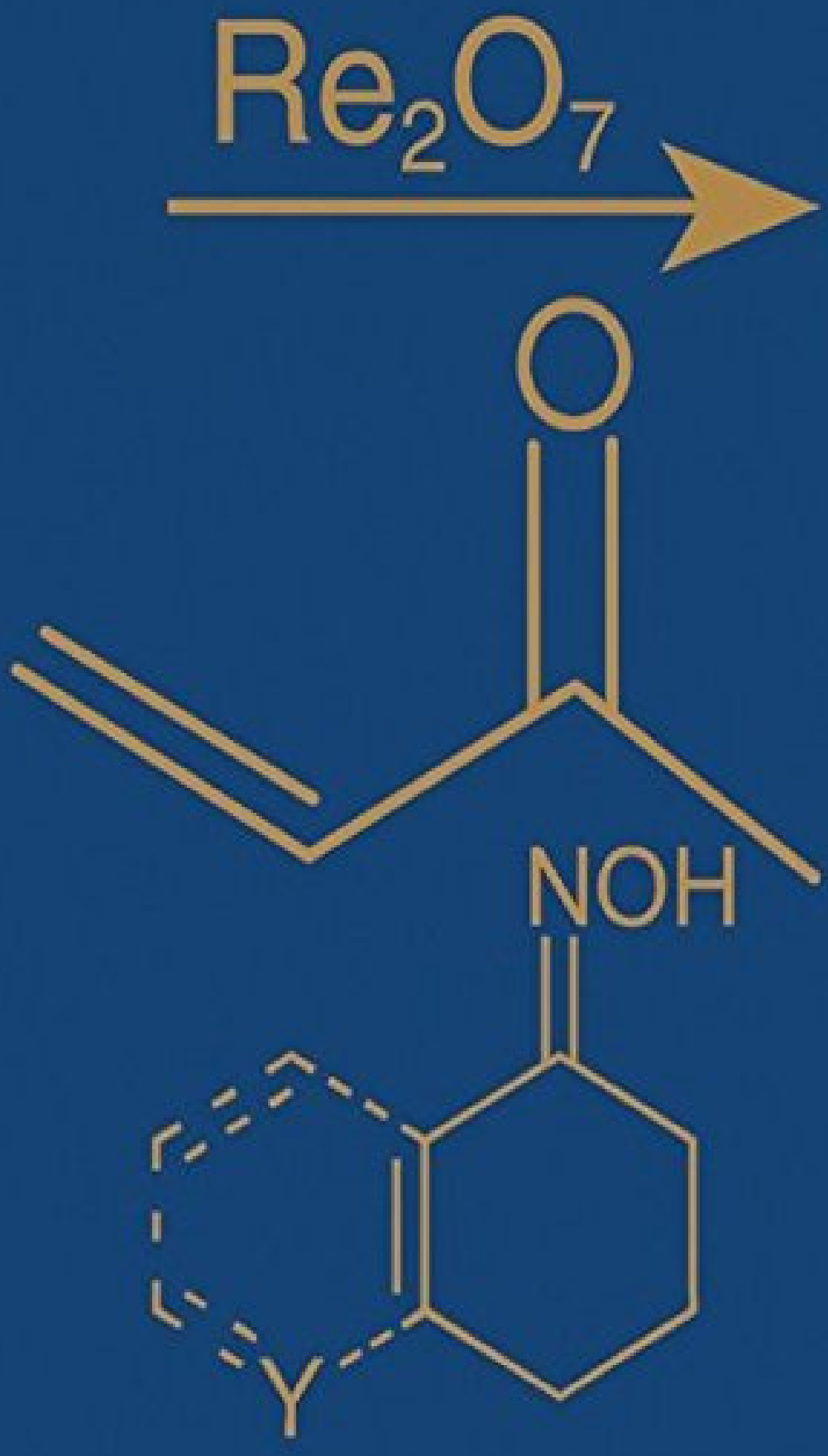

Re2O7
O
NOH
Y

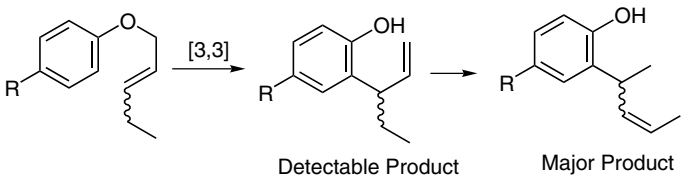
1

Abnormal Claisen Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

The first example of abnormal Claisen rearrangements was reported by Lauer and Filbert in 1936.[1] In contrast to the regular Claisen rearrangement ([3,3] σ migration),[2] the abnormal Claisen rearrangement[3] usually occurs for the allyl aromatic ethers. A similar reaction also occurs for the thermal rearrangement of cyclopropyl ketones to homoallylic ketones.[4] The abnormal Claisen rearrangement is believed to proceed via two consecutive processes, i.e., the normal *ortho* Claisen rearrangement of γ-alkylallyl aryl ether to an *o*-(α-alkylallyl) phenol and the isomerization of the resulting phenol. In general, this type of abnormal Claisen rearrangement does not occur smoothly, except when in the presence of Lewis acids $FeCl_3$, even though other Lewis acids (e.g., $HfCl_4$, $GaCl_3$, $ZrCl_4$) have limited ability to accelerate such reaction.[3a] It is reported that the abnormal Claisen rearrangement can be prevented by the application of 1,1,1,3,3,3-hexamethyldisilazane and *N*,*O*-bis(trimethylsilyl)acetamide.[5]

B. GENERAL REACTION SCHEME



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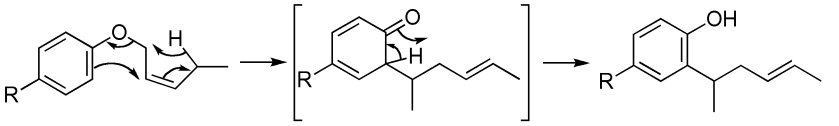
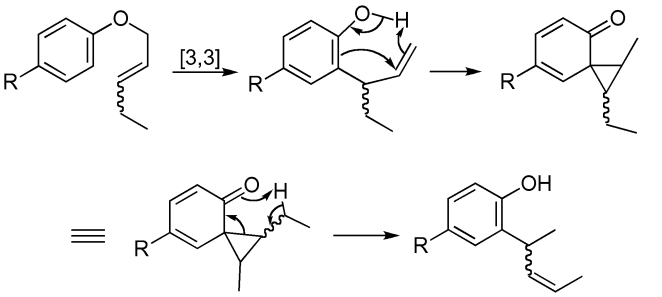
C. PROPOSED MECHANISMS

Two kinds of mechanisms have been proposed for the abnormal Claisen rearrangement: the concerted process (Scheme 1)[6] and the stepwise process consisting of two consecutive steps (Scheme 2).[4] However, much experimental evidence is inconsistent with the stepwise mechanism.



SCHEME 1. *Concerted mechanism for abnormal Claisen rearrangement.*



SCHEME 2. *Stepwise mechanism for abnormal Claisen rearrangement.*

D. MODIFICATION

N/A

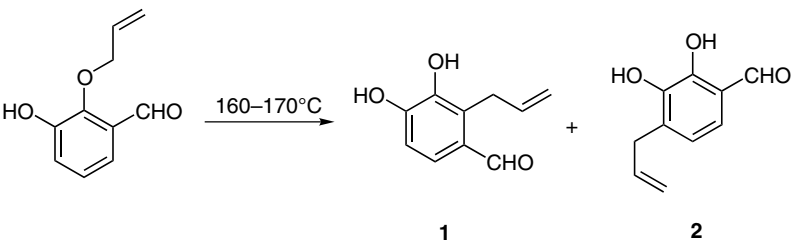
E. APPLICATIONS

This reaction has certain applications in organic synthesis.

F. RELATED REACTIONS

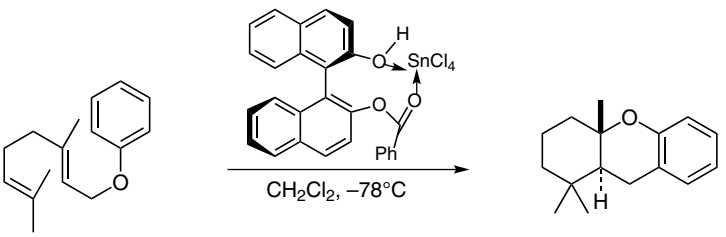
This reaction is related to the *Claisen Rearrangement*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

Caution! The reaction becomes vigorous and exothermic when heated above 200°C, especially on a large scale. To a 25-mL round-bottomed flask equipped with a magnetic stirring bar and an air condenser was added 5.06 g 3-hydroxy-2-(2-propenyloxy)benzaldehyde (28.43 mmol). The flask was gently heated to melt the solid and then placed in a Wood's metal bath at 165–170°C. After an induction period of a few minutes, the liquid in the flask darkened and evolved a gas. When the reaction was finished (detected by TLC) and cooled down, the mixture was triturated 10 times with boiling hexane. The dark, granular residue was dissolved in EtOAc and adsorbed on 10 silica. The mixture was separated by column chromatography using hexane/EtOAc/AcOH (65:35:1) as the eluent to give the major normal Claisen rearrangement product and the first abnormal Claisen rearrangement product, i.e., 2-allyl-3,4-dihydroxybenzaldehyde (**1**). The hexane extracts were evaporated and chromatographed on silica using hexane/EtOAc/AcOH (80:20:1) as eluent to give the second abnormal Claisen rearrangement product, i.e., 2,3-dihydroxy-4-allylbenzaldehyde (**2**) and other minor products.



Reference 3a.

General Procedure for the Preparation of Geranyl Phenyl Ether

To a stirred suspension of 176 mg sodium hydride (60% in oil, 4.4 mmol) in 20 mL THF at room temperature under argon atmosphere was added 0.376 g phenol (4.0 mmol) in portions followed by a catalytic amount of hydroquinone. The mixture was stirred for 0.5 h. HMPA (2 mL) and 0.74 mL geranyl chloride (4.0 mmol) were successively added. The whole mixture was stirred for 1 day. After decomposition of excess sodium hydride with 0.5 mL methanol, the mixture was poured onto ice water and extracted with ether. The combined organic layers were dried, concentrated, and purified by column chromatography on silica gel (hexane-dichloromethane as eluent).

General Procedure for the Enantioselective Cyclization of Geranyl Phenol Ether Promoted by the BINOL-$SnCl_4$ Complex

To a solution of BINOL (0.22 mmol) in 4 mL distilled CH_2Cl_2 was added 200 μL 1.0 M $SnCl_4$ in CH_2Cl_2 (0.2 mmol) at −78°C under argon atmosphere. After the mixture was stirred for several minutes at the same temperature, 0.230 g geranyl phenyl ether (0.1 mmol) was added dropwise at −78°C. After the resulting mixture was stirred for 3 days at −78°C, 16 μL pyridine (0.2 mmol) was added. Then the mixture was poured onto a saturated $NaHCO_3$ solution and extracted with ether. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography using hexane/CH_2Cl_2 (4:1) as the eluent to give 98% of the rearrangement product as detected by GC.

Other references related to the abnormal Claisen rearrangement can be found in the literature.[8]

H. REFERENCES

1. Lauer, W. M. and Filbert, W. F., *J. Am. Chem. Soc.*, **1936**, *58*, 1388.
2. See *Claisen Rearrangement* herein (P. 649).
3. (a) Nakamura, S.; Ishihara, K. and Yamamoto, H., *J. Am. Chem. Soc.,* **2000**, *122*, 8131. (b) Patel, G. N. and Trivedi, K. N., *J. Indian Chem. Soc.,* **1988**, *65*, 192. (c) Shah, R. R. and Trivedi, K. N., *Curr. Sci.,* **1975**, *44*, 226. (d) Jain, A. C. and Gupta, R. K., *Chem. Lett*., **1974**, 1353. (e) Mahey, S.; Seshadri, T. R. and Mukerjee, S. K., *Indian J. Chem.,* **1973**, *11*, 1126. (f) Jain, A. C. and Jain, S. M., *Indian J. Chem.,* **1972**, *10*, 971. (g) Hansen, H. J., *Mech. Mol. Migr.,* **1971**, *3*, 177. (h) Jefferson, A. and Scheinmann, F., *J. Chem. Soc., C,* **1969**, 243. (i) Marvell, E. N. and Schatz, B. S., *Tetrahedron Lett.,* **1967**, 67. (j) Roberts, R. M. and Landolt, R. G., *J. Org. Chem.,* **1966**, *31*, 2699. (k) Jefferson, A. and Scheinmann, F., *Chem. Commun. (London),* **1966**, 239. (l) Marvell, E. N.; Anderson, D. R. and Ong, J., *J. Org. Chem.,* **1962**, *27*, 1109. (m) Habich, A.; Barner, R.; Roberts, R. M. and Schmid, H., *Helv. Chim. Acta,* **1962**, *45*, 1943.
4. (a) Roberts, R. M.; Landolt, R. G.; Greene, R. N. and Heyer, E. W. *J. Am. Chem. Soc.,* **1967**, *89*, 1404. (b) Roberts, R. M. and Landolt, R. G. *J. Am. Chem. Soc.,* **1965**, *87*, 2281.
5. Fukuyama, T.; Li, G. Q. and Peng, G., *Tetrahedron Lett.,* **1994**, *35*, 2145.
6. Lauer, W. M.; Doldouras, G. A.; Hileman, R. E. and Liepins, R., *J. Org. Chem.,* **1961**, *26*, 4785.
7. Kilenyi, S. N.; Mahaux, J. M. and Van Durme, E., *J. Org. Chem*., **1991**, *56*, 2591.
8. (a) Puranik, R.; Rao, Y. J. and Krupadanam, G. L. D., *Indian J. Chem. Section B: Org. Chem.,* **2002**, *41B*, 868. (b) Schobert, R.; Siegfried, S.; Gordon, G.; Mulholland, D.; Nieuwenhuyzen, M., *Tetrahedron Lett.,* **2001**, *42*, 4561. (c) Ito, H.; Sato, A. and Taguchi, T., *Tetrahedron Lett.*, **1997**, *38*, 4815. (d) Palani, N. and Balasubramanian, K. K., *Tetrahedron Lett.,* **1993**, *34*, 5001. (e) Grieco, P. A.; Clark, J. D. and Jagoe, C. T., *J. Am. Chem. Soc.,* **1991**, *113*, 5488. (f) Shah, R. R. and Trivedi, K. N., *Indian J. Chem., Section B: Org. Chem.,* **1981**, *20B*, 210. (g) Okely, H. M. and Grundon, M. F., *J. Chem. Soc., Perkin Trans. I,* **1981**, 897. (h) Yagodin, V. G.; Bunina-Krivorukova, L. I. and Bal'yan, K. V., *Zh. Org. Khim.,* **1970**, *6*, 2513. (i) Lauer, W. M. and Johnson, T. A., *J. Org. Chem.,* **1963**, *28*, 2913.

2

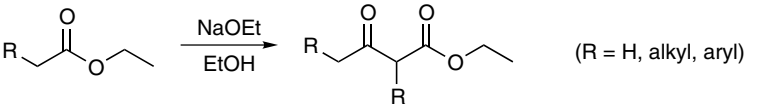
Acetoacetic Ester Condensation

(Claisen-Geuther Ester Condensation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Geuther in 1863[1] and subsequently studied by Claisen.[2] It is a self-condensation of ester in the presence of alkali alkoxide in alcohol to form β-keto esters (e.g. ethyl acetoacetate from ethyl acetate) and is generally known as acetoacetic ester condensation.[3] This reaction was extensively explored by McElvain in 1930s.[4] In general, it is carried out under basic conditions (e.g., NaOEt) to generate β-keto-esters from aliphatic carboxylic acid esters.

B. GENERAL REACTION SCHEME



(R = H, alkyl, aryl)

C. PROPOSED MECHANISMS

The general mechanism for acetoacetic ester condensation shown here uses ethyl acetate as an example.[3f,4]

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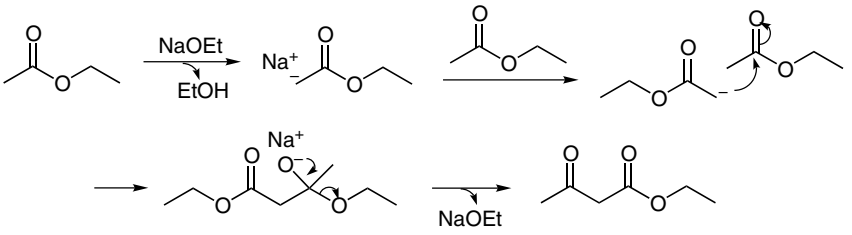


D. MODIFICATION

Three esters (ethyl isovalerate, ethyl *t*-butylacetate, and ethyl isobutyrate) do not undergo this type of condensation under normal conditions with sodium ethoxide, presumably due to the steric hindrance. However, their condensation proceeds readily when mesitylmagnesium bromide is applied as the base.[5] In addition, the acetoacetic ester condensation has been improved to give high yields using some quaternary ammonium salts of long aliphatic chains as the phase transfer catalyst in benzene.[6]

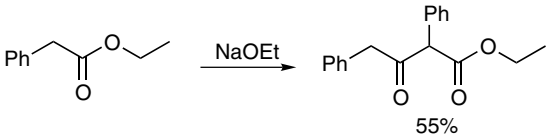
E. APPLICATIONS

This reaction is useful for the synthesis of a series of β-keto esters (both branched and unbranched). In addition, ethyl acetoacetate can be applied to the preparation of γ-diketones in reaction with epoxides followed by oxidation and decarboxylation.[7]

F. RELATED REACTIONS

This reaction is related to *Acetoacetic Ester Synthesis*.

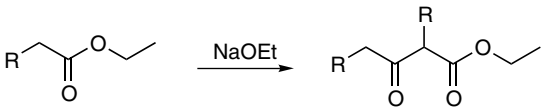
G. CITED EXPERIMENTAL EXAMPLES



Reference 3a.

To a 500-mL flask equipped with a sealed stirrer and a reflux condenser were added fresh NaOEt (prepared from 4.6 g sodium) and 70.0 g ethyl phenylacetate (0.42 mol). The flask was heated with stirring in a steam bath at about 95°C for 6 h; however, the solid material (NaOEt) in the reaction mixture completely disappeared after a few minutes of heating. Then the flask was cooled to room temperature and treated carefully with 15 mL acetic acid in 100 mL water. At this point, a considerable amount of ethyl α,γ-diphenylacetoacetate precipitated. Ether (150 mL) was added to return this precipitate to solution, and the

separated aqueous layer was further extracted with 50 mL ether. The combined ether layers were washed sufficiently with saturated sodium bicarbonate solution. After the removal of ether, the residue was allowed to crystallize, and the resulting crystalline mass was again added to 20 mL alcohol and kept at 0°C. The precipitate was filtered off by suction and dried over a porous plate, and 28 g of material was obtained. The filtrate was then distilled from an oil bath to remove alcohol, and the unreacted ethyl phenylacetate was collected at 5 mmHg. The residue was dissolved in another 10 mL hot alcohol and cooled to 0°C. An additional 3 g ethyl α,γ-diphenylacetoacetate was recovered. The yield was 55% on the basis of sodium ethoxide used, or 78% based on the ethyl phenylacetate recovered. The product has an m.p. 75 – 77°C.



$R = C_nH_{2n+1}$, $n = 1, 2, \ldots 12$

Reference 3f.

To a 125 mL Claisen flask equipped with a 35-cm-long fractioning column were placed 0.1 mol corresponding ester and 0.05 mol NaOEt. The fractioning column was attached to a receiving flask (without cooling) that was in turn attached through a soda lime tower and a safety bottle to a manometer and a water pump. The flask was then heated carefully in an oil bath to a temperature and under a pressure that caused a moderate, but not too vigorous, evolution of alcohol vapor, as shown by the ebullition of the reaction mixture. The required temperature and pressure varied with the boiling point of the esters; the lower esters required lower reaction temperatures and higher pressures to prevent the loss of ester. Consequently, the time necessary for the completion of the reaction in these cases was increased. After the reaction had proceeded for some time, the temperatures and pressures could be raised and lowered, respectively, until the reaction mass ceased ebullition. The reaction product after cooling was treated with the calculated quantity of 30% acetic acid and shaken vigorously until the sodium salt had been completely decomposed. The β-keto ester was then extracted with 25 mL ether followed by the standard workup procedure. This procedure was quite satisfactory for all of the esters except ethyl α-pelargonylpelargonate and ethyl α-caprylcaprate, both of which suffered a small amount of pyrolysis to the corresponding ketone.

Other references related to acetoacetic ester condensation are cited in the literature.[8]

H. REFERENCES

1. Geuther, A., *Arch. Pharm.,* **1863**, *106*, 97.
2. Claisen, R. L. and Lowman, O., *Ber*., **1887**, *20*, 651.
3. (a) Roberts, D. C and McElvain, S. M., *J. Am. Chem. Soc.,* **1937**, *59*, 2007. (b) Meincke, E. R. and McElvain, S. M., *J. Am. Chem. Soc,* **1935**, *57*, 1443. (c) Cox, R. F. B. and McElvain, S. M., *J. Am. Chem. Soc.*, **1934**, *56*, 2459. (d) Fisher, N. and McElvain, S. M., *J. Am. Chem. Soc.,* **1934**, *56*, 1766. (e) Thomas, W. B. and McElvain, S. M., *J. Am. Chem. Soc.*, **1934**, *56*, 1806. (f) Cox, R. F. B.; Kroeker, E. H. and McElvain, S. M., *J. Am. Chem. Soc.,* **1934,** *56*, 1173. (g) Briese, R.

R. and McElvain, S. M., *J. Am. Chem. Soc.,* **1933**, *55*, 1697. (h) Prill, E. A. and McElvain, S. M., *J. Am. Chem. Soc.,* **1933**, *55*, 1233. (i) Snell, J. M. and McElvain, S. M., *J. Am. Chem. Soc.*, **1933**, *55*, 416. (j) Snell, J. M. and McElvain, S. M., *J. Am. Chem. Soc.* **1931**, *53*, 2310. (k) Snell, J. M. and McElvain, S. M., *J. Am. Chem. Soc.,* **1931**, *53*, 750. (l) McElvain, S. M., *J. Am. Chem. Soc.,* **1929**, *51*, 3124.

4. Frampton, O. D. and Nobis, J. F., *Ind. Eng. Chem.*, **1953**, *45*, 404.
5. Spielman, M. A. and Schmidt, M. T., *J. Am. Chem. Soc*., **1937**, *59*, 2009.
6. Durst, H. D. and Liebeskind, L., *J. Org. Chem.*, **1974**, *39*, 3271.
7. Adams, R. M. and Vanderwerf, C. A., *J. Am. Chem. Soc.*, **1950**, *72*, 4368.
8. (a) Chandra, M. and Mehrotra, J. K., *J. Indian Chem. Soc.,* **1970**, *47*, 46. (b) Colonge, J. and Cayrel, J.-P., *Bull. Soc. Chim. Fr.,* **1965**, 3596. (c) Shivers, J. C.; Hudson, B. E. and Hauser, C. R., *J. Am. Chem. Soc.,* **1943**, *65*, 2051. (d) Hauser, C. R. and Hudson, B. E., *Org. React.,* **1942**, *1*, 266. (e) Roland, J. R. and McElvain, S. M., *J. Am. Chem. Soc.,* **1937**, *59*, 132. (f) Adickes, F., *Ber.,* **1932**, *65B*, 522. (g) Franklin, M. C. and Short, W. F., *J. Chem. Soc.,* **1928**, 591. (h) Scheibler, H. and Marhenkel, E., *Ann.,* **1927**, *458*, 1. (i) Scheibler, H., *Angew. Chem.,* **1923**, *36*, 6. (j) Branch, G. E. K. and Branch, H. E. H., *J. Am. Chem. Soc.,* **1918**, *40*, 1708.

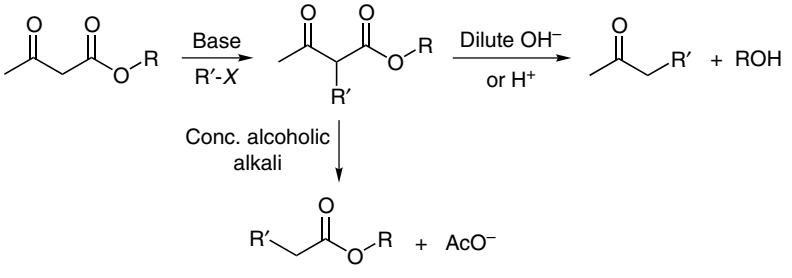
3

Acetoacetic Ester Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Simonsen in 1908;[1] unfortunately, it was not named after this inventor. It is the synthesis of α-substituted acetic acid esters or substituted acetones from acetoacetic ester by treatment of ethyl acetoacetate with a strong base, followed by alkylation and subsequent deacetylation or decarboxylation; it is known as acetoacetic ester synthesis.[2] Being adjacent to two electron-withdrawing groups (i.e., carbonyl and ester groups), the α-methylene protons in β-ketoesters (e.g., acetoacetic esters) are very acidic; the pKa of which could be as low as 10.[3] Therefore, the α-methylene proton is readily deprotonated, and the resulting α-carbanion can be alkylated or acylated. In addition, the acetoacetic esters can also be alkylated in acidic condition via the form of enol intermediate, although some unexpected products might form.[4] The new substituted β-ketoesters are then either treated with a concentrated base (normally strong base) to give substituted esters or are hydrolyzed under mild conditions (either acidic or basic) to give substituted acetones through decarboxylation.[5,6]

B. GENERAL REACTION SCHEME



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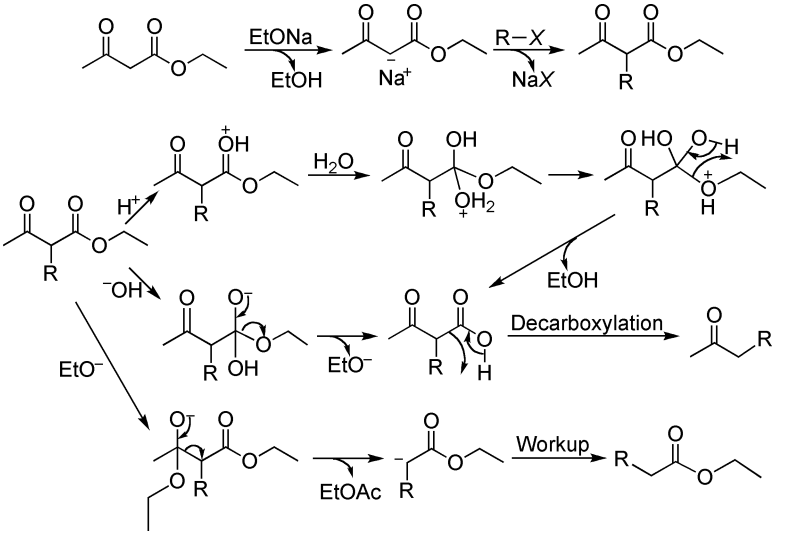
C. PROPOSED MECHANISMS

Displayed here is a general mechanism for acetoacetic ester synthesis from ethyl acetylacetate.

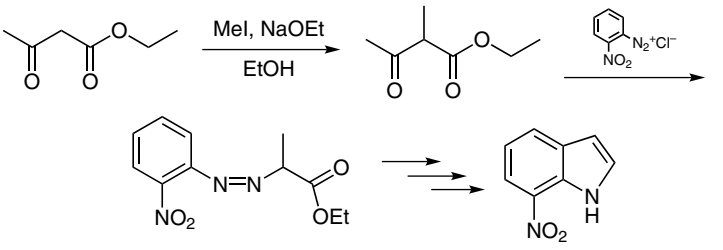


D. MODIFICATION

N/A

E. APPLICATIONS

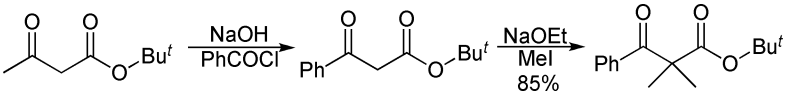
Besides the applications to synthesize ketones and esters, this reaction has been used to synthesize 7-nitro-indole by me in 1995, as shown in the following reaction route.



F. RELATED REACTIONS

This reaction is very closely related to *Acetoacetic Ester Condensation*; and mechanistically, the cleavage of β-ketoesters under strong base conditions is similar to the *Retro-Aldol Addition*.

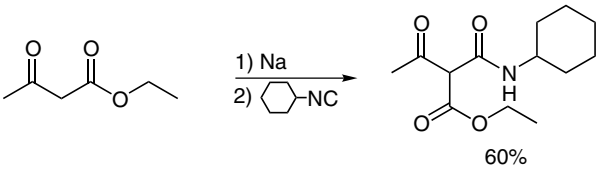
G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

To a 500-mL three-necked flask equipped with a mechanical stirrer and two pressure-equalizing dropping funnels was added a mixture of 100 mL water and 50 mL hexane. The flask was placed in an ice bath. To the cooled mixture was added 40 mL *tert*-butyl acetoacetate and 13 mL of a solution of 66 g NaOH in 200 mL water. Through the two dropping funnels were added 40 mL freshly distilled benzoyl chloride and 54 mL of the NaOH solution over a period of 2 h with stirring. The solution was then warmed to 35°C for 30 min. The layers were separated in a separatory funnel, and the aqueous layer was collected and stirred with 16 g NH_4Cl for 15 h. After filtration to remove solids, 18 g NaCl was added to the filtrate to induce the separation of phases. The organic layer was collected, and the aqueous layer was extracted with ether. The extracts combined with the organic layer were dried by addition of benzene and azeotropic evaporation on rotary evaporator. The residue was distilled at 115–116°C (0.5 mmHg) to afford *t*-butyl α-benzoylacetate.

To the three-necked flask equipped with a dropping funnel was added NaOEt solution prepared from 1.1 g sodium in 15 mL absolute ethanol. When the solution was cooled to 5°C, 4.5 g of *tert*-butyl benzoylacetate was added under stirring. After a while, 10.0 g iodomethane, which had been cooled to −17°C was added. The reaction flask was stoppered, and after 16 h the reaction mixture was refluxed gently to ensure completion of the reaction. Sodium iodide precipitated during the course of the reaction. The solution was filtered, and ethanol was removed by rotary evaporation. The flask was cooled to 5°C, and the solution was neutralized with an NH_4Cl solution prepared from 2.7 g ammonium chloride in 20 mL water. The solution was extracted with ether (2 × 100 mL), and the ether extracts were combined. The aqueous layer then was acidified with 10 mL 1 M HCl and then extracted again with ether. The combined ether extracts were dried over anhydrous sodium thiosulfate, a procedure that also removes iodine. After filtration and evaporation, the residue was distilled at 85–90°C (0.2 mmHg) to give 85% of *tert*-butyl α,α-dimethyl-benzoylacetate.



Reference 8.

To a three-necked flask were added 300 mL anhydrous ether and 4.6 g sodium ribbons (0.2 mol), followed by 25.5 mL ethyl acetoacetate (0.2 mol) dropwise under well stirring. Then an additional 300 mL anhydrous ether was added, and the reaction mixture was refluxed for 4 h. Then 25.5 mL freshly distilled cyclohexyl isonitrile (0.2 mol) was added dropwise to the resulting viscous mixture. After being refluxed for 50 h, the reaction mixture

was diluted with 150 mL benzene and neutralized by adding an aqueous phosphate buffer solution while stirring vigorously. The benzene extracts were washed with 5% $NaHCO_3$ and water and dried over $MgSO_4$. Upon removal of solvent by evaporation, about 31.0 g *N*-cyclohexyl β-ethoxycarbonyl acetoacetamide was obtained, in a yield of 60%. The product was purified by crystallization in hexane, with on m.p. of 47.2–48°C.

Other references related to acetoacetic ester synthesis are cited in the literature.[9]

H. REFERENCES

1. Simonsen, J. L., *J. Chem. Soc., Trans.,* **1908**, *93*, 1777.
2. (a) Ogawa, K.; Sasaki, M. and Nozaki, T., *Appl. Radiation Isotopes,* **1997**, *48*, 623. (b) Sommer, L. H. and Marans, N. S., *J. Am. Chem. Soc.,* **1950**, *72*, 1935. (c) Scheibler, H. and Ziegner, H., *Ber.,* **1922**, 55*B*, 789. (d) Michael, A., *Ber.,* **1900**, *33*, 3731.
3. Koltheff, I. M., *Treatise on Analytical Chemistry*, Interscience Encyclopedia Inc. New York, **1959**.
4. (a) Bottin-Strzalko, T.; Corset, J.; Froment, F.; Pouet, M. J; Seyden-Penne, J. and Simonnin, M. P., *J. Org. Chem.,* **1980**, *45*, 1270. (b) Surmatis, J. D.; Walser, A.; Gibas, J. and Thommen, R., *J. Org. Chem*., **1970**, *35*, 1053.
5. Hammond, G. S. and Cram, D. J., *Organic Chemistry,* McGraw Hill, New York, **1959**, p. 260.
6. Fieser, L. F. and Fieser, M., *Advanced Organic Chemistry,* Reinhold Pub. Corp., New York, **1961**, p. 446.
7. Kluger, R. and Brandl, M., *J. Org. Chem.,* **1986**, *51***,** 3964.
8. Wicks, Z. W. and Wu, K.-J., *J. Org. Chem.,* **1980**, *45*, 2446.
9. (a) Makarov, V. A.; Solov'eva, N. P.; Chernyshev, V. V.; Sonneveld, E. J. and Granik, V. G., *Chem. Heterocycl. Compd.,* **2000**, *36*, 70. (b) Schimelpfenig, C. W., *J. Chem. Edu.,* **1977**, *54*, 446. (c) Durst, H. D. and Liebeskind, L., *J. Org. Chem.,* **1974**, *39*, 3271. (d) Temnikova, T. I.; Astaf'eva, A. E. and Semenova, S. N., *Zh. Org. Khim.,* **1970**, *6*, 736. (e) Temnikova, T. I.; Markina, G. V.; Borodavko, V. A. and Yaskina, N. I., *Zh. Org. Khim.,* **1970**, *6*, 739. (f) Simonsen, J. L. and Storey, R., *Proc. Chem. Soc.,* **1910**, *25*, 290. (g) Simonsen, J. L. and Storey, R., *J. Chem. Soc., Trans.,* **1909**, *95*, 2106.

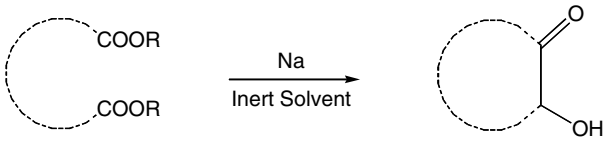
4

Acyloin Condensation
(Acyloin Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Bouveault and Blanc in 1903,[1] and was further extended by Bouveault and Locquin.[2] It is the synthesis of symmetrical α-hydroxy ketones via the reductive condensation of esters in an inert solvent in the presence of sodium. Since symmetrical α-hydroxy ketones, the aliphatic analogs of benzoins, are generally known as acyloins, the formation of α-hydroxy ketones from esters is simply referred to as acyloin condensation.[3] In a few cases, it is also referred to as acyloin reaction.[4] For the individual acyloin, the name is derived by adding the suffix *oin* to the stem name of corresponding acid, e.g., acetoin prepared from acetate.[5] The most common method used to make acyloin is the reductive condensation of aliphatic esters with sodium in inert solvents, such as ether, xylene or even in liquid NH_3.[3aaa] The yield of this reaction can be greatly improved when trimethylchlorosilane presents.[4d] Intromolecular acyloin condensation from aliphatic diesters affords cyclic ketones of different ring sizes.

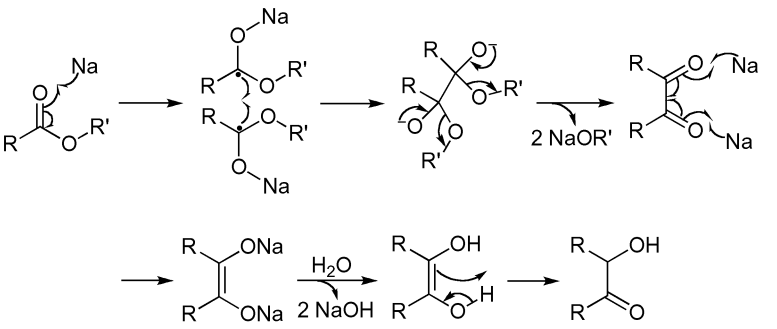
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

Under the reductive condition, the ester group is reduced to hemiacetal radical by sodium, and the coupling of the radical pairs accompanied with the elimination of alkoxide affords the α-dicarbonyl intermediate, which is further reduced by two sodium atoms to ene-diolate. Upon hydrolysis, the ene-diol tautomerizes to acyloin product.[6] A general mechanism for acyloin condensation is displayed below.



D. MODIFICATION

This reaction has been modified to form bis(trimethylsilyloxy) alkenes.[4d] In addition, C_8K[7] and thiazolium salt,[8] such as 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride,[3c] have been applied for the acyloin condensation.

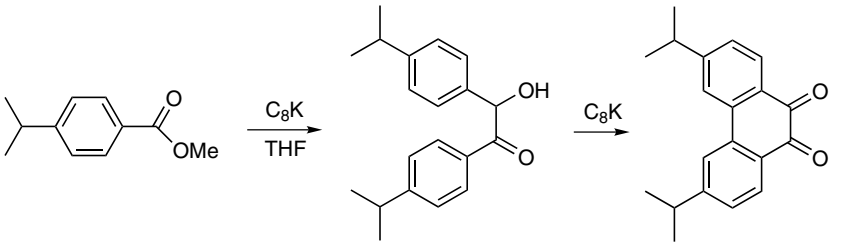
E. APPLICATIONS

This reaction has been used to synthesize cyclic ketones of intermediates to a large ring from diesters with long hydrocarbon chain between two ester groups.[9]

F. RELATED REACTIONS

This reaction is related to *Benzoin Condensation*, in which the benzoin is prepared from benzaldehyde.

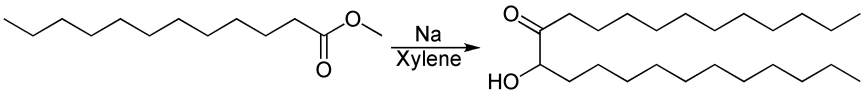
G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

Preparation of C_8K. To a 100 mL argon-flushed and flame-dried three-necked round-bottomed flask, were added 2.4 g of graphite powder, and magnetic stir bar. The graphite powder was heated to 150°C under argon atmosphere while stirring. After 15 minutes, 1 g of clean potassium metal (25 mmol) was added in slices. The stirring at 150°C was continued until the bronze-colored C_8K was formed. The reagent was cooled to room temperature and kept under argon.

The generally procedure for acyloin condensation. To the above flask (protected under argon) was added 50 mL of dry THF, and the flask was kept at 25°C under argon atmosphere. Then a solution of 710 mg of methyl *p*-isopropylbenzoate (4 mmol) in 50 mL of solvent was dropped into the reaction mixture over 20 minutes under stirring. The reaction was monitored by TLC. After the ester was totally consumed, the mixture was stirred for 1 hour and then cooled to 0°C, and 10 mL of water was added to the solution (no violent reaction occurred at this moment). The reaction mixture was filtered through a fritted glass funnel, and the filter cake was washed with two 25-mL portions of ether. The combined filtrate was washed twice with 20 mL of water, the organic phase was dried over $MgSO_4$, and removed by evaporation. The crude product (400 mg) was then purified on a chromatographic preparative plate. Crystallization from methanol gave 175 mg of 3,6-diisopropylphenanthrenequinone, in yield of 30%, m.p. 155-157°C.



Reference 10.

To a 5-L three-necked flask (equipped with a high speed stirrer and protected by nitrogen or other inert gas) was added a mixture of 115 g of sodium (5 mol) and 3 L of xylene. The mixture was heated to 105°C, and the sodium melted. The stirrer was started and the sodium dispersed in a finely divided state in the xylene. From a separatory funnel, 535 g of methyl laurate (2.5 mol) was then added into the flask. The addition was at such a rate that the temperature did not rise above 110°C. The addition of the ester required about 1 hour. Stirring was continued for one-half hour after the ester had been added. Small portion of unchanged sodium were decomposed by the addition of an excess of methanol (1–2 mol). After cooling to about 80°C, 0.5 to 1 L of water was added cautiously until the alkali had

dissolved, and the layers were separated by decantation. After one or two more washings of the xylene layer with water, the remaining alkali was neutralized with a slight excess of mineral acid, and this excess acid was finally neutralized with sodium bicarbonate. The xylene was removed by steam distillation, and the residual oily layer was poured into a suitable vessel to solidify. The impure product contains 80–90% of the lauroin, which can be purified through crystallization from 95% ethanol, m.p. 62°C.

Other references related to acyloin condensation are cited in literature.[11]

H. REFERENCES

1. (a) Bouveault, L. and Blanc, G., *Compt. Rend.,* **1903**, *137*, 60. (b) Bouveault, L. and Blanc, G., *Compt. Rend.,* **1903**, *137*, 328. (c) Bouveault, L. and Blanc, G., *Compt. Rend.,* **1903**, *137*, 1676. (d) Bouveault, L. and Blanc, G., *Bull. Soc. Chim. Fr.,* **1904**, *31*, 748. (e) Bouveault, L. and Blanc, G., *Bull. Soc. Chim. Fr.,* **1904**, *31*, 1213. (f) Bouveault, L. and Blanc, G., *Compt. Rend.,* **1904**, *138*, 148.
2. (a) Bouveault, L. and Loquin, R., *Compt. Rend,* **1905**, *140*, 1593. (b) Bouveault, L. and Loquin, R., *Compt. Rend,* **1905**, *140*, 1699.
3. (a) Saito, T.; Kimishima, A. and Nakata, T., *Heterocycles,* **2006**, *70*, 177. (b) Sanchez-Gonzalez, M. and Rosazza, J. P. N., *Adv. Synth. Catal.,* **2003**, *345*, 819. (c) Heck, R.; Henderson, A. P.; Kohler, B.; Retey, J. and Golding, B. T., *Eur. J. Org. Chem.,* **2001**, 2623. (d) Guo, Z.; Goswami, A.; Nanduri, V. B. and Patel, R. N.; *Tetrahedron: Asymmetry,* **2001**, *12*, 571. (e) Zhang, Y.-m.; Gao, D.-w.; Su, B.; Zhao, T.-q. and Meng, F.-y., *Jingxi Huagong,* **2000**, *17*, 358. (f) Guo, Z. W.; Goswami, A.; Mirfakhrae, K. D. and Patel, R. N., *Tetrahedron: Asymmetry,* **1999**, *10*, 4667. (g) Motesharei, K. and Myles, D. C., *J. Am. Chem. Soc.,* **1997**, *119*, 6674. (h) Yamashita, K.; Sasaki, S.-i.; Osaki, T.; Nango, M. and Tsuda, K., *Tetrahedron Lett.,* **1995**, *36*, 4817. (i) Cetinkaya, E. and Kucukbay, H., *Turk. J. Chem.,* **1995**, *19*, 24. (j) Friedrich, K.; Haesler, J. and Pulst, S., *J. Prakt. Chem./Chem.-Zeit.,* **1995**, *337*, 63. (k) Ebert, C.; Gardossi, L.; Gianferrara, T.; Linda, P. and Morandini, C., *Biocatalysis,* **1994**, *10*, 15. (l) Yamashita, K.; Osaki, T.; Sasaki, K.; Yokota, H.; Oshima, N.; Nango, M. and Tsuda, K., *J. Poly. Sci., Part A: Poly. Chem.,* **1994**, *32*, 1711. (m) Praefcke, K.; Psaras, P. and Bilgin, B., *Chem. Ber.,* **1992**, *125*, 285. (n) Stumpf, B. and Kieslich, K., *Appl. Microbiol. Biotech.,* **1991**, *34*, 598. (o) Fadel, A.; Canet, J. L. and Salaun, J., *Synlett,* **1990**, 89. (p) Yamashita, K.; Shimizu, Y.; Tokuda, H.; Kuromiya, T. and Tsuda, K., *J. Poly. Sci., Part A: Poly. Chem.,* **1989**, *27*, 4389. (q) Abraham, W. R. and Stumpf, B., *Zeit. Naturforsch., C: J. Biosci.,* **1987**, *42*, 559. (r) Tamarkin, D. and Rabinovitz, M., *J. Org. Chem.,* **1987**, *52*, 3472. (s) McGarvey, G. J. and Kimura, M., *J. Org. Chem.,* **1985**, 50, 4655. (t) Stetter, H. and Kuhlmann, H., *Org. Synth.,* **1984**, *62*, 170. (u) Matsumoto, T.; Ohishi, M. and Inoue, S., *J. Org. Chem.,* **1985**, *50*, 603. (v) Nallaiah, C., *J. Poly. Sci., Poly. Chem. Ed.,* **1984**, *22*, 3107. (w) Shinkai, S.; Hara, Y. and Manabe, O., *Bull. Chem. Soc. Jpn.,* **1983**, *56*, 770. (x) Hanson, J. R. and Triana, J., *J. Chem. Soc., Perkin Trans. I,* **1982**, 611. (y) Snyder, W. H. and Akef, N., *Poly. Preprints,* **1978**, *19*, 562. (z) Drusiani, A.; Plessi, L. and Porzi, G., *Chim. Ind. (Milan)*, **1978**, 60, 717. (aa) Bloomfield, J. J. and Nelke, J. M., *Org. Synth.,* **1977**, *57*, 1. (bb) Khachatryan, L. A.; Akhnazaryan, A. A.; Dzhivanshiryan, T. L. and Dangyan, M. T., *Zh. Org. Khim.,* **1977**, *13*, 2516. (cc) Babicheva, A. F.; Vovk, A. I. and Yasnikov, A. A., *Ukr. Khim. Zh.,* **1976**, *42*, 259. (dd) Bloomfield, J. J.; Owsley, D. C. and Nelke, J. M., *Org. React.,* **1976**, 23, 259. (ee) Bloomfield, J. J.; Owsley, D. C.; Ainsworth, C. and Robertson, R. E., *J. Org. Chem.,* **1975**, *40*, 393. (ff) Naoshima, Y.; Yamaguchi, M.; Kawai, M.; Ichimoto, I. and Ueda, H., *Agri. Biol. Chem.,* **1974**, *38*, 2273. (gg) Andryushina, V. A.; Popova, E. V.; Anisimova, O. S. and Grinenko, G. S., *Zh. Org. Khim.,* **1974**, *10*, 1212.

(hh) Delbaere, C. U. L. and Whitman, G. H., *J. Chem. Soc., Perkin Trans. I,* **1974**, 879. (ii) Yasnikov, A. A. and Babicheva, A. F., *Ukr. Khim. Zh.,* **1974**, *40*, 52. (jj) Tagaki, W. and Hara, H., *J. Chem. Soc., Chem. Commun.,* **1973**, 891. (kk) Babicheva, A. F.; Pokhodenko, V. D. and Yasnikov, A. A., *Ukr. Khim. Zh.,* **1973**, *39*, 472. (ll) Bloomfield, J. J.; Martin, R. A. and Nelke, J. M., *J. Chem. Soc., Chem. Commun.,* **1972**, 96. (mm) Strating, J.; Reiffers, S. and Wynberg, H., *Synthesis,* **1971**, 209. (nn) Ainsworth, C. and Chen, F., *J. Org. Chem.,* **1970**, *35*, 1272. (oo) Mori, T.; Nakahara, T. and Nozaki, H., *Can. J. Chem.,* **1969**, *47*, 3266. (pp) Detert, D. and Lindberg, B., *Acta Chem. Scand.,* **1969**, *23*, 690. (qq) Ames, D. E.; Hall, G. and Warren, B. T., *J. Chem. Soc. C,* **1968**, 2617. (rr) Bloomfield, J. J., *Tetrahedron Lett.,* **1968**, 591. (ss) Bloomfield, J. J., *Tetrahedron Lett.,* **1968**, 587. (tt) Russell, G. A. and Whittle, P. R., *J. Am. Chem. Soc.,* **1967**, 89, 6781. (uu) Fujita, E.; Fujita, T.; Katayama, H. and Kunishima, S., *Chem. Commun. (London),* **1967**, 258. (vv) Totten, E. L.; Camp, N. C.; Cooper, G. M.; Haywood, B. D. and Lewis, D. P., *J. Org. Chem.,* **1967**, *32*, 2033. (ww) Stepanov, F. N. and Danilenko, G. I., *Zh. Org. Khim.,* **1967**, *3*, 533. (xx) Bloomfield, J. J. and Irelan, J. R. S., *J. Org. Chem.,* **1966**, *31*, 2017. (yy) Binte, H. J. and Henseke, G., *Zeit. Chem.,* **1965**, 5, 268. (zz) Totton, E. L.; Kilpatrick, G. R.; Horton, N. and Blakeney, S. A., *J. Org. Chem.,* **1965**, *30*, 1647. (aaa) Finley, K. T., *Chem. Rev.,* **1964**, *64*, 573. (bbb) Taits, S. Z. and Gol'dfarb, Ya. L., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1963**, 1289. (ccc) Totton, E. L.; Freeman, R. C.; Powell, H. and Yarboro, T. L., *J. Org. Chem.,* **1961**, *26*, 343. (ddd) Gauglitz, E. J. and Malins, D. C., *J. Am. Oil Chem. Soc.,* **1960**, *37*, 425. (eee) Sheehan, J. C. and Erman, W. F., *J. Am. Chem. Soc.,* **1957**, *79*, 6050. (fff) Downes, J. E. and Sykes, P., *Chem. & Ind. (London),* **1957**, 1095. (ggg) Gorlich, B., *Chem. Ber.,* **1956**, *89*, 2145. (hhh) Juni, E. and Heym, G. A., *J. Biol. Chem.,* **1956**, *218*, 365. (iii) Sheehan, J. C.; Erman, W. F. and Cruickshank, P. A., *J. Am. Chem. Soc.,* **1957**, *79*, 147. (jjj) Juni, E. and Heym, G. A., *J. Biol. Chem.,* **1956**, *218*, 365. (kkk) Van Heyningen, E. M., *J. Am. Chem. Soc.,* **1955**, *77*, 4016. (lll) Mathes, W.; Sauermilch, W. and Klein, T., *Chem. Ber.,* **1954**, 87, 1870. (mmm) Cordon, M.; Knight, J. D. and Cram, D. J., *J. Am. Chem. Soc.,* **1954**, *76*, 1643. (nnn) Sheehan, J. C.; Coderre, R. A. and Cruickshank, P. A., *J. Am. Chem. Soc.,* **1953**, *75*, 6231. (ooo) Sheehan, J. C. and Coderre, R. C., *J. Am. Chem. Soc.,* **1953**, *75*, 3997. (ppp) Sheehan, J. C.; Coderre, R. C.; Cohen, L. A. and O'Neill, R. C., *J. Am. Chem. Soc.,* **1952**, *74*, 6155. (qqq) Van Heyningen, E., *J. Am. Chem. Soc.,* **1952**, *74*, 4861. (rrr) Sheehan, J. C. and O'Neill, R. C., *J. Am. Chem. Soc.,* **1950**, *72*, 4614. (sss) Sheehan, J. C.; O'Neill, R. C. and White, M. A., *J. Am. Chem. Soc.,* **1950**, *72*, 3376. (ttt) Cardon, S. Z. and Lankelma, H. P., *J. Am. Chem. Soc.,* **1948**, *70*, 4248. (uuu) Yamasaki, I. and Karashima, T., *Enzymologia,* **1937**, *3*, 271. (vvv) Dirscherl, W., *Z. Physiol. Chem.,* **1931**, *201*, 47.

4. (a) Henry-Riyad, H. and Tidwell, T. T., *Can. J. Chem.,* **2003**, *81*, 697. (b) Makosza, M. and Grela, K., *Synlett,* **1997**, 267. (c) Daynard, T. S.; Eby, P. S. and Hutchinson, J. H., *Can. J. Chem.,* **1993**, *71*, 1022. (d) Cookson, C. M. and Whitham, G. H., *J. Chem. Soc., Perkin Trans. I,* **1975**, 806.
5. McElvain, S. M. "*Chapter 4, The Acyloins*", in Organic Reactions, Ed. by Adams, R., John Wiley & Sons, Inc. New York, **1948**, Vol. 4, pp. 256-268.
6. Snell, J. M. and McElvain, S. M., *J. Am. Chem. Soc.* **1931**, *53*, 750.
7. Tamarkin, D. and Rabinovitz, M., *J. Org. Chem.,* **1987**, *52*, 3472.
8. Matsumoto, T.; Ohishi, M. and Inoue, S., *J. Org. Chem.,* **1985**, *50*, 603.
9. Bloomfield, J. J.; Owsley, D. C. and Nelke, J. M., *Org. React.,* **1976**, *23*, 259.
10. Hansley, V. L., *J. Am. Chem. Soc.,* **1935**, *57*, 2303.
11. (a) Stetter, H. and Daembkes, G., *Synthesis,* **1980**, 309. (b) Stetter, H. and Daembkes, G., *Synthesis,* **1977**, 403. (c) Woodward, R. B. and Blout, E. R., *J. Am. Chem. Soc.,* **1943**, *65*, 562. (d) Corson, B. B.; Benson, W. L. and Goodwin, T. T., *J. Am. Chem. Soc.,* **1930**, *52*, 3988.

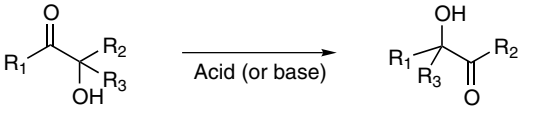
5

Acyloin Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

Acyloins are the general name of symmetrical α-hydroxy ketones, the aliphatic analogs of benzoins; and the individual name is derived by adding the suffix-*oin* to the stem name of the corresponding acid.[1] The acyloin rearrangement is the conversion of an α-hydroxycarbonyl compound into its structural isomer (also an α-hydroxylcarbonyl compound), which is accomplished by the interchange of the carbonyl group and migration of an alkyl group to the adjacent carbon atom.[2] While this rearrangement is usually promoted by acid[3] or base,[4] it also proceeds under pyrolytic conditions;[5] and the thermal acyloin rearrangement can be accelerated by high pressure.[6] The details of acyloin rearrangement are given in the literature.[7]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Both acid-(Scheme 1) and base-(Scheme 2) catalyzed reactions are displayed here.

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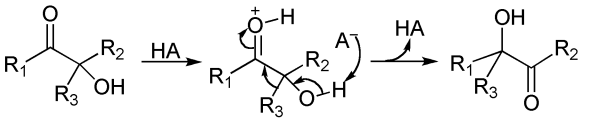
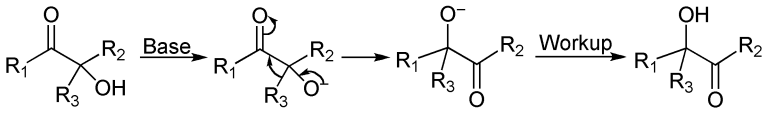


SCHEME 1. *An acid-catalyzed acyloin rearrangement.*



SCHEME 2. *Mechanism of a base-catalyzed acyloin rearrangement.*

D. MODIFICATION

N/A

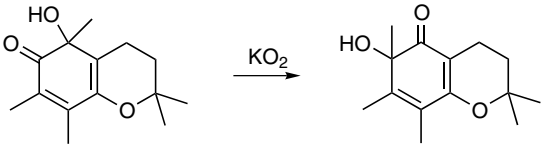
E. APPLICATIONS

This reaction has general applications in organic synthesis.

F. RELATED REACTIONS

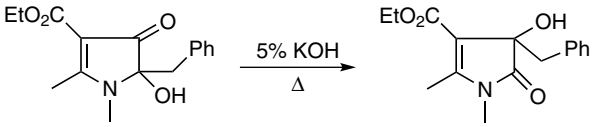
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 8.

A solution of 236 mg 5-hydroxy-2,2,5,7,8-pentamethylchroman-6(5H)-one (1 mmol) in 20 mL dry THF was added to a stirred suspension of 70 mg potassium superoxide (KO_2, 1 mmol) in 50 mL dry THF at 0°C. The reaction mixture was stirred for 1 h at 0°C. The excess amount of KO_2 was decomposed by the addition of 10 mL water. The resulting mixture was extracted with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and filtered. Upon removal of solvent under reduced pressure, the resulting solid residue was purified by silica gel column chromatography using a mixture of *n*-hexane and ethyl ether (1:l) as eluent to afford 224 mg 6-hydroxy-2,2,6,7,8-pentamethylchroman-5(6H)-one, in a yield of 95%.



Reference 9.

A mixture of 2.89 g 1,2-dimethyl-3-(ethoxycarbonyl)-5-benzyl-5-hydroxy-2-pyrrolin-4-one (10 mmol), 30 mL 5% aqueous potassium hydroxide (30 mL), and 30 mL chloroform was heated with stirring in a water bath at 65°C for 10 min. Then the mixture was allowed to stand at room temperature for 1 h. After filtration, the resulting solution was acidified with 6 *N* HCl. The precipitated hydroxypyrrolinone was extracted with $CHCl_3$ (2 × 40 mL). The combined organic layers were washed with water and dried over Na_2SO_4. Upon removal of the solvent under reduced pressure, the remaining white solid was recrystallized to give 1.74 g 1,2-dimethyl-3-(ethoxycarbonyl)-4-benzyl-4-hydroxy-2-pyrrolin-5-one, in a yield of 60%, m.p. 119°C.

Other references related to acyloin rearrangement are cited in the literature.[10]

H. REFERENCES

1. McElvain, S. M., "The Acyloins," in *Organic Reaction*, vol. 4, ed. Adams, R., John Wiley & Sons, New York, **1948**, pp. 256–268.
2. Ingold, C. K., *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N.Y., **1953**; p. 728.
3. Ooi, T.; Ohmatsu, K. and Maruoka, K., *J. Am. Chem. Soc.,* **2007**, *129*, 2410.
4. (a) Katayama, S. and Yamauchi, M., *Chem. Pharm. Bull.,* **2005**, *53*, 666. (b) Hall, A. J.; Ferreira, D. and Roux, D. G., *J. Chem. Soc., Perkin Trans. I,* **1980**, 1025. (c) Nishinaga, A.; Itahara, T.; Matsuura, T.; Berger, S.; Henes, G. and Rieker, A., *Chem. Ber.,* **1976**, *109*, 1530.
5. Grunewald, G. L.; Walters, D. E. and Kroboth, T. R., *J. Org. Chem.,* **1978**, *43*, 3478.
6. Li, Z. H.; Mori, A. and Takeshita, H., *Sogo Rikogaku Kenkyuka Hokoku*, **1991**, *12*, 375.
7. de Mayo, P., ed., *Molecular Rearrangements*, Wiley, New York, **1964**, chaps. 1, 13–16.
8. Matsumoto, S.; Matsuo, M. and Iitaka, Y., *J. Org. Chem.,* **1986**, *51*, 1435.
9. Gelin, S. and Gelin, R., *J. Org. Chem.,* **1979**, *44*, 808.
10. (a) Katayama, S.; Hiramatsu, H.; Aoe, K. and Yamauchi, M., *Chem. Pharm. Bull.,* **1997**, *45*, 1419. (b) Sato, T.; Nagata, T.; Maeda, K. and Ohtsuka, S., *Tetrahedron Lett.,* **1994**, *35*, 5027. (c) McIntosh, J. M. and Cassidy, K. C., *Can. J. Chem.,* **1991**, *69*, 1315. (d) Uno, H.; Yayama, A. and Suzuki, H., *Chem. Lett.,* **1991**, 1165. (e) Werstiuk, N. H.; Wade, G. I. and Martin, P. J. J., *Can. J. Chem.,* **1985**, *63*, 2582. (f) Clemens, A. H.; Hartshorn, M. P.; Richards, K. E.; Robinson, W. T.; Sutton, K. H.; Vaughan, J. and Wright, G. J., *Aust. J. Chem.,* **1983**, *36*, 67. (g) Bates, P. A.; Ditzel, E. J.; Hartshorn, M. P.; Huong, T. I.; Richards, K. E. and Robinson, W. T., *Tetrahedron Lett.,* **1981**, *22*, 2325. (h) Eckhardt, H. H.; Perst, H. and Marsch, M., *Tetrahedron Lett.,* **1979**, 4975. (i) Gokel, G. W. and Gerdes, H. M., *Tetrahedron Lett.,* **1979**, 3379. (j) Iriye, R., *Agri. Biol. Chem.,* **1978**, *42*, 1495. (k) Ishiguro, T.; Kondo, Y. and Takemoto, T., *Tetrahedron Lett.,* **1975**, 315. (l) Herz, W. and Baburao, V., *J. Org. Chem.,* **1971**, *36*, 3899. (m) Nye, M. J. and Tang, W. P., *J. Chem. Soc., Chem. Commun.,* **1971**, 1394. (n) Bartsch, H. and Hecker, E., *Ann.,* **1969**, *725*, 142.

6

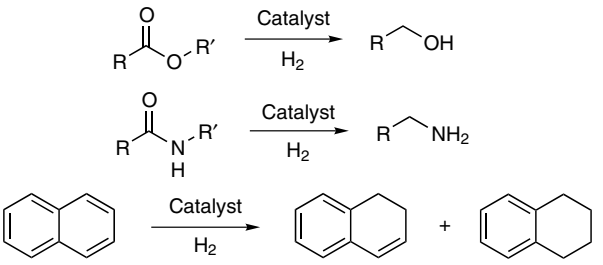
Adkins Catalyst

A. GENERAL DESCRIPTION OF THE REACTION

Adkins catalysts are kinds of metal complexes prepared from chromium, copper, nickel, platinum, etc. These catalysts were primarily developed by Homer Adkins and have been applied to many organic reactions, e.g., hydrogenation, dehydrogenation and decarboxylation. Hydrogenations include the hydrogenation of ester to alcohol,[1] hydrogenation of amide to amine,[2] and other hydrogenations.[3] Similarly, dehydrogenations include dehydrogenation of alcohol,[4] dehydrogenation of aromatic compounds,[5] and some other dehydrogenations.[6] The protocols for the preparation of these catalysts are also provided by Adkins.[7]

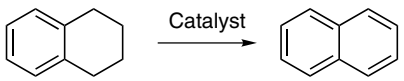
B. GENERAL REACTION SCHEME

Some representative reactions are illustrated here.



Hydrogenation

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

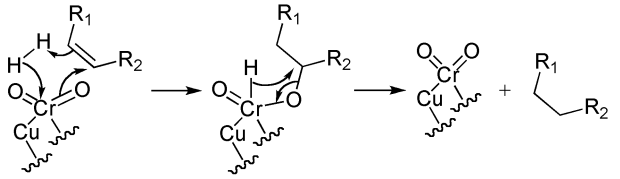


Dehydrogenation

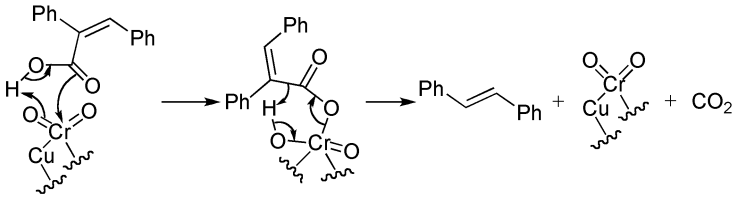
C. PROPOSED MECHANISMS

The mechanisms of a few representative reactions are illustrated: in the hydrogenation of alkene (Scheme 1), the decarboxylation of conjugated carboxylic acid (Scheme 2), and the dehydrogenation of diols (Scheme 3).

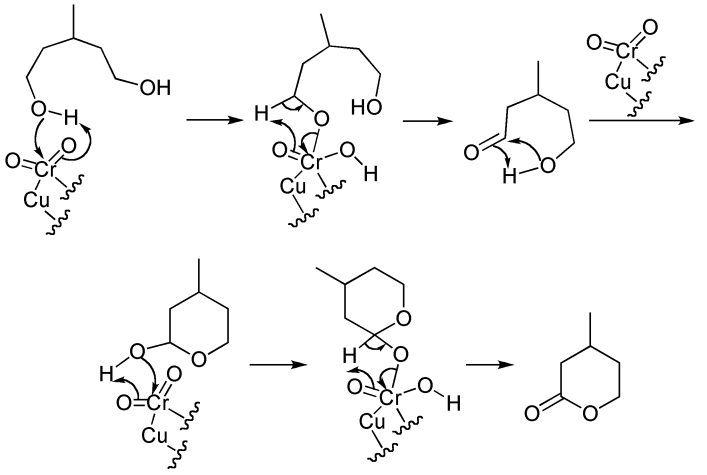
For hydrogenation, the Adkins catalyst will help the cleavage of a hydrogen-hydrogen bond so that the hydrogen can add to double bonds (Scheme 1).



SCHEME 1. *Hydrogenation of olefin over an Adkins catalyst.*



SCHEME 2. *Decarboxylation of α,β-unsaturated carboxylic acids.*



SCHEME 3. *Dehydrogenation of a diol.*

D. MODIFICATION

N/A

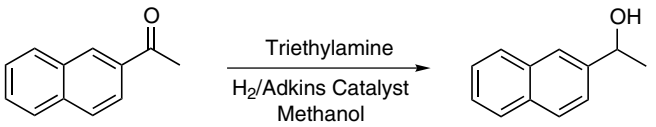
E. APPLICATIONS

This reaction has broad applications in organic synthesis, especially on a large reaction scale.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3g.

The Preparation of Catalyst HJS 2

To a 900 mL of a solution (at 25°C) prepared from 178 g sodium dichromate dihydrate ($Na_2Cr_2O_7 \cdot 2H_2O$) and 225 mL 28% NH_4OH was poured 900 mL of a solution (at 80°C) containing 260 g copper nitrate trihydrate ($Cu(NO_3)_2 \cdot 3H_2O$) and 31 g $Ba(NO_3)_2$. The orange precipitate was collected on a filter, washed with 200 mL of water in two portions, pressed and sucked as dry as possible, dried at 75–80°C for 12 h and pulverized. This product was decomposed in a 1-L four-necked flask held in a Woods metal bath at 350°C. The flask was equipped with a wide air condenser, a funnel for introducing a solid, a thermometer, and a stainless-steel stirrer with a 1.25-cm-wide and 10-cm-long crescent blade. The material to be decomposed was added through the funnel during a period of 15 min with rapid stirring. The product was heated with stirring at a bath temperature of 350°C for 20 min after all of the material had been added. The product from the decomposition was leached by stirring for 30 min with 600 mL 10% acetic acid at room temperature. The powder was washed with water (6 × 100 mL), dried at 125°C for 12 h and pulverized. The catalyst so obtained was brownish black and amounted to 160–170 g. The cooper-chromium oxide catalyst was activated by shaking the catalyst, suspended in methanol, under approximately 4000 psi of hydrogen at 100°C for 5 min. The reaction vessel was then cooled to room temperature, and the compound to be hydrogenated was added.

The Hydrogenation of Methyl 2-Naphthyl Ketone

A mixture of 17 g methyl 2-naphthyl ketone and 10 g of the activated catalyst (described above) in 100 mL methanol was stirred under a hydrogen pressure of 4000 psi. Methyl-2-naphthylcarbinol was obtained, m.p. 74–75°C.

Other references related to the Adkins catalyst are cited in the literature.[8]

H. REFERENCES

1. (a) Adkins, H. and Folkers, K., *J. Am. Chem. Soc*., **1931**, *53*, 1095. (b) Folkers, K. and Adkins, H., *J. Am. Chem. Soc.*, **1932**, *54*, 1145. (c) Adkins, H.; Wojcik, B. and Covert, L. W., *J. Am. Chem. Soc*., **1933**, *55*, 1669. (d) Sauer, J. and Adkins, H., *J. Am. Chem. Soc*., **1937**, *59*, 1. (e) Adkins, H. and Pavlic, A. A., *J. Am. Chem. Soc.*, **1947**, *69*, 3039. (f) Adkins, H. and Billica, H. R., *J. Am. Chem. Soc.,* **1948**, *70*, 3121.
2. (a) Winans, C. F. and Adkins, H., *J. Am. Chem. Soc.*, **1933**, *55*, 2051. (b) Adkins, H. and Wojcik, B., *J. Am. Chem. Soc.*, **1934**, *56*, 247. (c) Wojcik, B. and Adkins, H., *J. Am. Chem. Soc*., **1934**, *56*, 2419. (d) Sauer, J. C. and Adkins, H., *J. Am. Chem. Soc.*, **1938**, *60*, 402.
3. (a) Adkins, H.; Diwoky, F. F. and Broderick, A. E., *J. Am. Chem. Soc.*, **1929**, *51*, 3418. (b) Adkins, H.; Zartman, W. H. and Cramer, H., *J. Am. Chem. Soc.*, **1931**, *53*, 1425. (c) Adkins, H. and Connor, R., *J. Am. Chem. Soc*., **1931**, *53*, 1091. (d) Bowden, E. and Adkins, H., *J. Am. Chem. Soc.*, **1934**, *56*, 689. (e) Adkins, H., *Ind. Eng. Chem.*, **1940**, *32*, 1189. (f) Adkins, H. and Billica, H. R., *J. Am. Chem. Soc.*, **1948**, *70*, 3118. (g) Adkins, H.; Burgoyne, E. E. and Schneider, H. J., *J. Am. Chem. Soc*., **1950**, *72*, 2626.
4. (a) Lazier, W. A. and Adkins, H., *J. Am. Chem. Soc*., **1925**, *47*, 1719. (b) Adkins, H.; Kommes, C. E.; Struss, E. F. and Dasler, W., *J. Am. Chem. Soc.,* **1933**, *55*, 2992.
5. (a) Adkins, H. and Reid, W. A., *J. Am. Chem. Soc.*, **1941**, *63*, 741. (b) Adkins, H.; Richards, L. M. and Davis, J. W., *J. Am. Chem. Soc.*, **1941**, *63*, 1320. (c) Adkins, H. and Lundsted, L. G., *J. Am. Chem. Soc.,* **1949**, *71*, 2964.
6. Adkins, H. and Lazier, W. A., *J. Am. Chem. Soc.*, **1924**, *46*, 2291.
7. (a) Connor, R.; Folkers, K. and Adkins, H., *J. Am. Chem. Soc*., **1931**, *53*, 2012. (b) Connor, R.; Folkers, K. and Adkins, H., *J. Am. Chem. Soc*., **1932**, *54*, 1138.
8. (a) Furusawa, T. and Kunii, D., *J. Chem. Eng. Jpn.,* **1971**, *4*, 274. (b) Ohtsuka, H.; Aomura, K.; Tomita, N.; Hashimoto, K. and Takada, O., *Hokkaido Daigaku Kogakubu Iho,* **1966**, 199. (c) Lanchec, G.; Blouri, B. and Rumpf, P., *Bull. Soc. Chem. Fr.,* **1966**, 3978. (d) Falkum, E. and Glenn, R. A., *Fuel,* **1952**, *31*, 133. (e) Falkum, E. and Glenn, R. A., *Fuel,* **1950**, *29*, 178. (f) Miyake, R., *Yakugaku Zasshi*, **1948**, *68*, 38. (g) Miyake, R., *Yakugaku Zasshi*, **1948**, *68*, 29. (h) Miyake, R., *Yakugaku Zasshi*, **1948**, *68*, 26. (i) Miyake, R., *Yakugaku Zasshi*, **1948**, *68*, 22. (j) Miyake, R., *Yakugaku Zasshi*, **1948**, *68*, 18. (k) Miyake, R., *Yakugaku Zasshi*, **1948**, *68*, 14. (l) Miyake, R., *Yakugaku Zasshi*, **1948**, *68*, 8.

7

Ainley and King Synthesis
(Ainley-King-Sargent Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

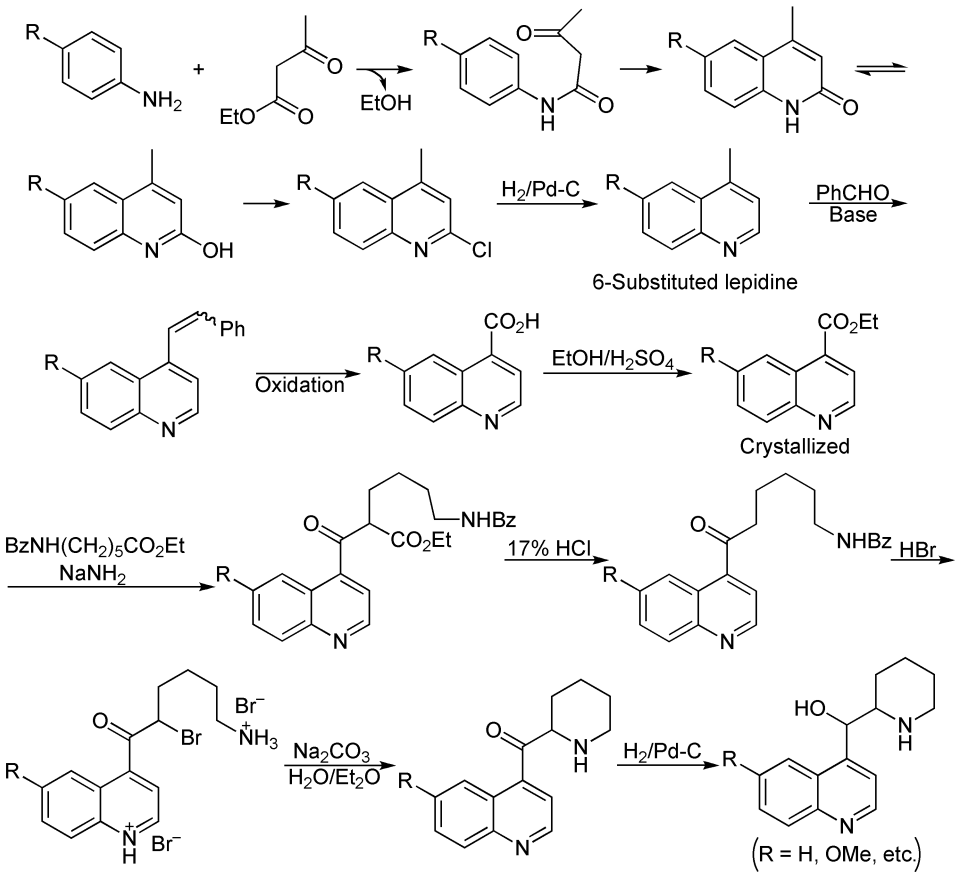
This reaction was reported first by Ruzicka et al. in 1924[1] and was extended by Ainley and King in 1935.[2] It is a multistep synthesis of α-piperidyl-4-quinolinemethanols[3] (or quinolyl-4-α-piperidylcarbinols[4]), involving the reaction of *(a)* amidation of *p*-anisidine by an acetoacetic ester, *(b)* electrophilic cyclization to give 2-hydroxy-lepidine, *(c)* replacement of the 2-hydroxyl group by a chlorine atom, *(d)* removal of chlorine by Pd/C catalyzed hydrogenation in AcOH, *(e)* condensation with benzaldehyde followed by oxidation to afford 4-quininic acid in 50% pyridine, *(f)* esterification of the 4-quininic acid, *(g)* Claisen-Geuther ester condensation[5] of ethyl quininate with ethyl ε-benzamidocaproate, *(h)* hydrolysis of the ester and β-decarboxylation, *(i)* α-bromination and cyclization, and *(j)* reduction of the carbonyl group to a secondary hydroxyl group via hydrogenation.[2,6] This reaction played an important role in the preparation of large quantities of quinine for antimalarial[3,4a,6,7] during the World War II and is generally known as the Ainley and King synthesis.[3,4a,6] Subsequently, this reaction has been modified by various researchers, especially by Sargent in 1946;[4] thus this synthesis is also referred to as the Ainley-King-Sargent synthesis.[8]

Compared to that of the Ruzicka protocol, the Claisen-Geuther ester condensation in this synthesis was optimized from 17% to 64% by replacement of sodium ethoxide with sodium or sodium amide. In addition, the cyclization to form the piperidinyl ring is carried out in a two-phase solvent system (H_2O and ether) using sodium carbonate as base.[2]

Among the subsequent modifications, it was found that, if the preparation of lepidine at the stage of dehalogenation is performed in warm alcoholic KOH in the presence of Raney nickel, the lepidine can be easily isolated; in addition, such dehalogenation can also be accomplished by zinc and acetic acid.[6] Moreover, the formation of quininic acid via oxidation in acetone was found to be superior to that in 50% pyridine due to the easy isolation of product.[5]

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Details of this multistep reaction are not shown because each step is very simple and obvious in modern organic synthesis.

D. MODIFICATION

Although the general reaction route of the Ainley and King synthesis is generally followed, each step has been modified in same way to produce large quantities of quinine. Some of the modifications are the removal of chlorine by zinc and acetic acid to form lepidine and the formation of quininic acid in acetone during the oxidation.[6]

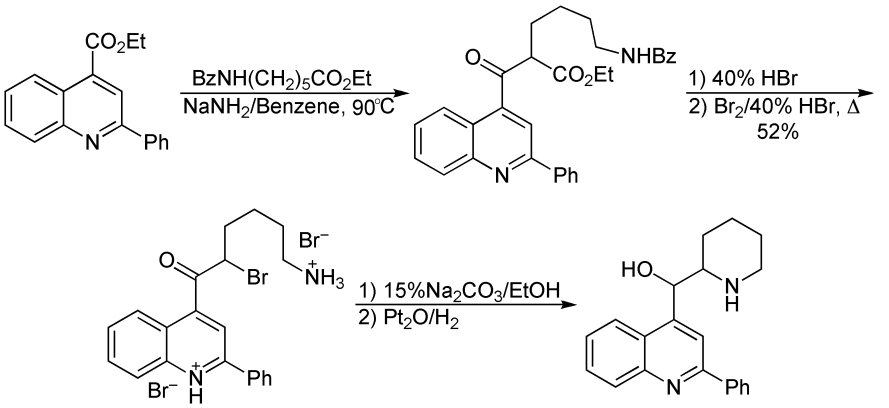
E. APPLICATIONS

This reaction provided the basic blueprint for the production of quinine in the 1940s, the product was widely used for the treatment of malaria.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3.

To a 5-L three-necked flask equipped with a Hirshberg stirrer and a condenser protected with a soda lime tube, were added 38.0 g powered sodium amide (1.65 mol), 360 g ethyl 2-phenylcinchoninate (1.30 mol), 345 g ethyl benzamidocaproate (1.31 mol), and 675 mL thiophene-free dry benzene. After the solution was stirred at 90°C for 22 h, the mixture was cooled in an ice water bath while a solution of 1.2 L concentrated HCl and 1 L water was added. The Hirshberg stirrer was then replaced with a stillhead, and the benzene steam distilled until the temperature of the vapor reached 108°C. After substituting a condenser for the stillhead, the remaining solution was refluxed for 40 h. The solution was then cooled and adjusted to pH 10–12 with 50% NaOH (920 mL). The ketone was extracted with 1.5 L $CHCl_3$ in portions and the combined organic layers were dried over Na_2SO_4. The chloroform solution of ketone was then extracted with 750 g 40% HBr, and chloroform was removed from the HBr layer by heating on a steam bath while stirring (30 min). The increase in weight of the solution was 304 g. (This part is not clearly stated, as the combined chloroform layers will be extracted with 48% HBr; it is not necessary to dry the chloroform solution with Na_2SO_4). Small amounts of ketone dihydrobromide can be isolated by cooling the solution; and recrystallization of the isolate solid in 96% ethanol is as yellow clusters of needles, with a m.p. of 225–227°C (dec.).

The solution of ketone dihydrobromide in 40% HBr was heated to 85°C and, under mechanical stirring, a solution of 138 g bromine in 275 mL 40% HBr was added over a period of 20 min, during which the temperature was maintained at 85–90°C. The product (ε-bromo-ε-(2-phenylcinchoninyl)-*N*-amylamine dihydrobromide) began to crystallize out before all the bromine was added. The mixture was heated to the boiling point and 250 mL 40% HBr was added, but the product did not dissolve. The reaction mixture was then chilled, and the precipitate was collected on a sintered glass funnel. It was washed by suspension in isopropanol to remove hydrobromic acid, then with acetone until the filtrate was colorless, and finally with ether. After drying in vacuo over NaOH, 334.5 g of a

light yellow powder was obtained, m.p. 210.5–212°C (dec.), and additional crop of 41 g of crystal was obtained after the mother liquors were concentrated to half volume. The total yield was 375 g (52%). (By acidifying the aqueous phase from the chloroform extraction of the ketone and washing the precipitate with ethanol to remove benzoic acid, 96 g of crude cinchophen was recovered.)

To a suspension of 140 g ε-bromo-ε-(2-phenylcinchoninyl)-*N*-amylamine dihydrobromide (0.25 mol) in 2.2 L absolute ethanol in a 4-L bottle was added 735 mL 15% (by weight) Na_2CO_3 solution. After displacing the air with nitrogen, the bottole was stoppered and shaken mechanically for 50 min. Then 3.0 g platinum oxide was added, and the bottle was filled with hydrogen. The reduction was performed at room temperature for 4 h, at which time the rate of hydrogen absorption had fallen from an initial 100 mL/min to 1 mL/min with the total uptake of 6.7 L. After removal of the catalyst and precipitated salts, ethanol was removed under reduced pressure. After decanting the aqueous phase, the residul oil was rinsed with water and dissolved in 1 L of absolute ethanol. The solution was filtered and 50 mL concentrated HCl was added. The precipitate was filtered, washed with acetone, and dried to give 71 g 2-phenyl-α-(2-piperidyl)-4-quinolinemethanol as a light pink powder, m.p. 226–228°C (dec.)

Other references related to the Ainley and King synthesis are cited in the literature.[9]

H. REFERENCES

1. Ruzicka, L.; Seidel, C. F. and Liebl, Fr., *Helv. Chim. Acta,* **1924**, *7*, 995.
2. Ainley, A. D. and King, H., *Proc. Royal Soc. London, Series B, Biol. Sci.,* **1938**, *125*, 60.
3. Rapport, M. M.; Senear, A. E.; Mead, J. F. and Koepfli, J. B., *J. Am. Chem. Soc.,* **1946**, *68*, 2697.
4. (a) Sargent, H., *J. Am. Chem. Soc.,* **1946**, *68*, 2688. (b) Buchman, E. R.; Sargent, H.; Myers, T. C. and Seneker, J. A., *J. Am. Chem. Soc.,* **1946**, *68*, 2692.
5. See *Acetoacetic Ester Condensation* herein (P. 5).
6. Campbell, K. N.; Tipson, R. S.; Elderfield, R. C.; Campbell, B. K.; Clapp, M. A.; Gensler, W. J.; Morrison, D. and Moran, W. J., *J. Org. Chem.,* **1946**, *11*, 803.
7. Mead, J. F.; Senear, A. E. and Koepfli, J. B., *J. Am. Chem. Soc.,* **1946**, *68*, 2708.
8. Winstein, S.; Jacobs, T. L.; Levy, E. F.; Seymour, D.; Linden, G. B. and Henderson, R. B., *J. Am. Chem. Soc.,* **1946**, *68*, 2714.
9. (a) Brasyunas, V. B.; Andreyanova, T. A.; Safonova, T. S.; Solov'eva, N. P.; Turchin, K. F. and Sheinker, Yu. N., *Chem. Heterocycl. Compd*., **1988**, *24*, 670. (b) Schultz, O. E. and Amschler, U., *Ann.,* **1970**, *740*, 192. (c) Harington, C. R., *Biograph. Memoirs Fellows Royal Soc.,* **1956**, *2*, 157. (d) Ramsey, V. G.; Baldwin, W. E. and Tipson, R. S., *J. Am. Chem. Soc.,* **1947**, *69*, 67. (e) Mead, J. F.; Rapport, M. M. and Koepfli, J. B., *J. Am. Chem. Soc.,* **1946**, *68*, 2704. (f) Work, T. S., *J. Chem. Soc.,* **1946**, 194. (g) Brown, R. F.; Jacobs, T. L.; Winstein, S.; Kloetzel, M. C.; Speath, E. C.; Florsheim, W. H.; Robson, J. H.; Levy, E. F.; Bryan, G. M.; Magnusson, A. B.; Miller, S. J.; Ott, M. L. and Terek, J. A., *J. Am. Chem. Soc.,* **1946**, *68*, 2705. (h) Buchman, E. R.; McCloskey, C. M. and Seneker, J. A., *J. Am. Chem. Soc.,* **1947**, *69*, 380. (i) Work, *J. Chem. Soc.,* **1942**, 426. (j) Rabe, P.; Huntenburg, W.; Schultze, A. and Volger, G., *Ber.,* **1931**, *64B*, 2487.

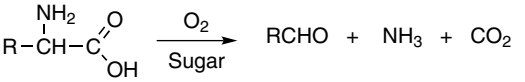
8

Akabori Amino Acid Reaction

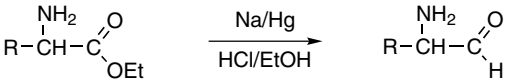
A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Akabori in 1931.[1] It is the synthesis of an aldehyde, an α-amino aldehyde, or a primary amine from α-amino acid under different reaction conditions. In the presence of a reducing agent (usually a reducing sugar), an α-amino acid is oxidized to an aldehyde and ammonia by molecular oxygen (Scheme 1). For comparison, the α-amino acid ester is reduced by sodium amalgam in alcoholic solution in the presence of hydrochloric acid to give an α-amino aldehyde (Scheme 2). However, under pyrolytic condition, the α-amino acid is converted to primary amine in the presence of benzaldehyde (Scheme 3).

B. GENERAL REACTION SCHEME



SCHEME 1. *Oxidation of α-amino acid to an aldehyde in the presence of a reducing sugar.*



SCHEME 2. *Formation of α-amino aldehydes via the reduction of α-amino acids or esters with sodium amalgam in the presence of ethanolic HCl.*

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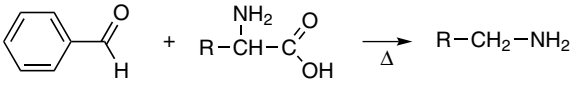
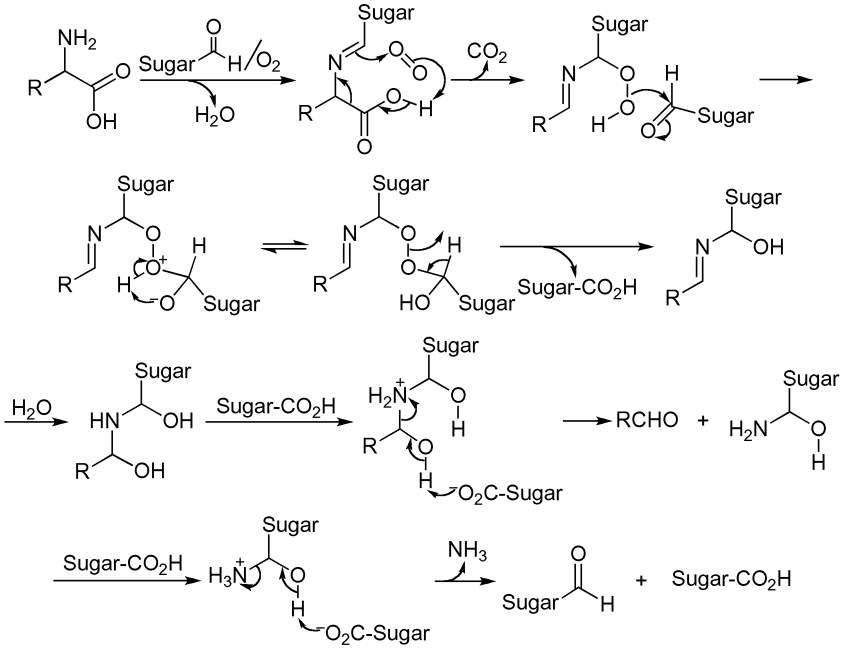


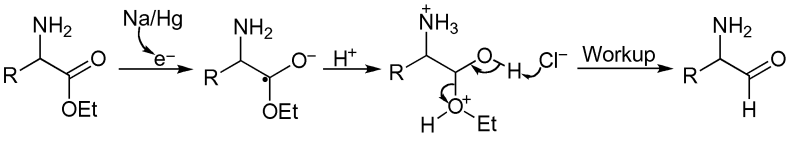
SCHEME 3. *Formation of a primary amine from the pyrolysis of an amino acid in the presence of an aromatic aldehyde (e.g., benzaldehyde).*

C. PROPOSED MECHANISMS

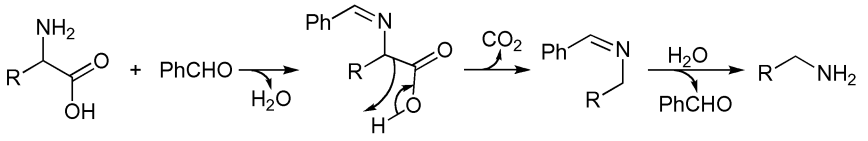
The mechanism for the conversion of α-amino acid to aldehyde in the presence of a reducing sugar (sugar was emphasized by the aldehyde group) is displayed in Scheme 4. The reduction of an α-amino acid or its ester derivatives to α-amino aldehyde by sodium amalgam in acidic alcohol is illustrated in Scheme 5, and the mechanism for the pyrolytic decarboxylation of an α-amino acid to a primary amine in the presence of an aromatic aldehyde is given in Scheme 6.



SCHEME 4. *Conversion of an α-amino acid into an aldehyde.*



SCHEME 5. *Reduction of an α-amino acid or its esters to α-amino aldehyde by a sodium amalgam.*



SCHEME 6. *Formation of primary amines via the pyrolysis of α-amino acids in the presence of an aromatic aldehyde.*

D. MODIFICATION

N/A

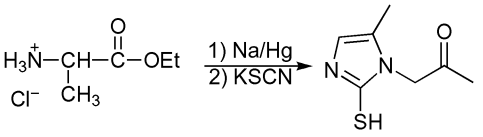
E. APPLICATIONS

This reaction has been used to synthesize dichlorophthalimido derivatives for the analysis of peptides, since the mass spectra of those derivatives are easily recognized due to the characteristic pattern of ions containing two chlorine atoms.[2] The simplicity of this technique is illustrated by the following general example, in which a few milligrams of a peptide is subjected to reaction with hydrazine dissolved in dimethlysulfoxide in a commercially available microwave oven for about 30 min. Samples are then removed from the solution in 5 min intervals, and the FAB MS of corresponding samples are recorded. In the case of oligopeptides, it is often possible to determine the entire sequence of amino acids via this application.

F. RELATED REACTIONS

N/A

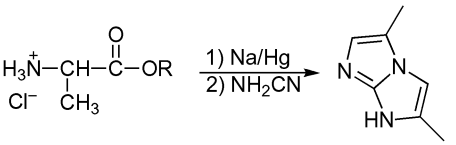
G. CITED EXPERIMENTAL EXAMPLES



Reference 3.

About 50 g of the hydrochloride salt of (DL)-α-alanine ethyl ester (0.56 mol) was subjected to reaction with 2 kg finely divided sodium amalgam (2.5%) at a pH between 2.0 and 4.5. The resultant mixture was then stirred for an additional 30 min. The solution was decanted from mercury and then filtered, and the pH of the filtrate was adjusted to 4.0 using a solution of sodium bicarbonate. Upon refluxing in the presence of 70 g potassium thiocyanate (0.72 mol), the solution acquired a dark brown color. After an additional 0.75-h reaction period, the solution was concentrated at atmospheric pressure until crystals began

to appear. The dark brown product was filtered off and subsequently recrystallized from water (charcoal was added to decolorize the solution), to give 16.5 g 1-acetyl-2-mercapto-5-methylglyoxaline as white blades, in a yield of 35%, m.p. 182–183°C.



Reference 4.

About 10 g of (DL)-α-alanine were first esterified with ethanol by standard methods. The resulting ester was then reduced with sodium amalgam using the reaction conditions described earlier. To the resultant 10 g solution of the aminoaldehyde, 10 g cyanamide in 60 mL 10% acetic acid aqueous solution was added, and the mixture was adjusted to pH 4.0–5.0 and then refluxed for 30 min. The cooled and filtered solution was then made alkaline by the addition of a solid sodium bicarbonate and extracted with ether to remove unused cyanamide and dicyandiamide. Sodium hydroxide was next added, and the solution was extracted with ether again. The ether solution was dried over Na_2SO_4 and evaporated. The residue was dissolved in a little anhydrous ether, and anhydrous hydrogen chloride was passed into the ether solution. The dark precipitated hydrochloride salt, in amount of 3.2 g, was recrystallized from ethanol to afford colorless prisms, m.p. 272°C (dec.).

Other references related to the Akabori amino acid reaction are cited in literature[5].

H. REFERENCES

1. Akabori, S., *Nippon Kagaku Kaishi,* **1931**, *52*, 606.
2. See www.pepnet.com/products/Antisera.pdf.
3. Lawson, A. and Morley, H. V., *J. Chem. Soc.,* **1955**, 1695.
4. Lawson, A., *J. Chem. Soc.,* **1956**, 307.
5. (a) Bose, A. K.; Ing, Y. H.; Lavlinskaia, N.; Sareen, C; Pramanik, B. N.; Bartner, P. L.; Liu, Y.-H. and Heimark, L., *J. Am. Soc. Mass Spectr.,* **2002**, *13*, 839. (b) Ambach, E. and Beck, W., *Chem. Ber.,* **1985**, *118*, 2722. (c) Belikov, V. M.; Vitt, S. V.; Kuznetsova, N. I.; Bezrukov, M. G. and Saporovskaya, M. B., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1969**, 2536. (d) Emoto, S. and Ando, M., *Nippon Nogei Kagaku Kaishi*, **1961**, *35*, 663. (e) Dose, K., *Ber.,* **1957**, *90*, 1251. (f) Takagi, E. and Mangyo, M., *Yakugaku Zasshi,* **1952**, 72, 812. (g) Takagi, E., *Yakugaku Zasshi,* **1951**, *71*, 648. (h) Akabori, S., *J. Chem. Soc.,* **1943**, *64*, 608. (i) Akabori, S., *Ber.,* **1933**, *66*, 143, 151.

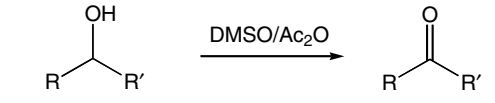
9

Albright-Goldman Oxidation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Albright and Goldman from the American Cyanamid Company in 1965.[1] It is a mild conversion of primary and secondary alcohols into corresponding aldehydes and ketones using the mixture of dimethyl sulfoxide and acetic anhydride as the oxidant. This reaction is particularly useful for the oxidation of the sterically hindered hydroxyl groups. In general, the oxidation is carried out by allowing a mixture of 1 mmol primary or secondary alcohol, 3 mL DMSO, and 2 mL (20 mmol excess) acetic anhydride to stand at room temperature for 18–24 h.[2]

B. GENERAL REACTION SCHEME

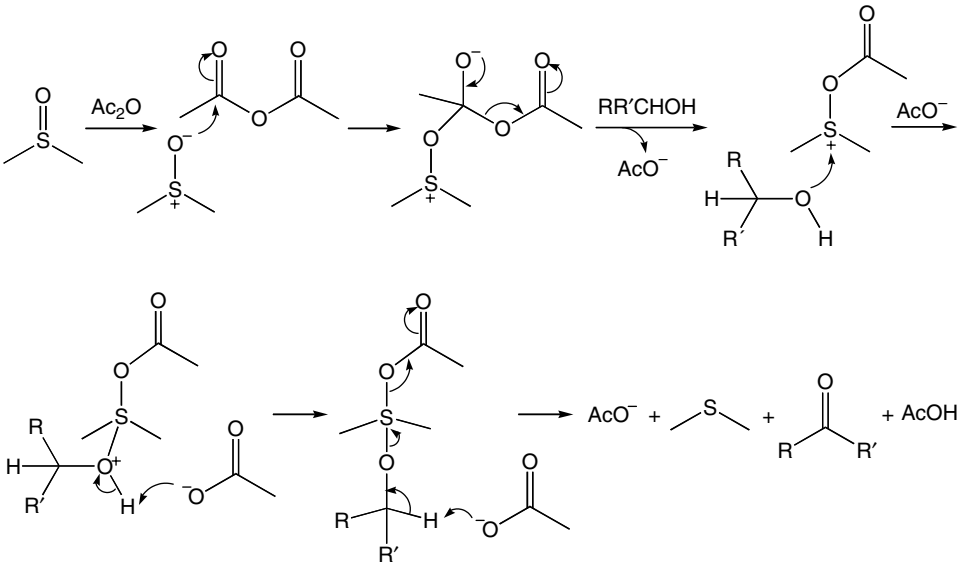


(R′ = H, alkyl or aryl)

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

Displayed here is a simple illustration of this reaction.



D. MODIFICATION

This reaction has been modified using the mixture of DMSO and one of the following reagents: benzoic anhydride, polyphosphoric acid, and phosphorus pentoxide. However, it seems that the mixture of acetic anhydride and DMSO is still the best combination for this reaction.[3]

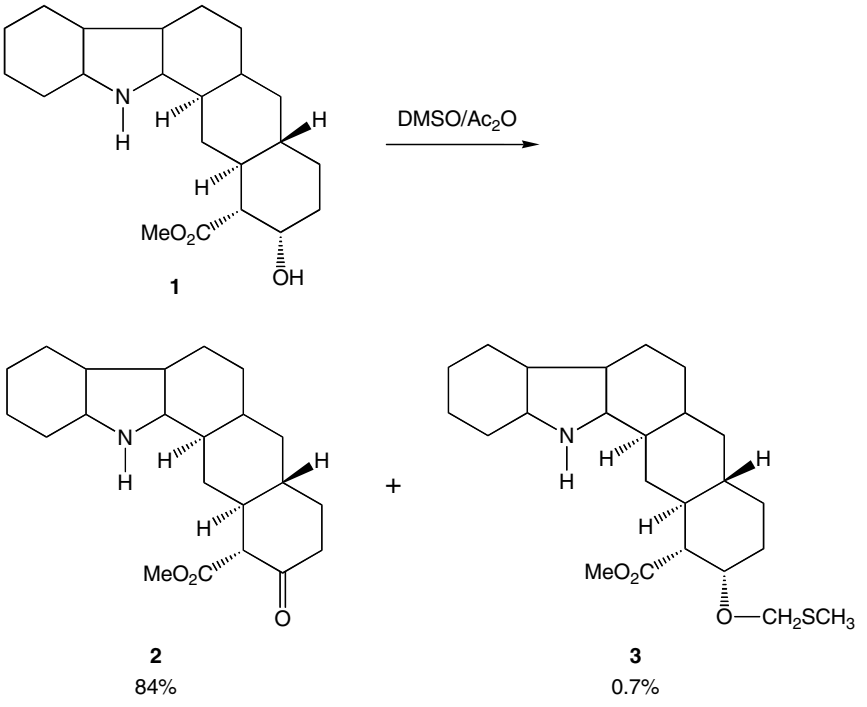
E. APPLICATIONS

This reaction has been used to convert primary and secondary alcohols into corresponding aldehydes and ketones, especially for the sterically hindered alcohols. This reaction has been commonly used in carbohydrate transformation. However, for the oxidation of phenols with DMSO/Ac_2O, the thiomethoxymethylation of the corresponding phenols occurs.[4]

F. RELATED REACTIONS

Other oxidation reactions using DMSO as an oxidant include the *Pfitzner-Moffatt Oxidation* (DMSO/dicyclohexylcarbodiimide), Swern oxidation (DMSO/oxalyl chloride or trifluoroacetic anhydride), Onodera oxidation (DMSO/phosphorus pentoxide), *Parikh-Doering Oxidation* (DMSO/pyridine-sulfur trioxide), *Corey-Kim Oxidation* (dimethyl sulfide/*N*-chlorosuccinimide), and Liu oxidation (DMSO/phenyl dichlorophosphate).

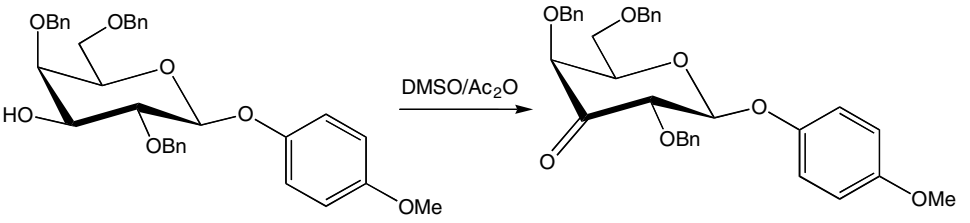
G. CITED EXPERIMENTAL EXAMPLES



Reference 3.

To a mixture of 886 g yohimbine (**1**) and 7.55 L dry dimethyl sulfoxide was added 5.05 L acetic anhydride. The mixture was stirred at room temperature for 18 h, then diluted with 16.8 L ethanol, stirred for 1 h, and mixed with 4.2 L water. Concentrated ammonium hydroxide (11 L) was added while maintaining the temperature at 15–30°C by cooling. The mixture was then diluted with 16.8 L water. Filtration gave a solid that was washed with water and dried to give 818 g (93%) of tan crystals, with a m.p. of 248–250°C (dec.). A slurry of this tan crystal was formed twice with 4 L ethanol, and 742 g methyl yohimban-17-one 16α-carboxylate **(2)** was obtained by filtration, in a yield of 84%, m.p. 253–254°C (dec.).

The filtrate from the first slurry with 4 L ethanol was concentrated to give a dark colored gum. The gum was dissolved in chloroform-acetone-ethanol (6:3:1) and filtered through synthetic magnesia silica gel. The filter cake was washed with acetone, and the combined filtrates were concentrated to give 40 g of dark gum. The gum (20 g) was chromatographed on a column of 300 g silica gel using chloroform-ethanol (99.3:0.7) as the eluting solvent and 250-mL cuts were collected. Evaporation of cuts 5–11 gave the product as a glass. The combined glass from two column purifications was crystallized from methanol to give 6.95 g (0.7%) methyl 17α-[(methylthio)methoxy]yohimban-l6α-carboxylate **(3)** as tan crystals, m.p. 195–198°C.



Reference 5.

To a mixture of 18 mL anhydrous DMSO and 15 mL acetic anhydride was added 2.93 g *p*-methoxyphenyl-2,4,6-tri-*O*-benzyl-β-D-galactopyranoside. The solution was stirred under nitrogen for 12 h at room temperature, then acetic anhydride was evaporated and the remaining solution was diluted with water and extracted with chloroform. The combined organic layers were washed with H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel using EtOAc/petroleum ether (1:3) as the eluent to give 2.45 g *p*-methoxyphenyl-2,4,6-tri-*O*-benzyl-β-D-xylo-hex-3-ulopyranoside as a light yellow solid, in a yield of 84%, m.p. 85–87°C; $\alpha_D^{23} = -52^\circ$ ($c = 1$, $CHCl_3$).

Other references related to the Albright-Goldman oxidation are cited in the literature.[6]

H. REFERENCES

1. Albright, J. D. and Goldman, L., *J. Org. Chem.*, **1965**, *30*, 1107.
2. Albright, J. D. and Goldman, L., *J. Am. Chem. Soc.*, **1965**, *87*, 4214.
3. Albright, J. D. and Goldman, L., *J. Am. Chem. Soc.*, **1967**, *89*, 2416.
4. Hayashi, Y. and Oda, R., *J. Org. Chem.*, **1967**, *32*, 457.
5. Bazin, H. G.; Du, Y. G.; Polat, T. and Linhardt, R., *J. Org. Chem.,* **1999**, 64,7254.
6. (a) Dodd, D. S. and Oehlschlager, A. C., *J. Org. Chem.,* **1992**, *57*, 2794. (b) Tadanier, J.; Martin, J, R.; Goldstein, A. W. and Hirner, E. A., *J. Org. Chem.,* **1978**, *43*, 2351. (c) Wikholm, R. J. and Moore, H. W., *J. Am. Chem. Soc.,* **1972**, *94*, 6152. (d) Dmitriev, B. A.; Kost, A. A. and Kochetkov, N. K., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1969**, 903. (e) Gabriel, T.; Chen, W. Y. and Nussbaum, A. L., *J. Am. Chem. Soc.,* **1968**, *90*, 6833. (f) Sweat, F. W. and Epstein, W. W., *J. Org. Chem.,* **1967**, *32*, 835. (g) Torssell, K., *Tetrahedron Lett.,* **1966**, 4445.

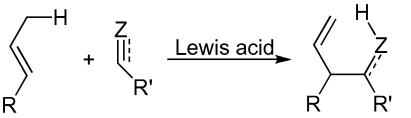
10

Alder Ene Reaction
(Conia Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Alder in 1943.[1] It is the reaction between an alkene of at least one allylic hydrogen (ene) and another unsaturated compound (i.e., enophile) to form a new olefinic compound with a new bond connecting the two unsaturated termini, and the allylic hydrogen is transferred to the enophile. Therefore, this reaction is generally known as the Alder ene reaction[2] and is occasionally referred to as ene cyclization,[3] ene functionalization,[4] or Alder ene synthesis.[5] This reaction has been extensively reviewed.[6]

B. GENERAL REACTION SCHEME



Z = C, N, O, S

(Lewis acid: $SnCl_4$, $BF_3{\bullet}Et_2O$, $Al(CH_3)_2Cl$, $CpRu(CH_3CN)_3PF_6$, etc.)

C. PROPOSED MECHANISMS

The mechanism of ene reaction is similar to that of *Diels-Alder Reaction*.

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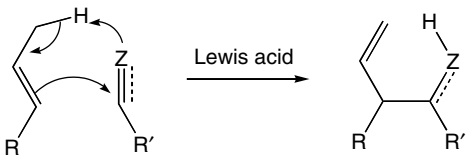


D. MODIFICATION

Conia has developed an intramolecular version of Alder ene reaction of unsaturated ketones, where the carbonyl group functions as the ene component via the tautomerization and the olefinic moiety serves as the enophile.[7] This kind of Alder ene reaction is generally known as a Conia reaction.[8]

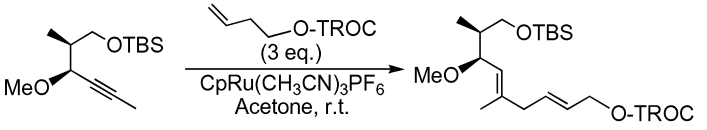
E. APPLICATIONS

This reaction has very wide applications in organic synthesis.

F. RELATED REACTIONS

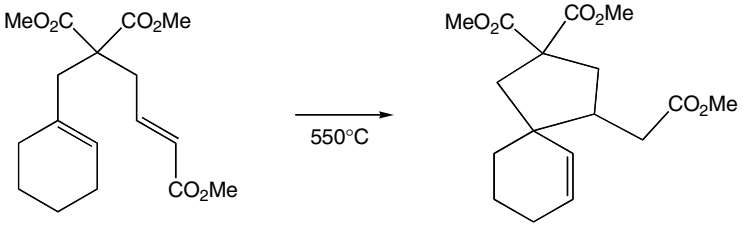
This reaction is related to *Pericyclic Reaction.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 9.

The mixture of 900 mg 1-*O*-(tert-butyldimethylsilyl)-2-methyl-3-methoxy-hex-4-yn-1-ol (3.5 mmol) and 2.6 g 3-butenyloxycarbonyloxy-2,2,2-trichloroethane (10.5 mmol) in 7.0 mL acetone was treated with 76 mg $CpRu(CH_3CN)_3PF_6$ (0.18 mmol) for 20 min at room temperature. The reaction mixture was concentrated and purified by silica gel flash column chromatography using ether/petroleum ether (1:9 to 1:3) as the eluent to afford 1.49 g (2E,5E)(7S,8S)-9-(*tert*-butyldimethylsilyloxy)-7-methoxy-5,8-di-methylnona-2,5-dienoxycarbonyloxy-2,2,2-trichloroethyl, in a yield of 85%.



Reference 10.

Methyl 5,5-bis(methoxycarbonyl)-6-(l-cyclo-hexenyl)-2(E)-hexenoate (40 mg, 0.17 mmol) was distilled at 180°C (0.1 mmHg) into a horizontally mounted nonpacked quartz tube that was heated in an oven at 550°C at a 0.1 mmHg vacuum. The product was collected in a dry ice trap. Flash chromatography (3:1 hexane-ether) gave 32 mg of 2,2-bis(methoxycarbonyl)-4-[(methoxycarbonyl)-methyl]spiro[4.5]dec-6-ene, in a yield of 80%.

Other references related to the Alder ene reaction are cited in the literature.[11]

H. REFERENCES

1. Alder, K.; Pascher, F. and Schmitz, A., *Ber.,* **1943**, *76B*, 27.
2. (a) Ashirov, R. V.; Balandina, A. A.; Kharlamov, S. V.; Appolonova, S. A.; Figadere, B.; Latypov, S. K. and Plemenkov, V. V., *Lett. Org. Chem.,* **2006**, *3*, 670. (b) Ashirov, R. V.; Appolonova, S. A.; Shamov, G. A. and Plemenkov, V. V., *Mendeleev Commun.,* **2006**, 276. (c) Brummond, K. M. and McCabe, J. M., *Tetrahedron,* **2006**, *62*, 10541. (d) Naerhi, K.; Franzen, J. and Baeckvall, J.-E., *J. Org. Chem.,* **2006**, *71*, 2914. (e) Struebing, D.; Neumann, H.; Huebner, S.; Klaus, S. and Beller, M., *Tetrahedron,* **2005**, *61*, 11345. (f) Naruse, Y.; Suzuki, T. and Inagaki, S., *Tetrahedron Lett.,* **2005**, *46*, 6937. (g) Brummond, K. M. and You, L. F., *Tetrahedron,* **2005**, *61*, 6180. (h) Pedrosa, R.; Andres, C.; Martin, L.; Nieto, J. and Roson, C., *J. Org. Chem.,* **2005**, *70*, 4332. (i) Hansen, E. C. and Lee, D. S., *J. Am. Chem. Soc.,* **2005**, *127*, 3252. (j) Chen, H. and Li, S. H., *Organometallics,* **2005**, *24*, 872. (k) Pedrosa, R.; Andres, C.; Martin, L.; Nieto, J. and Roson, C., *J. Org. Chem.,* **2005**, *70*, 4332. (l) Hansen, E. C and Lee, D. S., *J. Am. Chem. Soc.,* **2005**, *127*, 3252. (m) Hartley, J. P. and Pyne, S. G., *Synlett,* **2004**, 2209. (n) Nair, C. P. R. and Ninan, K. N., *Polymers & Polymer Composites,* **2004**, *12*, 55. (o) Gouri, C.; Nair, C. P. R. and Ramaswamy, R., *Polymers & Polymer Composites,* **2003**, *11*, 311. (p) Brummond, K. M.; Chen, H. F.; Sill, P. and You, L. F., *J. Am. Chem. Soc.,* **2002**, *124*, 15186. (q) Lei, A. W.; He, M. S.; Wu, S. L. and Zhang, X. M., *Angew. Chem. Int. Ed.,* **2002**, *41*, 3457. (r) Nair, C. P. R.; Sunitha, M. and Ninan, K. N., *Polymers & Polymer Composites,* **2002**, *10*, 457. (s) Lei, A. W.; He, M. S. and Zhang, X. M., *J. Am. Chem. Soc.,* **2002**, *124*, 8198. (t) Brummond, K. M; Chen, H. F.; Sill, P. and You, L. F., *J. Am. Chem. Soc.,* **2002**, *124*, 15186. (u) Lei, A. W.; He, M. S. and Zhang, X. M., *J. Am. Chem. Soc.,* **2002**, *124*, 8198. (v) Sunitha, M.; Nair, C. P. R.; Krishnan, K. and Ninan, K. N., *Thermochimica Acta,* **2001**, *374*, 159. (w) Gouri, C.; Nair, C. P. R. and Ramaswamy, R., *Polymer Int.,* **2001**, *50*, 403. (x) Bindu, R. L.; Nair, C. P. R. and Ninan, K. N., *J. Appl. Poly. Sci.,* **2001**, *80*, 737. (y) Gouri, C.; Nair, C. P. R. and Ramaswamy, R., *High Performance Polymers,* **2000**, *12*, 497. (z) Thompson, M. R.; Tzoganakis, C. and Rempel, G. L., *Polymer Eng. Sci.,* **1998**, *38*, 1694. (aa) Thompson, M. R.; Tzoganakis, C. and Rempel, G. L., *J. Poly. Sci., Part A: Poly. Chem.,* **1998**, *36*, 2371. (bb) Llerena, D.; Aubert, C. and Malacria, M., *Tetrahedron Lett.,* **1996**, *37*, 7027. (cc) Trost, B. M. and Li, Y., *J. Am. Chem. Soc.,* **1996**, *118*, 6625. (dd) Saito, S. and Yamamoto, Y., *Chemtracts: Inorg. Chem.,* **1995**, *7*, 206. (ee) Saito, S. and Yamamoto, Y., *Chemtracts: Org. Chem.,* **1995**, *8*, 300. (ff) Sarkar, T. K.; Ghoral, B. K.; Nandy, S. K. and Mukherjee, B., *Tetrahedron Lett.,* **1994**, *35*, 6903. (gg) Trost, B. M. and Muller, T. J. J., *J. Am. Chem. Soc.,* **1994**, *116*, 4985. (hh) Huang, B. and Huang, H. H., *Huaxue Shiji,* **1993**, *15*, 162. (ii) Friedrich, L. E.; Kampmeier, J. A. and Good, M., *Tetrahedron Lett.,* **1971**, 2783.
3. Trost, B. M.; Lautens, M.; Chan, C.; Jebaratnam, D. J. and Mueller, T., *J. Am. Chem. Soc.,* **1991**, *113*, 636.
4. Thompson, M. R.; Tzoganakis, C. and Rempel, G. L., *J. Appl. Poly. Sci.,* **1999**, *71*, 503.
5. Ashirov, R. V.; Appolonova, S. A. and Plemenkov, V. V., *Chem. Nat. Compd.,* **2006**, *42*, 434.

6. (a) Mikami, K. and Shimuzu, M., *Chem. Rev*., **1992**, *92*, 1021. (b) Mikami, K.; Terada, M.; Narisawa, S. and Nakai, T., *Synlett*, **1992**, 255. (c) Snider, B. B., *Comp. Org. Syn.,* **1991**, *5*, 1. (d) Snider, B. B., *Comp. Org. Syn*., **1991**, *2*, 527. (e) Rouessac, F.; Beslin, P. and Conia, J. M., *Tetrahedron Lett*., **1965**, 3319.
7. Conia, J. M. and Perchec, P. L., *Synthesis*, **1975**, 1.
8. (a) Ruedi, G.; Laikov, D. N. and Hansen, H.-J., *Helv. Chim. Acta,* **2004**, *87*, 1990. (b) Schobert, R.; Siegfried, S.; Gordon, G.; Nieuwenhuyzen, M. and Allenmark, S., *Eur. J. Org. Chem.,* **2001**, 1951. (c) Chung, W.-S. and Ho, C.-C., *Chem. Commun.,* **1997**, 317.
9. Trost, B. M.; Gunzner, J. L.; Dirat, O. and Rhee, Y. H., *J. Am. Chem. Soc*., **2002**, *124*, 10396.
10. Trost, B. M.; Lautens, M.; Chan, C.; Jebaratnam, D. J. and Mueller, T., *J. Am. Chem. Soc*., **1991**, *113*, 636.
11. (a) Becker, J. J.; van Orden, L. J.; White, P. S. and Gagné, M. R., *Org. Lett.*, **2002**, *4*, 727. (b) Brummond, K. M.; Chen, H. F.; Sill, P. and You, L. F., *J. Am. Chem. Soc.,* **2002**, *124*, 15186. (c) Lei, A. W.; He, M. S. and Zhang, X. M., *J. Am. Chem. Soc.,* **2002**, *124*, 8198. (d) Trost, B. M.; Probst, G. D. and Schoop, A., *J. Am. Chem. Soc.,* **1998**, *120*, *9228*. (e) Trost, B. M. and Li, Y., *J. Am. Chem. Soc.,* **1996**, *118*, 6625. (f) Johannsen, M. and Jørgensen, K. A., *J. Org. Chem.,* **1995**, *60*, 5757. (g) Trost, B. M. and Müller, T. J. J., *J. Am. Chem. Soc.,* **1994**, *116*, 4985. (h) Lai, Y.-C.; Mallakpour, S. E. and Butler, G. B., *J. Org. Chem.,* **1985**, *50*, 4378.

11

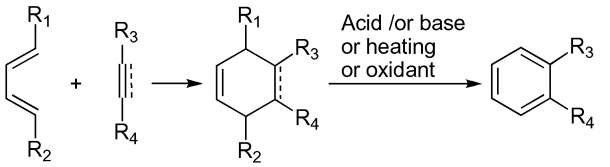
Alder-Rickert Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Alder and Rickert in 1936.[1] It is the extension of the *Diels-Alder Reaction* in which the Diels-Alder cycloadducts extrude the cleavable groups to give even more stable aromatic compounds[2] under thermal conditions or in the presence of either acid or base. Thus this reaction is generally known as the Alder-Rickert reaction.[3] In addition, the Diels-Alder cycloadducts can also be converted into aromatic compounds via rearrangement or oxidation.[4]

B. GENERAL REACTION SCHEME

Shown here is a typical Alder-Rickert reaction in which R_1 and R_2 are eliminated. Other groups are also possible to cleave.



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C. PROPOSED MECHANISMS

There are too many types of reactions to be generalized here; however, the formation of a stable aromatic ring will be the driving force for this reaction.

D. MODIFICATION

N/A

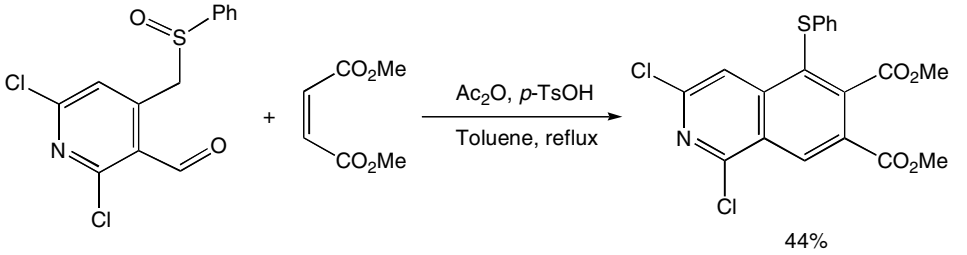
E. APPLICATIONS

This reaction has general applications in the formation of aromatic compounds.

F. RELATED REACTIONS

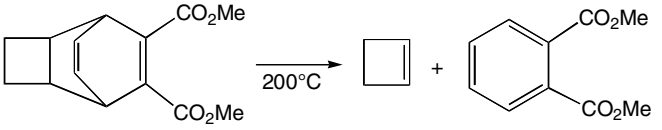
This reaction is related to *Diels-Alder Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



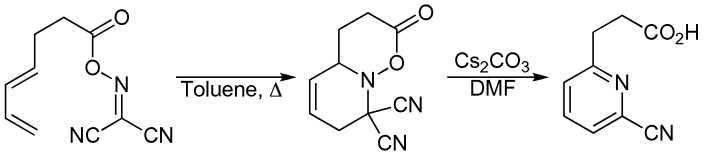
Reference 5.

To a flask equipped with a condenser were added 10 mL dry toluene, 3.0 mmol acetic anhydride, 0.15 mL dimethyl maleate (1.27 mmol), and a catalytic amount of *p*-toluenesulfonic acid. Under argon, 100 mg 2,6-dichloro-4-[(phenylsulfinyl)methyl]nicotinaldehyde (0.32 mmol) in toluene was added to above solution, dropwise over a period of 10 min. After the addition was complete, the yellow mixture was refluxed for an additional hour. The reddish yellow solution was cooled and washed with saturated aqueous $NaHCO_3$ solution. The organic layer was concentrated and purified by preparative layer chromatography to give dimethyl 1,3-dichloro-5-(phenylthio)isoquinoline-6,7-dicarboxylate, in a yield of 44% yield, m.p. 109–111°C.



Reference 6.

To a 5-mL flask with a capillary inlet attached to a source of dry nitrogen, was added 4.72 g of the Diels-Alder cycloadduct from cyclooctatriene and dimethyl acetylenedicarboxylate. The flask was connected to a 25-cm tube, which served as an air-cooled condenser, and which led to a trap cooled with liquid nitrogen. The system was evacuated at 100 mmHg, and the flask was heated in a bath at 200°C for 20 min. The flask was cooled, and nitrogen was admitted. The trap contained 0.97 g cyclobutene (95%), which was solid at the temperature of liquid nitrogen and liquefied when placed in a dry ice bath at −78°C. The residue from the pyrolysis of cycloadduct was shown to be dimethyl phthalate by comparing its infrared spectrum with the spectrum of an authentic sample and by saponification to phthalic acid, isolated by sublimation as phthalic anhydride.



Reference 7.

The solution of 205 mg 2-((*E*)-1-*oxo*-hepta-4,6-dienyloxyimino)malononitrile (1.01 mmol) in 200 mL dry toluene was stirred at reflux for 24 h. The solution was concentrated in vacuo to give a dark brown oil that was purified by flash column chromatography on silica gel eluting with hexanes/EtOAc (1:1) to give 139 mg 2-*oxo*-3,4,4a,7-tetrahydro-2H-pyridio[1,2-b]oxazine-8,8-dicarbonitrile as a thick brown oil, in a yield of 68%. The solution of 140 mg of the above cycloadduct (0.69 mmol) and 671 mg Cs_2CO_3 (2.06 mmol) in 5 mL dry DMF was stirred at room temperature for 18 h. The reaction mixture was diluted with 20 mL EtOAc and acidified to pH 2 with 10% aqueous HCl. The aqueous layer was extracted with 5 mL EtOAc three times. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give 87 mg 6-(2-carboxyethyl)pyridine-2-carbonitrile as a light tan solid, in a yield of 72%, m.p. 95–98.5°C.

Other references related to the Alder-Rickert reaction are cited in the literature.[8]

H. REFERENCES

1. Alder, K. and Rickert, H. F., *Ann*., **1936**, *524*, 180.
2. (a) Zhang, Y. and Herndon, J. W., *Tetrahedron Lett.,* **2001**, *42*, 777. (b) Cimetière, B.; Dubuffet, T.; Muller, O.; Descombes, J.-J.; Simonet, S.; Laubie, M.; Verbeuren, T. J. and Lavielle, G., *Bioorg. Med. Chem. Lett.,* **1998**, *8*, 1375. (c) Jackson, P. M. and Moody, C. J., *Tetrahedron*, **1992**, *48*, 7447. (d) Pérez, D.; Guitián, E. and Castedo, L., *J. Org. Chem.,* **1992**, *57*, 5911. (e) Jackson, P. M. and Moody, C. J., *J. Chem. Soc., Perkin Trans. I,* **1990**, 2156. (f) Moody, C. J. and Shah, P., *J. Chem. Soc., Perkin Trans I,* **1988**, 1407. (g) Kraus, G. A. and Pezzanite, J. O., *J. Org. Chem.,* **1982**, *47*, 4337. (h) Märkl, G. and Fuchs, R., *Tetrahedron Lett.,* **1972**, 4691.
3. (a) Goh, Y. W.; Danczak, S. M.; Lim, T. K. and White, J. M., *J. Org. Chem.,* **2007**, *72*, 2929. (b) Labadie, S. S., *Synth. Commun.,* **1998**, *28*, 2531. (c) Patterson, J. W., *J. Org. Chem.,* **1995**, *60*, 560. (d) Kanakam, C. C.; Ramanathan, H.; Rao, G. S. R. S. and Birch, A. J., *Curr. Sci.,* **1982**, *51*, 400.
4. (a) Matsushita, Y.-I.; Sakamoto, K.; Murakami, T. and Matsui, T., *Synth. Commun*., **1994**, *24*, 3307. (b) Karmarkar, K. S. and Samant, S. D., *Indian J. Chem., Sect. B*, **1993**, *32*, 1113. (c) van Broeck,

P. I.; van Doren, P. E.; Toppet, S. M. and Hoornaert, G. J., *J. Chem. Soc., Perkin Trans. I,* **1992**, 415. (d) Shimo, T.; Ohe, M.; Somekawa, K. and Tsuge, O., *J. Heterocycl. Chem.,* **1991**, *28*, 1831. (e) van Doren, P.; Vanderzande, D.; Toppet, S. and Hoornaert, G., *Tetrahedron,* **1989**, *45*, 6761. (f) Ahmed, S. A.; Bardshiri, E. and Simpson, T. J., *J. Chem. Soc., Chem. Commun.,* **1987**, 883. (g) Noguchi, M.; Kakimoto, S.; Kawakami, H. and Kajigaeshi, S., *Heterocycles*, **1985**, *23*, 1085. (h) Jung, M. E.; Lowe, J. A., III; Lyster, M. A.; Node, M.; Pfluger, R. W. and Brown, R. W., *Tetrahedron,* **1984**, *40*, 4751. (i) Saito, K.; Iida, S. and Mukai, T., *Bull. Chem. Soc. Jpn.,* **1984**, *57*, 3483. (j) Cano, P.; Echavarren, A.; Prados, P. and Farina, F., *J. Org. Chem.*, **1983**, *48*, 5373.

5. Sarkar, T. K.; Panda, N. and Basak, S., *J. Org. Chem*., **2003**, *68*, 6919.
6. Cope, A. C.; Haven, A. C.; Ramp, F. L. and Trumbull, E. R., *J. Am. Chem. Soc*., **1952**, *74*, 4867.
7. Bland, D. C.; Raudenbush, B. C. and Weinreb, S. M., *Org. Lett*., **2000**, *2*, 4007.
8. (a) Sarkar, T. K.; Panda, N. and Basak, S., *J. Org. Chem.,* **2003**, *68*, 6919. (b) Kranjc, K.; Polanc, S. and Kocevar, M., *Org. Lett.*, **2003**, *5*, 2833. (c) Padwa, A.; Kappe, C. O.; Cochran, J. E. and Snyder, J. P., *J. Org. Chem*., **1997**, *62*, 2786. (d) Padwa, A.; Dimitroff, M.; Waterson, A. G. and Wu, T.-H., *J. Org. Chem.,* **1997**, *62*, 4088. (e) Kappe, C. O. and Padwa, A., *J. Org. Chem.,* **1996**, *61*, 6166. (f) Padwa, A.; Cochran, J. E. and Kappe, C. O., *J. Org. Chem.*, **1996**, *61*, 3706. (g) Ho, T.-L., *Symmetry: A Basis for Synthesis Design,* John Wiley & Sons, Inc., New York, **1995**, p. 340. (h) Srivastava, S.; Marchand, A. P.; Vidyasagar, V.; Flippen-Anderson, J. L.; Gilardi, R.; George, C.; Zachwieja, Z. and le Noble, W. L., *J. Org. Chem.,* **1989**, *54*, 247. (i) Birch, A. J. and Wright, J. H., *Aust. J. Chem.,* **1969**, *22*, 2635. (j) Doering, R. F.; Miner, Jr., R. S.; Rothman, L. and Becker, E. I., *J. Org. Chem.,* **1958**, *23*, 520. (k) Cava, M. P.; Wilson, C. L. and Williams, C. J., *J. Am. Chem. Soc.,* **1956**, *78*, 2303. (l) Alder, K., *The Diene Synthesis* in *Newer Methods of Preparative Organic Chemistry*, ed. Foerst, W., Interscience, **1948**, pp. 381–512.

12

Aldol Reaction and Aldol Condensation

A. GENERAL DESCRIPTION OF THE REACTION

The aldol reaction[1] or aldol condensation,[2] first reported by Kane in 1838,[3] is one of the most important C-C bond formation reactions for aldehydes and ketones. Due to the electron-withdrawing characteristic of carbonyl groups in aldehydes and ketones, the α-methylene group is relatively acidic (with a pKa of 16–21[4]); therefore, aldehydes and ketones can isomerize into enolates or enols under basic or acidic conditions, respectively. The enolates or enols can further add to the carbonyl group in aldehydes or ketones,[5] giving β-hydroxyl carbonyl compounds known as aldols (aldehyde + alcohol). Enolates normally aggregate to form dimer, tetramer, or higher oliogmers and exist as monomer predominantly only in very dilute solutions.[6] In general, this reaction is complicated[7] because many possible reactions can occur at the same time. For example, the enolization of a ketone will give two possible enolates, which will add to the same molecule or another aldehyde or ketone (in a stepwise manner) to give aldols that differ in regioselectivity and stereoselectivity. In addition, the aldol products can undergo dehydration to form conjugated carbonyl molecules (α,β-unsaturated aldehydes or ketones, in this case; the whole process is also referred to as aldol condensation[8]), which might undergo the *Michael Addition* with the existing enolates. On the other hand, under the basic condition, the aldehydes can undergo disproportionation to give both carboxylic acid and alcohol (*Cannizzaro Disproportionation*) or to form the ester (*Tischenko Reaction*). Furthermore, the addition of an enolate to a carbonyl group could be complicated with either *O*-attack or *C*-attack.[6] If all of these possible reactions occur during the aldol reaction, then the aldol reaction will not be as useful. However, more selective methods have been developed to generate enolates

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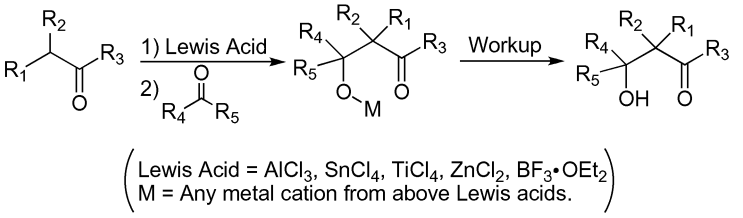
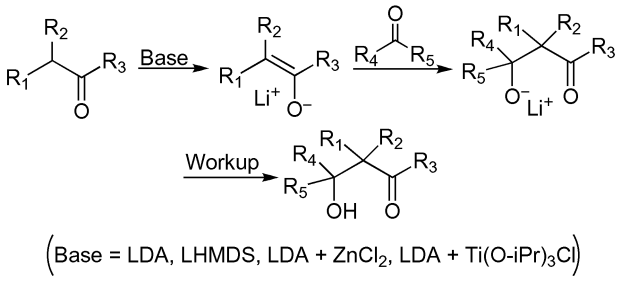
or enols, which selectively give the desired carbonyl molecules. Because this reaction is so important, it has been extensively reviewed in different aspects.[9]

B. GENERAL REACTION SCHEME

The aldol reaction or aldol condensation proceeds under either acidic (Scheme 1) or basic (Scheme 2) conditions.



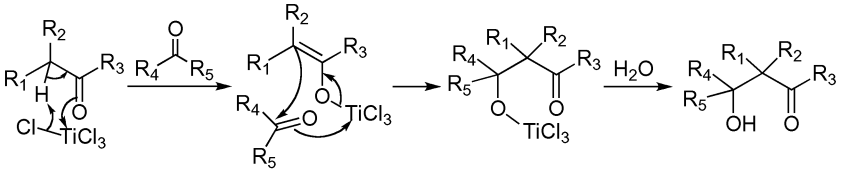
SCHEME 1. *Acid-catalyzed aldol reaction.*



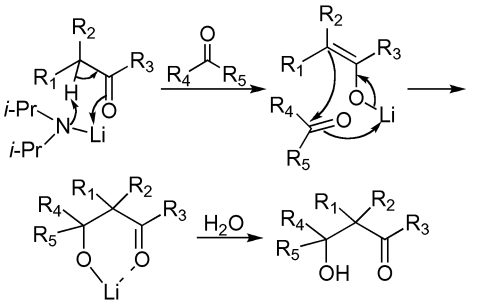
SCHEME 2. *Base-catalyzed aldol reaction.*

C. PROPOSED MECHANISMS

The mechanism is similar to that shown in Schemes 1 and 2 and illustrated in detail in Schemes 3 and 4.



SCHEME 3. *Mechanism of aldol reaction under acidic conditions.*



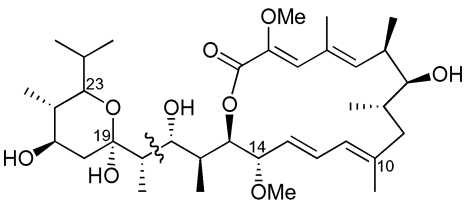
SCHEME 4. *Mechanism of aldol reaction under basic conditions.*

D. MODIFICATION

When aldehydes or ketones enolize to enols under acidic conditions, the enols are not as stable as aldehydes or ketones. However, the formed enols can be fixed or protected by a trimethylsilyl group to form trimethylsilyl vinyl ethers, which then undergo the aldol reaction. This modification is known as *Mukaiyama Aldol Reaction*.

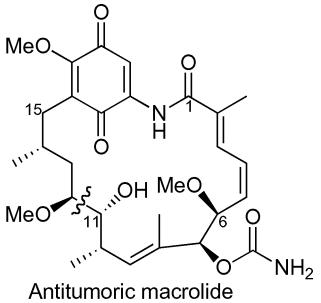
E. APPLICATIONS

Beside being used to form a variety of compounds (some of which are listed in the experimental section), the aldol reaction has been used to synthesize the following antibiotic macrolides, especially for the macrolide acutiphycin, which is primarily prepared by five steps of consecutive aldol reactions. Among the listed structures, the bonds arising from aldol reactions are labeled with many lines.



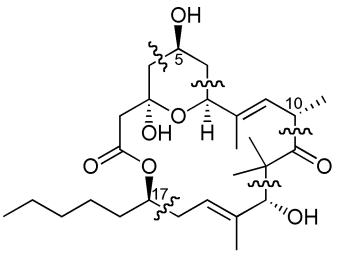
Macrolide antibiotic

(Ref. 10a).



Antitumoric macrolide

(Ref. 10b).



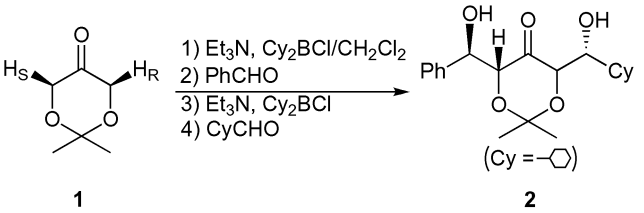
Synthesis of antineoplastic acutiphycin by consecutive aldol reactions

(Ref. 10c).

F. RELATED REACTIONS

Besides the aldol reaction to form β-hydroxyketone, *1,3-Dipolar Cycloaddition* can also form similar molecules. In addition to the *Mukaiyama Aldol Reaction*, the following are also similar or closely related to the aldol reaction: the *Claisen-Schmidt Condensation* (the aldol reaction between benzaldehyde and an aliphatic aldehyde or ketone in the presence of relatively strong bases to form an α,β-unsaturated aldehyde or ketone), the *Henry Reaction* (base-catalyzed addition of nitroalkane to aldehydes or ketones), the *Ivanov Reaction* (the addition of enediolates or aryl acetic acid to electrophiles, especially carbonyl compounds), the *Knoevenagel Reaction*[11] (the condensation of aldehydes or ketones with acidic methylene compounds in the presence of amine or ammonia), the *Reformatsky Reaction* (the condensation of aldehydes or ketones with organozinc derivatives of α-halo-esters), and the *Robinson Annulation Reaction* (the condensation of ketone cyclohexanone with methyl vinyl ketone or its equivalent to form bicyclic compounds).

G. CITED EXPERIMENTAL EXAMPLES

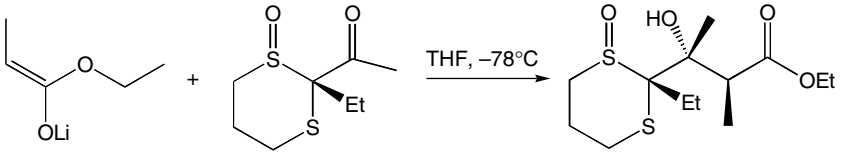


1 2

Reference 12 (a similar reaction condition is also found in Ref. 13).

To 10 mL CH_2Cl_2 was added 0.28 mL triethylamine (2.00 mmol), and the resulting solution was cooled to 0°C. To this solution, was added 2.0 mL 0.5 M dicyclohexylboron chloride in hexane (1.00 mmol), and the solution was stirred for 5 min. Then 0.13 g dioxanone (1.00 mmol) was added; and after being stirred for 15 min, 0.1 mL benzaldehyde (1.00 mmol) was added. After stirring for another 15 minutes, 0.28 mL of triethylamine (2.00 mmol) was added, followed by 2.0 mL of 0.5 M dicyclohexylboron chloride in hexane

(1.00 mmol). After another 15 minutes, 0.17 mL of cyclohexyl aldehyde (1.50 mmol) was added. After being stirred for an additional 15 min, the reaction mixture was quenched with 20 mL concentrated buffer (pH = 7). The resulting product was extracted with diethyl ether (3 × 50 mL). The combined extracts were washed with brine (2 × 10 mL) and dried over $MgSO_4$. Upon evaporation of the solvent, the residue was dissolved in 18 mL methanol and cooled to 0°C. To this solution were sequentially added 6 mL concentrated buffer (pH = 7) and 6 mL 30% H_2O_2. The solution was stirred at 0°C for 3 h and 150 mL Et_2O was then added; the separated organic layer was washed with saturated $NaHCO_3$ (2 × 15 mL) and 15 mL brine and was dried over $MgSO_4$. Upon removal of the solvent, four components were identified in the residual mixture as analyzed by ^1H NMR in a ratio of 83:9:6:2. The residue was isolated by DFC (9:1 hexane/CH_2Cl_2 followed by 9:1:2 hexane/CH_2Cl_2/AcOEt) to give 224 mg of the major product as a colorless liquid, in a yield of 64%.



Reference 14.

A solution of 4.5 mL 2.5 M n-BuLi in hexane (10.5 mmol) was slowly added to a cooled solution (−78°C) of 1.7 mL diisopropylamine (12.6 mmol) in 45 mL THF under a nitrogen atmosphere. After 30 min, a solution of 1.072 g ethyl propanoate (10.5 mmol) in 30 mL THF was slowly added. After being stirred for 30 min at the same temperature, a solution of 0.619 g 2-acetyl-2-ethyl-1,3-dithiane 1-oxide (3 mmol) in 20 mL THF was added dropwise via syringe, and the mixture was stirred for 5 min. Saturated aqueous NH_4Cl was added; and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with brine and dried over $MgSO_4$. Upon removal of the solvent under reduced pressure, the residue was purified either by flash chromatography or by crystallization.

Other references related to the aldol reaction are cited in the literature.[15]

H. REFERENCES

1. (a) Oisaki, K.; Zhao, D. B.; Kanai, M. and Shibasaki, M., *J. Am. Chem. Soc.,* **2007**, *129*, 7439. (b) Huang, W.-P.; Chen, J.-R.; Li, X.-Y.; Cao, Y.-J. and Xiao, W.-J., *Can. J. Chem.,* **2007**, *85*, 208. (c) Zhang, F. L.; Peng, Y. Y.; Liao, S. H. and Gong, Y. F., *Tetrahedron,* **2007**, *63*, 4636. (d) Fan, J.-F.; Wu, L.-F. and Sun, Y.-P., *Chinese J. Chem.,* **2007**, *25*, 472. (e) Abramite, J. A. and Sammakia, T., *Org. Lett.,* **2007**, *9*, 2103. (f) Corminboeuf, G.; Amrhein, M. and Naef, O., *Chemometrics & Intelligent Lab. Sys.,* **2007**, *86*, 168. (g) Valla, A.; Valla, B.; Le Guillou, R.; Cartier, D.; Dufosse, L. and Labia, R., *Helv. Chim. Acta,* **2007**, *90*, 512. (h) Shinisha, C. B. and Sunoj, R. B., *Org. Biomol. Chem.,* **2007**, *5*, 1287. (i) London, G.; Szoellosi, G. and Bartok, M., *J. Mol. Catal. A: Chem.,* **2007**, *267*, 98. (j) Terao, Y.; Miyamoto, K. and Ohta, H., *Chem. Lett.,* **2007**, *36*, 420. (k) Cergol, K. M.; Jensen, P.; Turner, P. and Coster, M. J., *Chem. Commun.,* **2007**, 1363. (l) Payne, A. D.; Skelton, B. W.; Wege, D. and White, A. H., *Eur. J. Org. Chem.,* **2007**, 1184. (m) Amedjkouh,

M., *Tetrahedron: Asymmetry,* **2007**, *18*, 390. (n) Kotani, S.; Hashimoto, S. and Nakajima, M., *Tetrahedron,* **2007**, *63*, 3122. (o) Alcaide, B.; Almendros, P. and Luna, A., *Tetrahedron,* **2007**, *63*, 3102. (p) Zhou, L. and Wang, L., *Chem. Lett.,* **2007**, *36*, 628. (q) Russo, A.; Botta, G. and Lattanzi, A., *Synlett*, **2007**, 795.

2. (a) Diez, V. K.; Apesteguia, C. R. and Di Cosimo, J. I., *J. Catal.,* **2006**, *240*, 235. (b) Guillena, G.; Hita, M. del C. and Najera, C., *Tetrahedron: Asymmetry,* **2006**, *17*, 729. (c) Arnold, A.; Markert, M. and Mahrwald, R., *Synthesis,* **2006**, 1099. (d) Kustrowski, P.; Sulkowska, D.; Chmielarz, L. and Dziembaj, R., *Appl. Catal. A: General,* **2006**, *302*, 317. (e) Hasni, M.; Prado, G.; Rouchaud, J.; Grange, P.; Devillers, M. and Delsarte, S., *J. Mol. Catal. A: Chem.,* **2006**, *247*, 116. (f) Behrendt, C.; Dabek, S.; Heck, J.; Courtney, D.; Manning, A. R.; McGlinchey, M. J.; Mueller-Bunz, H. and Ortin, Y., *J. Organomet. Chem.,* **2006**, *691*, 1183. (g) Terai, H.; Takaya, H. and Naota, T., *Tetrahedron Lett.,* **2006**, *47*, 1705.
3. (a) Kane, R., *Ann. Phys. Chem. Ser. 2*, **1838**, *44*, 475. (b) Kane, R., *J. Prakt. Chem.,* **1938**, *15*, 129.
4. (a) Bordwell, F. G. and Zhang, X. M., *Acc. Chem. Res.,* **1993**, *26*, 510. (b) Taft, R. W. and Bordwell, F. G., *Acc. Chem. Res*., **1988**, *21*, 463. (c) Bordwell, F. G., *Acc. Chem. Res.,* **1988**, *21*, 456. (d) Bell, R. P. *The Proton in Chemistry*, Cornell University Press, Ithaca, N. Y., **1959**. (e) Pearson, R. G. and Dillon, R. L., *J. Am. Chem. Soc*., **1953**, *75*, 2439.
5. (a) Kano, T.; Yamaguchi, Y.; Tanaka, Y. and Maruoka, K., *Angew. Chem. Int. Ed.,* **2007**, *46*, 1738. (b) Markert, M.; Mulzer, M.; Schetter, B. and Mahrwald, R., *J. Am. Chem. Soc.,* **2007**, *129*, 7258. (c) Shiomi, T. and Nishiyama, H., *Org. Lett.,* **2007**, *9*, 1651. (d) Luo, S. Z.; Xu, H.; Li, J. Y.; Zhang, L. and Cheng, J.-P., *J. Am. Chem. Soc.,* **2007**, *129*, 3074. (e) Shiomi, T.; Ito, J.-I.; Yamamoto, Y. and Nishiyama, H., *Eur. J. Org. Chem.,* **2006**, 5594.
6. (a) Wang, D. Z.; Kim, Y.-J. and Streitwieser, A., *J. Am. Chem. Soc,*, **2000**, *122*, 10754. (b) Streitwieser, A. and Wang, D. Z., *J. Am. Chem. Soc.*, **1999**, *121*, 6213. (c) Wang, D. Z. and Streitwieser, A., *J. Org. Chem.*, **1999**, *64*, 4860. (d) Wang, D. Z. and Streitwieser, A., *Can. J. Chem*., **1999**, *77*, 654.
7. Interested readers may refer to the 11 papers by H. O. House, published in *J. Org. Chem.* from **1963** to **1979** and to A. Streitwieser's work published from the late **1980s** to the **1990s**.
8. (a) Bazin, S.; Feray, L.; Vanthuyne, N.; Siri, D. and Bertrand, M. P., *Tetrahedron,* **2007**, *63*, 77. (b) Gonzalez, V. A.; Cabriales, R. C.; Moggio, I. and Arias, E., *Polymer Bull.,* **2007**, *58*, 627. (c) Tai, J. R. and Davis, R. J., *Catal. Today,* **2007**, *123*, 42.
9. General reviews: (a) Nielsen, A. T. and Houlihan, W. J. "The Aldol Condensation," in *Organic Reactions*, vol. 16, ed. Cope, A. C., John Wiley & Sons, New York. **1968**, (the whole issue discusses the aldol reaction). (b) Mukaiyama, T., *Org. React.,* **1982**, *28*, 203. The application of lithium and magnesium enolates: (c) Heathcock, C. H., *Comp. Org. Syn.,* **1991**, *2*, 181. Application of boron enolates: (d) Kim, B. M. *Comp. Org. Syn.,* **1991**, *2*, 239. Application of transition metal enolates: (e) Paterson, I., *Comp. Org. Syn.,* **1991**, *2*, 301. (f) Johnson, J. S. and Evans, D. A., *Acc. Chem. Res*., **2000**, *33*, 325. Stereoselective reactions of ester and thioester enolates: (g) Braun, M. and Sacha, H., *J. Prakt. Chem.,* **1993**, *335*, 653. Vinylogous aldol reaction: (h) Casiraghi, G.; Zanardi, F.; Appendino, G. and Rassu, G., *Chem. Rev.,* **2000**, *100*, 1929. Asymmetric catalysis: (i) Denmark, S. E. and Stavenger, R. A., *Acc. Chem. Res.,* **2000**, *33*, 432. (j) Mahrwald, R., *Chem. Rev*., **1999**, *99*, 1095. Historical perspective (k) Heathcock, C. H., *Comp. Org. Syn.,* **1991**, *2*, 133.
10. (a) Roush, W. R.; Bannister, T. D.; Wendt, M. D.; Jablonowski, J. A. and Scheidt, K. A., *J. Org. Chem.,* **2002**, *67*, 4275. (b) Andrus, M. B.; Meredith, E. L. and Sekhar, B. B. V. S., *Org. Lett*., **2001**, *3*, 259. (c) Kiyooka, S.-I. and Hena, M. A., *J. Org. Chem.,* **1999**, *64*, 5511.
11. See *Knoevenagel Condensation* herein (P. 1621).
12. Majewski, M. and Nowak, P., *J. Org. Chem.,* **2000**, *65*, 5152.

13. Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P. and Sereinig, N., *J. Am. Chem. Soc.,* **2001**, *123*, 9535.

14. Ruano, J. L. G.; Barros, D.; Maestro, M. C.; Slawin, A. M. Z. and Page, P. C. B., *J. Org. Chem.,* **2000**, *65*, 6027.

15. (a) Wang, X.-J.; Zhao, Y. and Liu, J.-T., *Org. Lett.,* **2007**, *9*, 1343. (b) Ma, B.; Parkinson, J. L. and Castle, S. L., *Tetrahedron Lett.,* **2007**, *48*, 2083. (c) Guizzetti, S.; Benaglia, M.; Raimondi, L. and Celentano, G., *Org. Lett.,* **2007**, *9*, 1247. (d) Gryko, D.; Zimnicka, M. and Lipinski, R., *J. Org. Chem.,* **2007**, *72*, 2258. (e) Wang, Y.-J.; Shen, Z.-X.; Ding, J. and Zhang, Y.-W., *Youji Huaxue,* **2007**, *27*, 235. (f) Pandey, J.; Dwivedi, N.; Singh, N.; Srivastava, A. K.; Tamarkar, A. and Tripathi, R. P., *Bioorg. Med. Chem. Lett.,* **2007**, *17*, 1321. (g) Ma, G.-N.; Zhang, Y.-P. and Shi, M., *Synthesis,* **2007**, 197. (h) Kumaraswamy, G. and Markondaiah, B., *Tetrahedron Lett.,* **2007**, *48*, 1707. (i) Jiang, J.; He, L.; Luo, S.-W.; Cun, L.-F. and Gong, L.-Z., *Chem. Commun.,* **2007**, 736. (j) Fu, Y.-Q.; Li, Z.-C.; Ding, L.-N.; Tao, J.-C.; Zhang, S.-H. and Tang, M.-S., *Tetrahedron: Asymmetry,* **2007**, *17*, 3351. (k) Villano, R.; Acocella, M. R.; Massa, A.; Palombi, L. and Scettri, A., *Tetrahedron: Asymmetry,* **2007**, *17*, 3332. (l) Inokuchi, T. and Kawafuchi, H., *J. Org. Chem.,* **2007**, *72*, 1472. (m) Chen, X.-H.; Luo, S.-W.; Tang, Z.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z. and Gong, L.-Z., *Chem. Eur. J.,* **2007**, *13*, 689. (n) Gryko, D.; Zimnicka, M. and Lipinski, R., *J. Org. Chem.,* **2007**, *72*, 964. (o) Yanagisawa, A.; Ichikawa, T. and Arai, T., *J. Organomet. Chem.,* **2007**, *692*, 550. (p) Deng, D.-S. and Cai, J. W., *Helv. Chim. Acta,* **2007**, *90*, 114. (q) Chheda, J. N. and Dumesic, J. A., *Catal. Today,* **2007**, *123*, 59. (r) Lutic, D.; Hulea, V.; Coq, B.; Durand, R. and Tichit, D., *Prog. Catal.,* **2006**, *15*, 31. (s) Zeidan, R. K. and Davis, M. E., *J. Catal.,* **2007**, *247*, 379. (t) Ciszewski, A. and Rydzynska, B., *J. Power Source,* **2007**, *166*, 526. (u) Sunden, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L. and Cordova, A., *Chem. Eur. J.,* **2007**, *13*, 574. (v) Abello, S.; Medina, F.; Tichit, D.; Perez-Ramirez, J.; Sueiras, J. E.; Salagre, P. and Cesteros, Y., *Appl. Catal. B: Environ.,* **2007**, *70*, 577. (w) Masuyama, Y.; Ohtsuka, M. and Kondo, A., *Synlett,* **2006**, 3346. (x) Wang, Y.; Wei, S. Y. and Sun, J., *Synlett,* **2006**, 3319. (y) Enders, D.; Niemeier, O. and Straver, L., *Synlett,* **2006**, 3399. (z) Chen, G.; Wang, Y.; He, H. P.; Gao, S.; Yang, X. S. and Hao, X. J., *Heterocycles,* **2006**, *68*, 2327. (aa) Bennett, G. D., *J. Chem. Edu.,* **2006**, *83*, 1871. (bb) Bhagat, S.; Sharma, R. and Chakraborti, A. K., *J. Mol. Catal. A: Chem.,* **2006**, *260*, 235. (cc) Schramm, O. G. and Mueller, T. J. J., *Synlett,* **2006**, 1841. (dd) Ouyang, Y.; Dong, D. W.; Pan, W.; Zhang, J. and Liu, Q., *Tetrahedron,* **2006**, *62*, 10111. (ee) Kriis, K.; Kanger, T.; Laars, M.; Kailas, T.; Muurisepp, A.-M.; Pehk, T. and Lopp, M., *Synlett,* **2006**, 1699. (ff) Jung, J.-C.; Kim, J.-C.; Moon, H.-I. and Park, O.-S., *Tetrahedron Lett.,* **2006**, *47*, 6433. (gg) Kamiguchi, S.; Nishida, S.; Takahashi, I.; Kurokawa, H.; Miura, H. and Chihara, T., *J. Mol. Catal. A: Chem.,* **2006**, *255*, 117. (hh) Li, J. H.; Tai, J. R. and Davis, R. J., *Catal. Today,* **2006**, *116*, 226. (ii) Lian, J.-J.; Lin, C.-C.; Chang, H.-K.; Chen, P.-C. and Liu, R.-S., *J. Am. Chem. Soc.,* **2006**, *128*, 9661. (jj) Guillena, G.; Hita, M. del C. and Najera, C., *Tetrahedron: Asymmetry,* **2006**, *17*, 1027. (kk) Barrett, C. J.; Chheda, J. N.; Huber, G. W. and Dumesic, J. A., *Appl. Catal. B: Environ.,* **2006**, *66*, 111. (ll) Narang, G.; Jindal, D. P.; Jit, B.; Bansal, R.; Potter, B. S. and Palmer, R. A., *Helv. Chim. Acta,* **2006**, *89*, 258. (mm) Das, B.; Thirupathi, P.; Mahender, I. and Reddy, K. R., *J. Mol. Catal. A: Chem.,* **2006**, *247*, 182. (nn) Yamashita, Y.; Ishitani, H.; Shimizu, H. and Kobayashi, S., *J. Am. Chem. Soc*., **2002**, *124*, 3292. (oo) Sakthivel, K.; Notz, W.; Bui, T. and Barbas, C. F.,*J. Am. Chem. Soc.,* **2001**, *123*, 5260. (pp) Crimmins, M. T.; King, B. W.; Tabet, E. A. and Chaudhary, K., *J. Org. Chem.,* **2001**, *66*, 894.

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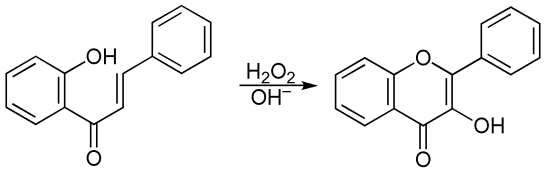
Algar-Flynn-Oyamada (AFO) Reaction

(Algar-Flynn-Oyamada Oxidation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Algar and Flynn[1] and concurrently by Oyamada[2] in 1934. It is the synthesis of flavones via oxidative cyclization of 2′-oxychalcones with hydrogen peroxide under alkaline conditions. Therefore, this reaction is generally known as the Algar-Flynn-Oyamada reaction.[3] In addition, this reaction has also been referred to as the Algar-Flynn oxidation,[4] Algar-Flynn-Oyamada oxidation,[5] Algar-Flynn-Oyamada (AFO) reaction,[6] Algar-Flynn-Oyamada condensation,[7] and AFO cyclization.[8] It has been found that a variety of 2-hydroxychalcones with methoxy groups in different positions in the two aromatic nuclei smoothly undergo the AFO oxidation.[9]

B. GENERAL REACTION SCHEME



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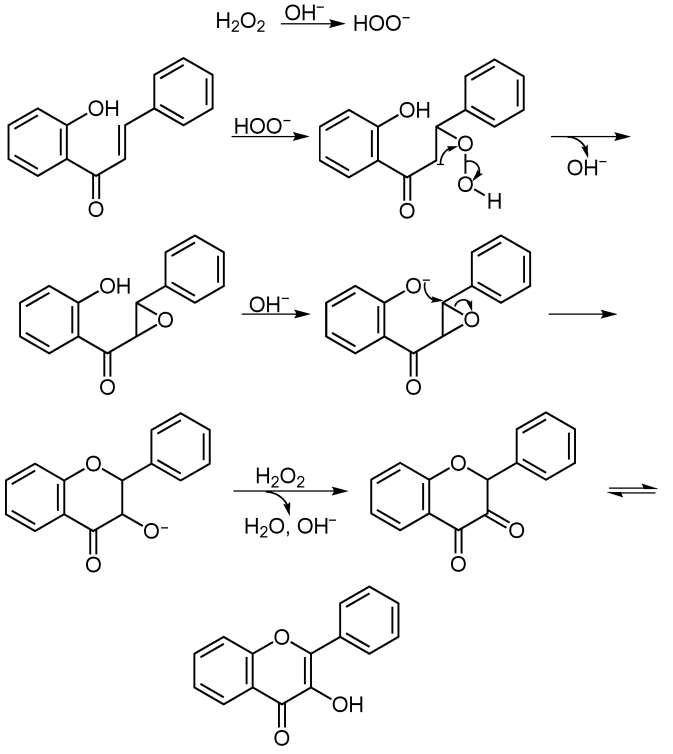
C. PROPOSED MECHANISMS

The mechanism of this reaction is somewhat controversial. The initial formation of flavanone from 2′-hydroxychalcone and subsequent oxidation to flavonol has been postulated by Oyamada,[10] but the prior oxidation of 2′-hydroxychalcone into either an epoxide or a glycol followed by intramolecular cyclization to afford flavonol has been favored by Algar and Flynn.[1] However, because flavanones readily undergo ring-opening under alkaline conditions to the salts of the corresponding 2′-hydroxychalcones,[9] the mechanism proposed by Oyamada is difficult to validate.[11] In comparison, although a chalcone epoxide intermediate would lead to a flavone or a benzalcoumaranone,[1] no trace of a chalcone epoxide has ever been isolated.[3e] The α-attack is predominant for the intromolecular cyclization of the corresponding 2′-hydroxychalcone epoxide, yielding a diasteroisomeric mixture of aurone hydrates, which can be sustained for several days in an aqueous media at neutral pH.[8] Displayed here is one kind of reaction mechanism.



D. MODIFICATION

This reaction has been modified to convert 2′-hydroxychalcones into flavones via SeO_2 oxidation;[4] in addition, flavone has recently been prepared via a polystyrene-supported selenenyl bromide followed by H_2O_2 oxidation.[12]

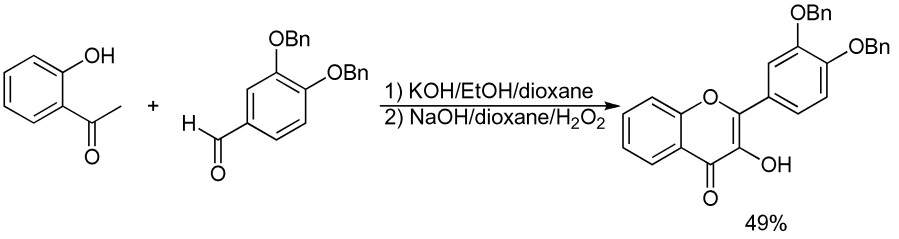
E. APPLICATIONS

This reaction is widely used for the preparation of flavones and flavonols.

F. RELATED REACTIONS

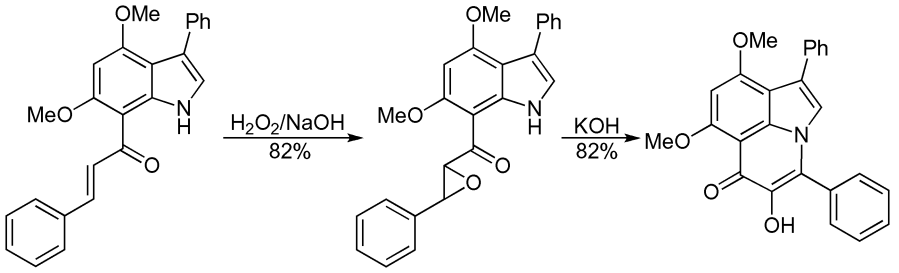
This reaction is related to the *Auwers Synthesis, Baker-Ollis Reaction*, *Kostanecki-Robinson Reaction* and *Allan-Robinson Annulation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 3g.

A suspension of 10.0 g 3,4-dibenzyloxybenzaldehyde (31.4 mmol) and 4.28 g 2-hydroxyacetophenone (31.4 mmol) in 80 mL ethanol and 50 mL dioxane was cooled to 10°C, and 25 mL 40% w/v KOH solution was added dropwise. The reaction mixture was stirred for 66 h at room temperature. CH_2Cl_2 (400 mL) was added, and the organic layer was washed with H_2O (3 × 50 mL), dried over Na_2SO_4 and concentrated in vacuo. The oily residue was dissolved in 110 mL dioxane and 300 mL ethanol, and 100 mL of 5.4% (w/v) NaOH solution was added, followed by 11.4 mL of 35% H_2O_2 dropwise. The reaction mixture was stirred in an ice bath for 2 h and subsequently at room temperature overnight, resulting in a yellow suspension. After acidification with 100 mL 2 *M* HCl, the precipitate was filtered and washed with 500 mL H_2O. The crude product was recrystallized from ethanol to give 7.0 g 3′,4′-dibenzyloxy-3-hydroxyflavone as a light yellow solid, in a yield of 49%, m.p. 145.8–146.8°C.



Reference 3e.

To a solution of 0.69 g 1-(4,6-dimethoxy-3-phenylindol-7-yl)-3-phenyl-2-propen-1-one (1.8 mmol) in 30 mL aqueous THF was added 10 mL saturated NaOH; the mixture was stirred at room temperature for 5 min. To this mixture was added 15 mL 30% H_2O_2 dropwise, and the resulting mixture was stirred for 6–8 h. Water was added, and the resulting pale yellow precipitate was filtered, washed, and dried. After flash chromatography with dichloromethane and recrystallization (dichloromethane/petroleum ether), 0.59 g 1-(4,6-dimethoxy-3-phenylindol-7-yl)-3-phenyl-2,3-epoxypropan-1-one was obtained as a pale yellow powder, in a yield of 82%, m.p. 217–219°C. To a solution of 0.17 g 1-(4,6-dimethoxy-3-phenylindol-7-yl)-3-phenyl-2,3-epoxypropan-1-one (0.42 mmol) in 13 mL aqueous THF was added 3 mL saturated KOH solution and 0.3 g solid KOH (5.3 mmol). The reaction mixture was stirred at room temperature for 4 h. Water was added, and the resulting pale yellow precipitate was filtered, washed, dried, and flash column chromatographed (dichloromethane/methanol = 97:3). After recrystallization from dichloromethane/petroleum ether, 0.14 g 5-hydroxy-7,9-dimethoxy-1,4-diphenyl-6-oxo-6H-pyrrolo-[3,2,1-*ij*]quinoline was obtained, in a yield of 82%, m.p. 250°C.

Other references related to the Algar-Flynn-Oyamada reaction are cited in the literature.[13]

H. REFERENCES

1. Algar, J. and Flynn, J. P., *Proc. Royal Irish Acad., Sect. B,* **1934**, *42*, 1.
2. Oyamada, T., *Nippon Kagaku Kaishi,* **1934**, *55*, 1256.
3. (a) Hasan, A.; Rasheed, L. and Malik, A., *Asian J. Chem.,* **2007**, *19*, 937. (b) Zhu, A.; Wang, B.; White, J. O. and Drickamer, H. G., *J. Phys. Chem. B,* **2004**, *108*, 891. (c) Lévai, A., *ARKIVOC,* **2004**, (*vii*), 15. (d) Falkovskaia, E.; Pivovarenko, V. G. and del Valle, J. C., *J. Phys. Chem. A,* **2003**, *107*, 3316. (e) Black, D. St. C.; Kumar, N. and Mitchell, P. S. R., *J. Org. Chem.,* **2002**, *67*, 2464. (f) Ameer-Beg, S.; Ormson, S. M.; Brown, R. G.; Matousek, P.; Towrie, M.; Nibbering, E. T. J.; Foggi, P. and Neuwahl, F. V. R., *J. Phys. Chem. A,* **2001**, *105*, 3709. (g) van Acker, F. A. A.; Hageman, J. A.; Haenen, G. R. M. M.; van der Vijgh, W. J. F.; Bast, A. and Menge, W. M. P. B., *J. Med. Chem.,* **2000**, *43*, 3752. (h) Roshal, A. D.; Grigorovich, A. V.; Doroshenko, A. O.; Pivovarenko, V. G. and Demchenko, A. P., *J. Phys. Chem. A,* **1998**, *102*, 5907. (i) Patonay, T.; Lévai, A.; Nemes, C.; Timár, T.; Tóth, G. and Adam, W., *J. Org. Chem.,* **1996**, *61*, 5375. (j) Donnelly, J. A. and Farrell, D. F., *J. Org. Chem.,* **1990**, *55*, 1757. (k) Prasad, K. J. R.; Iyer, C. S. R. and Iyer, P. R., *Indian J. Chem., Sect. B,* **1983**, *22B*, 693. (l) Jain, A. C.; Gupta, S. M. and Sharma, A., *Bull. Chem. Soc. Jpn.,* **1983**, *56*, 1267. (m) Dubnitskaya, V. I.; Oganesyan, E. T. and Shinkarenko, A. L., *Izv. Severo-Kavkazskogo Nauch. Tsent. Vysshei Shkoly, Estest. Nauki,* **1975**, *3*, 74. (n) Gormley, T. R. and O'Sullivan, W. I., *Tetrahedron,* **1973**, *29*, 369. (o) O'Sullivan, W. I.; Brady, B. A. and Philbin, E. M., *J. Chem. Soc., Chem. Commun.,* **1970**, 1435. (p) Bellino, A. and Venturella, P., *Atti Accad. Sic., Lett. Arti Palermo,* **1962**, *21*, 17. (q) Venturella, P. and Bellino, A., *Ann. Chim. (Rome, Italy),* **1960**, *50*, 1510.
4. Shah, D. N.; Parikh, S. K. and Shah, N. M., *J. Am. Chem. Soc.,* **1955**, *77*, 2223.
5. (a) Beutler, J. A.; Hamel, E.; Vlietinck, A. J.; Haemers, A.; Rajan, P.; Roitman, J. N.; Cardellina, J. H. and Boyd, M. R., *J. Med. Chem.,* **1998**, *41*, 2333. (b) de Meyer, N.; Haemers, A.; Mishra, L.; Pandey, H.-K.; Pieters, L. A. C.; Berghe, D. A. V. and Vlietinck, A. J., *J. Med. Chem.,* **1991**, *34*, 736. (c) Rao, A. V. S. and Rao, N. V. S., *Curr. Sci.,* **1974**, *43*, 477. (d) Cullen, W. P.; Donnelly, D. M. X.; Keenan, A. K.; Lavin, T. P.; Melody, D. P. and Philbin, E. M., *J. Chem. Soc., C,* **1971**, 2848.

6. (a) Bennett, M.; Burke, A. J. and O'Sullivan, W. I., *Tetrahedron,* **1998**, *54*, 9911. (b) Bennet, M.; Burke, A. J. and O'Sullivan, W. I., *Tetrahedron,* **1996**, *52*, 7163. (c) Stefanovic, M.; Krstic, L.; Rihter, B. and Mladenovic, S., *J. Serb. Chem. Soc.,* **1987**, *52*, 61. (d) Cullen, W. P.; Donnelly, D. M. X.; Keenan, A. K.; Kennan, P. J. and Ramdas, K., *J. Chem. Soc., Perkin Trans. I,* **1975**, 1671. (e) Ramakrishnan, V. T. and Kagan, J., *J. Org. Chem.,* **1970**, *35*, 2898. (f) Adams, J. H., *J. Org. Chem.,* **1967**, *32*, 3992.
7. Parsapour, F. and Kelley, D. F., *J. Phys. Chem.,* **1996**, *100*, 2791.
8. Stevens, J. F.; Miranda, C. L.; Frei, B. and Buhler, D. R., *Chem. Res. Toxicol.,* **2003**, *16*, 1277.
9. Geissman, T. A. and Fukushima, D. K., *J. Am. Chem. Soc.,* **1948**, *70*, 1686.
10. Oyamada, T., *Bull. Chem. Soc. Jpn.,* **1935**, *10*, 182.
11. Reichel, L. and Steudel, J., *Ann.,* **1942**, *553*, 83.
12. Huang, X.; Tang, E.; Xu, W.-M. and Cao, J., *J. Comb. Chem.,* **2005**, *7*, 802.
13. (a) Wang, Q.-A.; Fang, W.-Q. and Liao, T.-G., *J. Hunan Univ. (Nat. Sci.)*, **2006**, *33*, 98. (b) Peng, W.-J.; Han, X.-W. and Yu, B., *Chin. J. Chem.,* **2006**, *24*, 1154. (c) Su, B.; Hackett, J. C.; Diaz-Cruz, E. S.; Kim, Y. W. and Brueggemeier, R. W., *Bioorg. Med. Chem.*, **2005**, *13*, 6571. (d) Zhu, A.; Wang, B.; White, J. O. and Drickamer, H. G., *J. Phys. Chem. B,* **2003**, *107*, 9973. (e) Zhu, A.; Wang, B.; White, J. O. and Drickamer, H. G., *J. Phys. Chem. A,* **2003**, *107*, 6932. (f) Fougerousse, A.; Gonzalez, E. and Brouillard, R., *J. Org. Chem.,* **2000**, *65*, 583. (g) Ormson, S. M.; Brown, R. G.; Vollmer, F. and Rettig, W., *J. Photochem. Photobiol. A,* **1994**, *81*, 65. (h) Pfister, J. R.; Wymann, W. E.; Schuler, M. E. and Roszkowski, A. P., *J. Med. Chem.,* **1980**, *23*, 335. (i) Bhardwaj, D. K.; Jain, S. C. and Sharma, G. C., *Indian J. Chem., Sect. B,* **1977**, *15B*, 860. (j) Clark-Lewis, J. W. and Mahandru, M. M., *Aust. J. Chem.,* **1974**, *27*, 2689. (k) Smith, M. A.; Neumann, R. M. and Webb, R. A., *J. Heterocycl. Chem.,* **1968**, *5*, 425. (l) Clark-Lewis, J. W. and Skingle, D. C., *Aust. J. Chem.,* **1967**, *20*, 2169. (m) Dean, F. M. and Podimuang, V., *J. Chem. Soc.*, **1965**, 3978. (n) Chen, F. C.; Chang, C. T. and Chen, T. S., *J. Org. Chem.,* **1962**, *27*, 85. (o) Cummins, B.; Donnelly, D. M. X.; Philbin, E. M.; Swirski, J.; Wheeler, T. S. and Wilson, R. K., *Chem. Ind. (London),* **1960**, 348. (p) Murakami, M. and Irie, T., *Proc. Imperial Acad. (Tokyo),* **1935**, *11*, 229.

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Alkene Metathesis
(Olefin Metathesis)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Eleuterio in 1963[1] and concurrently by Bailey in 1964;[2] it was subsequently extended primarily by Grubbs et al.[3] It is the swap of olefinic substituents between two alkenes in the presence of a metallo-carbene complex. Therefore, it is generally known as the alkene metathesis[4] or olefin metathesis.[5] Occasionally, it is also referred to as the Grubbs metathesis,[6] Grubbs olefin metathesis,[7] and olefin disproportionation.[2] It is a synthetically powerful chemical transformation, enabling the synthesis of complicated molecular structures for the preparation of novel pharmaceuticals and is the basis of many important industrial processes. The catalyst used in this reaction is generally referred to as the Grubbs catalyst.[8] It is generally proposed that the alkene metathesis proceeds via insertion (or oxidative addition) followed by reductive elimination to afford the final product in the presence of only a catalytic amount of the Grubbs catalyst. During the development of alkene metathesis, different types of ruthenium-based metallo-carbene complexes were designed and are referred to as first-generation Grubbs catalysts, second-generation Grubbs catalysts, first-generation Hoveyda-Grubbs catalysts, and second-generation Hoveyda-Grubbs catalyst,[9] as shown. Many new ruthenium-based metallo-carbene complexes have recently been synthesized.[10]

According to the nature of alkene metathesis, this general reaction can be divided into different subgroups: cross-metathesis (CM),[11] ring-closing metathesis (RCM),[12] ring-opening metathesis polymerization (ROMP),[13] and acyclic diene metathesis polymerization (ADMET).[14] From an industrial perspective, a more cost-effective method for alkene metathesis is to generate the metallo-carbene *in situ*.[15] This reaction has been extensively reviewed.[16]

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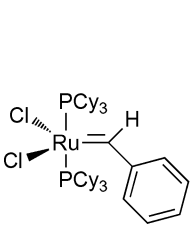
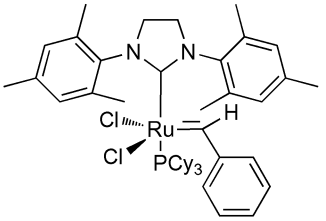
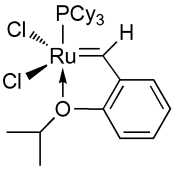


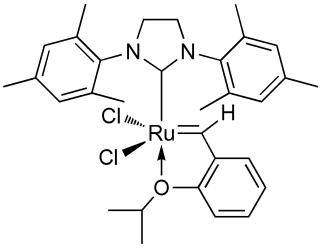
First-generation
Grubbs catalyst



Second-generation
Grubbs catalyst

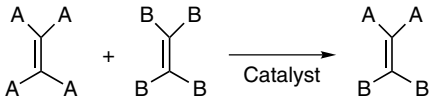


First-generation
Hoveyda-Grubbs catalyst



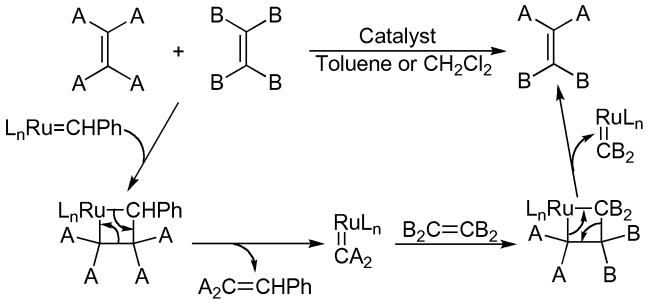
Second-generation
Hoveyda-Grubbs catalyst

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

This reaction generally involves insertion and subsequent reductive elimination.



D. MODIFICATION

This reaction has been modified to generate the catalyst *in situ*.[15]

E. APPLICATIONS

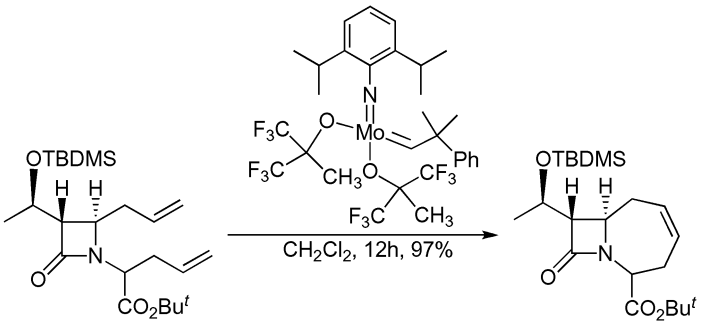
Besides its extensive application in industrial processes, e.g., ROMP and ADMET, the alkene metathesis has been applied to drug discovery and peptide synthesis. Examples include the synthesis of antifungal lactone (-)-gloeosporone,[17] the cross-metathesis of the amino acid homoallylglycine,[18] the introduction of carbon-carbon cross-linkages into

peptides,[19] and ring-closing olefin metathesis of non-natural α-amino acids.[20] Other applications are the synthesis of polymer bound olefins,[21] stereoselective preparation of cyclic 1-amino-1-carboxylic acids,[22] asymmetric synthesis of a potent inhibitor of HIV reverse transcriptase,[23] synthesis of the potential anticancer drugs epothilone A and B in solution and on solid support[24] (as well as the solution-phase combinatorial synthesis[25]), efficient synthesis of [2]-catenanes,[26] template-directed synthesis and polymerization of unsaturated crown ethers,[27] and synthesis of bridged oligocalix[4]arenes.[28] Moreover, this reaction has been applied to the general field of material sciences.[16]

F. RELATED REACTIONS

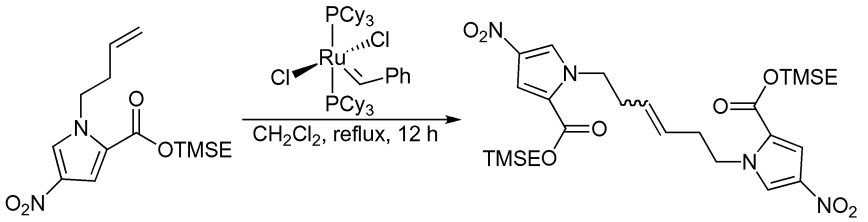
This reaction is related to *Tebbe Olefination*.[29]

G. CITED EXPERIMENTAL EXAMPLES



Reference 30.

The catalyst was added to a mixture of (2*R*)-*tert*-butyl 2-{(3*S*,4*R*)-3-[(1*R*)-(*tert*-butyldimethyl-silyloxy)ethyl]-2-oxo-4-(2-propenyl)-1-azetidinyl}-4-pentenoate and (2*S*)-*tert*-butyl 2-{(3*S*,4*R*)-3-[(1*R*)-(*tert*-butyldimethylsilyloxy)ethyl]-2-oxo-4-(2-propenyl)-1-azetidinyl}-4-pentenoate in CH_2Cl_2 (2 mL). The mixture was stirred for 12 h before destruction of the catalyst by exposure to air. The mixture was then evaporated, and the residue was chromatographed to afford a colorless oil as a mixture of the following-inseparable diastereoisomers: (2*R*,7*R*,8*S*)-*tert*-butyl-1-aza-8-[(1*R*)-(*tert*-butyldimethylsilyloxy)ethyl]-9-oxobicyclo[5.2.0]non-4-ene-2-carboxylate and (2*S*,7*R*,8*S*)-*tert*-butyl 1-aza-8-[(1*R*)-(*tert*-butyldimethyl-silyloxy)ethyl]-9-oxobicyclo[5.2.0]non-4-ene-2-carboxylate, in a yield of 97%, $R_f = 0.41$ (Et_2O:hexanes = 3:2).



Reference 31.

To 90 mL anhydrous CH_2Cl_2 was added 12.3 g 1,1,1-trimethylsilylethyl (4-nitro-1-but-3-enyl)-pyrrole-2-carboxylate (39.6 mmol); the resulting solution was purged with argon for 15 min. Then 0.760 g Grubbs catalyst (1.98 mmol, 2.5 mol %) was added to the solution, and the solution was refluxed while stirred under argon for 24 h. Another 0.76 g Grubbs catalyst was added, and the stirring/refluxing was continued for another 12 h until the reaction was complete as determined by TLC analysis. The solvent was removed in vacuo, and the residue was chromatographed on silica using hexane/EtOAc (5:1) as an eluent. Two isomers (*E* and Z) were collected in total amount of 8.71 g, in a yield of 74%.

Other references related to the Alkene metathesis are cited in the literature.[32]

H. REFERENCES

1. Eleuterio, H. S., *U.S. Pat.,* Jan. 22, **1963**, 3,074,918.
2. Banks, R. L. and Bailey, G. C., *Ind. Eng. Chem., Prod. Res. Develop.,* **1964**, *3*, 170.
3. Grubbs, R. H., *Adv. Synth. Catal.,* **2007**, *349*, 34.
4. (a) Jordaan, M. and Vosloo, H. C. M., *Adv. Synth. Catal.,* **2007**, *349*, 184. (b) Boisvert, L.; Beaumier, F. and Spino, C., *Can. J. Chem.,* **2006**, *84*, 1290. (c) Lewanzik, N.; Oeser, T.; Bluemel, J. and Gladysz, J. A., *J. Mol. Catal. A: Chem.,* **2006**, *254*, 20. (d) Correa da Costa, R. and Gladysz, J. A., *Chem. Commun.,* **2006**, 2619. (e) Bruneau, C. and Dixneuf, P. H., *Angew. Chem. Int. Ed.,* **2006**, *45*, 2176. (f) Nawara, A. J.; Shima, T.; Hampel, F. and Gladysz, J. A., *J. Am. Chem. Soc.,* **2006**, *128*, 4962. (g) Perez-Ruiz, R.; Miranda, M. A.; Alle, R.; Meerholz, K. and Griesbeck, A. G., *Photochem. Photobiol. Sci.,* **2006**, *5*, 51. (h) Tsipis, A. C.; Orpen, A. G. and Harvey, J. N., *Dalton Trans.,* **2005**, 2849. (i) Castarlenas, R.; Eckert, M. and Dixneuf, P. H., *Angew. Chem. Int. Ed.,* **2005**, *44*, 2576. (j) Matsugi, M. and Curran, D. P., *J. Org. Chem.,* **2005**, *70*, 1636. (k) Connon, S. J. and Blechert, S., *Top. Organomet. Chem.,* **2004**, *11*, 93. (l) Reddy, D. S. and Kozmin, S. A., *J. Org. Chem.,* **2004**, *69*, 4860.
5. (a) Salameh, A.; Joubert, J.; Baudouin, A.; Lukens, W.; Delbecq, F.; Sautet, P.; Basset, J. M. and Coperet, C., *Angew. Chem. Int. Ed.,* **2007**, *46*, 3870. (b) Schrodi, Y. and Pederson, R. L., *Aldrichimica Acta,* **2007**, *40*, 45. (c) Chattopadhyay, S. K.; Ghosh, D. and Neogi, K., *Synth. Commun.,* **2007**, *37*, 1535. (d) Juarez Garcia, M.-E.; Froehlich, U. and Koert, U., *Eur. J. Org. Chem.,* **2007**, 1991. (e) Fournier, P.-A. and Collins, S. K., *Organometallics,* **2007**, *26*, 2945. (f) Zhao, Y. and Truhlar, D. G., *Org. Lett.,* **2007**, *9*, 1967. (g) Hong, S. H. and Grubbs, R. H., *Org. Lett.,* **2007**, *9*, 1955. (h) Blanc, F.; Thivolle-Cazat, J.; Basset, J.-M.; Coperet, C.; Hock, A. S.; Tonzetich, Z. J.; Sinha, A. and Schrock, R. R., *J. Am. Chem. Soc.,* **2007**, *129*, 5779. (i) Occhipinti, G.; Jensen, V. R. and Bjorsvik, H.-R., *J. Org. Chem.,* **2007**, *72*, 3561. (j) Thurier, C.; Fischmeister, C.; Bruneau, C.; Olivier-Bourbigou, H. and Dixneuf, P. H., *J. Mol. Catal. A: Chem.,* **2007**, *268*, 127. (k) Vougioukalakis, G. C. and Grubbs, R. H., *Organometallics,* **2007**, *26*, 2469. (l) Matos, J. M. E.; Batista, N. C.; Carvalho, R. M.; Santana, S. A. A.; Puzzi, P. N.; Sanches, M. and Lima-Neto, B. S., *Quim. Nova,* **2007**, *30*, 431. (m) Feyen, F.; Jantsch, A. and Altmann, K.-H., *Synlett,* **2007**, 415. (n) Giudici, R. E. and Hoveyda, A. H., *J. Am. Chem. Soc.,* **2007**, *129*, 3824. (o) Salameh, A.; Coperet, C.; Basset, J.-M.; Bohm, V. P. W. and Roper, M., *Adv. Synth. Catal.,* **2007**, *349*, 238. (p) Coperet, C. and Basset, J.-M., *Adv. Synth. Catal.,* **2007**, *349*, 78.
6. (a) Faulkner, J.; Edlin, C. D.; Fengas, D.; Preece, I.; Quayle, P. and Richards, S. N., *Tetrahedron Lett.,* **2005**, *46*, 2381. (b) Maishal, T. K.; Mondal, B.; Puranik, V. G.; Wadgaonkar, P. P.; Lahiri, G. K. and Sarkar, A., *J. Organomet. Chem.,* **2005**, *690*, 1018. (c) Dinger, M. B. and Mol, J. C., *Eur. J. Inorg. Chem.,* **2003**, 2827. (d) Dinger, M. B. and Mol, J. C., *Organometallics,* **2003**, *22*, 1089.
7. Edlin, C. D.; Faulkner, J.; Fengas, D.; Knight, C. K.; Parker, J.; Preece, I.; Quayle, P. and Richards, S. N., *Synlett,* **2005**, 572.

8. Mukai, C. and Itoh, R., *Tetrahedron Lett.,* **2006**, *47*, 3971.
9. see www.sigmaaldrich.com/suite7/Brands/Fluka_Riedel_Home/Miscellaneous/Reagent_of_the_Year/1998.html.
10. (a) Tanaka, K.; Boehm, V. P. W.; Chadwick, D.; Roeper, M. and Braddock, D. C., *Organometallics,* **2006**, *25*, 5696. (b) Vehlow, K.; Maechling, S.; Koehler, K. and Blechert, S., *Tetrahedron Lett.,* **2006**, *47*, 8617.
11. (a) Bell, T. D. M.; Ghiggino, K. P.; Haynes, A.; Langford, S. J. and Woodward, C. P., *J. Porphyrins & Phthalocyanines,* **2007**, *11*, 455. (b) Paul, T. and Andrade, R. B., *Tetrahedron Lett.,* **2007**, *48*, 5367. (c) Morita, A. and Kuwahara, S., *Tetrahedron Lett.,* **2007**, *48*, 3163. (d) Raju, R.; Allen, L. J.; Le, T.; Taylor, C. D. and Howell, A. R., *Org. Lett.,* **2007**, *9*, 1699. (e) Moiese, J.; Arseniyadis, S. and Cossy, J., *Org. Lett.,* **2007**, *9*, 1695. (f) Storcken, R. P. M.; Panella, L.; van Delft, F. L.; Kaptein, B.; Broxterman, Q. B.; Schoemaker, H. E. and Rutjes, F. P. J. T., *Adv. Synth. Catal.,* **2007**, *349*, 161. (g) Tischer, S. and Metz, P., *Adv. Synth. Catal.,* **2007**, *349*, 147. (h) Fomine, S. and Tlenkopatchev, M. A., *J. Organomet. Chem.,* **2006**, *691*, 5189.
12. (a) Zhang, X. J.; Hsung, R. P. and Li, H. Y., *Chem. Commun.,* **2007**, 2420. (b) Murray, A. J.; Parsons, P. J. and Hitchcock, P., *Tetrahedron,* **2007**, *63*, 6485. (c) Wojtkielewicz, A. and Morzycki, J. W., *Steroids,* **2007**, *72*, 552. (d) Virolleaud, M.-A. and Piva, O., *Eur. J. Org. Chem.,* **2007**, 1606. (e) Fujioka, H.; Okitsu, T.; Ohnaka, T.; Sawama, Y.; Kubo, O.; Okamoto, K. and Kita, Y., *Adv. Synth. Catal.,* **2007**, *349*, 636. (f) Lo, C.; Cariou, R.; Fischmeister, C. and Dixneuf, P. H., *Adv. Synth. Catal.,* **2007**, *349*, 546. (g) Mohapatra, D. K.; Ramesh, D. K.; Giardello, M. A.; Chorghade, M. S.; Gurjar, M. K. and Grubbs, R. H., *Tetrahedron Lett.,* **2007**, *48*, 2621. (h) Feyen, F.; Jantsch, A. and Altmann, K.-H., *Synlett,* **2007**, 415. (i) Berlin, J. M.; Campbell, K.; Ritter, T.; Funk, T. W.; Chlenov, A. and Grubbs, R. H., *Org. Lett.,* **2007**, *9*, 1339. (j) Pathak, R.; Panayides, J.-L.; Jeftic, T. D.; de Koning, C. B. and van Otterlo, W. A. L., *South Afri. J. Chem.,* **2007**, *60*, 1. (k) Sharma, G. V. M. and Reddy, K. L., *Tetrahedron: Asymmetry,* **2007**, *17*, 3197. (l) Ramana, C. V.; Salian, S. R. and Gurjar, M. K., *Tetrahedron Lett.,* **2007**, *48*, 1013. (m) Galletti, E.; Avramova, S. I.; Renzulli, M. L.; Corelli, F. and Botta, M., *Tetrahedron Lett.,* **2007**, *48*, 751. (n) Simpkins, S. M. E.; Kariuki, B. M. and Cox, L. R., *J. Organomet. Chem.,* **2006**, *691*, 5517. (o) Gardiner, J.; Aitken, S. G.; McNabb, S. B.; Zaman, S. and Abell, A. D., *J. Organomet. Chem.,* **2006**, *691*, 5487. (p) Clavier, H.; Petersen, J. L. and Nolan, S. P., *J. Organomet. Chem.,* **2006**, *691*, 5444. (q) Schiltz, S.; Ma, C.; Ricard, L. and Prunet, J., *J. Organomet. Chem.,* **2006**, *691*, 5438. (r) Matovic, R.; Ivkovic, A.; Manojlovic, M.; Tokic-Vujosevic, Z. and Saicic, R. N., *J. Org. Chem.,* **2006**, *71*, 9411. (s) Lebrun, S.; Couture, A.; Deniau, E. and Grandclaudon, P., *Synthesis,* **2006**, 3490. (t) Lejkowski, M.; Gais, H.-J.; Banerjee, P. and Vermeeren, C., *J. Am. Chem. Soc.,* **2006**, *128*, 15378. (u) Gracias, V.; Gasiecki, A. F.; Moore, J. D.; Akritopoulou-Zanze, I. and Djuric, S. W., *Tetrahedron Lett.,* **2006**, *47*, 8977. (v) Wang, C.; Rath, N. P. and Covey, D. F., *Tetrahedron Lett.,* **2006**, *47*, 7837. (w) Le Flohic, A.; Meyer, C. and Cossy, J., *Tetrahedron,* **2006**, *62*, 9017. (x) Yee, N. K.; Farina, V.; Houpis, I. N.; Haddad, N.; Frutos, R. P.; Gallou, F.; Wang, X.-J.; Wei, X. D.; Simpson, R. D.; Feng, X. W.; Fuchs, V.; Xu, Y. B.; Tan, J.; Zhang, L.; Xu, J. H.; Smith-Keenan, L. L.; Vitous, J.; Ridges, M. D.; Spinelli, E. M.; Johnson, M.; Donsbach, K.; Nicola, T.; Brenner, M.; Winter, E.; Kreye, P. and Samstag, W., *J. Org. Chem.,* **2006**, *71*, 7133. (y) Karanjule, N. S.; Markad, S. D. and Dhavale, D. D., *J. Org. Chem.,* **2006**, *71*, 6273. (z) Schmidt, B. and Hermanns, J., *Curr. Org. Chem.,* **2006**, *10*, 1363.
13. (a) Maj, A. M.; Delaude, L.; Demonceau, A. and Noels, A. F., *J. Organomet. Chem.,* **2007**, *692*, 3048. (b) Nishihara, Y.; Inoue, Y.; Saito, A. T.; Nakayama, Y.; Shiono, T. and Takagi, K., *Poly. J. (Tokyo, Japan),* **2007**, *39*, 318. (c) Sutthasupa, S.; Terada, K.; Sanda, F. and Masuda, T., *Polymer,* **2007**, *48*, 3026. (d) Chen, F. X.; Shi, J. X.; Han, H. J.; Dang, J. Y.; Kong, Y. and Xie, M. R., *Gaofenzi Xuebao,* **2007**, 383. (e) Kong, B.; Lee, J. K. and Choi, I. S., *Langmuir,* **2007**, *23*, 6761. (f) Nakayama, Y.; Tanimoto, M. and Shiono, T., *Macromol. Rapid Commun.,* **2007**, *28*, 646. (g) Sandholzer, M.; Lex, A.; Trimmel, G.; Saf, R.; Stelzer, F. and Slugovc, C., *J. Poly. Sci., Part A: Poly. Chem.,* **2007**, *45*, 1336. (h) Bielawski, C. W. and Grubbs, R. H., *Prog. Poly. Sci.,* **2007**, *32*,

1. (i) Mingotaud, A.-F.; Kraemer, M. and Mingotaud, C., *J. Mol. Catal. A: Chem.,* **2007**, *263*, 39. (j) South, C. R. and Weck, M., *Macromolecules*, **2007**, *40*, 1386. (k) Switek, K. A.; Chang, K.; Bates, F. S. and Hillmyer, M. A., *J. Poly. Sci., Part A: Poly. Chem.,* **2007**, *45*, 361. (l) Zheng, L. D.; Chen, F. X.; Xie, M. R.; Han, H. J.; Dai, Q.; Zhang, Y. Q. and Song, C. M., *React. Funct. Poly.,* **2007**, *67*, 19. (m) Alb, A. M.; Enohnyaket, P.; Craymer, J. F.; Eren, T.; Coughlin, E. B. and Reed, W. F., *Macromolecules*, **2007**, *40*, 444. (n) Feng, J. X.; Stoddart, S. S.; Weerakoon, K. A. and Chen, W., *Langmuir,* **2007**, *23*, 1004. (o) Gao, W.; Hagver, R.; Shah, V.; Xie, W. C.; Gross, R. A.; Ilker, M. F.; Bell, C.; Burke, K. A. and Coughlin, E. B., *Macromolecules,* **2007**, *40*, 145. (p) Larin, G. E.; Bernklau, N.; Kessler, M. R. and DiCesare, J. C., *Poly. Eng. Sci.,* **2006**, *46*, 1804. (q) Yu, C.-Y. and Turner, M., *Angew. Chem. Int. Ed.,* **2006**, *45*, 7797. (r) Ganem, B. and Ding, Z. B., *Can. J. Chem.,* **2006**, *84*, 1254. (s) Belfield, K. D. and Zhang, L., *Chem. Mater.,* **2006**, *18*, 5929. (t) Singh, R.; Verploegen, E.; Hammond, P. T. and Schrock, R. R., *Macromolecules,* **2006**, *39*, 8241. (u) Gautrot, J. E. and Zhu, X. X., *Angew. Chem. Int. Ed.,* **2006**, *45*, 6872. (v) Liaw, D.-J.; Huang, C.-C. and Hong, S.-M., *J. Poly. Sci., Part A: Poly. Chem.,* **2006**, *44*, 6287. (w) Matos, J. M. E. and Lima-Neto, B. S., *J. Mol. Catal. A: Chem.,* **2006**, *259*, 286. (x) Vygodskii, Y. S.; Shaplov, A. S.; Lozinskaya, E. I.; Filippov, O. A.; Shubina, E. S.; Bandari, R. and Buchmeiser, M. R., *Macromolecules*, **2006**, *39*, 7821. (y) Gatschelhofer, C.; Schmid, M. G.; Schreiner, K.; Pieber, T. R.; Sinner, F. M. and Guebitz, G., *J. Biochem. Biophys. Methods,* **2006**, *69*, 67. (z) Frech, C. M; Blacque, O. and Berke, H., *Pure & Appl. Chem.,* **2006**, *78*, 1877.

14. (a) Karabulut, S.; Aydogdu, C.; Duez, B. and Imamoglu, Y., *J. Inorg. Organomet. Poly. Mat.,* **2007**, *17*, 313. (b) Karabulut, S.; Aydogdu, C.; Duez, B. and Imamoglu, Y., *J. Inorg. Organomet. Poly. Mat.,* **2007**, *17*, 517. (c) Petkovska, V. I.; Hopkins, T. E.; Powell, D. H. and Wagener, K. B., *Anal. Chem.,* **2006**, *78*, 3624. (d) Nomura, K.; Miyamoto, Y.; Morimoto, H. and Geerts, Y., *J. Poly. Sci., Part A: Poly. Chem.,* **2005**, *43*, 6166. (e) Wu, Z. Z.; Papandrea, J. P.; Apple, T. and Interrante, L. V., *Macromolecules,* **2004**, *37*, 5257. (f) Qin, H. H.; Chakulski, B. J.; Rousseau, I. A.; Chen, J. Z.; Xie, X.-Q.; Mather, P. T.; Constable, G. S. and Coughlin, E. B., *Macromolecules,* **2004**, *37*, 5239. (g) Courchay, F. C.; Sworen, J. C. and Wagener, K. B., *Polymer Preprints,* **2003**, *44*, 940. (h) Nomura, K.; Morimoto, H.; Imanishi, Y.; Ramhani, Z. and Geerts, Y., *J. Poly. Sci., Part A: Poly. Chem.,* **2001**, *39*, 2463. (i) Brzezinska, K. R. and Deming, T. J., *Macromolecules,* **2001**, *34*, 4348. (j) Watson, M. D. and Wagener, K. B., *Macromolecules,* **2000**, *33*, 8963. (k) Kellam, E. C.; Hofmann, M. A. and Allcock, H. R., *Polymer Preprints,* **2000**, *41*, 1233. (l) Joo, S.-H.; Yun, Y.-K.; Jin, J.-I.; Kim, D.-C. and Zin, W.-C., *Macromolecules,* **2000**, *33*, 6704. (m) Watson, M. D. and Wagener, K. B., *Macromolecules,* **2000**, *33*, 5411. (n) Wagener, K. B. and Pawlow, J. H., *Poly. Mat. Sci. Eng.,* **1999**, *80*, 433. (o) Gomez, F. J.; Abboud, K. A. and Wagener, K. B., *J. Mol. Catal. A: Chem.,* **1998**, *133*, 159. (p) Tang, F. C.; Wu, Q. and Lu, Z. J., *Gaofenzi Tongbao,* **1997**, 65. (q) Miao, Y.-J. and Bazan, G. C., *Macromolecules,* **1997**, *30*, 7414. (r) Walba, D. M.; Keller, P.; Shao, R. F.; Clark, N. A.; Hillmyer, M. and Grubbs, R. H., *J. Am. Chem. Soc.,* **1996**, *118*, 2740. (s) Nubel, P. O.; Lutman, C. A. and Yokelson, H. B., *Macromolecules,* **1994**, *27*, 7000. (t) Wagener, K. B.; Patton, J. T.; Forbes, M. D. E.; Myers, T. L. and Maynard, H. D., *Poly. Int.,* **1993**, *32*, 411. (u) Konzelman, J. and Wagener, K. B., *Polymer Preprints,* **1992**, *33*, 110. (v) Wagener, K. B. and Smith, D. W., *Macromolecules,* **1991**, *24*, 6073. (w) Wagener, K. B.; Boncella, J. M.; Nel, J. G.; Duttweiler, R. P. and Hillmyer, M. A., *Makromol. Chem.,* **1990**, *191*, 365. (x) Nel, J. G.; Wagener, K. B. and Boncella, J. M., *Polymer Preprints,* **1989**, *30*, 130. (y) Wagener, K. B., *Poly. Mat. Sci. Eng.,* **1988**, *58*, 101.

15. Nubel, P. O. and Hunt, C. L., *J. Mol. Catal A: Chem*., **1999**, *145*, 323.

16. (a) Grubbs, R. H., ed. *Handbook of Metathesis*, Wiley-VCH, Weinhein, Germany, **2003**. (b) Imamoglu, Y. and Bencze, L., *Novel Metathesis Chemistry: Well-Defined Initiator Systems for Specialty Chemical Synthesis, Tailored Polymers, and Advanced Material Applications*, Kluwer Academic Publishers, Dordrecht, **2003**. (c) Khosrari, E. and Szymanska-Buzar, T., ed., *Ring Opening Metathesis Polymerisation and Related Chemistry* Kluwer Academic Publishers, Dordrecht, **2002**. (d) Furstner, A. *Alkene Metathesis in Organic Synthesis*, Springer-Berlin, **1998**.

(e) Imamoglu, Y., *Metathesis Polymerization of Olefins and Polymerization of Alkynes*, Kluwer Academic Publishers, Dordrecht, **1998**. (f) Imamoglu, Y.; Zümreoglu-Karan, B. and Amass, A. J., *Olefin Metathesis and Polymerization Catalysts: Synthesis, Mechanism and Utilization*, Kluwer Academic Publishers, Dordrecht, **1990**. (g) Quirk, R. P. and Hoff, R. E., *Transition Metal Catalyzed Polymerizations: Ziegler-Natta and Metathesis Polymerizations*, Cambridge University Press, Cambridge, **1989**. (h) Ivin, K. J., *Olefin Metathesis*, Academic Press, London, **1983**.

17. Fristner, A. and Langemann, K., *J. Am. Chem. Soc*., **1997**, *119*, 9130.
18. Gibson, S. E.; Gibson, V. C. and Keen, S. P., *Chem. Commun.,* **1997**, 1107.
19. Miller, S. J.; Blackwell, H. E. and Grubbs, R. H., *J. Am. Chem. Soc*., **1996**, *118*, 9606.
20. Rutjes, F. P. J. T. and Schoemaker, H. E., *Tetrahedron Lett.,* **1997**, *38*, 677.
21. Van Maarseveen, J. H.; den Hartog, J. A. J.; Engelen, V.; Finner, E.; Visser, G. and Kruse, C. G., *Tetrahedron Lett.,* **1996**, *37*, 8249.
22. Hammer, K. and Undheim, K., *Tetrahedron,* **1997**, *53*, 2309.
23. Crimmins, M. T. and King, B. W., *J. Org. Chem.,* **1996**, *61*, 4129.
24. Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumix, D.; Yang, Z.; Li, T.; Giannakakou, P. and Hamel, E., *Nature,* **1997**, *387*, *268*.
25. Boger, D. L.; Wenying, C.; Ozer, R. S. and Anderson, C. M., *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 463.
26. Mohr, B.; Weck, M.; Sauvage, J. P. and Grubbs, R. H., *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, 1308.
27. Marsella, M. J.; Maynard, H. D. and Grubbs, R. H., *Angew. Chem.,* **1997**, *109*, 1147.
28. McKervey, M. A. and Pitarch, M., *Chem. Comm. (Cambridge)*, **1996**, 1689.
29. (a) Burton, J. W.; Clark., J. S.; Derrer, S.; Stork, T. C.; Bendall, J. G.; Holmes, A. B., *J. Am. Chem. Soc.,* **1997**, *119*, 7483. (b) Tebbe, F. N.; Parshall, G. W. and Reddy, G. S., *J. Am. Chem. Soc.,* **1978**, *100*, 3270.
30. Barrett, A. G. M.; Ahmed, M.; Baker, S. P.; Baugh, S. P. D.; Braddock, D. C.; Procopiou, P. A.; White, A. J. P. and Williams D. J., *J. Org. Chem.,* **2000**, *65*, 3716.
31. Olenyuk, B.; Jitianu, C. and Dervan, P. B., *J. Am. Chem. Soc.,* **2003**, *125*, 4741.
32. (a) Chauvin, Y., *Adv. Synth. Catal.,* **2007**, *349*, 27. (b) Grubbs, R. H., *Adv. Synth. Catal.,* **2007**, *349*, 23. (c) Murruzzu, C. and Riera, A., *Tetrahedron: Asymmetry,* **2007**, *18*, 149. (d) Madsen, R., *Eur. J. Org. Chem.,* **2007**, 399. (e) Pattabiraman, V. R.; Stymiest, J. L.; Derksen, D. J.; Martin, N. I. and Vederas, J. C., *Org. Lett.,* **2007**, *9*, 699. (f) Macnaughtan, M. L.; Johnson, M. J. A. and Kampf, J. W., *Organometallics,* **2007**, *26*, 780. (g) Pilyugina, T. S.; Schrock, R. R.; Mueller, P. and Hoveyda, A. H., *Organometallics,* **2007**, *26*, 831. (h) Siaj, M.; Oudghiri-Hassani, H.; Maltais, C. and McBreen, P. H., *J. Phys. Chem. C,* **2007**, *111*, 1725. (i) Blanc, F.; Thivolle-Cazat, J.; Basset, J.-M.; Coperet, C.; Hock, A. S.; Tonzetich, Z. J. and Schrock, R. R., *J. Am. Chem. Soc.,* **2007**, *129*, 1044. (j) Zheng, X. L.; Jones, C. W. and Weck, M., *J. Am. Chem. Soc.,* **2007**, *129*, 1105. (k) Schrodi, Y., *Special Chem. Mag.,* **2006**, *26*, 34. (l) Katz, T. J., *New J. Chem.,* **2006**, *30*, 1844. (m) Chen, W.-Z.; Protasiewicz, J. D.; Shirar, A. J. and Ren, T., *Eur. J. Inorg. Chem.,* **2006**, 4737. (n) Yoshida, K.; Kawagoe, F.; Iwadate, N.; Takahashi, H. and Imamoto, T., *Chem. Asian J.,* **2006**, *1*, 611. (o) Hock, A. S.; Schrock, R. R. and Hoveyda, A. H., *J. Am. Chem. Soc.,* **2006**, *128*, 16373. (p) Ledoux, N.; Allaert, B.; Schaubroeck, D.; Monsaert, S.; Drozdzak, R.; Van Der Voort, P. and Verpoort, F., *J. Organomet. Chem.,* **2006**, *691*, 5482. (q) Edlin, C. D.; Faulkner, J. and Quayle, P., *Tetrahedron Lett.,* **2006**, *47*, 1145. (r) Banerjee, S.; Nayek, A.; Sinha, S.; Bhaumik, T. and Ghosh, S., *J. Mol. Catal. A: Chem.,* **2006**, *254*, 85. (s) Kwon, Y. and Kim, K.-H., *Macromol. Res.,* **2006**, 14, 424. (t) Royer, F.; Vilain, C.; Elkaý1m, L. and Grimaud, L., *Org. Lett*., **2003**, *5*, 2007. (u) Vasbinder, M. M. and Miller, S. J., *J. Org. Chem.,* **2002**, *6*7, 6240. (v) Fu1rstner, A.; Thiel, O. R. and Ackermann, L., *Org. Lett*., **2001**, *3*, 449. (w) Barrett, A. G. M.; Beall, J. C.; Braddock, D. C.; Flack, K.; Gibson, V. C. and Salter, M. M., *J. Org. Chem.,* **2000**, *65*, 6508.

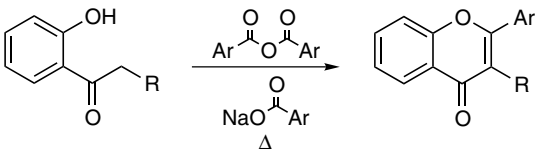
15

Allan-Robinson Condensation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Allan and Robinson in 1924.[1] It is the synthesis of flavones or isoflavones derivatives by means of the condensation between *o*-hydroxyaryl ketones and an anhydride of aromatic acid in the presence of the sodium salt of corresponding acid in the anhydride. Thus this reaction is known as the Allan-Robinson condensation,[2] Allan-Robinson's flavone synthesis,[3] Allan-Robinson reaction,[4] and Allan-Robinson synthesis.[5]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A general illustration of the reaction mechanism is provided here.

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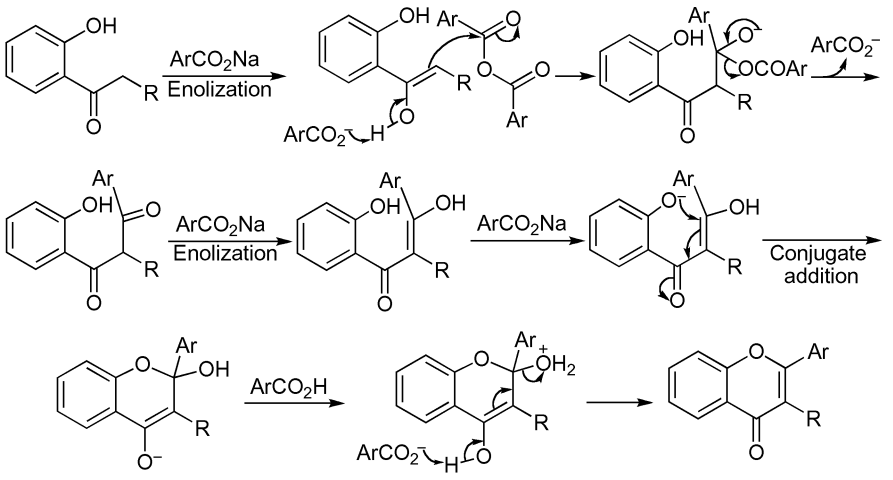


D. MODIFICATION

N/A

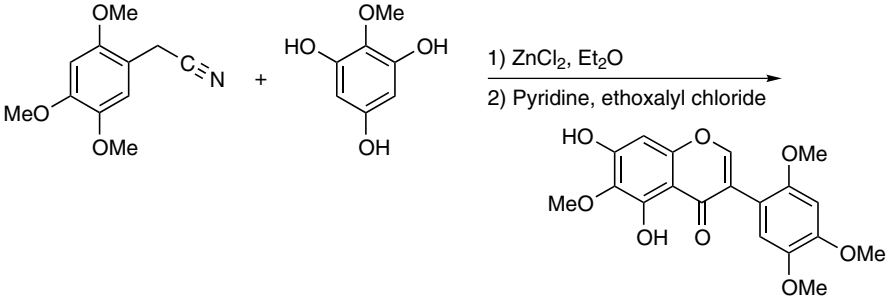
E. APPLICATIONS

This reaction has been used to synthesize the structurally disparate flavonoids and isoflavones.[6]

F. RELATED REACTIONS

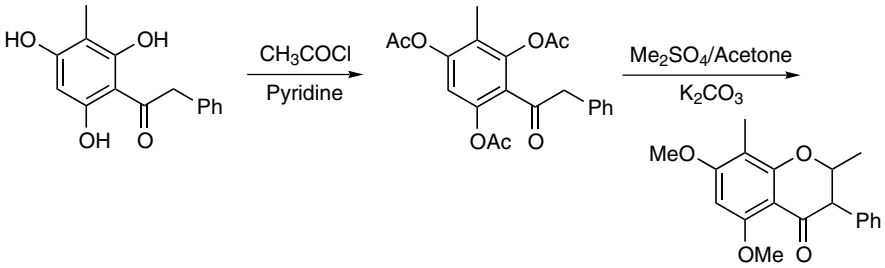
This reaction is closely related to the *Baker-Venkataraman Rearrangement* and *Kostanecki-Robinson Reaction*. Regarding the synthesis of flavone derivatives, the Allan-Robinson condensation is also related to the *Algar-Flyn-Oyamada (AFO) Reaction* and *Auwers Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

To a mixture of 4.2 g iretol, 6.0 g 2,4,5-trimethoxybenzyl cyanide and 5.0 g anhydrous zinc chloride in 150 mL anhydrous ether was bubbled with dried hydrogen chloride for 5 h at 0°C. After remaining at 0°C for 1 week, the ether solution was decanted from the oily layer of the ketimine hydrochloride-zinc chloride complex, which had separated. The oily layer was shaken with dry ether (2 × 250 mL) then heated under a nitrogen atmosphere on a steam bath with 400 mL water, which had been previously boiled with a stream of nitrogen bubbling through it. After cooling and standing, the product was collected and recrystallized from aqueous ethanol to afford 5.9 g of ketone as almost colorless rhombs, in a yield of 60%, m.p. 211–212°C. A part of the ketone (2.48 g) was dissolved in 50 mL dry pyridine, and 4.5 mL ethoxalyl chloride was added with shaking at 0°C. After remaining at 0°C for 3 days, it was poured into water and extracted with chloroform. The combined extracts were washed with dilute sulfuric acid and water, dried over $MgSO_4$, and evaporated to yield 3.18 g 2-carbethoxyisoflavone as an oil.



Reference 6d.

To a mixture of 1.0 g 2,4,6-trihydroxy-3-methyldeoxybenzoin and 20 mL pyridine was added 1.4 mL freshly distilled acetyl chloride at 0°C with stirring. After remaining for 24 h at 0°C, crushed ice was added and the solution was extracted several times with ether. The combined extracts were washed with ice cold hydrochloric acid, then with water, and then dried. Upon removal of ether via distillation, 1.4 g of a reddish brown semisolid mass was obtained.

About 0.2 g of this product (m.p. 224–225°C) was co-heated with 2 mL methyl sulfate and 5.0 g potassium carbonate in 150 mL dry acetone for 50 h. The product on repeated crystallization from methanol separated into 90 mg of colorless shining needles, m.p. 176–177°C. The second product, which separated from methanol as colorless needles (60 mg, m.p. 184–186°C), was characterized as the final product.

Other references related to the Allan-Robinson condensation are cited in the literature.[8]

H. REFERENCES

1. Allan, J. and Robinson, R., *J. Chem. Soc.*, **1924**, *125*, 2192.
2. Boers, F.; Deng, B.-L.; Lemière, G.; Lepoivre, J.; de Groot, A.; Dommisse, R. and Vlietinck, A. J., *Arch. Pharm.,* **1997**, *330*, 313.
3. Fukui, K.; Nakayama, M. and Horie, T., *Cell. Mol. Life Sci.,* **1968**, *24*, 769.
4. Goudard, M. and Chopin, J., *Compt. Rend. Sean. Acad. Sci., Ser. C.: Sci. Chem.,* **1976**, *282*, 683.
5. Patwardhan, S. A. and Gupta, A. S., *J. Chem. Res. (S),* **1984**, 395.

6. (a) Corey, E. J. and Gin, D. Y., *Tetrahedron Lett.,* **1996**, *37*, 7163. (b) Reddy, B. P. and Krupadanam, G. L. D., *J. Heterocycl. Chem.,* **1996**, *33*, 1561. (c) Horie, T.; Kawamura, Y.; Tsukayama, M. and Yoshizaki, S., *Chem. Pharm. Bull.,* **1989**, *37*, 1216. (d) Makrandi, J. K. and Kumari, V., *Synth. Commn.,* **1989**, *19*, 1919. (e) Horie, T.; Tsukayama, M.; Kawamura, Y. and Seno, M., *J. Org. Chem*., **1987**, *52*, 4702. (f) Horie, T.; Tsukayama, M.; Kawamura, Y. and Yamamoto, S., *Chem. Pharm. Bull.,* **1987**, *35*, 4465. (g) Patwardhan, S. A. and Gupta, A. S., *J. Chem. Res (S),* **1984**, 395. (h) Dutta, P. K.; Bagchi, D. and Pakrashi, S. C., *Indian J. Chem., Sect. B,* **1982**, *21B*, 1037. (i) Wagner, H.; Maurer, I.; Farkas, L. and Strelisky, J., *Tetrahedron*, **1977**, *33*, 1405. (j) Szell, T.; Dozsai, L.; Zarandy, M. and Menyharth, K., *Tetrahedron*, **1969**, *25*, 715.

7. Dyke, S. F.; Ollis, W. D. and Sainsbury, M., *J. Org. Chem.,* **1961**, *26*, 2453.

8. (a) Lee, Y. R. and Kim, D. H., *Synthesis,* **2006**, 603. (b) Guarna, A.; Lombardi, E.; Machetti, F.; Occhiato, E. G. and Scarpi, D., *J. Org. Chem.,* **2000**, *65*, 8093. (c) Dyker, G.; Grundt, P.; Markwitz, H. and Henkel, G., *J. Org. Chem.,* **1998**, *63*, 6043. (d) Corey, E. J. and Gin, D. Y., *Tetrahedron Lett.,* **1996**, *37*, 7163. (e) Mohanty, S.; Makrandi, J. K. and Grover, S. K., *Indian J. Chem., Sect. B,* **1989**, *28B*, 766. (f) Fukui, K.; Matsumoto, T.; Nakayama, M. and Horie, T., *Experientia,* **1969**, *25*, 349. (g) Fukui, K.; Matsumoto, T.; Nakamura, S.; Nakayama, M. and Horie, T., *Bull. Chem. Soc. Jpn.,* **1968**, *41*, 1413. (h) Fukui, K.; Matsumoto, T. and Matsuzaki, S., *Bull. Chem. Soc. Jpn.,* **1964**, *37*, 265. (i) Grover, S. K.; Jain, A. C.; Mathur, S. K. and Seshadri, T. R., *Indian J. Chem.,* **1963**, *1*, 382. (j) Rahman, W. and Nassim, K. T., *J. Org. Chem.,* **1962**, *27*, 4215. (k) Rao, K. V.; Seshadri, T. R. and Viswanadham, N., *Proc. Indian Acad. Sci., Sect. A,* **1949**, *29A*, 72.

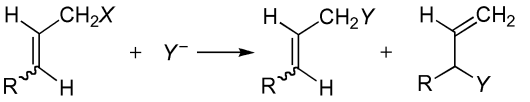
16

Allylic Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Claisen in 1912.[1] It is a migration of a carbon-carbon double bond within a three-carbon system (i.e., allylic), often occurring on the nucelophilic substitution of allylic systems in which the nucleophile adds to the carbon-carbon double bond along with the cleavage of the allylic leaving group. Thus this reaction is generally known as the allylic rearrangement,[2] and occasionally referred to as the allylic isomerization,[3] allylic transposition,[4]and allylic 1,3-rearrangement.[5] Because the allylic cation is relatively stable, the allylic rearrangement is often competed with regular S_N1 and S_N2 substitutions; therefore, the allylic rearrangement is also known as the S_N1' or S_N2' reaction. The allylic rearrangement can be promoted by light,[6] enzymes,[7] solvents,[8] acid,[6,9] (especially the Lewis acids such as $Eu(fod)_3$[10] PBr_3[11] and $NiCl_2$[12]) and transition metal catalysts (including tungsten,[13] rhodium,[14] cobalt[15] and palladium[16]). In addition, the allylic rearrangement also occurs under the conditions of electrophilic substitution.[17]

B. GENERAL REACTION SCHEME



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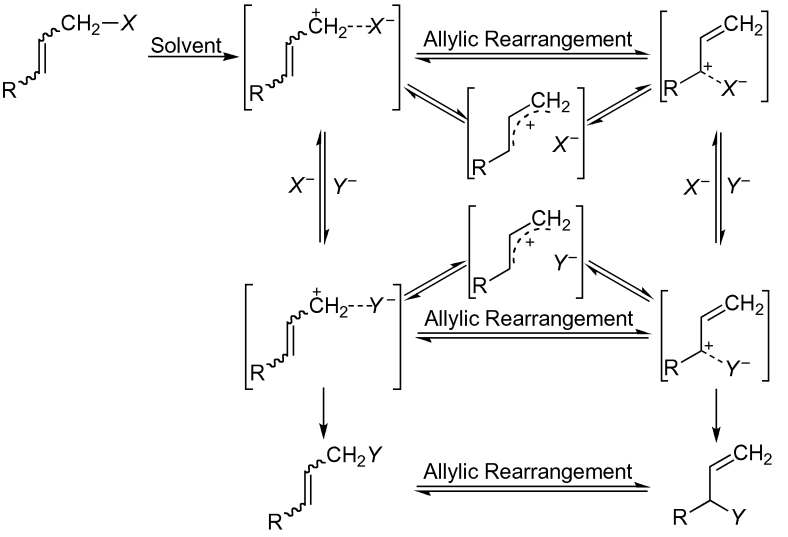
C. PROPOSED MECHANISMS

This reaction is proposed to occur through what is referred to as "super-conjugation" between α-methylene hydrogen and the π-double bond. The positive charge thus formed can be distributed to the double bond, especially under S_N1 conditions, forming a three-center two-electron system. On the other hand, the allylic cation can also isomerize to another resonance structure, via the distribution of the positive charge, resulting a relatively stable allylic cation. When a nucleophilic group attacks the allylic cation, it can bind to either one of the two positions as shown (a proposed mechanism).



D. MODIFICATION

This reaction has been extended to proceed via the promotion by means of enzymes, Lewis acids, transition metal complexes, and so on.

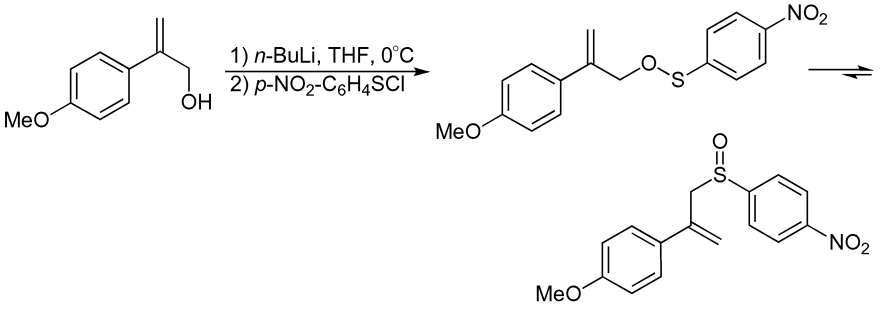
E. APPLICATIONS

The allylic rearrangement is so common in organic chemistry that it has been extensively used to synthesize a variety of organic molecules.

F. RELATED REACTIONS

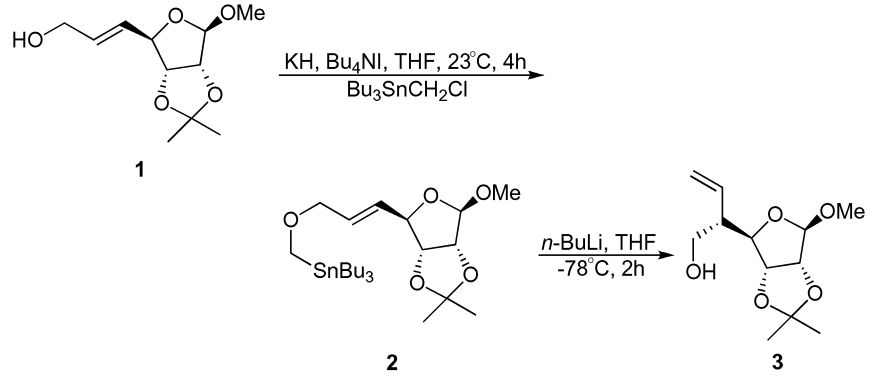
This reaction is similar to the *Chapman Reaction.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 18.

Under nitrogen atmosphere, 1.0 mL 2.0 M butyllithium in hexane (2.0 mmol) and 398 mg 4-nitrobenzenesulfenyl chloride (2.1 mmol) were added sequentially to a solution of 328 mg 2-(4-methoxyphenyl)-prop-2-en-1-ol (2.0 mmol) in anhydrous THF at 0°C. After being stirred for 30 min, the reaction mixture was diluted with EtOAc, washed with aqueous phosphate buffer (400 mM, pH 6.8) and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel with hexane/EtOAc (2:1) as an eluent to afford 2-(4-methoxyphenyl)prop-2-en-1-yl-4-nitrophenyl sulfoxide as a yellow solid, in a yield of 55%, m.p. 99.9–100.7°C, $R_f = 0.25$ (hexane/EtOAc = 2:1).



Reference 19.

To a suspension of 418 mg KH (10.4 mmol, prewashed with hexane) and 25 mg tetrabutylammonium iodide in 10 mL dry THF at 0°C was added dropwise a solution of 1.2 g (methyl (*E*)-5,6-dideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hept-5-enofuranoside (**1**) (5.23 mmol) in 2 mL THF. The resulting red suspension was allowed to warm to 23°C, and the mixture was stirred for 1 h. The reaction was cooled to 0°C, and 2.1 g Bu_3SnCH_2I (6.8 mmol) in 2 mL THF was added dropwise over a period of 2 min. The mixture was stirred at 0–23°C for 4 h. Then the reaction was quenched with 10 mL saturated NH_4Cl solution. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4. Evaporation of the solvents provided the allyl stannylmethyl ether (**2**) as a colorless oil. This material was used for the next reaction without further purification. An analytical sample of structure **2** was obtained by flash chromatography over silica gel (5% EtOAc in hexane).

To a stirred solution of the formed crude stannyl ether **2** in 10 mL of THF at −78°C was added 3.2 mL 2.5 M *n*-BuLi in hexane (8 mmol) dropwise by a syringe pump over a period of 1 h. The resulting mixture was stirred for 2 h at −78°C. Then the reaction was quenched with saturated NH_4Cl solution, and the resulting mixture was warmed to 23°C. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Upon evaporation of the solvents, the residue was chromatographed over silica gel using EtOAc/hexane (1:4) as an eluent to furnish 1.07 g of an inseparable mixture of methyl 5-(*S*)-deoxy-5-vinyl-2,3-*O*-isopropylidene-*β*-D-*ribo*-hexanofuranoside (**3**) and its epimer (4.4:1 by ^1H NMR) as a colorless oil, in a yield of 84%.

Other references related to allylic rearrangement are cited in the literature.[20]

H. REFERENCES

1. Claisen, L., *Ber.* **1912**, *45*, 3157.
2. (a) Tachi, Y.; Dai, W.-M.; Tanabe, K. and Nishimoto, S.-I., *Bioorg. Med. Chem.,* **2006**, *14*, 3199. (b) Shanmugasundaram, B.; Bose, A. K. and Balasubramanian, K. K., *Tetrahedron Lett.,* **2002**, *43*, 6795. (c) Konno, T.; Daitoh, T.; Ishihara, T. and Yamanaka, H., *Tetrahedron: Asymmetry,* **2001**, *12*, 2743. (d) Dai, W.-M.; Wu, A. and Hamaguchi, W., *Tetrahedron Lett.,* **2001**, *42*, 4211. (e) Reizelman, A. and Zwanenburg, B., *Synthesis,* **2000**, 1952. (f) Blattner, R.; Ferrier, R. J. and Furneaux, R. H., *Tetrahedron: Asymmetry,* **2000**, *11*, 379. (g) Hattori, T.; Suzuki, Y.; Uesugi, O.; Oi, S. and Miyano, S., *Chem. Commun.,* **2000**, 73. (h) Faigl, F.; Barcza, T.; Agai, B. and Toke, L., *ACH-Models Chem.,* **1999**, *136*, 593. (i) Maksakov, V. A.; Kirin, V. P.; Tkachev, S. V. and Golovin, A. V., *Russ. Chem. Bull.,* **1999**, *48*, 2158. (j) Bellemin-Laponnaz, S.; Le Ny, J. P. and Dedieu, A., *Chem. Eur. J.,* **1999**, *5*, 57. (k) Dai, W.-M.; Fong, K. C.; Lau, C. W.; Zhou, L.; Hamaguchi, W. and Nishimoto, S.-I., *J. Org. Chem.,* **1999**, *64*, 682. (l) Suzuki, H.; Sako, M. and Hirota, K., *Chem. Pharm. Bull.,* **1998**, *46*, 1314. (m) Westermann, B. and Dubberke, S., *Liebigs Ann./Rec.,* **1997**, 375. (n) Jarosz, S. and Kozlowska, E., *Carbohydr. Lett.,* **1996**, *2*, 213. (o) Pop, E.; Rachwal, S. and Brewster, M. E., *Int. J. Quant. Chem.,* **1996**, *60*, 105. (p) Dai, W.-M. and Fong, K. C., *Tetrahedron Lett.,* **1996**, *37*, 8413. (q) Clayden, J.; Collington, E. W.; Elliott, J.; Martin, S. J.; McElroy, A. B.; Warren, S. and Waterson, D., *J. Chem. Soc., Perkin Trans. I,* **1993**, 1849. (r) Schiesser, C. H. and Wu, H., *Aust. J. Chem.,* **1993**, *46*, 1437. (s) Hideg, K.; Sar, C. P.; Hankovszky, O. H.; Tamas, T. and Jerkovich, G., *Synthesis,* **1993**, 390. (t) Belgacem, J.; Kress, J. and Osborn, J. A., *J. Am. Chem. Soc.,* **1992**, *114*, 1501. (u) Erman, M. B.; Cherkaev, G. V.; Yakover, L. L. and Mochalin, V. B., *Zh. Org. Khim.,* **1991**, *27*, 1873. (v) Huot, J. F.; Outurquin, F. and Paulmier, C., *Chem. Lett.,* **1991**, 1957. (w) O'Sullivan, M. C.; Schwab, J. M.; Zabriskie, T. M.; Helms, G. L. and Vederas, J. C., *J. Am. Chem. Soc.,* **1991**, *113*, 3997. (x) Zacharias, M. T.; Pushpakumari, T.; Sreevalsan, S. V. and Pillai, G. N., *Indian J. Chem., Sect. B,* **1991**, 30*B*, 59. (y) Oehler, E. and Zbiral, E., *Chem. Ber.,* **1991**, *124*, 175. (z) Rotto, N. T.; Coates, R. M., *J. Am. Chem. Soc.,* **1989**, *111*, 8941. (aa) Davies, A. G. and Kinart, W. J., *J. Chem. Res. (S),* **1989**, 22. (bb) Davies, A. G.; Davison, I. G. E. and Schiesser, C. H., *J. Chem. Soc., Chem. Commun.,* **1989**, 742. (cc) De March, P.; Moreno-Manas, M. and Roca, J. L., *J. Org. Chem.,* **1988**, *53*, 5149. (dd) Thibblin, A., *J. Chem. Soc., Perkin Trans. II,* **1987**, 1629. (ee) Tsuboi, S.; Kurihara, Y.; Watanabe, T. and Takeda, A., *Synth. Commun.,* **1987**, *17*, 773. (ff) Kurihara, T.; Miki, M.; Santo, K.; Harusawa, S. and Yoneda, R., *Chem. Pharm. Bull.,* **1986**, *34*, 4620. (gg) Ananda, G. D. S.; Slawin, A. M. Z.; Stoodley, R. J. and Williams, D. J., *J. Chem. Soc., Chem. Commun.,* **1986**, 165. (hh) Kiss, J.; Wyss, P. C.; Flesch, G.; Arnold, W.; Noack, K. and Schonholzer, P., *J. Carbohydr. Chem.,* **1985**, *4*, 347. (ii) Katz, H. E. and Starnes, W. H., *J. Org. Chem.,* **1984**, *49*, 2758. (jj) Robert,

J. F. and Panouse, J. J., *J. Heterocycl. Chem.,* **1982**, *19*, 343. (kk) Gambaro, A.; Marton, D. and Tagliavini, G., *J. Organomet. Chem.,* **1981**, *210*, 57. (ll) Bunton, C. A.; Cori, O.; Hachey, D. and Leresche, J. P., *J. Org. Chem.,* **1979**, *44*, 3238. (mm) Bessiere, Y.; Reca, E.; Chatzopoulos-Ouar, F. and Boussac, G., *J. Chem. Res (S),* **1977**, 302. (nn) Ferrier, R. J. and Vethaviyasar, N., *Carbohydr. Res.,* **1977**, *58*, 481. (oo) Maruyama, K. and Yamamoto, Y., *J. Am. Chem. Soc.,* **1977**, *99*, 8068. (pp) Holmes, B. N.; Leonard, N. J., *J. Org. Chem.,* **1976**, *41*, 568. (qq) Moriwaki, M.; Yamamoto, Y.; Oda, J. and Inouye, Y., *J. Org. Chem.,* **1976**, *41*, 300. (rr) Leonard, N. J. and Frihart, C. R., *J. Am. Chem. Soc.,* **1974**, *96*, 5894. (ss) Hayashi, T., *Tetrahedron Lett.,* **1974**, 339. (tt) Frihart, C. R. and Leonard, N. J., *J. Am. Chem. Soc.,* **1973**, *95*, 7174. (uu) Takeda, A. and Tsuboi, S., *J. Org. Chem.,* **1973**, *38*, 1709.

3. (a) Goncalves, O.; Dintinger, T.; Lebreton, J.; Blanchard, D. and Tellier, C., *Biochem. J.,* **2000**, *346*, 691. (b) Dakoji, S.; Shin, I.; Becker, D. F.; Stankovich, M. T. and Liu, H.-W., *J. Am. Chem. Soc.,* **1996**, *118*, 10971.
4. (a) Heravi, M. M.; Nooshabadi, M. A. and Aghapoor, K., *Phosphorus Sulfur Silicon Relate. Elem.,* **2000**, *164*, 95. (b) Martin, C.; Bortolussi, M. and Bloch, R., *J. Chem. Res. (S),* **1998**, 416. (c) Clayden, J. and Warren, S., *J. Chem. Soc., Perkin Trans. I,* **1994**, 1529. (d) Panek, J. S. and Sparks, M. A., *J. Org. Chem.,* **1990**, *55*, 5564.
5. Ogura, K.; Iihama, T.; Kiuchi, S.; Kajiki, T.; Koshikawa, O.; Takahashi, K. and Iida, H., *J. Org. Chem.,* **1986**, *51*, 700.
6. Fehr, T. and Stadler, P. A., *Helv. Chim. Acta,* **1975**, *58*, 2484.
7. (a) Schwab, J. M. and Henderson, B. S., *Chem. Rev.,* **1990**, *90*, 1203. (b) Schwab, J. M. and Klassen, J. B., *J. Am. Chem. Soc.,* **1984**, *106*, 7217. (c) Schwab, J. M. and Klassen, J. B., *J. Chem. Soc., Chem. Commun.,* **1984**, 298. (d) Schwab, J. M. and Klassen, J. B., *J. Chem. Soc., Chem. Commun.,* **1984**, 296.
8. Lebedeva, T. L.; Vointseva, I. I.; Gil'man, L. M.; Petrovskii, P. V. and Larina, T. A., *Russ. Chem. Bull.,* **1997**, *46*, 732.
9. Yamakawa, K.; Nishitani, K. and Mashiko, T., *Chem. Pharm. Bull.,* **1984**, *32*, 3263.
10. (a) Dai, W.-M. and Mak, W.-L., *Chinese J. Chem.,* **2003**, *21*, 772. (b) Dai, W.-M.; Wu, A.; Lee, M. Y. H. and Lai, K. W., *Tetrahedron Lett.,* **2001**, *42*, 4215.
11. Babler, J. H., *J. Org. Chem.,* **1976**, *41*, 1262.
12. Lu, X. Y. and Zhu, J. Y., *J. Organomet. Chem.,* **1986**, *304*, 239.
13. Hosogai, T.; Fujita, Y.; Ninagawa, Y. and Nishida, T., *Chem. Lett.,* **1982**, 357.
14. Campi, E. M.; Jackson, W. R.; McCubbin, Q. J. and Trnacek, A. E., *J. Chem. Soc., Chem. Commun.,* **1994**, 2763.
15. Kirsch, S. F.; Overman, L. E. and Watson, M. P., *J. Org. Chem.,* **2004**, *69*, 8101.
16. (a) Falck-Pedersen, M. L.; Benneche, T. and Undheim, K., *Acta Chem. Scand.,* **1993**, *47*, 63. (b) Dunkerton, L. V.; Brady, K. T.; Mohamed, F. and McKillican, B. P., *J. Carbohydr. Chem.,* **1988**, *7*, 49.
17. Young, D. and Kitching, W., *Tetrahedron Lett.,* **1983**, *24*, 5793.
18. Zhou, Z. S.; Flohr, A. and Hilvert, D., *J. Org. Chem.,* **1999**, *64*, 8334.
19. Ghosh, A. K. and Wang, Y., *J. Org. Chem.,* **1998**, *63*, 6735.
20. (a) Overman, L. E. and Carpenter, N. E., *Org. React.,* **2005**, *66*, 1. (b) Takasu, H.; Tsuji, Y.; Sajiki, H. and Hirota, K., *Tetrahedron,* **2005**, *61*, 11027. (c) Dai, W.-M., *Curr. Med. Chem.,* **2003**, *10*, 2265. (d) Gais, H.-J. and Böhme, A., *J. Org. Chem.,* **2002,** *67*, 1153. (e) Ferrier, R. J., *Top. Curr. Chem.,* **2001**, *215*, 153. (f) Bouvet, D.; Sdassi, H.; Ourevitch, M. and Bonnet-Delpon, D., *J. Org. Chem.,* **2000**, *65*, 2104. (g) Wennerberg, J.; Olofsson, C. and Frejd, T., *J. Org. Chem.,* **1998**, *63*, 3595. (h) Butts, C. P.; Eberson, L.; Hartshorn, M. P. and Robinson, W. T., *Aust. J. Chem.,* **1995**, *48*, 1989. (i) March, J., *Advanced Organic Chemistry*, 4th ed., Wiley-Interscience, New York, **1992**, pp. 327–330. (j) Wickham, G.; Young, D. and Kitching, W., *Organometallics*,

1988, *7*, 1187. (k) Sicinski, R. R. and Szczepek, W. J., *Tetrahedron Lett.,* **1987**, *28*, 5729. (l) Tamaru, Y.; Yoshida, Z.; Yamada, Y.; Mukai, K. and Yoshioka, H., *J. Org. Chem.*, **1983**, *48*, 1293. (m) Kwart, H. and Benko, D. A., *J. Am. Chem. Soc.,* **1979**, *101*, 1277. (n) Goering, H. L. and Vlazny, J. C., *J. Am. Chem. Soc.,* **1979**, *101*, 1801. (o) Babler, J. H.; Coghlan, M. J. and Giacherio, D. J., *J. Org. Chem.*, **1977**, *42*, 2172. (p) Olsen, D. O. and Babler, J. H., *J. Org. Chem.,* **1975**, *40*, 255. (q) Takeda, A. and Tsuboi, S., *J. Org. Chem.,* **1970**, *35*, 2690. (r) Cristol, S. J. and Lee, G. A., *J. Am. Chem. Soc.,* **1969**, *91*, 7554. (s) DeWolfe, R. H. and Young W. G., Chapter 10, Allylic Reactions, in *The Chemistry of Alkenes,* Patai, S. ed. Interscience, New York, **1964**, pp. 681–738. (t) Mackenzie, K. Chapter 7, Alkene Rearrangement, in *The Chemistry of Alkenes,* Patai, S. ed. Interscience, New York, **1964**, pp. 387–467. (u) de la Mare, P. B. D., Rearrangements in the Chemistry of Allylic Compounds, in *Molecular Rearrangements*, Part 1, de Mayo, P. ed. John Wiley & Sons, New York, **1963**, pp. 27–110. (v) Young, W. G., *J. Chem. Ed.,* **1962**, *39*, 455. (w) Goering, H. L. and Greiner, R. W., *J. Am. Chem. Soc.,* **1957**, *79*, 3464. (x) DeWolfe, J. R.; and Young, W. G., *Chem. Rev.,* **1956**, *56*, 753. (y) Lyle, G. G.; Perlowski, E. F. and Lyle, R. E., *J. Org. Chem.,* **1956**, *21*, 423. (z) Kundiger, D. G. and Haney, H. N., *J. Am. Chem. Soc.,* **1954**, *76*, 615. (aa) Webb, I. D. and Young, W. G., *J. Am. Chem. Soc.,* **1951**, *73*, 777. (bb) Wilson, K. W.; Roberts, J. D. and Young, W. G., *J. Am. Chem. Soc.,* **1949**, *71*, 2019. (cc) Gilman, H. and Greuer, F., *J. Am. Chem. Soc.,* **1934**, *56*, 1127. (dd) Young, W. G. and Prater, A. N., *J. Am. Chem. Soc.,* **1932**, *54*, 404.

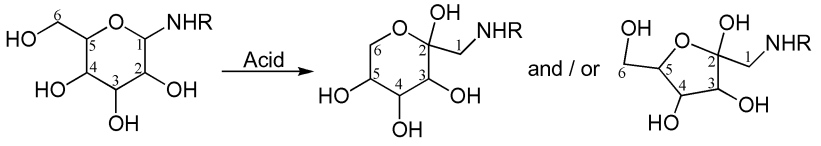
17

Amadori Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Amadori in 1925.[1] It is the transformation of *N*-glycosides of aldoses into *N*-glycosides of corresponding ketoses under acidic condition, or more generally the conversion of aldimines into ketoamines.[2] Thus this reaction is commonly known as the Amadori rearrangement.[3] This reaction often occurs in the formation of complex glycation end products[4] that have been potulated to play very important roles in biological processes. For example, in the *Maillard Reaction* pathway, the Amadori rearrangement appears to be involved in the manifestations of the pathological effects of diabetes, Alzheimer disease, and aging processes in general. Unfortunately, in its non-vivo applications, the Amadori rearrangement suffers from a variety of preparative shortcomings. This reaction is different from the so-called glycosylation in which the products are glycosides. This reaction has been extensively reviewed.[5]

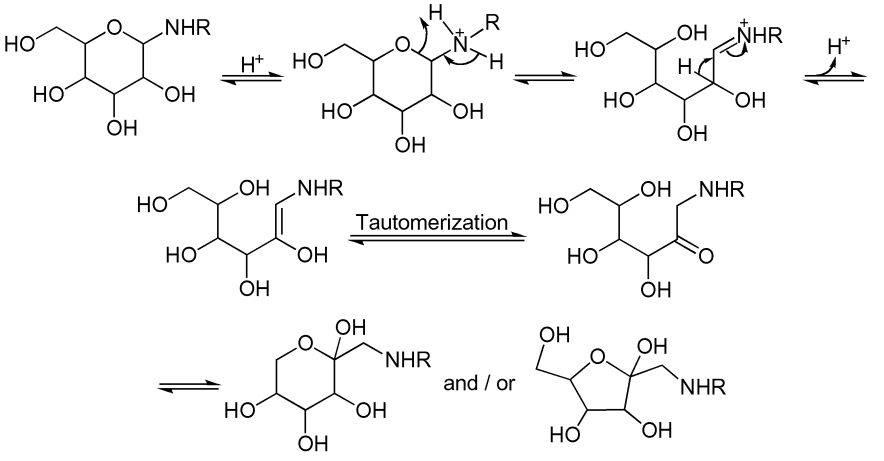
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

A general illustration of the reaction detail is displayed here.



D. MODIFICATION

There is a Hodge and Rist modification of Amadori rearrangement, as shown in the first experimental protocol provided here.[6]

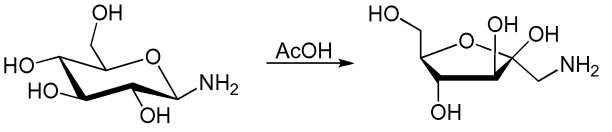
E. APPLICATIONS

This reaction has been extensively applied to the preparation of glycoproteins, via the reaction of the reducing sugars with the amino termini or the side chains of lysine and arginine residues in proteins. In addition, the Amadori rearrangement has been used for the synthesis of aminopolysaccharides.[7]

F. RELATED REACTIONS

This reaction is related to the *Lobry de Bruyn-van Ekenstein transformation* of aldoses involving the rearrangement of *N*-alkylamino-D-glucopyranosides into 1-alkylamino-1-deoxy-D-fructoses.[8]

G. CITED EXPERIMENTAL EXAMPLES



Reference 6.

The Preparation of β-D-Glucopyranosylamine

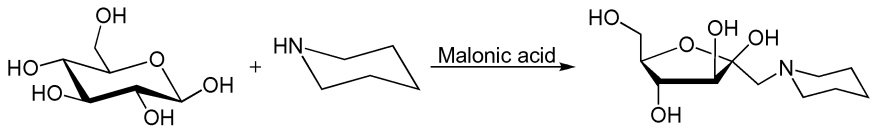
To 50 mL methanol, were added 20 g D-glucose and 0.5 g ammonium chloride, and the mixture was treated with ammonia gas at 0°C until the sugar dissolved. The solution was stored at 0°C until satisfactory crystallization had occurred. The first crystallization was slow and required storage of the solution for about a month. Subsequent recrystallizations with the aid of seed crystals were more rapid, but maximum yields required storage for a week or two. The crystals were separated, washed with methanol, and dried over sodium hydroxide in a vacuum desiccator. The crude product, 17 g, was dissolved in 17 mL water, and the solution was diluted with 170 mL methanol and sufficient ethanol to produce turbidity. After 48 h, the crystalline material was separated, washed with methanol, and stored over sodium hydroxide in an atmosphere of ammonia for 2 days.

Amadori Rearrangement of D-Glucopyranosylamine in Acetic Acid

To 10 mL glacial acetic acid was added 0.5 g β-D-glucopyranosylamine, and the solution was kept at 20°C. The optical rotation, $[\alpha]_D^{20}$, changed from a +18° to a value of −18° in 1 h and to a value of −65° after a period of 18 h. The solution had then become amber colored after this period. The acetic acid was removed by the repeated addition of toluene and evaporation in a rotary film evaporator apparatus. The residue, still containing a small amount of acetic acid, was redissolved in 10 mL water for hydrolysis to take place. After several hours, the solution was again concentrated; this treatment caused decomposition of any remaining D-glucosylamine. The residue was dissolved in 10 mL water and passed through a column containing 20 mL cation exchange resin (amberlite IR120-H, Rohm & Haas Co., Philadephia, Pa.); the resin was then washed with water, and the wash liquor was discarded. The basic materials held on the resin were eluted with 20 mL 1 *N*-hydrochloric acid. The eluent and wash liquor were combined, concentrated, and then adjusted to a volume of 0.1 mL. The specific rotation, $[\alpha]_D^{20}$ was −58°. Production of the stable basic substance having a levo-rotation (−58° in this case) indicates the presence of 1-amino-1-deoxy-D-fructose.

Hodge and Rist Modification of the Amadori Rearrangement

To 5 mL dimethylsulfoxide were added 0.2 g D-glucosylamine and 5 mL diethyl malonate. The mixture was heated for 90 min at 80°C and, after cooling back down to room temperature, was kept at room temperature overnight. The resultant brown solution was diluted with water and allowed to stand for several hours for effective hydrolysis of the remaining D-glycosylamines. The solution was then extracted several times with chloroform, and the aqueous portion was filtered through decolorizing carbon, concentrated using rotary film evaporation, and adjusted to a volume of 10 mL. The optical rotation, $[\alpha]_D^{20}$, was −43.5°, based on the weight of the original D-glucosylamine.



Reference 9.

The mixture of 90 g anhydrous D-glucose (0.50 mol) and 57 g piperidine (0.67 mol) was stirred mechanically at 60–75°C until a homogeneous amber sirup was obtained (~20 min). After the heating bath was removed, 18 g malonic acid (0.17 mol) was added slowly to the stirred sirup over a period of 10 min. The temperature rose to 80°C, and the color of the sirup deepened to a reddish hue. After stirring for 5 min longer, 70 mL ethanol was added; and the resulting solution was heated at 75°C for 30 min. After the addition of 70 mL acetone, seed crystals appeared; and after 1 h at 25°C, the first batch of D-glucose piperidine furanose was obtained (28 g), m.p. 123–125°C (dec.). Reheating the mother liquors at 95–100°C was required to produce further crystallization at 0°C without long waiting periods. A total of 37.0 g of crude product was obtained, in a yield of 30%. Recrystallization from 200 mL of hot ethanol and 200 mL acetone gave 33 g of pure product as colorless, glistening plates, in a yield of 27%, m.p. 126–127°C (dec.).

Other references related to the Amadori rearrangement are cited in the literature.[10]

H. REFERENCES

1. (a) Amadori, M., *Atti Accad. Nazl. Lincei,* **1925**, *2*, 337. (*Chem. Abstr*., **1926**, *20*, 902.) (b) Amadori, M., *Atti Accad. Nazl. Lincei*. **1929**, *9*, 68. (*Chem. Abstr*., **1929**, *23*, 3211.) (c) Amadori, M., *Atti Accad. Nazl. Lincei.,* **1929**, *9*, 226. (*Chem. Abstr.,* **1929**, *23*, 3443.)
2. Acharya, A. S.; Roy, R. P. and Dorai, B., *J. Protein Chem.,* **1991**, *10*, 345.
3. (a) Yaylayan, V. A. and Locas, C. P., *Mol. Nutrition Food Res.,* **2007**, *51*, 437. (b) Jalbout, A. F.; Shipar, M. A. H. and Navarro, J. L., *Food Chem.,* **2007**, *103*, 919. (c) Yaylayan, V. A., *Food Sci. Tech. Res.,* **2003**, *9*, 1. (d) Fernandez-Bolanos, J. G.; Ulgar, V.; Maya, I.; Fuentes, J.; Dianez, M. J.; Estrada, M. D.; Lopez-Castro, A. and Perez-Garrido, S., *Tetrahedron: Asymmetry,* **2003**, *14*, 1009. (e) Hrnciar, P.; Ueda, Y.; Huang, S.; Leet, J. E. and Bronson, J. J., *J. Org. Chem.,* **2002**, *67*, 8789. (f) Hakojima, T. and Maita, N., *Kagaku (Kyoto),* **2001**, *56*, 62. (g) Liedke, R. and Eichner, K., *Lebensmittelchemie,* **2000**, *54*, 136. (h) Cremer, D. R.; Vollenbroeker, M. and Eichner, K., *Eur. Food Res. Tech.,* **2000**, *211*, 400. (i) Turner, J. J.; Wilschut, N.; Overkleeft, H. S.; Klaffke, W.; van der Marel, G. A.; van Boom, J. H., *Tetrahedron Lett.,* **1999**, *40*, 7039. (j) Kadokawa, J.-I.; Hino, D.; Karasu, M.; Tagaya, H. and Chiba, K., *Chem. Lett.,* **1998**, 383. (k) Zu, J.; Kato, M.; Nishikawa, S. and Kashimura, N., *Bull. Faculty Bioresources, Mie Univ.,* **1997**, *18*, 47. (l) Wrodnigg, T. M.; Stutz, A. E. and Withers, S. G., *Tetrahedron Lett.,* **1997**, *38*, 5463. (m) Zu, J.; Nishikawa, S. and Kashimura, N., *Biosci. Biotech. Biochem.,* **1997**, *61*, 188. (n) Yaylayan, V. A. and Huyghues-Despointes, A., *Carbohydr. Res.,* **1996**, *286*, 179. (o) Zu, J.; Morita, J.; Nishikawa, S. and Kashimura, N., *Carbohydr. Lett.,* **1996**, *1*, 457. (p) Iwamoto, T.; Kan, T.; Katsumura, S. and Ohfune, Y., *Synlett,* **1996**, 169. (q) Saleh, M. A.; Abdo, M. A.; Abdel-Megeed, M. F. and El-Hiti, G. A., *Indian J. Chem., Sect. B,* **1996**, *35B*, 147. (r) Noomen, S. N.; Breel, G. J. and Winkel, C., *Rec. Trav. Chim. Pays-Bas,* **1995**, *114*, 321. (s) Hommel, U.; Eberhard, M. and Kirschner, K., *Biochemistry,* **1995**, *34*, 5429. (t) Yaylayan, V. A. and Huyghues-Despointes, A., *Critic. Rev. Food Sci. & Nutri,* **1994**, *34*, 321. (u) Gyurcsik, B.; Gajda, T.; Nagy, L.; Burger, K.; Rockenbauer, A. and Korecz, L., *Inorg. Chim. Acta,* **1993**, *214*, 57. (v) Yaylayan, V. A.; Mandeville, S. and Pare, J. R. J., *Spectroscopy (Amsterdam),* **1991**, *9*, 73. (w) Yuan, C. W. and Richard, H., *Youji Huaxue,* **1991**, *11*, 55. (x) Yaylayan, V. and Forage, N. G., *J. Agri. Food Chem.,* **1991**, *39*, 364. (y) Yaylayan, V. and Sporns, P., *Food Chem.,* **1989**, *33*, 81. (z) Yaylayan, V. and Sporns, P., *J. Agri. Food Chem.,* **1989**, *37*, 978. (aa) Pokorny, J.; Pilkova, L.; Davidek, J. and Valentova, H., *Nahrung,* **1988**, 32, 767. (bb) Mori, N. and Manning, J. M., *Anal. Biochem.,* **1986**, *152*, 396. (cc) Kolka, S., *Pol. J. Chem.,* **1984**, *58*, 689. (dd) Xenakis, D.; Moll, N. and Gross, B., *Synthesis,* **1983**, 541. (ee) Acharya, A. S.; Sussman, L. G. and Manning, J. M., *J. Biol. Chem.,* **1983**,

258, 2296. (ff) Ramos, J. V. and Gonzalez C. O., *Revista Latinoamer. Quim.,* **1982**, *13*, 113. (gg) Altena, J. H.; van den Ouweland, G. A. M.; Teunis, C. J. and Tjan, S. B., *Carbohydr. Res.,* **1981**, *92*, 43. (hh) Acharya, A. S. and Manning, J. M., *J. Biol. Chem.,* **1980**, *255*, 7218. (ii) Klemer, A. and Funcke, W., *Liebigs Ann. Chem.,* **1979**, 1682. (jj) Funcke, W., *Ann.,* **1978**, 2099. (kk) Funcke, W.; Klemer, A. and Meissner, E., *Ann.,* **1978**, 2088. (ll) Turchina, R. P.; Vigdorchik, M. M.; Turchin, K. F. and Suvorov, N. N., *Zh. Org. Khim.,* **1977**, *13*, 1316. (mm) Ramos, J. R. and Gonzalez C., O., *Revista Latinoamer. Quim.,* **1977**, *8*, 94. (nn) Hashiba, H., *J. Agri. Food Chem.,* **1976**, *24*, 70. (oo) Tjan, S. B. and van den Ouweland, A. A. M., *Tetrahedron,* **1974**, *30*, 2891. (pp) Alfimova, R. N.; Andreeva, N. A.; Khoroshikh, N. I. and Shishkin, Yu. L., *Zh. Strukt. Khim.,* **1974**, *15*, 938. (qq) Vigdorchik, M. M.; Olad'ko, R. P.; Kostyuchenko, N. P. and Suvorov, N. N., *Zh. Org. Khim.,* **1974**, *10*, 1256. (rr) Kolka, S. and Sokolowski, J., *Roczniki Chem.,* **1974**, *48*, 439. (ss) Das, S. K.; Abernethy, J. L. and Quin, L. D., *Carbohydr. Res.,* **1973**, *30*, 379. (tt) Parekh, H.; Parikh, A. R. and Thaker, K. A., *Indian J. Chem.,* **1973**, *11*, 299. (uu) Kolka, S. and Sokolowski, J., *Roczniki Chem.,* **1972**, *46*, 147. (vv) Heyns, K.; Chiemprasert, T. and Baltes, W., *Chem. Ber.,* **1970**, *103*, 2877. (ww) Simon, H. and Kraus, A., *Fortsch. Chem. Forsch.,* **1970**, *14*, 430. (xx) Wolf, W. A. and Brown, G. M., *Biochim. Biophys. Acta, Gen. Subj.,* **1969**, *192*, 468. (yy) Yoshimura, J.; Funabashi, M. and Simon, H., *Carbohydr. Res.,* **1969**, *11*, 276. (zz) Micheel, F.; Degener, S. and Dijong, I., *Ann.,* **1967**, *701*, 233. (aaa) Micheel, F.; Heinemann, K. H.; Schwieger, K. H. and Frowein, A., *Tetrahedron Lett.,* **1965**, 3769. (bbb) Paulsen, H., *Ann.,* **1965**, *683*, 187. (ccc) Palm, D. and Simon, H., *Z. Naturfors.,* **1965**, *20B*, 32. (ddd) Paulsen, H., *Tetrahedron Lett.,* **1964**, 451. (eee) Palm, D. and Simon, H., *Z. Naturfors.,* **1963**, *18B*, 419. (fff) Hodge, J. E. and Fisher, B. E., *Methods Carbohydr. Chem.,* **1963**, *2*, 99. (ggg) Micheel, F., *Rev. Chim., Acad. Rep. Populaire Roumaine,* **1962**, *7*, 1077. (hhh) Micheel, F. and Dijong, I., *Ann.,* **1962**, *658*, 120. (iii) Micheel, F. and Dijong, I., *Tetrahedron Lett.,* **1962**, 20. (jjj) Micheel, F. and Heiskel, E., *Chem. Ber.,* **1961**, *94*, 143. (kkk) Onodera, K.; Uehara, T. and Kitaoka, S., *Bull. Agri. Chem. Soc. Jpn.,* **1960**, *24*, 703. (lll) Enselme, J. and Chapot, A., *Bull. Soc. Chim. Biol.,* **1960**, *42*, 279. (mmm) Heyns, K. and Baltes, W., *Chem. Ber.,* **1960**, *93*, 1616. (nnn) Micheel, F. and Buning, R., *Chem. Ber.,* **1957**, *90*, 1606. (ooo) Micheel, F. and Frowein, A., *Chem. Ber.,* 1957, *90*, 1599. (ppp) Weygand, F.; Simon, H. and Ardenne, R. V., *Chem. Ber.,* **1959**, *92*, 3117. (qqq) Isbell, H. S. and Frush, H. L., *J. Org. Chem.,* **1958**, *23*, 1309. (rrr) Nordin, P. and Kim, Y. S., *J. Agri. Food Chem.,* **1958**, *6*, 765. (sss) Rosen, L.; Woods, J. W. and Pigman, W., *J. Am. Chem. Soc.,* **1958**, *80*, 4697. (ttt) Rosen, L.; Woods, J. W. and Pigman, W., *Chem. Ber.,* **1957**, *90*, 1038. (uuu) Adachi, S., *Chem. Ind. (London),* **1957**, 956. (vvv) Friedberg, F. and Kaplan, L., *J. Am. Chem. Soc.,* **1957**, *79*, 2600. (www) Micheel, F. and Schleppinghoff, B., *Chem. Ber.,* **1956**, *89*, 1702. (xxx) Hodge, J. E., *Adv. Carbohydr. Chem.,* **1955**, *10*, 169. (yyy) Hodge, J. E. and Rist, C. E., *J. Am. Chem. Soc.,* **1953**, *75*, 316. (zzz) Weygand, F., *Ber.,* **1940**, *73B*, 1259. (aaaa) Kuhn, R. and Birkofer, L., *Ber.,* **1938**, *71B*, 621. (bbbb) Kuhn, R. and Weygand, F., *Ber.,* **1937**, *70B*, 769.

4. (a) Venkatraman, J.; Aggarwal, K. and Balaram, P., *Chem. Biol.,* **2001**, *8*, 611. (b) Avigad, G.; Kniep, A. and Bailin, G., *Biochem. Mol. Biol. Int.,* **1996**, *40*, 273. (c) Lal, S.; Chithra, P. and Chandrakasan, G., *Mol. Cell Biochem.*, **1996**, *154*, 95. (d) Nacharaju, P. and Acharya, A. S., *Biochemistry,* **1992**, *31*, 12673. (e) Ghiggeri, G. M.; Candiano, G.; Ginevri, F.; Oleggini, R.; Piccardo, M. T.; Bertelli, R.; Perfumo, F. and Gusmano, R., *Analyst (Cambridge),* **1988**, *113*, 1101.
5. (a) Wrodnigg, T. J. and Eder, B.,*Topics Curr. Chem.*, **2001**, *215*, 115. (b) Steinborn, D. and Junicke, H., *Chem. Rev.*, **2000**, *100*, 4280. (c) Maruoka, K. and Yamamoto, H., *Comp. Org. Syn.,* **1991**, *6*, 789. (d) Lemieux, R. U., *Rearrangements and Isomerizations in Carbohydrate Chemistry,* in *Molecular Rearrangements*, Part 2, de Mayo, P. Wiley-Interscience, New York, **1964**, p 753. (e) Pigman, W. W., *The Carbohydrates: Chemistry, biochemistry, Physiology, Academic Press,* New York, **1957**, p. 422. (f) Pigman, W. W. and Goepp, R. M., *Chemistry of the Carbohydrates*, Academic Press, New York, **1948**, p. 405.
6. Isbell, H. S. and Frusch, H. L., *J. Org. Chem.,* **1958**, *23*, 1309.

7. Kadokawa, J.; Hino, D.; Karasu, M.; Tagaya, H. and Chiba, K., *Eur. Polymer J.,* **2000**, *36*, 225.
8. Wander, J. D. and Horton, D., *Adv. Carbohydr. Chem. Biochem.*, **1976**, *32*, 15.
9. Hodge, J. E. and Rist, C. E., *J. Am. Chem. Soc*., **1953**, *75*, 316.
10. (a) Davidek, T.; Clety, N.; Aubin, S. and Blank, I., *J. Agric. Food Chem.,* **2002**, *50*, 5472. (b) Davis, B. G., *Chem. Rev*., **2002**, *102*, 579. (c) Sanz, M. L.; del Castillo, M. D.; Corzo, N. and Olano, A., *J. Agric. Food Chem.,* **2001**, *49*, 5228. (d) Hofmann, T. and Schieberle, P., *J. Agric. Food Chem*., **2000**, *48*, 4301. (e) Cremer, D. R.; Vollenbroeker, M. and Eichner, K., *Eur. Food Res. Tech.,* **2000**, *211*, 400. (f) Mossine, V. V.; Linetsky, M.; Glinsky, G. V.; Ortwerth, B. J. and Feather, M. S., *Chem. Res. Toxicol.,* **1999**, *12*, 230. (g) Turner, J. J.; Wilschut, N.; Overkleeft, H. S.; Klaffke, W.; van der Marel, G. A. and van Boom, J. H., *Tetrahedron Lett.,* **1999**, *40*, 7039. (h) Kadokawa, J.-I.; Hino, D.; Karasu, M.; Tagaya, H. and Chiba, K., *Chem. Lett.,* **1998**, 383. (i) Wrodnigg, T. M.; Stutz, A. E. and Withers, S. G., *Tetrahedron Lett.,* **1997**, *38*, 5463. (j) Yaylayan, V. A. and Huyghues-Despointes, A., *Carbohydr. Res.,* **1996**, *286*, 187. (k) Harrowfield, J. M.; Mocerino, M.; Skelton, B. W.; Wei, W. Y. and White, A. H., *J. Chem. Soc., Dalton Trans.,* **1995**, 783. (l) Brownlee, M., *Diabetes*, **1994**, *43*, 836. (m) Baynes, J. W., *Diabetes*, **1991**, *40*, 405. (n) Brownlee, M., Vlassara, H. and Cerami, A., *Ann. Int. Med.,* **1984**, *101*, 527. (o) Stepanenko, B. N.; Kaletina, N. I. and Zelenkova, V. V., *Dokl. Akad. Nauk SSSR,* **1971**, *200*, 609. (p) Simon, H. and Kraus, A., *Fortsch. Chem. Forsch.,* **1970**, *14*, 430. (q) Micheel, D., *Ann*., **1962**, *658*, 120. Kuhn, R.; Baer, H. H.; Bister, W.; Brossmer, R.; Gauhe, A.; Haas, H. J.; Haber, F.; Kruger, G.; Tiedemann, H. and Weiser, D., *Angew. Chem.,* **1957**, *69*, 23. (r) Weygand, F., *Ber.*, **1940**, *73*, 1259. (s) Kuhn, R. and Birkofer, L., *Ber.*, **1938**, *71*, 621. (t) Kuhn, R. and Weygand, F., *Ber.*, **1937**, *70*, 769. (u) Kuhn, R. and Dansi, A., *Ber.*, **1936**, *69*, 1745.

18

Andrussow Process

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Andrussov (Andrussow) in 1927.[1] It is primarily an industrial process used to manufacture hydrogen cyanide from methane, ammonia, and oxygen over a catalyst of 90% Pt–10% Rh in the form of a pad of woven screens at 1050–1100°C and 2 atm.[2] Therefore, this reaction is known as Andrussow process.[3] In this process, the catalytic gauze is 3–5 mm thick, and when the high gas velocities are employed, the contact times achieved are of the order of a few milliseconds. The effluent stream contains about 8% HCN and a number of byproducts such as hydrogen, CO, and CO_2.[2b] It was reported that in 1978 the output of hydrogen cyanide exceeded 600 million pounds in the United States alone.[2b]

B. GENERAL REACTION SCHEME

$$CH_4 + NH_3 + O_2 \xrightarrow{90\%\ Pt - 10\%\ Rh} HCN + H_2O$$

C. PROPOSED MECHANISMS

The mechanism for the oxidation of ammonia has been discussed by Zawadski;[4] however, at least three theories have been proposed for the Andrussow process.[5] Bodenstein and Krauss proposed the mechanism of the initial oxidation of ammonia with adsorbed oxygen to

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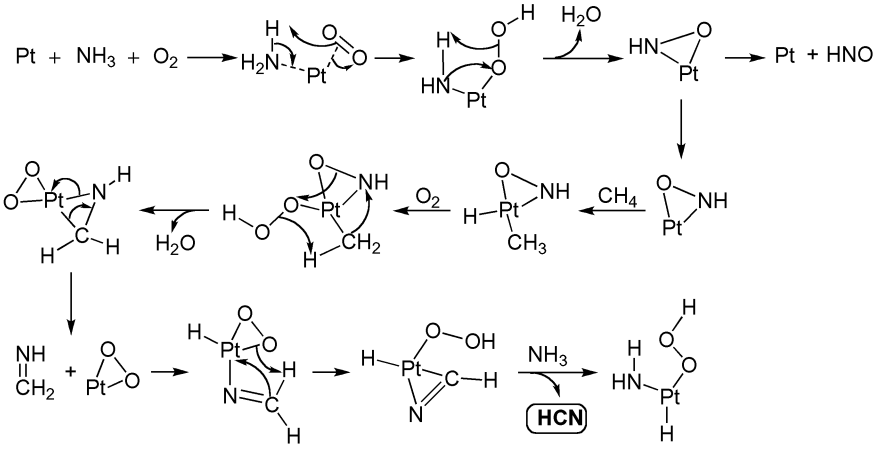
form hydroxylamine,[6] while Zawadski believed that the imide (NH) was initially formed.[4] The third mechanism, proposed by Andrussov, is that the initial oxidation of ammonia with oxygen forms nitroxyl (HNO).[7] Later experimental evidence supported Andrussow's postulation.[5,8] Although 90% Pt–10% Rh rhudium is used as a catalyst, it is believed that platinum is the actually catalytic center. Therefore, the mechanism of this reaction is tentatively given here.



D. MODIFICATION

As rhodium is not the actual catalytic center and is very expensive, modifications have been done on both the catalyst and the starting materials. For example, one modification used α-Al_2O_3-supported platinum as a catalyst, and mixture of C_2H_6, NH_3, and oxygen as the reactants.[2a] In other modification, the combination of manganese oxide and bismuth oxide was tested as a catalyst.[5]

E. APPLICATIONS

This reaction is usually used to manufacture hydrogen cyanide.

F. RELATED REACTIONS

Homogenous oxidation of ammonia followed by hydration to form HNO_3 is called the Ostwald process.[9,10] On the other hand, the strongly endothermic process in which methane and ammonia react over platinum catalysts in the absence of air at 1150–1250°C is called the Degussa (or BMA) process,[11] which holds the advantages of higher HCN yield, higher NH_3 conversion per pass, and a fairly high purity of the byproduct hydrogen but has the disadvantage of needing external heating.

G. CITED EXPERIMENTAL EXAMPLES

$$CH_4 + NH_3 + O_2 \xrightarrow{68\%\ CuCl_2 - 32\%\ KCl} HCN + H_2O$$

Reference 5.

The fused salt (68% $CuCl_2$/32% KCl) reactor (which consisted of a 22-mm inside diameter glass tube, 15 in. in length) was heated externally. The preheated gaseous reactants were introduced near the bottom of the tube below the surface of the salt. Analysis of the products was made after steady state conditions were obtained.

Additional references about the Andrussow process are cited in the literature.[12]

H. REFERENCES

1. Andrussow, L., *Ber*., **1927**, *60B*, 2005.
2. (a) Bharadwaj, S. S. and Schmidt, L. D., *Ind. Eng. Chem. Res.,* **1996**, *35*, 1524. (b) McKenna, E. A.; Othoneos, A.; Kiratzis, N. and Stoukides, M., *Ind. Eng. Chem. Res*., **1993**, *32*, 1904. (c) Waletzko, N. and Schmidt, L. D., *AZChE J.,* **1988**, *34*, 1146.
3. Gorywoda, M. and Lund, J., *Eur. Pat. Appl*., **2001**, 1086928.
4. Zawadzki, J., *Discuss. Faraday Soc.,* **1950**, 140.
5. Johnstone, H. F.; Houvourasl, E. T. and Schowalter, W. R., *Ind. Eng. Chem.*, **1954**, *46*, 702.
6. (a) Bodenstein, M., *Trans. Electwchenz. Soc.,* **1937**, *71*, 353. (b) Krauss, W., *Z. Elektrochem.,* **1949**, *53*, 320; (c) Krauss, W., Z. *Elektrochem*., **1950**, *54*, 264.
7. Andrussow, L., *Angew. Chem.,* **1951**, *63*, 21.
8. Hickman, D. A. and Schmidt, L. D., *Ind. Eng. Chem. Res*., **1991**, *30*, 50.
9. Satterfield, C. N., *Heterogeneous Catalysis in Practice*, McGraw-Hill, New York, **1980**, pp. 214–221.
10. Twigg, M. V., *Catalyst Handbook,* Wolfe Publishing, Ltd., London, **1989**, pp. 470–489.
11. Koberstein, E., *Ind. Eng. Chem. Process Des. Dev.,* **1973**, *12*, 444.
12. (a) Gryn, G.; Prezhdo, O.; Trusov, N. and Prezhdo, V., *Pol. J. Appl. Chem.,* **2002**, *46*, 95. (b) Bockholt, A.; Harding, I. S. and Nix, R. M., *J. Chem. Soc., Faraday Trans*., **1997**, *93*, 3869. (c) Thomas, J. M., *Angew. Chem*., **1994**, *106*, 963; (d) Thomas, J. M., *Angew. Chem. Int. Ed. Engl.,* **1994**, *33*, 913. (e) Hickman, D. A.; Huff, M. and Schmidt, L. D., *Ind. Eng. Chem. Res.,* **1993**, *32*, 809. (f) Hasenberg, D. and Schmidt, L. D., *J. Catal*., **1987**, *104*, 441. (g) Kiratzis, N. and Stoukides, M., *J. Electrochem. Soc.,* **1987**, *134*, 1925. (h) Hasenberg, D. and Schmidt, L. D., *J. Catal*., **1986**, *97*, 156. (i) Molinari, E.; Cramarossa, F.; Pullo, A. and Triolo, L., *J. Catal.,* **1965**, *4*, 341. (j) Kunz, W. and Krauch, H., *Chemiker Ztg*., **1959**, *83*, 82. (k) Andrussow, L., *Ber.,* **1938**, *71B*, 776. (l) Andrussov, L., *Angew. Chem.,* **1935**, *48*, 593. (m) Raschig, F., *Angew. Chem.,* **1927**, *40*, 1183.

19

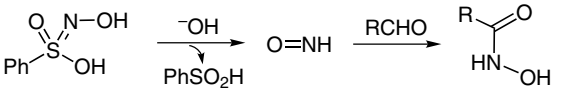
Angeli-Remini Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Angeli in 1896.[1] It is the preparation of hydroxamic acids from aldehyde and benzosulfohydroxamic acid. As an important class of reagents, hydroxamic acids have found a variety type of applications in inorganic, organic and pharmaceutical chemistry, including antibiotics,[2] inhibitors,[3] and strong metal ion-chelators,[4] etc. As of today, many other methods have been developed to prepare different hydroxamic acids.[5]

B. GENERAL REACTION SCHEME

The original version of the Angeli-Remini reaction is displayed below.



C. PROPOSED MECHANISMS

The mechanism for the original Angeli-Remini reaction is proposed below.

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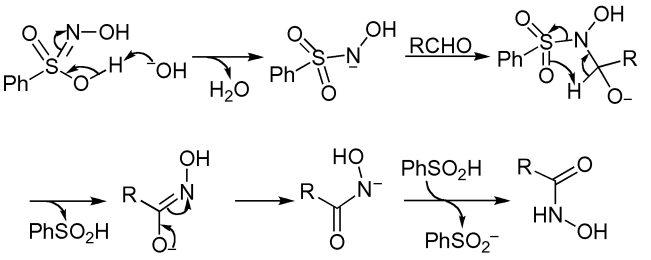


D. MODIFICATION

Different methods for the preparation of hydroxamic acids have been developed.[5]

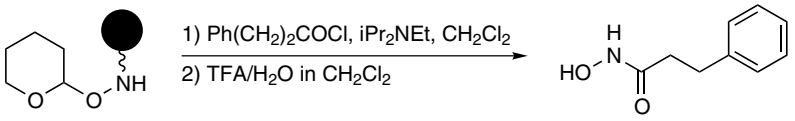
E. APPLICATIONS

This reaction is useful for the preparation of hydroxamic acids.

F. RELATED REACTIONS

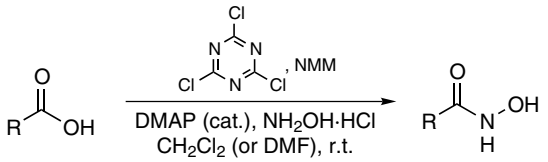
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 6.

The mixture of 300 mg of alkoxyamine resin, 126 μL of diisopropylethylamine (0.72 mmol, 10 equiv.), and 53.4 μL of hydrocinnamoyl chloride (0.36 mmol, 5.0 equiv.) was shaken for 18 hours at room temperature under nitrogen. The resin was filtered and washed sequentially with MeOH (3×5 mL) and dichloromethane (2×5 mL). The resin was then treated with a solution of 2.5% TFA and 1% H_2O in 4 mL of dichloromethane, and the mixture was shaken for 1 hour. Resin was filtered and washed sequentially with MeOH (3×5 mL) and dichloromethane (2×5 mL), and then retreated with a solution of 50% TFA and 1% H_2O in 4 mL of dichloromethane under shaking for 1 hour. The resin was filtered, and the filtrate was concentrated in vacuo to give crude product which was purified by preparative TLC (5% MeOH in dichloromethane) to give 6.75 mg of hydroxamic acid, in yield of 88%.



Reference 7.

To a solution of 2.24 g of (*S*)-(*N*-benzyloxycarbonyl)proline (9.0 mmol), 1.0 g of *N*-methylmorpholine (NMM, 9.9 mmol), 0.01 g of DMAP (0.1 mmol) and 0.68 g of hydroxylamine hydrochloride (9.8 mmol) in 20 mL of dichloromethane, was added 0.5 g of cyanuric chloride (3.0 mmol) at 0 °C under stirring. The mixture was warmed to room temperature and stirred for 12 hours and then filtered on Celite. The organic phase was washed three times with 15 mL of 1 *N* HCl and then brine, dried over Na_2SO_4 and evaporated to give 2.3 g of (*S*)-(*N*-benzyloxycarbonyl)proline hydroxamate without further purification, in yield of 96%.

Other examples about the preparation and application of hydroxamic acids are cited in literature[8].

H. REFERENCES

1. Angeli A., *Gazz. Chim. Ital.*, **1896**, *26*, II, 17.
2. (a) Kazmiersky, W. M.; Wolberg, G.; Wilson, J. G.; Smith, S. R.; Williams, D. S.; Thorp, H. H. and Molina, L., *Proc. Natl. Acad. Sci. U.S.A.,* **1996**, *93*, 9138. (b) Kurzak, B.; Kozlowski, H. and Farkas, E., *Coord. Chem. Rev.,* **1992**, *114*, 169. (c) Miller, M. J., *Chem. Rev.,* **1989**, *89*, 1563. (d) Summers, J. B.; Mazdiyasni, H.; Holm, J. H.; Ratajczyk, J. D.; Dyer, R. D. and Carter, G. W., *J. Med. Chem.,* **1987**, *30*, 574. (e) Miller, M. J., *Acc. Chem. Res.,* **1986**, *19*, 49. (f) Young, C. W.; Schachetman, C. S.; Hodas, S. and Bolis, M. C., *Cancer Res.,* **196**7, *27*, 535. (g) Stearn, B.; Losee, K. A. and Bernstein, J., *J. Med. Chem.,* **1963**, *6*, 201.
3. (a) Cheng, M.; De, B.; Pikul, S.; Almstead, N. G.; Natchus, M. G.; Anastasio, M. V.; McPhail, S. J.; Snider, C. E.; Taiwo, Y. O.; Chen, L.; Dunaway, C. M.; Gu, F.; Dowty, M. E.; Mieling, G. E.; Janusz, M. J. and Wang-Weigang, S., *J. Med. Chem.,* **2000**, *43*, 369. (b) Whittaker, M.; Floyd, C. D.; Brown, P. and Gearing, A. J. H., *Chem. Rev.*, **1999**, *99*, 2735. (c) Nishino, N. and Powers, J. C., *Biochemistry,* **1979**, *18*, 4340. (d) Nishino, N. and Powers, J. C., *Biochemistry,* **1978**, *17*, 2846. (e) Snow, G. A., *Bacteriol. Rev.,* **1970,** *34*, 99. (f) Neilands, J. B., *Science*, **1967**, *156*, 1443.
4. (a) Boukhris, S.; Souizi, A. and Robert, A., *Tetrahedron Lett.,* **1996**, *37*, 179. (b) Kurzak, B.; Kozlowski, H. and Farkas, E., *Coord. Chem. Rev.*, **1992**, *114*, 169.
5. (a) Sibi, M. P.; Hasegawa, H. and Ghorpade, S. R., *Org. Lett.,* **2002**, *4*, 3343. (b) Staszak, M. A. and Doecke, C. W., *Tetrahedron Lett.,* **1994**, *33*, 6021. (c) Tamaki, K.; Ogita, T.; Tanzawa, K. and Sugimura, Y., *Tetrahedron Lett.,* **1993**, *34*, 683. (d) Altenburger, J. M.; Mioskowski, C.; d'Orchymont, H.; Schirlin D.; Schalk, C. and Tarnus, C., *Tetrahedron Lett.,* **1992**, *33*, 5055. (e) Sicker, D.; Reifegerste, D.; Hauptmann, S.; Wilde, H. and Mann, G., *Synthesis*, **1985,** 331. (f) Ando, W. and Tsumaki, H., *Synth. Commun.,* **1983**, *13*, 1053. (g) Matlin, S. A.; Sammes, P. G. and Upton, R. M., *J. Chem. Soc*., *Perkin Trans. I,* **1979**, 2481. (h) Matlin, S. A, and Sammes, P. G., *J. Chem. Soc.*, *Chem. Commun*., **1972**, 1222. (i) Noble, D. and Wibberley, D. G., *J. Med. Chem.,* **1966**, *9*, 974. (j) F. Mathis, *Bull. Soc. Chim. Fr.,* **1953**, *5*, D9. (k) Yale, H. L., *Chem. Rev*., **1943**, *43*, 209.

6. Ngu, K. and Patel, D. V., *J. Org. Chem.*, **1997**, *62*, 7088.
7. Giacomelli, G.; Porcheddu, A. and Salaris, M., *Org. Lett*., **2003**, *5*, 2715.
8. (a) Letchamo, W.; Korolyuk, E. A. and Tkachev, A. V., *J. Essential Oil Res.,* **2005**, *17*, 396. (b) Lim, N. C.; Morton, M. D.; Hilary, H. A.; Jenkins, A. and Brückner, C., *J. Org. Chem.,* **2003**, *68*, 9233. (c) Sawa, M.; Kiyoi, T.; Kurokawa, K.; Kumihara, H.; Yamamoto, M.; Miyasaka, T.; Ito, Y.; Hirayama, R.; Inoue, T.; Kirii, Y.; Nishiwaki, E.; Ohmoto, H.; Maeda, Y.; Ishibushi, E.; Inoue, Y.; Yoshino, K. and Kondo, H., *J. Med. Chem.,* **2002**, *45*, 919. (d) Leggio, A.; Liguori, A.; Napoli, A.; Siciliano, C. and Sindona, G., *J. Org. Chem.,* **2001**, *66*, 2246. (e) Munson, J. W., "*Hydroxamic Acids*," in *The Chemistry of Acid Derivative*s, ed. Patai, S., John Wiley and Sons, New York, **1992**, Suppl. B, *Vol. 2*, p 849. (f) Buchbauer, G.; Spreitzer, H. and Kotlan, U., *Z. Naturfors., B: Chem. Sci.,* **1991**, *46*, 1272. (g) Murahashi, S.-I.; Oda, T.; Sugahara, T. and Masui, Y., *J. Org. Chem.,* **1990**, *55*, 1744. (h) Agrawal, Y. K. and Thomas, J. K., *J. Chem. Eng. Data,* **1985**, *30*, 493. (i) Miller, M. J.; Mattingly, P. G.; Morrison, M. A. and Kerwin, Jr., J. F., *J. Am. Chem. Soc.,* **1980**, *102*, 7026. (j) Robinson, C. H.; Gnoj, O.; Mitchell, A.; Wayne, R.; Townley, E.; Kabasakalian, P.; Oliveto, E. P. and Barton, D. H. R., *J. Am. Chem. Soc*., **1961**, *83*, 1771. (k) Stolberg, M. A.; Mosher, W. A. and Wagner-Jauregg, T., *J. Am. Chem. Soc.*, **1957**, *79*, 2615. (l) Safir, S. R. and Williams, J. H., *J. Org. Chem*., **1952**, *17*, 1298. (m) Shaw, E. and McDowell, J., *J. Am. Chem. Soc*., **1949**, *71*, 1691. (n) Angeli A., Angelico E., *Gazz. Chim. Ital.*, **1904**, *34*, 50.

20

ANRORC Rearrangement
(Degenerate Ring Transformation of Heterocycles)

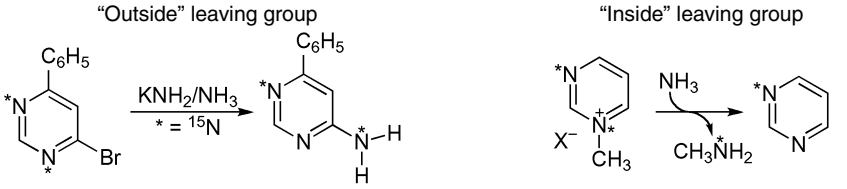
A. GENERAL DESCRIPTION OF THE REACTION

ANRORC rearrangement occurs in nucleophilic substitution of heterocyclic compounds, and stands for a whole process of the initial **A**ddition of a **N**ucleophile, followed by the **R**ing **O**pening and **R**ing **C**losure during the substitution. This transformation, known as S_N(ANRORC) reaction[1] or degenerate ring transformation,[2] is a very common transformation for heterocycles, and has been discovered for more than a century already. One example is the well-known *Dimroth Rearrangement*.[3] In ANRORC rearrangement, one (or more) of the ring atoms(s) will be replaced by one (or more) identical atom(s) present in the nucleophilic reagent that can be divided into two subgroups, including the reactions with the leaving group as a substituent on the heterocyclic ring ("outside" leaving group) and those with the leaving group as an integral part of the heterocyclic system ("inside" leaving group).[4]

B. GENERAL REACTION SCHEME

Listed below are two examples of such reaction with either an "outside" leaving group or "inside" leaving group.[5,6]

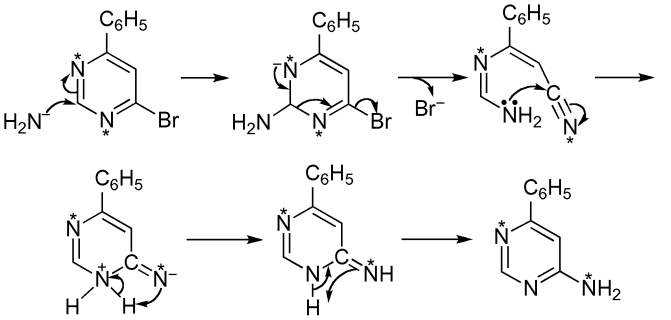
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang



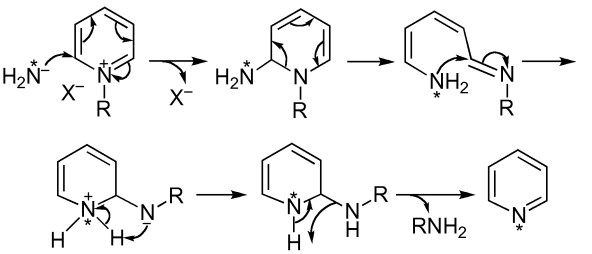
C. PROPOSED MECHANISMS

This reaction involves three consecutive steps: addition of nucleophile, ring opening and ring closure.

"Outside" leaving group



"Inside" leaving group



D. MODIFICATION

N/A

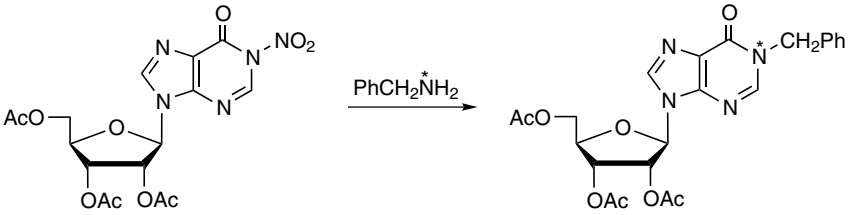
E. APPLICATIONS

This reaction has wide applications in heterocycle chemistry.

F. RELATED REACTIONS

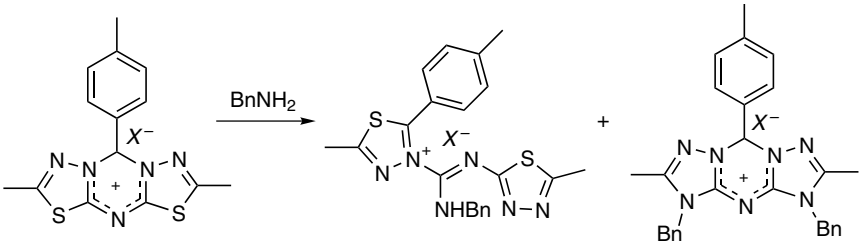
Dimroth Rearrangement is a special type of ANRORC rearrangement.

G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

To a small flask, were added 132 mg of nitroinosine (0.30 mmol) and 6.0 mL of CH_2Cl_2. After being cooled to -78°C, 64 mg of benzylamine (0.60 mmol) in 1.0 mL of CH_2Cl_2 was added. The resulting mixture was left overnight at -20°C. The mixture was then allowed to warm to room temperature and was stirred for 2 days (until no nitroinosine remained). After being treated with 46 μL of CF_3COOH (0.60mmol) for 35 hours, solvent was removed and the residue was purified by column chromatography to give final product.



Reference 8.

To a 250 mL of flask, were added 60.0 mL pyridine and 5.0 mmol of bis(1,3,4-thiadia-zolo)-1,3,5-triazinium halide. Triazinium halide will suspend in pyridine under stirring. To this suspension, 10 mmol of benzylamine was added and the mixture was stirred for 24 hours at room temperature. This procedure gave a clear solution with a slight red coloring, while the smell of hydrogen sulfide was observed. After the reaction, pyridine was removed via rotatory evaporation, the crude product was extracted with *tert*-butyl methyl ether and the solid residue was washed with water. After filtration and drying in vacuo, two main products were isolated by column chromatography on silica gel 60 (0.063 – 0.200 mm): *N*-benzyl-5-methyl-2-(4-methylphenyl)-*N*′-(5-methyl-1,3,4-thiadiazol-2-yl)-1,3,4-thiadiazole-3(2*H*)-carboximidamide (0.78 g, m.p. 161°C, in yield of 37%) and 3,5-dibenzyl-2,6-dimethyl-9-(4-methylphenyl)-3H,5H,9H-di[1,2,4]-triazolo[1,5-a:1′,5′-d][1,3,5]triazine-8-ium bromide (0.65 g, m.p. 238°C, in yield of 24%).

Other references related to ANRORC rearrangement are cited in the literature.[9]

H. REFERENCES

1. Wermann, K.; Walther, M.; Gunther, W.; Gorls, H. and Anders, E., *Eur. J. Org. Chem.,* **2003**, 1389.
2. (a) van der Plas, H. C., *J. Heterocycl. Chem.,* **2000**, *37*, 427. (b) van der Plas, H. C., *Adv. Heterocycl. Chem.,* **1999**, *74*, 1. (c) de Bie, D. A.; Geurtsen, B. and van der Plas, H. C., *J. Org. Chem.,* **1986**, *51*, 71.
3. (a) Dimroth, O., *Ann.,* **1909**, *364***,** 183. (b) Dimroth, O., *Ann*., **1927**, *459*, 39.
4. van der Plas, H. C., "*Degenerate Ring Transformations of Heterocyclic Compounds*," *Advances in Heterocyclic Chemistry*, edited by Katritzky, A. R. FRS, Academic Press, San Diego, **1999**.
5. de Valk, J. and van der Plas, H. C., *Recl. Trav. Chim. Pays-Bas*, **1971**, *90*, 1239.
6. Oostveen, E. A.; van der Plas, H. C. and Jongejan, H., *Recl. Trav. Chim. Pays-Bas*, **1974**, *93*, 58.
7. Ariza, X.; Bout, V. and Vilarrasa, J., *J. Am. Chem. Soc.,* **1995**, *117*, 3665.
8. Wermann, K.; Walther, M.; Günther, W.; Görls, H. and Anders, E., *Eur. J. Org. Chem*., **2003**, 1389.
9. (a) Palumbo Piccionello, A.; Pace, A.; Pibiri, I.; Buscemi, S. and Vivona, N., *Tetrahedron,* **2006**, *62*, 8792. (b) Chattopadhyay, G. and Saha, T. K., *Indian J. Chem., Sect. B,* **2004**, *43B*, 1558. (c) Kozhevnikov, V. N.; Kozhevnikov, D. N.; Rusinov, V. L. and Chupakhin, O. N., *Chem. Heterocycl. Compd.,* **1999**, *35*, 470. (d) Fabian, W. M. F.; Bakulev, V. A. and Kappe, C. O., *J. Org. Chem.,* **1998**, *63*, 5801. (e) Nishiwaki, N.; Wang, H.-P.; Matsuo, K.; Tohda, Y. and Ariga, M., *J. Chem. Soc., Perkin Trans, I,* **1997**, 2261. (f) Nishiwaki, N.; Tohda, Y. and Ariga, M., *Synthesis*, **1997**, 1277. (g) Rusinov, V. L.; Chupakhin, O. N. and van der Plas, H. C., *Heterocycles*, **1995**, *40*, 441. (h) Babaev, E. V.; Lushnikov, D. E. and Zefirov, N. S., *J. Am. Chem. Soc.,* **1993**, *115*, 2416. (i) Hermecz, I.; Breining, T.; Sessi, J. and Podanyi, B., *J. Heterocycl. Chem*., **1991**, *28*, 783. (j) Marcelis, A. T. M.; Tondys, H. and van der Plas, H. C., *J. Heterocycl. Chem.,* **1988**, *25*, 831. (k) Brouwer, A. C. and van der Plas, H. C., *J. Heterocycl. Chem.*, **1987**, *24*, 1657. (l) Breuker, K.; van der Plas, H. C. and van Veldhuizen, A., *Isr. J. Chem*., **1986**, *27*, 67. (m) Sladowska, H.; de Meester, J. W. G. and van der Plas, H. C., *J. Heterocycl. Chem.*, **1986**, *23*, 477. (n) Tondys, H.; van der Plas, H. C. and Wozniak, M., *J. Heterocycl. Chem.*, **1985**, *22*, 353. (o) de Bie, D.; Geurtsen, B. and van der Plas, H. C., *J. Org. Chem*., **1985**, *50*, 484. (p) Rykowski, A. and van der Plas, H. C., *Synthesis*, **1985**, 884. (q) Charushin, V. N. and van der Plas, H. C., *Recl. Trav. Chim. Pays-Bas*, **1983**, *102*, 373. (r) Hara, H. and van der Plas, H. C., *J. Heterocycl. Chem.,* **1982**, *19*, 1285. (s) Hara, H. and van der Plas, H. C., *J. Heterocycl. Chem*., **1982**, *19*, 1527. (t) Reinheimer, J. D.; Mayle, L. L.; Dolnikowski, G. G. and Gerig, J. T., *J. Org. Chem*., **1980**, *45*, 3097. (u) Rasmussen, C. A. H. and van der Plas, H. C., *Recl. Trav. Chim. Pays-Bas*, **1979**, *98*, 5. (v) Hirota, K.; Watanabe, K. A. and Fox, J. J., *J. Org. Chem.,* **1978**, *43*, 1193. (w) Geerts, J. P. and van der Plas, H. C., *J. Org. Chem.*, **1978**, *43*, 2682. (x) Rasmussen, C. A. H. and van der Plas, H. C., *Tetrahedron Lett.,* **1978**, 3841. (y) Peereboom, R.; van der Plas, H. C. and Koudijs, A., *Recl. Trav. Chim. Pays-Bas*, **1974**, *93*, 58. (z) den Hertog, H. J.; Boer, H.; Streef, J. W.; Vekemans, F. C. A. and van Zoest, W. J., *Recl. Trav. Chim. Pays-Bas*, **1974**, *93*, 195. (aa) Sanders, G. M.; van Dijk, M. and den Hertog, H. J., *Recl. Trav. Chim. Pays-Bas*, **1974**, *93*, 198. (bb) Zoltewica, J. A.; Helmick, L. S.; Oestrich, T. M.; King, R. W. and Kandetzki, E., *J. Org. Chem.,* **1973**, *38*, 1947. (cc) van der Plas, H. C. and Koudijs, A., *Rec. Trav. Chim. Pays-Bas,* **1973**, *92*, 711. (dd) Bunnett, J. F., *Acc. Chem. Res.,* **1972**, *5*, 139. (ee) Zoltewica, J. A. and Helmick, L. S., *J. Am. Chem. Soc*., **1972**, *94*, 682. (ff) Kim, K. K. and Bunnett, J. F., *J. Am. Chem. Soc.,* **1970**, *92*, 7463. (gg) Kim, K. K. and Bunnett, J. F., *J. Am. Chem. Soc*., **1970**, *92*, 7465. (hh) van der Plas, H. C.; Zuurdeeg, B. and van Meeteren, H. W., *Recl. Trav. Chim. Pays-Bas*, **1969**, *88*, 1156. (ii) Streef, J. W. and den Hertog, H. J., *Recl. Trav. Chim. Pays-Bas*, **1969**, *88*, 1391. (jj) van der Plas, H. C. and Zuurdeeg, B., *Recl. Trav. Chim. Pays-Bas*, **1969**, *88*, 426. (kk) Wahren, M., *Tetrahedron*, **1968**, *24*, 441. (ll) den Hertog, H. J. and Buurman, D. J., *Recl. Trav. Chim. Pays-Bas,* **1967**, *86*, 187. (mm) van der Plas, H. C.; Haase, B.; Zuurdeeg, B. and Vollering, M. C., *Recl. Trav. Chim. Pays-Bas*, **1966**, *85*, 1101. (nn) den Hertog, H. J.; van der Plas, H. C.; Pieterse, M. J. and Streef, J. W., *Recl. Trav. Chim. Pays-Bas*, **1965**, *84*, 1569.

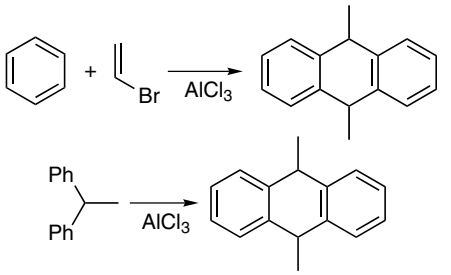
21

Anschütz Anthracene Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially studied by Anschütz between 1879 and 1886.[1] It is the synthesis of anthracene from vinyl bromide and benzene in the presence of aluminum chloride. In addition, methyl phenyl carbinol or 1,1-diphenyl ethane can also be converted into anthracene derivative in the presence of aluminum chloride.

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The reaction mechanism is similar to that of *Friedel-Crafts Alkylation.*

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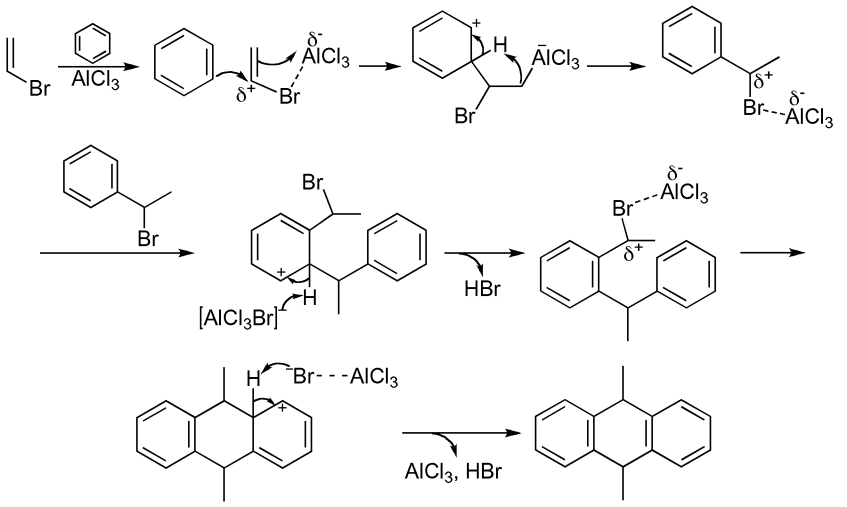


D. MODIFICATION

N/A

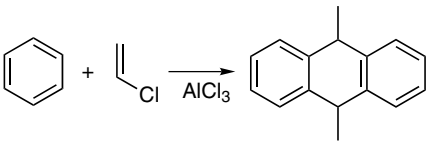
E. APPLICATIONS

N/A

F. RELATED REACTIONS

N/A

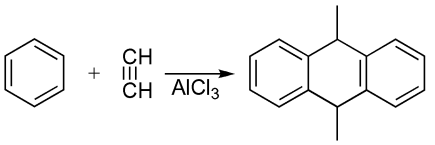
G. CITED EXPERIMENTAL EXAMPLES



Reference 2.

To a 1-L three-necked flask equipped with condenser, thermometer and gas inlet tube were added 300 mL thiophene-free benzene and 50 g $AlCl_3$. The solution was agitated using a stirrer at 1000–1400 rpm until the aluminum chloride was in a finely divided state. Then vinyl chloride gas was passed into the flask at such a rate that only a few bubbles of gas escaped from an alkali trap connected to the condenser. The reaction was kept at 0–5°C. No hydrogen chloride was evolved until an initial period of 15–20 min.

After 90 g vinyl chloride gas had been added, all of the hydrogen chloride apparently had been evolved. The reaction mixture was poured into ice and acidified with hydrochloric acid. After the heavy black layer had completely disappeared, the fluorescent brown top layer was separated, washed with water, and steam distilled. The distillate, consisting chiefly of unreacted benzene, was dried and fractionated. Besides benzene, some ethylbenzene was obtained in the fraction, boiling at 130–135°C. In no case was a styrene fraction (140–145°C) obtained. The residue from the steam distillation was a viscous, fluorescent greenish oil. Water was removed first at a pressure of 50 mmHg, after which unsymmetrical diphenylethane distilled at 130–140°C at 12 mmHg. The latter was a nearly colorless oil but possessed a strong violet fluorescence. On redistillation, most of the fraction boiled at 134–130°C (12 mmHg). Above 140°C the pressure was reduced to 0.5 mmHg, and traces of 9,10-dimethyldihydro-anthracene was sublimed at 180–200°C. The residue was poured into a beaker and solidified on cooling to a dark green resin having a reddish fluorescence when in solution. Occasionally, the residue from the steam distillation crystallized on standing. In this event, the solid was filtered and crystallized from alcohol. It was identified as 9,10-dimethyldihydro-anthracene and possessed the following characteristics: yellow platelets, melting at 179–181°C, and purplish fluorescence in solution.



Reference 3.

To a 1-L three-necked flask equipped with condenser, thermometer, and gas inlet tube were added 200 g benzene and 50 g $AlCl_3$. The acetylene, after being purified by passing through a solution of chromic acid, was washed and stored in gasometers from which it was led at a nearly constant rate (20 L/h) through a drying bottle to the three-necked flask. This flask was provided with an efficient return condenser through which the unabsorbed gas was discharged to a large bottle, where its volume was measured approximately. No gas escape if the pressure was 150 mmHg above atmospheric pressure. Provision was made for heating or cooling the reaction flask, and the mixture was shaken frequently during the course of the reaction. After passing 30–45 L acetylene through the reaction mixture, a reddish brown material was obtained that was hydrolyzed and distilled with steam to give two volatile fractions and a black tarry residue. The first fraction was unreacted benzene. A small portion of a material, b.p. 140–145°C, was also obtained. This gave evidence of the presence of styrene, which, however, was not present in sufficient quantity to be isolated. The second fraction, which came over slowly (in 4–6 h), when dried, boiled at 280–290°C and was identified as 1,1-diphenylethane, b.p. 286°C, by oxidation to benzophenone and the formation of benzophenone oxime, m.p. 140°C. The other fraction, which distilled above 360°C, solidified and, after several recrystallizations from alcohol, yielded long brown needles, m.p. 181°C. It was, therefore, identified as the 9,l0-dimethyl-anthracene hydride of Anschutz.

Other references related to the synthesis of anthracene are cited in the literature.[4]

H. REFERENCES

1. (a) Anschütz, von R. and Schultz, G., *Ann.,* **1879**, *196*, 32. (b) Angelbis, A. and Anschütz, R., *Ber.*, **1884**, *17*, 165, 167. (c) Anschütz, R. and Immendorf, H., *Ber.,* **1885**, *18*, 657. (d) Anschütz, R., *Ann.,* **1886**, *235*, 159, 299.
2. Davidson, J. M. and Lowy, A., *J. Am. Chem. Soc*., **1929**, *51*, 2978.
3. Cook, O. W. and Chambers, V. J., *J. Am. Chem. Soc.*, **1921**, *43*, 334.
4. (a) Huston, R. C. and Friedemann, T. E., *J. Am. Chem. Soc*., **1918**, *40*, 785. (b) Nenitzescu, C. D., *Angew. Chem.,* **1939**, *52*, 231.

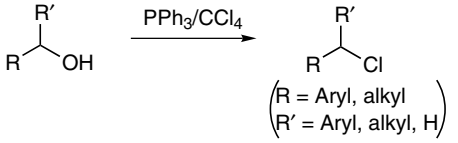
22

Appel Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported in 1966 by Lee et al.,[1] after the initial work of Horner et al. for the halogenation of alcohol using triarylphosphine dihalides in 1959.[2] In this reaction, primary and secondary alcohols are transformed into corresponding chlorides with a remarkable tendency of inversion of the configuration when the alcohols react with triphenylphosphine and carbon tetrachloride. This reaction has been extensively reviewed by Appel[3] and is generally known as the Appel reaction.[4] Likewise, the mixture of triphenylphosphine and carbon tetrachloride is referred to as the Appel reagent[5] and Appel agent.[6]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is believed that this reaction involves the initial halophilic substitution between triphenylphosphine and carbon tetrachloride (i.e., triphenyl phosphine attacks the chlorine atom in carbon tetrachloride instead of the carbon atom in a traditional S_N2 substitution) and

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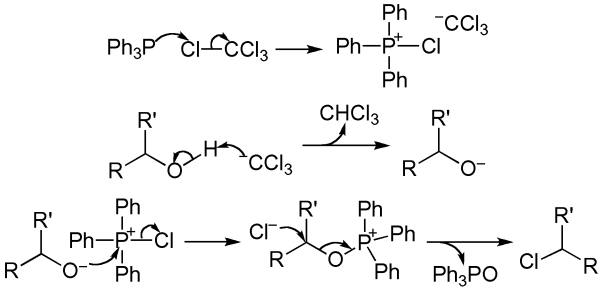
subsequent proton abstraction of alcohol from trichloromethyl anion, the attack of alkoxide on phosphonium chloride, and final S_N2 substitution from chloride, as shown. It is reported that chloride and four valent phosphine species form a tight ion pair that does not react with externally added nucleophiles (e.g., CN^-).[5]



D. MODIFICATION

The pair of both hexachloroacetone/triphenylphosphine[7] and dichloroselenurane/triphenylphosphine[4] are also applied to the chlorination of alcohol, and the first pair has been extensively studied in the chlorination of allyl alcohol.

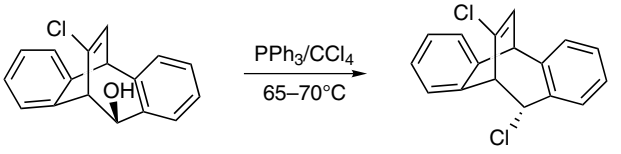
E. APPLICATIONS

This reaction has general applications for the preparation of alkyl chlorides.

F. RELATED REACTIONS

N/A

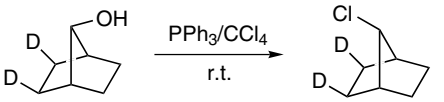
G. CITED EXPERIMENTAL EXAMPLES



Reference 8.

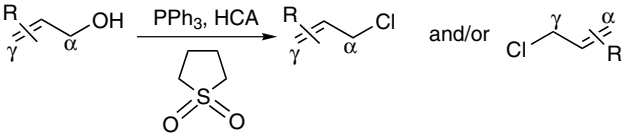
To a reaction flask, were added 1.08 g 6-chloro-2,3:8,9-dibenzobicyclo[3.2.2]nona-2,6,8-trien-*exo*-4-ol (4.0 mmol), 7.0 mL carbon tetrachloride, and 1.06 g triphenylphosphine (4.0 mmol). The solution was heated at 65–70°C for 36 h, and the reaction mixture was cooled and filtered. The yellow solution was chromatographed over a silica gel column with

hexane. The solution was evaporated, and solid was crystallized from 95% ethanol to give 0.80 g of a white crystalline solid, in a yield of 70%, m.p. 113°C.



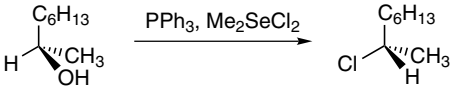
Reference 5.

A solution of 1.14 g *exo*,*exo*-2,31-dideuterio-*anti*-7-hydroxybicyclo[2.2.1] heptane (0.01 mol) and 2.88 g triphenylphosphine (0.011 mol) in 6 mL carbon tetrachloride was stirred in a closed flask for 24 h at room temperature. Solvent was distilled at $\leq$ 35°C (at 30 mmHg) in a dry atmosphere. The residue was heated slowly at 16 mmHg pressure to 175°C. The distillate, collected in a dry ice trap (1.15 g), was sublimed and eluted on a 1.5-g Florisil column first with pentane and then with methanol. Pentane was carefully distilled, and the residue obtained was sublimed at 55–70°C to give *exo*,*exo*-2,3-dideuterio-*syn*-7-chlorobicyclo[2.2.1] heptane, m.p. 43–45°C. (*Note*: After the solvent is removed, the residue can be directly purified via column chromatography.)



Reference 7a.

In a 100-mL, round-bottomed flask equipped with a magnetic stirrer were placed ~0.03 mol of the alcohol and (usually) a slight excess of Ph_3P in 10–15 mL of sulfolane. To the cooled (10°C), stirred solution was added hexachloroacetone (HCA) in ~10 mL sulfolane dropwise; after an initial temperature rise and formation of a precipitate, the temperature gradually dropped to ambient as the rest of the HCA solution was added. The reaction mixture was allowed to come to room temperature. Immediate flash distillation at 4–5 mmHg into a dry ice/acetone cooled receiver gave product. In most instances, the material was exclusively the allylic or saturated chloride.



Reference 4j.

The Preparation of Dimethyldichloroselenurane

To a stirred solution of 3.76 g dimethyl selenide (20 mmol) in 20 mL ethyl ether was added dropwise 2.70 g sulfuryl chloride (20 mmol) at 0°C. Stirring was continued for an additional 15 min. The crystals formed during the addition of sulfuryl chloride were filtered off, washed with anhydrous benzene, and dried under reduced pressure to give 5.82 g analytically pure dimethyldichloroselenurane, in a yield of 100%, m.p. 46–49°C.

General Procedure for Chlorination of Chiral Alcohols

In a 10-mL flask, 1.0 mmol alcohol and 1.0 mmol triphenylphosphine were dissolved in 3 mL of the appropriate solvent (benzene). To this solution was added 1.0 mmol dimethyldichloroselenurane in small portions over a few minutes. When the addition of the dimethyldichloroselenurane was completed, the solvent was removed under reduced pressure, and 10–15 mL of hexane was added to the residue. The precipitated triphenylphosphine oxide was filtered off. To remove the remaining traces, the hexane solution was passed through a short silica gel column. Removal of the solvent gave virtually pure chloride.

Other references using triphenylphosphine and carbon tetrachloride to produce chlorides are cited in literature.[9]

H. REFERENCES

1. (a) Downie, J. M.; Holmes, J. B. and Lee, J. B., *Chem. Ind.,* **1966**, 900. (b) Lee, J. B., *J. Am. Chem. Soc.,* **1966**, *88*, 3440.
2. Horner, L.; Oediger, H. and Hoffmann, H., *Ann*., **1959**, *626*, 26.
3. Appel, R., *Angew. Chem., Int. Ed. Engl.,* **1975**, *14*, 801.
4. (a) Bikbulatov, R. V.; Yan, F.; Roth, B. L. and Zjawiony, J. K., *Bioorg. Med. Chem. Lett.,* **2007**, *17*, 2229. (b) Roethle, P. A.; Hernandez, P. T. and Trauner, D., *Org. Lett.,* **2006**, *8*, 5901. (c) Zhong, M. H.; Nowak, I.; Cannon, J. F. and Robins, M. J., *J. Org. Chem.,* **2006**, *71*, 4216. (d) Agota, S.; Janos, W.; Erzsebet, M.; Renata, M.; Arpad, M.; George, F. and Gyula, S., *Steroids,* **2006**, *71*, 141. (e) Barros, M. T. and Phillips, A. M. F., *Molecules,* **2006**, *11*, 177. (f) Yin, Q.; Ye, Y.; Tang, G. and Zhao, Y.-F., *Spectrochimica Acta, Part A: Mol. Biomol. Spectr.,* **2006**, *63A*, 192. (g) Nawrot, B.; Michalak, O.; Nowak, M.; Okruszek, A.; Dera, M. and Stec, W. J., *Tetrahedron Lett.,* **2002**, *43*, 5397. (h) Scheurer,A.; Mosset, P.; Bauer, W. and Saalfrank, R. W., *Eur. J. Org. Chem.,* **2001**, 3067. (i) Seebach, D.; Pichota, A.; Beck, A. K.; Pinkerton, A. B.; Litz, T.; Karjalainen, J. and Gramlich, V., *Org. Lett.,* **1999**, *1*, 55. (j) Drabowicz, J.; Luczak, J. and Mikolajczyk, M., *J. Org. Chem.,* **1998**, *63,* 9565. (k) Baraniak, J. and Stec, W. J., *Tetrahedron Lett.,* **1985**, *26*, 4379. (l) Zhmurova, I. N.; Yurchenko, V. G. and Pinchuk, A. M., *Zh. Obsh. Khim.,* **1985**, *55*, 321. (m) Beres, J.; Bentrude, W. G.; Parkanji, L.; Kalman, A. and Sopchik, A. E., *J. Org. Chem.,* **1985**, *50*, 1271. (n) Lensink, C.; de Ruiter, B. and van de Grampel, J. C., *J. Chem. Soc., Dalton Trans.,* **1984**, 1521. (o) Zhmurova, I. N.; Yurchenko, V. G. and Pinchuk, A. M., *Zh. Obsh. Khim.,* **1981**, *51*, 2462. (p) Zhmurova, I. N. and Yurchenko, V. G., *Zh. Obsh. Khim.,* **1980**, *50*, 52. (q) Pinter, I.; Kovacs, J. and Messmer, A., *Magyar Kemiai Folyoirat,* **1977**, *83*, 231. (r) Pinter, I.; Kovacs, J. and Messmer, A., *Carbohydr. Res.,* **1977**, *53*, 117.
5. Weiss, R. G. and Snyder, E. I., *J. Org. Chem*., **1970**, *35*, 1627.
6. Nishida, Y.; Shingu, Y.; Dohi, H. and Kobayashi, K., *Org. Lett.,* **2003**, *5*, 2377.
7. (a) Magid, R. M.; Talley, B. G. and Souther, S. K., *J. Org. Chem.,* **1981**, *46*, 824. (b) Magid, R. M.; Fruchey, O. S.; Johnson, W. L. and Allen, T. G., *J. Org. Chem.,* **1979**, *44*, 359.
8. Cristol, S. J.; Strom, R. M. and Stull, D. P., *J. Org. Chem*., **1978**, *43*, 1150.
9. (a) Bergin, E.; O'Connor, C. T.; Robinson, S. B.; McGarrigle, E. M.; O'Mahony, C. P. and Gilheany, D. G., *J. Am. Chem. Soc.,* **2007**, *129*, 9566. (b) Wölfling, J.; Szájli, Á.; Vörös, L.; Gáspár, M. and Schneider, G., *Monatsh. Chem.,* **2006**, *137*, 1099. (c) Vicente, V.; Fruchier, A.; Taillefer, M.; Combes-Chamalet, C.; Scowen, I. J.; Plenat, F. and Cristau, H.-J., *New J. Chem.,* **2004**, *28*, 418. (d) Cho, H. I. and Lee, K.-J., *Bull. Korean Chem. Soc.,* **2003**, *24*, 189. (e) Desmaris,

L.; Percina, N.; Cottier, L. and Sinou, D., *Tetrahedron Lett.*, **2003**, *44*, 7589. (f) Lim, J.-S. and Lee, K.-J., *J. Heterocycl. Chem.,* **2002**, *39*, 975. (g) Arstad, E.; Barrett, A. G. M.; Hopkins, B. T. and Koebberling, J., *Org. Lett.,* **2002**, *4*, 1975. (h) Zhmurova, I. N.; Yurchenko, V. G. and Pinchuk, A. M., *Zh. Obsh. Khim.,* **1985**, *55*, 321. (i) Castro, B. R., *Org. React.,* **1983**, *29*, 1. (j) Appel, R.; Kleinstuck, R. and Ziehn, A., *Angew. Chem. Int. Ed. Engl.,* **1971**, *10*, 132. (k) Downie, I. M.; Lee, J. E. and Matough, M. F., *Chem. Commun.,* **1968**, 1360. (l) Weiss, R. G. and Snyder, E. I., *Chem. Commun.,* **1968**, 1358. (m) Ried, W. and Appel, R., *Ann.,* **1964**, *670*, 61.

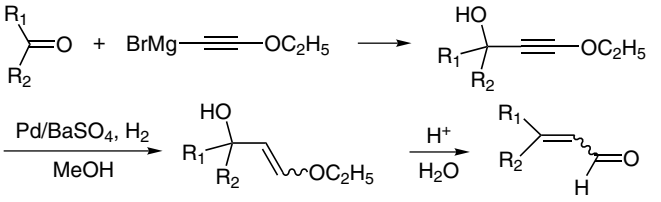
23

Arens-van Dorp Reaction
(Isler Modification)

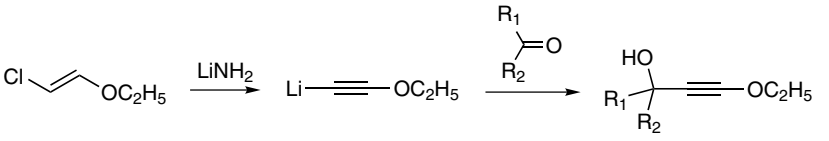
A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Arens et al. in 1947.[1] It is the synthesis of α,β-unsaturated aldehyde from the reaction of ethoxyethynemagnesium bromide and ketone or aldehyde and is known as the Arens and van Dorp reaction.[2] Because the preparation of ethoxyacetylene is tedious, this reaction has been modified to generate lithium ethoxyacetylene by treatment of β-chlorovinyl ether with lithium amide, which then reacts with a ketone or aldehyde to form α,β-unsaturated aldehyde.[3] This new protocol is referred to as the Isler modification.

B. GENERAL REACTION SCHEME



Isler modification



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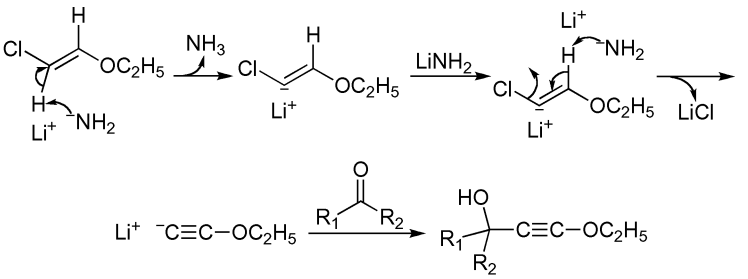
C. PROPOSED MECHANISMS

The mechanism of the Arens-van Dorp reaction is clearly illustrated in the original reaction scheme; therefore, it is not necessary to repeat the mechanism here. The mechanism of the Isler modification is shown here.



D. MODIFICATION

In the presence of a chiral catalyst (BINOL), substituted acetylene and diethyl zinc can react with aldehyde to give chiral alkynyl alcohols of up to 99% e.e.[4]

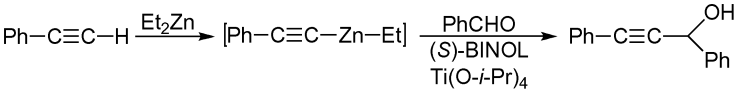
E. APPLICATIONS

N/A

F. RELATED REACTIONS

This reaction is related to the *Favorskii-Babayan Synthesis* and *Nef Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4.

To a 25-mL flask were added 1 mL toluene, 226 μL phenylacetylene (2.0 mmol), and 210 μL diethylzinc (2.0 mmol), and the mixture was refluxed for 1 h under nitrogen. After the solution was cooled to room temperature, 57.2 mg (*S*)-BINOL (>99% e.e., 0.2 mmol), 8 mL diethyl ether, and 150 μL $Ti(OiPr)_4$ (0.5 mmol) were added sequentially. The solution was stirred for 1 h more, and 0.5 mmol 4-methylbenzaldehyde was added. After 4 h, the reaction was quenched with saturated ammonium chloride. The resulting mixture was extracted with methylene chloride and concentrated under vacuum. Pure propargylic alcohol was obtained via short silica gel column chromatography, in a yield of 93% and 97% e.e.

Other references related to the Arens-van Dorp reaction are cited in the literature.[5]

H. REFERENCES

1. (a) van Dorp, D. A. and Arens, J. F., *Nature*, **1947**, *160*, 189. (b) Arens, J. F. and van Dorp, D. A., *Rec. Trav. Chim. Pays-Bas Belg.,* **1949**, *68*, 604. (c) Graham, W.; van Dorp, D. A. and Arens, J. F., *Rec. Trav. Chim. Pays-Bas Belg.,* **1949**, *68*, 609.
2. Naves, Y. R. and Ardizio, P., *Bull. Soc. Chim. Fr.,* **1951**, 374.
3. Isler, O.; Montavon, M.; Rüegg, R. and Zeller, P., *Helv. Chim. Acta,* **1956**, *39*, 259.
4. Gao, G.; Moore, D.; Xie, R.-G. and Pu, L., *Org. Lett*., **2002**, *4*, 4143.
5. (a) Lakhvich, F. A.; Lis, L. G. and Akhrem, A. A., *Russ. Chem. Rev.,* **1984**, *53*, 582. (b) Arens, J. F., *Advances in Organic Chemistry: Methods and Results*, Raphael, R. A.; Taylor E. C. and Wynberg, H. ed., Interscience Publishers, New York, **1960**, 2, 117–212. (c) Heusser, H.; Eichenberger, K. and Plattner, P. A., *Helv. Chim. Acta,* **1950**, *33*, 370. (d) Meerwein, H., *Houben-Weyl,* **1965**, *6/3*, 189. (e) Isler, O.; Lindlar, H.; Montavon, M.; Ruegg, R. and Zeller, P., *Helv. Chim. Acta,* **1956**, *39*, 249. (f) Isler, O.; Lindlar, H.; Montavon, M.; Ruegg, R. and Zeller, P., *Helv. Chim. Acta,* **1956**, *39*, 274. (g) Julia, M., *Compt. Rend.,* **1948**, *227*, 1374.

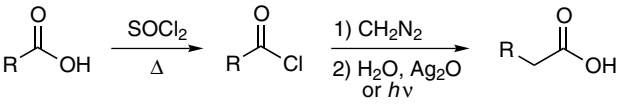
24

Arndt-Eistert Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Arndt and Eistert in 1935.[1] It is the extension of carboxylic acid by one CH_2 unit via the reaction of acyl chloride with diazomethane and is generally known as the Arndt-Eistert synthesis.[2] In addition, this reaction is also occasionally referred to as the Arndt-Eistert acid synthesis,[3] Arndt-Eistert homologation,[4] and Arndt-Eistert reaction.[5] This reaction has been extensively reviewed.[2x,6] Other reagents instead of diazomethane have been similarly applied to extend the length of the carboxylic acids.[7]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A general mechanism for the Arndt-Eistert synthesis is provided here.

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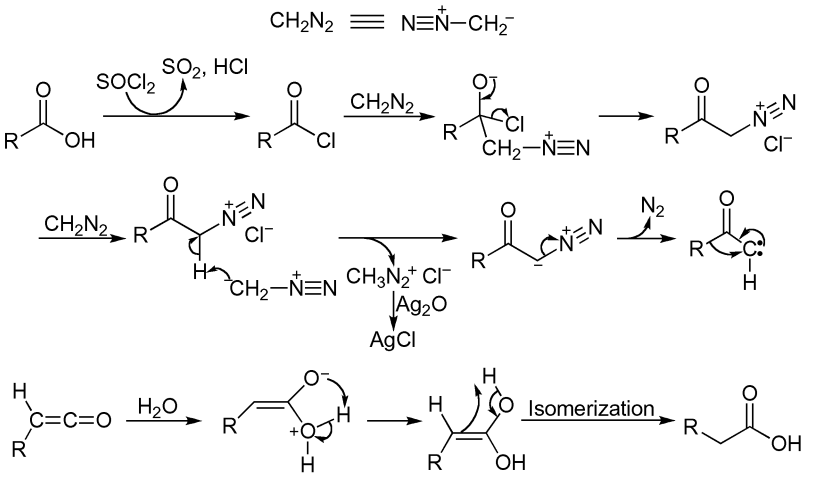


D. MODIFICATION

This reaction has been modified using other reagents than diazomethane to elongate the carboxylic acid chain.[7]

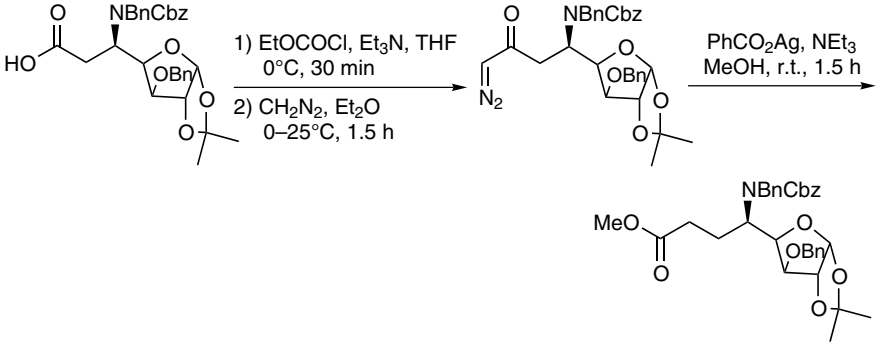
E. APPLICATIONS

This method has been used to synthesize unsaturated diazoketone[8] and amino acids.[9] Other early applications of such reactions to prepare carboxylic acids are cited in Ref. 10.

F. RELATED REACTIONS

This reaction is similar to the *Wolff Rearrangement* and *Nierenstein Reaction*.

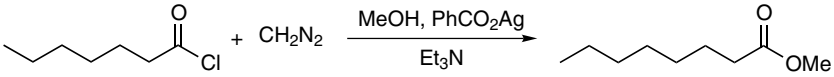
G. CITED EXPERIMENTAL EXAMPLES



Reference 11.

A solution of 0.80 g ethyl 3-*O*-benzyl-5-(*N*-benzyl-*N*-benzoxycarbonylamino)-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*gluco*-hepto-furan-uronic acid (1.42 mmol) in 10 mL THF was cooled to 0°C under dry nitrogen, then 0.16 g triethylamine (1.57 mmol) and 0.17 mL ethylchloroformate (1.57 mmol) were added one after another. After 15 min, the suspension was allowed to warm to 25°C and filtered through celite. To the filtrate was added a freshly prepared solution of diazomethane in diethyl ether [(prepared from *N*-nitrosomethyl urea (1.02 g, 7.12 mmol) and 2 g KOH] dropwise over a period of 30 min. The mixture was stirred for 1.5 h, during which the reaction slowly come to room temperature. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography using petroleum ether/EtOAc (9:1) as an eluent to give 0.52 g 5,6,8-trideoxy-1,2-*O*-isopropylidene-3-*O*-benzyl-5-(*N*-benzyl-*N*-benzoxy carbonyl amino)-8-diazo-α-D-*gluco*-octo-1,4-furan-7-ulose as a thick liquid, in yield of 62%. R_f = 0.35 (*n*-hexane/EtOAc = 7:3); $[R]_D = -12.2^\circ$ (*c*4.0, $CHCl_3$).

To a solution of 0.5 g 5,6,8-trideoxy-1,2-*O*-isopropylidene-3-*O*-benzyl-5-(*N*-benzyl-*N*-benzoxy carbonyl amino)-8-diazo-α-D-*gluco*-octo-1,4-furan-7-ulose (0.85 mmol) in 12 mL anhydrous MeOH was added dropwise a solution of 0.06 g silver benzoate (0.27 mmol) in 1 mL triethylamine under dry nitrogen. The mixture was stirred at 25°C for 1.5 h. The solvent was evaporated, and the residue was purified by column chromatography using petroleum ether/EtOAc (95:5) to give 0.42 g methyl 3-*O*-benzyl-5-(*N*-benzyl-*N*-benzoxycarbonyl-amino)-5,6,7-trideoxy-1,2-*O*-isopropylidene-α-D-*gluco*-octo-1,4-furanuronate as a thick liquid, in a yield of 83%. R_f = 0.46 (*n*-hexane/EtOAc = 7:3); $[R]_D = -50.87^\circ$ (*c*3.0, $CHCl_3$).



Reference 25.

To a 1000-mL three-necked, round-bottomed flask equipped with a condenser, mechanical stirrer, and a dropping funnel were added 0.15 mol diazomethane in 150 mL dry ether, and the solution was cooled to −10°C. To this solution was added 8 g 7-octynoyl chloride (0.05 mol) in 50 mL dry ether. After stirring for 1 h, the solvent and excess of diazomethane were removed under reduced pressure at room temperature. The yellow oily residue did not solidify on cooling in attempted crystallization. It was, therefore, dissolved in 70 mL methanol and placed in a 500-mL three-necked, round-bottomed flask fitted with a mercury-sealed mechanical stirrer, a dropping-funnel, and a condenser connected to an azotometer. A solution of 1 g dry silver benzoate (prepared by mixing equivalent portions of silver nitrate and sodium benzoate) in 9 g triethylamine was then added dropwise over a period of 90 min. The reaction mixture turned black, and the evolution of nitrogen commenced immediately. A total of 93% of the theoretical amount of gas was collected. The reaction mixture was then refluxed for 5 min and filtered. Most of the alcohol was removed under a vacuum; the residue was dissolved in ether and washed successively with hydrochloric acid, sodium hydroxide, and water. After drying over magnesium sulfate, distillation yielded 13 g (80%) of product, b.p. 97–100°C at 8 mmHg.

Other references related to the Arndt-Eistert synthesis are cited in the literature.[12]

H. REFERENCES

1. Arndt, F. and Eistert, B., *Ber.,* **1935**, *68* 200.
2. (a) Cesar, J. and Sollner Dolenc, M., *Tetrahedron Lett.,* **2001**, *42*, 7099. (b) Desai, K. R. and Pathak, M. M., *J. Indian Chem. Soc.,* **1984**, *61*, 814. (c) Kuo, Y. C.; Aoyama, T. and Shioiri, T., *Chem. Pharm. Bull.,* **1982**, *30*, 899. (d) Aoyama, T. and Shioiri, T., *Chem. Pharm. Bull.,* **1981**, *29*, 3249. (e) Vasi, I. G. and Acharya, R. H., *Indian J. Chem., Sect. B,* **1981**, *20B*, 509. (f) Aoyama, T. and Shioiri, T., *Tetrahedron Lett.,* **1980**, *21*, 4461. (g) Vasi, I. G. and Nanavati, N. T., *J. Indian Chem. Soc.,* **1980**, *57*, 744. (h) Vasi, I. G. and Nanavati, N. T., *J. Inst. Chem. (India),* **1980**, *52*, 107. (i) Hudlicky, T. and Sheth, J. P., *Tetrahedron Lett.,* **1979**, 2667. (j) Vasi, I. G. and Nanavati, N. T., *J. Indian Chem. Soc.,* **1977**, *54*, 426. (k) Vasi, I. G. and Nanavati, N. T., *J. Inst. Chem. (India),* **1976**, *48*, 198. (l) Vasi, I. G. and Desai, K. R., *J. Inst. Chem. (India),* **1974**, *46*, 126. (m) Vasi, I. G. and Desai, K. R., *J. Inst. Chem. (India),* **1972**, *44*, 77. (n) Vasi, I. G. and Desai, K. R., *J. Inst. Chem. (India),* **1972**, *44*, 133. (o) Wilds, A. L.; van der Berghe, J.; Winestock, C. H.; Trebra, R. L. V. and Woolsey, N. F., *J. Am. Chem. Soc.,* **1962**, *84*, 1503. (p) Saldabols, N., *Latvijas PSR Zinatnu Akad. Vestis,* **1958**, 75. (q) Fles, D. and Markovac-Prpic, A., *Croat. Chem. Acta,* **1957**, *29*, 79. (r) Fles, D. and Markovac-Prpic, A., *Croat. Chem. Acta,* **1956**, *28*, 73. (s) Wotiz, J. H. and Buco, S. N., *J. Org. Chem.,* **1955**, *20*, 210. (t) Kasturi, T. R. and Iyer, B. H., *J. Indian Inst. Sci.,* **1955**, *37A*, 258. (u) Links, J. and de Groot, M. S., *Rec. Trav. Chim. Pays-Bas Belg.,* **1953**, *72*, 57. (v) Smith, T. B. and Muth, C. W., *Proc. West Virginia Acad. Sci.,* **1953**, *25*, 42. (w) Wilds, A. L. and Meader, A. L., *J. Org. Chem.,* **1948**, *13*, 763. (x) Bachmann, W. E. and Struve, W. S., *Org. React.,* **1942**, *1*, 38.
3. Roedig, A. and Lunk, H., *Chem. Ber.,* **1954**, *87*, 971.
4. Vasanthakumar, G. R. and Babu, V. V. S., *Indian J. Chem., Sect. B,* **2003**, *42B*, 1691.
5. (a) Liao, B.-R.; Hong, Y.-Y.; Xu, J. and Liu, B., *Youji Huaxue,* **2004**, *24*, 63. (b) Knollmann, R. and Dyong, I., *Chem. Ber.,* **1975**, *108*, 2021. (c) Sobocinska, M.; Witczuk, B. and Kupryszewski, G., *Roczniki Chem.,* **1974**, *48*, 1103. (d) Park, J. D.; Larsen, E. R.; Holler, H. V. and Lacher, J. R., *J. Org. Chem.,* **1958**, *23*, 1166. (e) Brown, F. and Musgrave, W. K. R., *J. Chem. Soc.,* **1953**, 2087. (f) Vandenheuvel, F. A. and Yates, P., *Can. J. Res.,* **1950**, *28B*, 556. (g) Huggett, C.; Arnold, R. T. and Taylor, T. I., *J. Am. Chem. Soc.,* **1942**, *64*, 3043.
6. (a) Gill, G. B., *Comp. Org. Syn.,* **1991**, *3*, 888–889. (b) Eistert, B., *Newer Methods in Preparative Organic Chemistry*, *Vol. 1*, Interscience, New York, **1948**, pp. 513–570.
7. Katritzky, A. R.; Zgang, S. and Fang, Y., *Org. Lett*., **2000**, *2*, 3789.
8. (a) Gademann, K.; Ernst, M.; Hoyer, D. and Seebach, D., *Angew. Chem. Int. Ed.,* **1999**, *38*, 1223. (b) Winum, J.-Y.; Kamal, M.; Leydet, A.; Roque, J.-P. and Montero, J.-L., *Tetrahedron Lett.,* **1996**, *37*, 1781.
9. (a) DeVita, R. J.; Goulet, M. T.; Wyvratt, M. J.; Fisher, M. H.; Lo, J.-L.; Yang, Y. T.; Cheng, K. and Smith, R. G., *Bioorg. Med. Chem. Lett.,* **1999**, *9,* 2621. (b) Marti, R. E.; Bleicher, K. H. and Bair, K. W., *Tetrahedron Lett.,* **1997**, *38*, 6145.
10. (a) Podlech, J. and Seebach, D., *Angew. Chem. Int. Ed. Engl*., **1995**, *34*, 471. (b) Adelfang, J. L. and Daub, G. H., *J. Org. Chem*., **1958**, *23*, 749. (c) Kunz, K., *Chemiker Ztg*., **1958**, *82*, 868.
11. Patil, N. T.; Tilekar, J. N. and Dhavale, D. D., *J. Org. Chem.,* **2001**, *66*, *1065*.
12. (a) Hughes, A. B. and Sleebs, B. E., *Aust. J. Chem.,* **2005**, *58*, 778. (b) Vasanthakumar, G.-R. and Babu, V. V. S., *Synth. Commun.,* **2002**, *32*, 651. (c) Dran, R.; Decock-Le Reverend, B. and Polveche, M., *Bull. Soc. Chim. Fr.,* **1971**, 2114. (d) Kucsman, A. and Kremmer, T., *Acta Chim. Acad. Sci. Hung.,* **1962**, *34*, 75. (e) Adelfang, J. L. and Daub, G. H., *J. Am. Chem. Soc*., **1957**, *79*, 1751.

25

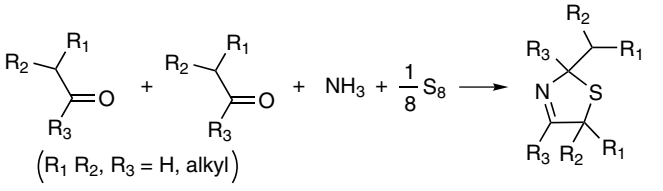
Asinger Reaction

(Asinger Multicomponent Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Friedrich Asinger in 1956.[1] It is a multicomponent reaction for preparing 3-thiazolines from ketones, ammonia, and sulfur[2] and is generally known as the Asinger reaction.[3] This reaction was subsequently extended to the synthesis of *m*-thiazines.[4] The Asinger reaction, together with other multicomponent reactions (MCRs)—such as the *Ugi Reaction*, *Biginelli Reaction*, *Passerini Reaction*, and *Hantzsch Dihydropyrimidine Synthesis*—have attracted more attention recently and have been commonly applied to the process of drug and agrochemicals discovery, because these reactions are highly atom economic and can efficiently produce a variety of molecular libraries of small molecular weight and structural diversity.[5] So far, more than 20 molecular scaffolds have been prepared from these MCRs.[5]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

As proposed by Asinger, this reaction contains two steps. The first step is an α-thiolation catalyzed by amine to form α-surfhydryl ketone, and the second step is an α-aminoalkylation

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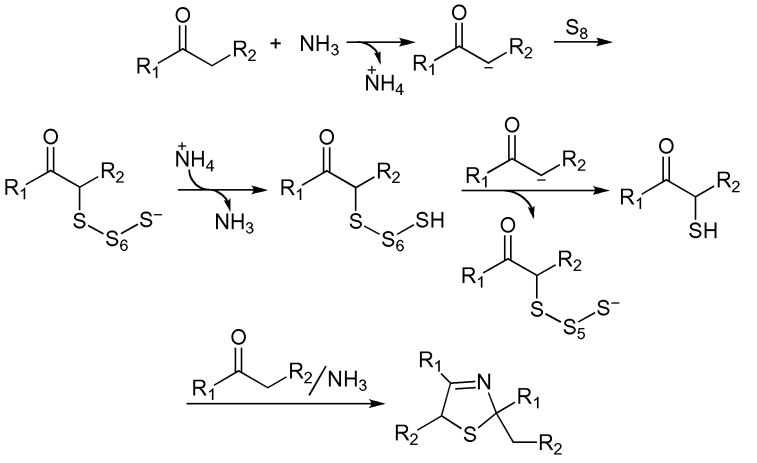
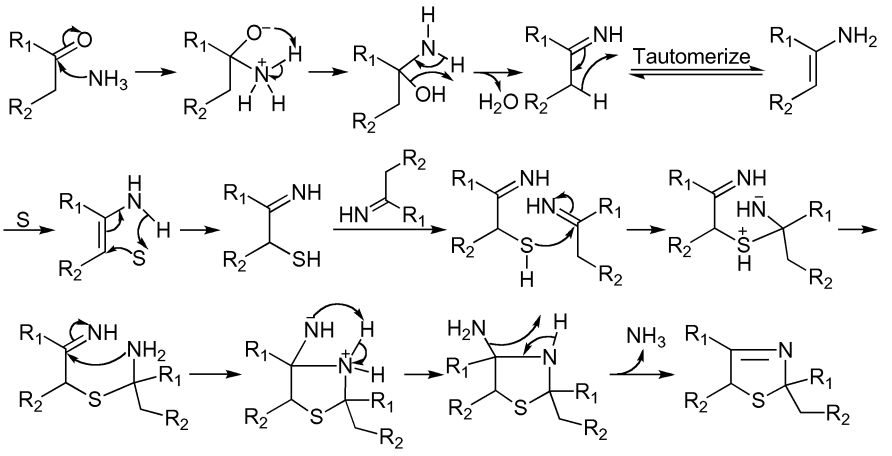
of an SH acid and subsequent stabilization via ring closure with elimination of water (similar to the *Mannich Condensation*). The details are illustrated here.[6]



At least two weaknesses exist in this mechanism: (a) NH_3 is not strong enough to abstract an α-proton from ketone and (b) no detail is given about the formation of final 3-thiazolines. Therefore, an alternative mechanism is proposed here, as shown.



D. MODIFICATION

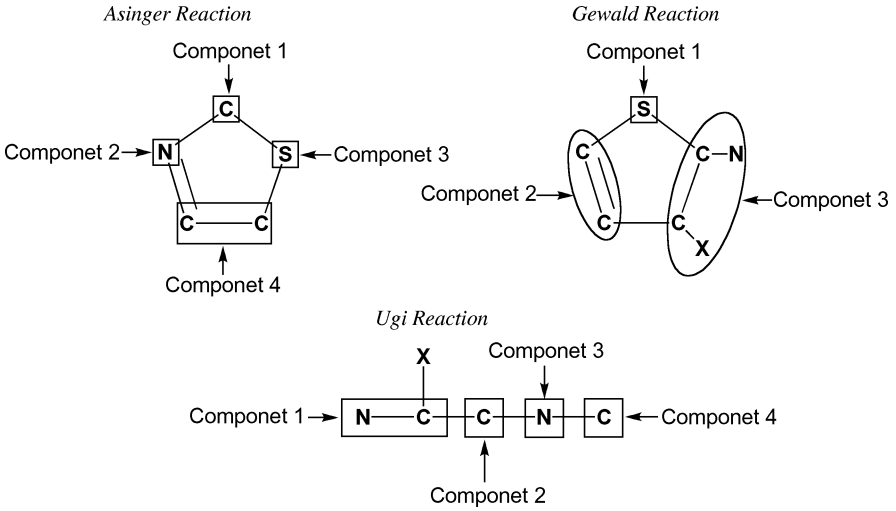
N/A

E. APPLICATIONS

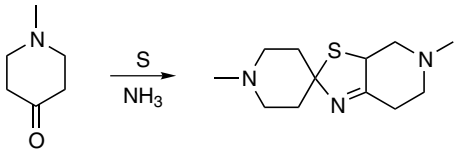
This reaction is useful in the preparation of 3-thiazoline derivatives.

F. RELATED REACTIONS

Being an MCR, the Asinger reaction shares similarities with other MCRs (e.g., Ugi, Gewald) in that more than one bond is formed in the final product. These reactions are shown here.[5]



G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

To a three-necked flask equipped with gas inlet and outlet were added a stir bar, 6.0 g sulfur, and 40.0 g 1-methyl-4-piperidone. The flask was cooled with ice, and under stirring ammonia gas was bubbled into the mixture. The temperature of the reaction was maintained between 40 and 50°C. The introduction of ammonia was continued until the last traces of sulfur disappeared (usually 2 h). The excess ammonia was removed by connecting the gas outlet to vacuum while stirring. The warm, viscous liquid was diluted with 200 mL 50% potassium carbonate solution, and the mixture was extracted with five 100-mL portions of ether. The ether solution was dried over potassium carbonate, filtered, and treated with hydrogen chloride. A yellow precipitate of 1,6′-dimethyl-2′,4′,5′,6′,7′,7a′-hexahydrospiro[piperidine-4,2′-thiazolo[5,4-c]-pyridine]dihydrochloride formed immediately, which was filtered, washed with ether, and dried under reduced pressue over $CaCl_2$ to afford 53.5 g of product, m.p. 200–205°C. An analytical sample was prepared by

recrystallization of this solid from a mixture of ethanol and isopropyl alcohol and melted at 240–241°C. The pure 1,6′-dimethyl- 2′,4′,5′,6′,7′,7a′-hexahydrospiro-[piperidine-4,2′-thiazolo[5,4-c]pyridine] was formed in quantitative yield from its dihydrochloride salt by neutralization with potassium carbonate solution. The base thus formed was purified by distillation under reduced pressure, and the fraction, b.p. 198–202°C at 16 mmHg was collected.

Other references related to the Asinger reaction are cited in the literature.[8]

H. REFERENCES

1. Asinger, F., *Angew. Chem.,* **1956**, *68*, 413.
2. (a) Schlemminger, I.; Janknecht, H.-H.; Maison, W.; Saak, W. and Martens, J., *Tetrahedron Lett.,* **2000**, *41*, 7289. (b) Martens, J. and Janknecht, H. H., *Sulfur Lett.,* **1990**, *11*, 263. (c) Lyle, R. E.; Munk, R. and Ladd, L., *J. Org. Chem.,* **1965**, *30*, 293.
3. (a) Asinger, F., *Ann*., **1964**, *674*, 103. (b) Asinger, F., *Ann*., **1964**, *674*, 134. (c) Asinger, F., *Ann*., **1964**, *674*, 156. (d) Asinger, F., *Ann*., **1964**, *674*, 179. (e) Asinger, F., *Ann*., **1959**, *627*, 195. (f) Asinger, F., *Ann*., **1958**, *619*, 145. (g) Asinger, F., *Ann*., **1958**, *619*, 169. (h) Thiel, M.; Asinger, F. and Schmiedel, K., *Ann*., **1958**, *611*, 121. (i) Asinger, F.; Thiel, M. and Pallas, E., *Ann*., **1957**, *602*, 37. (j) Asinger, F.; Thiel, M. and Esser, G., *Ann*., **1957**, *610*, 33. (k) Asinger, F., *Ann*., **1957**, *606*, 67. (l) Asinger, F., Thiel, M. and Kalzendorf, I., *Ann*., **1957**, *610*, 25. (m) Asinger, F., *Ann*., **1957**, *610*, 33. (n) Asinger, F., *Ann*., **1957**, *610*, 49.
4. (a) Asinger, F.; Offermanns, H.; Muller, P. and Andree, H., *Monatsh. Chem.,* **1968**, *99*, 2059. (b) Asinger, F. and Gentz, F., *Angew. Chem., Int. Ed. Engl.,* **1963**, *2*, 397. (c) Asinger, F.; Thiel, M. and Höringklee, W., *Ann*., **1957**, *610*, 1. (d) Thiel, M. and Asinger, F., *Ann*., **1957**, *610*, 17.
5. Dömling, A., *Curr. Opinion Chem. Biol.*, **2000**, *4*, 318.
6. Asinger, F. and Offermanns, H., *Angew. Chem. Int. Ed. Engl*., **1967**, *6*, 907.
7. Lyle, R. E.; Munk, R. and Ladd, L., *J. Org. Chem*. **1965**, *30*, 293.
8. (a) Ugi, I., *Pure & Appl. Chem.*, **2001**, *73*, 187. (b) Schlemminger, I.; Willecke, A.; Maison, W.; Koch, R.; Lützen, A. and Martens, J., *J. Chem. Soc., Perkin Trans. 1*, **2001**, 2804. (c) Galantay, E.; Engel, H.; Szabo, A. and Fried, J., *J. Org. Chem.,* **1964**, *29*, 3560. (d) Gaines, J. R. and Lidel, D. D., *J. Org. Chem.,* **1963**, *28*, 1032.

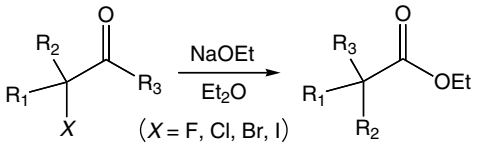
26

Aston-Greenburg Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

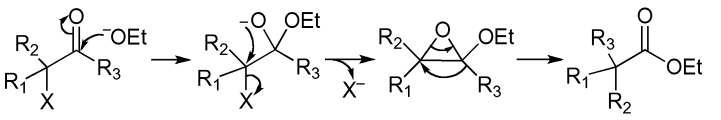
This reaction was first reported by Aston and Greenburg in 1940.[1] It is the transformation of α-haloketone into ester along with the migration of one of the alkyl (or aryl) moieties in this ketone to the α-position of another moiety when the α-haloketone is treated with alkali alkoxide (e.g., NaOEt, NaOMe). In many cases, this rearrangement is used to prepare the esters of tertiary α-carbon.

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

This reaction involves the following steps: the addition of an alkoxyl group to the carbonyl group, the formation of epoxide, and the migration of the alkyl group, as illustrated below.



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D. MODIFICATION

N/A

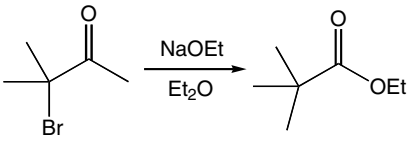
E. APPLICATIONS

N/A

F. RELATED REACTIONS

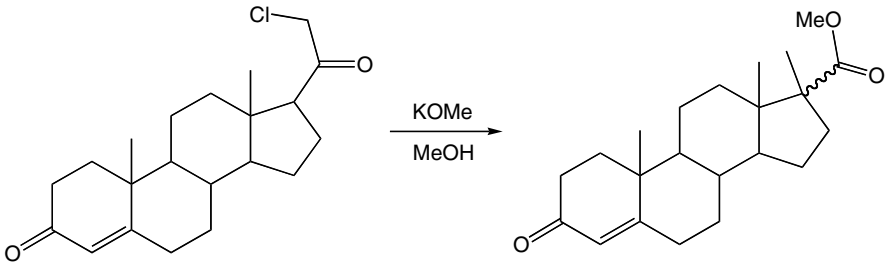
This reaction has a similar mechanism to the *Favorskii Rearrangement*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 1.

To a flask equipped with condenser were added 500 mL ether, 29.2 mL absolute ethanol (0.5 mol), and 11.5 g sodium (0.5 mol). This mixture was refluxed for 48 h to ensure the completion of reaction and then cooled in ice. After that, 82.5 g 3-bromo-3-methyl-2-butanone (0.5 mol) was added over a period of 2 h. The solution was refluxed 3 h, then water was added to dissolve the precipitated sodium bromide. The organic layer was separated and fractionated via distillation, and 39.8 g ethyl trimethylacetate was obtained, in a yield of 61.3%, b.p.116°C at 725 mmHg, n_D^{20} 1.3912, d_4^{20} 0.856g/cm^3.



Reference 2.

To a flask equipped with condenser, were added 220 mL absolute methanol and 2.1 g potassium. After the potassium disappeared, 9.615 g chloroprogesterone was added to the solution in portions. The mixture was refluxed for 2 h with exclusion of moisture. After cooling, the solution was poured into water, and the product was extracted with ether. The organic layers were combined and washed until neutral, and 9.687 g oil was

obtained after removal of the solvent. This mixture was purified using 250 g aluminum oxide with petroleum ether-benzene (4:1 to 1:1) as an eluent. This fraction after drying and recrystallization from acetone-hexane gave 2.945 g methyl Δ^4-3-keto-17α-methyletienate, m.p. 173–173.5°C. Another fraction from the column using benzene and benzene-ether as an eluent yielded 378 mg methyl Δ^4-3-keto-17-isoetienate after removal of the solvent and recrystallization, m.p. 155.5–156°C. The rest of the mass was a mixture of the two products.

Other references related to the Aston-Greenburg rearrangement are cited in the literature.[3]

H. REFERENCES

1. Aston, J. G. and Greenburg, R. B., *J. Am. Chem. Soc.*, **1940**, *62*, 2590.
2. Engel, C. R. and Just, G., *J. Am. Chem. Soc.*, **1954**, *76*, 4909.
3. (a) Engel, C. R., *J. Am. Chem. Soc.*, **1955**, *77*, 1064. (b) Heusser, H.; Engel, C. R.; Herzig, P. T. and Plattner, P. A., *Helv. Chim. Acta*, **1950**, *33*, 2229. (c) Plattner, P. A.; Heusser, H. and Herzig, P. T., *Helv. Chim. Acta,* **1949**, *32*, 270. (d) Plattner, P. A.; Heusser, H. and Boyce, S. F., *Helv. Chim. Acta*, **1948**, *31*, 603. (e) Marker, R. E. and Wagner, R. B., *J. Am. Chem. Soc.*, **1943**, *64*, 1273. (f) Marker, R. E. and Wagner, R. B., *J. Am. Chem. Soc.*, **1942**, *64*, 216.

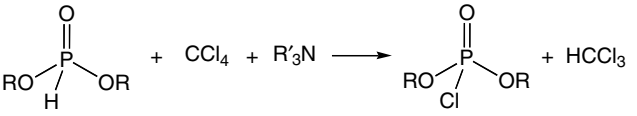
27

Atherton-Todd Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Atherton and Todd et al. in 1945.[1] It is a transformation of dialkylphosphite into dialkyl chlorophosphate in the presence of carbon tetrachloride and a base (usually tertiary amine, secondary amine, or primary amine). Therefore, it is generally known as the Atherton-Todd reaction.[2] In general, the formed dialkyl chlorophosphate is too reactive to be isolated, which further reacts with alcohol or amine to give phosphate or phosphoramidate. Only a few dialkyl chlorophosphates have been separated so far.[3]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The commonly known mechanism for the Atherton-Todd reaction is based primarily on the early kinetic investigations.[4] It is believed that the initial step is the deportonation of the dialkyl phosphonate $(RO)_2P(O)H$ by a base to give a dialkyl phosphite anion that undergoes the halophilic substitution with CCl_4, as illustrated here.

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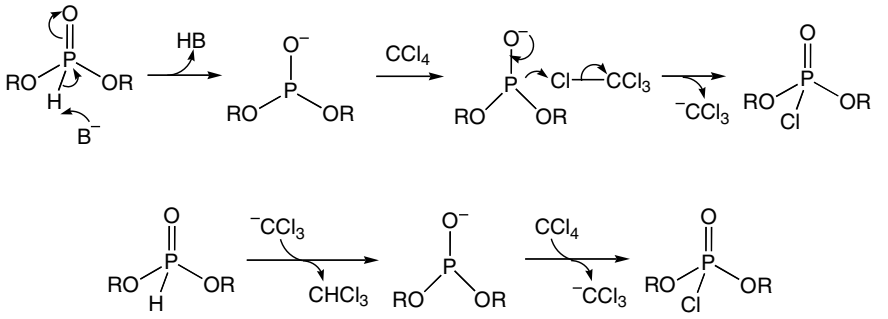
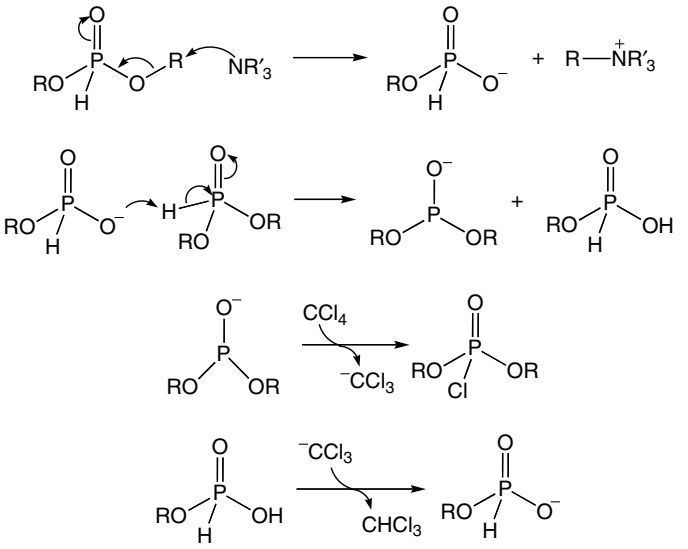


However, it has been established that, in the initial step, amines as a base are actually alkylated and not protonated at the nitrogen by dialkyl phosphonates.[5] Therefore, an alternative mechanism is proposed in agreement with both experimental and computational results.[21]



D. MODIFICATION

It is reported that the original process can be improved effectively by employing an aqueous base and a phase-transfer catalyst.[6] After this modification, many mixed trialkyl phosphates, dialkylphosphorylated amines, hydrazines, and hydroxylamines can be easily prepared.

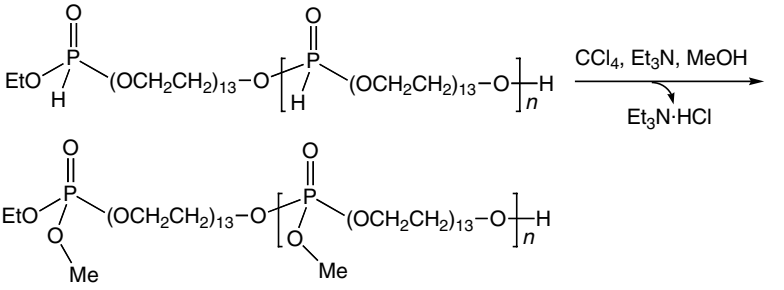
E. APPLICATIONS

This reaction has general applications in the preparation of trialkyl phosphates, dialkylphosphorylated amines hydrazines, and hydroxylamines.

F. RELATED REACTIONS

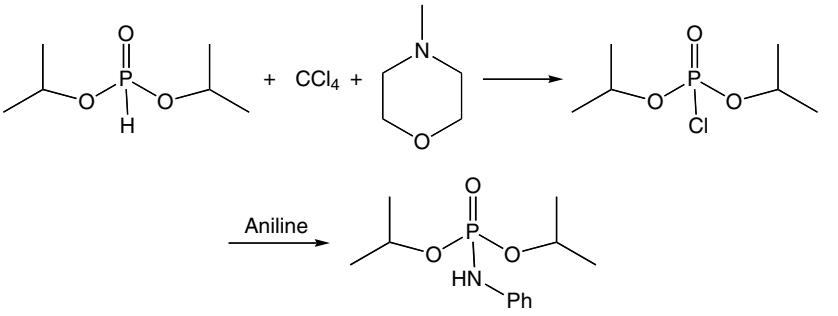
This reaction is related to the *Appel Chlorination*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

To a three-necked flask equipped with a magnetic stirrer, thermometer, reflux condenser, and a dropping funnel were added 9 mL dichloromethane, 22.5 mL carbon tetrachloride, 0.94 g triethylamine, and 0.72 mL methanol. Then 13.5 mL dichloromethane solution containing 2.3 g polymer (0.0036 mol of repeating units) was added dropwise at ambient temperature under continuous stirring. The reaction was allowed to proceed for 24 h. After filtration of the precipitated triethylamine hydrochloride, the filtrate was concentrated and the polymer product was precipitated by addition of diethyl ether. The product of poly(oxyethylene phosphate) was purified by dissolution in *N,N*-dimethylformamide (DMF) and reprecipitation in diethyl ether. The isolated product was dried at 30–40°C under reduced pressure (1 mmHg) to give 2.6 g of a polymer product, in a yield of 100%.



Reference 1.

To a 500 mL flask, were added 150 mL carbon tetrachloride and 83.0 g diisopropyl phosphite (0.5 mol). To this solution was added 50.5 g *N*-methylmorpholine (0.5 mol), no apparent reaction occurred until refluxing. After 3 h the solvent was removed in vaccum (distillate contained chloroform); the residue was stirred with 200 mL light petroleum; and

28.0 g of *N*-methylmorpholine hydrochloride (solid material) was obtained by filtration, washing with light petroleum, and drying. The ligroin solution was evaporated on a water bath, and the residue was distilled under reduced pressure. The main fraction (70.0 g) contained traces of solid and on filtration and redistillation afforded 58.0 g of colorless diisopropyl chlorophosphonate. When diisopropyl chlorophosphonate was treated with two equivalents of aniline, both aniline hydrochloride and diisopropylanilinophosphonate were obtained. The latter one has a m.p. of 121°C.

Other references related to the Atherton-Todd reaction are cited in the literature.[8]

H. REFERENCES

1. Atherton, F. R.; Openshaw, H. T. and Todd, A. R., *J. Chem. Soc.*, **1945**, 660.
2. (a) Chen, X. L.; Yu, Y. Z.; Qu, L. B.; Liao, X. C. and Zhao, Y. F., *Synth. Commun.,* **2004**, *34*, 493. (b) Karlova, E. K. and Erzhonov, K. B., *Izv. Nat. Akad. Nauk Resp. Kazakhstan, Ser. Khim.,* **2003**, 19. (c) Shishkin, V. E.; Yukhno, Yu. M.; Ufimtsev, S. V. and No, B. I., *Russ. J. Gen. Chem.,* **2002**, *72*, 1820. (d) Zhao, G.; Li, Y.-M.; Luo, S.-Z.; Han, B. and Zhao, Y.-F., *Gaodeng Xuexiao Huaxue Xuebao,* **2001**, *22*, 2034. (e) Ding, Y. X.; Liu, Z. F.; Zhou, H. Y. and Wang, W. H., *Phosphorus, Sulfur & Silicon and Related Elements,* **1998**, 134/135, 531. (f) Zhu, S. Z.; Zhang, J.; Xu, B. and Qin, C. Y., *Org. Prep. Proc. Int.,* **1997**, *29*, 352. (g) Cao, R.-Z.; Zeng, X.-Z.; Liu, Y.-N. and Liu, L.-Z., *Org. Prep. Proc. Int.,* **1996**, *28*, 490. (h) Liu, L. Z.; Li, G. W.; Zeng, X. Z.; Fu, L. B. and Cao, R. Z., *Heteroatom Chem.,* **1996**, *7*, 131. (i) Oussaid, B.; Soufiaoui, M. and Garrigues, B., *Synth. Commun.,* **1995**, *25*, 871. (j) Ding, Y. X. and Zhou, S. F., *Phosphorus, Sulfur & Silicon and Related Elements,* **1994**, *92*, 219. (k) Safta, M. and Csunderlik, C., *Revistade Chim. (Romania),* **1994**, *45*, 14. (l) Mazieres, M. R.; Houalla, D.; Monje, M. C. and Sanchez, M., *Phosphorus, Sulfur & Silicon and Related Elements,* **1993**, *83*, 157. (m) Georgiev, E. M.; Kaneti, J.; Troev, K. and Roundhill, D. M., *J. Am. Chem. Soc.,* **1993**, *115*, 10964. (n) No, B. I.; Yukhno, Yu. M.; Eremin, S. N.; Shishkin, V. E.; Mednikov, E. V. and Tikhomirov, P. V., *Zh. Obsh. Khim.,* **1992**, *62*, 228. (o) Georgiev, E.; Roundhill, D. M. and Troev, K., *Inorg. Chem.,* **1992**, *31*, 1965. (p) Houalla, D.; Bounja, Z. and Skouta, S., *Tetrahedron Lett.,* **1992**, *33*, 2817. (q) Abdullaev, N. B.; Galmyzhanov, S. A.; Biguzina, K. S.; Erzhanova, M. S. and Promonenkov, V. K., *Izv. Akad. Nauk Kazakhskoi SSR, Ser. Khim.,* **1991**, 71. (r) Troev, K.; Kirilov, E. M. G. and Roundhill, D. M., *Bull. Chem. Soc. Jpn.,* **1990**, *63*, 1284. (s) Gryaznov, S. M. and Azhaev, A. V., *Bioorg. Khim.,* **1989**, *15*, 994. (t) Gryaznov, S. M.; Sokolova, N. I. and Shabarova, Z. A., *Vest. Moskov. Univ., Ser. 2: Khim.,* **1986**, *27*, 421. (u) Lukanov, L.; Venkov, A. and Mollov, N., *Synth. Commun.,* **1986**, *16*, 767. (v) Lukanov, L.; Venkov, A. and Mollov, N., *Synthesis,* **1985**, 971. (w) Makarov, A. M.; Matevosyan, G. L. and Zavlin, P. M., *Zh. Obsh. Khim.,* **1985**, *55*, 937. (x) Kotovich, B. P., *Vestn. L'vov. Un-ta. Ser. Khim.,* **1983**, 71.
3. Gajda, T. and Zwierzak, A., *Synthesis*, **1976**, 243.
4. Steinberg, G. M., *J. Org. Chem.,* **1950**, 15,637.
5. Troev, K.; Roundhill, D. M., *Phosphorus and Sulfur*, **1988**, *73*, 189, (and references therein).
6. (a) Zwierzak, A., *Synthesis,* **1976**, 305. (b) Zwierzak, A. and Sulewska, A., *Synthesis,* **1976**, 835. (c) Zwierzak, A., *Synthesis,* **1975**, 507. (d) Zwierzak, A. and Brylikowska, J., *Synthesis,* **1975**, 712. (e) Zwierzak, A., *Synthesis,* **1975**, 270.
7. Georgieva, R.; Tsevi, R.; Kossev, K.; Kusheva, R.; Balgjiska, M.; Petrova, R.; Tenchova, V.; Gitsov, I. and Troev, K., *J. Med. Chem.,* **2002**, *45*, 5797.
8. (a) Bennett, S. N. L. and Hall, R. G., *J. Chem. Soc., Perkin Trans. I,* **1995**, 1145. (b) Zhu, S.-Z., *J. Chem. Soc., Perkin Trans. I,* **1994**, *15*, 2077. (c) Gryaznov, S. and Chen, J.-K.,

J. Am. Chem. Soc., **1994**, *116*, 3143. (d) Houalla, D.; Bounja, Z.; Skouta, S.; Rieael, L.; Lindemann, D., *Phosphorus, Sulfur Silicon,* **1993**, *77*, 216. (e) Gryaznov, S. M. and Letsinger, R. L., *Nucleic Acids Res.,* **1992**, *20*, 3403. (f) Brosse, J.-C.; Derouet, D.; Fontaine, L., and Chairatanathavorn, S., *Makromol. Chem.,* **1989**, *190*, 2339. (g) Kong, A. and Engel, R., *Bull. Chem. Soc. Jpn.,* **1985**, 58, 3671. (h) Nifantiev, E. E.; Blagowestenskij, A. M. and Sokorenko, A. M., Skljarskij, L. *S., Zh. Obsh. Khim.,* **1974**, *44*, 108. (i) Atherton, F. R. and Todd, A. R., *J. Chem. Soc.*, **1947**, 674.

28

Auwers-Skita Rule
(Conformational Rule)

A. GENERAL DESCRIPTION OF THE REACTION

Auwers-Skita rule,[1] also called conformational rule, is an empirical rule related to the physical properties of geometrical isomers and their configurations. This rule was initially proposed by von Auwers,[2] and Skita[3] separately and was restated by Allinger.[4] This rule was extensively applied during the assignment of the structures of isomers before the NMR techniques were commonly available. This rule, applying to alicyclic epimers not differing in dipole moment, states that the isomer of smaller molecular volume and therefore higher physical constants (e.g., density, index of refraction, and boiling point) has the higher heat content (enthalpy),[4e,5] however, molecules of higher enthalpy have a lower melting point.[6] Between the pair of *cis*- and *trans*- isomers, *cis*-compounds are higher in specific gravity and refractive index but smaller in molecular refraction.[2,3] Between stereoisomers, the *trans*-form of a pair of stereoisomers has the lower density, boiling point, and refractive index.[7] This rule can even be used to assign the conformers, in which the conformer of higher enthalpy has a lower molecular volume.[8] In cyclic stereoisomers, when the substituents are bound to configurationally identical ring systems, the isomer with the higher density and the higher refractive index is that which has the higher heat content.[9] Usually, the (higher) boiling point and (lower) molar refraction can be related in a similar manner. In other words, isomers having the greater number of axial substituents within a series will have the higher boiling point and refractive index and the greater density.[10] Although this rule has been proved successful with a variety of disubstituted cyclohexanes,[11] it is recognized that such an empirical rule is of limited reliability, especially in complex systems, such as the configuration for isopinocampheol,[12] 3-methylcyclohexanol,[13] thiabicyclo[3.3.0]-octanes,[14] and other 1,3-disubstituted cyclohexenes.[15]

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME

N/A

C. PROPOSED MECHANISMS

N/A

D. MODIFICATION

N/A

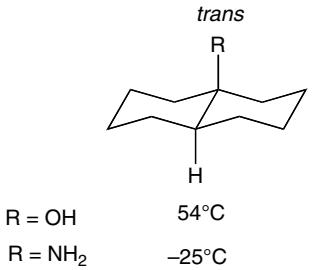
E. APPLICATIONS

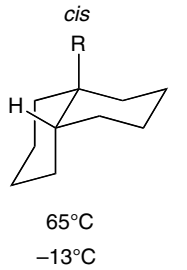
This rule was extensively used to assign the structures between stereoisomers before the era of NMR.

F. RELATED REACTIONS

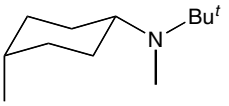
The van Arkel Rule (i.e., dipole rule) describes the relationship between physical properties and the dipole moment of geometrically isomeric olefins, i.e., the isomer of higher dipole moment has the higher boiling point, refractive index, and density.[4e,16]

G. CITED EXPERIMENTAL EXAMPLES

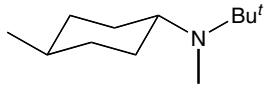




Reference 17.



Cis-*N*-methyl-*N*-neopentyl-4-methylcyclohexylamine, n_D^{20} = 1.4569, b.p. 90–91°C (4.5 mmHg).[5a]



trans-*N*-methyl-*N*-neopentyl-4-methylcyclohexylamine, n_D^{20} = 1.4527, b.p. 88–89°C (4.5 mmHg).[5a]

Other applications of the Auwers-Skita rule are also cited in Ref. 18 and Ref. 19 (Ref. 19 were located by keyword *Skita*).

H. REFERENCES

1. (a) Wiberg, K. B.; Hammer, J. D.; Castejon, H.; Bailey, W. F.; DeLeon, E. L. and Jarret, R. M., *J. Org. Chem.,* **1999**, *64*, 2085. (b) Stapp, P. R. and Weinberg, D. S., *J. Org. Chem.,* **1969**, *34*, 3592. (c) Feltkamp, H. and Thoma, K. D., *Ann.,* **1965**, *685*, 148. (d) Schuetz, R. D. and Caswell, L. R., *J. Org. Chem.,* **1962**, *27*, 486. (e) van Bekkum, H.; van Veen, A.; Verkade, P. E. and Wepster, B. M., *Rec. Trav. Chim. Pays-Bas,* **1961**, *80*, 1310. (f) Eastman, R. H. and Quinn, R. A., *J. Am. Chem. Soc.,* **1960**, *82*, 4249. (g) Kazanskii, B. A.; Liberman, A. L. and Tyun'kina, N. I., *Dokl. Akad. Nauk SSSR,* **1960**, *134*, 93. (h) Kazanskii, B. A.; Liberman, A. L.; Tyun'kina, N. I. and Kuznetsova, I. M., *Dokl. Akad. Nauk SSSR,* **1958**, *122*, 1025. (i) Liberman, A. L.; Lapshina, T. V. and Kazanskii, B. A., *Proc. Acad. Sci. USSR, Sect. Chem.,* **1956**, *107*, 141. (j) Liberman, A. L.; Lapshina, T. V. and Kazanskii, B. A., *Dokl. Akad. Nauk SSSR,* **1956**, *107*, 93.
2. (a) von Auwers, K., *Ann.,* **1920**, *420*, 91. (b) von Auwers, K., *Ann.,* **1920**, *420*, 84.
3. (a) Skita, A., *Ber.,* **1920**, *53*, 1792. (b) Skita, A. and Schneck, A., *Ber.*, **1922**, *55*, 144 . (c) Skita, A., *Ann*., **1922**, *427*, 275. (d) Skita, A., *Ber*., **1923**, *56*, 1014. (e) Skita, A., *Ber.,* **1923**, *56*, 2234. (f) Skita, A., *Ann*., **1923**, *431*, 1.
4. (a) Alllinger, N. L., *Experientia,* **1954**, *10*, 328. (b) Allinger, N. L., *J. Org. Chem.,* **1956**, *21*, 915. (c) Allinger, N. L., *J. Am. Chem. Soc.,* **1958**, *80,* 1953 (d) Allinger, N. L. and Curby, R. J., *J. Org. Chem.,* **1961**, *26,* 933. (e) Allinger, N. L., *J. Am. Chem.* Soc., **1957**, *79*, 3443.
5. (a) Goldberg, S. I. and Lam, F.-L., *J. Am. Chem. Soc.,* **1969**, *91*, 5113. (b) McGovern, T. P. and Beroza, M., *J. Org. Chem*., **1966**, *31*, 1472. (c) Eliel, E. L., *Stereochemistry of Carbon Compounds*, McGraw-Hill Book Co., New York, **1962**, p. 216. (d) Eliel, E. L. and Haber, R. G., *J. Org. Chem.,* **1958**, *23*, 2041.
6. Daly, J. W.; Green, F. C. and Eastman, R. H., *J. Am. Chem. Soc.*, **1958**, *80*, 6330.
7. Banthorpe, D. V. and Whittaker, D., *Chem. Rev.,* **1966**, *66*, 643.
8. (a) Martinez, A. G.; Vilar, E. T.; Fraile, A. G. and Martinez-Ruiz, P., *J. Phys. Chem. A,* **2002**, *106,* 4942. (b) Wiberg, K. B.; Hammer, J. D.; Castejon, H.; Bailey, W. F.; DeLeon, E. L. and Jarret, R. M., *J. Org. Chem.,* **1999**, *64,* 2085. (c) Eliel, E. L. and Wilen, S. H., *Stereochemistry of Organic Compounds,* Wiley, New York, **1994**, p 620.
9. Bottiki, A. T. and Vanetten, R. L., *J. Org. Chem*., **1965**, *30*, 2994.
10. Dauben, W. G. and Pitzer, K. S., Conformational Analysis, in *Steric Effects in Organic Chemistry*, ed. Newman, M. S., John Wiley & Sons, New York, **1956**, Chap. 1.
11. (a) Selin, T. G. and West, R., *J. Am. Chem. Soc*., **1962**, *84*, 1856. (b) Kelly, R. B., *Can. J. Chem.,* **1957**, *35*, 149.
12. (a) Hückel, W. and Nag, D. S., *Ann*., **1961**, *645*, 101. (b) Bose, K., *J. Org. Chem.,* **1955**, *20*, 1003. (c) Schmidt, H., *Ber.,* **1944**, *77,* 544 .
13. Noyce, D. S. and Denney, D. B., *J. Am. Chem. Soc.*, **1952**, *74*, 5912.
14. (a) Birch, S. F.; Dean, R. A.; Hunter, N. J. and Whitehead, E. V., *J. Org. Chem.,* **1955**, *20,* 1178. (b) Owen, L. N. and Peto, A. G., *Chem.* & *Ind. (London),* **1955**, 65.
15. (a) Eastmann, R. H. and Quinn, R. A., *J. Am. Chem. Soc.,* **1960**, *82*, 4249. (b) Noyce, D. S. and Nagel, R. I., *J. Am. Chem. Soc*., **1953**, *75*, 127. (c) Russini, F. and Pitrer, K., *Science*, **1947**, *106*, 117.
16. (a) van Arkel, A. E., *Rec. Trav. Chim*., **1934**, *53*, 246. (b) van Arkel, A. E., *Rec. Trav. Chim.,* **1932**, *51*, 1081.
17. Dauben, W. G.; Tweit, R. C. and MacLean, R. L., *J. Am. Chem. Soc*., **1955**, *77*, 48.
18. (a) Pines, H.; Kannan, S. V. and Stalick, W. M., *J. Org. Chem.,* **1971**, *36*, 2308. (b) Bottiki, A. T. and Vanatten, R. L., *J. Org. Chem.,* **1965**, *30*, 2994. (c) Searles, S.; Hays, H. and Lutz, E. F., *J. Org. Chem.,* **1962**, *27*, 2828. (d) Schuetz, R. D. and Caswell, L. R., *J. Org. Chem.,*

1962, *27*, 486. (e) Van Tamelen, E. E. and Timmons, R. J., *J. Am. Chem. Soc.,* **1962**, *84*, 1067. (f) Stiles, A. R.; Reilly, C. A.; Pollard, G. R.; Tieman, C. H.; Ward, L. F.; Phillips, D. D.; Soloway, S. B. and Whetstone, R. R., *J. Org. Chem*., **1961**, *26*, 3960. (g) Neureiter, N. P. and Bordwell, F. G., *J. Am. Chem. Soc.,* **1959**, *81*, 578. (h) Birch, S. F.; Dean, R. A. and Whitehead, E. V., *J. Org. Chem.,* **1958**, *23*, 783. (i) Ramirez, F. and Sargent, J., *J. Am. Chem. Soc.*, **1955**, *77*, 6297. (j) Haggis, G. A. and Owen, L. N., *J. Chem. Soc.,* **1953**, 408. (k) Barton, D. H., *J. Chem. Soc.,* **1953**, 1027. (l) Corey, E. J., *J. Am. Chem. Soc.*, **1952**, *76*, 2301. (m) Serijan, K. T.; Wise, P. H. and Gibbons, L. C., *J. Am. Chem. Soc.,* **1949**, *71*, 2265. (n) Owen, L. N. and Robins, P. A., *J. Chem. Soc.,* **1949**, 320. (o) Chiurdoglu, G., *Bull. Soc*. *Chim. Belg.,* **1944**, *68,* 45. (p) Ellinghoe, E. and Fuson, R. C., *J. Am. Chem.* Soc., **1934**, *66,* 1774. (q) von Braun, J. and Anton, E.*, Ber.*, **1927**, *60*, 2438. (r) Vogel, A. I., *J. Chem. Soc.,* **1922**, 1985.

19. (a) Kut, O. M.; Dätwyler, U. R. and Gut, G., *Ind. Eng. Chem. Res.,* **1988**, *27*, 219. (b) Hückel, W.; Mayer, M.; Jordan, E. and Seeger, W., *Ann*., **1958**, *616*, 46. (c) Augustine, R. L., *J. Org. Chem.,* **1958**, *23*, 1853. (d) Siegel, S., *J. Am. Chem. Soc.,* **1953**, *75*, 1317. (e) Smith, H. A. and Pennekamp, E. F. H., *J. Am. Chem. Soc.,* **1945**, *67*, 279. (f) Campbell, K. N. and Campbell, B. K., *Chem. Rev.,* **1942**, *31*, 77. (g) Linstead, R. P.; Doering, W. E.; Davis, S. B.; Levine, P. and Whetstone, R. R., *J. Am. Chem. Soc.,* **1942**, *64*, 1985. (h) Skita, A. and Rossler, R., *Ber.,* **1939**, *72*, 265. (i) Skita, A. and Rossler, R., *Ber.,* **1939**, *72*, 461.

29

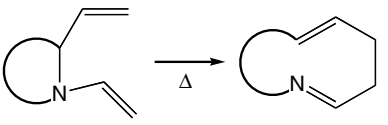
Aza-Claisen Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

Similar to normal *Claisen Rearrangement*, the *aza*-Claisen rearrangement[1] involves the cleavage of one bond and the formation of a new bond; however, in this reaction, one allyl carbon atom is displaced by a nitrogen atom and the carbon-nitrogen bond is the bond to break. In general, the nitrogen atom in *aza*-Claisen rearrangement is either in a heterocycle or a quaternary amine (ammonium salt), and the extension of heterocycle ring or cleavage of ammonium salt is probably the driving force for this reaction. Although one of the earliest examples of the *aza*-Claisen rearrangement—the reaction between *N*-methylpyrrole and dimethyl acetylenedicarboxylate (DMAD)—was reported by Alder in 1931,[2] this reaction is currently receiving renewed attention.[3–14]

B. GENERAL REACTION SCHEME

This reaction is represented by a general nitrogen-containing heterocycle, as illustrated here.



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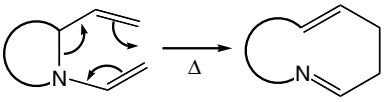
C. PROPOSED MECHANISMS

This rearrangement will be similar to a regular [3,3]-sigmatropic rearrangement.



D. MODIFICATION

N/A

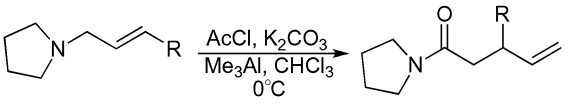
E. APPLICATIONS

This reaction has been used to prepare a variety types of nitrogen-containing compounds.[3−14]

F. RELATED REACTIONS

Conceptually, this rearrangement is related to the *Bellus-Claisen Rearrangement*, in terms of ring expansion.[8b,14g,14i] This reaction is also related to the regular *Claisen Rearrangement* and *Cope Rearrangement*.

G. CITED EXPERIMENTAL EXAMPLES

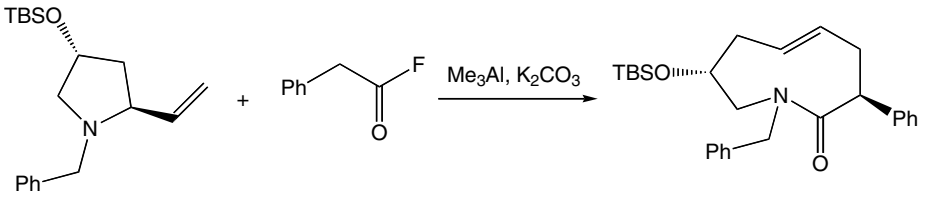


Reference 1ff.

Standard Procedure for the Zwitterionic *aza*-Claisen Rearrangement

To 35 mL dry $CHCl_3$ was added 1.6 g dry K_2CO_3 (11.6 mmol) under argon. The suspension was cooled to 0°C. *N*-allylpyrrolidine (5 mmol) and 6 mmol of acetyl chloride were added subsequently by means of a syringe. After about 30 min of stirring at 0°C, 0.25 mL 2 M Me_3Al in toluene (0.50 mmol) was added via syringe. The resulting mixture was also stirred at 0°C. After 24 h, a second volume of Me_3Al was injected. After 2–3 days, the reaction was stopped by quenching dropwise with saturated aqueous $NaHCO_3$ (5–10 mL) at 0°C until the Al_2O_3/K_2CO_3 precipitated. Then the organic layer was decanted, the solid residue was extracted with CH_2Cl_2 (5 × 20 mL), and the combined organic layers were dried over $MgSO_4$. The solvent was removed, and the crude mixture of diastereomeric amides and von Braun type products was purified by column chromatography. If necessary,

diastereomers were separated via HPLC or column chromatography on silica gel. If the crude product contained more than 10% of allylic amine (occurred in the majority of the experiments), the mixture was subjected to these reaction conditions for a second cycle.



Reference 4a.

To a small flask were added 70 mg dry K_2CO_3(0.5 mmol) and 15 mL CH_2Cl_2 under argon. The mixture was cooled to 0°C, then 320 mg of *N*-allylpyrrolidine (1 mmol) and 3–6 mmol of acid fluoride were added subsequently via a syringe. After about 15 min of stirring at 0°C, 0.75–1.5 mL Me_3Al in *n*-heptane (1.5–3 mmol) was added via syringe, and CH_4 evolved. The mixture was allowed to warm to room temperature, and the reaction was completed within hours (groups other than phenyl may take up to 2 days). In some cases, the addition of a second amount of acid fluoride and Me_3Al was necessary to achieve a complete conversion of the reactant. After the reaction, the mixture was diluted with Et_2O and filtrated through a short silica gel column to remove the polar impurities. The residual organic layer was washed with saturated $NaHCO_3$ solution and dried over $MgSO_4$. When solvent was removed below 20°C, (*p*S)*E*-3*S*,8*R*-1-benzyl-8-(*tert*-butyldimethylsilyloxy)-3-phenyl-2,3,4,7,8,9-hexahydro-1*H*-azonin-2-one was yielded. (*Note*: Heating to 40 – 60°C led to a fast epimerization to give the *p*R-lactams).

Other references related to the *aza*-Claisen rearrangement are cited in the literature.[15]

H. REFERENCES

1. (a) Swift, M. D. and Sutherland, A., *Tetrahedron Lett.*, **2007**, *48*, 3771. (b) Jamieson, A. G. and Sutherland, A., *Org. Lett.*, **2007**, *9*, 1609. (c) Jautze, S.; Seiler, P. and Peters, R., *Angew. Chem. Int. Ed.*, **2007**, *46*, 1260. (d) Jamieson, A. G. and Sutherland, A., *Tetrahedron*, **2007**, *63*, 2123. (e) Yasui, H.; Yorimitsu, H. and Oshima, K., *Chem. Lett.*, **2007**, *36*, 32. (f) Weiss, M. E.; Fischer, D. F.; Xin, Z. Q.; Jautze, S.; Schweizer, W. B. and Peters, R., *Angew. Chem. Int. Ed.*, **2006**, *45*, 5694. (g) Jamieson, A. G. and Sutherland, A., *Org. Biomol. Chem.*, **2006**, *4*, 2932. (h) Tenza, K.; Northen, J. S.; O'Hagan, D. and Slawin, A. M. Z., *Beilstein J. Org. Chem.*, **2005**, *1*, 13. (i) Swift, M. D. and Sutherland, A., *Org. Biomol. Chem.,* **2006**, *4*, 3889. (j) Jamieson, A. G. and Sutherland, A., *Org. Biomol. Chem.,* **2006**, 4, 2932. (k) Fanning, K. N.; Jamieson, A. G. and Sutherland, A., *Org. Biomol. Chem.,* **2005**, *3*, 3749. (l) Kim, S. C.; Gowrisankar, S. and Kim, J. N., *Bull. Korean Chem. Soc.,* **2005**, *26*, 1001. (m) Nubbemeyer, U., *Top. Curr. Chem.*, **2005**, *224*, 149. (n) Moyano, A.; Rosol, M.; Moreno, R. M.; Lopez, C. and Maestro, M. A., *Angew. Chem. Int. Ed.*, **2005**, *44*, 1865. (o) Jamieson, A. G. and Sutherland, A., *Org. Biomol. Chem.*, **2005**, *3*, 735. (p) Bremner, J. B. and Perkins, D. F., *Tetrahedron*, **2005**, *61*, 2659. (q) Yoon, Y.-J.; Chun, M.-H.; Joo, J.-E.; Kim, Y.-H.; Oh, C.-Y.; Lee, K.-Y.; Lee, Y.-S. and Ham, W.-H., *Arch. Pharm. Res.*, **2004**, *27*, 136. (r) Roe, J. M.; Webster, R.A. B. and Ganesan, A., *Org. Lett.*, **2003**, *5*, 2825. (s) Honda, K.; Yasui, H. and Inoue, S., *Synlett*, **2003**, 2380. (t) Davies, S. G.; Garner, A. C.; Nicholson, R. L.; Osborne, J.; Savory, E. D. and Smith, A. D., *Chem. Commun.*, **2003**, 2134. (u) Kang,

J.; Kim, T. H.; Yew, K. H. and Lee, W. K., *Tetrahedron: Asymmetry*, **2003**, *14*, 415. (v) Kang, J.; Yew, K. H.; Kim, T. H. and Choi, D. H., *Tetrahedron Lett.*, **2002**, *43*, 9509. (w) Majumdar, K. C. and Bhattacharyya, T., *J. Indian Chem. Soc.*, **2002**, *79*, 112. (x) Majumdar, K. C. and Samanta, S. K., *Synthesis*, **2002**, 121. (y) Majumdar, K. C. and Samanta, S. K., *Tetrahedron*, **2001**, *57*, 4955. (z) Jiang, Y. T.; Longmire, J. M. and Zhang, X. M., *Tetrahedron Lett.*, **1999**, *40*, 1449. (aa) Laabs, S.; Scherrmann, A.; Sudau, A.; Diederich, M.; Kierig, C. and Nubbemeyer, U., *Synlett*, **1999**, 25. (bb) Uozumi, Y.; Kato, K. and Hayashi, T., *Tetrahedron: Asymmetry,* **1998**, *9*, 1065. (cc) Shabany, H. and Spilling, C. D., *Tetrahedron Lett.*, **1998**, *39*, 1465. (dd) Ammenn, J.; Altmann, K. H. and Bellus, D., *Helv. Chim. Acta*, **1997**, *80*, 1589. (ee) Diederich, M. and Nubbemeyer, U., *Chem. Eur. J.*, **1996**, *2*, 894. (ff) Nubbemeyer, U., *J. Org. Chem.*, **1996**, *61*, 3677. (gg) Suh, Y.-G.; Lee, J.-Y.; Kim, S.-A. and Jung, K.-K., *Synth. Commun.*, **1996**, *26*, 1675. (hh) Estieu, K.; Ollivier, J. and Salaun, J., *Tetrahedron Lett.*, **1995**, *36*, 2974. (ii) Ito, S. and Tsunoda, T., *Pure & Appl. Chem.*, **1994**, *66*, 2071. (jj) Gilbert, J. C. and Cousins, K. R., *Tetrahedron*, **1994**, *50*, 10671. (kk) Tsunoda, T.; Tatsuki, S.; Kataoka, K. and Ito, S., *Chem. Lett.*, **1994**, 543. (ll) Walters, M. A. and Hoem, A. B., *J. Org. Chem.*, **1994**, *59*, 2645. (mm) Vedejs, E. and Gingras, M., *J. Am. Chem. Soc.*, **1994**, *116*, 579. (nn) Gonda, J.; Helland, A. C.; Ernst, B. and Bellus, D., *Synthesis*, **1993**, 729. (oo) Tsunoda, T.; Tatsuki, S.; Shiraishi, Y.; Akasaka, M. and Ito, S., *Tetrahedron Lett.,* **1993**, *34*, 3297. (pp) Tsunoda, T.; Sakai, M.; Sasaki, O.; Sako, Y.; Hondo, Y. and Ito, S., *Tetrahedron Lett.*, **1992**, *33*, 1651. (qq) Molina, P.; Alajarin, M. and Lopez-Leonardo, C., *Tetrahedron Lett.*, **1991**, *32*, 4041. (rr) Tsunoda, T.; Sasaki, O. and Ito, S., *Tetrahedron Lett.,* **1990**, *31*, 727. (ss) Vogler, B.; Bayer, R.; Meller, M.; Kraus, W. and Schell, F. M., *J. Org. Chem.,* **1989**, *54*, 4165. (tt) Kurth, M. J. and Brown, E. G., *Synthesis*, **1988**, 362. (uu) Kurth, M. J. and Soares, C. J., *Tetrahedron Lett.*, **1987**, *28*, 1031. (vv) Kurth, M. J. and Decker, O. H. W., *J. Org. Chem.*, **1986**, *51*, 1377. (ww) Danishefsky, S. J. and Phillips, G. B., *Tetrahedron Lett.,* **1984**, *25*, 3159. (xx) Gilbert, J. C. and Senaratne, K. P. A., *Tetrahedron Lett.*, **1984**, *25*, 2303. (yy) Padwa, A. and Cohen, L. A., *J. Org. Chem.*, **1984**, *49*, 399. (zz) Kurth, M. J. and Decker, O. H. W., *Tetrahedron Lett.*, **1983**, *24*, 4535. (aaa) Padwa, A. and Cohen, L. A., *Tetrahedron Lett.,* **1982**, *23*, 915. (bbb) Laurent, A.; Mison, P.; Nafti, A. and Pellissier, N., *Tetrahedron Lett.*, **1982**, *23*, 655. (ccc) Hill, R. K. and Khatri, H. N., *Tetrahedron Lett.*, **1978**, 4337. (ddd) Mariano, P. S.; Dunaway-Mariano, D.; Huesmann, P. L. and Beamer, R. L., *Tetrahedron Lett.*, **1977**, 4299. (eee) McCurry, P. M. and Singh, R. K., *Tetrahedron Lett.*, **1973**, 3325.

2. Diels, O. and Alder, K., *Ann.*, **1931**, *490,* 267.
3. (a) Walters, M. A., *J. Am. Chem. Soc.*, **1994**, *116,* 11618. (b) Walters, M. A.; McDonough, C. S.; Brown, P. S. Jr. and Hoem, A. B., *Tetrahedron Lett.*, **1991**, *32*, 179.
4. (a) Sudau, A.; Muünch, W.; Nubbemeyer, U. and Bats, J. W., *J. Org. Chem.*, **2000,** *65,* 1710. (b) Sudau, A. and Nubbemeyer, U., *Angew. Chem*., **1998**, *110*, 1178. (c) Diederich, M. and Nubbemeyer, U., *Angew. Chem*., **1995**, *107*, 1095. (d) Nubbemeyer, U., *Synthesis*, **1993**, 1120.
5. (a) Kurth, M. J.; Decker, O. H. W.; Hope, H. and Yanuck, M. D., *J. Am. Chem. Soc.*, **1985**, *107*, 443. (b) Kurth, M. J. and Decker, O. H. W., *J. Org. Chem*., **1985**, *50*, 5769.
6. (a) Molina, P.; Alajarin, M.; Lopez-Leonardo, C. and Alcantara, J., *Tetrahedron*, **1993**, *49*, 5153. (b) Molina, P.; AlajarIn, M. and Vidal, A., *J. Org. Chem.*, **1990**, *55*, 6140.
7. (a) Lai, G. and Anderson, W. K., *Tetrahedron*, **2000**, *56*, 2583. (b) Anderson, W. K. and Lai, G., *Synthesis*, **1995**, 1287. (c) Lai, G. and Anderson, W. K., *Tetrahedron Lett.*, **1993**, *34*, 6849. (d) Beholz, L. G. and Stille, J. R., *J. Org. Chem*., **1993**, *58*, 5095.
8. (a) Cid, M. M. and Pombo-Villar, E., *Helv. Chim. Acta*, **1993**, *76*, 1591. (b) Cid, M. M.; Eggnauer, U.; Weber, H. P. and Pombo-Villar, E., *Tetrahedron Lett*., **1991**, *32*, 7233.
9. (a) Baxter, E. W.; Labaree, D.; Ammon, H. L. and Mariano, P. S., *J. Am. Chem. So*c., **1990**, *112*, 7682. (b) Baxter, E. W.; Labaree, D.; Chao, S. and Mariano, P. S., *J. Org. Chem*., **1989**, *54*, 2839. (c) Chao, S.; Kunng, F.-A.; Gu, J.-M.; Ammon, H. L. and Mariano, P. S., *J. Org. Chem*., **1984**, *49*, 2708. (d) Chen, Y.; Huesmann, P. L. and Mariano, P. S., *Tetrahedron Lett.*, **1983**, *24,* 1021.

(e) Kunng, F.-A.; Gu, J.-M.; Chao, S.; Chen, Y. and Mariano, P. S., *J. Org. Chem*., **1983**, *48*, 4262. (f) Mariano, P. S.; Dunaway-Mariano, D. and Huesmann, P. L., *J. Org. Chem.*, **1979**, *44*, 124.

10. (a) Hill, R. K. and Newkome, G. R., *Tetrahedron Lett.*, **1968**, *9*, 5059. (b) Hill, R. K. and Gilman, N. W., *Tetrahedron Lett.*, **1967**, *8*, 1421.
11. (a) Houdewind, P. and Pandit, U. K., *Tetrahedron Lett.*, **1974**, *15*, 2359. (b) Houdewind, P.; Pandit, U. K.; Bose, A. K.; Brambilla, R. J. and Trainor, G. L., *Heterocycles*, **1973**, *1, 53.*
12. (a) Cook, G. R.; Barta, N. S. and Stille, J. R., *J. Org. Chem.*, **1992**, *57*, 461. (b) Cook, G. R. and Stille, J. R., *J. Org. Chem.*, **1991**, *56*, 5578.
13. (a) Irie, K.; Isaka, T.; Iwata, Y.; Yanai, Y.; Nakamura, Y.; Koizumi, F.; Ohigashi, H.; Wender, P. A.; Satomi, Y. and Nishino, H., *J. Am. Chem. Soc.*, **1996**, *118,* 10733. (b) Irie, K.; Koizumi, F.; Iwata, Y.; Ishii, T.; Yanai, Y.; Nakamura, Y.; Ohigashi, H. and Wender, P. A., *Bioorg. Med. Chem. Lett.,* **1995**, *5*, 453. (c) Irie, K.; Kajiyama, S.; Funaki, A.; Koshimizu, K.; Hayashi, H. and Arai, M., *Tetrahedron*, **1990**, *46*, 2773.
14. (a) Cooper, M. A.; Lucas, M. A.; Taylor, J. M.; Ward, A. D. and Williamson, N. M., *Synthesis*, **2001**, 621. (b) McComsey, D. F. and Maryanoff, B. E., *J. Org. Chem.*, **2000,** *65,* 4938. (c) Kazmaier, U., *Liebigs Ann./Recueil,* **1997**, 285. (d) Enders, D.; Knopp, M. and Schiffers, R., *Tetrahedron: Asymmetry*, **1996**,*7*, 1847. (e) Bamatraf, M. M. M.; Vernon, J. M. and Wilson, G. D., *J. Chem. Soc., Perkin Trans. I,* **1995**, 1647. (f) Pereira, S. and Srebnik, M., *Aldrichimica Acta*, **1993**, *26*, 17. (g) Edstrom, E. D., *J. Am. Chem. So*c., **1991**, *113*, 6690. (h) Barmettler, P. and Hansen, H.-J., *Helv. Chim. Acta*, **1990**, *73*, 1515. (i) Roberts, S. M.; Smith, C. and Thomas, R. J., *J. Chem. Soc., Perkin Trans. I,* **1990**, 1493. (j) Ito, S. and Tsunoda, T., *Pure & Appl. Chem.*, **1990**, *62*, 1405. (k) Vogler, B.; Bayer, R.; Meller, M.; Kraus, W. and Shell, F. M., *J. Org. Chem.,* **1989,** *54,* 4165. (l) Ishida, M.; Muramaru, H. and Kato, S., *Synthesis*, **1989**, 562. (m) Schwan, A. L. and Warkentin, J., *Can. J. Chem*., **1988**, *66*, 1686. (n) Murahashi, I.; Makabe, Y. and Kunita, K., *J. Org. Chem.*, **1988**, *53,* 4489. (o) Kandeel, K. A. and Vernon, J. M., *J. Chem. Soc., Perkin Trans. I*, **1987**, 2023. (p) Grandberg, I. I., *Russ. Chem. Rev.*, **1987**, *56*, 477. (q) Hassner, A. and Wiegand, N., *J. Org. Chem.*, **1986**, *51*, 3652. (r) Hayakawa, K.; Fujii, I. and Kanematsu, K., *J. Org. Chem.*, **1983**, *48*, 166. (s) Hoogsteen, K. and Hirshfield, J., *J. Org. Chem.*, **1983**, *48*, 173. (t) Hoogsteen, K. and Hirshfield, J., *J. Org*. *Chem.*, **1982**, *47,* 752. (u) Babayan, A. T., *Zh. Org. Khim.*, **1982**, *28*, 2442. (v) Hayakawa, K.; Motohiro, S.; Fujii, I. and Kanematsu, K., *J. Am. Chem. Soc.*, **1981**, *103*, 4605. (w) Laird, T.; Ollis, W. D. and Sutherland, I. O., *J. Chem. Soc., Perkin Trans. I*, **1980**, 1477. (x) Secrist, J. A. and Winter, W. J., Jr., *J. Am. Chem. Soc.*, **1978**, *100,* 2554. (y) Katayama, H., *Chem. Pharm. Bull.*, **1978**, *26*, 2027. (z) Jolidon, S. and Hansen, H.-J., *Helv. Chim. Acta*, **1977**, 60, 978. (aa) Ireland, R. E. and Willard, A. K., *J. Org. Chem.*, **1974**, *39,* 421. (bb) Schmid, M.; Hansen, H.-J. and Schmid, H., *Helv. Chim. Acta*, **1973**, *56*, 105. (cc) Taka-matsu, N.; Inoue, S. and Kishi, Y., *Tetrahedron Lett.,* **1971**, 4661. (dd) Opitz, G., *Ann.*, **1961**, *650*, 122. (ee) Brannock, K. C. and Burpitt, R. D., *J. Org. Chem.*, **1961**, *26*, 3576.
15. (a) Zheng, J.-F.; Jin, L.-R. and Huang, P.-Q., *Org. Lett*., **2004**, *6*, 1139. (b) Kuhn, C.; Skaltsounis, L.; Monneret, C. and Florent, J.-C., *Eur. J. Org. Chem.*, **2003**, 2585. (c) Lindström, U. M. and Somfai, P., *J. Am. Chem. Soc.*, **1997,** *119,* 8385. (d) Walters, M. A.; Hoem, A. B.; Arcand, H. R.; Hegeman, A. D. and McDonough, C. S., *Tetrahedron Lett.*, **1993**, *34*, 1453.

30

Baddeley Isomerization

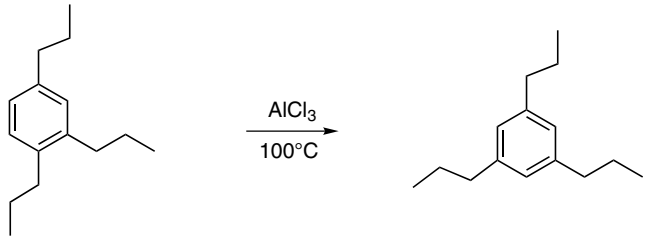
A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Baddeley in 1930s.[1] It is the migration of alkyl groups in polyalkylbenzenes or polynuclear aromatic compounds in the presence of anhydrous aluminum chloride or the mixture of protonic acid and Lewis acid. In one of Baddeley's experiments, when 1,3,4-tri-*n*-propylbenzene was warmed with $AlCl_3$ at 100°C, the 1,3,5-tri-*n*-propyl was formed, along with the lower and higher alkylated benzenes.[1b] After extensive studies, it was found that the amount of α-isomer can be reduced by the addition to the reaction mixture of a variety of substances (e.g., nitrobenzene and excess acid chloride) that complex strongly with aluminum chloride.[2,3] Likewise, less α-isomer has been observed when this reaction is carried out in nitrobenzene. In addition, isomerization of hindered aromatic ketones occurs if the ketones are melted with an excess amount of aluminum chloride and sodium chloride.[4]

B. GENERAL REACTION SCHEME

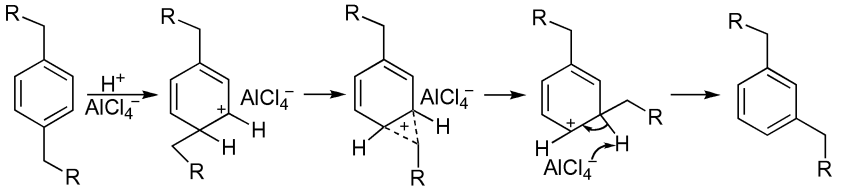
The reaction is simply illustrated by the isomerization of 1,2,4-tri-*n*-propylbenzene to 1,3,5-tri-*n*-propylbenzene in Baddeley's initial work.

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang



C. PROPOSED MECHANISMS

It is proposed that in the presence of a protonic acid and a Lewis acid, a direct [1,2] alkyl shift is involved in this isomerization, which is displayed here.[5]



However, in the absence of protonic acid, the Baddeley isomerization may involves the reaction of $AlCl_3$ with two aromatic molecules.[6]

D. MODIFICATION

N/A

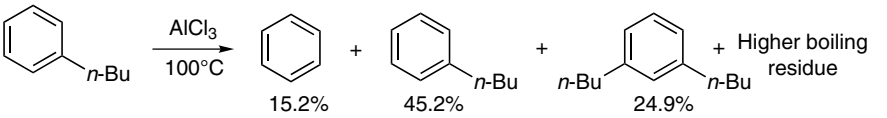
E. APPLICATIONS

N/A

F. RELATED REACTIONS

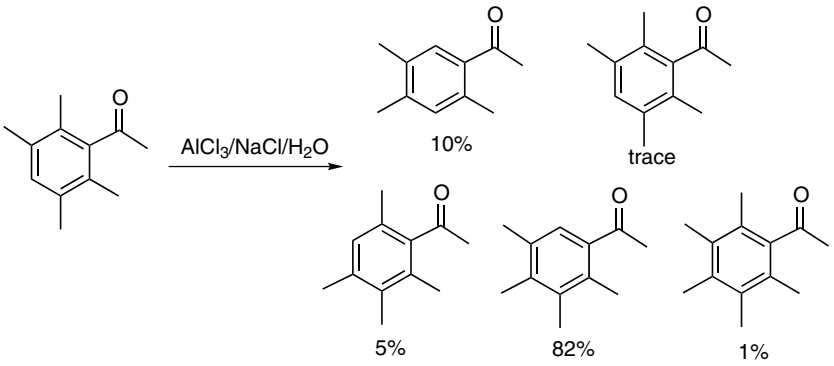
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 6a.

To a flask equipped with a condenser were added 202.5 g *n*-butylbenzene and 40.0 g anhydrous aluminum chloride (sublimed). The mixture was stirred for 3 h at 100°C to form two layers, the lower being of relatively small volume and dark in color. After the reaction, the mixture was poured over cracked ice; and the organic layer was separated, washed with water, and dried over anhydrous calcium chloride. A total of 192.8 g hydrocarbon was recovered at this step. Careful fractionation of this hydrocarbon gave 15.2% benzene, 45.2% *n*-butylbenzene, b.p. 98.5–97.5°C at 50 mmHg (99.4 mol % *n*-butylbenzene and 0.6 mol % *s*-butylbenzene by mass spectrometer analysis), 27.7% dibutylbenzene, b.p. 160–162°C at 50 mmHg (at least 90 mol % *m*-di-*n*-butylbenzene), and 11.9% of a higher boiling residue.



Reference 7.

To a flask equipped with a refluxing condenser were added 7.5 g 2,3,5,6-tetramethylacetophenone (0.043 mol), 15 g anhydrous $AlCl_3$ (0.11 mol), 90 mg H_2O (0.005 mol), and 1 g NaCl (0.02 mol). The mixture was stirred at 100°C for 2 h. The reaction mixture was cooled, poured onto ice, and neutralized with saturated $NaHCO_3$ solution. The organic material was extracted with a total of 30 mL C_6H_6, washed with H_2O, saturated $NaHCO_3$ solution, and H_2O and dried over Na_2SO_4. Analysis of the mixture by GC (150 ft. MBMS column at 160°C, helium pressure 30 psi) showed the product distribution as 2,4,5-trimethylacetophenone (10%), 2,3,4,6-tetramethylacetophenone (starting material, trace), 2,3,4,6-tetramethylacetophenone (5%), 2,3,4,5-tetramethylacetophenone (82%), and pentamethylacetophenone (1%).

Other references related to the isomerization of polyalkyl aromatic compound in the presence of Lewis acids are cited in the literature.[8]

H. REFERENCES

1. (a) Baddeley, G. and Bennett, G. M., *J. Chem. Soc.,* **1933**, 261. (b) Baddeley, G. and Kenner, J., *J. Chem. Soc.,* **1935**, 303. (c) Baddeley, G. and Kenner, J., *Ber.,* **1936**, *69B*, 902.
2. (a) Baddeley, G., *J. Chem. Soc.*, **1949**, S-99. (b) Chopin, M., *Bull. Soc. Chim.,* **1924**, *35*, 610.
3. Fieser, L. F., *The Chemistry of Natural Products Related to Phenanthrene*, Reinhold Publishing, New York, **1936**, p. 74.
4. Baddeley, G. and Pendleton, A. G., *J. Chem. Soc.,* **1952**, 807.

5. (a) Roberts, R. M. G., *J. Org. Chem*. **1982**, *47*, 4050. (b) Brown, H. C. and Jungk, H., *J. Am. Chem. Soc.*, **1955**, *77*, 5579.

6. (a) Kinney, R. E. and Hamilton, L. A., *J. Am. Chem. Soc.*, **1954**, *76*, 786. (b) Neissner, P. and French Jr., F. E., *J. Am. Chem. Soc*., **1952**, *74*, 1000.

7. Schlosberg, R. H. and Woodbury, R. P., *J. Org. Chem*., **1972**, *37*, 2627.

8. (a) Perchonock, C. D. and Finkelstein, J. A., *J. Org. Chem.,* **1980**, *45*, 2000. (b) DeHaan, F. P. and Brown, H. C., *J. Am. Chem. Soc.*, **1969**, *91*, 4844. (c) Fry, A. J. and Farnham, W. B., *J. Org. Chem*., **1969**, *34*, 2314. (d) Ransley, D. L., *J. Org. Chem.*, **1966**, *31*, 3595. (e) Allen, R. H., and Yats, L. D., *J. Am. Chem. Soc.*, **1959**, *81*, 5289. (f) Roberts, R. M. and Panayides, S. G., *J. Org. Chem.*, **1958**, *23*, 1080. (g) Olah, G. A. and Kuhn, S. J., *J. Am. Chem. Soc.*, **1958**, *80*, 6535. (h) Jensen, F. R., *J. Am. Chem. Soc*., **1957**, *79*, 1226. (i) Brown, H. C. and Young, H. L., *J. Org. Chem*., **1957**, *22*, 719. (j) Baddeley, G. and Williamson, R., *J. Chem. Soc*., **1956**, 4647. (k) Burwell, R. L. and Shields, A. D., *J. Am. Chem. Soc.*, **1955**, *77*, 2766. (l) Baddeley, G., *Quart Rev. (London),* **1954**, *8*, 355. (m) McCaulay, D. A. and Lien, A. P., *J. Am. Chem. Soc.*, **1952**, *74*, 6246. (n) Baddeley, G.; Holt, G. and Voss, D., *J. Chem. Soc.* **1952**, 100. (o) Baddeley, G. and Pendleton, A. G., *J. Chem. Soc*., **1952**, 807. (p) Baddeley, G., *J. Chem. Soc*., **1950**, 944. (q) Baddeley, G., *J. Chem. Soc.,* **1943**, 627. (r) Pitzer, K. J. and Scott, D. W., *J. Am. Chem. Soc.*, **1943**, *65*, 803. (s) Nightingale, D. and Smith, L. I., *J. Am. Chem. Soc.*, **1939**, *61*, 101. (t) Norris, J. F. and Rubinstein, D., *J. Am. Chem. Soc.*, **1939**, *61*, 1163.

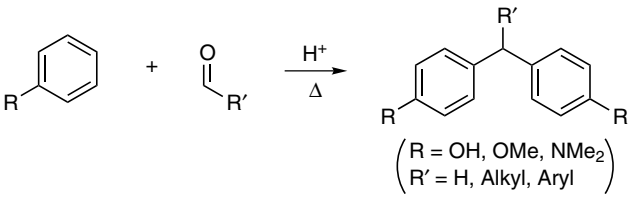
31

Baeyer Diarylmethane Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially studied by von Baeyer in 1872.[1] It is an acid-catalyzed condensation of aromatic compounds with formaldehyde or formaldehyde derivatives. In normal conditions, the reactive benzene derivatives such as phenols and arylamines are applied to condense with formaldehyde; however, a small number of less-reactive aromatics have also been used in this reaction, including benzene,[2a] toluene,[2b,c] benzyl chloride,[2b,c] biphenyl,[2b,c] iodobenzene,[2d] naphthalene,[2e] and mesitylene.[2f] Although no yields were given in the early studies, it is reasonable to obtain 70–80% yield for this type of reaction. Many other reactions have been developed to synthesize diarylmethanes, including Katritzky's benzotriazole method,[3] Kochi's dealkylative coupling,[4] Fukuzaw's 1,3-propandiol method,[5] and the reduction method.[6] In general, the condensation occurs at the *para*-position of substituted aromatics.

B. GENERAL REACTION SCHEME



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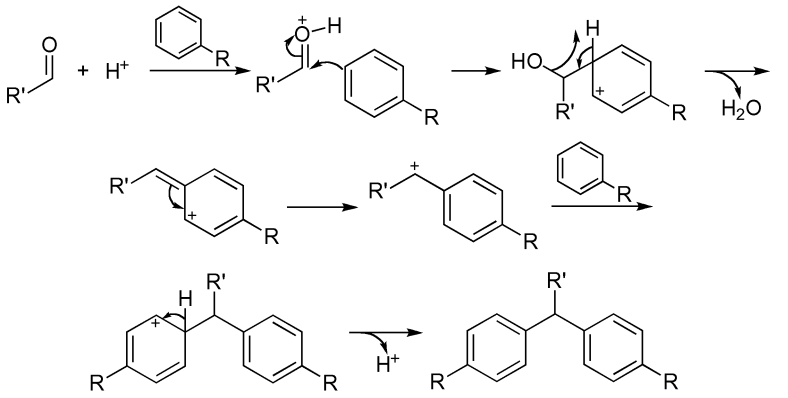
C. PROPOSED MECHANISMS

The mechanism is similar to that of the *Friedel-Crafts Alkylation*.



D. MODIFICATION

N/A

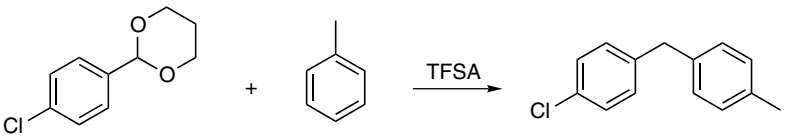
E. APPLICATIONS

This reaction can be applied to prepare diarylmethanes.

F. RELATED REACTIONS

This reaction is related to the *Baekeland-Lederer-Manasse Reaction*, which gives resinous product from the reaction between phenol and formaldehyde. In addition, this reaction is related to *Zinke Synthesis*.

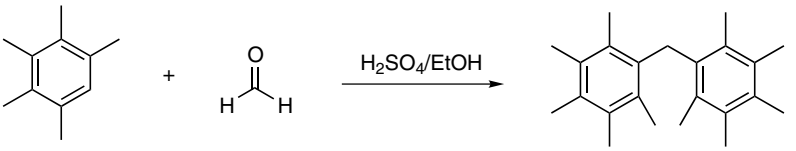
G. CITED EXPERIMENTAL EXAMPLES



Reference 5b.

To a solution of 199 mg 2-(4-chlorophenyl)-1,3-dioxane (1.0 mmol) in 5.0 mL toluene was added 8.0 mg TFSA (0.05 mmol) at room temperature while stirring. The mixture was refluxed for 17 h, then cooled down to room temperature and poured into aqueous $NaHCO_3$.

The organic layer was separated, and the aqueous phase was extracted with diethyl ether. The combined organic extracts were washed with brine and dried over $MgSO_4$. The product distribution was analyzed by GC/MS, using naphthalene as standard and comparing with an authentic sample. The *ortho*/*meta*/*para* ratio was found to be 27:7:56, in a yield of 81% on the basis of dioxane.



Reference 7.

To a 500-mL three-necked flask equipped with a reflux condenser, mechanical stirrer, and thermometer were added 0.67 mol pentamethyl benzene and 0.17 mol paraformaldehyde. The mixture was warmed to 75°C by a water bath. In a separate beaker was placed 170 mL 95% ethanol, and 68 mL 96% sulfuric acid was poured into at the side of the beaker ($EtOH/H_2SO_4$ = 2.5:1). This alcoholic solution was stirred and cooled to 5°C below the desired reaction temperature (75°C), and then poured into the flask. The heterogeneous mixture was stirred vigorously at 75°C for 1 h. When the solution was cooled down to room temperature, it was poured into 250 mL water, and 250–300 mL benzene was added to extract the product. The benzene extract was fractionated by distillation using a 10-in. Vigreux column to afford 86% of product, m.p. 220.6–221.2°C. Other polyalkylbenzenes react at different temperatures, and different solvents were used to extract the corresponding product. Yields were found between 50% and 86%.

Other references for making diarylmethanes can be found in the literature.[8]

H. REFERENCES

1. (a) von Baeyer, A., *Ber*., **1872**, *5*, 25. (b) von Baeyer, A., *Ber*., **1872**, *5*, 280. (c) von Baeyer, A., *Ber*., **1872**, *5*, 1094.
2. (a) von Baeyer, A., *Ber.,* **1873**, *6*, 221. (b) Weiler, J., *Ber*., **1874**, *7*, 1181. (c) Reichstein, T. and Oppenauer, K., *Helv. Chim. Acta*, **1933**, *16*, 1373. (d) Nastukov, A. M. and Shelyagin, V. V., *J. Prakt. Chem.* **1928**, *119*, 303. (e) Grabowski, J., *Ber*., **1874**, *7*, 1605. (f) von Baeyer, A., *Ber*., **1872**, *6*, 1098.
3. (a) Katritzky, A. R.; Zhang, Z. X.; Lang, H. Y. and Lan, X. F., *J. Org. Chem.,* **1994**, *59*, 7209. (b) Katritzky, A. R.; Lan, X. F. and Lam, J. N., *J. Org. Chem*., **1991**, *56*, 4397.
4. Rathore, R. and Kochi, J. K., *J. Org. Chem.,* **1995**, *60*, 7479.
5. (a) Tsuchimoto, T.; Tobita, K.; Hiyama, T. and Fukuzawa, S.-I., *J. Org. Chem.,* **1997**, *62*, 6997. (b) Fukuzawa, S.-I.; Tsuchimoto, T. and Hiyama, T., *J. Org. Chem.,* **1997,** *62*, 151. (c) Tsuchimoto, T.; Hiyama, T. and Fukuzawa, S.-I., *Chem. Commun.,* **1996**, 2345. (d) Tsuchimoto, T.; Tobita, K.; Hiyama, T. and Fukuzawa, S.-I., *Synlett,* **1996**, 557.
6. Tour, J. M.; Rawlett, A. M.; Kozaki, M.; Yao, Y. X.; Jagessar, R. C.; Dirk, S. M.; Price, D. W.; Reed, M. A.; Zhou, C.-W.; Chen, J.; Wang, W. Y. and Campbell, I., *Chem. Eur. J.,* **2001**, *7*, 5118.
7. Welch, C. M. and Smith, H. A., *J. Am. Chem. Soc*., **1951**, *73*, 4391.

8. (a) Kobayashi, S.; Sugiura, M.; Kitagawa, H. and Lam, W. W. L., *Chem. Rev*., **2002**, *102*, 2227. (b) Maulding, D. R.; Lotts, K. D. and Robinson, S. A., *J. Org. Chem*., **1983,** *48*, 2938. (c) Hart, H., *Acc. Chem. Res.,* **1971**, *4*, 337. (d) Schnell, W. and Krimm, H., *Angew. Chem*., **1962**, *75*, 622. (e) Foster, H. M. and Hein, D. W., *J. Org. Chem.,* **1961**, *26*, 2539. (f) Deno, K. C.; Peterson, H. J. and Saines, G. S., *Chem. Rev*., **1960**, *60*, 7. (g) Hultzsch, K., *Chemie der Phenolharze*, Springer, Berlin, **1950**, 193. (h) Wagner, E. C., *J. Am. Chem. Soc*., **1934**, *56*, 1944.

32

Baeyer-Drewson Reaction
(Baeyer-Drewson Indigo Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

Indigo is one of the oldest and most important coloring agents obtained from the vegetable kingdom. von Baeyer initially developed a protocol to synthesize indigos in the 1880s and 1890s[1] via the condensation of 2-nitrobenzaldehyde with acetone in the presence of dilute NaOH or Na_2CO_3.[2] Therefore, this reaction is known as the Baeyer-Drewson reaction.[3] After the pioneering work of von Baeyer, many other methods have been developed to synthesize indigos, including the acidic hydrolysis of the dimethyl acetal of *o*-amino-phenylglyoxal,[4a] reduction of l-*o*-nitrophenyl-2-nitroethanol by the basic dithionite,[4b] acid or base treatment of 2-anilinoindoxyl,[4c] treatment of 2-oximinoindoxyl with sulfuric acid,[4d] reduction of *o*-nitrobenzoylacetic acid by base and glucose,[4e,f] and reduction of 2-chloroindolone.[4g,h] In addition, the *Heumann Indigo Process* was the industrial manufacturing process applied to making indigo in large quantitles.[5] The original indigo synthesis was developed for testing for *o*-nitrobenzaldehyde in alkaline acetone solution (not applicable to *o*-nitrobenzaldehydes with *meta*- or *para*-hydroxyl groups, otherwise, a second nitro group is needed to form 2,6-dinitroisovanillin.)[3,6] The Baeyer-Drewsen indigo synthesis in combination with the *Lieben Iodoform Reaction* has been developed to differentiate methylcarbinols from methyl ketones. As an example, a positive iodoform reaction and a negative indigo reaction indicate a methylcarbinol; a positive iodoform reaction and a positive indigo reaction indicate a methyl ketone; whereas a negative iodoform reaction can rule out both methylcarbonols and methyl ketones.[7]

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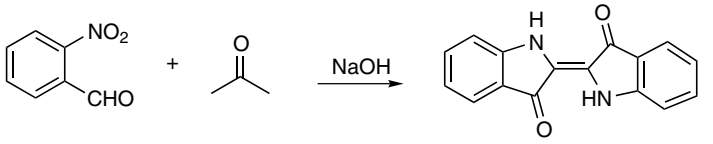
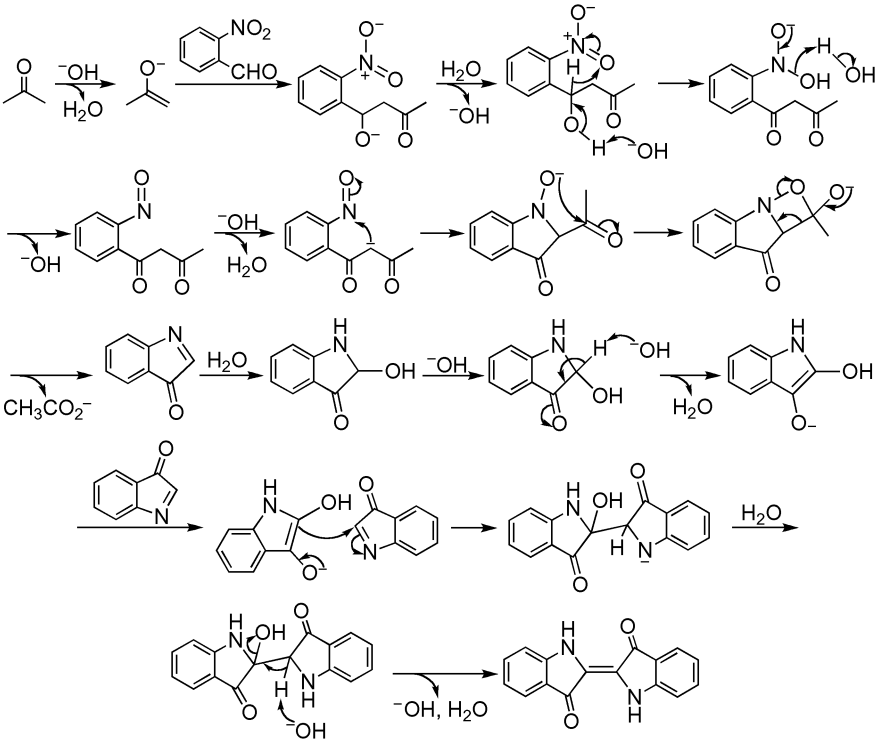
B. GENERAL REACTION SCHEME

Indigo should be the *trans*-isomer, preferentially stabilized by intramolecular hydrogen bonding available only in the *trans*-configuration.[8]



C. PROPOSED MECHANISMS

It is believed that this reaction occurs via the addition of an enolate, followed by the reduction of the nitro group and the final ring closure, as illustrated here.[7]



D. MODIFICATION

N/A

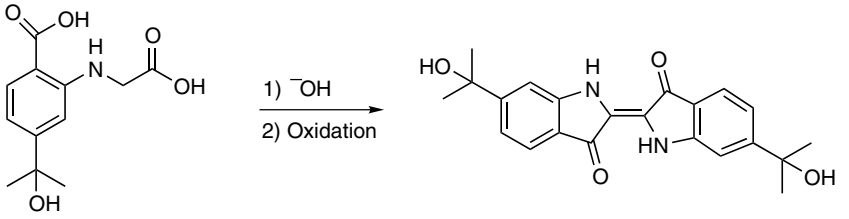
E. APPLICATIONS

This reaction is useful for the preparation of indigo derivatives; in addition, it can be applied for testing the presence of methyl ketones.

F. RELATED REACTIONS

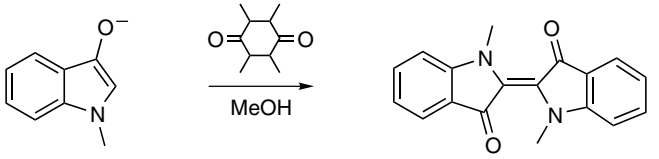
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 9.

A mixture of 10.1 g 2-amino-acetic-4-(α-hydroxyisopropyl)-benzoic acid (0.04 mol) and 50.5 g potassium hydroxide (0.90 mol) were fused in a nickel crucible to exclude air. The fusion was conducted initially at 180–200°C and was completed at 220–230°C within 15 min. Then the reddish yellow mass was cooled and dissolved in water. A current of air was led through the solution until a test portion no longer produced a bluish precipitate when air was drawn through. The oxidation product then formed was filtered off, washed successively with water and with very dilute hydrochloric acid, and finally dried to give 2.32 g of the shown product, in a yield of 31.0%. (*Note*: The name of the starting material has been changed from the original paper.)



Reference 10.

N,*N*′-dimethylindigo was prepared by the oxidation of 1 .05 mmol *N*-methylindoxyl acetate in 9 mL methanol by 2.2 mmol duroquinone under nitrogen and in the presence of 8.8 mmol sodium methoxide. After 15 min the mixture was acidified with hydrochloric acid and chromatographed on silica gel with chloroform to give 0.44 mmol pure *N*,*N*′-dimethylindigo, in a yield of 84%. Alternately, this *N*,*N*′-dimethylindigo can also be prepared according to the procedure of Ettinger and Friedlaender by oxidation of *N*-methylindoxyl in aqueous ammonia.[11] Recrystallization from heptanem under nitrogen

yielded 28% of needles, m.p. 180°C. No impurities were found by TLC or mass spectrometric (parent peak m/z 290).

Other references related to the Baeyer-Drewson reaction are cited in the literature.[12]

H. REFERENCES

1. Adams, R., *Ind. Eng. Chem*., **1926**, *18*, 1182.
2. (a) von Baeyer, A. and Drewson, V., *Ber*., **1882**, *15*, 2856. (b) von Baeyer, A. and Drewson, V. B., *German Pat.*, **1882**, Feb. 24, 19768. (c) von Baeyer, A. and Drewson, V. B., *U.S. Pat.*, **1882**, May 9, 257,812. (d) Baeyer, A. and Wirth, E., *Ann.,* **1895**, *284*, 154.
3. (a) McKee, J. R. and Zanger, M., *J. Chem. Edu.,* **1991**, *68*, A242, A244. (b) Hinkel, L. E.; Ayling, E. E. and Morgan, W. H., *J. Chem. Soc.,* **1932**, 985.
4. (a) Ziegler, E. and Kappe, T., *Angew. Chem.,* **1964**, *76*, 921. (b) Harley-Mason, J., *J. Chem. Soc*., **1950**, 2907. (c) Pummerer, R. and Gottler, M., *Ber.,* **1910**, *43*, 1376. (d) Wieland, H. and Gmelin, E., *Ber.,* **1908**, *41*, 3512. (e) von Baeyer, A., *Ber.,* **1880**, *13*, 2254, (f) von Baeyer, A., *Ber.* **1881**, *14*, 1741. (g) von Baeyer, A., *Ber.,* **1878**, *11*, 1296. (h) von Baeyer, A., *Ber*., **1879**, *12*, 456.
5. (a) Schmidt, H., *Chem. Unserer Zeit,* **1997**, *31*, 121. (b) Heuman, K., *U.S. Pat.*, **1899**, 622139. (c) Heumann, K., *U.S. Pat.*, February 28, **1899**, 620442. (d) Heumann, K., *U.S. Pat.*, February 21, **1899**, 619884. (e) Heumann, K., *U.S. Pat.*, January 10, **1899**, 617652. (f) Hentschel, W., *J. Prakt. Chem.,* **1898**, *57*, 198.
6. Tanasescu, I. and Tanasescu, E., *Bull. Soc. Chim. Fr.,* **1936**, *3*, 865.
7. Kamlet, J., *Ind. Eng. Chem.,* **1944**, *16*, 362.
8. (a) Weinstein, J. and Wyman, G. M., *J. Am. Chem. Soc.,* **1956**, *78*, 2387. (b) Madelung, W. and Wilhelmi, O., *Ber.,* **1924**, *57*, 237.
9. Phillips, M., *J. Am. Chem. Soc.,* **1922**, *44*, 1775.
10. Russell, G. A. and Kaupp, G., *J. Am. Chem. Soc.*, **1969**, *91*, 3851.
11. Ettinger, L. and Friedlaender, P., *Ber*., **1912**, *45*, 2074.
12. (a) Cooksey, C. J. and Dronsfield, A. T., *Dyes in History & Archaeology,* **2002**, *18*, 13. (b) Wu, Q., *Huaxue Tongbao,* **2001**, 527. (c) McKee, J. R. and Zanger, M., *J. Chem. Edu.,* **1991**, *68*, A242, A244. (d) Preston, P. N. and Tennant, G., *Chem. Rev.*, **1972**, *72*, 627. (e) Hassner, A.; Haddadin, M. J. and Catsoulacos, P., *J. Org. Chem.*, **1966**, *31*, 1363. (f) E. Ziegler and T. Kappe, *Angew. Chem.,* **1964**, *76*, 921. (g) Loudon, J. D. and Tennant, *G., Quart. Rev. (London),* **1964**, *18*, 389. (h) Hassner, A. and Haddadin, M. J., **1962**, 975. (i) Harley-Mason, J., *J. Chem. Soc*., **1950**, 2907. (j) Van Order, R. B. and Lindwall, H. G., *Chem. Rev*., **1942**, *42*, 69. (k) Tanasescu, I. and Tanasescu, E., *Bull. Soc. Chim. Fr.,* **1936**, *3*, 865. (l) Tanasescu, I. and Georgescu, A., *J. Prakt. Chem*., **1934**, *139*, 189. (m) Tanasescu, I. and Georgescu, A., *Bull. Soc. Chim. Fr.,* **1932**, *51*, 234. (n) Overmyer, C. J., *J. Am. Chem. Soc*., **1926**, *48*, 454. (o) Heller, G.; Lauth, H., and Buchwaldt, A , *Ber.,* **1922**, *55*, 483. (p) Friedlander, P. and Schenck, O., *Ber.,* **1914**, *47*, 3040. (q) Pummerer, R. and Gottler, M., *Ber.,* **1910**, *43*, 1376. (r) Wieland, H. and Gmelin, E., *Ber*., **1908**, *41*, 3512. (s) Baeyer, A. and Drewson, V. B., *Ber*., **1883**, *16*, 2205. (t) Baeyer, A., *Ber*., **1883**, *16*, 2204. (u) Baeyer, A. and Drewson, V. B., *Ber*., **1882**, *15*, 2856. (v) Baeyer, A., *Ber.*, **1881**, *14*, 1741. (w) Baeyer, A., *Ber*., **1880**, *13*, 2254. (x) Baeyer, A., *Ber.,* **1879**, *12*, 456. (y) Baeyer, A., *Ber*., **1878**, *11*, 1296.

33

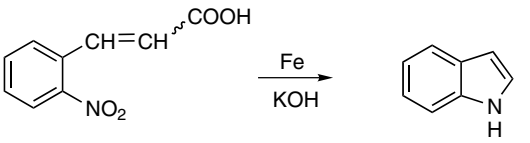
Baeyer Indole Synthesis

(Baeyer-Emmerling Indole Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Baeyer and Emmerling in 1869.[1] It is the synthesis of indole via the alkaline reduction of *o*-nitro-cinnamic acid by iron. Although the *Fischer Indole Synthesis* has been considered as the most versatile approach for the indole derivatives,[2] a few methods similar to Baeyer indole synthesis have also been developed so far.[3]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Displayed here is the mechanism of Baeyer indole synthesis.

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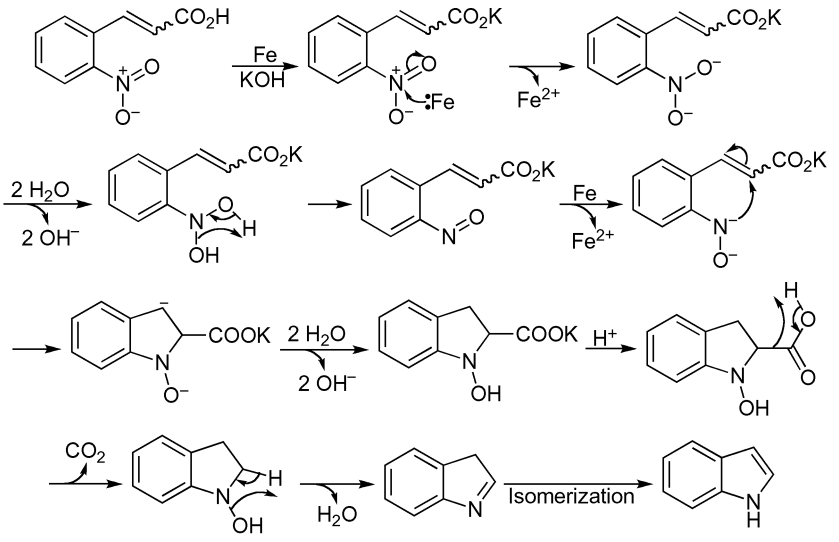


D. MODIFICATION

A few modifications have been developed, as described in detail in Cited Experimental Examples.[3]

E. APPLICATIONS

N/A

F. RELATED REACTIONS

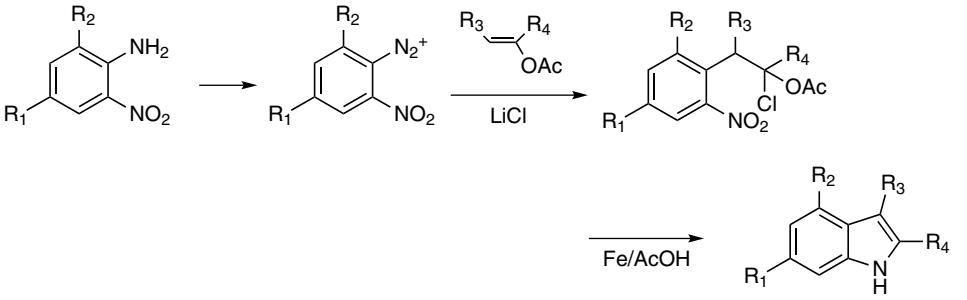
This reaction is related to the *Reissert Indole Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES

Reference 3a.

The preparation of chromium-copper-on-charcoal catalyst has been reported elsewhere.[4] It is prepared by adding acid-washed charcoal to a strong hot solution of $Ca(NO_3)_2$, KNO_3, or KH_2PO_4. The amount of salt adsorbed was determined by filtering off the catalyst after a few minutes, evaporating the filtrate to dryness, and weighing the residue. (Interested readers should see Ref. 4 for details because chromium and copper salt were not mentioned here.)

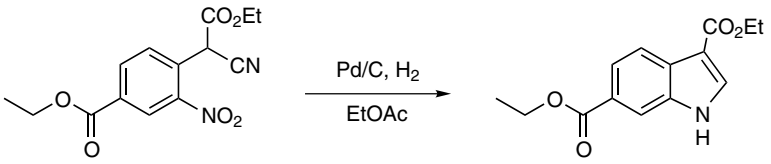
The apparatus was similar to the reported one;[5] however, in the runs above 625°C, a catalyst tube made from Corning 172 glass was used instead of the usual Pyrex. In the experiment, 10 mL of catalyst was used and preceded by about 10 mL of quartz chips, which served as a preheater for the incoming vapors. Before use, the catalyst was reduced *in situ* there with a slow stream of hydrogen for 30 min at 150–200°C, and then for 1 h at a few degrees above the actual reaction temperature. The *o*-ethyl aniline was passed through the reaction tube. The indole and skatole were isolated from the condensate by first extracting the unconverted aniline and aminostyrene with dilute hydrochloric acid and then steam distilling the residue to obtain the pure indole. The amount of indole present in the skatole was determined by repeated crystallization from water and alcohol.



Reference 3b.

2-Nitroaniline hydrochloride, prepared from heating a mixture of 1.38 g 2-nitroaniline (10.0 mmol) and 2.50 mL 12 M HCl (30.0 mmol) for several minutes, was cooled to −5°C in an ice salt bath. A cold solution of 725 mg sodium nitrite (10.5 mmol) in 3 mL water was added over 15 min with stirring, while the temperature of the reaction was held between −5° and 2°C. The mixture was stirred for an additional 15 min, and 30 mg urea (0.60 mmol) in 5.0 mL cold water was added. This cold solution was added over 10 min to a stirred mixture of 2.77 mL vinyl acetate (30.0 mmol) and 0.85 g LiCl (20.0 mmol) in 50 mL acetone-water mixture (v/v = 65:35) in a 100-mL two-necked flask fitted with a gas bubbler that was cooled to −5°C under an argon atmosphere. A cold solution of 0.26 g cupric chloride dihydrate (1.5 mmol) in 5 mL water was then added over 10 min, and the evolution of nitrogen commenced. The temperature of the reaction mixture was held between 3° and 10°C for 2 h and then warmed to room temperature over 2 h. After an additional 2 h, nitrogen evolution ceased, and the acetone was evaporated. The reaction mixture was poured into 50 mL water and extracted with dichloromethane (3 × 30 mL). The combined extracts were washed successively with water and brine and dried over anhydrous magnesium sulfate. Evaporation of the solvent and purification by flash column chromatography on 70 g silica gel using 35% dichloromethane in hexanes as an eluent gave 1.21 g l-acetoxy-l-chloro-2-(2-nitrophenyl)ethane as a light yellow oil, in a yield of 50%.

To a 250-mL one-necked flask fitted with a reflux condenser were added 1.22 g l-acetoxy-l-chloro-2-(2-nitrophenyl)ethane (5.00 mmol), 0.98 g 200 mesh iron powder (17.5 mmol), 2.10 g acetic acid (35.0 mmol), 0.68 g sodium acetate dihydrate (5.0 mmol), and 100 mL 80:20 (v/v) ethanol/water. The mixture was refluxed with stirring for 2 h under an atmosphere of argon. The reaction mixture was cooled, the ethanol was evaporated, and the residue was extracted with dichloromethane (3 × 30 mL). The combined extracts were washed successively with water and brine and dried over potassium carbonate. Evaporation of the solvent and purification by flash column chromatography on 50 g silica gel (50:50 dichloromethane-hexanes eluent) gave 0.53 g indole, in a yield of 90%.



Reference 3d.

A solution of 6.12 g ethyl 2-nitro-4-carbethoxyphenylcyanoacetate in 60 mL freshly distilled ethyl acetate was placed in a pressure bottle with 1 g 30% palladium-on-carbon. Hydrogenation was performed at a hydrogen pressure of 56 psi at 22°C. Approximately 3 mol of hydrogen per mole of starting material was absorbed during the first 15 min. The temperature was raised to 85–90°C, and another mole of hydrogen was absorbed during the next 2 h. The product, insoluble in ethyl acetate, was collected by filtration along with the catalyst. The product was dissolved in ethanol, filtered to remove the catalyst, and recrystallized twice from ethanol water. Finally, 4.70 g 3,6-dicarbethoxyindole was obtained, in a yield of 90%, m.p., 134–136°C.

Other references related to the Baeyer indole synthesis are cited in the literature.[6]

H. REFERENCES

1. von Baeyer, A. and Emmerling, A., *Ber*., **1869**, *2*, 679.
2. Robinson, B., *Chem. Rev*., **1963**, *63*, 373.
3. (a) Raucher, S. and Koolpe, G. A., *J. Org. Chem.*, **1983**, *48*, 2066. (b) Odle, R.; Blevins, B.; Ratcliff, M. and Hegedus, L. S., *J. Org. Chem*., **1980**, *45*, 2709. (c) Snyder, H. R.; Merica, E. P.; Force, C. G. and White, E. G., *J. Am. Chem. Soc.*, **1958**, *80*, 4622. (d) Hansch, C. and Helmkamp, G., *J. Am. Chem. Soc.*, **1951**, *73*, 3080.
4. Hansch, C.; Crosby, D. G.; Sadoski, M.; Leo, A. and Percival, D., *J. Am. Chem. Soc*., **1951**, *73*, 704.
5. Hoog, H.; Verheus, J. and Zuiderweg, F. J., *Trans. Faraday Soc*., **1939**, *35*, 993.
6. (a) Foster, H. M. and Hein, D. W., *J. Org. Chem*., **1961**, *26*, 2539. (b) van Order, R. B. and Lindwall, H. G., *Chem. Rev*., **1942**, *42*, 69. (c) Carrasco, O. and Padoa, M., *Gazz. Chim. Ital.*, **1907**, *37*, 49. (d) Carrasco, O. and Padoa, M., *Atti Accad. Nazl. Lincei*, **1906**, *15*, 699. (e) Baeyer, A., and Tutein, F., *Ber.,* **1889**, *22*, 2178. (f) Baeyer, A. and Caro, H., *Ber*., **1877**, *10*, 692. (g) Beilstein, F. and Kuhlberg, A., *Ann*., **1872**, *163*, 141. (h) Baeyer, A., *Ann*., **1866**, *140*, 295.

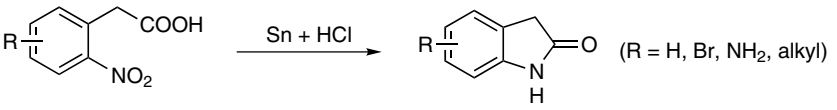
34

Baeyer Oxindole Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by von Baeyer in 1878.[1] It is the synthesis of oxindole via the acidic reduction of *o*-nitrophenylacetic acid by tin and the subsequent cyclization of the resulting reduced intermediate. Besides such reaction conditions, other acidic reducing combinations can also be applied to the preparation of oxindole, including Zn + H_2SO_4, Zn + HOAc, and Fe + HOAc, $SnCl_2$ + NH_4Cl. Recently, other methods have been developed for preparing oxindoles.[2]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Displayed is the mechanism for the formation of oxindole.

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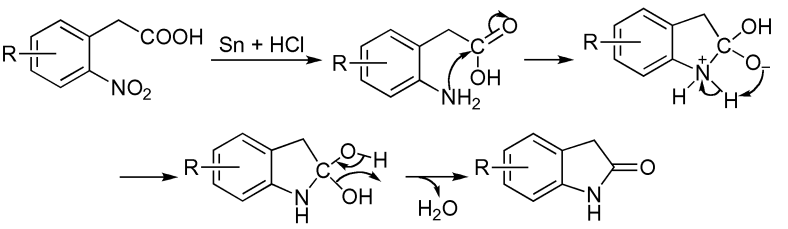


D. MODIFICATION

The reaction has been modified using a palladium catalyst as the coupling reagent, as shown in Cited Experimental Examples.

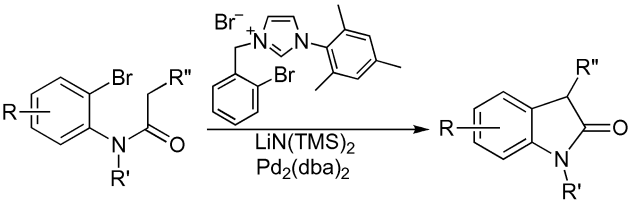
E. APPLICATIONS

This reaction has general usage for the preparation of oxindoles.

F. RELATED REACTIONS

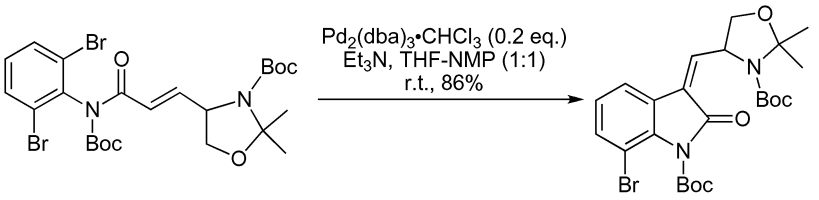
This reaction is related to the *Béchamp Reduction* and *Hinsberg Oxindole Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2a.

The reaction was carried out in THF using a certain amount of substrate, 1.5–3 mol % $Pd_2(dba)_2$, 3–6 mol % 1-mesitylimidazoium salt, and 1.5–2 eq. of $LiN(TMS)_2$. The reaction mixture was stirred at 68°C for 1–4 h and monitored by TLC. After the reaction, the solvent was evaporated, and the residue was directly purified by column chromatography. Normally, the isolated yield was in the range of 40–95%. (*Note*: This reference did not provide experimental details.)



Reference 2b.

To the mixed solvent of THF and NMP (1:1), were added certain amount of starting material, 0.2 eq. of $Pd_2(dba)_2{\cdot}CHCl_3$, and Et_3N. The mixture was stirred at room temperature and monitored by TLC. After the reaction, the solvent was evaporated, and the residue was purified on column chromatography. The yield was 86% with a Z:E selectivity of more than 95%. (Z:E > 20:1). The reaction temperature is crucial for the regioselectivity of this reaction, as an example, the Z:E ratio of the shown product was decreased to 3:1 when the reaction was conducted at 50°C. (*Note*: Experimental details were not given in this reference; interested readers should see Ref. 3).

Other references related to the synthesis of oxindole are cited in the literature.[4]

H. REFERENCES

1. von Baeyer, A., *Ber*., **1878**, *11*, 582.
2. (a) Zhang, T. Y. and Zhang, H. B., *Tetrahedron Lett*., **2002**, *43*, 193. (b) Inoue, M.; Furuyama, H.; Sakazaki, H. and Hirama, M., *Org. Lett*., **2001**, *3*, 2863.
3. Lin, S. and Danishefsky, S. J., *Angew. Chem. Int. Ed*., **2001**, *40*, 1967.
4. Laird, T.; Hermitage, S. A. and Tilstam, U., *Org. Proc. Res. Dev.*, **2002**, *6*, 90.

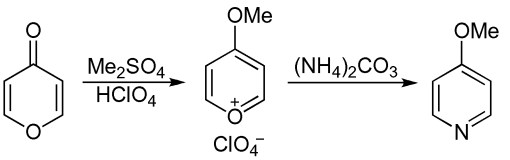
35

Baeyer Pyridine Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by von Baeyer in 1910.[1] It is the transformation of γ-pyrones or other pyrone derivatives into pyridines via pyronium salt intermediates, which subsequently react with an ammonium salt, such as ammonium carbonate. This reaction can be applied to the preparation of other types of heterocycles containing nitrogen. Besides this reaction, other methods have been developed to synthesize pyridines, which have been extensively reviewed by Bergstrom.[2] Other methods not included in Bergstrom's review include distillation of allylethylamine over heated lead oxide,[3a] passing a mixture of acetylene and hydrocyanic acid through a red-hot tube,[3b] heating pyrrole with sodium methylate and methylene iodide to 200°C,[3c] heating isoamyl nitrate with phosphorus pentoxide,[3d] and heating piperidine in acetic acid with silver acetate.[3e] These methods normally give low yields of pyridine derivatives.

B. GENERAL REACTION SCHEME



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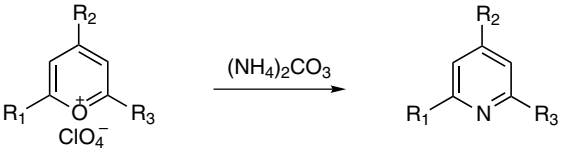
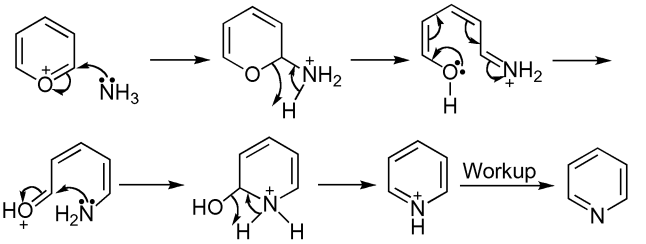
Starting from any pyronium salt:



C. PROPOSED MECHANISMS

It is believed that this reaction involves the following steps: the addition of amine, opening of the pyronium ring, closure of the ring, and elimination of water. This mechanism is similar to that of *ANRORC Rearrangement*.



D. MODIFICATION

N/A

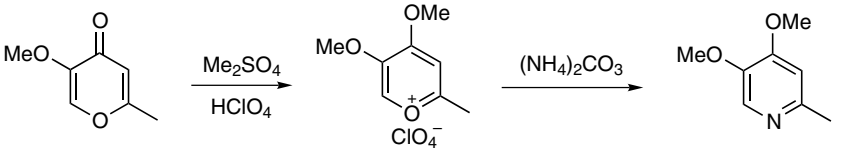
E. APPLICATIONS

This reaction has general application in the formation of pyridines.

F. RELATED REACTIONS

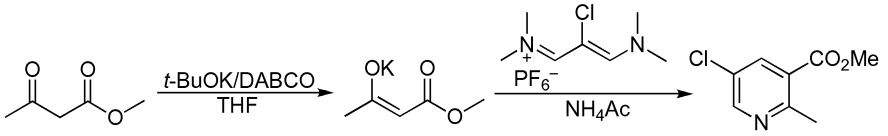
This reaction is related to the *Clauson-Kaas Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4.

To a flask equipped with a condenser were added 70 g 2-methyl-5-methoxy γ-pyrone (0.2 mol) and 31 g dimethyl sulfate (0.25 mol). The mixture was heated at 50°C for 2 h, and was then poured into 3 eq. of ice-cooled 20% $HClO_4$. After 2 h, the pyronium perchlorate salt was filtered and added to 175 mL 10% ammonium carbonate solution saturated with ammonium sulfate. After the reaction, the product was extracted with EtOAc. The product was obtained via evaporation of solvent and vacuum distillation, b.p. 75–80°C (1 mmHg). The product can also be converted to hydrochloride salt, m.p. 164°C.



Reference 5.

To a suspension of 2.9 g methyl acetoacetate (25 mmol) in 50 mL dry THF was added 16.4 mL 20 wt % *t*-BuOK in THF (26.3 mmol, 1.05 eq.) at 0°C. The slurry was warmed to room temperature and stirred for 45 min, then 1.0 eq. DABCO was added followed by 11.5 g vinamidinium hexafluorophosphate salt (37.5 mmol, 1.5 eq.) in one portion. The mixture was stirred for 45°C for 3 h, and 2 eq. ammonium acetate was added in one portion. The resulting dark solution was heated at reflux for 6 h and concentrated under reduced pressure. The yield was found to be 84%, m.p., 186–187°C. The residue was directly purified by chromatography on silica gel. Alternatively, the residue after evaporation of the THF can be extracted with EtOAc, and washed with water and saturated sodium chloride solution after the purification.

Other references related to Baeyer pyridine synthesis are cited in the literature.[6]

H. REFERENCES

1. von Baeyer, A., *Ber*., **1910**, *43*, 2337.
2. Bergstrom, F. M., *Chem. Rev*., **1945**, *45*, 77.
3. (a) Konigs, W., *Ber*., **1879**, *12*, 234. (b) Ramsay, W., *Ber*., **1877**, *10*, 736. (c) Dennstedt, M. and Zimmermann, J., *Ber*., **1885**, *18*, 3316. (d) Chapman, E. T. and Smith, M. H., *Ann*., **1868**, *6* (suppl.) 329. (e) Tafel, J., *Ber*., **1892**, *25*, 1619.
4. Balaban, A. T. and Nenitzescu, C. D., *Ann*., **1959**, *625*, 74.
5. Marcoux, J.-F.; Marcotte, F.-A.; Wu, J.; Dormer, P. G.; Davies, I. W.; Hughes, D. and Reider, P. J., *J. Org. Chem.* **2001,** *66*, 4194.
6. (a) Dimroth, K., *Angew. Chem.,* **1960**, *72*, 331. (b) Herzenberg, J. and Boccato, G., *Chim. Ind. (Paris),* **1958**, *80*, 248. (c) Goldman, M. and Becker, E. I., *Nature,* **1952**, *170*, 35. (d) Cavallieri, L. F., *Chem. Rev*., **1947**, *41*, 525. (e) King, H. and Ware, L. L., *J. Chem. Soc*., **1939**, 875. (f) Dilthey, W.; Nusslein, J.; Meyer, H. and Kaffer, H., *J. Prakt. Chem*., **1922**, *104*, 28. (g) Dilthey, W.; Bauriedel, G.; Burger, B.; Geisselbrecht, G.; von Ibach, F.; Kiefer, F.; Seeger, A.; Simon, O.; Taucher, R. and Winkler, J., *J. Prakt. Chem*., **1921**, *102*, 209. (h) Baeyer, A. and Piccard, J., *Ann*., **1911**, *384*, 217.

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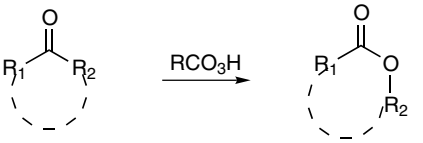
Baeyer-Villiger Oxidation

(Baeyer-Villiger Reaction, Baeyer-Villiger Rearrangement)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Baeyer and Villiger in 1899.[1] It is the oxidation of ketones or cyclic ketones into esters or lactones by peracids or hydrogen peroxide. This reaction is thus known as the Baeyer-Villiger oxidation,[2] Baeyer-Villiger reaction,[3] and Baeyer-Villiger rearrangement.[4] Typical peracids in this oxidation include peroxybenzoic acid, *m*-chloroperoxybenzoic acid (*m*CPBA), peroxyacetic acid, and trifluoroperoxyacetic acid. In this reaction, the more substituted group often migrates preferentially, and the migratory aptitudes of these groups are tertiary > secondary > cyclohexyl > benzyl > phenyl > primary > methyl. More importantly, both the stereochemistry and chirality of the migrating group are retained during the migration. This reaction has been extensively reviewed.[5]

B. GENERAL REACTION SCHEME



Dashed line, cyclic ketone.

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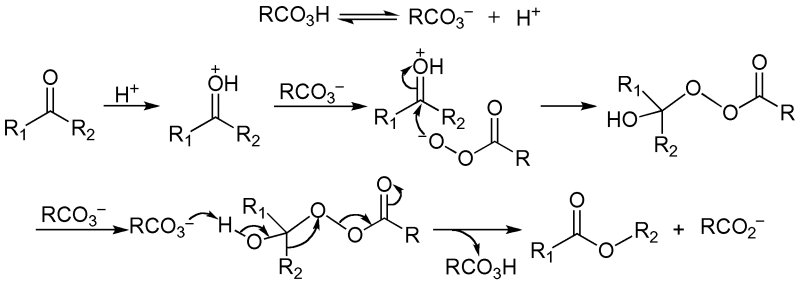
C. PROPOSED MECHANISMS

A general mechanism is displayed here.



D. MODIFICATION

Because alkenes react readily with peroxyacids to form epoxides, the Baeyer-Villiger oxidation has been modified using bis[trimethylsilyl]peroxide[6a] or basic hydrogen peroxide.[6b] Recently, a modification of Baeyer-Villiger oxidation on cyclohexanone using tin-infused zeolite as catalyst and hydrogen peroxide as oxidation reagent has been developed.[6c,6d] This method can be extended to other ketones with high selectivity. It is said that this route is more environmentally friendly than the traditional manufacturing methods for caprolactone and other lactones. Moreover, as an environmentally friendly reagent, hydrogen peroxide has been widely applied for the Baeyer-Villiger oxidation under various conditions: (*a*) using $[(triphosPO)Pt]^{2+}$,[7a] montmorillonite-supported $SnCl_2$,[7b] Sn-palygorskite,[7c] organoselenium,[7d] selenoxides,[7e] aminomethyl polystyrene resin-supported tin complex,[7f] and water-tolerant Lewis acid in molecular sieves[7g] as catalysts; (*b*) using H_2O_2/nitrile as oxidant, such as H_2O_2/nitrile over $Mg(OH)_2$ or MgO,[7h] Mg/Al hydrotalcite,[7i] and H_2O_2/benzonitrile over hydrotalcite;[7j,7k] and *(c)* with tailoring Pt(II) chiral catalyst[7l] and Pt(II) catalyst[7m] or CH_3ReO_3/H_2O_2 in ionic liquids.[7n] In addition, other kinds of reagents have been applied as oxidant for the Baeyer-Villiger oxidation, including potassium peroxomonosulfate,[8a,8b] bis-cationic platinum (II) complex ($[[Pt(mu\text{-}OH)(Pom\text{-}Pom)]_2[BF_4]_2$ [Pom-Pom = $(OMe)_2PCH_2CH_2P(OMe)_2$]),[8c] and molecular oxygen/benzaldehyde.[8d] Furthermore, microbial[9a] and enzymatic[9b,9c] Baeyer-Villiger oxidation (e.g., monooxygenases,[9d–9h] cunninghamella echinulata NRRL 3655,[9i] and arabidopsis CYP85A2[9j]).

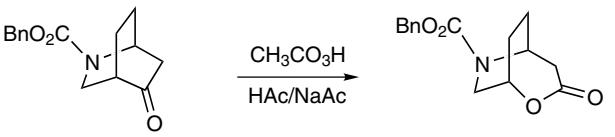
E. APPLICATIONS

This reaction has broad applications in organic synthesis for the preparation of esters and lactones.

F. RELATED REACTIONS

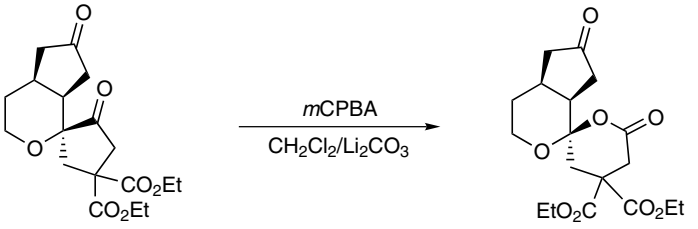
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 10.

To a solution of 400 mg *N*-carbobenzyloxy-2-azabicyclo[2.2.2]octan-5-one (1.53 mmol) in 1 mL acetic acid containing 0.1 g sodium acetate was added 1 mL 28% peracetic acid. After the mixture was stirred in the dark for 24 h, 10 mL methylene chloride was added, and the solution was washed with saturated sodium sulfite (4 × 5 mL) followed by saturated sodium bicarbonate (2 × 5 mL). After removal of the solvent, the residue was purified by flash chromatography, and 338.0 mg 6-(benzyloxycarbonyl)-2-*oxa*-3-*oxo*-6-azabicyclo[3.2.2]-nonane was obtained, in a yield of 80%, b.p. 145–150°C (0.025 mmHg).



Reference 11.

To a solution of 0.045 mmol 4,4-dicarbethoxy-3,7β-dioxa-8,2-dioxobicyclo[4.3.0]-nonane-2-*spiro*-1′-cyclopentane in 1.0 mL dichloromethane were added a catalytic amount of Li_2CO_3 and 0.068 mmol *m*CPBA. The mixture was stirred for 5 h at room temperature and quenched by 0.5 mL 10% $Na_2S_2O_4$ solution. The product was extracted with chloroform (3 × 5 mL), and the combined organic layers were washed with 10% K_2CO_3 and brine and then dried over Na_2SO_4. Upon removal of solvent, the residue was purified by flash chromatography to afford 70–75% of 5,5′-dicarbethoxy-3,7β,2β-trioxa-8,3-dioxobicyclo[4.3.0]nonane-2-nonane-1-cyclohexane.

Other references related to the Baeyer-Villiger oxidation are cited in the literature.[12]

H. REFERENCES

1. (a) von Baeyer, A. and Villger, V., *Ber*., **1899**, *32*, 3625. (b) von Baeyer, A. and Villiger, V., *Ber*., **1900**, *33*, 858.
2. (a) Cernuchova, P. and Mihovilovic, M. D., *Org. Biomol. Chem.,* **2007**, *5*, 1715. (b) Huang, J.; Li, J. X.; Dai, W. L.; Cao, Y. and Fan, K. N., *Shiyou Huagong,* **2007**, *36*, 200. (c) Li, C. L.; Wang, J. Q.; Yang, Z. W.; Hu, Z. G. and Lei, Z. Q., *Catal. Commun.,* **2007**, *8*, 1202. (d) Li, C.-L.; Yang, Z.-W.; Wu, S. and Lei, Z.-Q., *React. Funct. Polymers,* **2007**, *67*, 53. (e) Llamas, R.; Jimenez-Sanchidrian, C. and Ruiz, J. R., *React. Kinet. Catal. Lett.,* **2007**, *90*, 309. (f) Sgarbossa, P.; Scarso, A.; Michelin,

R. A. and Strukul, G., *Organometallics,* **2007**, *26*, 2714. (g) Sgarbossa, P.; Scarso, A.; Pizzo, E.; Sbovata, S. M.; Tassan, A.; Michelin, R. A. and Strukul, G., *J. Mol. Catal. A: Chem.,* **2007**, *261*, 202. (h) Zhang, Q. H.; Wang, S. F. and Lei, Z. Q., *Chinese Chem. Lett.,* **2007**, *18*, 4. (i) Baldwin, C. V. F. and Woodley, J. M., *Biotechnol. Bioeng.,* **2006**, *95*, 362. (j) Fantin, G.; Giovannini, P. P.; Guerrini, A.; Maietti, S.; Medici, A. and Pedrini, P., *Biotechnol. Lett.,* **2006**, *28*, 805. (k) Grein, F.; Chen, A. C.; Edwards, D. and Crudden, C. M., *J. Org. Chem.,* **2006**, *71*, 861. (l) Hilker, I.; Baldwin, C.; Alphand, V.; Furstoss, R.; Woodley, J. and Wohlgemuth, R., *Biotechnol. Bioeng.,* **2006**, *93*, 1138. (m) Iwaki, H.; Wang, S. Z.; Grosse, S.; Bergeron, H.; Nagahashi, A.; Lertvorachon, J.; Yang, J. Z.; Konishi, Y.; Hasegawa, Y. and Lau, P. C. K., *Appl. Environ. Microbio.,* **2006**, *72*, 2707. (n) Koopmans, C.; Iannelli, M.; Kerep, P.; Klink, M.; Schmitz, S.; Sinnwell, S. and Ritter, H., *Tetrahedron,* **2006**, *62*, 4709. (o) Mihovilovic, M. D., *Curr. Org. Chem.,* **2006**, *10*, 1265. (p) Mihovilovic, M. D.; Mueller, B.; Spina, M.; Durrani, A. I.; Stanetty, P.; Dazinger, G. and Kirchner, K., *Monatsh. Chem.,* **2006**, *137*, 785. (q) Mihovilovic, M. D.; Snajdrova, R. and Groetzl, B., *J. Mol. Catal. B: Enzymatic,* **2006**, *39*, 135. (r) Mikami, K.; Yamanaka, M.; Islam, Md. N.; Tonoi, T.; Itoh, Y.; Shinoda, M. and Kudo, K., *J. Fluor. Chem.,* **2006**, *127*, 592. (s) Scafato, P.; Larocca, A. and Rosini, C., *Tetrahedron: Asymmetry,* **2006**, *17*, 2511. (t) Wang, B.; Shen, Y.-M. and Shi, Y., *J. Org. Chem.,* **2006**, *71*, 9519. (u) Zhang, M.; Wei, J.-F. and Shi, Z., *Xibei Daxue Xuebao, Ziran Kexueban*, **2006**, *36*, 403. (v) Corma, A. and Renz, M., *Coll. Czech. Chem. Commun.,* **2005**, *70*, 1727. (w) Hilker, I.; Wohlgemuth, R.; Alphand, V. and Furstoss, R., *Biotechnol. Bioeng.,* **2005**, *92*, 702. (x) Mihovilovic, M. D.; Snajdrova, R.; Winninger, A. and Rudroff, F., *Synlett,* **2005**, 2751.

3. (a) Yamabe, S. and Yamazaki, S., *J. Org. Chem.,* **2007**, *72*, 3031. (b) Bolm, C., *Asymmetric Synthesis,* **2007**, 57. (c) Frison, J.-C.; Palazzi, C. and Bolm, C., *Tetrahedron,* **2006**, *62*, 6700. (d) Zhang, P.; Yang, M.; Lue, X. P. and Han, P. F., *Huaxue Tongbao*, **2005**, *68*, 897. (e) Song, Z.-G.; Li, J.; Liu, Q.-W.; Li, Y.-Z. and Huang, H.-M., *Gaodeng Xuexiao Huaxue Xuebao*, **2005**, *26*, 2264. (f) Iglesias-Arteaga, M. A.; Velazquez-Huerta, G. A.; Mendez-Stivalet, J. M.; Galano, A. and Alvarez-Idaboy, J. R., *ARKIVOC*, **2005**, (*vi*) 109. (g) Bolm, C.; Palazzi, C. and Beckmann, O., *Trans. Metal Org. Synth.,* **2004**, *2*, 267. (h) Snowden, M.; Bermudez, A.; Kelly, D. R. and Radkiewicz-Poutsma, J. L., *J. Org. Chem.,* **2004**, *69*, 7148. (i) Bolm, C.; Frison, J.-C.; Zhang, Y. and Wulff, W. D., *Synlett,* **2004**, 1619. (j) Bernini, R.; Coratti, A.; Fabrizi, G. and Goggiamani, A., *Tetrahedron Lett.,* **2003**, *44*, 8991. (k) Sever, R. R. and Root, T. W., *J. Phys. Chem. B,* **2003**, *107*, 10848. (l) Sever, R. R. and Root, T. W., *J. Phys. Chem. B,* **2003**, *107*, 10521. (m) Ito, Y., *Organomet. News*, **2002**, 140. (n) Murahashi, S.-I.; Ono, S. and Imada, Y., *Angew. Chem. Int. Ed.,* **2002**, *41*, 2366. (o) Peng, Y.; Feng, X.; Yu, K.; Li, Z.; Jiang, Y. and Yeung, C.-H., *J. Organomet. Chem.,* **2001**, *619*, 204.

4. (a) Alvarez-Idaboy, J. R.; Reyes, L. and Cruz, J., *Org. Lett.,* **2006**, *8*, 1763. (b) Reyes, L.; Castro, M.; Cruz, J. and Rubio, M., *J. Phys. Chem. A,* **2005**, *109*, 3383. (c) Bernini, R.; Mincione, E.; Cortese, M.; Aliotta, G.; Oliva, A. and Saladino, R., *Tetrahedron Lett.,* **2001**, *42*, 5401. (d) Cadenas, R.; Reyes, L.; Lagunez-Otero, J. and Cetina, R., *THEOCHEM*, **2000**, *497*, 211. (e) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Alvarez-Manzaneda, R.; Chahboun, R.; Meneses, R. and Aparicio B., M., *Synlett,* **1999**, 713. (f) Zhu, Y. J., *Daxue Huaxue*, **1998**, *13*, 48. (g) Bhaumik, A.; Kumar, P. and Kumar, R., *Catal. Lett.,* **1996**, *40*, 47. (h) Alcaide, B.; Aly, M. F. and Sierra, M. A., *Tetrahedron Lett.,* **1995**, *36*, 3401. (i) Paryzek, Z. and Blaszczyk, K., *Liebigs Ann.,* **1995**, 341. (j) Gordon, N. J. and Evans, S. A., *J. Org. Chem.,* **1993**, *58*, 4516. (k) Mak, A. Y. and Swinney, D. C., *J. Am. Chem. Soc.,* **1992**, *11*, 8309. (l) Kuo, Y. H.; Shih, K. S. and Lee, S. M., *J. Photochem. Photobio. A: Chem.,* **1988**, *45*, 97. (m) Levin, D. and Warren, S., *Tetrahedron Lett.,* **1986**, *27*, 2265. (n) Boger, D. L. and Coleman, R. S., *J. Org. Chem.,* **1986**, *51*, 5436. (o) Trost, B. M.; Buhlmayer, P. and Mao, M., *Tetrahedron Lett.,* **1982**, *23*, 1443. (p) Stoute, V. A.; Winnik, M. A. and Csizmadia, I. G., *J. Am. Chem. Soc.,* **1974**, *96*, 6388. (q) Rodewald, W. and Achmatowicz, B., *Roczniki Chem.*, **1972**, *46*, 2193. (r) Isaka, I.; Kojima, T. and Murakami, M., *Yakugaku Zasshi*, **1968**, *88*, 71. (s) Granger, R.; Orzalesi, H. and Joyeux, P., *Compt. Rend.*, **1965**, *260*, 923. (t) Mislow, K. and Brenner, J., *J. Am. Chem. Soc.,* **1953**, *75*, 2318.

5. (a) Brink, G.-J. T.; Arends, I. W. C. E. and Sheldon, R. A., *Chem. Rev.,* **2004**, *104*, 4105. (b) Krow, G. R., *Org. React*., **1993**, *43*, 251. (c) Krow, G. R., *Comp. Org. Syn*., **1991**, *7*, 671. (d) Lee, J. B. and Uff, B. C., *Quart. Rev. Chem. Soc*., **1967**, *21*, 429. (e) Smith, P. A. S., in *Molecular Rearrangements*, ed., de Mayo, P., Wiley-Interscience, New York, **1963**, part 1. (f) Hassal, C. H., *Org. React.*, **1957**, *9*, 73.
6. (a) Suzuki, M.; Takada, H. and Noyori, R., *J. Org. Chem*., **1982**, *47*, 902. (b) Trost, B. M., *Acc. Chem. Res*., **1974**, *7*, 85. (c) Corma, A.; Nemeth, L. T.; Renz, M. and Valencia, S., *Nature*, **2001**, *412*, 423.
7. (a) Brunetta, A.; Sgarbossa, P. and Strukul, G., *Catal. Today,* **2005**, *99*, 227. (b) Lei, Z. Q.; Ma, G. F. and Jia, C. G., *Catal. Commun.,* **2007**, *8*, 305. (c) Lei, Z. Q.; Zhang, Q. H.; Wang, R. M.; Ma, G. F. and Jia, C. G., *J. Organomet. Chem.,* **2006**, *691*, 5767. (d) Ichikawa, H.; Usami, Y. and Arimoto, M., *Tetrahedron Lett.,* **2005**, *46*, 8665. (e) Goodman, M. A. and Detty, M. R., *Synlett,* **2006**, 1100. (f) Zhang, Q. H.; Wen, S. X. and Lei, Z. Q., *React. Funct. Polymers,* **2006**, *66*, 1278. (g) Corma, A.; Fornes, V.; Iborra, S.; Mifsud, M. and Renz, M., *J. Catal.,* **2004**, *221*, 67. (h) Llamas, R.; Jimenez-Sanchidrian, C. and Ruiz, J. R., *Appl. Catal. B: Environ.,* **2007**, *72*, 18. (i) Llamas, R.; Jimenez-Sanchidrian, C. and Ruiz, J. R., *Tetrahedron,* **2007**, *63*, 1435. (j) Jimenez-Sanchidrian, C.; Hidalgo, J. M.; Llamas, R. and Ruiz, J. R., *Appl. Catal. A: General,* **2006**, *312*, 86. (k) Ruiz, J. R.; Jimenez-Sanchidrian, C. and Llamas, R., *Tetrahedron,* **2006**, *62*, 11697. (l) Colladon, M.; Scarso, A. and Strukul, G., *Synlett,* **2006**, 3515. (m) Conte, V.; Floris, B.; Galloni, P.; Mirruzzo, V.; Scarso, A.; Sordi, D. and Strukul, G., *Green Chem.,* **2005**, *7*, 262. (n) Bernini, R.; Coratti, A.; Fabrizi, G. and Goggiamani, A., *Tetrahedron Lett.,* **2005**, *46*, 6169.
8. (a) Gonzalez-Nunez, M. E.; Mello, R.; Olmos, A. and Asensio, G., *J. Org. Chem.,* **2006**, *71*, 6432. (b) Gonzalez-Nunez, M. E.; Mello, R.; Olmos, A. and Asensio, G., *J. Org. Chem.,* **2005**, *70*, 10879. (c) Sgarbossa, P.; Scarso, A.; Pizzo, E.; Sbovata, S. M.; Tassan, A.; Michelin, R. A. and Strukul, G., *J. Mol. Catal. A: Chem.,* **2007**, *261*, 202. (d) Kawabata, T.; Fujisaki, N.; Shishido, T.; Nomura, K.; Sano, T. and Takehira, K., *J. Mol. Catal. A: Chem.,* **2006**, *253*, 279.
9. (a) Luna, A.; Gutierrez, M.-C.; Furstoss, R. and Alphand, V., *Tetrahedron: Asymmetry,* **2005**, *16*, 2521. (b) Ottolina, G.; de Gonzalo, G.; Carrea, G. and Danieli, B., *Adv. Synth. Catal.,* **2005**, *347*, 1035. (c) Moonen, M. J. H.; Westphal, A. H.; Rietjens, I. M. C. M. and van Berkel, W. J. H., *Adv. Synth. Catal.,* **2005**, *347*, 1027. (d) Mihovilovic, M. D.; Mueller, B.; Spina, M.; Durrani, A. I.; Stanetty, P.; Dazinger, G. and Kirchner, K., *Monatsh. Chem.,* **2006**, *137*, 785. (e) Mihovilovic, M. D.; Rudroff, F.; Winninger, A.; Schneider, T.; Schulz, F. and Reetz, M. T., *Org. Lett.,* **2006**, *8*, 1221. (f) Mihovilovic, M. D.; Rudroff, F.; Groetzl, B. and Stanetty, P., *Euro. J. Org. Chem.,* **2005**, 809. (g) Lee, W.-H.; Park, Y.-C.; Lee, D.-H.; Park, K. and Seo, J.-H., *Appl. Biochem. Biotechnol.,* **2005**, 121. (h) Reetz, M. T.; Brunner, B.; Schneider, T.; Schulz, F.; Clouthier, C. M. and Kayser, M. M., *Angew. Chem. Int. Ed.,* **2004**, *43*, 4075. (i) Fairlamb, I. J. S.; Grant, S.; Grogan, G.; Maddrell, D. A. and Nichols, J. C., *Org. Biomol. Chem.,* **2004**, *2*, 1831. (j) Kim, T.-W.; Hwang, J.-Y.; Kim, Y.-S.; Joo, S.-H.; Chang, S. C.; Lee, J. S.; Takatsuto, S. and Kim, S.-K., *Plant Cell,* **2005**, *17*, 2397.
10. Krow, G. R.; Johnson, C. A.; Guare, J. P.; Kubrak, D.; Henz, K. J.; Shaw, D. A.; Szczepanski, W. and Carey, J. T., *J. Org. Chem*., **1982**, *47*, 5239.
11. Haddad, N.; Rukhman, I. and Abramovich, Z., *J. Org. Chem.,* **1997**, *62*, 7629.
12. (a) Cotarca, L.; Delogu, P.; Nardelli, A.; Maggioni, P.; Bianchini, R.; Sguassero, S.; Alini, S.; Dario, R.; Clauti, G.; Pitta, G.; Duse, G. and Goffredi, F., *Org. Proc. Res. Dev*., **2001**, *5*, 69. (b) Laird, T. and Hermitage, S. A., *Org. Proc. Res. Dev*., **2001**, *5*, 544. (c) Rychnovsky, S. D. and Dahanukar, V. H., *J. Org. Chem*., **1996**, *61*, 7648. (d) Carling, R. W.; Clark, S. J.; Holmes, A. B., *J. Chem. Soc., Perkin Trans. I*, **1992**, 83. (e) Wilson, S. R. and Di Grandi, M. J., *J. Org. Chem.*, **1991**, *56*, 4766. (f) Garland, R. B.; Miyano, M. M.; Pireh, D.; Clare, M.; Finnegan, P. M. and Swenton, L., *J. Org. Chem*., **1990**, *55*, 5854. (g) Hammond, M. L.; Kopka, I. E.; Zambiaz, R. A.; Caldwell, C. G.; Boger, J.; Baker, F.; Bach, T.; Luell, S. and MacIntyre, D. E., *J. Med. Chem*., **1989**, *32*, 1006. (h) Shishido, K.; Takahashi, K. and Fukumoto, J., *J. Org. Chem*., **1987**, *52*, 5704.

(i) Zibuck, R.; Liverton, N. J. and Smith. A. B., *J. Am. Chem. Soc.*, **1986**, *108*, 2451. (j) Klunder, A. J. H.; Ariaans, G. J. A.; Loop, E. A. R. M. and Zwanenburg, B., *Tetrahedron*, **1986**, *42*, 1903. (k) Sosnowski, J. J.; Danaher, E. B. and Murray, R. K., *J. Org. Chem*., **1985**, *50*, 2759. (l) Hart, D. J. and Tsia, Y.-M., *J. Am. Chem. Soc.*, **1984**, *106*, 8209. (m) Mergelsberg, I.; Langhals, H. and Ruchardt, C.,*Ber*., **1983**, *116*, 360. (n) Krafft, G. A. and Katzenellenbogen, J. A., *J. Am. Chem. Soc*., **1981**, *103*, 5459. (o) Hudrlik, P. F.; Hudrlik, A. M.; Nagendrappa, G.; Yimenu, T.; Zellers, E. T. and Chin, E., *J. Am. Chem. Soc*., **1980**, *102*, 6894. (p) Hannan, R. L.; Barber, R. B. and Rapoport, H., *J. Org. Chem*., **1979**, *44*, 2153. (q) Baldwin, S. W. and Wilkinson, J. M., *Tetrahedron Lett*., **1979**, *20*, 2657. (r) Salomon, R. G.; Coughlin, D. J. and Easler, E. M., *J. Am. Chem. Soc.*, **1979**, *101*, 3961. (s) Marron, N. A. and Cano, J. E., *J. Am. Chem. Soc.*, **1976**, *98*, 4653. (t) Dauben, W. G. and Aoyagi, E. I., *J. Org. Chem*., **1976**, *37*, 251. (u) Trost, B. M. and Bodganowicz, M. J., *J. Am. Chem. Soc.*, **1973**, *95*, 5321. (v) Trost, B. M. and Bogdanowicz, M. J., *J. Am. Chem. Soc.*, 1973, 95, 5321. (w) Bogdanowicz, M. J.; Ambelang, T. and Trost, B. M., *Tetrahedron Lett*., **1973**, 923. (x) Weinshenker, N. M. and Stephenson, R., *J. Org. Chem*., **1972**, *37*, 3741. (y) Grieco, P. A., *J. Org. Chem*., **1972**, *37*, 2373. (z) Klunder, A. J. H. and Zwanenburg, B., *Tetrahedron Lett*., **1972**, *28*, 4131. (aa) Eadon, G., Popov, S. and Djerassi, C., *J. Am. Chem. Soc.*, **1972**, *94*, 1282. (bb) Zwanenburg, B. and Klunder, A. J. H., *Tetrahedron Lett*., **1971**, 1717. (cc) Tsuda, Y.; Tanno, T.; Ukai, A. and Isobe, K., *Tetrahedron Lett*., **1971**, 2009. (dd) Corey, E. J. and Ravindranathan, T., *Tetrahedron Lett*., **1971**, 4753. (ee) Meinwald, J.; Labana, L. L. and Wheeler, T. N., *J. Am. Chem. Soc.*, **1970**, *92*, 1006. (ff) Horton, J. A.; Laura, M. A.; Kalbag, S. M. and Petterson, R. C., *J. Org. Chem*., **1969**, *34*, 3366. (gg) Robertson, J. C. and Swelim, A., *Tetrahedron Lett*., **1967**, *30*, 2871. (hh) Pinhey, J. T. and Schaffner, K., *Tetrahedron Lett*., **1965**, 601. (ii) Mateos, J. L. and Menchaca, H., *J. Org. Chem*., **1964**, *29*, 2026. (jj) Cope, A. C. and Woo, G. L., *J. Am. Chem. Soc.*, **1963**, *85*, 3601. (kk) Mcclure, J. D. and Williams, P. H., *J. Org. Chem*., **1962**, *27*, 24. (ll) Hawthorne, M. F.; Emmons, W. D. and McCallum, K. S., *J. Am. Chem. Soc.*, **1958**, *80*, 6393. (mm) Hawthorne, M. F. and Emmons, W. D., *J. Am. Chem. Soc.*, **1958**, *80*, 6398. (nn) Sager, W. and Duckworth, A., *J. Am. Chem. Soc.*, **1955**, *77*, 188. (oo) Emmons, W. D. and Lucas, G. B., *J. Am. Chem. Soc.*, **1955**, *77*, 2287. (pp) Buu-Hoi, N. P. and Lavit, D., *J. Org. Chem*., **1955**, *20*, 1191. (qq) Mislow, K. and Brenner, J., *J. Am. Chem. Soc.*, **1953**, *75*, 2318. (rr) Friess, S. L. and Pinson, R., *J. Am. Chem. Soc.* **1952**, *74*, 1302. (ss) Turner, R. B., *J. Am. Chem. Soc.*, **1950**, *72*, 878. (tt) Rivera, D. G.; Pando, O.; Suardiaz, R. and Coll, F., *Steroids,* **2007**, *72*, 466. (uu) Yoshida, A.; Yoshimura, M.; Uehara, K.; Hikichi, S. and Mizuno, N., *Angew. Chem. Int. Ed.,* **2006**, *45*, 1956. (vv) Boronat, M.; Corma, A.; Renz, M.; Sastre, G. and Viruela, P. M., *Chem. Eur. J.,* **2005**, *11*, 6905. (ww) Jastrzebska, I. and Morzycki, J. W., *Pol. J. Chem.,* **2005**, *79*, 1245. (xx) Imada, Y.; Iida, H.; Murahashi, S.-I. and Naota, T., *Angew. Chem. Int. Ed.,* **2005**, *44*, 1704. (yy) Cristau, H.-J.; Marat, X.; Vors, J.-P.; Virieux, D. and Pirat, J.-L., *Curr. Org. Synth.,* **2005**, *2*, 113. (zz) Yadav, J. S.; Reddy, B. V. S.; Basak, A. K. and Narsaiah, A. V., *Chem. Lett.,* **2004**, *33*, 248. (aaa) Watanabe, A.; Uchida, T.; Irie, R. and Katsuki, T., *Proc. Nat. Acad. Sci. USA,* **2004**, *101*, 5737. (bbb) Moulines, J.; Bats, J.-P.; Lamidey, A.-M. and Da Silva, N., *Helv. Chim. Acta,* **2004**, *87*, 2695. (ccc) Mihovilovic, M. D.; Rudroff, F. and Groetzl, B., *Curr. Org. Chem.,* **2004**, *8*, 1057. (ddd) Hilker, I.; Gutierrez, M. C.; Alphand, V.; Wohlgemuth, R. and Furstoss, R., *Org. Lett.,* **2004**, *6*, 1955. (eee) Kosaka, N.; Hiyama, T. and Nozaki, K., *Macromolecules,* **2004**, *37*, 4484. (fff) Laurent, M.; Ceresiat, M. and Marchand-Brynaert, J., *J. Org. Chem.,* **2004**, *69*, 3194. (ggg) Fukuda, O.; Sakaguchi, S. and Ishii, Y., *Tetrahedron Lett.,* **2001**, *42*, 3479. (hhh) Crudden, C. M.; Chen, A. C. and Calhoun, L. A., *Angew. Chem. Int. Ed. Engl.,* **2000**, *39*, 2851. (iii) Hickman, Z. L.; Sturino, C. F. and Lachance, N., *Tetrahedron Lett*., **2000**, *41*, 8217. (jjj) Renz, M. and Meunier, B., *Eur. J. Org. Chem*., **1999**, *4*, 737. (kkk) Bolm, C. and Beckmann, O., *Compr. Asymmetric Catal. I-III*, **1999**, *2*, 803. (lll) Becker, D. and Birnbaum, D., *J. Org. Chem*., **1980**, *45*, 570.

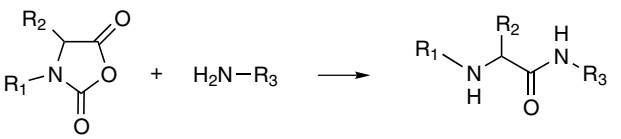
37

Bailey Peptide Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

Several methods have been developed to synthesize peptides, of which one is to use *N*-carboxyanhydrides (NCAs). The most successful application of the NCA method in peptide synthesis is the one developed by Bailey in 1949,[1] in which amino acids and peptide esters condense with NCAs at low temperatures in organic solvents.[2] This reaction is known as the Bailey peptide ester synthesis.[3] This method for peptide synthesis has the a great advantage of rapid acylation of an amino acid so that the reaction completes in a few minutes to a few hours to give a peptide in very high yield.[4] In addition, the reaction of NCAs with amino acids or peptides can be accomplished without protection of the functional group of the amino acids or the peptides. This method, therefore directly gives a free peptide from an amino acid. Although a by-product sometimes exists, *N*-substituted NCA has been developed so that the formed by-product can be easily removed from the conventional washing of the product with an acid or base.[5]

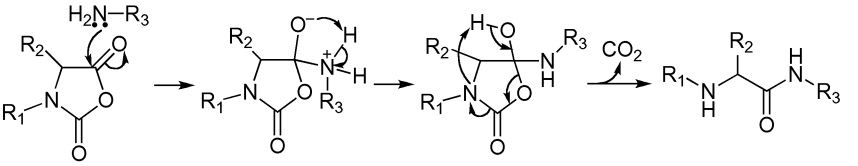
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

Displayed here is a simple illustration of this reaction.



D. MODIFICATION

N-substituted amino acid NCA has been applied to a similar reaction.[6b]

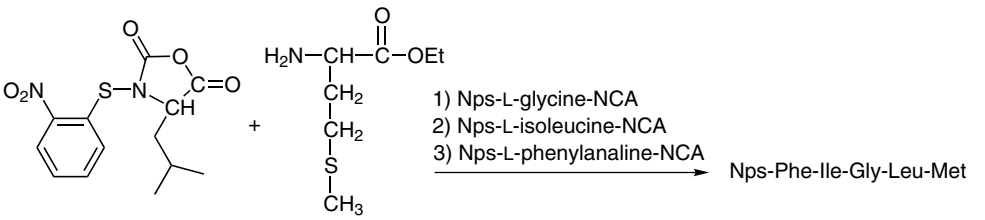
E. APPLICATIONS

N/A

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 4.

To a solution of 10.7 g L-methionine ethyl ester hydrochloride (0.05 mol) in 200 mL THF was added 7.0 mL triethylamine (0.05 mol). The resulting salt was filtered. To the solution, 17.0 g (0.055 mol) Nps-leucine NCA was added and stirred at room temperature for 2 h. Then the solvent was evaporated under reduced pressure at 35°C, the residual oil was dissolved in 200 mL ethyl acetate, and the solution was washed with 5% of citric acid, 5% of sodium bicarbonate, and water; and dried over Na_2SO_4. The solution was concentrated in vacuum at 40°C to give an oil, which was crystallized by adding *n*-hexane. Further purification can be done from recrystallization in ethyl acetate.

Then 13.3 g (0.03 mol) purified Nps-L-leucyl-L-methionine ethyl ester was dissolved in 150 mL methanol saturated with ammonia, and the solution was allowed to stand for 3 days. The solvent was evaporated to give a yellow solid, which was again dissolved in 150 mL methanol. The solution was concentrated, and diethyl ether was added to the residue. The resulting crystals of the Nps-dipeptide amide were obtained in 96% yield. The Nps-dipeptide amide was dissolved in 50 mL 1 N hydrochloric acid in methanol. After the solvent was evaporated, 300 mL diethyl ether was added. The resulting solid of the hydrochloride was isolated and washed with diethyl ether until the yellow color disappeared. The dipeptide amide hydrochloride (8.35 g, 0.028 mol) was dissolved in 150 mL tetrahydrofuran and treated with 4.2 mL (0.03 mol) triethylamine. After the crystals of the salt were removed by filtration, 7.6 g (0.03 mol) Nps-glycine NCA was added and allowed to react for 2 h at room temperature. The solvent was evaporated at 35°C. The residue was dissolved in 400 mL ethyl acetate, washed with 5% citric acid, 5% sodium bicarbonate, and water, and dried over sodium sulfate. The filtrate was concentrated to crystallize the Nps-tripeptide amide. The product was recrystallized from warm tetrahydrofuran. The Nps-protecting group of the tripeptide amide was removed by dissolving in 50 mL 1 N hydrochloric acid in methanol. Glycyl-L-leucyl-L-methionine amide hydrochloride was isolated by adding 400 mL diethyl ether, followed by filtration, and the filtrate was washed with diethyl ether. The tripeptide amide hydrochloride was dissolved in 200 mL tetrahydrofuran and treated with triethylamine, followed by 9.3 g (0.03 mol) Nps-L-isoleucine NCA. The isolation and purification of the product were done by the same procedure of Nps-tripeptide amide to give a pure Nps-tetrapeptide amide. The Nps group of 11.7 g (0.02 mol) Nps-L-isoleucylglycyl-L-leucyl-L-methionine amide was removed by action of hydrochloric acid. The tetrapeptide amide hydrochloride was treated in the presence of 3 mL (0.0214 mol) triethylamine with 7.8 g (0.022 mol) Nps-L-phenylalanine NCA in 300 mL tetrahydrofuran. The solvent was removed by evaporation, and the residue was diluted with 400 mL water to crystallize the Nps-pentapeptide amide. The product was collected by filtration and washed with 5% citric acid, 5% sodium bicarbonate, and water and then dried in vacuo over P_2O_5. The yield was 93%, m.p. 232–234°C.

Other references related to the Bailey peptide synthesis have been cited in the literature.[6]

H. REFERENCES

1. (a) Bailey, J. L., *Nature* (*London*), **1949**, *164*, 889. (b) Bailey, J. L., *J. Chem. Soc*., **1950**, 3461.
2. Hirschmann, R.; Strachan, R. G.; Schwam, H.; Schoenewaldt, E. F.; Joshua, H.; Barkemeyer, B.; Veber, D. F.; Paleveda, W. J.; Jacob, T. A.; Beesley, T. E. and Denkewalter, R. G., *J. Org. Chem*., **1967**, *32*, 3415.
3. Langenbeck, W. and Kresse, P., *J. Physiologie (Paris),* **1955**, *2*, 261.
4. Katakai, R., *J. Org. Chem*., **1975**, *40*, 2697.
5. Greenstein, J. P. and Winitz, M., *Chemistry of the Amino Acids*, Wiley, New York, **1961**, p 943.
6. (a) Bailey, J. L., *Techniques in Protein Chemistry*, Elsevier Publishing. New York, **1962**. (b) Xue, C.-B. and DeGrado, W. F., *J. Org. Chem*., **1996**, *60*, 946. (c) Fuller, W. D.; Cohen, M. P.; Shabankareh, M.; Blair, R. K.; Goodman, M. and Naider, F. R., *J. Am. Chem. Soc*., **1990**, *112*, 7414. (d) Kricheldorf, H. R., *α-Aminoacid-N-Carboxy-Anhydrides and Related Heterocycles: Syntheses, Properties, Peptide Synthesis, Polymerization,* Springer-Verlag, Berlin, **1987**, pp. 22–23. (e) Akiyama, M.; Hasegawa, M.; Takeuchi, H. and Shimizu, K., *Tetrahedron Lett*., **1979**,

28, 2599. (f) Banerjee, S. N. and Ressler, C.*, J. Org. Chem.*, **1976**, *41*, 3056. (g) Katakai, R.; Oya, M.; Toda, F.; Uno, K. and Iwakura, Y., *J. Org. Chem*., **1974**, *39*, 180. (h) Grovestine, E. M.; Langlois, J. R. and Williams, R. E., *Can. J. Chem*., **1973**, *51*, 1284. (i) Katakai, R.; Oya, M.; Uno, K. and Iwakura, Y., *J. Org. Chem*., **1972**, *37*, 327. (j) Gait, R. J.; Langlois, J. R. and Williams, R. E., *Can. J. Chem*., **1972**, *50*, 299. (k) Maher, J. J.; Furey, M. E. and Greenberg, L. J., *Tetrahedron Lett*., **1972**, 1581. (l) Katakai, R.; Oya, M.; Uno, K. and Iwakura, Y., *Biopolymers*, **1971**, *10*, 2199. (m) Hirschmann, R.; Schwam, H.; Strachan, R. G.; Schoenewaldt, E. F.; Barkemeyer, H.; Miller, S. M.; Conn, J. B.; Garsky, V.; Veber, D. F. and Denkewalter, R. G., *J. Am. Chem. Soc*., **1971**, *93*, 2746. (n) Dewey, R. S.; Schoenewaldt, E. F.; Joshua, H.; Paleveda, W. J.; Schwam, H.; Barkemeyer, H.; Arison, B. H.; Veber, D. F.; Strachan, R. G.; Milkowski, J.; Denkewalter, R. G. and Hirschmann, R., *J. Org. Chem*., **1971**, *36*, 49. (o) Iwakura, Y.; Uno, K.; Oya, M. and Katakai, R., *Biopolymers*, **1970**, *9*, 1419. (p) Kirk, K. L. and Cohen, L. A., *J. Org. Chem*., **1969**, *34*, 384. (q) Kipple, K. D.; Saito, T. and Ohnishi, M., *J. Org. Chem*., **1969**, *34*, 1631. (r) Denkewalter, R. G.; Veber, D. F.; Holly, F. W. and Hirschmann, R., *J. Am. Chem. Soc*., **1969**, *91*, 502. (s) Veber, D. F.; Hirschmann, R. and Denkewalter, R. G., *J. Org. Chem*., **1969**, *34*, 753. (t) Dewey, R. S.; Schoenewaldt, E. F.; Joshua, H.; Paleveda, W. J.; Schwam, H.; Barkermeyer, H.; Arison, B. H.; Veber, D. F.; Denkewalter, R. G. and Hirschmann, R., *J. Am. Chem. Soc.,* **1968**, *90*, 3254. (u) Denkewalter, R. G.; Schwam, H.; Strachan, R. G.; Beesley, T. E.; Veber, D. F.; Schoenewaldt, E. F.; Barkemeyer, H.; Paleveda, W. J.; Jacob, T. A. and Hirschmann, R., *J. Am. Chem. Soc*., **1966**, *88*, 3163. (v) Fridkin, M.; Patchornik, A. and Katchalski, E., *J. Am. Chem. Soc*., **1965**, *87*, 4646. (w) Panayotis, B. and Ratsoyannis, G., *J. Am. Chem. Soc*., **1961**, *83*, 4053. (x) Bartlett, P. D.; Jones, R. H.*, J. Am. Chem. Soc*., **1957**, *79*, 2153. (y) Overell, B. G. and Petrow, V., *J. Chem. Soc*., **1955**, 232. (z) Honzyl, J. and Rudinger, J., *Coll. Czech. Chem. Commun*., **1955**, *20*, 1190. (aa) Schlögl, I.; Wessely, F. and Wawersich, E., *Monatsh. Chem.*, **1953**, *84*, 705. (bb) Honzl, J. and Rudinger, J., *Collect. Czech. Chem. Commum.,* **1953**, *84*, 705. (cc) Rudinger, J. and Sorm, F., *Coll. Czech. Chem. Commun*., **1951**, *16*, 214. (dd) Wessely, F.; Schlogl, K. and Korger, G., *Monatsch. Chem.,* **1951**, *82*, 671.

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Bakelite Process

(Baekeland-Manasse-Lederer Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

Orthohydroxy benzyl alcohol,[1] oxybenzylalcohol,[2] or simply phenol alcohol or saligenin[2,3] was first isolated by Piria in 1843.[1] It can be converted into resin (known as "saliretins"[4]) on heating. The reaction between phenol and aldehyde was first reported by von Baeyer in 1872,[5] who used an iron pressure cooker he invented, called a "bakelizer,"[2] and resulted in a sticky substance that he dismissively called "Schmiere". The actual reaction between formaldehyde and phenol was independently studied by Manasse[6] and Lederer in 1894,[7] after formaldehyde became a commercial product.

In Manasse's protocol, phenol was treated with an equivalent of strong alkali base in aqueous solution for several days until the odor of formaldehyde disappeared, whereas in Lederer's process, phenol was heated with weak base until the completion of the reaction.[1] Therefore, the reaction of phenol and formaldehyde under basic condition is referred to as the Manasse-Lederer reaction.[8] The resulting products, known as "shellac substitutes,"[2] are soluble in alcohol, acetone, and alkaline hydroxide and melt on heating and resolidify after cooling. In addition, the heating and melting can be repeated indefinitely.[3] It was Baekeland who in 1909 developed a process to make phenolic thermosetting resin from phenol and formaldehyde in an apparatus that provided external pressure[2] to balance the internal pressure.[2,3,9] Formaldehyde was heated with an excess of phenol and in the presence of an acid condensing agent to form fusible, soluble resins. This process consists of three phases. In the first phase, the product is referred to as initial condensation product, designated by Baekeland as Bakelite A, which at ordinary temperatures may be liquid, viscous, pasty, or

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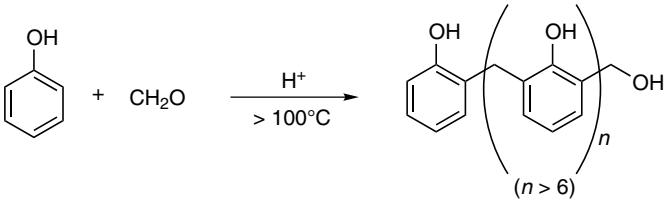
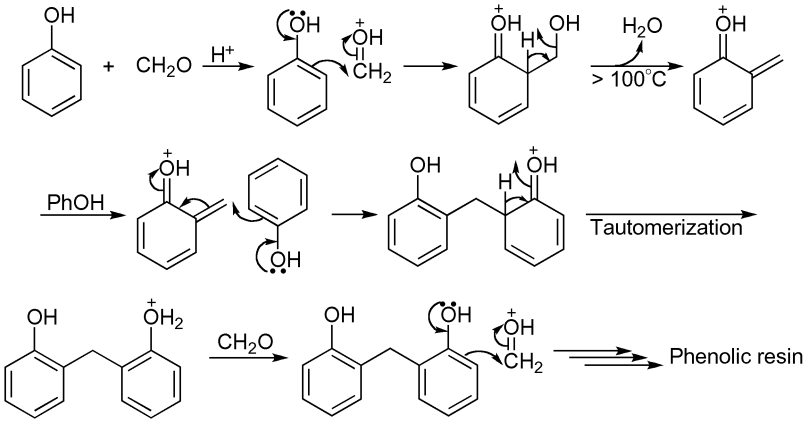
solid. Bakelite A is soluble in alcohol, acetone, phenol, and NaOH solution.[2] The product from the second phase—the so-called intermediate condensation product—is designated as Bakelite B, which is solid at all temperatures and insoluble in all solvents but may swell in acetone, phenol, or terpineol. It softens decidedly but does not melt and becomes elastic during heating and becomes again hard and brittle upon cooling. The product of the third phase is called the final condensation product, or Bakelite C, which is infusible, insoluble in all solvents, and indifferent to ordinary acids and alkaline solutions. Other properties of Bakelite C include poor conductivity of heat and electricity and excellent thermal stability. For example, Bakelite C can stand boiling with dilute H_2SO_4 and does not soften to any serious extent if heated (but chars without entering into fusion). It stands at temperatures as high as to 300°C.[2,9k] Therefore, the process to make Bakelite is referred to as the Bakelite process,[10] and Bakelite is the trademark of oxybenzylmethylen-glycolanhydride.[9k]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

This reaction should involve multiple condensation between formaldehyde and phenol, as shown here.



D. MODIFICATION

N/A

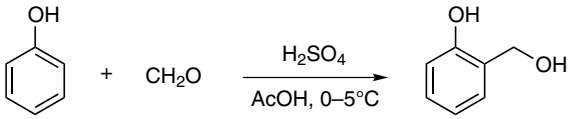
E. APPLICATIONS

This reaction has important applications in industry for making phenolic resins.

F. RELATED REACTIONS

This reaction is related to the *Rothemund Condensation* and *Zinke Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 8f.

A substituted phenol (0.1 mol) was dissolved in 20 mL glacial acetic acid, and a cold solution of 20 g of conc. H_2SO_4 in 40 mL glacial acetic acid was then added. Over a period of 2.5 h, 4.2 mL 40% formaldehyde (0.055 mol) was added to the mixture at 0–5°C. The reaction mixture was stirred cold for an additional 3 h and was then stirred at room temperature for 24 h after the beginning of the reaction. The reaction mixture was poured into cold water, and the precipitate was filtered off and neutralized with sodium bicarbonate solution. The product was purified by crystallization.

Other references related to the Bakelite process are cited in the literature.[11]

H. REFERENCES

1. Granger, F. S., *Ind. Eng. Chem.,* **1932**, *24*, 442.
2. Baekeland, L. H., *J. Ind. Eng. Chem.,* **1909**, *1*, 149.
3. Baekeland, L. H., *J. Ind. Eng. Chem.,* **1911**, *3*, 932.
4. Granger, F. S., *Ind. Eng. Chem.,* **1937**, *29*, 860.
5. (a) von Baeyer, A., *Ber*., **1872**, *5*, 25. (b) von Baeyer, *Ber*., **1872**, *5*, 280. (c) von Baeyer, A., *Ber*., **1872**, *5*, 1094.
6. (a) Manasse, O., *Ber.,* **1894**, *27*, 2409. (b) Manasse, O., *U.S. Pat.,* **1894**, Oct. 2, 526,786.
7. (a) Lederer, L., *J. Prakt. Chem.,* **1894**, *50*, 224. (b) Lederer, L., *U.S. Pat.,* **1896**, July 14, 563,975.
8. (a) Alonso, M. V.; Rodriguez, J. J.; Oliet, M.; Rodriguez, F.; Garcia, J. and Gilarranz, M. A., *J. Appl. Poly. Sci.,* **2001**, *82*, 2661. (b) Zhao, L.-W.; Griggs, B. F.; Chen, C.-L.; Gratzl, J. S. and Hse, C-Y., *J. Wood Chem. Technol.,* **1994**, *14*, 127. (c) Green, M.; Sayigh, A. A. and Ulrich, H., *U.S. Pat.,* **1966**, Feb. 22, 3,236,898. (d) Kametani, T. and Ogasawara, K., *J. Chem. Soc.,* **1964**, 4142. (e) Nozoe, T.; Mukai, T. and Takase, K., *Sci. Rept. Tohoku Univ.,* **1952**, *36*, 40. (f) Faith, E. H., *J. Am. Chem. Soc.,* **1950**, *72*, 837. (g) Adler, E.; Tingstam, S. and Caspersson, O., *Arkiv Kemi, Mineral. Geol.,* **1942**, 15*B*, 1. (h) Auwers, K. and Traun, F. A., *Ber.,* **1899**, *32*, 3309.
9. (a) Baekeland, L. H., *U. S. Pat.,* **1909**, Nov. 16, 939,966. (b) Baekeland, L. H., *U. S. Pat.,* **1909**, Nov. 30, 941,605. (c) Baekeland, L. H., *U. S. Pat.,* **1909**, Dec. 7, 942,699. (d) Baekeland,

L. H., *U. S. Pat.,* **1909**, Dec. 7, 942,700. (e) Baekeland, L. H., *U. S. Pat.,* **1909**, Dec. 7, 942,808. (f) Baekeland, L. H., *U. S. Pat.,* **1909**, Dec.7, 942,809. (g) Baekeland, L. H., *U. S. Pat.,* **1909**, Dec. 7, 942,852. (h) Baekeland, L. H., *U. S. Pat.,* **1910**, Feb. 15, 949,671. (i) Baekeland, L. H., *U. S. Pat.,* **1910**, Apr. 12, 954,666. (j) Baekeland, L. H., *U. S. Pat.,* **1910**, May 3, 957,137. (k) Baekeland, L. H., *J. Ind. Eng. Chem.*, **1909**, 1, 545. (l) Baekeland, L. H., *Trans. Am. Electrochem, Soc*., **1909**, *15*, 593. (m) Baekeland, L. H., *Angew. Chem.,* **1910**, *22*, 2006. (n) Baekeland, L. H., *J. Ind. Eng. Chem.*, **1910**, 2, 478. (o) Baekeland, L. H., *J. Ind. Eng. Chem*., **1912**, *4*, 737. (p) Baekeland, L. H., *J. Ind. Eng. Chem*., **1913**, *5*, 506. (q) Baekeland, L. H., *J. Ind. Eng. Chem*., **1935**, *27*, 538.

10. (a) Cassidy, P. E.; Marvel, C. S. and Ray, S., *J. Poly. Sci., Part A: General Papers,* **1965**, *3*, 1553. (b) Harold, P. K., *J. Appl. Poly. Sci.,* **1964**, *8*, 1443.

11. (a) Ahmaruzzaman, M. and Sharma, D. K., *Energy & Fuels,* **2007**, *21*, 891. (b) Ahmaruzzaman, M. and Sharma, D. K., *Energy & Fuels,* **2006**, *20*, 2498. (c) Martuscelli, E., *Chim. Ind. (Milan)*, **1998**, 80, 355. (d) Reusova, L. A.; Lykov, M. V.; Petrilenkova, E. B.; Bogoslovskii, V. E. and Zhigalov, V. G., *Plast. Massy,* **1969**, 38. (e) Griengl, H.; Appenroth, M.; Dax, K. and Schwarz, H., *Monatsh. Chem.,* **1969**, *100*, 316. (f) Schaar, B. E., *Chemistry,* **1967**, *40*, 19. (g) Traverso, G., *Gazz. Chim. Ital.,* **1958**, *88*, 517. (h) Goethals, G., *Natuurwetenschappelijk Tijdschrift (Ghent)*, **1936**, *18*, 249. (i) Zinzow, W. A. and Hazen, T., *Ind. Eng. Chem.,* **1935**, *27*, 899. (j) Kremlevskii, P. A., *Zavodskaya Lab.,* **1933**, 16. (k) Issinskii, P. A., *Lesokhimicheskaya Promyshlennost,* **1932**, *1*, 3. (l) Redman, L. V. and Mory, A. V. H., *Ind. Eng. Chem.,* **1931**, *23*, 595. (m) Redman, L. V., *Ind. Eng. Chem.,* **1928**, *20*, 1274. (n) Abonyi, A. L., *Kunststoffe,* **1926**, 16, 30. (o) Clement, R., *Chem. Ind. (Paris),* **1922**, *8*, 38. (p) Flight, W. S., *BEAMA,* **1921**, *9*, 542. (q) Matsumoto, G., *J. Chem. Ind. Jpn.,* **1915**, *18*, 434. (r) Redman, L. V.; Weith, A. J. and Brock, F. P., *J. Ind. Eng. Chem.,* **1913**, *6*, 3. (s) Auwers, K., *Ber.,* **1907**, *40*, 2524. (t) Auwers, K. and Traun, F. A., *Ber.,* **1899**, *32*, 3309.

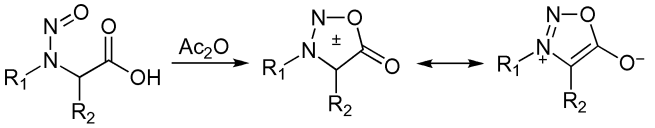
39

Baker-Ollis Sydnones Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

The sydnones, of both biological and structural importance, were first reported by Earl and Wackney in 1935[1] but were not studied intensively until 1946 and thereafter.[2] The structural importance of this type of compound is that no single valence structure can adequately explain the chemical and physical properties of sydnones, although many controversial structures have been proposed to solve this problem.[3] The most commonly used structure is the one proposed by Baker and Ollis in 1957.[4] From the structural point of view, sydnones represent only 1 of some 288 possible five-membered ring systems having similar electronic characteristics, of which relatively few have yet been prepared.[5] Generally, sydnones can be simply synthesized from *N*-nitroso derivatives of *N*-substituted α-amino acids with certain dehydrating agents, such as acetic anhydride.[6] The sydnones were reviewed by Stewart in 1964.[7]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The formation of sydnone is shown here.

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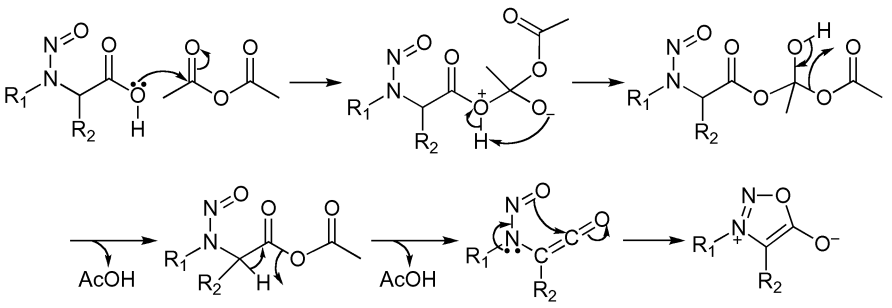


D. MODIFICATION

Trifluoroacetic anhydride,[2h,6c] thionyl chloride,[2h] and carbonyl chloride[8] have been applied as dehydrating reagents. When trifluoroacetic anhydride is used, a reaction that usually takes a few days can be completed in seconds. In aqueous solution, *N*,*N*-diisopropylcarbodiimide[8] has been used in this reaction at room temperature.

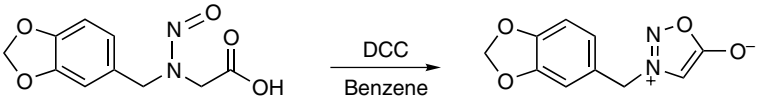
E. APPLICATIONS

N/A

F. RELATED REACTIONS

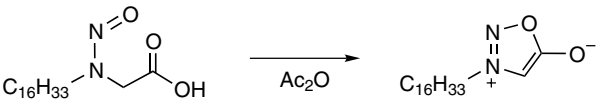
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 9.

To a solution of 4 g *N*-nitroso-*N*-piperonylglycine in 150 mL dry benzene at 70°C was added a 50 mL dry benzene solution (also 70°C) containing enough *N*,*N*-dicyclohexylcarbodiimide (DCC), and *N*,*N*-dicyclohexylurea immediately precipitated. The mixture was stirred at 50–60°C for 2 h and filtered while hot. The filtrate was evaporated to dryness in *vacuo*, and the residue was recrystallized from 75 mL toluene; 2.7 g 3-piperonylsydnone (shiny needles) was obtained, in a yield of 72.4%, m.p. 158–159°C. A parallel run was also carried out using acetic anhydride as a cyclizing reagent, and a comparable yield was obtained.



Reference 10.

A mixture of 0.5 g nitroso acid and 10 mL acetic anhydride was kept at room temperature in the dark for 3–4 days, with gentle warming at intervals to maintain complete solution. The excess anhydride was decomposed with water, and the precipitated *N*-hexadecylsydnone was filtered off, washed, and recrystallized from aqueous ethanol to afford 0.33 g product as colorless needles, in a yield of 70%, m.p. 63.5–64.5°C.

Other references related to sydnones are cited in the literature.[11,12]

H. REFERENCES

1. Earl, J. C. and Wackney, A. W., *J. Chem. Soc*., **1935**, 899.
2. (a) Hammick, D. L. and Roe, A. M., *Chem. Ind.*, **1963**, 900. (b) Hammick, D. L.; Roe, A. M. and Voaden, D. J., *Chem. Ind.*, **1954**, 251. (c) Kruger, S., *Chem. Ind.*, **1954**, 465. (d) Earl, J. C., *Chem. Ind.*, **1953**, 746. (e) Earl, J. C., *Chem. Ind.*, **1953**, 1284. (f) Hill, R. A. W. and Sutton, L. E., *J. Chem. Soc.*, **1953**, 1482. (g) Earl, J. C.; LeFevre, R. J. W.; Pulford, A. G. and Walsh, A., *J. Chem. Soc*., **1951**, 2207. (h) Baker, W.; Ollis, W. D. and Poole, V. D., *J. Chem. Soc*., **1950**, 1542. (i) Hill, R. A. W. and Sutton, L. E., *J. Chim. Phys.Phys.-Chim. Biol.*, **1949**, *46*, 244. (j) Hill, R. A. W. and Sutton, L. E., *J. Chem. Soc*., **1949**, 746. (k) Baker, W.; Ollis, W. D. and Poole, V. D., *J. Chem. Soc.*, **1949**, 307. (l) Earl, J. C.; LeFevre, R. J. W. and Wilson, I. R., *J. Chem. Soc*., **1949**, S103. (m) Earl, J. C.; Leake, E. M. W. and LeFevre, R. J. W., *J. Chem. Soc*., **1948**, 2269. (n) Eade, R. A. and Earl, J. C., *J. Chem. Soc*., **1948**, 2307. (o) Baker, W.; Ollis, W. D.; Poole, V. D.; Barltrop, J. A.; Hill, R. A. W. and Sutton, L. E., *Nature*, **1947**, *160*, 366. (p) Kenner, J. and MacKay, K., *Nature*, **1947**, *160*, 465. (q) Baker, W. and Ollis, W. D., *Nature*, **1946**, *158*, 703. (r) Earl, J. C., *Nature*, **1946**, *158*, 910. (s) Kenner, J. and Mackay, K., *Nature*, **1946**, *158*, 909.
3. (a) Tien, J. M. and Hunsberger, I. M., *J. Am. Chem. Soc.*, **1961**, *83*, 178. (b) Baker, W., *Proc. Chem. Soc*., **1959**, 75. (c) Kato, H. and Ohta, M., *Bull. Chem. Soc. Jpn*., **1957**, *30*, 210. (d) Katritzky, A. R., *Chem. Ind. (London)*, **1955**, 1391.
4. Baker, W. and Ollis, W. D., *Quart. Rev. (London),* **1957**, *11*, 15.
5. Bieber, T. I., *Chem. Ind. (London),* **1955**, 1055.
6. (a) Stewart, F. H. C., *J. Chem. Soc.,* **1963**, 701. (b) Stewart, F. H. C., *J. Chem. Soc.,* **1963**, 2099. (c) Daeniker, H. U. and Druey, J., *Helv. Chim. Acta,* **1957**, *40*, 918. (d) Eade, R. A. and Earl, J. C., *J. Chem. Soc*., **1946**, 591.
7. Stewart, F. H. C., *Chem. Rev*., **1964**, *64*, 129.
8. Pütter, R. W., and Wolfrom, G., *Brit. Pat.*, **1959**, Nov. 4, 823,001 [*Chem. Abstr*. **1960**, *54*, 8854].
9. Nyberg, W. H. and Cheng, C. C., *J. Med. Chem*., **1965**, *8*, 531.
10. Stewart, F. H. C., *Aust. J. Chem.,* **1961**, *14*, 654.
11. (a) Ollis, W. D. and Ramsden, C. A., "Meso-ionic compounds" in *Advances in Heterocyclic Chemistry*, Vol. 19, ed., Katritzky, A. R. and Boulton, A. J., Academic Press, New York, **1976**, pp. 1–122. (b) Thiessen, W. E. and Hope, H., *J. Am. Chem. Soc*., **1967**, *89*, 5977. (c) Metz, F. I.; Servoss, W. C. and Welsh, F. E., *J. Phys. Chem*., **1962**, *66*, 2466. (d) Yashunskii, V. G.; Vasil'eva, V. F. and Sheinker, Y. N., *Zh. Obsh. Khim.,* **1959**, *29*, 2712. (e) Henry, R. A.; Finnegan, W. G.

and Lieber, E., *J. Am. Chem. Soc*., **1954**, *76*, 2894. (f) Baker, W.; Ollis, W. D. and Poole, V. D., *J. Chem. Soc*., **1950**, 3389. (g) Baker, W.; Ollis, W. D. and Poole, V. D., *J. Chem. Soc*., **1949**, 307.

12. (a) Sherigara, B. S.; Shivaraj, Y.; Mascarenhas, R. J.; Rainoji, S. and Kallurayac, B., *Croat. Chem. Acta,* **2006**, *79*, 273. (b) Mascarenhas, R. J.; Shivaraj, Y.; Sherigara, B. S.; Mahadevan, K. M. and Kalluraya, B., *Russ. J. Electrochem.,* **2006**, *42*, 776. (c) Moustafa, M. A.; Nasr, M. N.; Gineinah, M. M. and Bayoumi, W. A., *Arch. Pharm. Pharm. Med. Chem.,* **2004**, *337*, 164. (d) Yashunskii, V. G. and Kholodov, L. E., *Russ. Chem. Rev.,* **1980**, *49*, 28. (e) Fridman, A. L.; Mukhametshin, F. M. and Novikov, S. S., *Russ. Chem. Rev.,* **1971**, *40*, 34. (f) Bowie, J. H.; Eade, R. A. and Earl, J. C., *Aust. J. Chem.,* **1968**, *21*, 1665. (g) Stille, J. K. and Bedford, M. A., *J. Poly. Sci., Part B: Poly. Lett.,* **1966**, *4*, 329. (h) Tin-Lok, C.; Miller, J. and Stansfield, F., *J. Chem. Soc.*, **1964**, 1213.

40

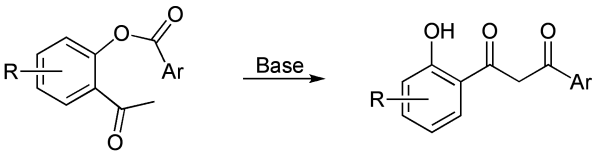
Baker-Venkataraman Rearrangement

(Baker-Venkataraman Transformation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first and concurrently reported by Baker[1] and Venkataraman[2] in 1933. It is the rearrangement of *o*-acyloxyketones into β-diketones under basic conditions and is generally known as the Baker-Venkataraman rearrangement[3] or Baker-Venkataraman transformation.[4] In addition, this reaction is also referred to as the Baker-Venkataraman reaction,[5] and Baker-Venkataraman synthesis.[6] Although this intramolecular acyl transfer reaction has become a major reaction in flavone chemistry,[7] the migration of acyl group has been confined to aromatic or heteroaromatic acyl group.[8] The resulting molecules can be applied to the synthesis of chromones and flavones and has been extensively reviewed.[9]

B. GENERAL REACTION SCHEME



(R = alkyl, OH, alkoxyl)

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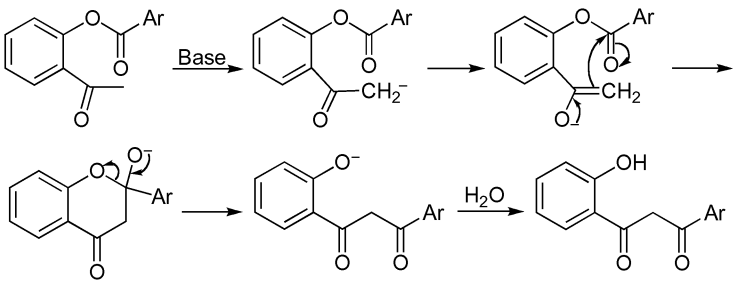
C. PROPOSED MECHANISMS

Even though the mechanism of this reaction has been discussed elsewhere,[10] shown here is another illustration of this reaction.



D. MODIFICATION

N/A

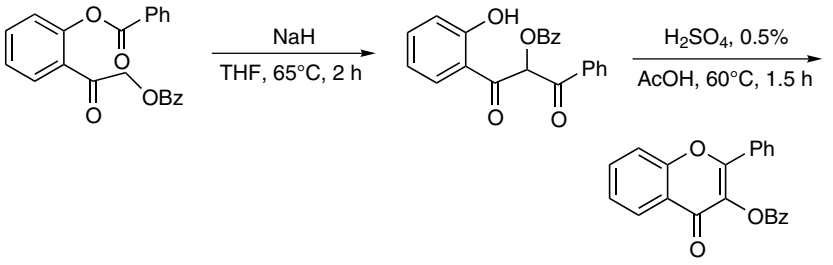
E. APPLICATIONS

This reaction has been applied to synthesize other types of molecules.[11]

F. RELATED REACTIONS

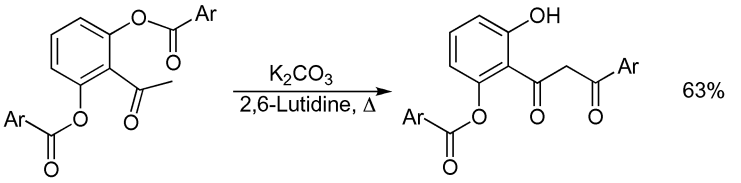
This reaction is related to the *Allan-Robinson Annulation* and *Kostanecki Acylation* in terms of the formation of flavones. In mechanism, this reaction is related to the *Fries Rearrangement*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 12.

To a suspension of 48.0 mg NaH (2.0 mmol) in 10 mL dry THF was added 250 mg 2,2′-dibenzoyloxyacetophenone (0.7 mmol) in 10 mL THF. The mixture was refluxed for 90 min, and then the cooled mixture was poured into a mixture of 120 g ice and 2 mL concentrated HCl. The precipitated crude β-diketone was washed with water and dried. This β-diketone was added to 10 mL acetic acid, and 0.25 mL conc. H_2SO_4 was added dropwise. The reaction mixture was heated at 60˚C for 90 minutes with stirring, and the solution was poured over 60 g ice. The precipitate was filtered, washed with water, and recrystallized from ethanol to yield 150 mg pure 2-phenyl-3-benzoyloxy-4-oxo-4H-1-benzopyran as colorless needles, in a yield of 63%.



Reference 13.

To a three-necked flask equipped with stirrer and condenser were added 10 g 2,6-bis(methoxybenzoxyl)-acetophenone, 12 g anhydrous potassium carbonate, and 100 mL 2,6-lutidine (or pyridine). The mixture was refluxed for 2 h. The resulting yellow precipitate and 2,6-lutidine (or pyridine) were dissolved in water and poured cautiously into an excess of ice cold 6 N HCl solution. The resulting pale yellow to bright orange precipitate was collected by filtration and dried. This product was not purified further and was subjected into cyclization to give flavone directly.

Other references related to the Baker-Venkataraman rearrangement are cited in the literature.[14]

H. REFERENCES

1. Baker, W., *J. Chem. Soc.,* **1933**, 1381.
2. (a) Mahal, H. S. and Venkataraman, K., *Curr. Sci.,* **1933**, *4*, 214. (b) Mahal, H. S.; Venkataraman, K., *J. Chem. Soc.,* **1934**, 1767.
3. (a) Krohn, K.; Tran-Thien, H. T.; Vitz, J. and Vidal, A., *Eur. J. Org. Chem.,* **2007**, 1905. (b) Krohn, K.; Vidal, A.; Vitz, J.; Westermann, B.; Abbas, M. and Green, I., *Tetrahedron: Asymmetry*, **2006**, *17*, 3051. (c) Thasana, N. and Ruchirawat, S., *Tetrahedron Lett.,* **2002**, *43*, 4515. (d) Kalinin, A. V. and Snieckus, V., *Tetrahedron Lett.,* **1998**, *39*, 4999. (e) Kalinin, A. V.; Da Silva, A. J. M.; Lopes, C. C.; Lopes, R. S. C. and Snieckus, V., *Tetrahedron Lett.,* **1998**, *39*, 4995. (f) Krohn, K.; Roemer, E. and Top, M., *Liebigs Ann.,* **1996**, 271. (g) Song, G.-Y. and Ahn, B.-Z., *Arch. Pharm. Res.,* **1994**, *17*, 434. (h) Dua, S.; Amemiya, S. and Bowie, J. H., *Rapid Commun. Mass Spectr.,* **1994**, *8*, 475. (i) Bowden, K. and Chehel-Amiran, M., *J. Chem. Soc., Perkin Trans. II,* **1986**, 2039. (j) Prasad, K. J. R.; Iyer, C. S. R. and Iyer, P. R., *Indian J. Chem., Section B,* **1983**, *22B*, 278. (k) Wurm, G. and Geres, U., *Arch. Pharm.,* **1977**, *310*, 609. (l) Wurm, G. and Geres, U., *Arch. Pharm.,* **1977**, *310*, 230. (m) Wurm, G. and Geres, U., *Arch. Pharm.,* **1976**, *309*, 273. (n) Wurm, G. and Lachmann, Ch., *Arch. Pharm.,* **1975**, *308*, 389. (o) Wurm, G., *Arch. Pharm.,* **1975**, *308*, 259. (p) Looker, J. H.; Edman, J. R. and Dappen, J. I., *J. Heterocycl. Chem.,* **1964**,1,

141. (q) Re, P. D. and Cimatoribus, L., *Experientia*, **1962**, *18*, 67. (r) Schmid, H. and Banholzer, K., *Helv. Chim. Acta,* **1954**, *37*, 1706.

4. (a) Barros, A. I. R. N. A., *Heterocycl. Commun.,* **2006**, *12*, 141. (b) Lamba, M. S.; Kumar, S. and Makrandi, J. K., *J. Chem. Res.,* **2006**, 133. (c) Miya, M. B.; Ramadas, S. and Krupadanam, G. L. D., *Indian J. Chem., Sect. B,* **1998**, *37B*, 579. (d) Reddy, B. P. and Krupadanam, G. L. D., *J. Heterocycl. Chem.,* **1996**, *33*, 1561. (e) Pinto, D. C. G. A.; Silva, A. M. S. and Cavaleiro, J. A. S., *Heterocycl. Commun.,* **1996**, *2*, 145. (f) Reddy, M. S.; Reddy, Ch. R.; Krupadanam, G. L. D. and Srimannarayana, G., *Indian J. Chem., Sect. B,* **1989**, *28B*, 1057. (g) Makrandi, J. K. and Kumari, V., *Synth. Commun.,* **1989**, *19*, 1919. (h) Reddy, C. R.; Krupadanam, G. L. D. and Srimannarayana, G., *Indian J. Chem., Sect. B,* **1987**, *26B*, 974. (i) Saxena, S.; Makrandi, J. K. and Grover, S. K., *Synthesis,* **1985**, 697. (j) Srimannarayana, G. and Rao, N. V. S., *Indian J. Chem.,* **1969**, *7*, 940. (k) Srimannarayana, G. and Rao, N. V. S., *Indian J. Chem.,* **1968**, *6*, 696. (l) Rao, A. V. S. and Rao, N. V. S., *Curr. Sci.,* **1966**, *35*, 149. (m) Jain, A. C.; Mathur, S. K. and Seshadri, T. R., *J. Sci. Ind. Res., Sect. B,* **1962**, *21B*, 214. (n) Gupta, V. N. and Seshadri, T. R., *J. Sci. Ind. Res., Sect. B,* **1957**, *16B*, 116. (o) O'Farrell, M. P.; Wheeler, D. M. S.; Wheeler, M. M. and Wheeler, T. S., *J. Chem. Soc.,* **1955**, 3986. (p) Philbin, E. M.; O'Sullivan, W. I. A. and Wheeler, T. S., *J. Chem. Soc.,* **1954**, 4174. (q) Gowan, J. E. and Wheeler, T. S., *J. Chem. Soc.,* **1950**, 1925. (r) Nowlan, N. V.; Slavin, P. A. and Wheeler, T. S., *J. Chem. Soc.,* **1950**, 340.
5. (a) Zhang, X.-Q.; Shi, J.; Xue, D. and Zhang, Z.-T., *Xibei Daxue Xuebao, Ziran Kexueban,* **2006**, *36*, 575. (b) Mani, R. I.; Powers, P. F. and Drummond, L., *J. Tennessee Acad. Sci.,* **1993**, *68*, 83. (c) Henning, H. G.; Schwabe, B.; Kernchen, F. and Westphal, G., *J. Prakt. Chem. (Leipzig),* **1984**, *326*, 491. (d) Kraus, G. A.; Fulton, B. S. and Wood, S. H., *J. Org. Chem.,* **1984**, *49*, 3212.
6. Jain, P. K.; Makrandi, J. K. and Grover, S. K., *Synthesis,* **1982**, 221.
7. Thakar, K. A. and Muley, P. R., *Indian. J. Chem., Sect. B*,**1975**, *14*, 226.
8. Only a few examples involve the migration of aliphatic acyl groups. (a) Ullal, V. V.; Shah, R. C. and Wheeler, T. S., *J. Chem. Soc*., **1940**,1499. (b) Virkar, V. V. and Wheeler, T. S., *J. Chem. Soc*., **1939**, 1679.
9. (a) Gripenberg, J., *Flavones* in *The Chemistry of Flavonoid Compounds*, ed. Geissman, T., Macmillan Co., New York, **1962**, p. 410. (b) Venkataraman, K., *Progress in the Chemistry of Organic Natural Products*, ed. Zechmeister, T., Springer-Verlag, Vienna **1959**, *17*, p. 2. (c) Hauser, C. R.; Swamer, F. W. and Adams, J. T., *Org. React. (N. Y.),* **1954**, *8*, 168. (d) Jurd, L., *Spectral Properties of Flavonoid Compounds* in *The Chemistry of Flavonoid Compounds*, ed. Geissman, T. A., Macmillan, New York, **1962**, pp. 107–155.
10. Bowden, K. and Chehel-Amiran, M., *J. Chem. Soc. Perkin Trans. II,* **1986**, 2039.
11. (a) Pinto, D. C. G. A.; Silva, A. M. S. and Cavaleiro, J. A. S., *New. J. Chem*., **2000**, *24*, 85. (b) Zhu, J. P.; Wang, Q. and Li, Y. L., *Chem. Commun.,* **1988**, 1549. (c) Ollis, W. D. and Weight, D., *J. Chem. Soc*., **1952**, 3826. (d) Doyle, B. G.; Gogan, F.; Gowan, J. E.; Keane, J. and Wheeler, T. S., *Sci. Proc. Roy. Dublin Soc.,* **1948**, *24*, 291.
12. Fougerousse, A.; Gonzales, E. and Brouillard, R., *J. Org. Chem*., **2000**, *65*, 583.
13. Looker, J. H. and Hanneman, W. W., *J. Org. Chem*., **1962**, *27*, 3261.
14. (a) Barros, A. I. R. N. A. and Silva, A. M. S., *Monatsh. Chem.,* **2006**, *137*, 1505. (b) Bauvois, B.; Puiffe, M.-L.; Bongui, J.-B.; Paillat, S.; Monneret, C. and Dauzonne, D., *J. Med. Chem.,* **2003**, 46,3900. (c) Horton, D. A.; Bourne, G. T. and Smythe, M. L., *Chem. Rev*., **2003**, *103*, 893. (d) Kahnberg, P., Lager, E.; Rosenberg, C.; Schougaard, J.; Camet, L.; Sterner, O.; Nielsen, E. Ø.; Nielsen, M. and Liljefors, T., *J. Med. Chem.,* **2002**, 45,4188. (e) Galietta, L. J. V.; Springsteel, M. F.; Eda, M.; Niedzinski, E. J.; By, K.; Haddadin, M. J.; Kurth, M. J.; Nantz, M. H. and Verkman, A. S., *J. Biol. Chem.,* **2001**, *276*, 19723. (f) Kumar, P. and Bodas, M. S., *Org. Lett*., **2000**, *2*, 3821. (g) Dekermendjian, K.; Kahnberg, P.; Witt, M.-R.; Sterner, O.; Nielsen, M. and Liljefors, T., *J. Med. Chem.,* **1999**, *42*, 4343. (h) Aitken, R. A.; Bibby, M. C.; Double, J. A.; Laws, A. L.; Ritchie, R. B. and Wilson, D. W. J., *Arch. Pharm. Pharm. Med. Chem.,* **1997**, *330*, 215. (i) Ares, J. J.; Outt, P.

E.; Randall, J. L.; Murray, P. D.; Weisshaar, P. S.; Obrien, L. M.; Ems, B. L.; Kakodkar, S. V.; Kelm, G. R.; Kershaw, W. C.; Werchowski, K. M. and Parkinson, A., *J. Med. Chem.,* **1996**, *38*, 4937. (j) Mohakhud, P. K.; Goyal, S.; Grover, N.; Saradhi K. P. and Parthasarathy, M. R., *Indian J. Chem., Sect. B*, **1996**, *25B*, 904. (k) Ares, J. J.; Outt, P. E.; Kakodkar, S. V.; Buss, R. C.and Geiger, J. C., *J. Org. Chem*., **1993**, *58*, 7903. (l) Horie, T.; Tominaga, H.; Kawamura, Y.; Hada, T.; Ueda, N.; Amano, Y. and Yamamoto, S., *J. Med. Chem.,* **1991**, *34*, 2169. (m) McGarry, L. W. and Detty, M. R., *J. Org. Chem.,* **1990**, *55*, 4349. (n) Wu, E. S. C.; Cole, T. E.; Davidson, T. A.; Dailey, M. A.; Doring, K. G.; Fedorchuk, M.; Loch, J. T.; Thomas, T. L.; Blosser, J. C.; Borrelli, A. R.; Kinsolving, C. R.; Parker, R. B.; Strand, J. C. and Watkins, B. E., *J. Med. Chem.,* **1989**, *32*, 183. (o) Kraus, G. A. and Fulton, B. S., *J. Org. Chem.,* **1985**, *50*, 1782. (p) Looker, J. H.; Edman, J. R. and Kingsbury, C. A., *J. Org. Chem*., **1984**, *49*, 645. (q) Looker, J. H., McMechan, J. H. and Mader, J. W., *J. Org. Chem*., **1978**, *43*, 2344. (r) Thomas, M. B. and Mabry, T. J., *J. Org. Chem*., **1967**, *32*, 3254. (s) Farkass, L.; Nogradi, M.; Sudarsanam, V. and Herz, W., *J. Org. Chem*., **1966**, *31*, 3228. (t) Yates, P. and Anderson, C. D., *J. Am. Chem. Soc*., **1963**, *85*, 2937. (u) Wheeler, T. S., *Org. Syn. Coll., 40*, **1963**, *4*, 478. (v) Jurd, L., *J. Org. Chem*., **1962**, *27*, 872. (w) Looker, J. H. and Hanneman, W. W., *J. Org. Chem*., **1962**, *27*, 381. (x) Rahman, W. and Nasim, K. T.,*J. Org. Chem*., **1962**, *27*, 4215. (y) Simpson, T. H. and Wright, R. S., *J. Org. Chem*., **1961**, *28*, 4686. (z) Devitt, P. F.; Timoney, A. and Vickars, M. A., *J. Org. Chem*., **1961**, *26*, 4941. (aa) Clarke, R. and Hunter, W. T., *J. Am. Chem. Soc*., **1958**, *80*, 5304. (bb) Gallagher, K. M.; Hughes, A. C.; O'Donnell, M.; Philbin, E. M. and Wheeler, T. S., *J. Chem. Soc*., **1953**, 3777. (cc) Dunne, A. T. M.; Gowan, J. E.; Keane, J.; O'Kelly, B. M.; O'Sullivan, D.; Roche, M. M.; Ryan, P. M. and Wheeler, T. S., *J. Chem. Soc.,* **1950**, 1252. (dd) Baker, W., *J. Chem. Soc*., **1941**, 662.

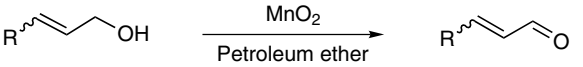
41

Ball-Goodwin-Morton Oxidation

A. GENERAL DESCRIPTION OF THE REACTION

Manganese dioxide has been considered a specific reagent for oxidation of allyl alcohol to allyl aldehyde or ketones, and several different types of manganese dioxide have been used for this type of oxidation. The first type of these manganese dioxides was initially reported by Ball, Goodwin, and Morton in 1948.[1] In their original study, vitamin A alcohol was oxidized to vitamin A aldehyde using manganese dioxide suspended in petroleum ether. Other oxidations of alcohol using manganese dioxide include the oxidation of unsaturated steroidal alcohol,[2] polyene alcohol,[3] acetylenic alcohol,[4] ferrocene alcohol,[5] and benzyl alcohols.[6] It is interesting that manganese dioxide prepared by heating the corresponding carbonate or oxalate in air will oxidize benzyl alcohols dissolved in petroleum ether (or preferably in ethyl ether) to aldehyde in good yield but not the allylic alcohols.[1,2d,6] However, acid-washed manganese dioxide suspended in petroleum ether will oxidize allylic alcohols to corresponding aldehydes in good yield, but not for saturated alcohols.[6]

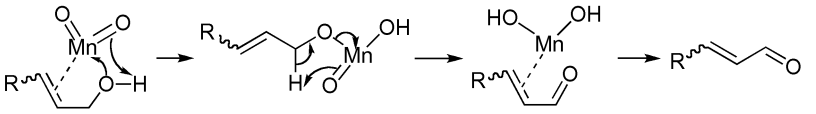
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

Displayed is the oxidation mechanism; a similar mechanism has been proposed by Goldman for the oxidation of benzyl alcohols.[7]



D. MODIFICATION

N/A

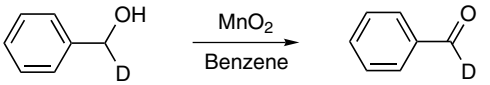
E. APPLICATIONS

N/A

F. RELATED REACTIONS

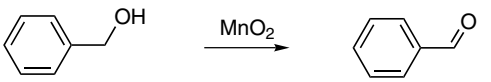
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 8.

The active manganese dioxide was prepared by azeotropic removal of water according to the reported procedure.[9] To 125 mL benzene were added 1 g deuterated benzyl alcohol (C_6H_5CHD-OH) and 10.5 g activated manganese dioxide under nitrogen (from 25 g wet manganese dioxide). The mixture was stirred for 1 h and then filtered through Celite, and benzene was removed carefully under reduced pressure. The product was analyzed directly after the purification by GLPC or distillation, the yield is 91.7%.



Reference 7a.

To a 500-mL flask were added 100 g activated manganese dioxide and ~ 300 mL solvent. The flask was immediately swirled and, if necessary, sealed and shaken vigorously to wet all of the MnO_2. Then 25 g of the alcohol to be oxidized was added, and the flask was stoppered and shaken in a shaking machine at a rate sufficient to keep the MnO_2 suspended for the time given, generally about 3 days. The solid then was separated from the solution

by suction filtration, using an inorganic filter aid when necessary (e.g., Celite), and the solid was washed with more solvent. The combined solution was concentrated to give the corresponding aldehydes.

Procedures for preparing different types of manganese dioxides have been reported.[7a,10] Other references related to this type of oxidation are cited in the literature.[11]

H. REFERENCES

1. Ball, S.; Goodwin, T. V. and Morton, R. A., *Biochem. J.,* **1948**, *42,* 516.
2. (a) Sugasawa, S. and Mizukami, K., *Pharm. Bull.,* **1955**, *3,* 393. (b) Sugasawa, S. and Mizukami, K., *Pharm. Bull.,* **1954**, *2,* 341.
3. (a) Rosenkranz, G.; Sondheimer, F. and Mancera, O., *Experientia,* **1953**, *9,* 62. (b) Rosenkranz, G.; Sondheimer, F. and Amendolla, C., *J. Am. Chem. Soc.,* **1953**, *75,* 5930. (c) Rosenkranz, G.; Sondheimer, F. and Amendolla, C., *J. Am. Chem. Soc.,* **1953**, *75,* 5932. (d) Rosenkranz, G.; Sondheimer, F. and Mancera, O., *J. Chem. Soc.,* **1953**, 2189.
4. (a) Bharucha, K. R., *J. Chem. Soc.,* **1956**, 2446. (b) Attenburrow, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. M.; Hems, B. A.; Jansen, A. B. A. and Walker, T., *J. Chem. Soc.,* **1952**, 1094. (c) Braude, E. A. and Coles, J. A., *J. Chem. Soc.,* **1952**, 1430. (d) Cama, H. R.; Dalvi, P. D.; Morton, R. A.; Salah, M. B.; Steinberg, G. R. and Stubbs, A. L., *Biochem. J.,* **1952**, *52,* 535. (e) Braude, E. A. and Forbes, W. F., *J. Chem. Soc.,* **1951**, 1755. (f) Weedon, B. C. and Woods, R. J., *J. Chem. Soc.,* **1951**, 2687. (g) Wendler, N. L.; Slates, H. L.; Trenner, K. R. and Tishler, M., *J. Am. Chem. Soc.,* **1951**, *73,* 719.
5. Bell, I.; Jones, E. R. and Whiting, M. C., *Chem. & Ind. (London),* **1956**, 548.
6. Lindsay, J. K. and Hauser, C. R., *J. Org. Chem.,* **1957**, *22,* 355.
7. (a) Harfenist, M.; Bavley, A. and Lazier, W., *J. Org. Chem.,* **1954**, *19,* 1608. (b) Turner, D. L., *J. Am. Chem. Soc.,* **1954**, *76,* 5175.
8. Goldman, I. M., *J. Org. Chem.,* **1969**, *34,* 3289.
9. Goldman, I. M., *J. Org. Chem.,* **1969**, *34,* 1979.
10. Gritter, R. J. and Wallace, T. J., *J. Org. Chem.,* **1959**, *24,* 1051.
11. (a) Lai, T. K.; Banerji, J.; Chatterjee, A. and Basak, B., *Indian J. Chem., Sect. B,* **2005**, *44B*, 1309. (b) Wang, X.-M. and Li, Q.-H., *Hecheng Huaxue,* **2004**, *12,* 408. (c) Tsuboi, S.; Ishii, N.; Sakai, T.; Tari, I. and Utaka, M., *Bull. Chem. Soc. Jpn.,* **1990**, *63,* 1888. (d) Eremin, S. V.; Mitsner, B. I.; Khodonov, A. A. and Evstigneeva, R. P., *Bioorg. Khim.,* **1984**, *10,* 256. (e) Kobayashi, M.; Koyama, T.; Ogura, K.; Seto, S.; Ritter, F. J. and Brueggemann-Rotgans, I. E. M., *J. Am. Chem. Soc.,* **1980**, *102,* 6602. (f) Knudsen, C. G.; Carey, S. C. and Okamura, W. H., *J. Am. Chem. Soc.,* **1980**, *102,* 6355. (g) Bedoukian, R. H. and Wolinsky, J., *J. Org. Chem.,* **1975**, *40,* 2154. (h) Papadopoulos, E. P.; Jarrar, A. and Issidorides, C. H., *J. Org. Chem.,* **1966**, *31,* 615. (i) Elkik, E., *Bull. Soc. Chim. Fr.,* **1964**, 2258. (j) Harrison, J. T., *Proc. Chem. Soc.,* **1964**, 110. (k) Gritter, R. J. and Wallace, T. J., *J. Org. Chem.,* **1959**, *24,* 1051. (l) Barakat, M. Z.; Abdel-Wahab, M. F. and El-Sadr, M. M., *J. Chem. Soc.,* **1956**, 4685. (m) Heilmann, R. and Glenat, R., *Bull. Soc. Chim. Fr.,* **1955**, 1586. (n) Highet, R. J. and Wildman, W. C., *J. Am. Chem. Soc.,* **1955**, *77,* 4399. (o) Harfenist, M.; Bavley, A. and Lazier, W. A., *J. Org. Chem.,* **1954**, *19,* 1608. (p) Sondheimer, F. and Rosenkranz, G., *Experientia,* **1953**, *9,* 62. (q) Wendler, N. L.; Rosenrlum, C. and Tishler, M., *J. Am. Chem. Soc*., **1950**, *72,* 235. (r) Wendler, N. L.; Slates, H. L. and Tishler, M., *J. Am. Chem. Soc*., **1949**, *71,* 3267. (s) von Braun, J. and Keller, W., *Ber*., **1933**, *66B*, 215.

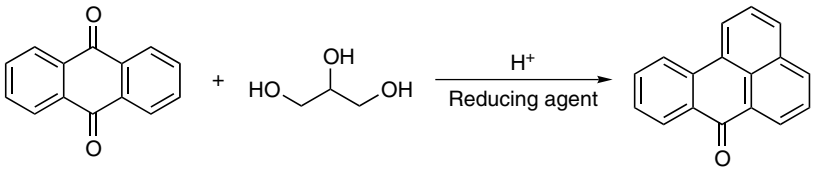
42

Bally-Scholl Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Bally in 1905[1] and was investigated again by Bally and Scholl in 1911.[2] It is the synthesis of benzanthrone from the condensation of anthraquinone with acrolein in the presence of an acidic condensing agent, especially sulfuric acid. In addition, the formation of acrolein from glycerol and sulfuric acid was carefully studied by Scholl in 1936.[3] Therefore, this reaction is known as the Bally reaction,[4] Bally benzanthrone synthesis,[5] or Bally-Scholl reaction.[6] The yield of this reaction is usually 50–60%.[7] In industry, benzanthrone is produced from the reaction among anthraquinone, glycerol, and iron in concentrated H_2SO_4, where acrolein can be generated *in situ*, and 9,10-anthraquinone is reduced to anthracene-9(10H)-one.[8] Nevertheless, it has been applied to make different types of dye molecules.[9]

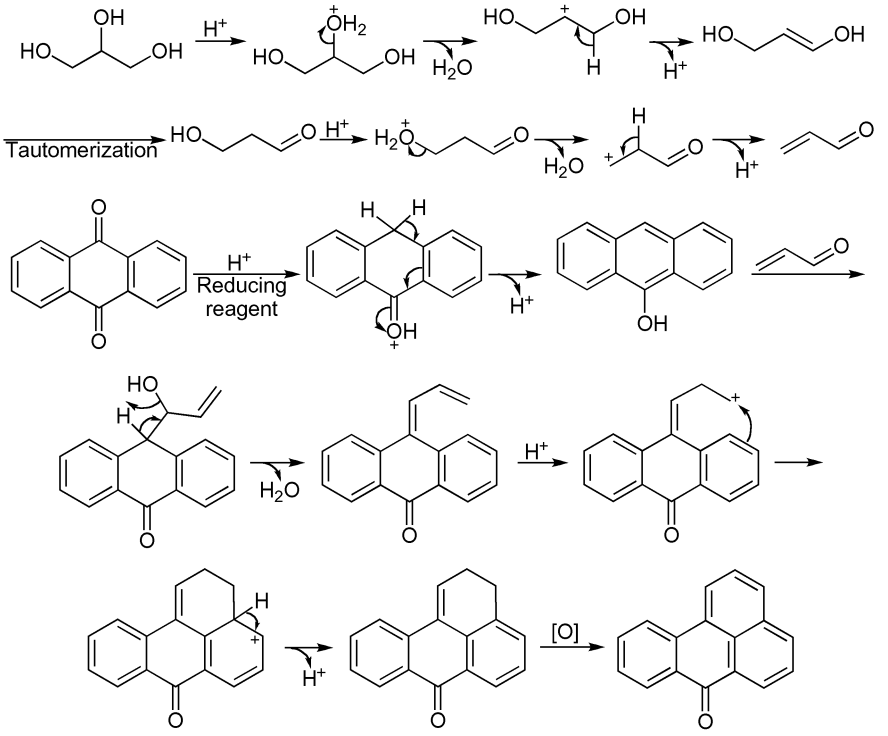
B. GENERAL REACTION SCHEME



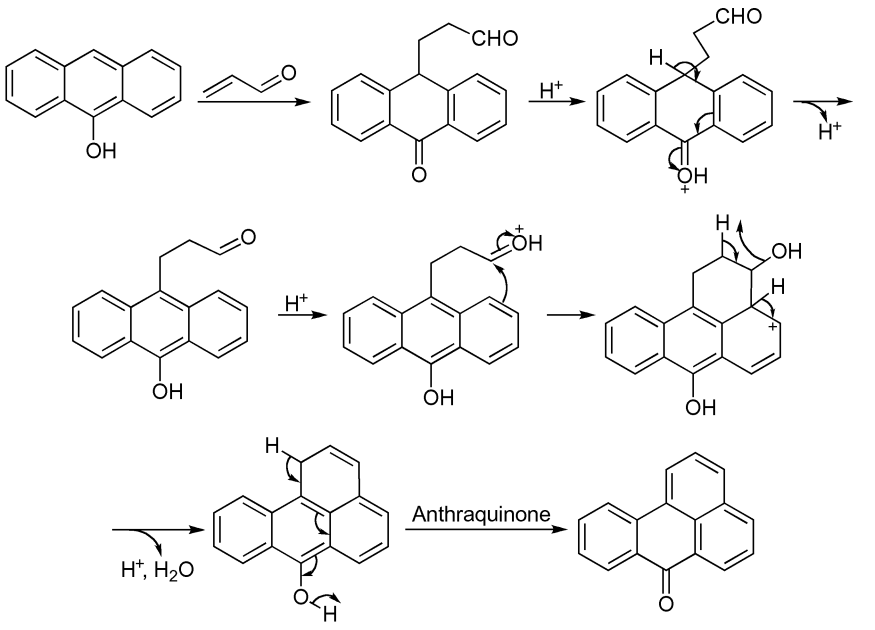
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

It is generally accepted[2,8,10] that this reaction involves the conversion of glycerol into acrolein and reduction of anthraquinone to anthrone, the latter undergoing the *Aldol Condensation* with acrolein.[2] After that, the consecutive dehydration, cyclization, and oxidation afford the final product of benzanthrone.[8] An illustration of the reaction mechanism is displayed here.



It may be possible that the anthrone undergoes the *Michael Reaction* with acrolein, and the cyclized product is then oxidized by anthraquinone and the latter is reduced to anthrone, as shown by the partial illustration of the mechanism. This route is consistent with the relatively low yield of 50–60%.[7]



D. MODIFICATION

This reaction has been modified to proceed from glycerol and anthraquinone in sulfuric acid in the presence of iron,[8] copper,[11] or a reducing agent of anthrone[12] or sodium hypophosphite.[13] Moreover, a reaction between hydroanthraquinone and acrolein in sulfuric acid to afford benzanthrone has also been developed.[14] Another modification is the reaction between anthraquinone-1-diazonium salt and α-methylacronitrile or α-methyl vinyl acetate in monovalent alcohol (e.g., MeOH, EtOH) in the presence of a catalytic amount of cuprous chloride.[15]

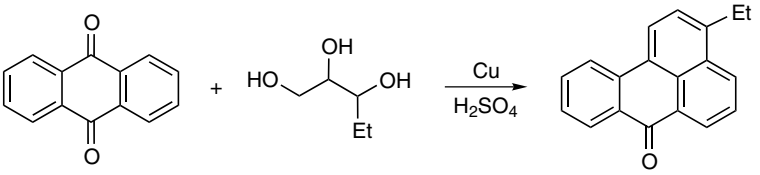
E. APPLICATIONS

This reaction has general application in preparation of benzanthrone.

F. RELATED REACTIONS

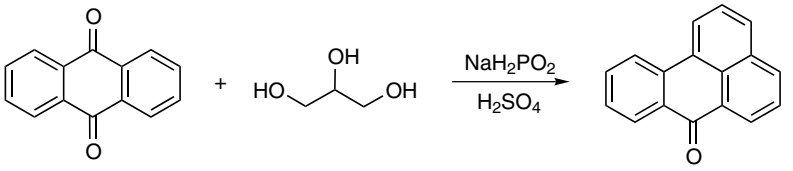
This reaction is related to the *Skraup Reaction* and *Scholl Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4.

To 132 mL H_2SO_4 (2.4 mol) stirred at room temperature was slowly added 9.0 g anthraquinone (0.043 mol). When all of anthraquinone had dissolved, 5 mL water was added. The resulting mixture was maintained at 38–42°C while 6.0 g freshly precipitated copper (0.01 mol) was added over 90 min; after 3 h the copper had dissolved, and the mixture acquired a yellow-brown color with separation of some anthranol. A mixture of 14.4 g α-ethylglycerol (0.12 mol) and 14 mL water was added over 50 min while the temperature was raised to 80°C, and the whole solution was then maintained at 100°C for 2.5 h. The progress of the reaction was shown by the development of a red color; and considerable care was exercised in heating to avoid charring, which occurred quite readily. The whole mixture was cooled and poured into 500 mL boiling water, and the resulting mixture was boiled for a few minutes and kept overnight. The precipitate was collected, washed with water, and boiled with 150 mL 1% NaOH for 40 min to dissolve unchanged anthranol. The solution, which could not be filtered, was shaken several times with benzene, and the emulsion was centrifuged into two layers. The combined benzene extracts were boiled for 2 h with animal charcoal and then filtered. The solvent was removed principally by distillation and finally by evaporation in a vacuum at the ordinary temperature. The crystals that separated were pressed on a porous plate to remove an oily material and recrystallized from methanol, from which 0.5 g 1′-ethylmesobenzanthrone was separated in yellow needles, m.p. 106°C.



Reference 13.

Anthraquinone (208 g) was dissolved in 1000 g conc. H_2SO_4 at 80–110°C. Then a solution of 96 g sodium hypophosphite in 240 g glycerol was added in a manner such that a reaction temperature of 100°C could be maintained. The mixture was then heated to 120°C and kept at this temperature for 3 h. After that, the reaction mixture was poured into 3 L water, and the product that precipitated was filtered off. The solid was washed with hot water until the runnings were almost colorless, and the filter cake was then suspended in 1.5 L water and the suspension was rendered weakly alkaline and boiled up. After renewed filtration of the product, washing with hot water, and drying at 100°C, 200–225 g 92–97% pure benzanthrone was obtained, in the yield of 80–93%.

More procedures with experimental details for the preparation of benzanthrone can be found in the literature.[11,12,14,15] Other references related to the Bally-Scholl reaction are cited the literature.[16]

H. REFERENCES

1. Bally, O., *Ber.*, **1905**, *38*, 194.
2. Bally, O. and Scholl, R., *Ber.*, **1911**, *44*, 1656.
3. Scholl, R. and Meyer, H. K., *Ber.,* **1936**, *69B*, 152.
4. Baddar, F. G. and Warren, F. L., *J. Chem. Soc.,* **1938**, 401.
5. (a) Fieser, L. F., *J. Am. Chem. Soc.,* **1929**, *51*, 1620. (b) Houben, J. and Fischer, W., *Anthracene and Anthraquinones, and Their Polynuclear Systems,* Georg Thieme, Leipzig, Germany, **1929**.
6. Boger, E.; O'Malley, R. F. and Sardella, D. J., *J. Fluor. Chem.,* **1976**, *8*, 513.
7. Allen, C. F. H. and Overbaugh, S. C., *J. Am. Chem. Soc.,* **1935**, *57*, 1322.
8. Zollinger, H., *Color Chemistry: Syntheses, Properties, and Applications of Organic Dyes and Pigments*, Verlag Helvetica Chimica Acta AG, Zurich, and Wiley-VCH GmbH & Co., KGaA, Weinheim, **2003**, pp. 286–287.
9. Rodd, E. H., *Chemistry of Carbon Compounds IIIB*, Elsevier, New York, **1956**, p. 1496.
10. (a) Kwon, T.-W. and Watts, B. M., *Anal. Chem.,* **1963**, *35*, 733. (b) Pfliegel, T., *Chem. Prumysl*, **1955**, *5*, 370.
11. Macleod, L. C. and Allen, C. F. H., *Org. Synth. Coll. Vol. II,* **1943**, 62.
12. Bürli, M.; Bersier, J.; Plattner, E. and Herrmann, H.-U., *U.S. Pat.* **1985**, December 17, 4,559,176.
13. Schroeder, J., *U.S. Pat.* **1981**, October 20, 4,296,043.
14. Matsuura, R.; Nakatani, S.; Nagaoka, K.; Kusabe, K. and Kaseda, M., *U.S. Pat.,* **1978**, Nov. 28, 4,127,595.
15. Ribaldone, G. and Borsotti, G., *U.S. Pat.,* **1977**, July 19, 4,036,859.
16. (a) Herbst, W.; Hunger, K.; Wilker, G.; Ohleier, H. and Winter, R., *Industrial Organic Pigments*, 3rd ed., Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, **2004**. (b) Kendall, J. K. and Shechter, H., *J. Org. Chem.,* **2001**, *66*, 6643. (c) Pogodin, S. and Agranat, I., *Org. Lett.,* **1999**, *1*, 1387. (d) Deshpande, R. J., *Indian J. Chem., Sect. B,* **1978**, *16B*, 389. (e) Kastner, V. M., *U.S. Pat.* **1964**, June 23, 3,138,612. (f) Calcott, W. S.; Tinker, J. M. and Weinmayr, V., *J. Am. Chem. Soc.,* **1939**, *61*, 949. (g) Gallotti, M. and Beretta, A., *Annali Chim. App.,* **1932**, *22*, 691. (h) Sokolov, P. I. and Gurevich, L., *Zh. Khim. Promyshlen.,* **1928**, *5*, 308.

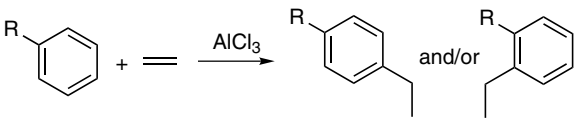
43

Balsohn Alkylation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Balsohn in 1879,[1] just two years after Friedel and Crafts's acylation and alkylation with $AlCl_3$.[2] In its initial reaction, benzene was directly alkylated with ethylene in the presence of $AlCl_3$, and the prolonged reaction favored a higher yield of polyethylbenzenes, including pentaethylbenzene. Since then, many other acidic catalysts have been applied to similar reactions, and these catalysts include sulfuric acid,[3] phosphorus acid,[4] phosphorus pentoxide,[5] and boron trifluoride.[6] It should be pointed out that the Balsohn alkylation is not limited to ethylene itself but works for other alkenes[1,7] as well, and even for acetylene.[8] Other aromatics such as phenol also react in a similar fashion.[9] When higher alkenes react with aromatics, the less substituted end of the alkenes always reacts and attaches to the aromatic ring, whereas when acetylene is used, diphenylethane and 9,10-dimethyl-9,10-dihydroanthracene will form.[8] When sulfuric acid is used as catalyst, two other side reactions—polymerization and formation of ester—also compete with the actual alkylation.[3] Some of the reactions have been used on a large scale for industrial production.[10] In addition, the Balsohn alkylation follows the *para/ortho regio*-selectivity as shown in the *Friedel-Crafts Acylation* and *Friedel-Crafts Alkylation*.

B. GENERAL REACTION SCHEME



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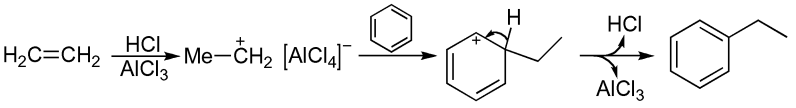
C. PROPOSED MECHANISMS

Kinetic studies showed that this reaction is similar to that of ethylation of benzene with ethyl bromide when aluminum bromide presents; therefore, it is believed that this reaction occurs via the generation of carbocation as the first step,[11] as illustrated here.



D. MODIFICATION

N/A

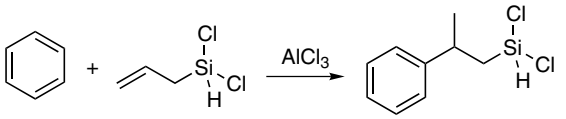
E. APPLICATIONS

N/A

F. RELATED REACTIONS

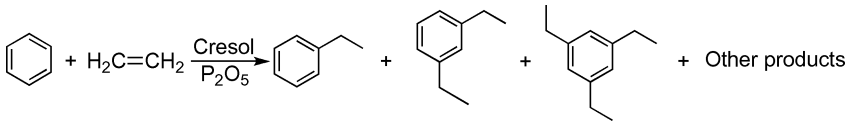
This reaction is related to the *Friedel-Crafts Alkylation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 12.

To mixture of 13.9 g benzene (178 mmol) and 0.4 g anhydrous aluminum chloride (3 mmol) was added dropwise 5.0 g allyldichlorosilane (36 mmol) at room temperature. The mixture was stirred for 30 min, and 2.0 g sodium chloride (34 mmol) was added to the mixture, which then was warmed to 70°C and stirred for 1 h. After the salts were filtrated and the mixture was evaporated to remove benzene, the residue was subjected to vacuum distillation to give 5.7 g 3-phenyl-1,1-dichloro-1-silabutane (26 mmol), in a yield of 72%. (b.p., 64 – 67°C/0.6 mmHg). In addition, 0.6 g di-adducts was obtained.



Reference 13.

A mixture of 780 g benzene (10 mol), 50 g phosphorus pentoxide, 24 g lampblack and 10 g cresol were heated in an autoclave for 100 min at 250°C with agitation, while a approximate pressure of 27 atm was maintained by a periodic introduction of ethylene. The weight of the liquid in the autoclave was increased by 527.7 g, indicating that 18.86 mol ethylene had been absorbed. The reaction mixture was fractionated into five portions, corresponding to benzene (1.6%), monoethylbenzene, (23.1%), diethylbenzene isomers (42.3%), triethyl benzene isomers (24.4%), and higher ethylbenzene isomers (8.5%) by volume.

Other references related to the Balsohn reaction are cited in the literature.[14]

H. REFERENCES

1. Balsohn, M., *Bull. Soc. Chim. Fr.,* **1879**, *31*, 539.
2. (a) Friedel, C. and Crafts, J. M., *Compt. Rend.,* **1877**, *84*, 1392. (b) Friedel, C. and Crafts, J. M., *Compt. Rend.,* **1877**, *84*, 1450.
3. Ipatieff, V. N.; Corson, B. B. and Pines, H., *J. Am. Chem. Soc*., **1936**, *68*, 919.
4. Ipatieff, V. N.; Pines, H. and Komarewsky, V. I., *J. Ind. Eng. Chem.,* **1936**, *28*, 222.
5. Truffault, R., *Compt. Rend*., **1936**, *202*, 1286.
6. Ipatieff, V. N. and Grosse, A. V., *J. Am. Chem. Soc*., **1935**, *57*, 1616.
7. Gilman, H. and Calloway, N. O., *J. Am. Chem. Soc*., **1933**, *55*, 4197.
8. (a) Cook, J. W. and Hewett, C. L., *J. Chem. Soc.*, **1933**, 1408. (b) Boeseken, J. and Adler, A. A., *Rec. Trav. Chim. Pays-Bas Belg*., **1929**, *48*, 474. (c) Bastet, M. C., *Chem. Ztg*., **1914**, *37*, 564.
9. (a) Niederl, J. B. and Riley, C. H., *J. Am. Chem. Soc*., **1934**, *56*, 2412. (b) Sowa, F. J.; Hinton, H. D. and Nieuwland, J. A., *J. Am. Chem. Soc*., **1932**, *54*, 3694.
10. (a) Huellmann, M.; Mayr, H. and Becker, R., *German Pat.*, **1991**, Sept. 4,008,694 [*Chem. Abstr*., **1991**, *116*, 6262]. (b) Polubentaeva, M. F.; Tolmacheva, I. I.; Duganova, V. V. and Lipovich, V. G., *Zh. Obsh. Khim.*, **1990**, *60*, 927. (c) Swain, C. G.; Unger, S. H.; Rosenquist, N. R. and Swain, M. S., *J. Am. Chem. Soc.,* **1983**, *105*, 492. (d) Tiltacher, H. and Faustmann, J., *Chem. Ing. Tech.*, **1981**, *53*, 396. (e) Kulsvestha, G. N.; Shanker, U.; Pathania, B. S. and Bhattacharyya, K. K., *Indian J. Chem. Sect. B*., **1981**, *20B*, 298. (f) Hattori, S.; Wakabayashi, K. and Sano, S., *Jpn. Tokkyo Koho*, **1978**, *78*, 43,486 [*Chem. Abstr*., **1978**, *90*, 86974p].
11. (a) Hodnett, E. M. and Feldman, C. F., *J. Am. Chem. Soc*., **1959**, *81*, 1638.
12. Lee, B. W.; Yoo, B. R.; Kim, S.-I., and Jung, I. N., *Organometallics,* **1994**, *13*, 1312.
13. Malishev, B. W., *J. Am. Chem. Soc*., **1935**, *57*, 883.
14. (a) Radici, P.; Cozzi, P.; Giuffrida, G. and Zatta, A., *U. S. Pat.*, Nov. 17, 1996, 5, 574, 198. (b) Shook, J. J., *U. S. Pat.,* **1968**, Jan. 23, 3,365,509. (c) De Pierri, W. G.; Edwards, W. R. and Boynton, H. G., *U. S. Pat.,* **1962**, Sept. 4, 3,052,741. (d) Olson, A. C., *Am. Chem. Soc., Div. Petrol. Chem., Preprints,* **1959**, *4*, 89. (e) Ipatieff, V. N.; Pines, H. and Schmerling, L., *J. Am. Chem. Soc.,* **1938**, *60*, 1163. (f) Grosse, A. V. and Ipatieff, V. K., *J. Org. Chem.*, **1938**, *60*, 447. (g) Simons, J.

H. and Archer, S., *J. Am. Chem. Soc*., **1938**, *60*, 2952. (h) Ipatieff, V. N.; Pines, H. and Schmerling, L., *J. Am. Chem. Soc*., **1938**, *60*, 353. (i) Slanina, S. J.; Sowa, F. J. and Nieuwland, J. A., *J. Am. Chem. Soc*., **1935**, *67*, 1547. (j) Sullivan, F. W.; Voorhees, V.; Neeley, A. W. and Shankland, R. V., *Ind. End. Chem.*, **1931**, *23*, 604. (k) Berry, T. M. and Reid, E. E., *J. Am. Chem. Soc*., **1927**, *49*, 3142. (l) Brochet, A., *Compt. Rend*., **1893**, *117*, 115. (m) Kraemer, G. and Spilker, A., *Ber.,* **1890**, *23*, 84.

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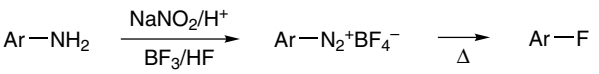
Balz-Schiemann Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Balz and Schiemann in 1927.[1] It is the most popular reaction to introduce a fluorine atom into aromatic rings through the thermal decomposition of diazonium tetrafluoroborate by diazotization of the corresponding aromatic amines. Therefore, this reaction is generally known as the Balz-Schiemann reaction[2] or Schiemann reaction[3] and is referred to as the Balz-Schiemann decomposition[4] as well. This reaction is especially important for synthesizing the specifically fluorinated aromatic compounds, of which the decomposition in the absence of solvent normally affords a fairly good yield of aromatic fluorides. The general procedure can be directly extended for preparing other aromatic halides. The Balz-Schiemann reaction has been extensively reviewed.[5]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Although the mechanism was studied by Swain et al.[6a] and Olah et al.,[6b] an illustrative detail of this reaction is proposed here.

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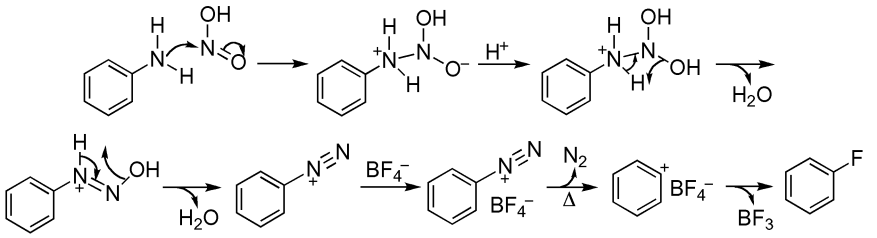


D. MODIFICATION

This reaction has been extensively modified for different conditions, using a large excess of HF,[7a] HPF_6 instead of HBF_4,[7b] $NaBF_4$ rather than HBF_4,[7c] microwave accelerated multiphase reaction,[7d] and photo-Balz-Schiemann reaction.[7e–7i] Other modifications of this reaction are cited in Refs.[7j–7t]

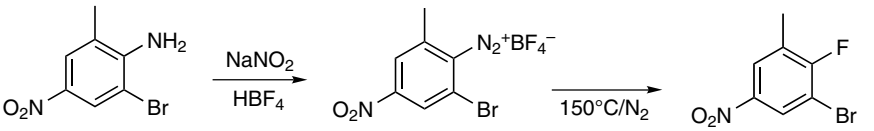
E. APPLICATIONS

This reaction has general application in the preparation of aromatic halides.

F. RELATED REACTIONS

The metal-catalyzed *Sandmeyer Reaction* is also widely used to prepare fluorinated aromatic compounds;[8] unfortunately, it is often accompanied by unwanted side reactions.

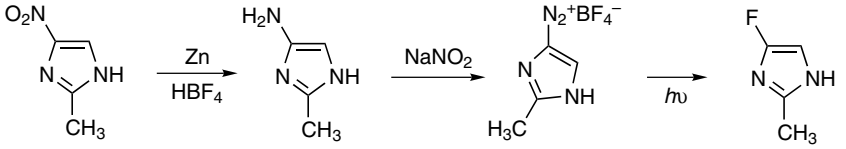
G. CITED EXPERIMENTAL EXAMPLES



Reference 9.

To a 400-mL beaker were added 110 mL fluoroboric acid and 57.75 g 2-amino-3-bromo-5-nitrotoluene (0.25 mol). The beaker was placed in an ice bath, and the solution was efficiently stirred while adding a 35 mL of a cold solution of sodium nitrite (17 g, 0.25 mol) dropwise. When the addition was complete, the mixture was stirred for 15 min and filtered by suction on a sintered glass funnel. The solid diazonium salt was washed with fluoroboric acid, twice with ethanol, and several times with ether; 57.57 g diazonium fluoroborate was obtained, in a yield of 70%. This solid was subjected to thermal decomposition without further purification and was mixed with 150 g acid-washed sand. The mixture was placed in a three-necked flask, and a nitrogen supply was attached to allow a constant flow of

nitrogen through the apparatus during decomposition. The reaction was initiated by heating to 150°C for 10 min. The vigorous reaction was allowed to continue until the evolution of BF_3 gas had ceased. The nitrogen supply was removed, and the dark mass was cooled. The residue was dissolved in 600 mL dichloromethane, and the sand was filtered off. The solvent was removed, under reduced pressure, and the residue was purified by chromatography on alumina using dichloromethane as the eluent, and 20 g 2-fluoro-3-bromo-5-nitrotoluene was obtained, in a yield of 40%.



Reference 7e.

The solution of 5.08 g 2-methyl-4-nitroimidazole in 200 mL 42% tetrafluoroboric acid was cooled to -10°C; to this cooled solution was added 5.08 g zinc dust (78 mmol) in portions of ~ 0.1 g with rapid stirring. Each addition was made only after the prior portion had dissolved and the temperature had fallen to at least -5°C. The addition took about 1 h. Small aliquots were removed, diluted with water, and examined by UV. Total loss of the chromophore at 310 nm indicated the completion of reduction. Then a solution 2.04 g sodium nitrite (44 mmol) in 10 mL water was added dropwise. The resulting solution of the diazonium salt was diluted to 380 mL with cold 42% tetrafluoroboric acid and was irradiated under argon in a Pyrex immersion-well photoreactor using a 400-W high-pressure mercury lamp (Riko 400-HA). After 90 min, the diazonium chromophore at 280 nm had disappeared. The solution was cooled to -10°C with dry ice, neutralized slowly with 25% aqueous sodium hydroxide to pH 5–6, and extracted with EtOAc (5 × 200 mL). The combined extracts were dried over Na_2SO_4 and evaporated. The residual material was purified on 100 mL silica gel with EtOAc as an eluent to give 1.06 g 4-fluoro-2-methylimidazole, in a yield of 27%, m.p. 142–144°C.

Other references related to the Balz-Schiemann reaction are cited in the literature.[10]

H. REFERENCES

1. Balz, G. and Schiemann, G., *Ber.*, **1927**, *60*, 1186.
2. (a) Laali, K. K. and Gettwert, V. J., *J. Fluor. Chem.,* **2001**, *107*, 31. (b) Tsuge, A.; Moriguchi, T.; Mataka, S. and Tashiro, M., *J. Chem. Res. (S),* **1995**, 460. (c) Mueller, A.; Roth, U.; Siegert, S. and Miethchen, R., *Zeitsch. Chem.,* **1986**, *26*, 169. (d) Matsumoto, J.; Miyamoto, T.; Minamida, A.; Nishimura, Y.; Egawa, H. and Nishimura, H., *J. Heterocycl. Chem.,* **1984**, *21*, 673. (e) Al'sing, T. K. and Sochilin, E. G., *Zh. Org. Khim.,* **1971**, *7*, 530. (f) Suschitzky, H., *Adv. Fluor. Chem.,* **1965**, *4*, 1. (g) Pavlath, A. and Olah, G., *Acta Chim. Acad. Sci. Hungaricae,* **1956**, *10*, 227.
3. (a) Heredia-Moya, J. and Kirk, K. L., *J. Fluor. Chem.,* **2007**, *128*, 674. (b) Fu, J.-L., *Huanan Ligong Daxue Xuebao, Ziran Kexueban,* **2000**, *28*, 86. (c) Fu, J. L. and Ding, G. Y., *Huanan Ligong Daxue Xuebao, Ziran Kexueban,* **1995**, *23*, 31. (d) Matsumoto, J. and Yoshida, K., *Yuki Gosei Kagaku Kyokaishi,* **1995**, *53*, 822. (e) Deng, Y., *Acta Chim. Sinica,* **1989**, 422. (f) Al'sing, T. K. and Boldyrev, A. G., *Zh. Org. Khim.,* **1970**, *6*, 627. (g) Montgomery, J. A. and Hewson, K.,

J. Org. Chem., **1969**, *34*, 1396. (h) Yasuda, S.; Yamanaka, K.; Kurihara, T. and Saito, N., *Yakugaku Zasshi,* **1968**, *88*, 209. (i) Yasuda, S.; Yamanaka, K.; Kurihara, T. and Saito, N., *J. Pharm. Soc. Jpn.,* **1968**, *88*, 209. (j) Al'sing, T. K. and Boldyrev, A. G., *Zh. Org. Khim.,* **1967**, *3*, 2249. (k) Montgomery, J. A.; Hewson, K., *J. Heterocycl. Chem.,* **1967**, *4*, 463. (l) Brill, E., *J. Chem. Soc. C,* **1966**, 748. (m) Fatutta, S., *Ric. Sci., Rend. Sez. A,* **1962**, *2*, 656. (n) Rutherford, K. G.; Redmond, W. and Rigamonti, J., *J. Org. Chem.,* **1961**, *26*, 5149. (o) Fletcher, T. L. and Namkung, M. J., *Chem. Ind. (London),* **1961**, 179. (p) Olah, G. and Tolgyesi, W. S., *J. Org. Chem.,* **1961**, *26*, 2053. (q) Roe, A. and Teague, C. E., *J. Am. Chem. Soc.,* **1951**, *73*, 687. (r) Roe, A., *Org. React.,* **1949**, *5*, 193. (s) Roe, A. and Hawkins, G. F., *J. Am. Chem. Soc.,* **1949**, *71*, 1785. (t) Roe, A. and Hawkins, G. F., *J. Am. Chem. Soc.,* **1947**, *69*, 2443.

4. Knoechel, A. and Zwernemann, O., *Appl. Radiation & Isotopes,* **1991**, 42, 1077.
5. (a) Lal, G. S.; Pez, G. P. and Syvret, R. G., *Chem. Rev*., **1996**, *96*, 1737. (b) Wilkinson, J. A., *Chem. Rev*., **1992**, *92*, 505. (c) Silvester, M. J., *Aldrichimica Acta*, **1991**, *24*, 31. (d) Hewitt, C. D. and Silvester, M. J., *Aldrichimica Acta*, **1988**, *21*, 3. (e) Becker, H. G. O. and Israel, G., *J. Prakt. Chem.,* **1979**, *321*, 579. (f) Alsing, T. K. and Sochilin, E. G., *Zh. Org. Khim.,* **1971**, *7*, 530. (g) Suschitzky, H., *The Balz-Schiemann Reaction*, in *Advances in Fluorine Chemistry*, ed., Stasey, M.; Tatlow, J. C. and Sharpe, A. G., Butterworths, Washington, **1965**. (h) Roe, A., *Org. React.*, **1949**, *5*, 193.
6. (a) Swain, C. G. and Rogers, R. J., *J. Am. Chem. Soc.*, **1975**, *97*, 799. (b) Olah, G. A. and Tolgyesi, W. S., *J. Org. Chem*., **1961**, *26*, 2053.
7. (a) Christe, K. O. and Pavlath, A. E., *J. Org. Chem*., **1965**, *30*, 3170. (b) Haroutounian, S. A.; DiZio, J. P. and Katzenellenbogen, J. A., *J. Org. Chem*., **1991**, *56*, 4993. (c) Roe, A. and Fleishman, H. L., *J. Am. Chem. Soc*., **1947**, *69*, 509. (d) de Mas, N.; Günther, A.; Schmidt, M. A. and Jensen, K. F., *Ind. Eng. Chem. Res*., **2003**, *42*, 698. (e) Hayakawa, Y.; Kimoto, H.; Cohen, L. A. and Kirk, K. L., *J. Org. Chem*., **1998**, *63*, 9448. (f) Kirk, K. L. and Cohen, L. A., *J. Am. Chem. Soc*., **1973**, *95*, 4619. (g) Kirk, K. L.; Nagai, W. and Cohen, L. A., *J. Am. Chem. Soc*., **1973**, *95*, 8389. (h) Kirk, K. L. and Cohen, L. A. *J. Org. Chem*., **1973**, *38*, 3647. (i) Kirk, K. L. and Cohen, L. A. *J. Am. Chem. Soc*., **1971**, *93*, 3060. (j) de Viedma, A. G.; Martínez-Barrasa, V.; Burgos, C.; Izquierdo, M. L. and Alvarez-Builla, J., *J. Org. Chem*., **1999**, *64*, 1007. (k) Mulder, P. P. J.; Ramakrishna, N. V. S.; Cremonesi, P.; Rogan, E. G. and Cavalieri, E. L., *Chem. Res. Toxicol.*, **1993**, *6*, 657. (l) Ng, J. S.; Katzenellenbogen, J. A. and Kilbourn, M. R., *J. Org. Chem*., **1981**, *46*, 2520. (m) Honore, T. and Hjeds, H., *Eur. J. Med. Chem.-Chim. Ther.,* **1979**, *14*, 285. (n) Becker, H. G. O. and Israel, G., *J. Prakt. Chem.,* **1979**, *321*, 579. (o) Fabra, F.; Vilarraaa, J. and Coll, J., *J. Heterocycl. Chem.,* **1978**, *15*, 1447. (p) Hartmann, G. D. and Biffer, S. E., *J. Org. Chem.,* **1977**, *42*, 1468. (q) Sweeny, A.; Blair, R. D.; Chang, A. and Clark, L., *J. Fluor. Chem.,* **1976**, *6*, 389. (r) Doyle, M. P.; Whitefleet, J. L. and Zaleta, M. A., *Tetrahedron Lett.,* **1975**, 4201. (s) Reepmeyer, J. C.; Kirk, K. L. and Cohen, L. A., *Tetrahedron Lett.,* **1975**, 4107. (t) Aelony, D., *J. Am. Chem. Soc*., **1934**, 2063.
8. (a) Hodgson, H. H. and Ward, E. R., *J. Chem. Soc*., **1947**, 127. (b) Hodgson, H. H. and Marden, E., *J. Chem. Soc*., **1944**, 22. (c) Meerwein, H.; Buechner, F. and von Emster, K., *J. Prakt. Chem*., **1939**, *152*, 237. (d) Hantsch, A. and Vock, R., *Ber.,* **1903**, *36*, 2060. (e) Gatterman, L. and Cantzler, A., *Ber*., **1899**, *32*, 1136. (f) Gatterman, L., *Ber*., **1890**, *23*, 1218. (g) Gatterman, L. and Cantzler, A.,*Ber*., **1890**, *23*, 1225. (h) Sandmeyer, T., *Ber.,* **1884**, *17*,1633. (i) Sandmeyer, T., *Ber*., **1884**, *17*, 2650.
9. O'Neill, P. M.; Willock, D. J.; Hawley, S. R.; Bray, P. G.; Storr, R. C.; Ward, S. A. and Park, B. K., *J. Med. Chem*., **1997**, *40*, 437.
10. (a) Thibault, C.; L'Heureux, A.; Bhide, R. S. and Ruel, R., *Org. Lett*., **2003**, *5*, 5023. (b) Gourves, J.-P.; Ruzziconi, R. and Vilarroig, L., *J. Org. Chem*., **2001**, *66*, 617. (c) Laali, K. K. and Gettwert, V. J., *J. Fluor. Chem.,* **2001**, *107*, 31. (d) Adenier, A.; Bernard, M.-C.; Chehimi, M. M.; Cabet-Deliry, E.; Desbat, B.; Fagebaume, O.; Pinson, J. and Podvorica, F., *J. Am. Chem. Soc.,* **2001**, *123*, 4541. (e) Kiryanov, A. A.; Seed, A. J. and Sampson, P., *Tetrahedron Lett.,* **2001**, *42*, 8797. (f) Suschitzky,

H. and Wakefield, B. J., *Fluor. Chem. Millennium,* **2000**, 463. (g) Marriere, E.; Rouden, J.; Tadino, V. and Lasne, M.-C., *Org. Lett*., **2000**, *2*, 1121. (h) Dolle, F.; Dolci, L.; Valette, H.; Hinnen, F.; Vaufrey, F.; Guenther, I.; Fuseau, C.; Coulon, C.; bottlaender, M. and Crouzel, C., *J. Med. Chem.,* **1999**, *42*, 2251. (i) Lui, N.; Marhold, A. and Rock, M. H., *J. Org. Chem*., **1998**, *63*, 2493. (j) Davis, F. A.; Han, W. and Murphy, C. K., *J. Org. Chem*., **1996**, *60*, 4730. (k) Cecchetti, V.; Clementi, S.; Cruciani, G.; Fravolini, A.; Pagella, I. G.; Savino, A. and Tabarrini, O., *J. Med. Chem*., **1995**, *38*, 973. (l) Farooq, O. and Tiers, G. V. D., *J. Org. Chem.,* **1994**, *59*, 2122. (m) Wilbur, D. S., From: D. Scott Wilbur, *Bioconjugate Chem*., **1992**, *3*, 433. (n) Milner, J. D., *Synth. Commun*., **1992**, *22*, 73. (o) Purrington, S. T. and Woodard, D. L., *J. Org. Chem*., **1991**, *56*, 142. (p) Satyamurthy, N.; Barrio, J. R.; Schmidt, D. G.; Kammerer, C.; Elida, G. T. and Phelps, M. E., *J. Org. Chem*., **1990**, *55*, 4560. (q) Snow, K. M. and Smith, K. M., *J. Org. Chem*., **1989**, *54*, 3270. (r) Yoneda, N.; Suzuki, A. and Fukuhara, T., *J. Fluor. Chem.,* **1988**, *38*, 435. (s) Calli, C., *Chem. Rev*., **1988**, *88*, 765. (t) Andrews, L. E.; Bonnett, R.; Kozyrev. A. N. and Appelman, E. H. *J. Chem. Soc*., *Perkin Trans. I,* **1988**, 1735. (u) Belanger, P. C.; Lau, C. K.; Williams, H. W. R.; Dufresne, C. and Scheigetz, J., *Can. J. Chem.,* **1988**, *66*, 1479. (v) Nishimura, Y. and Matsumoto, J., *J. Med. Chem.,* **1987**, *30*, 1622. (w) Horwitz, J. P.; Iyer, V. K.; Vardhan, H. B.; Corombos, J. and Brooks, S. C., *J. Med. Chem.,* **1986**, *29*, 692. (x) Shani, J.; Gazit, A.; Livshitz, T. and Birant, S., *J. Med. Chem*., **1985**, *28*, 1504. Shani, J.; Gazit, A.; Livshitz, T. and Biran, S., *J. Med. Chem.,* **1985**, *28*, 1504. (y) Jovanovic, M. V., *Heterocycles,* **1984**, *22*, 1105. (z) Matsumoto, J.; Miyamoto, T.; Minamida, A.; Nishimura, Y.; Egawa, H. and Nishimura, H., *J. Med. Chem.,* **1984**, *27*, 292. (aa) Matsumoto, J.; Miyiamoto, T.; Minamida, A.; Nishimura, Y.; Egawa, H. and Nishimura, Y., *J. Heterocycl. Chem.,* **1984**, *21*, 673. (bb) Lerman, O.; Tor, Y.; Hebel, D. and Rozen, S., *J. Org. Chem*., **1984**, *49*, 806. (cc) Barrio, J. R.; Satyamurthy, N.; Ku, H. and Phelps, M. E., *J. Chem. Soc*., *Chem. Commun*., **1983**, 443. (dd) Lerman, O.; Tor, Y. and Rozen, S., *J. Org. Chem*., **1981**, *46*, 4629. (ee) Stephenson, M. T. and Shine, H. J., *J. Org. Chem*., **1981**, *46*, 3139. (ff) Barrio, J. R.and Ku, H., *J. Nucl. Med*., **1981**, *22*, 13. (gg) Heiman, D. F.; Senderoff, S. G.; Katzenellenbogen, J. A. and Neeley, R. J., *J. Med. Chem*., **1980**, *23*, 994. (hh) Patrick, T. B.; Cantrell, G. L.; Chang, C., *J. Am. Chem. Soc.,* **1979**, *101*, 7434. (ii) Olah, G. A.; Welch, J. T.; Vankar, Y. D.; Nojima, M.; Kerekes, I. and Olah, J. A., *J. Org. Chem*., **1979**, *44*, 3872. (jj) Tewson, T. J. and Welch, M. J., *J . Chem. Soc*., *Chem. Commun*. **1979**, 1149. (kk) Gougoutas, J. Z., *J. Am. Chem. Soc.,* **1979**, *101*, 5672. (ll) Rosenfeld, M. N. and Widdowson, D. A., *J. Chem. Soc., Chem. Commun.,* **1979**, 914. (mm) Gougoutas, J. Z. and Johnson, J., *J. Am. Chem. Soc*., **1978**, *100*, 5816. (nn) Hesse, R. H., *Isr. J. Chem*., **1978**, *17*, 60. (oo) Patrick, T. B.; Schield, J. A. and Kirchnerl, D. G., *J. Org. Chem.,* **1974**, *39*, 1758. (pp) Desai, P. B., *J. Chem. Soc., Perkin Trans. I,* **1973**, 1865. (qq) Petterson, R. C.; DeMaggio, A.; Herbert, A. L.; Haley, T. J.; Mykytka, J. P. and Sarkar, I. M., *J. Org. Chem*., **1971**, *36*, 631. (rr) Shaw, M. J.; Hyman, H. H. and Filler, R., *J. Am. Chem. Soc*., **1970**, *92*, 6498. (ss) Hyman, H. H.; Shaw, M. J. and Filler, R., *J. Am. Chem. Soc.,* **1970**, *92*, 6498. (tt) Gruenert, C.; Schellong, H. and Wiechert, K., *Zeit. Chem.,* 1970, 10, 116. (uu) Hart, H. and Janssen, J. F., *J. Org. Chem*., **1970**, *35*, 3637. (vv) Saflers, C. and Sustisky, H., *J. Chem. Soc*., C **1966**, 2317. (ww) Hamer, J., *J. Org. Chem.,* **1963**, *28*, 1666. (xx) Sweeny, A.; Benz, M. L. and Chiainti, J. A., *J. Org. Chem*., **1962**, *27*, 336. (yy) Rutherford, K. G.; Redniond, W. and Rigamonti, J., *J. Org. Chem*., **1961**, *26*, 5149. (zz) Fletcher, T. L. and Nankung, J. J., *Chem. Ind. (London)*, **1961**, 179. (aaa) Olah, G. A. and Tolgyesi, W. S., *J. Org. Chem*., **1961**, *26*, 2319. (bbb) Bachman, G. B. and Hokama, T., *J. Am. Chem. Soc*., **1957**, *79*, 4370. (ccc) Finger, G. C. and Kruse, C. W., *J. Am. Chem. Soc.,* **1956**, *78*, 6034. (ddd) Butt-Hot, N. P.; Lavit, D. and Xuong, N. D., *J. Org. Chem*., **1954**, 1617. (eee) Suschitsky, H., *J. Chem. Soc*., **1953**, 3042. (fff) Ellia, J. F. and Musgrave, W. K. R., *J. Chem. Soc*., **1953**, 1063.. (ggg) Lewis, E. S. and Hinds, W. H., *J. Am. Chem. Soc*., **1952**, *74*, 304. (hhh) Roe, A. and Teague, C. E., *J. Am. Chem. Soc.,* **1951**, *73*, 687. (iii) Ferm, R. L. and VanderWerf, C. A., *J. Am. Chem. Soc.*, **1950**, *78*, 4809. (jjj) Ellia, J. F. and Musgrave, W. K. R., *J. Chem. Soc*., **1950**, 3608. (kkk) Roe, A. and Hawkins, G. F., *J. Am. Chem. Soc*., **1949**, *71*, 1785. (lll) Check, P. H.; Wiley, R. H. and Roe, A., *J. Am. Chem. Soc*., **1949**, *71*, 1863. (mmm) Ray, F. E. and Albertson, C. E., *J. Am. Chem. Soc.,* **1948**, *70*, 1954. (nnn) Roe, A. and Hawkins, G. F.,

J. Am. Chem. Soc., **1947**, *69*, 2443. (ooo) Fosdick, L. S.; Fancher, O. and Urbach, K. F., *J. Am. Chem. Soc.,* **1946**, *68*, 840. (ppp) Flood, D. T., *Org. Syn. Coll. II*, **1943**, 295. (qqq) Schiemann, G. and Winkelmuller, W., *Org. Syn. Coll. II*, **1943**, 299. (rrr) Fosdick, L. S. and Dodds, A. F., *J. Am. Chem. Soc.,* **1943**, *65*, 2305. (sss) Dunker, M. F. W. and Starkey, E. B., *J. Am. Chem. Soc.,* **1939**, *61*, 3005. (ttt) Gottlieb, H. B., *J. Am. Chem. Soc.,*, **1938**, *68*, 532. (uuu) Booth, H. S.; Elsvy, H. M. and Burchfield, P. E., *J. Am. Chem. Soc.,*, **1935**, *57*, 2066. (vvv) Schiemann, G.; Winkelmuller, W.; Basler, E. and Ley, E. *J. Prakt. Chem.,* **1935**, *143*, 18. (www) Booth, H. S.; Elsey, H. M. and Burchfield, P. E., *J. Am. Chem. Soc.,* **1935**, *57*, 2064. (xxx) Balz, G. and Schiemann, G., *U.S. Pat.*, **1933**, July 4, 1,916,327. (yyy) Stoughton, R. W. and Adams, R., *J. Am. Chem. Soc.,* **1932**, *54*, 4426. (zzz) Schiemann, G. and Pillarsky, R., *Ber*., **1929**, *62*, 3035. (aaaa) Blicke, F. F. and Smith, F. D., *J. Am. Chem. Soc*., **1929**, *51*, 1865.

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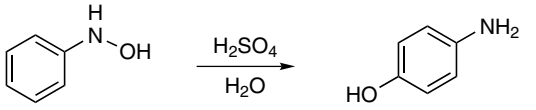
Bamberger Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Bamberger in 1894.[1] It is an intermolecular rearrangement of *N*-phenylhydroxylamines in acidic aqueous solution to afford the corresponding 4-aminophenols, e.g., in aqueous sulfuric acid. Thus this reaction is generally known as the Bamberger rearrangement.[2] Occasionally, it is also termed the Bamberger reaction.[3] It is believed that in this rearrangement the hydroxyl group is introduced into the aromatic ring via a nucleophilic attack of a hydrosulfate ion on the anilenium ion, which is generated by the heterolytic N-O bond cleavage of *O*-protonated *N*-phenylhydroxylamine.[4] It has been found that alkoxy, halogen, phenoxy are incorporated into the aromatic ring when the rearrangement of *N*-phenylhydroxylamine is carried out in nucleophilic solvents, such as alcohols, hydrogen halides, and phenols.[5] There is much mechanistic evidence to favor the heterolytic N-O bond cleavage.[6] This rearrangement has been reviewed.[7]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Under acidic conditions, phenylhydroxylamine is first protonated and subsequently transformed into anilenium by releasing a water molecule, during which the aromatic ring carries

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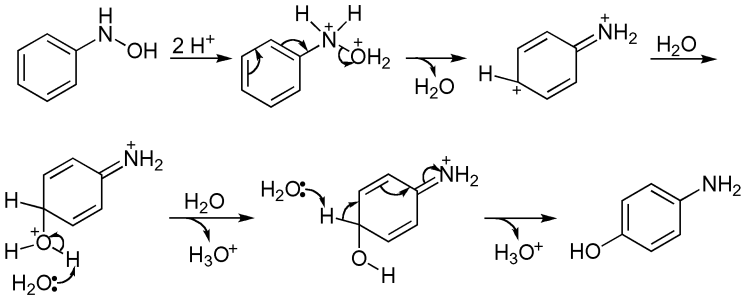
a partial positive charge so that the nucleophilic attacking occurs at the *para* position (the amino group is an *ortho* and *para*-determining group). The mechanism of this rearrangement has been extensively studied in detail.[2g,4,6g,8]



D. MODIFICATION

This type of rearrangement has been extended to pyridines and isoquinolones.[9a] It is reported that the nitro group (NO_2) will migrate to the *ortho* position when it is connected to nitrogen atom of aniline.[9b–d] However, in the case of *O*-phenylhydroxylamine, the amino group will migrate to both the *ortho* and the *para* positions.[4] It has been found that when hydrogen is replaced by a sulfur atom in phenylhydroxylamine [i.e, PhN(OH)SR], the rearrangement rate will be 10^6 as fast as normal Bamberger rearrangement.[10]

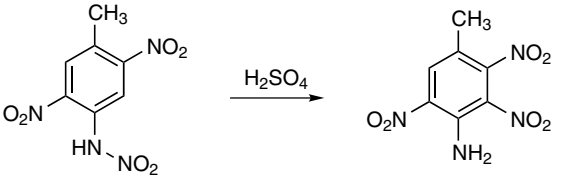
E. APPLICATIONS

N/A

F. RELATED REACTIONS

N/A

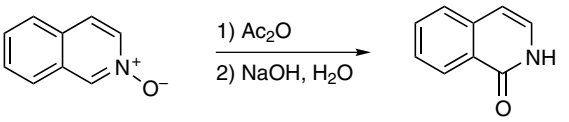
G. CITED EXPERIMENTAL EXAMPLES



Reference 9b.

To a flask were added 10 mL conc. H_2SO_4 and 0.5 g 4-amino-*N*,2,5-trinitrotoluene (2.06 mmol). The mixture was cooled at 0°C, stirred for 69 h, and then poured into 100 mL ice water. The resulting precipitate was filtered off and washed with water to give 0.44 g

4-amino-2,3,5-trinitrotoluene, in a yield of 88%, m.p., 145–151°C. Further recrystallization from hot ethanol gave pure 4-amino-2,3,5-trinitrotoluene, in 40% of recovery, m.p., 150–153°C.



Reference 9a.

In a typical experiment, 18.12 g isoquinoline-*N*-oxide was added to 150 mL acetic anhydride and refluxed gently for 5 h. The liquid soon turned dark red. The acetic anhydride was removed under an aspirator vacuum, and the residue was distilled. The volatile portion was collected in one fraction, which boiled at ~ 142°C (0.9 mmHg); however, an appreciable non-volatile portion remained. The solid distillate was heated on the steam bath with 4 g NaOH and 75 mL water for 40 min and then allowed to stand at room temperature overnight. A pale yellow solid was filtered off and washed with water to give 9.02 g isocarbostyril, in a yield of 53%, m.p., 208.0–209.5°C.

Other references related to the Bamberger rearrangement are cited in literature.[11]

H. REFERENCES

1. (a) Bamberger, E., *Ber.,* **1894**, *27*, 1347. (b) Bamberger, E., *Ber.,* **1894**, *27*, 1548.
2. (a) Schenzle, A.; Lenke, H.; Spain, J. C. and Knackmuss, H.-J., *J. Bacteriology,* **1999**, *181*, 1444. (b) Naicker, K. P.; Pitchumani, K. and Varma, R. S., *Catal. Lett.,* **1998**, *54*, 165. (c) Hughes, J. B.; Wang, C.; Yesland, K.; Richardson, A.; Bhadra, R.; Bennett, G. and Rudolph, F., *Environ. Sci. Technol.,* **1998**, *32*, 494. (d) Fishbein, J. C. and McClelland, R. A., *Can. J. Chem.,* **1996**, *74*, 1321. (e) Shcherbinin, M. B.; Erusalimskii, G. B.; Bal'tser, A. E.; Bazanov, A. G. and Ostrovskii, V. A., *Zh. Org. Khim.,* **1995**, *31*, 1829. (f) Zoran, A.; Khodzhaev, O. and Sasson, Y., *J. Chem. Soc., Chem. Commun.,* **1994**, 2239. (g) Fishbein, J. C. and McClelland, R. A., *J. Am. Chem. Soc.,* **1987**, *109*, 2824. (h) Moehrle, H. and Mieger, T., *Pharmazie,* **1986**, *41*, 26. (i) Corbett, M. D.; Corbett, B. R. and Doerge, D. R., *J. Chem. Soc., Perkin Trans. I,* **1982**, 345. (j) Matschiner, H.; Tanneberg, H. and Maschmeier, C. P., *J. Prakt. Chem.,* **1981**, *323*, 924. (k) Sone, T.; Hamamoto, K.; Seiji, Y.; Shinkai, S. and Manabe, O., *J. Chem. Soc., Perkin Trans. II,* **1981**, 1596. (l) Krylov, A. I. and Stolyarov, B. V., *Zh. Org. Khim.,* **1981**, *17*, 811. (m) Sone, T.; Tokuda, Y.; Sakai, T.; Shinkai, S. and Manabe, O., *J. Chem. Soc., Perkin Trans. II,* **1981**, 298. (n) Sone, T.; Karikura, M.; Shinkai, S. and Manabe, O., *Nippon Kagaku Kaishi,* **1980**, 245. (o) Sone, T.; Karikura, M.; Shinkai, S. and Manabe, O., *Nippon Kagaku Kaishi,* **1979**, 1532.
3. Tordeux, M. and Wakselman, C., *J. Fluor. Chem.,* **1995**, *74*, 251.
4. Haga, N.; Endo, Y.; Kataoka, K.-I.; Yamaguchi, K. and Shudo, K., *J. Am. Chem. Soc*., **1992**, *114*, 9795.
5. (a) Bamberger, E., *Ann.,* **1921**, *424*, 233. (b) Bamberger, E., *Ann.,* **1912**, *390*, 131. (c) Bamberger, E. and Lugutt, J., *Ber.,* **1898**, *31*, 1500. (d) Bamberger, E., *Ber.,* **1895**, *28*, 245.
6. (a) Novak, M. and Lagerman, R. K., *J. Org. Chem.,* **1988**, *53*, 4762. (b) Novak, M.; Pelecanou, M. and Pollack, L., *J. Am. Chem. Soc*., **1986**, *108*, 112. (c) Kohnstam, G.; Petch, W. A. and Williams, D. L. H., *J. Chem. Soc., Perkin Trans. II*, **1984**, 423. (d) Gassman, P. G. and Granrud, J. E., *J. Am. Chem. Soc*., **1984**, *106*, 1498. (e) Novak, M.; Pelecanou, M.; Roy, A. K.; Andronico, A. F.; Plourde, F. M.; Olefirowicz, T. M. and Curtin, T. J., *J. Am. Chem. Soc*., **1984**, *106*, 5623. (f) Sone,

T.; Tokudo, Y.; Sakai, T.; Shinkai, S. and Manabe, O., *J. Chem. Soc., Perkin Trans. II*, **1981**, 298. (g) Sone, T.; Hamamoto, K.; Seiji, Y.; Shinkai, S. and Manabe, O., *J. Chem. Soc., Perkin Trans. II*, **1981**, 1596. (h) Gassman, P. G.; Campbell, G. and Frederick, R., *J. Am. Chem. Soc.,* **1972**, *94*, 3884. (i) Gassman, P. G. and Campbell, G., *J. Am. Chem.* Soc., **1972**, *94*, 3891. (j) Gassman, P. G. and Campbell, G., *J. Am. Chem.* Soc., **1971**, *93*, 2567. (k) Heller, H. E.; Hugh, E. D. and Ingold, K. C., *Nature,* **1951**, *168*, 909.

7. (a) Shine, H. J., *Aromatic Rearrangements*, Elsevier, Amsterdam, **1967**, pp. 182–190. (b) Dewar, M. J. S., Aromatic Rearrangements, in *Molecular Rearrangements*, ed., de Mayo, P., Interscience, New York, **1963**, pp. 295–344. (c) Ingold, K. C., *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N.Y., **1953**, pp. 621–624
8. Bolton, J. L. and McClelland, R. A., *J. Am. Chem. Soc*., **1989**, *111*, 8172.
9. (a) Robison, M. M. and Robison, B. L., *J. Org. Chem*., **1957**, *21*, 1337. (b) Nielsen, A. T.; Christian, S. L.; Chafin, A. P. and Wilson, W. S., *J. Org. Chem*., **1994**, *59*, 1714. (c) Atkins, R. L. and Wilson, W. S., *J. Org. Chem.,* **1986**, *51*, 2572. (d) White, W. N. and Klink, J. R., *J. Org. Chem*., **1970**, *35*, 965.
10. Kazanis, S. and McClelland, R. A., *J. Am. Chem. Soc*., **1992**, *114*, 3052.
11. (a) Hughes, J. B.; Wang, C.; Yesland, K.; Richardson, A.; Bhadra, R.; Bennett, G. and Rudolph, F., *Environ. Sci. Technol*., **1998**, *32*, 494. (b) Preuss, A.; Rieger, P.-G., Anaerobic Transformation of 2,4,6-Trinitrotoluene and Other Nitroaromatic Compounds, in *Biodegradation of Nitroaromatic Compounds*, Spain, J. C., Plenum Press: New York, **1995**; *49*, pp 69–86. (c) Corbett, M. D.; Corbett, B. R., *Biodegradation of Nitroaromatic Compounds*, ed., Spain, J. C., Plenum Press: New York, **1995**; *49*, pp 151–182. (d) M. Tordeux, C. Wakselman, *J. Fluor. Chem.,* **1995**, *74*, 251. (e) Olszewski, J. D.; Marshalla, M.; Sabat, M. and Sundberg, R. J., *J. Org. Chem.,* **1994**, *59*, 4285. (f) Nishino, S. F.; Spain, J. C., *Appl. Environ. Microbiol*., **1993**, *59*, 2520. (g) Sakamoto, Y.; Yoshioka, T. and Uematsu, T., *J. Org. Chem.,* **1989**, *54*, 4449. (h) Johnston, D. and Elder, D., *J. Labelled Compd. Radiopharm.,* **1988**, *25*, 1315. (i) Novak, M.; Bonham, G. A.; Mohler, L. K. and Peet, K. M., *J. Org. Chem*., **1988**, *53*, 3903. (j) McClelland, R. A.; Panicucci, R. and Rauth, A. M., *J. Am. Chem. Soc.,* **1985**, *107*, 1762. (k) Sternson, L. A. and Chandrasakar, R., *J. Org. Chem.,* **1984**, *49*, 4295. (l) Sone, T.; Tokudo, Y.; Sakai, T.; Shinkai, S.; Manabe, O., *J. Chem. Soc., Perkin Trans. II,* **1981**, 298. (m) Shudo, K.; Ohta, T. and Okamoto, T., *J. Am. Chem. Soc.,* **1981,** *103*, 645. (n) Buncel, E., *Acc. Chem. Res*., **1975**, *8*, 132. (o) Mudge, P. R.; Salter, D. A. and Scilly, N. R. *J. Chem. Soc., Chem. Commun.,* **1975,** 509. (p) Patrick, J. A.; Schield, J. A. and Kirchner, D. J., *J. Org. Chem*., **1974**, *39*, 1758. (q) Hughes, E. D. and Ingold, C. K. Q., *Chem. Soc. Rev.,* **1952**,*6*, 34. (r) Dewar, M. J. S., *Nature (London),* **1946,** *156*, 784. (s) Reese, J. S., *Chem. Rev*., **1933**, *33*, 55. (t) Bamberger, E., *Ann.,* **1925**, *441*, 297. (u) Bamberger, E., *Ann.*, **1921**, *424*, 230. (v) Bamberger, E., *Ann.,* **1921**, *424*, 233. (w) Bamberger, E., *Ber.*, **1918**, *51*, 636. (x) Bamberger, E., *Ann.,* **1912**, *390*, 131. (y) Johnson, T. B. and Guest, H. H., *J. Am. Chem. Soc*., **1910**, *32*, 1279. (z) Bamberger, E., *Ber.,* **1907**, *40*, 1906. (aa) Bamberger, E. and Rising, A., *Ber.,* **1901**, *34*, 229. (bb) Bamberger, E., *Ber.,* **1900**, *33*, 3600. (cc) Bamberger, E., *Ber.,* **1895**, *28*, 251. (dd) Bamberger, E., *Ber.,* **1894**, *27*, 1522. (ee) Bamberger, E. and Landsteiner, K., *Ber.,* **1893**, *26*, 485.

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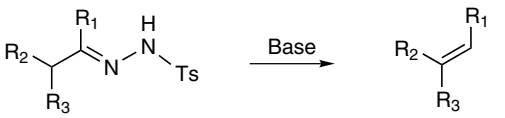
Bamford-Stevens Reaction
(Bamford-Stevens Olefination)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Bamford and Stevens in 1952.[1] It is the transformation of ketones and aldehydes into alkenes through the base-promoted thermal or photolytic decomposition of *p*-toluenesulfonylhydrazones of the corresponding ketones or aldehydes.[2] Therefore, this reaction is generally known as the Bamford-Stevens reaction.[3] In addition, this reaction is also referred to as the Bamford-Stevens olefination.[4] The bases used in this reaction are strong bases, including NaOMe, LiH, NaH, $NaNH_2$, and BuLi. The alkenes formed are normally the thermodynamic product, i.e., the highly substituted alkenes. Depending on the reaction conditions (e.g., bases used, solvents), other types of products rather than alkenes can be prepared as well, including diazo compounds,[5] carbenes,[2e–h] cyclopropyl compounds,[2e–h,6] and alcohols.[7] This is because during the pyrolysis, *p*-toluenesulfonylhydrazone salts first lose *p*-toluenesulfinate anion to generate a diazo intermediate, and the diazo intermediate can change into different species, depending on the reaction conditions, such as solvents (protic vs. aprotic),[8] metal cations[9] and the type and concentration of alkali.[10]

B. GENERAL REACTION SCHEME



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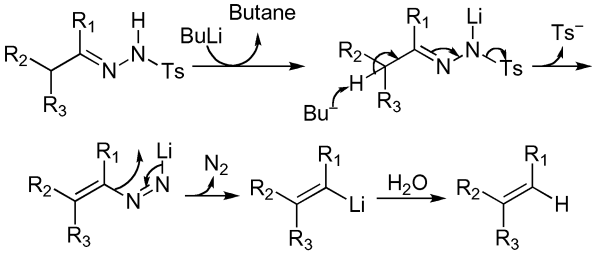
C. PROPOSED MECHANISMS

The mechanism is illustrated by the reaction with butyl lithium.



D. MODIFICATION

Hoffman has modified this reaction to generate diazo compounds *in situ*.[11]

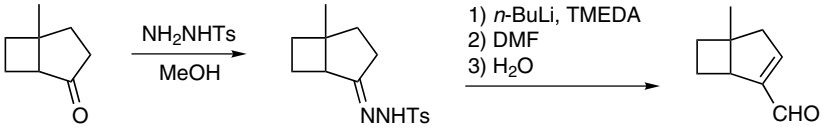
E. APPLICATIONS

This reaction has wide applications in the preparation of alkenes.

F. RELATED REACTIONS

This reaction is closely related to the *Shapiro Reaction* developed 15 years later.[12] The *Shapiro Reaction* is also the decomposition of *p*-toluenesulfonylhydrazones of ketones and aldehydes and is carried out under mild conditions to form less-substituted alkenes.

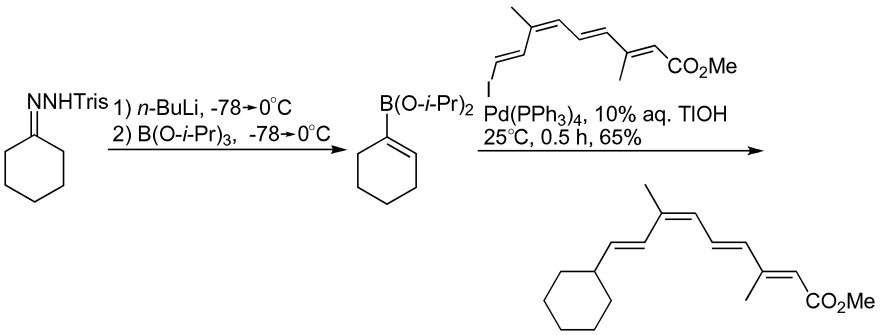
G. CITED EXPERIMENTAL EXAMPLES



Reference 13.

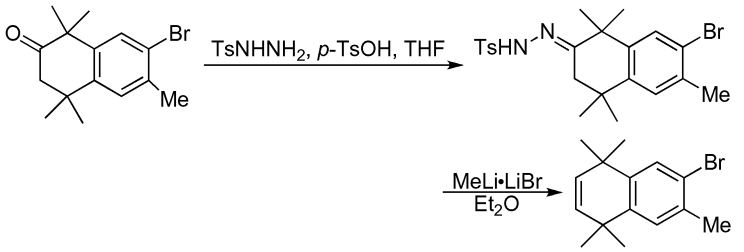
To a flask, were added 46 mL 60% aqueous MeOH and 3.53 g tosylhydrazine (18.9 mmol), and the mixture was heated to 60°C. Then 2.33 g (1*S*R,5*S*R)-methylbicyclo[3.2.0]heptan-2-one (18.8 mmol) was added dropwise to the solution. The reaction mixture was immediately stored at 5°C for 15 h. The resultant white crystals were filtered, washed with 60% aqueous MeOH, and air-dried for 10 min. A mixture of 4.91 g *E* and *Z* isomers of tosylhydrazone (*N*-1-[(1*S*R,5*S*R)-5-methylbicyclo[3.2.0]hep-2-yliden]-4-methyl-1-toluenesulfonoylhydrazone) was obtained as white crystals, in a yield of 89%, m.p. 174–176°C.

Caution: Nitrogen is produced in this reaction and allowance must be made for its escape. Do not use a sealed system. A suspension of 1.04 g of tosylhydrazone (3.59 mmol) in 15 mL TMEDA was cooled to −78°C, under a nitrogen atmosphere. Then 4.6 mL 2.3 M *n*-BuLi (10.58 mmol) was added dropwise to the frozen suspension, and the solution generated was kept at −78°C for 15 min and then allowed to warm to ambient temperature, whereupon it turned a dark red color. This solution was stirred for a further 5 h. When the solution was cooled to 0°C, 0.4 mL DMF (5.18 mmol) was added, and the solution was stirred at ambient temperature overnight. It was then poured into 60 mL 7.5% HCl (aq.) and extracted with CH_2Cl_2 (4 × 40 mL). The combined organic phases were washed with 40 mL sat. NaCl (aq.) and dried; solvent was removed in vacuum. The crude material was used directly in the next reaction. A small portion was purified by flash chromatography using CH_2Cl_2 as the eluent to give a pure sample for spectroscopic analysis.



Reference 14.

To a cold (−78°C) suspension of 0.14 g hydrazone (0.38 mmol) in 1.0 mL THF was added 0.37 mL 3.07 M *n*-BuLi (1.14 mmol), and the solution was stirred for 30 min. Nitrogen evolution was observed when the temperature was taken up to 0°C, before cooling to −78°C for the addition of 0.17 mL triisopropyl borate (0.75 mmol). The mixture was stirred for 1 h at 0°C and then warmed to room temperature. Then 0.035 g $Pd(PPh_3)_4$ (0.030 mmol) followed by iodide dissolved in 1.0 mL THF were added. After 10 min of stirring, a 2.6 mL of 10% aqueous solution of TlOH (1.16 mmol) was added, and the final mixture was stirred at 25°C for 30 min. It was then diluted with Et_2O and filtered through Celite. The filtrate was washed with a saturated $NaHCO_3$ solution three times, dried over Na_2SO_4, and evaporated. The crude residue was purified by column chromatography (SiO_2, 90:10 hexane/EtOAc) to afford 0.06 g ethyl (2*E*,4*E*,6*Z*,8*E*)-(cyclohex-1-en-1-yl)-3,7-dimethylnona-2,4,6,8-tetraenoate as a yellow solid, in a yield of 65%, m.p. 77.5°C (recrystallized from hexane/EtOAc).



Reference 15.

A suspension of 30.5 g 7-bromo-1,1,4,4,6-pentamethyl-1,3,4-trihydronaphtha-len-2-one (0.10 mol), 22.1 g *p*-toluene-sulfonylhydrazide (0.119 mol), and 4.92 g of *p*-toluenesulfonic acid monohydrate (25.9 mmol) in 611 mL MeOH was refluxed under nitrogen for 24 h. The resultant reaction slurry was cooled for 1 h in an ice bath, filtered, and rinsed with 150 mL cold MeOH to give 36.8 g [*aza*-(7-bromo-1,1,4,4,6-pentamethyl(2-1,3,4-trihydro-naphthylidene))methyl][(4-methylphenyl)-sulfonyl]-amine, in a yield of 77%.

A suspension of 20.0 g [*aza*-(7-bromo-1,1,4,4,6-pentamethyl(2-1,3,4-trihydro-naphthyl-idene))methyl][(4-methylphenyl)-sulfonyl]-amine (43.2 mmol) in 400 mL MTBE was treated with 86.3 mL of a 1.5 M solution of MeLi complexed with LiBr in Et_2O (0.13 mol) at room temperature under nitrogen. The reaction was stirred at room temperature for 1 h, cooled to 0°C, and quenched with 500 mL water. The reaction was extracted with 1 L MTBE. The organic layer was dried over $MgSO_4$, and the solvent was removed in vacuo to give 12.0 g -bromo-1,1,4,4,7-pentamethyl-1,4-dihydronaphtha-lene as a white solid, in a yield of 99%.

Other references related to the Bamford-Stevens reaction are cited in the literature.[16]

H. REFERENCES

1. Bamford, W. R. and Stevens, T. S., *J. Chem. Soc.,* **1952,** 4735.
2. (a) Nickon, A., *Acc. Chem. Res*., **1993**, *26*, 84. (b) Regitz, M. and Maas, G., *Diazo Compounds: Properties and Synthesis*, Academic Press, Orlando, Florida, **1986**. (c) Brown, R. F. C., *Pyrolytic Methods in Organic Chemistry*, Academic Press, New York, **1980**. (d) Shapiro, R. H., *Org. React.,* **1976**, *23*, 405. (e) Barom, W. J.; Decamp, M. R.; Hendrick, M. E.; Jones, M. Jr.; Levin, R. H. and Sohn, M. B., *Carbenes From Diazo Compounds* in *Carbenes*, ed. Jones, M. Jr. and Moss, R. A., John Wiley & Sons, New York, **1973**, *I*, Chap. 1. (f) Kirmse, W., *Carbene Chemistry*, 2nd ed. Academic Press, New York, **1971**. (g) R. A. More O'Ferrall, *Advan. Phys. Org. Chem.,* **1967**, *5*, 331. (h) Kirmse, W., *Prog. Org. Chem.,* **1964**, 164.
3. (a) Chandrasekhar, S.; Rajaiah, G.; Chandraiah, L. and Swamy, D. N., *Synlett,* **2001**, 1779. (b) Khripach, V. V.; Zhabinskii, V. N.; Kotyatkina, A. I.; Fando, G. P.; Lyakhov, A. S.; Govorova, A. A.; van der Louw, J.; Groen, M. B. and de Groot, A., *Mendeleev Commun.,* **2001**, 144. (c) Dzikovskaya, L. M. and Ganushchak, N. I., *Russ. J. Org. Chem.,* **2000**, *36*, 1346. (d) Olmstead, K. K. and Nickon, A., *Tetrahedron,* **1999**, *55*, 7389. (e) Olmstead, K. K. and Nickon, A., *Tetrahedron,* **1999**, *55*, 3585. (f) Olmstead, K. K. and Nickon, A., *Tetrahedron,* **1998**, *54*, 12161. (g) Morioka, M.; Kato, M.; Yoshida, H. and Ogata, T., *Heterocycles,* **1996**, *43*, 1759. (h) Banciu, M. D.; Bangiu, A.; Draghici, C.; Petride, A. and Chiraleu, F., *Rev. Roumaine Chim.,* **1995**, *40*, 1165. (i) Chandrasekhar, S.; Mohapatra, S. and Lakshman, S., *Chem. Lett.,* **1996**, 211. (j) Stern, A. G.; Ilao, M. C. and Nickon, A., *Tetrahedron,* **1993**, *49*, 8107. (k) Nickon, A.; Stern, A. G. and Ilao, M. C., *Tetrahedron Lett.,* **1993**, *34*, 1391. (l) Kuznetsova, T. S.; Kozhushkov, S. I.; Gromov, A. V.; Vatlina, L. P.; Kozlovskii, V. I. and Zefirov, N. S., *Zh. Org. Khim.,* **1992**, *28*, 317. (m) Jin, F. Q.; Xu, Y. Y. and Ma, Y. L., *Tetrahedron Lett.,* **1992**, *33*, 6161. (n) Sarkar, T. K. and Ghorai, B. K., *J. Chem. Soc., Chem. Commun.,* **1992**, 1184. (o) Zefirov, N. S.; Kuznetsova, T. S.; Gromov, A. V.; Kozhushkov, S. I.; Vatlina, L. P. and Kozlovskii, V. I., *Zh. Org. Khim.,* **1990**, *26*, 1432. (p) Vlad, R. and Banciu, M., *Rev. Roumaine Chim.,* **1985**, *30*, 1001. (q) Stadler, H.; Rey, M. and Dreiding, A. S., *Helv. Chim. Acta,* **1984**, *67*, 1379. (r) Shafiullah, S. and Khan, B. Z., *J. Indian Chem. Soc.,* **1981**, *58*, 919. (s) Nickon, A. and Zurer, P. St. J., *J. Org. Chem.,* **1981**, *46*, 4685. (t) Bondavalli, F.; Ranise, A.; Schenone, P. and Lanteri, S., *J. Chem. Soc., Perkin Trans.*

I, **1979**, 885. (u) Yue, V. T.; Courson, C. J.; Brinkman, M. R. and Gaspar, P. P., *J. Org. Chem.,* **1978**, *43*, 4873. (v) Bondavalli, F.; Schenone, P.; Ranise, A. and Lanteri, S., *Chim. Ind. (Milan),* **1977**, *59*, 301. (w) Casanova, J. and Waegell, B., *Bull. Soc. Chim. Fr.,* **1975**, 922. (x) Chapleo, C. B. and Dreiding, A. S., *Helv. Chim. Acta,* **1974**, *57*, 1259. (y) Chapleo, C. B. and Dreiding, A. S., *Helv. Chim. Acta,* **1974**, *57*, 873. (z) Ege, G. and Jooss, G., *Chem. Ber.,* **1973**, *106*, 1678. (aa) Nickon, A. and Werstiuk, N. H., *J. Am. Chem. Soc.,* **1972**, *94*, 7081. (bb) Geibel, K. and Maeder, H., *Chem. Ber.,* **1970**, *103*, 1645. (cc) Wilt, J. W. and Kraemer, J. F., *J. Org. Chem.,* **1968**, *33*, 4267. (dd) Ahmad, M. S. and Sharma, R. P., *Aust. J. Chem.,* **1968**, *21*, 527. (ee) Bayless, J. H.; Friedman, L.; Cook, F. B. and Shechter, H., *J. Am. Chem. Soc.,* **1968**, *90*, 531. (ff) Prelog, V. and Smolinski, S., *Helv. Chim. Acta,* **1966**, *49*, 2275. (gg) Nickon, A. and Werstiuk, N. H., *J. Am. Chem. Soc.,* **1966**, *88*, 4543. (hh) Dannenberg, H. and Gross, H. J., *Tetrahedron,* **1965**, *21*, 1611. (ii) Caglioti, L.; Grasselli, P. and Maina, G., *Chim. Ind. (Milan),* **1963**, *45*, 559. (jj) Farnum, D. G., *J. Org. Chem.,* **1963**, *28*, 870.

4. Krief, A.; Lorvelec, G. and Jeanmart, S., *Tetrahedron Lett.,* **2000**, *41*, 3871.
5. (a) Nikiforov, G. A.; Plekhanova, L. G.; De Jonge, K. and Ershov, V. V., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1978**, *12*, 2752. (b) Farnum, D. G., *J. Org. Chem*., **1963**, *28*, 870. (c) Ried, W. and Dietrich, R., *Ber*., **1961**, *94*, 387.
6. (a) Angle, S. R. and Neitzel, M. L., *J. Org. Chem*., **2000**, *65*, 6458. (b) Rudolph, A. and Weedon, A. C., *Can. J. Chem*., **1990**, *68*, 1590. (c) Cook, F.; Schechter, H.; Bayless, J.; Firedman, L.; Folz, R. L. and Randall, R., *J. Am. Chem. Soc*., **1966**, *88*, 3870. (d) Nickon, A. and Werstiuk, N. H., *J. Am. Chem. Soc*., **1966**, *88*, 4543. (e) Wiberg, K. B. and Lavanish, J. M., *J. Am. Chem. Soc*., **1966**, *88*, 5272.
7. (a) Edamura, F. Y. and Nickon, A., *J. Org. Chem.,* **1970**, *35*, 1509. (b) Wilt, J. W.; Stein, R. G. and Wagner, W. J., *J. Org. Chem*., **1967**, *32*, 2097. (c) Wilt, J. W.; Schneider, C. A.; Dabek, H. F.; Kraemer, J. F. and Wagner, W. J., *J. Org. Chem*., **1966**, *31*, 1543.
8. (a) Nickon, A. and Werstiuk, N. H., *J. Am. Chem.* Soc., **1972**, *94*, 7081. (b) Kirmse, W., *Carbene Chemistry*, 2nd ed, Academic Press, New York, **1971**, pp. 30–32. (c) Shapiro, R. H.; Duncan, J. H. and Clopton, J. C., *J. Am. Chem. Soc.,* **1967**, *89*, 471. (d) Nickon, A. and Werstiuk, N. H., *J. Am. Chem. Soc*., **1966**, *88*, 4543. (e) Smith, J. A.; Shechter, H.; Bayless, J. and Friedman, L., *J. Am. Chem. Soc*., **1965**, *87*, 661. (f) Clarke, P.; Whiting, M. C.; Papenmaier. G. and Reusch, W., *J. Org. Chem.,* **1962**, *27*, 3356. (g) Powell, J. W. and Whiting, M. C., *Tetrahedron,* **1959**, *7*, 305. (h) Friedman, L. and Shechter, H., *J. Am. Chem. Soc.,* **1959**, *81*, 5512.
9. (a) Shapiro, R. H.; Duncan, J. H. and Clopton, J. C., *J. Am. Chem. Soc*., **1967**, *89*, 1442. (b) Shapiro, R. H., *Tetrahedron Lett.,* **1966**, 3401.
10. (a) Biellmann, J. F. and Pete, J. P., *Bull. Soc. Chim. Fr*., **1967**, 675. (b) Kirmse, W.; von Bulow, B.-G. and Schepp, H., *Ann.*, **1966**, *691*, 41.
11. (a) Hoffman, R. V.; Orphanides, G. G. and Shechter, H., *J. Am. Chem. Soc.,* **1978**, *100*, 7927. (b) Hoffman, R. V. and Shechter, H., *J. Am. Chem. Soc.,* **1971**, *93*, 5940.
12. See *Shapiro Reaction* herein (P. 2563).
13. Hamon, D. P. G. and Tuck, K. L., *J. Org. Chem.,* **2000**, *65*, 7839.
14. Pazos, Y., Iglesias, B. and de Lera, A. R., *J. Org. Chem.,* **2001**, *66*, 8483.
15. Faul, M. M., Ratz, A. M., Sullivan, K. A., Trankle, W. G. and Winneroski, L. L., *J. Org. Chem.,* **2001**, *66*, 5772.
16. (a) Nordvik, T.; Mieusset, J.-L. and Brinker, U. H., *Org. Lett*., **2004**, *6*, 715. (b) Zhu, S. F.; Liao, Y. X. and Zhu, S. Z., *Org. Lett.,* **2004**, *6*, 377. (c) Guldi, D. M.; Nuber, B.; Bracher, P. J.; Alabi, C. A.; MacMahon, S.; Kukol, J. W.; Wilson, S. R. and Schuster, D. I., *J. Phys. Chem. A,* **2003**, *107*, 3215. (d) May, J. A. and Stoltz, B. M., *J. Am. Chem. Soc*., **2002**, *124*, 12426. (e) Toth, M. and Somsak, L. *J. Chem. Soc., Perkin Trans. I,* **2001**, 942. (f) Angle, S. R. and Neitzel, M. L., *J. Org. Chem.,* **2000**, *65*,6458. (g) Knol, J. and Hummelen, J. C., *J. Am. Chem. Soc.,* **2000**, *122*, 3226.

(h) Pezacki, J. P.; Pole, D. L.; Warkentin, J.; Chen, T.; Ford, F.; Toscano, J. P.; Fell, J. and Platz, M. S., *J. Am. Chem. Soc.,* **1997**, *119*, 3191. (i) Albers, R. and Sander, W., *J. Org. Chem.,* **1997**, *62*, 761. (j) Ohno, M.; Itoh, M.; Umeda, M.; Furuta, R.; Kondo, K. and Eguchi, S., *J. Am. Chem. Soc.,* **1996**, *118*, 7075. (k) Trost, B. M. and Higuchi, R. I., *J. Am. Chem. Soc.,* **1996**, *118*, 10094. (l) Aller, E.; Brown, D. S.; Cox, G. G.; Miller, D. J. and Moody, C. J., *J. Org. Chem.,* **1995**, *60*, 4449. (m) Hummelen, J. C.; Knight, B. W.; LePeq, F.; Wudl, F.; Yao, J. and Wilkins, C. L., *J. Org. Chem.,* **1995**, *60*, 532. (n) An, Y.-Z.; Rubin, Y.; Schaller, C. and McElvany, S. W., *J. Org. Chem.,* **1994**, *59*, 2927. (o) Sarkar, T. K. and Ghorai, B. K., *Chem. Commun.,* **1992**, 1184. (p) Maruka, K. and Yamamoto, H., *Comp. Org. Syn.,* **1991**, *6*, 776. (q) Brinker, U. H.; Schrievers, T. and Xu, L., *J. Am. Chem. Soc.,* **1990**, *112*, 8609. (r) Schlecht, M. F.; Tsarouhtsis, D.; Lipovac, M. N. and Debler, E. A., *J. Med. Chem.,* **1990**, *33*, 386. (s) Majchrzak, M. W.; Bézhazi, M.; Tse-Sheepy, I. and Warkentin, J., *J. Org. Chem.,* **1989**, *54*, 1842. (t) Brinker, U. H. and Weber, J., *Tetrahedron Lett.,* **1986**, *27*, 5371. (u) Huffman, J. W.; Shanmugasundaram, G.; Sawdaye, R.; Raveendranath, P. C. and Desai, R. C., *J. Org. Chem*. **1985**, *50*, 1460. (v) Brinker, U. H. and Boxberger, M. *Angew. Chem. Int. Ed. Engl.,* **1984**, *23*, 974. (w) Mohamadi, F. and Collum, D. B., *Tetrahedron Lett.,* **1984**, *25*, 271. (x) Adlington, R. M. and Barrett, A. G. M., *Acc. Chem. Res.*, **1983**, *16*, 55. (y) Loeschorn, C. A.; Nakajima, M.; McCloskey, P. and Anselme, J.-P., *J. Org. Chem*., **1983**, *48*, 4407. (z) Brinker, U. H. and König, L., *Ber*., **1983**, *116*, 882. (aa) Hacker, N. P. and Turro, N. J., *Tetrahedron Lett.,* **1982**, 1771. (bb) Hirsl-Starcevic, S. and Majerski, Z., *J. Org. Chem.,* **1982**, *47*, 2520. (cc) Nickon, A. and Zurer, P. St. J., *J. Org. Chem*., **1981**, *46*, 4685. (dd) Yue, V. T.; Courson, C. J.; Brinkman, M. R. and Gaspar, P. P., *J. Org. Chem*., **1978**, *43*, 4873. (ee) Nickon, A.; Kwasnik, H. R.; Mathew, C. T.; Swartz, T. D.; Williams, R. O. and DiGiorgio, J. B., *J. Org. Chem*., **1978**, *43*, 3904. (ff) Chamberlin, A. R. and Bond, F. T., *J. Org. Chem*., **1978**, *43*, 154. (gg) Chamberlin, A. R.; Stemke, J. E. and Bond, F. T., *J. Org. Chem.,* **1978**, *43*, 147. (hh) Borowiecki, L. and Welniak, M., *Pol. J. Chem.,* **1978**, *52*, 2173. (ii) Kyba, E. P. and John. A. M., *J. Am. Chem. Soc*., **1977**, *99*, 8329. (jj) Kyba, E. P. and Hudson, C. W., *J. Am. Chem. Soc*., **1976**, *98*, 5696. (kk) Kirmse, W. and Knöpfel, N., *J. Am. Chem. Soc.,* **1976**, *98*, 4672. (ll) Nickon, A.; Huang, F.-C.; Weglein, R.; Matsuo, K. and Yagi, H., *J. Am. Chem. Soc*., **1974**, *96*, 5264. (mm) Mizuno, Y.; Endo, T.; Miyaoka, T. and Ikeda, K., *J. Org. Chem.,* **1974**, *39*, 1260. (nn) Murahashi, S. I.; Okumura, K.; Maeda, Y.; Sonoda, A, and Moritani, I., *Bull. Chem. Soc. Jpn.,* **1974**, *47*, 2420. (oo) Ojima, I. and Kondo, K., *Bull, Chem. Soc., Jpn.*, **1973**, *46*, 1539. (pp) Greene, F. D.; Camp, R L.; Abegg, V. P. and Pierson, G. O., *Tetrahedron Lett.,* **1973**, 4091. (qq) Kondo, K. and Ojima, I, *J. Chem.* Soc., *Chem. Commun.,* **1972**, *62*. (rr) Nickon, A. and Werstiuk, N. H., *J. Am. Chem. Soc*., **1972**, *94*, 7081. (ss) Moss, R. A. and Dolling, U. H., *Tetrahedron Lett*., **1972**, 5117. (tt) Moss, R. A.; Dolling, U. H., Whittle, J. R., *Tetrahedron Lett*., **1971**, 931. (uu) Edamura, F. Y. and Nickon, A., *J. Org. Chem.*, **1970**, *35*, 1509. (vv) Jones, W. M. and Ennis, C. L., *J. Am. Chem. Soc*., **1969**, *91*, 6391. (ww) Wilt, J. W. and Kraemer, J. F., *J. Org. Chem*., **1968**, *33*, 4267. (xx) Bayless, J. H.; Friedman, I. L.; Cook, F. B. and Shechter, H., *J. Am. Chem. Soc*., **1968**, *90*, 531. (yy) Kirmse, W.; von Scholz, H. D. and Arold, H., *Ann.,* **1968**, *711*, 22. (zz) Robson, J. H. and Shechter, H., *J. Am. Chem. Soc*., **1967**, *89*, 7112. (aaa) Moser, R. E.; Fritsch, J. M.; Westman, T. L.; Kliss, R. M. and Mathews, C. M., *J. Am. Chem. Soc*., **1967**, *89*, 5673. (bbb) Masamune, S.; Chin, C. G.; Hojo, K. and Seidner, R. T., *J. Am. Chem. Soc*., **1967**, *89*, 4808. (ccc) Muchowski, J. M., *Tetrahedron Lett.,* **1966**, 1773. (ddd) Nickon, A.; Lambert, J. L. and Oliver, J. E., *J. Am. Chem. Soc*., **1966**, *88*, 2787. (eee) Nickon, A. and Werstiuk, N. H., *J. Am. Chem. Soc*., **1966**, *88*, 4543. (fff) Masamune, S.; Fukumoto, K.; Yasunari, Y. and Darwish, D., *Tetrahedron Lett*., **1966**, 193. (ggg) Kirmse, W. and Pook, K.-H., *Angew. Chem. Int. Ed. Engl*., **1966**, *5*, 594. (hhh) Chapman, J. R., *Tetrahedron Lett*., **1966**, 113. (iii) Cope, A. C.; Brown, M. and Woo, G. L., *J. Am. Chem. Soc.*, **1965**, *87*, 3107. (jjj) Gianturco, M. A.; Friedel, P. and Flanagan, V. *Tetrahedron Lett*., **1965**, 1847. (kkk) Wilt, J. W.; Kosturik, J. and Orlowski, R. C., *J. Org. Chem*., **1965**, *30*, 1052. (lll) Buchi, G. and White, J. D., *J. Am. Chem. Soc*., **1964**, *86*, 2884. (mmm) Lemal, D. M. and Fry, A. J., *J. Org. Chem.,* **1964**, *29*, 1673. (nnn) Lemal, D. M. and Fry, A. J., *J. Org. Chem*., **1964**, *29*, 1673. (ooo) Cristol, S. and Harrington, J. K., *J. Org. Chem.,* **1963**, *28*, 1413. (ppp) Closs, G. L.; Closs, L. E. and Boll,

W., *J. Amer. Chem. Soc.,* **1963**, *85*, 3796. (qqq) Freeman, P. K.; George, D. E. and Rao, V. N. M., *J. Org. Chem.,* **1963**, *28*, 3234. (rrr) Cristol, S. J. and Harrington, J. K., *J. Org. Chem.,* **1963**, *28*, 1413. (sss) Farum, D. G., *J. Org. Chem.,* **1963**, *28*, 870. (ttt) Dauben, W. G. and Willey, F. G., *J. Am. Chem.* Soc., **1962**, *84*, 1498. (uuu) Friedman, L. and Shechter, H., *J. Am. Chem.* Soc., **1959**, *81*, 5512. (vvv) Powell, J. W. and Whiting, M. C., *Tetrahedron*, **1957**, *7*, 305.

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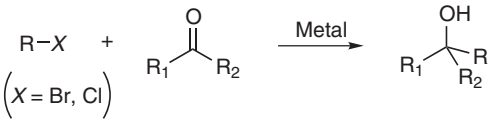
Barbier Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Barbier in 1898,[1] just 2 years earlier than the well-known but closely related *Grignard Reaction*.[2] In the *Grignard Reaction*, alkyl halides react first with magnesium to form Grignard reagents, which further attack the carbonyl groups to form carbon-carbon bonds; however, in the Barbier reaction,[3] both alkyl halides and carbonyl compounds are simultaneously mixed with magnesium turnings and form carbon-carbon bonds in one-step. In the latter case, a much smaller excess of the toxic halide can be used,[4] and similar results, including the R:S ratio, with respect to the *Grignard Reaction* can be obtained.[5] Therefore, the purification procedure is considerably simplified.[4,6] This reaction is known to be preferable for halides, like allyl and benzyl bromides,[7] and is believed to go through the single-electron transfer (SET) process.[8] Currently, many zero-valent metals have been successfully applied to similar reaction conditions, particularly lithium,[9] because it often results in exceptional yields.[10] Even metal halides instead of metal have been applied to this reaction.[11] One important advantage associated with the Barbier reaction over the *Grignard Reaction* is that this reaction tolerates water; and, in fact, many metals have been reported to be effective in mediating the aqueous Barbier reaction, including aluminum,[12a] antimony,[12b] bismuth,[12c,12d] cadmium,[12e] gallium,[12f] indium,[12g–12r] lead,[12s,12t] magnesium,[3b,5,12u] manganese,[12v,12w] samarium,[11d,12x–12ad] tin,[12ae–12jj] and zinc.[12kk–12yy] It has been reported that nonpolar solvents favor R-regioselection,[13a,13b] whereas polar solvents, such as DMSO, which is strongly coordinated[12x–12dd] with the tin of an allylic tin, lead to *γ-syn* selection.[13c] The versatility and mildness of this reaction[12ee–12jj] has been extensively reviewed.[14]

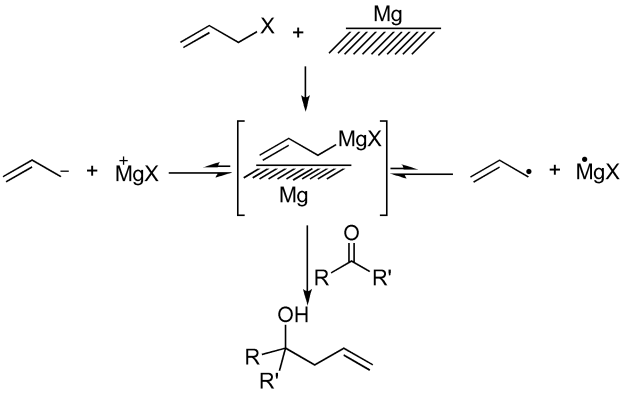
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The mechanism of both the Barbier reaction and the *Grignard Reaction* have been extensively studied.[15]It is believed that this reaction occurs at least partially via SET,[8] as illustrated here.[16]



D. MODIFICATION

Compared to the initial reaction conditions, the applications of other metals to this reaction can be considered modifications.

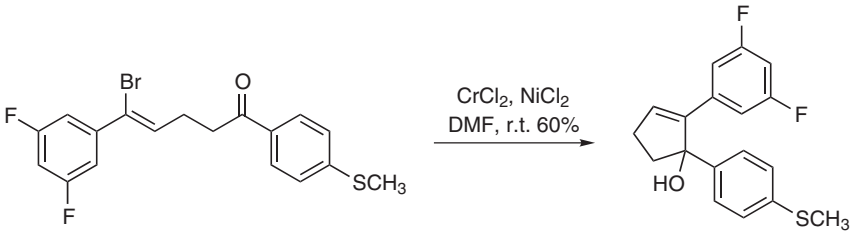
E. APPLICATIONS

This reaction has wide applications in organic synthesis.

F. RELATED REACTIONS

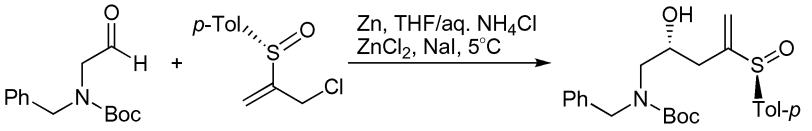
This reaction is closely related to the *Grignard Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



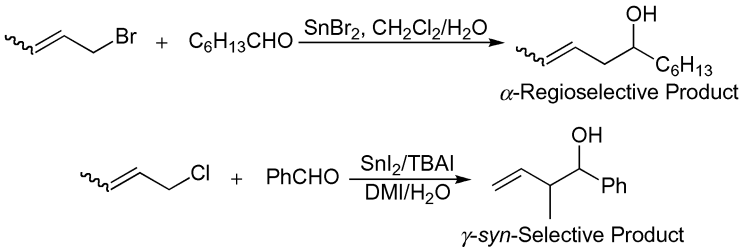
Reference 17.

To a flask in a dry box were added 154 mg chromium(II) chloride (1.25 mmol) and 65 mg nickel(II) chloride (0.5 mmol), and the flask was sealed under argon. To this flask was added a solution of 100 mg 5-bromo-5-(3,5-difluorophenyl)-1-(4-methylsulfanylphenyl)pent-4-en-1-one (0.25 mmol) in 2 mL DMF, and the solution was stirred for overnight at room temperature. The crude reaction mixture was then loaded directly to a silica gel column (3/1 petroleum ether/ethyl ether) to give 48 mg 2-(3,5-difluorophenyl)-1-(4-methylsulfanylphenyl)cyclopent-2-enol as a colorless oil, in a yield of 60%, as well as 12 mg of unreacted starting material (20%). This product was found to be unstable and needed to react in the next step very quickly to prevent decomposition. $R_f = 0.28$ (3/1 petroleum ether/ethyl ether).



Reference 7d.

To a solution of 320 mg (*S*)-allyl chloride (1.5 mmol) in 1 mL THF was added 670 mg NaI (4.5 mmol) under argon. After being stirred for 5 min at room temperature, a solution of the 1.5 mmol aldehyde in 0.5 mL THF was added, followed by the addition of 610 mg $ZnCl_2$ (4.4 mmol) in portions and 7.5 mL saturated aqueous NH_4Cl solution. The reaction mixture was then cooled in an ice water bath, and 150 mg Zn dust (2.3 mmol) was added in portion. After stirring at 0°C for 2 h, the reaction mixture was extracted with 10 mL CH_2Cl_2/Et_2O (1:2) and worked up in the usual way to obtain an oil, which was purified by flash chromatography to give the desired sulfinylamino alcohol, in a yield of 90%, as a 3:1 mixture of diastereomers.



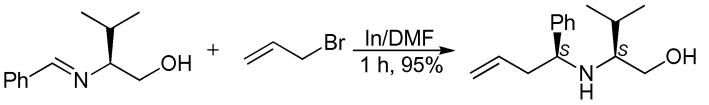
Reference 7f.

α-Regioselective Carbonyl Allylation by 1-Bromobut-2-ene with $SnBr_2$

A typical procedure is as follows: To a solution of 0.56 g $SnBr_2$ (2 mmol) and 0.27 g 1-bromobut-2-ene (2 mmol) in 6 mL mixed solvent of CH_2Cl_2-H_2O (1:1), was added 0.11 g heptanal (1 mmol) at ambient temperature under a nitrogen atmosphere. After being stirred for 24 h, the mixture was diluted with 120 mL of a mixed solvent (ether/dichloromethane = 2:1) and washed successively with 10 mL aqueous 10% HCl solution, 10 mL aqueous $NaHCO_3$ solution, 10 mL water, and 10 mL brine. The extracts were dried over anhydrous $MgSO_4$, and 0.082 g undec-2-en-5-ol (0.48 mmol) was obtained after evaporation of solvent and column chromatography (hexane/EtOAc = 7.1), in a yield of 48%.

γ−*Syn*-Selective Carbonyl Allylation by 1-Chlorobut-2-Ene with SnI_2 and TBAI

A typical procedure is as follows: To a solution of 0.74 g SnI_2 (2.0 mmol), 0.074 g TBAI (0.20 mmol), and 0.30 g NaI (2.0 mmol) in mixed solvent of 3 mL DMI and 0.1 mL H_2O, was added 0.19 mL 1-chlorobut-2-ene (2.0 mmol), followed by 0.10 mL benzaldehyde (1.0 mmol) at ambient temperature under a nitrogen atmosphere. After being stirred for 41 h, the mixture was diluted with 100 mL CH_2Cl_2 and was washed successively with 10 mL aqueous 10% HCl solution, 10 mL aqueous $NaHCO_3$ solution, 10 mL water, and 10 mL brine. The extracts were dried over anhydrous $MgSO_4$ and evaporated to give 0.13 g 2-methyl-1-phenylbut-3-en-1-ol as a colorless oil after column chromatography (hexane/EtOAc = 10:1), in a yield of 83%.



Reference 7e.

General Procedure for the Barbier-Type Allylation

A mixture of 1 mmol imine, 1.5 mmol indium and 1.5 mmol allyl bromide in 5 mL DMF was stirred for 1 h at room temperature under nitrogen. The reaction mixture was evaporated, and EtOAc and 1 N aqueous HCl were added to the resulting suspension and stirred for 30 min. Then 30% NaOH was added to neutralize the resulting solution, which was further stirred for 10 min. The mixture was extracted with EtOAc and washed with brine, dried over anhydrous potassium carbonate, and concentrated under reduced pressure. The mixture was purified by flash silica gel column chromatography with hexane/EtOAc (8:1) to give the product in 95% yield.

Other references related to the Barbier reaction are cited in the literature.[18,19]

H. REFERENCES

1. Barbier, P., *Comp. Rend.*, **1898**, *128*, 110.
2. Grignard, V., *Comp. Rend.*, **1900**, *130*, 1322.

3. (a) Brahma, S.; Maity, S. and Ray, J. K., *J. Heterocycl. Chem*., **2007**, *44*, 29. (b) Erdik, E. and Kocoglu, M., *Tetrahedron Lett*., **2007**, *48*, 4211. (c) Saito, T.; Takeuchi, T.; Matsuhashi, M. and Nakata, T., *Heterocycles*, **2007**, *72*, 151. (d) Lee, A. S.-Y.; Tsao, K.-W.; Chang, Y.-T. and Chu, S.-F., *J. Chin. Chem. Soc*., **2007**, *54*, 519. (e) Lee, A. S.-Y.; Chu, S.-F.; Chang, Y.-T. and Wang, S.-H., *Tetrahedron Lett*., **2004**, *45*, 1551. (f) Sinha, P. and Roy, S., *Organometallics*, **2004**, *23*, 67. (g) Oudeyer, S.; Aaziz, A.; Leonel, E.; Paugam, J. P. and Nedelec, J.-Y., *Synlett*., **2003**, 485. (h) Zha, Z. G.; Wang, Y. S.; Yang, G.; Zhang, L. and Wang, Z. Y., *Green Chem*., **2002**, *4*, 578. (i) Huang, Z. Z.; Jin, H. W. and Duan, D. H., *Synth. Commun*., **2002**, *32*, 565. (j) Ennis, D. S.; Lathbury, D. C.; Wanders, A. and Watts, D., *Org. Proc. Res. Dev*., **1998**, *2*, 287. (k) Lee, A. S.-Y. and Dai, W.-C., *Tetrahedron*, **1997**, *53*, 859. (l) Russo, D. A., *Chem. Ind. (Dekker)*, **1996**, *64*, 405. (m) Aurell, M. J.; Danhui, Y.; Einhorn, C. and Luche, J. L., *Synlett*., **1995**, 459. (n) Massey, A. G., *Appl. Organomet. Chem*., **1995**, *9*, 159. (o) Stephenson, G. R., *Chem. Ind. (London)*, **1995**, 271.
4. Bernlind, C. and Oscarson, S., *J. Org. Chem*., **1998**, *63*, 7780.
5. Blomberg, C. and Hartog, F. A., *Synthesis*, **1977**, 18.
6. (a) Gyenes, F.; Bergmann, K. E. and Welch, J. T., *J. Org. Chem*., **1998**, *63*, 2824. (b) Aurell, M. J.; Einhorn, C.; Einhorn, J. and Luche, J. L., *J. Org. Chem*., **1995**, *60*, 8.
7. (a) Legros, J.; Meyer, F.; Coliboeuf, M.; Crousse, B.; Bonnet-Delpon, D. and Bégué, J.-P., *J. Org. Chem*., **2003**, *68*, 6444. (b) Skaanderup, P. R. and Madsen, R., *J. Org. Chem*., **2003**, *68*, 2115. (c) Tan, X.-H.; Shen, B.; Deng, W.; Zhao, H.; Liu, L. and Guo, Q.-X., *Org. Lett*., **2003**, *5*, 1833. (d) Márquez, F.; Montoro, R.; Llebaria, A.; Lago, E.; Molins, E. and Delgado, A., *J. Org. Chem*., **2002**, *67*, 308. (e) Yanada, R.; Kaieda, A. and Takemoto, Y., *J. Org. Chem*., **2001**, *66*, 7516. (f) Ito, A.; Kishida, M.; Kurusu, Y. and Masuyama, Y., *J. Org. Chem*., **2000**, *65*, 494. (g) Hyldtoft, L. and Madsen, R., *J. Am. Chem. Soc*., **2000**, *122*, 8444. (h) Li, C.-J. and Zhang, W.-C., *J. Am. Chem. Soc*., **1998**, *120*, 9102.
8. Dubois, J. E.; Bauer, P. and Kaddani, B., *Tetrahedron Lett*., **1985**, *26*, 57.
9. (a) Choi, H.; Pinkerton, A. A. and Fry, J. L., *J. Chem. Soc., Chem. Commun*., **1987**, 225. (b) Luche, J. L. and Damiano, J. C., *J. Am. Chem. Soc*., **1980**, *102*, 7926. (c) Scilly, N. F., *Synthesis*, **1973**, 160. (d) Pearce, P. J.; Richards, D. H. and Scilly, N. F., *J. Chem. Soc., Perkin Trans. I*, **1972**, 1655. (e) Richards, D. H. and Scilly, N. F., *J. Chem. Soc., C*, **1969**, 55.
10. Molle, G. and Bauer, P., *J. Am. Chem. Soc*., **1982**, *104*, 3481.
11. (a) Chan, T. H. and Yang, Y., *J. Am. Chem. Soc*., **1999**, *121*, 3228. (b) Dubner, F. and Knochel, P., *Angew. Chem., Int. Ed*., **1999**, *38*, 379. (c) Yi, X.-H.; Meng, Y.; Hua, X.-G. and Li, C. J., *J. Org. Chem*., **1998**, *63*, 7472. (d) Curran, D. P.; Gu, X.; Zhang, W. and Dowd, P., *Tetrahedron*, **1997**, *53*, 9023. (e) Yanagisawa, A.; Habaue, S.; Yasue, K. and Yamamoto, H., *J. Am. Chem. Soc*., **1994**, *116*, 6130.
12. (a) Araki, S.; Jin, S. J.; Idou, Y. and Butsugan, Y., *Bull. Chem. Soc. Jpn*., **1992**, *65*, 1736. (b) Li, L. H. and Chan, T. H., *Tetrahedron Lett*., **2000**, *41*, 5009. (c) Ren, P.-D.; Pan, S.-F.; Dong, T.-W. and Wu, S.-H., *Chin. J. Chem*., **1996**, *14*, 462. (d) Wada, M.; Ohki, H. and Akiba, K. Y., *Bull. Chem. Soc. Jpn*., **1990**, *63*, 2751. (e) Kobayashi, S.; Aoyama, N. and Manabe, K., *Synlett*., **2002**, 483. (f) Wang, Z.; Yuan, S. and Li, C.-J., *Tetrahedron Lett*., **2002**, *43*, 5097. (g) Li, J. M.; Zha, Z. G.; Sun, L. L.; Zhang, Y. and Wang, Z. Y., *Chem. Lett*., **2006**, *35*, 498. (h) Gong, J. H.; Lee, K. Y.; Son, J. S. and Kim, J. N., *Bull. Korean Chem. Soc*., **2003**, *24*, 507. (i) Yadav, J. S.; Madhuri, C.; Reddy, B. V. S.; Reddy, G. S. K. K. and Sabitha, G., *Synth. Commun*., **2002**, *32*, 2771. (j) Hilt, G.; Smolko, K. I. and Waloch, C., *Tetrahedron Lett*., **2002**, *43*, 1437. (k) Vogel, S.; Stembera, K.; Hennig, L.; Findeisen, M.; Giesa, S.; Welzel, P. and Lampilas, M., *Tetrahedron*, **2001**, *57*, 4139. (l) Steurer, S. and Podlech, J., *Adv. Synth. Catal*., **2001**, *343*, 251. (m) Canac, Y.; Levoirier, E. and Lubineau, A., *J. Org. Chem*., **2001**, *66*, 3206. (n) Nair, V. and Jayan, C. N., *Tetrahedron Lett*., **2000**, *41*, 1091. (o) Loh, T. P.; Zhou, J. R. and Yin, Z., *Org. Lett*., **1999**, *1*, 1855. (p) Paquette, L. A. and Mitzel, T. M., *J. Am. Chem. Soc*., **1996**, *118*, 1931. (q) Cintas, P., *Synlett*., **1995**, 1087.

(r) Chan, T. H.; Li, C. J.; Lee, M. C. and Wei, Z. Y., *Can. J. Chem*., **1994**, *72*, 1181. (s) Zhou, J.-Y.; Sun, G.-F.; Zhang, M.-F.; Jia, Y. and Wu, S.-H., *Chin. J. Chem*., **1997**, *15*, 361. (t) Tanaka, H.; Hamatani, T.; Yamashita, S. and Torii, S., *Chem. Lett*., **1986**, 1461. (u) Li, C.-J.; Meng, Y.; Yi, X.-H.; Ma, J. and Chan, T.-H., *J. Org. Chem*., **1997**, *62*, 8632. (v) Cahiez, G. and Chavant, P. Y., *Tetrahedron Lett*., **1989**, *30*, 7373. (w) Basu, M. K. and Banik, B. K., *Tetrahedron Lett*., **2001**, *42*, 187. (x) Huang, Z.-Z.; Jin, H.-W.; Duan, D.-H. and Huang, X., *J. Chem. Res. (S)*, **1999**, 564. (y) Takeya, T.; Ohguchi, A. and Tobinaga, S., *Chem. Pharm. Bull*., **1994**, *42*, 438. (z) Sasaki, M.; Collin, J. and Kagan, H. B., *New J. Chem*., **1992**, *16*, 89. (aa) Curran, D. P. and Wolin, R. L., *Synlett*., **1991**, 317. (bb) Curran, D. P.; Fevig, T. L. and Totleben, M. J., *Synlett*., **1990**, 773. (cc) Zou, C.-L.; Zha, Z.-G.; Wang, Z.-Y.; Wu, J.-H. and Zhang, J.-H., *Chin. J. Chem*., **2002**, *20*, 718. (dd) Zha, Z.-G.; Xie, Z.; Zhou, C.-L.; Wang, Z.-Y. and Wang, Y.-S., *Chin. J. Chem*., **2002**, *20*, 1477. (ee) Sinha, P. and Roy, S., *Chem. Commun*., **2001**, 1798. (ff) Chan, T. H.; Yang, Y. and Li, C. J., *J. Org. Chem*., **1999**, *64*, 4452. (gg) Majumdar, K. K., *Tetrahedron: Asymmetry*, **1997**, *8*, 2079. (hh) Wu, S. H.; Huang, B. Z.; Zhu, T. M.; Yiao, D. Z. and Chu, Y. L., *Acta Chim. Sin*., **1990**, *48*, 372. (ii) Wu, S. H. and Zhu, T., *Acta Chim. Sin*., **1987**, *45*, 1135. (jj) Mukaiyama, T. and Harada, T., *Chem. Lett*., **1981**, 1527. (kk) Keinicke, L.; Fristrup, P.; Norrby, P. and Madsen, R., *J. Am. Chem. Soc*., **2005**, *127*, 15756. (ll) Resende, G. O.; Aguiar, L. C. S. and Antunes, O. A. C., *Synlett*., **2005**, 119. (mm) Jairaj, V. and Burton, D. J., *J. Fluor. Chem*., **2001**, *111*, 233. (nn) Luche, J.-L. and Sarandeses, L. A., *Organozinc Reagents*, **1999**, 307. (oo) Bieber, L. W.; Storch, E. C.; Malvestiti, I. and Da Silva, M. F., *Tetrahedron Lett*., **1998**, *39*, 9393. (pp) Bieber, L. W.; da Silva, M. F.; da Costa, R. C. and Silva, L. O. S., *Tetrahedron Lett*., **1998**, *39*, 3655. (qq) Yi, X. H.; Haberman, J. X. and Li, C. J., *Synth. Commun*., **1998**, *28*, 2999. (rr) Marton, D.; Stivanello, D. and Tagliavini, G., *J. Org. Chem*., **1996**, *61*, 2731. (ss) Makosza, M. and Grela, K., *Synth. Commun*., **1996**, *26*, 2935. (tt) Makosza, M. and Grela, K., *Tetrahedron Lett*., **1995**, *36*, 9225. (uu) Deng, D.-L. and Lu, Z.-H., *Chin. Chem. Lett*., **1994**, *5*, 173. (vv) Hong, F.; Tang, X. Q. and Hu, C. M., *J. Chem. Soc., Chem. Commun*., **1994**, 289. (ww) Petrier, C. and Luche, J. L., *J. Org. Chem*., **1985**, *50*, 910.

13. (a) Masuyama, Y.; Hayakawa, A.; Kurusu, Y., *J. Chem. Soc., Chem. Commun*., **1992**, 1102. (b) Masuyama, Y.; Hayakawa, A.; Kishida, M.; Kurusu, Y., *Inorg. Chim. Acta*, **1994**, *220*, 155. (c) Takahara, J. P.; Masuyama, Y. and Kurusu, Y., *J. Am. Chem. Soc*., **1992**, *114*, 2577.

14. (a) Krief, A. and Laval, A.-M., *Chem. Rev*., **1999**, *99*, 745. (b) Lubineau, A.; Auge, J. and Queneau, Y., Chapter 4, Carbonyl Additions and Organometallic Chemistry in Water, in *Organic Synthesis in Water*, ed. Grieco, P. A., Blackie Academic & Professional, London, **1998**. (c) Paquette, L. A., Opportunities Offered by Indium-Promoted Carbon-Carbon Bond-Forming Reactions in Water, in *Green Chemistry-Frontiers in Benign Chemical Syntheses and Processes*, ed. Anastas, P. T. and Williamson, T. C., Oxford University Press, New York, **1998**. (d) Li, C. J. and Chan, T. H., *Organic Reactions in Aqueous Media*, John Wiley & Sons, New York, **1997**. (e) Chan, T. H. and Isaac, M. B., *Pure & Appl. Chem*., **1996**, *68*, 919. (f) Marshall, J. A., *Chem. Rev*., **1996**, *96*, 31. (g) Wakefield, B. J., Organomagnesium Methods in Organic Chemistry, in *Organomagnesium Methods in Organic Synthesis*, *Best Synthetic Methods Series*, eds. Katritzky, A. R.; Meth-Cohn, O. and Rees, C. W., Academic Press, San Diego, **1995**. (h) Lubineau, A.; Auge, J. and Queneau, Y., *Synthesis*, **1994**, 741. (i) Thomas, E. J., *Chemtracts-Org. Chem*., **1994**, *7*, 207. (j) Masuyama, Y., Palladium-catalyzed Carbonyl Allylation via π-Allypalladium Complexes, in *Advances in Metal-Organic Chemistry*, ed. Liebeskind, L. S., JAI Press, Greenwich, Conn., **1994**; *3*, p 255. (k) Li, C. J., *Chem. Rev*., **1993**, *93*, 2023. (l) Yamamoto, Y. and Asao, N., *Chem. Rev*., **1993**, *93*, 2207. (m) Blomberg, C., *The Barbier Reaction and Related One-Step Processes*, Springer-Verlag, New York, **1993**. (n) Cintas, P., *Synthesis*, **1992**, 248. (o) Rousch, W. R., Uncatalyzed Additions of Nucleophilic Alkenes to C-X, in *Comprehensive Organic Synthesis*, eds. Trost, B. M.; Fleming, I. and Heathcock, C. H., Pergamon Press, Oxford, **1991**, *2*, pp. 1-53. (p) Lai, Y. H., *Synthesis*, **1981**, 585. (q) Courtois, G. and Miginiac, L., *J. Organomet. Chem*., **1974**, *69*, 1. (r) Ioffe, S. T.

and Nesmeyanov, A. N., *The Organic Compounds of Magnesium, Beryllium, Calcium, Strontium and Barium*, North-Holland, Amsterdam, **1976**.

15. (a) Walborsky, H. M. and Zimmermann, C., *J. Am. Chem. Soc*., **1992**, *114*, 4996. (b) Walling, C., *Acc. Chem. Res*., **1991**, *24*, 255. (c) Garst, J. F., *Acc. Chem. Res*., **1991**, *24*, 95. (d) Walborsky, H. M., *Acc. Chem. Res*., **1990**, *23*, 286. (e) Lawrence, L. M. and Whitesides, G. M., *J. Am. Chem. Soc*., **1980**, *102*, 2493. (f) Gomberg, M. and Bachmann, W. E., *J. Am. Chem. Soc*., **1927**, *49*, 236.
16. Zhang, W.-C. and Li, C.-J., *J. Org. Chem*., **1999**, *64*, 3230.
17. Trost, B. M. and Pinkerton, A. B., *J. Org. Chem*., **2001**, *66*, 7714.
18. (a) Tamiya, H.; Goto, K. and Matsuda, F., *Org. Lett*., **2004**, *6*, 545. (b) Sugimoto, O.; Yamada, S. and Tanji, K.-I., *J. Org. Chem*., **2003**, *68*, 2054. (c) Lombardo, M.; Morganti, S. and Trombini, C., *J. Org. Chem*., **2003**, *68*, 997. (d) Aoyama, N.; Hamada, T.; Manabe, K. and Kobayashi, S., *J. Chem. Soc*., *Chem. Commun*., **2003**, 676. (e) Keh, C. C. K.; Wei, C.-M. and Li, C.-J., *J. Am. Chem. Soc*., **2003**, *125*, 4062. (f) Thadani, A. N. and Batey, R. A., *Org. Lett*., **2002**, *4*, 3827. (g) Shin, J.; Gerasimov, O. and Thompson, D. H., *J. Org. Chem*., **2002**, *67*, 6503. (h) Sugimoto, O.; Yamada, S. and Tanji, K.-I., *Tetrahedron Lett*., **2002**, *43*, 3355. (i) Márquez, F.; Llebaria, A. and Delgado, A., *Tetrahedron: Asymmetry*, **2001**, *12*, 1625. (j) Balskus, E. P., Mendez-Andino, J., Arbit, R. M. and Paquette, R. A., *J. Org. Chem*., **2001**, *66*, 6695. (k) Bernardelli, P.; Moradei, O. M.; Friedrich, D.; Yang, J.; Gallou, F.; Dyck, B. P.; Doskotch, R. W.; Lange, T. and Paquette, L. A., *J. Am. Chem. Soc*., **2001**, *123*, 9021. (l) Molander, G. A.; Le Huérou, Y. and Brown, G. A., *J. Org. Chem*., **2001**, *66*, 4511. (m) Li, C. J. and Venkatraman, S., *Tetrahedron Lett*., **2001**, *42*, 781. (n) Loh, T.-P.; Tan, K.-T.; Yang, J.-Y. and Xiang, C.-L., *Tetrahedron Lett*., **2001**, *42*, 8701. (o) Loh, T.-P.; Tan, K.-T. and Hu, Q.-Y., *Tetrahedron Lett*., **2001**, *42*, 8705. (p) Omotowa, B. A. and Shreeve, J. M., *Organometallics*, **2000**, *19*, 2664. (q) Alcaide, B.; Almendros, P. and Aragoncillo, C., *Org. Lett*., **2000**, *2*, 1411. (r) Anwar, U.; Grigg, R. and Sridharan, V., *Chem. Commun*., **2000**, 933. (s) Márquez, F.; Llebaria, A. and Delgado, A., *Org. Lett*., **2000**, *2*, 547. (t) Miller, R. S.; Sealy, J. M.; Shabangi, M.; Kuhlman, M. L.; Fuchs, J. R. and Flowers, R. A., *J. Am. Chem. Soc*., **2000**, *122*, 7718. (u) Gryko, D. and Jurczak, J., *Helv. Chim. Acta*, **2000**, *83*, 2705. (v) Trost, B. M. and Pinkerton, A. B., *Org. Lett*., **2000**, *2*, 1601. (w) Williams, D. R.; Clark, M. P.; Emde, U. and Berliner, M. A., *Org. Lett*., **2000**, *2*, 3023. (x) Luche, J.-L. and Sarandeses, L. A., Zinc-mediated Barbier Reactions, in *Organozinc Reagents-A Practical Approach,* ed. Knochel, P. and Jones, P., Oxford University Press, Oxford, **1999**; p. 307. (y) Marshall, J. A., McNulty, L. M. and Zou, D., *J. Org. Chem*., **1999**, *64*, 5193. (z) Chen, X.-T.; Bhattacharya, S. K.; Zhou, B.; Gutteridge, C. E.; Pettus, T. R. R. and Danishefsky, S. J., *J. Am. Chem. Soc*., **1999**, *121*, 6563. (aa) Urban, D.; Skrydstrup, T. and Beau, J.-M., *J. Org. Chem*., **1998**, *63*, 2507. (bb) Chen, C., *Synlett*., **1998**, 1311. (cc) Abad, A.; Agullo, C.; Arno, M.; Cunat, A. C.; Meseguer, B. and Zaragoza, R. J., *J. Org. Chem*., **1998**, *63*, 5100. (dd) Rübsam, F.; Seck, S.; and Giannis, A., *Tetrahedron*, **1997**, *53*, 2823. (ee) Hanessian, S.; Park, H. and Yang, R. Y., *Synlett*., **1997**, *4*, 353. (ff) Loh, T.-P.; Li, X.-R., *Angew. Chem., Int. Ed. Engl*., **1997**, *36*, 980. (gg) Paquette, L. A.; Mitzel, T. M.; Isaac, M. B.; Crasto, C. F. and Schomer, W. W., *J. Org. Chem*., **1997**, *62*, 4293. (hh) Li, C. J., *Tetrahedron*, **1996**, *52*, 5643. (ii) Paquette, L. A. and Mitzel, T. M., *Tetrahedron Lett*., **1995**, *36*, 6863. (jj) Isaac, M. B. and Chan, T.-H., *Tetrahedron Lett*., **1995**, *36*, 8957. (kk) Molander, G. A. and Harris, C. R., *J. Am. Chem. Soc*., **1995**, *117*, 3705. (ll) Kinishima, M.; Hioki, K.; Kono, K.; Sakuma, T.; Tani, S., *Chem. Pharm. Bull*., **1994**, *42*, 2190. (mm) Gil, J. F.; Ramon, D. J. and Yus, M., *Tetrahedron*, **1994**, *50*, 3437. (nn) Masuyama, Y., *Jpn. J. Synth. Org. Chem*., **1992**, *50*, 202. (oo) Molander, G. A. and McKie, J. A., *J. Org. Chem*., **1991**, *56*, 4112. (pp) Barner, B. A.; Liu, Y. and Rahman, M. A., *Tetrahedron*, **1989**, *45*, 6101. (qq) Rieke, R. D., *Science*, **1989**, *246*, 1260. (rr) de Souza-Barboza, J. C., Pbtrier, C. and Luche, J.-L., *J. Org. Chem*., **1988**, *53*, 1212. (ss) Auvray, P.; Knochel, P. and Normant, J. F., *Tetrahedron*, **1988**, *44*, 4495. (tt) Lannoye, G.; Sambadvarao, K.; Wehrli, S.; Cook, J. M. and Webs, U., *J. Org. Chem*., **1988**, *53*, 2327. (uu) Lannoye, G. and Cook, J. M., *Tetrahedron Lett*., **1988**, *29*, 171. (vv) Molander, G. A.; Etter,

J. B. and Zinke, P. W., *J. Am. Chem. Soc*., **1987**, *109*, 453. (ww) Suginome, H. and Yanada, S., *Tetrahedron Lett*., **1987**, *28*, 3983. (xx) Molander, G. A. and Etter, J. B., *Synth. Commun*., **1987**, *17*, 901. (yy) Auvray, P.; Knochel, P. and Normant, J. F., *Tetrahedron Lett*., **1986**, 5091. (zz) Molander, G. A. and Etter, J. B., *J. Org. Chem*., **1986**, *51*, 1778.

19. (a) Lee, A. S.-Y.; Chang, Y.-T.; Chu, S.-F. and Tsao, K.-W., *Tetrahedron Lett*., **2006**, *47*, 7085. (b) Lombardo, M.; Gianotti, K.; Licciulli, S. and Trombini, C., *Tetrahedron*, **2004**, *60*, 11725. (c) Zha, Z. G.; Xie, Z.; Zhou, C. L.; Chang, M. X. and Wang, Z. Y., *New J. Chem*., **2003**, *27*, 1297. (d) Lannou, M.-I.; Helion, F. and Namy, J.-L., *Tetrahedron Lett*., **2002**, *43*, 8007. (e) Ivkovic, A.; Matovic, R. and Saicic, R. N., *J. Serb. Chem. Soc*., **2002**, *67*, 141. (f) Martelli, G.; Morri, S. and Savoia, D., *Synlett*., **2002**, 158. (g) Jogi, A. and Maeorg, U., *Molecules*, **2001**, *6*, 964. (h) Lee, A. S.-Y. and Lin, L.-S., *Tetrahedron Lett*., **2000**, *41*, 8803. (i) Chandrasekhar, S. and Sridhar, M., *Tetrahedron Lett*., **2000**, *41*, 4685. (j) Costello, D. P. and Geraghty, N. W. A., *Synth. Commun*., **1999**, *29*, 3083. (k) Ringom, R. and Benneche, T., *J. Fluor. Chem*., **1999**, *95*, 121. (l) Machrouhi, F.; Parlea, E. and Namy, J.-L., *Eur. J. Org. Chem*., **1998**, 2431. (m) Peters, D.; Zur, C. and Miethchen, R., *Synthesis*, **1998**, 1033. (n) Lee, A. S.-Y. and Kung, C.-C., *J. Chin. Chem. Soc*., **1997**, *44*, 65. (o) Shih-Yuan, A. and Dai, W.-C., *Tetrahedron Lett*., **1996**, *37*, 495. (p) Aurell, M. J.; Einhorn, C.; Einhorn, J. and Luche, J. L., *J. Org. Chem*., **1995**, *60*, 8. (q) Yang, D. H.; Einhorn, J.; Einhorn, C.; Aurell, M. J. and Luche, J.-L., *J. Chem. Soc., Chem. Commun*., **1994**, 1815. (r) Guijarro, A. and Yus, M., *Tetrahedron Lett*., **1994**, *35*, 253. (s) Yamataka, H.; Nishikawa, K. and Hanafusa, T., *Bull. Chem. Soc. Jpn*., **1994**, *67*, 242. (t) Zhang, W. and Dowd, P., *Tetrahedron Lett*., **1993**, *34*, 2095. (u) Kihara, M.; Kashimoto, M. and Kobayashi, Y., *Tetrahedron*, **1992**, *48*, 67. (v) Waldmann, H., *Liebigs Ann*., **1991**, 1317. (w) Moyano, A.; Pericas, M. A.; Riera, A. and Luche, J. L., *Tetrahedron Lett*., **1990**, *31*, 7619. (x) Waldmann, H., *Synlett*., **1990**, 627. (y) Kihara, M.; Kashimoto, M.; Kobayashi, Y. and Kobayashi, S., *Tetrahedron Lett*., **1990**, *31*, 5347. (z) Shih, N. Y.; Mangiaracina, P.; Green, M. J. and Ganguly, A. K., *Tetrahedron Lett*., **1989**, *30*, 5563. (aa) De Souza-Barboza, J. C.; Luche, J. L. and Petrier, C., *Tetrahedron Lett*., **1987**, *28*, 2013. (bb) Einhorn, J. and Luche, J. L., *Tetrahedron Lett*., **1986**, *27*, 501. (cc) Auvray, P.; Knochel, P. and Normant, J. F., *Tetrahedron Lett*., **1985**, *26*, 2329. (dd) Molander, G. A. and Etter, J. B., *Tetrahedron Lett*., **1984**, *26*, 3281. (ee) Girard, P.; Namy, J. L. and Kagan, H. B., *J. Am. Chem. Soc*., **1980**, *102*, 2693. (ff) Bauer, P. and Molle, G., *Tetrahedron Lett*., **1978**, 4853.

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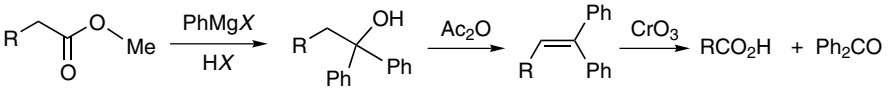
Barbier-Wieland Degradation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was reported independently by Wieland in 1912[1] and Barbier in 1913.[2] However, this reaction is generally known as the Barbier-Wieland degradation.[3] In this reaction, higher-order aliphatic acids (particularly in steroid side chains[3g,3j,4] and side chains of other cyclic compounds[5]) will degrade to the next lower homologs via the consecutive processes of (*a*) the formation of ester, (*b*) the reaction with phenylmagnesium bromide to form carbinol, (*c*) the dehydration to form diphenyl alkenes, and (*d*) the oxidation of alkenes by CrO_3 to give aliphatic acid. This method has been an important method for the elucidation of aliphatic acid structures, although it has failed in a few cases,[6] such as in cyclopropyl acetic acid[7] and lactone.[8] Currently, this method has been modified by using different oxidation reagents,[9] Grignard reagents,[10] and dehydration reagents.[11]

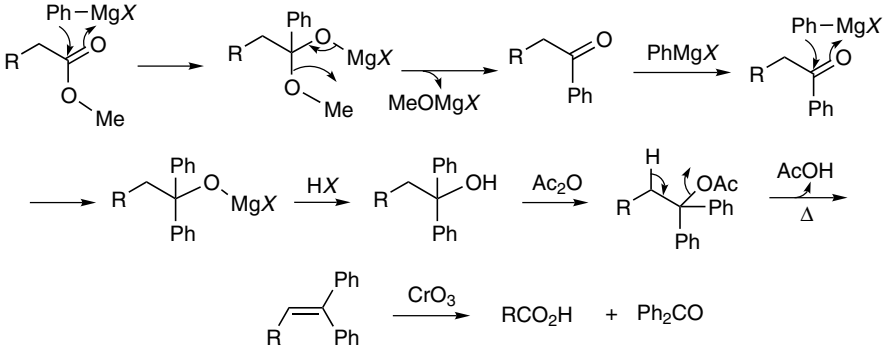
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

This reaction is believed to proceed via the process illustrated below.



D. MODIFICATION

The whole process has been modified using different oxidation reagents, such as the mixture of ruthenium tetroxide and sodium metaperiodate;[9] different Grignard reagents, such as methyl magnesium iodide[10] and different dehydration reagents, such as boric acid.[11] Other modifications are cited in Ref. 4b and Ref. 12.

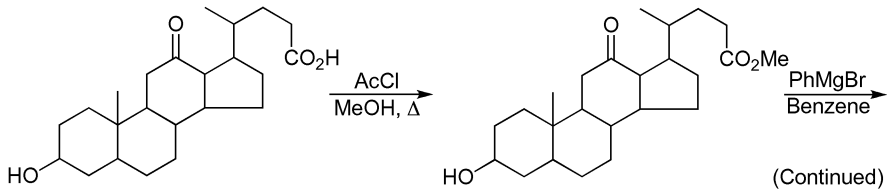
E. APPLICATIONS

This reaction was extensively applied to structural elucidations in the 1930s through the 1950s. Its recent synthetic applications are cited in Ref. 13.

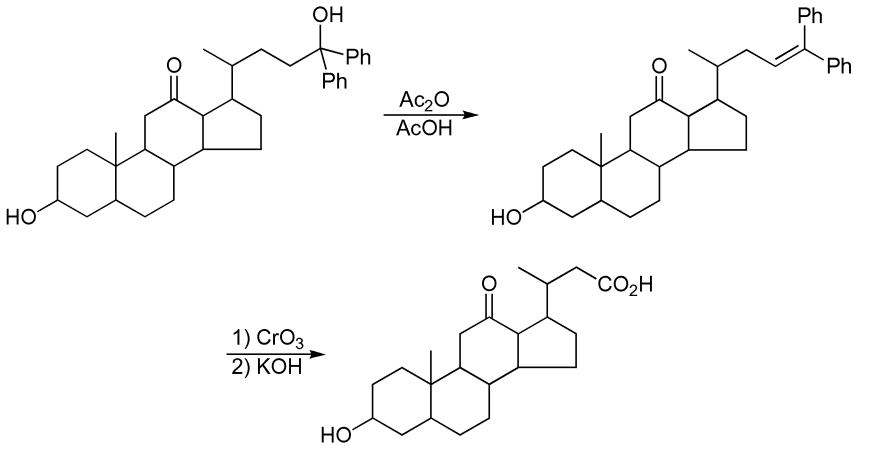
F. RELATED REACTIONS

This reaction is related to the *Miescher Degradation*.

G. CITED EXPERIMENTAL EXAMPLES



(Continued)



Reference 4g.

Preparation of Ester of Methyl 3-Hydroxy-12-Ketocholanate

To a solution of 5.95 g 3-hydroxy-12-ketocholanic acid in 50 mL methanol was added 2 mL acetyl chloride. The solution was refluxed for 15 min and then allowed to stand at room temperature for 3 h. The ester was obtained in crystalline form by carefully diluting the solution to 175 mL with water, in the amount of 5.10 g (99% yield), m.p., 110–112°C.

Preparation of Carbinol of 3-Hydroxy-12-Keto-Nor-Cholanyldiphenylcarbinol

A solution of phenylmagnesium bromide was prepared from 7.78 g magnesium (0.32 mol) and 37.5 mL bromobenzene in 150 mL dry ether. To this solution was added slowly with stirring a solution of 8.05 g methyl 3-hydroxy-12-ketocholanate (0.02 mol) in 150 mL dry benzene. The resulting solution was refluxed for 3.5 h and then decomposed by pouring it into a mixture of 500 mL ice and 50 mL conc. hydrochloric acid. The layers were separated, and the aqueous layer was extracted with ether. The combined ether extracts were washed with dilute hydrochloric acid, water, 5% sodium carbonate solution, and finally with water. The residue left after removing the solvent was steam distilled for 2 h, collected, and dried to give 13.27 g 3-hydroxy-12-keto-nor-cholanyldiphenylcarbinol.

Dehydration of Carbinol

A sample of 7.2 g of the crude 3-hydroxy-12-keto-nor-cholanyldiphenylcarbinol dissolved in 50 mL acetic acid and 25 mL acetic anhydride was refluxed for 2.5 h. The solvent was removed by vacuum distillation, and the gummy residue was dissolved in hot acetone. On standing in the cold room, 1.454 g 3-acetoxy-12-keto-bis-nor-cholanyldiphenylethylene was separated as crystals, in a yield of 24% (based on methyl 3-hydroxy-12-ketocholanate), m.p. 175–178°C

Oxidation of Alkene

To a suspension of 1 g 3-acetoxy-12-keto-bisnor-cholanyldiphenylethylene in 1 mL chloroform and 5 mL acetic acid was added slowly with stirring a solution of 0.63 g chromic acid in 0.5 mL water and 3 mL acetic acid. The temperature was kept at 3.5°C by slight cooling during the addition, which required ~30 min. After stirring for ~5 min more, the excess chromic acid was reduced by adding 2 mL methanol while cooling. The reaction mixture was concentrated in vacuum at room temperature until quite viscous. Water and ether were added, and the aqueous layer was repeatedly extracted with ether. The combined ether extracts were washed several times with dilute hydrochloric acid and then with water. The clear, colorless ether solution was extracted several times with 1% sodium hydroxide solution (total ~70 mL). The basic solution was concentrated to 30–35 mL and 2 g solid sodium hydroxide was added. After refluxing for 1.5 h, it was diluted with water and filtered into 20 mL 6N hydrochloric acid. The 3-hydroxy-12-keto-nor-cholanic acid that precipitated was separated and dried. It weighed 0.470 g and melted at 230–245°C. Crystallization from ethanol gave material melting at 248–250°C, which did not depress the melting point of an authentic sample.

Other references related to the Barbier-Wieland degradation are cited in the literature.[14]

H. REFERENCES

1. Wieland, H., *Ber*., **1912**, *45*, 484.
2. Barbier, P. and Locquin, R., *Compt. Rend*., **1913**, *156*, 1443.
3. (a) Hora, J., *Coll. Czech. Chem. Commun.,* **1966**, *31*, 2737. (b) Fetizon, M.; Golfier, M. and Rassat, A., *Compt. Rend.*, **1961**, *252*, 139. (c) Baker, W.; Curtis, R. F.; McOmie, J. F. W.; Olive, L. W. and Rogers, V., *J. Chem. Soc.,* **1958**, 1007. (d) Yanuka, Y. and Sarel, S., *Bull. Res. Council Isr.,* **1957**, *6A*, 286. (e) Kasturi, T. R. and Iyer, B. H., *J. Indian Inst. Sci.,* **1955**, *37A*, 258. (f) Bhati, A., *Curr. Sci.,* **1953**, *22*, 341. (g) Turner, R. B.; Mattox, V. R.; McGuckin, W. F. and Kendall, E. C., *J. Am. Chem. Soc.,* **1952**, *74*, 5814. (h) Chamberlin, E. M.; Ruyle, W. V.; Erickson, A. E.; Chemerda, J. M.; Aliminosa, L. M.; Erickson, R. L.; Sita, G. E. and Tishler, M., *J. Am. Chem. Soc.,* **1951**, *73*, 2396. (i) Buu-Hoi; J. J., *Bull. Soc. Chim. Fr.,* **1946**, 147. (j) Riegel, B. and Moffett, R. B., *J. Am. Chem. Soc.,* **1943**, *65*, 1971.
4. (a) Johnson, W. S.; Collins, J. C.; Pappo, R.; Rubin, M. B.; Kropp, P. J.; Johns, W. F.; Pike, J. E. and Bartmann, W., *J. Am. Chem. Soc.,* **1963**, *85*, 1409. (b) Mattox, V. R.; Turner, R. B.; McGuckin, W. F.; Chu, E. J. H. and Kendall, E. C., *J. Am. Chem. Soc*., **1952**, *74*, 5818. (c) MacPhillamy, H. B. and Scholz, C. R., *J. Org. Chem*., **1949**, *14*, 643. (d) Riegel, B. and Meyer, E. W., *J. Am. Chem. Soc*., **1946**, *68*, 1097. (e) Moffett, R. B.; Stafford, J. E.; Linsk, J. and Hoehn, W. M., *J. Am. Chem. Soc.,* **1946**, *68*, 1857. (f) Hoehn, W. M. and Mason, H. L., *J. Am. Chem. Soc*., **1938**, *60*, 1493.
5. (a) Wilt, J. W.; Zawadzki, J. F. and Schultenover, D. G., *J. Org. Chem*., **1966**, *31*, 876. (b) Büchi, G.; Erickson, R. E. and Wakabayashi, N., *J. Am. Chem. Soc*., **1961**, *83*, 927. (c) Gutsche, C. D., *J. Am. Chem. Soc.*, **1948**, *70*, 4150.
6. Moore, J. A. and Habraken, C. L., *J. Org. Chem*., **1965**, *30*, 1889.
7. Smith, L. I. and McKenzie, S., *J. Org. Chem*., **1950**, *15*, 75.
8. Johns, W. F., *J. Org. Chem*., **1964**, *29*, 2545.
9. Sarel, S. and Yanuka, Y., *J. Org. Chem.,* **1959**, *24*, 2018.
10. Smith, L. I. and Spillane, L. J., *J. Am. Chem. Soc*., **1943**, *65*, 202.

11. Cope, A. C. and Brown, M., *J. Am. Chem. Soc*., **1958**, *80*, 2859.

12. Ireland, R. E. and Kierstead, R. C., *J. Org. Chem*., **1966**, *31*, 2543.

13. (a) Schteingart, C. D. and Hofmann, A. E., *J. Lipid Res*., **1988**, *29*, 1387. (b) Wilcox, S. C. and Guadino, J. J., *J. Am. Chem. Soc*., **1986**, *108*, 3102.

14. (a) Demnitz, F. W. J.; Philippini, C. and Raphael, R. A., *J. Org. Chem*., **1995**, *60*, 5114. (b) Dias, J. R. and Ramachandra, R., *Tetrahedron Lett.,* **1976**, 3685. (c) House, H. O. and Blankly, C. J., *J. Org. Chem*., **1968**, *33*, 47. (d) Bhati, A., *J. Org. Chem.,* **1962**, *27*, 4485. (e) Eigenmann, G. W. and Arnold, R. T., *J. Am. Chem. Soc*., **1959**, *81*, 3440. (f) Baker, W.; Curtis, R. F.; McOmie, J. F. W.; Oliol, L. W. and Rogers, V., *J. Chem. Soc*., **1958**, 1007. (g) Haworth, R. D. and Turner, A. F., *J. Chem. Soc*., **1958**, 1240. (h) Zeiss, H. H. and Grant, F. W., *J. Am. Chem. Soc*., **1957**, *79*, 1201. (i) Stork, G. and Schulenberg, J. W., *J. Am. Chem. Soc*., **1956**, *78*, 250. (j) Herz, W., *J. Am. Chem. Soc.,* **1956**, *78*, 1485. (k) Weisenborn, F. L.; Remy, D. C. and Jacobs, T. L., *J. Am. Chem. Soc*., **1954**, *76*, 552. (l) Bhati, A., *Curr. Sci.,* **1953**, *22*, 341. (m) Dauben, W. G.; Hoerger, E. and Petersen, J. W., *J. Am. Chem. Soc*., **1953**, *75*, 2347. (n) Gutsche, C. D., *J. Am. Chem. Soc*., **1951**, *73*, 786. (o) Davy, G. S.; Jones, E. R. H. and Halsall, T. G., *Rec. Trav. Chim*., **1950**, *69*, 368. (p) Stadtman, E. R.; Stadtman, T. C. and Barker, H. A., *J. Bio. Chem.,* **1949**, *118*, 677. (q) Blomquist, A. T. and Holley, R. W., *J. Am. Chem. Soc*., **1948**, *70*, 36. (r) Shoppee, C. W., *Ann. Repts*. *Prog. Chem. (Chem. Soc., London),* **1948**, *44*, 170. (s) Shoppee, C. W., *Ann. Repts*. *Prog. Chem. (Chem. Soc., London),* **1947**, *43*, 200. (t) Meystre, C. and Miescher, K., *Helv. Chim. Acta*, **1946**, *29*, 33. (u) Long, W. P.; Marshall, C. W. and Gallagher, T. F., *J. Biol. Chem*., **1946**, *165*, 197. (v) Turner, R. B.; Mattox, V. R.; Engel, L. L.; McKenzie, B. F. and Kendall, E. C., *J. Biol. Chem.,* **1946**, *166*, 345. (w) Ruzicka, L.; Huer, W. and Jeger, O., *Helv. Chim. Acta*, **1945**, *28*, 195. (x) Riegel, B.; Moffett, R. B. and McIntosh, A. V., *Org. Syn.*, **1944**, *24*, 38. (y) Riegel, B.; Moffett, R. B. and McIntosh, A. V., *Org. Syn*., **1944**, *24*, 41. (z) Lane, J. F. and Wallis, E. S., *J. Am. Chem. Soc*., **1941**, *63*, 1674. (aa) Hoehn, W. M. and Mason, H. L., *J. Am. Chem. Soc*., **1940**, *62*, 569. (bb) Marker, R. E. and Krueger, J., *J. Am. Chem. Soc*., **1940**, *62*, 79. (cc) Kumura and Sugiyama, *J. Biochem. (Tokyo)*, **1939**, *29*, 409. (dd) Wieland, H.; Schlichting, O. and Jacobi, R., *Z. Physiol. Chem*., **1926**, *161*, 80.

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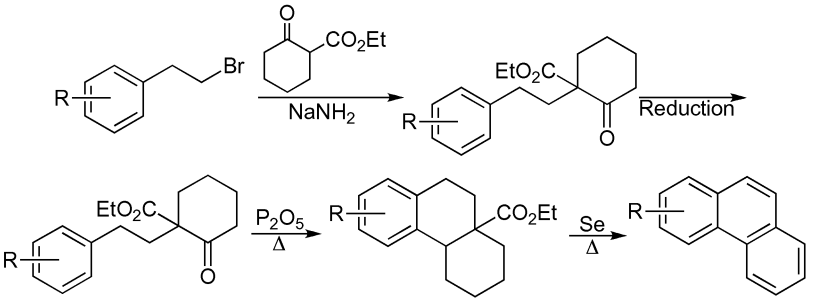
Bardhan Sengupta Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Bardhan and Sengupta in 1932.[1] It is the synthesis of phenanthrene via the following consecutive processes: the alkylation of arylethyl halide with cyclohexanone under basic conditions, the reduction of the carbonyl group, cyclization to an aromatic ring in the presence of phosphorus pentoxide, and dehydrogenation to phenanthrene with selenium. Therefore, this reaction is known as the Bardhan-Sengupta synthesis.[2] Unfortunately, Bardhan and Sengupta's original claim of 1,4-dimethylphenanthrene prepared by this reaction has proven to be the 1,3-dimethylphenanthrene.[3] In this reaction, some side products, including the *spiro* compound, might form.[4] The synthesis of phenanthrene has been reviewed.[5]

B. GENERAL REACTION SCHEME

The whole reaction process is illustrated here.



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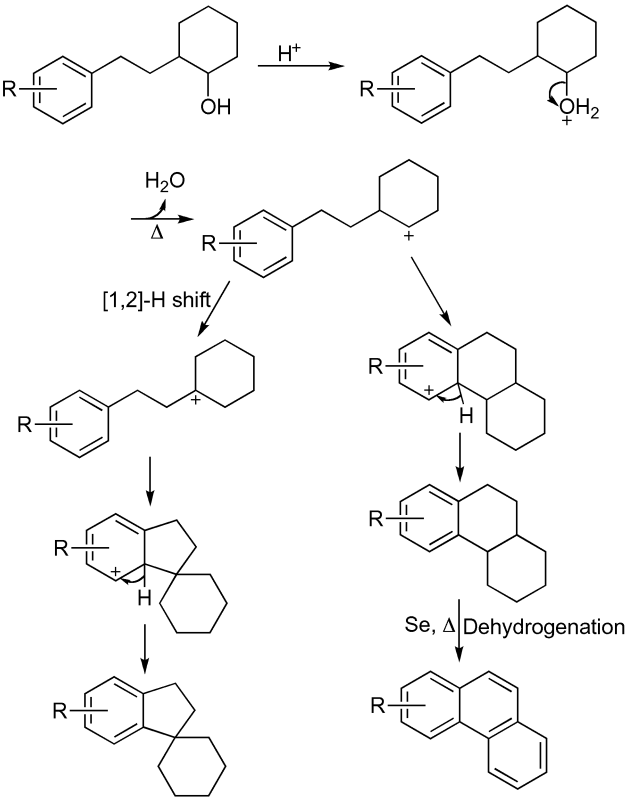
C. PROPOSED MECHANISMS

Because the mechanism of this reaction has been studied[6] and is clearly shown in the reaction scheme, only a part of the mechanism is given here. The presence of an ester group in cyclohexanol will prevent the formation of *spiro* cyclics.



D. MODIFICATION

A few modifications have been carried out for this reaction.[6,7] The dehydrogenation of octahydrophenanthrene can also be carried out using sulfur.[8]

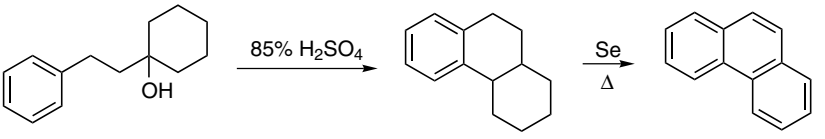
E. APPLICATIONS

This reaction is a general method for synthesizing different phenanthrenes and can be extended to other higher polynuclear aromatics.

F. RELATED REACTIONS

This reaction is related to the *Haworth Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4.

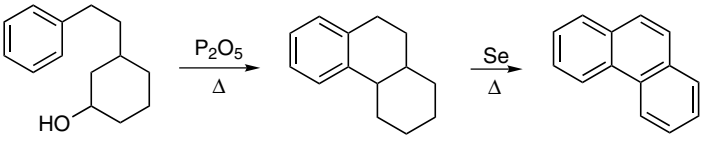
1-β-Phenylethylcyclohexanol was obtained from the *Grignard Reaction* between phenylethyl bromide and cyclohexanone, in a yield of 54%.

Dehydration of Carbinol

1-β-phenylethylcyclohexanol was added slowly with stirring to two volumes of 85% sulfuric acid cooled by ice pack (90% sulfuric acid is needed for the secondary alcohol). When all the alcohol had been added, the stirring was continued for 15–20 min at room temperature, and the mixture was then extracted with petroleum ether. The extract was agitated vigorously two or three times with cold 85% sulfuric acid, until the ether layer was a pale lemon yellow. The reaction mixture was washed with a 10% sodium carbonate followed by a 10% sodium sulfate solution, dried over anhydrous potassium carbonate, and fractioned under vacuum to give 90% yield of octahydrophenanthrene, b.p. 135–137°C at 10 mmHg.

Dehydrogenation of Octahydrophenanthrene by Selenium

The mixture of octahydrophenanthrene and 1.5–2 Eq. selenium in a flask equipped with a long Pyrex tube, which functioned as an air condenser, was heated in a potassium nitrate–sodium nitrate bath at 290–320°C for 14–15 h. The dehydrogenation product was extracted with benzene; the benzene extract was distilled at atmospheric pressure, and the residual was crystallized to give phenanthrene, m.p. 99.5°C.



Reference 6.

Dehydration of Carbinol

The procedure was precisely the same as used by Bardhan and Sengupta by which 5.5 g β-phenylethylcyclohexanol-3 was treated with 11.0 g phosphorus pentoxide, and the product upon distillation over sodium afford 4.1 g 1,2,3,4,4a,9,10,10a-octahydrophenanthrene, in a yield of 81.8%, b.p. 131°C at 5.0 mmHg.

Dehydrogenation of Octaphenanthrene

Octahydrophenanthrene (4.0 g) was heated with 4.0 g 10% palladized charcoal at 210–270°C for ~3 h in a slow steam of carbon dioxide. The mass was cooled and thoroughly extracted with ether. The solvent was removed, and 3.5 g crude phenanthrene was purified through its picrate, affording 3.0 g phenanthrene, m.p., 100°C.

Other refereces related to the Bardhan-Sengupta synthesis are cited in the literature.[9]

H. REFERENCES

1. (a) Bardhan, J. C. and Sengupta, S. C., *J. Chem. Soc*., **1932**, 2520. (b) Bardhan, J. C. and Sengupta, S. C., *J. Chem. Soc*., **1932**, 2798.
2. Chatterjee, A. and Banerjee, D., *J. Indian Chem. Soc.,* **1968**, *45*, 78.
3. (a) Mukherji, S. M. and Bhattacharyya, N. K., *J. Org. Chem.,* **1952**, *16*, 1202. (b) Johnson, Goldman and Schseider, *J. Am. Chem. Soc.,* **1945**, *67*, 1357. (c) Bachmann, W. E. and Edgerton, R. O., *J. Am. Chem. Soc.,* **1940**, *62*, 2219. (d) Bliss, R.; Stamatoff, G. S. and Bogert, M. T., *J. Am. Chem. Soc.,* **1937**, *59*, 1268.
4. Perlman, D.; Davidson, D. and Bogert, M. T., *J. Org. Chem*., **1937**, *2*, 288.
5. Floyd, A. J.; Dyke, S. F. and Ward, S. E., *Chem. Rev*., **1976**, *76*, 509.
6. Pal, B. C., *J. Am. Chem. Soc.,* **1955**, *77*, 3397.
7. (a) Walker, G. N., *J. Am. Chem. Soc.,* **1957**, *79*, 3508. (b) Barnes, R. A.; Hirschler, H. P. and Bluestein, B. R., *J. Am. Chem. Soc.,* **1952**, *74*, 32. (c) Renfrow, W. B.; Renfrow, A.; Shoun, E. and Sears, C. A., *J. Am. Chem. Soc.,* **1951**, *73*, 317. (d) Fieser, L. F. and Hershberg, E. B., *J. Am. Chem. Soc.,* **1935**, *57*, 2192.
8. Fulton, J. D. and Robinson, R., *J. Chem. Soc*., **1933**, 1463.
9. (a) Brisse, F.; Lectard, A. and Schmidt, C., *Can. J. Chem.,* **1974**, *52*, 1123. (b) Tatta, K. R. and Bardhan, J. C., *J. Chem. Soc., C,* **1968**, 893. (c) Bardhan, J. C.; Bhattacharyya, K. C. and Bala, S., *Indian J. Chem*., **1967**, *5*, 100. (d) Gensler, W. J.; Chakravarti, S. C. and Johnson, F., *J. Org. Chem.,* **1962**, *27*, 857. (e) Carruthers, W. and Gray, J. D., *J. Chem. Soc*., **1957**, 2422. (f) Ray, M.; Bardhan, J. C. and Bhattacharyya, K. C., *J. Chem. Soc*., **1956**, 1344. (g) Bardhan, J. C.; Adhya, R. N. and Bhattacharyya, K. C., *J. Chem. Soc.,* **1956**, 1346. (h) Bardhan, J. C.; Nasipuri, D. and Adhya, R. N., *J. Chem. Soc*., **1956**, 355. (i) Fieser, L. F. and Fieser, M., *Natural Products Related to Phenanthrene*, Reinhold, New York, **1949**, p. 88. (j) Adkins, H. and Hager, G. F., *J. Am. Chem. Soc.,* **1949**, *71*, 2965. (k) Engel, B. G.; Ronco, A.; Berse, K.; Plattner, P. A. and Ruzicka, L., *Helv. Chim. Acta,* **1949**, *32*, 1713. (l) Heilbronner, E.; Daniker, H. U. and Plattner, P. A., *Helv. Chim. Acta*, **1949**, *32*, 1723. (m) Barnes, R. A. and Gordon, L., *J. Am. Chem. Soc.,* **1949**, *71*, 2644. (n) Bachmann, W. E.; Gregg, R. A. and Pratt, E. F., *J. Am. Chem. Soc.,* **1943**, *65*, 2314. (o) Hewett, C. L. and Martin, R. H., *J. Chem. Soc.,* **1940**, 1396. (p) Papa, D.; Perlman, D. and Bogert, M. T., *J. Am. Chem. Soc.,* **1938**, *60*, 319. (q) Bogert, M. T. and Perlman, D., *J. Am. Chem. Soc*.,

1937, *59*, 2534. (r) Linstead, R. P., *Ann. Repts. (Chem. Soc., London),* **1936**, *33*, 319. (s) Bardhan, J. C., *J. Chem. Soc*., **1936**, 1848. (t) Bardhan, J. C., *Nature,* **1934**, *134*, 217. (u) Haworth, R. D.; Mavin, C. R. and Sheldrick, G., *J. Chem. Soc*., **1934**, 454. (v) Cook, J. W. and Hewett, C. L., *J. Chem. Soc*., **1933**, 1098. (w) Kon, G. A. R., *J. Chem. Soc*., **1933**, 1081. (x) Bogert, M. T., and Stamatoff, G. S., *Rec. Trav. Chim.,* **1933**, *52*, 583. (y) Bogert, M. T., *Science*, **1933**, *77*, 289.

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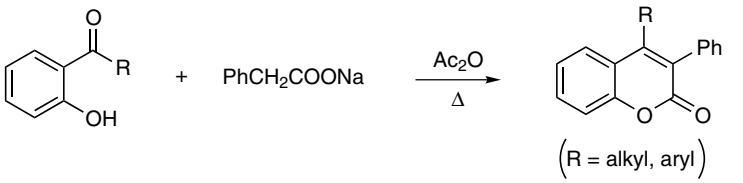
Bargellini Condensation
(Bargellini Coumarin Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Bargellini in 1925.[1] It is the synthesis of coumarins from the reaction between *o*-oxyarylketones and sodium phenylacetates in the presence of acetic anhydride. This reaction is based on Bargellini's earlier work in which benzoylacetonitriles condense with polyhydric phenols, such as resorcinol, in the presence of concentrated sulfuric acid to give the corresponding coumarins.[2] Thus this reaction is known as the Bargellini condensation.[3] This reaction is inconvenient from the practical point of view and generally leads to poor yields,[4] so other methods have been developed for preparing coumarins.[5] The Bargellini condensation has been modified via the condensation of *o*-methoxybenzaldehydes with arylacetonitrile and demethylation with pyridine hydrochloride[6] and via 2,5-dimethoxycinnamic acid with boron tribromide.[7]

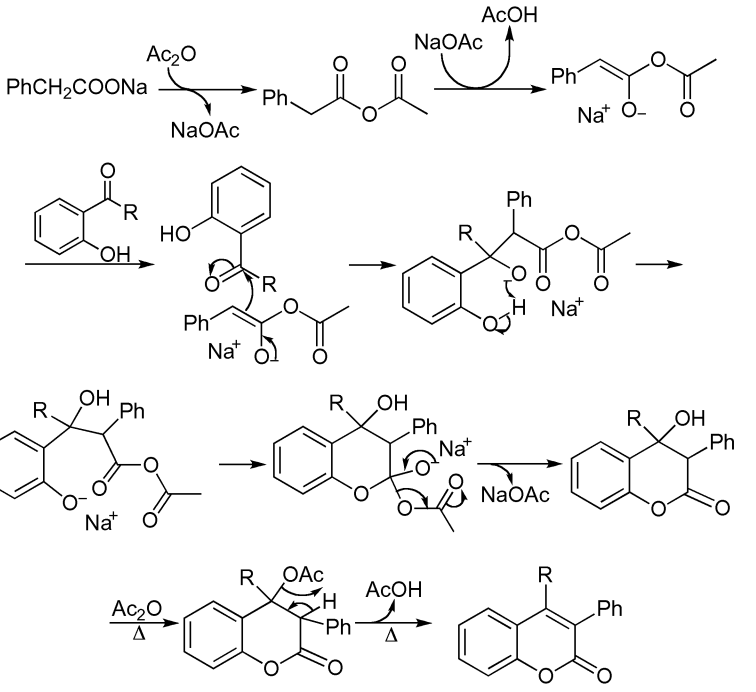
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

An exemplary mechanism is displayed below.



D. MODIFICATION

This reaction has been modified by the condensation of *o*-methoxybenzaldehydes with arylacetonitrile[6] or from the condensation of 2,5-dimethoxycinnamic acid with boron tribromide.[7]

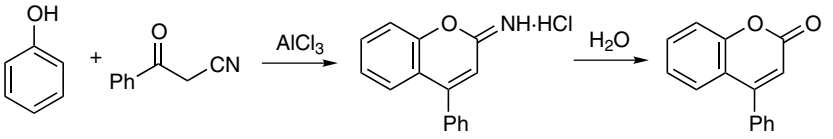
E. APPLICATIONS

This reaction has been applied to the synthesis of different coumarins.

F. RELATED REACTIONS

This reaction is related to the *Perkin Reaction* and *Pechmann Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



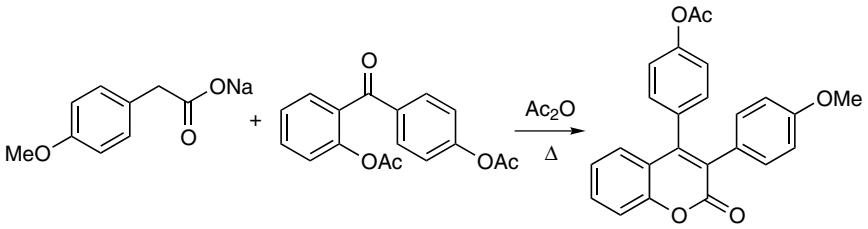
Reference 8.

General Procedure for the Acid-Catalyzed Reaction Between Phenol and Benzoylacetonitrile

To a stirred suspension of 0.1 mol anhydrous aluminum chloride in 15 mL isopropyl ether was added dropwise at 20–30°C a solution of 0.05 mol phenol and 0.05 mol benzoylacetonitrile in 60 mL isopropyl ether. The mixture, into which dry hydrogen chloride was continuously passed, was gradually heated at 50–60°C and kept for 5 h. The resulting mixture was chilled and poured over water containing crushed ice and concentrated hydrochloric acid. After it was stirred for 0.5 h, filtration and drying gave the crude intermediate shown. (Substitution of isopropyl ether for an inert solvent such as *sym*-tetrachloroethane afforded a lower yield of such intermediate.) The formation of such intermediate can also be carried out without any solvent but at a higher temperature (e.g., 70–80°C).

Conversion to Coumarin

The mixture of 0.6 g intermediate and 6 mL water was heated on a steam bath for 3 h. Upon cooling to room temperature, the solution was filtered to give 0.5 g coumarin, in a yield of 95%, m.p. 246–247°C. One recrystallization from the ethanol gave pure coumarin, m.p. 249–250°C.



Reference 4a.

A mixture of sodium *p*-methoxyphenylacetate (prepared from 5.56 g *p*-methoxyphenylacetic acid and 7.20 g 25% methanolic sodium methoxide) and 2,4′-diacetoxybenzophenone was refluxed in 50 mL acetic anhydride for 40 h. When the solution was cooled to room temperature, it was poured into water and stirred for 2 h. The aqueous phase was removed by decantation, and the organic gum was dissolved in methylene chloride. This solution was washed in turn with aqueous-saturated $NaHCO_3$, water, and brine and taken to dryness in vacuo. The residue was recrystallized once from methanol and twice from aqueous acetic acid to give 1.85 g 3-(*p*-methoxyphenyl)-4-(*p*-acetoxyphenyl)-coumarin.

Other references related to the Bargellini condensation are cited in the literature.[9]

H. REFERENCES

1. Bargellini, G., *Gazz. Chim. Ital.*, **1925**, *55*, 945.
2. Bargellini, G. and Forti-Forli, G., *Gazz, Chim. Ital*., **1911**, *41*, 747.
3. (a) Biswas, B.; Sen, P. K. and Venkateswaran, R. V., *Tetrahedron*, **2007**, *63*, 12026. (b) Biswas, B.; Sen, P. K. and Venkateswaran, R. V., *Tetrahedron Lett.,* **2006**, *47*, 4019. (c) Sen, P. K.; Biswas, B. and Venkateswaran, R. V., *Tetrahedron Lett.,* **2005**, *46*, 8741.
4. (a) Lednicer, D.; Lyster, S. C. and Duncan, G. W., *J. Med. Chem*., **1965**, *8*, 725. (b) Buu-Hoï, N. P.; Ekert, B. and Royer, R., *J. Org. Chem.*, **1954**, *19*, 1548.
5. (a) Meerwein, H.; Buchner, E. and van Emster, K., *J. Prakt. Chem*., **1939**, *162*, 237. (b) Badhwar, I. C.; Baker, W.; Menon, B. K. and Venhataraman, K., *J. Chem. Soc*., **1931**, 1541. (c) Baker, W., *J. Chem. Soc*., **1927**, 2898. (d) Baker, W. and Robinson, R., *J. Chem. Soc*., **1925**, *127*, 1981.
6. Buu-Hoï, N. P.; Hoán, N. and Khenissi, M. R., *J. Chem. Soc*., **1951**, 2307.
7. Degraw, J. I. and Tsakotellis, P., *J. Chem. Eng. Data*, **1969**, *14*, 509.
8. Sato, K. and Amakasu, T., *J. Org. Chem*., **1968**, *33*, 2446.
9. (a) Geissman, T. A. and Fukushima, D. K., *J. Am. Chem. Soc.*, **1948**, *70*, 1686. (b) Bargellini, G., *Gazz. Chim. Ital*., **1927**, *67*, 457. (c) Ellison, T. E., *J. Chem. Soc.,* **1927**, 1720. (d) Sonn, A., *Ber.*, **1918**, *61*, 821. (e) Sonn, A., *Ber.,* **1918**, *51*, 1829. (f) Sonn, A., *Ber.,* **1918**, *51*, 821. (g) Ghosh, B. N., *J. Chem. Soc*., **1916**, *109*, 105. (h) Bargellini, G. and Monti, L., *Gazz. Chim. Ital.,* **1915**, *45*, 90.

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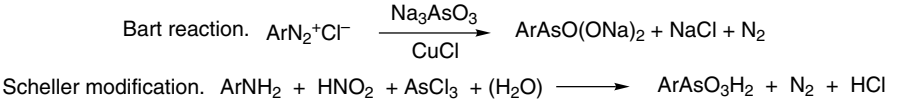
Bart Reaction
(Scheller Modification)

A. GENERAL DESCRIPTION OF THE REACTION

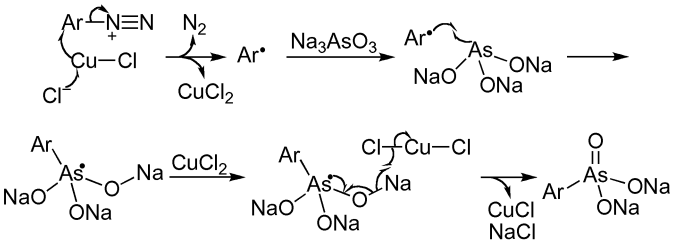
This reaction was first reported by Bart in 1910.[1] It is the synthesis of arylarsenic acids from aromatic diazonium compounds with alkali arsenites in the presence of cupric salts, powdered silver, or copper. Therefore, this reaction is generally known as the Bart reaction.[2] In addition, the reaction between aromatic diazonium and arsenious chloride in the presence of trace amounts of cuprous chloride is referred to as the Scheller modification.[3] Besides the Scheller modification, the Sakellarios modification is the reaction between sulfanilamide and phenyldisodium arenite.[4]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is believed that this reaction proceeds via a radical mechanism, as proposed here.



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D. MODIFICATION

A few modifications have been developed for the Bart reaction, including the Scheller modification and the Sakellarios modification. The most useful and famous one is the Scheller modification.

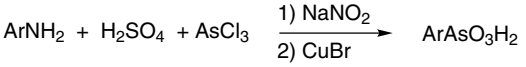
E. APPLICATIONS

This reaction can be applied for synthesizing aromatic arsenic acid, which has important applications in the pharmaceutical industry for isotopic labeling (^{76}As has a half-life of 26 h).[5] In addition, this reaction can be used to prepare arylstibonic acid,[6] and even other metals can be bounded to the aromatic ring in a similar fashion to form metallic aromatics, such as mercury,[7] tin,[8] lead,[9] and bismuth.[10]

F. RELATED REACTIONS

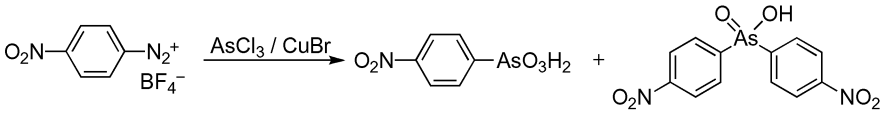
This reaction is related to the *Béchamp Reduction, Sandmeyer Reaction*, and *Rosenmund Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 11.

To a mixture of 0.1 mol aromatic amine, 10 g sulfuric acid, and 28 g arsenous chloride ($AsCl_3$) in 250 mL absolute alcohol cooled at 0°C was added an equivalent amount of saturated aqueous solution of sodium nitrite, using starch-iodide paper to protect the end point. Then, and not before, 1 g cuprous bromide was added to the mixture, and the resulting mixture was stirred vigorously. The solution was warmed to 60°C until no more nitrogen was evolved, then the reaction mixture was steam distillated to afford the corresponding arsonic acid, which can be further purified via recrystallization.



Reference 12.

To a two-necked flask equipped with a sealed stirrer and an outlet tube connected to a water trap were added 125 mL solvent and 0.1 mol *p*-nitrobenzenediazonium fluoroborate,

then 0.1 mol arsenic trichloride and 2 g catalyst (CuBr or CuCl) were added. In the majority of experiments, nitrogen was evolved immediately upon starting the stirring. After the evolution of nitrogen, the mixture was steam distilled to remove the organic solvent and volatile by-product. The residual liquid in the flask was condensed to 100 mL; on cooling, the precipitate was filtered and dissolved in sodium carbonate solution to remove the small amount of impurity. The filtrate was acidified to congo red with concentrated hydrochloric acid, and the mixture of *p*-nitrobenzenearsonic and *bis*-(*p*-nitropheny1)-arsinic acids was removed by filtration. The mixture was extracted with boiling water. The primary acid crystallized out of this solution and was purified by two recrystallizations from hot water. The water-insoluble portion, which consisted of crude secondary acid, was recrystallized from hot alcohol.

Other references related to the Bart reaction are cited in the literature.[13,14]

H. REFERENCES

1. (a) Bart, H., *German Pat.*, Jan. 8, **1910**, DE 250,264. (b) Bart, H., *German Pat.*, Dec. 8, **1910**, DE 254,092. (c) Bart, H., *German Pat.*, Nov. 9, **1910**, DE 264,924. (d) Bart, H., *German Pat.*, Sep. 12, **1913**, DE 268,172. (e) Bart, H., *Ann.,* **1922**, *429*, 55.
2. (a) Nakai, R. and Yamakawa, Y., *Bull. Inst. Chem. Res., Kyoto Univ.,* **1950**, *22*, 91. (b) Mingoia, Q. and Poggi, S., *Arquiv. Biol. (Sao Paulo),* **1945**, *29*, 119. (c) Ruddy, A. W.; Starkey, E. B. and Hartung, W. H., *J. Am. Chem. Soc.,* **1942**, *64*, 828. (d) Doak, G. O., *J. Am. Chem. Soc.,* **1940**, *62*, 167.
3. (a) Doak, G. O.; Steinman, H. G. and Eagle, H., *J. Am. Chem. Soc.,* **1940**, *62*, 3012. (b) Steinkopf, W. and Jaeger, P., *J. Prakt. Chem*., **1930**, *128*, *63*. (c) Scheller, E., *Chem. Zentr*., **1927**, *98, II,* 229. (d) Scheller, E., *French Pat.*, June 7, **1927**, 624,028. (e) Scheller, E., *British Pat.*, Aug. 10, **1927**, 261,026.
4. Sakellarios, E., *Ber.,* **1924**, *57B*, 1514.
5. see http://www.webelements.com/webelements/elements/text/As/radio.html.
6. Doak, G. O. and Steinman, H. G., *J. Am. Chem. Soc*., **1946**, *68*, 1987.
7. (a) Nesmejanow, A. N., *Ber*., **1929**, *62*, 1010. (b) Nesmejanow, A. N. and Kahn, E. J., *Ber*., **1929**, *62*, 1018.
8. (a) Kocheshkov, K. A.; Nesmeyanow, A. N. and Klimova, V. A., *J. Gen. Chem. (U. S. S. R.),* **1936**, *6*, 167. (b) Kocheshkov, K. A.; Nesmeyanow, A. N. and Klimova, V. A., *Chem. Abstr*., **1936**, *30*, 4834. (c) Nesmejanow, A. N.; Kocheshkov, K. A. and Klimova, V. A., *Ber*., **1935**, *68*, 1877.
9. (a) Kocheshkov, K. A.; Nesmeyanow, A. N. and Gipp, N. K., *J. Gen. Chem. (U. S. S. R.),* **1936**, 6, 172. (b) Kocheshkov, K. A.; Nesmeyanow, A. N. and Gipp, N. K., *Chem. Abstr*., **1936**, *30*, 4834.
10. Gilman, H. and Yablunky, H. L., *J. Am. Chem. Soc.*, **1941**, *63*, 949.
11. Doak, G. O., *J. Am. Chem. Soc.,* **1940**, *62*, 167.
12. Doak, G. O. and Freedman, L. D., *J. Am. Chem. Soc.,* **1951**, *73*, 5656.
13. (a) Doak, G. O. and Freedman, L. D., *Organometallic Compounds of Arsenic, Antimony, and Bismuth*, John Wiley & Sons, Ltd., **1970**. (b) Garascia, R. J.; Batzis, G. W. and Kroeger, J. O., *J. Org. Chem*., **1960**, *25*, 1271. (c) Freedman, L. D. and Doak, G. O., *J. Am. Chem. Soc.,* **1955**, *77*, 6374. (d) Freedman, L. D. and Doak, G. O., *J. Am. Chem. Soc.,* **1953**, *75*, 4905. (e) Cowdry, W. A. and Davies, D. S., *Quart. Rev.,* **1952**, *6*, 363. (f) Doak, G. O. and Freedman, L. D., *J. Am. Chem. Soc.,* **1951**, *73*, 5658. (g) Doak, G. O. and Freedman, L. D., *J. Am. Chem. Soc.,* **1951**, *73*, 5656. (h) Ray, F. E. and Garascia, R. J., *J. Org. Chem.,* **1950**, *15*, 1233. (i) Saunders, K. H., *Aromatic*

Diazo-Compounds and Their Technical Applications, E. Arnold & Co. London, **1949**, p. 330. (j) Doak, G. O. and Steinman, H. G., *J. Am. Chem. Soc.,* **1946**, *68*, 1987. (k) Doak, G. O.; Steinman, H. G. and Eagle, H., *J. Am. Chem. Soc.,* **1945**, *67*, 719. (l) Hamilton, C. F. and Morgan, J. F., *Org. React.,* **1944**, *2*, 415. (m) Doak, G. O.; Steinman, H. G. and Eagle, H., *J. Am. Chem. Soc.,* **1944**, *66*, 194. (n) Doak, G. O.; Steinman, H. G. and Eagle, H., *J. Am. Chem. Soc.,* **1944**, *66*, 197. (o) Ruddy, A. W.; Starkey, E. B. and Hartung, W. H., *J. Am. Chem. Soc.,* **1942**, *64*, 828. (p) Doak, G. O.; Eagle, H. and Steinman, H. G., *J. Am. Chem. Soc*., **1942**, *64*, 1064. (q) Oneto, J. F. and Way, E. L., *J. Am. Chem. Soc.,* **1941**, *63*, 3068. (r) Doak, G. O.; Eagle, H. and Steinman, H. G., *J. Am. Chem. Soc.,* **1940**, *62*, 3010. (s) Oneto, J. F. and Way, E. L., *J. Am. Chem. Soc.,* **1940**, *62*, 2157. (t) Raiziss, G. W.; Clemence, L. W.; Severac, M. and Moetsch, J. C., *J. Am. Chem. Soc.*, **1939**, *61*, 2763. (u) Robertson, G. R. and Stieglitz, J., *J. Am. Chem. Soc*., **1921**, *43*, 179.

14. (a) Ambushev, F. D.; Kovyrzina, V. P.; Shagidullin, R. R.; Gorchakova, L. A.; Fedotov, B. G.; Bespalov, Yu. A.; Nikiforov, M. D.; Kokorev, G. I. and Khalitov, F. G., *Zh. Obsh. Khim.,* **1981**, *51*, 2232. (b) Fredrickson, R. L.; Bocchieri, S. F.; Glenn, H. J. and Overby, L. R., *J. Assoc. Official Agri. Chem.,* **1965**, *48*, 10. (c) Hobin, T. P., *SCI Monograph,* **1961**, *13*, 303. (d) Jones, E. R. H. and Mann, F. G., *J. Chem. Soc.,* **1958**, 294. (e) Lukin, A. M. and Petrova, G. S., *Zh. Obsh. Khim.,* **1957**, *27*, 2171. (f) Mann, F. G. and Wilkinson, A. J., *J. Chem. Soc.,* **1957**, 3336. (g) Margerum, D. W.; Byrd, C. H.; Reed, S. A. and Banks, C. V., *Anal. Chem.,* **1953**, *25*, 1219. (h) Feitelson, B. N. and Petrow, V., *J. Chem. Soc.,* **1951**, 2279. (i) Orlando, A. M., *Rev. Fac. Cienc. Quim.,* **1950**, *25*, 97. (j) Hewett, C. L.; Lermit, L. J.; Openshaw, H. T.; Todd, A. R.; Williams, A. H. and Woodward, F. N., *J. Chem. Soc.,* **1948**, 292. (k) Krishnan, P. P.; Iyer, B. H. and Guha, P. C., *J. Indian Chem. Soc*., **1947**, *24*, 285. (l) Kraft, M. Ya. and Rossina, S. A., *Dokl. Akad. Nauk SSSR, Ser. A,* **1947**, *55*, 821. (m) Mann, F. G. and Watson, J., *J. Chem. Soc.,* **1947**, 505. (n) Ruddy, A. W. and Starkey, E. B., *Org. Synth.,* **1946**, *26*, 60. (o) Doak, G. O.; Steinman, H. G. and Eagle, H., *J. Am. Chem. Soc.,* **1944**, 66, 192. (p) Doak, G. O.; Steinman, H. G. and Eagle, H., *J. Am. Chem. Soc.,* **1941**, *63*, 99. (q) Oneto, J. F. and Way, E. L., *J. Am. Chem. Soc.,* **1939**, *61*, 2105. (r) Walton, E., *J. Chem. Soc.,* **1939**, 156. (s) Banks, C. K. and Hamilton, C. S., *J. Am. Chem. Soc.,* **1939**, *61*, 357. (t) Oneto, J. F., *J. Am. Chem. Soc.,* **1938**, *60*, 2058. (u) Binkley, S. B. and Hamilton, C. S., *J. Am. Chem. Soc.,* **1938**, *60*, 134. (v) Davies, W. C. and Othen, C. W., *J. Chem. Soc.,* **1936**, 1236. (w) Sweet, L. A. and Hamilton, C. S., *J. Am. Chem. Soc.,* **1934**, *56*, 2408. (x) Barnett, M. M.; Gillieson, A. H. C. P. and Kermack, W. O., *J. Chem. Soc.,* **1934**, 433. (y) Das-Gupta, H. N., *J. Indian Chem. Soc.,* **1932**, *9*, 393. (z) Goswami, M. and Das-Gupta, H. N., *J. Indian Chem. Soc.*, **1932**, *9*, 91. (aa) Gump, W. and Stoltzenberg, H., *J. Am. Chem. Soc.,* **1931**, *53*, 1428. (bb) Slater, R. H., *J. Chem. Soc.,* **1931**, 107. (cc) Barber, H. J., *J. Chem. Soc.,* **1930**, 2047. (dd) Phillips, M. A., *J. Chem. Soc.,* **1930**, 2685. (ee) Slater, R. H., *J. Chem. Soc.,* **1930**, 1209. (ff) Barber, H. J., *J. Chem. Soc.,* **1929**, 2333. (gg) Foldi, Z., *Ber.,* **1923**, *56B*, 2489.

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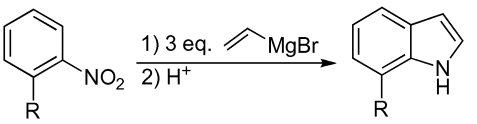
Bartoli Indole Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Giuseppe Bartoli in 1989.[1] It is the treatment of an *ortho*-substituted nitroarenes with 3 eq. of vinylmagnesium bromide to afford 7-substituted indole,[2] and is generally known as the Bartoli indole synthesis.[3] Currently, this reaction has rapidly become the shortest and most flexible approach for indoles with 7-substituents.[2] In fact, this reaction is based on Bartoli's earlier work, in which he had extensively studied the reaction between nitroarenes and a lesser amount of Grignard reagents and found that aromatic nitroso compounds can be formed by using 2 eq. of vinylmagnesium bromide and nitroarenes.[4]

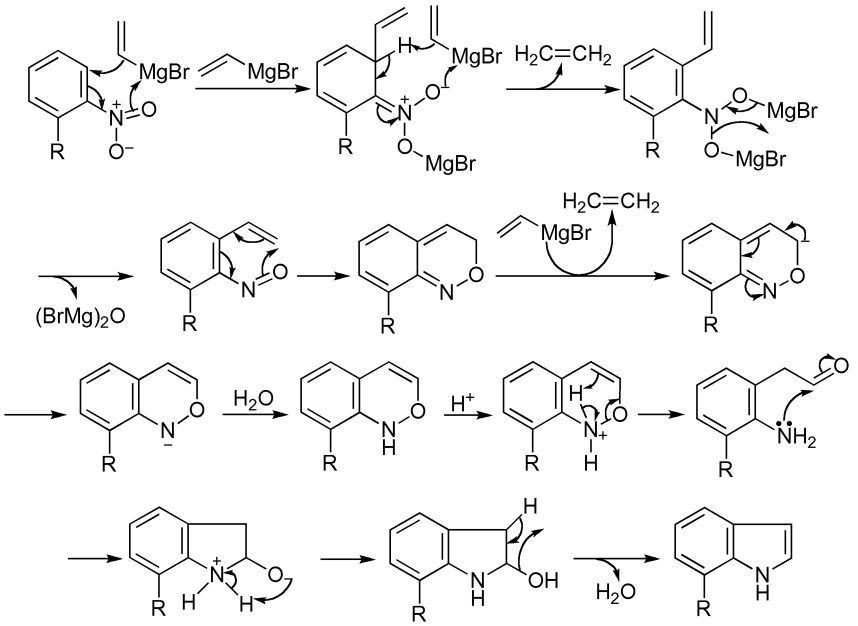
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The mechanism for Bartoli indole synthesis is proposed[5] as shown below, according to the fact that nitroso compounds may be generated from nitroarenes and 2 equivalents of Grignard reagents.[4]

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang



D. MODIFICATION

The reaction has been modified to take place on solid-state supporting material.[6]

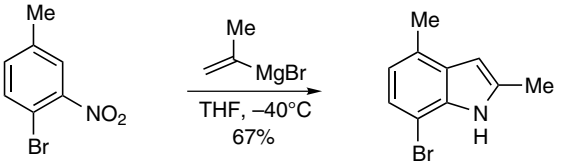
E. APPLICATIONS

Besides the general application in the preparation of 7-substituted indoles,[1,2] Bartoli indole synthesis has found other applications, including the synthesis of azaindoles[7] and optically pure 7-alkoxyltryptophan.[8]

F. RELATED REACTIONS

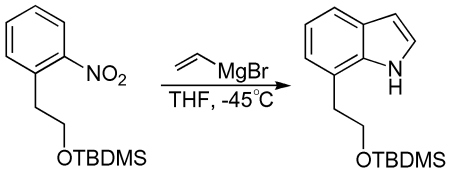
N/A

G. CITED EXPERIMENTAL EXAMPLES



Referece 2a.

To a two-necked flask equipped with a gas inlet (argon) and rubber septum was added 5.0 mmol 3-nitro-4-bromo-toluene. The flask was purged several times with argon before the addition of 35–40 mL dry THF and being cool to between -40° and -45°C. Then 15.0 mmol isopropenyl magnesium bromide (3 eq.) was added rapidly in one portion to the THF solution and stirred for a further 30–60 min (the exact length of time had no effect on the yield). Saturated ammonium chloride solution was added to the reaction mixture (at $\sim -40^\circ$C) before the mixture was allowed to warm to room temperature. The mixture was thoroughly extracted with diethyl ether (2×200 mL); the ether extracts were combined and thoroughly washed with a further 300 mL saturated ammonium chloride, 300 mL water, and 300 mL brine. They were dried over $MgSO_4$. Evaporation of the solvent and flash column chromatography (hexane/EtOAc = 9:1) afford 67% of 2,4-dimethyl-7-bromo-indole.



Reference 9.

The solution of 85.6 g *tert*-butyldimethyl[2-(2-nitrophenyl)ethoxy]silane (304 mmol) in 1000 mL THF was cooled to -65°C, and 913 mL 1.0 M solution of vinylmagnesium bromide in THF (913 mmol) was introduced while maintaining a temperature below -60°C. The reaction was stirred for 15 min at -45°C, then an additional 152 mL vinylmagnesium bromide (152 mmol) was added, and the reaction was stirred at -45°C for 30 min. The cold reaction solution was poured into 800 mL saturated NH_4Cl and extracted with EtOAc (500 mL, 200 mL, and 200 mL). The organic layers were combined, washed with 400 mL brine, and dried over $MgSO_4$. Upon removal of the solvent in vacuo, the residue was purified by silica gel chromatography using hexane/EtOAc (95:5) as the eluent to give 47.1 g 7-[2-(*tert*-butyldimethylsilanyloxy)ethyl]-1H-indole, in a yield of 56%.

Other references related to the Bartoli indole synthesis are cited in the literature.[10]

H. REFERENCES

1. Bartoli, G.; Palmieri, G.; Bosco, M. and Dalpozzo, R., *Tetrahedron Lett*., **1989**, *30*, 2129.
2. (a) Dobbs, A., *J. Org. Chem.,* **2001**, *66*, 638. (b) Dobbs, A. P.; Jones, K. and Veal, K. T., *Tetrahedron Lett.,* **1997**, *38*, 5379. (c) Dobson, D.; Gilmore, J. and Long, D. A., *Synlett,* **1992**, *79*. (d) Dobson, D. P.; Todd, A. and Gilmore, J., *Synth. Commun*., **1991**, *21*, 611. (e) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Palmieri, G. and Marcantoni, E., *J. Chem. Soc.*, *Perkin Trans. I,* **1991**, 2757.
3. (a) Dalpozzo, R. and Bartoli, G., *Curr. Org. Chem.,* **2005**, *9*, 163. (b) Knepper, K. and Braese, S., *Org. Lett.,* **2003**, *5*, 2829.
4. (a) Bartoli, G., *Acc. Chem. Res.,* **1984**, *17*, 109. (b) Bartoli, G.; Bosco, M. and Baccolini, G., *J. Org. Chem.,* **1980**, *45*, 522.
5. Bosco, M.; Dalpozzo, R.; Bartoli, G.; Palmieri, G. and Petrini, M., *J. Chem. Soc*., *Perkin Trans. II,* **1991**, 657.
6. Knepper, K. and Bräse, S., *Org. Lett*., **2003**, *5*, 2829.

7. Zhang, Z. X.; Yang, Z.; Meanwell, N. A.; Kadow, J. F. and Wang, T., *J. Org. Chem*., **2002**, *67*, 2345.
8. Berthelot, A.; Piguel, S.; Le Dour, G. and Vidal, J., *J. Org. Chem*., **2003**, *68*, 9835.
9. Faul, M. M.; Engler, T. A.; Sullivan, K. A.; Grutsch, J. L.; Clayton, M. T.; Martinelli, M. J.; Pawlak, J. M.; LeTourneau, M.; Coffey, D. S.; Pedersen, S. W.; Kolis, S. P.; Furness, K.; Malhotra, S.; Al-awar, R. S. and Ray, J. E., *J. Org. Chem.,* **2004**, *69*, 2967.
10. (a) Ziegert, R. E.; Knepper, K. and Braese, S., *Targets Heterocycl. Systems,* **2005**, *9*, 230. (b) Somei, M. and Yamada, F., *Nat. Prod. Rep*., **2003**, *20*, 216. (c) Pirrung, M. C.; Wedel, M. and Zhao, Y., *Synlett,* **2002**, 143. (d) Garg, N. K.; Sarpong, R. and Stoltz, B. M., *J. Am. Chem. Soc*., **2002**, *124*, 13179. (e) Sanchez, J. D.; Avendaòo, C. and Menéndez, J. C., *Sixth International Electronic Conference on Synthetic Organic Chemistry*, **2002**, September 1–30. http://www.mdpi.org/ecsoc-6. (f) Dobbs, A. P., Voyle, M., and Whittall, N., *Synlett,* **1999**, 1594. (g) Mewshaw, R. E.; Webb, M. B.; Marquis, K. L.; McGaughey, G. B.; Shi, X. J.; Wasik, T.; Scerni, R.; Brennan, J. A. and Andree, T. H., *J. Med. Chem.,* **1999**, *42*, 2007.

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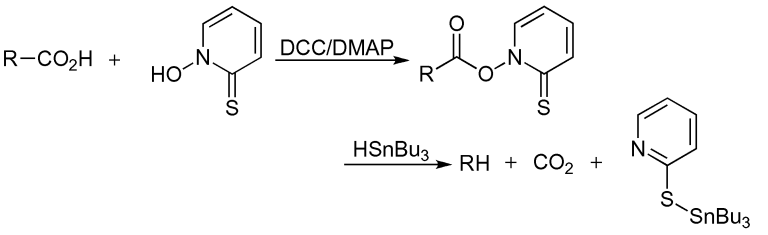
Barton Decarboxylation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Barton in 1983.[1] It is a radical decarboxylation of organic acids to generate alkanes via a two-step process: the formation of thiohydroxamic acid esters of the corresponding organic acid[2] and the addition of a radical initiator and the radical transfer reagents of a good H-atom donor such as tri-*n*-butyltin hydride [$HSnBu_3$],[3] *t*-butylmercaptan [*t*-BuSH],[4] phenylselenol [PhSeH],[4] and tri(trimethylsilyl)silane [$(Me_3Si)_3SiH$].[5] Therefore, this reaction is generally known as the Barton decarboxylation,[6] or by the less common name Barton's radical decarboxylation.[7] However, THF cannot be applied as the H-atom donor,[8] besides the application of a radical initiator, the Barton decarboxylation can also be initiated by either photolysis[9] or sonication.[10] This important reaction has been extensively reviewed.[11]

B. GENERAL REACTION SCHEME



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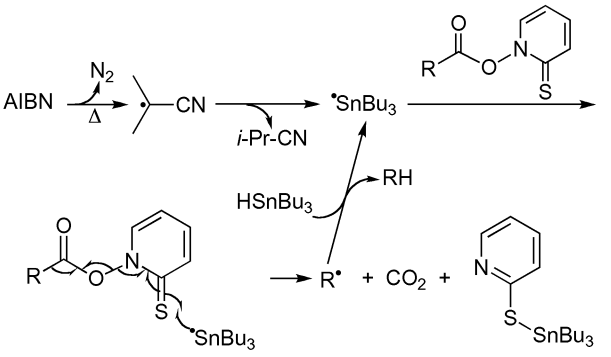
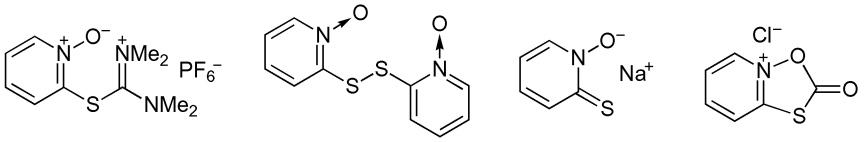
C. PROPOSED MECHANISMS

Displayed here is the mechanism for the Barton decarboxylation.



D. MODIFICATION

The formation of thiohydroxamic acid esters has been modified using different sources, including S-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium hexafluorophosphate,[12a] 2,2-dithiopyridine-1,1-dioxide,[5] sodium salt of *N*-hydroxy-2-thiopyridine,[12b] and thiocarbonate.[12c] The structures of these thiohydroxamic acid sources are illustrated below. On the other hand, the decarboxylation has been modified using other good H-atom sources,[4,5] and via initiation from photolysis[9] and sonication.[10] When thiohydroxamic acid ester reacts with diphenyldiselenide, phenylselenide forms.[12c]



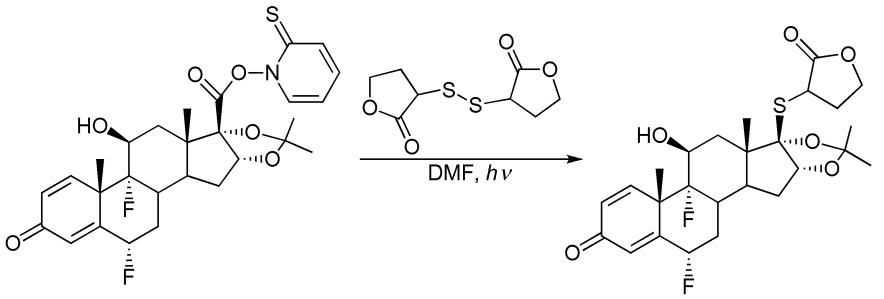
E. APPLICATIONS

This reaction is generally applied for removing the carboxylic group on organic compounds.

F. RELATED REACTIONS

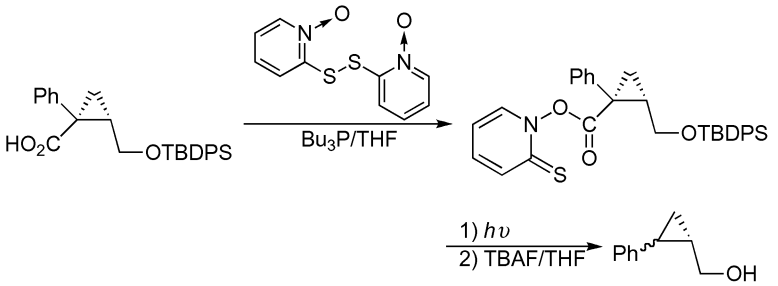
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 13.

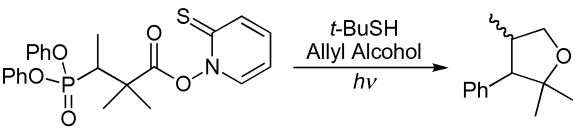
A solution of 2.50 g 2-thioxo-2H-pyridin-1-yl ester of 6α,9α-difluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-3-oxoandrosta-1,4-diene-17β-carboxylic acid (4.57 mmol) in 15 mL dry DMF was added to a stirred suspension of 2.15 g butyrolactone disulfides (9.17 mmol) in 15 mL dry DMF under nitrogen at 0°C. The resulting mixture was then subjected to irradiation by two 200-W tungsten filament light bulbs for approximately 4 h. The reaction mixture was diluted with 650 mL EtOAc and washed with brine, water, 2 M HCl, water, saturated $NaHCO_3$, water and brine (200 mL each). The organic solution was dried, the solvent was removed under reduced pressure, and the residue was chromatographed on silica gel using $CHCl_3$/MeOH (50:1) as the eluent. The concentrated product was further purified by HPLC (60% MeCN-H_2O) to give 635 mg 6α,9α-difluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-17β-(2-oxo-tetrahydrofuran-3-ylsulfanyl)androsta-1,4-dien-3-one as a white crystalline solid, in a yield of 27%.



Reference 5.

A mixture of 86.0 mg (1*S*,2*R*)-1-(*tert*-butyldiphenylsilyloxy)methyl)-2-carboxy-2-phenylcyclopropane (0.20 mmol), 61.0 mg 2,2-dithiopyridine-1,1-dioxide (0.24 mmol), 125 μL Bu_3P (0.50 mmol), and 1.0 mmol of a hydrogen donor (5 eq.) in 5 mL solvent (THF, benzene, or chlorobenzene) was stirred at room temperature under shading. After the disappearance of (1*S*,2*R*)-1-(*tert*-butyldiphenylsilyloxy)methyl-2-carboxy-2-phenylcyclopropane on TLC, the radical reaction was carried out by the addition of an initiator (Et_3B and Me_2Zn, 0.3 eq. or AIBN, 0.2 eq.) or irradiation with a high-pressure mercury lamp (300 W). The resulting reaction mixture was evaporated, and the residue was partitioned between EtOAc and H_2O. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography (silica gel,

hexane/*i*-Pr_2O, 100:1) to give the reductive decarboxylation products as an oil. A mixture of the oil and 400 μL TBAF (1.0 M in THF, 0.40 mmol) in 5 mL THF was stirred at room temperature for 12 h and then evaporated. The residue was partitioned between EtOAc and H_2O, and the organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography (silica gel, hexane/EtOAc, 9:1) to afford 1-phenyl-2-hydroxymethyl-propane as an oil.



Reference 14.

A solution of 0.107 g carboxylic acid, 2-thioxo-2H-pyridin-1-yl ester (0.2 mmol), and 45.3 μL *tert*-butylthiol (0.4 mmol) in 4.0 mL allyl alcohol in a Pyrex flask was photolyzed at room temperature with a 250-W Philips krypton lamp for 1 h. After removal of the volatiles under vacuum, ^1H and ^{31}P NMR spectra indicated a clean reaction and complete conversion of carboxylic acid, 2-thioxo-2H-pyridin-1-yl ester with essentially quantitative formation of diphenyl phosphate (^{31}P NMR δ -10.36 in $CDCl_3$). Purification by preparative TLC (hexane/EtOAc = 20:1) gave 32.0 mg *cis/trans*-2,2,4-trimethyl-3-phenyltetrahydrofuran as the major product, in a yield of 82%.

Other references related to the Barton decarboxylation are cited in the literature.[15]

H. REFERENCES

1. Barton, D. H. R.; Crich, D. and Motherwell, W. B., *J. Chem. Soc., Chem. Commun.,* **1983**, 939.
2. (a) Barton, D. H. R.; Crich, D. and Motherwell, W. B., *U.S. Pat.*, **1987**, May 26, 4,668,356. (b) Barton, D. H. R. and Zard, S. Z., *Pure & Appl. Chem.,* **1986**, *58*, 675. (c) Barton, D. H. R.; Crich, D. and Motherwell, W. B., *Tetrahedron,* **1985**, *41*, 3901.
3. Ballestri, M.; Chatgilialoglu, C.; Cardi, N. and Sommazzi, A., *Tetrahedron Lett.,* **1992**, *33*, 1787.
4. Gawronska, K.; Gawronski, J. and Walborsky, H. M., *J. Org. Chem.*, **1991**, *56*, 2193.
5. Yamaguchi, K.; Kazuta, Y.; Abe, H.; Matsuda, A. and Shuto, S., *J. Org. Chem.*, **2003**, *68*, 9255.
6. (a) Stojanovic, A. and Renaud, P., *Synlett,* **1997**, 181. (b) Eaton, P. E.; Nordari, N.; Tsanaktsidis, J. and Upadhyaya, S. P., *Synthesis,* **1995**, 501. (c) Gawronska, K.; Gawronski, J. and Walborsky, H. M., *J. Org. Chem.,* **1991**, *56*, 2193. (d) Magnus, P.; Ladlow, M.; Kim, C. S. and Boniface, P., *Heterocycles,* **1989**, *28*, 951. (e) Winkler, J. D.; Hey, J. P. and Williard, P. G., *J. Am. Chem. Soc.,* **1986**, *108*, 6425.
7. Zhu, J.; Klunder, A. J. H. and Zwanenburg, B., *Tetrahedron,* **1995**, *51*, 5099.
8. Newcomb, M. and Park, S. U., *J. Am. Chem. Soc.,* **1986**, *108*, 4132.
9. (a) Barton, D. H. R., *Pure & Appl. Chem.,* **1994**, *66*, 1943. (b) Barton, D. H. R., *Tetrahedron,* **1992**, *48*, 2529. (c) Crich, D., *Aldrichimica Acta,* **1987**, *20*, 35.
10. Dauben, W. G.; Bridon, D. P. and Kowalczyk, B. A., *J. Org. Chem.*, **1990**, *55*, 376.
11. (a) Zard, S. Z., *Radical Reactions in Organic Synthesis*, Oxford University Press, Oxford **2004**. (b) Togo, H., *Advanced Free Radical Reactions for Organic Synthesis*, Elsvier, Amsterdam **2004**. (c) Chatgilialoglu, C.; Crich, D.; Komatsu, M. and Ryu, I., *Chem. Rev.*, **1999**, *99*, 1991. (d) Barton,

D. H. R. and Parekh, S. I., *Half a Century of Free Radical Chemistry*, Cambridge University Press, Cambridge, **1993**. (e) Crich, D. and Quintero, L., *Chem. Rev.,* **1989**, *89*, 1413.

12. (a) Takasu, K.; Mizutani, S.; Noguchi, M.; Makita, K. and Ihara, M., *J. Org. Chem.,* **2000**, *65*, 4112. (b) Dauben, W. G.; Bridon, D. P. and Kowalczyk, B. A., *J. Org. Chem*., **1989**, *54*, 6101. (c) Meza-León, R. L.; Crich, D.; Bernès, S. and Quintero, L., *J. Org. Chem.,* **2004**, *69*, 3976.
13. Procopiou, P. A.; Biggadike, K.; English, A. F.; Farrell, R. M.; Hagger, G. N.; Hancock, A. P.; Haase, M. V.; Irving, W. R.; Sareen, M.; Snowden, M. A.; Solanke, Y. E.; Tralau-Stewart, C. J.; Walton, S. E. and Wood, J. A., *J. Med. Chem.,* **2001**, *44*, 602.
14. Crich, D.; Huang, X. and Newcomb, M., *J. Org. Chem.,* **2000**, *65*, 523.
15. (a) Ling, T. T.; Poupon, E.; Rueden, E. J. and Theodorakis, E. A., *Org. Lett*., **2002**, *4*, 819. (b) Masterson D. S. and Porter, N. A., *Org. Lett*., **2002**, *4*, 4253. (c) Ling, T. T.; Poupon, E.; Rueden, E. J.; Kim, S. H. and Theodorakis, E. A., *J. Am. Chem. Soc.,* **2002**, *124*, 12261. (d) Camps, P. and Muñoz-Torrero, D., *Mini Rev. Med. Chem*., **2001**, *1*, 163. (e) Bennasar, M.-L.; Vidal, B.; Kumar, R.; Lázaro, A. and Bosch, J., *Eur. J. Org. Chem*., **2000**, 3919. (f) Badia, A.; Baños, J. E.; Camps, P.; Contreras, J.; Görbig, D. M.; Muñoz-Torrero, D.; Simón, M. and Vivas, N. M., *Bioorg. Med. Chem*., **1998**, *6*, 427. (g) Ishihara, J.; Nonaka, R.; Terasawa, Y.; Shiraki, R.; Yabu, K.; Kataoka, H.; Ochiai, Y. and Tandano, K.-I., *J. Org. Chem.,* **1998**, *63*, 2679. (h) Ziegler, F. E. and Belema, M., *J. Org. Chem.,* **1997**, *62*, 1083. (i) Patterson, D. R. and Spangler, L. A., *Org. Proc. Res. Dev.*, **1997**, *1*, 172. (j) Stamos, D. P.; Chen, S. S. and Kishi, Y., *J. Org. Chem.,* **1997**, *62*, 7552. (k) Crich, D.; Hwang, J.-T. and Yuan, H. W., *J. Org. Chem.,* **1996**, *61*, 6189. (l) Schultz, A. G.; Holoboski, M. A. and Smyth, M. S., *J. Am. Chem. Soc.,* **1996**, *118*, 6120. (m) Trost, B. M. and Higuchi, R. I., *J. Am. Chem. Soc.,* **1996**, *118*, 10094. (n) Eaton, P. E.; Nordari, N.; Tsanaktsidis, J. and Upadhyaya, S. P., *Synthesis*, **1995**, 501. (o) Corey, E. J. and Hong, B.-C., *J. Am. Chem. Soc.,* **1994**, *116*, 3149. (p) Hatakeyama, S.; Kawamura, M. and Takano, S., *J. Am. Chem. Soc.,* **1994**, *116*, 4081. (q) Barton, D. H. R. and Samadi, M., *Tetrahedron,* **1992**, *48*, 7083. (r) Barton, D. H. R.; Chen, C. and Wall, G. M., *Tetrahedron,* **1991**, *47*, 6127. (s) Gawronska, K.; Gawronski, J. and Walborsky, H. M., *J. Org. Chem*., **1991**, *56*, 2193. (t) Barton, D. H. R. and Sas, W., *Tetrahedron,* **1990**, *46*, 3419. (u) Reich, L. and Reich, H. J., *J. Org. Chem.,* **1990**, *55*, 2282. (v) Dauben, W. G.; Kowalczyk, B. A. and Bridon, D. P., *Tetrahedron Lett*., **1989**, *30*, 2461. (w) Barton, D. H. R.; Herve, Y.; Potier, P.; Thierry, J., *Tetrahedron,* **1988**, *44*, 5479. (x) Barton, D. H. R.; Bridon, D. and Zard, S. Z., *Tetrahedron,* **1987**, *43*, 5307. (y) Newcomb, M. and Deeb, T., *J. Am. Chem. Soc.,* **1987**, *109*, 3163. (z) Barton, D. H. R.; Bridon, D. and Zard, S. Z., *Heterocycles,* **1987**, *25*, 449. (aa) Barton, D. H. R.; Crich, D. and Kretzschmar, G., *J. Chem.* Soc., *Perkin Trans. I,* **1986**, 39. (bb) Della, E. W. and Tsanaktsidis, J., *Aust. J. Chem.,* **1986**, *39*, 2061. (cc) Barton, D. H. R.; Crich, D.; Herve, Y.; Potier, P. and Thierry, J., *Tetrahedron,* **1985**, *41*, 4347. (dd) Barton, D. H. R.; Herve, Y.; Potier, P. and Thierry, J., *J. Chem. Soc., Chem. Commun.,* **1984**, 1298. (ee) Ito, H.; Takeguchi, S.; Kawagishi, T. and Iguchi, K., *Org. Lett.,* **2006**, *8*, 4883. (ff) Sadeghi-Khomami, A.; Blake, A. J.; Wilson, C. and Thomas, N. R., *Org. Lett.,* **2005**, *7*, 4891. (gg) Bennasar, M.-L.; Vidal, B.; Kumar, R.; Lazaro, A. and Bosch, J., *Eur. J. Org. Chem.,* **2000**, 3919. (hh) Tagat, J. R.; Nazareno, D. V.; Puar, M. S.; McCombie, S. W. and Ganguly, A. K., *Bioorg. Med. Chem. Lett.,* **1994**, *4*, 1101. (ii) Winkler, J. D.; Hey, J. P. and Williard, P. G., *Tetrahedron Lett.,* **1988**, *29*, 4691.

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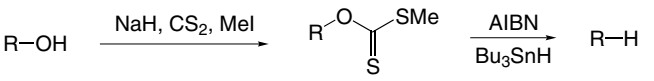
Barton Deoxygenation
(Barton-McCombie Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Barton and McCombie in 1975.[1] It is a two-step process for removing the hydroxyl group of an alcohol involving the initial acylation of such alcohol to the corresponding xanthate followed by a reductive cleavage of the resultant thiocarbonyl compound in the presence of a good H-atom donor/radical initiation system. Therefore, this reaction is generally known as the Barton deoxygenation[2] or the Barton-McCombie reaction.[3] The H-atom donor/radical initiation system used in this reaction includes tributyltin hydride/AIBN, tributyltin hydride/Et_3B,[4] diphenylsilane/peroxide (or Et_3B),[5] trialkylsilane/peroxide/thiol,[6] 5,10-dihydrosilanthrene/AIBN,[3c] tris(trimethylsilyl)silane/AIBN,[7] dibutylphosphine oxide/AIBN (or Et_3B),[8] phosphine-borane/AIBN,[9] H_3PO_2/Et_3N/AIBN,[10] and tetraphenyldisilane/AIBN.[11] As of today, this reaction has become the most effective and practical deoxygenation method of the hydroxyl group in organic compounds (especially carbohydrates, nucleosides, and nucleotides) and has found widespread application in synthetic organic chemistry. Due to some intrinsic problems with the Barton deoxygenation—toxic tin hydride and disposal problems—the original procedure has been modified via the preparation of different xanthates (with CH_3, SCH_3, Ph, OPh, or imidazolyl on xanthates)[12] and the application of different reduction systems.[3c,5–10] Other modifications include the application of a catalytic amount of tributyltin hydride rather than 1.5–3 equivalents of Bu_3SnH at the reduction step under normal conditions[13] and a single-step procedure that does not use the metal hydride reagent.[14] The reactivity of Barton deoxygenation is observed in the following order: primary alcohol > secondary alcohol > tertiary alcohol. This reaction has been extensively reviewed.[15]

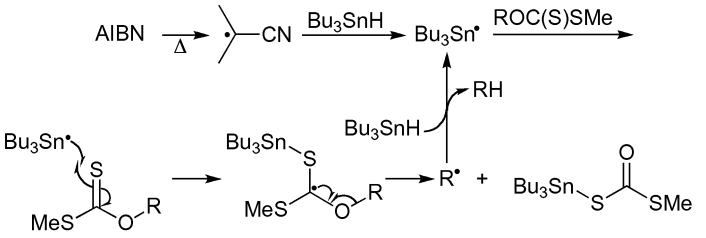
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is believed that this reaction involves a rapid, reversible addition of the stannyl radical to the thiocarbonyl group followed by a slower fragmentation of the radical, with cleavage of the carbon oxygen bond.[3f,4b,4e,15]



D. MODIFICATION

The original procedure has been extensively modified, including the preparation of different xanthates, the application of different reduction systems, and the use of a catalytic amount of tributyltin hydride. Other modifications are collected in the literature[16] including the photolysis of a carbazole in the presence of $Mg(ClO_4)_2$[16a] or benzoates[16b] and the formation of alkyl halide using carbon tetrachloride or bromotrichloromethane as the solvent instead of the tin hydride.[16c]

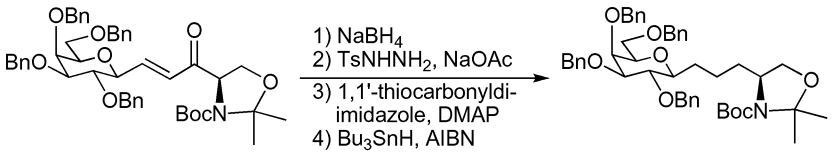
E. APPLICATIONS

This reaction has found widespread application in organic synthesis, especially in the preparation of deoxy carbohydrates, deoxy nucleosides, and nucleotides. In addition, this reaction can also be applied for converting aldehydes/ketones to alkanes after the reduction of the carbonyl groups.[17] Unfortunately, this reaction has failed in a few circumstances.[18]

F. RELATED REACTIONS

N/A

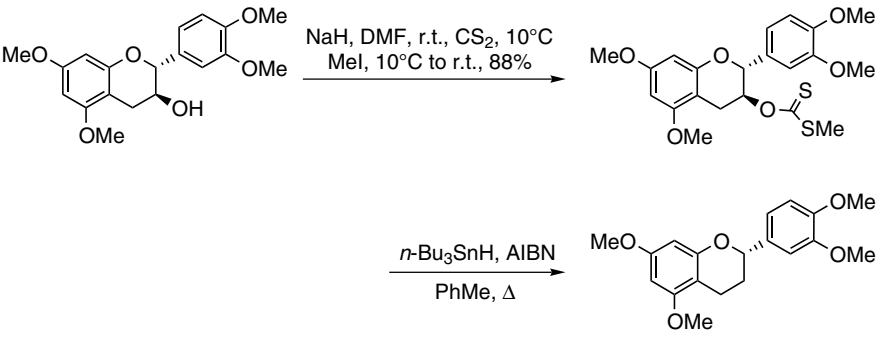
G. CITED EXPERIMENTAL EXAMPLES



Reference 19.

To a solution of 400 mg (E)-6,10-anhydro-7,8,9,11-tetra-*O*-benzyl-2,4,5-trideoxy-1,2-*N*,*O*-isopropylidene-2-(*tert*-butoxycarbonylamino)-D-*threo*-L-*galacto*-undec-4-en-3-ulose (0.51 mmol) in a mixed solvent of 1.5 mL MeOH and 1.5 mL Et_2O cooled at 0°C, was added 41 mg $NaBH_4$ (1.07 mmol) under stirring. The mixture was stirred at 0°C for 10 min and at room temperature for 10 min, then diluted with 1.0 mL acetone and partially concentrated. The residue was suspended in 100 mL CH_2Cl_2, washed with H_2O (2 × 10 mL), dried over $MgSO_4$, and concentrated. To the solution of crude allylic alcohol and 285 mg freshly recrystallized *p*-tolenesulfonylhydrazide (1.53 mmol) in 7 mL dimethoxyethane at 85°C was added 1.53 mL 1 M aqueous sodium acetate in six portions over 3 h. After an additional 2.5 h at 85°C, the mixture was diluted with 5 mL H_2O and extracted with CH_2Cl_2 (2 × 30 mL). The organic phase was dried over $MgSO_4$ and concentrated. The residue was eluted from a silica gel column with cyclohexane/EtOAc (from 9:1 to 4:1) to give 311 mg of a ~6:1 mixture of diastereomeric alcohol 3-hydroxy-6,10-anhydro-7,8,9,11-tetra-*O*-benzyl-2,4,5-trideoxy-1,2-*N*,*O*-isopropylidene-2-(*tert*-butoxycarbonylamino)-D-*lyxo*-D-*manno*- and -D-*altro*-undecitol (**1**, 3R/3*S* = ~1:1) and their C-5 transposed isomers 5-hydroxy-6,10-anhydro-7,8,9,11-tetra-*O*-benzyl-2,4,5-trideoxy-1,2-*N*,*O*-isopropylidene-2-(*tert*-butoxy-carbonylamino)-D-*lyxo*-D-*manno*- and -D-*altro*-undecitol (**2**, 5R/5*S* = ~1:1), in a yield of 78%. An analytical sample of 3-hydroxy-6,10-anhydro-7,8,9,11-tetra-*O*-benzyl-2,4,5-trideoxy-1,2-*N*,*O*-isopro-pylidene-2-(*tert*-butoxy-carbonylamino)-D-*lyxo*-D-*manno*- and -D-*altro*-undecitol was obtained by preparative TLC (2.5:1 cyclohexane/EtOAc).

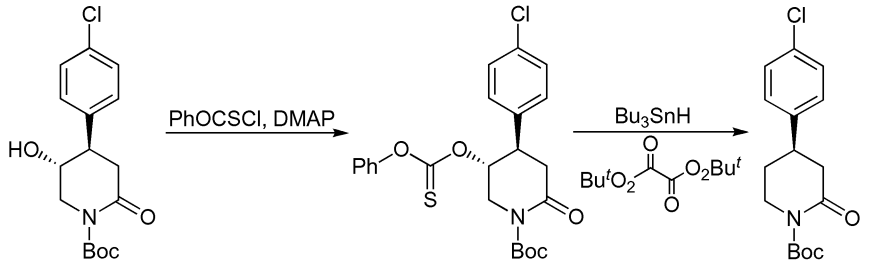
To the solution of 300 mg of a ~6:1 mixture of **1** and **2** (0.38 mmol) in 3 mL anhydrous THF at 70°C, were added 677 mg 1,1′-thiocarbonyldiimidazole (3.80 mmol) and 696 mg 4-*N*,*N*-(dimethylamino)pyridine (5.70 mmol) under stirring. After an additional 6 h at 70°C, the mixture was concentrated. The residue was eluted from a short silica gel column (1.5 × 8 cm, d × h) with 2.5:1 cyclohexane/EtOAc to give 285 mg of the corresponding thiocarbonylimidazolides (83%), which were slightly contaminated by uncharacterized by-products. To a solution of 285 mg thiocarbonylimidazolides (~ 0.32 mmol) in 3.0 mL anhydrous toluene at 85°C were added 0.86 mL Bu_3SnH (3.20 mmol) and 5.3 mg AIBN (0.032 mmol) under stirring. The solution was stirred at 85°C for an additional 2 h and then concentrated. The residue was eluted from a silica gel column (3.5 × 15 cm, d × h) with 10:1 cyclohexane/EtOAc to give 185 mg 6,10-anhydro-7,8,9,11-tetra-*O*-benzyl-2,4,5-trideoxy-1,2-6,10-anhydro-7,8,9,11-tetra-*O*-benzyl-2,3,4,5-tetradeoxy-1,2-*N*,*O*-isopropylidene-2-(*tert*-butoxycarbonyl-amino)-D-*threo*-L-*galacto*-undecitol as a syrup, in a yield of 63%.



Reference 20.

To a solution of 1.84 g 5,7,3′,4′-tetra-*O*-methylcatechin (5.31 mmol) in 5 mL DMF was added 0.25 g 60% NaH in oil (6.4 mmol) all at once. The mixture was stirred with a powerful magnetic stirrer at room temperature (mild exotherm) for 10 min while hydrogen evolved, and then it was immersed in a +10°C water bath; 0.48 mL of CS_2 (8.0 mmol) was added dropwise in 5 min, and stirred at +10°C for 10 min. To the resulting yellow to amber suspension was added 0.50 mL MeI (8.0 mmol) dropwise in 5 min. Halfway through the addition, the stirrer stopped, and the mildly exothermic addition was continued without cooling to reduce viscosity. The reaction mixture remained pasty and soon hardened; it was left at room temperature for 20 min and then dissolved in the mixed solvent of 40 mL H_2O and 60 mL toluene. The phases were separated, and the aqueous phase was extracted with 20 mL toluene. The combined organic phases were washed with 40 mL H_2O and concentrated, and the residue was chromatographed on SiO_2 first with CH_2Cl_2/hexane (1:1) to remove a forerun and then with CH_2Cl_2/EtOAc (19:1) to elute the product. Mixed fractions with a nonpolar contaminant were again subjected to column chromatography (SiO_2, EtOAc/CH_2Cl_2/hexane 1:7:12 for forerun, 1:19:0 for product), and all product-containing fractions were combined, evaporated, and dried in vacuo to yield 2.04 g 5,7,3′,4′-tetra-*O*-methyl-3-*O*-[[(methylthio)thiocarbonyl]-oxy]catechin as a yellowish solid, in a yield of 88%.

A stirred solution of 4.17 g intermediate 5,7,3′,4′-tetra-*O*-methyl-3-*O*-[[(methylthio)thiocarbonyl]-oxy]catechin (9.55 mmol) in 150 mL anhydrous toluene was heated to reflux under nitrogen and a solution of 10.3 mL *n*-Bu_3SnH (38.2 mmol) and 0.31 g AIBN (1.9 mmol) in 80 mL anhydrous toluene was added dropwise through the reflux condenser over a period of 4.25 h. Reflux was continued for 4 h. The cooled reaction mixture was directly chromatographed on SiO_2. A forerun was eluted using toluene, and then a mixture of (2*S*)-5,7,3′,4′-tetramethoxyflavan and a slightly more polar impurity was eluted using toluene/EtOAc (12:1). A late fraction containing mostly impurity was set aside for the isolation of the impurity; from the remaining mixture, (2*S*)-5,7,3′,4′-tetramethoxyflavan was isolated by further column chromatography on SiO_2 with EtOAc/$CHCl_3$/hexane (1:7:12). Evaporation and drying in vacuo yielded 2.52 g (2*S*)-5,7,3′,4′-tetramethoxyflavan as a colorless glass, in a yield of 80%.



Reference 21.

To a solution of 0.31 g (*R*)-1-(*tert*-butyloxycarbonyl)-4-(4-chlorophenyl)-5-hydroxyl-2-piperidone (0.93 mmol) and 0.20 g phenyl chlorothionoformate (1.14 mmol) in 15 mL CH_2Cl_2 was added a solution of 2.17 g 4-(dimethylamino)pyridine (DMAP) (17.8 mmol) in 15 mL CH_2Cl_2 under nitrogen and within a period of 15 min. After stirring for 18 h at 25°C, the reaction mixture was quenched with 1 M HCl, and then 40 mL CH_2Cl_2 was added. The organic phase was washed twice with 1 M HCl and subsequently with a saturated aqueous solution of $NaHCO_3$ and brine. The dried organic phase over Na_2SO_4 was evaporated, and the residue was subjected to column chromatography (light petroleum-EtOAc) to give 0.37 g phenyl thiocarbonate, in a yield of 85%, m.p. 153–154°C, $[R]_D^{20} = +31^\circ$ (c = 1.2, CH_2Cl_2).

To a solution of 0.35 g (4*R*,5*R*)-1-(*tert*-butyloxycarbonyl)-4-(4-chlorophenyl)-5-[*O*-(phenyloxythiocarbonyl) hydroxy]-2-piperidone (0.75 mmol) in 50 mL acetone were added 0.30 g tributyltin hydride (1.39 mmol) and subsequently 10 mg di-*tert*-butyl peroxyoxalate. The solution was left at 25°C for 18 h. The opalescent solution was evaporated, and the oily residue was subjected to column chromatography (light petroleum-EtOAc) to give 0.22 g (*R*)-1-(*tert*-butyloxycarbonyl)-4-(4-chlorophenyl)-2-piperidone, in a yield of 94%, m.p. 95.0–96.0°C, $[R]_D^{20} = +22^\circ$ (c = 2.1, CH_2Cl_2).

Other references related to the Barton deoxygenation (or the Barton-McCombie reaction) are cited in the literature.[22]

H. REFERENCES

1. Barton, D. H. R. and McCombie, S. W., *J. Chem. Soc., Perkin Trans. I*, **1975**, 1574.
2. (a) Bensasson, C. S.; Cornforth, J.; Du, M.-H. and Hanson, J. R., *Chem. Commun.,* **1997**, 1509. (b) Crich, D.; Beckwith, A. L. J.; Chen, C.; Yao, Q. W.; Davison, I. G. E.; Longmore, R. W.; Anaya de Parrodi, C.; Quintero-Cortes, L. and Sandoval-Ramirez, J., *J. Am. Chem. Soc.,* **1995**, *117*, 8757. (c) Barker, P. J. and Beckwith, A. L. J., *J. Chem. Soc., Chem. Commun.,* **1984**, 683.
3. (a) Quiclet-Sire, B. and Zard, S. Z., *Tetrahedron Lett.,* **1998**, *39*, 9435. (b) Jung, P. M. J.; Burger, A. and Biellmann, J.-F., *J. Org. Chem.,* **1997**, *62*, 8309. (c) Gimisis, T.; Ballestri, M.; Ferreri, C. and Chatgilialoglu, C., *Tetrahedron Lett.,* **1995**, *36*, 3897. (d) Kirwan, J. N.; Roberts, B. P. and Willis, C. R., *Tetrahedron Lett.,* **1990**, *31*, 5093. (e) Kirwan, J. N.; Roberts, B. P. and Willis, C. R., *Tetrahedron Lett.,* **1990**, *31*, 5093. (f) Forbes, J. E. and Zard, S. Z., *Tetrahedron Lett.,* **1989**, *30*, 4367.

4. (a) Barton, D. H. R.; Parekh, S. I. and Tse, C.-L., *Tetrahedron Lett.,* **1993**, *34*, 2733. (b) Barton, D. H. R.; Jang, D. O. and Jaszberenyi, J. C., *Tetrahedron Lett.,* **1990**, *31*, 3991. (c) Barton, D. H. R. and Jaszberenyi, J. C., *Tetrahedron Lett.,* **1989**, *30*, 2619. (d) Nozaki, K.; Oshima, K. and Utimoto, K., *Tetrahedron Lett.,* **1988**, *29*, 6125. (e) Barton, D. H. R.; Crich, D.; Lobberding, A. and Zard, S. Z., *Tetrahedron,* **1986**, *42*, 2329. (f) Barton, D. H. R.; Crich, D.; Lobberding, A. and Zard, S. Z., *J. Chem. Soc., Chem. Commun*., **1985**, 646. (g) Robins, M. J.; Wilson, J. S. and Hansske, F., *J. Am. Chem. Soc*., **1983**, *105*, 4059. (h) Barton, D. H. R.; Hartwig, W.; Hay-Motherwell, R. S.; Motherwell, W. B. and Stange, A., *Tetrahedron Lett.,* **1982**, *23*, 2019. (i) Barton, D. H. R.; Motherwell, W. B. and Stange, A., *Synthesis,* **1981**, 743. (j) Rasmussen, J. R.; Slinger, C. J.; Kordish, R. J. and Newman-Evans, D. D., *J. Org. Chem*., **1981**, *46*, 4843.
5. (a) Barton, D. H. R.; Jang, D. O. and Jaszberenyi, J. C., *Synlett,* **1991**, 435. (b) Barton, D. H. R.; Jang, D. O. and Jaszberenyi, J. C., *Tetrahedron Lett.,* **1990**, *31*, 4681.
6. (a) Cole, S. J.; Kirwan, J. N.; Roberts, B. P. and Willis, C. R., *J. Chem. Soc., Perkin Trans. 1,* **1991**, 103. (b) Allen, R. P.; Roberts, B. P. and Willis, C. R., *Chem. Commun*., **1989**, 1387.
7. Chatgilialoglu, C., *Acc. Chem. Res*., **1992**, *25*, 188.
8. (a) Jang, D. O.; Cho, D. H. and Barton, D. H. R., *Synlett,* **1998**, 39. (b) Barton, D. H. R.; Jang, D. O. and Jaszberenyi, J. C., *Tetrahedron Lett.,* **1992**, *33*, 5709.
9. Barton, D. H. R. and Jacob, M., *Tetrahedron Lett.,* **1998**, *39*, 1331.
10. Barton, D. H. R.; Jang, D. O. and Jaszberenyi, J. C., *J. Org. Chem.,* **1993**, *58*, 6838.
11. Togo, H.; Matsubayashi, S.; Yamazaki, O. and Yokoyama, M., *J. Org. Chem.,* **2000**, *65*, 2816.
12. (a) Ojida, A.; Tanoue, F. and Kanematsu, K., *J. Org. Chem.,* **1994**, *59*, 5970. (b) Paquette, L. A.; Sauer, D. R.; Cleary, D. G.; Kinsell, M. A.; Blackwell, C. M. and Anderson, L. G., *J. Am. Chem. Soc.,* **1992**, *114*, 1315. (c) Boyd, S. A.; Mantei, R. A.; Hsiao, C.-N. and Baker, W. R., *J. Org. Chem.,* **1991**, *56*, 438. (d) Robin, M. J. and Wilson, J. S., *J. Am. Chem. Soc.,* **1981**, *103*, 932.
13. Lopez, R. M.; Hays, D. S. and Fu, G. C., *J. Am. Chem. Soc.,* **1997**, *119*, 6949.
14. Graham, A. E.; Thomas, A. V. and Yang, R., *J. Org. Chem.,* **2000**, *65*, 2583.
15. (a) Renaud, P. and Sibi, M. P., eds. *Radicals in Organic Synthesis*, Wiley-VCH, Weinheim, **2001**. (b) Barton, D. H. R.; Ferreira, J. A.; and Jaszberenyi, J. C., "Free Radical Deoxygenation of Thiocarbonyl Derivatives of Alcohols," in *Preparative Carbohydrate Chemistry,* ed. Hanessian, S., Marcel Dekker, New York, **1997**, pp. 15–172. (c) Chatgilialoglu, C. and Ferreri, C., *Res. Chem. Intermed.* **1993**, 755. (d) Motherwell, W. B. and Crich, D., *Free Radical Chain Reactions in Organic Synthesis,* Academic Press, London, **1992**, chap. 3. (e) McCombie, S. W., Reduction of C=X to C=H, in *Comprehensive Organic Synthesis*, ed. Trost, B. M., Pergamon, New York, **1991,** *8*, 811–833. (f) Crich, D. and Quintero, L., *Chem. Rev.,* **1989**, *89*, 1413. (g) Pereyre, M.; Quintard, J.-P. and Rahm, A., *Tin in Organic Synthesis*, Butterworths, Boston, **1987**, pp. 84–96. (h) Hartwig, W., *Tetrahedron,* **1983**, *39*, 2609.
16. (a) Wang, Z. W.; Prudhomme, D. R.; Buck, J. R.; Park, M. and Rizzo, C. J., *J. Org. Chem.,* **2000**, *65*, 5969. (b) Saito, I.; Ikehira, H.; Kasatani, R.; Watanabe, M. and Matsuura, T., *J. Am. Chem. Soc.,* **1986**, *108*, 3115. (c) Cristol, S. J. and Seapy, D. G., *J. Org. Chem.,* **1982**, *47*, 132. (d) Bhattacharjee, A.; Soltani, O. and De Brabander, J. K., *Org. Lett*., **2002**, *4*, 481. (e) Prudhomme, D. R.; Wang, Z. W. and Rizzo, C. J., *J. Org. Chem.,* **1997**, *62*, 8257.
17. Mander, L. N. and Thomson, R. J., *Org. Lett*., **2003**, *5*, 1321.
18. (a) Lecomte, V.; Stéphan, E.; Rager, M.-N. and Jaouen, G., *J. Org. Chem.,* **2004**, *69*, 3216. (b) Wee, A. G. H. and McLeod, D. D., *J. Org. Chem.,* **2003**, *68*, 6268. (c) White, J. D.; Wang, G. Q. and Quaranta, L., *Org. Lett*., **2003**, *5*, 4109. (d) Snider, B. B.; Kiselgof, J. Y. and Foxman, B. M., *J. Org. Chem.,* **1998**, *63*, 7945. (e) Kulkarni, Y. S.; Niwa, M.; Ron, E. and Snider, B. B., *J. Org. Chem.,* **1987**, *52*, 1568.
19. Dondoni, A.; Marra, A. and Massi, A., *J. Org. Chem.,* **1999**, *64*, 933.
20. Kozikowski, A. P.; Tuckmantel, W. and George, C., *J. Org. Chem.,* **2000**, *65*, 5371.

21. Karla, R., Ebert, B., Thorkildsen, C., Herdeis, C., Johansen, T. N., Nielsen, B. and Krogsgaard-Larsen, P., *J. Med. Chem.,* **1999**, *42*, 2053.

22. (a) Vanheusden, V.; Busson, R.; Herdewijn, P. and Calenbergh, S. V., *J. Org. Chem.,* **2004**, *69*, 4446. (b) Rhee, J. U.; Bliss, B. I. and RajanBabu, T. V., *J. Am. Chem. Soc.,* **2003**, *125*, 1492. (c) Horiguchi, T.; Rithner, C. D.; Croteau, R. and Williams, R. M., *J. Org. Chem*., **2002**, *67*, 4901. (d) Hodgson, D. M.; Bebbington, M. W. P. and Willis, P., *Org. Lett*., **2002**, *4*, 4353. (e) Poupon, J. C.; Lopez, R.; Prunet, J. and Férézou, J. P., *J. Org. Chem.,* **2002**, *67*, 2118. (f) Ling, T. T.; Chowdhury, C.; Kramer, B. A.; Vong, B. G.; Palladino, M. A. and Theodorakis, E. A., *J. Org. Chem.,* **2001**, *66*, 8843. (g) Luzzio, F. A. and Fitch, R. W., *J. Org. Chem.,* **1999**, *64*, 5485. (h) Rudolf, M. T.; Li, W. H.; Wolfson, N.; Traynor-Kaplan, A. E. and Schultz, C., *J. Med. Chem.,* **1998**, *41*, 3635. (i) Volpini, R.; Camaioni, E.; Costanzi, S.; Vittori, S. and Cristalli, G., *Helv. Chim. Acta,* **1998**, *81*, 2326. (j) Meade, E. A.; Wotring, L. L.; Drach, J. C. and Townsend, L. B., *J. Med. Chem.*, **1997**, *40*, 794. (k) Crich, D.; Beckwith, S. A. L. J.; Chen. C.; Yao, Q. W.; Davison, I. G. E.; Longmore, R. W.; de Parrodi, C. A.; Quintero-Cores, L. and Sandoval-Ramirezs, J., *J. Am. Chem. Soc.,* **1995**, *117*, 8757. (l) Oba, M. and Nishiyama, K., *Tetrahedron,* **1994**, *50*, 10193. (m) Kumar, A.; Khan, S. I.; Manglani, A.; Khan, A. K. and Katti, S. B., *Nucleosides Nucleotides,* **1994**, *13*, 1049. (n) Rizzo, C. J.; Dougherty, J. P. and Breslow, R., *Tetrahedron Lett.,* **1992**, *33*, 4129. (o) Barton, D. H. R.; Blundell, P.; Dorchak, J.; Jang, D. O. and Jaszberenyi, J. C., *Tetrahedron,* **1991**, *43*, 8969. (p) Barton, D. H. R.; Jang, D. O. and Jaszberenyi, J. C., *Tetrahedron Lett.,* **1991**, *32*, 2569. (q) Kulicke, K. J. and Giese, B., *Synlett,* **1990**, 91. (r) Chatgilialoglu, C.; Guerrini, A. and Seconi, G., *Synlett,* **1990**, 219. (s) Giese, B.; Kopping, B. and Chatgilialoglu, C., *Tetrahedron Lett.,* **1989**, *30*, 681. (t) Araki, Y.; Endo, T.; Tanji, M.; Nagasawa, J. and Ishido, Y., *Tetrahedron Lett.,* **1988**, *29*, 351. (u) Chatgilialoglu, C.; Griller, D. and Lesage, M., *J. Org. Chem.,* **1988**, *53*, 3641. (v) Bachi. M. D. and Bosch. E., *J. Chem. Soc., Perkin Trans. I,* **1988**, 1517. (w) Crich, D., *Tetrahedron Lett.,* **1988**, *29*, 5805. (x) Barker, P. J. and Beckwith, A. L. J., *J. Chem. Soc., Chem. Commun.,* **1988**. *683*. (y) Hanessian, S.; Dhanoa, D. S. and Beaulieu, P. L., *Can. J. Chem.,* **1987**, *65*, 1859. (z) RajanBabu, T. V., *J. Am. Chem. Soc.,* **1987**, *109*, 609. (aa) Keck, G. E. and Enholm, E. J., *Tetrahedron,* **1985**, *41*, 4079. (bb) Hansske, F. and Robins, M. J., *Tetrahedron Lett.,* **1985**, *26*, 4295. (cc) Dolan, S. C. and MacMillan, J., *J. Chem. Soc., Chem. Commun.,* **1985**, 1588. (dd) Clive, D. L. J.; Beaulieu, P. L. and Set, L., *J. Org. Chem.,* **1984**, *49*, 1313. (ee) Giese, B.; González-Goméz, J. A. and Witzel, T., *Angew. Chem. Int. Ed. Engl*., **1984**, *23*, 69. (ff) Hansske, F. and Robins, M. J., *J . Am. Chem. Soc.,* **1983**, *105*, 6736. (gg) Hart, D. J. and Tsai, Y.-M., *J. Org. Chem.,* **1982**, *47*, 4403. (hh) Barton. D. H. R.; Hanwig. W. and Mothewell. W. B., *J. Chem. Soc., Chem. Commun.,* **1982**, 447. (ii) Lessor, R. A. and Leonard, N. J., *J . Org. Chem.,* **1981**, *46*, 4300. (jj) Barrett, A. G. M.; Barton, D. H. R. and Bielski, R., *J. Chem. Soc., Perkin Trans. I,* **1979**, 2378. (kk) Barton, D. H. R. and Subramanian, R., *J. Chem. Soc., Perkin Trans. I,* **1977**, 1718. (ll) Barrett, A. G. M.; Barton, D. H. R.; Bielski, R. and McCombie, *S*.W., *J. Chem. Soc., Chem. Commun.,* **1977**, 866. (mm) Alibés, R.; de March, P.; Figueredo, M.; Font, J.; Racamonde, M and Parella, T., *Org. Lett*., **2004**, *6*, 1449. (nn) Sato, T.; Aoyagi, S. and Kibayashi, C., *Org. Lett*., **2003**, *5*, 3839. (oo) Reynolds, A. J.; Scott, A. J.; Turner, C. I. and Sherburn, M. S., *J. Am. Chem.. Soc.,* **2003**, *125*, 12108. (pp) Boydell, A. J.; Jeffery, M. J.; Bürkstümmer, E. and Linclau, B., *J. Org. Chem.,* **2003**, *68*, 8252. (qq) Itoh, T.; Yamazaki, N. and Kibayashi, C., *Org. Lett*., **2002**, *4*, 2469. (rr) Durand, T.; Guy, A.; Vidal, J.-P. and Rossi, J.-C., *J. Org. Chem.* **2002**, *67*, 3615. (ss) Kerr, W. J.; McLaughlin, M.; Morrison, A. J. and Pauson, P. L, *Org. Lett.,* **2001**, *3*, 2945. (tt) Calter, M. A.; Liao, W. S. and Struss, J. A., *J. Org. Chem.,* **2001**, *66*, 7500. (uu) Padwa, A.; Brodney, M. A.; Dimitroff, M.; Liu, B. and Wu, T. H., *J. Org. Chem.,* **2001**, *66*, 3119. (vv) Hanessian, S. and Rogel, O., *J. Org. Chem.,* **2000**, *65*, 2667. (ww) Boussaguet, P.; Delmond, B.; Dumartin, G. and Pereyre, M., *Tetrahedron Lett.,* **2000**, *41*, 3377. (xx) Durand, T.; Guy, A.; Vidal, J.-P.; Viala, J. and Rossi, J.-C., *Tetrahedron Lett*., **2000**, *41*, 3859. (yy) Cassayre, J. and Zard, S. Z., *J. Am. Chem. Soc.* **1999**, *121*, 6072. (zz) Ballereau, S.; Guédat, P.; Poirier, S. N.; guillemette, G.; Spiess, B. and Schlewer, G., *J. Med. Chem.,* **1999**, *42*, 4824. (aaa) Guy, A.; Durand, T.; Roland, A.;

Cormenier, E. and Rossi, J.-C., *Tetrahedron Lett*., **1998**, *39*, 6181. (bbb) Hays, D. S. and Fu, G. C., *J. Org. Chem.,* **1998**, *63*, 2796. (ccc) Padwa, A.; Harring, S. R. and Semones, M. A., *J. Org. Chem.,* **1998**, *63*, 44. (ddd) Padwa, A.; Brodney, M. A.; Marino, J. P. and Sheehan, S. M., *J. Org. Chem.,* **1997**, *62*, 78. (eee) Jung, P. M. J.; Burger, A. and Biellmann, J., *J. Org. Chem.,* **1997**, *62*, 8309. (fff) Beckwith, A. L. J.; Crich, D.; Duggan, P. J. and Yao, Q. W., *Chem. Rev.,* **1997**, *97*, 3273. (ggg) Desmaële, D.; Mekouar, K. and d'Angelo, J., *J. Org. Chem.,* **1997**, *62*, 3890. (hhh) Corey, E. J.; Luo, G. L. and Lin, L. S. Z., *J. Am. Chem. Soc.,* **1997**, *119*, 9927. (iii) Witter, D. J. and Vederas, J. C., *J. Org. Chem.,* **1996**, *61*, 2613. (jjj) Nicolaou, K. C.; Theodorakis, E. A.; Rutjes, F. P. J. T.; Sato, M.; Tiebes, J.; Xiao, X. Y.; Hwang, C. K.; Duggan, M. E.; Yang, Z.; Couladouros, E. A.; Sato, F.; Shin, J.; He, H. M. and Bleckman, T., *J. Am. Chem. Soc*., **1995**, *117*, 10239. (kkk) Kakiuchi, K.; Nakamura, I.; Matsuo, F.; Nakata, M.; Ogura, M.; Tobe, Y. and Kurosawa, H., *J. Org. Chem.,* **1995**, *60*, 3318. (lll) Rondot, B.; Durand, T.; Vidal, J.-P.; Girard, J.-P. and Rossi, J.-C., *J. Chem. Soc.*, *Perkin Trans. II,* **1995**, 1589. (mmm) Newcomb, M. and Chestney, D. L., *J. Am. Chem. Soc.,* **1994**, 116,9753. (nnn) Barton, D. H. R.; Jang, D. O. and Jaszberenyi, J. C., *Tetrahedron,* **1993**, *49*, 2793. (ooo) Liu, W. G.; Steffens, J. J.; Goswami, A. and Rosazza, J. P. N., *J. Org. Chem.,* **1993**, *58*, 6329. (ppp) Rondot, B.; Durand, T.; Girard, J.-P.; Rossi, J.-C.; Schio, L.; Khanapure, S. P. and Rokach, J., *Tetrahedron Lett*., **1993**, *34*, 8245. (qqq) Chatgilialoglu, C., *Acc. Chem Res*., **1992**, *25*, 188. (rrr) Barton, D. H. R.; Dorchak, D. and Jaszberenyi, J. C., *Tetrahedron,* **1992**, *48*, 7435. (sss) Barton D. H. R., *Tetrahedron* **1992**, *48*, 2529. (ttt) Barton, D. H. R.; Jang, D. O. and Jaszberenyi, J. C., *Tetrahedron Lett.,* **1992**, *33*, 2311. (uuu) Valverde, S.; Lopez, J. C.; Gomez, A. M. and Garcia-Ochoa, S., *J. Org. Chem.,* **1992**, *57*, 1613. (vvv) Barton, D. H. R.; Jang, D. O. and Jaszberenyi, J. C., *Tetrahedron Lett.,* **1991**, *32*, 7187. (www) Ballestri, M.; Chatgilialoglu, C.; Clark, D.; Giese, B. and Kopping, B., *J. Org. Chem*., **1991**, *56*, 678. (xxx) Dickhaut, J. and Giese, B., *Org. Synth.,* **1991**, *70*, 164. (yyy) France, C. J.; McFarlane, I. M.; Newton, C. G.; Pitchen, P. and Barton, D. H. R., *Tetrahedron,* **1991**, *47*, 6381. (zzz) Lesage, M. M.; SimBes, J. A. and Griller, D., *J. Org. Chem*., **1990**, *55*, 5413. (aaaa) Chu. C. K.; Bhadti, V. S.; Doboszewski, B.; Gu, Z. P.; Kosuai, Y.; Pullaiah, K. C. and Van Roey, P., *J. Org. Chem.,* **1989**, *54*, 2217. (bbbb) Serafinowski, P., *Synthesis,* **1990**, 411. (cccc) Ziegler, F. E. and Zheng, Z. L., *J. Org. Chem.,* **1990**, *55*, 1416. (dddd) Muher, J.; Steffen, U.; Zorn, L.; Schneider, C.; Weinhold, E.; Miinch, W.; Rudert, R.; Luger, P. and Hartli, H., *J. Am. Chem. Soc.,* **1988**, *110*, 4640. (eeee) Prisbe, E. J. and Martin, J. C., *Synth. Commun.,* **1985**, *15*, 401. (ffff) Palmisano, G.; Danieli, B.; Lesma, G.; Riva, R.; Riva, S.; Demartin, F. and Masciocchi, N., *J. Org. Chem*., **1984**, *49*, 4138. (gggg) Barton, D. H. R. and Motherwell, W. B., *Pure & Appl. Chem.,* **1981**, *53*, 15.

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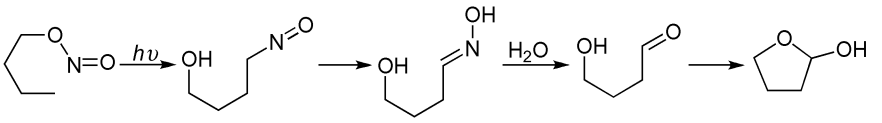
Barton Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was reported by Barton in 1960.[1] It is the transformation of a nitrite ester into a nitroso alcohol under photolytic conditions and involves the homolytic cleavage of a nitrogen-oxygen bond followed by an intramolecular δ-hydrogen abstraction with the resulting oxygen-centered radical.[2] Thus this reaction is known as the Barton reaction.[3] The formed nitroso compound can tautomerize to an oxime derivative that further hydrolyzes to aldehyde[1] or can be oxidized to nitrile.[4] This reaction is useful in the conversion of the angular methyl groups (Δ methyl groups) in steroids into carbonyl groups.[1,5]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Although the mechanism of this reaction has been extensively studied,[4,6] it is believed that the homolytic cleavage of the nitrogen-oxygen bond is reversible, which initially

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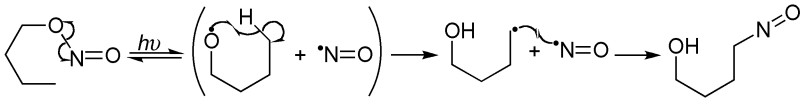
conforms to a geminate recombination.[4] However, in the subsequent stages, the partners are separated; therefore, the "solvent cage" effect is not shown in this reaction, as illustrated here in detail for the transformation of nitrite ester into nitroso compound.



D. MODIFICATION

N/A

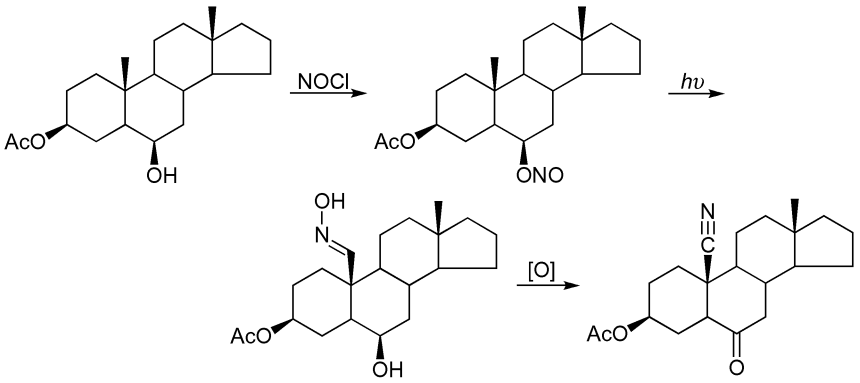
E. APPLICATIONS

This reaction has been applied for activating the methyl group that is three carbon atoms away from the hydroxyl group, especially for methyl groups occurring in steroids.

F. RELATED REACTIONS

N/A

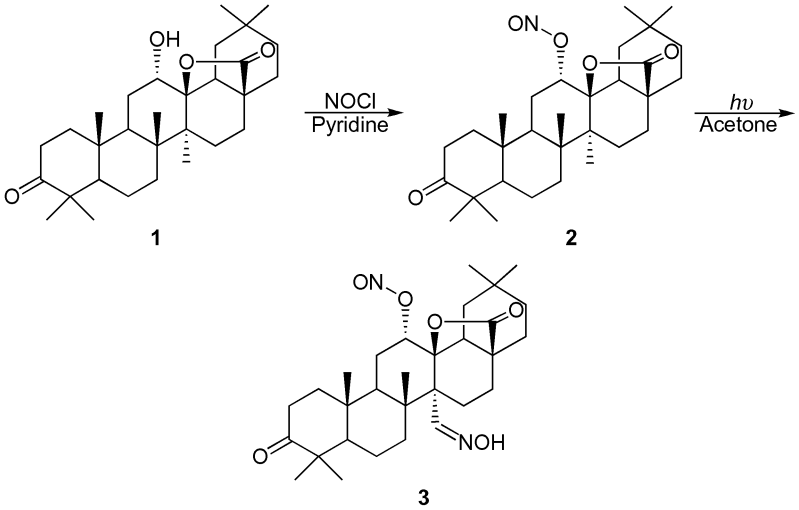
G. CITED EXPERIMENTAL EXAMPLES



Reference 4.

A solution of 600 mg 3β-acetoxy-6β-hydroxyandrostane in 10 mL pyridine at 0°C was treated with an excess of nitrosyl chloride. The product was worked up as usual (extraction); after crystallization from methylene chloride-hexane, 500 mg 3β-acetoxyandrostan-6β-yl nitrite was obtained, m.p. 135–138°C.

A solution of 70 mg 3β-acetoxyandrostan-6β-yl nitrite in 2 mL toluene was photolyzed in a Pyrex test tube at 4°C using a 200-w Hanovia high-pressure mercury arc lamp. After 15 min the nitroso dimmer was filtered off and washed with toluene. The dimmer was refluxed in 5 mL isopropyl alcohol for 1 h. Evaporation of the solvent furnished a noncrystalline oxime. This oxime in 2 mL pyridine was treated with 200 mg chromium trioxide in 7 mL pyridine at room temperature overnight and worked up as usual. Crystallization from methylene chloride-methanol gave 25 mg 3β-acetoxy-19-nitriloandrostan-6-one, m.p. 230–236°C.



1 2 3

Reference 7.

A stream of NOCl, generated from 87.4 g $NaNO_2$ and 509 mL 35% HCl, was introduced to an ice cold solution of 298 g alcohol **1** (0.634 mol) in 3 L pyridine at −40°C over 30 min. The mixture was stirred at −40°C for 30 min and poured into 4.4 L ice water. The resulting precipitate was collected by filtration and washed with 2.5 L H_2O. The wet precipitate was dissolved in a mixture of 2.9 L CH_2Cl_2 and 52 mL pyridine, and the organic layer was separated and concentrated. The residue was triturated with 1.2 L hexane, and the white powder was filtered and washed with 0.5 L hexane to give 296 g nitrite ester **2**, in yield of 94%, m.p. 254–258°C (dec.), $R_f = 0.68$ (CH_2Cl_2/EtOAc = 8/1).

A solution of 20 g nitrite ester **2** in 1.2 L acetone containing a small amount of pyridine (0.16 mL) was irradiated with a high-pressure mercury lamp (400 W) through a Pyrex filter under nitrogen atmosphere for 1 h. A total of 14 batches of the photoreaction mixture were combined and concentrated, and 1.4 L 1,2-dichloroethane was added to the residue; the solution was refluxed for 1.5 h. The resulting slurry was collected by filtration and washed with dichloroethane to give 206 g oxime **3** as white crystals, in a yield of 74%. The filtrate was concentrated to 1.2 kg, and an additional 31 g oxime **3** was obtained (11%) as a crystalline powder. The total yield was 85%, m.p. 285–289°C (dec.), $R_f = 0.16$ (CH_2Cl_2/EtOAc = 8:1).

Other references related to the Barton reaction are collected in the literature.[8]

H. REFERENCES

1. (a) Barton, D. H. R.; Beaton, J. M.; Geller, L. E. and Pechet, M. M., *J. Am. Chem. Soc*., **1960**, *82*, 2640. (b) Barton, D. H. R.; Beaton, J. M.; Geller, L. E. and Pechet, M. M., *J. Am. Chem. Soc*., **1961**, *83*, 4076.
2. (a) Hesse, R. H., *Adv. Free Radical Chem*., **1969**, *3*, 83. (b) Akhtar, M., Some Recent Developments in the Photochemistry of Organic Nitries and Hypohalites in *Advances in Photochemistry*, ed. Noyes, W. A. Jr.; Hammond, G. S. and Pitts, J. N. Jr., John Wiley & Sons, New York, **1964**, *2*, p. 263. (c) Nussbaum, A. L. and Robinson, C. H., *Tetrahedron*, **1962**, *17*, 35.
3. Grossi, L., *Chem. Eur. J.,* **2005**, *11*, 5419.
4. Akhtar, M. and Pechet, M. M., *J. Am. Chem. Soc.,* **1964**, *86*, 265.
5. Erikson, J. M. and Forbes, D. L., in *Steroid Reactions*, ed. Djerassi, C., Holden-Day, Inc., San Francisco, **1963**, p. 341, 343, 358, 364.
6. (a) Burke, S. D.; Silks, L. A. and Strickland, S. M. S., *Tetrahedron Lett.,* **1988**, *29*, 2761. (b) Barton, D. H. R.; Hesse, R. H.; Pechet, M. M. and Smith, L. C., *J. Chem. Soc., Perkin Trans. I,* **1979**, 1159. (c) Nickon, A.; Ferguson, R.; Bosch, A. and Iwadare, T., *J. Am. Chem. Soc.,* **1977**, *99*, 4518.
7. Konoike, T.; Takahashi, K.; Araki, Y. and Horibe, I., *J. Org. Chem.,* **1997**, 62,960.
8. (a) Hakimelahi, G. H.; Li, P.-C.; Moosavi-Movahedi, A. A.; Chamani, J.; Khodarahmi, G. A.; Weily, T.; Valiyev, F.; Leong, M. K.; Hakimelahi, S.; Shia, K.-S. and Chao, I., *Org. Biomol. Chem*., **2003**, *1*, 2461. (b) Puchowicz, D.; Adamus, J. and Gebicki, J. *J. Chem. Soc., Perkin Trans. II*, **2000**, 1942. (c) Herzog, A.; Knobler, C. B. and Hawthorne, M. F., *Angew. Chem. Int. Ed.,* **1998**, *37*, 1552. (d) Sejbal, J.; Klinot, J. and Budesinsky, M., *Coll. Czech. Chem. Commun*., **1996**, *61*, 1360. (e) Suginome, H., "Barton Nitrite Photolysis" in *Organic Photochemistry and Photobiology,* ed. Horspol, W. M. and Song, P.-S., CRC Press, Boca Raton, Fla., **1995**, p. 1007. (f) Barton, D. H. R. and Parekh, S. I., *Half a Century of Free Radical Chemistry*, Cambridge, Cambridge University Press. **1993**. (g) Green, M. M.; Boyle, B. A.; Vairamani, M.; Mukhopadhyay, T.; Saunders, W. H.; Bowen, P. and Allinger, N. L., *J. Am. Chem. Soc*., **1986**, *108*, 2381. (h) Jakus, C. and Smets, G., *Macromolecules,* **1982**, *15*, 435. (i) Hobbs, P. D. and Magnus, P. D., *J. Am. Chem. Soc*., **1976**, *98*, 4594. (j) Barton, D. H. R., *Pure & Appl. Chem*., **1968**, *16*, 1. (k) Heusler, K. and Kalvoda, J., *Angew. Chem. Int. Ed. Engl*., **1964**, *8*, 525. (l) Khtar, M. A.; Barton, D. H. R. and Sammes, P. G., *J. Am. Chem. Soc*., **1964**, *86*, 3394. (m) Sneen, R. A. and Matheny, N. P., *J. Am. Chem. Soc.,* **1964**, *86*, 5503. (n) Jen, T. and Wolff, M. E., *J. Org. Chem*., **1963**, *28*, 1573. (o) Akhtar, M.; Barton, D. H. R.; Beaton, J. M. and Hortmann, A. G., *J. Am. Chem. Soc*., **1963**, *85*, 1512. (p) Kabasakalian, P. and Townley, E. R., *J. Am. Chem. Soc.,* **1962**, *84*, 2724. (q) Kabasakalian, P. and Townley, E. R., *J. Org. Chem*., **1962**, *27*, 2918. (r) Akhtar, M. and Barton, D. H. R., *J. Am. Chem. Soc*., **1962**, *84*, 1496. (s) Barton, D. H. R. and Beaton, J. M., *J. Am. Chem. Soc*., **1962**, *84*, 199. (t) Kabasakalian, P.; Townley, E. R. and Yudis, M. D., *J. Am. Chem. Soc.,* **1962**, *84*, 2716. (u) Barton, D. H. R. and Beaton, J. M., *J. Am. Chem. Soc*., **1961**, *83*, 4083.

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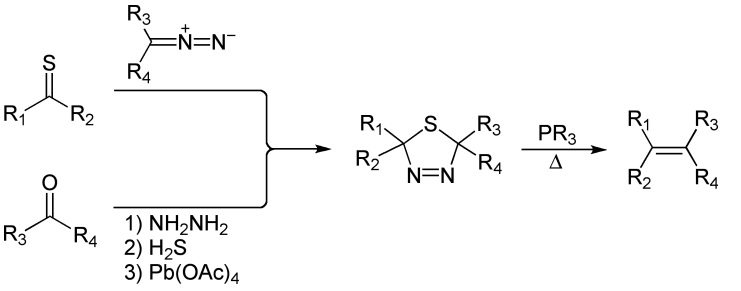
Barton-Kellogg Olefination

(Barton-Kellogg Olefin Synthesis; Barton-Kellogg Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Barton[1] and Kellogg[2] concurrently in 1970. It is the coupling of two ketones into alkenes, particularly applicable to the synthesis of moderately to highly hindered alkenes. Therefore, it is generally known as the Barton-Kellogg olefination,[3] Barton-Kellogg olefin synthesis,[4] or Barton-Kellogg reaction.[5] In this reaction, the steric constraints are gradually introduced via sequential processes involving a *1,3-Dipolar Cycloaddition* to form five-membered Δ^3-1,3,4-thiadiazoline, followed by the nitrogen elimination to three-membered episulfide, and finally the sulfur extrusion to afford the alkenes.[6] Although this reaction can be used for the synthesis of asymmetric alkenes from two different ketones, symmetric alkenes will always be formed as by-products.

B. GENERAL REACTION SCHEME



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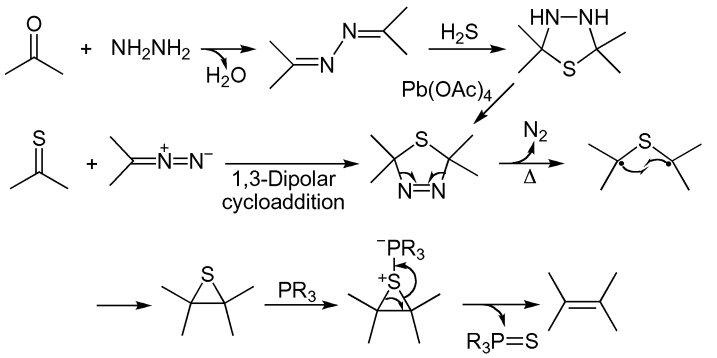
C. PROPOSED MECHANISMS

Displayed below is the olefination mechanism.



D. MODIFICATION

N/A

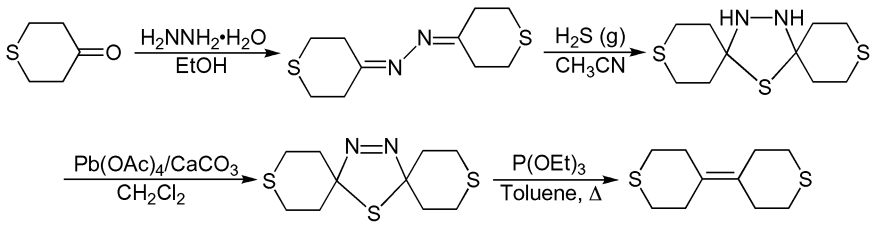
E. APPLICATIONS

This reaction has been applied for synthesizing alkenes, especially those overcrowded alkenes.[7]

F. RELATED REACTIONS

The *McMurry Reaction* is similar to the Barton-Kellogg reaction. However, the *McMurry Reaction* is unsuccessful for preparing some of the overcrowded alkenes, such as tetra-*tert*-butylethylene.[8]

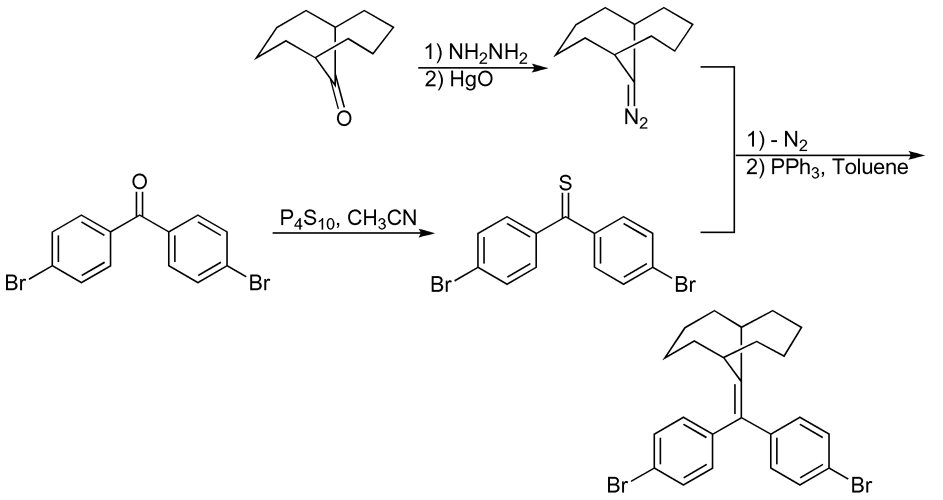
G. CITED EXPERIMENTAL EXAMPLES



Reference 7b.

A solution of 5.0 g tetrahydro-4*H*-thiopyran-4-one (43.0 mmol) in 125 mL ethanol at reflux temperature was added dropwise to mixed solution of 1.06 mL $H_2NNH_2 \cdot H_2O$ (>99%, 21.6 mmol) and 50 mL ethanol. The mixture was refluxed overnight. After cooling to room

temperature and the removal of solvent in vacuo, 4.90 g pure tetrahydro-4H-thiopyran-4-on azine was obtained, in a yield of 100%. The 4.90 g tetrahydro-4H-thiopyran-4-on azine was dissolved in 150 mL CH_3CN and stirred under H_2S (g) atmosphere for 5 days. After evaporation of the solvent, 5.54g pure 3,7,11-trithia-14,15-diazadispiro[5.1.5.2]pentadecane was obtained as a light yellow solid, in a yield of 98%. This compound (21.1 mmol) was oxidized with a mixture of 13.0 g $Pb(OAc)_4$ (29.3 mmol) and 13.0 g $CaCO_3$(0.13 mol) in 160 mL dry CH_2Cl_2. After work up, 5.87 g brown solid was obtained, which was recrystallized from hot EtOAc to yield 3.39 g pure 3,7,11-trithia-14,15-diazadispiro[5.1.5.2]pentadec-14-ene, in a yield of 62%. This solid (13.0 mmol) was mixed with 12.0 mL triethyl phosphite (70 mmol) and 200 mL toluene and refluxed for 24 h. After cooling to room temperature, the solvent was removed in vacuo, and the solid residue was triturated with 25 mL methanol. The solid was filtered off and subsequently, sublimed (80°C at 0.1 mmHg) to give 1.93 g of pure 4,4-bis(tetrahydro-4H-thiopyranylidene) in a yield of 74%, m.p., 144.1°C.



Reference 7c.

To a 25-mL flask were added 1.2 g bicyclo[4.4.1]-undecan-11-one (7.25 mmol), 10 g hydrazine monohydrate (200 mmol, 10 mL), and 1.0 g hydrazine sulfate (9 mmol). The mixture was refluxed for 4 days, and upon cooling a solid precipitated. The mixture was extracted with Et_2O, washed twice with H_2O, once with saturated brine, and dried over Na_2SO_4. Solvent removal gave a white solid, which was used directly for the next step in the reaction.

To a flask containing 2.0 g yellow HgO (9.23 mmol) was added a solution of 300 mg bicyclo[4.4.1]undecan-11-one hydrazone (1.67 mmol) in 30 mL Et_2O; then 2.0 g Na_2SO_4 (14.08 mmol) was added, followed by a few drops of a saturated ethanolic solution of NaOH. The resulting yellow suspension was stirred for 14 h, filtered, and evaporated to yield a crystalline orange solid. This solid was used for next step in the reaction without further purification.

To a suspended mixture of 2.0 g 4,4-dibromobenzophenone and 4.02 g P_4S_{10} (9.05 mmol) in 20 mL acetonitrile, was added 3.1 g $NaHCO_3$ (36 mmol). The mixture was stirred at 50°C for 12 h, during which time it became dark blue. After cooling, the mixture was transferred to a separatory funnel containing Et_2O and H_2O, and the resulting

blue organic layer was washed three times with saturated aqueous $NaHCO_3$, washed once with saturated brine, and then dried over Na_2SO_4. The solvents were removed to give a blue solid, which was recrystallized (argon was blown over the solution during boiling and cooling) from MeOH to give dark blue microcrystals of the product (the thioketone). This material was contaminated ($\sim$ 25% by ^{1}H NMR) with starting material; however, the subsequent reaction was unaffected by such contamination so that no additional purification was attempted.

To a 50-mL flask were added 1.14 g the thioketone (3.25 mmol) and 5 mL THF (deep blue). Then the orange solution of 580 mg diazoalkane (3.25 mmol) in 15 mL THF was added, causing gas evolution. The resulting blue solution was protected from light and refluxed for 12 h. After removal of THF, the residue was subjected to radial chromatography (SiO_2, petroleum ether) to give 1.06 g bis(4′,4″-bromophenyl)methylenebicyclo[4.4.1]-undecane episulfide as a colorless solid, in a yield of 66%.

This episulfide (1.06 g, 2.13 mmol) and 1.12 g triphenylphosphine (4.26 mmol) were dissolved in 15 mL toluene and refluxed for 2 nights. After cooling, the reaction mixture was filtered through SiO_2, and evaporated, and the residue was subjected to radial chromatography (SiO_2, petroleum ether) to afford 0.815 g bis(4′,4″-bromophenyl) methylenebicyclo[4.4.1]-undecane, as a colorless solid, in a yield of 87%.

Other references related to the Barton-Kellogg reaction are cited in the literature.[9]

H. REFERENCES

1. (a) Barton, D. H. R. and Willis, B. J., *J. Chem. Soc., Chem. Commun.,* **1970**, 1226. (b) Barton, D. H. R. and Willis, B. J., *J. Chem. Soc., Perkin Trans. I,* **1972**, 305.
2. (a) Kellogg, R. M. and Wassenaar, S., *Tetrahedron Lett.,* **1970**, 1987. (b) Kellogg, R. M.; Wassenaar, S. and Buter, J., *Tetrahedron Lett*., **1970**, 4689. (c) Buter, J.; Wassenaar, S. and Kellogg, R. M., *J. Org. Chem.,* **1972**, *37*, 4045.
3. Kaepplinger, C.; Beckert, R.; Braunerova, G.; Zahajska, L.; Darsen, A. and Goerls, H., *Sulfur Lett.,* **2003**, *26*, 141.
4. Hoogesteger, F. J.; Havenith, R. W. A.; Zwikker, J. W.; Jenneskens, L. W.; Kooijman, H.; Veldman, N. and Spek, A. L., *J. Org. Chem.,* **1995**, *60*, 4375.
5. Garratt, P. J.; Payne, D. and Tocher, D. A., *J. Org. Chem.,* **1990**, *55*, 1909.
6. (a) de Lange, B.; Feringa, B. L. and Jager, W. F., *Mol. Cryst. Liq. Cryst.,* **1992**, *217*, 129. (b) Jager, W. F.; Feringa, B. L.; and de Lange, B., *Mol. Cryst. Liq. Cryst.,* **1992**, *217*, 133.
7. (a) Koumura, N.; Geertsema, E. M.; van Gelder, M. B.; Meetsma, A. and Feringa, B. L., *J. Am. Chem. Soc.,* **2002**, *124*, 5037. (b) Marsman, A. W.; Havenith, R. W. A.; Bethke, S.; Jenneskens, L. W.; Gleiter, R.; van Lenthe, J. H.; Lutz, M. and Spek, A. L., *J. Org. Chem.,* **2000**, *65*, 4584. (c) Shultz, D. A.; Boal, A. K.; Lee. H. Y. and Farmer, G. T., *J. Org. Chem.,* **1999**, *64*, 4386. (d) Anderson, K. K.; Shultz, D. A. and Dougherty, D. A., *J. Org. Chem.,* **1997**, *62*, 7575. (e) Hoogesteger, F. J.; Havenith, R. W. A.; Zwikker, J. W.; Jenneskens, L. W.; Kooijman, H.; Veldman, N. and Spek, A. L., *J. Org. Chem.,* **1995**, *60*, 4375. (f) Collazo, L. R. and Guziec, F. S., *J. Org. Chem.,* **1993**, *58*, 43. (g) Feringa, B. L.; Jager, W. F.; de Lange, B. and Meijert, E. W., *J. Am. Chem. Soc*., **1991**, *113*, 5468. (h) Bee, L. K.; Beeby, J.; Everett, J. W. and Garratt, P. J., *J. Org. Chem.,* **1975**, *40*, 2212. (i) Schaap, A. P. and Faler, G. R., *J. Org. Chem.,* **1973**, *38*, 3061.
8. Sulzbach, H. M.; Bolton, E.; Lenoir, D.; Schleyer, P. v. R. and Schaefer, H. F., *J. Am. Chem. Soc.,* **1996**, *118*, 9908.

9. (a) Van Delden, R. A.; ter Wiel, M. K. J.; de Jong, H.; Meetsma, A. and Feringa, B. L., *Org. Biomol. Chem*., **2004**, *2*, 1531. (b) Kaepplinger, C.; Beckert, R.; Braunerova, G.; Zahajska, L.; Darsen, A. and Goerls, H., *Sulfur Lett*., **2003**, *26*, 141. (c) Feringa, B. L.; van Delden, R. A.; Koumura, N. and Geertsema, E. M., *Chem. Rev*., **2000**, *100*, 1789. (d) Koumura, N.; Geertsema, E. M.; Meetsma, A. and Feringa, B. L., *J. Am. Chem. Soc.,* **2000**, *122*, 12005. (e) Wagner, K.; Weiss, D. and Beckert, R., *Eur. J. Org. Chem.,* **2000**, 3001. (f) Schwab, P. F. H.; Levin, M. D. and Michl, J., *Chem. Rev.,* **1999**, *99*, 1863. (g) Novak, J. A.; Jain, R. and Dougherty, D. A., *J. Am. Chem. Soc.,* **1989**, *111*, 7618. (h) Kabe, Y.; Takata, T.; Ueno, K. and Ando, W., *J. Am. Chem. Soc.,* **1984**, *106*, 8174. (i) McMurry, J. E.; Haley, G. J.; Matz, J. R.; Clardy, J. C.; van Duyne, G.; Gleiter, R.; Schafer, W. and White, D. H., *J. Am. Chem. Soc.* **1984**, *106*, 5018. (j) Ando, W.; Kabe, Y. and Takata, T., *J. Am. Chem. Soc.,* **1982**, *104*, 7314. (k) Bachi, M. D.; Goldberg, O. and Gross, A., *Tetrahedron Lett.* **1978**, 4167. (l) Bee, K. K.; Everett, J. W. and Garratt, P. J., *Tetrahedron,* **1977**, *33*, 2143. (m) Barton, D. H. R.; Guziec, F. S.; Shahak, I. J., *J. Chem. Soc., Perkin Trans. I,* **1974**, 1794. (n) Krapcho, A. P. and Jahngen, E. G. E., *J. Org. Chem.,* **1974**, *39*, 1650. (o) Everett, I. W. and Garratt, P. J., *J. Chem. Soc., Chem. Commun.,* **1972**, 642.

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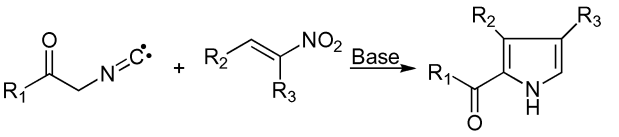
Barton-Zard Pyrrole Synthesis

(Barton-Zard Pyrrole Condensation; Barton-Zard Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Barton and Zard in 1985.[1] It is the synthesis of 2-substituted pyrroles (2-pyrrole-carboxylates or 2-sulfonyl pyrroles) via the basic condensation between alkyl isocyanoacetate (or tosylmethyl isocyanide) and α,β-unsaturated nitroalkenes (or β-nitroacetates). Therefore, this reaction is generally known as the Barton-Zard pyrrole synthesis,[2] Barton-Zard pyrrole condensation,[3] or the Barton-Zard reaction.[4] This reaction is convenient for the synthesis of pyrroles with various substituents at the β positions (R_2 and R_3) but is not applicable for the synthesis of pyrroles without a substituent at position 2. The yields of this reaction are generally high (80–90%), however, if R_2 is hydrogen, the yield is moderate. A nonionic strong base, such as DBU and guanidine, is generally used in this reaction. Currently, this method has been developed for preparing polypyrroles and porphyrins fused with various aromatic rings or bicyclic frameworks, starting from aromatic nitro compounds and ethyl isocyanoacetate.[5] The formed polypyrroles and porphyrins can be applied as functional dyes. The reaction has been reviewed.[6]

B. GENERAL REACTION SCHEME



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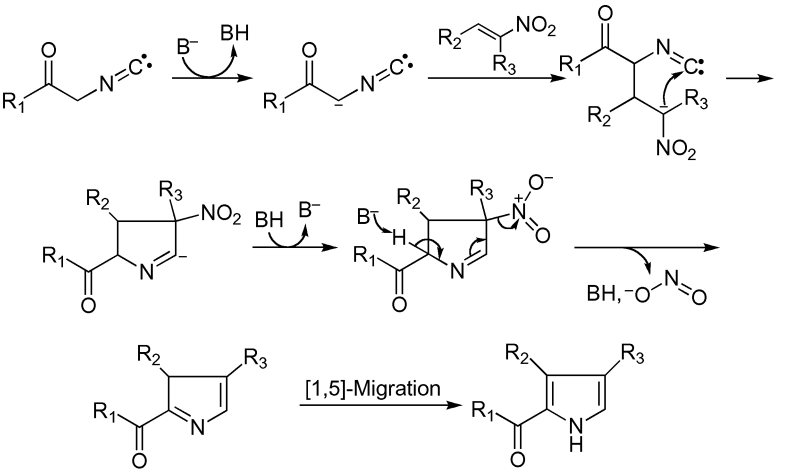
C. PROPOSED MECHANISMS

The reaction mechanism is shown below.



D. MODIFICATION

A few modifications have been developed for this reaction.[7]

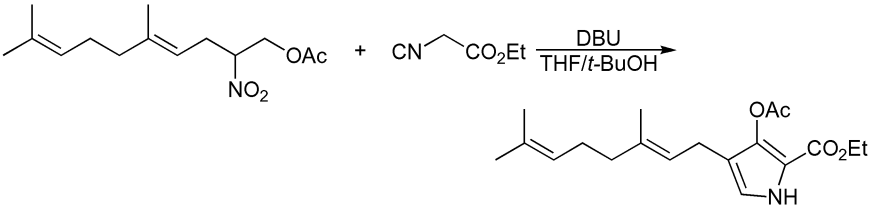
E. APPLICATIONS

This reaction has been applied for preparing polypyrroles and porphyrins.[5] Although the substituted isoindoles can also be prepared from substituted nitrobenzenes, the simple isoindole cannot be prepared in this manner because nitrobenzene does not react with ethyl isocyanoacetate.[8]

F. RELATED REACTIONS

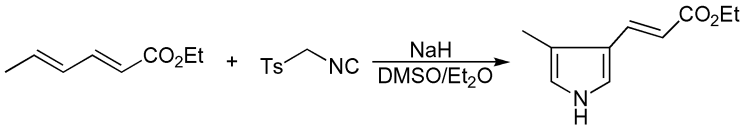
This reaction is similar to the *Leusen Pyrrole Condensation*,[9] based on the reaction of tosylmethyl isocyanide and electron-deficient alkenes (a toluenesulfinate anion is eliminated).[10] The most important advantage of this reaction is that α-free pyrroles can be obtained directly.

G. CITED EXPERIMENTAL EXAMPLES



Reference 11.

To a stirred solution of 3.04 g (*E*)-5,9-dimethyl-2-nitrodeca-4,8-dienyl acetate (11.29 mmol) in 28 mL of a mixed solvent of anhydrous THF/*t*-BuOH (1:1) were added 1.23 mL ethyl isocyanoacetae (11.29 mmol) and 3.38 mL DBU (22.58 mmol) dropwise while cooling at 0°C. After stirring for 26 h, 30 mL water and 30 mL EtOAc were added. The mixture was extracted with EtOAc (2 × 20 mL) and the combined organic layers were washed with water (2 × 20 mL) and 30 mL brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane = 1:9) to give 2.36 g ethyl 4-(3,7-dimethylocta-2,6-dienyl)pyrrole-2-carboxylate as a yellow oil, in a yield of 18%.



Reference 10k.

A solution of 15 g tosylmethyl isocyanide (75 mmol) and 10.0 g ethyl sorbate (71.3 mmol) in 50 mL dry DMSO and 100 mL ether was added to an ice cold suspension of 3.6 g NaH (88.5 mmol, 59% dispersion in oil) in 100 mL ether. The mixture was stirred for 3 h at 20°C, poured into 50 mL saturated aqueous NH_4Cl solution, and extracted with ether (4 × 50 mL). The combined extracts were washed with saturated aqueous NH_4Cl solution, and dried over $MgSO_4$. Evaporation of the extract gave 13.0 g of crude ethyl 3-(4-methyl-3-pyrrolyl)acrylate. Crystallization from EtOH gave 10.6 g of pure product, in a yield of 80%; m.p. 88–89°C.

Other references related to the Barton-Zard pyrrole synthesis are cited in the literature.[12]

H. REFERENCES

1. (a) Barton, D. H. R. and Zard, S. Z., *J. Chem. Soc., Chem. Commun.*, **1985**, 1098. (b) Barton, D. H. R.; Kervagoret, J. and Zard, S. Z., *Tetrahedron*, **1990**, *46*, 7587.
2. (a) Bhattacharya, A.; Cherukuri, S.; Plata, R. E.; Patel, N.; Tamez, V.; Grosso, J. A.; Peddicord, M. and Palaniswamy, V. A., *Tetrahedron Lett.,* **2006**, *47*, 5481. (b) Bobal, P. and Lightner, D. A., *J. Heterocycl. Chem.,* **2001**, *38*, 527.
3. (a) Lash, T. D.; Wijesinghe, C.; Osuma, A. T. and Patel, J. R., *Tetrahedron Lett.,* **1997**, *38*, 2031. (b) Lash, T. D.; Novak, B. H. and Lin, Y. N., *Tetrahedron Lett.,* **1994**, *35*, 2493.
4. (a) Liao, Y.-G.; Song, J.-X.; Wang, H.-B. and Guo, C.-C., *Huaxue Shiji,* **2006**, *28*, 663. (b) Pelkey, E. T.; Chang, L. and Gribble, G. W., *Chem. Commun.,* **1996**, 1909.
5. (a) Ono, N.; Tsukamura, C.; Nomura, Y.; Hironaga, H.; Murashima, T. and Ogawa, T., *Adv. Mater.*, **1997**, *9*, 149. (b) Ono, N.; Hironaga, H.; Ono, K.; Kaneko, S.; Murashima, T.; Ueda, T.; Tsukamura, C. and Ogawa, T., *J. Chem. Soc., Perkin Trans. I*, **1996**, 417. (c) Chandrasekar, P. and Lash, T. D., *Tetrahedron Lett.*, **1996**, *28*, 4873. (d) Lash, T. D. and Novak, B. H., *Angew. Chem. Int. Ed. Engl.*, **1995**, *34*, 683. (e) Ono, N.; Hironaga, H.; Simidzu, K.; Ono, K. and Ogawa, T., *J. Chem. Soc., Chem. Commun.*, **1994**, 1019.
6. Ono, N., *Synthesis of Heterocyclic Compounds* in *The Nitro Group in Organic Synthesis*, ed. Ono, N., Wiely-VCH, New York, **2001**.

7. (a) Fumoto, Y.; Uno, H.; Tanaka, K.; Tanaka, M.; Murashima, T. and Ono, N., *Synthesis*, **2001**, 399. (b) Uno, H.; Ito, S.; Wada, M.; Watanabe, H.; Nagai, M.; Hayashi, A.; Murashima, T. and Ono, N., *J. Chem. Soc., Perkin Trans. I*, **2000**, 4347.
8. Ito, S.; Murashima, T.; Uno, H. and Ono, N., *Chem. Commun*., **1998**, 1661.
9. Van Leusen, A. M.; Siderius, H.; Hoogenboom, B. E. and van Leusen, D., *Tetrahedron Lett.,* **1972**, 5337.
10. (a) Have, R. and van Leusen, A. M., *Tetrahedron*, **1998**, *54*, 1913. (b) Boelle, J.; Schneider, R.; Gerardin, P. and Loubinoux, B., *Synthesis*, **1997**, 1451. (c) Have, R.; Leusink, F. R. and van Leusen, A. M., *Synthesis*, **1996**, 871. (d) Disant, R.; Costar, R.; Massa, S. and Artisco, M., *Synth. Commun.,* **1995**, *25*, 819. (e) Leusink, F. R.; Have, R.; van Berg, K. J. and van Leusen, A. M., *J. Chem. Soc., Chem. Commun.,* **1992**, 1401. (f) Ono, N.; Muratani, E. and Ogawa, T., *J. Heterocyclic Chem.,* **1991**, *28*, 2053. (g) Van Leusen, D.; Flentge, E. and van Leusen, A. M., *Tetrahedron*, **1991**, *47*, 4639. (h) Magnus, P.; Danikeiwicz, W.; Katoh, T.; Huffman, J. C. and Folting, K., *J. Am. Chem. Soc.,* **1990**, *112*, 2465. (i) Aoyagi, K.; Toi, H.; Aoyama, Y. and Ogoshi, H., *Chem. Lett.,* **1988**, 1891. (j) Hoogenboom, B. E.; Oldenziel, O. H. and van Leusen, A. M., *Org. Synth*., **1988**, *6*, 987. (k) Magnus, P.; Gallagher, T.; Schultz, J.; Or, Y. S. and Magnus, P., *J. Am. Chem. Soc.,* **1987**, *109*, 2706. (l) Carter, P.; Fitzjohn, S.; Halazy, S. and Magnus, P., *J. Am. Chem. Soc.,* **1987**, *109*, 2711. (m) Van Leusen, A. M.; Siderius, H.; Hoogenboom, B. E. and van Leusen, D., *Tetrahedron Lett.,* **1972**, 5337.
11. Fumoto, Y.; Eguchi, T.; Uno, H and Ono, N., *J. Org. Chem.,* **1999**, *64*, 6518.
12. (a) Montalban, A. G.; Herrera, A. J.; Johannsen, J.; Beck, J.; Godet, T.; Vrettou, M.; White, A. J. P. and Williams, D. J., *Tetrahedron Lett.,* **2002**, *43*, 1751. (b) Finikova, O.; Cheprakov, A.; Beletskaya, I. and Vinogradov, S., *Chem. Commun.*, **2001**, 261. (c) Adamczyk, M.; Johnson, D. D. and Reddy, R. E., *Angew. Chem. Int. Ed. Engl.,* **1999**, *38*, 3537. (d) Kakiuchi, T.; Kinoshita, H. and Inomata, K., *Synlett,* **1999**, 901. (e) Uno, H.; Tanaka, M.; Inoue, T. and Ono, N., *Synthesis*, **1999**, 471. (f) Ono, N.; Miyagawa, H.; Ueta, T.; Ogawa, T. and Tani, H., *J. Chem. Soc., Perkin Trans I*, **1998**, 1595. (g) Knapp, S.; Vasudevan, J.; Emge, T. J.; Arison, B. H.; Potenza, J. A. and Schugar, H. J., *Angew. Chem. Int. Ed. Engl.,* **1998**, *37*, 2368. (h) Abel, Y.; Haake, E.; Haake, G.; Schmidt, W.; Struve, D.; Walter, A. and Montforts, F.-P., *Helv. Chim. Acta*, **1998**, *81*, 1978. (i) Adamczyk, M.; Fishpaugh, J. R.; Heuser, K. J.; Ramp, J. M.; Reddy, R. E. and Wong, M., *Tetrahedron*, **1998**, *54*, 3093. (j) Ito, S.; Murashima, T. and Ono, N., *J. Chem. Soc., Perkin Trans. I*, **1997**, 3161. (k) Vicente, M. G. H.; Tome, A. C.; Walter, A. and Caveleiro, J. A. S., *Tetrahedron Lett.,* **1997**, *38*, 3639. (l) Adamczyk, K. and Reddy, R. E., *Tetrahedron Lett.,* **1996**, *37*, 2325. (m) Adamczyk, K. and Reddy, R. E., *Tetrahedron*, **1996**, *52*, 14689. (n) Burns, D. H.; Jabara, C. S. and Burden, M. W., *Synth. Commun.,* **1995**, *25*, 379. (o) Adamczyk, K. and Reddy, R. E., *Tetrahedron Lett.,* **1995**, *36*, 7983. (p) Adamczyk, K. and Reddy, R. E., *Tetrahedron Lett.,* **1995**, *36*, 9121. (q) Fursho, Y.; Tsunoda, A. and Aida, T., *J. Chem. Soc., Perkin Trans. I*, **1995**, 183. (r) Ono, N.; Katayama, H.; Nishiyama, S. and Ogawa, T., *J. Heterocyclic Chem.,* **1994**, *31*, 707. (s) Lash, T. D.; Bellettini, J. R.; Bastian, J. A. and Couch, K. B., *Synthesis*, **1994**, 170. (t) Haake, G.; Struve, D. and Montforts, F.-P., *Tetrahedron Lett.*, **1994**, *35*, 9703. (u) Yuan, C. and Huang, W., *Synthesis*, **1993**, 473. (v) Ono, N.; Bougauchi, M. and Maruyama, K.*Tetrahedron Lett.,* **1992**, *33*, 1629. (w) Ono, N.; Kawamura, H. and Maruyama, K., *Bull. Chem. Soc. Jpn.,* **1989**, *62*, 3386. (x) Ono, N. and Maruyama, K., *Bull. Chem. Soc. Jpn.,* **1988**, *61*, 4470.

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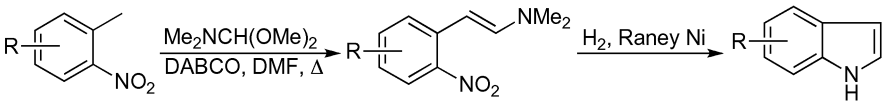
Batcho-Leimgruber Indole Synthesis

(Leimgruber-Batcho Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Batcho and Leimgruber in 1971.[1] It is a general, mild, two-step process for indole synthesis that consists of the condensation between substituted *o*-nitrotoluene and *N*,*N*-dimethylformamide dimethyl acetal to give an *o*-nitrophenylacetaldehyde enamine, and the subsequent reductive cyclization to furnish the indole. Therefore, this reaction is known as the Batcho-Leimgruber indole synthesis[2] or the Leimgruber-Batcho reaction.[3] The reagents used to reduce the nitro group can be Fe(II), hydrogen, dithionite,[4] and hydrazine hydrate-Raney Nickel,[5] etc.; and the reductive cyclization using the combination of hydrazine hydrate-Raney Nickel generally gives better yield than other reducing reagents reported.[6] This reaction is a particular useful method for synthesizing indoles with substituents at the benzene ring rather than at the heterocyclic pyrrole ring.

B. GENERAL REACTION SCHEME



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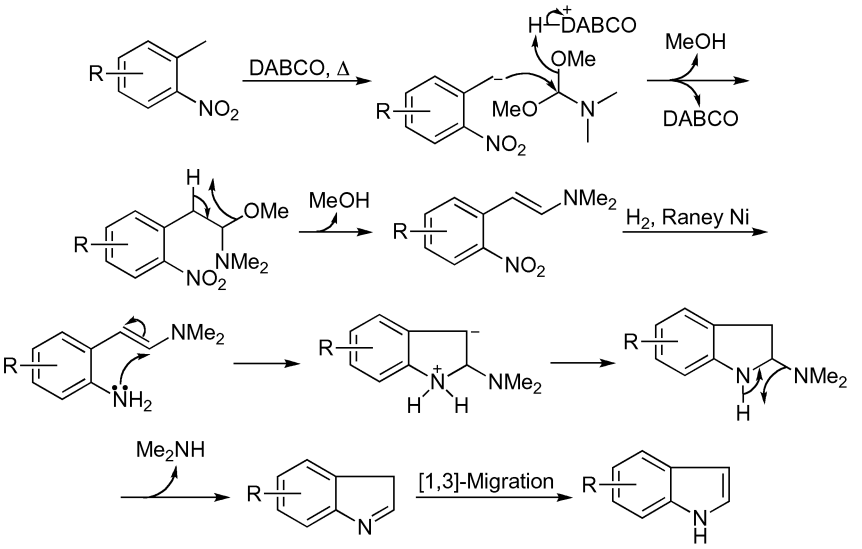
C. PROPOSED MECHANISMS

The *ortho* electron-withdrawing nitro group enables the proton abstraction from the methyl group, forming an anion that attacks the electrophilic carbon of the dimethylformamide dimethyl acetal to form the enamine. Upon the reduction of nitro group, ring closure occurs and eliminates dimethylamine to afford indole. The mechanism is illustrated below.



D. MODIFICATION

The modification of this reaction includes the variation of the applied base, the reducing reagents, and the available acetals of dimethylformamide. Some of the modifications are collected in the literature.[7]

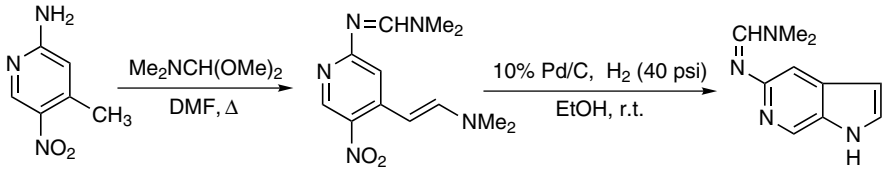
E. APPLICATIONS

This reaction has been applied for synthesizing indoles with substitutents in the benzene ring rather than the pyrrole moiety of the indole ring. In addition, this method has been adapted for synthesizing amides and esters via solid-support synthesis.[8]

F. RELATED REACTIONS

This reaction is closely related to the *Reissert Indole Synthesis*, which consists of a decarboxylation in the final step.[4]

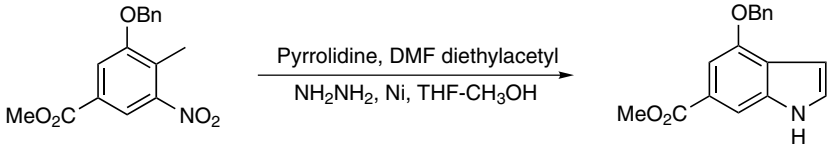
G. CITED EXPERIMENTAL EXAMPLES



Reference 7a.

To a solution of 10.0 g 2-amino-4-methyl-5-nitropyridine (65.3 mmol) in 90 mL DMF was added 87.0 mL *N*,*N*-dimethylformamide dimethyl acetal (653.0 mmol) in one portion. The deep red reaction mixture was heated at 110°C overnight and then cooled to room temperature and concentrated in vacuo to provide 17.7 g *N*,*N*-dimethyl-*N*-[4-(2-dimethylamino)vinyl)-5-nitropyridin-2-yl]formamidine as a red solid, in a yield of 100%. An analytical sample was purified by recrystallization from benzene, m.p. 149–151°C.

A mixture of 8.0 g *N*,*N*-dimethyl-*N*-[4-(2-dimethylamino)vinyl)-5-nitropyridin-2-yl]formamidine (30.4 mmol) and 2.0 g 10% palladium on carbon in 80 mL EtOH was hydrogenated at room temperature under 40 psi of hydrogen pressure for 24 h, and the mixture was filtered through Celite and concentrated in vacuo. The resulting dark brown foam was chromatographed (10–20% 2 M NH_3-MeOH/CH_2Cl_2) to provide 3.4 g *N*, *N*-dimethyl-*N*′-(1H-pyrrolo[2,3-c]pyridin-5-yl)formamidine, in a yield of 60%, m.p. 162–166°C.



Reference 9.

To a solution of 29.0 g methyl 3-(benzyloxy)-4-methyl-5-nitrobenzoate (0.0962 mol) in 60.0 mL DMF was added 12.0 mL freshly distilled pyrrolidine (0.144 mol) and 19.0 mL *N*, *N*-dimethylformamide dimethyl acetal (of 94% purity, 0.134 mol). The dark red colored reaction mixture was heated at 110°C for 3.5 h and concentrated on a rotary evaporator. Then 350 mL CH_3OH and 15 mL CH_2Cl_2 were added to the residue, and the solution was stored at 6°C for 12 h. The garnet colored precipitate was filtered and carefully washed with cold CH_3OH. Upon removal of the solvent under high vacuum, 23.24 g of a 10:1 mixture of pyrrolidino-styrene and *N*, *N*-dimethylamino-styrene was obtained, in a yield of 64%.

To a solution of 21.5 g of the nitrostyrenes in 300 mL of mixed solvent (THF/CH_3OH = 1:1) at room temperature was added 1 mL Raney nickel (50% slurry) at pH 9.0. Then 5 mL 55% hydrazine hydrate was added dropwise under stirring accompanied by vigorous evolution of gas. When the evolution of gas subsided (∼1.3 h), an additional 5 mL hydrazine hydrate was added, and the reaction mixture was warmed to 43°C. Over the next 3 h, two additional portions of hydrazine hydrate (4 mL, 1 mL) were added, and the reaction mixture was stirred until gas evolution ceased. The Raney nickel was filtered on a pad of Celite and washed with CH_2Cl_2. The filtrate was worked up. Flash chromatography of the residue

(EtOAc/hexanes = 3:7) afforded 14.06 g methyl 4-(benzyloxy)-1H-indole-6-carboxylate as a white solid, in a yield of 88%, m.p. 165.0–166.8°C.

Other references related to the Batcho-Leimgruber indole synthesis are cited in the literature.[10]

H. REFERENCES

1. (a) Batcho, A. D. and Leimgruber, W., *U.S. Pat*., **1971**, Aug. 5, 3732245. (b) Batcho, A. D. and Leimgruber, W., *German Pat*., **1971**, May 27, 2057840. (c) Batcho, A. D. and Leimgruber, W., *Chem. Abstr*., **1971**, *75*, P63605v. (d) Leimgruber, W. and Batcho, A. D., *Third International Congress of Heterocyclic Chemistry*, Sendai, Japan, **1971**, p. 462 [abstract].
2. (a) Xu, Y.-Z. and Chen, C. P., *J. Labelled Compd. & Radiopharm.,* **2006**, *49*, 897. (b) Fetter, J.; Bertha, F.; Poszavacz, L. and Simig, G., *J. Heterocycl. Chem.,* **2005**, *42*, 137. (c) Edin, M. and Grivas, S., *ARKIVOC,* **2001**, *2 (1)*, 144. (d) Edin, M. and Grivas, S., *ARKIVOC,* **2000**, *1 (1)*, 1. (e) Grivas, S., *Curr. Org. Chem.,* **2000**, *4*, 707. (f) Showalter, H. D. H.; Sun, L.; Sercel, A. D.; Winters, R. T.; Denny, W. A. and Palmer, B. D., *J. Org. Chem.,* **1996**, *61*, 1155. (g) Taylor, E. C.; Young, W. B. and Ward, C. C., *Tetrahedron Lett.,* **1993**, *34*, 4595. (h) Feldman, P. L. and Rapoport, H., *Synthesis,* **1986**, 735.
3. (a) Zhu, J. L.; Wong, H.; Zhang, Z. X.; Yin, Z. W.; Meanwell, N. A.; Kadow, J. F. and Wang, T., *Tetrahedron Lett.,* **2006**, *47*, 5653. (b) Watson, S. E., *Synth. Commun.,* **2005**, *35*, 2695. (c) Bentley, J. M.; Davidson, J. E.; Duncton, M.; Giles, P. R. and Pratt, R. M., *Synth. Commun.,* **2004**, *34*, 2295. (d) Siu, J.; Baxendale, I. R. and Ley, S. V., *Org. Biomol. Chem.,* **2004**, *2*, 160. (e) Söderberg, B. C. and Shriver, J. A., *J. Org. Chem.,* **1997**, *62*, 5838. (f) Toste, F. D. and Still, I. W. J., *Org. Pre. Proc. Int.,* **1995**, *27*, 576. (g) Stanetty, P. and Koller, H., *Arch. Pharm.,* **1992**, *325*, 433.
4. Pozikowski, A. P. and Greco, M. N., *J. Am. Chem. Soc.,* **1980**, *102*, 1165.
5. (a) Batcho, A. D. and Leimgruber, W., *Org. Synth*., **1984**, *63*, 214. (b) Maehr, H. and Smallheer, J. M., *J. Org. Chem.,* **1981**, *46*, 1752. (c) Dellar, G.; Djura, P. and Sargent, M. V., *J. Chem. Soc., Perkin Trans. I*, **1981**, 1679.
6. (a) Kozikowski, A. P.; Ishida, H. and Chen, Y.-Y., *J. Org. Chem.,* **1980**, *45*, 3350. (b) Ponticello, G. S. and Baldwin, J. J., *J. Org. Chem.,* **1979**, *44*, 4003.
7. (a) Filla, S. A.; Mathes, B. M.; Johnson, K. W.; Phebus, L. A.; Cohen, M. L.; Nelson, D. L.; Zgombick, J. M.; Erickson, J. A.; Schenck, K. W.; Wainscott, D. B.; Branchek, T. A. and Schaus, J. M., *J. Med. Chem.,* **2003**, *46*, 3060. (b) Schumacher, R. W. and Davidson, B. S., *Tetrahedron*, **1999**, *55*, 935. (c) Taylor, E. C. and Young, W. B., *J. Org. Chem.,* **1995**, *60*, 7947. (d) Toste, D. F. and Still, I. W. J., *OPPI Briefs,* **1995**, *27*, 576. (e) Moyer, M. P.; Shiurba, J. F. and Rapoport, H., *J. Org. Chem.,* **1986**, *51*, 5106. (f) Lloyd, D. H. and Nichols, D. E., *Tetrahedron Lett.,* **1983**, *24*, 4561.
8. Todd, M. H.; Oliver, S. F. and Abell, C., *Org. Lett*., **1999**, *1*, 1149
9. Mahboobi, S.; Teller, S.; Pongratz, H.; Hufsky, H.; Sellmer, A.; Botzki, A.; Uecker, A.; Beckers, T.; Baasner, S.; Schächtele, C.; Überall, F.; Kassack, M. U.; Dove, S. and Böhmer, F.-D., *J. Med. Chem.,* **2002**, *45*, 1002.
10. (a) Grivas, S., *Curr. Org. Chem*., **2000**, *4*, 707. (b) Gribble, G. W. *J. Chem. Soc., Perkin Trans. I,* **2000**, 1045. (c) Ziegler, F. E. and Belema, M., *J. Org. Chem.,* **1997**, *62*, 1083. (d) Ezquerra, J.; Pedregal, C.; Lamas, C.; Barluenga, J.; Pérez, M.; Garcia-Martin, M. A.; González, J. M. *J. Org. Chem*. **1996**, *61*, 5804. (e) Jacobs, R. T.; Brown, F. J.; Crank, L. A.; Aharony, D.; Buckner, C. K.; Kusner, E. J.; Kirkland, K. M. and Neilson, K. L., *J. Med. Chem.,* **1993**, *36*, 394. (f) Gribble,

G. W.; Saulnier, M. G.; Obaza-Nutaitis, J. A. and Ketcha, D. M., *J. Org. Chem.,* **1992**, *57*, 5891. (g) Mahadevan, I. and Rasmussen, M., *J. Heterocycl. Chem*. **1992**, *29*, 359. (h) Webb, R. R.; Venuti, M. C. and Eigenbrott, C., *J. Org. Chem.,* **1991**, *56*, 4706. (i) Cournoyer, R.; Evans, D. H.; Stroud, S. and Boggs, R., *J. Org. Chem.,* **1991**, *56*, 4576. (j) Batcho, A. D. and Leimgruber, W., *Org. Synth. Coll.,* **1990**, *7*, 34–41. (k) Bergman, J. and Sand, P., *Tetrahedron,* **1990**, *46*, 6085. (l) Rajeswari, S.; Drost, K. J. and Cava, M. P., *Heterocycles,* **1989**, *29*, 415. (m) Makosza, M.; Danikiewicz, W. and Wojciechowski, K., *Liebigs Ann. Chem*., **1988**, 203. (n) Lloyd, D. H. and Nichols, D. E., *J. Org. Chem*. **1986**, *51*, 4294. (o) Nrubaker, A. N. and Colley, M., *J. Med. Chem.,* **1986**, *29*, 1528. (p) Buchi, G.; Lee, G. C. M.; Yang, D. and Tannenbaum, S. R., *J. Am. Chem. Soc.,* **1986**, *108*, 4115. (q) Repke, D. B.; Grotjahn, D. B. and Shulging, A. T., *J. Med. Chem.,* **1985**, *28*, 892. (r) Clark, R. D. and Repke, D. B., *Heterocycles,* **1984**, *22*, 195. (s) Maehr, H. and Smallheer, J. M., *J. Org. Chem.,* **1984**, *49*, 1549. (t) Sundberg, R. J., *Pyrroles and Their Benzo Derivatives* in *Comprehensive Heterocyclic Chemistry*, ed. Katritzky, A. R. and Rees, C. W., Pergamon, New York, **1984**, *4*. 313–376. (u) Cannon, J. G.; Lee, T.; Ilhan, M.; Koons, J. and Long, J. P., *J. Med. Chem.*, **1984**, *27*, 386. (v) Kline, T. B.; Benington, F.; Morin, R. D. and Beaton, J. M., *J. Med. Chem.,* **1982**, *25*, 908. (w) Kozikowski, A. P.; Greco, M. N. and Springert, J. P., *J. Am. Chem. Soc.,* **1982**, *104*, 7622. (x) Kozikowski, A. P., *Heterocycles* **1981**, *16,* 267. (y) Somei, M.; Inoue, S.; Tokutake, S.; Yamada, F. and Kaneko, C., *Chem. Pharm. Bull*., **1981**, *29*, 726. (z) Maehr, H.; Smallheer, J.; Blount, J. F. and Todaro, L. J., *J. Org. Chem.,* **1981**, *46*, 5019. (aa) Kozikowski, A. P.; Ishida, H. and Chen, Y.-Y., *J. Org. Chem.,* **1980**, *45*, 3352. (bb) Kozikowski, A. P.; Ishida, H. and Chen, Y. Y., *J. Org. Chem.,* **1980**, *45*, 2236. (cc) Flaugh, M. E.; Crowell, T. A.; Clemens, J. A. and Sawyer, B. D., *J. Med. Chem.,* **1979**, *22*, 63. (dd) Hengartner, U.; Valentine, D.; Johnson, K. K.; Larscheid, M. E.; Pigott, F.; Scheidl, F.; Scott, J. W.; Sun, R. C.; Townsend, J. M. and Williams, T. H., *J. Org. Chem.,* **1979**, *44*, 3741. (ee) Hengartner, U.; Batcho, A. D.; Blount, J. F.; Leimgruber, W.; Larscheid, M. E. and Scott, J. W., *J. Org. Chem.,* **1979**, *44*, 3748. (ff) Batcho, A. D. and Leimgruber, W., *Chem. Abstr.,* **1977**, *86*, 29624. (gg) Gassman, P. G. and Schenk, W. N., *J. Org. Chem.,* **1977**, *42,* 3240. (hh) Bennington, F.; Morin, R. D. and Bradley, R. J., *J. Heterocycl. Chem.,* **1976**, *13*, 749. (ii) Battersby, A. R.; McDonald, E.; Wurziger, H. K. W. and James, K. J., *J. Chem. Soc., Chem. Commun*., **1975**, 493. (jj) Garcia, E. E. and Fryer, R. I., *J. Heterocycl. Chem.,* **1974**, *11,* 219.

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Baudisch Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Baudisch in 1939.[1] It is the synthesis of *o*-nitrosophenols from benzene (or its derivatives), hydroxylamine, and hydrogen peroxide in the presence of copper salts and is generally known as the Baudisch reaction.[2] In contrast to conventional nitrosation of phenol with HNO_2, which always leads to *p*-nitrosophenols, the Baudisch reaction proceeds via the simultaneous introduction of the nitroso and hydroxyl group into the adjacent position on the aromatic nucleus to form reddish violet copper salts.[3] Besides the copper salts, other metal salts (Ni^{2+}, Fe^{2+}, etc) can also be applied to this reaction.[4] The free *o*-nitrosophenols, due to the formation of intramolecular hydrogen bonding, is volatile[2e] and can be obtained via acidifying the complexes with HCl followed by extraction in petroleum ether.[5] It is known that the presence of copper salts is necessary to stabilize the nitrosyl radical to form stable complexes and to prevent the further oxidation of *o*-nitrosophenols to *o*-nitrophenols or the rearrangement to *p*-quinone monoximes.[6] If the reaction is applied to phenols instead of nonhydroxyl benzene derivatives, similar products are obtained with higher yields in a much shorter reaction period, because the higher solubility of phenols in water.[7] However, the Baudisch reaction is not applicable to aromatic aldehydes and primary amines because the aldehyde group will react with the nitrosyl radical or hydroxylamine directly to form hydroxamic acid or oxime (i.e., the *Angeli Remini Reaction*), and primary amine will react with the nitrosyl radical to form diazo compounds.[5] Some of the aromatic nitroso compounds have shown some antiviral activity, such as against HIV.[8]

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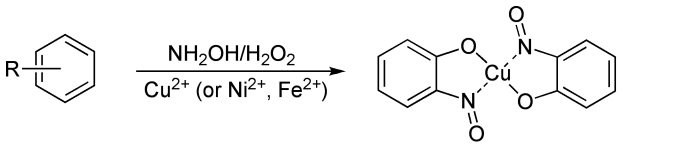
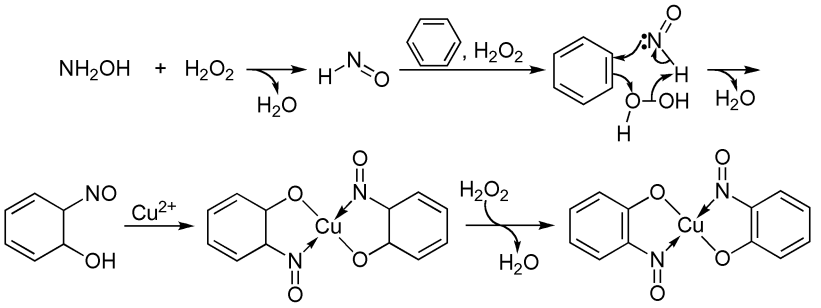
B. GENERAL REACTION SCHEME



(R = alkyl, phenyl, Cl, Br, NO_2, etc.)

C. PROPOSED MECHANISMS

Baudisch[9] and Cronheim[6a] postulated that some of the cupric ion which is reduced to cuprous ion, which forms the complex $[Cu(NO)]^-$ with nitrosyl radicals that were generated via the prior oxidation-reduction reactions among the various reagents. Then this complex attacks the aromatic ring, leading to nitrosation, followed by the hydroxylation adjacent to the position of nitrosation. However, this mechanism has been questioned.[2e] A tentative mechanism is thus proposed here.



D. MODIFICATION

N/A

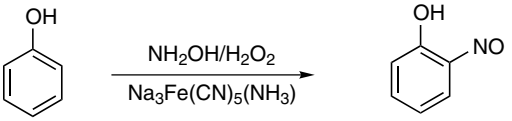
E. APPLICATIONS

This reaction has been used to prepare more than 50 *o*-nitrosophenols.

F. RELATED REACTIONS

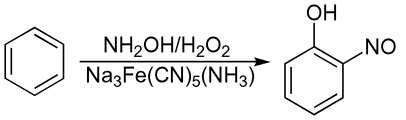
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 2e.

A total of 4 mL 30% hydrogen peroxide was added to a solution of 1 g phenol, 4 g hydroxylamine hydrochloride, and 2 g sodium pentacyanoaminneferrate(II) in 200 mL water and 60 mL petroleum ether (b.p. 30–70°C). The mixture was stirred at room temperature for 1 h, the ether layer was separated, and the aqueous layer was extracted with petroleum ether repeatedly until the green color was scarcely found in the ether layer. The petroleum ether extracts of *o*-nitrosophenol were transferred to a flask, which was connected to an empty flask by means of a T-tube fitted with a glass stopcock. After air was pumped out through the stopcock, the empty flask was cooled with an ice-salt mixture, and the flask containing the extract was warmed with hot water. *o*-Nitrosophenol, which was volatilized with the petroleum ether, was condensed in the ice-cooled flask.



Reference 10.

Sodium pentacyano-ammine-ferroate (2 g) was dissolved in 100 mL water; then 25 mL benzene and 50 mL ligroin (a kind of petroleum ether) were added, and the mixture was cooled with ice water. Then 2 g hydroxylamine chloride was added (color changes from brown to grass green), followed by 4 mL Merck superoxol (color changes from grass green to deep brownish violet). After the mixture was shaken violently for 1 h, the color of the benzene-ligroin layer was deep green, due to the formation of large amounts of *o*-nitrosophenol. The green benzene-ligroin layer was separated, washed with ice water, and shaken with a dilute copper sulfate solution; a deep red, water-soluble *o*-nitrosophenol copper salt was formed while the benzene-ligroin became entirely colorless and was used for further extraction of the aqueous layer. After undergoing shaking for 1 or 2 h, the deep green benzene-ligroin was again separated and *o*-nitrosophenol was converted into the red copper salt. The copper salt solutions were combined and acidified in presence of petroleum ether with hydrochloric acid. The deep green petroleum ether was washed with ice water free from excess acid. The solution, kept away from light in the cold, lasts for weeks without any change.

Other references related to the Baudisch reaction are cited in the literature.[11]

H. REFERENCES

1. (a) Baudisch, O., *Naturwissenschaften*, **1939**, *27*, 768. (b) Baudisch, O. and Smith, S. H., *Naturwissenschaften*, **1939**, *27*, 769.
2. (a) Maruyama, K. and Tanimoto, I., *Bull. Chem. Soc. Jpn.,* **1971**, *44*, 3120. (b) Tanimoto, I., *Bull. Chem. Soc. Jpn.,* **1970**, *43*, 1182. (c) Tanimoto, I., *Bull. Chem. Soc. Jpn.,* **1970**, *43*, 139. (d) Bartos, J., *Ann. Pharm. Fr.,* **1969**, *27*, 759. (e) Maruyama, K.; Tanimoto, I. and Goto, R., *J. Org. Chem.,* **1967**, *32*, 2516. (f) Maruyama, K.; Tanimoto, I. and Goto, R., *Tetrahedron Lett.,* **1966**, 5889.
3. Kukushkin, V. Y. and Pombeiro, A. J. L., *Coord. Chem. Rev*., **1999**, *181*, 147.
4. Konecny, J. O., *J. Am. Chem. Soc*., **1955**, *77*, 5748.
5. Cronheim, G., *J. Org. Chem.,* **1947**, *12*, 7.
6. (a) Cronheim, G., *J. Org. Chem*., **1947**, *12*, 1. (b) Cronheim, G., *J. Org. Chem*., **1947**, *12*, 20.

7. Charalambous, J.; Thomas, T. A.; Howarth, O. and Whiteley, R. N., *Polyhedron*, **1996**, *15*, 3851.
8. Rice, W. G.; Schaeffer, C. A.; Harten, B.; Villinger, F.; South, T. L.; Summers, M. F.; Henderson, L. E.; Bess, J. W. Jr.; Arthur, L. O.; McDougal, J. S.; Orloff, S. L.; Mendeleyev, J. and Kun, E., *Nature,* **1993**, *361*, 473.
9. (a) Baudisch, O., *Arch. Biochem*., **1944**, *5*, 301. (b) Baudisch, O., *Science*, **1940**, *92*, 336.
10. Baudisch, O., *J. Am. Chem. Soc.,* **1941**, *63*, 622.
11. (a) Ishikawa, T.; Watanabe, T.; Tanigawa, H.; Saito, T.; Kotake, K.-I.; Ohashi, Y. and Ishii, H., *J. Org. Chem.,* **1996**, *61,* 2774. (b) Cone, M. C.; Melville, C. R.; Carney, J. R.; Gore, M. P. and Gould, S. J., *Tetrahedron,* **1995**, *51*, 3095. (c) Coombes, R. G., "Nitro and Nitroso Compounds" in *Comprehensive Organic Chemistry*, ed. Barton, D. and Ollis, W. D., Pergamon Press, Oxford, **1979**, *2*, pp. 305–381. (d) Benson, W. R., and Gajan, R. J., *J. Org. Chem*., **1966**, *31*, 2498. (e) Perry, M. H. and Serfass, E. J., *Anal. Chem.,* **1950**, *22*, 565. (f) Audisch, O., *Am. Scientist,* **1943**, *31*, 211. (g) Cronheim, G. and Wink, W., *Ind. Eng. Chem., Anal. Ed.,* **1942**,*14*, 447. (h) Baudisch, O., *J. Am. Chem. Soc.,* **1941**, *63,* 672.

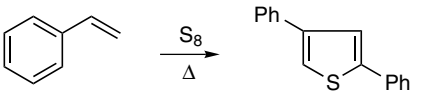
60

Baumann-Fromm Thiophene Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Baumann and Fromm in 1891.[1] It is the synthesis of 2,4-diarylthiophenes via the reaction between substituted styrenes and sulfur. Besides the major product of 2,4-diarylthiophene, some minor 2,5-diarylthiophenes are also found in this reaction.[2] Similarly, butadiynes can react with hydrogen sulfide to afford thiophenes.[3] However, at 600°C in the presence of a ferrous sulfide-alumina catalyst, styrene reacted with hydrogen sulfide to give 60% benzothiophene.[4] On the other hand, thiophenes can also be prepared via the reaction between ethylbenzene and sulfur,[5] acetophene and hydrogen sulfide,[6] or 1,4-diketones and phosphorus trisulfide (or phosphorus pentasulfide).[7] The preparation of 2,4-diarylthiophene has been reviewed.[8]

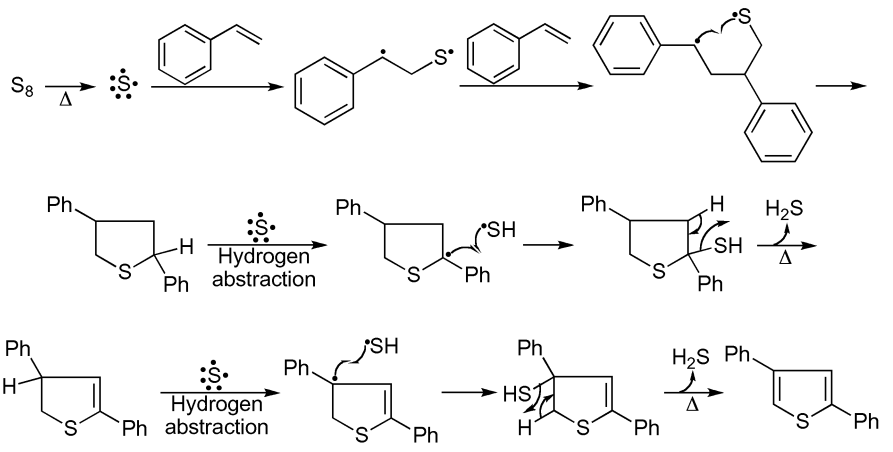
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is believed that this reaction proceeds through a radical mechanism, similar to the vulcanization of rubber.[5] A tentative mechanism is illustrated here.

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang



D. MODIFICATION

This reaction has been modified using different starting materials, such as ethylbenzene[5] and acetophenone.[6]

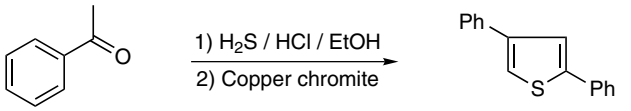
E. APPLICATIONS

This reaction has been used to prepare 2,4-diarylthiophene.

F. RELATED REACTIONS

This reaction is related to the *Bogert-Herrera Reaction*[8] and *Volhard-Erdmann Cyclization*.[9]

G. CITED EXPERIMENTAL EXAMPLES

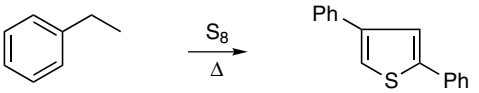


Reference 10.

Acetophenone (40 g) was dissolved in 300 mL absolute alcohol and cooled to 0°C in an ice salt bath. Dry hydrogen chloride was passed in for a few minutes until the rate of gas influx could be regulated, and then hydrogen sulfide was also passed in at a slow rate. Approximately 140 g dry hydrogen chloride (the amount calculated to saturate the alcohol) was passed into the solution over a period of 6 h during which time the reaction flask was kept in the ice-salt bath. When all the hydrogen chloride was used, the bath was

allowed to come to room temperature, while hydrogen sulfide was passed continuously into the flask for 8 h longer. About 3 h later, white crystals began to form in the flask, and a purple resin precipitated. After 14 h, the gas-inlet tubes were removed, and the flask was stored in the refrigerator overnight. The white crystals were stirred up and filtered from the mother liquor, leaving the purple resin of thioacetophenone in the flask. The crystals of "anhydroacetophenone disulfide" were washed once with alcohol and dried. The crude product melted from 106–109°C. The yield was 23.5 g, or 57% of the theoretical level. After two recrystallizations from acetone, the product was obtained in white hexagonal bars, m. p. 107–108°C (corrected).

"Anhydroacetophenone disulfide" (3 g) was dissolved in 35 mL dry xylene, and 10 g copper chromite powder was added, and the mixture was refluxed. No hydrogen sulfide was evolved during the course of 3 h. At the end of this time, the mixture was cooled and filtered. The residual catalyst was washed thoroughly with xylene, and the combined washings and filtrate were distilled under a water-pump vacuum to remove xylene. The brown residue solidified on cooling. It was dissolved in 80 mL boiling methanol and treated with norite. Upon cooling, white flaky crystals deposited. These were recrystallized from methanol and dried, and 1.5 g 2,4-diphenylthiophene was obtained, in a yield of 83%.



Reference 11.

Ethylbenzene (4.1 mol) and sulfur (6.2 mol) were placed in a 800 mL bomb, and heated to 340–350°C for 40 min, at which time a small leak in the bomb head developed and heating was stopped. Hydrogen sulfide at high pressures seemed to attack the brass threads of the valve very rapidly. After releasing 78 g hydrogen sulfide, the heating was continued for a second time until the leaking happened again. A total of 378 g liquid containing a small amount of solid was removed from the bomb. The solid was filtered off, and the liquid was distilled. The residue in the distilling flask, along with the solid filtered from the original reaction mixture, was extracted with hot alcohol; this solution on cooling deposited 86.5 g 2,4-diphenylthiophene as a light yellow crystalline substance, which on recrystallization had a melting point of 119.5–120.5°C.

Other references related to the Baumann-Fromm thiophene synthesis are cited in the literature.[12]

H. REFERENCES

1. (a) Baumann, E. and Fromm, E., *Ber.,* **1891**, *24*, 1456. (b) Baumann, E. and Fromm, E., *Ber.,* **1895**, *28*, 890. (c) Baumann, E. and Fromm, E., *Ber*., **1895**, *28*, 895. (d) Baumann, E. and Fromm, E., *Ber*., **1895**, *28*, 907.
2. Mayo, F. R., *J. Am. Chem. Soc.,* **1968**, *90*, 1289.
3. Schulte, K. E.; Reisch, J. and Hörner, L., *Ber.,* **1962**, *95*, 1943.
4. Moore, R. J. and Greensfelder, B. S., *J. Am. Chem. Soc.,* **1947**, *69*, 2008.
5. Horton, A. W., *J. Org. Chem.,* **1949**, *14*, 761.

6. Campaigne, E.; Reid, W. B. and Pera, J. D., *J. Org. Chem.,* **1959**, *24*, 1229.
7. Paal, C., *Ber.,* **1885**, *18*, 2251.
8. Bogert, M. T. and Hcrrera. P. P., *J. Am. Chem. Soc.,* **1923**, *45*, 238.
9. Volhard, J. and Erdmann, H., *Ber.,* **1885**, *18*, 454.
10. Campaigne, E., *J. Am. Chem. Soc.,* **1944**, *66*, 684.
11. Glass, H. B. and Reid, E. E., *J. Am. Chem. Soc.,* **1929**, *51*, 3428.
12. (a) Pasto, D. J. and Servs, M. P., *J. Org. Chem.,* **1962**, *27*, 4665. (b) Schmitt, J. and Lespagnol, A., *Bull. Soc. Chim. Fr.,* **1950**, 459. (c) Emerson, W. S., *Chem. Rev*., **1949**, *49*, 183. (d) Demerseman, P.; Buu-Hoi, Ng.; Royer, R. and Cheutin, A., *J. Chem. Soc*., **1954**, 2720. (e) Meyer, K. H. and Hohenemser, W., *Helv. Chim. Acta*, **1935**, *18*, 1061. (f) Baumann, E. and Fromm, E., *Ber*., **1897**, *30*, 110.

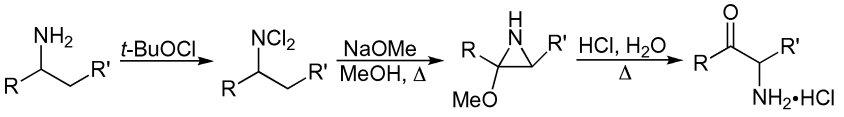
61

Baumgarten α-Amino Ketone Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Baumgarten in 1954.[1] It is the synthesis of α-amino ketones from the rearrangement of *N*,*N*-dichloro-*sec*-alkylamines by means of the treatment of sodium methoxide.[2] *N*,*N*-Dichloro-*sec*-alkylamines were initially prepared via the chlorination of *sec*-alkylamine by chlorine.[1]

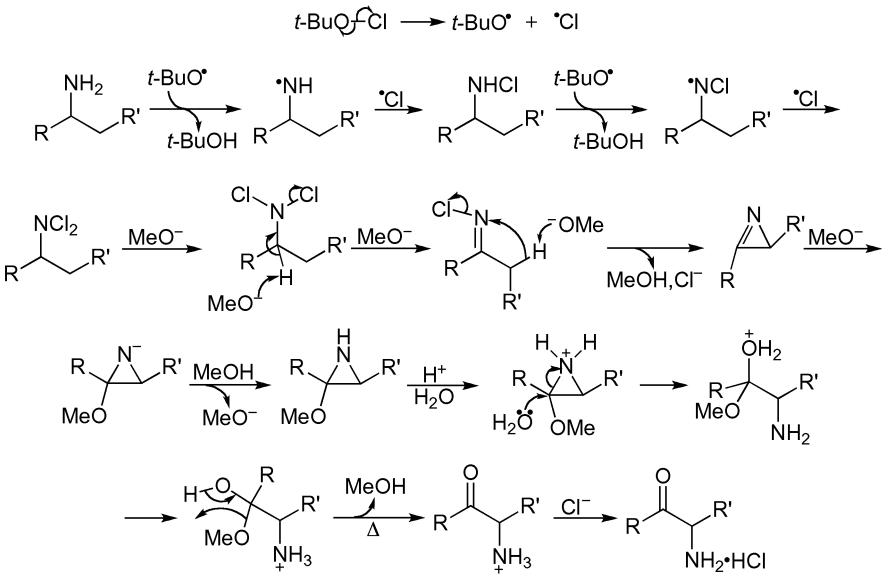
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is believed that the reaction proceeds via *N*-chloro-imine intermediate, as illustrated here.

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang



D. MODIFICATION

It has been modified for preparing α-amino ketones from the reaction between more generally available nitriles and a Gringard reagent.[2] In addition, this reaction has been applied to the synthesis of α-amino acids.[2b]

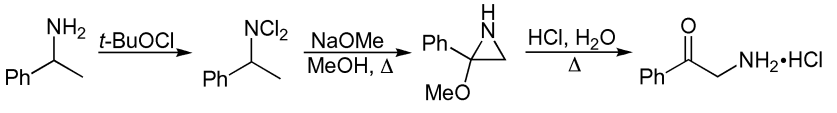
E. APPLICATIONS

It is a specific method to synthesize α-amino ketones and α-amino acids.

F. RELATED REACTIONS

N/A

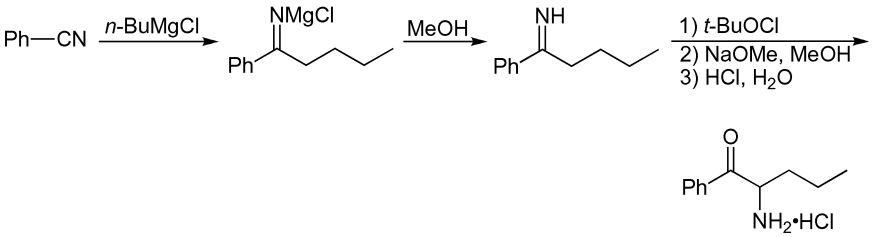
G. CITED EXPERIMENTAL EXAMPLES



Reference 3.

In a thoroughly dry 500-mL three-necked round-bottomed flask fitted with a mechanical stirrer, dropping funnel, and a Y-tube containing a calcium chloride drying tube and a thermometer were placed 24.2 g α-phenylethylamine (26 mL, 0.20 mol) and 50 mL dry

benzene. The solution was cooled in an ice-salt bath to 5°C, and a solution of 44.5 g (50 mL, 0.41 mol) of *tert*-butyl hypochlorite in 50 mL dry benzene was added at such a rate as to maintain the temperature below 10°C. After the addition of the *tert*-butyl hypochlorite solution was complete, the reaction mixture was stirred at room temperature for 1–4 h. The Y-tube was replaced by a reflux condenser fitted with a calcium chloride drying tube, and a freshly prepared solution of 13.8 g (0.60 mol) sodium in 140 mL anhydrous methanol was added to the benzene solution of *N*,*N*-dichloro-α-phenylethylamine at such a rate as to maintain gentle reflux. After the addition of the sodium methoxide was complete, the reaction mixture was refluxed until a negative test was obtained with acidified starch-iodide paper (45–70 min). The reaction mixture was cooled in an ice water bath, and the precipitated NaCl was removed by filtration through a Büchner funnel. The filter cake was washed with three 25-mL portions of dry benzene. The combined filtrates were added, slowly with shaking or stirring, to 150 mL 2 *N* HCl contained in a 1-L beaker. The layers were separated, and the benzene layer was extracted with three 50-mL portions of 2 *N*HCl. The combined acid extracts were washed twice with 50-mL portions of ether. The ether extracts were discarded. The pale amber to yellow aqueous solution was evaporated to dryness at a temperature not greater than 40°C. The residue was transferred to a 1-L round-bottomed flask fitted with a reflux condenser to which was added 400 mL isopropyl alcohol-hydrochloric acid solution. The mixture was refluxed for at least 30 min and was filtered hot through a Büchner funnel. The residual solid was returned to the flask and extracted in the same manner with a 150-mL portion of the isopropyl alcohol-hydrochloric acid solution. The solid residue NaCl was discarded. The two extracts were cooled separately in the refrigerator overnight and then filtered on a Büchner funnel. The nearly colorless crystals were washed on the filter with two 50-mL portions of dry ether. Each of the filtrates was diluted with an equal volume of dry ether (400 mL and 150 mL, respectively) and allowed to stand in the refrigerator overnight. From these diluted filtrates additional crops of crystals were collected. The combined yield of the three to four crops of phenacylamine hydrochloride was 18.9–24.8 g (55–72%), m.p. 185–186°C (dec.). Normally the product is sufficiently pure for use without further purification; however, the product may be recrystallized from an isopropyl alcohol-hydrochloric acid solution, using 100 mL of the solution for each 6 g of compound. The recovery is ~5.5 g per 6.0 g of crude product.



Reference 2a.

Only the procedure of making *n*-butyl phenyl ketimine is given, the rest of procedures are similar to the first example.

To a solution of 84 mL 3 M *n*-butylmagnesium chloride (0.25 mol) and 150 mL dry ether, was added a solution of 10.3 mL benzonitrile (0.1 mol) in 10 mL of dry ether dropwise at such a rate as to maintain a slight reflux. After the addition was complete, the gray solution containing a precipitate was refluxed for 10 h in an oil bath and cooled in an ice bath. To this

cooled solution, 60 mL dry methanol was added dropwise, during which the first portion was added slowly and cautiously because the reaction was quite vigorous. After the addition was complete, the reaction mixture containing a finely divided white precipitate was stirred at room temperature for 20 min. The mixture was then cooled in ice and filtered by suction through a 0.25-in. layer of Celite in a Büchner funnel. The filter cake was washed with three 25-mL portions of dry ether, which were added to the filtrate. The ether was evaporated, and to the remaining yellowish residue was added 80 mL dry benzene. Usually a small amount of precipitate either remained after evaporation or formed on addition of the benzene, and this was removed by filtering the mixture through a Büchner funnel into a tarred flask. The evaporator flask was washed with small portions of dry benzene for a total of 30 mL. After weighing the flask plus filtrate and washings, weighed samples of the solution were taken for analysis. The apparent yield of the *n*-butyl phenyl ketimine was 70–86%.

Other references related to the Baumgarten α-amino ketone synthesis are cited in the literature.[4]

H. REFERENCES

1. Baumgarten, H. E. and Bower, F. A., *J. Am. Chem. Soc.,* **1954**, *76*, 4561.
2. (a) Baumgarten, H. E.; Petersen, J. M. and Wolf, D. C., *J. Org. Chem.,* **1963**, *28*, 2369. (b) Baumgarten, H. E.; Dirks, J. E.; Petersen, J. M. and Wolf, D. C., *J. Am. Chem. Soc.,* **1960**, *82*, 4422.
3. Baumgarten, H. E. and Petersen, J. M., *Org. Synth. Coll.* **1973**, *5*, 909.
4. Baumgarten, H. E. and Petersen, J. M., *J. Am. Chem. Soc.,* **1960**, *82*, 459.

62

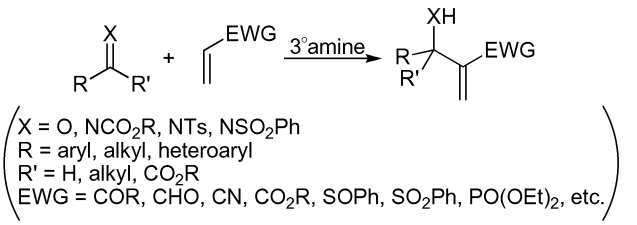
Baylis-Hillman Reaction
(Morita-Baylis-Hillman Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

Although the Baylis-Hillman reaction[1] has been primarily credited to Baylis and Hillman from Celanese Corporation, from their initial work patented in 1972,[2] the initial discovery of this reaction has roots back to 1968, when Morita et al. reported a tricyclohexylphosphine catalyzed reaction between an aldehyde and acrylic compounds.[3] Therefore, this reaction is also widely referred to as the Morita-Baylis-Hillman reaction.[4] The Baylis-Hillman reaction is essentially a three-component reaction involving the coupling of the α-position of activated alkenes with carbon electrophiles (i.e., aldehydes) under the influence of a catalyst/catalyst system, with the characteristics of atom efficiency and the formation of dense functionality. Likewise, the corresponding reaction between alkenes and imines under similar conditions is referred to as the aza-Baylis-Hillman reaction[5] or aza-Morita-Baylis-Hillman reaction.[6] In a few cases, this reaction is also cited as Morita reaction,[7] Morita-Baylis-Hillman alkylation,[8] and Morita-Baylis-Hillman cyclization.[9] In this reaction, the activated alkenes include acrylonitrile, acrolein, acrylates, and α,β-unsaturated ketones. The catalysts applied include tricyclohexylphosphine (the original Morita condition),[3] a variety of tertiary amines (1,4-diazabicyclo[2.2.2]octane (DABCO, the standard amine catalyst), 3-hydroxyquinuclidine (an optimal catalyst), DBU 3-quinuclidone, quinuclidine, and indolizine),[10] and chalcogenides.[4ij,11] Unfortunately, this reaction also has some drawbacks, such as the slow reaction rate (up to weeks in an extreme case),[12] being limited to electrophilic α,β-unsaturated carbonyl compounds; and almost exclusively occuring in the reactions involving β-unsubstituted α,β-unsaturated carbonyl compounds and cyclic enones.[13] Therefore, different measures have been taken to optimize this reaction, including the application of activated alkenes,[14] reactive electrophiles,[15] aqueous medium,[16] high pressure,[17] microwave irradiation,[18] and Lewis acids.[19] This reaction has been extensively reviewed.[10c,10g,20]

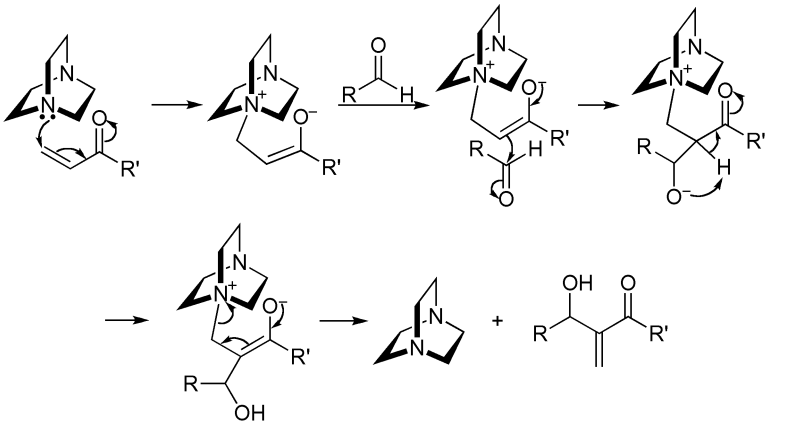
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The accepted mechanism is similar to the one originally proposed by Morita (as illustrated here) and is supported mainly by kinetic studies.[14c,21] However, none of the zwitterionic intermediates shown in the mechanism has been isolated to date.



D. MODIFICATION

This reaction has been extensively studied recently and modified in many aspects compared to the original reaction conditions, including the application of reactive alkenes, electrophiles, aqueous medium, high pressure and Lewis acid catalysts.

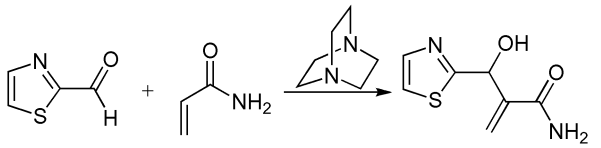
E. APPLICATIONS

Owing to its atom efficiency and the generation of dense functionality, this reaction has wide applications in producing of variety a molecules. Some of the Baylis-Hillman adducts have shown promising biological activities.[22]

F. RELATED REACTIONS

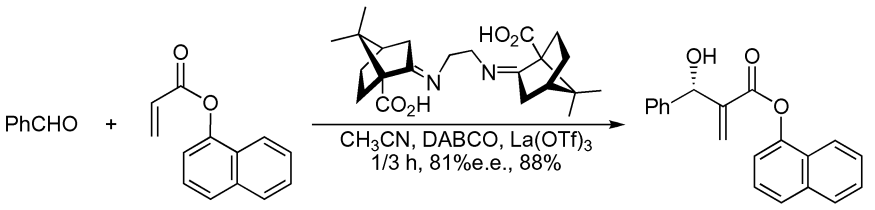
N/A

G. CITED EXPERIMENTAL EXAMPLES



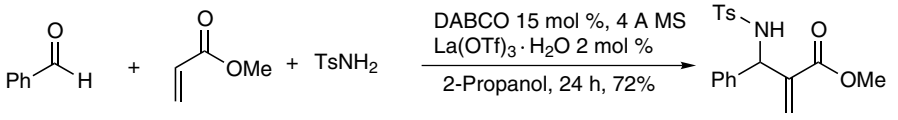
Reference 23.

A clear solution of 2.0 mmol aldehyde and 2.0 mmol acrylamide in 5 mL 1,4-dioxane was slowly charged with 5 mL deionized water under stirring. The homogeneous reaction mixture was stirred at ambient temperature in the presence of 1 Eq DABCO, and the reaction progress was monitored by TLC. Upon completion or as indicated, the reaction mixture was partitioned with 250 mL ethyl acetate and 20 mL brine. The aqueous layer was extracted with chloroform (3×60 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate and/or methanol to give the desired product, in a yield of 99%. (*Note*: Acrylamide was considered to be unreactive in the Baylis-Hillman reaction.[20b])



Reference 19a

To a solution of 12 mg chiral ligand (0.03 mmol) in 2.6 mL CH_3CN was added 9 mg $La(OTf)_3$ (0.015 mmol) at room temperature under a nitrogen atmosphere. After stirring for 10 min, 54 mg benzaldehyde (0.51 mmol), 0.10 g α-naphthyl acrylate (0.51 mmol), and 17 mg DABCO (0.15 mmol) were added sequentially. The resulting mixture was stirred for 20 min and the reaction was quenched with 5 mL H_2O. The mixture was extracted with 10 mL CH_2Cl_2, and the layers were separated. The organic layer was washed with 10 mL brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel using 8:1 hexane/EtOAc as an eluent to give 0.13 g alcohol as a white solid, in a yield of 88%. The enantiomeric ratios were determined as 81% e.e. by HPLC analyses using a chiral column.



Reference 24a.

In a dry flask were added 855 mg tosylamide (5 mmol), 84 mg DABCO (0.75 mmol), and 58.5 mg $La(OTf)_3 \cdot H_2O$ (0.1 mmol) together with 900 mg 4-Å molecular sieves. Then 2.5 mL *iso*-PrOH, 505 μL benzaldehyde (5 mmol), and 450 μL methyl acrylate (5 mmol) were added, and the reaction mixture was stirred for 48 h at ambient temperature. The mixture was filtered through a thin layer of Celite, which was rinsed three times with 10 mL *iso*-PrOH. The solvent was evaporated, and to the crude mixture were added 25 mL methanol and 10 mL 1 M sulfuric acid. The solution was stirred for 1 h, and then methanol was evaporated. The remaining acidic solution was diluted with water and extracted with dichloromethane (3×30 mL). The organic phase was then successively washed with saturated $NaHCO_3$, 1 M NaOH, water, and saturated NaCl solution and dried over Na_2SO_4. Evaporation of the solvent gave 1.38 g pure methyl α-methylene-β-[(*p*-toluenesulfonyl)-amino]-3-phenylpropionate as a white crystalline material, in a yield of 80%, m.p. 76–77°C.

Other references related to the Baylis-Hillman reaction are cited in the literature.[25,26]

H. REFERENCES

1. (a) Zhao, S.-H.; Zhao, M.-G.; Zhang, H.-R. and Chen, Z.-B., *Youji Huaxue*, **2007**, *27*, 322. (b) Kang, S.-Y.; Park, K.-S.; Kim, J. Y.; Chong, Y. H. and Choo, H., *Bull. Korean Chem. Soc.*, **2007**, *28*, 179. (c) Davies, H. J.; Ruda, A. M. and Tomkinson, N. C. O., *Tetrahedron Lett.*, **2007**, *48*, 1461. (d) Shah, B. A.; Taneja, S. C.; Sethi, V. K.; Gupta, P.; Andotra, S. S.; Chimni, S. S. and Qazi, G. N., *Tetrahedron Lett.*, **2007**, *48*, 955. (e) Marcucci, E.; Martelli, G.; Orena, M. and Rinaldi, S., *Monatsh. Chem.*, **2007**, *138*, 27. (f) Park, K.-S.; Kim, J. Y.; Choo, H. and Chong, Y. H., *Synlett*, **2007**, 395. (g) Chen, P.-Y.; Chen, H.-M.; Chen, L.-Y.; Tzeng, J.-Y.; Tsai, J.-C.; Chi, P.-C.; Li, S.-R. and Wang, E.-C., *Tetrahedron*, **2007**, *63*, 2824. (h) Santos, L. S.; Da Silveira Neto, B. A.; Consorti, C. S.; Pavam, C. H.; Almeida, W. P.; Coelho, F.; Dupont, J. and Eberlin, M. N., *J. Phys. Org. Chem.*, **2006**, *19*, 731. (i) de Souza, R. O. M. A.; Fregadolli, P. H.; Goncalves, K. M.; Sequeira, L. C.; Pereira, V. L. P.; Filho, L. C.; Esteves, P. M.; Vasconcellos, M. L. A. A. and Antunes, O. A. C., *Lett. Org. Chem.*, **2006**, *3*, 936. (j) Song, H. S.; Song, Y. S. and Lee, K.-J., *J. Heterocycl. Chem.*, **2006**, *43*, 1533. (k) Xu, J. Y.; Guan, Y. Y.; Yang, S. H.; Ng, Y. R.; Peh, G. R. and Tan, C.-H., *Chem. Asian J.*, **2006**, *1*, 724. (l) Trifonov, V. V.; Goncharov, V. I. and Aksenov, A. V., *Chem. Heterocycl. Compd.*, **2006**, *42*, 955. (m) Nenajdenko, V. G.; Druzhinin, S. V. and Balenkova, E. S., *Mendeleev Commun.*, **2006**, 273. (n) Majhi, T. P.; Neogi, A.; Ghosh, S.; Mukherjee, A. K. and Chattopadhyay, P., *Tetrahedron*, **2006**, *62*, 12003. (o) Vasbinder, M. M.; Imbriglio, J. E. and Miller, S. J., *Tetrahedron*, **2006**, *62*, 11450. (p) Nakano, A.; Takahashi, K.; Ishihara, J. and Hatakeyama, S., *Org. Lett.*, **2006**, *8*, 5357. (q) Wu, Z. G.; Zhou, G. F.; Zhou, J. Y. and Guo, W., *Synth. Commun.*, **2006**, *36*, 2491. (r) Ding, Y.-P.; Ding, Y.; Shen, Z.-X.; Li, B. and Zhang, Y.-W., *Youji Huaxue*, **2006**, *26*, 1306. (s) Das, B.; Banerjee, J.; Chowdhury, N.; Majhi, A. and Mahender, G., *Helv. Chim. Acta*, **2006**, *89*, 1265. (t) Tang, H. Y.; Zhao, G. F.; Zhou, Z. H.; Zhou, Q. L. and Tang, C. C., *Tetrahedron Lett.*, **2006**, *47*, 5717. (u) Lee, S. W.; Lee, C. H. and Lee, K.-J., *Bull. Korean Chem. Soc.*, **2006**, *27*, 769. (v) Gausepohl, R.; Buskens, P.; Kleinen, J.; Bruckmann, A.; Lehmann, C. W.; Klankermayer, J. and Leitner, W., *Angew. Chem. Int. Ed.*, **2006**, *45*, 3689. (w) Das, B.; Banerjee, J.; Chowdhury, N.; Majhi, A. and Mahender, G., *Helv. Chim. Acta*, **2006**, *89*, 876. (x) Pan, W.; Dong, D. W.; Sun, S. G. and Liu, Q., *Synlett*, **2006**, 1090. (y) He, K.; Zhou, Z. H.; Zhao, G. F. and Tang, C. C., *Heteroatom Chem.*, **2006**, *17*, 317. (z) Gong, H.; Cai, C.-Q.; Yang, N.-F.; Yang, L.-W.; Zhang, J. and Fan, Q.-H., *J. Mol. Catal. A: Chem.*, **2006**, *249*, 236. (aa) Mamaghani, M.; Radmogadam, K. and Badrian, A., *Asian J. Chem.*, **2006**, *18*, 840. (bb) Acke, D. R. J. and Stevens, C. V., *Org. Proc. Res. Dev.*, **2006**, *10*, 417. (cc) He, Z. R.; Tang, X. F.; Chen, Y. M. and He, Z. J., *Adv. Synth. Catal.*, **2006**, *348*, 413. (dd) Krishna, P. R.; Reddy,

P. S.; Narsingam, M.; Sateesh, B. and Sastry, G. N., *Synlett*, **2006**, 595. (ee) Coelho, F.; Diaz, G.; Abella, C. A. M. and Almeida, W. P., *Synlett*, **2006**, 435. (ff) Nakano, A.; Takahashi, K.; Ishihara, J. and Hatakeyama, S., *Heterocycles*, **2005**, *66*, 371. (gg) Chapuis, C.; Buchi, G. H. and Wuest, H., *Helv. Chim. Acta*, **2005**, *88*, 3069. (hh) Shi, Y.-L. and Shi, M., *Tetrahedron*, **2005**, 62, 461. (ii) Porzelle, A.; Williams, C. M.; Schwartz, B. D. and Gentle, I. R., *Synlett*, **2005**, 2923. (jj) He, K.; Zhou, Z. H.; Tang, H. Y.; Zhao, G. F. and Tang, C. C., *Chinese Chem. Lett.,* **2005**, *16*, 1427. (kk) Gong, H.; Yang, N.-F.; Yang, L.-W.; Huang, W.-S. and Fan, M.-Y., *Huaxue Shiji*, **2005**, *27*, 392. (ll) Radha Krishna, P.; Manjuvani, A. and Kannan, V., *Tetrahedron: Asymmetry*, **2005**, *16*, 2691. (mm) Chen, S.-H.; Hong, B.-C.; Su, C.-F. and Sarshar, S., *Tetrahedron Lett.*, **2005**, *46*, 8899. (nn) Caumul, P. and Hailes, H. C., *Tetrahedron Lett.*, **2005**, *46*, 8125. (oo) Pereira, S. I.; Adrio, J.; Silva, A. M. S. and Carretero, J. C., *J. Org. Chem.*, **2005**, *70*, 10175.

2. (a) Baylis, A. B. and Hillman, M. E. D., *German Pat*., **1972**, 2,155,113. (b) Baylis, A. B. and Hillman, M. E. D., *U. S. Pat*., **1973**, 3,743,669. [*Chem. Abstr*., **1972**, *77*, 34174].
3. Morita, K.; Suzuki, Z. and Hirose, H., *Bull. Chem. Soc. Jpn.*, **1968**, *41*, 2815.
4. (a) Yoshizawa, K. and Shioiri, T., *Tetrahedron*, **2007**, *63*, 6259. (b) Reetz, M. T.; Mondiere, R. and Carballeira, J. D., *Tetrahedron Lett.*, **2007**, *48*, 1679. (c) Kwong, C. K.-W.; Huang, R.; Zhang, M. J.; Shi, M. and Toy, P. H., *Chem. Eur. J.*, **2007**, *13*, 2369. (d) Seidel, F. and Gladysz, J. A., *Synlett*, **2007**, 986. (e) Myers, E. L.; de Vries, J. G. and Aggarwal, V. K., *Angew. Chem. Int. Ed.*, **2007**, *46*, 1893. (f) Mack, J. and Shumba, M., *Green Chem.*, **2007**, *9*, 328. (g) Shi, M.; Liu, Y.-H. and Chen, L.-H., *Chirality*, **2007**, *19*, 124. (h) Zhao, S.-H.; Zhang, H.-R.; Feng, L.-H. and Chen, Z.-B., *J. Mol. Catal. A: Chem.*, **2006**, *258*, 251. (i) Xu, J. H.,*THEOCHEM*, **2006**, *767*, 61. (j) Berkessel, A.; Roland, K. and Neudoerfl, J. M., *Org. Lett.*, **2006**, *8*, 4195. (k) Rodgen, S. A. and Schaus, S. E., *Angew. Chem. Int. Ed.*, **2006**, *45*, 4929. (l) Krafft, M. E. and Wright, J. A., *Chem. Commun.*, **2006**, 2977. (m) Dadwal, M.; Mobin, S. M. and Namboothiri, I. N. N., *Org. Biomol. Chem.*, **2006**, *4*, 2525. (n) He, L. and Ng, S. W., *Acta Cryst., Sect. E: Struct. Reports Online*, **2006**, *E62*, 5517. (o) Areces, P.; Carrasco, E.; Mancha, A. and Plumet, J., *Synthesis*, **2006**, 946. (p) Shi, M. and Liu, Y.-H., *Org. Biomol. Chem.*, **2006**, *4*, 1468. (q) Lin, Y. S.; Lin, C.-Y.; Liu, C.-W. and Tsai, T. Y. R., *Tetrahedron*, **2006**, *62*, 872. (r) Teng, W.-D.; Huang, R.; Kwong, C. K.-W.; Shi, M. and Toy, P. H., *J. Org. Chem.*, **2006**, *71*, 368. (s) Kataoka, T. and Kinoshita, H., *Phosphorus, Sulfur & Silicon & Related Elements*, **2005**, *180*, 989. (t) Krafft, M. E.; Seibert, K. A.; Haxell, T. F. N. and Hirosawa, C., *Chem. Commun.*, **2005**, 5772. (u) Zhao, S.-H. and Chen, Z.-B., *Synth. Commun.*, **2005**, *35*, 3045. (v) Wang, J.; Li, H.; Yu, X. H.; Zu, L. S. and Wang, W., *Org. Lett.*, **2005**, *7*, 4293. (w) Ito, H.; Takenaka, Y.; Fukunishi, S. and Iguchi, K., *Synthesis*, **2005**, 3035. (x) Back, T. G.; Rankic, D. A.; Sorbetti, J. M. and Wulff, J. E., *Org. Lett.*, **2005**, 7, 2377. (y) Nair, V. and Abhilash, K. G., *Synthesis*, **2005**, 1967. (z) Aroyan, C. E.; Vasbinder, M. M. and Miller, S. J., *Org. Lett.*, **2005**, *7*, 3849. (aa) Lin, Y.-S.; Liu, C.-W. and Tsai, T. Y. R., *Tetrahedron Lett.*, **2005**, *46*, 1859. (bb) Mi, X. L.; Luo, S. Z. and Cheng, J.-P., *J. Org. Chem.*, **2005**, *70*, 2338. (cc) Kataoka, T. and Kinoshita, H., *Eur. J. Org. Chem.*, **2005**, 45. (dd) Sagar, R.; Pant, C. S.; Pathak, R. and Shaw, A. K., *Tetrahedron*, **2004**, *60*, 11399. (ee) McDougal, N. T.; Trevellini, W. L.; Rodgen, S. A.; Kliman, L. T. and Schaus, S. E., *Adv. Synth. Catal.*, **2004**, *346*, 1231. (ff) Rastogi, N.; Namboothiri, I. N. N. and Cojocaru, M., *Tetrahedron Lett.*, **2004**, *45*, 4745. (gg) Kinoshita, H.; Kinoshita, S.; Munechika, Y.; Iwamura, T.; Watanabe, S.-I. and Kataoka, T., *Eur. J. Org. Chem.*, **2003**, 4852. (hh) McDougal, N. T. and Schaus, S. E., *J. Am. Chem. Soc.*, **2003**, *125*, 12094. (ii) Kinoshita, H.; Osamura, T.; Kinoshita, S.; Iwamura, T.; Watanabe, S.-I.; Kataoka, T.; Tanabe, G. and Muraoka, O., *J. Org. Chem.*, **2003**, *68*, 7532. (jj) Zanardi, F.; Appendino, G. and Casiraghi, G., *Chemtracts*, **2002**, *15*, 490. (kk) Mergott, D. J.; Frank, S. A. and Roush, W. R., *Org. Lett.*, **2002**, *4*, 3157. (ll) Bauer, T. and Tarasiuk, J., *Tetrahedron: Asymmetry*, **2001**, *12*, 1741. (mm) Sergeeva, N. N.; Golubev, A. S. and Burger, K., *Synthesis*, **2001**, 281. (nn) Ciganek, E., *Org. React.*, **1997**, *51*, 201.
5. (a) Raheem, I. T. and Jacobsen, E. N., *Adv. Synth. Catal.*, **2005**, *347*, 1701. (b) Buskens, P.; Klankermayer, J. and Leitner, W., *J. Am. Chem. Soc.,* **2005**, *127*, 16762.

6. (a) Sorbetti, J. M.; Clary, K. N.; Rankic, D. A.; Wulff, J. E.; Parvez, M. and Back, T. G., *J. Org. Chem.*, **2007**, *72*, 3326. (b) Gao, J.; Ma, G.-N.; Li, Q.-J. and Shi, M., *Tetrahedron Lett.*, **2006**, *47*, 7685. (c) Liu, Y.-H.; Chen, L.-H. and Shi, M., *Adv. Synth. Catal.*, **2006**, *348*, 973. (d) Matsui, K.; Takizawa, S. and Sasai, H., *Synlett*, **2006**, 761. (e) Matsui, K.; Tanaka, K.; Horii, A.; Takizawa, S. and Sasai, H., *Tetrahedron: Asymmetry*, **2006**, *17*, 578. (f) Shi, M. and Chen, L.-H., *Pure & Appl. Chem.*, **2005**, *77*, 2105. (g) Shi, M.; Chen, L.-H. and Teng, W.-D., *Adv. Synth. Catal.*, **2005**, *347*, 1781. (h) Liu, X. Y.; Chai, Z.; Zhao, G. and Zhu, S. Z., *J. Fluor. Chem.*, **2005**, *126*, 1215. (i) Matsui, K.; Takizawa, S. and Sasai, H., *J. Am. Chem. Soc.*, **2005**, *127*, 3680.
7. Keck, G. E. and Welch, D. S., *Org. Lett.*, **2002**, *4*, 3687.
8. (a) Krafft, M. E. and Seibert, K. A., *Synlett*, **2006**, 3334. (b) Krafft, M. E.; Haxell, T. F. N.; Seibert, K. A. and Abboud, K. A., *J. Am. Chem. Soc.*, **2006**, *128*, 4174.
9. (a) Pigge, F. C.; Dhanya, R. and Hoefgen, E. R., *Angew. Chem. Int. Ed.*, **2007**, *46*, 2887. (b) Krafft, M. E. and Haxell, T. F. N., *J. Am. Chem. Soc.*, **2005**, *127*, 10168. (c) Methot, J. L. and Roush, W. R., *Org. Lett.*, **2003**, *5*, 4223.
10. (a) Aggarwal, V. K. and Mereu, A., *Chem. Commun.*, **1999**, 2311. (b) Hayashi, Y.; Okado, K.; Ashimine, I.; Shoji, M., *Tetrahedron Lett.*, **2002**, *43*, 8683. (c) Basavaiah, D.; Dharma Rao, P. and Suguna Hyma, R., *Tetrahedron*, **1996**, *52*, 8001. (d) Ameer, F.; Drewes, S. E.; Freese, S. and Kaye, P. T., *Synth. Commun.*, **1988**, *18*, 495. (e) Aggarwal, V. K.; Dean, D. K.; Mereu, A. and Williams, R., *J. Org. Chem.*, **2002,** 67,510. (f) Aggarwal, V. K.; Emme, I. and Fulford, S. Y., *J. Org. Chem.*, **2003**, *68*, 692. (g) Langer, P., *Angew. Chem. Int. Ed.*, **2000**, *39*, 3049.
11. (a) Kataoka, T.; Iwama, T.; Kinoshita, H.; Tsurukami, Y.; Tsujiyama, S.; Fujita, M.; Honda, E.; Iwamura, T. and Watanabe, S.-I., *J. Organomet. Chem.*, **2000**, *611*, 455. (b) Iwama, T.; Kinoshita, H. and Kataoka, T., *Tetrahedron Lett.*, **1999**, *40*, 3741. (c) Kataoka, T.; Iwama, T.; Kinoshita, H.; Tsujiyama, S.; Tsurukami, Y.; Iwamura, T. and Watanabe, S., *Synlett*, **1999**, 197. (d) Kataoka, T.; Iwama, T. and Tsujiyama, S.-I., *Chem. Commun.*, **1998**, 197. (e) Kataoka, T.; Iwama, T.; Tsujiyama, S.-i.; Iwamura, T. and Watanabe, S.-I., *Tetrahedron*, **1998**, *54*, 11813.
12. Rafel, S. and Leahy, J. W., *J. Org. Chem.*, **1997**, *62*, 1521.
13. Perna, F. M.; Capriati, V.; Florio, S. and Luisi, R., *J. Org. Chem.*, **2002**, *67*, 8351.
14. (a) Perlmutter, P.; Puniani, E. and Westman, G., *Tetrahedron Lett.* **1996**, *37*, 1715. (b) Fort, Y.; Berthe, M. C. and Caubere, P., *Tetrahedron*, **1992**, *48*, 6371. (c) Bode, M. L. and Kaye, P. T., *Tetrahedron Lett.*, **1991**, *32*, 5611.
15. Basavaiah, D. and Gowriswari, V. V. L., *Synth. Commun*., **1989**, *19*, 2461.
16. (a) Luo, S. Z.; Mi, X. L.; Wang, P. G.; and Cheng, J.-P., *Tetrahedron Lett*., **2004**, *45*, 5171. (b) Yu, C., Liu, B. and Hu, L., *J. Org. Chem.*, **2001**, 66,5413. (c) Auge, J.; Lubin, N. and Lubineau, A., *Tetrahedron Lett.*, **1994**, *35*, 7947.
17. (a) Schuurman, R. J. W.; V. D. Linden, A.; Grimbergen, R. P. F.; Nolte, R. J. M. and Scheeren, H. W., *Tetrahedron*, **1996**, *52*, 8307. (b) Hill, J. S. and Isaacs, N. S., *J. Chem. Res. (S)*, **1988**, 330. (c) Hill, J. S. and Isaacs, N. S., *Tetrahedron Lett.*, **1986**, *27*, 5007.
18. Kundu, M. K.; Mukherjee, S. B.; Balu, N.; Padmakumar, R. and Bhat, S. V., *Synlett,* **1994**, 444.
19. (a) Yang, K.-S., Lee, W.-D., Pan, J.-F. and Chen, K., *J. Org. Chem.*, **2003**, *68*, 915. (b) Kataoka, T.; Kinoshita, H.; Kinoshita, S. and Iwamura, T., *J. Chem. Soc., Perkin Trans. I*, **2002**, 2043. (c) Li, G.; Wei, H.-X.; Gao, J. J. and Caputo, T. D., *Tetrahedron Lett.*, **2000**, *41*, 1. (d) Taniguchi, M.; Hino, T. and Kishi, Y., *Tetrahedron Lett*., **1986**, *27*, 4767.
20. (a) Basavaiah, D.; Rao, A. J. and Satyanarayana, T., *Chem. Rev.*, **2003**, *103*, 811. (b) Ciganek, E., *The Morita-Baylis-Hillman Reaction* in *Organic Reactions*, Vol. 51; ed., Paquette, L. A., John Wiley & Sons, New York, **1997**, pp. 201–350. (c) Drewes, S. E. and Roos, G. H. P., *Tetrahedron*, **1988**, *44*, 4653.
21. Hill, J.S. and Isaacs, N. S., *J. Phys. Org. Chem.*, **1990**, *3*, 285.

22. (a) Hamilton, D. S.; Ding, Z.; Ganem, B. and Creighton, D. J., *Org. Lett.*, **2002**, *4*, 1209. (b) Gonzalez, A. G.; Silva, M. H.; Padron, J. I.; Leon, F.; Reyes, E.; Alvarez-Mon, M.; Pivel, J. P.; Quintana, J.; Estevez, F. and Bermejo, J., *J. Med. Chem.*, **2002**, *45*, 2358. (c) Zhu, S.; Hudson, T. H.; Kyle, D. E. and Lin, A. J., *J. Med. Chem.*, **2002**, *45*, 3491. (d) Pregabalin, P., *Drugs Future*, **2002**, *27*, 426. (e) Kundu, M. K.; Sundar, N.; Kumar, S. K.; Bhat, S. V.; Biswas, S. and Valecha, N., *Bioorg. Med. Chem. Lett.*, **1999**, *9*, 731.

23. Yu, C. and Hu, L., *J. Org. Chem.*, **2002**, *67* 219.

24. Balan, D. and Adolfsson, H., *J. Org. Chem.*, **2001**, *66*, 6498.

25. (a) Xu, Y.-M. and Shi, M., *J. Org. Chem.*, **2004**, *69*, 417. (b) Ramachandran, P. V.; Pratihar, D.; Biswas, D.; Srivastava, A. and Reddy, M. V. R., *Org. Lett.*, **2004**, *6*, 481. (c) Kabalka, G. W.; Venkataiah, B. and Dong, G., *J. Org. Chem.*, **2004**, *69*, 5807. (d) Luo, S. Z.; Wang, P. G. and Cheng, J. P., *J. Org. Chem.*, **2004**, *69*, 555. (e) Ribière, P.; Enjalbal, C.; Aubagnac, J.-L.; Yadav-Bhatnagar, N.; Martinez, J. and Lamaty, F., *J. Comb. Chem.*, **2004**, *6*, 464. (f) Kannan, V., *Synlett*, **2004**, 1120. (g) Park, J. B.; Ko, S. H.; Hong, W. P. and Lee, K.-J., *Bull. Korean Chem. Soc*., **2004**, *25*, 927. (h) Alcaide, B.; Almendros, P.; Aragoncillo, C. and Rodríguez-Acebes, R., *J. Org. Chem.*, **2004**, *69*, 826. (i) Galeazzi, R.; Martelli, G.; Mobbili, G.; Orena, M. and Rinaldi, S., *Org. Lett.*, **2004**, *6*, 2571. (j) Kawahara, S.; Nakano, A.; Esumi, T.; Iwabuchi, Y. and Hatakeyama, S., *Org. Lett.*, **2003**, *5*, 3103. (k) Basavaiah, D.; Sreenivasulu, B. and and Rao, A. J., *J. Org. Chem.*, **2003**, *68*, 5983. (l) Trost, B. M.; Thiel, O. R. and Tsui, H.-C., *J. Am. Chem. Soc.*, **2003**, *125*, 13155. (m) Shi, M. and Chen, L.-H., *Chem. Commun*., **2003**, 1310. (n) Radha Krishna, P.; Kannan, V.; Sharma, G. V. M. and Ramana Rao, M. H. V., *Synlett*, **2003**, 888. (o) Radha Krishna, P.; Raja Sekhar, E. and Kannan, V., *Tetrahedron Lett.*, **2003**, *44*, 4973. (p) Kabalka, G. W.; Venkataiah, B. and Dong, G., *Org. Lett.*, **2003**, *5*, 3803. (q) Zhao, G.-L.; Huang, J.-W. and Shi, M., *Org. Lett.*, **2003**, *5*, 4737. (r) Shi, M. and Jiang, Y., *J. Chem. Res. (S)*, **2003**, 564. (s) Evans, C. A. and Miller, S. C., *J. Am. Chem. Soc.*, **2003**, *125*, 12394. (t) Wang, M.-X. and Wu, Y., *Org. Biomol. Chem.*, **2003**, *1*, 535. (u) Shi, M. and Xu, Y.-M., *J. Org. Chem.*, **2003**, *68*, 4784. (v) Matsuya, Y., Hayashi, K. and Nemoto, H., *J. Am. Chem. Soc*., **2003**, *125*, 646. (w) Reddy, M. V. R., Rudd, M. T. and Ramachandran, P. V., *J. Org. Chem.*, **2002**, *67*, 5382. (x) Cai, J. X.; Zhou, Z. H.; Zhao, G. F. and Tang, C. C., *Org. Lett.*, **2002**, *4*, 4723. (y) Basavaiah, D., Sharada, D. S., Kumaragurubaran, N. and Reddy, R. M., *J. Org. Chem.*, **2002**, *67*, 7135. (z) Kim, J. N.; Lee, H. J.; Lee, K. Y. and Gong, J. H., *Synlett*, **2002**, 173. (aa) Kim, J. N. and Lee, K. Y., *Curr. Org. Chem.*, **2002**, *6*, 627. (bb) Trost, B. M.; Thiel, O. R. and Tsui, H.-C., *J. Am. Chem. Soc.*, **2002**, *124*, 11616. (cc) Shi, M. and Xu, Y.-M., *Angew. Chem. Int. Ed*., **2002**, *41*, 4507. (dd) Kaye, P. T. and Nocanda, X. W., *J. Chem. Soc., Perkin Trans. I*, **2002**, 1318. (ee) Shi, M.; Jiang, J.-K. and Li, C.-Q., *Tetrahedron Lett.*, **2002**, *43*, 127. (ff) Aggarwal, V. K.; Castro, A. M. M.; Mereu, A. and Adams, H., *Tetrahedron Lett*., **2002**, *43*, 1577. (gg) Luo, S. Z.; Zhang, B. L.; He, J. Q.; Janczuk, A.; Wang, P. G. and Cheng, J.-P., *Tetrahedron Lett*., **2002**, *43*, 7369. (hh) Balan, D. and Adolfsson, H., *J. Org. Chem.*, **2002**, *67*, 2329. (ii) Aumann, R.; Fu, X. L.; Holst, C. and Fröhlich, R., *Organometallics*, **2002**, *21*, 4356. (jj) Patra, A.; Batra, S.; Joshi, B. S.; Roy, R.; Kundu, B. and Bhaduri, A. P., *J. Org. Chem.*, **2002**, *67*, 5783. (kk) Chung, Y. M.; Im, Y. J. and Kim, J. N., *Bull. Korean Chem. Soc*., **2002**, *23*, 1651. (ll) Sammelson, R. E; Gurusinghe, C. D.; Kurth, J. M.; Olmstead, M. M. and Kurth, M. J., *J. Org. Chem.*, **2002**, 67,876. (mm) Rajesh, S.; Banerji, B. and Iqbal, J., *J. Org. Chem.*, **2002**, *67*, 7852. (nn) Shi, M. and Feng, Y.-S., *J. Org. Chem.*, **2001**, *66*, 406. (oo) Jauch, J., *J. Org. Chem.*, **2001**, 66,609. (pp) Richards, E. L.; Murphy, P. J.; Dinon, F.; Fratucello, S.; Brown, P. M.; Gelbrich, T. and Hursthouse, M. B., *Tetrahedron*, **2001**, *57*, 7771. (qq) Basavaiah, D.; Kumaragurubaran, N. and Sharada, D. S., *Tetrahedron Lett*., **2001**, *42*, 85. (rr) Basavaiah, D. and Kumaragurubaran, N., *Tetrahedron Lett*., **2001**, *42*, 477. (ss) Basavaiah, D. and Satyanarayana, T., *Org. Lett.*, **2001**, *3*, 3619. (tt) Kim, J. N.; Kim, H. S.; Gong, J. H. and Chung, Y. M., *Tetrahedron Lett*., **2001**, *42*, 8341. (uu) Radha Krishna, P.; Kannan, V.; Ilangovan, A. and Sharma, G. V. M., *Tetrahedron: Asymmetry*, **2001**, *12*, 829. (vv) Alcaide, B., Almendros, P. and Aragoncillo, C., *J. Org. Chem.*, **2001**, *66*, 1612. (ww) Iwabuchi, Y.; Sugihara, T.; Esumi, T. and Hatakeyama, S., *Tetrahedron*

Lett., **2001**, *42*, 7867. (xx) Li, G. G.; Wei, H.-X.; Pehlps, B. S.; Purkiss, D. W. and Kim, S. H., *Org. Lett.*, **2001**, *3*, 823. (yy) Iwamura, T.; Fujita, M.; Kawakita, T.; Kinoshita, S.; Watanabe, S.-I. and Kataoka, T., *Tetrahedron*, **2001**, *57*, 8455. (zz) Iwabuchi, Y.; Furukawa, M.; Esumi, T. and Hatakeyama, S., *Chem. Commun.*, **2001**, 2030. (aaa) Trost, B. M.; Tsui, H.-C. and Toste, F. D., *J. Am. Chem. Soc.*, **2000**, *122*, 3534. (bbb) Basavaiah, D.; Krishnamacharyulu, M. and Rao, A. J., *Synth. Commun*., **2000**, *30*, 2061. (ccc) Shi, M.; Jiang, J.-K. and Feng, Y.-S., *Org. Lett.*, **2000**, *2*, 2397. (ddd) Li, G.-G.; Gao, J.-J.; Wei, H.-X. and Enright, M., *Org. Lett*., **2000**, *2*, 617. (eee) Räcker, R.; Döring, K. and Reiser, O., *J. Org. Chem.*, **2000**, *65*, 6932. (fff) Kaye, P. T. and Nocanda, X. W., *J. Chem. Soc., Perkin Trans. I*, **2000**, 1331. (ggg) Yang, K.-S. and Chen, K. M., *Org. Lett.*, **2000**, *2*, 729. (hhh) Youn, S. W.; Park, H. S. and Kim, Y. H., *Chem. Commun.*, **2000**, 2005. (iii) Katoaka, T.; Kinoshita, H.; Kinoshita, S.; Iwamura, T. and Watanabe, S.-I., *Angew. Chem. Int. Ed.*, **2000**, *39*, 2358. (jjj) Kim, J. N.; Lee, K. Y.; Kim, H. S. and Kim, T. Y., *Org. Lett*., **2000**, *2*, 343. (kkk) Ayed, T. B.; Villiéras, J. and Amri, H., *Tetrahedron*, **2000**, *56*, 805. (lll) Li, W. G.; Zhang, Z. G.; Xiao, D. M. and Zhang, X. M., *J. Org. Chem.*, **2000**, *65*, 3489.

26. (a) Nemoto, T.; Fukuyama, T.; Yamamoto, E.; Tamura, S.; Fukuda, T.; Matsumoto, T.; Akimoto, Y. and Hamada, Y., *Org. Lett.*, **2007**, *9*, 927. (b) Utsumi, N.; Zhang, H.; Tanaka, F. and Barbas, Carlos F., *Angew. Chem. Int. Ed.*, **2007**, *46*, 1878. (c) Pathak, R.; Singh, V.; Nag, S. N.; Kanojiya, S. and Batra, S., *Synthesis*, **2006**, 813. (d) Miller, S. J., *Acc. Chem. Res*., **2004**, *37*, 601. (e) Cho, C.-W.; Kong, J.-R. and Krische, M. J., *Org. Lett.*, **2004**, *6*, 1337. (f) Martínez, I.; Andrews, A. E.; Emch, J. D.; Ndakala, A. J.; Wang, J. and Howell, A. R., *Org. Lett.*, **2003**, *5*, 399. (g) Frank, S. A., Mergott, D. J. and Roush, W. R., *J. Am. Chem. Soc*., **2002**, *124*, 2404. (h) Wang, L.-C.; Luis, A. L.; Agapiou, K.; Jang, H.-Y. and Krische, M. J., *J. Am. Chem.. Soc.*, **2002**, *124*, 2402. (i) Kisanga, P. B. and Verkade, J. G., *J. Org. Chem.*, **2002**, *67*, 426. (j) Dinon, F.; Richards, E.; Murphy, P. J.; Hibbs, D. E.; Hursthouse, M. B. and Malik, K. M. A., *Tetrahedron Lett.*, **1999**, *40*, 3279. (k) Kulkarni, B. A. and Ganesan, A., *J. Comb. Chem.*, **1999**, *1*, 373. (l) Li, G. G.; Wei, H.-X.; Whittlesey, B. R. and Batrice, N. N., *J. Org. Chem.*, **1999**, *64*, 1061. (m) Akiyama, H.; Fujimoto, T.; Ohshima, K.; Hoshino, K.; Yamamoto, I. and Iriye, R., *Org. Lett.*, **1999**, *1*, 427. (n) Basavaiah, D.; Kumaragurubaran, N. and Padmaja, K., *Synlett*, **1999**, 1630. (o) Alcaide, B.; Almendros, P. and Aragoncillo, C., *Chem. Commun.*, **1999**, 1913. (p) Basavaiah, D.; Krishnamacharyulu, M.; Hyma, R. S.; Sarma, P. K. S. and Kumaragurubaran, N., *J. Org. Chem.*, **1999**, *64*, 1197. (q) Jauch, J., *Synlett*, **1999**, 1325. (r) Pringle, W. and Sharpless, K. B., *Tetrahedron Lett.*, **1999**, *40*, 5151. (s) Basavaiah, D.; Hyma, R. S.; Padmaja, K. and Krishnamacharyulu, M., *Tetrahedron*, **1999**, *55*, 6971. (t) Sugahara, T. and Ogasawara, K., *Synlett*, **1999**, 419. (u) Nayak, S. K.; Thijs, L. and Zwanenburg, B., *Tetrahedron Lett.*, **1999**, *40*, 981. (v) Kawamura, M. and Kobayashi, S., *Tetrahedron Lett*., **1999**, *40*, 1539. (w) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N. and Hatakeyama, S., *J. Am. Chem. Soc.*, **1999**, *121*, 10219. (x) Harrowven, D. and Hannam, J. C. *Tetrahedron* **1999**, *55*, 9341. (y) Rezgui, F. and Gaied, M. M. E. *Tetrahedron Lett*. **1998**, 5965. (z) Barrett, A. G. C.; Cook, A. S. and Kamimura, A., *Chem. Commun.*, **1998**, 2533. (aa) Aggarwal, V. K.; Mereu, A.; Tarver, G. J. and McCague, R., *J. Org. Chem.*, **1998**, *63*, 7183. (bb) Nagaoka, Y. and Yomioka, K., *J. Org. Chem*., **1998**, *63*, 6428. (cc) Richter, H. and Jung, G., *Tetrahedron Lett*., **1998**, *39*, 2729. (dd) Familoni, O. B.; Kaye, P. T. and Klaas, P. J., *Chem. Commun.*, **1998**, 2563. (ee) Almeida, W. P. and Coelho, F., *Tetrahedron Lett.*, **1998**, *39*, 8609. (ff) Bussolari, J. C.; Beers, K.; Lalan, P.; Murray, W. V.; Gauthier, D. and McDonnell, P., *Chem. Lett.*, **1998**, 787. (gg) Lee, H. J.; Seong, M. R. and Kim, J. N., *Tetrahedron Lett.,* **1998**, *39*, 6223. (hh) Basavaiah, D. and Bakthadoss, M., *Chem. Commun.*, **1998**, 1639. (ii) Kumareswaran, R. and Vankar, Y. D., *Synth. Commun.*, **1998**, *28*, 2291. (jj) Matsumoto, S. and Mikami, K., *Synlett*, **1998**, 469. (kk) Basavaiah, D. and Muthukumaran, K., *Tetrahedron*, **1998**, *54*, 4943. (ll) Matsumoto, S.; Okubo, Y. and Mikami, K., *J. Am. Chem. Soc.*, **1998**, *120*, 4015. (mm) Jenn, T. and Heissler, D., *Tetrahedron*, **1998**, *54*, 97. (nn) Hayase, T.; Shibata, T.; Soai, K. and Wakatsuki, Y., *Chem. Commun*., **1998**, 1271. (oo) Kamimura, A.; Mitsudera, H.; Asano, S.; Kakehi, A. and Noguchi, M., *J. Chem. Soc., Chem. Commun.*, **1998**, 1095. (pp) Li, G.; Wei, H. X. and Willis, S., *Tetrahedron Lett.*, **1998**, *39*, 4607. (qq) Brzezinski, L. J.; Rafael, S. and Leahy, J. W., *Tetrahedron*, **1997**, *53*, 16423. (rr) Black, G. P.;

Francesca, D.; Fratucello, S.; Murphy, P. J.; Nidelsen, M.; Williams, H. L. and Waishe, N. D. A., *Tetrahedron Lett.*, **1997**, *38*, 8561. (ss) Basavaiah, D.; Krishnamacharyulu, M.; Hyma, R. S. and Pandiaradju, S., *Tetrahedron Lett.*, **1997**, *38*, 2141. (tt) Drewes, S. E. and Rohwer, M. B., *Synth. Commun.*, **1997**, *27*, 415. (uu) Marko, I. E.; Giles, P. R. and Hindley, N. J., *Tetrahedron,* **1997**, *53*, 1015. (vv) Brzezinski, L. J.; Rafel, S. and Leahy, J. W., *J. Am. Chem. Soc.*, **1997**, *119*, 4317. (ww) Basavaiah, D.; Rao, P. D. and Hyma, R. S., *Tetrahedron*, **1996**, *52*, 801. (xx) Hadimani, S. B.; Padmakumar, R. and Bhat, S. V. *Synth. Commun.* **1996**, *26*, 3527. (yy) Basavaiah, D.; Pandiaraju, S. and Padmaja, K., *Synlett*, **1996**, 393. (zz) Basavaiah, D. and Hyma, R. S., *Tetrahedron*, **1996**, *52*, 1253. (aaa) Barrett, A. G. M. and Kamimura, A., *J. Chem. Soc., Chem. Commun.*, **1995**, 1755. (bbb) Byun, H. S.; Reddy, K. C. and Bittman, R., *Tetrahedron Lett*., **1994**, *35*, 1371. (ccc) Oishi, T.; Oguri, H. and Hirama, M., *Tetrahedron: Asymmetry*, **1995**, *6*, 1241. (ddd) Perlmutter, P. and McCarthy, T. D., *Aust. J. Chem.,* **1993**, *46*, 253. (eee) Bode, M. L. and Kaye, P. T., *J. Chem. Soc., Perkin Trans. I*, **1993**, 1809. (fff) Khan, A. A.; Emslie, N. D.; Drewes, S. E.; Field, J. S. and Ramesar, N.,*Ber.*, **1993**, *126*, 1477. (ggg) Drewes, S. E.; Khan, A. A. and Rowland, K., *Synth. Commun.*, **1993**, *23*, 183. (hhh) Drewes, S. E.; Emslie, N. D. and Khan, A. A., *Synth. Commun.*, **1993**, *23*, 1215. (iii) Kunidig, E. P.; Xu, L. H.; Romanens, P. and Bernardinelli, G., *Tetrahedron Lett*., **1993**, *34*, 7049. (jjj) Drewes, S. E.; Njamela, O. L.; Emslie, N. D.; Ramesar, N. and Field, J. S., *Synth. Commun.*, **1993**, *23*, 2807. (kkk) Roth, F.; Gygax, P. and Fráter, G., *Tetrahedron Lett.*, **1992**, *33*, 1045. (lll) Gilbert, A.; Heritage, T. W. and Isaacs, N. S., *Tetrahedron: Asymmetry*, **1991**, *2*, 969. (mmm) Basavaiah, D.; Gowriswari, V. V. L.; Sarma, P. K. S. and Rao, P. D., *Tetrahedron Lett.*, **1990**, *31*, 1621. (nnn) Drewes, S. E.; Emslie, N. D.; Karodia, N. and Khan, A. A.,*Ber.*, **1990**, *123*, 1447. (ooo) Basavaiah, D. and Gowriswari, V. V. L., *Tetrahedron Lett*.,**1986**, *27*, 2031.

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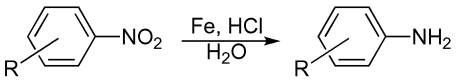
Béchamp Reduction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Béchamp in 1854.[1] It is the reduction of aromatic nitro compounds to the corresponding aromatic amines by iron, ferrous salts, or iron catalyst in aqueous acid. Thus this reaction is generally referred to as the Béchamp reduction.[2] Besides iron, zinc and tin are often used to reduce the aromatic nitro compounds in the presence of an acid;[3] however, the reduction of aromatic nitro compounds often stops at an intermediate stage, yielding hydroxylamines,[4] hydrazines,[5] azoarenes,[6] or azoxyarenes.[7] These intermediates definitely indicate some aspects of the mechanism. Although the main drawbacks of the Béchamp reduction include the slow reaction rate and costly steam distillation compared with the catalytic hydrogenation of aromatic nitro compounds, the Béchamp reduction usually shows higher selectivity to the desired product.[8] In addition, this reaction might give much better results if some neutral organic solvents were added to the aqueous reaction mixture, such as acetonitrile and propylene carbonate.[9] Recently, a highly chemoselective catalytic hydrogenation of nitrobenzenes using homogeneous iron complex catalysts has been reported.[10] The Béchamp reduction has been reviewed.[11]

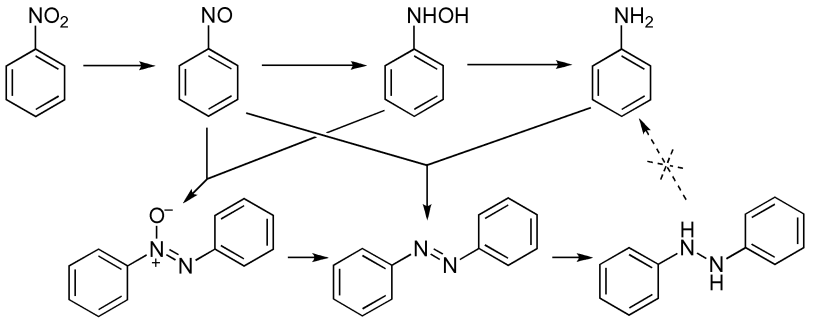
B. GENERAL REACTION SCHEME



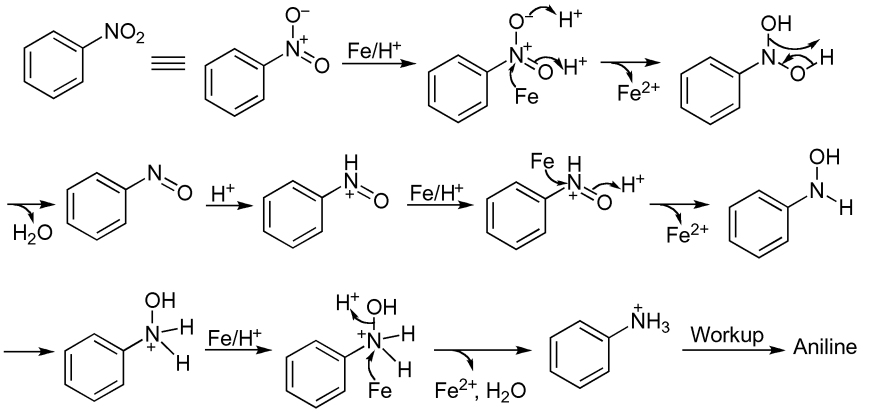
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

It is proposed that the nitro group is reduced via a multistep process, as shown below.[10,12]



A tentative mechanistic detail of the Béchamp reduction is also illustrated below.



D. MODIFICATION

N/A

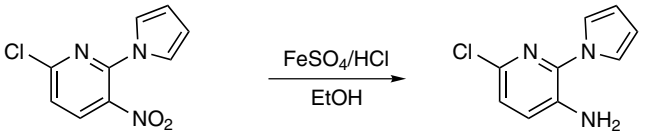
E. APPLICATIONS

This reaction is generally used to reduce aromatic nitro compounds into aromatic amines.

F. RELATED REACTIONS

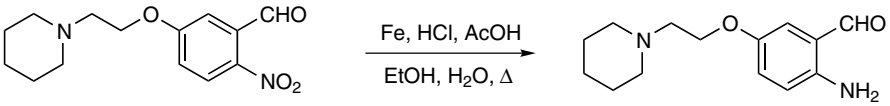
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 13.

To 300 mL EtOH was added 9.27 g 6-chloro-3-nitro-2-pyrrolopyridine (41 mmol), followed by 115.25 g $FeSO_4 \cdot 7H_2O$ (414 mmol), 0.5 mL 10 N HCl, and 5 mL water. The mixture was heated at 80°C for 90 min, while a 30% ammonia solution was added in little fractions to maintain a basic pH. After cooling, EtOH was evaporated under vacuum. The residue was poured in 100 mL water and extracted with Et_2O. After the usual treatment, the first amount of the product was obtained. The aqueous phase was alkalinized with ammonia solution and extracted with EtOAc. Finally, 4.59 g 3-amino-6-chloro-2-pyrrolopyridine was obtained as a beige powder, in a yield of 57%, m.p. 89°C (recrystallization from 80% Et_2O and 20% *n*-hexane).



Reference 14.

To mixture of 1.2 g iron (21.6 mmol), 0.25 mL 10 N HCl, 10 mL acetic acid, 10 mL ethanol and 5 mL water was added 1.0 g 2-nitro-5-(2-piperidin-1-ylethoxy)benzaldehyde (3.6 mmol). The mixture was refluxed for 15 min with stirring, and iron was removed by filtration. The product was worked up as usual.

Other references related to the Béchamp reaction are cited in the literature.[15]

H. REFERENCES

1. Béchamp, A. J., *Ann. Chim. Phys.,* **1854**, *42*, 186.
2. (a) Lund, R. B. and Brown, G. W., *Eur. Pat. Appl.*, **1987**, June 5, 221,021. (b) Vojir, V., *Chem. Prumysl,* **1981**, *31*, 74. (c) Terc, J.; Vokal, J. and Prachensky, J., *Chem. Prumysl,* **1981**, *31*, 20. (d) Medvedeva, V. S. and Belotsvetov, A. V., *Zh. Org. Khim.,* **1972**, *8*, 1335.
3. (a) Coleman, G. H.; McClosky, S. M. and Suart, F. A., *Org. Syn. Coll.,* **1955**, *3*, 668–670. (b) Hartman, W. W.; Dickey, J. B. and Stampfli, J. G., *Org. Syn. Coll.,* **1949**, *2*, 175–178.
4. (a) Rondestvedt, C. S. and Johnson, T. A., *Synthesis*, **1977**, 850. (b) Entwistle, I. D.; Gilkerson, T.; Johnstone, R. A. W. and Telford, R. P., *Tetrahedron,* **1978**, *34*, 213. (c) Oxley, P. W.; Adger, B. M.; Sasse, M. J. and Forth, M. A., *Org. Synth Coll., 8*, **1993**, 16. (d) Yanada, K.; Yamaguchi, H.; Meguri, H. and Uchida, S., *J. Chem. Soc., Chem. Commun.,* **1986**, 1655. (e) Feuer, H.; Bartlett, R. S.; Vincent, B. F. and Anderson R. S., *J. Org. Chem.*, **1965**, *30*, 2880.
5. (a) Furst, A. and Moore, R. E., *J. Am. Chem. Soc.,* **1957**, *79*, 5492. (b) Olah, G. A., *J. Am. Chem. Soc.,* **1959**, *81*, 3165.

6. Hutchins, R. O.; Lamson, D. W.; Rua, L.; Milewski, C. and Maryanoff, B., *J. Org. Chem.,* **1971**, *36*, 803.
7. (a) Osuka, A.; Shimizu, H. and Suzuki, H., *Chem. Lett.,* **1983**, 1373. (b) Azoo, J. A. and Grimshaw, J., *J. Chem. Soc.*, *Sect. C,* **1968**, 2403. (c) Ohe, K.; Uemura, S.; Sugita, N.; Masuda, H. and Taga, T., *J. Org. Chem.,* **1989**, *54*, 4169. (d) Ogata, Y. and Mibae, J., *J. Org. Chem*., **1962**, *27*, 2048. (e) Hutton, J. and Waters, W. A., *J. Chem. Soc. B,* **1968**, 191. (f) Porta, F.; Pizzotti, M. and Cenini, S., *J. Organomet. Chem.,* **1981**, *222*, 279.
8. Mukhopadhyay, S.; Gandi, G. K. and Chandalia, S. B., *Org. Proc. Res. Dev.,* **1999**, *3*, 201.
9. (a) Kolchinski, A. G. and Alcock, N. W., *J. Org. Chem.,* **1998**, *63*, 4515. (b) Riesgo, E. C.; Jin, X. and Thummel, R. P., *J. Org. Chem*., **1996**, *61*, 3017.
10. Deshpande, R. M.; Mahajan, A. N.; Diwakar, M. M.; Ozarde, P. S. and Chaudhari, R. V., *J. Org. Chem.,* **2004**, *69*, 4835.
11. (a) Vogt, P. F. and Gerulis, J. J., "*Amines*, *Aromatic*" in *Ullmann's Encyclopedia of Industrial Chemistry,* 5th ed.; Gerhartz, W., ed., VCH, Weinheim, **1985,** *A2*, pp. 37–55. (b) Hamilton, C. S. and Morgan, J. F., *Org. React.*, **1944**, *2*, 428.
12. Yu, C. Z.; Liu, B. and Hu, L. Q., *J. Org. Chem.,* **2001**, *66*, 919.
13. Prunier, H.; Rault, S.; Lancelot, J.-C.; Robba, M.; Renard, P.; Delagrange, P.; Pfeiffer, B.; Caignard, D.-H.; Misslin, R.; Guardiola-Lemaitre, B. and Hamon, M., *J. Med. Chem.,* **1997**, *40*, 1808.
14. Perzyna, A.; Marty, C.; Facompré, M.; Goossens, J.-F.; Pommery, N.; Colson, P.; Houssier, C.; Houssin, R.; Hénichart, J.-P. and Bailly, C., *J. Med. Chem.,* **2002**, *45*, 5809.
15. (a) Blaser, H. U. and Studer, M., *Appl. Catal.,* **1999**, *189*, 191. (b) Courtin, A., *Helv. Chim. Acta,* **1980**, *62*, 2280. (c) Knifton, J. F., *J. Org. Chem*., **1976**, *41*, 1200. (d) J. R. Geigy A.-G., *Belgian Pat.*, **1962**, 611,833 [*Chem. Abstr*., **1962**, *57*, P16578h]. (e) Yagi, S.; Miyauchi, T. and Yeh, C. Y., *Bull. Chem. Soc. Jpn.,* **1956**, *29*, 194. (f) Smith, L. I. and Opie, J. W., *Org. Syn. Coll.*, **1955**, *3*, 56. (g) Wertheim, E., *Org. Syn. Coll.,* **1949**, *2*, 16. (h) Werner, J., *Ind. Eng. Chem.,* **1949**, *41*, 1841. (i) Werner, J., *Ind. Eng. Chem.,* **1948**, *40*, 1575. (j) Brown, H. P. and Hamilton, C. S., *J. Am. Chem. Soc.,* **1934**, *56*, 151. (k) Ehrlich, P. and Bertheim, A., *Ber*., **1907**, *40*, 3292. (l) Béchamp, A. J., *Compt. Rend*., **1863**, *56*, 1172.

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Beckmann Rearrangement and Beckmann Fragmentation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Beckmann in 1886.[1] It is the rearrangement of an oxime to its corresponding amide in the presence of an acid and is generally known as the Beckmann rearrangement.[2] Oximes of cyclic ketones give lactams as the final products, resulting in the ring enlargements. An important example is the conversion of cyclohexanone oxime into ε-caprolactam, which is a basic component for the fabrication of nylon 6.[3] The oxime is formed by the reaction of a ketone with hydroxyamine. The Beckmann rearrangement of oxime derivatives proceeds stereospecifically, and the stereo-configuration of the migrating group is retained. The migrating substituent is the electrofuge that can better stabilize a partially positive charge.[4] This rearrangement has been applied to the construction of a variety of nitrogen-containing compounds, including amines (via imines),[5] amidines,[6] thioimidates,[7] imidoyl halides,[8] iminophosphonates,[9] and enaminones.[10] However, certain oximes, particularly those having a quarternary carbon *anti* to the hydroxyl, are likely to undergo the rearrangement to form nitriles instead of amides. This type of transformation is called the Beckmann fragmentation,[11,12] which was first reported by Werner and Piguet in 1904.[13] Because this kind of transformation is so different from the regular Beckmann rearrangement, it is sometimes called abnormal Beckmann rearrangement,[2y,4,11a,11f,14] secondary Beckmann rearrangement,[15] Beckmann fission,[16] etc. Besides those oximes having a quarternary carbon *anti* to the hydroxyl group, other oximes such as the bridged bicyclic ketoximes[17] and oximes with an electron-donating substituent at the α-carbon also undergo fragmentation rather than rearrangement under Beckmann rearrangement conditions. A variety of substituents, notably alkyl, aryl, hydroxy, alkoxy, amino, and thioalkoxy

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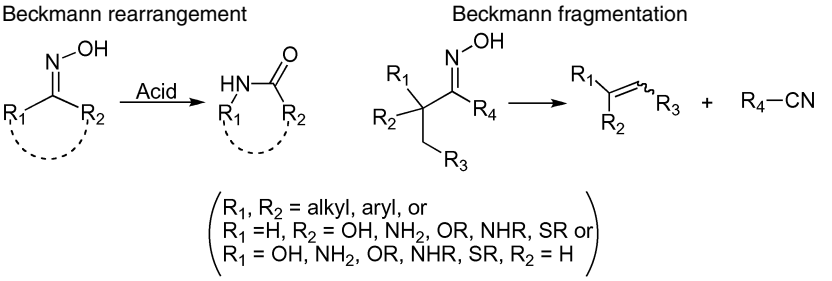
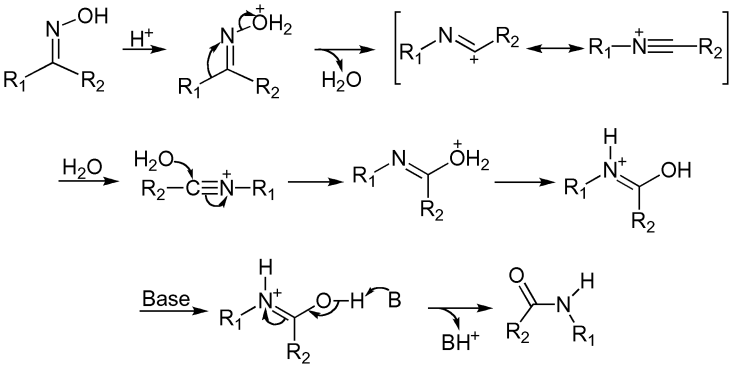
(thioether) can stabilize the intermediate carbonium ion and facilitate fragmentation.[2y,18] The Beckmann fragmentation has been applied to the modification of steroids and other organic syntheses.[19] Owing to their importance, both the Beckmann rearrangement and the Beckmann fragmentation have been extensively reviewed.[20] Currently, the Beckmann rearrangement has been carried out under mild conditions[21] and in supercritical water;[22] it has also been modified to be catalytic.[23]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is commonly assumed that the reaction involves an initial protonation at the oxygen atom of the oxime moiety, giving an oxonium cation, and is followed by the migration of an alkyl group plus the departure of a water molecule to give the nitrilium cation. The latter ion is, in turn, hydrolyzed in a basic solution to finally yield an amide.[24] The mechanism is illustrated below.



D. MODIFICATION

This reaction has been modified to be catalytic[23] and to occur under mild conditions,[21] in supercritical water,[22] and under photo-irradiation.[25]

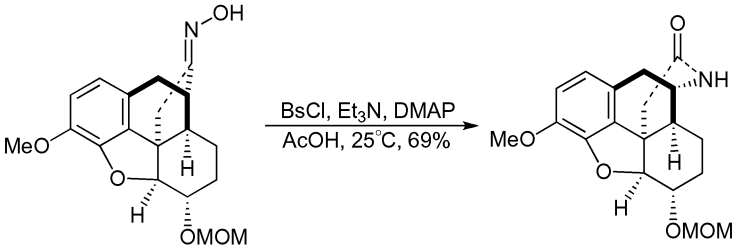
E. APPLICATIONS

This reaction has been used to synthesize different types of nitrogen-containing compounds.

F. RELATED REACTIONS

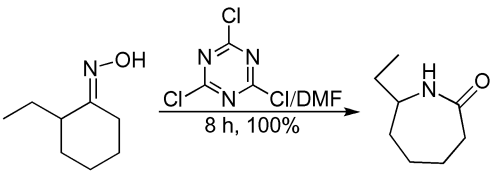
This reaction is related to the *Schmidt Reaction* and *Tiemann Rearrangement*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 26.

A solution of 25 mg (1*R*,4*S*,12*S*,13*S*,16*R*)-9-methoxy-13-(methoxymethoxy)-11-oxapentacyclo[8.6.1.$0^{1,12}$.$0^{4,16}$.$0^{6,17}$]-heptadeca-6(17),7,9-trienone oxime (0.072 mmol), 28 mg *p*-bromobenzenesulfonyl chloride (0.11 mmol), 16 μL Et_3N (0.12 mmol), and a catalytic amount of DMAP in 5 mL CH_2Cl_2 was stirred for 1 h at ambient temperature. The solvent was removed under reduced pressure, and the residue was taken up by 2 mL acetic acid. The resulting solution was stirred for 1 h and was neutralized with saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2, washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue on silica gel column (6 g, EtOAc/MeOH, 12:1) gave 17 mg (1*R*,5*S*,13*S*,14*S*,17*S*)-10-methoxy-14-(methoxymethoxy)-12-oxa-4-azapentacyclo[9.6.1.$0^{1,13}$.$0^{5,17}$.$0^{7,18}$]-octadeca-7(18),8,10-trien-3-one as a colorless oil, in a yield of 69%. $[R]_D^{23}$ = +114.2 (c 1.47, $CHCl_3$).



Reference 21.

To 2 mL DMF was added 1.83 g 2,4,6-trichloro-[1,3,5]triazine (TCT, 10.0 mmol) at 25°C. After the formation of a white solid, the reaction was monitored by TLC until the complete disappearance of TCT, then 1.41 g ethylcyclohexanone oxime (10.0 mmol) in 15 mL DMF was added. After the addition, the mixture was stirred at room temperature and monitored by TLC until completion (~8 h). Then 20 mL water was added, and the product was extracted with organic solvent. The organic phase was washed with 15 mL of a

saturated solution of Na_2CO_3, followed by 1 N HCl and brine. The organic layer was dried over Na_2SO_4, and evaporation of the solvent gave 1.41 g 7-ethylazepan-2-one without other purifications, in a yield of 100%, m.p. 91°C.

Other references related to the Beckmann rearrangement and the Beckmann fragmentation are cited in the literature.[27]

H. REFERENCES

1. (a) Beckmann, E., *Ber*., **1886**, *19*, 988. (b) Beckmann, E., *Ber*., **1887**, *20*, 1507.
2. (a) Fernandez, A. B.; Lezcano-Gonzalez, I.; Boronat, M.; Blasco, T. and Corma, A., *J. Catal.,* **2007**, *249*, 116. (b) Zhang, Y. J.; Wang, Y. Q.; Bu, Y. F.; Wang, L.; Mi, Z. T.; Wu, W.; Min, E. Z.; Fu, S. B.; Zhu, Z. H.; He, F. and Han, S., *Reaction Kinetics & Catal. Lett.,* **2007**, *90*, 365. (c) Forni, L.; Fornasari, G.; Trifiro, F.; Aloise, A.; Katovic, A.; Giordano, G. and Nagy, J. B., *Microporous & Mesoporous Mater.,* **2007**, *101*, 161. (d) Bonelli, B.; Forni, L.; Aloise, A.; Nagy, J. B.; Fornasari, G.; Garrone, E.; Gedeon, A.; Giordano, G. and Trifiro, F., *Microporous & Mesoporous Mater.,* **2007**, *101*, 153. (e) Sardarian, A. R.; Shahsavari-Fard, Z.; Shahsavari, H. R. and Ebrahimi, Z., *Tetrahedron Lett.,* **2007**, *48*, 2639. (f) Thomas, B. and Sugunan, S., *Microporous & Mesoporous Mater.,* **2006**, *96*, 55. (g) Marthala, V. R. R.; Jiang, Y. J.; Huang, J.; Wang, W.; Glaeser, R. and Hunger, M., *J. Am. Chem. Soc.,* **2006**, *128*, 14812. (h) Fernandez, A.-B.; Marinas, A.; Blasco, T.; Fornes, V. and Corma, A., *J. Catal.,* **2006**, *243*, 270. (i) Xiao, L. F.; Peng, J. J. and Xia, C. G., *Chinese Chem. Lett.,* **2006**, *17*, 617. (j) Yoo, K. H.; Choi, E. B.; Lee, H. K.; Yeon, G. H.; Yang, H. C. and Pak, C. S., *Synthesis,* **2006**, 1599. (k) Curtis, M.; Bunnelle, W.; Pagano, T.; Gopalakrishnan, M. and Faghih, R., *Synth. Commun.,* **2006**, *36*, 321. (l) Blaszczyk, K.; Koenig, H.; Mel, K. and Paryzek, Z., *Tetrahedron,* **2006**, *62*, 1069. (m) Ngamcharussrivichai, C.; Wu, P. and Tatsumi, T., *J. Catal.,* **2005**, *235*, 139. (n) Mao, D. S.; Lu, G. Z. and Chen, Q. L., *J. Mol. Catal. A: Chem.,* **2005**, *240*, 164. (o) Li, W.-C.; Lu, A.-H.; Palkovits, R.; Schmidt, W.; Spliethoff, B. and Schueth, F., *J. Am. Chem. Soc.,* **2005**, *127*, 12595. (p) Sirijaraensre, J.; Truong, T. N. and Limtrakul, J., *J. Phy. Chem. B,* **2005**, *109*, 12099. (q) Fernandez, A. B.; Boronat, M.; Blasco, T. and Corma, A., *Angew. Chem. Int. Ed.,* **2005**, *44*, 2370. (r) Bucko, T.; Hafner, J. and Benco, L., *J. Phys. Chem. A,* **2004**, *108*, 11388. (s) Wu, M. S.; Chen, R. Y. and Huang, Y., *Synthesis,* **2004**, 2441. (t) Chang, J.-C. and Ko, A.-N., *Reaction Kinetics & Catal. Lett.,* **2004**, *83*, 283. (u) Chang, J.-C. and Ko, A.-N., *Catal. Today,* **2004**, *97*, 241. (v) Forni, L.; Fornasari, G.; Giordano, G.; Lucarelli, C.; Katovic, A.; Trifiro, F.; Perri, C. and Nagy, J. B., *Phys. Chem. Chem. Phys.,* **2004**, *6*, 1842. (w) Takuwa, T.; Minowa, T.; Onishi, J. Y. and Mukaiyama, T., *Chem. Lett.,* **2004**, *33*, 322. (x) Gui, J. Z.; Deng, Y. Q.; Hu, Z. D. and Sun, Z. L., *Tetrahedron Lett.,* **2004**, *45*, 2681. (y) Wang, C. D.; Jiang, X.; Shi, H. J.; Lu, J.; Hu, Y. F. and Hu, H. W., *J. Org. Chem.,* **2003**, *68*, 4579. (z) Chandrasekhar, S. and Gopalaiah, K., *Tetrahedron Lett.,* **2001**, *42*, 8123.
3. Hendrickson, J. B; Cram, D. J. and Hammond, G. S., *Organic Chemistry*, 3rd ed., McGraw-Hill, Tokyo, **1970**, p. 708.
4. Rosenberg, M. G.; Haslinger, U. and Brinker, U. H., *J. Org. Chem.,* **2002**, *67*, 450.
5. (a) Hattori, K.; Maruoka, K. and Yamamoto, H., *Tetrahedron Lett*., **1982**, *23*, 3395. (b) Hattori, K.; Matsumura, Y.; Miyazaki, T.; Maruoka, K. and Yamamoto, H., *J. Am. Chem. Soc*., **1981**, *103*, 7368.
6. Oxley, P. and Short, W. F., *J. Chem. Soc*., **1948**, 1514.
7. Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K. and Yamamoto, H., *J. Am. Chem. Soc*., **1983**, *105*, 2831.
8. Ishida, Y.; Sasatani, S.; Maruoka, K. and Yamamoto, H., *Tetrahedron Lett*., **1983**, *24*, 3255.
9. Yokomatsu, T.; Minowa, T.; Yoshida, Y. and Shibuya, S., *Heterocycles* **1997**, *44*, 111.

10. Matsumura, Y.; Fujiwara, J.; Maruoka, K. and Yamamoto, H., *J. Am. Chem. Soc*., **1983**, *105*, 6312.

11. (a) Rakitin, O. A.; Rees, C. W.; Williams, D. J. and Torroba, T., *J. Org. Chem.,* **1996**, *61*, 9178. (b) Hill, R. K. and Cullison, D. A., *J. Am. Chem. Soc.,* **1973**, *95*, 2933. (c) Sasaki, T.; Eguchi, S. and Toru, T., *Tetrahedron Lett*., **1971**, 1109. (d) Stevens, T. E., *J. Org. Chem.,* **1969**, *34*, 2451. (e) Huitric, A. C. and Nelson, S. D., *J. Org. Chem.,* **1969**, *34*, 1230. (f) Conley, R. T. and Nowak, B. E., *J. Org. Chem.,* **1962**, *27*, 1965. (g) Bencee, W. L. and Allen, M. J., *J. Org. Chem.,* **1957**, *22*, 352. (h) Burrows, W. D. and Eastman, R. H., *J. Am. Chem. Soc.,* **1957**, *79*, 3756. (i) Regan, B. M. and Hayes, F. N., *J. Am. Chem. Soc.,* **1956**, *78*, 639. (j) Bartlett, P. D. and Stiles, M., *J. Am. Chem. Soc.,* **1955**, *77*, 2806. (k) Lyle, K. E.; Fielding, H. L.; Crtnquil, G. and Rouaand, J., *J. Org. Chem.,* **1955**, *20*, 623. (l) Hatch, M. J. and Cram, D. J., *J. Am. Chem. Soc.,* **1953**, *75*, 38. (m) Kaufmann, S., *J. Am. Chem. Soc.,* **1951**, *73*, 1779. (n) Price, C. C. and Mueller, G. P., *J. Am. Chem. Soc.,* **1944**, *66*, 634. (o) Perkin, W. H. and Titley, A. F., *J. Chem. Soc.,* **1921**, *119*, 1089. (p) Schroeter, G., *Ber*., **1911**, *44*, 1201. (q) Glover, W. H., *J. Chem. Soc.,* **1908**, *93*, 1285. (r) Wallach, O., *Ann*., **1890**, *259*, 309. (s) Leuckart, R. and Bach, E., *Ber.,* **1887**, *20*, 104.

12. (a) Cao, L. Y.; Sun, J. W.; Wang, X. Y.; Zhu, R.; Shi, H. J. and Hu, Y. F., *Tetrahedron,* **2007**, *63*, 5036. (b) Wang, C. D.; Rath, N. P. and Covey, D. F., *Tetrahedron Lett.,* **2006**, *47*, 7837. (c) Passacantilli, P.; Centore, C.; Ciliberti, E.; Piancatelli, G. and Leonelli, F., *Eur. J. Org. Chem.,* **2004**, 5083. (d) Garcia Martinez, A.; Teso Vilar, E.; Garcia Fraile, A.; de la Moya Cerero, S. and Lora Maroto, B., *Tetrahedron,* **2004**, *60*, 9447. (e) Garcia Martinez, A.; Teso ilar, E.; Garcia Fraile, A.; De la Moya Cerero, S. and Lora Maroto, B., *Eur. J. Org. Chem.,* **2002**, 781. (f) Laxmisha, M. S. and Rao, G. S. R. S., *Tetrahedron Lett.,* **2000**, *41*, 3759. (g) Kirihara, M.; Niimi, K.; Okumura, M. and Momose, T., *Chem. Pharm. Bull.,* **2000**, *48*, 220. (h) Coskun, N.; Tat, F. T. and Guven, O. O., *Synth. Commun.,* **1999**, *29*, 3889. (i) Petukhov, P. A. and Tkachev, A. V., *Tetrahedron,* **1997**, *53*, 2535. (j) Pejanovic, V. M.; Petrovic, J. A.; Csanadi, J. J.; Stankovic, S. M. and Miljkovic, D. A., *Tetrahedron,* **1995**, *51*, 13379. (k) Garcia Martinez, A.; Teso Vilar, E.; Garcia Fraile, A.; de la Moya Cerero, S.; Diaz Oliva, C.; Subramanian, L. R. and Maichle, C., *Tetrahedron: Asymmetry,* **1994**, *5*, 949. (l) Fujioka, H.; Miyazaki, M.; Kitagawa, H.; Yamanaka, T.; Yamamoto, H.; Takuma, K. and Kita, Y., *J. Chem. Soc., Chem. Commun.,* **1993**, 1634. (m) Petukhov, P. A. and Tkachev, A. V., *Synlett,* **1993**, 580. (n) Fujioka, H.; Kitagawa, H.; Yamanaka, T. and Kita, Y., *Chem. Pharm. Bull.,* **1992**, *40*, 3118. (o) Fujioka, H.; Yamamoto, H.; Miyazaki, M.; Yamanaka, T.; Takuma, K. and Kita, Y., *Tetrahedron Lett.,* **1991**, *32*, 5367. (p) Fujioka, H.; Yamanaka, T.; Takuma, K.; Miyazaki, M. and Kita, Y., *J. Chem. Soc., Chem. Commun.,* **1991**, 533. (q) Fujioka, H.; Miyazaki, M.; Yamanaka, T.; Yamamoto, H. and Kita, Y., *Tetrahedron Lett.,* **1990**, *31*, 5951. (r) Bakale, R. P.; Scialdone, M. A. and Johnson, C. R., *J. Am. Chem. Soc.,* **1990**, *112*, 6729. (s) VerHaeghe, D. G.; Weber, G. S. and Pappalardo, P. A., *Tetrahedron Lett.,* **1989**, *30*, 4041. (t) Hill, R. K.; McKinnie, B. G.; Conley, R. T.; Darby, P. S.; Van Halbeek, H. and Holt, E., *Tetrahedron,* **1988**, *44*, 3405. (u) Nishiyama, H.; Sakuta, K.; Osaka, N.; Arai, H.; Matsumoto, M. and Itoh, K., *Tetrahedron,* **1988**, *44*, 2413. (v) Nishiyama, H.; Sakuta, K. and Itoh, K., *Tetrahedron Lett.,* **1984**, *25*, 223. (w) Nishiyama, H.; Sakuta, K.; Osaka, N. and Itoh, K., *Tetrahedron Lett.,* **1983**, *24*, 4021. (x) Bosch, J.; Moral, M. and Rubiralta, M., *Heterocycles,* **1983**, *20*, 509. (y) Oxenrider, B. C. and Rogic, M. M., *J. Org. Chem.,* **1982**, *47*, 2629. (z) Redeker, U.; Engel, N. and Steglich, W., *Tetrahedron Lett.,* **1981**, *22*, 4263. (aa) Miljkovic, D. and Petrovic, J., *J. Org. Chem.,* **1977**, *42*, 2101. (bb) Bondavalli, F.; Schenone, P. and Longobardi, M., *Gazz. Chim. Ital.,* **1975**, *105*, 1317. (cc) Maeda, K.; Moritani, I.; Hosokawa, T. and Murahashi, S., *J. Chem. Soc., Chem. Commun.,* **1975**, 689. (dd) Grob, C. A. and Ide, J., *Helv. Chim. Acta,* **1974**, *57*, 2562. (ee) Grob, C. A. and Ide, J., *Helv. Chim. Acta,* **1974**, *57*, 2571. (ff) Miljkovic, D.; Petrovic, J.; Stajic, M. and Miljkovic, M., *J. Org. Chem.,* **1973**, *38*, 3585. (gg) Hill, R. K. and Cullison, D. A., *J. Am. Chem. Soc.,* **1973**, *95*, 2923. (hh) Autrey, R. L. and Scullard, P. W., *J. Am. Chem. Soc.,* **1968**, *90*, 4924. (ii) Eisele, W.; Grob, C. A.; Renk, E. and Von Tschammer, H., *Helv. Chim. Acta,* **1968**, *51*, 816. (jj) Stevens, T. E., *Tetrahedron Lett.,* **1967**, 3017.

13. (a) Werner, A. and Piguet, A., *Ber.,* **1904**, *37*, 4295. (b) Werner, A. and Detscheff, T., *Ber.,* **1905**, *38*, 69.

14. (a) Confalone, P. N. and Huie, E. M., *J. Org. Chem.,* **1987**, *52*, 79. (b) Palmere, R. M.; Conley, R. T. and Rabikowitz, J. L., *J. Org. Chem.,* **1972**, *37*, 4095. (c) Hill, R. K.; Conley, R. T. and Chortyk, O. T., *J. Am. Chem. Soc.,* **1965**, *87*, 5646. (d) Conley, R. T. and Nowak, B. E., *J. Org. Chem.,* **1961**, *86*, 692. (e) Graham, S. H. and Williams, A. J. S., *J. Chem. Soc.,* **1959**, 4066. (f) Lyle, R. E. and Lyle, G. G., *J. Org. Chem.,* **1953**, *18*, 1058.
15. (a) Cavä, M. P. and Ahmed, Q. A., *J. Org. Chem.,* **1968**, *33*, 2440. (b) Autrey, R. L. and Scullard, P. W., *J. Am. Chem. Soc.,* **1965**, *87*, 3284. (c) Freemam, J. P., *J. Org. Chem.,* **1961**, *26*, 3507.
16. (a) Ikeda, M.; Uno, T.; Homma, K.; Ohno, K.; Tamura, Y., *Synth. Commun.*, **1980**, *10*, 437. (b) Huitric, A. C. and Nelson, S. D., *J. Org. Chem.,* **1969**, *34*, 1230.
17. (a) Gates, M. and Malchick, S. P., *J. Am. Chem. Soc.,* **1957**, *79*, 5546. (b) Hall, H. K., *J. Am. Chem. Soc.,* **1960**, *82*, 1209.
18. (a) Conley, R. T. and Ghosh, S., *Mech. Mol. Migr.,* **1971**, *4*, 197. (b) Ohno, M. and Terasawa, I., *J. Am. Chem. Soc.,* **1966**, *88*, 5683. (c) Hill, R. K., *J. Org. Chem.,* **1962**, *27*, 29. (d) Hill, R. K. and Conley, R. T., *J. Amer. Chem. Soc.,* **1960**, *82*, 645.
19. (a) Catsoulacos, P. and Catsoulacos, D., *J. Heterocycl. Chem.,* **1993**, *30*, 1. (b) Oka, K. and Hara, S., *J. Org. Chem.,* **1978**, *43*, 3790. (c) Paisley, J. K. and Weiler, L., *Tetrahedron Lett*., **1972**, 261. (d) Olson, E. S. and Richards, J. H., *J. Org. Chem.,* **1968**, *33*, 434. (e) Singh, H. and Parashar, V. V., *Tetrahedron Lett*., **1966**, 983. (f) Cava, M. P.; Glamkowski, E. J.; and Weintraub, P. M., *J. Org. Chem.,* **1966**, *31*, 2755. (g) Ohta, G.; Takegoshi, T.; Ueno, K. and Shimizu, M., *Chem. Pharm. Bull.* (*Tokyo*), **1965**, *13*, 1445. (h) Doorenbos, N. J. and Havranek. R. E., *J. Org. Chem.,* **1965**, *30*, 2474. (i) Shoppee, C. W.; Lack, R. E.; Mirrington, R. N. and Smith, C. R., *J. Chem. Soc.,* **1965**, 5868. (j) Shoppee, C. W.; Lack, R. K. and Newman, B. C., *J. Chem. Soc.,* **1964**, 3388. (k) Shoppee, C. W.; Akhtar, M. I. and Lack, R. E., *J. Chem. Soc.,* **1964**, 3392. (l) Mazur, R., *J. Org. Chem.,* **1963**, *28*, 248. (m) Shoppee, C. W.; Kruger, G. and Mirrington. R. N., *J. Chem. Soc.,* **1962**, 1050. (n) Shoppee, C. W.; Killick, R. W. and Kruger, G., *J. Chem. Soc.,* **1962**, 2275. (o) Zderic, J. A. and Iriarte, J., *J. Org. Chem.,* **1962**, *27*, 1756. (p) Hassner, A. and Pomerants, I. H., *J. Org. Chem.,* **1962**, *27*, 1760. (q) Shoppee, C. W. and Kruger, G., *J. Chem. Soc.,* **1961**, 3641. (r) Knof, L., *Ann*., **1961**, *642*, 194. (s) Blickenstaff, R. T. and Foster, E. L., *J. Org. Chem.,* **1961**, *26*, 5029. (t) Bladon, P. and McMeekin, W., *J. Chem. Soc.,* **1961**, 3504. (u) Jacobs, T. A. and Brownfield, B. B., *J. Am. Chem. Soc.,* **1960**, *82*, 4033. literature covered up to 1960. (v) Litvan, F. and Robinson, R., *J. Chem. Soc.,* **1938**, 1997.
20. (a) Hauske, J. R., *Comp. Org. Syn.,* **1991**, *1*, 98. (b) Maruoka, K. and Yamamoto, H., *Comp. Org. Syn.,* **1991**, *6*, 763. (c) Carig, D., *Comp. Org. Syn.,* **1991**, *6*, 689. (d) Hesse, M., *Ring Enlargement in Organic Chemistry*, VCH, Weinheim, **1991**. (e) Jochims, J. C.; Hehl, S. and Herzberger, S., *Synthesis,* **1990**, 1128. (f) Gawley, R. E., *Org. React.,* **1988**, *35*, 1. (g) Conley, R. T. and Ghosh, S., Abnormal Beckmann rearrangements, in *Mechanisms of Molecular Migrations* ed. Thyagarajan, B. S., Wiley-Interscience, New York, **1971**, pp. 197–308. (h) McCarty, C. G., *Syn-anti* Isomerizations and Rearrangements, in *The Chemistry of the Carbon-Nitrogen Double Bond,* ed. Patai, S., Interscience, New York, **1970**, pp. 408–438. (i) Beckwith, A. L. J., Synthesis of Amides, in *The Chemistry of Amides*, ed. Zabicky, J., Interscience, New York, **1970**; p. 131. (j) Hornke, G.; Krauch, H. and Kunz, W., *Chem. Ztg.,* **1965**, *89*, 525. (k) Smith, P. A. S., Rearrangements Involving Migration to an Electron-Deficient Nitrogen or Oxygen, in *Molecular Rearrangements*, ed. de Mayo, P., Interscience: New York, **1963**, p 45. (l) Donaruma, L. G. and Heldt, W. Z., *Org. React.,* **1960**, *11*, 1. (m) Popp, F. D. and McEwen, W. E., *Chem. Rev.,* **1958**, *58*, 370. (n) Moller, F., Amine nach Speziellen Methoden, In *Methoden der Organischen Chemie*, ed. Muller, E., Thieme Verlag, Stuttgart, **1957**, *XI*, Part 1, p. 892. (o) Jones, B., *Chem. Rev.,* **1944**, *35*, 335. (p) Blatt, A. H., *Chem. Rev.,* **1933**, *12*, 215.
21. Luca, L. D., Giacomelli, G. and Porcheddu, A., *J. Org. Chem.,* **2002**, *67*, 6272.
22. (a) Boero, M.; Ikeshoji, T.; Liew, C. C.; Terakura, K. and Parrinello, M., *J. Am. Chem. Soc.,* **2004**, *126*, 6280. (b) Ikushima, Y.; Hatakeda, K.; Sato, O.; Yokoyama, T. and Arai, M., *J. Am. Chem. Soc.,* **2000**, *122*, 1908. (c) Sato, O.; Ikushima,Y. and Yokoyama, T., *J. Org.Chem*., **1998**, *63*, 9100.

23. (a) Arisawa, M. and Yamaguchi, M., *Org. Lett.,* **2001**, *3*, 311. (b) Kusama, H.; Yamashita, Y. and Narasaka, K., *Bull. Chem. Soc. Jpn*., **1995**, *68*, 373. (c) Narasaka, K.; Kusama, H.; Yamashita, Y. and Sato, H., *Chem. Lett*., **1993**, 489. (d) Mukaiyama, T. and Harada, T., *Chem. Lett*., **1991**, 1653. (e) Harada, T.; Ohno, T.; Kobayashi, S. and Mukaiyama, T., *Synthesis,* **1991**, 1216. (f) Izumi, Y., *Chem. Lett*., **1990**, 2171.
24. Nguyen, M. T.; Raspoet, G. and Vanquickenborne, L. G., *J. Am. Chem. Soc.,* **1997**, *119*, 2552.
25. (a) Smith, B. T.; Wendt, J. A. and Aubé, J., *Org. Lett.,* **2002**, 4, 2577. (b) Ogata, Y.; Takagi, K. and Mizuno, K., *J. Org. Chem.,* **1982**, *47*, 3684. (c) Suginome, H. and Takahashi, H., *Bull. Chem. Soc. Jpn*., **1975**, 576. (d) Sasaki, T.; Eguchi, S. and Tom, T., *J. Chem. Soc., D,* **1970**, 1239. (e) Oine, T. and Mukai, T., *Tetrahedron Lett*., **1969**, 157. (f) Taylor, R. T.; Douek, M. and Just, G., *Tetrahedron Lett*., **1966**, 4143. (g) Amin, J. H. and de Mayo, P., *Tetrahedron Lett*., **1963**, 1585.
26. White, J. D., Hrnciar, P. and Stappenbeck, F., *J. Org. Chem.* **1999**, *64*, 7871.
27. (a) Lee, G. S.; Nakagawa, Y.; Hwang, S. G.; Davis, M. E.; Wagner, P.; Beck, L. and Zones, S. I., *J. Am. Chem. Soc.,* **2002**, *124*, 7024. (b) Boruah, M. and Konwar, D., *J. Org. Che*m, **2002**, *67*, 7138. (c) Jiang, X.; Wang, C.; Hu, Y.; Hu, H. and Covey, D. F., *J. Org. Chem*., **2000**, *65*, 3555. (d) Katritzky, A. R.; Monteux, D. A. and Tymoshenko, D. O., *Org. Lett.,* **1999**, *1*, 577. (e) Krow, G. R., Szczepanski, S. W., Kim, J. Y., Liu, N., Sheikh, A., Xiao, Y. and Yuan, J., *J. Org. Chem.,*. **1999**, *64*, 1254. (f) Kuhl, A.; Karele, H. and Kreiser, W., *Helv. Chim. Acta,* **1999**, *82*, 30. (g) Holderich, W. F.; Roseler, J.; Heitmann, G. and Liebens, A. T., *Catal. Today,* **1997**, *37*, 353. (h) Han, M. and Covey, D. F., *J. Org. Chem*., **1996**, *61*, 7614. (i) Krow, G. R.; Cheung, O. H.; Hu, Z. and Lee, Y. B., *J. Org. Chem.,* **1996**, *61*, 5574. (j) Yokomatsu, T.; Yoshida, Y.; Nakabayashi, N. and Shibuya, S., *J. Org. Chem.,* **1994**, *59*, 7562. (k) Nikolaropoulos, S.; and Catsoulacos, P., *J. Heterocycl. Chem.,* **1990**, *27*, 1997. (l) Dolle, R. E.; Allaudeen, H. S. and Kruse, L. I., *J. Med. Chem*., **1990**, *33*, 877. (m) Burguet, M. C.; Aucejo, A. and Corma, A., *Can. J. Chem. Eng.,* **1987**, *65*, 944. (n) Fráter, G.; Müller, U. and Günther, G., *Tetrahedron Lett.,* **1984**, *25*, 1133. (o) Sakane, S.; Matsumura, Y.; Yamamura, Y.; Ishida, Y.; Maruoka, K. and Yamamoto, H., *J. Am. Chem. Soc.,* **1983**, *105*, 672. (p) Krow, G. and Szczepanski, S., *J. Org. Chem.* **1982**, *47*, 1153. (q) Carter, K. N. and Hulse, J. E., *J. Org. Chem.,* **1982**, *47*, 2208. (r) Novoselov, E. F.; Isaev, S. D.; Yurchenko, A. G.; Vodichka, L. and Trshiska, Y., *J. Org. Chem. USSR,* **1981**, *17*, 2284. (s) Hattori, K.; Matsumura, Y.; Miyazaki, T.; Maruoka, K. and Yamamoto, H., *J. Am. Chem. Soc.,* **1981**, *103*, 1368. (t) Krow, G. R., *Tetrahedron,* **1981**, *37*, 1283. (u) Pfenninger, J. and Graf, W., *Helv. Chim. Acta,* **1980**, *63*, 2338. (v) Schlatter, H.-R. and Graf, W., *Helv. Chim. Acta,* **1980**, *63*, 1554. (w) Olah, G. A. and Fung, A. P., *Synthesis,* **1979**, 537. (x) Sasaki, T.; Eguchi, S. and Hiroaki, O., *J. Org. Chem.,* **1976**, *41*, 1803. (y) Mammato, D. C. and Eadon, G. A., *J. Org. Chem.,* **1975**, *40*, 1784. (z) Chapman, J. C. and Pinhey, J. T., *Aust. J. Chem*., **1974**, *27*, 2421. (aa) Cohen, K. F.; Kazlauskas, R. and Pinhey, J. T., *J. Chem. Soc., Perkin Trans. 1*, **1973**, 2076. (bb) Moriconi, E. J. and Stemniski, M. A., *J. Org. Chem.,* **1972**, *37*, 2035. (cc) Ogura, H.; Takayanaqi, H. and Miyahara, C., *J. Org. Chem.,* **1972**, *37*, 519. (dd) Kelly, K. K. and Matthews, J. S., *J. Org. Chem.,* **1971**, *36*, 2159. (ee) Sasaki, T.; Eguchi, S. and Toru, T., *J. Org. Chem.,* **1971**, *36*, 2454. (ff) Fenselau, A. H.; Hamamura, E. H. and Moffatt, J. G., *J. Org. Chem.,* **1970**, *35*, 3546. (gg) Sasaki, T.; Eguchi, S. and Toru, T., *J. Org. Chem.,* **1970**, *35*, 4109. (hh) Korsloot, J. G.; Keizer, V. G. and Schlatmann, J. L. M. A., *Recl. Trav. Chim. Pays-Bas*, **1969**, *88*, 447. (ii) Narayanan, V. L. and Setescak, L., *J. Heterocycl. Chem.,* **1969**, *6*, 445. (jj) Korsloot, J. G. and Keizer, V. G., *Tetrahedron Lett*., **1969**, 3517. (kk) Potti, N. D. and Nobles, W. L., *J. Pharm. Sci.,* **1968**, *57*, 1785. (ll) Lansbury, P. T. and Mancuso, N. R., *J. Am. Chem. Soc.,* **1966**, *88*, 1205. (mm) Morita, K.-I, and Suzuki, Z., *J. Org. Chem.,* **1966**, *31*, 233. (nn) Hassner, A. and Wentworth, W. A., *Chem. Commun.,* **1965**, 44. (oo) Grob, C. A.; Fischer, H. P.; Raudenbusch, W. and Zergenyi, J., *Helv. Chim. Acta*, **1964**, *47*, 1003. (pp) Conley, R. T., *J. Org. Chem*., **1963**, *28*, 278. (qq) Conley, R. T. and Lange, R. J., *J. Org. Chem.,* **1963**, *28*, 210. (rr) Conley, R. T. and Annis, M. C., *J. Org. Chem.,* **1962**, *27*, 1961. (ss) Hill, R. K. and Chortyk, O. T., *J. Am. Chem. Soc*., **1962**, *84*, 1064. (tt) Conley, R. T. and Frainier, L. J., *J. Org. Chem.,* **1962**, *27*, 3844.

(uu) Lansbury, P. T. and Colson, J. G., *J. Am. Chem. Soc.,* **1962**, *84*, 4167. (vv) Elderfield, R. C. and Losin, E. T., *J. Org. Chem.,* **1961**, *26*, 1703. (ww) Ferris, A. F., *J. Org. Chem*., **1960**, *25*, 12. (xx) Hill, R. K. and Conley, R. T., *Chem. Ind. (London)*, **1956**, 1314. (yy) Snyder, H. R. and Elston, C. T., *J. Am. Chem. Soc.,* **1954**, *76*, 3039. (zz) Shechter, H. and Kirk, J. C., *J. Am. Chem. Soc.,* **1951**, *73*, 3087. (aaa) Sanford, J. K.; Blair, F. T.; Arroya, J. and Sherk, K. W., *J. Am. Chem. Soc.,* **1945**, *67*, 1941. (bbb) Blatt, A. H. and Barnes, R. P., *J. Am.. Chem. Soc*., **1934**, *56*, 1148.

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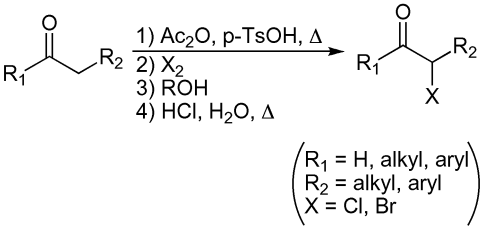
Bedoukian Halogenation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Bedoukian in 1944.[1] It is a reaction for preparing α-brominated ketones or aldehydes via a sequential process, including the formation of enol acetate, the addition of bromine to enol acetate, and the acidic hydrolysis of the resulting intermediate addition.[2]

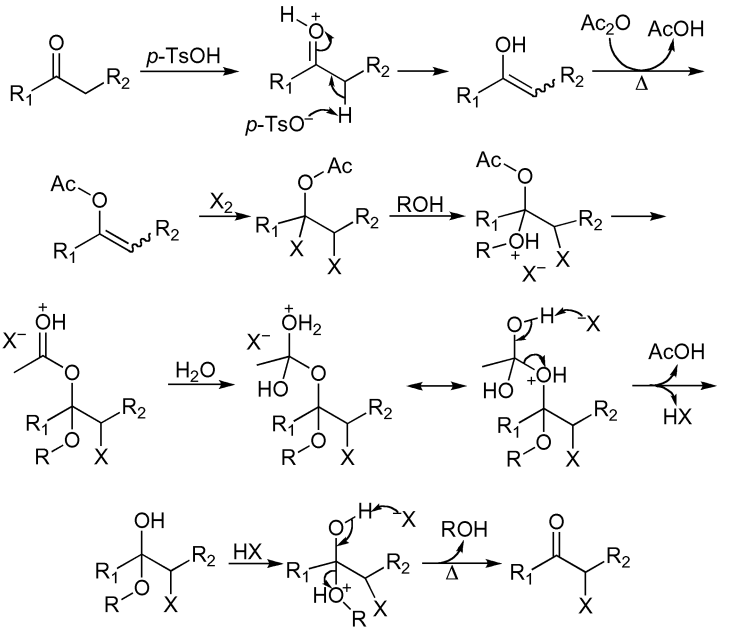
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Displayed here is the general mechanism of the halogenation.

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang



D. MODIFICATION

This reaction has been modified for preparing α-halogenated ketones via enol tosylate,[3] enol ethers,[4] and enol silyl ether.[5]

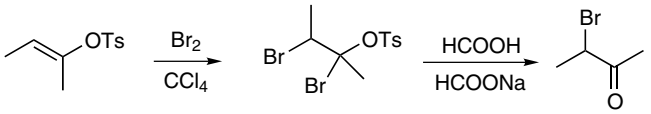
E. APPLICATIONS

This reaction provides an alternative method for preparing α-halogenated carbonyl compounds.

F. RELATED REACTIONS

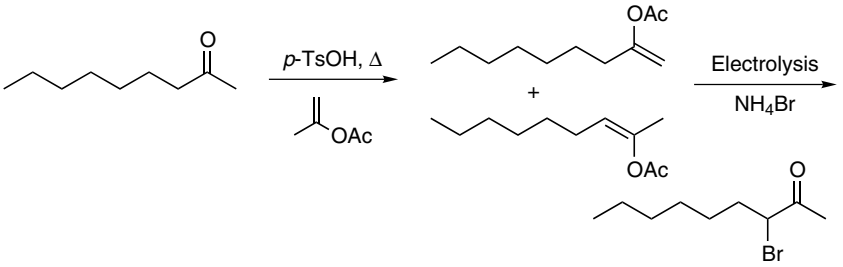
This reaction is related to the *Hell-Volhard-Zelinsky Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



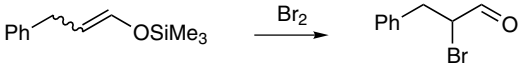
Reference 3.

To a solution of 0.5 mL CCl_4 containing 0.0358 g 2-buten-2-yl tosylate (0.01585 mmol) cooled in an ice bath was added 0.025 g bromine (0.1585 mmol); the mixture was kept cold until the completion of the addition. Evaporation of solvent gave the crude product. The flask containing erythro-2,3-dibromo-2-butyl tosylate was added the 0.125 M buffer of formic acid–sodium formate, and the reaction was monitored to completion. Then the solution was neutralized with $NaHCO_3$ and extracted with CCl_4. Removal of the solvent afforded 3-bromo-2-butanone. (*Note*: No complete experimental procedure was given in the original literature.)



Reference 2a.

A mixture of 1.02 g 2-octanone (7.92 mmol), 1.9 g isopropenyl acetate (19 mmol), and 50 mg *p*-TsOH was refluxed for 48 h. The mixture was worked up in the usual manner to give 1.32 g 1- and 2-octen-2-yl acetates, in a yield of 90%, b.p. 54–57°C (at 11 mmHg). To an electrolysis apparatus (an undivided cell equipped with two platinum electrodes (3 cm^2), a gas lead pipe, and a thermometer) were added 30 mg enol acetate, 19.7 mg NH_4Br (0.201 mmol), 6 mL acetonitrile, and 2 mL water. This solution was under a constant current of 6.7 mA/cm^2 at 3.0–5.0 V (anode voltage −0.75 V vs. Ag wire) at 20–25°C. After 2.3 F/mol of electricity was passed, the mixture was concentrated, and the residue was taken up in benzene:EtOAc (1:l). The usual workup gave 33.3 mg 3-bromo-2-octanone, in a yield of 95%. (*Note*: The corresponding chemical in the original literature was not relevant.)



Reference 5.

To a solution of 25 mL CCl_4 containing 6.2 g silyl enol ether was added slowly, over several hours, 1 equivalent of bromine in carbon tetrachloride. The rate of addition was maintained so that the solution was always colorless to pale orange. After the usual workup, 4.9 g 2-bromo-3-phenylpropanal was obtained as a colorless liquid, in a yield of 77%, b.p. 70–75°C (at 2 mmHg).

Other references for the preparation of α-halogenated carbonyl compounds are cited in the literature.[6]

H. REFERENCES

1. (a) Bedoukian, P. Z., *J. Am. Chem. Soc.*, **1944**, *66*, 1326. (b) Bedoukian, P. Z., *J. Am. Chem. Soc.*, **1945**, *67*, 1430.

2. (a) Torii, S.; Inokuchi, T.; Misima, S. and Kobayashi, T., *J. Org. Chem*., **1980**, *45*, 2731. (b) Rozen, S. and Menahem, Y., *Tetrahedron Lett*., **1979**, 725. (c) Cambie, R. C.; Hayward, R. C.; Jurlina, J. L.; Rutledge, P. S. and Woodgate, P. D., *J. Chem. Soc., Perkin Trans.*, **1978**, 126. (d) Jones, E. R. H. and Wluka, D. J., *J. Chem. Soc*., **1959**, 907. (e) Leonard, N. J. and Owens, F. H., *J. Am. Chem. Soc*., **1958**, *80*, 6039. (f) Bedoukian, P. Z., *Org. Synth. Coll.,* **1955**, *3*, 127. (g) Djerassi, C. J. and Lenk, C. T., *J. Am. Chem. Soc*., **1953**, *75*, 3493.
3. Peterson, P. E. and Indelicato, J. M., *J. Org. Chem*., **1970**, *35*, 531.
4. (a) Hall, S. S.; Weber, G. F. and Duggan, A. J., *J. Org. Chem*., **1978**, *43*, 667. (b) Thiem, J.; Karl, H. and Schwentner, J., *Synthesis*, **1978**, 696. (c) Duggan, A. J. and Hall, S. S., *J. Org. Chem*., **1977**, *42*, 1057. (d) Georgonlis, C. and Kopytona, L. P., *Bull. Soc. Chim. Fr.*, **1975**, 1431. (e) Gaydou, E. M., *Tetrahedron Lett*., **1972**, 4055. (f) Lessard, J.; Driguez, H. and Vermes, J. P., *Tetrahedron Lett*., **1970**, 4887. (g) Schank, K. and Pack, W., *Ber*., **1969**, *102*, 1892. (h) Shelton, J. R. and Kasuga, T., *J. Org. Chem*., **1963**, *28*, 2841. (i) Jones, D. G. and Bremer, J. G. M., *Brit. Pat.*, Oct. 2, **1948**, 598080 [*Chem. Abstr*., **1948**, *42*, 4614a].
5. Reuss, R. H. and Hassner, A., *J. Org. Chem*., **1974**, *39*, 1785.
6. (a) Olah, G. A.; Ohannesian, L.; Arvanaghi, M. and Parakash, G. K. S., *J. Org. Chem*., **1984**, *49*, 2032. (b) Hamaoka, T. and Brown, H. C., *J. Org. Chem*., **1975**, *40*, 1190. (c) Bigley, D. S. and Payling, D. W., *J. Chem. Soc*., **1965**, 3974. (d) Tiollais, R., *Bull. Chem. Soc., Fr.*, **1964**, 1205. (e) Allinger, N. L.; Allinger, J.; Freiberg, L. A.; Czaja, R. F. and Lebel, N. A., *J. Am. Chem. Soc*., **1960**, *82*, 5876. (f) Bedoukian, P. Z., *J. Am. Chem. Soc*., **1944**, *66*, 1325.

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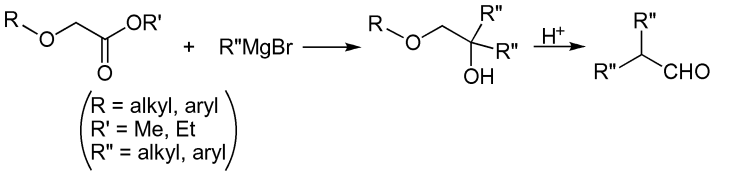
Béhal-Sommelet Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Béhal and Sommelet in 1904.[1] It is the transformation of methyl β-hydroxylalkyl ethers into aldehydes in the presence of acids, preferably oxalic acid. The methyl β-hydroxylalkyl ethers can be prepared via the *Grignard Reaction* between the Grignard reagents and esters of α-methoxy acetic acids.

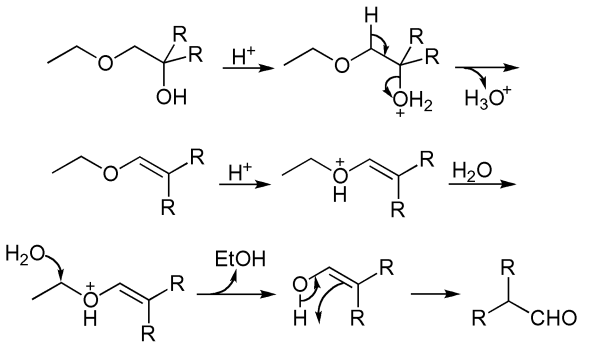
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is believed that this reaction undergoes dehydration in the presence of an acid to form an intermediate of vinyl ether that breaks down to the aldehyde. Some insight about the mechanism can be found in the rearrangement of methylallyl alcohol into isobutyraldehyde.[2]

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang



D. MODIFICATION

The formation of methyl β-hydroxylalkyl ethers has been modified using Grignard reagents and esters of α-phenoxyacetic acids because this reaction is easier to handle. The formed phenyl β-hydroxyalkyl ethers are further converted into ethyl β-hydroxyalkyl ether by heating under pressure with alcoholic potassium hydroxide because the ethoxy compounds are more readily converted into the aldehydes.[3] In the presence of oxalic acid, the hydrocarbon chain of aldehydes can be extended while reacting with vinyl ether.[4] It has been found that the reaction between a Grignard reagent and ethoxymethyleneaniline also affords aldehyde.[5] In addition, vinyl ether can be converted into aldehyde when heated at 215°C over SiO_2.[6]

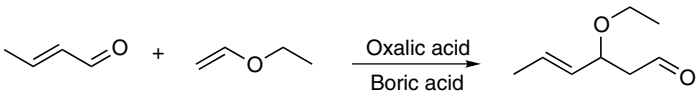
E. APPLICATIONS

It is a general method for preparing α-branched aldehydes.

F. RELATED REACTIONS

This reaction is related to the *Serini Reaction*.

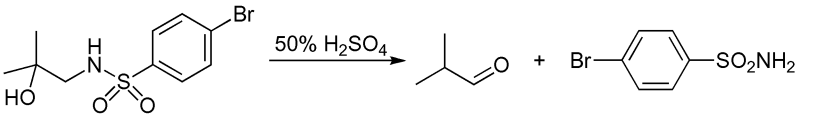
G. CITED EXPERIMENTAL EXAMPLES



Reference 4.

To a mixture of 630.0 g crotonaldehyde (9.0 mol) and 0.42 g boric acid–oxalic acid, was added 216.0 g vinyl ethyl ether (3.0 mol) over a period of 26 min while maintaining a reaction temperature of 40°C by periodic cooling. The red solution was stirred for an additional 15 min followed by neutralization of the catalyst with 5 g sodium carbonate in 200 mL water. Neutralization of the catalyst caused a color change from red to pale

yellow. The organic layer was distilled to provide 469 g wet crotonaldehyde and 195 g 3-ethoxy-4-hexenal, which distilled at 60–65°C (at 10 mmHg), in a yield of 46%.



Reference 7.

A total of 5 g l-*p*-bromobenzenesulfonamide-2-methyl-2-propanol was added to 60 mL 50% sulfuric acid, and the mixture was steam distilled until 100 mL distillate had been collected. To this distillate was added 4 g methone in 50 mL alcohol and a few drops of glacial acetic acid. The mixture was allowed to stand at room temperature for 8–9 days, after which the white crystals were removed by filtration and washed with aqueous alcohol to give 1.43 g methone derivative of isobutyraldehyde, m.p. 146–149°.

To the acid residue from the steam distillation was added an equal volume of water. The solid that separated was washed with water to afford 2.80 g *p*-bromobenzenesulfonamide, in a yield of 73%, m.p., 158–160°C.

Other references related to the synthesis of aldehydes are cited in the literature.[8]

H. REFERENCES

1. Béhal M. M. A. and Sommelet M., *Bull. Soc. Chim. Fr.*, **1904**, *31*, 300.
2. Currell, D. and Fry, A., *J. Am. Chem. Soc.,* **1956**, *78*, 4377.
3. Smith, L. I. and Nichols, J., *J. Org. Chem.,* **1941**, *6*, 489.
4. Hoaglin, R. I.; Kubler, D. G. and Leech, R. E., *J. Am. Chem. Soc.,* **1958**, *80*, 3069.
5. (a) Gattermann, L., *Ann.*, **1913**, *393*, 215. (b) Monier-Williams, G. W., *J. Chem. Soc.,* **1906**, *89*, 273.
6. Emerson, W. S. and Agnew, E. P., *J. Am. Chem. Soc.,* **1945**, *67*, 518.
7. Cairns, T. and Fletcher, J., *J. Am. Chem. Soc.,* **1941**, *63*, 1034.
8. (a) Johnson, K. and Degering, E., *J. Org. Chem.,* **1943**, *8*, 10. (b) Hersh, J. and Nelson, R., *J. Am. Chem. Soc.,* **1936**, *58*, 1631. (c) Stoermer, R., *Ber.,* **1906**, *39*, 2288. (d) Sommelet, M., *Ann. Chim. Phys.,* **1906**, *9*, 484. (e) Béhal M. M. A. and Sommelet M., *Comp. Rend*., **1904**, *138*, 89.

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Beirut Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Haddadin and Issodorides in 1965.[1] It is the preparation of quinoxaline-1,4-dioxides from the cycloaddition between benzofuroxan (i.e., benzofurazan *N*-oxide) and dienes, α,β-unsaturated ketones, enamines, or enolates. Unfortunately, this reaction is not named after the authors who discovered it; instead it is known as the Beirut reaction[2] after the city in which the inventors carried out is the initial work.[3] In most cases, ketones,[4] β-diketones,[5] β-ketoesters,[5b] β-ketonitrile,[2e] 1,3-dinitrile,[2d,2e,6] and β-ketoamides[7] all are suitable for this reaction, and the corresponding enolates can be easily prepared in the presence of a weak base such as triethylamine.[2a,2d,2e,5b] In addition, even phenolic enolates from phenol, resorcinol, hydroquinone, or benzoquinone undergo a similar dehydrative condensation with benzofuroxan under mild conditions (e.g., $NaOH/H_2O$, H_2O, $MeOH/RNH_2$, SiO_2/MeCN at room temperature), to give phenazine N,N'-dioxide derivatives.[3]

It should be pointed out that the Beirut reaction from unsymmetrically monosubstituted-benzofuroxanes affords two regio-isomers;[2e,5a] however, often only one regio-isomer is obtained after the workup and purification process,[2e] as shown in the reaction between 5-substituted benzofurxanes with benzoylacetonitrile, which gives only 7-substituted quinoxaline-1,4-dioxides.[8] Such high practical regioselectivity is probably due to the fact that the monosubstituents in benzofuroxanes do not have a directing effect on the formation of quinoxaline-1,4-dioxides.[5a] When aroylacetophenones are applied as the enolate precursors, the *ortho*-substituents have shown some directing effect, possibly owing to the steric hindrance, and the *para*-substituents do not have such effect.[5a] Besides the formation of quinoxaline N,N'-dioxides, the Beirut reaction can be used for quinoxaline mono-*N*-oxides as well.[2k]

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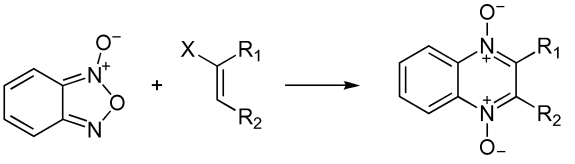
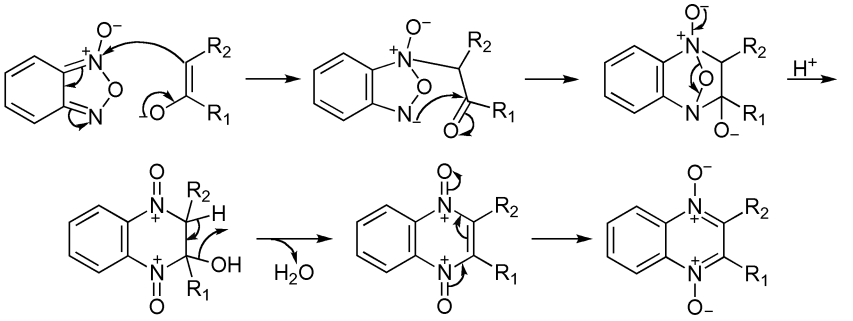
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

This reaction is assumed to involve the initial conjugate addition of enolate (or enamine) to the benzofuroxane ring, followed by the attack of nitrogen atom on the resumed carbonyl group,[3,5b] as shown below. In addition, the fused benzo moiety in benzofuroxane plays an important role, which provides the extra driving force for the Beirut reaction owing to the rearomatization of such a fused benzene ring. Furoxanes without a fused benzene ring are inactive in the Beirut reaction.[2f]



D. MODIFICATION

This reaction has been extended to use different phenolic enolates in the preparation of phenazine derivatives.[3]

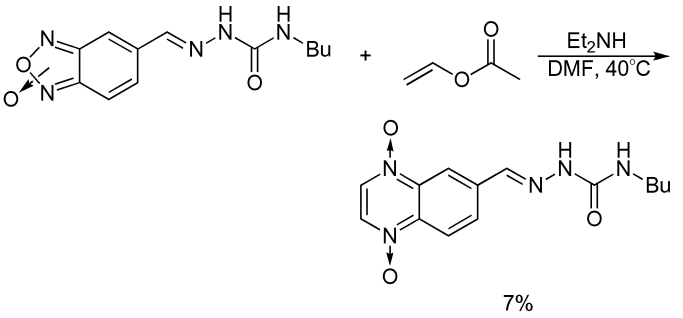
E. APPLICATIONS

This reaction provides a general tool for phenazine derivatives via the reduction of quinoxaline-1,4-dioxides.[1] Such reduction can be achieved by catalytic hydrogenation (e.g., complex hydrides, H_2-Pd/C, or dissolving metals)[9] or other reducing reagents, such as sodium dithionite ($Na_2S_2O_4$),[5b,10] sodium hyposulfite ($Na_2S_2O_3$),[11] PCl_3.[7] In addition, under light illumination, quinoxaline-1,4-dioxides easily rearrange to benzimidazolone derivatives via an oxaziridine intermediate, as shown by the conversion of 2-benzoyl-3-phenylquinoxaline-1,4-dioxide to 1,3-dibenzoylbenzimidazolone.[12]

F. RELATED REACTIONS

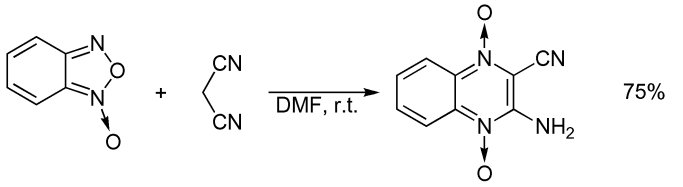
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 2d.

To a solution of 0.2 g 4-butyl-1-[(benzo[1,2-*c*]1,2,5-oxadiazol-5(6)-yl-N_1-oxide) methylidene]semicarbazide (0.72 mmol) and 0.07 mL Et_2NH in 0.5 mL DMF, was added 0.13 mL vinyl acetate (1.44 mmol) over 10 min at 0°C. The reaction mixture was then stirred at 40°C for 24 h. An additional 1.3 mL vinyl acetate (14.4 mmol) and 1.0 mL Et_2NH were added, and the stirring was continued at 40°C for 48 h. After that, the solvent was removed in vacuo and the oily residue was co-evaporated with toluene (3 × 10 mL). The residue was purified by silica gel column chromatography using CH_2Cl_2 as the eluent to afford 7% 4-butyl-1-[(quinoxalin-6-yl-N_1,N_4-dioxide)methylidene] semicarbazide as colorless oil.



Reference 6.

To a solution of 1.36 g benzofuroxan (10 mmol) and 0.7 g malononitrile (10.6 mmol) in 4 mL DMF cooled at 0°C in an ice bath was added a solution of 0.2 mL Et_3N in 3.0 mL DMF. The resulting mixture was stirred below ambient temperature for 1.5 h, after that solution was filtered, the solid was washed with Et_2O to give 1.51 g 3-amino-2-quinoxalinecarbonitrile 1,4-dioxide, in a yield of 75%, m.p. 190°C (dioxane).

Other references related to the Beirut reaction are cited in the literature.[13]

H. REFERENCES

1. Haddadin, M. J. and Issodorides, C. H., *Tetrahedron Lett.,* **1965**, 3253.
2. (a) Zarranz, B.; Jaso, A.; Lima, L. M.; Aldana, I.; Monge, A.; Maurel, S. and Sauvain, M., *Braz. J. Pharm. Sci.,* **2006**, *42*, 357. (b) Gali-Muhtasib, H. U.; Diab-Assef, M. and Haddadin, M. J., *J. Med. Liban.,* **2002**, *50*, 175. (c) Turker, L. and Dura, E., *J. Mol. Struct.: THEOCHEM,* **2002**, *593*, 143. (d) Cerecetto, H.; Maio, R. D.; González, M.; Risso, M.; Saenz, P.; Seoane, G.; Denicola, A.; Peluffo, G.; Quijano, C. and Olea-Azar, C., *J. Med. Chem.,* **1999**, *42*, 1941. (e) Monge, A.; Palop, J. A.; de Ceráin, A. L.; Senador, V.; Martínez-Crespo, F. J.; Sainz, Y.; Narro, S.; García, E.; de Miguel, C.; González, M.; Hamilton, E.; Barker, A. J.; Clarke, E. D. and Greenhow, D. T., *J. Med. Chem.,* **1995**, *38*, 1786. (f) Heathcock, C. H. and Smith, S. C., *J. Org. Chem.,* **1994**, *59*, 6828. (g) Haddadin, M. J. and Issidorides, C. H., *Heterocycles,* **1993**, *35*, 1503. (h) Lin, S. K., *Youji Huaxue (Chin. J. Org. Chem.)*, **1991**, *11*, 106. (i) Clemens, R. J., *Chem. Rev.,* **1986**, *86*, 241. (j) Kluge, A. F.; Maddox, M. L. and Lewis, G. S., *J. Org. Chem.,* **1980**, *45*, 1909. (k) Edwards, M. L.; Bambury, R. E. and Ritter, H. W., *J. Med. Chem.,* **1976**, *19*, 330.
3. Laursen, J. B. and Nielsen, J., *Chem. Rev.,* **2004**, *104*, 1663.
4. (a) Chupakhin, O. N.; Kotovskaya, S. K.; Perova, N. M.; Baskakova, Z. M. and Charushin, V. N., *Chem. Heterocycl. Compd.,* **1999**, *35*, 459. (b) Kotovskaya, S. K.; Charushin, V. N.; Chupakhin, O. N. and Kozhevnikova, E. O., *Russ. J. Org. Chem.,* **1998**, *34*, 369.
5. (a) Haddadin, M. J.; Agopian, G. and Issidorides, C. H., *J. Org. Chem.,* **1971**, *36*, 514. (b) Issidorides, C. H. and Haddadin, M. J., *J. Org. Chem.,* **1966**, *31*, 4067.
6. Monge, A.; Palop, J. A.; Castillo, J. C. D.; Calderó, J. M.; Roca, J.; Romero, G.; Río, J. D. and Lasheras, B., *J. Med. Chem.,* **1993**, *36*, 2745.
7. Haddadin, M. J. and Issidorides, C. H., *Heterocycles,* **1976**, *4*, 767.
8. Tennant, G. and Mason, J. C., *J. Chem. Soc. D,* **1971**, 586.
9. Römer, A. and Sammet, M., *Z. Naturforsch., Teil B: Anorg. Chem., Org. Chem.,* **1983**, *38B*, 866.
10. (a) Haddadin, M. J.; Zahr, G. E.; Rawdah, T. N.; Chelhot, N. C. and Issodorides, C. H., *Tetrahedron,* **1974**, *30*, 659. (b) El-Haj, M. J. A.; Dominy, B. W.; Johnston, J. D.; Haddadin, M. J. and Issidorides, C. H., *J. Org. Chem.,* **1972**, *37*, 589.
11. Vivian, D. L., *J. Am. Chem. Soc.,* **1951**, *73*, 457.
12. Masoud, N. A. and Olmsted, J., *J. Phys. Chem.,* **1975**, *79*, 2214.
13. (a) Itani, W.; Geara, F.; Haykal, J.; Haddadin, M. and Gali-Muhtasib, H., *Radiation Oncology,* **2007**, *2*, 1. (b) Gali-Muhtasib, H.; Sidani, M.; Geara, F.; Mona, A.-D.; Al-Hmaira, J.; Haddadin, M. J. and Zaatari, G., *Int. J. Oncology,* **2004**, *24*, 1121. (c) Zarranz, B.; Aldana, I.; Jaso, A. and Monge, A., *Bioorg. Med. Chem.,* **2004**, *12*, 3711. (d) Panasyuk, P. M.; Mel'nikova, S. F. and Tselinskii, I. V., *Russ. J. Org. Chem.,* **2001**, *37*, 892. (e) Kotovskaya, S. K.; Perova, N. M.; Charushin, V. N. and Chupakhin, O. N., *Mendeleev Commun.,* **1999**, 76. (f) Wu, Y. F.; Zhang, W. S.; Chen, X.; Hu, X.; Li, W. L.; Tang, L. X.; Li, X. Y. and Shen, X., *Zhongguo Yaowu Huaxue Zazhi,* **1997**, *7*, 157. (g) Wang, J. L. and Liu, F. C., *Hecheng Huaxue,* **1996**, *4*, 171. (h) El-Abadelah, M. M.; Nazer, M. Z.; El-Abadla, N. S. and Meier, H., *Heterocycles,* **1995**, *41*, 2203. (i) Atfah, A. and Hill, J., *J. Chem. Soc., Perkin Trans. I,* **1989**, 221. (j) Lin, S. K., *Yingyong Huaxue,* **1988**, *5*, 17. (k) Dirlam, J. P.; Czuba, L. J.; Dominy, B. W.; James, R. B.; Pezzullo, R. M.; Presslitz, J. E. and Windisch, W. W., *J. Med. Chem.,* **1979**, *22*, 1118. (l) Haddadin, M. J. and Salameh, A. S., *J. Org. Chem.,* **1968**, *33*, 2127.

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Belluš-Claisen Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Malherbe and Belluš in 1978.[1] It is a variant of the *Claisen Rearrangement* involving the reaction of an allylic ether, thioether, or amine with a ketene to form a γ,δ-unsaturated ester, thioester, or amide, of which the double bond is in *trans* configuration. Thus this reaction is known as the Belluš-Claisen rearrangement,[2] Belluš-Claisen reaction,[3] or the Belluš reaction.[4] In addition, this reaction is also referred to as the acyl-Claisen rearrangement,[4,5] ketene-Claisen reaction,[3] and ketene Claisen rearrangement,[6] ignoring the contribution from Belluš. For the specific reaction of allylic amine, the corresponding rearrangement is also cited as the *Aza-Claisen Rearrangement*[7] and zwitterionic *Aza-Claisen Reaction*.[8]

In the absence of heteroatom at the allylic position, alkenes usually undergo *[2+2] Cycloaddition* with ketenes to give cyclobutanones;[9] in contrast, in the case of allyl ether, thioether, or amine, the heteroatom (oxygen, nitrogen, sulfur, etc.) can chelate with ketene to form zwitterions, which undergo [3,3] sigmatropic rearrangement under the help of a base or a Lewis acid to afford γ,δ-unsaturated ester, thioester, and amide. In a special case, the Belluš-Claisen rearrangement of cyclic allyl ethers, thioethers, and amines can lead to the formation of ring-enlarged lactones, thiolactones, and lactams with *trans*-configurated double bonds by adding four carbon atoms to the rings.[2] It should be pointed out that when the heteroatom is oxygen or sulfur, the corresponding allyl ether or thioether reacts only with electrophilic ketenes, with a reactivity order of dichloroketene $\approx$ chloro(trichloroethyl)ketene $>>$ chloro(methyl)ketene $>$ chloroketene $\approx$ chloro(cyano)ketene.[2] In comparison, when the heteroatom is nitrogen, the allylic amines

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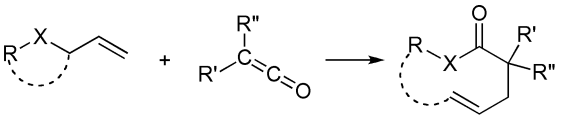
can react with ketenes preformed,[10] or generated *in situ*[2] by zinc-induced dehalogenation of a 2-chloroacyl chloride,[11] photolysis of a chromium-carbene complex,[12] or dehydrohalogenation of an acyl halide[13] (with Et_3N[9e]). However, for this type of rearrangement, the presence of sane ring strain on the allylamines is necessary, otherwise a strong Lewis acid (e.g., Me_2AlCl) is required to promote the reaction.[12]

Even though the non-electrophilic ketenes are not feasible for the Belluš-Claisen rearrangement with oxygen and sulfur as heteroatoms, the reaction of halogenated ketenes provides an alternative route for those ketenes because the halogen atoms in the resulting esters and thioesters can be easily removed by various methods, such as the treatment with Zn/AcOH,[1] catalytic hydrogenation,[14] and radical dechlorination.[15] During the rearrangement, the original stereochemistry can be transferred into corresponding products.[12,16]

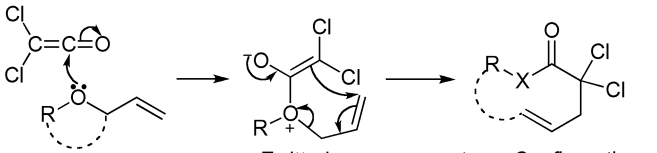
B. GENERAL REACTION SCHEME



R = alkyl, aryl, etc.
R' = alkyl, aryl, Cl, etc.
R" = alkyl, aryl, H, Cl, etc.
X = O, S, NR

C. PROPOSED MECHANISMS

Being a [3,3] sigmatropic rearrangement, this reaction is especially facilitated by the negative charge at the C_2 position,[17] the positive charge at the heteroatom, and the ring strain in the starting material, so that the Belluš-Claisen rearrangement often proceeds easily at room temperature.[2] Shown below is a representative mechanism between the reaction of an allylic ether and a dichloroketene.



Zwitterion *trans*-Configuration

D. MODIFICATION

Although this reaction is still at an early stage of development, a few modifications have been exploited. These modifications include the extension of the Belluš-Claisen rearrangement to ring strain molecules (such as 2-vinyloxetane,[3] 2-vinyloxirane,[13] and 2-vinylaziridines[13]) and to tertiary allyl amines,[3,12] the application of chiral Lewis acid derived from MgI_2 and bis(oxazolinyl)aryl ligands,[4] and the implementation of electron-rich ketene equivalents (e.g., alkoxyketenes, aminoketenes) by the photolysis of chromium carbene complexes.[12]

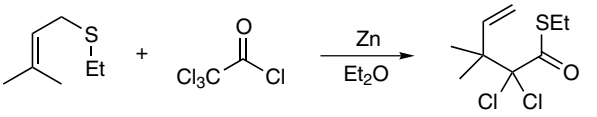
E. APPLICATIONS

This reaction has great potential in organic synthesis.

F. RELATED REACTIONS

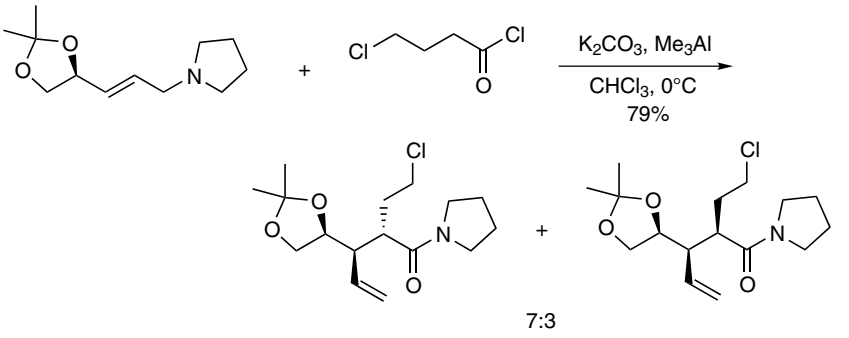
This reaction is closely related to the *Aza-Claisen Rearrangement*, *Claisen Rearrangement*, and *Abnormal Claisen Rearrangement*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 14.

To a 750-mL flame-dried, five-necked flask equipped with a condenser, addition funnel, stirrer, thermometer, and nitrogen inlet were added 13.0 g ethyl 3-methyl-2-butenyl sulfide (0.10 mol), 7.2 g activated zinc (0.11 mol), and 200 mL anhydrous ether. Under stirring, a solution of 11.5 mL trichloroacetyl chloride (18.5 g, 0.105 mol) in 100 mL anhydrous ether was added to the suspension over a period of 4 h. After that, an additional 3.5 g activated zinc (0.05 mol) was added to the flask, and the mixture was stirred for an additional hour. Pentane (200 mL) was added to precipitate the zinc salts, and the solution was decanted from the residue. The residue was washed twice with ether-pentane (50 mL), and the combined solutions was washed successively with water, a cold solution of 10% $NaHCO_3$, and brine and then dried over $MgSO_4$. Upon removal of solvent under vacuum, 17.2 g of crude ethyl thioester of 2,2-dichloro-3,3-dimethyl-4-pentenoic acid was obtained which was further purified by vacuum distillation to give 9.1 g product, in a yield of 38% (should be >38%), b.p. 66°C 0.25 mmHg.



Reference 6a.

To a suspension of 3.2 g K_2CO_3 (23.2 mmol) in 60 mL dry $CHCl_3$ at 0°C under an argon atmosphere were added 2.35 g *N*-allylpyrrolidine (11.12 mmol) and 13 mmol ε-chlorobutanoyl chloride by means of a syringe. After being stirred at 0°C for 30 min,

a solution of 0.50 mL 2 M Me_3Al in toluene (1.02 mmol) was added via syringe. The mixture was stirred at 0°C, and after 24 h, a second volume of Me_3Al was injected. After 6 days, the reaction was quenched by addition of 5–10 mL saturated aqueous $NaHCO_3$ at 0°C dropwise until the Al_2O_3/K_2CO_3 precipitated. Then the organic layer was decanted, the solid residue was extracted with CH_2Cl_2 (5 × 20 mL), and the combined organic layers were dried over $MgSO_4$. Upon removal of solvent, the residue was purified by column chromatography using EtOAc/hexanes (1:1) to 2.77 g (2*S*,3*R*,4*S*)-2-(2-chloroethyl)-3-ethenyl-4,5-(isopropylidendioxy) pentanoic acid pyrrolidinamide (R_f = 0.17) and (2*R*,3*R*,4*S*)-2-(2-chloroethyl)-3-ethenyl-4,5-(isopropylidendioxy) pentanoic acid pyrrolidinamide (R_f = 0.22), in a yield of 79%. These diastereomeric amides (7:3) can be isolated by preparative HPLC (5% 2-propanol in hexanes) to afford 1.94 g of the major diasteromer, in a yield of 55%.

Other references related to the Belluš-Claisen rearrangement are cited in the literature.[18]

H. REFERENCES

1. Malherbe, R. and Belluš, D., *Helv. Chim. Acta,* **1978**, *61*, 3096.
2. (a) Craig, D.; King, N. P. and Mountford, D. M., *Chem. Commun.,* **2007**, 1077. (b) Gonda, J., *Angew. Chem. Int. Ed.,* **2004**, *43*, 3516.
3. Yoon, T. P.; Dong, V. M. and MacMillan, D. W. C., *J. Am. Chem. Soc.,* **1999**, *121*, 9726.
4. Yoon, T. P. and MacMillan, D. W. C., *J. Am. Chem. Soc.,* **2001**, *123*, 2911.
5. (a) Castro, A. M. M., *Chem. Rev.,* **2004**, *104*,2939. (b) Dong, V. M. and MacMillan, D. W. C., *J. Am. Chem. Soc.,* **2001**, *123*, 2448.
6. (a) Nubbemeyer, U., *J. Org. Chem.,* **1996**, *61*, 3677. (b) Nubbemeyer, U., *J. Org. Chem.,* **1995**, *60*, 3773.
7. (a) Ichikawa, Y.; Egawa, H.; Ito, T.; Isobe, M.; Nakano, K. and Kotsuki, H., *Org. Lett.,* **2006**, *8*, 5737. (b) Xu, Q. and Rozners, E., *Org. Lett.,* **2005**, *7*, 2821.
8. Diederich, M. and Nubbemeyer, U., *Angew. Chem. Int. Ed. Engl.,* **1995**, *34*, 1026.
9. (a) Namyslo, J. C. and Kaufmann, D. E., *Chem. Rev.,* **2003**, *103*, 1485. (b) Hyatt, J. A. and Reynolds, P. W., *Org. React.,* **1994**, *45*, 159. (c) Valenti, E.; Pericas, M. A. and Moyano, A., *J. Org. Chem.,* **1990**, *55*, 3582. (d) Snider, B. B., *Chem. Rev.,* **1988**, *88*, 793. (e) Snider, B. B. and Hui, R. A. H. F., *J. Org. Chem.,* **1985**, *50*, 5167.
10. (a) Maurya, R.; Pittol, C. A.; Pryce, R. J.; Roberts, S. M.; Thomas, R. J. and Williams, J. O., *J. Chem. Soc., Perkin Trans. I,* **1992**, 1617. (b) Roberts, S. M.; Smith, C. and Thomas, R. J., *J. Chem. Soc., Perkin Trans I.,* **1990**, 1493.
11. Edstrom, E. D., *Tetrahedron Lett.,* **1991**, *32*, 5709.
12. Deur, C. J.; Miller, M. W. and Hegedus, L. S., *J. Org. Chem.,* **1996**, *61*, 2871.
13. Ishida, M.; Muramaru, H. and Kato, S., *Synthesis,* **1989**, 562.
14. Malherbe, R.; Rist, G. and Belluš, *J. Org. Chem.,* **1983**, *48*, 860.
15. Kling, M. R.; McNaughton-Smith, G. A. and Taylor, R. J. K., *J. Chem. Soc., Chem. Commun.,* **1993**, 1593.
16. Öhrlein, R.; Jeschke, R.; Ernst, B. and Belluš, D., *Tetrahedron Lett.,* **1989**, *30*, 3517.
17. Kazmeier, U.; Mues, H. and Krebs, A., *Chem. Eur. J.,* **2002**, *8*, 1850.
18. (a) Nubbemeyer, U., *Synthesis,* **1993**, 1120. (b) Nubbemeyer, U.; Öhrlein, R.; Gonda, J.; Ernst, B. and Belluš, D., *Angew. Chem. Int. Ed. Engl.,* **1991**, *30*, 1465.

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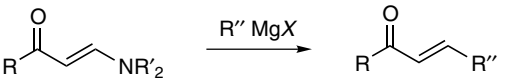
Bénary Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Bénary in 1909.[1] It is the reaction between a Grignard reagent (or an organolithium reagent) and an enamino ketone or aldehyde to yield an α,β-unsaturated ketone or aldehyde.[2] Therefore, it is generally known as the Bénary reaction.[3] The Bénary reaction is a general reaction for preparing not only α,β-unsaturated ketones and aldehydes but also α,β-unsaturated esters with stereoselectivity.[3a] The reaction might occur via different mechanisms—for example, in the case of β-amino vinyl ketones, the reaction seems to proceed through a 1,4-addition-elimination,[3a,4] whereas β-aminopropenals seems to react with organomagnesium and organolithium reagents mainly via a 1,2-addition at the carbonyl group.[3a] For the Bénary reaction, it is found that higher yields can be obtained when the reactions are carried out in toluene with Grignard reagents.[5]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is believed that the reaction occurs mainly via 1,4-addition followed by the elimination,[3,4] as shown below.

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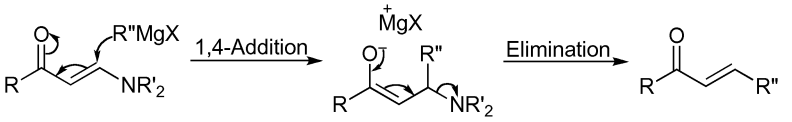
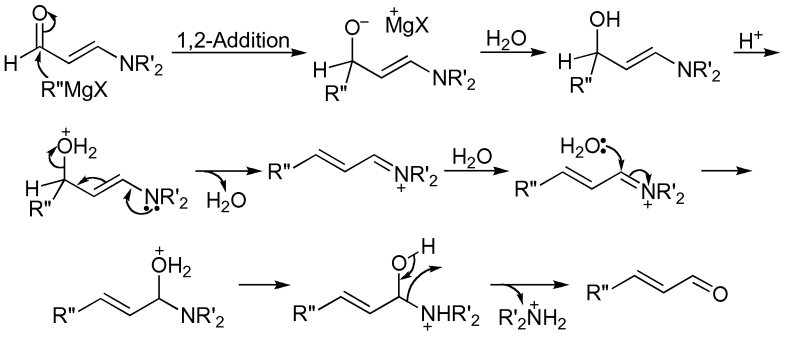
1,4-Addition–elimination mechanism.



1,2-Addition mechanism.



D. MODIFICATION

This reaction has been modified via the conjugate addition (1,4-addition) and elimination of alkenyl-dialkylboranes with enones to prepare highly functionalized dienones.[6]

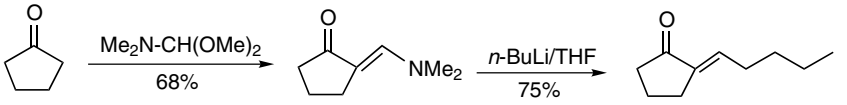
E. APPLICATIONS

This reaction has a general application in the preparation of α,β-unsaturated ketones, aldehydes, and esters.

F. RELATED REACTIONS

N/A

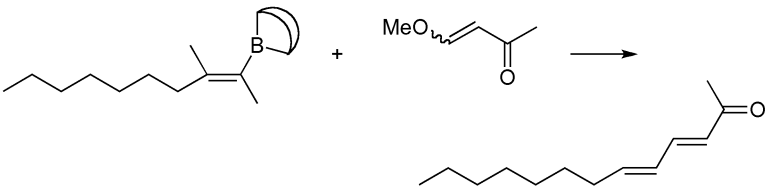
G. CITED EXPERIMENTAL EXAMPLES



Reference 4.

A mixture of 8.4 g cyclopentanone (0.1 mol) and 11.9 g *N*,*N*-dimethylformamide dimethyl acetal (0.1 mol) was refluxed under nitrogen at 110°C for 12 h. The resulting mixture was stripped of methanol and distilled in a Kugelrohr apparatus to afford 12.2 g 2-[(dimethylamino)methylene]-cyclopentanone as an amber oil, in a yield of 88%.

To 350 mL THF at −30°C under nitrogen was added 11.12 g 2-[(dimethylamino)methylene]-cyclopentanone and 57.2 mL 1.6 M *n*-butyllithium (1.1 eq.) dropwise over 30 min. The mixture was stirred to room temperature over 2 h. The excess *n*-butyllithium was destroyed with 5.0 mL water, and the solvent was removed in vacuo. The oily residue was treated with 100 mL water and extracted five times with 100-mL portions of ether. The ether was washed with water, dried over $MgSO_4$, and evaporated in vacuo (40°C, 10 mmHg) to afford 9.4 g 2-pentylidenecyclopentanone, in a yield of 75%, b.p., 100–102°C (8 mmHg).



Reference 6.

A dry nitrogen-flushed, 25-mL centrifuge tube equipped with a Teflon-coated magnetic stirring bar and capped with a rubber septum was charged with 2.46 g *B-trans*-l-nonen-l-yl-9-BBN (10 mmol), 0.34 g *n*-octane (3 mmol) as an internal standard, and 7.6 mL anhydrous diethyl ether. To the resulting solution was added 1.2 g 4-methoxy-3-buten-2-one (12 mmol). The reaction mixture was stirred for 24 h at 25°C and then quenched with 0.61 g ethanolamine (10 mmol). A precipitate of 9-BBN-ethanolamine adduct was formed almost immediately. After the resulting slurry was stirred for 1 h, the reaction mixture was centrifuged. Analysis of the supernatant by GC revealed that *trans*,*trans*-3,5-tridecadien-2-one was formed in 100% yield. The supernatant was decanted from the solid, and the volatiles were removed in vacuo. There remained 1.85 g *trans,trans*-tridecadien-2-one in a yield of 95%, with a purity > 95% by GC.

Other references related to Bénary reaction are cited in the literature.[7]

H. REFERENCES

1. Bénary, E., *Ber*., **1909**, *42*, 3912.
2. (a) Patai, S. and Rappoport, Z., *The Chemistry of Enamines,* ed. Rappoport, Z., Wiley, Chichester **1994**, chap. 10. (b) Mukaiyama, T. and Ohsumi, T., *Chem. Lett.,* **1983**, 875. (c) Bénary, E., *Ber*., **1931**, *64*, 2543.
3. (a) Näf, F. and Decorzant, R., *Helv. Chim. Acta,* **1974**, *57*, 1309. (b) Pasteur, A.; Riviere, H. and Tchoubar, B., *Bull. Soc. Chim. Fr*., **1965**, 2328.
4. Abdulla, R. F. and Fuhr, K. H., *J. Org. Chem*., **1978**, *43*, 4248.

5. Fontenas, C.; Aýt-Haddou, H.; Bejan, E. and Balavoine, G. G. A., *Synth. Commun*., **1998**, *28*, 1743.
6. Molander, G. A.; Singaram, B. and Brown, H. C., *J. Org. Chem*., **1984**, *49*, 5024.
7. (a) Chinchilla, R. and Nájera, C., *Chem. Rev*., **2000**, *100* 1891. (b) Bartoli, G.; Cimarelli, C.; Marcantoni, E.; Palmieri, G. and Petrini, M., *J. Chem. Soc., Chem. Commun*., **1994**, 715. (c) Schottenberger, H.; Buchmeiser, M.; Polin, J. and Schwarzhans, K.-E., *Z. Naturforsch*., **1993**, *48B*, 1524. (d) Crenshaw, R. R.; Essery, J. M. and Jeffries, A. T., *J. Org*. *Chem*., **1967**, *32*, 3132. (e) Everett, G. W. and Holm, R. H., *J. Am. Chem. Soc*., **1966**, *88*, 2442. (f) Everett, G. W. and Holm, R. H., *J. Am. Chem. Soc*., **1965**, *87*, 2117. (g) Ostercamp, D. L., *J. Org. Chem*., **1965**, *30*, 1169. (h) Everett, G. W. and Holm, R. H., *Proc. Chem. Soc.,* **1964**, 238. (i) Cuvigny, T. and Normant, H., *Bull. Soc. Chim. Fr*., **1960**, 515. (j) Jutz, C., *Ber*., **1958**, *91*, 1867. (k) Royals, E. E. and Covington, E. R., *J. Am. Chem. Soc*., **1955**, *77*, 3155. (l) Hauser, C. R. and Adams, J. T., *J. Am. Chem. Soc*., **1944**, *66*, 345. (m) Bénary, E., *Ber*., **1931**, *64*, 2543. (n) Bénary, E., *Ber*., **1930**, *63*, 1573. (o) Bénary, E., *Ber*., **1927**, *60*, 1826. (p) Bénary, E., *Ber*., **1926**, *59*, 2198. (q) Bénary, E.; Reiter, F. and Soenderop, H., *Ber*., **1917**, *50*, 65.

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Benkeser Reduction

A. GENERAL DESCRIPTION OF THE REACTION

Although Dumanskii initially reported the reduction of simple aromatics to mono-olefins by lithium in liquid ammonia and calcium hexaamine $[Ca(NH_3)_6]^{2+}$ suspended in anhydrous ethyl ether in 1916,[1] these procedures were cumbersome and usually gave highly impure products;[2] thus the reduction of aromatic compounds using lithium or calcium was not developed until Benkeser's work in 1952.[3] The generaly known Benkeser reduction[4] is the reduction of aromatic and olefinic compounds with lithium or calcium to unsaturated olefins and fully reduced hydrocarbons in the presence of low molecular weight amines. In fact, Benkeser found that low molecular weight monoamines, particularly methylamine and ethylamine, were excellent media for reduction with lithium.[5] In neat monoamines, aromatic compounds are reduced to mono olefins,[5a,5d,5f] whereas in monoamine-alcohol solution, di-olefins are obtained.[5c] Although ethylenediamine, with the same nitrogen-carbon ratio as methylamine but with less volatility, has been applied as an alternative solvent for the Benkeser reduction,[6] the Benkeser reduction in ethylenediamine frequently results in overreduction of the substrate, giving a mixture of products. This drawback has been overcome by using 1 mole of ethylenediamine or *N*,*N*′-dimethylethylenediamine per gram-atom of lithium with or without the proton donor (alcohol).[7] So far, the lithium-reducing systems have been applied to the reduction of furan or benzofuran,[8] aryl halides,[9] carbazole,[10] epoxide,[11] carboxamide,[12] fluorene,[13] carboxylic acid,[14] quinoline, isoquinoline,[15] etc. Under certain conditions, the amination to hydrocarbon also occurs, besides the normal reduction.[16] Compared to the reduction of aromatics and olefins by lithium, the reduction by calcium in methylamine or ethylenediamine resembles the lithium-amine-reducing system and holds the advantage of donating two electrons per atom.[17] The calcium-reducing systems have also been applied extensively to the reduction of aromatic hydrocarbons,[2,18]

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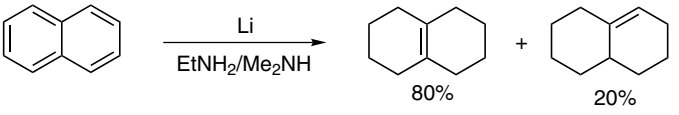
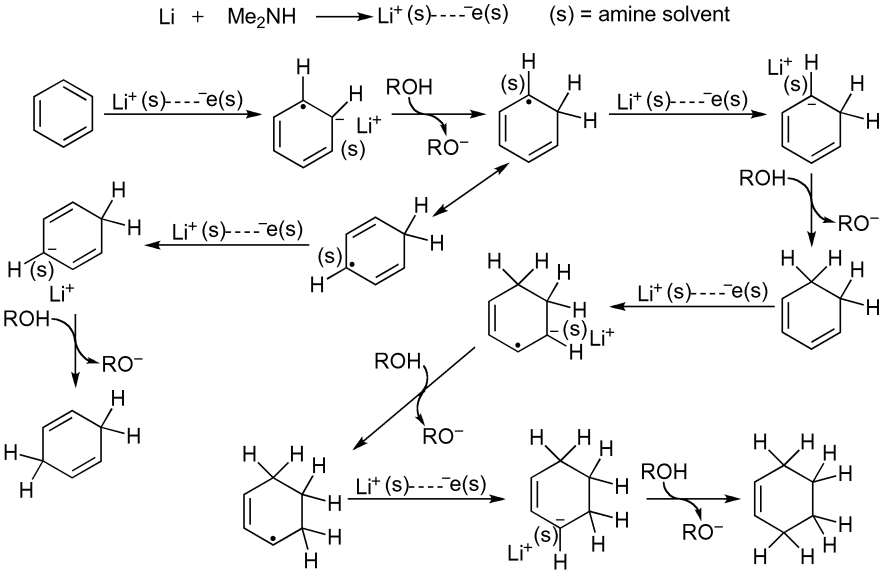
carbon-carbon double[2] and triple bonds,[19] benzyl ether,[19a] allylic ether,[11] epoxide,[11,19a] ester,[21] aliphatic nitrile,[22] dithiane,[21,23] thiophenyl, and sulfonyl groups.[19a] Similar reduction systems include the reduction by sodium in low molecular weight amine[24] and hexamethylphosphamide (HMPA) with alcohol.[25] In addition to these reducing systems, Benkeser also studied the electrochemical-reducing systems extensively,[26] which have also been extended by other research groups.[27]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is believed that this reaction occurs via a radical mechanism, and the solvated electron is the real reducing reagent. Details of the Benkeser reduction are illustrated here, using benzene as an example.[28]



D. MODIFICATION

The reaction has been modified for reducing aromatics under electrochemical conditions.[26,27]

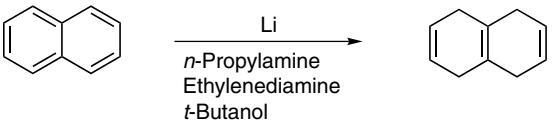
E. APPLICATIONS

This reaction has broad applications in the reduction of a variety of molecules.[2,8–15,18–25]

F. RELATED REACTIONS

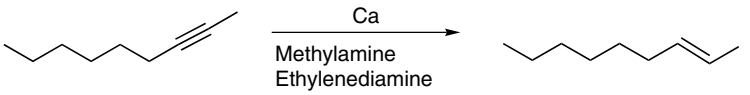
This reaction is closely related to the *Birch Reduction*, in which the alkali metals and alcohols are used in liquid ammonia. However, in laboratories, the Benkeser reduction is more commonly used because the solvent is safer and more convenient than liquid ammonia.[29]

G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

To a cold solution (-6°C) of 12.8 g naphthalene (0.10 mol) in 100 mL *n*-propylamine, 30 g ethylenediamine (0.5 mol) and 44.4 g *t*-butanol (0.6 mol), was added 3.5 g lithium (0.5 mol) portionwise in small pieces. The solution was warmed to 20°C and maintained by the addition of lithium. After1.5 h, the reaction mixture was poured over 150 g ice and 100 mL water and then extracted with ether. The ether was washed with water, brine, and evaporated under reduced pressure to give 12.2 g of a colorless solid that was triturated with methanol, filtered, and dried to give crude product. Recrystallization from 50 mL methanol gave 9.8 g 1,4,5,8-tetrahydronaphthalene, in a yield of 74%, with a purity of 93% by GLPC.



Reference 19b.

Methylamine (75 mL) was distilled through a potassium hydroxide drying tube into a 500-mL three-necked, round-bottomed flask equipped with a mechanical stirrer, gas inlet tube, and a reflux condenser through which ethylene glycol was circulated (-25°C). All exits were protected with a U-tube of mercury. Then 50 mmol 2-nonyne, 2.51 g calcium shot (0.0625 mol), and 75 mL ethylenediamine freshly distilled from sodium were placed in the reaction flask. The mixture was then stirred for the indicated amount of time. If the reaction became too vigorous, it was controlled with a dry ice–acetone bath or by surrounding the flask with a small amount of dry ice. Prolonged cooling caused the reaction to stop (it resumed when allowed to warm up) and the ethylenediamine to solidify. A gray solid formed during the reaction, which often sparked when dry upon exposure to the atmosphere and reacted vigorously with water. The methylamine was allowed to evaporate by disconnecting the cooling liquid from the condenser. The flask was cooled to 0°C (ice water bath) and 200 mL diethyl ether was added. The mixture was hydrolyzed by the cautious, dropwise addition of 200 mL 2 M aqueous NH_4C1. A vigorous reaction accompanied this addition. The layers were separated, and the aqueous layer was extracted with two 75-mL portions of diethyl ether. The organic extracts were combined with the organic phase from the reaction mixture and washed with two 75-mL portions of water, two 75-mL portions of NH_4C1,

75 mL 5% $NaHCO_3$, and 75 mL brine and then dried over anhydrous Na_2SO_4. The solvent was removed by fractional distillation through a 4-in. vacuum-jacketed column. A short-path distillation of the remaining oil gave the product (*trans*-2-alkene) in a yield of 75–88%.

Other references related to reduction by either lithium or calcium are cited in the literature.[30]

H. REFERENCES

1. Dumanskii, A. V. and Zvyereva, A. V., *J. Russ. Phys. Chem. Soc*., **1916**, *48*, 994.
2. Benkeser, R. A.; Belmonte, F. G and Kang, J., *J. Org. Chem*., **1983**, *48*, 2796.
3. Benkeser, R. A.; Robinson, R. E. and Landesman, H., *J. Am. Chem. Soc*., **1952**, *74*, 5699.
4. (a) Eaborn, C.; Jackson, R. A. and Pearce, R., *J. Chem. Soc., Perkin Trans. I*, **1975**, 475. (b) Traynham, J. G., *J. Org. Chem*., **1960**, *25*, 833.
5. (a) Benkeser, R. A.; Agnihotri, R. E.; Burrous, M. L.; Kaiser, E. M.; Malland, J. M. and Ryan, P. W., *J. Org. Chem*., **1964**, *29*, 1313. (b) Benkeser, R. A. and Kaiser, E. M., *J. Org. Chem*., **1964**, *29*, 955. (c) Benkeser, R. A.; Burrous, M. L.; Hazdra, J. J. and Kaiser, E. M., *J. Org. Chem*., **1963**, *28*, 1094. (d) Benkeser, R. A.; Agnihotri, R. K. and Burrous, M. L., *Tetrahedron Lett*., **1960**, *16*, 1. (e) Benkeser, R. A.; Hazdra, J. J.; Lambert, R. F. and Ryan, P. W., *J. Org. Chem*., **1959**, *24*, 854. (f) Benkeser. R. A.; Robinson, R. E.; Sauve, D. M. and and Thomas, O. H.,*J. Am. Chem. Soc*., **1955**, *77*, 3230. (g) Benkeser, R. A.; Schroll, G. and Sauve, D. M., *J. Am. Chem. Soc*., **1955**, *77*, 3378. (h) Benkeser, R. A.; Arnold, C.; Lambert, R. F. and Thomas, O. H., *J. Am. Chem. Soc*., **1955**, *77*, 6042.
6. (a) Mejer, S.; Gawecka, K. and Jablonski, L., *Roczn. Chem*., **1977**, *51*, 2477. (b) Mejer, S.; Porycki, J. and Jablonski, L., *Roczn. Chem*., **1977**, *51*, 1755. (c) Jablonski, L.; Kotlarek, W. and Mejer, S., *Bull. Acad. Polon. Sci. Ser. Sci. Chim*., **1975**, *24*, 101. (d) Brown, H. C.; Ikegami, S. and Kawakami, J. H., *J. Org. Chem*., **1970**, *35*, 3243. (e) Brooks, J. D.; Durie, R. A. and Silberman, H., *Aust. J. Chem*., **1964**, *17*, 55. (f) Reggel, L.; Friedel, R. A. and Wender, I., *J. Org. Chem*., **1958**, *23*, 1136. (g) Reggel, L.; Friedel, R. A. and Wender, I., *J. Am. Chem. Soc*., **1957**, *22*, 891.
7. Garst, M. E.; Dolby, L. J.; Esfandiari, S.; Fedoruk, N. A.; Chamberlain, N. C. and Avey, A. A., *J. Org. Chem*., **2000**, *65,* 7098.
8. (a) Bedenbaugh, A. O.; Bedenbaugh, J. H.; Adkins, J. D. and Bergin, W. A., *J. Org. Chem*., **1970**, *35*, 543. (b) Darling, S. D. and Wills, K. D., *J. Org. Chem*., **1967**, *32*, 2794. (c) Brust, D. P. and Tarbell, D. S., *J. Org. Chem*., **1966**, *31*, 1251.
9. (a) Mosher, H. S. and Blanz, E. J., *J. Org. Chem*., **1957**, *22*, 445. (b) Benkeser, R. A. and Deboer, C. E., *J. Org. Chem*., **1956**, *21*, 281.
10. Dressler, H. and Baum, M. E., *J. Org. Chem*., **1961**, *26*, 102.
11. Benkeser, R. A.; Rappa, A. and Wolsieffer, L. A., *J. Org. Chem*., **1986**, *51*, 3391.
12. Bedenbaugh, A. O.; Payton, A. L. and Bedenbaugh, J. H., *J. Org. Chem*., **1979**, *44*, 4703.
13. Adamski, R. J. and Cannon, J. G., *J. Org. Chem*., **1964**, *29*, 3693.
14. Burgstahler, A. W.; Worden, L. R. and Lewis, T. B., *J. Org. Chem*., **1963**, *28*, 2918.
15. Gray, A. P. and Heitmeier, D. E., *J. Am. Chem. Soc*., **1958**, *80*, 6274.
16. (a) Eisenbraun, E. J.; Bansal, R. C.; Hertzler, D. V. and Duncan, W. P., *J. Org. Chem*., **1970**, *35*, 1265. (b) Bansal, R. C.; Eisenbraun, E. J. and Flanagan, P. W., *J. Am. Chem. Soc*., **1966**, *88*, 1837.
17. Hwu, J. R.; Wein, Y. S. and Leu, Y.-J., *J. Org. Chem*., **1996**, *61,* 1493.
18. Benkeser, R. A.; Laugal, J. A. and Rappa, A., *Tetrahedron Lett*., **1984**, *25*, 2089.

19. (a) Hwu, J. R.; Chua, V.; Schroeder, J. E.; Barrans, R. E. Jr.; Khoudary, K. P.; Wang, N. and Wetzel, J. M., *J. Org. Chem.*, **1986**, *51*, 4731. (b) Benkeser, R. A. and Belmonte, F. G., *J. Org. Chem.*, **1984**, *49*, 1662. (c) van Tamelen, E. E. and Hwu, J. R., *J. Am. Chem. Soc.*, **1983**, *105*, 2490.

20. Zhou, J.; Lu, G.; Huang, X. and Wu, S., *Synth. Commun.*, **1991**, *21*, 435.

21. Hwu, J. R. and Furth, P. S., *J. Am. Chem. Soc.*, **1989**, *111*, 8842.

22. Doumaux, A. R., *J. Org. Chem.*, **1972**, *37*, 508.

23. (a) Hwu, J. R.; Wetzel, J. M.; Lee, J. S. and Butcher, R. J., *J. Organomet. Chem.*, **1993**, *453*, 21. (b) Hwu, J. R. and Wetzel, J. M., *J. Org. Chem.*, **1992**, *57*, 922.

24. (a) Dickson, L.; Matuszak, C. A. and Qazi, A. H., *J. Org. Chem.*, **1978**, *43*, 1007. (b) Nagendrappa, G.; Spivastava, R. K. and Devaprarhakara, D., *J. Org. Chem.*, **1970**, *35*, 347.

25. (a) House, H. O. and Kinloch, E. F., *J. Org. Chem.*, **1974**, *39*, 747. (b) Whitesides, G. M. and Ehmann, W. J., *J. Org. Chem.*, **1970**, *36*, 3565.

26. (a) Benkeser, R. A,; Belmonte, F. G. and Yang, M. H., *Synth. Commun.*, **1983**, *13*, 1103. (b) Benkeser, R. A. and Mels, S. J., *J. Org. Chem.*, **1970**, *35*, 261. (c) Benkeser, R. A.; Watanabe, H.; Mels, S. J. and Sabol, M. A., *J. Org. Chem.*, **1970**, *35*, 1210. (d) Benkeser, R. A. and Mels, S. J., *J. Org. Chem.*, **1969**, *34*, 3970. (e) Benkeser, R. A. and Tincher, C. A., *J. Org. Chem.*, **1968**, *33*, 2727. (f) Benkeser, R. A. and Tincher, C. A., *J. Organomet. Chem.*, **1968**, *13*, 139. (g) Benkeser, R. A.; Kaiser, E. M. and Lambert, R. F., *J. Am. Chem. Soc.*, **1964**, *86*, 5272. (h) Benkeser, R. A.; Kaiser, E. M. and Lambert, R. F., *J. Am. Chem. Soc.*, **1964**, *86*, 5272. (i) Benkeser, R. A, and Kaiser, E. M., *J. Am. Chem. Soc.*, **1963**, *85*, 2858.

27. (a) Meerholz, K. and Heinze, J., *J. Am. Chem. Soc.*, **1989**, *111,* 2325. (b) Pacut, R. I. and Kariv-Miller, E., *J. Org. Chem.*, **1986**, *51*, 3468. (c) Swenson, K. E.; Zemach, D.; Nanjundiah, C. and Kariv-Miller, E., *J. Org. Chem.*, **1983**, *48*, 1777. (d) Demortier, A. and Bard, A. J., *J. Am. Chem. Soc.*, **1973**, *95*, 3495. (e) Sternberg, H. W.; Marby, R. E.; Wender, I. and Mohilner, D. M., *J. Am. Chem. Soc.*, **1969**, *91*, 4191.

28. Krapcho, A. P. and Bothner-By, A. A., *J. Am. Chem. Soc.*, **1959**, *81*, 3658.

29. Kwart, H. and Conley, R. A., *J. Org. Chem.*, **1973**, *38*, 2011.

30. (a) Eckrich, R. and Kuck, D., *Synlett,* **1993**, 344. (b) Schultz, A. G. and Macielag, M., *J. Org. Chem.*, **1986**, *51*, 4983. (c) Benkeser, R. A.; Laugel, J. A. and Rappa, A., *Tetrahedron Lett.*, **1984**, *25*, 2089. (d) Benkeser, R. A. and Kang, J., *J. Org. Chem.*, **1979**, *44,* 3737. (e) Sedzik-Hibner, D., *Roczn. Chem.*, **1976**, *50*, 265. (f) Kaiser, E. M., *Synthesis,* **1972**, 391. (g) Biehl, E. R.; Smith, S. M.; Lapis, S. and Reeves, P. C., *J. Org. Chem.*, **1972**, *37*, 3529. (h) Harvey, R. G. and Urberg, K., *J. Org. Chem.*, **1968**, *33*, 2205. (i) Slaugh, L. H. and Raley, J. H., *J. Org. Chem.*, **1967**, *32*, 2861. (j) de Monteliano, B. R. O.; Loving, B. A.; Shields, T. C. and Gardner, P. D., *J. Am. Chem. Soc.*, **1967**, *89*, 3365. (k) Fried, J.; Abraham, N. A. and Santhanakrishnan, T. S., *J. Am. Chem. Soc.*, **1967**, *89*, 1044. (l) Krapcho, A. P. and Nadel, A. E., *J. Am. Chem. Soc.*, **1964**, *86*, 1096. (m) Patchornik, A.; Wilchek, M. and Sarid, S., *J. Am. Chem. Soc.*, **1964**, *86*, 1457. (n) Caspi, E. and Piatak, D. M., *J. Org. Chem.*, **1964**, *29*, 2948. (o) Benkeser, R. A.; Burrous, S. L.; Hazdra, J. J. and Kaiser, E. M., *J. Org. Chem.*, **1963**, *28*, 1064. (p) Leonard, N. J.; Steinhardt, C. K. and Lee, C., *J. Org. Chem.*, **1962**, *27*, 4027. (q) Benkeser, R. A.; Lambert, R. F.; Ryan, P. W. and Stoffey, D. G., *J. Am. Chem. Soc.*, **1958**, *80*, 6573. (r) Benkeser, R. A.; Robinson, R. E.; Sauve, D. M. and Thomas, O. H., *J. Am. Chem. Soc.*, **1954**, *76*, 631.

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Benzidine Rearrangement
(Semidine Rearrangement)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Hofmann in 1863.[1] It is an acid-catalyzed rearrangement of hydrazobenzenes (in general, the *N*,*N*′-diaryhydrazines) to 4,4′-diaminobiphenyls (benzidines) and is generally known as the benzidine rearrangement.[2] However, when hydrazobenzene contains a *para*-substituent, then the favored product is *p*-aminodiphenylamine, and such rearrangement is referred to as the semidine rearrangement.[3] In the benzidine rearrangement, besides the major product (4,4′-diaminobiaryls), other products may also be formed, including the 2,4′-diaminobiaryls, 2,2′-diaminobiaryls, and the *o*- and *p*-arylaminoanilines. The formation of different rearrangement products has led extensive studies on the reaction mechanisms, including the kinetic isotope effect,[2l−2n,2u,4] kinetic studies,[2a,2e,3i−3l,5] and other aspects of the mechanism (disproportionation,[6] salt formation,[7] intramolecular character,[8] effect of acid concentration,[9] effect of micelles,[2a,2c,10] Hückel molecular orbital calculation,[11] observation of dication intermediate,[3d,12] general acid catalysis,[13] photolytic rearrangement,[2a,2h,3h] etc.). The rearrangement to form benzidine is believed to occur via a [5,5]-sigmatropic shift in a concerted nature.[2k,2n,3c] Other mechanistic studies on benzidine rearrangement are available in Ref. 14.

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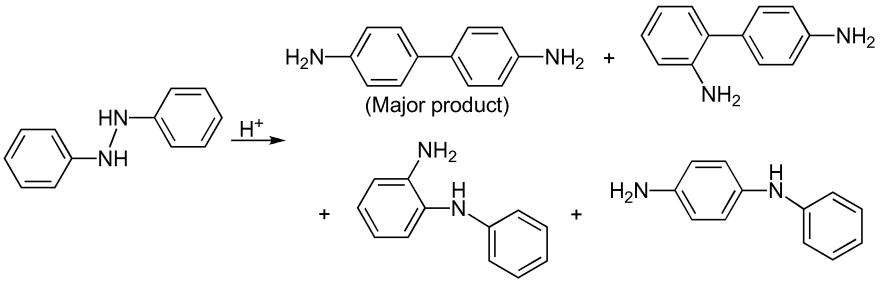
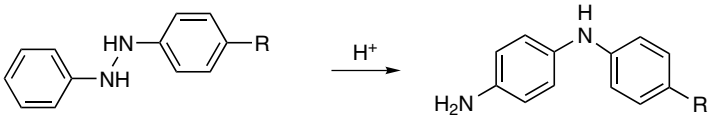
B. GENERAL REACTION SCHEME

Hydrazobenzene without *para*-substituent.



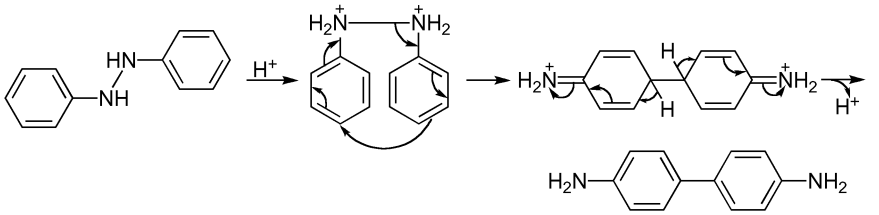
Hydrazobenzene with a *para*-substituent.



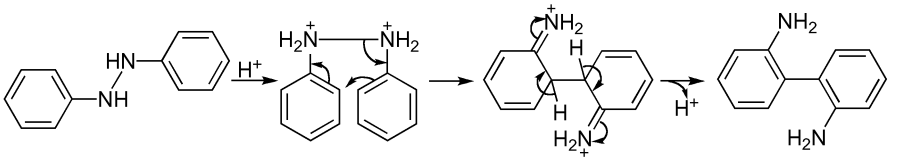
C. PROPOSED MECHANISMS

Based on extensive mechanism studies, it is believed that the rearrangement occurs via cationic intermediates, as illustrated here.

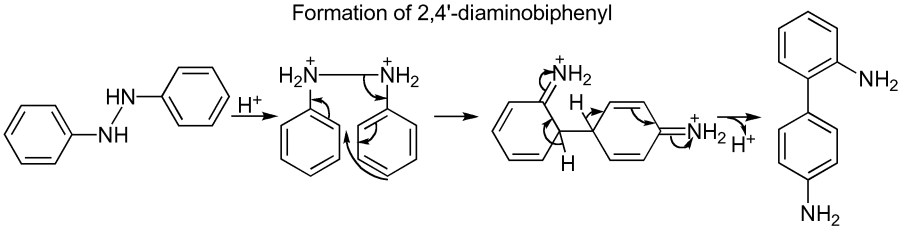
Formation of 4,4'-diaminobiphenyl



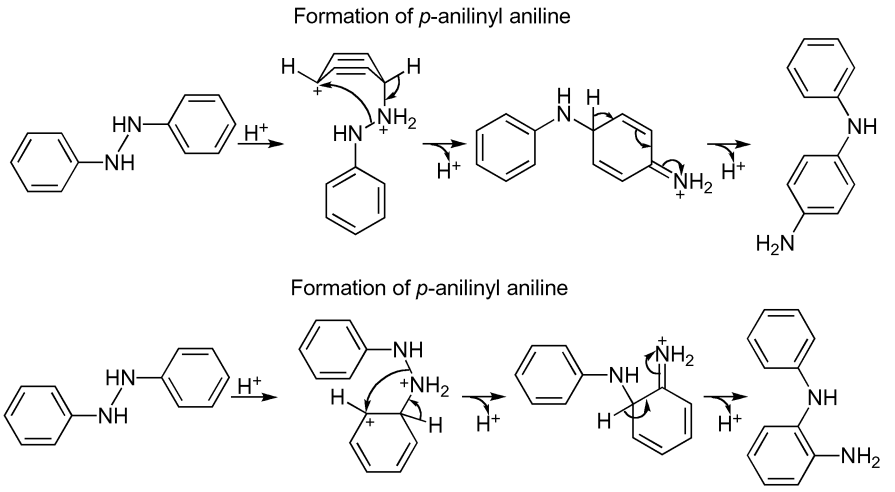
Formation of 2,2'-diaminobiphenyl



Formation of 2,4'-diaminobiphenyl



(Continued)



The last two pathways predominate in the rearrangements when a substituent exists at the *para*-position of one aryl group.[3c]

D. MODIFICATION

This rearrangement has been carried out using different acids as catalyst.

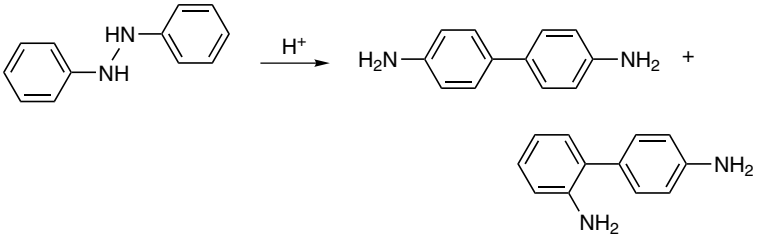
E. APPLICATIONS

This reaction has general application in the preparation of biphenyls with or without amino groups.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



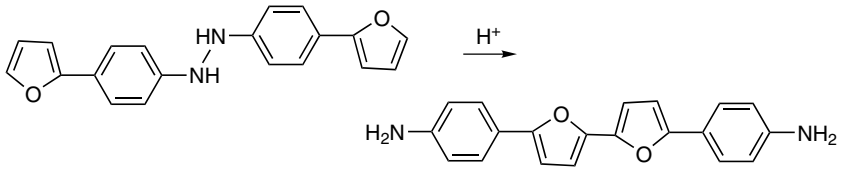
Reference 4.

Partial Conversion

Hydrazobenzene (2.2 g) was obtained by reduction of 2.4 g azobenzene in 150 mL acetone with 12 g zinc powder and 15 mL saturated NH_4Cl solution. After being dried for 12 h over $CaCl_2$ and under vacuum, 1.5 g hydrazobenzene (8.15 mmol) was dissolved in a mixture of 306 mL freshly distilled 95% EtOH and 102 mL water. Another solution was prepared from 10.5 g LiCl (248 mmol), 41 mL 2.0 N HCl and 61 mL water. Each solution was cooled to 0°C under argon. The two solutions were mixed under a flow of argon and kept at 0°C for 30 min, after which 50 mL saturated KOH solution was added quickly. Air was bubbled through the alkaline solution for 24 h to oxidize unused hydrazobenzene to azobenzene. The solution was evaporated to a smaller volume at room temperature. Approximately 10 mg azobenzene distilled in the evaporation. The mixture that remained was extracted with ether (4×100 mL). The ether solution was washed with 2 N HCl (3×100 mL) and water (2×50 mL). The ether solution was dried over $MgSO_4$ and evaporated in a rotary evaporator to give 1015 mg azobenzene (5.58 mmol, 68.5%). This was sublimed to give 989 mg azobenzene (5.38 mmol, 66%). The combined aqueous washings were made alkaline with saturated KOH solution and were extracted with ether (3×100 mL). Workup gave 379 mg residue. This was dissolved in 8 mL CH_2C1_2, and hexane was added slowly to the solution to precipitate 210 mg 4,4′-diaminobiphenyl, mp 125–126°C. After filtration, the solution was evaporated to give 126 mg residue. This was chromatographed on silica gel with cyclohexane/absolute EtOH (5:l) to give 11 mg unknowns (two or more), 47.6 mg (0.26 mmol, 3.2%) 2,4′-diaminobiphenyl as an oil, and 77.6 mg 4,4′-diaminobiphenyl, m.p. 125–126°C. The two portions of 4,4′-diaminobiphenyl were combined and crystallized from hot water to give 237 mg (1.29 mmol, 15.8%) 4,4′-diaminobiphenyl, m.p. 125–126°C.

Total Conversion

The procedure was as described but with a smaller amount of hydrazobenzene. The rearrangement mixture was kept in the refrigerator for 48 h and then made alkaline (the yields are 90–98%). Treatment with air was omitted.



Reference 2e.

A solution of 1.0 g bis[4-(2-furyl)phenyl]diazane (3.16 mmol) in 50 mL ethanol was cooled to 0°C under nitrogen. To this solution was added a solution of 3 mL conc. hydrochloric acid in 10 mL ethanol. The reaction mixture was allowed to stand in a refrigerator for 24 h, during which time the hydrochloride salt of benzidine rearrangement product was precipitated out from the solution and was almost free from impurities. The precipitate was filtered and neutralized with 1 N sodium bicarbonate solution. Further purification was

achieved by column chromatography using EtOAc/CH_2Cl_2 (1:1 v/v) as the eluting solvent to afford 0.75 g pure rearrangement product, in a yield of 75%, m.p. 203–205°C.

Other references related to the benzidine rearrangement and semidine rearrangement are cited in the literature.[15]

H. REFERENCES

1. Hofmann, A. W., *Proc. Roy. Soc. London,* **1863**, *12*, 576.
2. (a) Benniston, A. C.; Clegg, W.; Harriman, A.; Harrington, R. W.; Li, P. Y. and Sams, C., *Tetrahedron Lett.,* **2003**, *44*, 2665. (b) Buncel, E., *Can. J. Chem.,* **2000**, *78*, 1251. (c) Park, K. H.; Park, M.-K. and Cho, Y. H., *Bull. Korean Chem. Soc.,* **1998**, *19*, 1090. (d) Buncel, E. and Cheon, K.-S., *J. Chem. Soc., Perkin Trans. II,* **1998**, 1241. (e) Park, K. H. and Kang, J. S., *J. Org. Chem.,* **1997**, *62*, 3794. (f) Shine, H. J., *Bull. History Chem.,* **1996**, *19*, 77. (g) Rybinov, V. I.; Gorelik, M. V.; Tafenko, V. A.; Medvedev, S. V. and Gurvich, V. Y., *Zh. Org. Khim.,* **1989**, *25*, 1252. (h) Gunduz, T.; Kilic, E.; Kenar, A. and Oztas, S. G., *Analyst (Cambridge),* **1989**, *114*, 727. (i) Shine, H. J., *J. Chem. Edu.,* **1989**, *66*, 793. (j) Verma, K. K. and Sanghi, S. K., *Farmaco, Edizione Pratica,* **1988**, *43*, 13. (k) Shine, H. J.; Park, K. H.; Brownawell, M. L. and San Filippo, J., *J. Am. Chem. Soc.,* **1984**, *106*, 7077. (l) Shine, H. J.; Habdas, J.; Kwart, H.; Brechbiel, M.; Horgan, A. G. and San Filippo, J., *J. Am. Chem. Soc.,* **1983**, *105*, 2823. (m) Shine, H. J.; Zmuda, H.;Park, K. H.; Kwart, H.; Horgan, A. G. and Brechbiel, M., *J. Am. Chem. Soc.,* **1982**, *104*, 2501. (n) Shine, H. J.; Zmuda, H.; Park, K. H.; Kwart, H.; Horgan, A. G.; Collins, C. and Maxwell, B. E., *J. Am. Chem. Soc.,* **1981**, *103*, 955. (o) Abdallah, A. A., *Indian J. Chem., Sect. B,* **1981**, *20B*, 994. (p) Voegtle, F. and Boeckmann, K., *Chem. Ber.,* **1979**, *112*, 1400. (q) Allan, Z. J., *Ann.,* **1978**, 705. (r) Sheradsky, T. and Nov, E., *J. Chem. Soc., Perkin Trans. I,* **1977**, 1296. (s) Andreevskaya, O. I.; Furin, G. G. and Yakobson, G. G., *Zh. Org. Khim.,* **1977**, *13*, 1684. (t) Pinkus, J. L. and Goldman, L. S., *J. Chem. Edu.,* **1977**, *54*, 380. (u) Shine, H. J.; Henderson, G. N.; Cu, A. and Schmid, P., *J. Am. Chem. Soc.,* **1977**, *99*, 3719. (v) Nojima, M.; Ando, T. and Tokura, N., *J. Chem. Soc., Perkin Trans. I,* **1976**, 1504. (w) Matsui, Y.; Mochida, K.; Fukumoto, O. and Date, Y., *Bull. Chem. Soc. Jpn.,* **1975**, *48*, 3645. (x) Osugi, J.; Nakahara, M. and Horiguchi, M., *Rev. Phys. Chem. Jpn.,* **1975**, *45*, 27. (y) Shvedov, V. I.; Kurilo, G. N.; Cherkasova, A. A. and Grinev, A. N., *Khim. Gaterotsiklicheskikh Soedinenii,* **1975**, 1096. (z) Cheng, J.-D. and Shine, H. J., *J. Org. Chem.,* **1975**, *40*, 703. (aa) Allan, Z. J., *Monatsh. Chem.,* **1975**, *106*, 429. (bb) Bunton, C. A. and Rubin, R. J., *Tetrahedron Lett.,* **1975**, 59. (cc) Bunton, C. A. and Rubin, R. J., *Tetrahedron Lett.,* **1975**, 55. (dd) Sparatore, F.; Boido, V. and Pirisino, G., *Tetrahedron Lett.,* **1974**, 2371. (ee) Cox, J. R. and Dunn, M. F., *J. Org. Chem.,* **1972**, *37*, 4415. (ff) Lupes, M. E., *Rev. Roumaine Chim.,* **1972**, *17*, 1253. (gg) Svanholm, U.; Bechgaard, K.; Hammerich, O. and Parker, V. D., *Tetrahedron Lett.,* **1972**, 3675. (hh) Svanholm, U. and Parker, V. D., *J. Am. Chem. Soc.,* **1972**, *94*, 5507. (ii) Svanholm, U. and Parker, V. D., *J. Chem. Soc., Chem. Commun.,* **1972**, 440. (jj) Osugi, J. and Onishi, I., *Rev. Phys. Chem. Jpn.,* **1971**, *41*, 32. (kk) Allan, Z. J. and Podstata, J., *Coll. Czech. Chem. Commun.,* **1971**, *36*, 3053.
3. (a) Kisch, H.; Reisser, P. and Knoch, F., *Chem. Ber.,* **1991**, *124*, 1143. (b) Rhee, E. S. and Shine, H., *J. Am. Chem. Soc.,* **1986**, *108*, 1000. (c) Shine, H. J.; Zmuda, H.; Kwart, H.; Horgan, A. G. and Brechbiel, M., *J. Am. Chem. Soc.,* **1982**, *104*, 5181. (d) Heesing, A. and Schinke, U., *Chem. Ber.,* **1977**, *110*, 3319. (e) Paudler, W. W.; Zeiler, A. G. and Goodman, M. M., *J. Heterocycl. Chem.,* **1973**, *10*, 423. (f) Banthorpe, D. V. and Winter, J. G., *J. Chem. Soc., Perkin Trans. II,* **1972**, 868. (g) Banthorpe, D. V. and Winter, J. G., *J. Chem. Soc., Perkin Trans. II,* **1972**, 874. (h) Banthorpe, D. V.; Cooper, A.; Pearce, D. A. and Thomas, J. A., *J. Chem. Soc. B,* **1971**, 2057. (i) Banthorpe, D. V. and O'Sullivan, M., *J. Chem. Soc. B,* **1968**, 627. (j) Banthorpe, D. V.; Ingold, C.

K. and O'Sullivan, M., *J. Chem. Soc. B,* **1968**, 624. (k) Banthorpe, D. V. and Cooper, A., *J. Chem. Soc. B,* **1968**, 618. (l) Banthorpe, D. V. and O'Sullivan, M., *J. Chem. Soc. B,* **1968**, 615. (m) Shine, H. J.; Baldwin, C. M. and Harris, J. H., *Tetrahedron Lett.,* **1968**, 977. (n) Fischer, W. and Fahr, E., *Angew. Chem. Int. Ed. Engl.,* **1967**, *6*, 630. (o) Carlin, R. B. and Wich, G. S., *J. Am. Chem. Soc.,* **1958**, *80*, 4023. (p) Michaelis, A. and Schafer, A., *Ann.,* **1915**, *407*, 229.

4. Subotkowski, W.; Kupczyk-Subotkowska, L. and Shine, H. J., *J. Am. Chem. Soc.,* **1993**, *115*, 5073.
5. (a) Shine, H. J. and Chamness, J. T., *J. Org. Chem.,* **1963**, *28*, 1232. (b) Carlin, R. B. and Odioso, R. C., *J. Am. Chem. Soc.,* **1954**, *76*, 100. (c) Carlin, R. B. and Odioso, R. C., *J. Am. Chem. Soc.,* **1954**, *76*, 2345. (d) Croce, L. J. and Gettler, J. D., *J. Am. Chem. Soc.,* **1953**, *75*, 874. (e) Carlin, R. B.; Nelb, R. G. and Odioso, R. C., *J. Am. Chem. Soc.,* **1951**, *73*, 1002.
6. (a) Shine, H. J. and Chamness, J. T., *J. Org. Chem.,* **1967**, *32*, 901. (b) Shine, H. J. and Stanley, J. P., *J. Org. Chem.,* **1967**, *32*, 905.
7. Ritter, J. J. and Ritter, F. O, *J. Am. Chem. Soc.,* **1931**, *53*, 670.
8. Smith, D. H.; Schwartz, J. R. and Wieland, G. W., *J. Am. Chem. Soc.,* **1952**, *74*, 2282.
9. Hammond, G. S. and Shine, H. J., *J. Am. Chem. Soc.,* **1950**, *72*, 220.
10. Bunton, C. A. and Rubin, R. J., *J. Am. Chem. Soc.,* **1976**, *98*, 4236.
11. Snyder, L. C., *J. Am. Chem. Soc.,* **1962**, *84*, 340.
12. Olah, G. A.; Dunne, K.; Kelly, D. P. and Mo, Y. K., *J. Am. Chem. Soc.,* **1972**, *94*, 7438.
13. Cohen, M. D. and Hammond, G. S., *J. Am. Chem. Soc.,* **1953**, *75*, 880.
14. (a) Hartung, L. D. and Shine, H. J., *J. Org. Chem.,* **1969**, *34*, 1013. (b) Clovis, J. S. and Hammond, G. S., *J. Org. Chem.,* **1963**, *28*, 3290. (c) Hammond, G. S. and Clovis, J. S., *J. Org. Chem.,* **1963**, *28*, 3283. (d) Hammond, G. S.; Seidel, B. and Pincock, R. E., *J. Org. Chem.,* **1963**, *28*, 3275. (e) Carlin, R. B. and Foltz, G. E., *J. Am. Chem. Soc.,* **1956**, *78*, 1992. (f) Hammond, G. S. and Grundemeiek, W., *J. Am. Chem. Soc.,* **1955**, *77*, 2444. (g) Carlin, R. B. and Heinincer, S. A., *J. Am. Chem. Soc.,* **1955**, *77*, 2272. (h) Carlin, R. B.and Forshey, W. O., *J. Am. Chem. Soc.,* **1950**, *72*, 793.
15. (a) Xia, A., James, A. J. and Sharp, P. R., *Organometallics,* **1999**, *18,* 451. (b) Molina, A.; Martinez-Ortiz, F.; Ruiz, R. and Lopez-Tenes, M., *Coll. Czech. Chem. Commun*., **1997**, *62*, 709. (c) Williams, D. L. H., Rearrangement Reactions Involving the Amino, Nitro and Nitroso Groups, in *The Chemistry of Functional Groups*, ed. Rappoport, Z., ed., Wiley Interscience, New York, **1996**. (d) Rhee, E. S. and Shine, H. J., *J. Org. Chem.,* **1987**, *52*, 5633. (e) Nozoe, T.; Takase, K.; Saito, H.; Yamamoto, H. and Imafuku, K., *Chem. Lett.* **1986**, 1577. (f) Cox, R. A. and Buncel, E., Chapter 18: Rearrangements of Hydrazo, Azoxy and Azo Compounds, in *The Chemistry of Hydrazo, Azo and Azoxy Groups,* pt. 2, ed. S. Patai, S,. John Wiley & Sons, New York, **1975**, pp. 775–807. (g) Williams, D. L. H., Aromatic rearrangements, in *Comprehensive Chemical Kinetics,* ed. Bamford, C. H. and Tipper, C. F. H., Elsevier, New York, **1972**, *13*, pp. 437–448. (h) Miller, B. and Han, C.-H., *J. Chem. Soc. D,* **1970**, 623. (i) Wittig, G. and Grolig, J. E., *Ber*., **1961**, *94*, 2148. (j) Hughes, E. D. and Ingold, C. K., *Quart. Rev.,* **1952**, *6*, 53. (k) Robinson, R., *J. Chem. Soc.,* **1941**, 220. (l) Jacobson, P.; Henrich F. and Klein, J., *Ber*., **1893**, *26*, 688.

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Benzilic Acid Rearrangement

(Benzil-Benzilic Acid Rearrangement)

A. GENERAL DESCRIPTION OF THE REACTION

This rearrangement was first reported by von Liebig in 1838.[1] It is the conversion of benzil (α-diketone) into the salt of α-hydroxy acid by means of base treatment and is generally known as the benzilic acid rearrangement[2] or benzil-benzilic acid rearrangement.[3] It is one of the oldest and most widely studied carbon-carbon bond cleavage reactions[4] and is a specific hydroxide ion catalyzed rearrangement.[2mm,2bbb,2ccc,5] This rearrangement is normally carried out in the favored solvents of water and aqueous ethanol,[3d] and it can also be performed in other aqueous organic solvents, such as in aqueous dioxane[2mm,2bbb,2ccc,6] or even in solid state.[2f,7] The rearrangement may take up to 4 days at room temperature but completes within a few hours under refluxing.[3d] On the other hand, the counterion of the base also affects the reaction rate of the rearrangement when the reaction is carried out in aqueous organic solvents, whereas the metal cation effect is not important when the reaction occurs in water. For example, when 2,2′-dichlorobenzil was treated with base in 50% aqueous dioxane at 60.5°C, barium hydroxide caused the rearrangement to occur about 15 times faster than that with sodium hydroxide, whereas thallous hydroxide effected the reaction about 5 times faster than that with barium hydroxide;[6] in 67% aqueous dioxane at 49.5°C, only lithium hydroxide among the alkali hydroxides can increase the rate about

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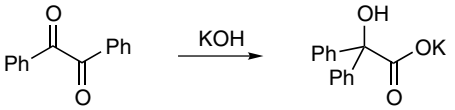
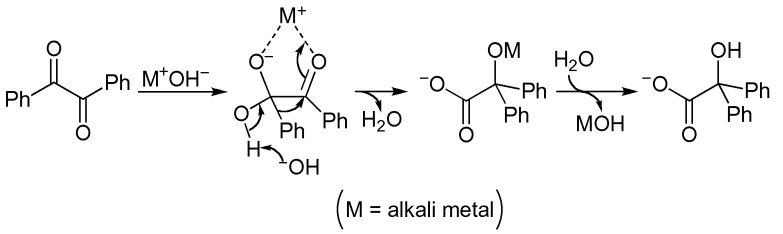
3 times of other alkali hydroxides.[2mm] For the rearrangement of unsymmetrically substituted benzils, rings containing electron-withdrawing substituents migrated preferentially to phenyl, while phenyl rearranges before the ring containing electron-donating substituents.[8] It is generally assumed that this rearrangement occurs via the preliminary reversible addition of hydroxide ion to benzil followed by an irreversible migration of a phenyl group and subsequent proton exchange.[2bbb] The coordination of metal cation also helps this rearrangement.[2mm]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A general mechanism is illustrated below for the reaction of simple benzil.



D. MODIFICATION

This reaction has recently been carried out under the irradiation of microwave which completed within 1 min.[3d]

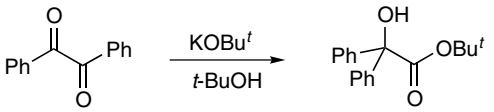
E. APPLICATIONS

This reaction has general application for preparing benzilic acids and their esters which have important biological activities.[9] The formed benzilic acid can be used as reducing reagent to transform α,β-unsaturated ketones into saturated ketones.[2b] In addition, the benzilic acid rearrangement on cyclic α-diketones will lead to ring contracted products.[2j,2ii,2kk,2nn]

F. RELATED REACTIONS

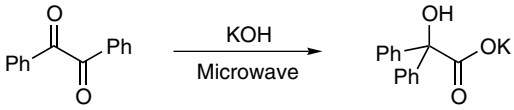
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 5.

A solution prepared from 2.5 g potassium in 100 mL *tert*-butyl alcohol (dried by distilling from sodium) in a flask protected from moisture was heated. With frequent flushing by nitrogen, 8.0 g benzil was added quickly with stirring. After being refluxed for 2 h, excess alcohol was removed by distillation, leaving a solid residue that was hydrolyzed with sodium bicarbonate solution and extracted with ether. Acidification of the aqueous layer gave 0.85 g benzilic acid (9.79%), m.p. 149–150°C after one recrystallization from water. The dried ether solution was concentrated to a residue that was crystallized once from carbon tetrachloride to afford 8.26 g crude *t*-butyl benzilate, in a yield of 76%, m.p. 53–55°C. Further recrystallization from carbon tetrachloride gave pure material, m.p. 60.0–60.2°C, which was soluble in ether and ethanol and insoluble in water.



Reference 3d.

The mixture of 0.56 g KOH (10 mmol) and 0.1 mL water was allowed to stand for 2 min. to dissolve the KOH, then 0.42 g powdered benzil (2 mmol) was added to the KOH solution, and the mixture was well ground with a pestle to form a milky material. Then 5 mL Celite was added, and the resulting mixture was ground again. The final mixture was irradiated in a domestic microwave oven (70% power) for 15s once and then three times for 10s. Diethyl ether (5 mL) was added to the mixture, which was stirred for a while and filtered. The mixture was acidified to pH 1.5 with 25 mL 3 M HCl and then extracted with 100 mL ethyl acetate. The organic phase was dried over $MgSO_4$ and concentrated to give 0.393 g benzilic acid as a white solid, in a yield of 86%, m.p. 146–148°C.

Other references related to the benzilic acid rearrangement are cited in the literature.[10]

H. REFERENCES

1. Von Liebig, J., *Ann.*, **1838**, *25*, 27.
2. (a) Wasserman, H. H.; Ennis, D. S.; Vu, C. B. and Schulte, G. K., *Tetrahedron Lett.,* **1991**, *32*, 6039. (b) Robinson, J. M.; Flynn, E. T.; McMahan, T. L.; Simpson, S. L.; Trisler, J. C. and Conn, K. B., *J. Org. Chem.,* **1991**, *56*, 6709. (c) Guo, J. S. and Liang, X. T., *Chinese Chem. Lett.,* **1991**, *2*, 189. (d) Kawai, M.; Ogura, T.; Butsugan, Y.; Taga, T. and Hayashi, M., *Tetrahedron,* **1991**, *47*, 2103. (e) Hayes, R. N.; Eichinger, P. C. H. and Bowie, J. H., *Rapid Commun. Mass Spectr.,* **1990**, *4*, 283. (f) Toda, F.; Tanaka, K.; Kagawa, Y. and Sakaino, Y., *Chem. Lett.,* **1990**, 373. (g) Askin, D.; Reamer, R. A.; Jones, T. K.; Volante, R. P. and Shinkai, I., *Tetrahedron Lett.,* **1989**, *30*, 671.

(h) Abe, K.; Okada, T.; Masui, Y. and Miwa, T., *Phytochem.,* **1989**, *28*, 960. (i) Dunlap, N. K.; Gross, R. S. and Watt, D. S., *Synth. Commun.,* **1988**, *18*, 13. (j) Trost, B. M. and Hiemstra, H., *Tetrahedron,* **1986**, *42*, 3323. (k) Dahn, H.; Dao, L. H. and Hunma, R., *Helv. Chim. Acta,* **1982**, *65*, 2458. (l) Akabori, S.; Ohtomi, M.; Takahashi, K.; Sakamoto, Y. and Ichinohe, Y., *Synthesis,* **1980**, 900. (m) Van der Westhuizen, J. H.; Ferreira, D. and Roux, D. G., *J. Chem. Soc., Perkin Trans. I,* **1977**, 1517. (n) Nakata, T.; Ohtsuka, Y.; Tahara, A. and Takada, S., *Chem. Pharm. Bull.,* **1975**, *23*, 2318. (o) Furukawa, M.; Yoshida, T. and Hayashi, S., *Chem. Pharm. Bull.,* **1975**, *23*, 580. (p) Osman, A. M.; Younes, M. E.-G. and Mokhtar, A., *Indian J. Chem.,* **1975**, *13*, 193. (q) Huu, L. D.; Dayer, F.; Duc, L.; Rode-Gowal, H. and Dahn, H., *Helv. Chim. Acta,* **1974**, *57*, 2215. (r) Furukawa, M. and Hayashi, S., *Synthesis,* **1974**, 132. (s) Rode-Gowal, H. and Dahn, H., *Helv. Chim. Acta,* **1973**, *56*, 2070. (t) Osman, A. M.; Younes, M. E.-G. and Sheta, A. E., *Egypt. J. Chem.,* **1972**, *15*, 269. (u) DeBoer, C. D., *J. Chem. Soc., Chem. Commun.,* **1972**, 377. (v) Tahara, A.; Nakata, T.; Ohtsuka, Y. and Takada, S., *Chem. Pharm. Bull.,* **1971**, *19*, 2653. (w) Dahn, H.; Gowal, H. and Schlunke, H. P., *Helv. Chim. Acta,* **1970**, *53*, 1598. (x) Vuori, J. and Krieger, H., *Suomen Kemistilehti B*, **1970**, *43*, 279. (y) Dahn, H. and Karoui, S., *Helv. Chim. Acta,* **1969**, *52*, 2491. (z) Black, D. S. C. and Srivastava, R. C., *Aust. J. Chem.,* **1969**, *22*, 1439. (aa) McKechnie, J. S. and Paul, I. C., *J. Am. Chem. Soc.,* **1968**, *90*, 2144. (bb) McKechnie, J. S. and Paul, I. C., *Experientia,* **1967**, *23*, 612. (cc) Kurath, P., *J. Org. Chem.,* **1967**, *32*, 3626. (dd) Dahn, H. and Donzel, A., *Helv. Chim. Acta,* **1967**, *50*, 1911. (ee) Nace, H. R.; Inaba, M. and Nelander, D. H., *Trans. New York Acad. Sci.,* **1962**, *25*, 23. (ff) Levisalles, J. and Tkatchenko, I., *Bull. Soc. Chim. Fr.,* **1966**, 1287. (gg) Kurath, P., *Experientia*, **1966**, *22*, 657. (hh) Bodendorf, K. and Kummer, H., *Arch. Pharm.*, **1964**, *297*, 566. (ii) Nace, H. R. and Nelander, D. H., *J. Org. Chem.,* **1964**, *29*, 1677. (jj) Georgian, V. and Kundu, N., *Tetrahedron,* **1963**, *19*, 1037. (kk) Nace, H. R. and Inaba, M., *J. Org. Chem.,* **1962**, *27*, 4024. (ll) Hirsjarvi, P.; Hilpi, A.; Klenberg, D. and Patala, M., *Suomen Kemistilehti B*, **1961**, *30*, 63. (mm) Puterbaugh, W. H. and Gaugh, W. S., *J. Org. Chem.,* **1961**, *26*, 3513. (nn) Kwart, H. and Sarasohn, I. M., *J. Am. Chem. Soc.,* **1961**, *83*, 909. (oo) Kuhn, R. and Trischmann, H., *Chem. Ber.,* **1961**, *94*, 2258. (pp) Kwart, H.; Spayd, R. W. and Collins, C. J., *J. Am. Chem. Soc.*, **1961**, *83*, 2579. (qq) Smith, P. A. S. and Kan, R. O., *J. Am. Chem. Soc.,* **1961**, *83*, 2580. (rr) O'Meara, D. and Richards, G. N., *J. Chem. Soc.,* **1960**, 1944. (ss) Chazerain, J. and Gardent, J., *Compt. Rend.*, **1959**, *249*, 1758. (tt) Eastham, J. F.; Nations, R. G. and Collins, C. J., *J. Org. Chem.,* **1958**, *23*, 1764. (uu) Franzen, V., *Chem. Zeit.,* **1958**, *82*, 105. (vv) Georgian, V. and Kundu, N., *Chem. Ind. (London),* **1958**, 1322. (ww) Hine, J. and Haworth, H. W., *J. Am. Chem. Soc.,* **1958**, *80*, 2274. (xx) Hirsjarvi, P. and Wuokko, M., *Suomen Kemistilehti B*, **1957**, *30B*, 78. (yy) Klosa, J., *Naturwissenschaften*, **1957**, *44*, 558. (zz) Blanksma, J. J. and Zaaijer, W. H., *Rec. Trav. Chim. Pays-Bas Belg.,* **1938**, *57*, 883. (aaa) Whitmore, F. C., *J. Am. Chem. Soc.,* **1938**, *60*, 2002. (bbb) Roberts, I. and Urey, H. C., *J. Am. Chem. Soc.,* **1938**, *60*, 880. (ccc) Westheimer, F. H., *J. Am. Chem. Soc.,* **1936**, *58*, 2209. (ddd) Evans, T. W. and Dehn, W. M., *J. Am. Chem. Soc.,* **1930**, *52*, 252. (eee) Schonberg, A., *Ber.,* **1925**, *58B*, 235. (fff) Scheuing, G., *Ber.,* **1924**, *57B*, 1963. (ggg) Schonberg, A., *Ber.,* **1924**, *57B*, 1396. (hhh) Schonberg, A. and Keller, K. T., *Ber.,* **1923**, *56B*, 1638. (iii) Staudinger, H. and Binkert, A., *Helv. Chim. Acta,* **1922**, *5*, 703. (jjj) Nicolet, B. H. and Pelc, J. J., *J. Am. Chem. Soc.,* **1921**, *43*, 935. (kkk) Schroeter, G., *Ber.,* **1909**, *42*, 2336.

3. (a) Patra, A.; Ghorai, S. K.; De, S. R. and Mal, D., *Synthesis,* **2006**, 2556. (b) Yamabe, S.; Tsuchida, N. and Yamazaki, S., *J. Org. Chem.,* **2006**, *71*, 1777. (c) Comisar, C. M. and Savage, P. E., *Green Chem.,* **2005**, *7*, 800. (d) Yu, H.-M.; Chen, S.-T.; Tseng, M.-J.; Chen, S.-T. and Wang, K.-T., *J. Chem. Res. (S),* **1999**, 62. (e) Polackova, V. and Toma, S., *Chem. Papers,* **1996**, *50*, 146. (f) Kuriakose, S. and Pillai, V. N. R., *Proc. Indian Acad. Sci., Chem. Sci.,* **1994**, *106*, 59. (g) Kuriakose, S. and Pillai, V. N. R., *Polymer,* **1994**, *35*, 1339. (h) Kuriakose, S. and Pillai, V. N. R., *Polym. Sci.,* **1991**, *1*, 444. (i) Pankaskie, M. C. and Small, L., *J. Chem. Edu.,* **1986**, *63*, 650.
4. (a) Gill, G. B., *Comp. Org. Syn.*, **1991**, *3*, p. 821. (b) Cram, D. J., *Fundamentals of Carbanion Chemistry,* Academic Press, New York **1965**, pp. 238–243. (c) Selman, S. and

Eastham, J. F., *Quart. Rev*., **1960**, *14*, 221. (d) Shemyakin, M. M. and Shihukina, L. A., *Quart. Rev*., **1956**, *10*, 261. (e) Ingold, C. K., *Ann. Repts. Progr. Chem. (Chem. Soc. London),* **1928**, *25*, 124.

5. Von E. Doering, W. and Urban, R. S., *J. Am. Chem. Soc.,* **1956**, *78*, 5938.
6. Pfeil, E.; Geissler, G.; Jacquemin, W. and Lomker, F., *Ber*., **1956**, *89*, 1210.
7. Toda, F., *Acc. Chem. Res*., **1995**, *28*, 480.
8. Clark, M. T.; Hendley, E. C. and Neville, O. K., *J. Am. Chem. Soc*., **1955**, *77*, 3280.
9. (a) Buehler, C. A.; Smith, H. A.; Glenn, D. M. and Nayak, K. V, *J. Org. Chem*., **1958**, *23*, 1432. (b) Shacklett, C. D. and Smith, H. A., *J. Am. Chem. Soc*., **1953**, *75*, 2654.
10. (a) Hatsui, T.; Wang, J.-J. and Takeshita, H., *Bull.Chem. Soc. Jpn.,* **1995**, *68*, 2393. (b) Hatsui, T.; Wang, J.-J. and Takeshita, H., *Bull. Chem. Soc. Jpn.,* **1994**, *67*, 2507. (c) Hatsui, T.; Ikeda, S. and Takeshita, H., *Chem. Lett.,* **1992**, 1891. (d) Hatsui, T.; Ikeda, S. and Takeshita, H., *Chem. Express,* **1991**, *6*, 845. (e) Hatsui, T.; Nojima, C. and Takeshita, H., *Bull. Chem. Soc. Jpn.,* **1989**, *62*, 2932. (f) Gowal, H.; Dao, L. H. and Dahn, H., *Helv. Chim. Acta,* **1985**, *68*, 173. (g) Screttas, C. G.; Micha-Screttas, M. and Cazianis, C. T., *Tetrahedron Lett*., **1983**, *24*, 3287. (h) Eastham, J. F. and Selman, S., *J. Org. Chem.*, **1961**, *26*, 293. (i) Cannon, J. G., *J. Org. Chem*., **1960**, *25*, 959. (j) Ott, D. B. and Smith, G. G., *J. Am. Chem. Soc*., **1955**, *77*, 2325. (k) Ott, D. B. and Smith, G. G., *J. Am. Chem. Soc*., **1955**, *77*, 2342. (l) Davis, H. W.; Grovenstein, E. and Neville, O. K., *J. Am. Chem. Soc*., **1953**, *75*, 3304. (m) Hendley, E. C. and Neville, O. K., *J. Am. Chem. Soc*., **1953**, *75*, 1995. (n) Collins, C. J. and Neville, O. K., *J. Am. Chem. Soc.,* **1951**, *73*, 2471. (o) Roberts, J. D.; Smith, D. R. and Lee, C. C., *J. Am. Chem. Soc*., **1951**, *73*, 619. (p) Von E. Doering, W.; Taylor, T. I. and Schoenwaldt, E. F., *J. Am. Chem. Soc*., **1948**, *70*, 445. (q) Neville, O. K., *J. Am. Chem. Soc.,* **1948**, *70*, 3199. (r) Swan, G., *J. Chem. Soc*., **1948**, 1408. (s) Westheimer, F. H., *J. Org. Chem*., **1936**, *1*, 339. (t) Kasiwagi, I., *Bull. Chem. Soc. Jpn*., **1926**, *1*, 66. (u) Lachman, A., *J. Am. Chem. Soc*., **1923**, *45*, 1509. (v) Lachman, A., *J. Am. Chem. Soc*., **1922**, *44*, 330. (w) Michael, A., *J. Am. Chem. Soc*., **1920**, *42*, 812. (x) Michael, A., *J. Am. Chem. Soc*., **1920**, *42*, 787. (y) Smith, A. J., *J. Chem. Soc.*, **1890**, *57*, 643. (z) Zinin, N., *Ann*., **1839**, 31, 329.

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Benzoin Condensation

A. GENERAL DESCRIPTION OF THE REACTION

Benzoin condensation,[1] sometimes known as the benzoin reaction,[2] is the condensation between aromatic aldehydes to form α-hydroxyl ketones (i.e., benzoins) in the presence of a catalyst. It should be pointed out that benzoin itself is not produced from benzaldehyde by acid or base catalysis or under thermal or free-radical conditions; in fact, benzoin is generated from benzaldehye in the presence of a catalyst.[3] The first benzoin condensation catalyzed by cyanide ion was reported by Stange in 1824,[1oo,4] and has been extensively studied by others since.[5] The interest in benzoin condensation is probably due to the fact that benzoins can be converted into 1,2-diphenyl amino ketones or 1,2-diphenyl amino alcohols, which have shown some important biological functions, such as tumor-necrotizing activities.[6] Since 1943, It has been known that thiamin (vitamin B_1) and related thiazolium salts can catalyze the benzoin condensation in the presence of a mild base.[1w,1ii,1ss,7] Currently, other catalytic systems have been developed, including *N*, *N*′-disubstituted *o*-phenylenediamines,[8] thiazolium cyclophane,[1o] and enzymes.[9] The benzoin cndensation is normally carried out in aqueous solution, and the addition of salt (LiCl, KCl) can increase the reaction rate;[1u] however, the condensation can also be performed in organic solvent, such as anhydrous petroleum ether.[5e] In contrast to the salt effect in aqueous solution, the addition of salt (LiCl, $LiClO_4$) into organic solvents (ethylene glycol, formamide, and DMSO) results in the decreasing of reaction rate.[1u] However, a few aldehydes were found not to form benzoin under the benzoin condensation condition; instead ethylenediol and ethanediol were formed.[10] This condensation when catalyzed by cyanide ion, is assumed

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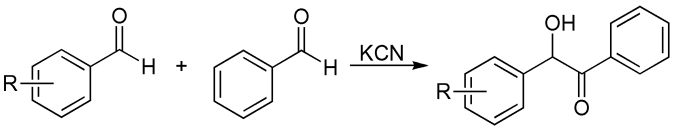
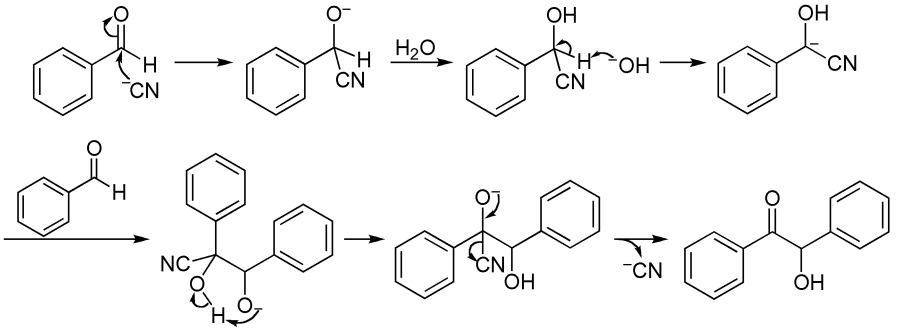
to occur via the addition of cyanide to an aldehyde group, deprotonation to form carbanion, and the addition of carbanion to a second aldehyde group to form benzoin.[1ee,5c,5j,7e,11] The mechanism is similar when catalyzed by thiazolium salt.[1n,1r,1w,1x,1dd,1gg,1ii,1jj,1ll,1pp,1rr]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A general mechanism in the presence of cyanide is displayed here.



D. MODIFICATION

The original benzoin condensation catalyzed by cyanide ion has been modified to use thiamin and a related thiazolium salt,[7] diamine,[8] or enzyme[9] as a catalyst. In addition, the aldehyde group can be replaced by a bisulfite group[1ddd] or converted to silyl-ester[12] to undergo the benzoin condensation.[1ddd]

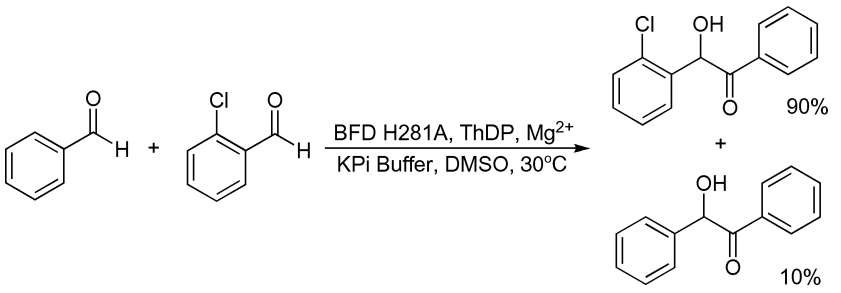
E. APPLICATIONS

This reaction is generally applied for preparing benzoins that can be oxidized to benzil,[1hhh] or converted to other diphenyl α-amino ketones or alcohols.

F. RELATED REACTIONS

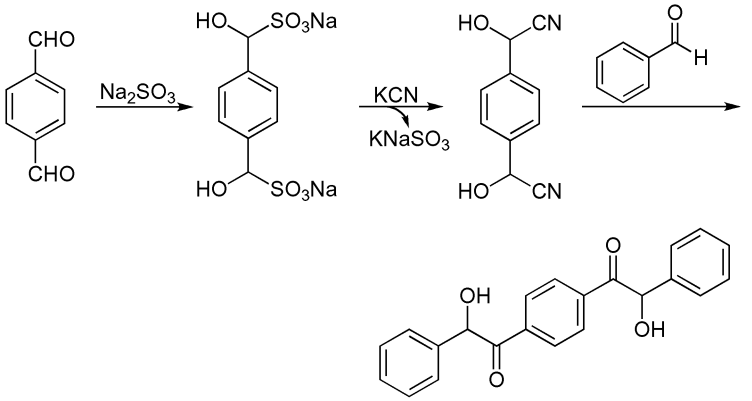
This reaction is related to the *Acyloin Condensation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 1ooo.

2-Chlorobenzaldehyde (113 μL, 1.0 mmol) was dissolved in 10 mL DMSO and 40 mL KPi buffer (50 mM, pH 7.0, ThDP 0.5 mM, $MgCl_2$ 2.5 mM) to give a 20 mM solution. After the addition of 102 μL benzaldehyde (1.0 mmol, 20 mM), 516 units BFD H281A was added, and the reaction mixture was stirred at 30°C for 26 h. The aqueous phase was extracted with 20 mL dichloromethane, the organic phase was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product (160 mg, 65%) was purified by column chromatography (hexane/EtOAc = 9:1) on a deactivated silica gel to yield 80 mg (*R*)-2′-chlorobenzoin as colorless needles, in a yield of 33%, e.e.: > 99%, m.p. 70°C; $[\alpha]_D^{21} = -338.0(0.1, CHCl_3)$.



Reference 1ddd.

Terephthalaldehyde biscyanohydrin was prepared from 10.0 g sodium bisulfite adduct (0.0292 mol) and the stoichiometric amount of potassium cyanide. This aqueous solution (which contained the inorganic reaction by-products) was then added to 18.9 g stirred benzaldehyde (0.178 mol) at 68°C over a period of 10 min. Subsequently, the reaction mixture was stirred at 68–70°C for 2 h. After cooling, the semisolid mass was washed with water and the excess benzaldehyde was removed under reduced pressure at 88–100°C. The bisbenzoin, $C_6H_5CH(OH)C(O)C_6H_4C(O)CH(OH)C_6H_5$, was isolated in 46% yield by treatment of the semisolid mass with benzene followed by crystyallization from methanol, m.p. 230–233°C. The bisbenzoin can be oxidized to bisbenzil as well, as described next.

The residue (14.8 g) was dissolved in 140 mL 80% acetic acid and heated with stirring at 101–105°C together with 20.0 g ammonium nitrate (0.2498 mol) and 0.2 g cupric acetate. On cooling, 6.39 g of yellow crystals appeared, in a yield of 64%, m.p. 116–119°C. Crystallization from ethanol gave 5.74 g pure 1,4-bis(phenylglyoxyloyl)benzene in a yield of 57%, m.p. 123.5–124.2°C.

Other references related to the benzoin condensation are cited in the literature.[13]

H. REFERENCES

1. (a) Estager, J.; Leveque, J.-M.; Turgis, R. and Draye, M., *Tetrahedron Lett.,* **2007**, *48*, 755. (b) Hagu, H.; Salmar, S. and Tuulmets, A., *Ultrason. Sonochem.,* **2007**, *14*, 445. (c) Tuulmets, A.; Hagu, H.; Salmar, S.; Cravotto, G. and Jaerv, J., *J. Phys. Chem. B,* **2007**, *111*, 3133. (d) Estager, J.; Leveque, J.-M.; Turgis, R. and Draye, M., *J. Mol. Catal. A: Chem.,* **2006**, *256*, 261. (e) Bag, S.; Vaze, V. V. and Degani, M. S., *J. Chem. Res.,* **2006**, 267. (f) Neo, A. G.; Delgado, J. and Marcos, C. F., *Chem. Educator,* **2006**, *11*, 328. (g) Chen, Q.; Yuan, Z. L. and Wu, H. X., *Shanghai Huagong,* **2005**, *30*, 19. (h) Storey, J. M. D. and Williamson, C., *Tetrahedron Lett.,* **2005**, *46*, 7337. (i) Xu, L.-W.; Gao, Y.; Yin, J.-J.; Li, L. and Xia, C.-G., *Tetrahedron Lett.,* **2005**, *46*, 5317. (j) Jiang, F. S.; Yu, H.; Gao, G. and Xie, R. G., *Chinese Chem. Lett.,* **2005**, *16*, 321. (k) Tachibana, Y.; Kihara, N. and Takata, T., *J. Am. Chem. Soc.,* **2004**, *126*, 13560. (l) Bhattacharya, A.; Purohit, V. C. and Beller, N. R., *J. Chem. Edu.,* **2004**, *81*, 1020. (m) Dudding, T. and Houk, K. N., *Proc. Nat. Acad. Sci., USA,* **2004**, *101*, 5770. (n) Tachibana, Y.; Kihara, N. and Takata, T., *J. Am. Chem. Soc.,* **2004**, *126*, 3438. (o) Duenkelmann, P.; Kolter-Jung, D.; Nitsche, A.; Demir, A. S.; Siegert, P.; Lingen, B.; Baumann, M.; Pohl, M. and Mueller, M., *J. Am. Chem. Soc.,* **2002**, *124*, 12084. (p) Gao, G.; Xiao, R.; Yuan, Y.; Zhou, C.-H.; You, J. S. and Xie, R.-G., *J. Chem. Res. (S),* **2002**, 262. (q) Enders, D. and Kallfass, U., *Angew. Chem. Int. Ed.,* **2002**, *41*, 1743. (r) White, M. J. and Leeper, F. J., *J. Org. Chem.,* **2001**, *66*, 5124. (s) Ikeda, H.; Horimoto, Y.; Nakata, M. and Ueno, A., *Tetrahedron Lett.,* **2000**, *41*, 6483. (t) Modler-Spreitzer, A.; Fritsch, R. and Mannschreck, A., *Coll. Czech. Chem. Commun.,* **2000**, *65*, 555. (u) Davis, J. H. and Forrester, K. J., *Tetrahedron Lett.,* **1999**, *40*, 1621. (v) Munawar, M. A.; Shahid, M. R.; Siddiq, M. and Athar, M., *J. Pure & Appl. Sci.,* **1998**, *17*, 45. (w) Knight, R. L. and Leeper, F. J., *J. Chem. Soc., Perkin Trans. I,* **1998**, 1891. (x) Dvorak, C. A. and Rawal, V. H., *Tetrahedron Lett.,* **1998**, *39*, 2925. (y) Suzuki, Y.; Takemura, Y.; Iwamoto, K.-I.; Higashino, T. and Miyashita, A., *Chem. Pharm. Bull.,* **1998**, *46*, 199. (z) Zhang, Y.-M. and Sun, P.-P., *Youji Huaxue,* **1997**, *17*, 362. (aa) Lopez-Calahorra, F.; Castro, E.; Ochoa, A. and Marti, J., *Tetrahedron Lett.,* **1996**, *37*, 5019. (bb) Lu, H. F.; Liu, Z. L. and Zhao, A. W., *Huaxue Shiji,* **1995**, *17*, 378. (cc) Marti, J.; Lopez-Calahorra, F. and Bofill, J. M., *THEOCHEM,* **1995**, *339*, 179. (dd) Lopez-Calahorra, F. and Rubires, R., *Tetrahedron,* **1995**, *51*, 9713. (ee) Breslow, R. and Connors, R. V., *J. Am. Chem. Soc.,* **1995**, *117*, 6601. (ff) Morkovnik, A. S.; Khrustalev, V. N.; Lindeman, S. V.; Struchkov, Y. T. and Morkovnik, Z. S., *Mendeleev Commun.,* **1995**, 11. (gg) Lopez-Celahorra, F.; Castells, J.; Domingo, L.; Marti, J. and Bofill, J. M., *Heterocycles,* **1994**, *37*, 1579. (hh) Kuriakose, S. and Pillai, V. N. R., *Eur. Poly. J.,* **1994**, *30*, 881. (ii) Breslow, R. and Kim, R., *Tetrahedron Lett.,* **1994**, *35*, 699. (jj) Lopez-Calahorrra, F. and Castells, J., *Afinidad,* **1993**, *50*, 461. (kk) Eevers, W.; Peeters, L. and Geise, H. J., *Bull. Soc. Chim. Belg.,* **1993**, *102*, 141. (ll) Lee, C. K.; Gong, J. S.; Sin, K. S. and Jun, J. G., *Bull. Korean Chem. Soc.,* **1993**, *14*, 29. (mm) Castells, J.; Domingo, L.; Lopez-Calahorra, F. and Marti, J., *Tetrahedron Lett.,* **1993**, *34*, 517. (nn) Lee, C. K.; Kim, M. S.; Gong, J. S. and Lee, I. S. H., *J. Heterocycl. Chem.,* **1992**, *29*, 149. (oo) Diederich, F. and Lutter, H. D., *J. Am. Chem. Soc.,* **1989**, *111*, 8438. (pp) van den Berg, H. J.; Challa, G. and Pandit, U. K., *J. Mol. Catal.,* **1989**, *51*, 13. (qq) Fan, B. Y.; Wang, G. Z. and Wang, M. Z., *Yaoxue Tongbao,* **1988**, *23*, 744. (rr) Zhao, C.; Chen, S. L.; Wu, P. Q. and Wen, Z., *Huaxue Xuebao,* **1988**, *46*, 784. (ss) Castells, J.; Lopez-Calahorra, F. and Domingo,

L., *J. Org. Chem.,* **1988**, *53*, 4433. (tt) Breslow, R. and Kool, E., *Tetrahedron Lett.,* **1988**, *29*, 1635. (uu) Kool, E. T. and Breslow, R., *J. Am. Chem. Soc.,* **1988**, *110*, 1596. (vv) Castells, J.; Lopez-Calahorra, F.; Geijo, F.; Perez-Dolz, R. and Bassedas, M. , *J. Heterocycl. Chem.,* **1986**, *23*, 715. (ww) Lutter, H. D. and Diederich, F., *Angew. Chem.,* **1986**, *98*, 1125. (xx) Nallaiah, C., *J. Poly. Mater.,* **1986**, *3*, 11. (yy) Castells, J.; Calahorra, F. L. and Domingo, L., *Tetrahedron Lett.,* **1985**, *26*, 5457. (zz) Rozwadowska, M. D., *Tetrahedron,* **1985**, *41*, 3135. (aaa) Castells, J. and Dunach, E., *Chem. Lett.,* **1984**, 1859. (bbb) Lappert, M. F. and Maskell, R. K., *J. Chem. Soc., Chem. Commun.,* **1982**, 580. (ccc) Tagaki, W.; Tamura, Y. and Yano, Y., *Bull. Chem. Soc. Jpn.,* **1980**, *53*, 478. (ddd) Kratzer, R. H.; Paciorek, K. L. and Karle, D. W., *J. Org. Chem.,* **1976**, *41*, 2230. (eee) Higashino, T.; Goi, M. and Hayashi, E., *Chem. Pharm. Bull.,* **1974**, *22*, 2493. (fff) Sheehan, J. C. and Hara, T., *J. Org. Chem.,* **1974**, *39*, 1196. (ggg) Solodar, J., *Tetrahedron Lett.,* **1971**, 287. (hhh) Levi, E. M. and Hauser, C. R., *J. Org. Chem.,* **1969**, *34*, 2482. (iii) Stockel, R. F.; Oppelt, J. C. and Arendt, V., *J. Chem. Edu.,* **1966**, *43*, 144. (jjj) Merz, K. W. and Plauth, D., *Chem. Ber.,* **1957**, *90*, 1744. (kkk) Bottari, F. and Carboni, S., *Gazz. Chim. Ital.,* **1957**, *87*, 1281. (lll) Sumrell, G.; Stevens, J. I. and Goheen, G. E., *J. Org. Chem.,* **1957**, *22*, 39. (mmm) Durr, G., *Compt. Rend.,* **1956**, *242*, 1630. (nnn) Phadke, R. J., *Curr. Sci.,* **1956**, *25*, 56. (ooo) Hensel, H. R., *Angew. Chem.,* **1953**, *65*, 491.

2. (a) Honjo, T., *Yuki Gosei Kagaku Kyokaishi*, **2007**, *65*, 370. (b) Iwamoto, K.-I.; Hamaya, M.; Hashimoto, N.; Kimura, H.; Suzuki, Y. and Sato, M., *Tetrahedron Lett.,* **2006**, *47*, 7175. (c) Hachisu, Y.; Bode, J. W. and Suzuki, K., *J. Am. Chem. Soc.,* **2003**, *125*, 8432. (d) Enders, D.; Breuer, K. and Teles, J. H., *Helv. Chim. Acta,* **1996**, *79*, 1217.
3. Sheehan, J. C. and Hara, T., *J. Org. Chem.,* **1974**, *39*, 1196.
4. Stange, C., *Buch. Rep. Pharm.,* **1824**, *93*, 16.
5. (a) Breslow, R.; Schmuck, C., *Tetrahedron Lett.,* **1996**, *37*, 8241. (b) Cheng, Y.-T.; Barletta, G. L.; Haghjoo, K.; Cheng, J. T. and Jordan, F., *J. Org. Chem.,* **1994**, *59*, 7714. (c) Kuebrich, J. P.; Schowen, R. L.; Wang, M. and Lupes, M. E., *J. Am. Chem. Soc.,* **1971**, *93*, 1214. (d) Ide, W. S. and Buck, J. S., *Org. React.,* **1948**, *4*, 269. (e) Morton, A. A. and Stevens, J. R., *J. Am. Chem. Soc.,* **1930**, *52*, 2031. (f) Lachman, A., *J. Am. Chem. Soc.,* **1924**, *46*, 708. (g) Stern, E., *Z. Phys. Chem.,* **1905**, *50*, 513. (h) Lapworth, A., *J. Chem. Soc.,* **1904**, *85*, 1206. (i) Bredig, G. and Stern, E. Z., *Electrochem.,* **1904**, *10*, 582. (j) Lapworth, A., *J. Chem. Soc.* **1903**, *83*, 995.
6. (a) Lutz, R. E. and Murphey, R. S., *J. Am. Chem.* Soc., **1949**, *71*, 478. (b) Lutz, R. E.; Freek, J. A. and Murphey, R. S., *J. Am. Chem.* Soc., **1948**, *70*, 2015. (c) Hartwell, J. L. and Kornberg, S. R. L., *J. Am. Chem. Soc.,* **1945**, *67*, 1606.
7. (a) Ugai, T.; Tanaka, S. and Dokawa, S., *J. Pharm. Soc. Jpn.* **1943**, *63*, 269. (b) Mohrig, J. R.; Hammond, C. N.; Morrill, T. C.; Neckers, D. C., *Experimental Organic Chemistry*, Freeman, New York, **1998**, pp. 419–427. (c) Mohrig, J. R. and Neckers, D. C., *Laboratory Experiments in Organic Chemistry*, 2nd ed, Van Nostrand, New York, **1973**, p. 868. (d) Gould, E. S., *Structure and Mechanism in Organic Chemistry*, Holt, New York, **1959**, pp. 394–397. (e) Breslow, R., *J. Am. Chem. Soc.,* **1958**, *80*, 3719.
8. Morkovnik, A. S.; Khrustalev, V. N.; Lindeman, S. V.; Struchkov, Y. T. and Morkovnik, Z. S., *Mendeleev Commun*., **1995**, *5*, 11.
9. (a) Demir, A. S.; Sesenoglu, Ö.; Eren, E.; Hosrik, B.; Pohl, M.; Janzen, E.; Kolter, D.; Feldmann, R.; Dünkelmann, P. and Müller, M., *Adv. Synth. Catal.,* **2002**, *344*, 96. (b) Demir, A. S.; Pohl, M.; Janzen, E. and Müller, M., *J. Chem. Soc., Perkin Trans. I,* **2001**, 633. (c) Iding, H.; Dünnwald, T.; Greiner, L.; Liese, A.; Müller, M.; Siegert, P.; Grötzinger, J.; Demir, A. S. and Pohl, M., *Chem. Eur. J.,* **2000**, *6*, 1483. (d) Demir, A. S.; Dünnwald, T.; Iding, H.; Pohl, M. and Müller, M., *Tetrahedron: Asymmetry,* **1999**, *10*, 4769.
10. (a) Buehler, C. A. and Edwards, S. P., *J. Am. Chem. Soc.,* **1952**, *74*, 977. (b) Buehler, C. A. and Harris, J. O., *J. Am. Chem. Soc.,* **1950**, *74*, 5015.
11. (a) Breslow, R., *Acc. Chem. Res.,* **2004**, *37*, 471. (b) Breslow, R., *Chem. Ind. (London),* **1957**, 893.

12. Linghu, X. and Johnson, J. S., *Angew. Chem.,* **2003**, *115*, 2638.

13. (a) Takikawa, H.; Hachisu, Y.; Bode, J. W. and Suzuki, K., *Angew. Chem. Int. Ed.,* **2006**, *45*, 3492. (b) Enders, D. and Balensiefer, T., *Acc. Chem. Res*., **2004**, *37*, 534. (c) Tachibana, Y.; Kihara, N. and Takata, T., *J. Am. Chem. Soc.,* **2004**, *126*, 3438. (d) Wildemann, H.; Dünkelmann, P.; Müller, M. and Schmidt, B., *J. Org. Chem.,* **2003**, *68*, 799. (e) Crundwell, G.; Meskill, T.; Sayers, D. and Kantardjieff, K., *Acta Cryst*., **2002**, *E58*, 666. (f) Pohl, M.; Lingen, B. and Müller, M., *Chem. Eur. J*., **2002**, *8*, 5289. (g) White, M. J. and Leeper, F. J., *J. Org. Chem.,* **2001**, *66*, 5124. (h) Kluger, R. and Moore, I. F., *J. Am. Chem. Soc.,* **2000**, *122*, 6145. (i) Miyashita, A.; Suzuki, Y.; Okumura, Y.; Iwamoto, K.-I. and Higashino, T., *Chem. Pharm. Bull.,* **1998**, *46*, 6. (j) Knight, R. L. and Leeper, F. J., *Tetrahedron Lett.,* **1997**, *38*, 3611. (k) Gerhard, A. U. and Leeper, F. J., *Tetrahedron Lett.,* **1997**, *38*, 3615. (l) Lopes-Calahorra, F.; Rubires, R., *Tetrahedron,* **1995**, *51*, 9713. (m) Hassner, A. and Rai, K. M. L., *Comp. Org. Syn.,* **1991**, *1*, p. 541. (n) Van den Berg, H. J.; Challa, G. and Pandit, U. K., *J. Mol. Catal.,* **1989**, *51*, 1. (o) Breslow, R. and Kool, E., *Tetrahedron Lett.,* **1988**, *29*, 1635. (p) Lappert, M. F. and Maskell, R. K., *J. Chem. Soc., Chem. Commun.,* **1982**. 580. (q) Yano, Y.; Tamura, Y. and Tagaki, W., *Bull. Chem. Soc. Jpn.,* **1980**, *53*, 740. (r) Lachmann, B.; Steinmaus, H. and Wanzlick, H. W., *Tetrahedron,* **1971**, *27*, 4085. (s) Sheehan, J. C. and Hunneman, D. H., *J. Am. Chem. Soc.,* **1966**, *88*, 3666. (t) Sumreli, G.; Stevens, J. I. and Goheen, G. E., *J. Org. Chem.,* **1957**, *22*, 39. (u) Roberts, T. G. and Teague, P. C., *J. Am. Chem. Soc.,* **1955**, *77*, 6258. (v) Shacklett and H. A. Smith, *J. Am. Chem. Soc.,* **1953**, *75*, 2655. (w) Ugai, T.; Dokawa, T. and Tsubokawa, S., *J. Pharm. Soc. Jpn.,* **1944**, *64*, 7A. 3. (x) Ugai, T.; Tanaka, R. and Dokawa, T., *J. Pharm. Soc. Jpn.,* **1943**, *63*, 296. (y) Adams, R. and Marvel, C. S., *Org. Syn. Coll. 1,* **1941–1994**, 94. (z) Buck, J. S. and Ide, W. S., *J. Am. Chem. Soc.,* **1931**, *53*, 2350. (aa) Anderson, E. and Jacobson, R. A., *J. Am. Chem. Soc.,* **1923**, *45*, 836. (bb) Staudinger, H., *Ber*., **1913**, *46*, 3530. (cc) Staudinger, H., *Ber*., **1913**, *46*, 3535. (dd) Bosler, M., *Ber.,* **1881**, *14*, 327.

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Bergius Process

A. GENERAL DESCRIPTION OF THE REACTION

This process, first invented by Bergius in 1913,[1] is based on Bergius's earlier research under high pressure in Hanover in 1909, in which cellulose was initially converted into a coal-like substance followed by the hydroliquefaction of the coal itself.[2] The generally known Bergius process[3] is a simple process for converting brown coal completely into crude oil in the presence of certain catalysts. In this process, the brown coal, also known as lignite, is ground into a fine powder and placed into a high-pressure reactor where the coal powder reacts with hydrogen gas at high temperature (425–480°C) and high pressure (200–700 atm). The initial catalyst for brown coal was molybdenum oxide in low concentration, along with sulfuric acid to partially neutralize the calcium humates in the brown coal.[2] Subsequently, iron, molybdenum, and tin, were commonly used as liquefaction catalysts in large-scale plants in Germany and England before World War II. Although iron remains the catalyst metal of choice because of the cost and availability, the effectiveness of well-dispersed molybdenum at low concentrations has led to much research on precursors based on that metal and on possible recovery and recycling of the catalyst.[4] Different from the regular hydrogenation reaction (or process) with Platinum or Palladium as catalyst, sulfur added to the reaction systems of the Bergius process is not only nonpoisonous to the catalyst, but also beneficial for increasing the efficiency of the catalyst.[5] After the development of the catalysts, Bergius won a Nobel Prize in 1931 for his contribution to industrial science.[6] This liquefaction of coal has also been carried out in supercritical fluids, such as in *sc*H_2O. Under this condition, the liquid hydrocarbons were extracted from the coal into the *sc*H_2O,

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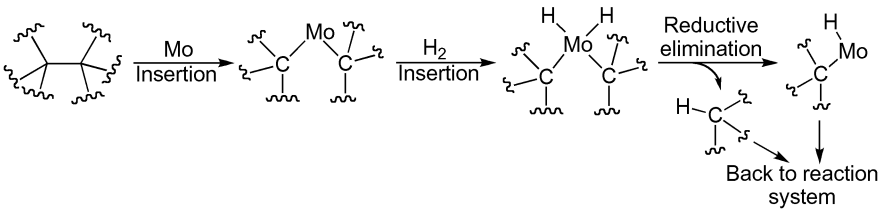
and the catalysts were recovered by precipitation induced by a pressure reduction. The advantages associated with such modification include the prevention of caking formation with coal, convenient separation of hydrocarbons from solvent, high efficiency by rendering the coal residue more porosity, and optimization of the yield up to 50 wt %.[7]

B. GENERAL REACTION SCHEME

$$C + H_2 \xrightarrow[\Delta,\ \text{high pressure}]{\text{Catalyst}} C_nH_{2n+2}$$

C. PROPOSED MECHANISMS

The hydroliquefaction of coal in the Bergius process is not a simple reaction or process; in fact, it involves a series of organometallic transformation, such as insertion, migration, and reductive elimination. Therefore, only a small part of the reaction scheme is displayed here to show a possible conversion.



D. MODIFICATION

This process has been modified using different metals as catalyst and has been carried out in supercritical fluids, such as $sc H_2O$.[6]

E. APPLICATIONS

This process has been used to produce hydrocarbons in the range of gasoline, diesel, and jet fuel from coal.

F. RELATED REACTIONS

The mechanism in Bergius process might be similar to the hydrogenation of alkenes using the *Adkins Catalyst*.

G. CITED EXPERIMENTAL EXAMPLES

$$C + H_2 \xrightarrow[420°C,\ 1500\ psi\ H_2]{MoS} C_nH_{2n+2}$$

Reference 8.

Experiments were run using 0.9%, 2.0%, 3.0%, and 5.0% sulfided molybdenum naphthenate (as the percent of molybdenum in the resid) to select a catalyst level. Standard conditions of 30 min at 420°C at a 3:1 tetralin/resid ratio, 3 wt % sulfided molybdenum naphthenate catalyst, and 1500 psi of hydrogen pressure were selected for determination of the relative reactivity to hydroconversion of the coal-derived vacuum resids. It was found that both catalyst concentration and hydrogen pressure have strong effect on the conversion of coal to hydrocarbon.

Other references related to the Bergius process are cited in the literature.[9]

H. REFERENCES

1. Bergius, F., *The Use of High Pressure in Chemical Reactions* [trans. from *Die Anwendung hoher drucke bei chemischen Vorgängen und eine nechbildung des Entstehungsprozesses der Steinkohle.*], Halle (Saale), W. Knapp, **1913**. [It is essentially unknown today.]
2. Weller, S. W., *Energy & Fuels,* **1994**, *8*, 415.
3. (a) Schuchardt, U.; Joekes, I. and Duarte, H. C., *J. Chem. Technol. Biotechnol.,* **1988**, *41*, 51. (b) Mitsui, K., *Nenryo Kyokaishi,* **1975**, *54*, 846. (c) Abe, R., *Kogyo Kagaku Zasshi,* **1932**, 35 (suppl. binding), *411*, 23, 19, 17. (d) Thate, H., *Rec. Trav. Chim. Pays-Bas Belg.,* **1931**, *50*, 77. (e) Gundermann, E., *Zentr. Zuckerindust.,* **1930**, *38*, 593. (f) Smith, E. W., *Times Trade & Eng. Suppl. (London)*, **1928**, *23*, 28. (g) Askew, H. O., *New Zealand J. Sci. Tech.,* **1928**, 321. (h) Strong, H. W., *Chem. Eng. & Mining Rev.,* **1927**, *19*, 449. (i) Heyn, M. and Dunkel, M., *Bernnstoff-Chem.,* **1926**, *7*, 245. (j) Heyn, M. and Dunkel, M., *Bernnstoff-Chem.,* **1926**, *7*, 81. (k) Spilker, A. and Zerbe, K., *Angew. Chem.,* **1926**, *39*, 1138. (l) Grebel, A., *Genie Civil*, **1926**, *88*, 176. (m) Broche, H., *Brennstoff-Chem.*, **1926**, 7, 140. (n) Fischer, F. and Tropsch, H., *Brennstoff-Chem.,* **1926**, *7*, 2. (o) Schuster, F., *Sparwirtschaft*, **1925**, *3*, 157. (p) Rheinfelder, L., *Mill. Schles. Kohlenforschungsinst. Kaiser-Wilhelm-Ges.*, **1925**, *2*, 34. (q) Dunkel, M. and Heyn, M., *Naturwissenschaften,* **1925**, *13*, 1021. (r) Shatwell, H. G., *Chem. Ind. (London),* **1925**, *44*, 471. (s) Nash, A. W. and Shatwell, H. G., *Colliery Guardian*, **1924**, *128*, 1435. (t) Kling, A., *Chaleur et Industrie*, **1924**, *11*, 1067. (u) Waterman, H. I. and Perquin, J. N. J., *Chim. Ind. (Paris),* **1923**, 200.
4. (a) Vasudevan, P. T. and Weller, S. W., *J. Catal.,* **1986**, *99*, 235. (b) Kalthod, D. G. and Weller, S. W., *J. Catal.,* **1986**, *98*, 572. (c) Kalthod, D. G. and Weller, S. W., *J. Catal.,* **1986**, *96*, 455. (d) Weller, S. W., in *Fourth Conference on the Chemistry and Uses of Molybdenum,* ed. Barry, H. F. and Mitchell, P. C. H., Climax Molybdenum Co., Ann Arbor, Mich., **1982**.
5. (a) Kotanigawa, T.; Yamamoto, M.; Sasaki, M.; Wang, N.; Nagaishi, H. and Yoshida, T., *Energy & Fuels,* **1997**, *11*, 190. (b) Ishii, T.; Sanada, Y. and Takeya, G., *Kogyo Kagaku Zasshi,* **1969**, *72*, 1269. (c) Ellis, C., *Hydrogenation of Organic Substauces*, D. Van Nostrand, Co. Inc., New York, **1930**.
6. See www.almaz.com.
7. Coenen, H.; Hagen, R. and Kriegel, E., *U. S. Pat.*, **1984**, Nov. 27 4,485,003.

8. Wang, S. J.; Huang, H.; Wang, K. Y.; Klein, M. T. and Calkins, W. H., *Energy & Fuels,* **1998**, *12*, 1335.
9. (a) Daintith, J., "Bergius Process" in *The Facts on File Dictionary of Chemistry*, ed. Daintith, J., Checkmark, New York, **2003**. (b) Jessop, P. G.; Ikariya, T. and Noyori, R., *Chem. Rev.,* **1999**, *99*, 475. (c) Derbyshire, F. J., *Catalysis in Coal Liquefaction: New Directions for Research. Int. Energy Agency Coal Res. Report, London,* **1988**. (d) Amestica, L. A. and Wolf, E. E., *Fuel,* **1986**, *65*, 1226. (e) Tanabe, K. and Hattori, H., *J. Pet. Soc. Jpn.*. **1986**, *29*, 280. (f) Nowacki, P., *Coal Liquefaction Processes*, Noyes Data Corporation, Park Ridge, N.J., **1979**. (g) Montano, P. P., *Fuel,* **1977**, *56*, 397. (h) Wu, W. R. K. and Storch, H. H., *Hydrogenation of Coal and Tar*., Bulletin-United States, Bureau of Mines, **1968,** No. 633, 195 pp. (i) Weller, S. W., "Catalysis in the Liquid-Phase Hydrogenation of Coal and Tar" in *Catalysis*, ed. Emmett, P. H., Reinhold, New York, **1966**; *4*, p 513. (j) Dpnath, E. D., "Hydrogenation of Coal and Tar" in *Chemistry of Coal Utilization,* Suppl. Vol., ed. Lowry, H. H., John Wiley & Sons, New York, **1963**. (k) Stranges, A. N., *J. Chem. Edu.,* **1963**, *60*, 617. (l) Weller, S. W.; Pelipetz, M. G.; Friedman, S. and Storch, H. H., *Ind. Eng. Chem.,* **1960**, *42*, 330. (m) Storch, H. H., "*Direct Hydrogenation of Coal and Tar*" in *Chemistry of Coal Utilization,* ed. Lowry, H. H., John Wiley & Sons, New York, **1945**, *2*, 1760. (n) Bergius, F., *Petroleum Z.*, **1926**, *22*, 76. (o) Bergius, F., *VDI Zeitschrift*, **1925**, *69*, 1313.

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Bergman Cyclization

A. GENERAL DESCRIPTION OF THE REACTION

The generally known Bergman cyclization[1] (or cyclisation[2]), sometimes also referred to as the Bergman cycloaromatization,[3] Bergman reaction,[4] and Masamune-Bergman cyclization,[5] is the formation of aromatic compounds from (*Z*)-enediynes via a 1,4-biradical intermediate. Although this reaction can be traced back to 1940–1950s,[6] it is Bergman who first proposed and proved the existence of the 1,4-aryldiradical intermediate in the gas phase for the thermal rearrangement of substituted 3-hexene-1,5-diynes in 1972.[7] Unfortunately, this reaction was largely ignored until the discovery of the enediyne class of anticancer antibiotics in the 1980s, including calicheamicin,[8]esperamicin,[9] dynemicin,[10] and kedarcidin.[11] These enediyne antibiotics are among the most potent antibiotic antitumor agents ever investigated.[12] Their reactivity is believed to be the action of the enediyne moiety, which undergoes a Bergman cyclization to generate a reactive diradical that can abstract hydrogen atoms from the backbone of DNA, thus cleaving the DNA.[13] The Bergman cyclization is an endothermic reaction (8.5 $\pm$ 1.0 Kcal/mol),[14] and the formed 1,4-biradical is believed to be a reactive σ,σ-biradical[15] that abstracts hydrogen from the proton donor (usually 1,4-cyclohexadiene) to give an aromatic compound; this intermediate sometimes also abstracts a chlorine atom from CCl_4 to form substituted 1,4-dichlorobenzenes or reacts with dissolved oxygen to form quinone.[16] The significant electronic configurational mixing from a closed-shell structure to the open-shell character of 1,4-biradical in this cyclization has led extensive mechanistic studies, mainly through computation.[1i,1p,1q,1w,1aa–1dd,1ff,1pp,1qq,1vv,1zz,4,17] The factors that affect the Bergman cyclization include solvent,[1ss] molecular strain energy,[1vv,19] the distance

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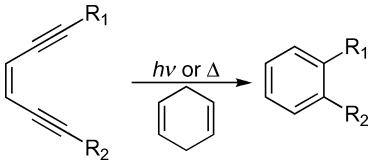
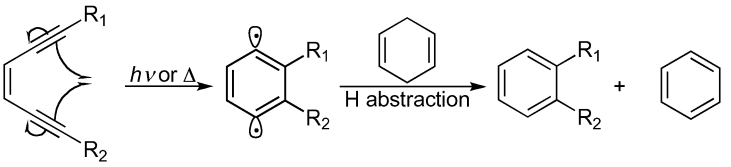
separating the acetylenic termini,[12] and electronic effect.[1gg,1uu,1xx,20] The Bergman cyclization can be carried out either thermally[1kk,1nn,13a,17c,21] or photochemically,[1b,1f,1u,1ff,21e,22] and the formed 1,4-biradical intermediate can either polymerize to give polymer[23] or initiate a radical polymerization process.[1r,24] When a carbon-carbon double bond (ethylene moiety) is replaced by a heteroatom (nitrogen), the corresponding cyclization is called aza-Bergman cyclization.[17f,25] Currently, this cyclization has been used to prepare macrocyclic compounds[26] and, more importantly, in photodynamic therapy[27] and biomedicine.[28]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A general mechanism is displayed below.



D. MODIFICATION

The original thermal cyclization has been modified to occur under photo irradiation.[1u,1ff,21e,22b–22e]

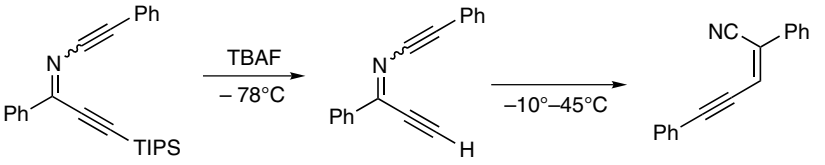
E. APPLICATIONS

This reaction can be applied to radical polymerization,[1r,23,24] the preparation of substituted quinones,[16] 1,4-dichlorobenzenes, macrocyclic compounds,[26] and heteroaromatic compounds (via aza-Bergman cyclization).[1f,25] However, the most important application of this reaction is in photodynamic therapy[27] and biomedicine.[28]

F. RELATED REACTIONS

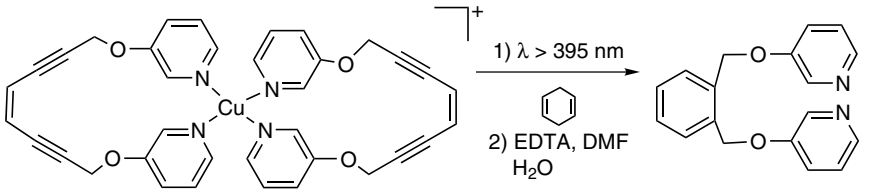
This reaction is related to the *Myers-Saito Cyclization* and *Schmittel Cyclization.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 29.

A solution of 68.0 mg 1,4-diphenyl-6-(triisopropylsilyl)-3-aza-3-ene-1,5-diyne (0.176 mmol) in 6.0 mL dry THF was cooled to –78°C and then a 1 M solution of TBAF (0.194 mmol) was added slowly. After being stirred at –78°C for 5–10 min the mixture was poured into 10 mL ice water and extracted by CH_2Cl_2 (2 × 15 mL). The dry organic solution was plugged through a small column before evaporation. The conversion of aza-enediyne to (*Z*)-2,5-diphenyl-pent-2-en-4-ynenitrile was followed by ^{1}H NMR and/or UV-vis spectroscopy. After the conversion was complete, the (*Z*)-2,5-diphenyl-pent-2-en-4-ynenitrile was purified by flash chromatography on silica gel (0–10% CH_2Cl_2 in hexanes) to afford 36.0 mg product as a yellow solid, in a yield of 89%, m.p. 79.3–80.7°C, R_f = 0.41 (50% CH_2Cl_2 in hexanes).



Reference 1u.

Under anaerobic condition, a Schlenk tube was charged with 20 mg $[Cu(bpod)_2]PF_6$ (0.03 mmol) dissolved in 20 mL dry, degassed (five freeze–pump–thaw cycles) CH_3CN. To this solution, either a 10-fold excess of degassed 1,4-cyclohexadiene or > 5000-fold excess of 2-propanol was added as a hydrogen-atom donor. In both cases, the final concentration of $[Cu(bpod)_2]PF_6$ in solution was 1 mM. These solutions were photolyzed with light of $\lambda \geq 395$ nm within a temperature-controlled bath (0–3°C) for 4 h (2-propanol) to 12 h (1,4-cyclohexadiene), depending on the concentration of the hydrogen-atom donor. Upon photolysis, the solutions change to a brown color, and a precipitate began to form within 1 h. To isolate the photoproduct, larger-scale photolysis was performed (∼275 mg) using the same ratios of hydrogen-atom donor. Upon completion of the photolysis, the solutions were concentrated, stirred with a 1:3 mixture of degassed ether/CH_3CN to precipitate the product, and filtered anaerobically. The solid was subsequently washed with ether and dried in vacuo to yield ∼135 mg (47%) of solid metal-containing photoproduct. The solid inorganic photoproduct (∼90 mg) was dissolved in 25 mL DMF. A 10-fold excess of aqueous Na_2EDTA solution was added to sequester the metal, and the mixture was allowed to be stirred gently at 0°C for 12 h. The precipitate was filtered and the uncomplexed organic material was extracted with dichloromethane. The organic layer was then washed with water, using a separatory funnel, and dried over anhydrous Na_2SO_4. The resulting brown oil was purified by flash chromatography (20% MeOH/CH_2Cl_2, R_f = 0.47) and had a

yield of 87% (based on 2 mol of ligand per mole of reacted complex) of the dark yellow Bergman-cyclized ligand.

Other references related to the Bergman cyclization are cited in the literature.[30]

H. REFERENCES

1. (a) Brzostowska, E. M.; Hoffmann, R. and Parish, C. A., *J. Am. Chem. Soc.,* **2007**, *129*, 4401. (b) Karpov, G. V. and Popik, V. V., *J. Am. Chem. Soc.,* **2007**, *129*, 3792. (c) Pickard, F. C.; Shepherd, R. L.; Gillis, A. E.; Dunn, M. E.; Feldgus, S.; Kirschner, K. N.; Shields, G. C.; Manoharan, M. and Alabugin, I. V., *J. Phys. Chem. A,* **2006**, *110*, 2517. (d) Zeidan, T. A.; Kovalenko, S. V.; Manoharan, M. and Alabugin, I. V., *J. Org. Chem.,* **2006**, *71*, 962. (e) Zeidan, T. A.; Manoharan, M. and Alabugin, I. V., *J. Org. Chem.,* **2006**, *71*, 954. (f) Kar, M.; Basak, A. and Bhattacharjee, M., *Bioorg. Med. Chem. Lett.,* **2005**, *15*, 5392. (g) Lewis, K. D. and Matzger, A. J., *J. Am. Chem. Soc.,* **2005**, *127*, 9968. (h) Basak, A.; Bag, S. S. and Das, A. K., *Eur. J. Org. Chem.,* **2005**, 1239. (i) Santos, J. C.; Andres, J.; Aizman, A.; Fuentealba, P. and Polo, V., *J. Phys. Chem. A,* **2005**, *109*, 3687. (j) Bhattacharyya, S.; Pink, M.; Baik, M.-H. and Zaleski, J. M., *Angew. Chem. Int. Ed.,* **2005**, *44*, 592. (k) Nath, M.; Pink, M. and Zaleski, J. M., *J. Am. Chem. Soc.,* **2005**, *127*, 478. (l) Basak, A.; Bag, S. S.; Majumder, P. A.; Das, A. K. and Bertolasi, V., *J. Org. Chem.,* **2004**, *69*, 6927. (m) Rule, J. D. and Moore, J. S., *Polymer Preprints,* **2004**, *45*, 87. (n) Rule, J. D.; Wilson, S. R. and Moore, J. S., *Polymer Preprints,* **2004**, *45*, 781. (o) Spence, J. D.; Cline, E. D.; Lagostera, D. M. and O'Toole, P. S., *Chem. Commun.,* **2004**, 180. (p) Puiggros, O. R.; Pittner, J.; Carsky, P.; Stampfuss, P. and Wenzel, W., *Coll. Czech. Chem. Commun.,* **2003**, *68*, 2309. (q) Gaffney, S. M.; Capitani, J. F.; Castaldo, L. and Mitra, A., *Int. J. Quant. Chem.,* **2003**, *95*, 706. (r) Rule, J. D.; Wilson, S. R. and Moore, J. S., *J. Am. Chem. Soc.,* **2003**, *125*, 12992. (s) Basak, A.; Mandal, S. and Bag, S. S., *Chem. Rev.,* **2003**, *103*, 4077. (t) Kundu, S. K.; Gupta, T. D.; Das, S. and Pramanik, A., *Indian J. Chem., Sect. B,* **2003**, *42B*, 1716. (u) Benites, P. J.; Holmberg, R. C.; Rawat, D. S.; Kraft, B. J.; Klein, L. J.; Peters, D. G.; Thorp, H. H. and Zaleski, J. M., *J. Am. Chem. Soc.,* **2003**, *125*, 6434. (v) Bhattacharyya, S.; Clark, A. E.; Pink, M. and Zaleski, J. M., *Chem. Commun.,* **2003**, 1156. (w) Chen, W.-C.; Zou, J.-W. and Yu, C.-H., *J. Org. Chem.,* **2003**, *68*, 3663. (x) Nath, M.; Huffman, J. C. and Zaleski, J. M., *Chem. Commun.,* **2003**, 858. (y) Kraft, B. J.; Coalter, N. L.; Nath, M.; Clark, A. E.; Siedle, A. R.; Huffman, J. C. and Zaleski, J. M., *Inorg. Chem.,* **2003**, *42*, 1663. (z) Alabugin, I. V. and Manoharan, M., *J. Phys. Chem. A,* **2003**, *107*, 3363. (aa) Pramanik, A. and Kundu, S. K., *Indian J. Chem., Sect. B,* **2002**, *41B*, 1707. (bb) Alabugin, I. V.; Manoharan, M. and Kovalenko, S. V., *Org. Lett.,* **2002**, *4*, 1119. (cc) Jones, G. B. and Warner, P. M., *J. Org. Chem.,* **2001**, *66*, 8669. (dd) Prall, M.; Wittkopp, A.; Fokin, A. A. and Schreiner, P. R., *J. Compt. Chem.,* **2001**, *22*, 1605. (ee) Chen, X. H.; Tolbert, L. M.; Hess, D. W. and Henderson, C., *Macromolecules,* **2001**, *34*, 4104. (ff) Clark, A. E.; Davidson, E. R. and Zaleski, J. M., *J. Am. Chem. Soc.,* **2001**, *123*, 2650. (gg) Jones, G. B. and Warner, P. M., *J. Am. Chem. Soc.,* **2001**, *123*, 2134. (hh) Schmitt, E. W.; Huffman, J. C. and Zaleski, J. M., *Chem. Commun.,* **2001**, 167. (ii) Abou-Hadeed, K., *Chimia,* **2000**, *54*, 763. (jj) Rawat, D. S. and Zaleski, J. M., *Chem. Commun.,* **2000**, 2493. (kk) Choy, N.; Blanco, B.; Wen, J. H.; Krishan, A. and Russell, K. C., *Org. Lett.,* **2000**, *2*, 3761. (ll) Choy, N.; Kim, C.-S.; Ballestero, C.; Artigas, L.; Diez, C.; Lichtenberger, F.; Shapiro, J. and Russell, K. C., *Tetrahedron Lett.,* **2000**, *41*, 6955. (mm) Debbert, S. L. and Cramer, C. J., *Int. J. Mass Spectr.,* **2000**, 201, 1. (nn) Benites, P. J.; Rawat, D. S. and Zaleski, J. M., *J. Am. Chem. Soc.,* **2000**, *122*, 7208. (oo) Kim, C.-S.; Diez, C. and Russell, K. C., *Chem. Eur. J.,* **2000**, *6*, 1555. (pp) Galbraith, J. M.; Schreiner, P. R.; Harris, N.; Wei, W.; Wittkopp, A. and Shaik, S., *Chem. Eur. J.,* **2000**, *6*, 1446. (qq) McMahon, R. J.; Halter, R. J.; Fimmen, R. L.; Wilson, R. J.; Peebles, S. A.; Kuczkowski, R. L. and Stanton, J. F., *J. Am. Chem. Soc.,* **2000**, *122*, 939. (rr) Basak, A.; Moh'd Bdour, H. and Shain, J. C., *J. Indian Chem. Soc.,* **1999**, *76*, 679. (ss) Kim, C.-S. and

Russell, K. C., *Tetrahedron Lett.,* **1999**, *40*, 3835. (tt) Hong, Y. P. and Kwon, S. H., *Bull. Korean Chem. Soc.,* **1998**, *19*, 1150. (uu) Kim, C.-S. and Russell, K. C., *J. Org. Chem.,* **1998**, *63*, 8229. (vv) Chen, W.-C.; Chang, N.-Y. and Yu, C.-H., *J. Phys. Chem. A,* **1998**, *102*, 2584. (ww) Pramanik, A.; Kalyanaraman, P. and Chandrasekhar, J., *Curr. Sci.,* **1997**, *73*, 527. (xx) Schmittel, M. and Kiau, S., *Chem. Lett.,* **1995**, 953. (yy) Warner, B. P.; Millar, S. P.; Broene, R. D. and Buchwald, S. L., *Science,* **1995**, *269*, 814. (zz) Kraka, E. and Cremer, D., *J. Am. Chem. Soc.,* **1994**, *116*, 4929. (aaa) Tour, J. M. and John, J. A., *Polymer Preprints,* **1993**, *34*, 372.

2. (a) Klein, M.; Walenzyk, T. and Koenig, B., *Coll. Czech. Chem. Commun.,* **2004**, *69*, 945. (b) Basak, A.; Sekhar Bag, S. and Bdour, H. M. M., *Chem. Commun.,* **2003**, 2614.
3. (a) Jones, G. B. and Russell, K. C., "*The Photo-Bergman Cycloaromatization of Enediynes*", in *CRC Handbook of Organic Photochemistry and Photobiology*, ed. Horspool, W. M. and Lenci, F., 2nd ed., CRC Press, Boca Raton, **2004**, 29/1. (b) Jones, G. B.; Wright, J. M.; Hynd, G.; Wyatt, J. K.; Warner, P. M.; Huber, R. S.; Li, A. W.; Kilgore, M. W.; Sticca, R. P. and Pollenz, R. S., *J. Org. Chem.,* **2002**, *67*, 5727. (c) Maier, M. E. and Greiner, B., *Liebigs Ann. Chem.,* **1992**, 855.
4. (a) Feldgus, S. and Shields, G. C., *Chem. Phys. Lett.,* **2001**, *347*, 505. (b) Graefenstein, J.; Hjerpe, A. M.; Kraka, E. and Cremer, D., *J. Phys. Chem. A,* **2000**, *104*, 1748.
5. Usuki, T.; Mita, T.; Lear, M. J.; Das, P.; Yoshimura, F.; Inoue, M.; Hirama, M.; Akiyama, K. and Tero-Kubota, S., *Angew. Chem. Int. Ed.,* **2004**, *43*, 5249.
6. (a) Wittig, C., *Naturwissenschaften,* **1942**, 696. (b) Roberts, J. D.; Semenow, D. A.; Simmons, H. E. Jr. and Carlsmith, L. A., *J. Am. Chem. Soc*., **1956**, *78*, 601. (c) Darby, N.; Kim, C. U.; Salaun, J. A.; Shelton, K. W.; Takada, S. and Masamune, S., *J. Chem. Soc., D,* **1971**, *23*, 1516. (d) Sander, W., *Acc. Chem. Res.,* **1999**, *32*, 669.
7. (a) Jones, R. R. and Bergman, R. G., *J. Am. Chem. Soc.,* **1972**, *94*, 660. (b) Bergman, R. G., *Acc. Chem. Res*., **1973**, *6*, 25.
8. (a) Wolkenberg, S. E., *Tetrahedron Lett*., **2001**, 1. (b) Hitchcock, S. A.; Chu-Moyer, M. Y.; Boyer, S. H.; Olson, S. H. and Danishefsky, S. J., *J. Am. Chem. Soc.,* **1995**, *117*, 5750. (c) Nicolaou, K. C., *Angew. Chem. Int. Ed. Engl.,* **1993**, *32*, 1377. (d) Lee, M. D.; Ellestad, G. A. and Borders, D. B., *Acc. Chem. Res.,* **1992**, *24*, 235. (e) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O. and Borders, D. B., *J. Am. Chem. Soc.,* **1987**, *109*, 3464. (f) Lockhardt, T. P.; Commita, P. B. and Bergman, R. G., *J. Am. Chem. Soc.,* **1981**, *103*, 4082.
9. Konishi, M.; Ohkuma, H.; Saitoh, K.; Kawaguchi, H.; Golik, J.; Dubay, G.; Groenewold, G.; Krishnan, B. and Doyle, T. W., *J. Antibiot.,* **1985**, *38*, 1605.
10. Konishi, M.; Ohkuma, H.; Matsumoto, K.; Tsuno, T.; Kamei, H.; Miyaki, T.; Oki, T.; Kawaguchi, H.; Van Duyne, G. D. and Clardy, J., *J. Antibiot.,* **1989**, *42*, 1449.
11. Leet, J. E.; Schroeder, D. R.; Hofstead, S. L.; Golik, J.; Colson, K. L.; Huang, S.; Klohy, S. E.; Doyle, T. W. and Matson, J. A., *J. Am. Chem. Soc.,* **1992**, *114*, 7946.
12. (a) Nicolaou, K. C. and Smith, A. L., *Acc. Chem. Res.,* **1992**, *25*, 497. (b) Nicolaou, K. C. and Dai, W.-M., *Angew. Chem.,* **1991**, *103*, 1453.
13. (a) Smith, A. L. and Nicolaou, K. C., *J. Med. Chem.,* **1996**, *39*, 2103. (b) Bergman, R. G. and Lockhart, T. P., *J. Am. Chem. Soc.,* **1981**, *103*, 4091.
14. Roth, W. R.; Hopf, H. and Horn, C., *Chem. Ber.,* **1994**, *127*, 1765.
15. (a) Saito, I.; Nagata, R.; Yamanaka, H. and Murahashi, E., *Tetrahedron Lett.,* **1990**, *31*, 2907. (b) Nicolaou, K. C.; Maligres, P.; Shin, J.; de Leon, E. and Rideout, D., *J. Am. Chem. Soc.,* **1990**, *112*, 7825.
16. Jones, L. H.; Harwig, C. W.; Wentworth P., Jr.; Simeonov, A.; Wentworth, A. D.; Py, S.; Ashley, J. A.; Lerner, R. A. and Janda, K. D., *J. Am. Chem. Soc*., **2001**, *123*, 3607.
17. (a) Alabugin, I. V. and Manoharan, M., *J. Am. Chem. Soc.,* **2003**, *125*, 4495. (b) Kawatkar, S. P. and Schreiner, P. R., *Org. Lett.,* **2002**, *4*, 3643. (c) König, B.; Pitsch, W.; Klein, M.; Vasold, R.;

Prall, M. and Schreiner, P. R., *J. Org. Chem.,* **2001**, *66*, 1742. (d) Schreiner, P. R. and Prall, M., *J. Am. Chem. Soc.,* **1999**, *121*, 8615. (e) Cramer, C. J. and Squires, R. R., *Org. Lett.,* **1999**, *1*, 215. (f) Cramer, C. J., *J. Am. Chem. Soc.,* **1998**, *120*, 6261. (g) Hoffner, J.; Schottelius, M. J.; Feichtinger, D. and Chen, P., *J. Am. Chem. Soc.,* **1998**, *120*, 376. (h) Schreiner, P. R., *J. Chem. Soc., Chem. Commun.,* **1998**, 483. (i) Schreiner, P. R., *J. Am. Chem. Soc.,* **1998**, *120*, 4184. (j) Cramer, C. J. and Squires, R. R., *J. Phys. Chem. A,* **1997**, *101*, 9191. (k) Kraka, E.; Cremer, D.; Bucher, G.; Wandel, H. and Sander, W., *Chem. Phys. Lett.,* **1997**, *268*, 313. (l) Cramer, C. J.; Nash, J. J. and Squires, R. R., *Chem. Phys. Lett.,* **1997**, *277*, 311. (m) Lindh, R. and Schütz, M., *Chem. Phys. Lett.,* **1996**, *258*, 409. (n) Logan, C. F. and Chen, P., *J. Am. Chem. Soc.,* **1996**, *118*, 2113. (o) Lindh, R.; Lee, T. J.; Bernhardsson, A.; Persson, B. J. and Karlström, G., *J. Am. Chem. Soc.,* **1995**, *117*, 7186. (p) Lindh, R. and Persson, B. J., *J. Am. Chem. Soc.,* **1994**, *116*, 4963. (q) Nicolaides, A. and Borden, W. T., *J. Am. Chem. Soc.,* **1993**, *115*, 11951. (r) Wierschke, S. G.; Nash, J. J. and Squires, R. R., *J. Am. Chem. Soc.,* **1993**, *115*, 11958. (s) Schreiner, A. C.; Schaefer, H. F. and Liu, B., *J. Am. Chem. Soc.,* **1989**, *111*, 3118.

18. Kim, C. and Russell, K. C., *Tetrahedron Lett.,* **1999**, *40*, 3835.
19. (a) Schreiner, P. R., *J. Am. Chem. Soc.,* **1998**, *120*, 4148. (b) Magnus, P.; Eisenbeis, S. A., *J. Am. Chem. Soc.,* **1993**, *115*, 953. (c) Magnus, P.; Fortt, S.; Pitterna, T. and Snyder, J. P., *J. Am. Chem. Soc.,* **1990**, *112*, 4986. (d) Snyder, J. P., *J. Am. Chem. Soc.,* **1990**, *112*, 5367.
20. (a) Jones, G. B. and Plourde, G. W., *Org. Lett.,* **2000**, *2*, 1757. (b) Choy, N. and Russell, K. C., *Heterocycles* **1999**, *51*, 13. (c) Semmelhack, M. F.; Neu, T. and Foubelo, F., *Tetrahedron Lett.,* **1992**, *3*, 3277.
21. (a) Coalter, N. L.; Concolino, T. E.; Streib, W. E.; Hughes, C. G.; Rheingold, A. L. and Zaleski, J. M., *J. Am. Chem. Soc.,* **2000**, *122*, 3112. (b) Grissom, J. W.; Guanwardena, G. U.; Klingberg, D. and Huang, D., *Tetrahedron,* **1996**, *52*, 6453. (c) Brückner, R.; Suffert, J.; Abraham, E. and Raeppel, S., *Liebigs Ann.,* **1996**, 447. (d) Nicolaou, K. C.; Smith, A. L., "The Enediyne Antibiotics" in *Modern Acetylene Chemistry*, ed. Stang, P. J. and Diederich, F., VCH, Weinheim, **1995**, p. 203. (e) Maier, M. E., *Synlett*, **1995**, 13.
22. (a) Fouad, F. S.; Crasto, C. F.; Lin, Y. Q. and Jones, G. B., *Tetrahedron Lett.,* **2004**, *45*, 7753. (b) Alabugin, I. V. and Kovalenko, S. V., *J. Am. Chem. Soc.,* **2002**, *124*, 9052. (c) Evenzahav, A. and Turro, N. J., *J. Am. Chem. Soc.,* **1998**, *120*, 1835. (d) Ramkumar, D.; Kalpana, M.; Varghese, B.; Sankararaman, S.; Jagadeesh, M. N. and Chandrasekhar, J., *J. Org. Chem.,* **1996**, *61*, 2247. (e) Funk, R. L.; Young, E. R. R.; Williams, R. M.; Flanagan, M. F. and Cecil, T. L., *J. Am. Chem. Soc*., **1996**, *118*, 3291.
23. (a) Johnson, J. P.; Bringley, D. A.; Wilson, E. E.; Lewis, K. D.; Beck, L. W. and Matzger, A. J., *J. Am. Chem. Soc.,* **2003**, *125*, 14708. (b) John, J. A. and Tour, J. M., *J. Am. Chem. Soc.,* **1994**, *116*, 5011.
24. Drumright, R. E.; Terbrueggen, R. H.; Priddy, D. B. and Koster, R. A., *U. S. Pat.*, **1997**, Apr. 8, 5,618,900.
25. David, W. M. and Kerwin, S. M., *J. Am. Chem. Soc.,* **1997**, *119*, 1464.
26. Wandel, H. and Wiest, O., *J. Org. Chem.,* **2002**, *67*, 388.
27. (a) Bonnett, R. and Martinez, G., *Tetrahedron,* **2001**, *57*, 9513. (b) Mody, T. M. and Sessler, J. L., eds., *Supramolecular Materials and Technologies*, Wiley, Chichester, UK, **1999**, *4*. (c) Ali, H. and van Lier, J. E., *Chem. Rev.,* **1999**, *99*, 2379. (d) Boyle, R. W. and Dolphin, D., *Photochem. Photobiol.,* **1996**, *64*, 469.
28. (a) North, J.; Neyndorff, H. and Lewis, J. G., *J. Photochem. Photobiol. B,* **1993**, *17*, 99. (b) Abramson, A. L.; Shikowitz, M. J.; Mullooly, V. M.; Steinberg, B. M.; Amella, C. A. and Rothstein, H. R., *Arch. Otolaryngol., Head Neck Surg.,* **1992**, *118*, 25. (c) Sieber, F.; O'Brien, J. M. and Gaffney, D. K., *Blood Cells,* **1992**, *18*, 117. (d) Sieber, F.; O'Brien, J. M. and Gaffney, D. K., *Semin. Hematol.,* **1992**, *29*, 79. (e) Matthews, J. L.; Sogandares-Bernal, F.; Judy, M.; Gulliya, K.; Newman, J.; Chanh, T. and Marengo-Rowe, A., *Blood Cells,* **1992**, *18*, 75.

29. Feng, L. P.; Kumar, D. and Kerwin, S. M., *J. Org. Chem.,* **2003**, *68*, 2234.

30. (a) Jones, G. B. and Fouad, F. S., *Front. Med. Chem.*, **2004**, *1*, 189. (b) Nath, M.; Huffman, J. C. and Zaleski, J. M., *J. Am. Chem. Soc.,* **2003**, *125*, 11484. (c) De Proft, F.; Schleyer, P. R.; van Lenthe, J. H.; Stahl, F. and Geerlings, P., *Chem. Eur. J.*, **2002**, *8*, 3402. (d) Eshdat, L.; Berger, H.; Hopf, H. and Rabinovitz, M., *J. Am. Chem. Soc.,* **2002**, *124*, 3822. (e) O'Connor, J. M.; Friese, S. J. and Tichenor, M., *J. Am. Chem. Soc.,* **2002**, *124*, 3506. (f) Stahl, F.; Moran, D.; von Ragué Schleyer, P.; Prall, M. and Schreiner, P. R., *J. Org. Chem.,* **2002**, *67*, 1453. (g) Liu, W.; Christenson, S. D.; Standage, S. and Shen, B., *Science,* **2002**, *297*, 1170. (h) Amegayibor, F. S.; Nash, J. J.; Lee, A. S.; Thoen, J.; Petzold, C. J. and Kenttämaa, H. I., *J. Am. Chem. Soc.,* **2002**, *124*, 12066. (i) Kraka, E. and Cremer, D., *J. Compt. Chem.,* **2001**, *22*, 216. (j) Sapse, A.-M.; Rothchild, R.; Kumar, R. and Lown, J. W., *Mol. Med.*, **2001**, *7*, 797. (k) Kaafarani, B. R. and Neckers, D. C., *Tetrahedron Lett.,* **2001**, *42*, 4099. (l) Kren, V. and Martínková, L., *Curr. Med. Chem*., **2001**, *8*, 1313. (m) de Visser, S. P.; Filatov, M. and Shaik, S., *Phys. Chem. Chem. Phys*., **2001**, *3*, 1242. (n) Bowles, D. M.; Palmer, G. J.; Landis, C. A.; Scott, J. L. and Anthony, J. E., *Tetrahedron,* **2001**, *57*, 3753. (o) Rawat, D. S. and Zaleski, J. M., *J. Am. Chem. Soc.,* **2001**, *123*, 9675. (p) Chandra, T.; Pink, M. and Zaleski, J. M., *Inorg. Chem.,* **2001**, *40*, 5878. (q) König, B., *Eur. J. Org. Chem.,* **2000**, 381. (r) Kraka, E. and Cremer, D., *J. Mol. Struct. (Theochem),* **2000**, *506*, 191. (s) Wenthold, P. G. and Lipton, M. A., *J. Am. Chem. Soc.* **2000**, *122*, 9265. (t) Liu, W. and Shen, B., *Antimicro. Agents & Chemother*., **2000**, *44*, 382. (u) McMahon, R. J.; Halter, R. J.; Fimmen, R. L.; Wilson, R. J.; Peebles, S. A.; Kuczkowski, R. L. and Stanton, J. F., *J. Am. Chem. Soc.,* **2000**, *122*, 8245. (v) Kim, J. H.; Ryoo, K. S.; Choi, J. H. and Hong, Y. P., *Bull. Korean Chem. Soc*., **2000**, *21*, 37. (w) Lindh, R.; Bernhardsson, R. and Schütz, M., *J. Phys. Chem. A,* **1999**, *103*, 9913. (x) Bunz, U. H. F.; Roidl, G.; Altmann, M.; Enkelmann, V. and Shimizu, K. D., *J. Am. Chem. Soc.,* **1999**, *121*, 10719. (y) Morao, I. and Cossio, F. P., *J. Org. Chem*., **1999**, *64*, 1868. (z) Koseki, S.; Fujimura, Y. and Hirama, M. J., *J. Phys. Chem. A,* **1999**, *103*, 7672. (aa) Xi, Z. and Goldberg, I., "*DNA Damaging Enediyne Compound,"* in *Comprehensive Natrual Products Chemistry*, ed. Barton, D. H. R. and Nakanishi, K., Pergamon, Oxford, **1999**; *7*, p. 553. (bb) Shah, H. V.; Brittain, S. T.; Huang, Q.; Hwu, S. J.; Whitesides, G. M. and Smith, D. W., *Chem. Mater.,* **1999**, *11*, 2623. (cc) Haberhauer, G. and Gleiter, R., *J. Am. Chem. Soc.,* **1999**, *121*, 4664. (dd) Butora, G.; Hudlicky, T.; Fearnley, S. P.; Stabile, M. R.; Gum, A. G. and Gonzalez, D., *Synthesis*, **1998**, 665. (ee) Manabe, T.; Yanagi, S. I.; Ohe, K. and Uemura, S., *Organometallics,* **1998**, *17*, 2942. (ff) Engels, B. and Hanrath, M., *J. Am. Chem. Soc.*, **1998**, *120*, 6356. (gg) Engels, B.; Lennartz, C.; Hanrath, M.; Schmittel, M. and Strittmatter, M., *Angew. Chem. Int. Ed. Engl*., **1998**, *37*, 1960. (hh) Wenthold, P. G.; Squires, R. R. and Lineberger, W. C., *J. Am. Chem. Soc.,* **1998**, *120*, 5279. (ii) Chen, W.-C.; Chang, N.-Y. and Yu C.-H., *J. Phys. Chem. A,* **1998**, *102*, 2548. (jj) Gräfenstein, J.; Kraka, E. and Cremer, D., *Chem. Phys. Lett.,* **1998**, *288*, 593. (kk) Tanaka, H.; Yamada, H.; Matsuda, A. and Takahashi, T., *Synlett,* **1997**, 381. (ll) McPhee, M. M. and Kerwin, S. M., *J. Org. Chem.,* **1996**, *61*, 9385. (mm) Tamao, K. and Yamaguchi, S., *Pure & Appl. Chem.,* **1996**, *68*, 139. (nn) Yamaguchi, S. and Tamao, K., *Tetrahedron Lett.,* **1996**, *37*, 2983. (oo) Roth, W.; Hopf, H.; Wasser, T.; Zimmermann, H. and Werner, C., *Liebigs Ann*., **1996**, 1691. (pp) Chen, P., *Angew. Chem.,* **1996**, *108*, 1584. (qq) König, B.; Hollnagel, H.; Ahrens, B. and Jones, P. G., *Angew. Chem. Int. Ed. Engl.,* **1995**, *34*, 2538. (rr) Wang, Y. S. and Finn, M. G., *J. Am. Chem. Soc.,* **1995**, *117*, 8045. (ss) Wenthold, P. G.; Wierschke, S. G.; Nash, J. J. and Squires, R. R., *J. Am. Chem. Soc.,* **1994**, *116*, 7378. (tt) Tamao, K.; Yamaguchi, S. and Shiro, M., *J. Am. Chem. Soc.,* **1994**, *116*, 11715. (uu) Grissom, J. W.; Calkins, T. L.; McMillen, H. A. and Jiang, Y. H., *J. Org. Chem.,* **1994**, *59*, 5833. (vv) Kraka, E. and Cremer, D., *Chem. Phys. Lett*., **1994**, *219*, 160. (ww) Kraka, E. and Cremer, D., *Chem. Phys. Lett.,* **1993**, *216*, 333. (xx) Yoshida, K.-I.; Minami, Y.; Azuma, R.; Saeki, M. and Otani, T., *Tetrahedron Lett*., **1993**, *34*, 2637. (yy) Magnus, P.; Carter, P.; Elliott, J.; Lewis, R.; Harling, J.; Pitterna, T.; Bauta, W. E. and Fortt, S., *J. Am. Chem. Soc.,* **1992**, *114*, 2544. (zz) Myers, A. G.; Dragovich, P. S. and Kuo, E. Y., *J. Am. Chem. Soc.,* **1992**, *114*, 9369. (aaa) Youngs, W. J.; Djebli, A. and Tessier, C. A., *Organomatallics,* **1991**, *10*, 2089. (bbb) Nicolau, K. C. and Dai, W.-M., *Angew. Chem. Int. Ed. Engl.,* **1991**, *30*, 1387. (ccc) Koga,

N. and Morokuma, K., *J. Am. Chem. Soc.,* **1991**, *113*, 1907. (ddd) Snyder, J. P., *J. Am. Chem. Soc.,* **1989**, *111*, 7630. (eee) Myers, A. G.; Kuo, E. Y. and Finney, N. S., *J. Am. Chem. Soc.,* **1989**, *111*, 8057. (fff) Saito, K.; Watanabe, T. and Takahashi, K., *Chem. Lett.,* **1989**, 2099. (ggg) Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishman, B.; Ohkuma, H.; Saitoh, K. and Doyle, T. W., *J. Am. Chem. Soc.,* **1987**, *109*, 3461. (hhh) Golik, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishman, B.; Ohkuma, H.; Saitoh, K. and Doyle, T. W., *J. Am. Chem. Soc.,* **1987**, *109*, 3462. (iii) Edo, K.; Mizugaki, M.; Koide, Y.; Seto, H.; Furihata, K. and Otake, N., *Tetrahedron Lett.,* **1985**, *26*, 331. (jjj) Hauptmann, H. and Mader, M., *Tetrahedron Lett.,* **1980**, *21*, 897. (kkk) Wong, H. N. C. and Sondheimer, F., *Tetrahedron Lett*., **1980**, *21*, 217.

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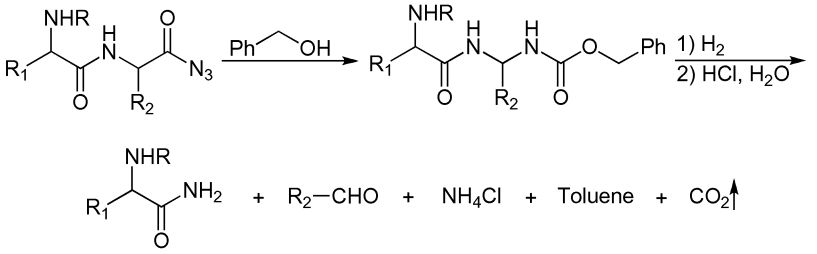
Bergmann Degradation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Bergmann in 1934.[1]It is a method of elucidating peptide sequences via carboxyl terminal (or C-terminal) peptide degradation,[2] involving the Curtis rearrangement of *N*-benzoylamino acids or *N*-benzoylpeptide hydrazides. The thermal rearrangement of the corresponding azides in the presence of benzyl alcohol yields the appropriate benzylurethanes. The removal of the *N*-benzyloxycarbonyl group is accomplished by catalytic hydrogenation in the presence of hydrochloric acid followed by boiling in water. This method removes the C-terminal amino acid residue as the next lower aldehyde in the homologous series and leaves the rest of the peptide in the form of its amide.[3] The acyl azide of C-terminal amino acid residue can be prepared in many ways, including the nitrosylation of *N*-formylaminoacyl hydrazide followed by nucleophilic displacement with sodium azide,[4] reaction with diphenylphosphoryl azide,[5] reaction between the mixed anhydride of amino acid and the TMS azide,[6] and other methods.[7]

B. GENERAL REACTION SCHEME



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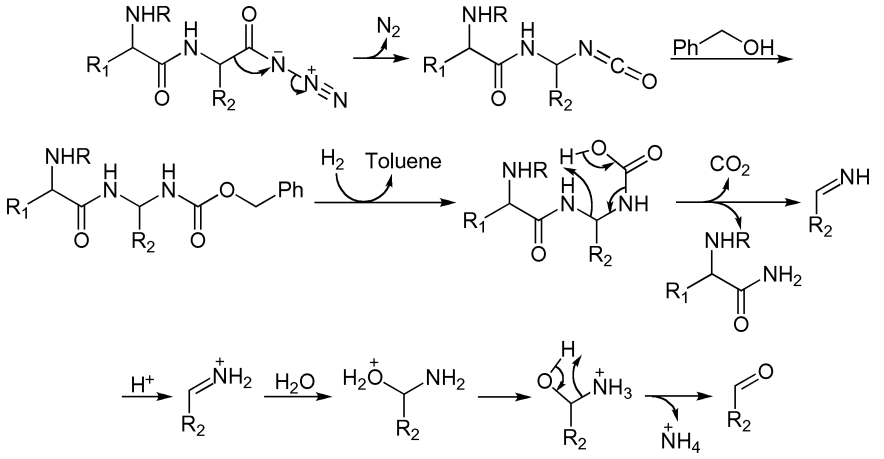
C. PROPOSED MECHANISMS

Displayed is the reaction mechanism, including the benzoylation, hydrogenation, and formation of aldehyde.



D. MODIFICATION

N/A

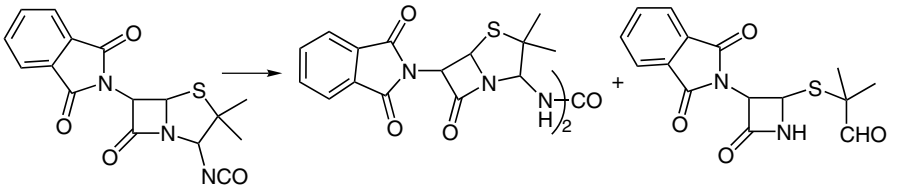
E. APPLICATIONS

This reaction has general application in protein and peptide sequencing. In addition, this method has been used to cleave the penicillin nucleus.[8]

F. RELATED REACTIONS

This reaction is related to *Curtius Rearrangement*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 8.

To a stirred solution of 3.68 mL 1 N HCl in 300 mL 50% aqueous tetrahydrofuran at room temperature was added dropwise over 3.25 h a solution of 1.26 g 2,2-dimethyl-6-phthalimido-3-penamyl isocyanate (3.68 mmol) in 200 mL THF. The reaction mixture was stirred for an additional 0.5 h after the addition of the isocyanate was complete. The reaction mixture was then extracted with CH_2Cl_2 (3×200 mL), and the combined methylene chloride extracts were washed with two 150-mL portions of water, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to an oil. From this oil was obtained 0.02 g *N*,*N*′-bis(2,2-dimethyl-6-phthalimido-3-penamyI)urea mixture by fractional crystallization from an ethanol-petroleum ether (b.p. 30–60°C), which after recrystallization from acetone-petroleum ether, was purifed as a hygroscopic crystalline solid, m.p. 184–185.5°C. The filtrate after removal of the urea was concentrated to a viscous oil, which on crystallization from benzene-ligroin (b.p. 90–100°C) yielded in four crops of 1.0 g 3-phthalimido-4-(1′-formyl-1′-methylethylthio)-2-aze-tidinone, in a yield of 76%, m.p. 101–105°C. Two recrystallizations from benzene-ligroin gave an analytical sample, m.p. 110–119°C.

Other references related to the Bergmann degradation are cited in the literature.[9]

H. REFERENCES

1. Bergmann, M., *Science,* **1934**, *79*, 439.
2. (a) Loudon, G. M.; Parham, M. E., *Tetrahedron Lett.,* **1978**, 437. (b) Parham, M. E. and Loudon, G. M., *Biochem. Biophys. Res. Commun.,* **1978**, *80*, 1.
3. (a) Loudon, G. M.; Radhakrishna, A. S.; Almond, M. R.; Blodgett, J. K. and Boutin, R. H., *J. Org. Chem.,* **1984**, *49*, 4212. (b) Chorev, M.; Willson, C. G. and Goodman, M., *J. Am. Chem. Soc.,* **1977**, *99*, 8975. (c) Synge, R. L. M., *Chem. Rev.,* **1943**, *32*, 135.
4. Chorev, M. and Goodman, M., *Int. J. Pept. Protein Res.,* **1983**, *21*, 258.
5. (a) Ninomiya, K.; Shioiri, T. and Yamada, S., *Tetrahedron,* **1974**, *30*, 2151. (b) Cremlyn, R. J. W., *Aust. J. Chem.* **1973**, *26*, 1591.
6. Fincham, C. I.; Higginbottom, M.; Hill, D. R.; Horwell, D. C.; O'Toole, J. C.; Ratcliffe, G. S.; Rees, D. C. and Roberts, E., *J. Med. Chem.,* **1992**, *35*, 1472.
7. (a) Rawal, V. H. and Zhong, H. M., *Tetrahedron Lett.,* **1994**, *35*, 4947. (b) Bodanszky, M., *Principles of Peptide Synthesis*, 2nd ed., Springer-Verlag, Berlin, **1993**. (c) Scriven, E. F. V. and Turnbull, K., *Chem. Rev.,* **1988**, *88*, 297. (d) Meienhofer, J., The Azide Method in Peptide Synthesis, in *The Peptides*: *Analysis, Synthesis, Biology*, ed. Gross, E. and Meienhofer, J., Academic, New York, **1979**, *1*, pp. 197–240. (e) Biffin, M. E. C.; Miller, J. and Paul, D. B., Introduction of the Azide Group, in *The Chemistry of the Azido Group*, ed. Patai, S., Interscience, London, **1971**, pp. 57–190. (f) Lwowski, W., Acyl Azides, in *The Chemistry of the Azido Group*, ed. Patai, S., Interscience, London, **1971**, pp. 503–554.
8. Sheehan, J. C. and Brandt, K. G., *J. Am. Chem. Soc.,* **1965**, *87*, 5468.
9. (a) Fletcher, M. D. and Campbell, M. M., *Chem. Rev.,* **1998**, *98,* 763. (b) Chorev, M.; Shavitz, R.; Goodman, M.; Minick, S. and Guillemin, R., *Science*, **1979**, *204*, 1210. (c) Willson, C. G.; Goodman, M.; Rivier, J. and Vale, W., Topochemically Related Hormone Structures. The synthesis of Retro-Analogs of LRF., in *Peptides: Proceedings of the 5th American Peptide Symposium*, ed. Goodman, M., and Meienhofer, J., Wiley, New York, **1977**, pp. 579–581. (d) Chorev, M.;

Willson, C. G. and Goodman, M., *J. Am. Chem. Soc.,* **1977**, *99*, 8075. (e) Springall, H. D., *The Structural Chemistry of Proteins*, Academic Press, New York, **1954**, p. 321. (f) Whitmore, F. C., *Organic Chemistry*, Van Nostrand, New York, **1951**, p. 514. (g) Trister, S. M., *J. Franklin Inst.,* **1941**, *232*, 500. (h) Bergmann, M. and Zervas, L., *J. Biol. Chem*., **1936**, *113*, 341.

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Bergmann-Stern Azlactone Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Bergmann and Stern and others in 1926.[1] It is the synthesis of peptides by aminolysis of azlactones from α-amino acids or corresponding esters and is generally known as the Bergmann-Stern azlactone synthesis.[2] This reaction involves the conversion of an acetylated amino acid and an aldehyde into an azlactone (also known as 5-oxazolone[3]) with an alkylidene side chain, the reaction of azlactone with the second amino acid to form an acylated unsaturated dipeptide along with the opening of the azlactone ring, the catalytic hydrogenation of the resulting *N*-acyl enamine, and final hydrolysis to give dipeptide. In fact, the first unsaturated azlactone was prepared by Plöchl, who condensed benzaldehyde with hippuric acid.[4] It was Erlenmeyer who coined the word of *azlactone* to describe the formed oxazolone and who initially showed the usefulness of these compounds in formation of α-keto acids and α-amino acids.[5] In comparison, the first saturated azlactone was reported by Mohr and Geis in 1908 by heating *N*-benzoyl-α-aminoisobutyric acid with acetic anhydride.[6] In most cases, the azlactone is racemic even though the starting material is optically active,[7]and the partly optically active azlactone racemizes more rapidly than it reacts with *p*-nitrophenol.[8] It was Bergmann who realized the racemization of *N*-acyl or benzoyl derivatives of α-amino acids in the presence of acetic anhydride, even in a catalytic amount, and who developed the method of synthesizing peptide.[9] This method has been greatly improved, and its scope has been extended by gently heating α-amino acid with trifluoroacetic anhydride to form 4-substituted-2-(trifluoromethyl)-6-oxazolone.[10] Overall,

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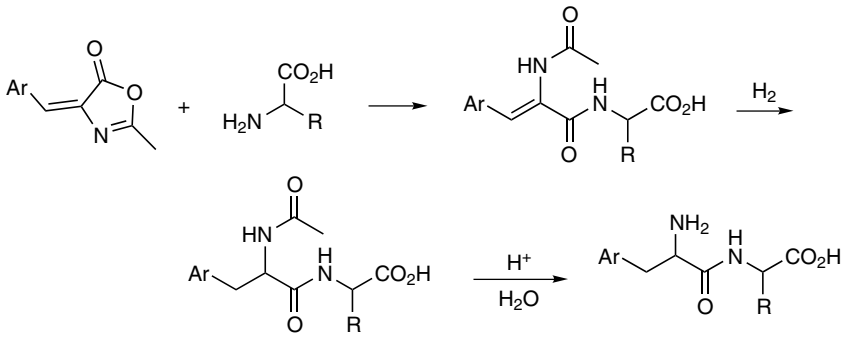
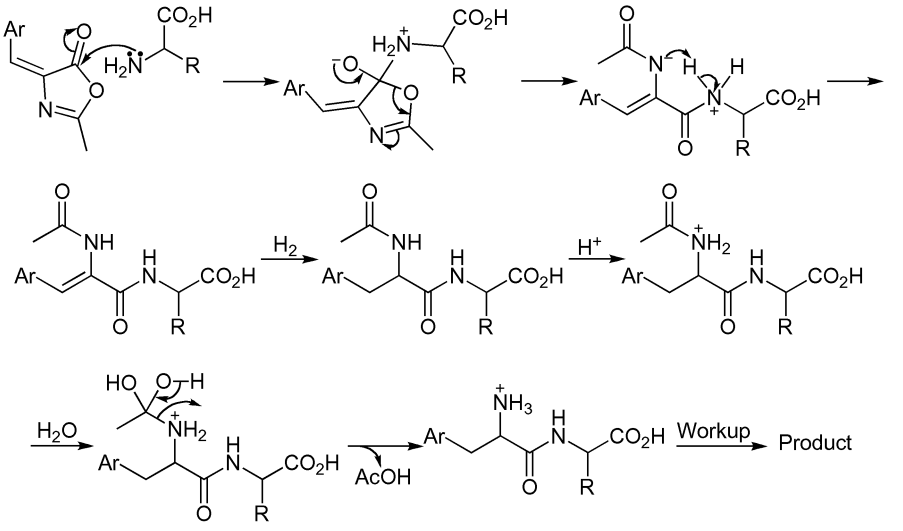
this reaction can be used to synthesize peptides containing tyrosine, arginine, histidine, glutamic acid, and other amino acids.[11] In addition, the formed azlactones can be converted into α-keto acids and α-amino acids.[5]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified to heat amino acid with trifluoroacetic anhydride to form 4-substituted-2-(trifluoromethyl)-6-oxazolone,[10] which can react with the succeeding amino acid to form peptide. The azlactone with a saturated side chain can be prepared from α-keto acid and subjected to the peptide synthesis.[12]

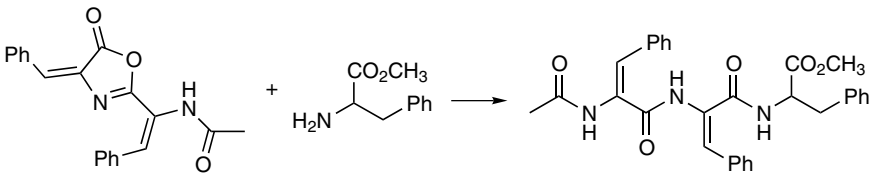
E. APPLICATIONS

This reaction has general application in the preparation of peptide. The azlactone itself can be converted into α-keto acid or α-amino acid.[5]

F. RELATED REACTIONS

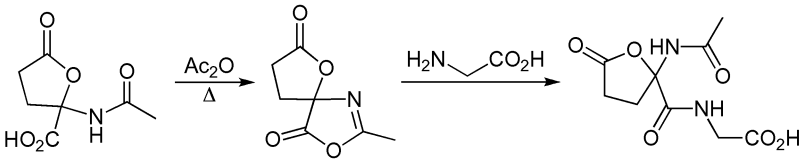
This reaction is related to the *Erlenmeyer-Plöchl Azlactone Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 13.

To a solution of 1.0 g azlactone (3.0 mmol) in 20 mL dry chloroform was added to a 5 mL $CHCl_3$ solution containing 0.64 g phenylalanine methyl ester hydrochloride (3.0 mmol) and 0.30 g NEt_3 (3.0 mmol). The reaction mixture was allowed to reflux for 8 h; then the solvent was removed under reduced pressure. The residue was washed with water and recrystallized from methanol-water and chloroform-petroleum ether to give methyl ester of Ac-(dehydro-Phe)$_2$-L-Phe, m.p. 188–189°C. (*Note*: No yield was given in the original reference.)



Reference 12.

A suspension of 3 g α-acetamino-α-hydroxyglutaric lactone in 60 mL acetic anhydride was heated on a boiling water-bath until all the material dissolved; 10–15 min was required,

during which time the solution became orange-yellow. After removal of the excess acetic anhydride in vacuo, the crude azlactone, a yellow viscous oil, was suspended in 30 mL acetone and treated immediately with a solution of 1.12 g glycine in 15 mL normal sodium hydroxide (1 N). The mixture, containing a trace of undissolved material, was shaken for 30 min, neutralized with 15 mL normal sulfuric acid (1 N), evaporated to dryness in vacuo, and extracted thoroughly with cold 95% alcohol. The alcoholic solution was evaporated to dryness; the residue was taken up in a small amount of water and decolorized with charcoal. The aqueous solution was then evaporated to dryness, and the residue was washed with cold alcohol. The 1.3 g of insoluble portion was recrystallized by suspension in hot alcohol with dropwise additions of water until solution took place. On cooling, 0.7 g of the lactone of α-acetamino-α-hydroxyglutarylglycine was separated from the solution.

Other references related to the Bergmann-Stern azlactone synthesis are cited in the literature.[14]

H. REFERENCES

1. (a) Bergmann, M.; Stern, F. and Witte, C., *Ann.,* **1926**, *449*, 271. (b) Bergmann, M.; Stern, F. and Witte, C., *Ann.,* **1926**, *449*, 277.
2. Steglich, W. and Hurnaus, R., *Tetrahedron Lett.,* **1966**, 383.
3. Fletcher, M. D. and Campbell, M. M., *Chem. Rev.,* **1998**, *98,* 763.
4. Plöchl, J., *Ber.,* **1883**, *16*, 2815.
5. (a) Erlenmeyer, E., *Ber*., **1900**, *33*, 2036. (b) Erlenmeyer, E., *Ber*., **1902**, *35*, 243.
6. Mohr, E. and Geis, T., *Ber*., **1908**, *41*,798.
7. Mohr, E. and Stroscheim, F., *Ber*., **1909**, *42*, 2521.
8. Goodman, M. and Levine, L., *J. Am. Chem.* Soc., **1964**, *86*, 2918.
9. (a) Bergmann, M. and Zervas, L., *Biochem. J.*, **1928**, *203, 280*. (b) Bergmann, M. and Zervas, L., *Hoppe-Seyler's J. Physiol. Chem.,* **1928**, *176*, 154.
10. (a) Weygand, F.; Steglich, W. and Tanner, H., *Ann*., **1962**, *658*, 128. (b) Weygand, F. and Reiher, M., *Ber*., **1955**, *88*, 26.
11. Sheehan, J. C. and Frank, V. S., *J. Am. Chem. Soc.,* **1959**, *71*, 1856.
12. Shemin, D. and Herbst, R. M., *J. Am. Chem. Soc.,* **1938**, *60*, 1951.
13. Pieroni, O.; Montagnoli, G.; Fissi, A.; Merlino, S. and Ciardellilc, F., *J. Am. Chem. Soc.,* **1975**, *97*, 6820.
14. (a) Cooper, A. J. L.; Ginos, J. Z. and Meister, A., *Chem. Rev.,* **1983**, *83,* 321. (b) Konno, S. and Stammer, C. H., *Int. J. Peptide Protein Res.,* **1978**, *12*, 222. (c) DeTar, D. F.; Silverstein, R. and Rogers, F. F., *J. Am. Chem. Soc.,* **1966**, *88*, 1024. (d) Greenstein, J. P. and Winitz, M., *Chemistry of the Amino Acids*, Wiley; New York, **1961**. (e) Pfleger, R. and Pelz, J., *Chem. Ber.,* **1957**, *90*, 1489. (f) Bergel, F. and Stock, J. A., *Proc. Chem. Soc.,* **1957**, 60. (g) Stoll, A.; Hofmann, A.; Leemann, H. G.; Ott, H. and Schenk, H. R., *Helv. Chim. Acta,* **1956**, *39*, 1165. (h) Baltazzi, E., *Quart. Rev. (London),* **1956**, *10*, 235. (i) Springall, H. D., *The Structural Chemistry of Proteins*, Academic Press, New York, **1954**, p. 29. (j) Archer, S., "*Azlactone*" in *Amino Acids and Proteins*, ed. Greenberg, D. M., Thomas, Springfield, IL., **1951**, p. 181. (k) Fruton, J. S., *Advances in Protein Chemistry V*, Academic Press, New York, **1949**, p. 15. (l) Cornforth, J. W. and Clarke, H. T., "*Oxazoles and Oxazolones*" in *Chemistry of Pencillin*, ed. Clarke, H. T., Princeton University Press, Princeton, N.J., **1949**, p. 783. (m) Dohefty, D. G.; Tietzman, J. E., and Bergmann, M., *J. Biol. Chem.,* **1943**, *147*, 617. (n) Dyer, E., *J. Am. Chem.*

Soc., **1941**, *63*, 265. (o) du Vigneaud, V. and Meyer, C. E., *J. Bio. Chem.,* 1932, 99, 143. (p) Bergmann, M. and Grafe, K., *Hoppe-Seyler's J. Physiol. Chem.,* **1930**, *187*, 183–186. *Chem. Abstr.,* **1930**, *24*, 2150. (q) Bergmann, M. and Grafe, K., *Hoppe-Seyler's J. Physiol. Chem.,* **1930**, *187*, 187–195. *Chem. Abstr.,* **1930**, *24*, 2150. (r) Bergmann, M. and Grafe, K., *Hoppe-Seyler's J. Physiol. Chem.,* **1930**, *187*, 196–202. *Chem. Abstr.,* **1930**, *24*, 2151.

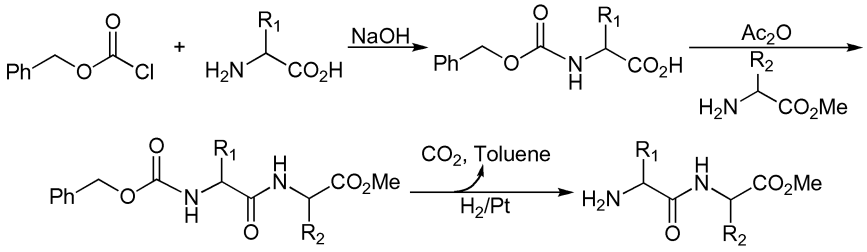
78

Bergmann-Zervas Peptide Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Bergmann and Zervas in 1932.[1] It is a synthesis of peptide involving the process of conversion of the amino acid into its *N*-carbobenzoxy derivative, activation of the carboxyl group, formation of peptide with the second amino acid, and deprotection via hydrogenolysis.[2] However, the original procedure did not lend itself to the preparation of cysteine or cystine peptides, as the catalyst (Pd, Pt) was not active enough in the presence of a sulfur-containing molecule. Therefore, the reductive removal of the carbobenzoxy group was modified by treatment of the resulting peptide with metallic sodium in liquid ammonia.[3] Moreover, other deprotection methods have been developed, such as the acidic hydrolysis using phosphonium iodide,[4] and hydrogen iodide in acetic acid.[4] In addition, the carbobenzoxy group can also be cleaved using hydrogen bromide[2,5] or hydrogen chloride.[6] This method has become a standard method for protecting amino groups in peptide synthesis.[7]

B. GENERAL REACTION SCHEME



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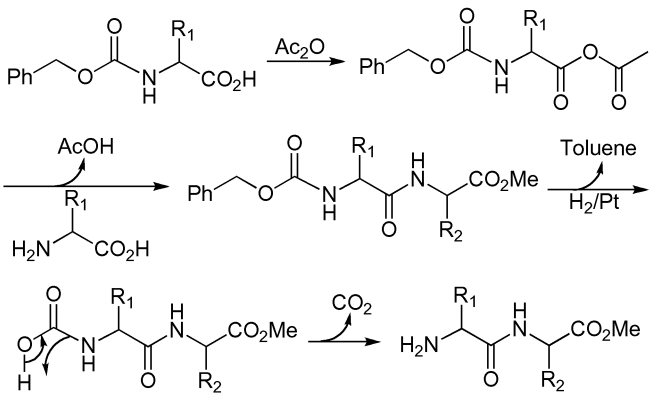
C. PROPOSED MECHANISMS



D. MODIFICATION

The removal of the carbobenzoxy group has been modified by reductive cleavage using sodium in liquid ammonia[3] or nonhydrolytic cleavage using acidic hydrolysis (HI, HBr or HCl).[2,4–6]

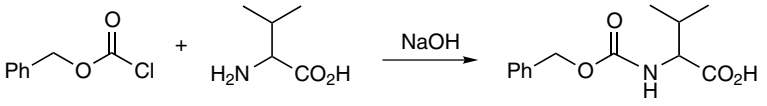
E. APPLICATIONS

This method has been extensively applied for peptide synthesis.[7]

F. RELATED REACTIONS

This reaction is related to the *Fischer Peptide Synthesis*.

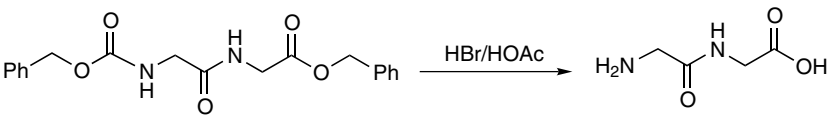
G. CITED EXPERIMENTAL EXAMPLES



Reference 7r.

DL-Valine (11.7 g, 0.10 mol) was dissolved in 25 mL 4 N sodium hydroxide. With cooling in an ice-bath, there were added simultaneously with stirring, over a period of 45 min, 25 mL 4 N sodium hydroxide and 23 mL carbobenzoxy chloride solution (from 200 g of 20% phosgene in toluene and 38 mL benzyl alcohol, allowed to react and then concentrate under reduced pressure to 80 g). The solution was acidified with hydrochloric acid, which

deposited an oil. The mass was crystallized by dissolving in dilute sodium hydroxide, reprecipitating with hydrochloric acid, and permitting it to stand overnight in the refrigerator to yield 21.0 g carbobenzoxy-DL-valine, in a yield of 84%, m.p. 75–77°C (uncor.). In later preparations, ether or ethyl acetate was used to extract the initial oil obtained upon acidification; the extracts were dried, and the solvent was removed by evaporation. The residue was crystallized by dissolving in benzene, precipitating with hexane, and seeding with material from the first preparation to yield 20.5 g carbobenzoxy-DL-valine, in a yield of 82%.



Reference 2.

Carbobenzoxyglycylglycine benzyl ester (5 g) was suspended in 25 mL glacial acetic acid, and a stream of dry hydrogen bromide was bubbled through the hot solution (60°C) for 1 h. During the reaction, the starting material dissolved, and after 15 minutes the dipeptide hydrobromide began to separate. Dry ether (100 mL) was then added, and the reaction flask was kept in the refrigerator for 4 h. The supernatant liquid was decanted, and the solid was washed with small portions of ether and dried in vacuo. To obtain the free peptide, the hydrobromide was dissolved in a minimum amount of water, excess pyridine was added, and the peptide was precipitated with absolute alcohol. It was filtered, washed with absolute alcohol and dry ether, and dried in vacuo over sulfuric acid for 48 h to afford glycylglycine, in a yield of 83%, m.p. 222°C (dec.).

Other references related to the Bergmann-Zervas peptide synthesis are cited in the literature.[8]

H. REFERENCES

1. Bergmann, M. and Zervas, L., *Ber.,* **1932**, *65*, 1192.
2. Ben-Ishai, D., *J. Org. Chem.,* **1954**, *19*, 62.
3. (a) du Vigneaud, V. and Miller, G. L., *J. Biol. Chem.,* **1936**, *116*, 469. (b) Sifferd, R. H. and du Vigneaud, V., *J. Biol. Chem.,* **1935**, *108*, 753. (c) du Vigneaud, V.; Audrieth, L. F. and Loring, H. S., *J. Am. Chem. Soc.,* **1930**, *52*, 4500.
4. Harington, C. and Mead, T., *Biochem. J.,* **1935**, *29*, 1603.
5. Albertson, N. F. and McKay, F. C., *J. Am. Chem. Soc.,* **1953**, *75*, 5323.
6. Barkdoll, A. E. and Ross, W. F., *J. Am. Chem. Soc.,* **1944**, *66*, 951.
7. (a) Greene, T. W., *Protective Groups in Organic Synthesis*, Wiley, New York, **1981**, p 239. (b) Shields, J. E. and Renner, H., *J. Am. Chem. Soc.,* **1966**, *88*, 2304. (c) Zervas, L.; Photaki, I. and Ghelis, N., *J. Am. Chem. Soc.,* **1963**, *85*, 1337. (d) Overby, L. R. and Ingersoll, A. W., *J. Am. Chem. Soc.,* **1960**, *82*, 2067. (e) Anderson, G. W. and Callahan, F. M., *J. Am. Chem. Soc.,* **1960**, *82*, 3359. (f) Zervas, L.; Winitz, M. and Greenstein, J. P., *J. Org. Chem.,* **1957**, *22*, 1515. (g) Springall, H. D. and Law, H. D., *Quart. Rev. (London)*, **1956**, *10*, 234. (h) Patchornik, A.; Berger, A. and Katchalski, E., *J. Am. Chem. Soc.,* **1957**, *79*, 6416. [both benzocarboxyl and decarboxy methods]. (i) Kenner, G. W., *J. Chem. Soc.,* **1956**, 3689. (j) Du Vigneaud, V., "A Trail of Sulfa Research: From Insulin to Oxytocin," Nobel lecture, **1955**, Dec. 12. (k) Vaughan, J. K. and Eici-Iler, J. A., *J. Am. Chem.*

Soc., **1954**, *76*, 2474 [preparation of peptide]. (l) Holley, R. W. and Sondheimer, E., *J. Am. Chem. Soc.,* **1954**, *76*, 1326. (m) Hofmann, K.; Rheiner, A. and Peckham, K. D., *J. Am. Chem. Soc.,* **1953**, *75*, 6083. (n) Katchalski, E. and Sela, M., *J. Am. Chem. Soc.,* **1953**, *75*, 5284 [preparation]. (o) Ben-Ishai, D. and Berger, A., *J. Org. Chem.,* **1952**, *17*, 1564. (p) Archer, S., "Azlactone" in *Amino Acids and Proteins,* ed. Greenberg, D. M., Charles C. Thomas, Springfield, IL., **1951**, p. 177. (q) Erlanger, B. F. and Brand, E., *J. Am. Chem. Soc.,* **1951**, *73*, 3508 [experiment]. (r) Fox, S. W.; Fling, M.; Wax, H. and Pettinga, C. W., *J. Am. Chem. Soc.,* **1950**, *72*, 1862 [experiment]. (s) Stevens, C. and Watanabe, R., *J. Am. Chem. Soc.,* **1950**, *72*, 725. (t) Rose, W. G., *J. Am. Chem. Soc.,* **1947**, *69*, 1384. (u) Bergstrom, N. C. and Martell, A. E., *J. Am. Chem. Soc.,* **1945**, *67*, 494. (v) Schmidt, C. L. A., *The Chemistry of the Amino Acids and Proteins*, Thomas, Springfield, IL., **1944**, p. 262. (w) Dyer, E., *J. Am. Chem. Soc.,* **1941**, *63*, 265. (x) Smith, C. S. and Brown, A. E., *J. Am. Chem. Soc.,* **1941**, *63*, 2605. (y) Bergmann M., Zervas L. and Ross W., *J. Biol. Chem.*, **1935**, *3*, 245. (z) Bergmann, M.; Zervas, L. and Rinke, H., *Z. Physiol. Chem.*, **1934**, *224*, 40.

8. (a) Fruton, J. S., *Trends Biochem. Sci.,* **1982**, *7*, 37. (b) Sus, O. and Hoffmann, H., *Ann.,* **1951**, *572*, 96. (c) Polglase, W. J. and Smith, E. L., *J. Am. Chem. Soc.,* **1949**, *71*, 3081. (d) Greenstein, J. P., *J. Biol. Chem.,* **1937**, *118*, 321. (e) Harington, C. R. and Mead, T. H., *Biochem. J.,* **1936**, *30*, 1598. (f) Abderhalden, E. and Neumann, A., *Fermentforschung*, **1934**, *14*, 133.

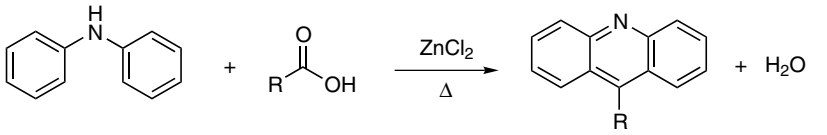
79

Bernthsen Reaction
(Bernthsen Acridine Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Bernthsen in 1878.[1] It is one of the earliest methods for the synthesis of acridine by heating diphenylamine hydrochloride with benzonitrile. Therefore, this reaction is generally known as the Bernthsen reaction.[2] In the modified method, the mixture of diphenylamine, an aromatic or aliphatic carboxylic acid, and zinc chloride is heated at 200–270°C for 20 h.[3,4] Heating zinc chloride with *N*-acyldiphenylamine[5] or a mixture of diphenylamine and acyl chloride also affords acridines.[6]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A tentative mechanism is proposed for this reaction, as shown here.

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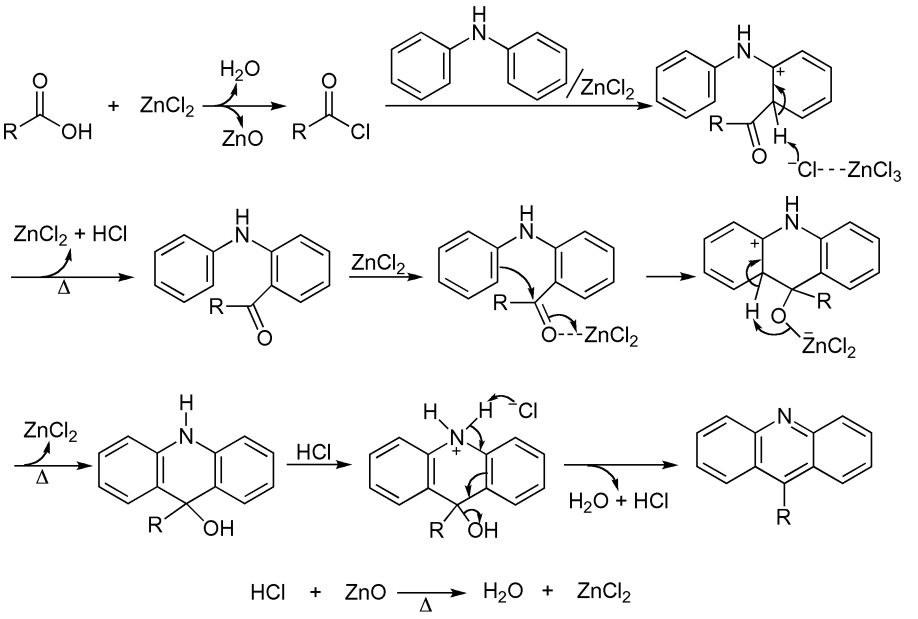


D. MODIFICATION

This reaction has been modified to form the intermediate of 2-acyltriphenylamine from triphenylamine.[2d]

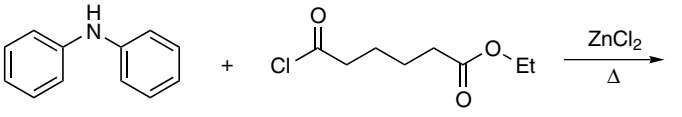
E. APPLICATIONS

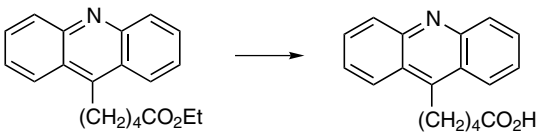
This reaction has generally been used to prepare substituted acridines, which can be converted into quinolines.[7]

F. RELATED REACTIONS

N/A

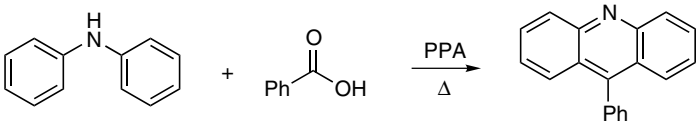
G. CITED EXPERIMENTAL EXAMPLES





Reference 6.

A mixture of equimolecular amounts of ethyl adipyl chloride and diphenylamine was heated with a small amount of anhydrous zinc chloride at temperatures ranging between 180°C and 220°C for 30 h. The dark brown liquid mixture was saponified by boiling with 8% ethanolic sodium hydroxide solution for 3 h. The solid sodium salt was dissolved in water, and unreacted diphenylamine was removed by ether extraction. The alkaline solution was acidified, extracted again to remove adipic acid, and then carefully neutralized to phenolphthalein. A brownish solid [6-(9-acridyl)valeric acid] precipitated, which was filtered and recrystallized from boiling pyridine. The yield was 12%. The compound dissolved to give a yellow solution in alkali and showed a green fluorescence in acids. It melted at 265–269°C (dec.) after some sintering.



Reference 2d.

A mixture of 0.06 mol diphenylamine, 0.03 mol benzoic acid, and 230–250 g polyphosphoric acid was heated with stirring at 195–205°C for 15 min. The reaction mixture was then poured onto ice and filtered or decanted. Examination of the infrared spectra of the gummy solid indicated that it contained mainly diphenylamine, a small amount of ketonic product, and possibly some 9-substituted acridine. Treatment of the solution with 25% sodium hydroxide solution caused the precipitation of a solid (while the solution was still acidic), which was apparently the phosphate salt of the 9-phenyl acridine. This product was washed with water and alcohol to give analytically pure material after drying in vacuo. The yield was 18%, m.p. 184–185°C.

Other references related to the Bernthsen reaction are cited in the literature.[8]

H. REFERENCES

1. Bernthsen, A., *Ann.,* **1878**, *192*, 1.
2. (a) Seijas, J. A.; Vazquez-Tato, M. P.; Martinez, M. M. and Rodriguez-Parga, J., *Green Chem.,* **2002**, *4*, 390. (b) Klemm, L. H.; Chiang, E. and O'Bannon, G. W., *J. Heterocycl. Chem.,* **1992**, *29*, 571. (c) Bhavsar, M. D. and Lakhani, J. D., *Man-Made Textiles India*, **1987**, *30*, 65. (d) Popp, F. D., *J. Org. Chem.,* **1962**, *27*, 2658.
3. (a) Acheson, R. M., "The Chemistry of Heterocyclic Compounds" in *Acridines*, ed. Weissberger, A., Interscience Publishers, New York, **1956**. pp. 19–25. (b) Albert, A., "The Acridines," in *Heterocyclic Compounds*, Vol. 4, ed. Elderfield, R. C., John Wiley & Sons, New York, **1952**, pp. 502–503.

4. (a) Bernthsen, A. and Fischer, O., *Ber.,* **1883**, *16*, 68. (b) Bernthsen, A. and Bender, *Ber.,* **1883**, *16*, 767. (c) Bernthsen, A. and Bender, F., *Ber.,* **1883**, *16*, 1802. (d) Fischer, O., *Ber.,* **1883**, *16*, 1820.
5. Bernthsen, A., *Ber.,* **1882**, *15*, 3011.
6. Graef, E.; Fredericksen, J. M. and Burger, A., *J. Org. Chem.,* **1946**, *11*, 257.
7. (a) Manske, R. H. F., *Chem. Rev.,* **1942**, *30*, 113. (b) Hepner, H., *Monatsh*., **1906**, *27*, 1045. (c) Knoevenagel, E. and Brunswig, R., *Ber.,* **1902**, *35*, 2172.
8. (a) Ray, J. K.; Roy, B. C. and Kar, G. K., *J. Org. Chem.* **1996**, *61*, 1863. (b) Rapaport, E.; Cass, M. W. and White, E. H., *J. Am. Chem. Soc.,* **1972**, *94*, 3160. (c) Thang, D. C.; Can, C. X.; Buu-Hoi, N. P. and Jacquignon, P., *J. Chem. Soc., Perkin Trans. I,* **1972**, 1932. (d) Staskun, B., *J. Org. Chem.,* **1968**, *33*, 3031. (e) Buu-Hoi, Ng. Ph.; Royer, R. and Hubert-Habart, M., *J. Chem. Soc.* **1955**, 1082. (f) Bradsher, C., *Chem. Rev*., **1946**, *38*, 447. (g) von Auwer, K. and Kraul, R., *Ber.,* **1925**, *58*, 543. (h) Friedländer, P. and Kunz, K., *Ber*., **1922**, *55*, 1597. (i) Stollé, R., *J. Prakt. Chem*., **1922**, *105*, 137. (j) Decker, K. and Hock, T., *Ber.,* **1904**, *37*, 1564. (k) Bernthsen, A., *Ann.,* **1884**, *224*, 1. (l) Fisher, O. and Kberner, G., *Ber*., **1884**, *17*, 101. (m) Bernthsen, A., *Ann.,* **1884**, *224*, 12.

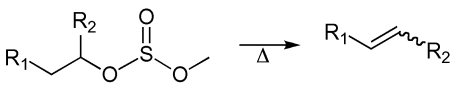
80

Berti Olefination

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Berti in 1954.[1] It is a reaction for preparing olefin via the pyrolysis of methyl sulfites of aliphatic or alicyclic alcohols. This reaction is similar to the *Chugaev Reaction* (the pyrolysis of xanthates of alcohols) but occurs via a *trans* pyrolytic elimination mechanism.[2] Different from the pyrolysis of other esters of alcohol (via the quasi six-membered ring transition sate[2]), the Berti olefination is evidenced to undergo a nonconcerted mechanism with the heterolysis of the carbon-oxygen bond, yielding ion pairs followed by direct proton loss or a 1,2-hydride shift and subsequent proton loss from the cationic species.[1,3,4] Important examples are the pyrolysis of *cis*-2-phenylcyclohexyl methyl sulfite to 1-phenylcyclohexene (78%) in preference to 3-phenylcyclohexene (22%)[1c] and the pyrolysis of 1,2-*cis*-cyclohexyl diol sulfite to cyclohexanone; the pyrolysis of 1,2-*trans*-cyclohexyl diol sulfite gives cyclopentaldehyde.[1b]

B. GENERAL REACTION SCHEME



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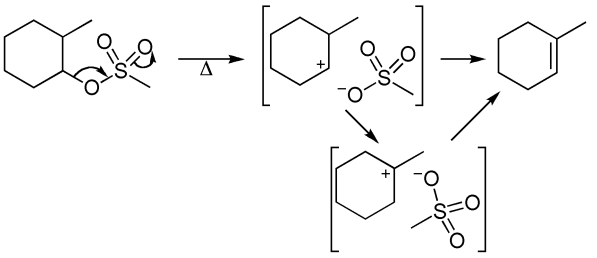
C. PROPOSED MECHANISMS

This reaction is evidenced to undergo a heterolytic cleavage of C–O bond to form olefins.[1,3,4]



D. MODIFICATION

N/A

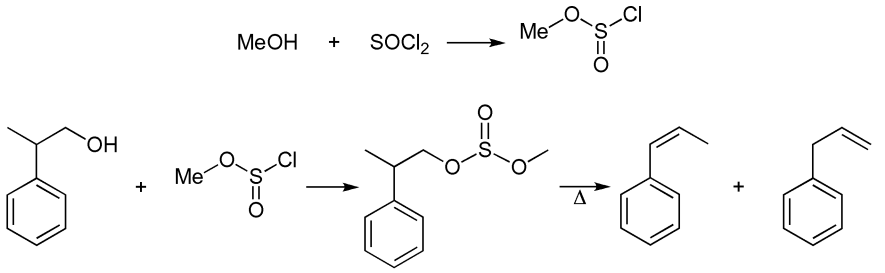
E. APPLICATIONS

This reaction has general applications for the preparation of olefins.

F. RELATED REACTIONS

This reaction is related to the *Chugaev Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 1c.

Methyl chlorosulfinate was prepared by the method of Carre and Libermann.[5] A 500-mL three-necked, round-bottomed flask, fitted with a mechanical stirrer, calcium chloride tube, and dropping funnel was used. To 260 g thionyl chloride, 64 g anhydrous methanol was added dropwise with stirring over 43 min. The reaction mixture was left 48 h at room temperature to allow for the reaction to complete. Then it was distilled under reduced pressure through a 50-cm Vigreux column; the fraction boiling between 35° and 36°C

(65 mmHg) was collected to give 199 g methyl chlorosulfinate, in a yield of 88%. The product can be stored for some time in the refrigerator, but it slowly undergoes decomposition.

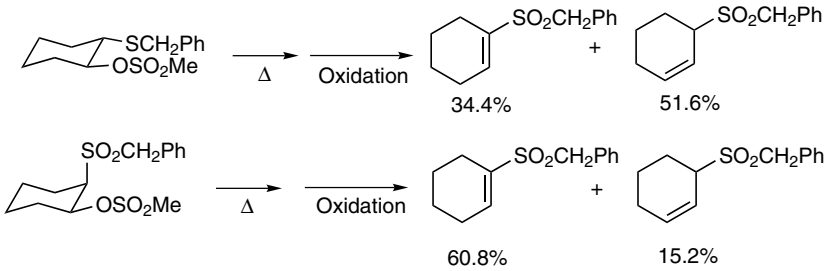
General Procedure for Preparation of Methyl Alkyl Sufites

Equimolar amounts of the alcohol and methyl chlorosulfinate were used. A slight excess (1.1–1.2 mol) of pyridine was employed. Dry ether was commonly used as the solvent, but dioxane and benzene gave equally good results. A solution of the alcohol and the pyridine was placed in a three-necked flask provided with a mercury-sealed stirrer and dropping funnel. Calcium chloride tubes surmounted the third neck and the top of the funnel. A solution of the chlorosulfinate was added slowly with stirring, controlling the temperature below 10°C. After the addition of the chlorosulfinate was completed, the stirring was continued for 30 min, then the precipitated pyridine hydrochloride was filtered off and the filtrate was washed with 0.1 N HC1, 5% sodium bicarbonate, and water. After drying over magnesium sulfate, the solvent was eliminated in vucuo.The residue may be purified by vacuum distillation or recrystallization. It also can be pyrolyzed without further purification.

Pyrolysis of Methyl α-Methyl-Phenethyl Sulfite

Method A The decomposition of this sulfite was found to start at 245°C. Methyl α-methylphenethyl sulfite (8 g) was heated at 285°C for 75 min. At the end of this time, 97% of the theoretical amount of sulfur dioxide had been absorbed in the sodium hydroxide solution. The distillate weighed 5 g, and 0.5 g tarry residue remained in the pyrolysis flask. The distillate was redistilled, and 4.15 g of the fraction boiling between 93° and 111°C (97 mmHg) was collected. This fraction was found to contain 2% dimethyl sulfite, 1% α-methylphenethyl alcohol, 53% propenylbenzene, and 43% allyl benzene.

Method B Through the column heated at 340–350°C, 21 g methyl α-methylphenethyl sulfite was dropped in about 1 h. After all the liquid had been passed through, the system was swept with nitrogen for 15 min, then the column was taken off and the receiver was stoppered and heated on a steam bath under a pressure of 5 mmHg to bring all volatile products into the dry ice trap. A residue of 4 g unchanged sulfite was left in the flask. The liquid that had collected in the dry ice trap was dissolved in ether and washed with water to eliminate sulfur dioxide and methanol. After the elimination of the ether, 9 g of liquid remained (96% based on unrecovered sulfite). The refractive index did not change after distillation from sodium.



Reference 2.

Pyrolysis of Methyl *cis*- and *trans*-2-*p*-Tolylthiocyclohexyl Sulfites.

These were pyrolyzed directly in a 25-mL distillation flask fitted with a 3-in. Vigreux head. The sulfite was heated to 200°C under nitrogen at atmospheric pressure for ~30 min. Vacuum (1 mmHg) was then applied, and the decomposition products were distilled slowly from the reaction mixture. The olefins were condensed in the air-cooled receiver, and the methanol and sulfur dioxide were allowed to pass into the dry ice trap. The yield of olefin was 86% from the *cis* isomer and 76% from the *trans* isomer. Analysis for the percentage of l-substituted and 3-substituted cyclohexene was made by oxidation to the sulfones, and the position of the absorption maximum in the ultraviolet spectra was determined. The oxidized product from the *cis* isomer had an absorption maximum at 229 mμ, corresponding to that of a mixture of 40% 1-*p*-tolylsulfonyl-1-cyclohexene and 60% 3-*p*-tolylsulfonyl-1-cyclohexene. The oxidized product from the *trans* isomer had its absorption maximum at 232 mμ, corresponding to 80% of the 1-substituted isomer.

Other references of the pyrolysis of esters (except for the *Chugaev Reaction*) to afford olefins are cited in literature.[6]

H. REFERENCES

1. (a) Price, C. C. and Berti, G., *J. Am. Chem. Soc.,* **1954**, *76*, 1207. (b) Price, C. C. and Berti, G., *J. Am. Chem. Soc.,* **1954**, *76*, 1211. (c) Berti G., *J. Am. Chem. Soc.*, **1954**, *76*, 1213.
2. Bordwell, F. G. and Landis, P. S., *J. Am. Chem. Soc.,* **1958**, *80*, 6379.
3. (a) Higgins, C. E. and Baldwin, W. H., *J. Org. Chem.,* **1965**, *30*, 3173. (b) Bordwell, F. G. and Landis, P. S., *J. Am. Chem. Soc.,* **1958**, *80*, 2450.
4. Briggs, W. S. and Djerassi, C., *J. Org. Chem.,* **1968**, *33*, 1625.
5. Carre, P. and Libermann, D., *Bull. Soc. Chim.,* **1933**, *53*, 1050.
6. (a) Hanneman, W. W. and Porter, R. S., *J. Org. Chem.,* **1964**, *29*, 2996. (b) Bailey, W. J. and Daly, J. J., *J. Org. Chem.,* **1964**, *29*, 1249. (c) Nace, H. R., *Org. React*., **1962**, *12*, 57. (d) McNamara, L. S. and Price C. C., *J. Org. Chem.*, **1962**, *27*, 1230. (e) Taylor, R.; Smith, G. G. and Wetzel, W., *J. Am. Chem. Soc.,* **1962**, *84*, 4817. (f) Haag, W. O. and Pines, H., *J. Am. Chem. Soc.,* **1960**, *82*, 2488. (g) Depuy, C. H. and King, R. W., *Chem. Rev.,* **1960**, *60*, 431. (h) Bailey, W. J. and Daly, J. J., *J. Am. Chem. Soc.,* **1959**, *81*, 5397. (i) Bordwell, F. G. and Landis, P. S., *J. Am. Chem. Soc.,* **1958**, *80*, 6383. (j) Bailey, W. J. and Bird, C. N., *J. Org. Chem.,* **1958**, *23*, 996. (k) Baumgarten, H. E. and Setterquist, R. A., *J. Am. Chem.* Soc., **1957**, *79*, 2605. (l) Baiely, W. J. and Daly, J. J., *J. Org. Chem.,* **1957**, *23*, 1189. (m) Bailey, W. J. and Hewitt, J. J., *J. Org. Chem.,* **1956**, *21*, 543. (n) Cram, D. J., "Olefins forming Elimination Reactions" in *Steric Effects in Organic Chemistry*, ed. Newman, M. S., John Wiley & Sons, Inc. New York, **1956**. (o) Bailey, W. J. and Turek, W. N., *J. Am. Oil Chemist Soc.,* **1956**, *33*, 817. (p) O'Connor, G. L. and Nace, H. R., *J. Am. Chem. Soc.,* **1955**, *77*, 1578. (q) Alexander, E. R. and Mudrak, A., *J. Am. Chem. Soc.,* **1951**, *73*, 59. (r) Libermann, D. and Rouiax, A., *Compt. Rend.*, **1948**, *226*, 2151.

81

Bertram-Walbaum Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Bertram and Walbaum in 1894.[1] It is a conversion of camphene into isoborneol by the treatment of camphene with 50% sulfuric acid[1] in acetic acid followed by saponification. Therefore, this reaction is generally known as the Bertram-Walbaum reaction[2] or Bertram-Walbaum method.[3] As a typical example, 20 g of camphene in 50 mL acetic acid was treated with 0.8 mL H_2SO_4 in 1.2 mL water at 50°–60°C for 3 h, then saponified and steam distilled to give 13.7 g crude isoborneol.[3] In addition, 98–100% formic acid[4] (with $BF_3{\cdot}Et_2O$[5]) is often applied as the reaction media for the Bertram-Walbaum reaction, instead of the combination of acetic acid and sulfuric acid; however, it is found that the application of acetic acid gives *exo*-norborneol in preference.[6] In this reaction, due to the nature of substituents, higher molecular weight by-products (e.g., dimers of olefins) might form in different amounts.[2b] For comparison, treatment of olefin in acetic acid containing 0.15 M acetamide and 0.1 M *p*-toluenesulfonic acid only allows the addition of acetic acid to olefins without any skeletal rearrangement.[7] It should be pointed out that the reversal reaction (i.e., from alcohol to olefin) under same conditions is also referred to as the Bertram-Walbaum reaction.[2a]

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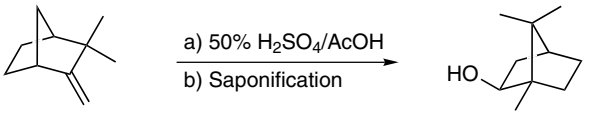
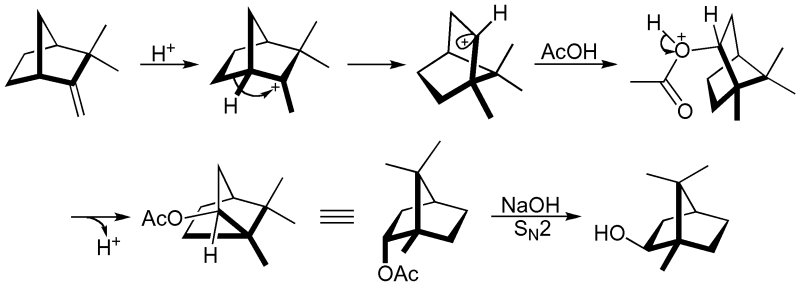
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is assumed that this reaction involves the protonation of *exo* double bond of camphene to generate a tertiary carbocation, followed by the carbon skeleton rearrangement to give a transient secondary carbocation, which is immediately trapped by acetic acid. Upon saponification via S_N2, the *endo* acetate is converted into *exo* alcohol as outlined in the mechanism shown here.



D. MODIFICATION

This reaction has been modified to undergo in concentrated formic acid.[4,5]

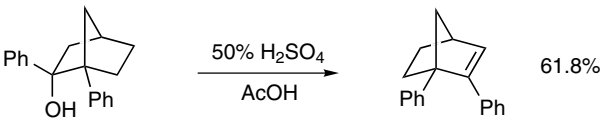
E. APPLICATIONS

This reaction has certain applications in terpene chemistry.

F. RELATED REACTIONS

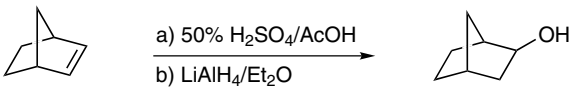
This reaction is related to the *Wagner-Meerwein Rearrangement, Demjanov Rearrangement, Tiffeneau-Demjanov Ring Expansion* and *Retropinacol Rearrangement* involving carbocation intermediates.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2b.

To a solution of 1.65 g 1,2-diphenyl-2-*endo*-norbornanol (6.25 mmol) in 30 mL acetic acid was added 1 mL 50% H_2SO_4; the resulting solution was stirred on a steam bath regulated at 70 ± 2°C for 2 h. When the solution was poured into water, a white solid formed immediately, which was filtered with suction, washed with water and dried to give 0.95 g 1,2-diphenyl-norbornene, in a yield of 61.8 %, m.p. 95.4–98.0°C (after four recrystallizations from ethanol).



Reference 6.

To 25 mL glacial acetic acid was added 4.9 g norbornene and ~0.5 mL 50% H_2SO_4. The solution was refluxed for 1 h, which quickly turned dark gray. The reaction mixture was poured into 400 mL water and extracted twice with ether. The combined organic phase was left overnight over solid Na_2CO_3, and the ether solution was washed twice with aqueous Na_2CO_3 and then dried over $MgSO_4$. Charcoal was added, and the solution was filtered then refluxed overnight in ether with excess $LiAlH_4$ to afford the *exo*-norborneol.

Other references related to the Bertram-Walbaum reaction are cited in the literature.[8]

H. REFERENCES

1. Bertram, J. and Walbaum, H., *J. Prakt. Chem.,* **1894**, *49*, 1.
2. (a) Grayson, D. H., *Nat. Prod. Reports,* **1997**, 477. (b) Hirao, N.; Kutsukake, K. and Kato, Y., *Kinki Daigaku Rikogakubu Kenkyu Hokoku*, **1978**, *13*, 53. (c) Krieger, H., *Suomen Kemistilehti B*, **1962**, *35B*, 127. (d) Krieger, H., *Suomen Kemistilehti B*, **1962**, *35B*, 71. (e) Kleinfelter, D. C. and Schleyer, P. von R., *J. Org. Chem.,* **1961**, *26*, 3740.
3. Charlton, R. W. and Day, A. R., *Ind. Eng. Chem.,* **1937**, *29*, 92.
4. (a) Bruson, H. A., *U. S. Pat.,* **1947**, Sep. 2, 2,426,725. (b) Bergmann, F. and Japhe, H., *J. Am. Chem. Soc.,* **1947**, *69*, 1826.
5. Schmerling, L.; Luvisi, J. P. and Welch, R. W., *J. Am. Chem. Soc.,* **1956**, *78*, 2819.
6. Bartlett, P. D. and Giddings, W. P., *J. Am. Chem. Soc.,* **1960**, *82*, 1240.
7. Trahanovsky, W. S.; Doyle, M. P. and Bartlett, P. D., *J. Org. Chem.,* **1967**, *32*, 150.
8. (a) Zubkov, F. I.; Nikitina, E. V.; Turchin, K. F.; Aleksandrov, G. G.; Safronova, A. A.; Borisov, R. S. and Varlamov, A. V., *J. Org. Chem.,* **2004**, *69*, 432. (b) Welniak, M., *J. Prakt. Chem.,* **1993**, *335*, 475. (c) Traylor, T. G. and Perrin, C. L., *J. Am. Chem. Soc.,* **1966**, *88*, 4934. (d) Rand, L. and Dolinski, R. J., *J. Org. Chem.,* **1966**, *31*, 4061. (e) Paasivirta, J., *Suomen Kemistilehti B*, **1963**, *36B*,

156. (f) Prelog, V.; Kaegi, H. H. and White, E. H., *Helv. Chim. Acta,* **1962**, *45*, 1658. (g) Berson, J. A.; Olsen, C. J. and Walia, J. S., *J. Am. Chem. Soc.,* **1962**, *84*, 3337. (h) Brewster, J. H., *J. Am. Chem. Soc.,* **1959**, *81*, 5483. (i) Funahashi, T., *J. Sci. Hiroshima Univ.,* **1955**, (Ser. A), *18*, 497. (j) Shaw, A. C., *J. Am. Chem. Soc.,* **1951**, *73*, 2859. (k) Bruson, H. A. and Riener, T. W., *J. Am. Chem. Soc.,* **1945**, *67*, 1178. (l) Kharasch, M. S.; Engelmann, F. and Urry, W. H., *J. Am. Chem. Soc.,* **1944**, *66*, 365. (m) Littmann, E. R., *J. Am. Chem. Soc.,* **1935**, *57*, 586. (n) Nametkin, S. S. and Shavrigin, A. I., *Ber.,* **1933**, *66B*, 511. (o) Hasselström, T., *J. Am. Chem. Soc.,* **1931**, *53*, 1097. (p) Dodge, F. D., *J. Am. Chem. Soc.,* **1902**, *24*, 649.

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Betti Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Betti in 1900.[1] It is a special case of the *Mannich Reaction* involving the components of an ammonia, a 2-naphthol, and at least one benzaldehyde to give either a phenyl β-naphtholaminomethane or a *m*-naphthoxazine derivative. The latter upon acidic hydrolysis (e.g., HCl) decomposes to the hydrochloride salt of former molecule along with a benzaldehyde.[1,2] Thus this reaction is known as Betti's condensation[3] or the Betti reaction;[4] likewise, the corresponding β-naphtholmethylamines are generally referred to as Betti's amines[5] or Betti bases.[6]

In this reaction, the course of condensation and the type of products formed depend on several factors, such as the nature of hydroxyaromatic compounds, amines, aldehydes, and the actual ratio of the components in the reaction system.[7] For examples, besides the initial ammonia, this reaction has been extended successfully to both primary amines[5] and secondary amines;[3]and among the secondary amines, the reaction particularly works for dimethylamine, diethylamine, and piperidine.[3] In addition, when one of the secondary amines exists in large excess or when dimethylamine or ammonia is removed from the reaction system via vaporization, good yields of pure products are often achievable.[6c] Besides the commonly used β-naphthol, many other hydroxyaromatic compounds are suitable for this reaction as well, such as phenols, and quinolinols.[3,4a] It is found that among kojic acid, 8-quinolinol, and 8-hydroxquinaldine, kojic acid is the most reactive compound for the Betti reaction, which reacts with benzylideneaniline in less than 1 day

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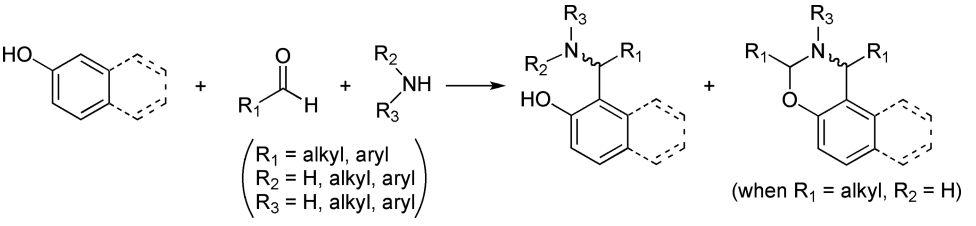
at room temperature; 8-quinolinol needs weeks and 8-hydroxquinaldine takes months for the corresponding reactions.[4a] On the other hand, when a stoichiometric amount of naphthol, amine, and 2 equivalents of aldehyde are used, the resulting Betti base can further react with additional aromatic aldehyde to afford the corresponding Schiff base, whereas naphthoxazine is yielded in the case of aliphatic aldehyde.[7] In addition, even in the case of benzaldehydes, it is found that the stability of Betti bases from monochlorobenzaldehydes is smaller than simple benzaldehyde, and that the stability of Betti bases from those monochlorobenzaldehydes decrease in the order of *m*-Cl > *o*-Cl > *p*-Cl.[5] When nitrobenzaldehyde is applied, more than 90% of nitrohydrobenzamide can be obtained from β-naphthol and alcoholic ammonia.[5] Moreoever, it is reported that reaction in benzene is advantageous over that in alcohol solvent.[7] All the generated Betti bases can decompose to give β-naphthol and benzaldehyde, especially in alkaline solution.[5]

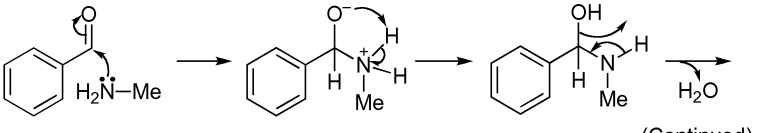
The importance of this reaction relies on the fact that the Betti bases can function as both excellent ligands and auxiliaries in asymmetric synthesis.[8] The racemic Betti amines can be separated into their optical antipodes.[5] In this respect, among the Betti bases from monochlorobenzaldehydes, only the *dextro* form of the *ortho* and *meta* chloro compounds could be resolved with satisfaction, while the *levo* antipodes are extremely difficult to obtain due to their higher solubilities.[5]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is agreed that Betti reaction involves the initial reaction between aldehyde and amine, followed by the second condensation of naphthol (or phenol or other active methylenes),[3] as shown by the reaction among β-naphthol, benzaldehyde, and methylamine.



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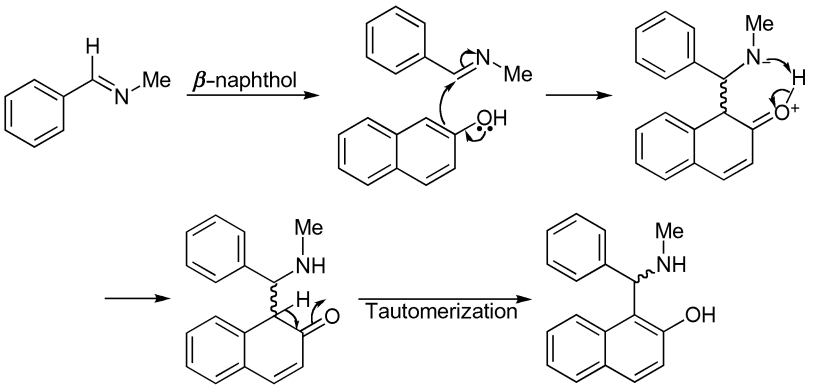


D. MODIFICATION

On the basis of Betti's initial work, the Betti reaction has been extended to both primary amines[5] and secondary amines.[3] The resulting Betti amines have been applied as ligands or chiral auxiliaries in asymmetric synthesis.[8] In addition, the Betti reaction has also been extended to the reaction among aldehydes, secondary amines, and compounds of active methylene moiety, such as dibenzyl ketones which can tautomerize to enols and mimic naphthol.[9] Moreover, the reaction of aromatic aldoximes and β-keto esters to afford isoxazolones should also be considered as an extension of the Betti reaction.[10]

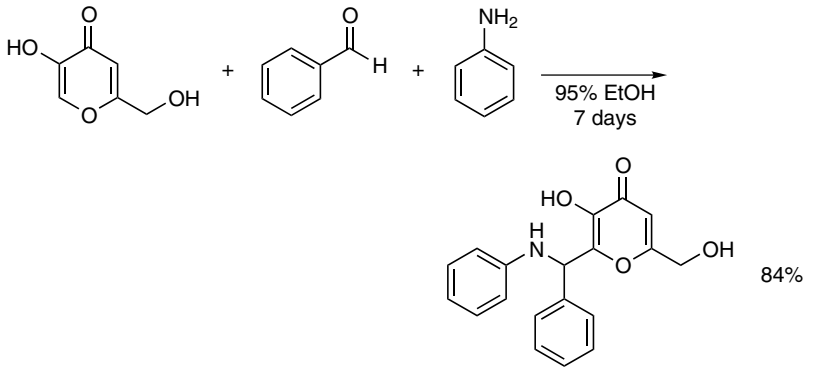
E. APPLICATIONS

This reaction should have wide applications for affording chiral ligands and auxiliaries for asymmetric synthesis.

F. RELATED REACTIONS

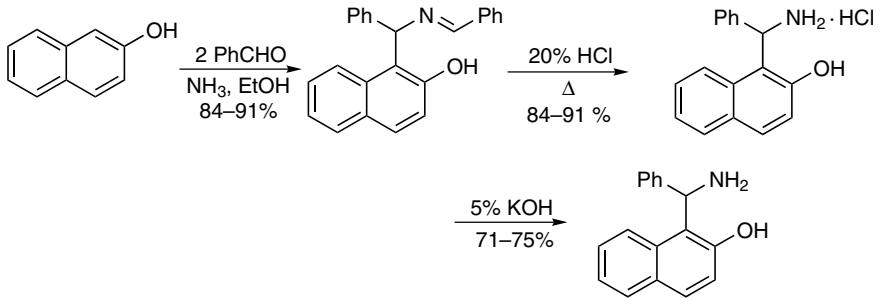
This reaction is closely related to the *Mannich Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4a.

To the solution of 5.31 g benzaldehyde (0.05 mol) and 4.66 g aniline (0.05 mol) in 50–100 mL 95% ethanol was added 7.11 g kojic acid. The mixture was stoppered and allowed to stand for 1 week, while the kojic acid derivatives precipitated within 1 day. The solid was filtered and washed, then purified by recrystallization from ethanol to afford 13.58 g of the Betti amine, in a yield of 84%, m.p. 176°C.



Reference 11.

To a cold solution of 144 g β-naphthol (1.0 mol) in 200 mL 95% ethanol in a 1-L round-bottomed flask were added first 212 g freshly distilled acid-free benzaldehyde (2.0 mol) and then ~200 mL 95% ethanol saturated with NH_3 at room temperature. The solution became red and warmed up spontaneously. The flask was stoppered and allowed to stand for 2 h. Then the stopper was removed, and the excess NH_3 was allowed to escape. After 12 h, the condensation product, which had separated as white needles, was filtered with suction and washed with 50 mL ethanol. The mother liquors on standing for 3 days deposited an additional quantity of the condensation product. The yield was 284–306 g (84–91% of the theoretical amount), m.p. 148 –150°C.

The condensation product thus obtained was introduced into a 5-L round-bottomed flask arranged for steam distillation, and treated with three to four times its volume of 20% HCl. The mixture was steam distilled to remove all the benzaldehyde formed by the hydrolysis (~2 h). Meanwhile, an abundant flocculent precipitate of light pink or white needles separated. The mixture in the flask was cooled thoroughly and filtered with suction. The yield was 240–260 g (84–91% of the theoretical amount), m.p. 190–220°C (dec.).

To obtain the amine, 200 g finely divided hydrochloride salt was placed in a 1500-mL beaker and stirred into a smooth paste with 300 mL water. To this was added 50 g crushed ice, and the mixture was cooled in an ice bath. Then 750–800 mL 5% KOH solution was added slowly under stirring until a nearly clear solution resulted. The cold solution was transferred to a separatory funnel and extracted eight to ten times with 300-mL portions of ether. The combined ether extract was dried overnight with 50 g anhydrous Na_2SO_4, filtered, and concentrated to ~300 mL. When the solution was cooled in an ice bath, the amine crystallized and was filtered with suction. The first crop of crystals weighed 112–115 g. Further concentration of the mother liquors to ~100 mL and cooling yield an additional 14–18 g of the product. The total yield was 127–131 g (73–75% of the theoretical amount), m.p. 124–125°C.

Other references related to the Betti reaction are cited in the literature. [12]

H. REFERENCES

1. Betti, M., *Gazz. Chim. Ital.*, **1900**, *30*, *II*, 301.
2. Betti, M., *Gazz. Chim. Ital.,* **1901**, *31*, *I*, 386.
3. Littman, J. B. and Brode, W. R., *J. Am. Chem. Soc.,* **1930**, *52*, 1655.
4. (a) Konopikova, M.; Uher, M.; Bransova, J.; Mastihuba, V. and Hudecova, D., *Chem. Papers,* **1994**, *48*, 182. (b) Möehrle, H.; Miller, C. and Wendisch, D., *Chem. Ber.,* **1974**, *107*, 2675. (c) Phillips, J. P. and Leach, J. T., *Trans. Kentucky Acad. Sci.*, **1964**, *24*, 95. (d) Phillips, J. P. and Barrall, E. M., *J. Org. Chem.,* **1956**, *21*, 692. (e) Phillips, J. P., *Chem. Rev.,* **1956**, *56*, 271.
5. Ray, F. E. and Moomaw, W. A., *J. Am. Chem. Soc.,* **1933**, *55*, 749.
6. (a) Dong, Y. M.; Li, R.; Lu, J.; Xu, X. N.; Wang, X. Y. and Hu, Y. F., *J. Org. Chem.,* **2005**, *70*, 8617. (b) Wang, X. Y.; Dong, Y. M.; Sun, J. W.; Xu, X. N.; Li, R. and Hu, Y. F., *J. Org. Chem.,* **2005**, *70*, 1897. (c) Snyder, H. R. and Brewster, J. H., *J. Am. Chem. Soc.,* **1948**, *70*, 4230.
7. Burke, W. J. and Reynolds, R. J., *J. Am. Chem. Soc.,* **1954**, *76*, 1291.
8. (a) Xu, X.; Lu, J.; Li, R.; Ge, Z.; Dong, Y. and Hu, Y., *Synlett*, **2004**, 122. (b) Xu, X.; Lu, J.; Dong, Y.; Li, R.; Ge, Z. and Hu, Y., *Tetrahedron: Asymmetry,* **2004**, *15*, 475. (c) Dong, Y.; Sun, J.; Wang, X.; Xu, X.; Cao, L. and Hu, Y., *Tetrahedron: Asymmetry,* **2004**, *15*, 1667. (d) Ji, J.; Qiu, L.; Yip, C. W. and Chan, A. S. C., *J. Org. Chem.,* **2003**, *68*, 1589. (e) Wang, Y.; Li, X. and Ding, K., *Tetrahedron: Asymmetry,* **2002**, *13*, 1291. (f) Lu, J.; Xu, X.; Wang, C.; He, J.; Hu, Y. and Hu, H., *Tetrahedron Lett.,* **2002**, *43*, 8367. (g) Lu, J.; Xu, X.; Wang, S.; Wang, C.; Hu, Y. and Hu, H., *J. Chem. Soc., Perkin Trans. I,* **2002**, 2900. (h) Cimarelli, C.; Mazzanti, A.; Palmieri, G. and Volpini, E., *J. Org. Chem.,* **2001**, *66*, 4759. (i) Liu, D.; Zhang, L.; Wang, Q.; Da, C.; Xin, Z.; Wang, R.; Choi, M. C. K. and Chan, A. S. C., *Org. Lett*., **2001**, *3*, 2733. (j) Palmieri, G., *Tetrahedron: Asymmetry,* **2000**, *11*, 3361. (k) Cardellicchio, C.; Ciccarella, G.; Naso, F.; Perna, F. and Tortorella, P., *Tetrahedron,* **1999**, *55*, 14685. (l) Cardelliccnio, C.; Ciccarella, G.; Naso, F.; Schingaro, E. and Scordari, F., *Tetrahedron: Asymmetry,* **1998**, *9*, 3667.
9. Dilthey, W. and Stallman, B., *Ber.,* **1929**, 62*B*, 1603.
10. (a) Minunni, G.; D'Urso, S.; Bellecci, V. and Ottaviano, I., *Gazz. Chim. Ital.,* **1929**, *59*, 32. (b) Minunni, G.; Ottaviano, I. and Spina, V., *Gazz. Chim. Ital.,* **1929**, *59*, 116. (c) Minunni, G. and D'Urso, S., *Gazz. Chim. Ital.,* **1928**, *58*, 485.
11. Betti, M., *Org. Synth. Coll.,* **1941**, *1*, 381.
12. (a) Smith, H. E. and Cooper, N. E., *J. Org. Chem.,* **1970**, *35*, 2212. (b) Sen, A. B.; Saxena, M. S. and Mehrotra, S., *J. Indian Chem. Soc*., **1960**, *37*, 640. (c) Phillips, J. P. and Duckwall, A. L., *J. Am. Chem. Soc.,* **1955**, *77*, 5504. (d) Phillips, J. P.; Keown, R. and Fernando, Q., *J. Org. Chem.,* **1954**, *19*, 907. (e) Phillips, J. P.; Keown, R. and Fernando, Q., *J. Am. Chem. Soc.,* **1953**, *75*, 4306. (f) Pirrone, F., *Gazz. Chim. Ital.,* **1941**, *71*, 320. (g) Pirrone, F., *Gazz. Chim. Ital.,* **1940**, *70*, 520. (h) Pirrone, F., *Gazz. Chim. Ital.,* **1937**, *67*, 529. (i) Donleavy, J. J. and Gilbert, E. E., *J. Am. Chem. Soc.,* **1937**, *59*, 1072. (j) Pirrone, F., *Gazz. Chim. Ital.,* **1936**, *66*, 518. (k) Brode, W. R. and Littman, J. B., *J. Am. Chem. Soc.,* **1931**, *53*, 1531. (l) Betti, M., *Gazz. Chim. Ital.,* **1907**, *36*, 392. (m) Betti, M., *Gazz. Chim. Ital.,* **1903**, *33* (no. 2), 2.

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Biginelli Reaction

A. GENERAL DESCRIPTION OF THE REACTION

Although in most cases the Biginelli reaction is cited from 1893,[1] the initial reaction was actually reported by Biginelli in 1891.[2] The Biginelli reaction is an one-pot, three-component condensation of β-dicarbonyl compounds (e.g., β-keto esters) with aldehydes and urea (or thiourea) in the presence of a catalytic amount of acid to form dihydropyrimidine derivatives with normal yields of 20–50%.[3] Therefore, besides the general name of Biginelli reaction,[4] this reaction is also referred to as the Biginelli condensation,[5] Biginelli cyclocondensation,[6] Biginelli multicomponent condensation,[7] Biginelli synthesis,[8] and Biginelli dihydropyrimidine synthesis.[5l,9] In addition, dihydropyrimidine itself is called the Biginelli compound.[5l,10] This reaction has attracted extensive attention recently, though it was ignored for a quite long time. This is because dihydropyrimidine derivatives have shown important biological activities,[11] and the reaction itself involves three components at the same time, which is a perfect example of a multicomponent reaction (MCR), used in the combinational synthesis.[7,12] In terms of its versatility and importance, the Biginelli reaction has been extensively modified to give high yields of product. So far, different Lewis acids—including BF_3,[13] $BiCl_3$,[14] $CeCl_3$,[15] $FeCl_3$,[16] $InCl_3$,[15,17] $LaCl_3$,[18] $LiClO_4$,[19] $Mn(OAc)_3$,[20] and $Yb(OTf)_3$,[21] — and protic acids — such as HCl,[9c,16] H_2SO_4,[5l] and acetic acid[22] have been applied as catalysts. The solvents often used are CH_3CN,[23] CH_2Cl_2,[23] THF,[23] and dioxane[9e] etc. Other modifications include the application of microwaves,[24] running a catalyst-free[23] or solvent-free[3,25] reaction, and carrying out the reaction in a polyphosphate ester[26] or fluorous phase.[7] The Biginelli reaction can be enantioselective when catalyzed by $InCl_3$ or $CeCl_3$ in the presence of chiral ligands.[15]

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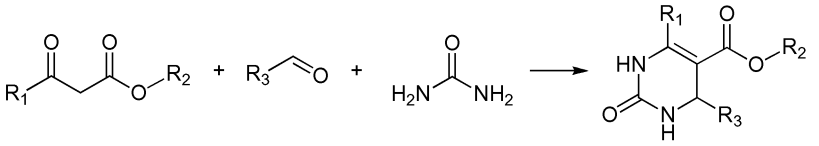
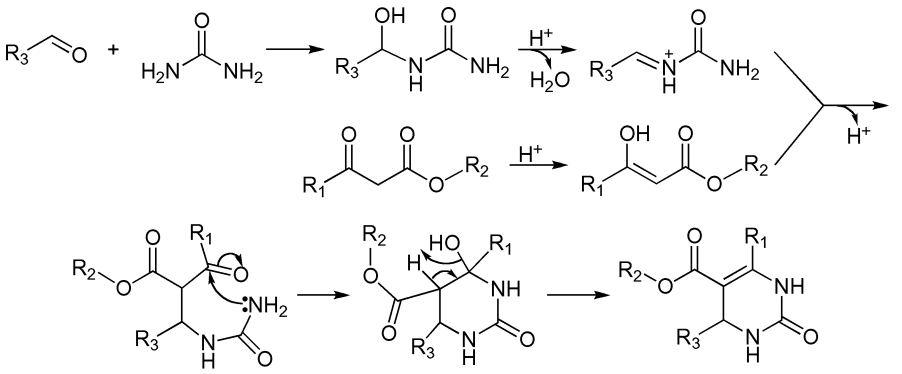
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It has been documented that the Biginelli reaction involves an aldehyde-urea condensation to form *N*-acyliminium ion as the key intermediate, followed by the addition of a π-nucleophile to the electron-deficient *N*-acyliminium ion and finally a ring closure,[9c,27] as illustrated below.



D. MODIFICATION

The original Biginelli procedure has been modified extensively to increase the overall yields, including the addition of Lewis acid catalyst,[13–21] application of polyphosphate ester[26] or fluorous solvent,[7] and introduction of microwaves[24] and even solvent-free[3,25] or catalyst-free[23] reaction conditions.

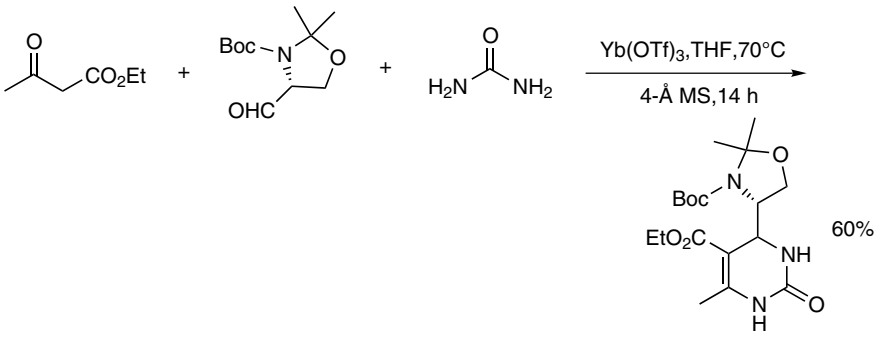
E. APPLICATIONS

This reaction has been successfully applied to the synthesis of complicated pentacyclic alkaloid ptilomycalin A,[5n,28] and other alkaloids, including crambine,[29] crambescidin,[30] and batzelladine.[5i,31]

F. RELATED REACTIONS

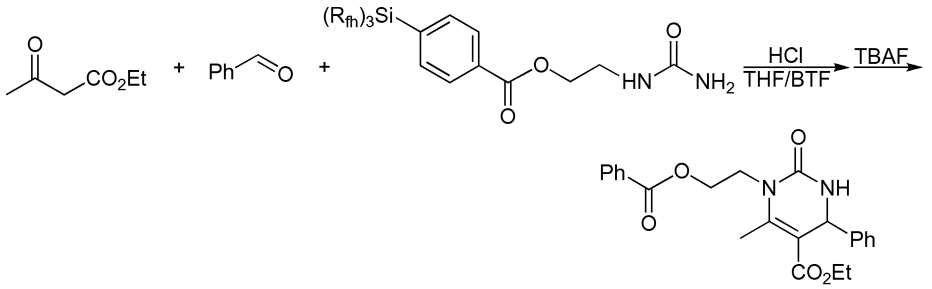
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 21.

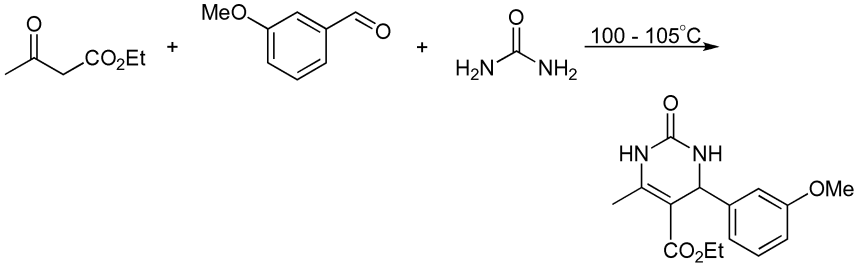
A screw-capped vial, containing a magnetic bar, was charged with 2.0 mmol Garner aldehyde, 255 μL ethyl acetoacetetate (2.0 mmol), 360.0 mg urea (6.0 mmol), 620 mg $Yb(OTf)_3$ (1.0 mmol), 200 mg powdered 4 Å molecular sieves, and 5 mL anhydrous THF. The mixture was stirred at 70°C for 14 h then cooled to room temperature, diluted with 100 mL EtOAc, filtered through a pad of Celite, and washed with H_2O (2 × 10 mL). The organic phase was dried over Na_2SO_4, concentrated, and eluted from a column of silica gel with cyclohexane-EtOAc (1:2, containing 0.3% Et_3N), to afford 460 mg diastereoisomers of (4*R*,4′S)- and (4*S*,4′S)-4-(3′-*tert*-butoxycarbonyl-2′,2′-dimethyl-oxazolidin-4′-yl)-6-methyl-2-oxo-1,2,3,4-tetra-hydropyrimidine-5-carboxylic acid ethyl esters (5:1 ratio), in a yield of 60%.



Reference 7.

A solution of 18 mg urea (9.6 μmol) in 0.75 mL THF/BTF (2:1) was treated at 25°C with 10 eq. ethyl acetoacetate, 10 eq. of benzaldehyde, and 1 μL HCl. After 3 days at 50°C, volatiles were removed in vacuo, and FC-84 and toluene (10 mL each) were added. The toluene phase was extracted with FC-84 (5 × 5 mL). The combined fluorous phases were filtered and concentrated. The resulting white solid was diluted with 0.5 mL THF/BTF (1:1) and treated dropwise with a 1 M tributylammonium fluoride (TBAF) solution in 10 μL THF (10 μmol). After the mixture was stirred for 0.5 h at 25°C, volatiles were removed in vacuo and FC-84 and toluene were added (10 mL each). The fluorous phase was extracted with toluene (3 × 5 mL). The combined toluene phases were extracted with saturated aqueous $NaHCO_3$ solution (3 × 10 mL) and brine (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated to afford 2.8 mg 1-(2-(benzoyloxy)ethyl)-6-methyl-

2-oxo-4-phenyl-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester, in a yield of 71%, m.p. 129°C.



Reference 23.

Solvent-Free and Catalyst-Free Conditions

Small-Scale (Milligram Level) A mixture of 272 mg freshly distilled 3-methoxybenzaldehyde (2 mmol), 260 mg freshly distilled ethyl acetoacetate (2 mmol), and 180 mg urea (3 mmol) was heated at 100–105°C under stirring. After few minutes during the progress of reaction, the solid started to separate out; after completion (1 h, TLC) the resulting solid was crushed, washed with cold water, filtered, and dried under vacuum to give the crude product, which was reasonably pure (>95% purity by ^{1}H NMR). However, recrystallization from hot ethanol provided 476 mg analytically pure product, in a yield of 82%, m.p. 207–208°C.

Large-Scale (Kilogram Level) A mixture of 530 g benzaldehyde (5 mol), 650 g ethyl acetoacetate (5 mol), and 360 g urea (6 mol) placed in a 2-L round-bottomed flask was stirred by a mechanical stirrer at room temperature for 2 min for uniform mixing, and then the temperature was raised to 100–105°C. No exothermic reaction was observed during addition and mixing. Stirring was continued for another hour at that temperature. During the progress of reaction (approximately during the first 20 min, all the urea dissolved and solids started to appear), the reaction mixture became a thick slurry, with the solids deposited. At this stage, although no efficient stirring or agitation could be made, the reaction was not affected. After 1 h the reaction mixture was cooled in an ice water bath (0–5°C), and 200 mL water was added. The solid was carefully broken into pieces with a spatula and filtered. The yellow solid was then washed with 100 mL cold water followed by 50 mL cold rectified spirit to provide 1.025 kg colorless solid that was practically pure (79% yield), m.p. 201–202°C. A portion of it was recrystallized from hot ethanol to give analytically pure sample.

Other references related to the Biginelli reaction are cited in the literature.[32]

H. REFERENCES

1. (a) Biginelli, P., *Gazz. Chim. Ital*., **1893**, *23*, 360-413 [the most cited paper]. (b) Biginelli, P., *Ber.,* **1893**, *26*, 447. (c) Biginelli, P., *Atti. Accad. Lincei,* **1894**, *3*, 195. (d) Biginelli, P., *Chem. Zentr*., **1894**, *65*, 823.

2. (a) Biginelli, P., *Ber.,* **1891**, *24*, 1317. (b) Biginelli, P., *Ber.,* **1891**, *24*, 2962.

3. Ma, Y.; Qian, C. T.; Wang, L. M. and Yang, M., *J. Org. Chem.,* **2000**, 65, 3864.

4. (a) Pourjavadi, A.; Salimi, H.; Barzegar, S. and Eftekhari-Sis, B., *Acta Chim. Slovenica,* **2007**, *54*, 140. (b) Ismaili, L.; Ubaldi, S.; Robert, J.-F.; Xicluna, A. and Refouvelet, B., *Heterocycles,* **2007**, *71*, 925. (c) Wang, S.-W.; Cao, W. and Li, M., *Shiyanshi Yanjiu Yu Tansuo*, **2007**, *26*, 100. (d) Chen, W.-Y.; Qin, S.-D. and Jin, J.-R., *Synth. Commun.,* **2007**, *37*, 47. (e) Ryabukhin, S. V.; Plaskon, A. S.; Ostapchuk, E. N.; Volochnyuk, D. M. and Tolmachev, A. A., *Synthesis,* **2007**, 417. (f) Novokshonov, V. V.; Novokshonova, I. A.; Ushakov, I. A. and Medvedeva, A. S., *Chem. Heterocycl. Compd.,* **2006**, *42*, 1492. (g) Kumar, J. A., *J. Teaching Res. Chem.,* **2006**, *13*, 68. (h) Mamedov, V. A.; Mustakimova, L. V.; Gubaidullin, A. T.; Vdovina, S. V.; Litvinov, I. A. and Reznik, V. S., *Chem. Heterocycl. Compd.,* **2006**, *42*, 1229. (i) Heravi, M. M.; Behbahani, F. K.; Zadsirjan, V. and Oskooie, H. A., *Heterocycl. Commun.,* **2006**, *12*, 369. (j) Chen, X.-H.; Xu, X.-Y.; Liu, H.; Cun, L.-F. and Gong, L.-Z., *J. Am. Chem. Soc.,* **2006**, *128*, 14802. (k) Suzuki, I.; Suzumura, Y. and Takeda, K., *Tetrahedron Lett*., **2006**, *47*, 7861. (l) Nilsson, B. L. and Overman, L. E., *J. Org. Chem.,* **2006**, *71*, 7706. (m) Debache, A.; Boumoud, B.; Amimour, M.; Belfaitah, A.; Rhouati, S. and Carboni, B., *Tetrahedron Lett.,* **2006**, *47*, 5697. (n) Fazaeli, R.; Tangestaninejad, S.; Aliyan, H. and Moghadam, M., *Appl. Catal., A: General,* **2006**, *309*, 44. (o) Rafiee, E. and Shahbazi, F., *J. Mol.Catal. A: Chem.,* **2006**, *250*, 57. (p) Manhas, M. S.; Ganguly, S. N.; Mukherjee, S.; Jain, A. K.; Bose, A. K., *Tetrahedron Lett.,* **2006**, *47*, 2423. (q) Wang, X. C.; Quan, Z. J.; Wang, F.; Wang, M. G.; Zhang, Z. and Li, Z., *Synth. Commun.,* **2006**, *36*, 451. (r) Azizian, J.; Mohammadi, A. A.; Karimi, A. R. and Mohammadizadeh, M. R., *Appl. Catal., A: General,* **2006**, *300*, 85. (s) Mabry, J. and Ganem, B., *Tetrahedron Lett.,* **2006**, *47*, 55. (t) Bhosale, R. S.; Hashmi, A. M.; Zubaidha, P. K. and Dongre, M. K., *Heterocycl. Commun.,* **2005**, *11*, 399. (u) Kappe, C. O., *Multicomponent Reactions*, **2005**, 95. (v) Huang, Y. J.; Yang, F. Y. and Zhu, C. J., *J. Am. Chem. Soc.,* **2005**, *127*, 16386. (w) Chari, M. A.; Shobha, D.; Kumar, T. K. and Dubey, P. K., *ARKIVOC,* **2005**, (xv), 74. (x) Wang, M.; Wang, Z.-C.; Sun, Z.-L. and Jiang, H., *Trans. Metal Chem.,* **2005**, *30*, 792. (y) Tajbakhsh, M.; Mohajerani, B.; Heravi, M. M. and Ahmadi, A. N., *J. Mol. Catal. A: Chem.,* **2005**, *236*, 216. (z) Reddy, Y. T.; Reddy, P. N.; Kumar, B. S.; Rao, G. V. P. and Rajitha, B., *Indian J. Chem., Sect. B,* **2005**, 44*B*, 1304. (aa) Putilova, E. S.; Kryshtal, G. V.; Zhdankina, G. M.; Troitskii, N. A. and Zlotin, S. G., *Russ. J. Org. Chem.,* **2005**, *41*, 512. (bb) Pasha, M. A.; Swamy, N. R. and Jayashankara, V. P., *Indian J. Chem., Sect. B,* **2005**, 44*B*, 823. (cc) Wang, Z.-T.; Wang, S.-C. and Xu, L.-W., *Helv. Chim. Acta,* **2005**, *88*, 986. (dd) Han, X. Y.; Xu, F.; Luo, Y. Q. and Shen, Q., *Eur. J. Org. Chem.,* **2005**, 1500. (ee) Cepanec, I.; Litvic, M.; Bartolincic, A. and Lovric, M., *Tetrahedron,* **2005**, *61*, 4275. (ff) Subhas Bose, D.; Sudharshan, M. and Chavhan, S. W., *ARKIVOC*, **2005**, (iii), 228. (gg) Bose, A. K.; Manhas, M. S.; Pednekar, S.; Ganguly, S. N.; Dang, H.; He, W. and Mandadi, A., *Tetrahedron Lett.,* **2005**, *46*, 1901. (hh) Xu, L.-W.; Wang, Z.-T.; Xia, C.-G.; Li, L. and Zhao, P.-Q., *Helv. Chim. Acta,* **2004**, *87*, 2608. (ii) Bose, A. K.; Pednekar, S.; Ganguly, S. N.; Chakraborty, G. and Manhas, M. S., *Tetrahedron Lett.,* **2004**, *45*, 8351. (jj) Xu, S. H., *Daxue Huaxue*, **2004**, *19*, 27. (kk) Thirupathi Reddy, Y.; Rajitha, B.; Narsimha Reddy, P.; Sunil Kumar, B. and Rao, V. P. G., *Synth. Commun.,* **2004**, *34*, 3821. (ll) Yadav, J. S.; Kumar, S. P.; Kondaji, G.; Rao, R. S. and Nagaiah, K., *Chem. Lett.,* **2004**, *33*, 1168. (mm) Srinivas, K. V. N. S. and Das, B., *Synthesis,* **2004**, 2091. (nn) Jenner, G., *Tetrahedron Lett.,* **2004**, *45*, 6195. (oo) Manjula, A.; Rao, B. V. and Neelakantan, P., *Synth. Commun.,* **2004**, *34*, 2665. (pp) Gangadasu, B.; Palaniappan, S.; Rao, V. J., *Synlett*, **2004**, 1285. (qq) Byk, G. and Kabha, E., *J. Comb. Chem.,* **2004**, *6*, 596. (rr) Bandyopadhyay, C.; Nag, P. P.; Sur, K. R.; Patra, R.; Banerjee, S.; Sen, A. and Ghosh, T., *J. Indian Chem. Soc.,* **2004**, *81*, 132. (ss) Tu, S. J.; Fang, F.; Zhu, S. L.; Li, T. J.; Zhang, X. J. and Zhuang, Q. Y., *J. Heterocycl. Chem.,* **2004**, *41*, 253. (tt) Tu, S. J.; Fang, F.; Zhu, S. L.; Li, T. J.; Zhang, X. J. and Zhuang, Q. Y., *Synlett,* **2004**, 537. (uu) Dzvinchuk, I. B.; Makitruk, T. V. and Lozinskii, M. O., *Chem. Heterocycl. Compd.,* **2003**, *39*, 455. (vv) Li, Y. X. and Bao, W. L., *Chinese Chem. Lett.,* **2003**, *14*, 993. (ww) Choudhary, V. R.; Tillu, V. H.; Narkhede, V. S.; Borate, H. B. and Wakharkar, R. D., *Catal. Commun.,* **2003**,

4, 449. (xx) Sabitha, G.; Reddy, G. S. K. K.; Reddy, Ch. S. and Yadav, J. S., *Synlett,* **2003**, 858. (yy) Xu, H. and Wang, Y.-G., *Chinese J. Chem.,* **2003**, *21*, 327. (zz) Maiti, G.; Kundu, P. and Guin, C., *Tetrahedron Lett.,* **2003**, *44*, 2757. (aaa) Martinez, S.; Meseguer, M.; Casas, L.; Rodriguez, E.; Molins, E.; Moreno-Manas, M.; Roig, A.; Sebastian, R. M. and Vallribera, A., *Tetrahedron,* **2003**, *59*, 1553. (bbb) Varala, R.; Alam, M. M. and Adapa, S. R., *Synlett,* **2003**, 67. (ccc) Reddy, A. V.; Reddy, V. L. N.; Ravinder, K. and Venkateswarlu, Y., *Heterocycl. Commun.,* **2002**, *8*, 459. (ddd) Dzvinchuk, I. B.; Makitruk, T. V. and Lozinskii, M. O., *Chem. Heterocycl. Compd.,* **2002**, *38*, 1000. (eee) Fu, N. Y.; Mei, L. P.; Yuan, Y. F. and Wang, J. T., *Chinese Chem. Lett.,* **2002**, *13*, 921. (fff) Lu, J.; Bai, J.-J.; Guo, Y.-H.; Wang, Z.-J. and Ma, H.-R., *Chinese J. Chem.,* **2002**, *20*, 681. (ggg) Jin, T. S.; Zhang, S. L. and Li, T. S., *Synth. Commun.,* 2002, 32, 1847. (hhh) Xue, S.; Shen, Y.-C.; Li, Y.-L.; Shen, X.-M. and Guo, Q.-X., *Chinese J. Chem.,* **2002**, *20*, 385. (iii) Lu, J. and Bai, Y. J., *Synthesis,* **2002**, 466. (jjj) Salmon, M.; Osnaya, R.; Gomez, L.; Arroyo, G.; Delgado, F. and Miranda, R., *Revista Soc. Quim. Mexico,* **2001**, *45*, 206. (kkk) Dondoni, A. and Massi, A., *Tetrahedron Lett.,* **2001**, *42*, 7975. (lll) Dondoni, A.; Massi, A. and Sabbatini, S., *Tetrahedron Lett.,* **2001**, *42*, 4495. (mmm) Yadav, J. S.; Reddy, B. V. S.; Reddy, P. T., *Synth. Commun.,* **2001**, *31*, 425. (nnn) Yadav, J. S.; Reddy, B. V. S.; Reddy, E. J. and Ramalingam, T., *J. Chem. Res. (S),* **2000**, 354. (ooo) Shutalev, A. D. and Sivova, N. V., *Chem. Heterocycl. Compd.,* **1998**, *34*, 848. (ppp) Rehani, R.; Shah, A. C. and Arya, V. P., *Indian J. Chem., Sect. B,* **1994**, 33*B*, 775. (qqq) Folkers, K. and Johnson, T. B., *J. Am. Chem. Soc.,* **1933**, *55*, 3784.

5. (a) Wang, C.-F.; Jiang, H.; Gong, H.; Wang, M. and Wang, Z.-C., *Youji Huaxue*, **2006**, *26*, 333. (b) Shaabani, A.; Bazgir, A. and Bijanzadeh, H. R., *Molecular Diversity*, **2004**, *8*, 141. (c) Aron, Z. D. and Overman, L. E., *Chem. Commun.*, **2004**, 253. (d) Shanmugam, P. and Perumal, P. T., *J. Chem. Res. (S),* **2003**, 601. (e) Wang, L. M.; Qian, C. T.; Tian, H. and Ma, Y., *Synth. Commun.,* **2003**, *33*, 1459. (f) Stadler, A.; Yousefi, B. H.; Dallinger, D.; Walla, P.; der Eycken, E. V.; Kaval, N. and Kappe, C. O., *Org. Proc. Res. Dev.,* **2003**, 7,707. (g) Pérez, R.; Beryozkina, T.; Zbruyev, O. I.; Haas, W. and Kappe, C. O., *J. Comb. Chem.,* **2002**, 4,501. (h) Lewandowski, F.; Murer, P.; Svec, F. and Fréchet, J. M. F., *J. Comb. Chem.,* **1999**, 1,105. (i) Cohen, F.; Overman, L. E. and Sakata, S. K. L., *Org. Lett.,* **1999**, *1*, 2169. (j) McDonald, A. I. and Overman, L. E., *J. Org. Chem.,* **1999**, 64,1520. (k) Franklin, A. S.; Ly, S. K.; Mackin, G. H.; Overman, L. E. and Shaka, A. J., *J. Org. Chem.*, **1999**, *64*, 1512. (l) Kappe, C. O., *Molecules,* **1998**, *3*, 1. (m) Kappe, C. O., *Molecules,* **1998**, *3*, 1. (n) Overman, L. E. and Rabinowitz, M. H., *J. Org. Chem.,* **1993**, *58*, 3235. (o) Folkers, K. Harwood, H. J. and Johnson, T. B., *J. Am. Chem. Soc.,* **1932**, *54*, 3751.
6. (a) Bose, D. S.; Fatima, L. and Mereyala, H. B., *J. Org. Chem.,* **2003**, *68*, 587. (b) Dondoni, A.; Massi, A.; Sabbatini, S. and Bertolasi, V., *J. Org. Chem.,* **2002**, *67*, 6979. (c) Bussolari, J. C. and McDonnell, P. A., *J. Org. Chem.,* **2000**, 65,6777.
7. Studer, A.; Jeger, P.; Wipf, P. and Curran, D. P., *J. Org. Chem.,* **1997**, *62*, 2917
8. (a) Zumpe, F. L.; Fluess, M.; Schmitz, K. and Lender, A., *Tetrahedron Lett.,* **2007**, *48*, 1421. (b) Shanmugam, P.; Sabastein, C. and Perumal, P. T., *Indian J. Chem., Sect. B,* **2004**, 43*B*, 135.
9. (a) Kappe, C. O., *Acc. Chem. Res.,* **2000**, *33*, 879. (b) Singh, K.; Singh, J.; Deb, P. K. and Singh, H., *Tetrahedron*, **1999**, *55*, 12873. (c) Kappe, C. O., *J. Org. Chem*., **1997**, *62*, 7201. (d) Wipf, P. and Cunningham, A., *Tetrahedron Lett*., **1995**, *36*, 7819. (e) Kappe, C. O., *Tetrahedron*, **1993**, *49*, 6937.
10. (a) Lin, H. X.; Ding, J. C.; Chen, X. T. and Zhang, Z. Y., *Molecules*, **2000**, *5*, 1240. (b) Kappe, C. O. and Roschger, P., *J. Heterocycl. Chem*., **1989**, *26*, 55.
11. (a) Rovnyak, G. C.; Atwal, K. S.; Hedberg, A.; Kimball, S. D.; Moreland, S.; Gougoutas, J. Z.; O'Reilly, B. C.; Schwartz, J. and Malley, M. F., *J. Med. Chem.,* **1992**, *35*, 3254. (b) Atwal, K. S.; Rovnyak, G. C.; Kimball, S. D.; Floyd, D. M.; Moreland, S.; Swanson, B. N.; Gougoutas, J. Z.; Schwartz, J.; Smillie, K. M. and Malley, M. F., *J. Med. Chem.,* **1990**, *33*, 2629. (c) Cho, H.; Ueda, M.; Shima, K.; Mizuno, A.; Hayashimatsu, M.; Ohnaka, Y.; Takeuchi, Y.; Hamaguchi, M.; Aisaka, K.; Hidaka, T.; Kawai, M.; Ishihara, T.; Funahashi, K.; Satah, F.; Morita, M. and Noguchi, T., *J. Med. Chem.,* **1989**, *32*, 2399.

12. (a) Lewandowski, K.; Murer, P.; Svec, F. and Frechet, J. M., *J. Chem. Soc., Chem. Commun*., **1998**, 2237. (b) Studer, A.; Hadida, S.; Ferritto, R.; Kim, S.-Y.; Jeger, P.; Wipf, P. and Curran, D. P., *Science,* **1997**, *275*, 823.
13. Hu, E. H.; Sidler, D. R. and Dolling, U. H., *J. Org. Chem.,* **1998**, *63*, 3454.
14. Ramalinga, K.; Vijayalakshmi, P. and Kaimal, T. N. B., *Synlett,* **2001**, 863.
15. Muñoz-Muñiz, O. and Juaristi, E., *ARKIVOC*, **2003**, 26.
16. Lu, J. and Ma, H. R., *Synlett,* **2000**, 63.
17. Ranu, B. C.; Hajra, A. and Jana, U., *J. Org. Chem*., **2000**, *65*, 6270.
18. Lu, J.; Bai, Y.; Wang, Z.; Yang, B. and Ma, H., *Tetrahedron Lett*., **2000**, *41*, 9075.
19. Yadav, J. S.; Reddy, B. V. S.; Srinivas, R.; Venugopal, C. and Ramalingam, T., *Synthesis,* **2001**, 1341.
20. Kumar, K. A.; Kasthuraiah, M.; Reddy, C. S. and Reddy, C. D., *Tetrahedron Lett*., **2001**, *42*, 7873.
21. Dondoni, A.; Massi, A.; Minghini, E.; Sabbatini, S. and Bertolasi, V., *J. Org. Chem.,* **2003**, *68*, 6172.
22. Tu, S.; Fang, F.; Miao, C.; Jiang, H.; Shi, D.; Wang, X., *J. Chem. Res. (S),* **2003**, 544.
23. Ranu, B. C.; Hajra, A. and Dey, S. S., *Org. Proc. Res. Dev.*, **2002**, *6*, 817.
24. (a) Hayes, B. L., *Microwave Synthesis: Chemistry at the Speed of Light*, CEM Publishing, Matthews, N.C., **2002**. (b) Stadler, A.; Kappe, C. O., *J. Chem. Soc., Perkin Trans. I*, **2000**, 1363. (c) Stefani, H. A.; Gatti, P. M., *Synth. Commun*., **2000**, *30*, 2165. (d) Kappe, C.O.; Kumar, D. and Varma, R. S., *Synthesis,* **1999**, 1799. (e) Gupta, R.; Paul, S. and Gupta, A. K., *Indian J. Chem. Technol*., **1998**, *5*, 340.
25. Bigi, F.; Carloni, S.; Frullanti, B.; Maggi, R. and Sartori, G., *Tetrahedron Lett*., **1999**, *40*, 3465.
26. (a) Kappe, C. O.; Falsone, S. F., *Synlett,* **1998**, 718. (b) Dixon, L. A., "Biginell: Dihydropyrimidine Synthesis" in *Encyclopedia of Reagents in Organic Chemistry,* ed. Paguette, L. A. Wiley, New York, **1995**, *6*, 4166.
27. Folkers, K. and Johnson, T. B., *J. Am. Chem. Soc*., **1933**, *55*, 3781.
28. (a) Ohtani, I.; Kusumi, T.; Kakisawa, H.; Kashman, Y. and Hirsh, S., *J. Am. Chem. Soc.,* **1992**, *114*, 8472. (b) Kashman, Y.; Hirsh, S.; McConnel, O. J.; Ohtani, I.; Takenori, K. and Kakisawa, H., *J. Am. Chem. Soc.,* **1989**, *111*, 8925.
29. Snider, B. B. and Shi, Z., *J. Org. Chem.,* **1993**, *58*, 3828.
30. (a) Coffey, D. S.; McDonald, A. I.; Overman, L. E.; Rabinowitz, M. H. and Renhowe, P. A., *J. Am. Chem. Soc.,* **2000**, *122*, 4893. (b) Coffey, D. S.; Overman, L. E. and Stappenbeck, F., *J. Am. Chem. Soc.,* **2000**, *122*, 4904. (c) Coffey, D. S.; McDonald, A. I.; Overman, L. E.; Stappenbeck, F., *J. Am. Chem. Soc.,* **1999**, *121*, 6944. (d) Coffey, D. S.; McDonald, A. I. and Overman, L. E., *J. Org. Chem.,* **1999**, *64*, 8741. (e) Overman, L. E.; Rabinowitz, M. H. and Renhowe, P. A., *J. Am. Chem. Soc.* **1995**, *117*, 2657.
31. Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; DeBrosse, C.; Mai, S.; Truneh, A.; Faulkner, D. J.; Carte, B.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westley, J. W. and Potts, B. C. M., *J. Org. Chem.* **1995**, *60*, 1182.
32. (a) Azizian, J.; Mohammadi, A. A.; Kohshari, M.; Karimi, A. R. and Mohammadizadeh, M. R., *J. Heterocycl. Chem.,* **2007**, *44*, 455. (b) Werner, S.; Turner, D. M.; Lyon, M. A.; Huryn, D. M. and Wipf, P., *Synlett,* **2006**, 2334. (c) Zhu, Y.-L.; Huang, S.-L. and Pan, Y.-J., *Eur. J. Org. Chem.,* **2005**, 2354. (d) Frost, C. G. and Hartley, J. P., *Mini-Rev. Org. Chem.,* **2004**, 1,1. (e) Gholap, A. R.; Venkatesan, K.; Daniel, T.; Lahoti, R. J. and Srinivasan, K. V., *Green Chem.,* **2004**, *6*, 147. (f) Kidwai, M.; Mohan, R. and Saxena, S., *Russ. Chem. Bull.,* **2003**, *52*, 2457. (g) Dzvinchuk, I. B.; Makitruk, T. V. and Lozinskii, M. O., *Chem. Heterocycl. Comp.*, **2003**, 536. (h) Kidwai, M.; Mohan, R. and Saxena, S., *Russ. Chem. Bull.,* **2003**, *52*, 2457. (i) Fu, N.-Y.; Yuan, Y.-F.; Cao, Z.; Wang, S.-W.; Wang, J.-T. and Peppe, C., *Tetrahedron*, **2002**, *58*, 4801. (j) Dzvinchuk, I. B.;

Makitruk, T. V. and Lozinskii, M. O., *Chem. Heterocycl. Comp.*, **2002**, 1141. (k) Fan, X.; Zhang, X. and Zhang Y., *J. Chem. Res. (S)*, **2002**, 436. (l) Holden, M. S. and Crouch, R. D., *J. Chem. Edu.*, **2001**, *78*, 1104. (m) Rani, V. R.; Srinivas, N.; Kishan, M. R.; Kulkarni, S. J. and Raghavan, K. V., *Green Chem.*, **2001**, *3*, 305. (n) Falsone, F. S. and Kappe, C. O., *ARKIVOC*, **2001**, 122. (o) Yadav, J. S.; Reddy, B. V. S.; Reddy, K. B.; Raj, K. S. and Prasad, A. R., *J. Chem. Soc., Perkin Trans. I,* **2001**, 1939. (p) Varma, R. S., *Pure & Appl. Chem.*, **2001**, *73*, 193. (q) Peng, J. and Deng, Y., *Tetrahedron Lett.,* **2001**, *42*, 5917. (r) Stadler, A. and Kappe, C. O., *J. Comb. Chem.,* **2001**, 3,624. (s) Overman, L. E. and Wolfe, J. P., *J. Org. Chem.,* **2001**, 66,3167. (t) Kappe, C. O., *Eur. J. Med. Chem.*, **2000**, *35*, 1043. (u) Kappe, C. O., *Bioorg. Med. Chem. Lett.*, **2000**, *10*, 49. (v) Saloutin, V. I.; Burgat, Ya. V.; Kuzueva, O. G.; Kappe, C. O. and Chupakhin, O. N., *J. Fluor. Chem.*, **2000**, *103*, 17. (w) Byk, G.; Gottlieb, H. E.; Herscovici, J. and Mirkin, F., *J. Comb. Chem.,* **2000**, 2,732. (x) Kappe, C. O.; Falsone, F.; Fabian, W. M. F. and Belaj, F., *Heterocycles*, **1999**, *51*, 77. (y) Hamper, B. C.; Gan, K. Z. and Owen, T. J., *Tetrahedron Lett.,* **1999**, 40,4973. (z) Shutalev, A. D.; Kishko, E. A.; Sivova, N. and Kuznetsov, A. Y., *Molecules,* **1998**, *3*, 100. (aa) Shutalev, A. D. and Sivova, N. V., *Khim. Geterotsikl. Soedin.*, **1998**, 979. (bb) Gupta, R.; Gupta, A. K.; Paul, S. and Kachroo, P. L., *Indian J. Chem.,* **1995**, 34*B*, 151. (cc) Wipf, P. and Cunningham, A., *Tetrahedron Lett.,* **1995**, 36,7816. (dd) Gupta, R.; Gupta, A. K.; Paul, S. and Kachroo, P. L., *Indian J. Chem.,* **1995**, 34*B*, 61. (ee) Sár, C. P.; Hankovszky, O. H.; Jerkovich, G.; Pallagi, I. and Hideg, K., *ACH - Models Chem.,* **1994**, *131*, 363. (ff) Marson, C. M.; Grabowska, U.; Fallah, A.; Walsgrove, T.; Eggleston, D. S. and Baures, P. W., *J. Org. Chem.,* **1994**, *59*, 291. (gg) Zavyalov, S. I. and Kulikova, L. B., *Khim.-Farm. Zh.,* **1992**, *26*, 116. (hh) Zavyalov, S. I. and Kulikova, L. B., *Khim.-Farm. Zh.,* **1992**, 1655. (ii) Atwal, K. S.; Rovnyak, G. C.; O'Reilly, B. C. and Schwartz, J., *J. Org. Chem.,* **1989**, *54*, 5898. (jj) Barluenga, J.; Tomas, M.; Ballesteros, A. and Lopez, L. A., *Tetrahedron Lett.*, **1989**, *30*, 4573. (kk) Fernàndez, M. V.; Herrera, F. J. L.; Cobos, T. L., *Heterocycles,* **1988**, *27*, 2133. (ll) O'Reilly, B. C. and Atwal, K. S., *Heterocycles,* **1987**, *26*, 1185. (mm) Atwal, K S.; O'Reilley, B. C.; Gougoutas, J. Z. and Malley, M. F., *Heterocycles,* **1987**, *26*, 1189. (nn) Fernàndez, M. V.; Herrera, F. J. L. and Cobos, T. L., *Heterocycles*, **1986**, *24*, 679. (oo) Barluenga, J.; Tomas, M.; Rubio, V. and Gotor, V. J., *J. Chem. Soc., Chem. Commun.,* **1979**. 675. (pp) Sastre, J. A. L. and Molina, J. M., *An. Quim.* **1978**, *74*, 353. (qq) Zaugg, H. E. and Martin W. B., *Org. React.,* **1965**, *14*, 88. (rr) Brown, D. J., *The Pyrimidines,* John Wiley & Sons., Inc. New York, **1962**, p. 440. (ss) Zee-Cheng, K. Y.; Robins, R. K. and Cheng, C. C., *J. Org. Chem.,* **1961**, *26*, 1877. (tt) Folkers, K. and Johnson, T. B., *J. Am. Chem. Soc.,* **1933**, *55*, 2886.

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Birch Reduction
(Metal-Ammonia Reduction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Wooster in 1937,[1] and subsequently by Hückel et al in 1939,[2] for the reduction of aromatic compounds by sodium in liquid ammonia with water; however, no structural information was provided. It was Birch who extended Wooster's protocol in 1944[3] and since then had extensively explored the reduction of benzene and aromatic derivatives with alkali metal (i.e., Li, Na, K) in liquid ammonia in the presence of an alcohol (as the proton donor) to produce corresponding cyclohexa-1,4-diene derivatives.[4] Therefore, the reduction of aromatic compounds by alkali metal in liquid ammonia in the presence of alcohol is generally known as the Birch reduction[5,6] or metal-ammonia reduction.[7] In addition, this reaction is also referred to as the Birch reaction,[6ddd,8] and in one instance is cited as the Birch-Hückel reduction.[9]

Different from the transition metal (e.g., Pd, Pt, etc.) catalyzed hydrogenation, by which aromatic compounds can be converted into the fully hydrogenated molecules,[5aa] the Birch reduction uses the ammonia-solvated electrons arising from alkali metal as the reducing agent, which bears the extremely negative single-electron redox potential;[10] thus even the electron-enriched aromatic systems (i.e., carrying electron-donating groups) can be reduced accordingly. In addition, once the solvated electron adds to aromatic system, the radical anion is quenched by alcohol, so that cyclohexa-1,4-diene derivatives are often produced from benzene derivatives without further reduced species. It should be pointed out that the existing alkali metal also reacts with alcohol to generate hydrogen, in a reaction known as the hydrogen reaction, which competes with the reduction of aromatic compounds.[5aa] It is reported that both the rate[5aa] and yield[11] of the Birch reduction decreases in the order of Li > Na > K; as a result, the relatively slower reduction of sodium with aromatic compounds

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(compared to lithium) may allow a simultaneous base-catalyzed isomerization from the isolated diene system to the more stable conjugated diene system, which in turn is further reduced to tetrahydro stage by the existing metal. In comparison, lithium has higher reducing power and does not tend to promote the isomerization of the isolated diene system.[6ww] Such difference between lithium and sodium presumably is the reason that Wooster et al did not exploit this reaction successfully. However, the combination of lithium-methylamine-alcohol can further reduce the aromatic system into tetrahydro derivatives.[6ggg] It should be pointed out that iron salts can strongly catalyze the sodium-based Birch reduction, but they have less effect on the lithium-based Birch reduction.[6hh] Although the Birch reduction and hydrogen reaction have a similar reaction order when the alkali metal concentration is around 0.01 M (or less), the hydrogen reaction decreases in an inverse order—that is, the reaction rate increases in the order of Li < Na < K.[5aa] Therefore, it is suggested that the reduction be carried out at the lowest possible temperature with methanol as the quenching agent to reduce the effect from the hydrogen reaction, because ethanol shows a faster rate than does butanol.[5aa,11d] Moreover, it is reported that both the Birch reduction and hydrogen reaction can be accelerated by the addition of an alkali cation common to the dissolved alkali metal (e.g., alkali bromide), whereas both reactions are disfavored by the addition of the complexing cryptands of the corresponding alkali cation, indicating that the formation of intermediate ion pairs or shifting pre-equilibria in which solvated electrons are involved. In addition, I propose that the added alkali cation might further stabilize the radical anion, causing a shift in the equilibrium to the end of product. Besides the commonly used alcohols, ethers and alkyl halides could be applied as anion quenchers,[9] and sometimes, a co-solvent such as THF[5x] is also added to the reaction system, presumably to alternate the solubility of aromatic compounds.

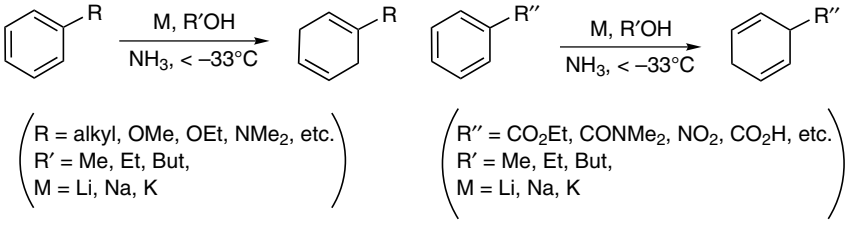
On the other hand, one of the advantages associated with the Birch reduction is its efficient steric control on the aromatic system—that is, the formed cyclohexa-1,4-diene system is the isomer with the maximum number of alkoxy and/or alkyl groups on the residual double bonds, known as the Birch rule.[5ccc,5mmm,12] In other words, the electron-withdrawing groups, (e.g., NO_2, COR, and CO_2H),[13] facilitate the formation of anion and subsequent reduction at the position on the aromatic ring bearing such group, leading to the formation of 1,4-dihydro derivatives via the addition of hydrogen *para* to the electron-withdrawing group;[14] whereas electron-donating groups (such as OMe, Me, NR_2, and $SiMe_3$) are deactivating substituents,[13] resulting in the generation of 2,5-dihydro derivatives by *meta* addition of hydrogen to the strongly deactivating group.[14] When both electron-withdrawing and electron-donating groups exist on the aromatic system, the former has a greater directing effect, whereas among the electron-donating groups, the ones with oxygen or nitrogen atoms outweigh the alkyl groups. Thus the empirical order for directing is as follows: carboxy > amino/alkoxyl > alkyl.[14] For the fused aromatic ring system, the ring with the most fusions to another aromatic ring is normally the one to undergo the Birch reduction;[14] however, the carbon skeleton for the fused aromatic system may rearrange during the Birch reduction. As an example, the reduction of biphenylene gives the expected 1,4,4a,8b-tetrahydrobiphenylene and the unexpected 4,5-benzobicyclo[4.2.0]octa-2,4-diene.[6ii] In the fused aromatic system, a ring with a hydroxyl group would be deactivated due to the formation of anion analogous to phenoxide.[14]

One of the most important applications of the Birch reduction is to convert aryl alkyl ethers into 1-alkoxycyclohexa-1,4-dienes which are then used as the starting materials in organic synthesis.[5x,13] Compared to the benzene series, the Birch reduction of naphthalenes may afford different products, depending on the position of the alkoxyl group.

For example, along with the loss of the methoxyl group, both 1-methoxy-2-naphthoic acid and 3-methoxy-2-naphthoic acid will be converted into 1,2,3,4-tetrahydro- or 1,2,3,4,5,8-hexahydro-2-naphthoic acid depending on the reaction conditions or proportion of reagents used, whereas 2-methoxy-1-naphthoic acid is mainly converted into 1,4,5,8-tetrahydro-2-methoxy-1-naphthoic acid without loss of the methoxyl group.[6s;6ii] Besides the reduction of aromatic systems, the Birch reaction has been found to reduce acetylenes stereospecifically to *trans*-olefins[15] and to hydrogenate graphite and carbon single-walled nanotubes (SWNTs).[16] However, the Birch reduction cannot reduce hexamethylbenzene and highly substituted benzene rings in [2*n*]-cyclophanes,[5oooo] probably due to the steric hindrance. In addition, the Birch reaction can also cleave the C-C bond in the presence of the aromatic system. For instance, the Birch reaction with lithium-ammonia can remove the tertiary cyano group,[17] whereas potassium sand in ether can cleave pentaphenyl ethane,[18] and sodium-potassium alloy is able to break 1,1,2,2-tetraphenylethane.[18] It is pointed out that the cleavage of 1,2-diarylethanes increases in the order of aryl = anthracene < naphthalene < benzene, with the alkali metal order of Li < Na < K, and the solvents in the order of NH_3 < THF < HMPA.[5ppp] It should be noted that the configuration is retained during the bond cleavage under Birch-like conditions.[14] Furthermore, the Birch reduction has often been used to generate hydroxyl groups by the removal of the benzyl-protecting group.[5i,20] It is interesting that in the absence of the harsh conditions of the Birch reduction, an enzyme-catalyzed reduction for the two-electron reduction of benzoyl-CoA to cyclohexa-1,5-diene-1-carbonyl-CoA has been observed, where a conjugated diene is formed instead of 1,4-diene in the Birch reduction.[10]

Nevertheless, the Birch reduction also has certain drawbacks, including the tedious experimental procedure, the use of strongly basic solutions, and sometimes the solubility problem of substrates.[5llll]

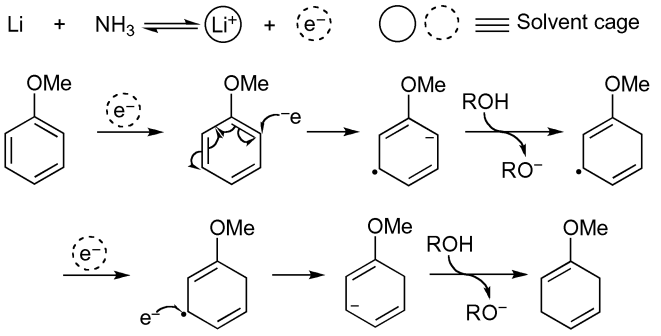
B. GENERAL REACTION SCHEME



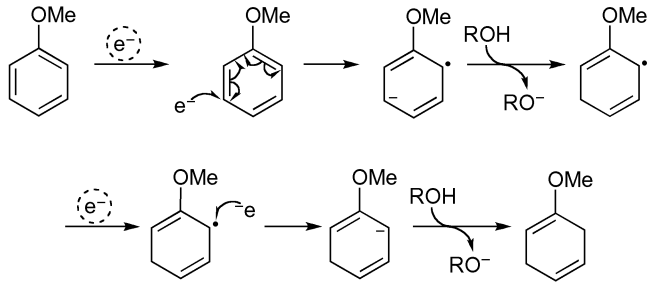
C. PROPOSED MECHANISMS

It is generally accepted that the metal ammonia solution (MAS) contains both the solvated electron and alkali cation, in which the solvated electron has extremely high single-electron redox potential[5aa] so that the solvated electron can even reduce electron-enriched aromatic systems. In this reduction, the solvated electron adds to the aromatic ring to generate a radical anion, which is protonated by an alcohol; then a second solvated electron adds to the ring to form a new radical anion, followed by alcohol

quenching to afford the unconjugated cyclohexa-1,4-diene.[5ccc,5mmm] The protonation of the radical anion by alcohol is the rate-limiting step.[5ccc,5mmm] However, there is disagreement about the electron density of the radical anion, for which Birch himself believed that the *meta* position of the radical anion formed from anisole had the highest electron density (Scheme 1),[21] whereas Zimmerman suggested the position *ortho* to the maximum number of substituents to be most electron rich, from the Hückel calculation (Scheme 2).[5ccc] Displayed here are Birch's mechanism and Zimmerman's explanation for the regioselectivity of the Birch reduction of anisole. The Birch reduction on a aromatic system with an electron-withdrawing group should have a similar reaction process but a different position for the solvated electron to attack.



SCHEME 1. *Birch's mechanism for the reduction of anisole.*



SCHEME 2. *Zimmerman's mechanism for the reduction of anisole.*

D. MODIFICATION

This reaction has been extensively modified. One of the important modifications is the quenching of radical anion by an alkylation agent to give an alkyl-substituted cyclohexa-1,4-diene derivative,[5xa,5nnnn,13,22] a condition known as the Birch reductive alkylation.[22b] On the other hand, a pyrrole nucleus bearing an extremely enriched electron density and

an acidic hydrogen atom normally does not undergo the Birch reduction;[5oo] however, the pyrrole nucleus has been successfully reduced to a dihydropyrrole derivative by replacing the acidic hydrogen atom with an *N*-*t*-butylcarboxyl (Boc) group.[5oo] In addition, an ammonia-free methodology has been developed by using a di-*tert*-butylbiphenyl radical anion (generated from di-*tert*-butylbiphenyl and lithium in THF) to provide electrons and bis(methoxyethyl)amine as an acid, so that a number of electrophiles, such as silyl halides, chloroformates, acid chlorides, and enolizable aldehydes, can be trapped by the radical anion.[5f] Furthermore, this reaction has been carried out via electrochemical reduction in an aqueous media,[5llll] using a concentrated aqueous solution of tetrabutylammonium hydroxide.[23] Moreover, calcium has been applied successfully for the ultrasound-promoted reduction of the aromatic compound;[24] likewise, a photo-reduction[6f] system has been developed to reduce aromatic compounds by irradiation of an acetonitrile/water (9:1) solution in the presence of $NaBH_4$ and *m*- or *p*-dicyanobenzene.[5wwww]

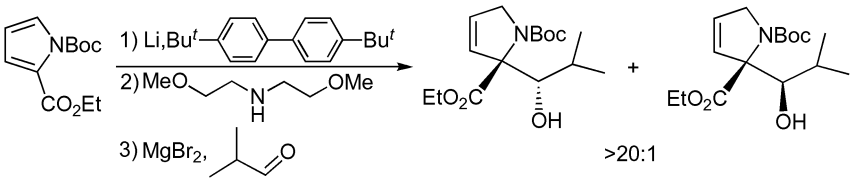
E. APPLICATIONS

This reaction has been widely used to convert the aryl alkyl ethers into 1-alkoxycyclohexa-1,4-diene derivatives. In addition, this reaction has been used to remove the benzyl group on oxygen, cleave the C-C bonds, and reduce acetylenes into *trans*-olefins stereospecifically.

F. RELATED REACTIONS

This reaction is closely related to the *Benkeser Reduction*.

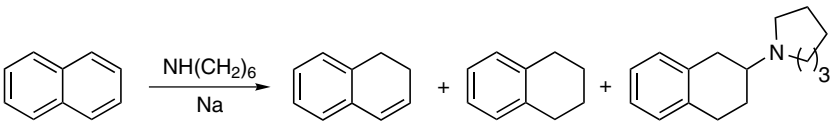
G. CITED EXPERIMENTAL EXAMPLES



Reference 5f.

A Schlenk tube containing 119 mg small strips of lithium ribbon (17.0 mmol), antibumping granules, and 4.5 g di-*tert*-butylbiphenyl (16.9 mmol) was evacuated and purged with argon several times. The mixture was ground with a magnetic stirrer until all the lithium became a dark powder. Freshly distilled THF (50 mL) was then added, and the mixture was cooled down to −78°C before a mixture of 1.1 g *N*-Boc ethyl 2-pyrrole carboxylate (4.4 mmol) and 0.8 mL bis-methoxyethylamine (5.3 mmol) in 25 mL freshly distilled THF was added dropwise to the turquoise solution. The mixture was then stirred at −78°C for a further 15 min after which 1.0 g freshly prepared $MgBr_2$ (5.4 mmol) in 20 mL THF was added, and the mixture was stirred for an additional 30 min. Distilled isobutyraldehyde

(0.7 mL, 7.0 mmol) was then added. After 30 min the reaction mixture was quenched with 10 mL saturated NH_4Cl aqueous solution. Stirring was continued at $-78^{\circ}C$ for a further 30 min and then the solution was warmed to ambient temperature. The reaction mixture was poured into a 50 mL 1 M HCl solution and extracted with Et_2O (3×60 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by gradient column chromatography by eluting with neat petroleum ether to recover the di-*tert*-butylbiphenyl and then 5% acetone in petroleum ether to afford 1.07 g product as a colorless oil, in a yield of 74%.



Reference 6ddd.

To a 500-mL three-necked flask equipped with a stirrer, air condenser, and nitrogen inlet tube were added 6.4 g naphthalene (0.05 mol) and 4.6 g dispersed sodium (0.2 mol), followed by 100 mL hexamethylenimine. A red color developed within 20 min. The mixture was stirred at 25°C for 12 h, and the unreacted sodium, which had agglomerated, was removed. The remaining solution was cooled and treated cautiously with water until the reaction mixture became colorless, then acidified with 10% aqueous HCl. After the hydrocarbons had been removed by extraction with ether, the aqueous layer was basified with dilute NaOH, and surplus hexamethylenimine was removed by steam distillation. The steam distillation residue was extracted with ether. Drying over anhydrous Na_2SO_4 and distillation yielded 6.2 g 2-*N*-hexamethylenyl tetralin, in a yield of 55%.

Other references related to the Birch reduction are cited in the literature.[25]

H. REFERENCES

1. Wooster, C. B. and Godfrey, K. L., *J. Am. Chem. Soc*., **1937**, *59*, 596.
2. Hückel, W. and Bretschneider, H., *Ann.,* **1939**, 540, 157.
3. Birch, A. J., *J. Chem. Soc.,* **1944**, 430.
4. (a) Birch, A. J., *J. Chem. Soc.,* **1945**, 809. (b) Birch, A. J., *Nature,* **1946**, *158*, 60. (c) Birch, A. J., *J. Chem. Soc.,* **1946**, 593. (d) Daunt, J. G.; Desirant, M.; Mendelssohn, K. and Birch, A. J., *Phys. Rev.,* **1946**, *70*, 219. (e) Birch, A. J. and MacDonald, D. K. C., *Trans. Faraday Soc.,* **1947**, *43*, 792. (f) Birch, A. J., *J. Chem. Soc.,* **1947**, 102. (g) Birch, A. J., *J. Chem. Soc.,* **1947**, 1642. (h) Birch, A. J. and MacDonald, D. K. C., *Nature,* **1947**, *159*, 811. (i) Birch, A. J., *Nature,* **1947**, *160*, 754. (j) MacDonald, D. K. C.; Mendelssohn, K. and Birch, A. J., *Phys. Rev.,* **1947**, *71*, 563. (k) Birch, A. J. and MacDonald, D. K. C., *Trans. Faraday Soc.,* **1948**, *44*, 735. (l) Birch, A. J. and MacDonald, D. K. C., *J. Chem. Phys.,* **1948**, *16*, 741. (m) Birch, A. J. and Mukherji, S. M., *J. Chem. Soc.,* **1949**, 2531. (n) Birch, A. J. and Mukherji, S. M., *Nature,* **1949**, *163*, 766. (o) Birch, A. J., *Quart. Revs. (London),* **1950**, *4*, 69. (p) Birch, A. J., *J. Proc. Royal Soc. New South Wales,* **1950**, *83*, 245. (q) Birch, A. J., *J. Chem. Soc.,* **1950**, 1551. (r) Birch, A. J.; Murray, A. R. and Smith, Herchel., *J. Chem. Soc.,* **1951**, 1945. (s) Birch, A. J. and Smith, H., *Quart. Revs. (London),* **1958**, *12*, 17. (t) Birch, A. J. and Rao, G. S. R. S., *Adv. Org. Chem.,* **1972**, *8*, 1. (u) Birch, A. J., *Pure & Appl. Chem.,* **1996**, *68*, 553.

5. (a) Kukula, P.; Dutly, A.; Rueegger, H. and Prins, R., *Tetrahedron Lett*., **2007**, *48*, 5657. (b) Tanaka, A.; Kawai, T.; Takabatake, T.; Oka, N.; Okamoto, H. and Bersohn, M., *Tetrahedron Lett*., **2006**, *47*, 6733. (c) Mena, M.; Valls, N.; Borregan, M. and Bonjoch, J., *Tetrahedron,* **2006**, *62*, 9166. (d) Casimiro-Garcia, A. and Schultz, A. G., *Tetrahedron Lett*., **2006**, *47*, 2739. (e) Castanedo, R.; Covarrubias-Zuniga, A. and Maldonado, L. A., *Tetrahedron Lett*., **2006**, *47*, 973. (f) Donohoe, T. J.; Sintim, H. O.; Sisangia, L.; Ace, K. W.; Guyo, P. M.; Cowley, A. and Harling, J. D., *Chem. Eur. J.,* **2005**, *11*, 4227. (g) Stanetty, P.; Kasemann, O.; Mereiter, K. and Mihovilovic, M. D., *ARKIVOC,* **2005**, (v), 83. (h) Kim, J. T. and Gevorgyan, V.,*J. Org. Chem.,* **2005**, *70*, 2054. (i) Taillier, C.; Bellosta, V.; Meyer, C. and Cossy, J., *Org. Lett.,* **2004**, *6*, 2145. (j) Turner, P. G.; Donohoe, T. J. and Cousins, R. P. C., *Chem. Commun.,* **2004**, 1422. (k) Malachowski, W. P. and Banerji, M., *Tetrahedron Lett*., **2004**, *45*, 8183. (l) Donohoe, T. J.; Guillermin, J.-B.; Calabrese, A. A. and Walter, D. S., *Tetrahedron Lett*., **2001**, *42*, 5841. (m) Del Campo, F. J.; Neudeck, A.; Compton, R. G.; Marken, F.; Bull, S. D. and Davies, S. G., *J. Electroanal. Chem.,* **2001**, *507*, 144. (n) Fuhry, M. A. M.; Colosimo, C. and Gianneschi, K., *J. Chem. Edu.,* **2001**, *78*, 949. (o) Guo, Z. H. and Schultz, A. G., *J. Org. Chem.,* **2001**, *66*, 2154. (p) Matsuoka, K.; Kurosawa, H.; Esumi, Y.; Terunuma, D. and Kuzuhara, H., *Carbohydr. Res.,* **2000**, *329*, 765. (q) Labadie, G. R.; Cravero, R. M. and Gonzalez-Sierra, M., *Synth. Commun.,* **2000**, *30*, 4065. (r) Donohoe, T. J.; Harji, R. R. and Cousins, R. P. C., *Tetrahedron Lett*., **2000**, *41*, 1331. (s) Ohta, Y.; Doe, M.; Morimoto, Y. and Kinoshita, T., *J. Heterocycl. Chem.,* **2000**, *37*, 751. (t) Vasil'ev, Y.; Wallis, D.; Drewello, T.; Nuchter, M.; Ondruschka, B. and Lobach, A., *Chem. Commun.,* **2000**, 1233. (u) Donohoe, T. J.; Guyo, P. M. and Raoof, A., *Targets in Heterocycl. Sys.,* **1999**, *3*, 117. (v) Schafer, A. and Schafer, B., *Tetrahedron*, **1999**, *55*, 12309. (w) Aniol, M., *Wiadomosci Chem.*, **1999**, *53*, 95. (x) Schultz, A. G., *Chem. Commun.,* **1999**, 1263. (y) Donohoe, T. J.; Guyo, P. M. and Helliwell, M., *Tetrahedron Lett*., **1999**, *40*, 435. (z) Takano, D.; Nakajima, Y.; Miyahara, I.; Hirotsu, K.; Tanaka, R.; Okada, K.; Morimoto, Y.; Kinoshita, T. and Yoshihara, K., *J. Heterocycl. Chem.,* **1998**, *35*, 1285. (aa) Greenfield, A. and Schindewolf, U., *Ber. Bunsen-Gesellschaft,* **1998**, *102*, 1808. (bb) Matsuoka, K.; Terabatake, M.; Saito, Y.; Hagihara, C.; Esumi, Y.; Terunuma, D. and Kuzuhara, H., *Bull. Chem. Soc. Jpn.,* **1998**, *71*, 2709. (cc) Schultz, A. G.; Guzi, T. J.; Larsson, E.; Rahm, R.; Thakkar, K. and Bidlack, J. M., *J. Org. Chem.,* **1998**, *63*, 7795. (dd) Sylvain, C.; Wagner, A. and Mioskowski, C., *Synthesis,* **1998**, 970. (ee) Ohta, Y.; Onoshima, M.; Tamura, M.; Tanaka, R.; Morimoto, Y.; Yoshihara, K. and Kinoshita, T., *J. Heterocycl. Chem.,* **1998**, *35*, 461. (ff) Donohoe, T. J.; Guyo, P. M.; Harji, R. R. and Helliwell, M., *Tetrahedron Lett*., **1998**, *39*, 3075. (gg) Donohoe, T. J.; Helliwell, M. and Stevenson, C. A., *Tetrahedron Lett.,* **1998**, *39*, 3071. (hh) Schultz, A. G. and Pettus, L., *J. Org. Chem.,* **1997**, *62*, 6855. (ii) Lawson, G. E.; Ma, B.; Rollins, H. R.; Hajduk, A. M. and Sun, Y.-P., *Res. Chem. Intermediates,* **1997**, 23, 549. (jj) Aniol, M. and Wawrzenczyk, C., *Heterocycles,* **1997**, *45*, 1069. (kk) Lin, Z.; Chen, J. H. and Valenta, Z., *Tetrahedron Lett*., **1977**, *38*, 3863. (ll) Schultz, A. and Li, Y.-J., *Tetrahedron Lett*., **1997**, *38*, 2071. (mm) Magnus, P.; Tavares, F. and Westwood, N., *Tetrahedron Lett*., **1997**, *38*, 1341. (nn) Beddoes, R. L.; Lewis, M. L.; Gilbert, P.; Quayle, P.; Thompson, S. P.; Wang, S. M. and Mills, K., *Tetrahedron Lett*., **1996**, *37*, 9119. (oo) Donohoe, T. J. and Guyo, P. M., *J. Org. Chem.,* **1996**, *61*, 7664. (pp) Kinoshita, T.; Ichinari, D. and Sinya, J., *J. Heterocycl. Chem.,* **1996**, *33*, 1313. (qq) Schultz, A. G. and Li, Y.-J., *Tetrahedron Lett*., **1996**, *37*, 6511. (rr) Schultz, A. G. and Kirincich, S. J., *J. Org. Chem.,* **1996**, *61*, 5631. (ss) Stanetty, P.; Kasemann, O. and Schmid, M., *J. Chem. Res. (S),* **1995**, 341. (tt) Schultz, A. G.; Kirincich, S. J. and Rahm, R., *Tetrahedron Lett*., **1995**, *36*, 4551. (uu) Aniol, M. and Wawrzenczyk, C., *Heterocycles,* **1994**, *38*, 2655. (vv) Wang, J. H.; Jiang, Y. Z. and Zhao, Z. Z., *Chinese Chem. Lett.,* **1994**, *5*, 925. (ww) Ali, A. S.; Liepa, A. J.; Thomas, M. D.; Wilkie, J. S. and Winzenberg, K. N., *Aust. J. Chem.,* **1994**, *47*, 1205. (xx) Aniol, M.; Lusiak, P. and Wawrzenczyk, C., *Heterocycles,* **1994**, *38*, 991. (yy) Govindaraj, A.; Rathna, A.; Chandrasekhar, J. and Rao, C. N. R., *Proc. Indian Acad. Sci., Chem. Sci.,* **1993**, *105*, 303. (zz) Li, Y. L. and He, X. C., *Youji Huaxue*, **1993**, *13*, 561. (aaa) D'Auria, M. and Volpe, F., *Gazz. Chim. Ital.,* **1993**, *123*, 527. (bbb) Banks, M. R.; Dale, M. J.; Gosney, I.; Hodgson, P. K. G.; Jennings, R. C. K.; Jones, A. C.; Lecoultre, J.; Langridge-Smith, P. R. R. and Maier, J. P.,

J. Chem. Soc., Chem. Commun., **1993**, 1149. (ccc) Zimmerman, H. E. and Wang, P. A., *J. Am. Chem. Soc.,* **1993**, *115*, 2205. (ddd) Rabideau, P. W. and Marcinow, Z., *Org. React.,* **1992**, *42*, 1. (eee) Kurzer, F. and Kapadia, Z., *Z. Naturforsch., B: Chem. Sci.,* **1992**, *47*, 579. (fff) Schultz, A. G.; Harrington, R. E. and Holoboski, M. A., *J. Org. Chem.,* **1992**, *57*, 2973. (ggg) Van Doorn, J. A.; Frijns, J. H. G. and Meijboom, N., *Rec. Trav. Chim. Pays-Bas,* **1991**, *110*, 441. (hhh) Beger, J.; Thomas, B.; Vogel, T.; Kirmse, K. and Lang, R., *J. Prakt. Chem.,* **1991**, *333*, 481. (iii) Saha, A.; Mahapatra, B. and Nasipuri, D., *Indian J. Chem., Sect. B,* **1991**, *30B*, 721. (jjj) Guzman, J. A.; Castanedo, R. and Maldonado, L. A., *Synth. Commun.,* **1991**, *21*, 1001. (kkk) Berkowitz, D. B., *Synthesis,* **1990**, 649. (lll) Box, V. G. S. and Yiannikouros, G. P., *Heterocycles,* **1990**, *31*, 971. (mmm) Zimmerman, H. E. and Wang, P. A., *J. Am. Chem. Soc.,* **1990**, *112*, 1280. (nnn) Marcinow, Z.; Clawson, D. K. and Rabideau, P. W., *Tetrahedron.,* **1989**, *45*, 5441. (ooo) Collins, D. J.; Downes, L. M.; Jhingran, A. G.; Rutschmann, S. B. and Sharp, G. J., *Aust. J. Chem.,* **1989**, *42*, 1235. (ppp) Marcinow, Z.; Hull, C. E. and Rabideau, P. W., *J. Org. Chem.,* **1989**, *54*, 3602. (qqq) Zhou, Q. S. and Weber, W. P., *Polymer Bulletin,* **1989**, *21*, 173. (rrr) Leonard, N. J.; Petric, A. and Rykowski, A., *J. Org. Chem.,* **1988**, *53*, 3873. (sss) Nishimura, J.; Ohbayashi, A.; Ueda, E. and Oku, A., *Chem. Ber.,* **1988**, *121*, 2025. (ttt) Schultz, A. G.; Macielag, M.; Podhorez, D. E.; Suhadolnik, J. C. and Kullnig, R. K., *J. Org. Chem.,* **1988**, *53*, 2456. (uuu) Collins, D. J. and Jacobs, H. A., *Aust. J. Chem.,* **1987**, *40*, 1989. (vvv) Van Doorn, J. A. and Meijboom, N., *J. Chem. Soc., Chem. Commun.,* **1987**, 1700. (www) Webster, F. X. and Silverstein, R. M., *Synthesis,* **1987**, 922. (xxx) Iwata, C.; Yamada, M.; Fusaka, T.; Miyashita, K.; Nakamura, A.; Tanaka, T.; Fujiwara, T. and Tomita, K., *Chem. Pharm. Bull.,* **1987**, *35*, 544. (yyy) Miyake, M.; Okamoto, E.; Nomura, M.; Shimada, H. and Nishijima, A., *Chem. Express,* **1987**, *2*, 241. (zzz) Kumamoto, T.; Hosoya, K.; Kanzaki, S.; Masuko, K.; Watanabe, M. and Shirai, K., *Bull. Chem. Soc. Jpn.,* **1986**, *59*, 3097. (aaaa) Moody, C. J. and Toczek, J., *Tetrahedron Lett*., **1986**, *27*, 5253. (bbbb) Schultz, A. G. and Macielag, M., *J. Org. Chem.,* **1986**, *51*, 4983. (cccc) Epling, G. A. and Florio, E., *Tetrahedron Lett*., **1986**, *27*, 1469. (dddd) Hook, J. M. and Mander, L. N., *Nat. Prod. Rep.,* **1986**, *3*, 35. (eeee) Schultz, A. G.; McCloskey, P. J.; Sundararaman, P. and Springer, J. P., *Tetrahedron Lett*., **1985**, *26*, 1619. (ffff) Hendrickson, J. B. and DeCapite, P. M., *J. Org. Chem.,* **1985**, *50*, 2112. (gggg) Schultz, A. G. and Puig, S., *J. Org. Chem.,* **1985**, *50*, 915. (hhhh) Mejer, S.; Respondek, S. and Lusiak, P., *Pol. J. Chem.,* **1984**, *58*, 1071. (iiii) Kreiser, W.; Rueschenbaum, V.; Bauer, H. and Buddrus, J., *Helv. Chim. Acta,* **1984**, *67*, 2231. (jjjj) Cotsaris, E. and Paddon-Row, M. N., *J. Chem. Soc., Perkin Trans. II,* **1984**, 1487. (kkkk) Chau, D. D.; Paddon-Row, M. N. and Patney, H. K., *Aust. J. Chem.,* **1983**, *36*, 2423. (llll) Kariv-Miller, E.; Swenson, K. E. and Zemach, D., *J. Org. Chem.,* **1983**, *48*, 4210. (mmmm) Sado, M.; Abe, H.; Inuzuka, N.; Shirai, K. and Kumamoto, T., *Bull. Chem. Soc. Jpn.,* **1983**, *56*, 1665. (nnnn) Taber, D. F.; Gunn, B. P. and Chiu, I. C., *Org. Synth.,* **1983**, *61*, 59. (oooo) Rohrbach, W. D. and Boekelheide, V., *J. Org. Chem.,* **1983**, *48*, 3673. (pppp) Cotsaris, E. and Paddon-Row, M. N., *J. Chem. Soc., Chem. Commun.,* **1982**, 1206. (qqqq) Toledano, J. C. and Olivella, S., *Anal. Quim., Ser. C: Quim. Org. Bioquim.,* **1982**, *78*, 187. (rrrr) Egli, P., *J. Labelled Compd. Radiopharm.,* **1981**, *18*, 1677. (ssss) Kosugi, K.; Anisimov, A. V.; Yamamoto, H.; Yamashiro, R.; Shirai, K. and Kumamoto, T., *Chem. Lett.,* **1981**, 1341. (tttt) Mochida, I.; Matsuoka, H.; Fujitsu, H.; Korai, Y. and Takeshita, K., *Carbon,* **1981**, *19*, 213. (uuuu) Casares, A.; Cardoso, J. M. L. and Maldonado, L. A., *Synth. Commun.,* **1981**, *11*, 223. (vvvv) Major, A.; Nagy, Z. and Nogradi, M., *Acta Chim. Acad. Sci. Hungaricae,* **1980**, *104*, 85. (wwww) Yasuda, M.; Pac, C. and Sakurai, H., *J. Org. Chem.,* **1980**, *46*, 788. (xxxx) Birch, A. J.; Hinde, A. L. and Radom, L., *J. Am. Chem. Soc.,* **1980**, *102*, 4074. (yyyy) Paddon-Row, M. N. and Hartcher, R., *Aust. J. Chem.,* **1980**, *33*, 785. (zzzz) Verchere, C. and Viel, C., *J. Heterocycl. Chem.,* **1980**, *17*, 49.

6. (a) Paddon-Row, M. N. and Hartcher, R., *J. Am. Chem. Soc.,* **1980**, *102*, 662. (b) Paddon-Row, M. N. and Hartcher, R., *J. Am. Chem. Soc.,* **1980**, *102*, 671. (c) Birch, A. J.; Hinde, A. L. and Radom, L., *J. Am. Chem. Soc.,* **1980**, *102*, 6430. (d) Birch, A. J.; Hinde, A. L. and Radom, L., *J. Am. Chem. Soc.,* **1980**, *102*, 3370. (e) Blenderman, W. G.; Joullie, M. M. and Preti, G., *Tetrahedron Lett*., **1979**, 4985. (f) Yasuda, M.; Pac, C. and Sakurai, H., *Kokagaku Toronkai Koen*

Yoshishu, **1979**, 262. (g) Tsujimoto, K.; Kamiyama, Y.; Furukawa, Y. and Ohashi, M., *Kokagaku Toronkai Koen Yoshishu*, **1979**, 208. (h) Blanch, C.; Camps, F. and Coll, J., *Anal. Quim.,* **1979**, *75*, 784. (i) Bhattacharyya, P. C., *Sci. Res. News,* **1979**, *1*, 102. (j) Divanfard, H. R.; Ibrahim, Y. A. and Joullie, M. M., *J. Heterocycl. Chem.,* **1978**, *15*, 691. (k) Humphreys, D. J.; Lawrence, P. M.; Newall, C. E.; Phillipps, G. H. and Wall, P. A., *J. Chem. Soc., Perkin Trans. I,* **1978**, *24*. (l) Vaidyanathaswamy, R.; Moorthy, S. N. and Devaprabhakara, D., *Indian J. Chem., Sect. B,* **1977**, *15B*, 309. (m) Hanson, A. W., *Acta Crystal., Sect, B,* **1977**, *B33*, 2003. (n) Ashmore, J. W. and Helmkamp, G. K., *Org. Prep. Proc. Int.,* **1976**, *8*, 223. (o) Beyerman, H. C.; Van Leeuwen, F. F.; Lie, T. S.; Maat, L. and Olieman, C., *Rec. Trav. Chim. Pays-Bas,* **1976**, *95*, 238. (p) Paddon-Row, M. N.; Hartcher, R. and Warrener. R. N., *J. Chem. Soc., Chem. Commun.,* **1976**, 305. (q) Junghans, K., *Chem. Ber.,* **1976**, *109*, 395. (r) Mizuno, K.; Okamoto, H.; Pac, C. and Sakarai, H., *J. Chem. Soc., Chem. Commun.,* **1975**, 839. (s) Oommen, P. K., *Aust. J. Chem.,* **1975**, *28*, 2095. (t) Kinoshita, T.; Miyano, K. and Miwa, T., *Bull. Chem. Soc. Jpn.,* **1975**, *48*, 1865. (u) Birch, A. J., *J. Chem. Edu.,* **1975**, *52*, 458. (v) Marshall, J. L.; Song, B.-H., *J. Org. Chem.,* **1975**, *40*, 1942. (w) Vaidyanathaswamy, R. and Devaprabhakara, D., *Indian J. Chem.,* **1975**, *13*, 287. (x) Eaborn, C.; Jackson, R. A. and Pearce, R., *J. Chem. Soc., Perkin Trans. I,* **1975**, 470. (y) Kocor, M.; Kaltenberg, O. P.; Kotlarek, W. and Sadlej, A. J., *Roczniki Chemii,* **1974**, *48*, 1951. (z) Pernemalm, P. A. and Dence, C. W., *Acta Chem. Scand., Ser. B,* **1974**, *28*, 453. (aa) Kinoshita, T. and Miwa, T., *J. Chem. Soc., Chem. Commun.,* **1974**, 181. (bb) Radlick, P.; Klem, R. and Crawford, H. T., *J. Org. Chem.,* **1974**, *39*, 1587. (cc) Radlick, P. and Crawford, H. T., *J. Chem. Soc., Chem. Commun.,* **1974**, 127. (dd) Murai, A.; Arita, K. and Masamune, T., *Bull. Chem. Soc. Jpn.,* **1973**, *46*, 3536. (ee) Jefford, C. W. and Delay, F., *Tetrahedron Lett*., **1973**, 3639. (ff) Kwart, H. and Conley, R. A., *J. Org. Chem.,* **1973**, *38*, 2011. (gg) Furusaki, A.; Hamanaka, N. and Matsumoto, T., *Bull. Chem. Soc. Jpn.,* **1973**, *46*, 434. (hh) Hamanaka, N.; Okuno, T.; Nakajima, T.; Furusaki, A. and Matsumoto, T., *Chem. Lett.,* **1972**, 1037. (ii) Matuszak, C. A. and Dickson, L., *J. Org. Chem.,* **1972**, *37*, 3345. (jj) Piers, E.; Phillips-Johnson, W. M. and Berger, C., *Tetrahedron Lett*., **1972**, 2915. (kk) Kaiser, E. M., *Synthesis*, **1972**, 391. (ll) Marshall, J. L. and Folsom, T. K., *Tetrahedron Lett*., **1971**, 757. (mm) Brannigan, L. H. and Tarbell, D. S., *J. Org. Chem.,* **1970**, *35*, 2339. (nn) Jenny, W. and Reiner, J., *Chimia,* **1970**, *24*, 69. (oo) Reiner, J. and Jenny, W., *Helv. Chim. Acta,* **1969**, *52*, 1624. (pp) Matuszak, C. A. and Niem, T. P.-F., *Chem. & Ind. (London),* **1969**, 952. (qq) Burnham, D. R., *Tetrahedron,* **1969**, *25*, 897. (rr) Rufer, C., *Ann.,* **1968**, *717*, 228. (ss) Phillips, D. K.; Wickham, P. P.; Potts, G. O. and Arnold, A., *J. Med. Chem.,* **1968**, *11*, 924. (tt) Camps, F.; Coll, J. and Pascual, J., *Anal. Quim.,* **1968**, *64*, 401. (uu) Masamune, T.; Kobayashi, K.; Takasugi, M.; Mori, Y. and Murai, A., *Tetrahedron,* **1968**, *24*, 3461. (vv) Remers, W. A. and Weiss, M. J., *Tetrahedron Lett*., **1968**, 81. (ww) Camps, F.; Coll, J. and Pascual, J., *J. Org. Chem.,* **1967**, *32*, 2563. (xx) Grewe, R.; Fischer, H. and Friedrichsen, W., *Chem. Ber.,* **1967**, *100*, 1. (yy) Fried, J.; Abraham, N. A. and Santhanakrishnan, T. S., *J. Am. Chem. Soc.,* **1967**, *89*, 1044. (zz) Mejer, S. and Respondek, S., *Bull. Acad. Polonaise Sci., Ser. Sci. Chim.,* **1966**, *14*, 611. (aaa) Brown, J. K.; Burnham, D. R. and Rogers, N. A. J., *Tetrahedron Lett*., **1966**, 2621. (bbb) Fentiman, A. F. and Poirier, R. H., *Chem. & Ind. (London),* **1966**, 813. (ccc) Hueckel, W.; Gupte, S. and Wartini, M., *Chem. Ber.,* **1966**, *99*, 1388. (ddd) Bensal, R. C.; Eisenbraun, E. J. and Flanagan, P. W., *J. Am. Chem. Soc.,* **1966**, *88*, 1837. (eee) Fried, J. and Abraham, N. A., *Tetrahedron Lett*., **1965**, 3505. (fff) Windholz, T. B.; Brown, R. D. and Patchett, A. A., *Steroids,* **1965**, *6*, 409. (ggg) Benkeser, R. A.; Burrous, M. I.; Hazdra, J. J. and Kaiser, E. M., *J. Org. Chem.,* **1963**, *28*, 1094. (hhh) Dryden, H. L.; Webber, G. M.; Burtner, R. R. and Cella, J. A., *J. Org. Chem.,* **1961**, *26*, 3237. (iii) Eliel, E. L. and Hoover, T. E., *J. Org. Chem.,* **1959**, *24*, 938. (jjj) Howell, F. H. and Taylor, D. A. H., *J. Chem. Soc.,* **1959**, 1607. (kkk) Huckel, W.; Graf, B. and Munkner, D., *Ann.,* **1958**, *614*, 47. (lll) Marchant, A. and Pinder, A. R., *Chem. & Ind. (London),* **1954**, 1261.

7. (a) Loewenthal, H. J. E. and Gottlieb, L., *J. Org. Chem.,* **1992**, *57*, 2631. (b) Marcinow, Z., *J. Chem. Res. (S),* **1991**, 186. (c) Smith, W. K.; Hardin, J. N. and Rabideau, P. W., *J. Org. Chem.,* **1990**, *55*, 5301. (d) Shimano, M.; Nagaoka, H. and Yamada, Y., *Chem. Pharm. Bull.,* **1990**, *38*, 276. (e) Marcinow, Z. and Rabideau, P. W., *J. Org. Chem.,* **1990**, *55*, 3812. (f) Rabideau,

P. W., *Tetrahedron,* **1989**, *45*, 1579. (g) Iwata, C.; Yamada, M.; Ida, Y.; Imao, T.; Miyagawa, H. and Miyashita, K., *Chem. Pharm. Bull.,* **1988**, *36*, 2864. (h) Gottlieb, L. and Loewenthal, H. J. E., *Tetrahedron Lett*., **1988**, *29*, 4473. (i) Marcinow, Z.; Sygula, A. and Rabideau, P. W., *J. Org. Chem.,* **1988**, *53*, 3603. (j) Marcinow, Z. and Rabideau, P. W., *J. Org. Chem.,* **1988**, *53*, 2117. (k) Toromanoff, E., *Bull. Soc. Chim. Fr.,* **1987**, 893. (l) Rabideau, P. W. and Karrick, G. L., *Tetrahedron Lett*., **1987**, *28*, 2481. (m) Holton, R. A. and Kennedy, R. M., *Tetrahedron Lett*., **1987**, *28*, 303. (n) De Vlieger, J. J.; Kieboom, A. P. G. and van Bekkum, H., *J. Org. Chem.,* **1986**, *51*, 1389. (o) Sasaki, S.; Grieco, P. A.; Huffman, J. C.; Callant, P. and Imamura, P. M., *J. Org. Chem.,* **1985**, *50*, 4880. (p) Bhattacharyya, S.; Basu, B. and Mukherjee, D., *Tetrahedron,* **1983**, *39*, 4221. (q) Rabideau, P. W. and Huser, D. L., *J. Org. Chem.,* **1983**, *48*, 4266. (r) Rabideau, P. W.; Husted, C. A. and Young, D. M., *J. Org. Chem.,* **1983**, *48*, 4149. (s) Huffman, J. W.; Desai, R. C. and LaPrade, J. E., *J. Org. Chem.,* **1983**, *48*, 1474. (t) Murthy, A. R.; Sundar, N. S. and Rao, G. S. R. S., *Tetrahedron,* **1982**, 38, 2831. (u) Sundar, N. S. and Rao, G. S. R. S., *J. Chem. Soc., Perkin Trans. I,* **1982**, 1381. (v) Rao, G. S. R. S. and Sundar, N. S., *J. Chem. Soc., Perkin Trans. I,* **1982**, 875. (w) Rabideau, P. W.; Peters, N. K. and Huser, D. L., *J. Org. Chem.,* **1981**, *46*, 1593. (x) Mejer, S.; Marcinow, Z. and Respondek, S., *Pol. J. Chem.,* **1980**, *54*, 2247. (y) Rabideau, P. W.; Burkholder, E. G. and Yates, M. J., *Synth. Commun.,* **1980**, *10*, 627. (z) Rabideau, P. W.; Huser, D. L. and Nyikos, S. J., *Tetrahedron Lett*., **1980**, *21*, 1401. (aa) Rabideau, P. W.; Nyikos, S. J.; Huser, D. L. and Burkholder, E. G., *J. Chem. Soc., Chem. Commun.,* **1980**, 210. (bb) Subba Rao, G. S. R.; Ramanathan, H. and Raj, K., *J. Chem. Soc., Chem. Commun.,* **1980**, 315. (cc) Subba Rao, G. S. R. and Shyama Sundar, N., *J. Chem. Res. (S),* **1979**, 282. (dd) Rabideau, P. W.; Jessup, D. W.; Ponder, J. W. and Beekman, G. F., *J. Org. Chem.,* **1979**, *44*, 4594. (ee) Coll Toledano, J. and Olivella, S., *Anal. Quim.,* **1979**, *75*, 107. (ff) Rabideau, P. W. and Burkholder, E. G., *J. Org. Chem.,* **1978**, *43*, 4283. (gg) Mejer, S. and Pacut, R., *Pol. J. Chem.,* **1978**, *52*, 529. (hh) Caine, D. and Smith, T. L., *J. Org. Chem.,* **1978**, *43*, 755. (ii) Mejer, S. and Marcinow, Z., *Roczniki Chemii*, **1977**, *51*, 1281. (jj) Butler, D. N., *Synth. Commun.,* **1977**, *7*, 441. (kk) Yamada, Y. and Nagaoka, H., *Synthesis,* **1977**, 577. (ll) Jessup, D. W.; Paschal, J. W. and Rabideau, P. W., *J. Org. Chem.,* **1977**, *42*, 2620. (mm) House, H. O. and Lusch, M. J., *J. Org. Chem.,* **1977**, *42*, 183. (nn) Birch, A. J. and Slobbe, J., *Aust. J. Chem.,* **1976**, *29*, 2737. (oo) Mejer, S. and Marcinow, Z., *Bull. Acad. Polonaise Sci., Ser. Sci. Chim.,* **1976**, *24*, 175. (pp) Wiberg, K. B.; Bailey, W. F. and Jason, M. E., *J. Org. Chem.,* **1976**, 41, 2711. (qq) Harvey, R. G.; Fu, P. P. and Rabideau, P. W., *J. Org. Chem.,* **1976**, *41*, 2706. (rr) Butler, D. N. and Koves, G., *Synth. Commun.,* **1975**, *5*, 471. (ss) Birch, A. J. and Slobbe, J., *Tetrahedron Lett*., **1975**, 627. (tt) Birch, A. J. and Lehman, P. G., *Tetrahedron Lett*., **1974**, 2395. (uu) Birch, A. J. and Lehman, P. C., *J. Chem. Soc., Perkin Trans. I,* **1973**, 2754. (vv) Harvey, R. G.; Lindow, D. F. and Rabideau, P. W., *J. Am. Chem. Soc.,* **1972**, *94*, 5412. (ww) Lindow, D. F.; Cortez, C. N. and Harvey, R. G., *J. Am. Chem. Soc.,* **1972**, *94*, 5406. (xx) Butler, D. N. and Milburn, R., *Can. J. Chem.,* **1972**, *50*, 1249. (yy) Harvey, R. G.; Lindow, D. F. and Rabideau, P. W., *Tetrahedron*, **1972**, *28*, 2909. (zz) Murphy, W. S. and Sullivan, D. F., *J. Chem. Soc., Perkin Trans. I,* **1972**, 999. (aaa) Harvey, R. G., *J. Org. Chem.,* **1971**, *36*, 3306. (bbb) Rabideau, P. W. and Harvey, R. G., *Tetrahedron Lett*., **1970**, 4139. (ccc) Harvey, R. G., *Synthesis,* **1970**, *2*, 161. (ddd) Rabideau, P. W. and Harvey, R. G., *J. Org. Chem.,* **1970**, *35*, 25. (eee) Harvey, R. G. and Davis, C. C., *J. Org. Chem.,* **1969**, *34*, 3607. (fff) Harvey, R. G. and Arzadon, L., *Tetrahedron,* **1969**, *25*, 4887. (ggg) Harvey, R. G.; Arzadon, L.; Grant, J. and Urberg, K., *J. Am. Chem. Soc.,* **1969**, *91*, 4535. (hhh) Birch, A. J. and Rao, G. S. R. S., *Aust. J. Chem.,* **1969**, *22*, 761. (iii) Jacobus, J. and Eastham, J. F., *Chem. Commun. (London),* **1969**, 138. (jjj) Coulombeau, A. and Rassat, A., *Chem. Commun. (London),* **1968**, 1587. (kkk) Huffman, J. W. and Charles, J. T., *J. Am. Chem. Soc.,* **1968**, *90*, 6486. (lll) Harvey, R. G. and Urberg, K., *J. Org. Chem.,* **1968**, *33*, 2206. (mmm) Harvey, R. G. and Urberg, K., *J. Org. Chem.,* **1968**, *33*, 2570. (nnn) Ortiz de Montellano, B. R.; Loving, B. A.; Shields, T. C. and Gardner, T. C., *J. Am. Chem. Soc.,* **1967**, *89*, 3365. (ooo) Svoboda, M.; Zavada, J. and Sicher, J., *Coll. Czech. Chem. Commun.,* **1965**, *30*, 413. (ppp) Brown, J. M., *Chem. & Ind. (London),* **1963**, 1689. (qqq) Phillips, D. K. and Manson, A. J., *J. Org. Chem.,* **1963**, *28*, 2886. (rrr) Devaprabhakara, D. and Gardner, P. D.,

J. Am. Chem. Soc., **1963**, *85*, 648. (sss) Birch, A. J.; Smith, H. and Thornton, R. E., *Chem. & Ind. (London),* **1956**, 1310.

8. (a) Chaussard, J.; Combellas, C. and Thiebault, A., *Tetrahedron Lett*., **1987**, *28*, 1173. (b) Verchere, C. and Viel, C., *J. Heterocycl. Chem.,* **1980**, *17*, 49. (c) Pernemalm, P. A. and Dence, C. W., *Acta Chem. Scand., Ser. B,* **1974**, *28*, 453. (d) Michailidis, A.; Brouard, J. P. and Resplandy, A., *Compt. Rend.,* **1972**, *275*, 961. (e) Przhiyalgovskaya, N. M. and Gaevskaya, S. R., *Zh. Org. Khim.,* **1970**, *6*, 2310.
9. Collins, C. J.; Hombach, H.-P.; Maxwell, B.; Woody, M. C. and Benjamin, B. M., *J. Am. Chem. Soc.,* **1980**, *102*, 851.
10. Möbitz, H. and Boll, M., *Biochemistry,* **2002**, *41*, 1752.
11. (a) Jacobus, O. J. and Eastham, J. F., *J. Am. Chem. Soc.,* **1965**, *87*, 5799. (b) Kelly, E. J.; Secor, H. V.; Keenan, C. W. and Eastham, J. F., *J. Am. Chem. Soc.,* **1962**, *84*, 3611. (c) Eastham, J. F.; Keenan, C. W. and Secor, H. V., *J. Am. Chem. Soc.,* **1959**, *81*, 6523. (d) Krapcho, A. P. and Bothner, A. A., *J. Am. Chem. Soc.,* **1959**, *81*, 3658.
12. Zimmerman, H. E., *Tetrahedron,* **1961**, *16*, 169.
13. Subba Rao, G. S. R., *Pure & Appl. Chem.,* **2003**, *75*, 1443.
14. Sinclair, S. and Jorgensen, W. L., *J. Org. Chem.,* **1994**, *59*, 762.
15. Boeckman, R. K. and Thomas, E. W., *J. Am. Chem. Soc.,* **1977**, *99*, 2805.
16. (a) Borondics, F.; Bokor, M.; Matus, P.; Tompa, K.; Pekker, S. and Jakab, E., *Fullerenes, Nanotubes, and Carbon Nanostructures,* **2005**, *13*, 375. (b) Pekker, S.; Salvetat, J.-P.; Jakab, E.; Bonard, J.-M. and Forró, L., *J. Phys. Chem., B,* **2001**, *105*, 7938.
17. Huang, P. Q.; Arseniyadis, S. and Husson, H.-P., *Tetrahedron Lett.,* **1987**, *28*, 547.
18. Bachmann, W. E., *J. Am. Chem. Soc.,* **1933**, *55*, 3005.
19. (a) Ziegler, K. and Thielmann, F., *Ber.,* **1923**, 56*B*, 2453. (b) Ziegler, K. and Thielmann, F., *Ber.,* **1923**, 56*B*, 1740.
20. (a) Hirama, M.; Oishi, T.; Uehara, H.; Inoue, M.; Maruyama, M.; Oguri, H. and Satake, M., *Science,* **2001**, *294*, 1904. (b) Kitano, K.; Sakata, S.; Kohgo, S.; Matsuoka, M.; Kodama, E.; Mitsuya, H. and Ohrui, H., *Nucleic Acids Symposium Ser.,* **2000**, *44*, 105.
21. Birch, A. J. and Nasipuri, D., *Tetrahedron,* **1959**, 148.
22. (a) Clive, D. L. J. and Sunasee, R., *Org. Lett.,* **2007**, *9*, 2677. (b) Lebeuf, R.; Robert, F. and Landais, Y., *Org. Lett.,* **2005**, *7*, 4557.
23. Swenson, K. E.; Zemach, D.; Nanjundiah, C. and Kariv-Miller, E., *J. Org. Chem.,* **1983**, *48*, 1777.
24. Pétrier, C. and Suslick, K., *Ultrason. Sonochem.,* **2000**, *7*, 53.
25. (a) Altundas, A.; Menzek, A.; Gultekin, D. D. and Karakaya, M., *Turk J. Chem.,* **2005**, *29*, 513. (b) Zvilichovsky, G. and Gbara-Haj-Yahia, I., *J. Org. Chem.,* **2004**, *69*, 5490. (c) Watanabe, H.; Yamaguchi, T.; Furuuchi, T.; Kido, M.; Bando, M. and Kitahara, T., *ARKIVOC,* **2003**, (*viii*), 267. (d) Böhm, C.; Austin, W. F. and Trauner, D., *Tetrahedron: Asymmetry,* **2003**, *14*, 71. (e) Overman, L. E.; Ricca, D. J. and Tran, V. D., *J. Am. Chem. Soc.,* **1997**, 119, 12031. (f) Saa, J. M.; Ballester, P., Deya, P. M.; Capo, M. and Garcias, X., *J. Org. Chem.,* **1996**, 61,1035. (g) Birch, A. J., *Steroids,* **1992**, *57*, 363. (h) Mander, L. N., *Synlett,* **1991**, 134. (i) Pacut, R. I. and Kariv-Miller, E., *J. Org. Chem.,* **1986**, *51*, 3468. (j) Kariv-Miller, E.; Swenson, K. E.; Lehman, G. K. and Andruzzi, R., *J. Org. Chem.,* **1985**, *50*, 556. (k) Birch, A. J.; Hinde, A. L. and Radom, L., *J. Am. Chem. Soc.,* **1981**, *103*, 284. (l) Haruna, M. and Ito, K., *J. Chem. Soc., Chem. Commun.,* **1976**, 345. (m) Pine, M. J., *Antimicro. Agents & Chemother.,* **1975**,7, 601. (n) Kotlarek, W., *J. Org. Chem.,* **1975**, *40*, 2841. (o) Marshall, J. L. and Song, B.-H., *J. Org. Chem.,* **1974**, *39*, 1342.

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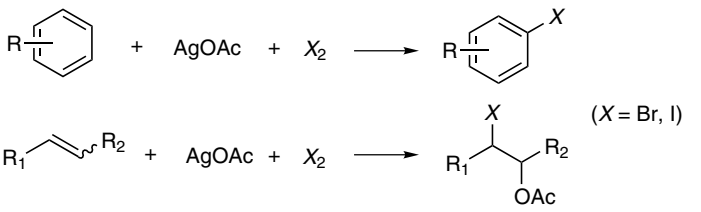
Birckenbach-Goubeau Halogenation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Birckenbach and Boubeau in 1932.[1] It is the halogenation of aromatic compounds with halide cations generated from halogen and silver perchlorate under anhydrous conditions. Especially when silver acetate is employed as the silver salt and acetic acid as the reaction medium, many aryl aliphatic acids can be halogenated.[2] In addition, the halogen cations can also be produced by mixing halogen with other metal halides (gold, copper, mercury, etc.), such as the iodination of cyclohexene in anhydrous ether with iodine and a slight excess of cuprous chloride to form *trans*-1-chloro-2-iodocyclohexane in an 80% yield.[3,4] However, when cyclohexene was treated with iodine and silver acetate at −80°C, 2-iodo-1-cyclohexanol acetate was produced.[4] Similarly, the mixture of bromine and silver acetate is an effective aromatic bromination agent and is an agent for converting alkenes to bromoacetates.[5]

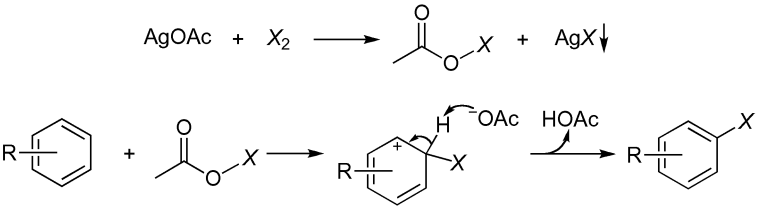
B. GENERAL REACTION SCHEME



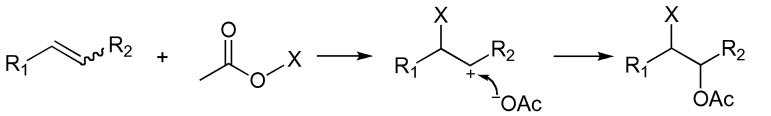
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

It is believed that acetyl hyperbromite[5] or hyperiodite[6] is formed as an intermediate when bromine or iodine reacts with silver acetate, giving bromine or iodine cation. Positive iodine has been stabilized via coordination with pyridine.[7] Therefore, a tentative mechanism is illustrated here.



In the case of reaction with alkenes, it will be:



D. MODIFICATION

Besides the original silver salt, different metal salts have been used in this reaction, including the salts of mercury,[5,8] gold,[9] copper,[9,10] and even zinc.[5]

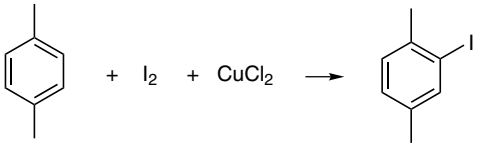
E. APPLICATIONS

This reaction can be used to prepare brominated or iodinated aromatic compounds or dihaloalkanes; the latter is produced from the mixture of metal halide and halogen with alkenes.[3,4]

F. RELATED REACTIONS

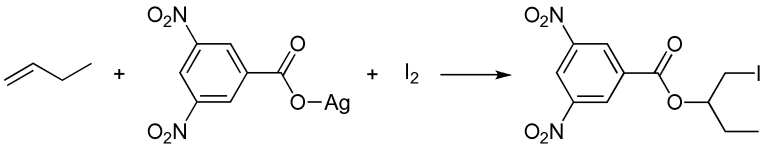
This reaction is related to the *Simonini Reaction* and *Hunsdiecker Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 10.

To a 500-mL flask equipped with a Teflon paddle stirrer and a reflux condenser was placed 70 mL xylene, 13.0 g iodine (0.05 mol), and 13.3 g $CuCl_2$ (0.1 mol). The reaction was stirred at 140°C for 5 h. The reaction mixture was cooled and filtered, and the filtrate was washed with 100 mL 20% sodium thiosulfate solution to discharge any residual iodine. The filtrate was dried over magnesium sulfate, the solution was filtered, and the excess xylene was removed on a rotary evaporator at 60°C (13 mmHg) to give 22.8 g of crude product, which was distilled to afford 19.8 g iodoxylenes, in a yield of 85%, b.p. 65–72°C (0.2 mmHg).



Reference 11.

To a mixture of 75 mL dry chloroform and 9.5 g silver 3,5-dinitrobenzoate (0.03 mol) cooled in an ice-salt mixture a solution of 0.03 mol iodine dissolved in 20 mL dry chloroform was added over 10–15 min with shaking. 1-Butene was then passed into the solution for 15 min with continuous shaking. The solid silver iodide that precipitated was removed, and the filtrate was washed with six 25-mL portions of 5% sodium carbonate solution. The chloroform solution was then dried over Drierite, the chloroform was removed by distillation, and boiling petroleum ether was added to dissolve the ester. The solution was then cooled, and 1-iodo-2-butanol 3,5-dinitrobenzoates was removed and purified by recrystallization from petroleum ether, in a yield of 46%.

Other references related to the Birckenbach-Goubeau halogenation are cited in the literature.[12]

H. REFERENCES

1. Birckenbach, L. and Goubeau, J., *Ber.*, **1932**, *65*, 395.
2. Birckenbach, L. and Goubeau, J., *Ber.*, **1933**, *66*, 1280.
3. Birckenbach, L. and Goubeau, J., *Ber.*, **1934**, *67*, 1420.
4. Birckenbach, L.; Goubeau, J. and Berninger, E., *Ber.,* **1932**, 65, 1339.
5. Hatanaka, Y.; Keefer, R. M. and Andrews, L. J., *J. Am. Chem. Soc.,* **1965**, *87*, 4280.
6. Birckenbach, L.; Goubeau, J. and Kolb, H., *Ber.,* **1934**, *67*, 1729.
7. (a) Colton, E., *J. Am. Chem. Soc.,* **1955**, *77*, 6190. (b) Zingaro, R. A.; Vanderwerf, C. A. and Kleinberg, J., *J. Am. Chem. Soc.,* **1950**, *72*, 5341.
8. Chen, E. M.; Keefer, R. M. and Andrews, L. J., *J. Am. Chem. Soc.,* **1967**, *89*, 428.
9. Baird, W. C.; Surridge, J. H. and Buza, M., *J. Org. Chem.,* **1971**, *36*, 2088.
10. Baird, W. C. and Surridge, J. H., *J. Org. Chem.,* **1970**, *35*, 3436.
11. Halperin, B. I.; Donahoe, H. B.; Kleinberg, J. and Vanderwerf, C. A., *J. Org. Chem.,* **1952**, *17*, 623.
12. (a) Woodward, R. B. and Brutcher, F. V., *J. Am. Chem. Soc.,* **1958**, *80*, 209. (b) Johnson, R. G. and Ingham, R. K., *Chem. Rev.,* **1956**, *56*, 219. (c) Janssen D. E., and Allen J., *J. Org. Chem.*,

1955, *20*, 1328. (d) Anbar, M. and Ginsburg, D., *Chem. Rev.,* **1954**, *54*, 925. (e) Crawford, G. H. and Simons, J. H., *J. Am. Chem. Soc.,* **1955**, *77*, 2605. (f) Abbott, D. C. and Arcus, C. L., *J. Chem. Soc.,* **1952**, 1515. (g) Dauben, W. G. and Tilles, H., *J. Am. Chem. Soc.,* **1950**, *72*, 3185. (h) Derbyshire D. H. and Waters W. A.,*J. Am. Chem. Soc.*, **1950**, *72*, 564, 573, 3694. (i) Arcus, C. L.; Campbell, A. and Kenyon, J., *J. Chem. Soc.,* **1949**, 1510. (j) Cason, J. and Way, R. L., *J. Org. Chem.,* **1949**, *14*, 31. (k) Doering, W. von E. and Farber, M., *J. Am. Chem. Soc.,* **1949**, *71*, 1514. (l) Arnold, R. T. and Morgan, P., *J. Am. Chem. Soc.,* **1948**, *70*, 4248. (m) Kleinberg, J., *Chem. Rev*., **1947**, *41*, 381. (n) Luttringhaus, A. and Schade, D., *Ber.,* **1941**, *74*, 1565. (o) Allen, C. F. H. and Wilson, C. V., *Org. Synth. Coll. 3*, **1955**, 578. (p) Birchenbach, L. and Meisenheimer, K., *Ber.,* **1936**, *69*, 723. (q) Bockemüller, W. and Hoffmann, F. W., *Ann.,* **1935**, *619*, 165. (r) Birckenbach, L.; Kellermann, K. and Stein, W., *Ber.,* **1932**, *66*, 1071. (s) Birckenbach, L. and Senxewald, K., *Ber.,* **1932**, *66*, 546.

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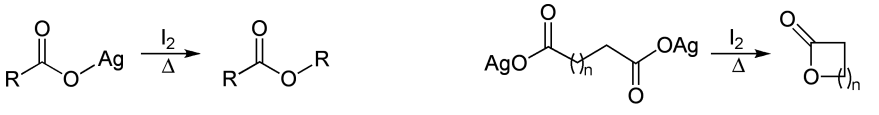
Birnbaum-Simonini Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction has initially been reported by Birnbaum[1] in 1869 and subsequently by Simonini[2] in 1892. It is the reaction for preparing esters by heating a mixture of silver salts of carboxylic acids and iodine and is generally known as the Birnbaum-Simonini reaction.[3] For comparison, the silver salts of dicarboxylic acids will form lactones when heated together with iodine.[4] Because of the cost and inconvenience of preparing and drying the silver salts, this reaction has been improved by heating the mixture of halogen with lead tetra-salts of carboxylic acids, giving comparable yields.[5] Such oxidative formation of esters from metal salts of carboxylic acids[1,2,3,5] has also been modified to the oxidation of carboxylic acids themselves,[6] and their corresponding peracids and peranhydrides.[7] However, in the presence of olefin, no ester is formed.[5]

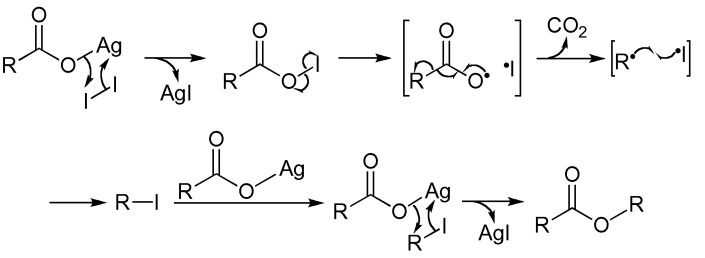
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is believed that carboxyl hyperiodite is formed as an intermediate, which might decompose to give alkyl radical after decarboxylation, as illustrated here.

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang



D. MODIFICATION

This reaction has been modified for preparing esters from a reaction between lead tetra-salts of carboxylic acids and iodine.[5] In this reaction, the mixture will be heated to $>100^{\circ}C$ to prevent caking or gelling of the reaction mixture; and *sym*-tetrachloroethane, *o*-dichlorobenzene, and mineral can be used as solvent. The yields depend markedly on the structure of the acid. For example, straight-chained aliphatic acids react quite satisfactorily, and the yields increase with the molecular weight of the acid. Unsaturated fatty acids give tars, and benzoic acid gives iodobenzene; fatty acids with one or two α-alkyl groups give diminished yields or no ester at all, respectively.

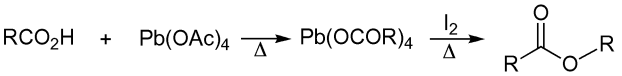
E. APPLICATIONS

This reaction can be used to prepare esters from carboxylic acids.

F. RELATED REACTIONS

This reaction is related to the *Birckenbach-Goubeau Halogenation* and *Hunsdiecker Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



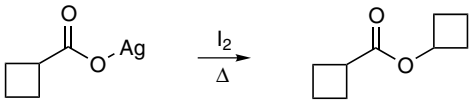
Reference 5.

Preparation of Lead Tetra-Salts

Lead tetraacetate (0.25 mol) and 1 mol of a carboxylic acid were heated together at 60–80°C, and the acetic acid was distilled at 10 mmHg pressure as it formed. The product was pure enough for further reactions without other treatment. When the lead tetra-salt melted > 80–100°C, a solvent, such as 1,1,2,2-tetrachloroethane, *o*-dichlorobenzene, or mineral oil, was used to prevent caking and local superheating of the product.

Generalized Preparation of Esters

A mixture of 0.25 mol of lead tetra-salt, 300 mL solvent, and 0.125 mol iodine was heated until gas evolution began and was maintained at 85–105°C until gas evolution ceased (~20 min). The temperature was then raised to 150–200°C (depending on the boing points of the solvent and alkyl iodide) for ~1 h. The workup of the reaction mixture depended on the relative boiling points of the solvent and the ester. For higher-boiling solvents, the ester was distilled from the reaction mixture, washed with dilute sodium carbonate solution, dried, and fractionated through a short column. For lower-boiling solvents, the solvent was distilled, the residue was triturated with 300 mL ether, filtered to remove lead salts. Then the ether solution was washed with sodium carbonate solution and sodium thiosulfate solution, dried, and fractionally distilled. For high-boiling esters, the product was not distilled but was recrystallized from a suitable solvent. Recovery of free carboxylic acids was accomplished by acidifying the sodium carbonate wash solutions with mineral acid and distilling or recrystallizing the nonaqueous phase that separated. For the case of lauric acid, the yield is 54%.



Reference 8.

Iodine (22 g) and 36.0 g silver cyclobutanecarboxylate (0.18 mol) were thoroughly ground with 1 g powdered, soft glass in a mortar. This mixture was rapidly transferred to a dry 2-L long-necked flask and warmed on the steam cone. At ~90°C, a vigorous reaction occurred, with the evolution of carbon dioxide and condensation of liquid on the walls of the flask. The reaction mixture was heated for an additional 30 min at 100°C. The liquid products were then lyophilized into a dry ice trap and taken up in ether. The ethereal solution was washed with 0.5 M sodium bisulfite solution and 1% sodium bicarbonate solution, water and dried over anhydrous magnesium sulfate. The ether was removed through a glass helix-packed column. The residue was fractionated through a microcolumn and yielded 1.1 g ester mixture, in yield of 8%, b.p. 92.5–93.5°C (20 mmHg).

Other references related to the Birnbaum-Simonini reaction are cited in the literature.[9]

H. REFERENCES

1. Birnbaum K., *Ann.*, **1869**, *152*, 111.
2. (a) Simonini A., *Monatsh.*, **1892**, *13*, 320. (b) Simonini A., *Monatsh.*, **1893**, *14*, 81.
3. (a) Mikulski, J. and Eckstein, Z., *Bull. Acad. Polonaise Sci., Ser. Sci. Chim.,* **1961**, *9*, 425. (b) Eckstein, Z. amd Mikulski, J., *Bull. Acad. Polonaise Sci., Ser. Sci. Chim.,* **1961**, *9*, 785. (c) Eckstein, Z.; Mikulski, J. and Sobotka, W., *Roczniki Chemii,* **1959**, *33*, 77. (d) Eckstein, Z.; Mikulski, J. and Sobotka, W., *Bull. Acad. Polonaise Sci., Classe III,* **1957**, *5*, 1085. (e) Darzens, G. and Meyer, M., *Compt. Rend.,* **1953**, *237*, 1334.
4. Winston, A.; Youngblood, G. T. and Wilder, P., *J. Org. Chem.,* **1957**, *22*, 876.
5. Bachman, G. B. and Wittmann, J. W., *J. Org. Chem.,* **1963**, *28*, 65.
6. Bacon, R. and Batt, R., *Chem. Ind. (London),* **1953**, 1287.

7. (a) Lau, H. H. and Hart, H., *J. Am. Chem. Soc.,* **1959**, *81*, 4897. (b) Walling, C., *Free Radicals in Solution*, John Wiley & Sons, Inc., New York, N.Y. **1957**, p. 491. (c) Swern, D., *Chem. Rev.,* **1949**, *45*, 1.

8. Roberts, J. D. and Simmons, H. E., *J. Am. Chem. Soc.,* **1951**, *73*, 5487.

9. (a) Bunce N. J. and Murray N. G.,*Tetrahedron*, **1971**, *71*, 5323. (b) Johnson, R. G. and Ingham, R. K., *Chem. Rev*., **1956**, *56*, 219. (c) Wilson, C., *Org. React*., **1956**, *9*, 332. (d) Oldham, J. W. H., *J. Chem. Soc.,* **1950**, 100. (e) Kleinberg, J., *Chem. Rev.,* **1947**, *41*, 381. (f) Demjanov, N. J., *J. Russ. Phys. Chem. Soc.,* **1929**, *61*, 1861. (g) Demjanov, N. J. and Dojarenko, M., *Ber.,* **1907**, *40*, 2594. (h) Birnbaum, K. and Reinherz, H., *Ber.,* **1882**, *15*, 456. (i) Birnbaum, K. and Gaier, J., *Ber.,* **1880**, *13*, 1270.

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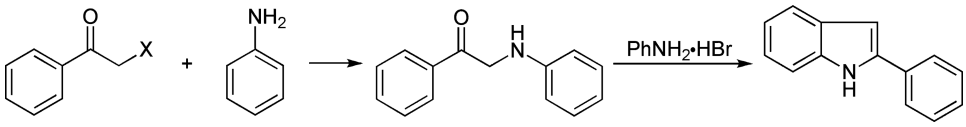
Bischler Reaction

(Möhlau-Bischler Indole Synthesis, Möhlau-Bischler Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Möhlau in 1881[1] and subsequently by Bischler in 1892.[2] It is the reaction for preparing 2-substituted indoles by heating α-haloketone, α-hydroxyketone, or α-anilinoketone with excess aniline via the cyclization of a 2-arylaminoketone intermediate. Therefore, this reaction is known as the Bischler reaction,[3] Mohlau-Bischler indole synthesis,[4] Mohlau-Bischler reaction,[5] or Mohlau-Bischler synthesis.[6] This reaction has been used for the preparation of a number of tetrahydrocarbazoles from anilines and 2-chlorocyclohexanones[7] and *N*-substituted indole-3-acetic acids and acetamides, which are useful for the preparation of tryptamines.[8] In addition, this reaction can be applied to the synthesis of benzofuran and benzothiophene.

B. GENERAL REACTION SCHEME



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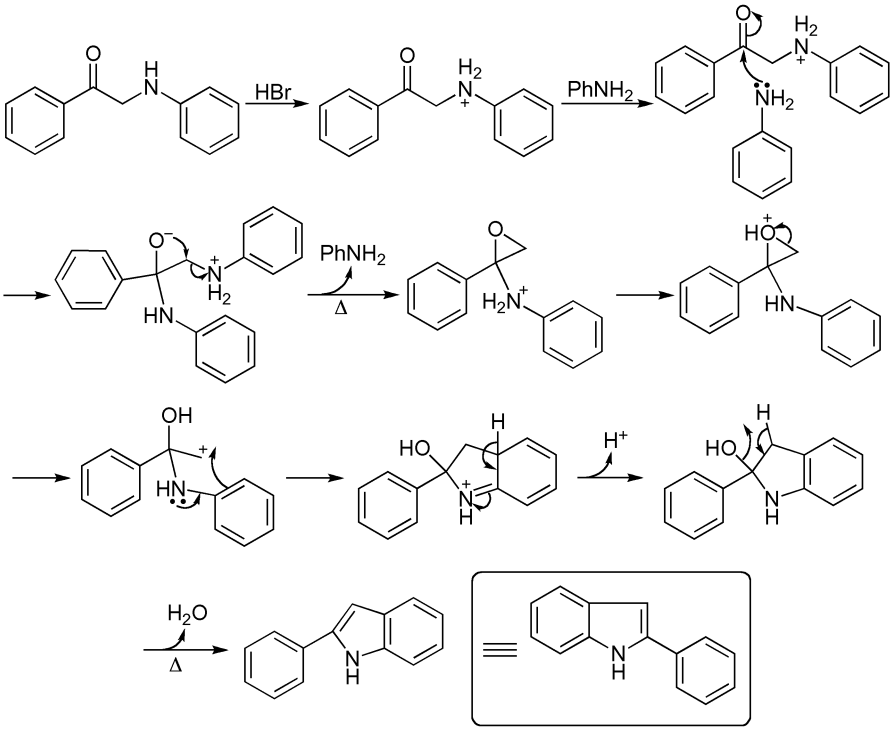
C. PROPOSED MECHANISMS

It is believed that this reaction occurs via a carbocation intermediate, as illustrated below.[9]



D. MODIFICATION

This reaction has been modified to react with α-chlorocyclohexanone.[7]

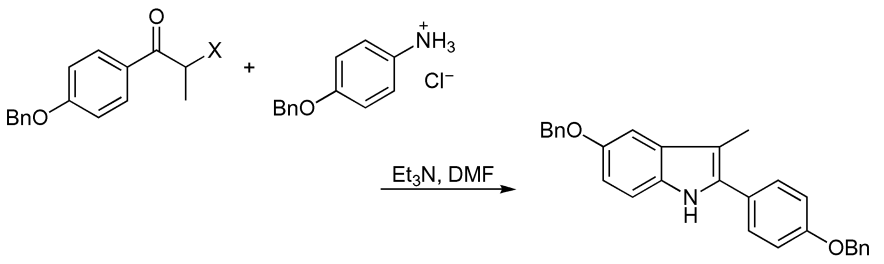
E. APPLICATIONS

This reaction is generally used to synthesize 2-substituted indoles; in addition, this reaction can also be used to prepare benzofuran, benzothiophene, and tetrahydrocarbazoles.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES

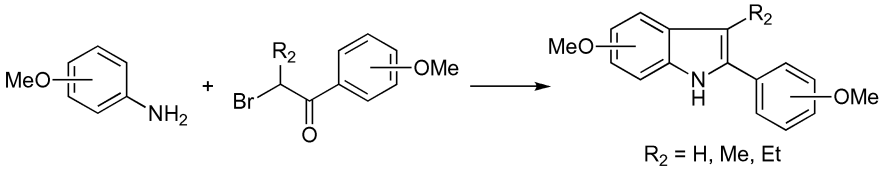


Reference 10.

To a flask were added 45.0 g 4-benzyloxyaniline hydrochloride (0.23 mol), 21.0 g 4′-benzyloxy-2-bromophenylpropiophenone (0.066 mol), and 50 mL DMF. The reaction was refluxed for 30 min and then cooled to room temperature and then partitioned between EtOAc and 1 N HCl. The EtOAc was washed with $NaHCO_3$ and brine, then dried over $MgSO_4$. The solution was concentrated, and the residue was taken up in CH_2Cl_2; hexanes were added to precipitate out 25.0 g of a crude solid. The solid was dissolved in CH_2Cl_2, evaporated onto silica gel, and chromatographed using CH_2Cl_2/hexane (1:5) to yield 9.2 g 2-phenyl-3-methyl-1H-indole as a tan solid, in a yield of 33%, m.p. 150–152°C.

Two-Step/One-Pot Procedure

Bromophenylpropiophenone (50 g, 0.16 mol) in 200 mL DMF was treated with 44.0 g aniline hydrochloride, and the reaction was purged with nitrogen for ∼10 min. Triethylamine (54.6 mL) was added, and the reaction was heated at 120°C for 2 h. TLC analysis (EtOAc/hexanes) showed the starting material had disappeared, forming a more polar spot. The reaction mixture was allowed to cool down, and an additional 48.0 g of the aniline hydrochloride was added. The reaction was heated to 150°C for 2 h. An additional 5.0 g of the aniline hydrochloride was added, and the reaction was heated at 150°C for an additional 30 min. The reaction mixture was allowed to cool to room temperature and then poured into ∼1.5 L water and extracted with 2 L EtOAc. The solids were dissolved with additional EtOAc as necessary. The EtOAc layer was washed with 1 L 1 N NaOH, 1 L water, and brine, then dried over $MgSO_4$ and filtered. The organic layers were concentrated down to yield a crude solid that was stirred with 500 mL of methanol and filtered. This solid was then stirred with 500 mL ethyl ether and filtered. The solid was stirred alternatively with methanol and ether until it was of whitish color and had a melting point of > 150°C. Reaction gave 36.0 g 2-phenyl-3-methyl-1H-indole, in a yield of 51%.



Reference 11.

General Procedure for Preparation of Methoxy-2-(Methoxypheny1)-1H-Indoles

A solution of 0.06 mol (2-bromoacy1)anisole was added slowly to a boiling mixture of 0.2 mol methoxyaniline and 35 mL *N*,*N*-dimethylaniline with stirring. After the addition, the mixture was kept at 170°C in a bath. After cooling, EtOAc was added and the mixture was extracted with 2 N HCl. The aqueous layer was extracted several times with EtOAc. After washing with 2 N HCl and water, the organic layer was dried over $MgSO_4$. The solvent was removed in vacuo and the resulting residue was chromatographed over SiO_2 with CH_2Cl_2 as the eluent. The product was recrystallized from EtOH, affording colorless crystals in a 10–50% yield.

Other references related to the Bischler reaction are cited in the literature.[12]

H. REFERENCES

1. (a) Möhlau, R., *Ber.,* **1881**, *14*, 171. (b) Möhlau, R., *Ber.,* **1882**, *15*, 2480.
2. (a) Bischler, A., *Ber.,* **1892**, *25*, 2860. (b) Bischler, A., *Ber.,* **1893**, *26*, 1336.
3. Bancroft, K. C. C.; Ward, T. J. and Brown, K., *J. Chem. Soc., Perkin Trans. I,* **1974**, 1852.
4. Nelson, K. L.; Robertson, J. C. and Duvall, J. J., *J. Am. Chem. Soc.,* **1964**, *86*, 684.
5. Buu-Hoi, N. P.; Saint-Ruf, G.; Deschamps, D.; Bigot, P. and Hieu, H. T., *J. Chem. Soc. C,* **1971**, 2606.
6. Bigot, P.; Saint-Ruf, G. and Buu-Hoi, N. P., *J. Chem. Soc., Perkin Trans. I,* **1972**, 2573.
7. (a) Campaigne, E. and Lake, R. D., *J. Org. Chem.,* **1959**, *24*, 478. (b) Ott, K., *German Pat.*, **1923**, Apr, 19, 374098 [*Chem. Abstr*., **1924**, *18*, 2175].
8. Revial, G.; Tabin, I.; Lim, S. and Pfau, M., *J. Org. Chem.,* **2002**, *67*, 2252.
9. Nelson, K. L. and Seefeld, R. L., *J. Am. Chem. Soc.,* **1958**, *80*, 5957.
10. Miller, C. P.; Collini, M. D.; Tran, B. D.; Harris, H. A.; Kharode, Y. P.; Marzolf, J. T.; Moran, R. A.; Henderson, R. A.; Bender, R. H. W.; Unwalla, R. J.; Greenberger, L. M.; Yardley, J. P.; Abou-Gharbia, M. A.; Lyttle, C. R. and Komm, B. S., *J. Med. Chem.,* **2001**, 44,1654.
11. Von Angerer, E.; Prekajac, J. and Strohmeier, J., *J. Med. Chem*., **1984**, *27*, 1439.
12. (a) Shikhaliev, K. S.; Leshcheva, E. V. and Solovév, A. S., *Chem. Heterocyclic Comp.*, **2003**, *39*, 335. (b) Bashford, K. E.; Cooper, A. L.; Kane, P. D.; Moody, C. J.; Muthusamy, S. and Swann, E., *J. Chem. Soc.*, *Perkin Trans. 1*, **2002**, 1672. (c) Gribble, G. W., *J. Chem. Soc*., *Perkin Trans. I*, **2000**, 1045. (d) Moody, C. J. and Swann, E., *Synlett*, **1998**, 135. (e) Henry, J. R. and Dodd, J. H., *Tetrahedron Lett.,* **1998**, *38*, 8763. (f) Brown, R. K., *Synthesis of the Indole Nucleus*, in *Chemistry of Heterocyclic Compounds*, ed. Weissberger, A. and Taylor, E. C., John Wiley & Sons, Chichister, **1972**, p. 317. (g) Sundberg, R. J., *The Chemistry of Indoles*, Academic Press, New York, **1970**, p. 164. (h) Morelli, G. and Stein, M. L., *J. Med. Chem*., **1960**, *2*, 79. (i) Weygand, F. and Richter, E., *Ber.,* **1955**, *88*, 499. (j) Julian, P. L.; Meyer, E. W. and Printy, H. C., *The Chemistry of Indole*, in *Heterocylic Compounds*, ed. Elderfield, R. C., John Wiley & Sons, New York, **1952**, *3*, pp. 22–35. (k) Mentzer, C.; Molho, D. and Berguer, J., *Bull. Soc. Chim. Fr.*, **1950**, *17*, 55. (l) Bradsher, C. K., *Chem. Rev.,* **1946**, *38*, 447. (m) Julian, P. L. and Pikl, J., *J. Am. Chem. Soc.,* **1933**, *55*, 2105. (n) Fischer, E and Schmitt, T., *Ber*., **1888**, *21*, 1071.

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Bischler-Napieralski Isoquinoline Synthesis

(Bischler-Napieralski Reaction; Bischler-Napieralski Cyclization)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Bischler and Napieralski in 1893.[1] It is a two-step reaction via the cyclization of *N*-acyl phenylethylamines with dehydrating agents to form 1-alkyl or 1-aryl 3,4-dihydroisoquinolines, followed by dehydrogenation or oxidation to afford isoquinolines.[2] Thus this reaction is generally known as the Bischler-Napieralski isoquinoline synthesis,[3] Bischler-Napieralski reaction[4] or Bischler-Napieralski cyclization.[5] The dehydrating agents used include phosphoric acid,[6] sulfonic acid derivative,[6] phosphorus oxychloride ($POCl_3$),[6,7] phosphorus pentoxide,[8,9] zinc chloride,[9] aluminum chloride,[9] and ferric chloride[9]. This reaction has been successfully used to synthesize numerous naturally occurring alkaloids, that including laudanosine, laudanine, and papaverine; cotarnine[10] and hydrastinine; salsoline, pectenine, and corypallin; the anhalonium alkaloids;[9] and takatonine[7f] and petaline.[7e] This reaction is generally carried out in boiling toluene or xylene in the presence of the listed dehydrating agents,[9] but it can be carried out in low boiling point solvents such as acetonitrile[7c] or dichloromethane[7e,7f] as well. In addition, this reaction can be used to synthesize thiophene derivatives.[11]

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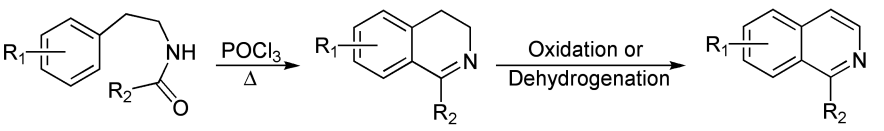
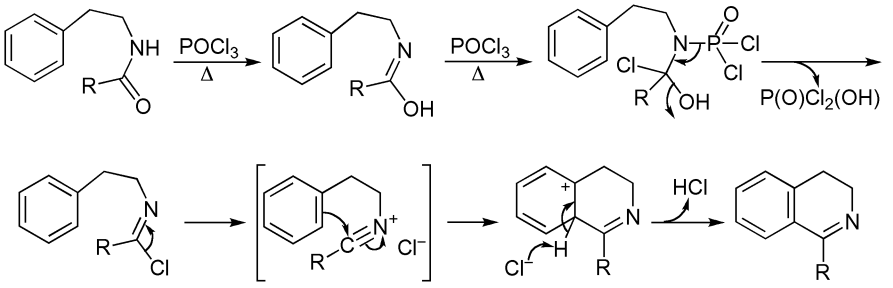
B. GENERAL REACTION SCHEME



(R_1 = alkyl, aryl, halogen, etc.
R_2 = alkyl, aryl)

C. PROPOSED MECHANISMS

It is believed that this reaction proceeds via initial formation of hydrochloric salts of imidoyl chloride when $POCl_3$, PCl_5, or $SOCl_2$ is used as a reagent, followed by the formation of imidoyl chloride by the loss of hydrogen chloride, which is in equilibrium with nitrilium salt.[12] Then the 3,4-dihydroisoquinoline is formed via the ring closure of nitrilium salt, as indicated in the direct formation of such dihydroisoquinoline via alkylation of nitrile with phenylethyl halide in the presence of a Lewis acid.[13] An exemplary mechanism of the Bischler-Napieralski reaction is illustrated here.



D. MODIFICATION

This reaction has been modified to occur in a solvent such as CH_3CN[7c] and CH_2Cl_2.[7e,7f] The synthesis of thiophene analogues of isoquinolines is another modification.[11]

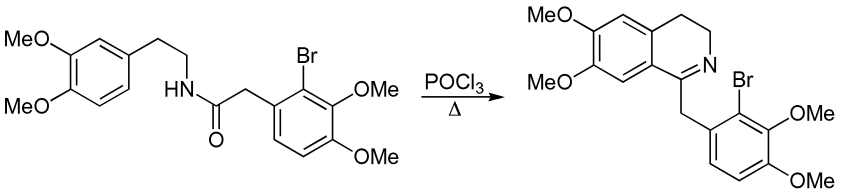
E. APPLICATIONS

This reaction has general applications in the preparation of alkaloids containing an isoquinoline skeleton.[7e,7f,9,10]

F. RELATED REACTIONS

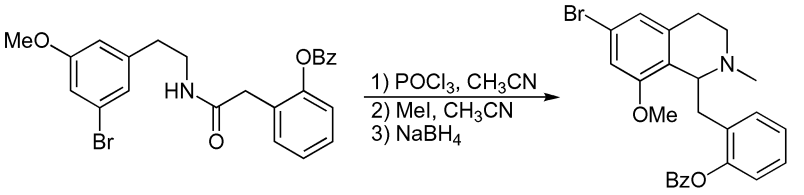
This reaction is related to the *Bradsher Pyridinium Salt Synthesis*, *Pictet-Gams Synthesis, Pictet-Spengler Reaction*, and *Skraup Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 14.

A mixture of 7.013 g *N*-(3,4-dimethoxyphenethyl)-2-bromo-3,4-dimethoxyphenylacetamide (16 mmol), 12.240 g $POCl_3$ (80 mmol), and 100 mL dry toluene (100 mL) was refluxed under nitrogen for 3 h. The cooled mixture was poured into 100 mL ice water and stirred for 2 h. The organic layer was discarded. The water layer and precipitates were then basified with 200 mL 2 N NaOH and extracted with CH_2Cl_2 (50 mL × 3). The extracts were washed with 100 mL water, dried over Na_2SO_4, and evaporated to give 5.731 g 1-(2-bromo-3,4-dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline as a solid, in a yield of 85%, m.p. 120–124°C. Recrystallization from benzene-Et_2O gave an analytical sample, m.p. 123–125°C; R_f = 0.15 on silica gel TLC plate (5% MeOH in CH_2Cl_2).



Reference 15.

A solution of 300 mg *N*-(3-bromo-5-methoxyphenethyl)-2-benzyloxyphenylacetamide (0.66 mmol) in 5.5 mL dry acetonitrile was treated with 0.6 mL phosphoryl chloride and refluxed under nitrogen for 1 h; the solvent was evaporated off, and the excess of reagent was removed in vacuo. A solution of the residue in $CHCl_3$ was rapidly washed with 1 N NaOH and H_2O, dried, and evaporated under reduced pressure. The unstable 3,4-dihydrobenzylisoquinoline was refluxed with 1.05 mL MeI (17 mmol) in 4 mL acetonitrile under nitrogen for 3 h. Evaporation gave the crude alkylammonium iodide, which was reduced in 1.1 mL $CHCl_3$ and 6.6 mL CH_3OH by adding 200 mg $NaBH_4$ (5.3 mmol) in

portions and then stirring for 30 min at room temperature. The solvent was evaporated off, H_2O was added, and the mixture was extracted with $CHCl_3$. The organic phase was dried, and the residue was chromatographed on silica gel, eluting with ethyl acetate, to afford 75 mg 1-(2-benzyloxybenzyl)-6-bromo-8-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, in a yield of 25%, $R_f = 0.26$ (EtOAc).

Other references related to the Bischler-Napieralski isoquinoline synthesis are cited in the literature. [16]

H. REFERENCES

1. Bischler, A. and Napieralski, B., *Ber*., **1893**, *26*, 1903.
2. Bergstrom, F. W., *Chem. Rev.,* **1944**, *35* 77.
3. (a) Doi, S.; Shirai, N. and Sato, Y., *J. Chem. Soc., Perkin Trans. I,* **1997**, 2217. (b) Fujitani, I. K. and Kishimoto, T., *J. Pharm. Soc. Jpn.,* **1964**, *84*, 329. (c) Fujitani, K.; Matsumoto, N.; Yoshioka, K.; Yoshida, I. and Inubushi, Y., *J. Pharm. Soc. Jpn.,* **1964**, *84*, 333.
4. (a) Hashimoto, N.; Miyatani, K.; Ohkita, K.; Ohishi, Y.; Kunitomo, J.-I.; Kawasaki, I.; Yamashita, M. and Ohta, S., *Heterocycles,* **2002**, *57*, 2149. (b) Croisy-Delcey, M.; Huel, C. and Bisagni, E., *J. Heterocycl. Chem.,* **1988**, *25*, 661. (c) Goszczynski, S. and Zielinski, W., *Roczniki Chemii,* **1970**, *44*, 109. (d) Ishiwata, S. and Itakura, K., *Chem. Pharm. Bull.,* **1969**, *17*, 2261. (e) Ishiwata, S. and Itakura, K., *Chem. Pharm. Bull.,* **1968**, *16*, 778. (f) Morimoto, Y., *Jpn. J. Pharmacology,* **1962**, *82*, 459. (g) Morimoto, Y., *Jpn. J. Pharmacology,* **1962**, *82*, 395. (h) Morimoto, Y., *Jpn. J. Pharmacology,* **1962**, *82*, 386.
5. (a) Sotomayor, N.; Dominguez, E. and Lete, E., *J. Org. Chem.,* **1996**, *61*, 4062. (b) Kametani, T.; Takagi, N.; Kanaya, N. and Honda, T., *Heterocycles,* **1982**, *19*, 535. (c) Kessar, S. V.; Jit, P.; Mundra, K. P. and Lumb, A. K., *J. Chem. Soc. C,* **1971**, 266.
6. Ishikawa, T.; Shimooka, K.; Narioka, T.; Noguchi, S.; Saito, T.; Ishikawa, A.; Yamazaki, E.; Harayama, T.; Seki, H. and Yamaguchi, K., *J. Org. Chem*., **2000**, *65*, 9143.
7. (a) Orito, K.; Miyazawa, M.; Kanbayashi, R.; Tokuda, M. and Suginome, H., *J. Org. Chem.,* **1999**, *64*, 658. (b) Couture, A.; Deniau, E.; Lebrun, S.; Grandclaudon, P. and Carpentier, J.-F., *J. Chem. Soc., Perkin Trans. I,* **1998**, 1403. (c) Ambros, R.; Schneider, M. R. and von Angerer, S., *J. Med. Chem.,* **1990**, *33*, 153. (d) Lida, H.; Aoyagi, S. and Kibayashi, C., *J. Chem. Soc., Perkin Trans. I,* **1975**, 2502. (e) Kametani, T.; Kobari, T.; Fukimoto, K. and Fujihara, M., *J. Chem. Soc. C,* **1971**, 1796. (f) Kubota, S.; Masui, T.; Fujita, E. and Kupchan, S. M., *J. Org. Chem.,* **1966**, *31*, 516.
8. Griffith, R. C.; Gentile, R. J.; Robichaud, R. C. and Frankenheim, J., *J. Med. Chem.,* **1984**, *27*, 995.
9. Manske, R. H., *Chem. Rev.,* **1942**, *30*, 145, and references therein.
10. Shirasaka, T.; Takuma, Y.; Shimpuku, T. and Imaki, N., *J. Org. Chem.,* **1990**, *55*, 3767.
11. (a) Herz, W. and Tsai, L., *J. Am. Chem. Soc.,* **1955**, *77*, 3529. (b) Herz, W., *J. Am. Chem. Soc.,* **1951**, *73*, 351.
12. (a) Nagubandi, S. and Fodor, G., *J. Heterocycl. Chem.,* **1980**, *17*, 1457. (b) Nagubandi, S. and Fodor, G., *Tetrahedron*, **1980**, *36*, 1279. (c) Fodor, G.; Gal, J. and Phillips, B. A., *Angew. Chem. Int. Ed. Engl*., **1972**, *11*, 919.
13. Lora-Tamayo, M.; Madroñero, R. and Muñoz, G.G., *Ber.,* **1959**, *93*, 289.
14. Orito, K.; Miyazawa, M.; Kanbayashi, R.; Tokuda, M. and Suginome, H., *J. Org. Chem.,* **1999**, *64*, 6583

15. Claudi, F.; Di Stefano, A.; Napolitani, F.; Cingolani, G. M.; Giorgioni, G.; Fontenla, J. A.; Montenegro, G. Y.; Rivas, M. E.; Rosa, E.; Michelotto, B.; Orlando, G. and Brunetti, L., *J. Med. Chem.,* **2000**, *43*, 599.

16. (a) Chrzanowska, M. and Rozwadowska, M. D., *Chem. Rev.,* **2004**, *104*, 3341 and references therein. (b) Huang, Q. H. and Larock, R. C., *J. Org. Chem.,* **2003**, *68*, 980 and references therein. (c) Pal, B.; Jaisankar, P. and Giri, V. S., *Syn. Commun.,* **2003**, 2339. (d) Judeh, Z. M. A.; Ching, C. B.; Bu, J. and McCluskey, A., *Tetrahedron Lett.,* **2002**, *43*, 5089. (e) Shklyaev, Y. V., *Chemistry and Computational Simulation. Butlerov Communications*, **2002**, 21. (f) Abu-Safieh, K. A.; El-Abadelah, M. M.; Sabri, S. S.; Voelter, W.; Mössmer, C. M. and Stroebele, M., *Z. Naturforsch*., **2002**, *57b*, 1327. (g) Bräse, S.; Gil, C. and Knepper, K., *Bioorg. Med. Chem*., **2002**, 2415. (h) Bermejo, A.; Andreu, I.; Suvire, F.; Léonce, F.; Caignard, D. H.; Renard, P.; Pierré, A.; Enriz, R. D.; Cortes, D. and Cabedo, N., *J. Med. Chem.,* **2002**, *45*, 5058. (i) Barun, O.; Chakrabarti, S.; Ha, H. and Junjappa, H., *J. Org. Chem.,* **2001**, *66*, 4457. (j) Bently, K. W., *Nat. Prod. Rep.,* **2001**, *18*, 148. (k) Banwell, M. G.; Harvey, J. E.; Hockless, D. C. R. and Wu, A. W., *J. Org. Chem.,* **2000**, *65*, 4241. (l) Coppola, G. M.; Zhang, Y. L. and Schuster, H. F., *Heterocycl. Commun.,* **2000**, *6*, 13. (m) Bergmeier, S. C. and Seth, P. P., *J. Org. Chem.,* **1999**, *64*, 3237. (n) von Nussbaum, F.; Miller, B.; Wild, S.; Hilger, C. S.; Schumann, S.; Zorbas, H.; Beck, W. and Steglich, W., *J. Med. Chem.,* **1999**, *42*, 3478. (o) Vedejs, E.; Trapencieris, P. and Suna, E., *J. Org. Chem.,* **1999**, *64*, 6724. (p) Hudlicky, T.; Gonzalez, D. and Gibson, D. T., *Aldrichimica Acta*, **1999**, *32*, 35. (q) Quirante, J.; Escolano, C.; Merino, A. and Bonjoch, J., *J. Org. Chem.,* **1998**, *63*, 968. (r) Desmaële, D.; Mekouar, K. and d'Angelo, J., *J. Org. Chem.,* **1997**, *62*, 3890. (s) Wender, P. A. and Smith, T. E., *J. Org. Chem.,* **1996**, *61*, 824. (t) Czarnocki, Z.; Mieczkowski, J. B. and Ziolkowski, M., *Tetrahedron: Asymmetry,* **1996**, *9*, 2711. (u) Rölfing, K.; Thiel, M. and Künzer, H., *Synlett,* **1996**, 1036. (v) Meutermans, W. D. F. and Alewood, P. F., *Tetrahedron Lett.,* **1995**, *36*, 7709. (w) Lögers, M.; Overman, L. E. and Welmaker, G. S., *J. Am. Chem. Soc.,* **1995**, *117*, 9139. (x) Aubé, J.; Ghosh, S. and Tanol, M., *J. Am. Chem. Soc.,* **1994**, *116*, 9009. (y) Sotomayor, N.; Vicente, T.; Domÿnguez, E.; Lete, E. and Villa, M. J., *Tetrahedron,* **1994**, *50*, 2207. (z) Flippin, L. A. and Muchowski, J. M., *J. Org. Chem.,* **1993**, *58*, 2631. (aa) Kammermeier, B. O. T.; Lerch, U. and Sommer, C., *Synthesis,* **1992**, *11*, 1157. (bb) Cobas, A.; Guitián, E. and Castedo, L., *J. Org. Chem.,* **1992**, *57*, 6765. (cc) Lienard, P.; Royer, J.; Quirion, J. C. and Husson, H.-P., *Tetrahedron Lett.*, **1991**, *32*, 2489. (dd) Hanessian, S. and Faucher, A.-M., *J. Org. Chem.,* **1991**, *56*, 2947. (ee) Lounasmaa, M. and Tolvanen, A., *J. Org. Chem*., **1990**, *55*, 4044. (ff) Yasuda, S.; Hirasawa, T.; Yoshida, S. and Hanaoka, M., *Chem. Pharm. Bull*., **1989**, *37*, 1682. (gg) Young, S. D.; Wiggins, J. M. and Huff, J. R., *J. Org. Chem.,* **1988**, *53*, 1114. (hh) Ishii, H.; Ichikawa, Y.-I.; Kawanabe, E.; Ishikawa, M.; Ishikawa, T.; Kuretani, K.; Inomata, M. and Hoshi, A., *Chem. Pharm. Bull*., **1985**, *33*, 4139. (ii) Fowler, F. W., in *Comprehensive Heterocycic Chemistry,* ed. Katrirzky, A. R. and Rees, C. W., Pergamon Press, Oxford, **1984**, *2*, pp. 410–416. (jj) Griffith, R. C.; Gentile, R. J.; Robichaud, R. C. and Frankenheim, J., *J. Med. Chem.,* **1984**, *27*, 995. (kk) Brooks, D. J.; Dowell, D. S.; Minter, D. E. and Villarreal, M. C., *J. Org. Chem.,* **1984**, *49*, 130. (ll) Walker, K. A.; Boots, M. R.; Stubbins, J. F.; Rogers, M. E. and David, C. W., *J . Med. Chem.,* **1983**, *26*, 174. (mm) Govindachari, T. R. and Rajeswari, S., *Indian J. Chem*., **1983**, *22B*, 531. (nn) Langlois, Y.; Pouilhès, A.; Génin, D.; Andriamialisoa, R. Z. and Langlois, N., *Tetrahedron,* **1983**, *39*, 3755. (oo) Nagubandi, S. and Fodor, G., *Heterocycles,* **1981**, *15*, 165. (pp) Ono, K.; Kawakami, H. and Katsube, J., *Heterocycles,* **1980**, *14*, 411. (qq) Herrmann, J. L.; Cregge, R. J.; Richman, J. E.; Kieczykowski, G. R.; Normandin, S. N.; Quesada, M. L.; Semmelhack, C. L.; Poss, A. J. and Schlessinger, R. H., *J. Am. Chem. Soc.,* **1979**, *101*, 1540. (rr) Pfäffli, P.; Oppolzer, W.; Wenger, R. and Hauth, H., *Helv. Chim. Acta,* **1975**, *58*, 1131. (ss) Iida, H.; Aoyagi, S. and Kibayashi, C. *J. Chem. Soc., Perkin Trans. I,* **1975**, 2502. (tt) Herrmann, J. L.; Cregge, R. J.; Richman, J. E.; Semmelhack, C. L. and Schlessinger, R. H., *J. Am. Chem. Soc.,* **1974**, *96*, 3702. (uu) Ott, H.; Hardtmann, G.; Denzer, M.; Frey, A. J.; Gogerty, J. H.; Leslie, G. H. and Trapold, J. H., *J. Med. Chem.,* **1968**, *11*, 777. (vv) Morrison, C. G.; Cetenko, W. and Shavel J., *J. Org. Chem*., **1964**, *29*, 2771. (ww) Tada, R.; Sakurawa, H. and Tokura, N., Bull. Chem. Soc. Japan, **1960**, *33*, 50.

(xx) Fujisawa, T. and Sugasawa, S., *Tetrahedron*, **1959**, *7*, 185. (yy) Buu-Hoï, N. P.; Long, C. T. and Xuong, N. D., *J. Org. Chem.,* **1958**, *23*, 42. (zz) Bentley, K. W. and Dyke, S. F., *J. Org. Chem.,* 1957, 22, 429. (aaa) Hey, D. H. and Paluel, A. L., *J. Chem. Soc*., **1956**, 4123. (bbb) Galat, A., *J. Am. Chem. Soc.,* **1953**, *75*, 1738. (ccc) Hill, A. J. and Hall, G. E., *J. Am. Chem. Soc.,* **1952**, *74*, 666. (ddd) Whaley, W. M. and Govindachari, T. R., *Org. React.,* **1951**, *6*, 74. (eee) Reeve, W. and Eareckson, W. W., *J. Am. Chem. Soc.,* **1950**, *72*, 5195. (fff) Whaley, W. M. and Hartung, W. H., *J. Org. Chem.,* **1949**, *14*, 650. (ggg) Mathew, K. K. and Menon, K. N., *Proc. Indian Acad. Sci.,* **1949**, *29A*, 361. (hhh) Schultz, E. M. and Arnold, R. T., *J. Am. Chem. Soc.,* **1949**, *71*, 1911. (iii) Hahn, G. and Rumpf, F., *Ber.,* **1938**, *71B*, 2141. (jjj) Hahn, G. and Hansel, A., *Ber.,* **1938**, *71B*, 2163. (kkk) Hahn, G. and Stiehl, K., *Ber.,* **1936**, *69B*, 2627. (lll) Harwood, H. J. and Johnson, T. B., *J. Am. Chem. Soc.,* **1933**, *55*, 2555.

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Black Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Black in 1986.[1] It is a 4-*N*,*N*-dimethylamino-pyridine (DMAP) catalyzed [1,3] translocation of an ester group (e.g., formate) from an oxygen atom to the adjacent α-carbon atom of the carbonyl group for the carbonate esters of benzofuran enolates. Therefore, this reaction is generally known as the Black rearrangement.[2] Similar to the competition between *O*-alkylation and *C*-alkylation in the reaction of enolate with alkylating agents,[3] the *O*-acylation and *C*-acylation also complete with each other in the reactions of enolates with acylating reagents. Although it has been reported that under several circumstances, the *C*-acylations are favored—such as the application of acyl chlorides rather than anhydrides as acylating agents,[4] the inverse addition of enolate to acyl chlorides[5] at low temperature,[6] and using enolates of divalent countercations instead of alkali[7] — the *O*-acylation may still predominate for certain types of substrates. As an example, the acylation of benzofuran enolates under the above-mentioned conditions affords *O*-acylated products in preference, with maximal *C*-acylation up to 30%.[8] Especially for the enolate of the diaryl acetic acid esters, only *O*-acylated products were isolated.[9] The high preference for *O*-acylation probably lies in the high electron density located at the negative oxygen atom, resulting in the kinetically favored products.[8]

In the presence of a catalytic amount of DMAP, the enol carbonates of benzofuran derived from *O*-acylation with alkyl chloroformates rearrange to the corresponding carbon-acylated isomers within a short period of time (usually <2 min).[8] Such rearrangement is often accompanied by the appearance of a transient deep blue color. In addition, in the presence of DMAP, the acylation and Black rearrangement can be run in an "one-pot" fashion resulting almost exclusively in *C*-acylation products of high yields.[8] Different from

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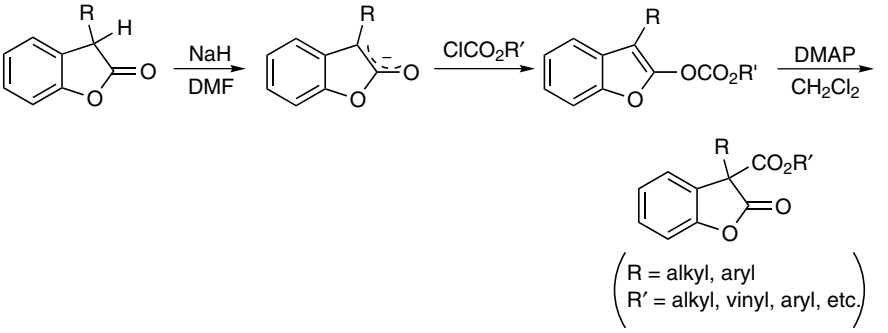
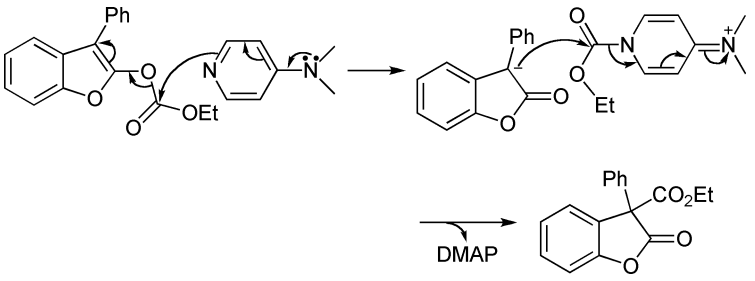
common acylations that take place under acidic conditions, the Black rearrangement can be applied in the basic conditions necessary for generating enolates.[8] Even though the solvent effect has been reported for this rearrangement, DMAP still retains its catalytic efficacy in a highly polar basic medium to maintain the regioselectivity.[8]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Due to the noticeable solvent effect of this rearrangement (e.g., slower rearrangement observed in DMF than in halogenated solvents), the rearrangement is assumed to involve polar donor-acceptor ion pairs.[8] Shown here is a representative mechanism for the carbonate ester of benzofuran.



D. MODIFICATION

This reaction has been extended to the translocation of the acyl group for indole derivatives.[10] In addition, a chiral planar DMAP derivative has been developed and applied for the enantioselective rearrangement of *O*-acylated azlactone[11] and the same catalyst recently has been used for an intermolecular reaction to form 1,3-diketones.[12] Moreover, 3-(2,2,2-triphenyl-1-acetoxyethyl)-4-(dimethylamino) pyridine (TADMAP) has been applied as a chiral nucleophilic catalyst to catalyze the carboxyl migration of oxazolyl, furanyl, and benzofuranyl enol carbonates with good to excellent levels of enantioselectivity. The rearrangement for oxazole derivatives are particularly efficient for giving chiral lactams and lactones.[2]

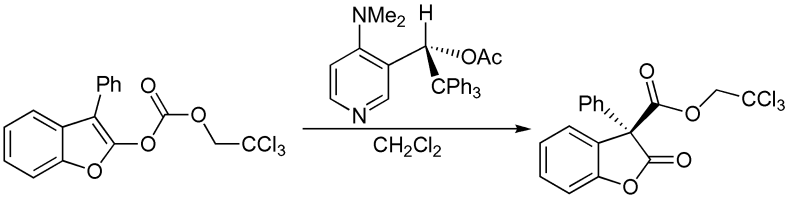
E. APPLICATIONS

This reaction has limited applications for the formation of quaternary chiral centers in benzofuran series.

F. RELATED REACTIONS

This reaction is related to the *Steglich Rearrangement* for benzofuran and indole derivatives.

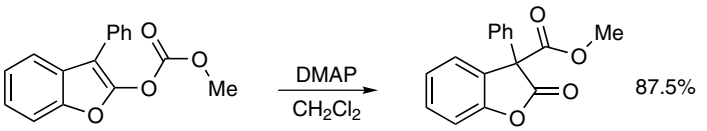
G. CITED EXPERIMENTAL EXAMPLES



92%, 86% *e.e.*

Reference 2.

After the solution of 38 mg 3-phenyl-benzofuran-2-yl 2′,2′,2′-trichloroethyl carbonate (0.10 mmol) and 8.7 mg (*R*)-3-(2,2,2-triphenyl-1-acetoxyethyl)-4-(dimethylamino) pyridine (TADMAP, 0.020 mmol) in 1 mL CH_2Cl_2 was prepared at $-78^{\circ}C$, the mixture was allowed to warm to $-40^{\circ}C$ and stirred at such temperature for 18 h. Then the solution was warmed to room temperature and concentrated under nitrogen stream. The residue was purified by flash chromatography (silica gel, 15 × 1.5 cm column) using EtOAc/hexanes (2:1) as the eluent. After elution with 200 mL EtOAc/hexanes (2:1), the column was further washed with 200 mL EtOAc. The first compound eluted within the first 80 mL and these fractions were evaporated to afford 35 mg of 2,3-dihydro-2-oxo-3-phenyl-3-benzofurancarboxylic acid 2′,2′,2′-trichloroethyl as a colorless oil, in a yield of 92% with 86% e.e., $R_f = 0.50$ (Et_2O/hexane = 1:1). Evaporation of further collected fractions from the column after 200 mL of solvent recovered 8.3 mg of the catalyst TADMAP, corresponding to 95% of catalyst recovery.



Reference 8.

To a 125-mL separatory funnel were charged 1 g carbonic acid, methyl 3-phenylbenzofur-2-yl ester and 20 mL CH_2Cl_2. The solution was effected by swirling. Then 40 mg DMAP was added, and the solution was briefly shaken. During the shaking, a deep blue/purple color developed immediately and disappeared after about 1 min. The solution was then washed successively with 5% HCl (3 × 20 mL) and 100 mL water, dried over $MgSO_4$; and con-

centrated. The residue was purified by bulb-to-bulb distillation (140–147°C, 0.05 mmHg) to afford 87.5% of 2,3-dihydro-2-oxo-3-phenyl-3-benzofurancarboxylic acid methyl ester as a clear, colorless oil that solidified after standing for several days to a white, crystalline solid, m.p. 68–70°C.

Other references related to the Black rearrangement are cited in the literature.[13]

H. REFERENCES

1. Black, T. H.; Arrivo, S. M.; Schumm, J. S. and Knobeloch, J. M., *J. Chem. Soc., Chem. Commun.,* **1986**, 1524.
2. Shaw, S. A.; Aleman, P.; Christy, J.; Kampf, J. W.; Va, P. and Vedejs, E., *J. Am. Chem. Soc.,* **2006**, *128*, 925.
3. (a) Wang, D. Z. R. and Streitwieser, A., *J. Org. Chem.,* **2003**, *68*, 8936. (b) Wang, D. Z. R.; Kim, Y.-J. and Streitwieser, A., *J. Am. Chem. Soc.,* **2000**, *122*, 10754. (c) Streitwieser, A.; Wang, D. Z. R. and Stratakis, M., *J. Org. Chem.,* **1999**, *64*, 4860. (d) Streitwieser, A. and Wang, D. Z. R., *J. Am. Chem. Soc.,* **1999**, *121*, 6213.
4. House, H. O. and Kramer, V., *J. Org. Chem.,* **1963**, *28*, 3362.
5. Beck, A. K.; Hoekstra, M. S. and Seebach, D., *Tetrahedron Lett.,* **1977**, 1187.
6. House, H. O.; Auerbach, R. A.; Gall, M. and Pett, R. P., *J. Org. Chem.,* **1973**, *38*, 514.
7. House, H. O.; Respess, W. L. and Whitesides, G. M., *J. Org. Chem.,* **1966**, *31*, 3128.
8. Black, T. H.; Arrivo, S. M.; Schumm, J. S. and Knobeloch, J. M., *J. Org. Chem.,* **1987**, *52*, 5425.
9. Nonhebel, D. C. and Smith, J., *J. Chem. Soc. C,* **1967**, 1919.
10. Lachia, M.; Poriel, C.; Slawin, A. M. Z. and Moody, C. J., *Chem. Commun.,* **2007**, 286.
11. (a) Fu, G. C., *Acc. Chem. Res.,* **2004**, *37*, 542. (b) Hills, I. D. and Fu, G. C., *Angew. Chem.,* **2003**, *115*, 4051. (c) Ruble, J. C. and Fu, G. C., *J. Am. Chem. Soc.,* **1998**, *120*, 11532.
12. Mermerian, A. H. and Fu, G. C., *J. Am. Chem. Soc.,* **2003**, *125*, 4050.
13. Vedejs, E. and Wang, J. B., *Org. Lett.,* **2000**, *2*, 1031.

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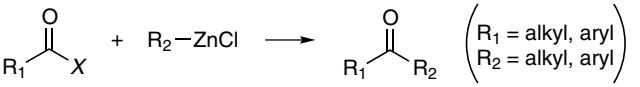
Blaise Ketone Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Blaise in 1907.[1] It is the reaction between an organozinc halide and acyl halide to form ketone,[1,2] and is generally known as the Blaise ketone synthesis.[3]In this reaction, organozinc chloride can be prepared by the reaction between anhydrous zinc chloride and a Grignard reagent;[3b] the resulting organozinc chloride is referred to as the Blaise reagent;[4] which can be applied directly to the coupling with acyl halide without any isolation.[3b] The yield of expected ketones can be as high as 80%, presumably due to the lower reactivity between organozinc chloride and ketones than that between the ketone and corresponding Grignard reagents.[3b] As a result, even a hydroxyl group can be tolerated in this reaction without protection.[5] In addition, the coupling between organozinc chloride and β-hydroxy carbonyl chloride to form β-hydroxy ketones and further conversion into α,β-unsaturated ketones in boiling dilute sulfuric acid is known as the Blaise-Maire reaction.[3a,6]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is obvious that the Blaise ketone synthesis proceeds via the nucleophilic addition of an organozinc reagent to the carbonyl group followed by the releasing of chloride, as displayed here.

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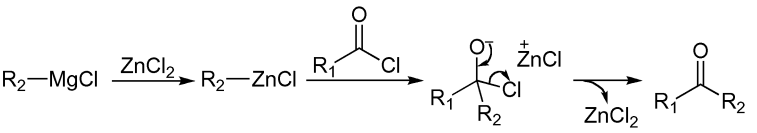


D. MODIFICATION

The Blaise ketone synthesis has been extended to the synthesis of α,β-unsaturated ketones, known as the Blaise-Maire reaction.[3a,6] In addition, the organozinc chloride has been replaced by an organocadmium reagent for a better yield.[3b]

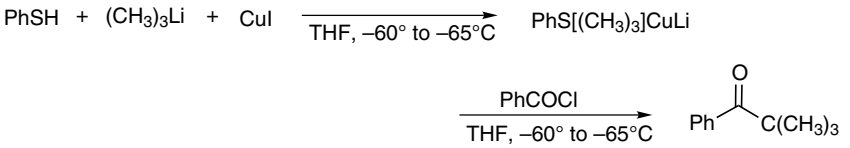
E. APPLICATIONS

This reaction has important applications in organic synthesis.

F. RELATED REACTIONS

This reaction is related to the *Grignard Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

A dry 200-mL round-bottomed flask was fitted with a magnetic stirring bar and a 100-mL pressure-equalizing dropping funnel, the top of which was connected to a nitrogen inlet. After the apparatus had been flushed with nitrogen, 50 mL 1.60 M *n*-butyllithium (0.080 mol) solution was placed in the flask and cooled with an ice bath. Under a nitrogen atmosphere, a solution of 8.81 g freshly distilled thiophenol (0.0801 mol) in 30 mL anhydrous THF was added dropwise to the cooled, stirred solution. An aliquot of the resulting solution was standardized by quenching in water, followed by titration with 0.10 N HCl to a green end point with a bromocresol indicator. The concentration of lithium thiophenoxide prepared in this manner was typically 1.0 M.

A dry 250-mL three-necked, round-bottomed flask was equipped with a sealed mechanical stirrer, a glass stopper, and a rubber septum through which were inserted hypodermic needles used to evacuate the flask and to admit nitrogen. After the apparatus had been flushed with nitrogen, 4.19 g purified copper(I) iodide (0.0220 mol) was added, and while warming with a flame, the apparatus was evacuated and then refilled with nitrogen. After

this procedure had been performed twice, the flask was allowed to cool, the stopper was replaced with a thermometer, and 45 mL anhydrous THF was added with a hypodermic syringe. With continuous stirring, 22 mL 1.0 M lithium thiophenoxide solution (0.022 mol) was added with a syringe to the slurry of copper(I) iodide. After 5 min, the resulting yellow solution was cooled, with continuous stirring, to −65°C with an acetone–dry ice cooling bath. Some copper(I) thiophenoxide usually separated from solution at ∼ −45°C. When the temperature of the mixture had reached ∼ −65°C, 13.6 mL 1.60 M *tert*-butyllithium (0.0218 mol) solution was added with a syringe to the stirred mixture at such a rate that the temperature of the mixture remained at −65° to −60°C. The resulting cloudy yellow-orange solution of the cuprate reagent was stirred at −65° to −60°C for 5 min.

With a syringe, a solution of 2.81 g freshly distilled benzoyl chloride (0.0200 mol) in 15 mL anhydrous THF was added dropwise, with stirring, to the cold solution (−65° to −60°C) of cuprate reagent. The resulting yellow-brown solution was stirred for 20 min (at −65° to −60°C) and quenched by the addition, with a syringe, of 5 mL anhydrous methanol. The red-orange reaction mixture was allowed to warm to room temperature and then poured into 100 mL aqueous saturated ammonium chloride. The copious precipitate of copper(I) thiophenoxide was separated by suction filtration and washed thoroughly with several 50-mL portions of diethyl ether. The combined filtrate was extracted with three 100-mL portions of ether. The combined ethereal solution was washed with two 50-mL portions of aqueous 1 N sodium hydroxide and with one 50-mL portion of aqueous 2% sodium thiosulfate. Each of the aqueous washes was extracted in turn with a fresh 50-mL portion of ether. The combined ethereal solution was dried with anhydrous $MgSO_4$, filtered, and concentrated by distillation through a short Vigreux column. The residual pale yellow liquid was distilled through a short column under reduced pressure, yielding 2.73–2.82 g of *tert*-butyl phenyl ketone as a colorless liquid, in a yield of 84–87%, b.p. 105–106°C (15 mmHg).

$$CH_3(CH_2)_{10}CH_2Br + Mg + ZnCl_2 \xrightarrow[\text{Benzene}]{ClC(O)(CH_2)_8CO_2Et} CH_3(CH_2)_{11}C(O)(CH_2)_8CO_2Et$$

Reference 8.

A Grignard reagent was prepared from 0.72 g magnesium and 7.5 g dodecyl bromide in 50 mL dry ether in a 500-mL flask fitted with the usual equipment and an inlet through which nitrogen was continuously passed. To the reagent was added 4.1 g freshly fused zinc chloride dissolved in 12 mL ether. After the mixture was refluxed for 30 min, 60 mL sodium-dried benzene was added to dissolve the white precipitate of dodecyl zinc chloride. With continuous stirring and refluxing, 6.0 g ω-carbethoxynonoyl chloride (prepared from ethyl hydrogen sebacate and thionyl chloride in 90% yield) dissolved in 50 mL dry benzene was slowly added. The reaction mixture was refluxed for another 2 h; decomposed with dilute HCl; and washed with dilute ammonium chloride solution, water, dilute sodium carbonate, and water. After removal of the solvent, the syrupy residue was saponified. The crystalline sodium salt was very insoluble in both cold water and cold benzene and was purified by thorough extraction with each. The filtered salt was digested with dilute HCl and the free acid crystallized from acetone-petroleum ether (b.p. 60–68°C) to give 5.3 g 10-ketodocosanoic acid as light, shiny crystals, in a yield of 62%. After one more crystallization, the melting point was 91.5°C.

Other references related to the Blaise ketone synthesis are cited in the literature.[9]

H. REFERENCES

1. (a) Blaise, E. E. and Maire, M., *Compt. Rend.,* **1907**, *145*, 73. (b) Blaise, E. E., *Compt. Rend.,* **1907**, *145*, 1285.
2. (a) Blaise, E. and Koehler, A., *Compt. Rend.,* **1909**, *148*, 489. (b) Blaise, E. E. and Koehler, A., *Bull. Soc. Chim.,* **1910**, *7*, 215. (c) Blaise, E. E. and Koehler, A., *Bull. Soc. Chim.,* **1910**, *5*, 681. (d) Blaise, E. E. and Picard, L., *Compt. Rend.,* **1911**, *152*, 446. (e) Blaise, E. E. and Picard, L., *Ann. Chim. Phys.,* **1912**, *26*, 258.
3. (a) Oyama, T.; Takamizawa, K. and Ogawa, Y., *Kobunshi Ronbunshu*, **1980**, *37*, 711. (b) Summerbell, R. K. and Bauer, L. N., *J. Am. Chem. Soc.,* **1936**, *58*, 759.
4. (a) Paleeva, I. E.; Sheverdina, N. I.; Abramova, L. V. and Kocheshkov, K. A., *Dokl. Akad. Nauk SSSR,* **1964**, *159*, 609. (b) Matsumoto, T. and Suzuki, A., *J. Org. Chem.,* **1960**, *25*, 1666.
5. Wang, F.-D. and Yue, J.-M., *Synlett,* **2005**, 2077.
6. (a) Lehmler, H.-J.; Bergosh, R. G.; Meier, M. S. and Carlson, R. M. K., *Biosci. Biotechnol. Biochem.,* **2002**, *66*, 523. b) Guha, P. C. and Ganapathi, K., *Ber.,* **1936**, 69*B*, 1183.
7. Posner, G. H. and Whitten, C. E., *Org. Synth. Coll.,* **1988**, *6*, 248.
8. Schneider, A. K. and Spielman, M. A., *J. Biol. Chem.,* **1942**, *142*, 345.
9. (a) Shirley, D. A., *Org. React.,* **1954**, *8*, 29. (b) Cason, J., *Chem. Rev.,* **1947**, *40*, 17. (c) Blaise, E. E., *Bull. Soc. Chim.,* **1916**, *19*, 10. (d) Blaise, E. E., *Bull. Soc. Chim.,* **1911**, *9*, 1. (e) Blaise, E. E. and Maire, M., *Ann. Chem. Phys.,* **1909**, *15*, 556. (f) Blaise, E. E. and Maire, M., *Bull. Soc. Chim.,* **1908**, *3*, 421. (g) Blaise, E. E. and Herman, I., *Compt. Rend.,* **1908**, *146*, 479. (h) Blaise, E. E. and Maire, M., *Compt. Rend.,* **1907**, *144*, 572. (i) Blaise, E. E. and Maire, M., *Compt. Rend.,* **1907**, *144*, 93.

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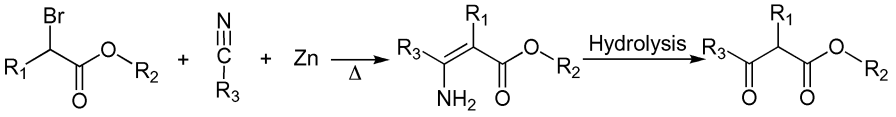
Blaise Reaction
(Blaise Condensation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Blaise in 1901.[1] It is the reaction between a nitrile and zinc reagent from an α-bromoester (i.e., the Reformatsky reagent) to give an enamino ester or the further product of a β-keto ester upon acidic hydrolysis.[2] Therefore, it is generally known as the Blaise reaction.[3] Occasionally, it is also referred to as the Blaise condensation.[4] Although it is a one-step synthesis of higher aliphatic β-keto esters from a stable and accessible starting material, the easy introduction of functionalities and the straightforward nature of the conversion have been overshadowed by the problems of low yield, narrow scope, and competing side reactions.[5] It is found that the structure of bromoester strongly affects the efficiency of this reaction–for example, esters of bromoacetic acid give no isolable yield of β-keto esters, whereas esters of α-bromopropionic acid and α-bromoisobutyric acid give β-keto esters in yields varying from 30% to 60%.[5d] However, when a Reformatsky reagent reacts with an excess amount of cyanogens $(CN)_2$, 30–60% of nitrile will form, resulting in a valuable method for synthesizing α-cyano ester, which is not easily obtained in good yields by other direct syntheses.[6] The original reaction procedure has been modified to a convenient preparation of enamino ester and β-keto ester by refluxing aliphatic or aromatic nitriles with 3–5 equivalents of α-bromo esters in THF in the presence of activated zinc dust.[2] This modification has been applied to the total synthesis of the paralytic shellfish poisons, saxitoxin, and gonyautoxin.[2]

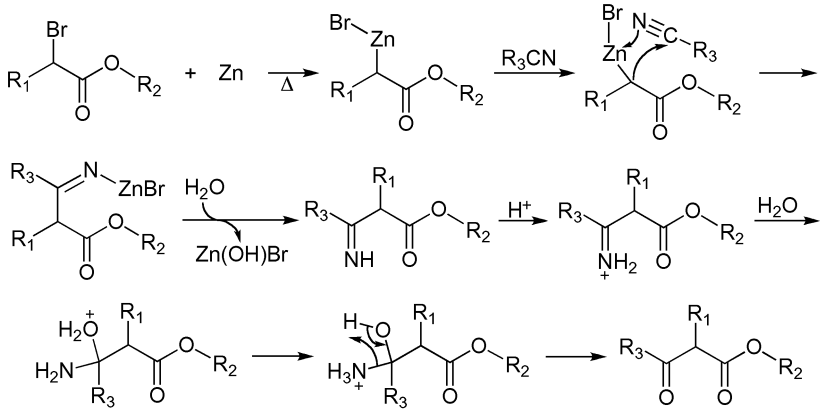
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

This reaction is believed to proceed by a mechanism analogous to that of the *Reformatsky Reaction*,[1] involving an initial condensation of the nitrile with the Reformatsky reagent; the intermediate is finally transformed into β-keto ester via acidic hydrolysis,[5d] as illustrated here.



D. MODIFICATION

This reaction has been modified via the generation of Reformatsky reagent *in situ* by refluxing the mixture of α-bromo esters and nitriles in the presence of activated zinc dust.[2] In addition, when a benzene solution of α-bromo esters are added slowly to a refluxing mixture of zinc and nitriles, a high yield of α,α-di and α-monosubstituted β-keto esters are obtained.[5c] On the other hand, the Blaise reaction has been improved by using a Zn-Ag couple under ultrasonic radiation. For example, the coupling by means of different forms of activated zinc instead of a zinc-silver couple or without the use of ultrasound does not occur or gives only poor yield.[3m] Moreover, it is reported that methanesulfonic acid can be used as an *in situ* activator of zinc to remove the induction period of the Blaise reaction.[3d] Furthermore, this reaction has been modified to afford β-amino esters via the reduction of the intermediate obtained by the hydrolysis of the reaction mixture with concentrated potassium carbonate.[2]

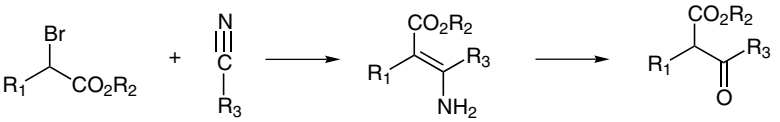
E. APPLICATIONS

This reaction can be generally applied to the preparation of enamino esters and β-keto esters, which can be asymmetrically reduced to yield chiral β-amino or hydroxyl esters and further hydrolyzed to β-amino or hydroxyl acids and cyclized to form β-lactams or lactones.[7] In addition, this reaction has been successfully used in the synthesis of the paralytic shellfish poisons, saxitoxin, and gonyautoxin.[2]

F. RELATED REACTIONS

This reaction is related to the *Reformatsky Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2.

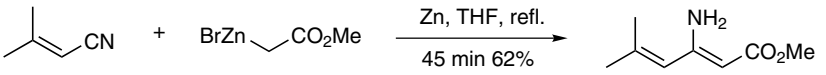
General Procedure for the Preparation of Enamino Esters

To a suspension of 327 mg activated zinc dust (5 eq.) in 3 mL refluxing anhydrous THF under nitrogen were added 4 drops α-bromo ester. After the appearance of the green color (this color is very evident with bromoacetates; when substituted bromo esters are used, however, the color may not appear), 1 mmol nitrile was added in one portion, and then 4 mmol α-bromo ester was injected by syringe pump over 45 min. The mixture was refluxed for an additional 10 min, diluted with 9 mL THF, and quenched with 1.3 mL 50% aqueous K_2CO_3. Rapid stirring for 30 min gave two cleanly separated layers. The upper organic layer was decanted, the residue was washed three times with THF, and the combined organic layers were dried with $MgSO_4$. Concentration and purification by PTLC (SiO_2 developed with 1:l hexanes/Et_2O, typically) gave the enamino ester product, contaminated with $< 25\%$ of its β-keto ester. Hydrolysis during purification could be minimized by avoiding contact of the enamino ester with dry silica gel. Column chromatography on solvent-wetted SiO_2 was an effective procedure for isolating pure enamino ester. Note that it was crucial to use the prescribed volumes of THF and K_2CO_3 solution. Otherwise, emulsions would form, and the clear, Zn^{2+}-free THF layer would not separate, making the workup tedious and decreasing the yield. For each mole of zinc salt produced, the cooled reaction mixture should be diluted to a total volume of 3 mL, and then 0.33 mL 50% aqueous K_2CO_3 should be added with vigorous stirring.

General Procedure for the Preparation of β-Keto Esters

The THF solution of crude enamino ester obtained as described earlier was subjected to acid hydrolysis as follows. The THF solution was treated with 1 mL 10% aqueous HCl at room temperature for 30 min, or a time sufficient for the UV-active enamino ester to be no

longer detectable by TLC. The mixture was concentrated, diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and purified by PTLC (SiO_2 developed with 1:l hexanes:Et_2O, typically) to yield the pure β-keto ester.



Reference 7b.

A suspension of 20.0 g activated zinc powder (0.3 mol) in 185 mL dry tetrahydrofuran was stirred at reflux while a few drops of methyl bromoacetate were added. After stirring a few minutes, the suspension color turned to dark green. A total of 5 g 3,3-dimethylacrylonitrile (62 mmol) was added in one portion, followed by 23 mL methyl bromoacetate (250 mmol), which was added over 1 h. After completion of the addition, the red reaction mixture was cooled, diluted with 550 mL tetrahydrofuran and then with 110 mL aqueous 50% potassium carbonate solution, and was vigorously stirred for 30 min. The mixture was then filtered through a pad of celite, and the filtrate was concentred in vacuo. The residue was taken up with 500 mL dichloromethane, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by chromatography (50% ether/pentane, $R_f = 0.7$) to give 5.95 g (2*Z*)-3-amino-5-methyl-2,4-hexadienoic acid methyl ester as a yellow oil, in a yield of 62%.

Other references related to the Blaise condensation are cited in the literature.[8]

H. REFERENCES

1. Blaise, E. E., *Compt. Rend*., **1901**, *132*, 478.
2. Hannick, S. M. and Kishi, Y., *J. Org. Chem*., **1983**, *48*, 3833.
3. (a) Peng, W. M.; Zhao, J. W. and Zhu, S. Z., *Synthesis,* **2006**, 1470. (b) Wang, F.-D. and Yue, J.-M., *Synlett,* **2005**, 2077. (c) Wang, F.-D. and Yue, J.-M., *Eur. J. Org. Chem.,* **2005**, 2575. (d) Choi, B. S.; Chang, J. H.; Choi, H.-W.; Kim, Y. K.; Lee, K. K.; Lee, K. E.; Lee, J. H.; Heo, T. H.; Nam, D. H. and Shin, H., *Org. Proc. Res. Dev.,* **2005**, *9*, 311. (e) Shin, H.; Choi, B. S.; Lee, K. K.; Choi, H.-W.; Chang, J. H.; Lee, K. W.; Nam, D. H. and Kim, N.-S., *Synthesis,* **2004**, 2629. (f) Deutsch, H. M.; Ye, X. C.; Shi, Q.; Liu, Z. Z. and Schweri, M. M., *Eur. J. Med. Chem.,* **2001**, *36*, 303. (g) Erian, A. W., *J. Prakt. Chem.,* **1999**, *341*, 147. (h) Narkunan, K. and Uang,B.-J., *Synthesis,* **1998**, 1713. (i) Syed, J.; Forster, S. and Effenberger, F., *Tetrahedron: Asymmetry,* **1998**, *9*, 805. (j) Lee, A. S.-Y.; Cheng, R.-Y. and Pan, O.-G., *Tetrahedron Lett.,* **1997**, *38*, 443. (k) Duffield, J. J. and Regan, A. C., *Tetrahedron: Asymmetry,* **1996**, *7*, 663. (l) Zylber, N.; Zylber, J.; Rollin, Y.; Dunach, E. and Perichon, J., *J. Organomet. Chem.,* **1993**, *444*, 1. (m) Beard, R. L. and Meyers, A. I., *J. Org. Chem.,* **1991**, *56*, 2091. (n) Krepski, L. R.; Lynch, L. E.; Heilmann, S. M. and Rasmussen, J. K., *Tetrahedron Lett.,* **1985**, *26*, 981. (o) Rigaudy, J., *Compt. Rend.,* **1949**, *229*, 662. (p) Horeau, A. and Jacques, J., *Bull. Soc. Chim. Fr.,* **1947**, 58. (q) Davies, R. R. and Hodgson, H. H., *J. Soc. Chem. Ind., London,* **1943**, *62*, 128.
4. Jager, H. and Keymer, R., *Arch. Pharm*., **1960**, *293*, 896.
5. (a) Konrad, J. and Jezo, I., *Chem. Zuesti,* **1980**, *34*, 125. (b) Lhommet, G.; Eskenazi, C. and Maitte, P., *C. R. Hebd. Seances Acad. Sci., Ser. C,* **1974**, *279*, 263. (c) Kagan, H. B. and Suen, Y.-H., *Bull. Soc. Chim. Fr*., **1966**, 1819. (d) Cason, J.; Rinehart, K. L. Jr. and Thornton, S. D., *J. Org. Chem.,* **1953**, *18*, 1594.

6. (a) Mowry, D. T., *Chem. Rev*., **1948**, *42*, 189. (b) Grignard, V.; Bellet, E. and Courtot, C., *Ann. Chim*., **1915**, *3*, 28; **1920**, *12*, 364. (c) Grignard, V. and Bellet, E., *Compt. Rend*., **1912**, *155*, 44; **1914**, *158*, 457. (d) Grignard, V., *Compt. Rend*., **1911**, *152*, 388.
7. (a) Dirat, O.; Kouklovsky, C.; Mauduit, M. and Langlois, Y., *Pure & Appl. Chem*., **2000**, *72*, 1721. (b) Mauduit, M.; Kouklovsky, C.; Langlois, Y. and Riche, C., *Org. Lett*., **2000**, *2*, 1053.
8. (a) Pospisil, J. and Markó, I. E., *J. Am. Chem. Soc.,* **2007**, *129*, 3516. (b) Hoang, C. T.; Alezra, V.; Guillot, R. and Kouklovsky, C., *Org. Lett.,* **2007**, *9*, 2521. (c) Çel, H., *J. Serb. Chem. Soc*., **2000**, *67*, 473. (d) Celik, H. and Ozeris, S., *Chim. Acta Turcica,* **1996**, *24*, 23. (e) Rathke, M. W. and Weipert, P., "Zinc Enolates: The Reformatsky and Blaise Reactions," in *Comprehensive Organic Synthesis*, ed. Trost, B. M., and Fleming, I., Pergamon Press, Oxford, **1991**, *2*, pp. 277–299. (f) Fukuyama, T. and Yung, Y. M., *Tetrahedron Lett*., **1981**, *22*, 3760. (g) Patil, B. B. and Bhattacharyya, S. C., *Indian J. Chem., Sect. B,* **1978**, *16B*, 355. (h) Breusch, F. L., Kirkali, A., *Fette Seifen Anstrichmittel,* **1965**, *67*, 4. (i) Vogel, A. I., *Practical Organic Chemistry*, 3rd ed. Longmans, Green and Co, **1961**, p. 367. (j) Lapin H.; Arsennievic V. and Horeau A., *Bull. Soc. Chim. Fr*., **1960**, 1700.

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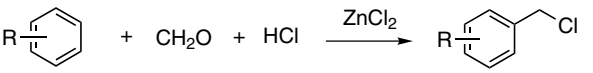
Blanc Chloromethylation
(Blanc Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Grassi-Cristaldi and Maselli in 1898[1] and subsequently extended by Blanc in 1923.[2] It is the reaction for introducing the chloromethyl group into aromatic rings when aromatic compounds are treated with formaldehyde and hydrogen chloride in the presence of zinc chloride. Therefore, this reaction is generally known as the Blanc chloromethylation.[3] Although aliphatic ketones could be chloromethylated in a similar manner, only those aromatic ketones carrying at least two alkyl groups could be chloromethylated in this reaction.[4] In fact, this reaction is a good indirect method for methylation of aromatic compounds if combined with subsequent reduction.[4,5] Chloromethylation of phenyl rings is important for the functionalization of resins, which provides an alternative to polymers employing functionalized monomer in the polymerization step.[6] Although the uncatalyzed chloromethylation of aromatic rings has been reported—such as chloromethylation using formaldehyde and HCl in acetic acid at 85°C[7] and using chloromethyl methyl ether in acetic acid at 100°C[8]—these results could not be repeated and are strongly questioned.[9] This reaction has been used to synthesize benzyl chloride, 6-chloromethyldehydroabietic acid,[10] hydrindene,[11] methylcholanthrene,[12] cyclophane,[13] Bakelite,[14] etc. This reaction has been reviewed.[15]

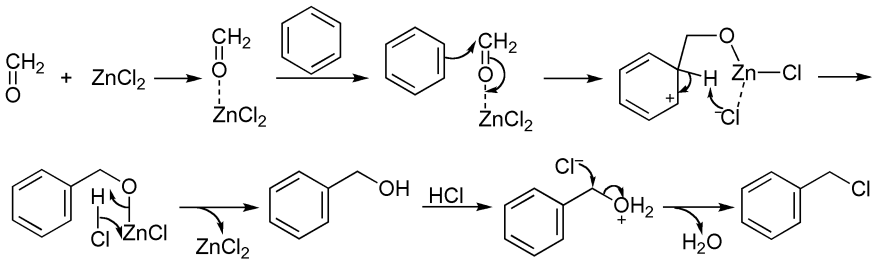
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

It is believed that the formation of complex between formaldehyde and zinc chloride polarizes formaldehyde so that the electrophilic aromatic substitution can occur, as displayed here.



D. MODIFICATION

Although the original Blanc procedure using paraformaldehyde (sometimes called trioxymethylene) and fused and pulverized zinc chloride is followed in many preparations,[16] this reaction has been modified by using either 85% phosphoric acid as catalyst[17] or $ZnCl_2$ as catalyst but with $AlCl_3$[12] or $NiCl_2$[18] as cocatalyst. In addition, 40% formaldehyde has been used for this reaction instead of paraformaldehyde.[18] Bromomethylation of aromatic compounds could be considered another modification.[19]

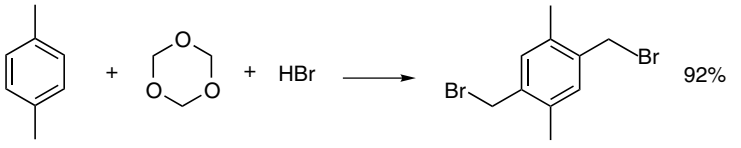
E. APPLICATIONS

This reaction is generally used to introduce the chloromethyl group into aromatic compounds.

F. RELATED REACTIONS

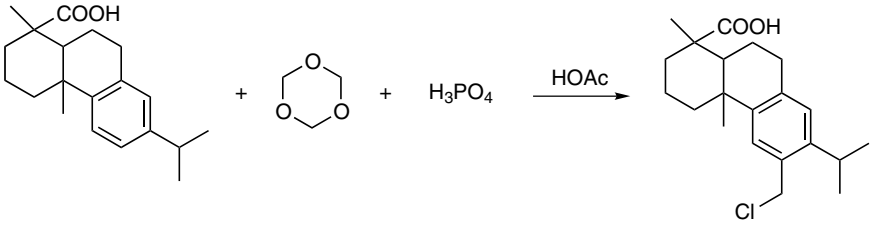
This reaction is related to the *Quelet Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



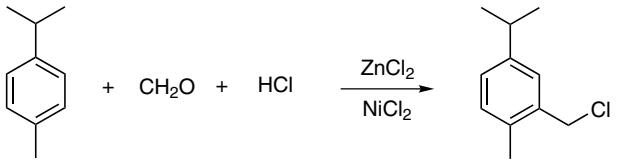
Reference 19.

To a solution of 95 mL 48% HBr (0.57 mol) in a 500-mL round-bottomed flask were added 7.65 g paraformaldehyde (0.25 mol) and 15.20 mL *p*-xylene (0.12 mol). After 28 h of refluxing, the mixture separated into two liquid phases and a white precipitate, which was filtered, yielding 34 g crude 1,4-dibromomethyl-*p*-xylene, in a yield of 97%. Recrystallization from CCl_4 gave 32 g of pure product as white needles, in a yield of 92%, m.p. 126–127°C.



Reference 17.

A solution of 25 g dehydroabietic acid, 3.3 g paraformaldehyde, and 5.2 mL 85% phosphoric acid in 50 mL glacial acetic acid was heated with vigorous stirring at 105–110°C for 11 h while treated with a stream of gaseous hydrogen chloride. The reaction mixture, which had separated into two layers, was diluted with water and extracted with ether. The ether extract was washed with water and dried over Drierite. Upon evaporation of the solvent, there was obtained a resinous, pale yellow residue, which was converted under reduced pressure to a froth that could be powdered and dried. The crude material (27.2 g) did not yield a crystalline product—that is, 6-chloromethyldehydroabietic acid.



Reference 18.

p-Cymene (50 g), 20 g anhydrous zinc chloride, 1 g nickel chloride, and 40 g 40% formaldehyde were stirred together at 60°C while hydrogen chloride was passed through. After 8 h, the reaction mixture was steam distilled. It was found that it was better to use the small quantities mentioned and to carry out many preparations rather than to use larger quantities. Forty-seven grams of colorless liquid was obtained by distillation at 123–124°C (20 mmHg), in a yield of 69%.

Other references related to the Blanc chloromethylation are cited in the literature.[20]

H. REFERENCES

1. Grassi-Cristaldi, G. and Maselli, M., *Gazz. Chim. Ital.,* **1898**, *20* , 477.
2. (a) Blanc, M. G., *Bull. Soc. Chim. Fr*., **1923**, *33,* 313. (b) Blanc, M. G., *Am. Perfumer,* **1923**, *17*, 541.

3. (a) Wang, Y.; Zheng, X.-Y. and Wu, Z.-L., *Shiyou Xuebao, Shiyou Jiagong*, **2007**, *23*, 12. (b) Liu, X. F.; Shen, D. S.; Ouyang, X. X.; Yang, G. Z. and Guan, X. Y., *Shiyou Huagong*, **2004**, *33,* 968. (c) Qiao, K. and Deng, Y.-Q., *Huaxue Xuebao*, **2003**, *61*, 133. (d) Chang, Y. H., *Jingxi Huagong Zhongjianti,* **2002**, *32*, 27.
4. (a) Fuson, R. C. and McKeever, C. H., *J. Am. Chem. Soc.,* **1940**, *62*, 784. (b) Colonge, *Bull. Soc. Chim.,* **1936**, *3*(5), 2116.
5. Braun, v. Braun, J. and Nelles, J., *Ber*., **1934**, *678*, 1094. and Nelles, *Ber*., **1934**, *67*, 1094.
6. (a) Kumar, K. S. and Pillai, V. N. R., *Tetrahedron,* **1999**, *55*, 10437. (b) Hori, M.; Gravert, D. J.; Wentworth, P. and Janda, K. D., *Bioorg. Med. Chem. Lett.,* **1998**, *8*, 2363.
7. Szmant, H. H. and Dudek, J., *J. Am. Chem. Soc.,* **1949**, *71*, 3763.
8. Vavon, G.; Bolle, J. and Calin, J., *Bull. Soc. Chim.,* **1939**, *6*(5), 1025.
9. Brown, H. C. and Nelson, K. L., *J. Am. Chem. Soc.,* **1953**, *75*, 6292.
10. Pratt, Y. T. (to Hercules Powder Company), *U.S. Pat.*, **1949**, July 6, 2,472,437 [*Chem. Abstr*. **1949**, *43*, 6665].
11. Fieser, L. F. and Seligman, A. M., *J. Am. Chem. Soc.,* **1935**, *57*, 228.
12. Fieser, L. F. and Seligman, A. M., *J. Am. Chem. Soc.,* **1935**, *57*, 942.
13. Akabori, S.; Sato, T. and Hata, K., *J. Org. Chem.,* **1968**, *33*, 3277.
14. See *Bakelite Process* here in (P. 160).
15. (a) Belen'kii, L. I.; Vol'kenshtein, Y. B. and Karmanova, I. B., *Russ. Chem. Rev*., **1977**, *46*, 891. (b) Olah, G. and Tolgyesi, W. S., "Blanc Rection" in *Friedel-Crafts and Related Reactions*, Vol. *2,* part 2, ed. Olah, G., Interscience, New York, **1963**, pp. 659–784. (c) Fuson, R. C. and McKeever, C. H., *Org. React.,* **1942**, *1*, 63.
16. (a) Benington, F.; Morin, R. D.; Clark, L. C. and Fox, R. P., *J. Org. Chem.,* **1959**, *27*, 1979. (b) Emerson, W. S.; Heyd, J. W.; Lucas, V. E.; Lyness, W. I.; Owens, G. R. and Shortridge, R. W., *J. Am. Chem. Soc.,* **1947**, *69*, 1905.
17. Pratt, Y. T., *J. Am. Chem. Soc.,* **1951**, *73*, 3803.
18. Whittleston, W. G., *J. Am. Chem. Soc.,* **1937**, *59*, 825.
19. Dahrouch, M. R.; Jara, P.; Mendez, L.; Portilla, Y.; Abril, D.; Alfonso, G.; Chavez, I.; Manriquez, J. M.; Rivière-Baudet, M.; Rivière, P.; Castel, A.; Rouzaud, J. and Gornitzka, H., *Organometallics,* **2001**, *20,* 5591.
20. (a) Sammelson, R. E. and Kurth, M. J., *Chem. Rev.,* **2001**, *101,* 137. (b) Franke, A.; Mattern, G. and Traber, W., *Helv. Chim. Acta,* **1975**, *58*, 283. (c) Grummitt, O. and Buck, A., *Org. Synth.,* **1944**, *24*, 30. (d) Darzens, G., *Compt. Rend.,* **1939**, *208*, 818. (e) Akin, R. B.; Stamatoff, G. S. and Bogert, M. T., *J. Am. Chem. Soc.,* **1937**, *59*, 1268. (f) Hill, P. and Short, W. F., *J. Chem. Soc.,* **1935**, 1123. (g) Brunner, A., *Chem. Zentralbl.,* **1933**, *2*, 609. (h) Blanc, G., *Perfumery Essent. Oil Record*, **1928**, *14*, 40. (i) Quelet, R., *Compt. Rend.,* **1933**, *196*, 1411.

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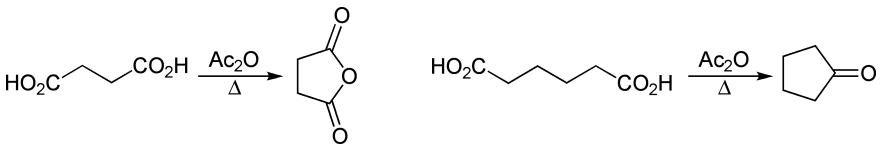
Blanc Rule

A. GENERAL DESCRIPTION OF THE REACTION

This rule was first generalized by Blanc in 1907,[1] although it was originally investigated by Lapworth in 1899[2] and subsequently by Perkin in 1904.[3] In 1907, Blanc reported[1] that glutaric acid on treatment with acetic anhydride formed an intramolecular anhydride, and when adipic and pimelic acids were subjected to the same treatment, cyclopentanone and cyclohexanone were generated correspondingly. Therefore, he summarized that when a dicarboxylic aliphatic acid was heated with acetic anhydride and distilled, the ketone of one less carbon atom would form, unless it was possible for a five- or six-membered cyclic anhydride to form. This generalization is called the Blanc rule.[4] It should be pointed out that the cyclizations can also be accomplished without the use of acetic anhydride by mere application of heat in a high vacuum.[5,6] This rule has been applied to a great number of substituted products of aliphatic dicarboxylic acids, especially in the constitutional analysis of the carbon skeleton of polycyclic systems, such as sterols and bile acids.[5,7,8] However, this rule has been found to be unsuccessful in a few cases,[9] and an alternative method has been developed to differentiate the cyclopentanones and cyclohexanones.[10] In this rule, the dicarboxylic aliphatic acids are normally heated $>200^{\circ}C$.[7]

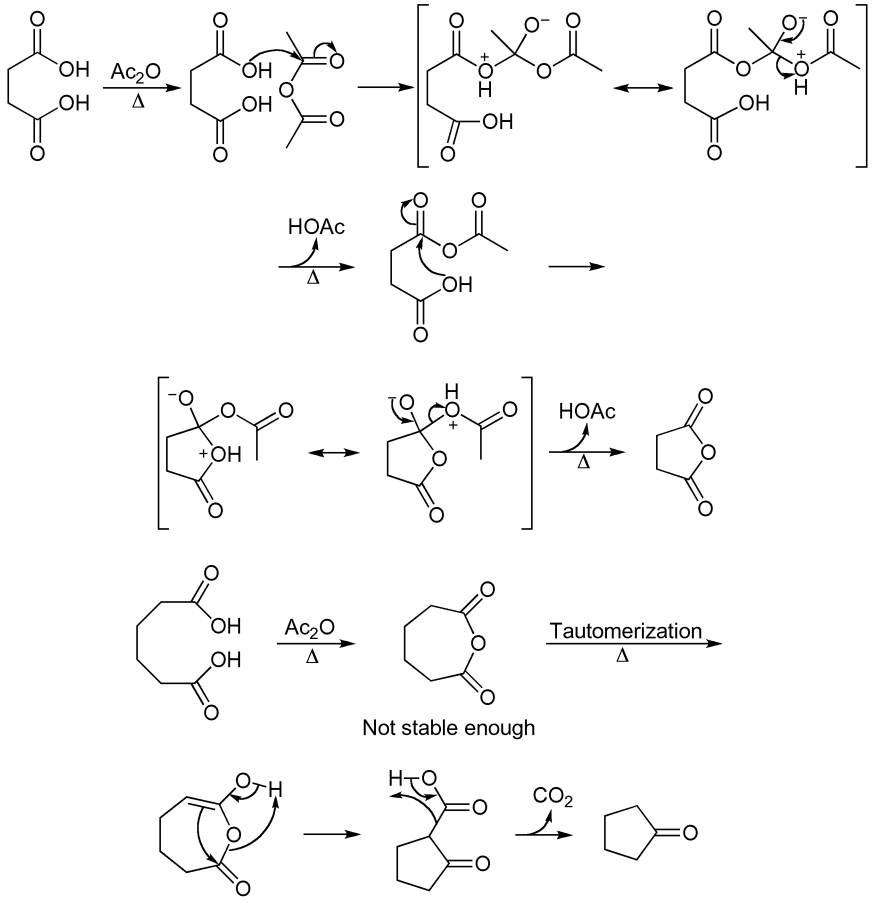
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

The mechanism is illustrated by showing the formation of succinic anhydride and cyclopentanone.



D. MODIFICATION

It has been modified by heating the dicarboxylic acid in the absence of acetic anhydride[6] and by using a mixture of acetic anhydride and potassium acetate.[7]

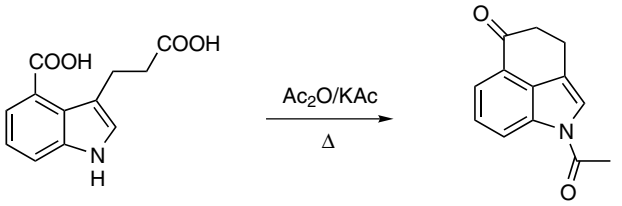
E. APPLICATIONS

This rule has been applied to characterize five-membered or six-membered ketone rings in steroid skeletons. In addition, this rule can also be used to prepare a variety of cycloketones.

F. RELATED REACTIONS

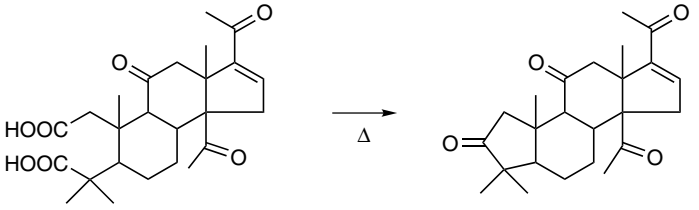
This rule is related to *Bredt's Rule*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

A solution of 143 mg β-(4-carboxy-3-indole)-propionic acid (0.6 mmol) and 15 mg potassium acetate (0.15 mmol) in 5 mL acetic anhydride was maintained at reflux temperature for 16 h. The acetic anhydride was distilled under reduced pressure. The residue was extracted with refluxing benzene. The solution was clarified by filtration and concentrated under diminished pressure. The remainder (125 mg) was recrystallized from a mixture of dichloromethane and ether to give 104 mg 1-acetyl-5-keto-1,3,4,5-tetrahydrobenz(ed) indole, m.p. 120–140°C. Further recrystallization from a mixture of dichloromethane and ether gave 90 mg pure product, in a yield of 71%, m.p. 147–152°C.



Reference 6

Dicarboxylic acid (2 g) was heated to 300°C for 2 h under a stream of nitrogen and at reduced pressure. Evolution of gas developed immediately. The residue was dissolved in benzene and chromatographed over 60 g alumina. The following fractions were collected: (a) benzene, 44 mg; (b) benzene-ether 3:1, 180 mg; (c) benzene-ether 1:1, 226 mg; (d) ether, 86 mg; and (e) chloroform, 340 mg. Fraction C crystallized, and further crystallizations from ether gave pure product, m.p. 195–197°C. No yield was given in original publication.

Other references related to the Blanc rule are cited in the literature.[11]

H. REFERENCES

1. (a) Blanc, H. G., *Compt. Rend.,* **1907**, *144*, 1356. (b) Blanc, H. G., *Bull. Soc. Chim.,* **1908**, *3*, 778.
2. (a) Lapworth, A. and Chapman, E. M., *J. Chem. Soc.,* **1899**, 1003. (b) Lapworth, A. and Chapman, E. M., *J. Chem. Soc.,* **1900**, 464.
3. (a) Perkin, W. H. and Thorpe, J. F., *J. Chem. Soc.,* **1904**, 128. (b) Perkin, W. H., *J. Chem. Soc.,* **1904**, 416. (c) Perkin, W. H., *J. Chem. Soc.,* **1906**, 1640.
4. (a) Davis, S. B.; Doering, W. E.; Levine, P. and Linstead, R. P., *J. Chem. Soc.,* **1950**, 1423. (b) Linstead, R. P. and Walpole, A. L., *J. Chem. Soc.,* **1939**, 850.

5. Sobotka, H., *Chem. Rev.,* **1934**, *15*, 311.
6. Lavie, D. and Willner, D., *J. Am. Chem. Soc.,* **1960**, *82*, 1668.
7. Smith, G. G. and Fahey, D. M., *J. Am. Chem. Soc.,* **1959**, *81*, 3391.
8. Uhle, F. C.; McEwen, C. M.; Schroter, H.; Yuan, C. and Baker, B. W., *J. Am. Chem. Soc.,* **1960**, *82*, 1200.
9. (a) Fieser, L. F. and Fieser, M., *Natural Pioducts Related to Phenanthrene*, Reinhold Publishing, New York, **1949**, pp. 134, 140. (b) Linstead, R. P. and Doering, W. E., *J. Am. Chem. Soc.,* **1942**, *64*, 1991.
10. Johnson, W. S. and Shelberg, W. E., *J. Am. Chem. Soc.,* **1945**, *67*, 1745.
11. (a) Bradbury, R. B., *Tetrahedron,* **1958**, *2*, 363. (b) Gascoigne, R. M. and Simes, J. J. H., *Quart. Rev.,* **1955**, *9*, 328. (c) Abu-Shady, H. A. and Soine, T. O., *J. Am. Pharm. Assoc.,* **1954**, *43*, 365. (d) Djerassi, C.; Wilfred, E.; Visco, L. and Lemin, A. J., *J. Org. Chem.,* **1953**,*18*, 1449. (e) Bachmann, W. E. and Deno, N. C., *J. Am. Chem. Soc.,* **1949**, *71*, 3540. (f) Ruzicka, L.; Rey, E. and Muhr, A. C., *Helv. Chim. Acta,* **1944**, *27*, 472. (g) Levitz, M.; Perlman, D. and Bogert, M. T., *J. Org. Chem.,* **1941**, *6*, 105. (h) Fieser, L. F. and Dunn, J. T., *J. Am. Chem. Soc.,* **1937**, *59*, 1021. (i) Bardhan, J. C., *J. Chem. Soc.,* **1936**, 1848. (j) Stange, O., *Z. Physiol. Chem.,* **1933**, *218*, 74. (k) Ruzicka, L.; Furter, M. and Thomann, G., *Helv. Chim. Acta,* **1933**, *16*, 327. (l) Wieland, H. and Dake, E., *Z. Physiol. Chem.,* **1932**, *210*, 268. (m) Windaus, A.; Westphal, K. and Stein, G., *Ber.,* **1928**, *61*, 1847. (n) Hückel, W. and Friederich, H., *Ann.,* **1927**, *451*, 153. (o) Adickes, F., *Ber.,* **1925**, *58*, 211. (p) Hückel, W., *Ann.,* **1925**, *444*, 14. (q) Windaus, A.; Hückel, W. and Reverey, G., *Ber.,* **1923**, *56*, 91.

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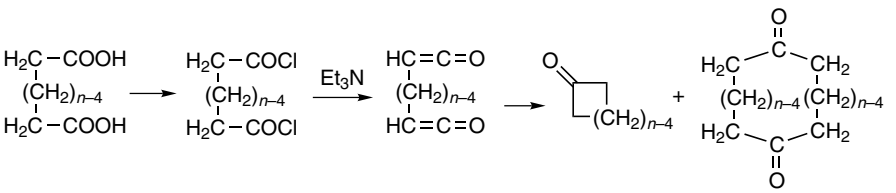
Blomquist Cyclic Ketone Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Blomquist in 1947.[1] It is the reaction to form intermediate to macrocyclic ketones via the process of intramolecular condensation of aliphatic diketenes at diluted concentration followed by hydrolysis and decarboxylation of cyclic ketene derivatives.[2] The intermolecular condensation of diketenes will form even larger macrocyclic diketones,[3] which can be converted into simple macrocyclic diketones.[4] The ketene can be easily obtained by the treatment of acyl chloride of dicarboxylic acid with tertiary amines, of which triethylamine gives the best result.[3] Although some polyketene products also form in this process, they can be easily removed.[3] Other methods for preparing macrocyclic ketones include the Ziegler,[5] Hunsdiecker,[6] Ruzicka,[7] and Gliński[8] reactions.

B. GENERAL REACTION SCHEME



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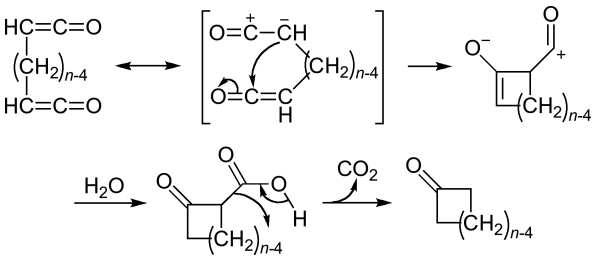
C. PROPOSED MECHANISMS

The mechanism is proposed as shown below.



D. MODIFICATION

N/A

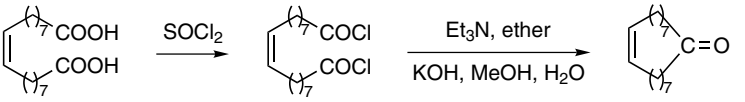
E. APPLICATIONS

This reaction has general application in the preparation of intermediate to macrocyclic ketones, such as muscone and civetone.[2]

F. RELATED REACTIONS

This reaction is related to the *Ruzicka Reaction.*

G. CITED EXPERIMENTAL EXAMPLES

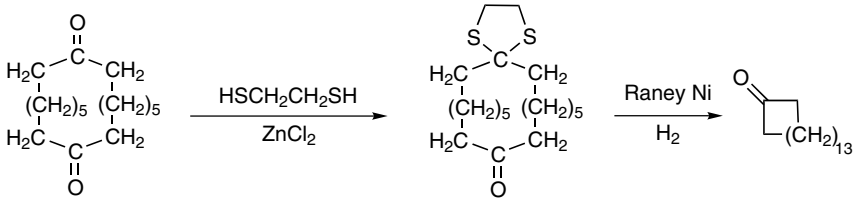


Reference 2.

A mixture of 1.8 g 9-octa-decene-1,18-dioic acid (5.8 mmol), 2 mL thionyl chloride (3.3 g, 28 mmol), and 5 mL absolute ether was warmed gently. Sulfur dioxide and hydrogen chloride distilled gradually. After 30 min, the temperature was raised to ~70°C, and the reaction was kept at this temperature for 1 h. Removal of excess thionyl chloride in vacuo at 50–60°C gave 2.03 g of the crude acid chloride, which still had an odor of thionyl chloride. A solution of the crude acid chloride in 200 mL absolute ether (Grignard dried) was added over a period of 15 h from a Hershberg dropping funnel down the condenser into a stirred, refluxing mixture of 500 mL absolute ether (Grignard dried) and 10 mL triethylamine. At the end of this time, the dropping funnel and condenser were rinsed with absolute ether, and

500 mL ether was removed by distillation of the combined ethereal solution. The remaining ethereal solution, triethylamine hydrochloride, and polymer were washed with 50-mL and 30-mL portions of 3 *N* HCl and finally with water until the washes were neutral to congo red. The ethereal solution was dried over anhydrous $MgSO_4$. The ether was distilled, and the residue weighed 1.72 g. To hydrolyze the ketene dimer, this material was dissolved in a solution of 2.0 g potassium hydroxide in 2.0 mL water and 30 mL methanol. The solution was kept at room temperature for 40 h and then was refluxed 1.5 h. The saponification mixture was cooled and diluted with water to ~200 mL; the neutral organic material was extracted repeatedly with ether. The combined ethereal solution was washed with water and dried over anhydrous $MgSO_4$. The ether was distilled, and 545 mg residue, crude civetone, was obtained. The material remaining in the aqueous layer was investigated sufficiently to ensure that no civetone was being lost as α-civetonecarboxylic acid.

The civetone was distilled at 0.2 mmHg pressure and a bath temperature of ~160°C. A nearly colorless distillate (476 mg) was obtained, in a yield of 33%.



Reference 4.

Conversion of 1,9-Cyclohexadecanedione to Its Ethylenedithioketal

After removing 50 mL benzene by distillation from a solution of 5.44 g 1,9-cyclohexadecanedione (0.0216 mol) in 200 mL of reagent-grade benzene, 2.03 g ethanedithiol (0.0216 mol), 20 g anhydrous Na_2SO_4, and 1.5 g freshly fused and powdered zinc chloride were added rapidly. The mixture, in a stoppered flask, was placed in the refrigerator overnight and allowed to stand 5 days at room temperature. The insoluble material was separated and thoroughly washed with benzene. The combined benzene filtrate and washings were evaporated to dryness and redissolved in hexane, leaving 1.0 g of insoluble material having a melting point of 204–210°C. This made up the crude bis-ethylenedithioketal. (An additional 1.1 g of this material—with a melting point of 206–210°C—was obtained by extracting the benzene-insoluble substances with water and chloroform and subsequently adding hexane to the chloroform extract.). Evaporation of the original hexane solution gave 4.66 g crude mono-ethylenedithioketal, which solidified in about 3 days. This crude product, containing unreacted diketone, was used for subsequent transformations without further purification.

Reductive Desulfurization of the 1,9-Cyclohexadecanedione Dithioketals

Crude 1,9-cyclohexadecandione dithioketal (4.66 g) was added to a suspension of 15 g Raney nickel in 200 mL ethanol, which had been previously refluxed for 1 h with 5 mL acetone. The mixture was refluxed for 3 h, cooled, and filtered. The filtered Raney nickel was allowed to stand under methanol. To the ethanolic filtrate was added a solution of 5 g semicarbazide hydrochloride and 10 g sodium acetate in 10 mL water. Although a white

precipitate formed immediately, the mixture was allowed to stand 24 h before filtration. The methanolic solution obtained after removal of the Raney nickel was treated similarly, and the resulting solid semicarbazone combined with that obtained earlier. The total semicarbazone precipitates were digested with 300-mL and 250-mL portions of boiling methanol. The insoluble material weighed 1.59 g and had a melting point of 221–227°C, corresponding to that of 1,9-cyclohexadecanedione disemicarbazone. An additional 0.29 g of impure disemicarbazone, (m.p. 186–191°C) separated when the methanolic filtrates stood at room temperature for 1 day. Concentration of the methanol solution gave three crystalline fractions of cyclohexadecanone semicarbazone: (a) 1.0 g with a melting point of 172–173°C, (b) 0.77 g with a melting point of 168–172°C, and (c) 1.25 g with a melting point of 170–175°C. The 3.02 g cyclohexadecanone semicarbazone corresponds to a 47% conversion from 1,9-cyclohexadecanedione. The yield, adjusted for recoverable diketone derivatives, was 90%.

Other references related to the synthesis of cyclic ketones are cited in the literature.[9]

H. REFERENCES

1. Blomquist, A. T. and Spencer, R. D., *J. Am. Chem. Soc.,* **1947**, *69*, 472.
2. Blomquist, A. T.; Holley, R. W. and Spencer, R. D., *J. Am. Chem. Soc.,* **1948**, *70*, 34.
3. Blomquist, A. T. and Spencer, R. D., *J. Am. Chem. Soc.,* **1948**, *70*, 30.
4. (a) Blomquist, A. T. and Wolinsky, J., *J. Am. Chem. Soc.,* **1955**, *77*, 5423. (b) Blomquist, A. T.; Prager, J. and Wolinsky, J., *J. Am. Chem. Soc.,* **1955**, *77*, 1804.
5. Ziegler, K.; Eberle, H. and Ohlinger, H., *Ann*., **1933**, *504*, 94.
6. Hunsdiecker, H., *Ber*., **1942**, *75B*, 1190.
7. Ruzicka, L. and Brugger, W., *Helv. Chim. Acta*, **1926**, *9*, 389.
8. Glinski, M. and Kaszubski, M., *Pol. J. Chem*., **2002**, *76*, 1037.
9. (a) Borgen, G. and Dale, J., *Acta Chem. Scand.,* **1972**, *26*, 952. (b) Schaefer, J. P. and Bloomfield, J. J., *Org. React.*, **1967**, *15*, 1. (c) Finley, K. T., *Chem. Rev*., **1964**, *64*, 573. (d) Meinwald, J. and Gassman, P., *J. Am. Chem. Soc.,* **1960**, *82*,2857. (e) Cava, M. P.; Little, R. L. and Napier, R. D., *J. Am. Chem. Soc.,* **1958**, *80*, 2257. (f) Walther, H.; Treibs, W. and Michaelis, K., *Chem. Ber.,* **1956**, *89*, 60. (g) Horner, L. and Spietscka, E., *Ber.,* **1954**, *88*, 934.

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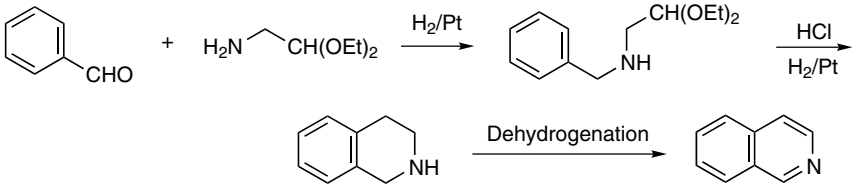
Bobbitt Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Bobbitt in 1965.[1] It is the reaction to synthesize 1,2,3,4-tetrahydroisoquinoline by cyclo-condensation of substituted benzylaminoacetals in the presence of hydrochloric acid, and is generally known as the Bobbitt reaction.[2] This reaction is not only good for the preparation of 1-substituted isoquinolines, but 4- and *N*-substituted isoquinolines as well. Although the initial preparation of 1-alkylisoquinolines has been developed by Quelet and Vinot,[3] the involvement of boron trifluoride as a cyclizing reagent has made it generally unsuitable for the synthesis of oxygenated isoquinolines. The Bobbitt reaction has overcome the potential problems via the addition of aliphatic Grignard reagents to the Schiff bases, followed by the cyclization[4] and its modification.[5] In addition, the *N*-substituted 1,2,3,4-isoquinoline can be easily prepared via the reductive alkylation of benzylamine and cyclization[6] and other related methods;[7] and the 4-substitued 1,2,3,4-isoquinoline (4-OH-1,2,3,4-isoquinoline[8]) could be synthesized via the condensation of 1,2-dihydroisoquinolines with aldehyde.[1b]

B. GENERAL REACTION SCHEME



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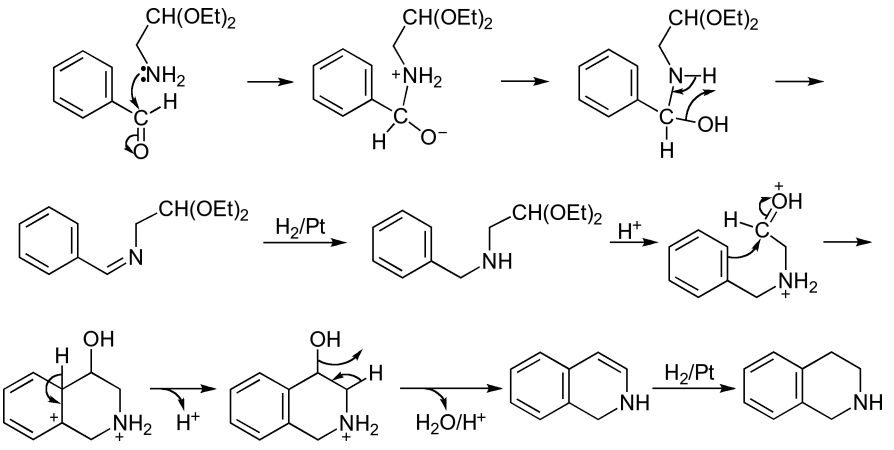
C. PROPOSED MECHANISMS

Displayed below is the illustration of reaction mechanism.



D. MODIFICATION

The 1-alkyl substituted isoquinolines have been modified via the reaction between imines and ethyl chloroformate followed by trimethyl phosphite to form carbamate phosphonate intermediates that cyclize into isoquinolines in the presence of Lewis acid.[5]

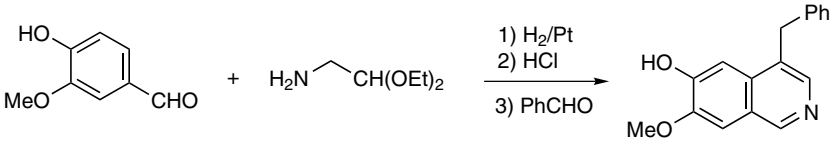
E. APPLICATIONS

This reaction has general application in synthesis of 1-, 4- and *N*-substituted 1,2,3,4-tetrahydroisoquinolines and 1-, and 4-substituted isoquinolines. In addition, this reaction has been applied to the synthesis of some alkaloids such as salsoline,[6] salsolidine,[6] carnegine,[6] and lophocerine.[9]

F. RELATED REACTIONS

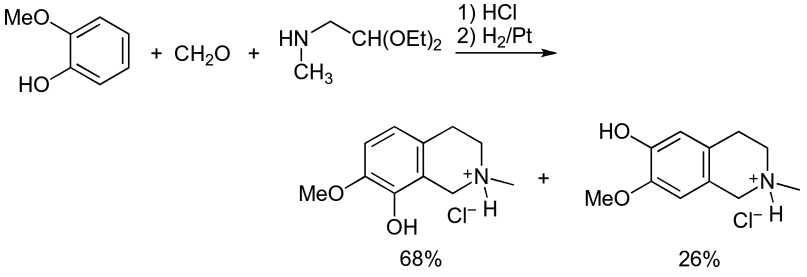
This reaction is related to the *Pomeranz-Fritsch Isoquinoline Synthesis.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 1b.

Vanillin (3.04 g, 0.02 mol), dissolved in a minimum amount of absolute ethanol, was combined with 2.66 g of aminoacetaldehyde diethylacetal (0.02 mol), and the mixture was diluted to 15 mL with absolute ethanol and hydrogenated at atmospheric pressure and room temperature over 200 mg of previously reduced platinum oxide. Hydrogen consumption stopped at about 90% completion after about 3 h. The catalyst was removed by filtration and the solvent was evaporated under vacuum. The residual oil was dissolved in 50 mL concentrated hydrochloric acid. The solution which had become hot was cooled and washed with three 30-mL portions of 3 : 2 ether-benzene to remove starting aldehyde. A two-fold excess of benzaldehyde (4.24 g, 0.04 mole) dissolved in 50 mL of ethanol was added to the acidic solution which was subsequently boiled for 30 min. The cooled solution was diluted with an equal volume of water and washed with three 50-mL portions of ether to remove the excess benzaldehyde. The solution was made basic with ammonium hydroxide to pH 8. The precipitate was removed by filtration and crystallized once from water-ethanol to give 3.33 g of 4-benzyl-6-hydroxy-7-methoxyisoquinoline, in a yield of 63%, m.p. 185–190°C. The analytical sample has m.p. at 192–193°C.



Reference 7a.

The mixture of 2.48 g guaiacol (0.02 mol), 3.0 g 40% aqueous formaldehyde (0.04 mol), and 3.6 g methylaminoacetaldehyde dimethyl acetal (0.03 mol) in 25 mL ethanol was stirred at room temperature for 24 h. The solvent was removed on a rotary evaporator and the resulting thick oil was dissolved in 50 mL cold 6 *N* HC1 and washed with ether. The acidic solution was stirred at room temperature for 15 h. The last traces of ether were removed on a rotary evaporator and the solution was hydrogenated over 4 g of 5% palladium on carbon at room temperature and atmospheric pressure until no more hydrogen was absorbed (about 0.02 mol). The catalyst was removed by filtration and the solution was concentrated on a rotary evaporator to a yellow syrup. The syrup was treated with 50 mL of hot ethanol and cooled. Crystals formed and were collected to yield 1.20 g of the crude hydrochloride of 2-methyl-6-hydroxyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline, in a yield of 26%, m.p. 281–284°C. The mother liquor after the removal of 2-methyl-6-hydroxyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride was concentrated and cooled to yield 3.12 g of crystalline crude hydrochloride of 2-methyl-7-methoxy-8-hydroxyl-1,2,3,4-tetrahydroisoquinoline, in a yield of 68%, m.p. 208–212°C.

Other references related to the Bobbitt reaction are cited in the literature.[10,11]

H. REFERENCES

1. (a) Bobbitt, J. M.; Kiely, J. M.; Khanna, K. L. and Ebermann, R., *J. Org. Chem.,* **1965**, *30*, 2247. (b) Bobbit J. M., Winter D. P. and Kiely J. M., *J. Org. Chem.*, **1965**, *30*, 2459.
2. (a) Lejay, P. and Viel, C., *Ann. Chim. (Paris),* **1977**, *2*, 127. (b) Lejay, P. and Viel, C., *Ann. Chim. (Paris),* **1977**, *2*, 87.
3. (a) Vinot, N. and Quelet, R., *Bull. Soc. Chim. Fr*., **1959**, 1164. (b) Vinot, N., *Ann. Chim.*, **1958**, *3*, 461.
4. Bobbitt, J. M.; Steinfeld, A. S.; Weisqraber, K. H. and Dutta, S., *J. Org. Chem.,* **1969**, *34*, 2478.
5. Hendrickson, J. B. and Rodríguez, C., *J. Org. Chem.,* **1983**, *48,* 3344.
6. Bobbitt, J. M.; Roy, D. N.; Marchand, A. and Allen, C. W., *J. Org. Chem.* **1967**, *32*, 2225.
7. (a) Bobbitt, J. M. and Dutta, C. P., *J. Org. Chem.,* **1969**, *34*, 2001. (b) Bobbit J. M. and Moore T. E., *J. Org. Chem.*, **1968**, *33*, 2958.
8. Bobbitt, J. M. and Sih, J. C., *J. Org. Chem.* **1968**, *33*, 856.
9. Bobbitt, J. M. and Chou, T.-T., *J. Org. Chem.,* **1959**, *24*, 1106.
10. For Reviews, see (a) Fukumi, H. and Kurihara, H., *Heterocycles,* **1978**, *9*, 1197. (b) Bobbitt, J. M., *Adv. Heterocycl. Chem.,* **1973**, *15*, 99.
11. (a) Kosciolowicz, A. and Rozwadowska, M. D., *Tetrahedron: Asymmetry,* **2006**, *17*, 1444. (b) Elkholy, Y. M., *Chem. Heterocyclic Comp.*, **2002**, *38*, 1342. (c) Durst, T.; Finke, J. A.; Huisgen, R. and Temme, R., *Helv. Chim. Acta*, **2000**, *83*, 2363. (d) Bobbitt, J. M. and Bourque, A. J., *Heterocycles,* **1987**, *25*, 601. (e) Coutta, I. G. C.; Hamblin, M. R.; Tinley, E. J. and Bobbitt, J. M., *J. Chem. Soc., Perkin Trans. I*, **1979**, 2744. (f) Gender, W. J.; Lawless, S. F.; Bluhm, A. L. and Dertouzos, H., *J. Org. Chem.* **1975**, *40*, 733. (g) Huffman, J. W. and Opliger, C. E., *J. Org. Chem.,* **1971**, *36*, 111. (h) Genster W. J.; Shamasundar K. T. and Marbury S., *J. Org. Chem.*, **1968**, *33*, 2861.

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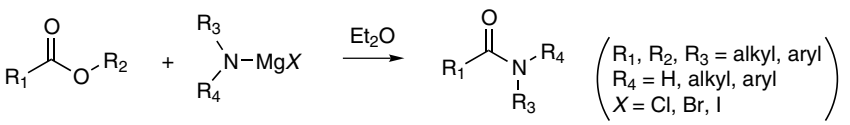
Bodroux Amide Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Bodroux in 1904.[1] It is the preparation of substituted amide from the reaction between a simple aliphatic or aromatic ester and an aminomagnesium halide (1:2 ratio) obtained by treatment of a primary or secondary amine with a Grignard reagent at room temperature. However, the direct aminolysis of carboxylic esters with primary amines requires high temperatures and the use of an autoclave.[2] Besides the magnesium amides,[1,3] other metal amides have also been developed, including the alkali,[4] aluminum,[5] tin,[6] and titanium amides.[7] This reaction has been modified as the reaction between esters and lithium aluminum amide prepared from the $LiAlH_4$ and amine (1:5 ratio of $LiAlH_4$ to amine for the best result) at 25°C in Et_2O.[2] The process for preparing lithium aluminum amide is indicated by the formation of a precipitate and usually is completed within 15–30 min for unhindered amines; it takes much longer time for hindered amine (e.g., overnight for *t*-$BuNH_2$).[2] More recent modifications for preparing amide include the reaction between a carboxylate, amine, and Grignard reagent in a 1:1:1.5 molar ratio.[8]

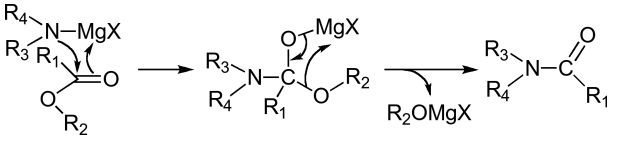
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

The mechanism is similar to the reaction between a Grignard reagent and ester, as illustrated here.



D. MODIFICATION

The original reaction procedure has been modified by using carboxylate, amine, and a Grignard reagent[8] and by using ester and lithium aluminum amides.[2]

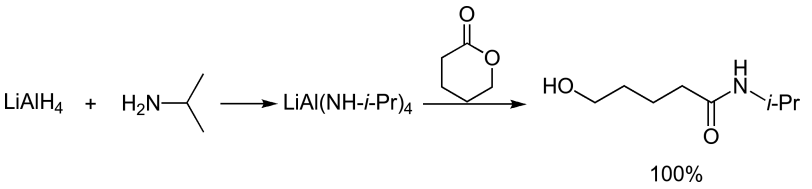
E. APPLICATIONS

This reaction is generally used to prepare substituted amides.

F. RELATED REACTIONS

This reaction is related to the *Willgerodt-Kindler Reaction*.

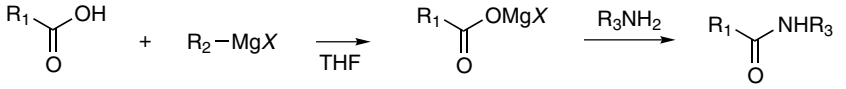
G. CITED EXPERIMENTAL EXAMPLES



Reference 2.

A suspension of 1 g $LiAlH_4$ (26 mmol) in 20 mL anhydrous Et_2O or THF was refluxed for 90 min. After the mixture was cooled to 25°C, 130 mmol of isopropylamine was added dropwise with stirring. After the addition was finished, stirring was maintained at 25°C until the precipitation was complete (15–30 min). After the addition of another 15 mL anhydrous Et_2O or THF, a ready-to-use-suspension was obtained. Then 26 mmol δ-valerolactone was added dropwise to the Et_2O suspension, and the new mixture was stirred at 25°C overnight (until the precipitate disappeared). The reaction was then carefully quenched by the successive addition of 1 mL H_2O, 1 mL 10% NaOH, and 3 mL H_2O. Stirring was maintained until the new precipitate became white and powdered. After filtration, the precipitate was carefully rinsed with CH_2C1_2 (5×10 mL), and the combined organic phases were dried over $MgSO_4$

and concentrated in vacuo to give the crude *N*-(1-methylethyl)-5-hydroxypentanamide as a pale yellow viscous liquid that could be purified via column chromatography, in a yield of 100%.



Reference 8.

The general procedure for the synthesis of the amides from carboxymagnesium halides is as follows. To a solution of 2 mmol alkylmagnesium halide was added 10–15 mmol of carboxylic acid at 0°C under nitrogen. After the reaction mixture had been stirred at 70°C for 15 min, 5 mmol amine was added at 0°C. The reaction vessel was heated at 70°C for 30 min to 3 h. The mixture was quenched with 25 mL 10% hydrochloric acid at 0°C and extracted with dichloromethane (2 × 20 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed on silica gel with ethyl acetate–light petroleum as the eluent. The reported yields were up to 65% if carried out in the noted conditions, and the tested amines include butylamine, diisopropylamine, morpholine, aniline, 1-phenylethylamine, and 1,2,3,4-tetrahydroisoquinoline. The best solvent for these conditions is THF, although Et_2O gives comparable yields. The mixture of THF and DMF (or THF/HMPA) does not afford any products. (*Note:* The procedure has been modified from the reported one for the purpose of easy follow-up.)

Other references related to the Bodroux amide synthesis are cited in the literature.[9]

H. REFERENCES

1. Bodroux, F., *Compt. Rend.,* **1904**, *138*, 1427.
2. Solladié-Cavallo, A. and Bencheqroun, M., *J. Org. Chem.,* **1992**, *57*, 5831.
3. Basset, H. L. and Thomas, C. R., *J. Chem. Soc.,* **1954**, 1188.
4. (a) Yang, K. W.; Cannon, J. C. and Rose, J. G., *Tetrahedron Lett.,* **1970**, 1791. (b) Huebner, C. F.; Lucas, R; McPhillamy, H. B. and Troxell, H. A., *J. Am. Chem. Soc*., **1955**, *77*, 469.
5. Baaha, A.; Lipton, M. and Weinreb, S. M., *Tetrahedron Lett.,* **1977**, 4171.
6. George, T. A. and Lappert, M. F., *J. Chem. Soc. C,* **1969**, 992.
7. Chandra, G.; George, T. A. and Lappert, M. F., *J. Chem. Soc C,* **1969**, 2565.
8. Aubert, C.; Huard-Perrio, C. and Lasne, M-C., *J. Chem. Soc., Perkin Trans. I,* **1997**, 2837.
9. (a) Kuhn, R. and Morris, C., *Ber.,* **1937**, *70*, 853. (b) Bodroux, F., *Bull. Soc. Chim. Fr.,* **1907**, 912. (c) Bodroux, F., *Bull. Soc. Chim. Fr.,* **1906**, *35*. (d) Bodroux, F., *Bull. Soc. Chim. Fr.,* **1906**, 519. (e) Bodroux, F., *Compt. Rend.,* **1906**, *142*, 401. (f) Bodroux, F., *Bull. Soc. Chim. Fr.,* **1905**, *33*. (g) Bodroux, F., *Bull. Soc. Chim. Fr.,* **1905**, 831. (h) Bodroux, F., *Compt. Rend.,* **1905**, *140*, 1108.

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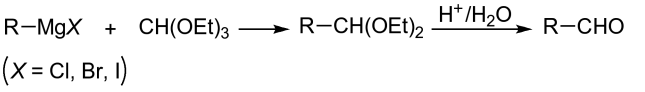
Bodroux-Chichibabin Reaction

A. GENERAL DESCRIPTION OF THE REACTION

Although this reaction had been initially reported by Gattermann and Maffezzoli[1] and concurrently by Chichibabin (or Tschitschibabin)[2] in 1903 and subsequently by Bodroux in 1904,[3] it was named after Bodroux and Chichibabin, as the Bodroux-Chichibabin reaction.[4] This reaction is the synthesis of aliphatic or aromatic aldehydes by treatment of ethyl orthoformate with corresponding Grignard reagents. In this reaction, after addition of the orthoformates to the ethereal solution of the Grignard reagent, and removal of solvent via distillation, the acetal will form and can be converted into aldehydes on treatment with acidic water. Other orthoformates can also be used for this reaction.[5] When ethyl orthoformate is applied in this reaction, the replacement of the first ethoxyl group is a slow reaction,[6] but the yields can be improved by refluxing the mixture of Grignard reagent and orthoformate.[6] It was found that in the reaction between the orthoformate (if prepared from 1,3-diol and alcohol) and the Grignard reagent, the acetals with axial 2-alkoxy groups react rapidly with a variety of Grignard reagents with high retention of configuration to give (very unstable) products with the axial 2-alkyl groups; in contrast, the diastereoisomers with equatorial 2-alkoxy groups appear to be unreactive and, under forcing conditions, give mixtures of several products.[7]

B. GENERAL REACTION SCHEME



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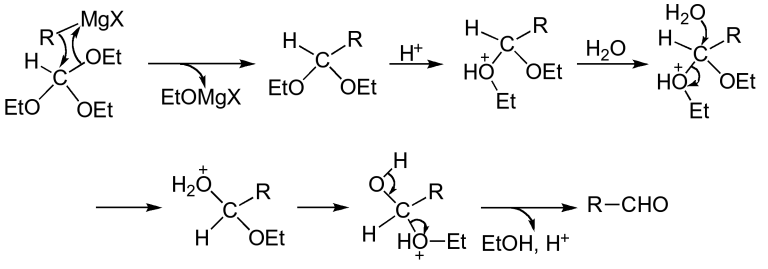
C. PROPOSED MECHANISMS

A general mechanism is displayed below.



D. MODIFICATION

N/A

E. APPLICATIONS

This reaction has been generally applied to the synthesis of aldehydes.

F. RELATED REACTIONS

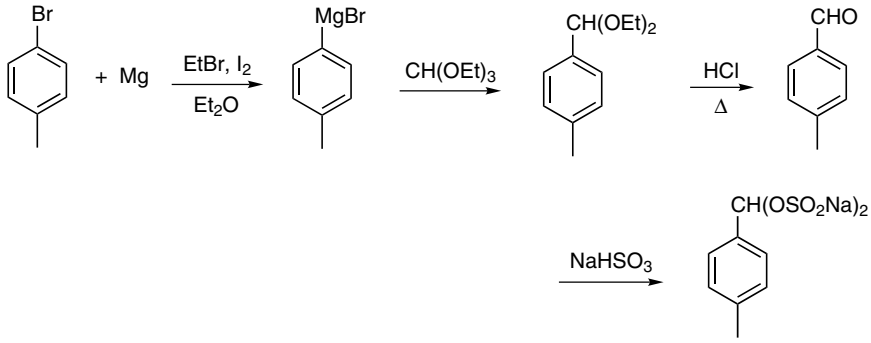
This reaction is related to the *Bouveault Reaction.*

G. CITED EXPERIMENTAL EXAMPLES

Reference 4c.

To a three-necked flask equipped with a dropping-funnel, mechanical stirrer, and condenser with openings protected by calcium chloride tubes was added fresh magnesium turnings. The flask was heated on a steam bath while a current of dry air was passed through. After the flask had cooled, 10 mL ether and a crystal of iodine were introduced. Then the alkyl halide (or aryl halide) in 10 mL ether was dropped onto the magnesium. After the reaction started, enough ether was added to the solution to bring the total amount of ether up to 4.5 moles per mole of alkyl halide. After the addition was complete, the mixture was refluxed and stirred for 15 min longer. Then, with stirring, the orthoformic ester, dissolved in an equal volume of ether, was added at the rate of about two drops per

second. No apparent reaction occurred. After the addition of the reagent was complete, the reaction mixture was refluxed and decomposed by the addition of ice and 5 N H_2SO_4 and refluxed for a few minutes to decompose the acetal. If the ether had been distilled off, the cooled mixture was extracted with ether three times (50 mL each time); otherwise, the ether layer was merely separated. The combined ethereal solutions were shaken vigorously with 50 mL saturated sodium bisulfite solution, and the filtrate was shaken with fresh bisulfite solution and again filtered. The combined solids were washed with 50 mL cold alcohol and then with 50 mL ether and spread in the air to dry. (*Note:* Readers should consult the original paper for details about this modified procedure.)



Reference 8.

The Grignard reagent was prepared by adding a solution of 20.8 g *p*-bromotoluene (0.122 mol) in 100 mL ether dropwise (45 min) to the suspension of 3.3 g magnesium powder (0.136 mol) in 20 mL ether under stirring. The reaction was started by the addition of 0.5 mL ethyl bromide and a crystal of iodine; after all the bromide was added, the solution was refluxed for 2 h. Ethyl orthoformate (22 g, 0.142 mol) in 30 mL ether was then rapidly added within 5 min and the reaction mixture was refluxed for 5 h. The ether was then distilled off on the steam bath; when practically all of it was removed, there was a sudden vigorous reaction. At this point, the flask was quickly immersed in an ice bath and allowed to remain there until all evidence of a reaction had disappeared. After standing overnight, 50 g ice and 125 mL cold 5 N HCl were added, the small residual amount of ether was evaporated, and the reaction mixture was refluxed for 30 min on the steam bath under an atmosphere of carbon dioxide. The aldehyde was then steam distilled in an atmosphere of carbon dioxide, and the distillate was extracted three times with ether (60 mL each time). The combined ether extracts were evaporated on the steam bath to remove solvent and propionic aldehyde (b.p., 50°C), and the residue of impure *p*-tolualdehyde was taken up in 20 mL ether. The ethereal solution was then vigorously shaken with a freshly prepared, saturated aqueous solution of sodium bisulfite, the solid was filtered off, and the filtrate was shaken again with fresh bisulfite solution and filtered. The combined solids were washed with ether and dried, and 20.3 g of solid was obtained, in a yield of 74.4%.

Other references related to the Bodroux-Chichibabin reaction are cited in the literature.[9]

H. REFERENCES

1. Gattermann, L. and Maffezzoli, F., *Ber.,* **1903**, *36*, 4152.
2. Chichibabin, A. E., *J. Russ. Phys. Chem. Soc.,* **1903**, *35*, 1284.
3. Bodroux, F., *Compt. Rend.,* **1904**, *138*, 92.
4. (a) Pasternak, Y. and Traynard, J. C., *Bull. Soc. Chim. Fr.,* **1966**, 356. (b) Kulka, K., *Amer. Perfumer & Aromatics,* **1958**, *71*, 51. (c) Smith, L. I. and Bayliss, M., *J. Org. Chem.,* **1941**, *6*, 437.
5. (a) Chichibabin, A. E. and Yelgasin, S. A., *Ber.,* **1914**, *47*, 48. (b) Chichibabin, A. E. and Yelgasin, S. A., *Ber.,* **1914**, *47*, 1843.
6. Bodroux, F., *Compt. Rend.,* **1904**, *138*, 700.
7. Eliel, E. L. and Nader, F., *J. Am. Chem. Soc.,* **1969**, *91*, 536.
8. Smith, L. I. and Nichols, J., *J. Org. Chem.,* **1941**, *6*, 489.
9. (a) Eliel, E. L. and Giza, C., *J. Org. Chem.,* **1968**, *33*, 3754. (b) Eliel, E. L. and Knoeber, M. C., *J. Am. Chem. Soc.,* **1968**, *90*, 3444. (c) Pasternak Y., Traynard J. C., *Bull. Soc. Chim. Fr.*, **1966**, 365. (d) Edwards, W. R. and Kammann, K. P., *J. Org. Chem.,* **1964**, *29*, 913. (e) Sisti, A.; Burgmaster, J. and Fudim, M., *J. Org. Chem.,* **1962**, *27*, 279. (f) Kharasch, M. and Reinmuth, O., *Grignard Reactions of Nonmetallic Substances,* Prentice-Hall, New York, **1954**, pp. 586–591. (g) Post, H. W., *The Chemistry of the Aliphatic Orthoesters,* Reinhold Publishing, New York, **1943**, pp. 96–105. (h) Bohlmann, F., *Ber*., **1933**, *86*, 63. (i) Bohlmann, F., *Ber*., **1933**, *86*, 657. (j) Chichibabin, A. E., *Ber.,* **1904**, *37*, 186. (k) Chichibabin, A. E., *Ber.,* **1904**, *37*, 850.

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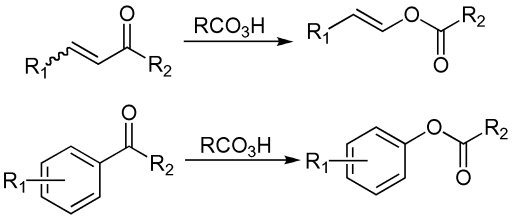
Böeseken Oxidation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Böeseken in 1929.[1] It is the reaction for transforming the α,β-unsaturated carbonyl compounds into enol esters[2] or aromatic carbonyl molecules (benzaldehys or phenyl ketones) into phenol esters[3] via oxygen insertion from the alkaline oxidation by peracids. The peracids used can be hydrogen peroxide,[4] peroxybenzoic acid,[5] peroxyacetic acid,[6] etc. This base-catalyzed oxidation of carbonyl compounds are different both in mechanism and in direction of cleavage from the acid-catalyzed oxidation (e.g., the *Baeyer-Villiger Oxidation*), indicating the migration of an alkyl or aryl group to an electron-deficient oxygen atom. The ease of cleavage and migratory aptitude of groups from ketone under alkaline peroxide oxidation is found in the order of primary alkyl > secondary alkyl > methyl and phenyl.[7] A faster and cleaner solid-state oxidation of hydroxylated benzaldehydes using urea-hydrogen peroxide as the oxidation reagent can be considered as the modification of this reaction.[3]

B. GENERAL REACTION SCHEME



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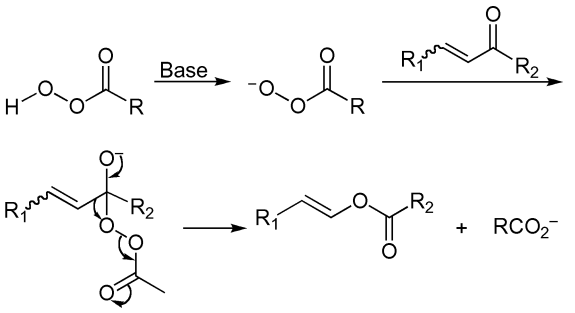
C. PROPOSED MECHANISMS

The mechanism for the alkaline oxidation of α,β-unsaturated carbonyl compound by peracids is proposed as shown below.



D. MODIFICATION

This reaction has been modified by using urea-hydrogen peroxide as an oxidizing reagent.[3]

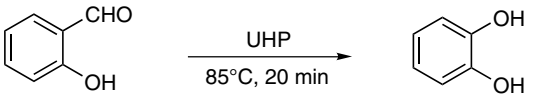
E. APPLICATIONS

This reaction can be used to prepare different phenols (e.g., via the oxidation of benzaldehydes or phenyl ketones), enol esters (from α,β-unsaturated carbonyl compounds) and aldehydes (from the further hydrolysis of corresponding enol esters).

F. RELATED REACTIONS

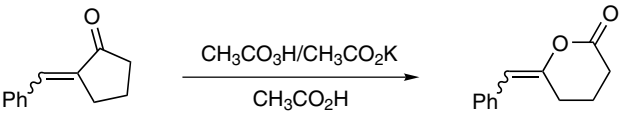
This reaction is related to the *Baeyer-Villiger Oxidation.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 3.

Benzaldehyde (2 mmol) was added to 376 mg finely powdered urea–hydrogen peroxide adduct (UHP, 4 mmol) in a glass test tube, and the reaction mixture was placed in an oil bath at 85°C for 20 min. After completion of the reaction (monitored by TLC, hexane/EtOAc = 8:2), the reaction mixture was extracted into ethyl acetate, and the combined extracts were washed with water and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford the crude product, which was purified by chromatography to deliver pure product, in a yield of 85%.



Reference 8.

To a solution of 14.05 g benzylidenecyclopentanone (0.082 mol) in 70 mL glacial acetic acid saturated with potassium acetate was added 12 mL commercial peroxyacetic acid (containing 0.076 mol peracid) within 10 min under stirring. After 40 min, 93% of the peroxyacetic acid and 53% of the hydrogen peroxide content of the reagent had been consumed; after 70 min 95% of peroxyacetic acid and 68% of the hydrogen peroxide content had been consumed. Ether and water (100 mL each) were added to the reaction mixture. The aqueous layer was separated and extracted with ether (2×50 mL). The ethereal solutions were combined, washed consecutively with water (3×50 mL), sodium carbonate solution (2×25 mL), and again with water (2×50 mL). After filtration through $MgSO_4$ and concentration on the steam bath, a residue was obtained, which solidified on cooling. Recrystallization from isopropyl ether yielded 8.4 g 6-phenyl-5-hydroxyl-5-hexenoic acid δ-lactone (colorless flakes), m.p. 79–80°C. Somewhat less pure additional material (1.0 g) was isolated from the recrystallization mother liquors. The total yield obtained was 67% on the basis of peroxyacetic acid and 82% on the basis of the ketone used.

Other references related to the Böeseken oxidation are cited in the literature.[9]

H. REFERENCES

1. Böeseken, J. and Elsen, G., *Rec. Trav. Chim. Pays-Bas Belg.,* **1929**, *48*, 363.
2. Gorodetsky, M.; Danieli, N. and Mazur, Y., *J. Org. Chem.,* **1967**, *32*, 760.
3. Varma, R. S. and Naicker, K. P., *Org. Lett.,* **1999**, *1*, 189.
4. Hassall, C. H., *Org. React.,* **1957**, *9*, 73.
5. Ogata, Y. and Sawaki, Y., *J. Org. Chem.,* **1969**, *34*, 3985.
6. Boeseken, J.; Cohen, W. D. and Kip, C. J., *Rec. Trav. Chim. Pays-Bas,* **1936**, *55*, 815.
7. House, H. O. and Wasson, R. L., *J. Org. Chem.,* **1957**, *22*, 1157.
8. Walton, H. M., *J. Org. Chem.,* **1957**, *22*, 1161.
9. (a) Pinhey, J. T. and Schaffner, K., *Tetrahedron Lett.,* **1965**, 601. (b) Caspi, E.; Chang, Y. W. and Dorfman, R. I., *J. Med. Pharm. Chem.,* **1962**, *5*, 714. (c) Crosby, D. G., *J. Org. Chem.*, **1961**, *26*, 2115. (d) Petrit, G. R. and Kasturi, T. R., *J. Org. Chem.,* **1961**, *26*, 986. (e) Petrit, G. R. and Kasturi, T. R., *J. Org. Chem.,* **1961**, *26*, 4557. (f) Payne, G. B. and Williams, P. H., *J. Org. Chem.*, **1959**, *24*, 284. (g) Turner, R. B., *J. Am. Chem. Soc.,* **1950**, *72*, 579. (h) Salamon, A., *Z. Physiol. Chem*., **1941**, *272*, 61. (i) Von. Wacek, A. and V. Bezard, A., *Oesterreichische Chemiker-Zeitung*, **1941**, *44*, 89. (j) Böeseken J. and Greup J., *Rec. Trav. Chim.*, **1939**, *58*, 528. (k) Böeseken J. and Jacobs, J., *Rec. Trav. Chim.*, **1936**, *55*, 786, 815. (l) Böeseken J. and Soesman, A. L., *Rec. Trav. Chim.,* **1933**, *52*, 874. (m) Kremer, A. and Böeseken, J., *Rec. Trav. Chim. Pays-Bas Belg.,* **1931**, *50*, 827. (n) Smit, W. C., *Rec. Trav. Chim. Pays-Bas Belg.,* **1930**, *49*, 686. (o) Smit, W. C., *Rec. Trav. Chim. Pays-Bas Belg.,* **1930**, *49*, 539. (p) Bodendorf, K., *Arch. Pharm.,* **1930**, *268*, 491.

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Bogert-Cook Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported almost coincidently by Cook[1] in 1932 and Bogert[2] in 1933. It is a two-step process for preparing octahydrophenanthrene derivatives from a *Grignard Reaction* between β-phenylethylmagnesium bromide and cyclohexanones followed by cyclodehydration of the tertiary alcohol with concentrated sulfuric acid, accompanied by a small amount of spirane. In this reaction, when the intermediate carbinol is treated with a milder dehydrating agent (e.g., iodine, potassium hydrogen sulfate, 50% sulfuric acid), it is converted into the corresponding olefin,[2] which can also cyclize to octahydrophenanthrene derivatives.[3] These experimental results led to the early idea that the mechanism of this reaction involved the initial dehydration followed by the cyclization of the olefin produced,[4] which is now known to be erroneous.[5] It is believed that three possible intermediates can be formed, depending on the acidity and temperature of the reaction.[5b] On the other hand, when an alkyl or alkoxyl group is at the position *meta* to the side chain in the phenyl ring, cyclization can proceed to yield the 5- or the 7-substituted phenanthrene derivatives.[6] The yields of spirane formed vary, depending on the reactivity of the aromatic nucleus at the cyclization position.[5b] The particular stereoisomer formed by cyclization of the carbinol intermediate with an unreactive aromatic nucleus (*o*-chlorophenyl) is different from that obtained from the corresponding carbinol with a more reactive nucleus (phenyl).[5b]

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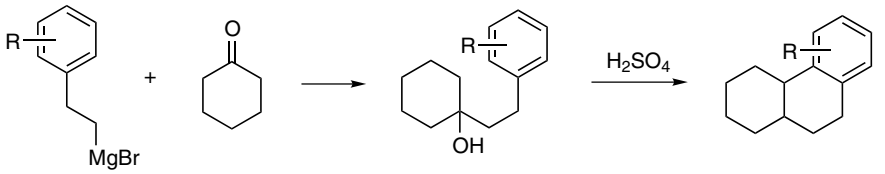
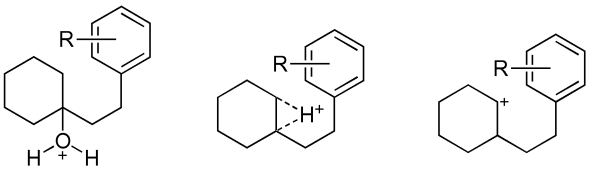
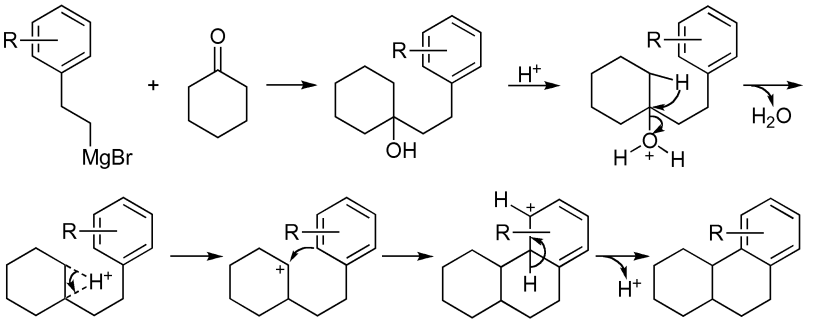
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



It is believed that three possible intermediates (**I**, **II**, and **III**) can be formed, depending on the acidity and temperature of the reaction.[5b] The bridged ion **II** is of appreciably lower energy than the free carbonium ion.[7] Under mild conditions, intermediate **I** predominates in the reaction, but only aryl groups with extremely reactive nuclear positions can cyclize; however, if the aromatic nucleus is moderately reactive, the cyclization occurs via the bridged ion **II**. If the aryl nucleus is unreactive, the cyclization takes place only after the higher energy carbonium ion (**III**) has formed to some extent. Nevertheless, an illustrative mechanism is shown for this reaction.



D. MODIFICATION

The cyclization of olefin has been modified using mercuric acetate and perchloric acid[8] or mercuric perchlorate in acetic acid.[9]

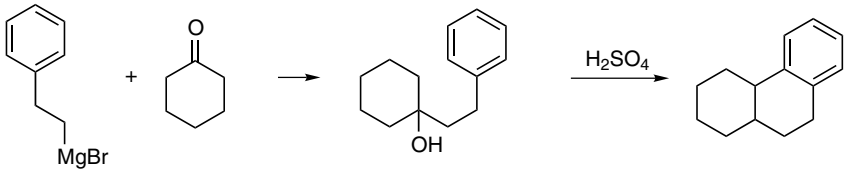
E. APPLICATIONS

This reaction has a general application in the preparation of polynuclear hydrocarbons containing a phenanthrene nucleus.

F. RELATED REACTIONS

This reaction is related to the *Bardhan Sengupta Synthesis*.

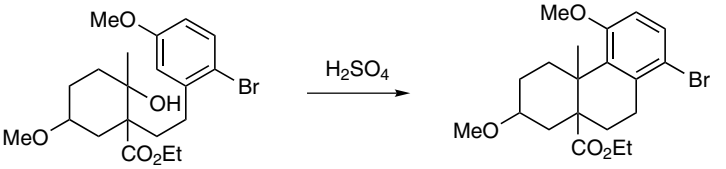
G. CITED EXPERIMENTAL EXAMPLES



Reference 4b.

The white needle-shaped 1-β-phenylethylcyclohexanol-1 was prepared from phenylethyl bromide and cyclohexanone, which was crystallized by making a saturated solution in warm petroleum ether and chilling it with an ice salt or solid carbon dioxide–alcohol mixture. The yield was 54%, m.p. 57°C, b.p. 145°C at 2–3 mmHg.

It is advised that 90% sulfuric acid be used for the secondary alcohols and 85% for the tertiary ones. The alcohol was added slowly with stirring to two volumes of the acid cooled by an ice pack. When all the alcohol had been added, the stirring was continued for 15–20 min at room temperature, and the mixture was then extracted with petroleum ether. The extract was agitated vigorously two or three times with cold 85% sulfuric acid, until the ether layer was a pale lemon yellow, then it was washed with a 10% sodium carbonate followed by a 10% sodium sulfate solution, dried over anhydrous potassium carbonate, and fractioned under diminished pressure to give *as*-octahydrophenanthrene, in a yield of 90%, b.p., 135–137°C (10 mmHg).



Reference 10.

The crude tertiary alcohol (5 g) was dissolved in 50 mL benzene and added to 107 g 90% sulfuric acid. The reaction mixture was stirred for 1 h at 0–2°C and then poured onto ice. After processing and evaporatively distilling at 150–155°C (0.15 mmHg), 1 g 2,5-dimethoxy-8-bromo-4a-methyl-10a-carbethoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene was obtained.

Other references related to the Bogert-Cook synthesis are cited in the literature.[11]

H. REFERENCES

1. Cook, J. W., *J. Chem. Soc.,* **1932**, 1472.
2. Bogert, M. T., *Science*, **1933**, *77*, 289.
3. Cook, J. W.; Hewett, C. L. and Robinson, A. M., *J. Chem. Soc.,* **1939**, 168.
4. (a) Bardhan, J. C. and Adhya, R. N., *J. Chem. Soc.,* **1956**, 260. (b) Perlmann, D.; Davidson, D. and Bogert, M. T., *J. Org. Chem.,* **1936**, *1*, 288.
5. (a) Barclay, L. R. C., "Cycloalkylation of Aromatics," in *Friedel-Crafts and Related Reactions*, ed. Olah, G. A., Interscience, New York, **1964**, *Vol. 2*, p. 785. (b) Barnes, R. A., *J. Am. Chem. Soc.,* **1953**, *75*, 3004.
6. (a) Christol, H.; Pietrasanta, Y. and Vernet, J. L., *C. R. Acad. Sci., Ser. C,* **1970**, *270*, 1477. (b) Haworth, R. D. and Moore, B. P., *J. Chem. Soc.,* **1946**, 633. (c) Haworth, R. D. and Barker, R. L., *J. Chem. Soc.,* **1939**, 1299. (d) Perlmann, D. and Bogert, M. T., *J. Am. Chem. Soc.,* **1937**, *59*, 2534. (e) Bogert, M. T.; Davidson, D. and Apfelbaum, P. M., *J. Am. Chem. Soc.,* **1934**, *56*, 959.
7. (a) Cram, D. J., *J. Am. Chem. Soc.,* **1952**, *74*, 2137. (b) Dewar, M. J. S., *Ann. Repts. Progr. Chem., (Chem. Soc. London),* **1951**, *48*, 118. (c) Pitzer, K. S., *J. Am. Chem. Soc.,* **1945**, *67*, 1126.
8. Julia, M. and Labia, R., *Tetrahedron Lett.,* **1969**, 501.
9. Julia, M. and Labia, R., *C. R. Acad. Sci., Ser. C.*, **1967**, *265*, 1492.
10. Barnes, R. A.; Hirschler, H. P. and Bluesteln, B. R., *J. Am. Chem. Soc.,* **1952**, *74*, 32.
11. (a) Evans, D. A.; Cain, P. A. and Wong, R. Y., *J. Am. Chem. Soc.,* **1977**, *99*, 7083. (b) Floyd, A. J.; Dyke, S. F and Ward, S. E., *Chem. Rev.,* **1976**, *76*, 509. (c) Schmidt C. and Thazhuthavectil J., *Can. J. Chem.*, **1973**, *51*, 3620. (d) Barnes, R. A. and Konort, M. D., *J. Am. Chem. Soc.*, **1953**, *75*, 303. (e) Barnes, R. A. and Gottesman, R. T.,*J. Am. Chem. Soc.,* **1952**, *74*, 35. (f) Barnes, R. A.; Hirschler, H. P. and Bluestein, B. R., *J. Am. Chem. Soc.,* **1952**, *74*, 4091. (g) Renfrow, W. B.; Renfrow, A.; Shoun, E. and Sears, C. A., *J. Am. Chem. Soc.,* **1951**, *73*, 317. (h) Barnes, R. A. and Gordon, L., *J. Am. Chem. Soc.,* **1949**, *71*, 2644. (i) Haworth, R. D. and Moore, E. P., *J. Chem. Soc*., **1946**, 633. (j) Cook, J. W.; McGinnis, N. A. and Mitchell, S., *J. Chem. Soc.,* **1944**, 286. (k) Begman, E., *Chem. Rev.*, **1941**, *29*, 535. (l) Sterling, E. C. and Bogert, M. T., *J. Org. Chem.,* **1939**, *4*, 20. (m) Perlmann, D.; Davidson, D. and Bogert, M. T., *J. Org. Chem.*, **1936**, *1*, 300. (n) van de Kamp, J. and Mosettig, E., *J. Am. Chem. Soc.,* **1936**, *58*, 1062. (o) Cook, J. W. and Hewett, C. L., *J. Chem. Soc.*, **1933**, 1098. (p) Cook, J. W. and Hewett, C. L., *J. Chem. Soc.*, **1933**, 398. (q) Cook, J. W. and Hewett, C. L., *J. Chem. Soc.,* **1933**, 451.

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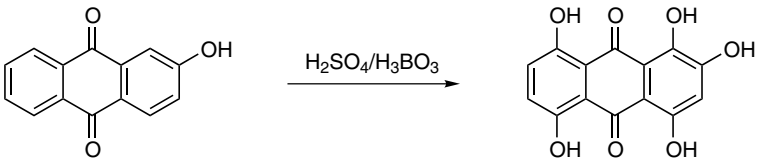
Bohn-Schmidt Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Bohn in 1889[1] and subsequently by Schmidt in 1891.[2] It is the introduction of hydroxyl groups into anthraquinone molecules containing at least one hydroxyl group by the oxidizing action of fuming sulfuric acid (i.e., oleum).[3] Therefore, it is generally known as the Bohn-Schmidt reaction.[3,4] It is reported that if boric acid is added to the reaction mixture, then ordinary concentrated sulfuric acid can be used instead of the oleum, and boric acid can form esters with hydroxyanthraquinones to prevent the further oxidation.[5] In addition, selenium, selenium oxide, and mercury can be added as catalytic agents.[6]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Because no illustrative mechanism is available, a tentative mechanism is proposed here for the reaction. It should be pointed out that oleum or even concentrated sulfuric acid has

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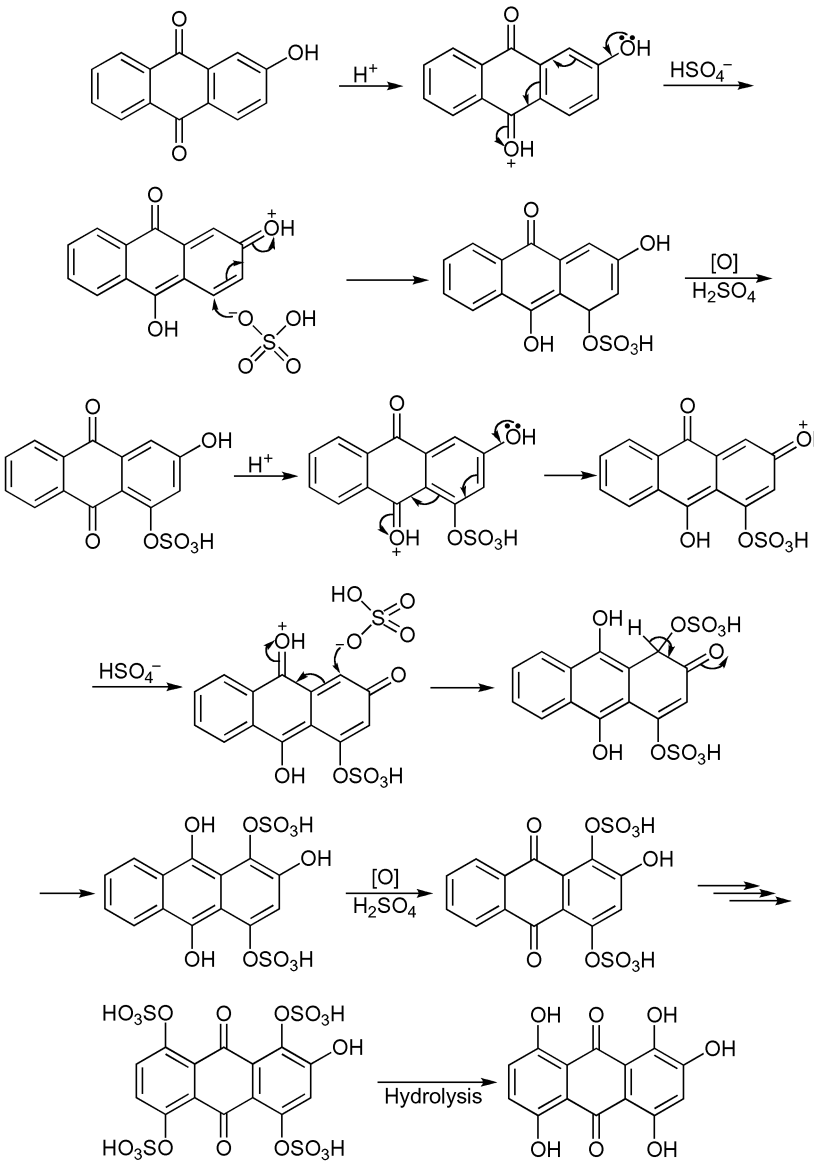
the oxidation power, and hydroquinone or semihydroquinone can be oxidized into quinone by sulfuric acid.



D. MODIFICATION

This reaction has been modified to proceed in the presence of selenium or selenium oxide as catalyst.[6]

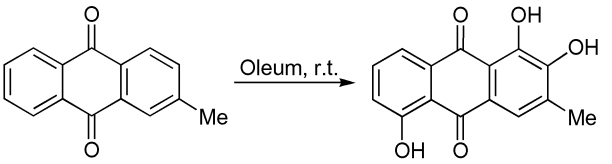
E. APPLICATIONS

This reaction has been applied to the technical preparation of important dyes such as Alizarin Green S, Alizarin Bordeaux, Alizarin Cyanine R, and Alizarin Cyanin Black.[3]

F. RELATED REACTIONS

This reaction is related to the *Boyland-Sims Oxidation* and *Elbs Persulfate Oxidation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

3-Methylalizarin (1 g) was treated with 6 mL 100% oleum at room temperature for 14–18 h. The reaction mixture was diluted with 50 mL concentrated H_2SO_4, and the resulting solution was poured onto 250 g crushed ice. The sulfuric ester that separated was filtered, and the wet cake was dissolved in 10% aqueous NaOH. The violet solution was acidified carefully with concentrated H_2SO_4, avoiding an excess of the acid. On boiling for 15 min, the precipitate was filtered and washed well. The dry precipitate (0.75 g) showed two spots on the oxalated silica gel plates using benzene as solvent. One spot corresponded to the starting material of 3-methylalizarin. The crude mixture was dissolved in DMF and then absorbed on column-grade silica gel. A dark violet band was eluted from the column upon elution with benzene. The eluate was concentrated to 1–2 mL, and to it was added 5 mL methanol. The compound crystallized in bright red microplates (80 mg) and was identified as 1,2,5-trihydroxy-3-methyl-anthraquinone, m.p. 220°C.

Other references related to the Bohn-Schmidt reaction are cited in the literature.[8]

H. REFERENCES

1. (a) Bohn, R., *German Pat.*, **1889**, Feb. 26, 46654. (b) Bohn, R., *German Pat.*, **1889**, April 9, 47252.
2. Schmidt, R. E., *German Pat.,* **1892**, Jan. 7, 60855.
3. Phillips, M., *Chem. Rev*., **1929**, *6*, 157.
4. (a) Confalone, P. N. and Pizzolato, G., *J. Am. Chem. Soc.,* **1981**, *103*, 4251. (b) Winkler, J. and Jenny, W., *Helv. Chim. Acta,* **1965**, *48*, 190. (c) Winkler, J. and Jenny, W., *Helv. Chim. Acta,* **1965**, *48*, 119. (d) Lecher, H. Z., *J. Am. Chem. Soc.,* **1955**, *77*, 6089. (e) Lubs, H. A., ed. *The Chemistry of Synthetic Dyes and Pigments*, American Chemical Society Monograph Series, Reinhold Publishing, New York, **1955**. (f) Fierz-David, H. E. and Blangey, L., *Fundamental Processes of Dye Chemistry,* Interscience Publishers, New York,

1949. (g) Waitkins, G. R. and Clark, C. W., *Chem. Rev.,* **1945**, *36*, 355. (h) Eckert, A., *Monatsch. Chem.,* **1914**, *34*, 1957.

5. (a) Schmidt, R. E., *German Pat.*, **1895**, May 14, 81481. (b) Schmidt, R. E., *German Pat.*, **1895**, June 13, 81961.
6. (a) Milbauer, J., *Chem. Obzor*., **1941**, *16*, 97. (b) Milbauer, J., and Mikolasek, J., *Chem. Obzor*., **1940**, *15*, 65. (c) Milbauer, J. and Mikolasek, J., *Chem. Obzor*., **1940**, *15*, 84. (d) Sreenivasan, A. and Sadisivan, V., *Ind. Eng. Chem., Anal. Ed.,* **1939**, *11*, 314. (e) Milbauer, J., *Chem. Obzor*., **1939**, *14*, 233. (f) Milbauer, J., *Chem. Obzor*., **1936**, *11*, 1. (g) Milbauer, J., *Chem. Obzor*., **1936**, *11,* 65. (h) Milbauer, J., *Chem. Obzor*., **1936**, *11,* 132. (i) Milbauer, J., *Chem. Obzor*., **1936**, *11,* 183. (j) Milbauer, J., *Chem. Obzor*., **1936**, *11,* 208. (k) Milbauer, J., *Chem. Obzor*., **1936**, *11*, 233.
7. Dhruva, B. R.; Patil, V. B. and Rao, A. V. R., *Indian J. Chem., Sect. B,* **1976**, *14B*, 622.
8. (a) Zollinger, H., *Color Chemistry: Syntheses, Properties, and Applications of Organic Dyes and Pigments*, Verlag Helvetica Chimica Acta AG, Zurich, and Wiley-VCH GmbH, Weinheim, **2003**, p. 273. (b) Morris, M. J. and Brown, J. R., *Tetrahedron Lett*., **1978**, 2937.

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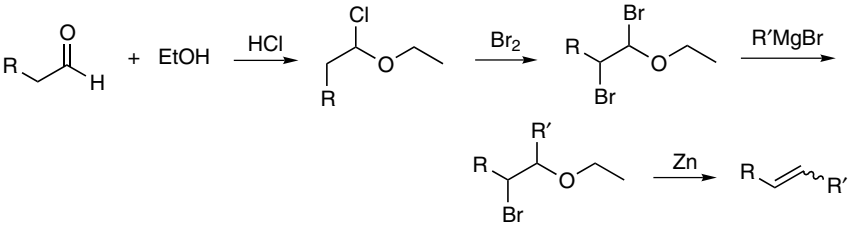
Boord Olefin Synthesis
(Boord Elimination)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Boord in 1930.[1] It is a general and flexible process for synthesizing different types of olefins with regio-specificity starting with the condensation of aldehydes with alcohol in the presence of hydrogen chloride gas, followed by the treatment with bromine to form α-bromo ether, and then further treatment with Grignard reagent, and zinc-induced reductive elimination of halogen and alkoxy groups. Therefore, this reaction is generally known as the Boord elimination,[2] or Boord olefin synthesis.[3] Unfortunately, the stereoselectivity of this reaction is poor, giving a mixture of *Z*- and *E*-olefins.[4,5] In zinc-induced reductive elimination, the larger the molecular weight of the alkoxy group, the slower the reaction rate. For example, the reactivity is found in the order of methoxy > ethoxy > butoxy > isobutoxy > 2-ethylhexoxy.[5]

B. GENERAL REACTION SCHEME



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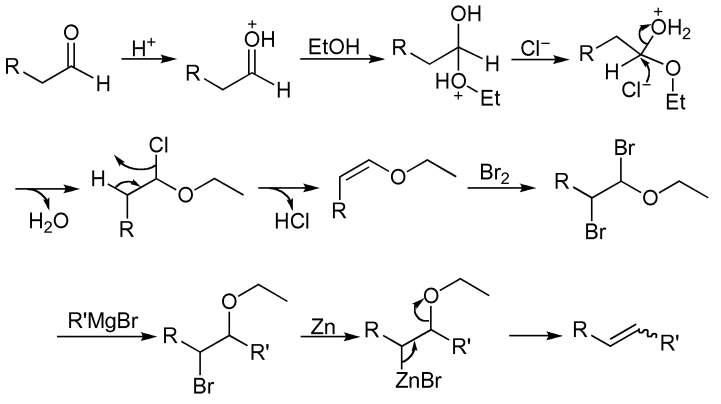
C. PROPOSED MECHANISMS

Although the mechanism is almost clearly shown in the reaction scheme, a tentative illustration is given here to show the reaction details.



D. MODIFICATION

When dibromides from alkyl vinyl ethers were condensed with Grignard reagents and the resulting β-bromoethers were treated with zinc, 53–84% of olefins could be yielded, which is 10–30% higher than the traditional procedure from aldehydes.[5]

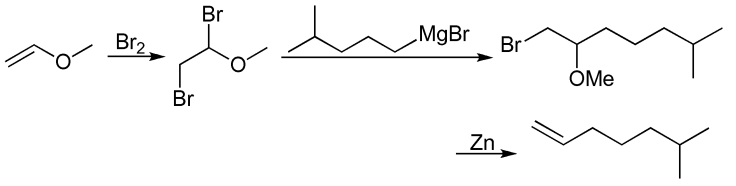
E. APPLICATIONS

This reaction has general application in preparation of different types of olefins.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 5.

Bromination of *Alkyl Vinyl Ethers*

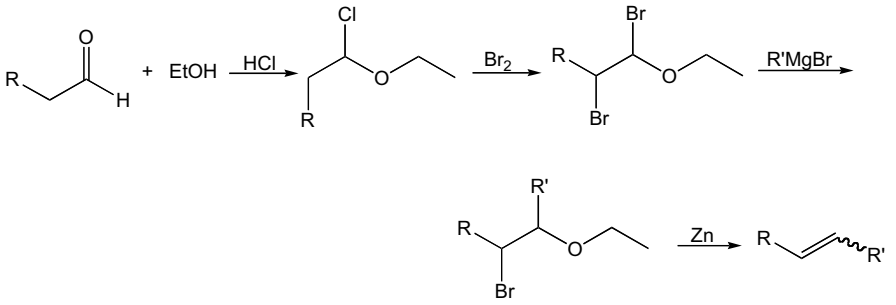
In a three-necked flask, suitably equipped and surrounded by a dry ice–acetone bath were placed 300–400 mL sodium-dried ethyl ether and 1 mol methyl vinyl ether. The theoretical amount of bromine was added, with stirring, at a rate of about 1 drop per second. The dibromides were not isolated from the ether solution, which were used as such in the *Grignard Reactions*.

Preparation of β-Bromoethers

The Grignard reagents from isoamyl chlorides (redistilled) were prepared in the manner described by Dreger.[6] The condensation was carried out in a conventional way, using a 20% excess of the Grignard reagent. After removal of the ethyl ether solvent by simple distillation, the β-bromoether was fractionated over solid sodium hydroxide at reduced pressure (column rated at about 10 theoretical plates at atmospheric pressure). The condensation with the dibromides was carried out in the customary way, the temperature of the reaction mixtures being maintained at 0–10°C. After distillation, 69% of 1-bromo-2-methoxy-5-methyl hexane was obtained, b.p. 98–99°C at 23 mmHg.

The Dealkoxybromination

The dealkoxybromination reaction was carried out as previously described.[1b] The olefin was purified only by washing with water and fractionation over metallic sodium at less than five-plate efficiency; yet the quality was obviously good. Finally, 84% of 5-methyl-1-hexene was obtained, b.p. 85.4–85.6°C.



Reference 1b.

Preparation of Alkyl-α-Chloroethyl Ether

The method[1a] has been generalized and extended to include the preparation of *n*-propyl- and *n*-butyl-α-chloroethyl ethers. It was found advisable for the purpose of synthesis to avoid distillation, the yield being diminished as much as 20–25% by a single fractionation. The upper ethereal layer was removed and dried over calcium chloride. For the α-chloroethyl ethers mentioned, the yield varies from 80 to 90% of crude or 60 to 69% of the distilled product.

Formation of Alkyl-α,β-Dibromoethyl Ethers (R-O-CHBr-CH_2Br)

The alkyl-α-chloroethyl ethers were brominated. The crude reaction product may be submitted directly to distillation under diminished pressure, but it was found advisable in this case to avoid distillation. The hydrogen chloride was removed under diminished pressure or by aspirating a slow current of air through the reaction mixture. The yields vary from 93 to 95% of crude or 88.5 to 91% of distilled product. For the case of *n*-butyl-α,β-dibromoethyl ether, the yield was 95.2%, b.p. 115°C at 36 mmHg.

Formation of Alkyl-β-Bromoethyl Ethers

A flask was surrounded by ice water, and the dibromoether—dissolved in an equal volume of anhydrous ether—was added through the dropping funnel at such a rate that the mixture remained cold. Mechanical stirring was used throughout the reaction which finished 15 min after the addition was completed. The reaction mixture was decomposed by pouring onto ice and acidifying with dilute hydrochloric acid. The ether layer was separated, dried over calcium chloride, and the ether was removed by distillation. The product was then transferred to a smaller flask, ~5% of its weight of solid sodium hydroxide was added, and it was then fractionated. α-Ethoxy-*n*-butyl bromide may be distilled at atmospheric pressure, but the higher members are best distilled under diminished pressure.

Synthesis of Olefins

For conversion into the olefin, the β-bromoether was dissolved in approximately 25 times its volume of 90% alcohol and placed in a three-necked flask under a spiral condenser. The flask was provided with a mechanical stirrer with a mercury seal. Zinc dust (2–3 eq.) was added, and the reaction mixture was digested at the boiling point for several hours. The lower bromoethers decomposed more slowly than those of higher molecular weight. β-ethoxy-*n*-amyl bromide yielded 60–65% of the crude pentene by treatment for 10 to 12 h, while β-ethoxyisoheptyl bromide gave a yield of 85–90% isoheptene in 5 h. The zinc dust tends to become coated with the basic salt produced. Mechanical stirring serves to obviate this difficulty in part, and there is some advantage in adding the zinc portion-wise. The separation of the olefin from the reaction mixture differed slightly, depending on its boiling point. In the case of α-pentene, the water in the spiral condenser was kept at 40°C so that the olefin volatilized from the reaction mixture continuously.

Other references related to the Boord olefin synthesis are cited in the literature.[7]

H. REFERENCES

1. (a) Swallen, L. C. and Boord, C. E., *J. Am. Chem. Soc.,* **1930**, *52*, 651. (b) Dykstra, H. B.; Lewis, J. F. and Boord, C. E., *J. Am. Chem. Soc.,* **1930**, *52*, 3396.
2. (a) Peppe, C.; Mello, P. de A. and Das Chagas, R. P., *J. Organomet. Chem.,* **2006**, *691*, 2335. (b) Beusker, P. H.; Aben, R. W. M.; Seerden, J.-P. G.; Smits, J. M. M. and Scheeren, H. W., *Eur. J. Org. Chem.,* **1998**, 2483. (c) Bowman, M. P.; Olofson, R. A.; Senet, J. P. and Malfroot, T., *J. Org. Chem.,* **1990**, *55*, 2240.
3. Marvel, C. S. and Garrison, W. E., *J. Am. Chem. Soc.,* **1959**, *81*, 4737.

4. Crombie, L., *Quart. Rev. (London),* **1952**, *6*, 131.
5. Rowlands, D. C.; Greenlee, K. W.; Derfer, J. M. and Boord, C. E., *J. Org. Chem.,* **1952**, *17*, 807.
6. Dreger, *Org. Synth. Coll.*, **1941**, *1* (2nd ed.), 306.
7. (a) Beusker, P. H.; Aben, R. W. M.; Seerden, J.-P. G.; Smits, J. M. M. and Scheeren, H. W., *Eur. J. Org. Chem.*, **1998**, 2483. (b) Yadav, J. S.; Ravishankar, R. and Lakshman, S., *Tetrahedron Lett.,* **1994**, *35*, 3617. (c) Bandart, P., *Bull. Soc. Chim.,* **1944**, *11*, 336. (d) Niemann, C. and Wagner, C. D., *J. Org. Chem*., **1942**, *7*, 227. (e) Swallen, L. C. and Boord, C. E., *J. Am. Chem. Soc.,* **1933**, *55*, 3293. (f) Soday, F. J. and Boord, C. E., *J. Am. Chem. Soc.,* **1933**, *55*, 3293. (g) Schurman, I. and Boord, C. E., *J. Am. Chem. Soc.,* **1933**, *55*, 4930. (h) Schmitt, C. G. and Boord, C. E., *J. Am. Chem. Soc.,* **1932**, *54*, 751. (i) Shoemaker, B. H. and Boord, C. E., *J. Am. Chem. Soc*., **1931**, *53*, 1505. (j) Schmitt, C. G. and Boord, C. E., *J. Am. Chem. Soc.,* **1931**, *53*, 2427.

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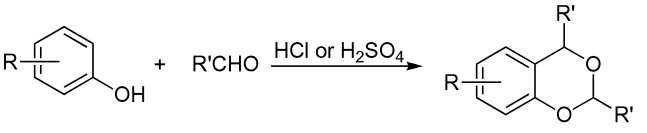
Borsche-Berkhout Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Borsche and Berkhout in 1904.[1] It is the reaction for preparing 1,3-benzodioxanes from phenols and aldehydes in the presence of acid, such as HCl and H_2SO_4. The formed 1,3-benzodioxanes can be oxidized into lactones[1,2] and converted into prodrugs of anti-inflammatory agents.[3] It is found that an electron-withdrawing group at position 8 will decrease the stability of such dioxane system toward alkali solution—for example, 6,8-dinitro-1,3-benzodioxane was easily cleaved in 1% of KOH solution to 2-hydroxy-3,5-dinitrobenzyl alcohol, whereas 6-nitro-1,3-benzodioxane was stable to boiling in 25% aqueous alkali or alcholic potassium ethoxide.[4]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Because no information about the reaction details is available, a tentative mechanism for the reaction between phenol and formaldehyde is proposed here.

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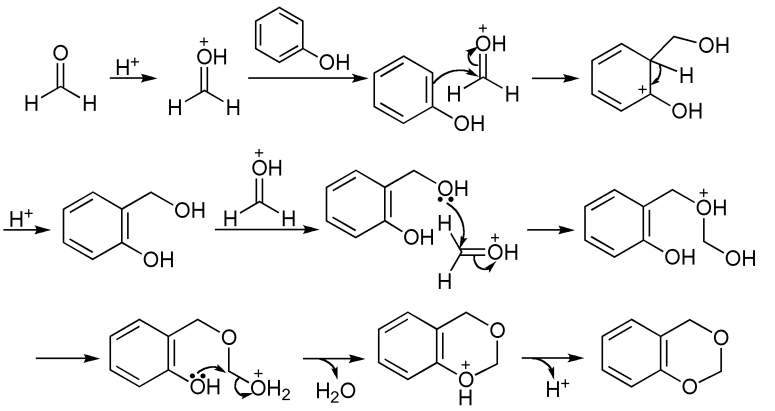


D. MODIFICATION

N/A

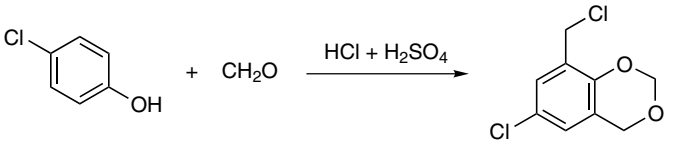
E. APPLICATIONS

This reaction can be generally applied to the synthesis of 1,3-benzodioxanes.

F. RELATED REACTIONS

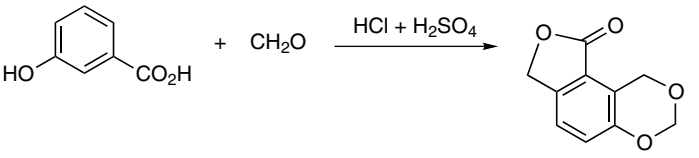
This reaction is related to *Bakelite Process*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2b.

To a mixture of 500 mL concentrated hydrochloric acid and 15 mL concentrated sulfuric acid warmed to 40°C were added 20 g *p*-chlorophenol and 80 mL 40% formaldehyde. Hydrogen chloride was bubbled rapidly through the stirred mixture and kept at 40°C for 1.5 h, at which point the solution had clarified with the separation of some solid. Crude solid (30 g) was crystallized three times from methanol to give 18.5 g 6-chloro-8-chloromethyl-1,3-benzodioxane, m.p. 103°C.



Reference 5.

To 1 L 40% formaldehyde in a three-necked flask (equipped with a mercury-sealed stirrer, a thermometer, and a glass tube with an opening of ~1 mm in diameter leading to the bottom of the flask for introducing dry hydrogen chloride) was added 50 g *m*-hydroxybenzoic acid. In ~5 min the acid had dissolved, and then 1 L concentrate hydrochloric acid and 50 mL concentrated sulfuric acid were added with stirring; hydrogen chloride was passed rapidly through the entire solution heated to 60°C. A white solid began to form after ~1.5 h, but the reaction was continued for a total of 3 h, at which time considerable more solid had separated. After cooling overnight in a refrigerator, the crystals were filtered off and washed until free from formaldehyde. One crystallization from methanol gave 21.5 g 6-hydroxymethyl-1,3-benzodioxane-5-carboxylic acid lactone, m.p. 176°C.

Other references related to the Borsche-Berkhout reaction are cited in the literature.[6]

H. REFERENCES

1. Borsche, W. and Berkhout, A. D., *Ann.*, **1904**, *330*, 92.
2. (a) Buehler, C. A.; Slack, A. V.; Shirley, D. A.; Sanguinetti, P. A. and Frey, S. H., *J. Am. Chem. Soc.,* **1951**, *73*, 2347. (b) Buehler, C. A.; Bass, B. C.; Darling, R. B. and Lubs, M. E., *J. Am. Chem. Soc.,* **1940**, *62*, 890.
3. Paris, G. Y.; Garmaise, D. L.; Cimon, D. G.; Swett, L.; Carter, G. W. and Young, P., *J. Med. Chem.,* **1980**, *23*, 79.
4. Hazy, A. C. and Karabinos, J. V., *J. Org. Chem.,* **1968**, *33*, 2557.
5. Buehler, C. A.; Harris, J. O.; Shacklett, C. and Block, B. P., *J. Am. Chem. Soc.,* **1946**, *68*, 574.
6. (a) Buehler, C. A. and Pruett, R. L., *J. Am. Chem. Soc.,* **1951**, *73*, 5506. (b) Ewing, G. W. and Steck, E. A., *J. Am. Chem. Soc.,* **1946**, *68*, 2181. (c) Buehler, C. A.; Brown, R. L.; Holbert, J. M.; Fulmer, J. G. and Parker, G. W., *J. Org. Chem.,* **1941**, *6*, 902. (d) Monti, L.; Cirelli, V. and Romano, B., *Gazz. Chim. Ital.,* **1936**, *66*, 42. (e) Borsche, W. and Berkhout, A. D., *Ann.*, **1904**, *330*, 82.

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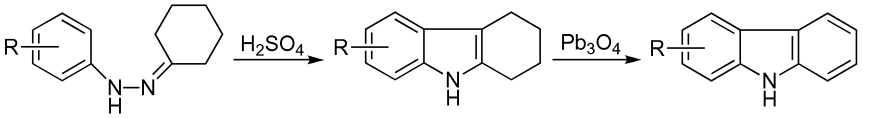
Borsche-Drechsel Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Drechsel[1] in 1888 and then by Borsche[2] in 1904. It is the reaction involving the cyclization of arylhydrazones of cyclohexanone to tetrahydrocarbazoles and the subsequent oxidation of tetrahydrocarbazoles into carbazoles. In this reaction, cyclohexanone phenylhydrazone is converted into tetrahydrocarbazole when heated with dilute sulfuric acid,[1,3] a process that is completely analogous to the *Fischer Indole Synthesis*. However, Borsche was the first to realize the full scope of this reaction, and had prepared many substituted tetrahydrocarbazoles.[4] Other acids can also be used in this reaction—for example, acetic acid has been found to give cleaner products.[5] Different oxidants have been applied for converting the tetrahydrocarbazoles into carbazoles, such as lead oxide,[4] mercury acetate,[5,6] palladium chloride,[7] and chloranil.[8] However, only chloranil was found to be a good reagent in this reaction. In addition, a mixture of cinnamic acid and palladium black is another excellent reagent for the preparation of carbazoles,[9] in which cinnamic acid was reduced to hydrocinnamic acid.

B. GENERAL REACTION SCHEME



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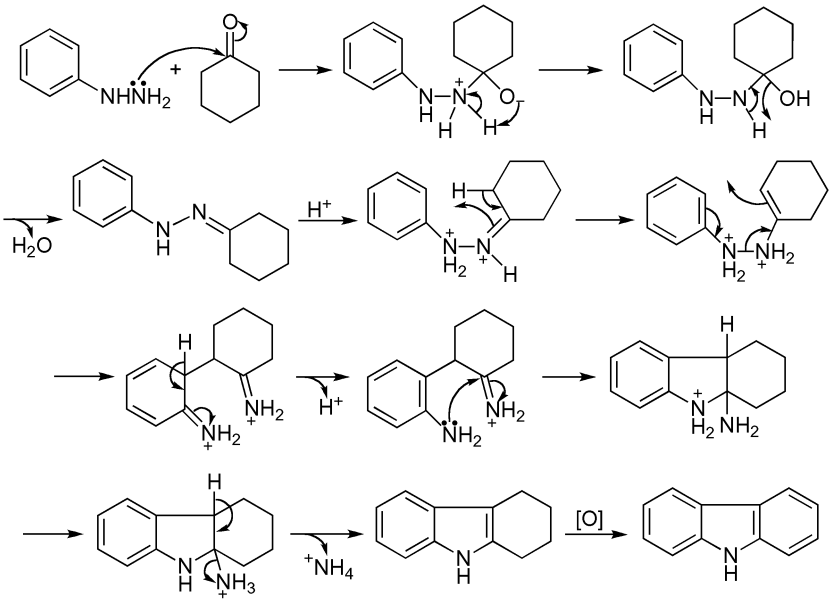
C. PROPOSED MECHANISMS

The mechanism is similar to the *Fischer Indole Synthesis* as outlined below.



D. MODIFICATION

The conversion of tetrahydrocarbazoles into carbazoles has been modified by using a mixture of cinnamic acid and palladium black.[9]

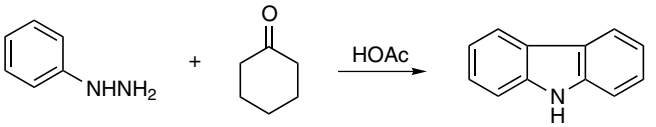
E. APPLICATIONS

This reaction has general application in the preparation of tetrahydrocarbazoles and carbazoles.

F. RELATED REACTIONS

This reaction is related to the *Bucherer Carbazole Synthesis, Fischer Indole Synthesis, Graebe-Ullmann Synthesis* and *Piloty-Robinson Pyrrole Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 10.

Phenylhydrazine (108 g, 1 mol) was added over 1 h to a stirred, refluxing solution of 98 g cyclohexanone (1 mol) in 360 g glacial acetic acid. After undergoing refluxing and stirring for an additional hour, the mixture was cooled to 5°C and filtered. The crude solid was washed with water, 75% methyl alcohol, and air dried to give 150 g 1,2,3,4-tetrahydrocarbazole, in a yield of 88%. Crystallization from methyl alcohol gave a first crop of 120 g and a second crop of 24 g. The reaction goes equally well if acetic acid is replaced by formic or propionic acid.

Other references related to the Borsche-Drechsel reaction are cited in the literature.[11]

H. REFERENCES

1. Drechsel, E., *J. Prakt. Chem*., **1888**, *38(2)*, 69.
2. Borsche, W. and Feise, M., *Ber*., **1904**, *20*, 378.
3. (a) Baeyer, A., *Ann.,* **1894**, *278*, 105. (b) Baeyer, A. and Tutein, F., *Ber.,* **1889**, *22*, 2178.
4. Borsche, W.; Witte, A. and Bothe, W., *Ann.,* **1908**, *369*, 52.
5. Perkin, W. H. and Plant, S. G. P., *J. Chem. Soc.,* **1921**, *119*, 1825.
6. Perkin, W. H. and Plant, S. G. P., *J. Chem. Soc.,* **1923**, *123*, 676.
7. Cooke, G. W. and Gulland, J. M., *J. Chem. Soc.,* **1939**, 872.
8. Campbell, N. and Barclay, B. M., *J. Chem. Soc.,* **1946**, 530.
9. Hoshino, T. and Takiura, K., *Bull. Chem. Soc. Jp.,* **1936**, *11*, 218.
10. Rogers, C. U. and Corsom, B. B., *J. Am. Chem. Soc.,* **1947**, *69*, 2910.
11. (a) Rousselle, D.; Gilbert, J. and Viel, C., *Compt. Rend.,* **1977**, *284*, 377. (b) Bruck, P., *J. Org. Chem.* **1970**, *35*, 2222. (c) Robinson, B., *Chem. Rev.,* **1962**, *62*, 373. (d) Rosnati, V. and Pelazzo, G., *Gazz. Chim. Ital*., **1954**, *84*, 644. (e) Sumpter, W. C., and Miller, F. M., "The Chemistry of Heterocyclic Compounds" in *Heterocyclic Compounds with Indole and Carbazole Systems*, ed. Weissberger, A., Interscience Publishers, New York, **1954**, p. 73. (f) Julian, P. L., Meyer, E. W., and Printy, H. C., "The Chemistry of indoles" in *Heterocyclic Compounds,* ed. Elderfield, R. C., Vol. 3, John Wiley & Sons, New York, and Chapman and Hall, London, **1952**, pp. 1–274. (g) Pausacker, K. H., Schubert C. I., *Nature*, **1949**, *103*, 289, 602. (h) Campbell, N. and Barclay, B. M., *Chem. Rev.,* **1947**, *40*, 359. (i) van Order, R. B. and Lindwall, H. G., *Chem. Rev*., **1942**, *30*, 69. (j) Robinson, R. and Robinson, G. M., *J. Chem. Soc.,* **1924**, *126*, 827. (k) Hollins, C., *The Synthesis of Nitrogen Ring Compounds Containing a Single Hetero-Atom (Nitrogen)*, Ernest Benn Ltd., London, **1924**, p. 168. (l) Robinson, R. and Robinson, G. M., *J. Chem. Soc.,* **1918**, *113*, 639. (m) Borsche, W., *Ann.,* **1908**, *359*, 49. (n) Borsche, A., *Ann.,* **1908**, *359*, 62. (o) Borsche, A., *Ann.,* **1908**, *359*, 52. (p) Baeyer, A., *Ann.,* **1904**, *278*, 88.

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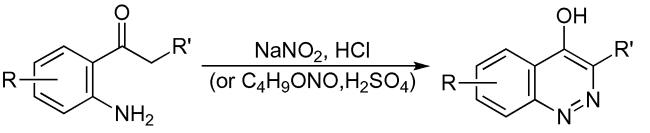
Borsche-Koelsch Cinnoline Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Borsche[1] in 1941 and Koelsch[2] in 1943. It is the reaction to form 4-hydroxycinnonlines[3] or 4-hydroxy-3-alkylcinnolines[4] via the diazotization of *ortho*-aminoarylketone followed by a slow step of cyclization.[5] In general, the aminoarylketone is diazotized in either aqueous solution or acetic acid solution, and the solution of the diazonium salt is allowed to stand in the dark at room temperature until it no longer gives a diazo coupling reaction with *p*-naphthol.[4] The time required for the completion of the cyclization under these conditions varies from a few days to 2–3 months. The reaction time appears to be a function of the basicity of the original amine. The yield of cinnoline obtained likewise depends on the character of the *o*-aminoarylketone used in its preparation. In general, the less basic the aminoarylketone, the shorter the time required for the cyclization and the greater the yield of corresponding cinnolines.[4] The substituted cinnolines are potential antimalarial drugs.[4]

B. GENERAL REACTION SCHEME



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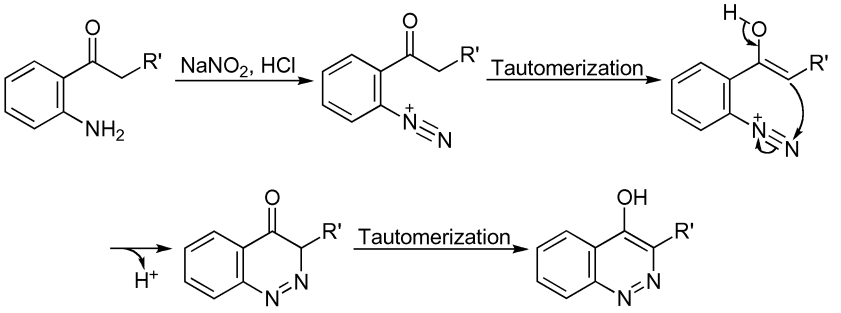
C. PROPOSED MECHANISMS



D. MODIFICATION

After the diazotization of *o*-aminoarylketone, 3-amino-cinnolines can be prepared in the presence of nitromethane;[6] on the other hand, the 4-alkyl-cinnolines can be synthesized similarly from *o*-amino-α-alkylstyrenes.[7]

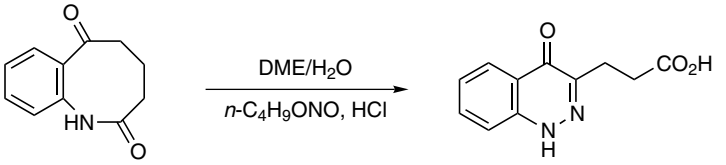
E. APPLICATIONS

This reaction is generally used to prepare 4-hydroxycinnolines.

F. RELATED REACTIONS

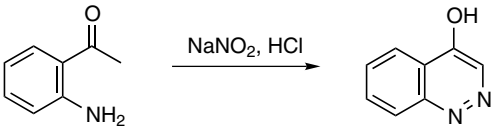
This reaction is related to the *Widman-Stoermer Synthesis* and *von Richter Cinnoline Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



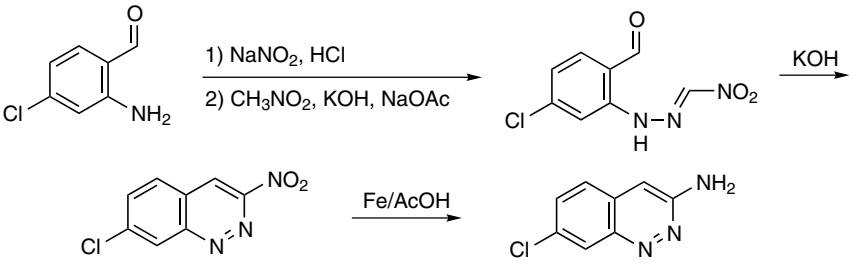
Reference 8.

To a suspension of 1 g of 4,5-dihydro-lH,3H-l-benzazocine-2,6-dione in 20 mL 1,2-dimethoxyethane and 0.1 mL water was added 0.84 g freshly prepared *n*-butyl nitrite. Hydrogen chloride gas was bubbled through the mixture at 25°C for 5 min; the resulting solution was stirred overnight at room temperature, after which time the intermediate diazonium chloride usually had separated. The solution or suspension was diluted with 10 mL water, the mixture was warmed for 5 min on a steam bath, and the resulting suspension was filtered. The solid residue was crystallized from aqueous ethanol to give 4-oxo-1,4-dihydro-cinnolin-3-ylpropionic acid, in a yield of 61%, m.p. 226–228°C.



Reference 4.

o-Aminoacetophenone (37.5 g, 0.278 mol) was dissolved in 120 mL water and 90 mL concentrated hydrochloric acid and diazotized between 0° and 7°C by the dropwise addition of 59 mL 5 N sodium nitrite solution. The solution was then treated with charcoal and filtered. A small amount of excess nitrous acid was removed from the filtrate by the addition of urea, and the solution was stored in the dark at room temperature until a diazonium reaction was no longer obtained with an alkaline solution of the anilide of 2-hydroxy-3-naphthoic acid (44 days). The reaction mixture consisted of a dark red solution in which was suspended some needle-like crystals and several globules of a red-brown oil. There was evidence of the evolution of a considerable amount of nitrogen. The solid material was removed by filtration. An additional crop of crystals was obtained by allowing the filtrate to stand for several hours at room temperature. After recrystallization from ethanol 17.4 g of product was obtained as slender white needles, in a yield of 42.9%, m.p. 236°C.



Reference 6a.

To a mixture of 7 g crude, moist 2-amino-4-chlorobenzaldehyde (~0.04 mol), 2.9 g sodium nitrite (0.042 mol) and 75 g crushed ice, made into a slurry in a Waring blender; a mixture of 9 mL concentrated hydrochloric (0.11 mol) acid and 50 g crushed ice was added in one portion. The mixture was blended for about 5 min until a clear solution was obtained. Small amounts of crushed ice were added periodically during the blending to keep the temperature low. The solution was filtered through a chilled funnel onto a small amount of crushed ice. Meanwhile a solution of 4.3 mL nitromethane (0.08 mol) in 5 mL ethanol was added slowly with stirring to a solution of 5.7 g potassium hydroxide (0.1 mol) in 3.5 L ice water. After the nitromethane had dissolved, 3.3 g sodium acetate (0.04 mol) was added to the solution. The diazonium solution was poured slowly into the solution of potassium *aci*-nitromethane. A yellow precipitate formed immediately. The mixture was allowed to stand for 20 min. The crude nitroformaldehyde 5-chloro-2-formylphenylhydrazone was collected by filtration and transferred to the Waring blender without further purification. A solution of 1.3 g potassium hydroxide in 50 mL water was added to the solid in the blender. A blood red color developed immediately. The mixture was blended until the red color faded into a chocolate brown (5–10 min). The mixture was poured into a beaker, allowed to stand for 2.5 h and filtered. The resultant brown solid was dried overnight in the vacuum desiccator. The crude material, 1.51 g, was recrystallized from acetone or, preferably, ethyl acetate,

giving 1.1 g (13%, based on 4-chloro-2-nitrobenzaldehyde) of 7-chloro-3-nitrocinnoline as pale yellow needles, m.p. 165.5–166°C

The reduction of 3.0 g 6-chloro-3-nitrocinnoline (0.014 mol) by iron in acetic acid gave 1.91 g of 3-amino-6-chlorocinnoline as bright yellow needles, in a yield of 74%, m.p. 215°C (dec.)

Other references related to the Borsche-Koelsch cinnoline synthesis are cited in the literature.[9]

H. REFERENCES

1. Borsche, W. and Herbert, A., *Ann.*, **1941**, *546*, 293.
2. Koelsch, C. F., *J. Org. Chem.*, **1943**, *8*, 295.
3. Leonard, N. J. and Boyd, S. N., *J. Org. Chem.,* **1946**, *11*, 405.
4. Leonard, N. J. and Boyd, S. N., *J. Org. Chem.,* **1946**, *11*, 419.
5. Baumgarten, H. E. and Debrunner, M. R., *J. Am. Chem. Soc.,* **1954**, *76*, 3489.
6. (a) Baumgarten, H. E.; Pedersen, D. L. and Hunt, M. W., *J. Am. Chem. Soc.,* **1958**, *80*, 1977. (b) Baumgarten, H. E. and Debrunner, M. R., *J. Am. Chem. Soc.,* **1954**, *76*, 3489.
7. Jacobs, T. L.; Winstein, S.; Henderson, R. B. and Spaeth, E. C., *J. Am. Chem. Soc.,* **1946**, *68*, 1310.
8. Holland, D.; Jones, G.; Marshall, P. W. and Tringham, G. W., *J. Med. Chem.,* **1976**, *19*, 1225.
9. (a) Bräse, S., *Acc. Chem. Res*., **2004**, *37*, 805. (b) Leonard, N. J., *Chem. Rev.,* **1945**, *37*, 269. (c) Schofield, K. and Simpson, J. C. E., *J. Chem. Soc.,* **1945**, 512.

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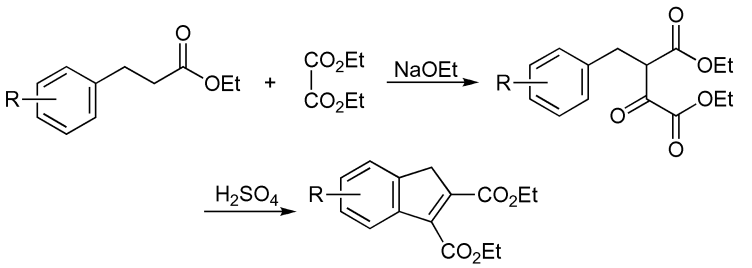
Bougault Reaction
(Bougault Cyclization)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Bougault in 1915.[1] It is the reaction for preparing indene derivatives via the condensation of β-arylpropionic acid ester with diethyl oxalate followed by the cyclization of the resulting glyoxylate ester with sulfuric acid. Thus this reaction is known as the Bougault cyclization[2] or Bougault reaction.[3] In this reaction, phosphoric acid may be the reagent of choice for cyclization, particularly when sulfuric acid leads to hydrolytic cleavage, ester exchange, or extensive sulfonation.[2] This reaction has been extended to the synthesis of dihydronaphthalenes[2] and phenanthrene.[4]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A general mechanism is displayed here.

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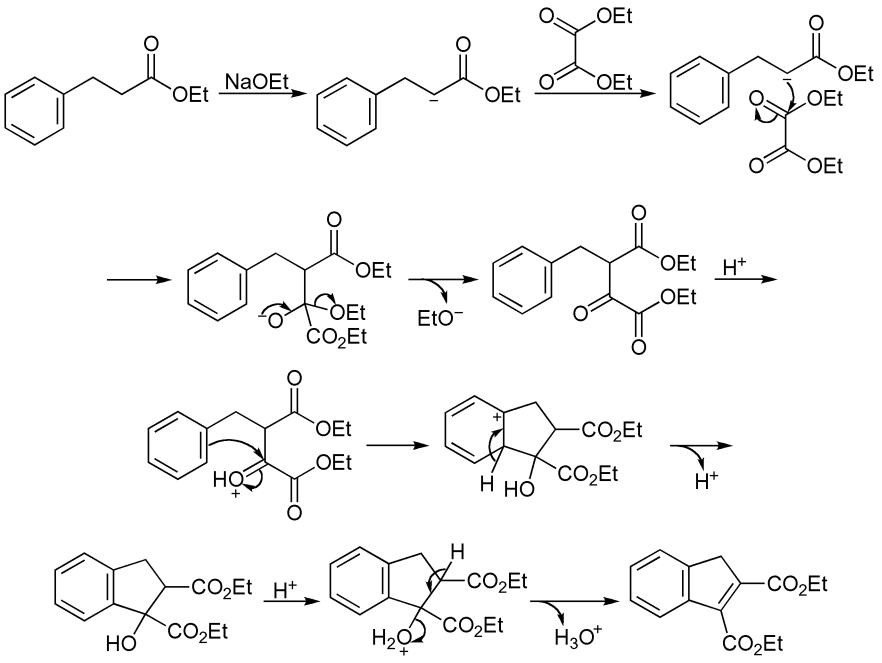


D. MODIFICATION

This reaction has been modified by the application of phosphoric acid as a cyclization reagent.

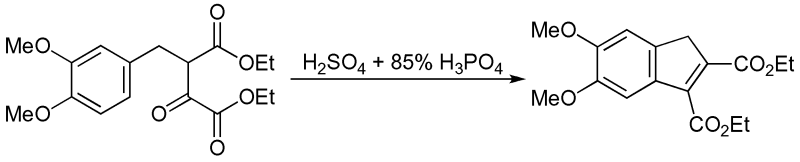
E. APPLICATIONS

This reaction can be applied to the synthesis of indene, dihydronaphthalene, and naphthalene derivatives.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 2.

A keto-ester (3.4 g, 0.01 mol) was added slowly to a mixture of 15 mL concentrated sulfuric acid and 15 mL 85% phosphoric acid at 0–5°C. After standing at room temperature for 3 h, the mixture was poured onto chopped ice. The product separated slowly in crystalline form, which was removed, dried, and recrystallized from benzene-hexane to give 1.8 g diethyl 5,6-dimethoxyindene-2,3-dicarboxylate in a yield of 55%, m.p., 159–160°C. This was the only product obtained under varying cyclization conditions with sulfuric-phosphoric acids.

Reference 4.

Potassium ethoxide was prepared from 1.95 g potassium and 9.2 mL absolute ethanol in 150 mL anhydrous ether. To this mixture 14.6 g diethyl oxalate was added. After 15 min, a solution of 13.5 g ethyl (3′-methoxy-2-biphenylyl)-acetate in 50 mL dry ether was added, and the mixture was refluxed for 51 h. The reaction mixture was cooled and extracted with 5% sodium hydroxide solution. The aqueous layer was saturated with carbon dioxide, and the precipitated oil was taken up in ether. Evaporation of the ether solution afforded 10.6 g crude diethyl α-keto-α'-(3-methoxy-2-biphenylyl)-succinate, which was used in subsequent experiments without purification. From the alkali-insoluble fraction, 4.2 g ethyl (3′-methoxy-2-biphenylyl)-acetate was recovered.

Cyclization of 5.9 g α-keto-α'-(3-methoxy-2-biphenylyl)-succinate was effected by stirring it vigorously with 30 mL 80% sulfuric acid for 10 min on a steam bath. By dilution of the reaction mixture with 300 mL water, 5.4 g dark yellow solid was obtained. This solid dissolved in 400 mL benzene, leaving only a small quantity of a black residue. The benzene solution contained two isomeric compounds. The lower-melting isomer, which was more abundant, was slightly less soluble in benzene and crystallized in fairly pure form from the dilute solution. When the lower-melting compound no longer crystallized in pure form, the solvent was evaporated, and the residue was taken up in glacial acetic acid. The higher-melting compound crystallized from acetic acid in a fairly pure condition as a flocculent mass. When hard kernels of impure material began to form, the acetic acid was replaced by benzene. The alternation between solvents was continued unti1 there was no residue left on evaporation. After a total of 37 crystallizations, 2.36 g 3-methoxyphenanthrene-9,10-dicarboxylic acid anhydride was obtained as yellow needles, m.p. 221.5–222°C.

Other references related to the Bougault reaction are cited in the literature.[5]

H. REFERENCES

1. Bougault, J.,*Compt. Rend.,* **1915**, *159*, 745.
2. Horning, E. C.; Koo, J. and Walker, G. N., *J. Am. Chem. Soc.,* **1951**, *73*, 5826.

3. Fieser, L. F. and Hershberg, E. B., *J. Am. Chem. Soc.,* **1935**, *57*, 1851.
4. Bradsher, C. K.; Brown, F. C. and Leake, P. H., *J. Am. Chem. Soc.,* **1957**, *79*, 1471.
5. (a) Horning, E. C. and Koo J., *J. Am. Chem. Soc.*, **1951**, *73*, 5828. (b) Geissman, T. A. and Tess, R., *J. Am. Chem. Soc*., **1940**, *62*, 514. (c) Schönberg, A. and Warren, F., *J. Chem. Soc.,* **1939**, 1838. (d) Fiesel, L. F. and Hershberg, E. B., *J. Am. Chem. Soc.*, **1935**, *57*, 1508. (e) Auwers, K., Möller, K., *J. Prakt. Chem.*, **1925**, *109*, 124.

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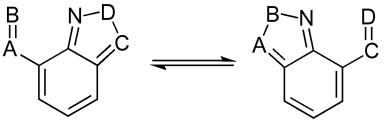
Boulton-Katritzky Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Boulton and Katritzky in 1962.[1] It is a type of monocyclic rearrangement of heterocycles[2] in the presence of either an acid[3] or a base[4] or under photoirradiation[5] and has been widely used in heterocyclic chemistry.[6] Therefore, this reaction is generally known as the Boulton-Katritzky rearrangement.[7] Occasionally, it is also referred to as the Boulton-Katritzky reaction.[8] This reaction has been reported to occur via a unimolecular one-step mechanism[7d] and suggested to be a [1,9]-sigmatropic rearrangement;[7n,9] but a recent computational study suggests a pseudo-pericyclic reaction.[4,7a] In addition, computational studies have shown that the pivotal nitrogen atom is not a mandatory prerequisite for this rearrangement,[4] although most of the reported rearrangements do involve nitrogen atoms, a rearrangement involving sulfur atoms is also known.[10] For example, the balance between substituted nitrobenzofuroxans depends on steric, electronic, conformational, and strain effects.[7i,11] The Boulton-Katritzky rearrangement has been extensively reviewed.[5,10b,12]

B. GENERAL REACTION SCHEME

This reaction is generally described as shown below.[13]



(A, C = N, N^+-O^-, N^+-$\bar{N}$-R, C-R
B, D = O, NR, S)

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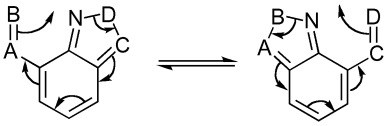
C. PROPOSED MECHANISMS

This reaction has been suggested to be a [1,9]-sigmatropic rearrangement,[7n,9] but has been proved to be a pseudo-pericyclic reaction from computational studies,[4,7a,7c,13] as illustrated here.



D. MODIFICATION

Because this reaction is general in heterocyclic chemistry, many individual reactions can be treated as modifications of the original reaction—for example, the substitution of nitrogen by sulfur atom in the ring system.[10]

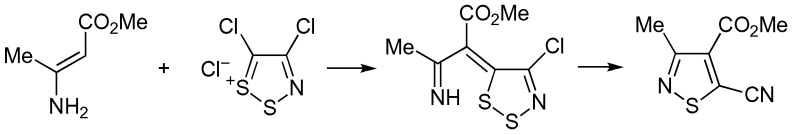
E. APPLICATIONS

This reaction has been widely used in heterocyclic chemistry for preparing certain types of nitrogeneous heterocycles, such as nitrobenzofuroxans, which have been used for the inhibition of nucleic acid and protein biosyntheses.[7c] Some interesting rearrangements are listed in experimental examples.

F. RELATED REACTIONS

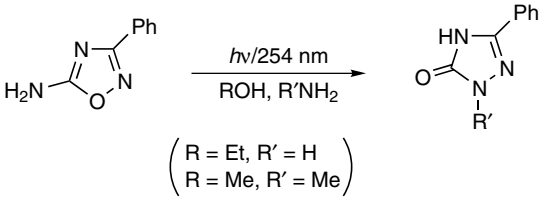
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 10a.

A mixture of 0.34 g methyl 3-aminocrotonate (3 mmol) and 0.63 g 4,5-dichloro-1,2,3-dithiazolium chloride (3 mmol) in 25 mL dichloromethane was stirred at room temperature for 1 h after which 0.49 mL pyridine (6 mmol) was added. The mixture was stirred for a further 30 min. The product was separated by flash chromatography on silica gel, eluting with dichloromethane/light petroleum (1:3) to give 0.43 g methyl 5-cyano-3-methylisothiazole-4-carboxylate, in a yield of 78%. Colorless crystals can form from dichloromethane–light petroleum, m.p. 55 – 56°C.



Reference 5.

To a solution of 0.5 g oxadiazole in 90 mL methanol was added 10 mL ethanolic methylamine (in a large excess). The solution was apportioned into two quartz tubes and then irradiated for 1.5 h. After removal of the solvent, the residue was chromatographed to give 10% of starting material and 60% of 1-methyl-3-phenyl-1,2,4-triazolin-5-one, m.p. 218–219°C. Similarly, irradiation of 0.5 g oxadizaole in the presence of 20 mL methanolic ammonia for 1.5 h, followed by the workup of the residue with minimum of methanol and filtration, afforded 0.25 g 3-phenyl-1,2,4-triazolin-5-one, m.p. 325–330°C. Chromatography of the mother liquor gave additional 0.05 g 3-phenyl-1,2,4-triazolin-5-one and 0.05 g starting material (10%); the total yield for this reaction was 60%.

Other references related to the Boulton-Katritzky rearrangement are collected in the literature.[14]

H. REFERENCES

1. Boulton, A. J. and Katritzky, A. R., *Proc. Chem. Soc.,* **1962**, 257.
2. Cosimelli, B.; Frenna, V.; Guernelli, S.; Lanza, C. Z.; Macaluso, G.; Petrillo, G. and Spinelli, D., *J. Org. Chem.,* **2002**, *67*, 8010.
3. Boulton, A. J. and Brown, R. C., *J. Org. Chem*., **1970**, *35*, 1662.
4. Rauhut, G., *J. Org. Chem.,* **2001,** *66*, 5444.
5. Buscemi, S.; Vivona, N. and Caronna, T., *J. Org. Chem.,* **1996,** *61*, 8397.
6. (a) Paton, R. M., 1,2,5-Oxadiazoles, in *Comprehensive Heterocyclic Chemistry II*, ed. Katritzky, A. R.; Rees, C. W. and Scriven, E. F. V., Pergamon Press, New York, **1995**, *4*. (b) Katritzky, A. R., *J. Heterocycl. Chem.,* **1994**, *31*, 569. (c) Katritzky, A. R. and Gordeev, M. F., *Heterocycles,* **1993**, *35*, 483. (d) Śliwa, W. and Thomas, A., *Heterocycles,* **1985**, *23*, 399. (e) Gasco, A. and Boulton, A. J., *Adv. Heterocycl. Chem.,* **1981**, *29*, 251. (f) Boulton, A. J. and Ghosh, P. B., *Adv. Heterocycl. Chem.,* **1969**, *10*, 1. (g) Harris, K. R.; Katritzky, A. R. and Majid-Hamid, A., *J. Chem. Soc.,* **1963**, 197.
7. (a) Pena-Gallego, A.; Rodriguez-Otero, J. and Cabaleiro-Lago, E. M., *J. Org. Chem.,* **2004**, *69*, 7013. (b) Crampton, M. R.; Pearce, L. M. and Rabbitt, L. C., *J. Chem. Soc., Perkin Trans. II,* **2002**, 257. (c) Eckert, F. and Rauhut, G., *J. Am. Chem. Soc.,* **1998**, *120*, 13478. (d) La Manna, G.; Buscemi, S. and Vivona, N., *THEOCHEM*, **1998**, *452*, 67. (e) Sonnenschein, H.; Schmitz, E.; Gruendemann, E. and Schroeder, E., *Liebigs Ann. Chem.,* **1994**, 1177. (f) Katayama, H.; Takatsu, N.; Sakurada, M. and Kawada, Y., *Heterocycles*, **1993**, *35*, 453. (g) Andrianov, V. G.; Makushenkov, S. V. and Eremeev, A. V., *Mendeleev Commun.,* **1992**, 129. (h) Belik, A. V.; Potemkin, V. A. and Belousov, D. V., *Izv. Vysshikh Uchebnykh Zavedenii, Khim. Khim. Tekh.,* **1992**, *35*, 49. (i) Takakis, I. M. and Hadjimihalakis, P. M., *J. Heterocycl. Chem.,* **1992**, *29*, 121. (j) Takakis, I. M.; Hadjimihalakis, P. M. and Tsantali, G. G., *Tetrahedron,* **1991**, *47*, 7157. (k) Belik, A. V. and Belousov, D. V., *Dokl. Akad. Nauk SSSR,* **1990**, *313*, 1127. (l) Ostrowski, S. and

Wojciechowski, K., *Can. J. Chem.,* **1990**, *68*, 2239. (m) Buncel, E.; Chuaqui-Offermanns, N. and Norris, A. R., *Can. J. Chem.,* **1979**, *57*, 2512. (n) Balli, H. and Gunzenhauser, S., *Helv. Chim. Acta,* **1978**, *61*, 2628.

8. D'Anna, F.; Frenna, V.; Noto, R.; Pace, V. and Spinelli, D., *J. Org. Chem.,* **2005**, *70*, 2828.
9. Parry, K. P. and Rees, W. C., *J. Chem. Soc., Chem. Commun.,* **1971**, 833.
10. (a) Clarke, D.; Emayan, K. and Rees, C. W., *J. Chem. Soc., Perkin Trans. I,* **1998**, 77. (b)Vivona, N.; Buscemi, S.; Frenna, V. and Cusmano, G., *Adv. Heterocycl. Chem.*, **1993**, *56*, 49.
11. Takakis, I. M.; Hadjimihalakis, P. M.; Tsantali, G. G. and Pilini, H., *J. Heterocycl. Chem.,* **1992**, *29*, 123.
12. (a) Katritzky, A. R. and Rees, C. W., eds.; *Comprehensive Heterocyclic Chemistry,* Pergamon, Oxford, **1984**; *Vols. 1-8*. (b) Ghosh, P. B.; Ternai, B. and Whitehouse, M. W., *Med. Res. Rev.,* **1981**, *1*, 159.
13. Eckert, F.; Rauhut, G.; Katritzky, A. R. and Steel, J. P., *J. Am. Chem. Soc.,* **1999**, *121*, 6700.
14. (a) Katritzky, A. R.; Wang, Z. Q.; Hall, C. D. and Akhmedov, N. G., *ARKIVOC*, **2003**, 49. (b) Katritzky, A. R.; Wang, Z.; Hall, C. D.; Ji, Y. and Akhmedov, N. G., *Tetrahedron Lett*., **2002**, *43*, 3449. (c) Guernelli, S.; Lagana, M. F.; Spinelli, D.; Lo Meo, P.; Noto, R. and Riela, S., *J. Org. Chem.,* **2002**, *67*, 2948. (d) Cosimelli, B.; Guernelli, S.; Spinelli, D.; Buscemi, S.; Frenna, V. and Macaluso, G., *J. Org. Chem.,* **2001**, *66*, 6124. (e) Katritzky, A. R. and Pozharskii, A. F., *Handbook of Heterocyclic Chemistry*, 2nd ed., Pergamon, Oxford, **2000**, pp. 101–102. (f) Billi, R.; Cosimelli, B.; Spinelli, D.; Leoni, A., *J. Heterocycl. Chem,.* **2000**, *37*, 875. (g) Billi, R.; Cosimelli, B.; Spinelli, D.; Andreani, A. and Leoni, A., *Tetrahedron,* **2000**, *56*, 6527. (h) Rauhut, G. and Eckert, F., *Sci. Prog.,* **1999**, *82*, 209. (i) Billi, R.; Cosimelli, B.; Spinelli, D. and Rambaldi, M., *Tetrahedron,* **1999**, *55*, 5433. (j) Bean, P. G., *J. Org. Chem.,* **1998**, *63*, 2497. (k) La Manna, G.; Buscemi, S. and Vivona, N., *THEOCHEM,* **1998**, *452*, 67. (l) Andreani, A.; Billi, R.; Cosimelli, B.; Mugnoli, A.; Rambaldi, M. and Spinelli, D., *J. Chem. Soc., Perkin Trans. II,* **1997**, 2407. (m) English, R. F.; Rakitin, O. A.; Rees C. W. and Vlasova, O. G., *J. Chem. Soc.*, *Perkin Trans. I*, **1997**, 201. (n) Besson, T. and Rees, C. W., *J. Chem. Soc.*, *Perkin Trans. I*, **1996**, 2857. (o) Besson, T. and Rees, C. W., *J. Chem. Soc.*, *Perkin Trans. I*, **1995**, 1659. (p) Buscemi, S.; Vivona, N. and Caronna, T., *J. Org. Chem.,* **1995**, *60*, 4096. (q) Besson, T.; Emayan K. and Rees, C. W., *J. Chem. Soc.*, *Perkin Trans. I*, **1995**, 2097. (r) Babaev, E. V.; Lushnikov, D. E. and Zefirov, N. S., *J. Am. Chem. Soc.,* **1993**, 115,2416. (s) Spinelli, D.; Mugnoli, A.; Andreani, A.; Rambaldi, M. and Frascari, S., *J. Chem. Soc., Chem. Commun.,* **1992**, 1394. (t) Bird, C. W., *Tetrahedron,* **1992**, *48*, 335. (u) Andrianov, V. G.; Makushenkov, S. V. and Eremeev, A. V., *Mendeleev Commun.,* **1992**, 129. (v) Takakis, I. M. and Hadjimihalakis, P. M., *J. Heterocycl. Chem.,* **1991**, 28,1373. (w) Takakis, I. M.; Hadjimihalakis, P. M. and Tsantali, G. G., *Tetrahedron,* **1991**, *47*, 7157. (x) La Manna, G.; Buscemi, S.; Frenna, V.; Vivona, N. and Spinelli, D., *Heterocycles,* **1991**, *32*, 1547. (y) Andrianov, V. G. and Eremeev, A. V., *Chem. Heterocyclic Compd.,* **1990**, *26*, 1199. (z) Katritzky, A. R.; Barczynsky, P.; Musumarra, G.; Pisano, D. and Szafran, M., *J. Am. Chem. Soc.,* **1989**, *111*, 7. (aa) Vivona, N.; Frenna, V.; Buscemi, S. and Ruccia, M., *J. Heterocycl. Chem*., **1986**, *22*, 97. (bb) Horváth, K.; Korbonits, D.; Náray-Szabó, G. and Simon, K., *THEOCHEM,* **1986**, *136*, 215. (cc) Bird, C. W., *Tetrahedron,* **1985**, *41*, 1409. (dd) LábbB, G., *J. Heterocycl. Chem*., **1984**, *21*, 627. (ee) Korbonits, D.; Kanzel-Szvoboda, I. and Horváth, K., *J. Chem. Soc.*, *Perkin Trans. I,* **1982**, 759. (ff) Ruccia, M.; Vivona, N.; Spinelli, D., *Adv. Heterocycl. Chem*., **1981**, *29*, 141. (gg) Frenna, V.; Vivona, N.; Consiglio, G.; Corrao, A. and Spinelli, D., *J. Chem. Soc.*, *Perkin Trans. II,* **1981**, 1325. (hh) Boulton, A. J.; Kan-Woon, T.; Balasubrahmanyam, S. N.; Mallick, I. M. and Radhakrishna, A. S., *J. Org. Chem.,* **1980**, *45*, 1653. (ii) Buncel, E.; Chuaqui-Offermanns, N. and Norris, A., *Can. J. Chem.,* **1979**, *57*, 2512. (jj) Vivona, N.; Cusmano, G.; Macaluso, G.; Frenna, V. and Ruccia, M., *J. Heterocycl. Chem.,* **1979**, *16*, 783. (kk) Korbonits, D.; Bakó, E. M. and Horváth, K., *J. Chem. Res. (S),* **1979**, 64; *J. Chem. Res.* (*M*),801. (ll) Korbonits, D.; Baks, E. M. and Harvath, K., *J. Chem. Res. (M)*, **1979**, 801. (mm) Afradi, S. A.; Katritzky, A. R. and Ramsden, A. C., *J. Chem. Soc., Perkin Trans. I,* **1976**, 315. (nn) Vivona, N.; Cusmano, G.;

Ruccia, M. and Spinelli, D., *J. Heterocycl. Chem.,* **1975**, *12*, 985. (oo) van der Plas, H. C., *Ring Transformations of Heterocycles*, Academic Press, London, **1973**, *1–2*. (pp) Ghosh, P. B.; Ternai, B. and Whitehouse, M. W., *J. Med. Chem.,* **1972**, *15*, 1255. (qq) Boulton, **A.** J.; Katritzky, A. R. and Hamid, A. M., *J . Chem. Soc.* C, **1967**, 2005. (rr)Boulton, A. J.; Ghosh, P. B. and Katritzky, A. R., *J. Chem. Soc. B,* **1966**, 1004. (ss) Boulton, A. J.; Ghosh, P. B. and Katritzky, A. R., *J. Chem. Soc. B,* **1966**, 1011. (tt) Boulton, A. J.; Ghosh, P. B. and Katritzky, A. R., *Angew. Chem. Int. Ed. Engl.,* **1964**, *3*, 693. (uu) Buscemi, S.; Pace, A.; Piccionello, A. P.; Pibiri, I.; Vivona, N.; Giorgi, G.; Mazzanti, A. and Spinelli, D., *J. Org. Chem.,* **2006**, *71*, 8106. (vv) Buscemi, S.; Pace, A.; Palumbo, P. A.; Macaluso, G.; Vivona, N.; Spinelli, D. and Giorgi, G., *J. Org. Chem.,* **2005**, *70*, 3288. (ww) Goumont, R.; Jan, E.; Makosza, M. and Terrier, F., *Org. Biomol. Chem.*, **2003**, *1*, 2192. (xx) Crampton, M. R.; Pearce, L. M. and Rabbitt, L. C., *J. Chem. Soc., Perkin Trans. II*, **2002**, 257. (yy) Ostrowski, S. and Wojciechowski, K., *Can. J. Chem.,* **1990**, *68*, 2239. (zz) Calzaferri, G.; Gleiter, R.; Knauer, K. H.; Martin, H. D. and Schmidt, E., *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 86. (aaa) Ghosh, P. B., *J. Chem. Soc. B,* **1968**, 334.

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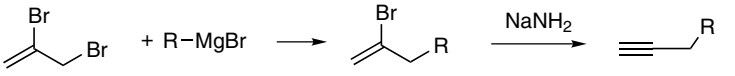
Bourgel Alkyne Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

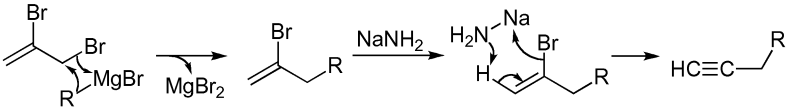
This reaction was first reported by Bourguel in 1925.[1] It is the synthesis of alkynes by the treatment of 2,3-dibromo-1-propene with a Grignard reagent to form a 3-substituted 2-bromo-1-propene, which further reacts with sodium amide. The yields are normally very high.[2] Another advantage of using sodium amide in the last step is that other internal alkynes can isomerize to terminal alkynes.[3]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A tentative mechanism for the generation of alkyne is illustrated below.



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D. MODIFICATION

N/A

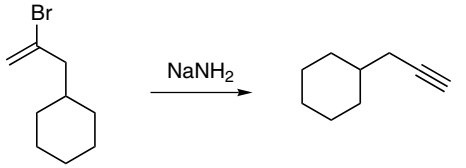
E. APPLICATIONS

This reaction has general application for the preparation of alkynes.

F. RELATED REACTIONS

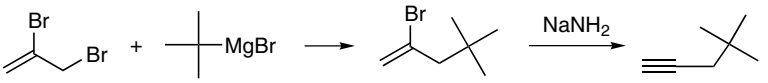
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 4.

A mixture of 120 g sodium amide (3.1 mol) and 200 mL purified mineral oil was ground together in a mortar until the amide was finely pulverized. This suspension was transferred to a 2-L round-bottomed, three-necked flask fitted with a reflux condenser holding a calcium chloride tube, a 500-mL separatory funnel, and an efficient mechanical stirrer through a mercury seal. The mortar and pestle were rinsed with an additional 250 mL of the oil, which was then added to the reaction flask. The mixture was heated in an oil bath maintained at 160–165°C, the stirrer was started, and 203 g cyclohexylbromopropene (1.0 mol) was dropped over 1.5 h. Ammonia was evolved, and was allowed to pass through the condenser and collected in water. After all the cyclohexylbromopropene had been run in, heating was continued for ~2 h; the mixture was cooled, and 500 mL ether was added. This mixture was poured onto 1.5 kg cracked ice in a 5-L flask and then acidified with 280 mL concentrated HCl. The ether layer was separated, dried over calcium chloride, and transferred to a 1-L modified Claisen flask for distillation. The ether was distilled at ordinary pressure, and then the cyclohexylpropyne was distilled under diminished pressure. The product, which was boiled up to 115°C (at 20 mmHg), was collected and fractionated. The cyclohexylpropyne boils at 58–63°C (20 mmHg). The higher-boiling material was chiefly unchanged cyclohexylbromopropene, which could be used again in a subsequent run. The amount of cyclohexylpropyne was 80 g, in a theoretical yield of 66%. The pure compound boils at 61–63°C at 24 mmHg.



Reference 5.

Formation of 4,4-Dimethyl-2-Bromo-1-Pentene

In a 3-L three-necked flask fitted with a mechanical stirrer, a reflux condenser, and a dropping funnel were placed 200 g 2-bromo-allyl bromide (1.0 mol) and 200 mL anhydrous ether. The flask was placed in an ice bath, and through the dropping funnel was added an ether solution of 1.33 mol *tert*-butylmagnesium chloride, which had been prepared and titrated previously. The Grignard reagent was added at such a rate that the ether boiled gently. The addition required 30–45 min. After the addition was complete, the ice bath was removed, and the mixture was gently refluxed on a water bath for ~2 h to ensure completion of the reaction. The mixture was then cooled and the excess Grignard reagent was decomposed by slowly adding a solution of 35 mL concentrated HCl in 350 mL water through the dropping funnel. The ether layer was separated, washed with a saturated sodium bicarbonate, dried over calcium chloride, and distilled. After the ether was removed, the 4,4-dimethyl-2-bromo-1-pentene was collected at 135–138°C. The yields varied from 80 to 110 g (45–62% of the theoretical amount).

Preparation of 4,4-Dimethyl1-Pentyne

Sodium amide (62 g) was ground in a mortar with 104 mL purified high-boiling mineral oil until a fine suspension was obtained. This was transferred to a round-bottomed, three-necked flask fitted with a reflux condenser protected with a calcium chloride tube, a 500-mL dropping funnel, and an efficient mechanical stirrer. An additional 125 mL mineral oil was used in transferring the suspension from the mortar to the reaction flask. The mixture was heated in an oil bath at 160–165°C, the stirrer was started, and 92 g 4,4-dimethyl-2-bromo-1-pentene was added through the dropping funnel. Heating and stirring were continued for 2 h after the addition of the bromo compound was complete. The mixture was then cooled, diluted with 250 mL xylene, and poured onto ~700 g cracked ice to which had been added 140 mL concentrated HCl. The oil layer was separated, washed with a saturated sodium bicarbonate, dried over calcium chloride, and distilled in a modified Claisen flask. In the first fractionation, the material boiling between 50° and 100°C was saved. On redistillation, the product boiling at 73-75°C at ordinary pressures was collected. There was some loss in the preparation due to the heptyne passing off with the ammonia. By using ice water in the condenser and washing the ammonia that escaped with the xylene, the yield was increased to 45%.

Other references related to the Bourguel alkyne synthesis are cited in the literature.[6]

H. REFERENCES

1. Bourguel, M., *Ann. Chim.,* **1925**, *3*, 231.
2. Johnson, J. R. and McEwen, W. L., *J. Am. Chem. Soc.,* **1926**, *48*, 469.
3. Hill, A. J. and Tyson, F., *J. Am. Chem. Soc.,* **1928**, *50*, 172.
4. Lespieau, R. and Bourguel, M., *Org. Syn. Coll.,* **1941**, *1* (2nd ed.) 191.
5. Ozanne, I. L. and Marvel, C. S., *J. Am. Chem. Soc.,* **1930**, *52*, 5267.
6. (a) Campbell, K. N.; Fatora, F. C. and Campbell, B. K., *J. Org. Chem.,* **1952**, *17*, 1141. (b) Anzilotti, W. F. and Vogt, R. R., *J. Am. Chem. Soc.,* **1939**, *61*, 572. (c) Ryden, L. L.; Glavis, F. J. and Marvel, C. S., *J. Am. Chem. Soc.,* **1937**, *59*, 1014. (d) Vaughen, T. H., *J. Am. Chem. Soc.,* **1933**, *55*, 3453. (e) Lespieau, R. and Bourguel, M., *Org. Syn. Coll.,* **1932**, *1*, 180. (f) Lespieau, R. and Bourguel, M., *Org. Syn.,* **1926**, *4*, 20. (g) Lespieau, R. and Bourguel, M., *Org. Synth.,* **1926**, *4*, 26.

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Bouveault Aldehyde Synthesis

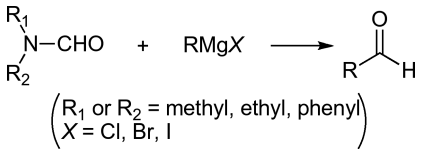
(Bouveault Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Bouveault in 1896.[1] It is the reaction for synthesizing aldehydes by the treatment of *N*,*N*-disubstituted formamides with either Grignard reagent or organic lithium reagent in an ether solvent. Thus this reaction is referred to as the Bouveault aldehyde synthesis[2] or Bouveault reaction.[3] It should be pointed out that this reaction works only in certain cases because the reaction is complicated and sometimes produces tertiary amines as the chief products.[4] For example, when *N*,*N*-disubstituted formamide is treated with 3 eq. Grignard reagent, the tertiary amine is the major product; however, when methylformamide or ethylformamide is treated with an equal amount of Grignard reagent, the major product is an aldehyde. Especially when diphenylformamide is used, the only product found is an aldehyde, whereas diethylformamide and piperidylformamide will give more amine than aldehyde when treated with Grignard reagent.[2] It is found that the greater the R group in the Grignard reagent, the more aldehyde is yielded.[2] It is suggested that the workup is easier when a slight excess of Grignard reagent is used in this reaction.[5] This reaction has been improved by either running in a co-solvent of ether-HMPA[6] or irradiating with high-frequency ultrasound in THF or tetahydropyran.[7]

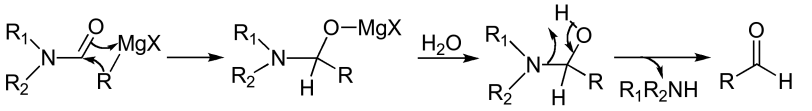
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A simple mechanism is displayed here.



D. MODIFICATION

This reaction has been modified by using co-solvent of ether-HMPA for a better yield.[6] In addition, when the reaction mixture is irradiated by a high-frequency ultrasound (50 kHz), the yield is increased more than 20% within a shorter reaction time.[7]

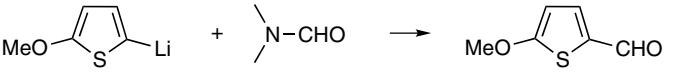
E. APPLICATIONS

This reaction has general application in the preparation of aldehydes.

F. RELATED REACTIONS

This reaction is related to the *Bodroux-Chichibabin Reaction*.

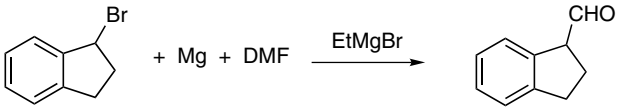
G. CITED EXPERIMENTAL EXAMPLES



Reference 5.

A solution of methoxythienyllithium, prepared from 10 mL 2-methoxythiophene and phenyllithium in 125 mL ether, was added in a slow stream to an ice cold solution of 8 mL dimethylformamide (0.11 mol) in 75 mL ether with efficient stirring. The yellow suspension was left at room temperature overnight, then poured onto ice. The ether layer was washed with water, dried over Na_2SO_4, and evaporated. The residue was distilled to give 9.27 g of 5-methoxy-2-thienaldehyde, in a yield of 67%, b.p. 79–81°C at 0.9 mmHg. A colorless

needle was obtained when the compound was crystallized from ether-hexane at –20°C, m.p. 24–26°C.



Reference 8.

To a stirred solution of 5 mmol ethylmagnesiumbromide in 100mL anhydrous THF containing magnesium turnings was added 5-bromoindane dropwise. The exothermic reaction initiated spontaneously and the remaining 5-bromoindane was added, taking care to keep the reaction from boiling over. When the reaction had returned to room temperature, the flask was cooled to 0°C. A solution of DMF in 75mL anhydrous THF was added over 15 min, causing a mild temperature rise. The flask was removed from the ice bath and allowed to stir for a further 2 h. The color changed from purple-brown to a light pea green during this period. The reaction was then quenched by the addition of ~80 mL 3 M HCl. The biphasic mixture was added to 500 mL water, and the product was extracted with ether (2 × 50 mL). The extracts were combined and washed with 100 mL water, 100 mL sodium bicarbonate solution, and 50 mL brine. Removal of the solvent and distillation under vacuum gave 10.1 g 5-formyl indane as a clear, colorless oil, boiling at 132 – 137°C, in a yield of 69%.

Other references related to the Bouveault aldehyde synthesis are cited in the literature.[9]

H. REFERENCES

1. Bouveault, L., *Bull. Soc. Chim.*, **1896**, *15*, 1014.
2. Smith, L. I. and Bayliss, M., *J. Org. Chem.,* **1941**, *6*, 437.
3. Petrier, C.; Gemal, A. L. and Luche, J. L., *Tetrahedron Lett.,* **1982**, *23*, 3361.
4. Smith, L. I. and Nichols, J., *J. Org. Chem.,* **1941**, *6*, 489.
5. Sicé, J., *J. Am. Chem. Soc.,* **1953**, *75*, 3697.
6. (a) Hansson, C. and Wickberg, B., *J. Org. Chem.,* **1973**, *38*, 3074. (b) Fauvarque, J.; Ducom, J. and Fauvarque, J. C., *C. R. Acad. Sci., Ser. C.,* **1972**, *275*, 511.
7. (a) Gains, P. W.; Martin, P. D. and Price, C. J., *Org. Proc. Res. Dev.,* **1998**, *2*, 34. (b) Pétrier, C.; Gemal, A. L. and Luche, J.-L., *Tetrahedron Lett.,* **1982**, *23*, 3361. (c) Luche, J.-L., *Ultrasonics*, **1987**, *25*, 40.
8. See www.erowid.org/archive/rhodium/chemistry/indane.formylation.html.
9. (a) Meier, H. and Aust, H., *J. Prakt. Chem.,* **1999**, *341***,** 466. (b) Einhorn, J. and Luche, J. L., *Tetrahedron Lett.*, **1986**, *27*, 1791. (c) Jones, E. R. H.; Skattebol, L. and Whiting, M. C., *J. Chem. Soc.* **1958**, 1054. (d) Evans, E. A., *Chem. Ind. (London),* **1957**, 1596. (e) Ferguson, L. K., *Chem. Rev*., **1946**, *38*, 227. (f) Barger, G. and Easson, A. P. T., *J. Chem. Soc.,* **1938**, 2100. (g) Maxim, N. and Mavrodineanu, R., *Bull. Soc. Chim.,* **1935**, *2*, 591; **1936**, *3*, 1084. (h) Maxim, N., *Bull. Soc. Chim.,* **1927**, *41*, 809. (i) Viguier, P., *Compt. Rend*., **1911**, *153*, 955. (j) Houben, J., and Doescher, H., *Ber.,* **1907**, *39*, 4576. (k) Bouveault, L., *Bull. Soc. Chim. Fr.*, **1904**, *31*, 1306. (l) Bouveault, L., *Bull. Soc. Chim. Fr.*, **1904**, *31*, 1322. (m) Bouveault, L., *Bull. Soc. Chim. Fr.,* **1897**, *17*, 363. (n) Bouveault, L., *Bull. Soc. Chim. Fr.,* **1897**, *17*, 940. (o) Bouveault, L., *Bull. Soc. Chim. Fr.,* **1897**, *17*, 943.

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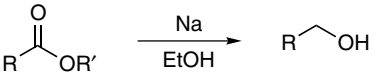
Bouveault-Blanc Reduction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Bouveault and Blanc in 1903.[1] It is the reduction of esters into alcohols with sodium in ethanol, in which sodium serves as a single electron-reducing agent and ethanol is the proton donor. Therefore, this reaction is generally known as the Bouveault-Blanc reduction.[2] Occasionally, it is also referred to as the Bouveault-Blanc reaction.[3] Besides ethanol, other alcohols can be applied as proton donors. However, in the absence of proton donor, the reduction of esters with sodium leads to the formation of acyloins (i.e., *Acyloin Condensation*). It should be pointed out that the Bouveault-Blanc reduction under appropriate conditions also effects the ring reduction of aromatic compounds (e.g., *Birch Reduction*). Although this method was widely used in the reduction of esters before lithium aluminum hydride appeared, it also sometimes failed.[4] For example, the reduction of methyl ester of isonoragathic acid gave alcohol in poor yield;[5] the reduction of methyl linoleate by the alcoholic sodium afforded octadecadiene-9,10-ol-1 and octadecadiene-10,12-ol-1.[6] It was found that the reduction of α-benzylamino-β-methoxy ester gave the unexpected de-methoxy amino alcohol.[7] Nevertheless, the Bouveault-Blanc reduction is an inexpensive substitute for lithium aluminum hydride reductions of esters in industrial production and was the "only alternative prior to the development of the metal hydride"[8] as the reducing agent. It has been proved that this reduction occurs via a radical mechanism, in which esters are first reduced to ketyl radicals and further to alcohols.[9] As a result, the ketyl radical can cyclize to form cyclic or spirocyclic molecules if a double bond exists in the appropriate location of the ester.[9] Recently, a reduction of organometallic complex was found to resemble the reduction behavior of the Bouveault-Blanc reduction.[10]

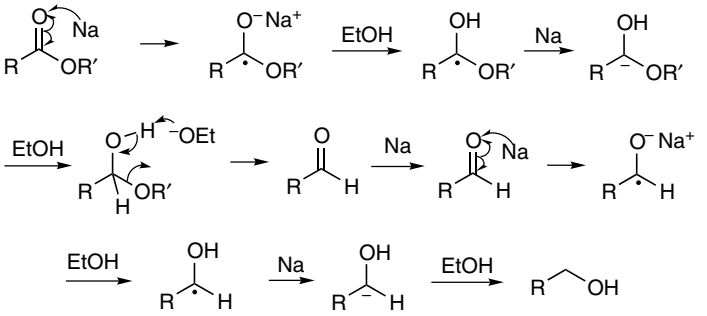
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A radical mechanism is proposed here.



D. MODIFICATION

The conversion of organometallic complex (η^2-formaldehyde complex: $Cp'_2Nb(Cl)(\eta^2\text{-}CH_2O)$) to the diamagnetic hydride complex ($Cp'_2Nb(H)(\eta^2\text{-}CH_2O)$) is an organometallic version of the Bouveault-Blanc reduction. This reaction provides access to reduction products that are not available with the use of hydridic reductants and requires the presence of alcohol to facilitate the second reduction event.[10]

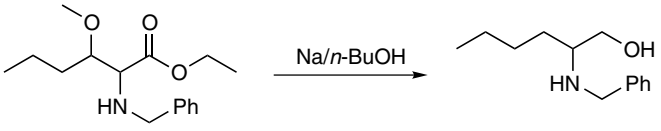
E. APPLICATIONS

This reaction can be generally used to reduce esters, aldehydes, and ketones to the corresponding alcohols. In addition, if a double bond exists on the appropriate location of the ester, a cyclic or spirocyclic alcohol will form.[9]

F. RELATED REACTIONS

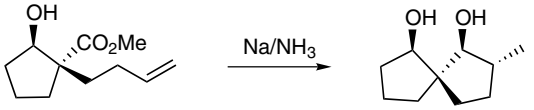
This reaction is related to the *Benkeser Reduction* and *Birch Reduction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

In a three-necked flask equipped with a mechanical stirrer and two reflux condensers was placed a solution of 55 g ethyl α-benzylamino-β-methoxy-*n*-caproate (0.197 mol) in 500 mL anhydrous *n*-butanol. The flask was placed in an oil bath maintained at 140°C. As soon as the contents of the flask had begun to boil, the burner was removed from under the bath and the temperature of the bath was permitted to fall to 115°C. At this point, 55 g sodium buck shot (2.4 mol) was added as rapidly as possible. The butanol was kept boiling vigorously until all of the sodium had dissolved, additional *n*-butanol was added at intervals to keep the sodium butoxide formed in solution. After all of the sodium metal had dissolved, the flask was cooled to 25°C, and 100 g ice was added. The solution was acidified with 6 *N* HCl. The solvents were then removed by distillation in vacuo. When an estimated 50 g sodium chloride had crystallized, the evaporation was interrupted, the sodium chloride was removed, and the distillation was continued until butanol no longer appeared in the distillate. The residue solidified on cooling to 25°C. The resultant paste was made strongly alkaline with 6 *N*NaOH and extracted with three 100-mL portions of ether. The combined ethereal extracts were washed with 25 mL water and dried over anhydrous magnesium sulfate. The solvent was removed, and the residue was distilled to give 25 g of a pale yellow oil, b.p. 130-133°C (0.1 mmHg). The distillate was caused to crystallize, and after two recrystallizations from acetone, the product was obtained as colorless needles, m.p. 46.5 – 47.5°C.



Reference 9.

To 150 mL liquid ammonia at –78°C, were added 0.3 g sodium in small pieces (12.0 mmol, 6.0 eq.). After 15 min, a solution of (±)-(1*RS*,2*SR*)-methyl 1-(but-3-enyl)-2-hydroxycyclopentane-1-carboxylate (2.0 mmol, 1.0 eq.) in 5 mL THF was added dropwise. The reaction mixture was warmed to -33°C and stirred in refluxing ammonia for 10 min. The excess of sodium was then destroyed by the addition of ammonium chloride, and the ammonia was evaporated under a stream of nitrogen (fume hood). Et_2O was added, and the reaction mixture was neutralized by a solution of 10% HCl. The residue was extracted with Et_2O. The organic layers were dried over $MgSO_4$ and filtered; the solvent was removed in vacuo. The crude oil was purified by crystallization in pentane, and 95% (±)-(1*SR*,2*RS*,5*SR*,6*RS*)-2-methyl-spiro[4.4]nonane-1,6-diol was obtained, m.p. 132 – 133°C, R_f = 0.10 (petroleum ether/EtOAc = 50:50).

Other references related to the Bouveault-Blanc reduction are cited in the literature.[11]

H. REFERENCES

1. (a) Bouveault, L. and Blanc, G., *Compt. Rend.*, **1903**, *136*, 1676. (b) Bouveault, L. and Blanc, G., *Compt. Rend.*, **1903**, *137*, 60.
2. (a) Zhang, Y. H. and Ding, C. Y., *Huaxue Tongbao*, **1997**, *36*. (b) Castells, J.; Grandes, D.; Moreno-Manas, M. and Virgili, A., *Anal. Quim.,* **1976**, *72*, 74. (c) Kanno, S. and Oyamada, T., *Kenkyu Hokoku - Asahi Garasu Kogyo Gijutsu Shoreikai*, **1967**, *13*, 631. (d) Akashi, H., *Kogyo Kagaku Zasshi*, **1961**, *64*, 315. (e) Masuyama, S., *Nippon Nogei-Kagaku Kaishi*, **1954**, *28*,

383. (f) Masuyama, S., *Nippon Nogei-Kagaku Kaishi*, **1952**, *26*, 622. (g) Masuyama, S., *Nippon Nogei-Kagaku Kaishi*, **1952**, *26*, 524.

3. (a) Poulain, F., *French Pat.,* **1954**, April 8, FR 1,061,101. (b) Palfray, L. and Anglaret, P., *Compt. Rend.,* **1946**, *223*, 860. (c) Blanc, G., *Amer. Perfumer Essent. Oil Rev.,* **1922**, *17*, 57.
4. Glattfeld, J. W. E. and Mochel, W. E., *J. Am. Chem. Soc.,* **1938**, *60*, 1011.
5. Ruzicka, L. and Jacobs, H., *Rev. Trav. Chim. Pays-Bas Bleg.,* **1938**, *57*, 509.
6. Kass, J. P.; Miller, E. S. and Burr, G. O., *J. Am. Chem. Soc.,* **1939**, *61*, 482.
7. Niemann, C. and Redemann, C. T., *J. Am. Chem. Soc.,* **1946**, *68*, 1932.
8. See www.organic-chemistry.org/namedreactions/bouveault-blanc-reduction.shtm.
9. Cossy, J.; Gille, B. and Bellosta, V., *J. Org. Chem.,* **1998**, 63,3141.
10. Thiyagarajan, B.; Michalczyk, L.; Bollinger, J. C.; Huffman, J. C. and Bruno, J. W., *Organometallics,* **1996**, 15,1989.
11. (a) Lapić, J. and Rapić, V., *Croatica Chem. Acta,* **2000**, *73*, 755. (b) Arosio, R. and Harris, R. G., *Speciality Chemicals*, **1999**, *19*, 198. (c) Seo, B.-I.; Lewis, D.E.; Wall, L.K.; Lee, H. and Buttrum, J. W., *Synth. Commun*., **1993**, *23*, 15. (d) Huffman, J. W.; Liao, W.-P. and Wallace, R. H., *Tetrahedron Lett.,* **1987**, *28*, 3315. (e) Pradhan, S. K., *Tetrahedron,* **1986**, *42*, 6351. (f) Rabideau, P. W.; Wetzel, D. M. and Young, D. M., *J. Org. Chem.,* **1984**, *49*, 1544. (g) Huffman, J. W., *Acc. Chem. Res.,* **1983**, *16*, 399. (h) Ohtani, Y.; Itoh, N.; Ogura, I. and Yamaguchi, M., *Kinki Daigaku Genshiryoku Kenkyusho Nenpo,* **1976**, *13*, 25. (i) Isaacs, N. S., *Reactive Intermediate in Organic Chemistry*, John Wiley & Sons, London **1974**, p370. (j) House, H. O., *Modern Synthetic Reactions*, 2nd ed., Benjamin, Menlo Park, Calif., **1972**, p. 150. (k) Gutsche, C. D.; Tao, I. Y. C. and Kozma, J., *J. Org. Chem.,* **1967**, *32*, 1782. (l) Decombe, J.; Ravoux, J. P. and Dormond, A., *Compt. Rend.,* **1964**, *258*, 2348. (m) Newman, M. S.; Renoll, M. W. and Auerbach, I., *J. Am. Chem. Soc.,* **1948**, *70*, 1023. (n) Hansley, V. L., *Ind. Eng. Chem*., **1947**, *39*, 35. (o) Palfray, L. and Anglaret, P., *Compt. Rend.,* **1947**, *224*, 404. (p) Darzens, G., *Compt. Rend.,* **1947**, *224*, 570. (q) Buser, K. and Rupe, H., *Helv. Chim. Acta*, **1943**, *26*, 859. (r) Manske, R. H., *Org. Synth. Coll. 2,* **1943**, 154. (s) Ford, S. G. and Marvel, C. S., *Org. Synth. Coll. 2*, **1943**, 372. (t) Crouch, W. W. and Lochte, H. L., *J. Am. Chem. Soc.,* **1941**, *63*, 1331. (u) Lucas, H. J. and Baumgarten, W., *J. Am. Chem. Soc.,* **1941**, *63*, 1653. (v) Goheen, G. E., *J. Ind. Eng. Chim.,* **1940**, *32*, 503. (w) Palfray, C. L. and Sabetay, *Chemie Industrie* (Special issue) (Congrès de Bruxelles), **1935**, p. 746. (x) Chablay, E., *Compt. Rend.,* **1913**, *156*, 1020. (y) Bouveault, L. and Blanc, G., *Bull. Soc. Chim. Fr.,* **1906**, *35*, 629. (z) Bouveault, L. and Locquin, R., *Compt. Rend*., **1905**, *140*, 1593, 1669. (aa) Bouveault, L. and Blanc, G., *Bull. Soc. Chim. Fr.,* **1904**, *31*, 666, 1203. (bb) Bouveault, L. and Blanc, G., *Chem. Zentr*., **1903**, *2*, 418. (cc) Bouveault, L. and Blanc, G., *Bull. Soc. Chim. Fr.*, **1903**, *29*, 787.

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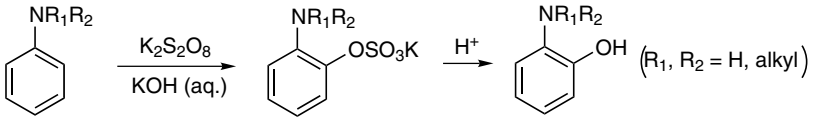
Boyland-Sims Oxidation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Boyland and Sims in 1953.[1] It is a two-step process involving the oxidation of aromatic amines by alkaline persulfate to give predominantly the *o*-amino aryl sulfates and subsequent conversion of *o*-amino aryl sulfates into *o*-hydroxy aryl amines through acid promoted hydrolysis. Therefore, this reaction is generally known as the Boyland-Sims oxidation.[2] Occasionally, it is also referred to as the Boyland-Sims peroxydisulfate oxidation.[3] In this reaction, primary, secondary, and tertiary aromatic amines all can be converted to the *o*-sulfate esters under this condition.[4] Even though the yields are generally 10–40%, the starting material is generally recoverable, even in the presence of an excess amount of persulfate.[2e] It is reported that a substantial amount of insoluble, brown amorphous materials appears in some of the oxidations.[1,4c,4d] Except for the oxidation of anthranilic acid,[5] the formation of *ortho* sulfate esters is exclusive for other aromatic amines;[2a,4] when both *ortho* positions of aromatic amines are blocked, the *para* substitution takes place.[1,4b–d] It is suggested that this reaction proceeds via a nucleophilic displacement on peroxide oxygen,[6] or an *ipso* attack followed by the rearrangement to *ortho* sulfate in the case of tertiary amines.[2d,7] The scope of this reaction has been extended to include indoles and aminopyrimidines,[8] and has been extensively reviewed.[9]

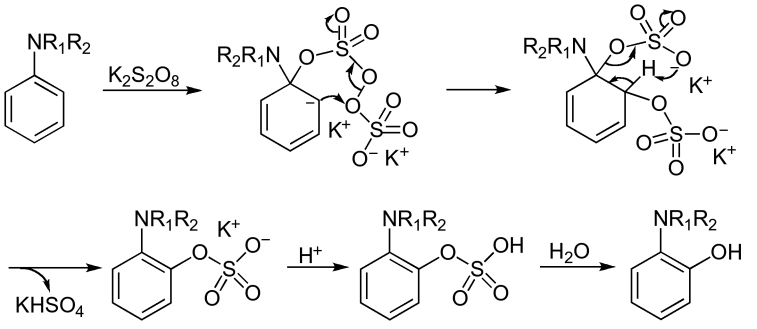
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is proposed that this reaction involves an *ipso* attack by peroxydisulfate followed by the cleavage of the peroxide bond to form the *ortho* sulfate ester, as illustrated below.[2d,7]



D. MODIFICATION

N/A

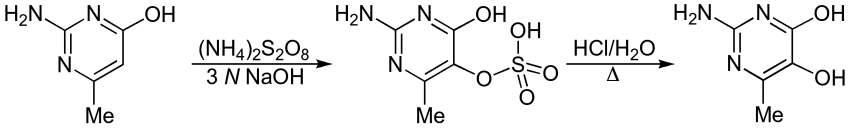
E. APPLICATIONS

This reaction has general application in the preparation of *o*-amino phenols.

F. RELATED REACTIONS

This reaction is related to the *Elbs Persulfate Oxidation*.

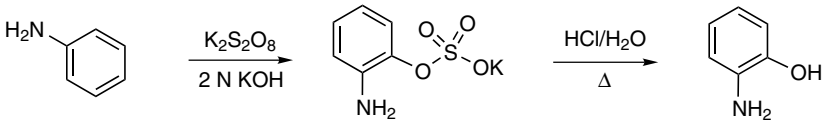
G. CITED EXPERIMENTAL EXAMPLES



Reference 8c.

To a stirred ice cold 3 N NaOH solution (220 mL) containing 12.5 g 2-amino-4-hydroxy-6-methylpyrimidine was added dropwise a solution of 34.2 g ammonium persulfate in 70 mL water over 1 h. After being stirred overnight, the solution was acidified with concentrated HCl, and 14.5 g 2-amino-4-hydroxy-6-methyl-5-pyrimidyl hydrogen sulfate was collected, m.p. 297°C (dec.). Recrystallization from water afforded the product as colorless prismatic needles, m.p. 311°C (dec.).

A solution of 76.0 g 2-amino-4-hydroxy-6-methyl-5-pyrimidyl hydrogen sulfate in 208 mL 5 N HCl was refluxed for 30 min, and then cooled. 2-Amino-4,5-dihydroxy-6-methylpyrimidine hydrochloride was collected and made into a slurry with sodium hydrogen carbonate solution and refiltered. The solid was purified by recrystallization from water to afford 30 g 2-amino-4,5-dihydroxy-6-methyl-5-pyrimidine as colorless prismatic needles, m.p. > 310°C.



Reference 1.

To a mixture of 5 g aniline, 500 mL water and 50 mL 2 N KOH solution at room temperature was added a saturated aqueous solution of 14.5 g potassium persulfate over 8 h with continuous stirring. The mixture was kept overnight, and the precipitate was collected, in an amount of 2.9 g. The filtrate was evaporated to 100 mL under reduced pressure, washed with ether (3 × 100 mL), and made acid to Congo red with 2 N H_2SO_4. The filtered solution was extracted with butanol (6 × 100 mL), and a slight excess of aqueous 2 N KOH was added to the combined organic phase. The butanol extract was evaporated to dryness under reduced pressure. The residue was extracted with hot 95% aqueous ethanol (4 × 100 mL), and the combined extracts were evaporated to 25 mL and kept at 0°C for some hours. *O*-Aminophenyl potassium sulfate (1.9 g, 15.5%) was obtained, separating from 90% ethanol containing a trace of aqueous KOH as a light brown plate.

A mixture of 500 mg *o*-aminophenyl potassium sulfate and 2 mL concentrated HCl was heated at 100°C for 30 min, and then partially neutralized with 2 N KOH to afford 245 mg of *o*-aminophenol as needles, in a yield of 90%, m.p. 173–174°C.

Other references related to the Boyland-Sims oxidation are cited in the literature.[10]

H. REFERENCES

1. Boyland, E.; Manson, D. and Sims, P., *J. Chem. Soc.,* **1953**, 3623.
2. (a) Behrman, E. J., *J. Org. Chem.,* **1992**, *57*, 2266. (b) Srinivasan, C.; Perumal, S. and Arumugam, N., *J. Chem. Soc., Perkin Trans. II,* **1985**, 1855. (c) Krishnamurthi, T. K. and Venkatasubramanian, N., *Indian J. Chem., Sect. A,* **1978**, *16A*, 28. (d) Behrman, E. J. and Behrman, D. M., *J. Org. Chem.,* **1978**, *43*, 4551. (e) Behrman, E. J., *J. Am. Chem. Soc.,* **1967**, *89*, 2424.
3. Behrman, E. J., *Beilstein J. Org. Chem.,* **2006**, *2*, 22.
4. (a) Sabesan, A. and Venkatasubramanian, N., *Aust. J. Chem*., **1971**, *24*, 1633. (b) Boyland, E. and Sims, P., *J. Chem. Soc.,* **1958**, 4198. (c) Sims, P., *J. Chem. Soc.,* **1958**, 44. (d) Boyland, E. and Sims, P., *J. Chem. Soc.,* **1954**, 980.

5. (a) May, E. L.; Millican, R. C. and Mehler, A. H., *J. Org. Chem.* **1962**, *27*, 2274. (b) Boyland, E.; Sims, P. and Williams, D. C., *Biochem. J.* **1956**, *62*, 546. (c) Dalgliesh, C. E., *Biochem. J.* **1955**, *61*, 334.
6. Behrman, E. J. and Edwards, J. O., *Prog. Phys. Org. Chem.,* **1967**, *4*, 93.
7. (a) Moodie, R. B. and Schofield, K., *Acc. Chem. Res.,* **1976**, *9*, 287. (b) Hartshorn, S. R.*, Chem. Soc. Rev*., **1974**, *3*, 167.
8. (a) Heacock, R. A. and Mahon, M. E., *Can. J. Biochem.,* **1965**, *43*, 1985. (b) Dalgliesh, C. E. and Kelley, W., *J. Chem. Soc.,* **1958**, 3726. (c) Hull, R., *J. Chem. Soc.,* **1956**, 2033.
9. Behrman, E. J., *Org. React.,* **1988**, *35*, 421.
10. (a) González, C. and Castedo, L., "Synthesis of Phenols" in *The Chemistry of Functional Groups*, ed. Rappoport, Z., John Wiley & Sons, Ltd., **2003**. (b) Gupta, V. K., *Reaction Kinetics & Catal. Lett.,* **1985**, *27*, 207. (c) Paul, D. F. and Haberfield, P., *J. Org. Chem.,* **1976**, *41*, 3170. (d) Juneja, T. R. and Dannenberg, H., *Tetrahedron*, **1975**, *31*, 695. (e) Juneja, T. R. and Dannenberg, H., *Tetrahedron*, **1975**, *31*, 701. (f) Gutschke, D. and Heesing, A., *Ber.,* **1973**, *106*, 2379. (g) Sabesan, A. and Venkatasubramanian, N., *Indian J. Chem.,* **1972**, *10*, 1092. (h) Venkatasubramanian, N. and Sabesan, A., *Can. J. Chem*., **1969**, *47*, 3710. (i) Tisue, G. T.; Grassmann, M. and Lwowski, W., *Tetrahedron*, **1968**, *24*, 999. (j) Truce, W. E.; Fieldhouse, J. W.; Vrencur, D. J.; Norell, J. R.; Campbell, R. W. and Brady, D. G., *J. Org. Chem.,* **1967**, *34*, 3097. (k) Boyland, E. and Manson, D., *Biochem. J*., **1966**, *101*, 84. (l) Boyland, E. and Nery, R., *J. Chem. Soc*., **1962**, 5217. (m) Huisgen, R.; Bayerlein, F. and Heydkamp, W., *Ber.,* **1959**, *92*, 3223. (n) Bacon, R. G. R.; Grime, R. and Munro, D. J., *J. Chem. Soc.,* **1954**, 2275.

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Bradsher Cyclization

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Bradsher in 1939.[1] It is a reaction for synthesizing a variety of polycyclic aromatic compounds, especially the phenanthrene series, by acid catalyzed cyclization. This reaction is sometimes called the Bradsher reaction,[2] Bradsher cyclization,[3] Bradsher-type aromatic cyclodehydration,[4] and *Parham Cyclization*.[5] So far, different types of functional groups linking to an aromatic ring have been found to be applicable for the general purpose of acid-catalyzed cyclization, and these groups include the carbonyl group in ketone[6] or aldehyde,[7] aldehyde derivative (e.g., acetal),[8] nitrile,[9] amino alcohol,[10] carbinol,[11] nitrile (converted to carbonyl by a Grignard reagent),[12] haloether,[13] olefin,[14] olefin oxide,[15] and glycols.[16] On the other hand, this cyclization can also be triggered via photoirradiation,[17] or a strong base.[18] In the cyclization involving a carbonyl group, this reaction is thought to proceed through four steps: (a) protonation of the carbonyl oxygen, (b) attacking of the positive carbon atom (of carbonyl) to the *ortho* position of the aromatic ring, (c) elimination of a proton, and (d) transannular elimination of water.[6e,19] However, no enol form of carbonyl group is found to be involved in this reaction.[20] The general mechanism should involve the arenium ion as an intermediate and final dehydration. This reaction has shown to be of significant value with a wide range of applications.[21] The cyclization of ketones or aldehydes have been reviewed.[22]

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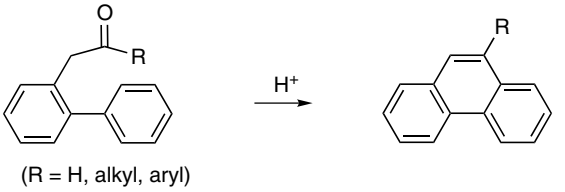
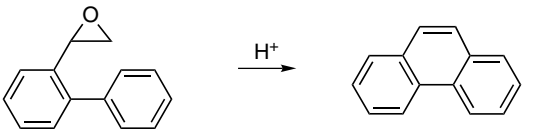
B. GENERAL REACTION SCHEME

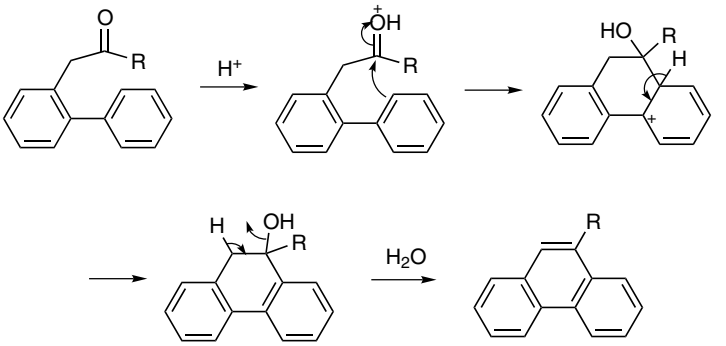


(R = H, alkyl, aryl)



C. PROPOSED MECHANISMS

A general mechanism is displayed below.



D. MODIFICATION

The initial reaction system has been extensively modified and adapted to different functional groups[1,6–16] and methods.[17]

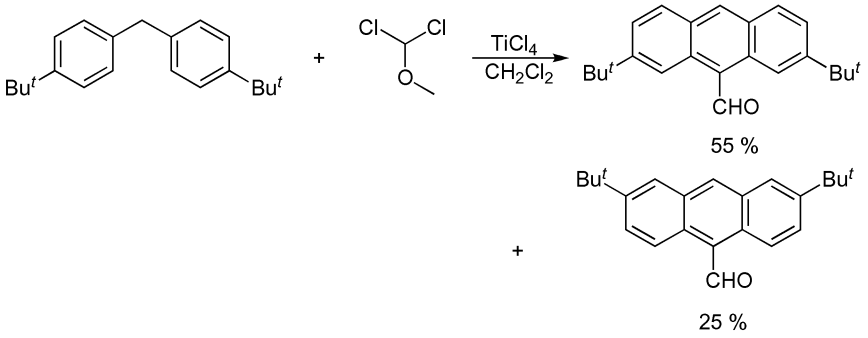
E. APPLICATIONS

This reaction has wide application in the preparation of a variety of polycyclic aromatic compounds[2a,20] and other molecules.[15]

F. RELATED REACTIONS

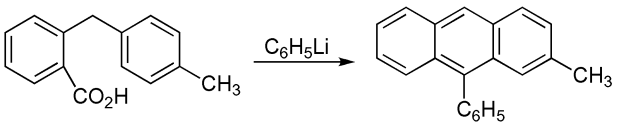
N/A

G. CITED EXPERIMENTAL EXAMPLES



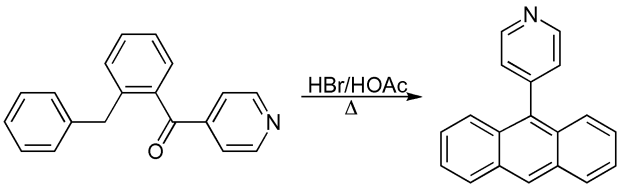
Reference 2a.

To a solution of 1.0 g 4,4′-di-*t*-butylphenylmethane (3.57 mmol) and 1.7 mL dichloromethyl methyl ether (19.2 mmol) in 50 mL CH_2Cl_2 was added a solution of 1.45 mL $TiCl_4$ (13.2 mmol) in 5 mL CH_2Cl_2 at 0°C. The reaction mixture was kept at room temperature for 1 h before the addition of 20 mL cold water; it was extracted with CH_2Cl_2 (30 mL × 3). The extract was washed with water (30 mL × 2), dried over Na_2SO_4, and concentrated. The residue was chromatographed over silica gel (Wako, C-300; 100 g) with hexane/benzene (1:1) as the eluent. The first fraction afforded a pale yellow solid, which was recrystallized from hexane to give 627 mg 2,7-di-*tert*-butyl-9-formylanthracene as pale yellow prisms, in a yield of 55%, m.p. 107–110°C. The second fraction afforded 285 mg 2,7-di-*tert*-butyl-10-formylanthracene as a pale yellow oil, in a yield of 25%.



Reference 18a.

To an ether solution of phenyllithium, a solution containing 5 g *o*-(4-methylbenzy1)benzoic acid in 150 mL dry ether was added gradually with stirring over a period of 30 min. The dark reaction mixture was stirred for 15 h at room temperature, and then ~ 200 mL ice water was added dropwise with cooling and stirring. The ether layer was separated, washed with water until neutral, and finally dried over sodium sulfate. The ether was removed on the steam bath, and the residue was dissolved in 50 mL dry benzene and chromatographed by passing it through a 2.5 × 35 cm column carefully packed with 125 g alumina (Merck and Co.). Benzene was used for the elution of the hydrocarbon fraction. Because no crystalline product was obtained, the chromatographic process was repeated, the benzene solution was concentrated, and the fluorescent residue was crystallized from ethanol to give 2.48 g 2-methyl-9-phenyl-phenanthracene as granular light yellow crystals, in a yield of 42%, m.p. 120°C.



Reference 3.

A mixture of 4.5 g 2-benzyl-phenyl 2-pyridyl ketone (0.017 mol), 25 mL 48% hydrobromic acid, and 50 mL glacial acetic acid was reflux for 52 h. The solution was neutralized with dilute NaOH, and the resultant precipitate was collected, washed with water, and dried; 3.9 g of 9-(2-pyridyl)anthracene was obtained, in a yield of 92%. The product was recrystallized from a mixture of ethanol and methanol to afford light yellow-green crystals, m.p. 163–165°C.

Other references related to the Bradsher cyclization are cited in the literature.[23]

H. REFERENCES

1. Bradsher, C. K., *J. Am. Chem. Soc.,* **1939**, *61*, 3131.
2. (a) Yamato, T.; Sakaue, N.; Shinoda, N. and Matsuo, K., *J. Chem. Soc., Perkin Trans. I,* **1997**, 1193. (b) Lupes, M. E. and Lupes, S. A., *Sci. Bull. Polytech. Inst. Bucharest, Chem. Mater. Sci.,* **1990**, *52*, 53. (c) Saraf, S. D. and Vingiello, F. A., *Synthesis*, **1970**, 655.
3. Bolitt, V.; Mioskowski, C.; Kollah, R. O.; Manna, S.; Rajapaksa, D. and Falck, J. R., *J. Am. Chem. Soc.,* **1991**, *113*, 6320.
4. (a) Vingiello, F. A. and Schlechter, D. A., *J. Org. Chem.,* **1963**, *28*, 2448. (b) Vingiello, F. A.; Borkovec, A., *J. Am. Chem. Soc.,* **1955**, *77*, 4823. (c) Vingiello, F. A.; Borkovec, A. and Shulman, J., *J. Am. Chem. Soc.,* **1955**, *77*, 2320.
5. Collado, M. I.; Manteca, I.; Sotomayor, N.; Villa, M.-J. and Lete, E., *J. Org. Chem.,* **1997**, *62*, 2080.
6. (a) Vingiello, F. A. and Greenwoods, E. J., *J. Org. Chem.,* **1964**, *29*, 1220. (b) Vingiello, F. A.; Spangler, M. O. L. and Bondurant, J. E., *J. Org. Chem.,* **1960**, *25*, 2091. (c) Vingiello, F. A.; Bořkovec, A. and Zajac, W., *J. Am. Chem. Soc.,* **1958**, *80*, 1714. (d) Bradsher, C. K and Kittila, R. S., *J. Am. Chem. Soc.,* **1950**, *72*, 277. (e) Bradsher, C. K. and Vingiello, F. A., *J. Am. Chem. Soc.,* **1949**, *71*, 1434.
7. Bradsher, C. K., *J. Am. Chem. Soc.,* **1942**, *64*, 1007.
8. Bradsher, C. K. and Wert, R. W., *J. Am. Chem. Soc.,* **1940**, *62*, 2806.
9. (a) Bradsher, C. K.; Little, E. D. and Beavers, D. J., *J. Am. Chem. Soc.,* **1956**, *78*, 2153. (b) Bradsher, C. K. and Beavers, D. J., *J. Org. Chem.,* **1956**, *21*, 1067. (c) Bradsher, C. K.; Beavers, D. J. and Little, E. D., *J. Am. Chem. Soc.,* **1954**, *76*, 948.
10. Orito, K.; Miyazawa, M.; Kanbayashi, R.; Tokuda, M. and Suginome, H., *J. Org. Chem.,* **1999**, *64*, 6583.
11. (a) Bradsher, C. K. and Tess, R. W. H., *J. Am. Chem. Soc.,* **1939**, *61*, 2184. (b) Bradsher, C. K. and Rosher, R., *J. Am. Chem. Soc.,* **1939**, *61*, 1524.
12. Bergmann, F. and Israflashwill, S., *J. Am. Chem. Soc.,* **1946**, *68*, 1.
13. Bradsher, C. K. and Jackson, W. J., *J. Am. Chem. Soc.,* **1954**, *76*, 4140.

14. Yamato, T.; Sakaue, N.; Shinoda, N. and Matsuo, K., *J. Chem. Soc., Perkin Trans. I,* **1997**, 1193.
15. Venkataramu, S. D.; MacDonell, G. D.; Purdum, W. R.; Dilbeck, G. A. and Berlin, K. D., *J. Org. Chem.,* **1977**, *42*, 2195.
16. (a) Shi, Z. J. and He, C., *J. Am. Chem. Soc.,* **2004**, *126*, 5964. (b) Bradsher, C. K.; Rapoport, L. and Anderson, P., *J. Am. Chem. Soc.,* **1946**, *68*, 2152. (c) Bradsher, C. K., *J. Am. Chem. Soc.,* **1944**, *66*, 1280. (d) Bradsher, C. K., *J. Am. Chem. Soc.,* **1943**, *65*, 2016. (e) Bradsher, C. K. and Amore, S. T., *J. Am. Chem. Soc.,* **1941**, *63*, 493.
17. Bradsher, C. K. and Wissow, L. J., *J. Am. Chem. Soc.,* **1943**, *65*, 2304.
18. (a) Bradsher, C. K. and Webster, S. T., *J. Org. Chem.,* **1958**, *23*, 482. (b) Bradsher, C. K. and Webster, S. T., *J. Am. Chem. Soc.,* **1957**, *79*, 393.
19. (a) Park, Y.-T.; Song, N. W.; Kim, Y.-H.; Hwang, C.-G.; Kim, S. K. and Kim, D., *J. Am. Chem. Soc.,* **1996**, *118*, 11399. (b) Dai-Ho, G. and Mariano, P. S., *J. Org. Chem.,* **1988**, *53*, 5113. (c) Kellogg, R. M.; Groen, M. B. and Wynberg, H., *J. Org. Chem.,* **1967**, *32*, 3093.
20. (a) Vingiello, F. A.; van Oot, J. G. and Hannabass, H. H., *J. Am. Chem. Soc.,* **1952**, *74*, 4546. (b) Bradsher, C. K. and Wissow, L. J., *J. Am. Chem. Soc.,* **1946**, *68*, 1094.
21. Bradsher, C. K. and Smith, E. S., *J. Am. Chem. Soc.,* **1943**, *65*, 1643.
22. (a) Bradsher, C. K., *Chem. Rev.,* **1987**, *87*, 1277. (b) Bradsher, C. K., *Chem. Rev.,* **1946**, *38*, 447.
23. (a) Quallich, G. J.; Fox, D. E.; Friedmann, R. C. and Murtiashaw, C. W., *J. Org. Chem.,* **1992**, *57*, 761. (b) Quillet, J. P. and Dreux, J., *Bull. Soc. Chim. Fr.,* **1966**, 645. (c) Vingielle, F. A.; Kramer, E.; Quo, S.-G.; Sheridan, J., *J. Org. Chem.,* **1961**, *26*, 2669. (d) Bradsher, C. K. and Jackson, W. J., *J. Am. Chem. Soc.,* **1954**, *76*, 734. (e) Bradsher, C. K. and Jackson, W. J., *J. Am. Chem. Soc.,* **1952**, *74*, 4890. (f) Bradsher, C. K. and Jackson, W. J., *J. Am. Chem. Soc.,* **1951**, *73*, 3235. (g) Vingiello, F. A. and van Oot, J. G., *J. Am. Chem. Soc.,* **1951**, *73*, 5070. (h) Berliner, E., *J. Am. Chem. Soc.,* **1944**, *66*, 533. (i) Bradsher, C. K. and Smith, E. S., *J. Am. Chem. Soc.,* **1943**, *66*, 451. (j) Bradsher, C. K. and Smith, E. S., *J. Am. Chem. Soc.,* **1943**, *65*, 854. (k) Berliner, E., *J. Am. Chem. Soc.,* **1942**, *64*, 2894.

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Bradsher Cycloaddition

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Bradsher in 1958[1] and was extensively explored by Bradsher and co-workers in the following two decades. It is the [4 + 2] cycloaddition of a common dienophile with cationic aromatic azadienes, such as acridizinium and isoquinolinium, to form a tricyclic system containing as many as four chiral centers and an iminium ion.[2] Therefore, this reaction is generally known as the Bradsher cycloaddition.[3] Furthermore, this reaction in some cases is referred to as the cationic polar cycloaddition[4] to distinguish cycloadditions employing cationic or anionic components from those employing dipolar or uncharged components.[5] Moreover, for compounds carrying a positive charge, such as acridizinium and isoquinolinium, the electron requirement of the diene-like part is different from that of traditional *Diels-Alder Cycloaddition*; therefore, the Bradsher cycloaddtion is also known as the inverse-electron-demand *Diels-Alder Reaction*,[2a,6] or simply the ionic *Diels-Alder Cycloaddition*.[7] This reaction has been proved to be exclusively regiospecific and often highly stereospecific.[8] The high stereospecificity and exclusive regiospecificity (*exo* addition) originate from the electrostatic interactions rather than from the secondary orbital interactions or steric effects.[8d,9] On the basis of a relatively large Hammett ρ-value (1.7) in the reaction between substituted acridizinium and styrene,[10] this reaction was initially proposed to occur via a two-step mechanism.[10,11] Lately it is thought to be via a weak charge-transfer complex existing along the reaction pathway,[8c,12] in a concerted but nonsynchronous manner,[8b] although the charge-transfer complex does not always play the role.[12b] It is reported that the substituent at position 9 of the acridizinium ring affects the reaction rate and that electron-withdrawing groups on acridizinium and electron-donating groups on styrene will accelerate the reaction.[13] Likewise, a nitro group at position 5 of the isoquinolinium salt will greatly enhance the reaction rate.[14] The dienophiles participating

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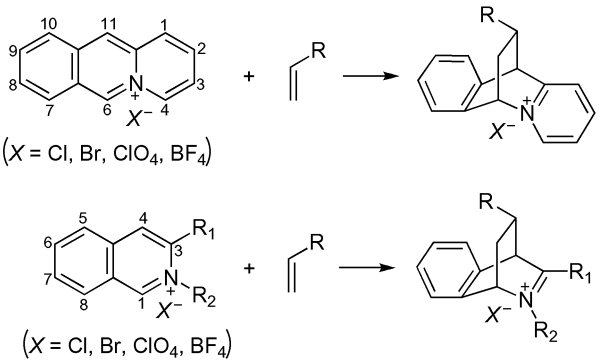
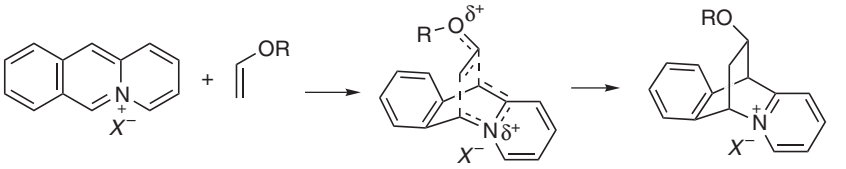
in this cycloaddition include alkenes, dienes, styrenes, benzynes, vinyl ethers, vinyl silyl ethers, enamines, ketene acetals, and ketene aminals.[6] This reaction has been modified for using 3-unsubstituted isoquinolines and has been used to synthesize 1-naphthaldehydes and 1-naphthylamines.[8a]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is believed that this reaction proceeds via a concerted but nonsynchronous cycloaddition with a weak charge-transfer complex along the reaction pathway.[12] Therefore, a tentative mechanism is outlined here.



D. MODIFICATION

This reaction has been modified to react with 3-unsubstituted isoquinolinium to form 1-naphthaldehydes and 1-naphthylamines.[8a]

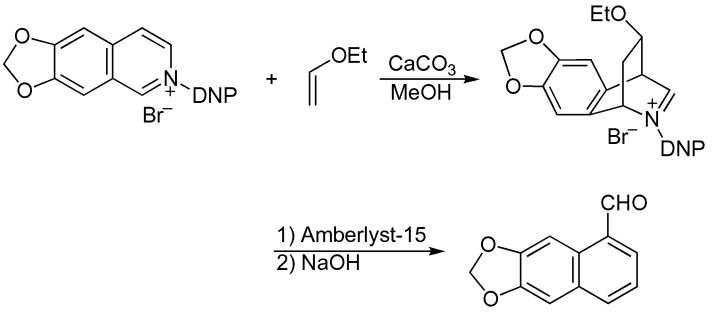
E. APPLICATIONS

This reaction is generally used for the preparation of tricyclic systems containing an iminium ion. In addition, this reaction has been used to synthesize the single diastereoisomer of *cis*-1,2-dideoxy-C-glucosides.[15] Other synthetic applications of this reaction, such as the preparation of angucycline antibiotics, have been published.[16]

F. RELATED REACTIONS

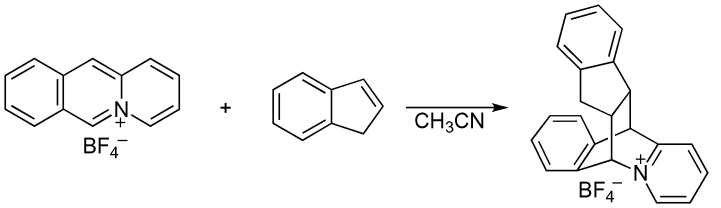
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 8a.

Cycloaddition and conversion to naphthaldehyde are best performed without purification of intermediates. To a stirred suspension of 0.503 g 2-(2,4-dinitrophenyl)-6,7-(methylenedioxy)isoquinolinium bromide (1.2 mmol) and 0.675 g powdered $CaCO_3$ in 4.0 mL MeOH was added 0.864 g ethyl vinyl ether (12 mmol). After 12 h, another portion of vinyl ether (12 mmol) was added, and stirring was continued for an additional 12 h [TLC (SiO_2): 15% MeOH/CH_2C1_2, $R_f \sim 0.78$]. The suspension was filtered over Celite, the filter cake was washed with CH_2C1_2, and the combined filtrate was evaporated. The crude adduct was stirred at 37°C with 300 mg Amberlyst-15 resin in 30 mL THF and 3 mL H_2O for 18 h. After filtration and evaporation, the residue was dissolved immediately in 5 mL THF and transferred to a solution of 0.4 g NaOH in 4 mL H_2O and 10 mL MeOH; it was then heated at reflux for 5 min. The resultant dark red solution was concentrated under reduced pressure, diluted with H_2O, extracted with EtOAc, and chromatographed (SiO_2, 1:l ether/hexanes) to give 230 mg 6,7-(methylenedioxy)naphthaldehyde, in a yield of 96%, m.p. 121°C after recrystallization from ether/hexane, $R_f \sim 0.50$ (SiO_2, ether/hexane = 2:1).



Reference 16.

A mixture of acridizinium tetrafluoroborate and a twofold excess of freshly distilled indene was refluxed for 6 h in acetonitrile with a small quantity of hydroquinone. The adduct was isolated by evaporation of the solvent under reduced pressure and trituration of the residue with ethyl acetate or anhydrous ethyl ether to remove any polymer that might have been formed. After the trituration, a 96% yield of adduct was obtained,

m.p., 172–178°C. Fractional crystallizations from ethanol afforded two compounds with melting points at 142–148°C and 194–195°C, respectively.

Other references related to the Bradsher cycloaddition are cited in the literature.[18]

H. REFERENCES

1. Bradsher, C. K. and Solomons, T. W. G., *J. Am. Chem. Soc.,* **1958**, *80*, 933.
2. (a) Gupta, R. B. and Franck, R. W., *J. Am. Chem. Soc.,* **1987**, *109*, 5393. (b) Cheng, Y.-S.; Ho, E.; Mariano, P. S. and Ammon, H. L., *J. Org. Chem.,* **1985**, *50*, 5678.
3. (a) Magnier, E. and Langlois, Y., *Tetrahedron Lett.,* **1998**, *39*, 837. (b) Sageot, O.; Monteux, D.; Langlois, Y.; Riche, C. and Chiaroni, A., *Tetrahedron Lett.,* **1996**, *37*, 7019. (c) Magnier, E.; Langlois, Y. and Merienne, C., *Tetrahedron Lett.,* **1995**, *36*, 9475. (d) Nicolas, T. E. and Franck, R. W., *J. Org. Chem.,* **1995**, *60*, 6904.
4. Van der Wel, G. K.; Wijnen, J. W. and Engberts, J. B. F. N., *J. Org. Chem.,* **1996**, *61*, 9001.
5. Schmidt, R. R., *Angew. Chem., Int. Ed. Engl.,* **1973**, *12*, 212.
6. Gupta, R. B.; Franck, R. W.; Onan, K. D. and Soll, C. E., *J. Org. Chem.,* **1989**, *54*, 1097.
7. Ritzberger-Baumgartner, W. and Schantl, J. G., *Molecules,* **1996**, *1*, 119.
8. (a) Manna, S.; Falck, J. R., and Mioskowski, C., *J. Org. Chem.,* **1982**, *47*, 5021. (b) Westerman, I. J. and Bradsher, C. K., *J. Org. Chem.,* **1979**, *44*, 727. (c) Bradsher, C. K.; Carlson, G. L. B.; Porter, N. A.; Westerman, I. J. and Wallis, T. G., *J. Org. Chem.,* **1978**, *43*, 822. (d) Bradsher, C. K. and Day, F. H., *J. Heterocycl. Chem.,* **1973**, *10*, 1031. (e) Bradsher, C. K. and Stone, J. A., *J. Org. Chem.,* **1968**, *33*, 519.
9. (a) Bradsher, C. K., *Adv. Heterocycl. Chem.,* **1974**, *16*, 289. (b) Bradsher, C. K.; Day, F. H.; McPhail, A. T. and Wong, P. S., *J. Chem. Soc., Chem. Commun.,* **1973**, 156. (c) Bradsher, C. K.; Day, F. H.; McPhail, A. T. and Wong, P. S., *Tetrahedron Lett.,* **1971**, 4205.
10. (a) Westerman, I. J. and Bradsher, C. K., *J. Org. Chem.,* **1971**, *36*, 969. (b) Bradsher, C. K. and Stone, J. A., *J. Org. Chem.,* **1969**, *34*, 1700.
11. Bradsher, C. K.; Miles, C. R.; Porter, N. A. and Westerman, I. J., *Tetrahedron Lett.,* **1972**, 4969.
12. Bradsher, C. K.; Carlson, G. L. B. and Adams, M. G., *J. Org. Chem.,* **1979**, *44*, 1199.
13. Porter, N. A.; Westerman, I. J.; Wallis, T. G. and Bradsher, C. K., *J. Am. Chem. Soc.,* **1974**, *96*, 5104.
14. Day, F. H.; Bradsher, C. K. and Chen, T.-K., *J. Org. Chem.,* **1975**, *40*, 1195.
15. (a) Franck, R. W. and Marzabadi, C. H., *J. Org. Chem.,* **1998**, *63*, 2197. (b) Gupta, R. B. and Franck, R. W., *J. Am. Chem. Soc.,* **1989**, *111*, 7668.
16. (a) Nicolas, T. E. and Franck, R. W., *J. Org. Chem.,* **1995**, *69*, 6904. (b) Yin, H.; Franck, R. W.; Chen, S. L.; Quigley, G. J. and Todaro, L., *J. Org. Chem.* **1992**, *57*, 644. (c) Bolitt, V. and Mioskowski, C., *J. Am. Chem. Soc.,* **1991**, *113*, 6320. (d) Hartman, G. D.; Phillips, B. T. and Halczenko, W., *J. Org. Chem.,* **1987**, *52*, 1136. (e) Hartman, G. D.; Halczenko, W. and Phillips, B. T., *J. Org. Chem.,* **1985**, *50*, 2427.
17. Westerman, I. J. and Bradsher, C. K., *J. Org. Chem.,* **1978**, *43*, 3002.
18. (a) Urban, D.; Duval, E. and Langlois, Y., *Tetrahedron Lett*., **2000**, *41*, 9251. (b) de Pascual Teresa, B. and Houk, K. N., *Tetrahedron Lett.,* **1996**, *37*, 1759. (c) Sageot, O.; Monteux, D.; Langlois, Y.; Riche, C. and Chiraroni, A., *Tetrahedron Lett.,* **1996**, *37*, 7019. (d) Magnier, E.; Langlois, Y. and Merienne, C., *Tetrahedron Lett.,* **1995**, *36*, 9475. (e) Gassman, P. G. and Gorman, D. B., *J. Am. Chem. Soc.,* **1990**, *112*, 8624. (f) Katritzky, A. R. and Dennis, N., *Chem. Rev.,* **1989**, *89*, 827. (g) Choudhury, A.; Franck, R. W. and Gupta, R. B., *Tetrahedron Lett.,* **1989**, *30*, 4921. (h) Boger,

D. L. and Weinreb, S. M., *Hetero Diels-Alder Methodology in Organic Synthesis*, Academic Press, New York, **1987**, pp. 239–299 (i) Franck, R. W. and Gupta, R. B.; *Tetrahedron Lett.* **1985**, 293. (j) Chen, T. K. and Bradsher, C. K., *J. Org. Chem.,* **1979**, *44*, 4680. (k) Bradsher, C. K.; Wallis, T. G.; Westerman, I. J. and Porter, N. A., *J. Am. Chem. Soc.,* **1977**, *99*, 2588. (l) Ashby, J.; Ayad, M. and Meth-Cohn, O., *J. Chem. Soc. Perkin Trans. I,* **1974**, 1744. (m) Bradsher, C. K. and Day, F. H., *J. Heterocycl Chem.,* **1974**, *11*, 23. (n) Bradsher, C. K.; Porter, N. A. and Wallis, T. G., *J. Org. Chem.,* **1974**, *39*, 1172. (o) Wallis, T. G.; Porter, N. A. and Bradsher, C. K., *J. Org. Chem.,* **1973**, *38*, 2917. (p) Schmidt, R. R., *Angew. Chem.*, **1973**, *6*, 235. (q) Ashby, J.; Ayad, M. and Meth-Cohn, O., *J. Chem. Soc., Perkin Trans. I,* **1973**, 1104. (r) Burnham, W. S. and Bradsher, C. K., *J. Org. Chem.,* **1972**, *37*, 355. (s) Parham, M. E.; Fraser, M. G. and Bradsher, C. K., *J. Org. Chem.,* **1972**, *37*, 358. (t) Bradsher, C.K.; Day, F. H., *Tetrahedron Lett.,* **1971**, 409. (u) Bradsher, C. K. and Harvan, D. J., *J. Org. Chem.,* **1971**, *36*, 3778. (v) Ahmed, M.; Ashby, J. and Meth-Cohn, O., *J. Chem. Soc., Chem. Commun.,* **1970**, 1094. (w) Katritzky, A. R. and Lunt, E., *Tetrahedron,* **1969**, *25*, 4291. (x) Fields, D. L.; Regan, T. H. and Dignan, J. C. *J. Org. Chem.* **1968**, *33*, 320. (y) Fields, D. L.; Regan, T. H. and Dignan, J. C., *J. Org. Chem.,* **1968**, *33*, 390. (z) Sauer, J. and Wiest, H., *Angew. Chem.*, **1962**, *74*, 353.

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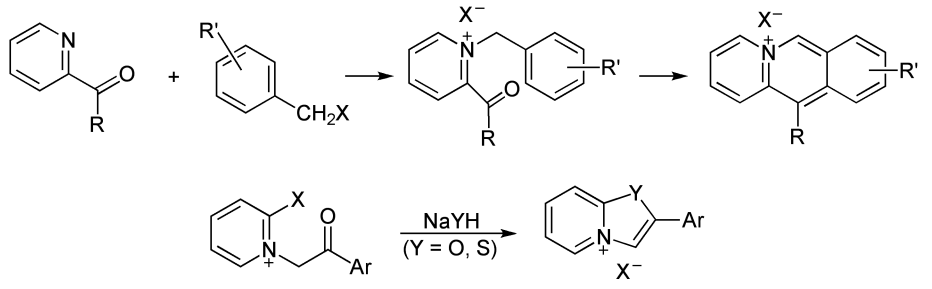
Bradsher Pyridinium Salt Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Bradsher in 1955.[1] It is a reaction for synthesizing pyridinium ring-containing heterocycles, such as oxazole[3,2-a] pyridinium,[2] thiooxazole[3,2-a]pyridinium,[3] and acridizinium salt.[1] The resulting quaternary ammonium salts are important versatile intermediates for complex heterocyclic skeletons used in pharmaceutical and materials chemistry. For example, the acridizinium salts are widely used for the *Bradsher Cycloaddition*[4] and the oxazole[3,2-a] pyridinium can undergo ring opening from either the 5-membered ring when reacting with alkali, hydrosulfide, ammonia and primary amines, CH-acids, etc. or the 6-membered ring in reaction with secondary amines.[4] The formation of quinolizinium ion has been reviewed.[5]

B. GENERAL REACTION SCHEME



(R = H, alkyl, aryl, X = Cl, Br, I, etc.)

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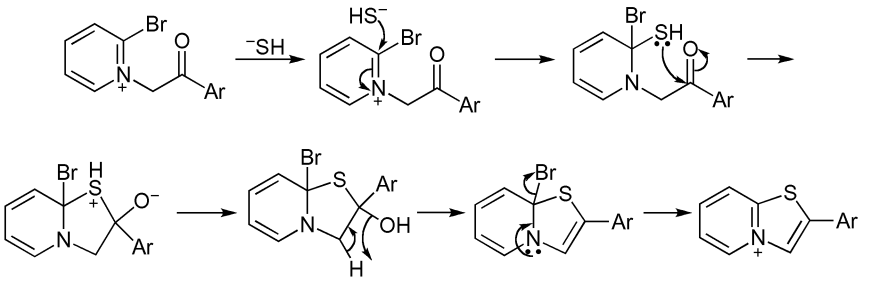
C. PROPOSED MECHANISMS

The mechanism for forming acridizinium salt is similar to the *Bradsher Cyclization* when a carbonyl group exists in the reaction system. However, the mechanism for forming oxazole[3,2-a] pyridinium is different from what is proposed here.



D. MODIFICATION

The preparation of quinolizinium salt from ketone has been extended to oxime,[6] nitrile,[7] and trimethylsilyl groups;[8] in addition, the quinolizinium salt has also been prepared directly from the reaction between pyridine and aryl halide under heating[9] or photoirradiation.[8,10] The preparation of thiooxazole[3,2-a]pyridinium has also been modified.[11]

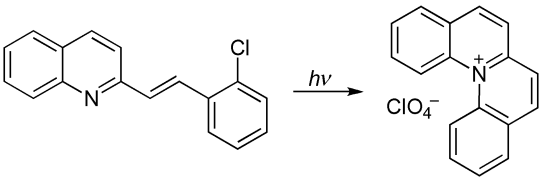
E. APPLICATIONS

The prepared quinolizinium salt or pyridinium salt can be generally used for *Bradsher Cycloaddition*. The formed oxazole[3,2-a]pyridinium or thio-analogues can be cleaved to afford different molecules from either 5-membered or 6-membered rings.[12]

F. RELATED REACTIONS

This reaction is related to the *Bradsher Cyclization*.

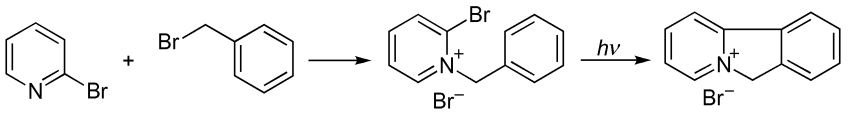
G. CITED EXPERIMENTAL EXAMPLES



Reference 10a.

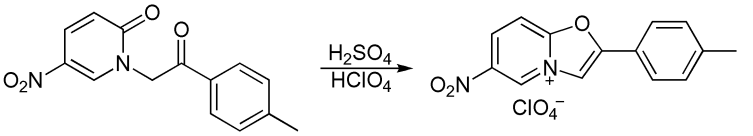
A solution containing 53 mg aryl chloride (0.2 mmol) in 1 L acetonitrile in a Pyrex reaction vessel was irradiated through an aqueous nickel sulfate filter with a 300-W high-pressure mercury lamp. The reaction mixture was magnetically stirred at room temperature,

and the progress of the photocyclization was monitored by UV spectroscopy. After the peak at 405 nm reached a maximum, the solvent was evaporated. The residue was dissolved in water and insoluble solids were filtered off. Saturated aqueous lithium perchlorate was added to the filtrate, and the resulting yellow solid was filtered off, washed with cold water, and recrystallized from ethanol to give 27 mg dibenzo[cf]quinolizinium perchlorate as yellow crystals, in a yield of 41%, m.p. 255–257°C.



Reference 10b.

A mixture of 7.9 g 2-bromopyridine (0.05 mol) and 8.3 g α-bromotoluene (0.05 mol) in 10 mL sulfolane were kept at 45°C for 4 days. The white solid that precipitated during this period was suspended in ether and collected. It was recrystallized from ethanol–ethyl acetate to afford 12.4 g *N*-benzyl-2-bromopyridinium bromide as colorless needles, m.p. 158–160°C. Then 2.0 g *N*-benzyl-2-bromopyridinium bromide in 430 mL water was irradiated with a water-cooled 450-W Hanovia UV source equipped with a Pyrex filter. The ultraviolet spectrum of the samples taken during the irradiation showed a shift from the absorption maximum of 278 nm for the starting material to two absorption maxima at 256 and 313 nm. The change was complete after 5 h. The dark green solution was then evaporated to small volume and treated with 0.5 g decolorizing charcoal. After filtering, the solution was evaporated to dryness; the residue was dissolved in a minimum quantity of ethanol and precipitated by careful addition of ethyl acetate to afford 0.8 g benz[a]indolizinium bromide as the hemihydrate, in a yield of 50%. The product had m.p. 207.5–209.5°C after one recrystalization from absolute ethanol. When 10% hydrobromic acid was used as the solvent in the irradiation, the use of decolorizing charcoal was unnecessary and 1.18 g product was isolated after an irradiation period of 8 h, in a yield of 75%.



Reference 11a.

N-Phenacyl-5-nitro-2-pyridone (10 mmol) was dissolved in 10 mL concentrated sulfuric acid, and the resulting solution was kept for 20–25 h. Then 2.5 mL 71% perchloric acid (25 mmol) was carefully added to the mixture; after being stirred for 10–15 min the solution was poured into 500 mL vigorously stirred diethyl ether. After being decanted the oily residue was mixed again with 500 mL fresh ether; this procedure was repeated until a pure white powder formed. The precipitate was filtered, washed with ether, and dried in vacuum over P_2O_5. The yield of 2-tolyl-6-nitrooxazo[3,2-a]pyridinium perchlorate was between 95% and 98%.

Other references related to the Bradsher pyridinium salt synthesis are cited in the literature.[13]

H. REFERENCES

1. Bradsher, C. K. and Beavers, L. E., *J. Am. Chem. Soc.,* **1955**, *77*, 4812.
2. Bradsher, C. K. and Zinn, M., *J. Heterocycl. Chem.,* **1967**, *4*, 66.
3. Bradsher, C. K.; Brandau, R. D.; Boilek, J. E. and Hough, T. L., *J. Org. Chem.,* **1969**, *34*, 2129.
4. Babaev, E. V., *J. Heterocycl. Chem.,* **2000**, *37*, 519.
5. Bradsher, C. K., *Acc. Chem. Res.,* **1969**, *2*, 181.
6. Bradsher, C. K.; Solomons, T. W. G. and Vaughan, F. R., *J. Org. Chem.,* **1960**, *25*, 757.
7. Bradsher, C. K. and Westerman, I. J., *J. Org. Chem.,* **1978**, *43*, 3536.
8. (a) Dai-Ho, G. and Mariano, P. S., *J. Org. Chem.,* **1988**, *53*, 5113. (b) Dai-Ho, G. and Mariano, P. S., *J. Org. Chem.,* **1987**, *52*, 704.
9. Alonso, C.; Olmstead, M. M.; Nantz, M. H. and Kurth, M. J., *Chem. Commun.,* **2001**, 639.
10. (a) Arai, S.; Ishikura, M. and Yamagishi, T., *J. Chem. Soc., Perkin Trans. I,* **1998**, 1561. (b) Fozard, A. and Bradsher, C. K., *J. Org. Chem.,* **1967**, *32*, 2966.
11. (a) Bush, A. A. and Babaev, E. V., *Molecules,* **2003**, *8*, 460. (b) Roth, B., *J. Med. Chem.,* **1969**, *12*, 227.
12. (a) Babaev, E. V. and Tsisevich, A. A., *J. Chem. Soc., Perkin Trans. I,* **1999**, 399. (b) Babaev, E. V.; Efimov, A. V.; Maiboroda, D. A. and Jug, K., *Eur. J. Org. Chem.,* **1998**, 193.
13. (a) Tovar, J. D. and Swager, T. M., *J. Org. Chem.,* **1999**, *64*, 6499. (b) Park, Y.-T.; Song, N. W.; Kim., Y.-H.; Hwang, C.-G.; Kim, S. K. and Kim, D., *J. Am. Chem. Soc.,* **1996**, *118*, 11399. (c) Pauls, H. and Krohnke, F., *Ber.,* **1976**, *109*, 3653. (d) Frazer, M. G. and Bradsher, C. K., *J. Org. Chem.,* **1971**, *36*, 2767. (e) Bradsher, C. K.; Burnham, W. S. and Zinn, M. F., *J. Heterocycl. Chem.,* **1970**, *7*, 779. (f) Bradsher, C. K. and Sherer, J. P., *J. Org. Chem.,* **1967**, *32*, 733. (g) Andrew, H. F. and Bradsher, C. K., *J. Heterocycl. Chem.,* **1967**, *4*, 577. (h) Fozard, A. and Bradsher, C. K., *J. Org. Chem.,* **1966**, *31*, 2346. (i) Bradsher, C. K. and McDonald, J. W., *J. Org. Chem.,* **1962**, *27*, 4482. (j) Bradsher, C. K. and Jones, J. H., *J. Am. Chem. Soc.,* **1959**, *81*, 1938. (k) Bradsher, C. K. and Jones, J. H., *J. Am. Chem. Soc.,* **1957**, *79*, 6033. (l) Bradsher, C. K. and Beavers, L. E., *J. Am. Chem. Soc.,* **1956**, *78*, 2459.

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Brandi-Guarna Reaction
(Brandi Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Brandi *et al.*, probably as early as in 1986.[1] It is a group of reactions for forming tetrahydropyridone derivatives. It involves the initial *1,3-Dipolar Cycloaddition* of nitrones and alkylidenecyclopropanes to yield the mixtures of isoxazolidine regioisomers with spiro-fused cyclopropane rings located on the C-4 and C-5, respectively, and the thermolysis of the 1,3-dipolar cycloadducts via a unique homolytic cleavage of the weak nitrogen-oxygen bond accompanying by the subsequent opening of the adjacent cyclopropane ring and closure of the diradical to afford tetrahydropyridones; *N*-bridgehead bicyclic ketones are ultimately formed from the cyclic nitrones. Therefore, this reaction is generally known as the Brandi-Guarna reaction[2] or simply the Brandi reaction.[3] In addition, the analogous reactions involving the *1,3-Dipolar Cycloaddition* of alkylidenecyclopropanes and nitrile oxides followed by similar ring enlargement to form *aza*-heterocycles are also referred to as the Brandi reaction.[4]

It should be pointed out that the alkylidenecyclopropanes are not stable due to the *exo* double bond and strained cyclopropane ring. The *1,3-Dipolar Cycloaddition* of alkylidenecyclopropanes with nitrones was reported by Akmanova in 1982 (i.e., the reaction between *N*-(phenylaminooxoethylidene) aniline *N*-oxide and 2,2-dimethylmethylenecyclopropane),[5] although the *1,3-Dipolar Cycloaddition* has been known since the 1960s.

For the *1,3-Dipolar Cycloaddition* of nitrones with methylenecyclopropane, generally a mixture of 5-spirocyclopropane isoxazolidines, and 4-spirocyclopropane isoxazolidines forms;[6] however, due to the steric effect, the 5-regioisomer is usually favored, with the ratio of 5-regioisomer to 4-regioisomer ranging from 2:1 to greater than 20:1.[4] In addition, the *1,3-Dipolar Cycloaddition* often proceeds via an *anti-anti* transition state, with each regioisomer arising from an *anti-anti exo* or *anti-anti endo* approach;[4,7] under these circumstances, there is generally no control over *exo-endo* selectivity.[7] It is possible that the

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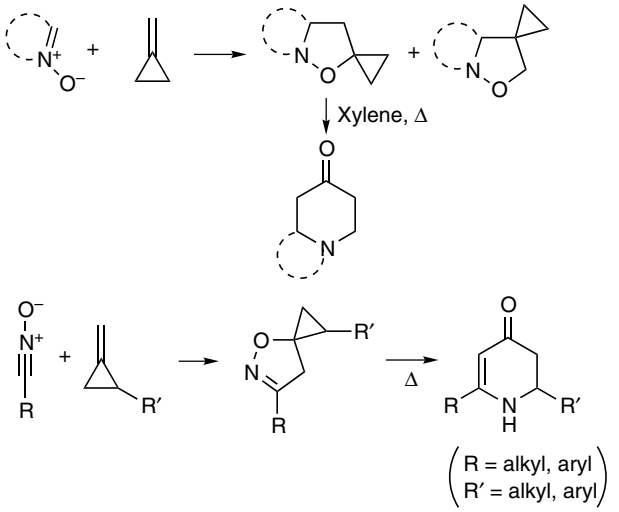
4-spirocyclopropane isoxazolidine regioisomers are formed from cycloreversion of primary cycloadducts and subsequent cycloaddition.[8]

Most of known isoxazolidines are quite stable at temperatures below 100°C and can be purified before thermolysis,[4] except for *N*-aryl-3-phenyl-4-(ethoxycarbonyl)-5-spirocyclopropane isoxazolidines, which quickly decompose at room temperature to give tetrahydropyridones.[9] In theory, flash vacuum thermolysis (FVT) is best for the Brandi reaction, due to the reduced possibility for intermolecular hydrogen exchange; in comparison, the thermal rearrangement in solution often leads to the formation of isomeric enaminones and lower selectivity between epimeric ketones.[7] For example, FVT on aryl-substituted dispiro-[2.0.3.3]oxazadecanes at 600°C exclusively gives azepan-4-ones.[10] However, the best practical conditions for the Brandi reaction is to reflux the cycloadducts in toluene.[7] In addition, it was found that the Brandi reaction may take alternative reaction routes in different solvents—for example, 1,2-tetrahydroisoquinoline fused 4-chloro-4-methoxycarbonyl-5-spirocyclopropane isoxazolidine thermolyzes in xylene at 150°C to afford 56% of α-ketolactam, whereas only 8% of α-ketolactam is obtained in DMSO at same temperature, along with 15% of benzoquinolizinone.[11] In addition, the effect of polar solvent has been observed in the formation of cyclobutane-annelated isoxazolidine when spirocyclopropane isoxazolidine is treated with the mild Lewis acid Al_2O_3 in CH_2Cl_2.[4]

On the other hand, in those spirocyclopropane isoxazolines with more than one cyclopropane ring, after the opening of the spirocyclopropane ring vicinal to the oxygen atom, the rest of the spirocyclopropane ring might also undergo ring enlargement,[12] although this type of reaction has not been extensively exploited yet.[4]

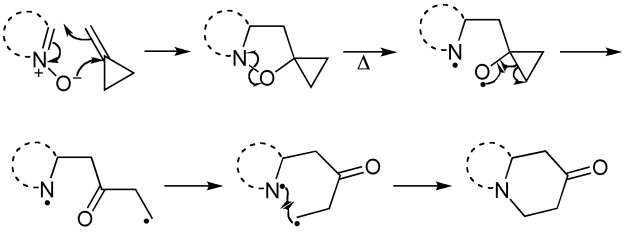
It should be pointed out that nitrile oxides are generally more reactive than corresponding nitrones, which are often prepared *in situ* due to the aptitude of self-dimerization for furoxans.[13] In addition, the cycloaddition of nitrile oxides with alkylidenecyclopropanes of either the electron-donating or the electron-withdrawing group shows a slightly lower regioselectivity than the corresponding nitrones but holds higher regioselectivity with small methylidenecyclopropane than the nitrones.[4]

B. GENERAL REACTION SCHEME

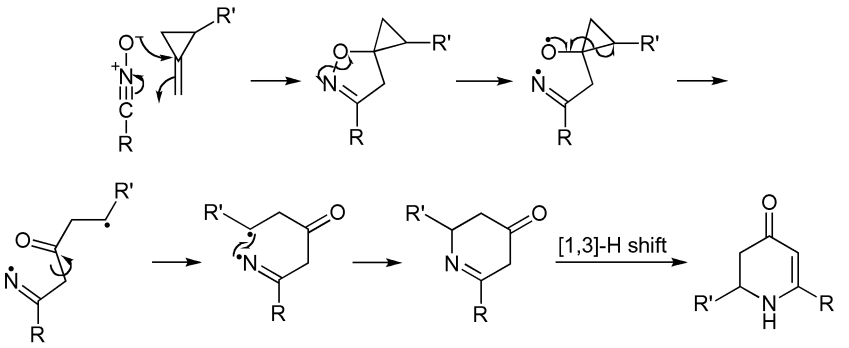


C. PROPOSED MECHANISMS

The reaction combines a *1,3-Dipolar Cycloaddition* and the thermolysis of cycloadducts, and the rearrangement of isoxazolidine intermediate proceeds via the initial cleavage of the weak nitrogen-oxygen bond, followed by the ring opening of the spirocyclopropane ring adjacent to oxygen atom and the final closure of the C,N-diradical.[14] Shown below are two simple mechanisms for the reaction with nitrone (Scheme 1) and with nitrile oxide (Scheme 2).



SCHEME 1. *Brandi-Guarna reaction from nitrones.*



SCHEME 2. *Brandi-Guarna reaction from nitrile oxides.*

D. MODIFICATION

The *1,3-Dipolar Cycloaddition* of nitrones has been extended to bicyclopropylidene, which could be combined with the subsequent thermolysis in a one-pot manner to afford spirocyclopropane-tetrahydropyridones efficiently due to the absence of the regioisomeric problem and higher boiling point (100°C) of bicyclopropylidene.[15] In addition, two intramolecular versions of the Brandi reaction have been developed, with the chain connecting either to nitrone functionality or to the cyclopropane ring.[4] Moreover, the thermolysis has been extended to proceed in the presence of a protic acid, resulting in a ring contraction along with the extrusion of ethylene to give β-lactams from isoxazolidines.[16]

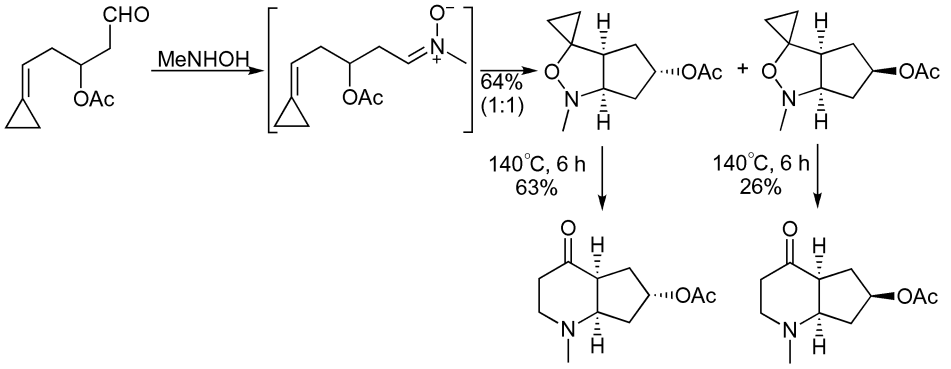
E. APPLICATIONS

This reaction has broad application in the preparation of heterocycles.

F. RELATED REACTIONS

N/A

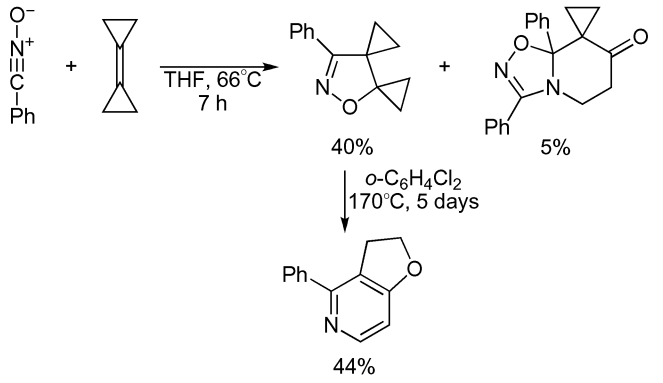
G. CITED EXPERIMENTAL EXAMPLES



Reference 16a.

To a solution of 850 mg 3-(acetyloxy)-5-cyclopropylidenepentanal (4.7 mmol) in 235 mL Et_2O, were added 468 mg *N*-methylhydroxylamine hydrochloride (5.6 mmol) and 453 μL pyridine (5.6 mmol) at room temperature. The resulting solution was stirred at room temperature overnight, and the salt was filtered through a short pad of Celite. Upon removal of the solvent, the residue was purified by silica gel column chromatography using pentane/Et_2O (1:3) as the eluent to afford 379 mg (3a*R*,5*R*,6a*S*)-1,3a,4,5,6,6a-hexahydro-1-methylspiro[3*H*-cyclopent[*c*]isoxazole-3,1-cyclopropan]-5-yl acetate (32%, $R_f = 0.25$) and 379 mg (3a*R*,5*S*,6a*S*)-1,3a,4,5,6,6a-hexahydro-1-methylspiro[3*H*-cyclopent[*c*]isoxazole-3,1-cyclopropan]-5-yl acetate (32%, $R_f = 0.14$).

A solution of 51 mg (3a*R*,5*R*,6a*S*)-1,3a,4,5,6,6a-hexahydro-1-methylspiro[3*H*-cyclopent[*c*]isoxazole-3,1-cyclopropan]-5-yl acetate (0.24 mmol) in 30 mL xylenes was refluxed for 6 h. After being cooled at room temperature, the solution was passed through a short pad of silica gel, eluting first with petroleum ether to remove the high-boiling solvent and then with MeOH to recover the product. After removal of MeOH, the residue was purified by silica gel chromatography using MeOH/Et_2O (1:9) as the eluent to afford 27 mg (4a*R*,6*R*,7a*S*)-6-(acetyloxy)-octahydro-1-methyl-4*H*-cyclopenta[*b*]pyridin-4-ones as a colorless oil (53%) and 5 mg (4a*R*,6*S*,7a*S*)-6-(acetyloxy)-octahydro-1-methyl-4*H*-cyclopenta[*b*]pyridin-4-ones as a colorless oil (10%).



Reference 15.

To a refluxing solution of 240 mg bicyclopropylidene (3.0 mmol) in 3 mL THF containing 277 mg $NaHCO_3$ (3.3 mmol) was added a solution of 513 mg benzohydroximoyl chloride (3.3 mmol) in 10 mL of THF dropwise over a period of 6 h, and the solution was stirred for an additional hour. After being cooled to room temperature, the salts were filtered off over Celite. Removal of the solvent in vacuo gave a crude mixture, which was purified by silica gel flash chromatography using petroleum ether/Et_2O (4:1) to afford 240 mg 9-phenyl-7-oxa-8-azadispiro[2.0.2.3]non-8-ene as a white solid, in a yield of 40%, m.p. 87–89°C (hexane), $R_f = 0.34$. In addition, 44 mg spiro[cyclopropane-1,8′-3,8a-diphenyl-7-oxo-5,6,8,8a-tetrahydro-7H-1,2,4-oxadiazolo[4,5-a]pyridine was also obtained as a pale yellow solid, in a yield of 5%, m.p. 84–86°C, $R_f = 0.39$.

A solution of 19.9 mg 9-phenyl-7-oxa-8-azadispiro[2.0.2.3]non-8-ene (0.1 mmol) in 1 mL *o*-dichlorobenzene in a sealed tube was heated at 170°C for 5 days. After being cooled to room temperature, the mixture was loaded to a short pad of silica gel and initially washed with petroleum ether to remove the *o*-dichlorobenzene followed by petroleum ether/Et_2O (3:8) to afford 8.7 mg 4-phenyl-2,3-dihydrofuro[3,2-c]pyridine as an oil, in a yield of 44%, $R_f = 0.33$.

Other references related to the Brandi-Guarna reaction are cited in the literature.[18]

H. REFERENCES

1. Brandi, A.; Guarna, A.; Goti, A. and De Sarlo, F., *Tetrahedron Lett.,* **1986**, *27*, 1727.
2. (a) de Meijere, A.; Kozhushkov, S. I. and Schill, H., *Chem. Rev.,* **2006**, *106*, 4926. (b) Zanobini, A., "Synthesis of New Spirocyclopropanated β-Lactams and Their Application as Building Blocks for β-Amino Acid Peptides," doctoral thesis, der Georg-August Universität zu Göttingen, **2005**. (c) Hassner, A. and Stumer, C., *Organic Syntheses Based on Name Reactions*, 2nd ed., Tetrahedron Organic Chemistry Series, Vol. 22, Pergamon, Amsterdam, **2002**, p. 42. (d) Gensini, M., "Synthesis of Potentially Biologically Active Cyclopropane- and Spirocyclopropane-annelated Oligoazaheterocycles," doctoral thesis, der Georg-August-Universität zu Göttingen, **2002**.
3. Ochoa, E.; Mann, M.; Sperling, D. and Fabian, J., *Eur. J. Org. Chem.,* **2001**, 4223.
4. Brandi, A.; Cicchi, S.; Cordero, F. M. and Goti, A., *Chem. Rev.,* **2003**, *103*, 1213.

5. Akmanova, N. A.; Sagitdinova, Kh. F. and Balenkova, E. S., *Khim. Geterotsikl. Soedin.,* **1982**, 1192 [*Chem. Abstr.,* **1982**, *97*, 216064].
6. (a) Cordero, F. M.; De Sarlo, F. and Brandi, A., *Monatsh. Chem.,* **2004**, *135*, 649. (b) Brandi, A.; Cordero, F. M.; Goti, A.; de Sarlo, F. and Guarna, A., *Synlett,* **1993**, 1.
7. Cordero, F. M.; Brandi, A.; Querci, C.; Goti, A.; De Sarlo, F. and Guarna, A., *J. Org. Chem.,* **1990**, *55*, 1762.
8. Bianchi, G. and Gandolfi, R., "1,3-Dipolar Cycloreversions" in *1,3-Dipolar Cycloaddition Chemistry*, ed. Padwa, A., Wiley-Interscience, New York, **1984**, *2*, pp. 451–543.
9. (a) Cordero, F. M.; Barile, I.; De Sarlo, F. and Brandi, A., *Tetrahedron Lett.,* **1999**, *40*, 6657. (b) Cordero, F. M.; Goti, A.; De Sarlo, F.; Guarna, A. and Brandi, A., *Tetrahedron,* **1989**, *45*, 5917.
10. de Meijere, A.; von Seebach, M.; Kozhushkov, S. I.; Boese, R.; Blaser, D.; Cicchi, S.; Dimoulas, T. and Brandi, A., *Eur. J. Org. Chem.,* **2001**, 3789.
11. Zorn, C.; Goti, A.; Brandi, A.; Johnsen, K.; Noltemeyer, M.; Kozhushkov, S. I. and de Meijere A., *J. Org. Chem.,* **1999**, *64*, 755.
12. (a) Cordero, F. M.; Barile, I.; Brandi, A.; Kozhushkov, S. I. and de Meijere, A., *Synlett,* **2000**, 1034. (b) Zorn, C.; Anichini, B.; Goti, A.; Brandi, A.; Kozhushkov, S. I.; de Meijere, A. and Citti, L., *J. Org. Chem.,* **1999**, *64*, 7846.
13. (a) Grünanger, P. and Vita-Finzi, P., "*Isoxazoles, Part 1*" in *The Chemistry of Heterocyclic Compounds,* ed. Taylor, E. C. and Weissberger, A., Wiley, New York, **1991**, *49*. (b) Caramella, P. and Grünanger, P., "Nitrile Oxides and Imines" in *1,3-Dipolar Cycloaddition Chemistry,* ed. Padwa, A., Wiley-Interscience, New York, **1984**, *1*, pp. 291–392. (c) Grundmann, C. and Grünanger, P., *The Nitrile Oxides,* Springer-Verlag, New York, **1971**.
14. Namyslo, J. C. and Kaufmann, D. E., *Chem. Rev.,* **2003**, *103*, 1485.
15. Goti, A.; Anichini, B.; Brandi, A.; Kozhushkov, S.; Gratkowski, C. and de Meijere, A., *J. Org. Chem.,* **1996**, *61*, 1665.
16. (a) Cordero, F. M.; Pisaneschi, F.; Salvati, M.; Paschetta, V.; Ollivier, J.; Salaün, J. and Brandi, A., *J. Org. Chem.,* **2003**, *68*, 3271. (b) Cordero, F. M.; Pisaneschi, F.; Goti, A.; Ollivier, J.; Salaün, J. and Brandi, A., *J. Am. Chem. Soc.,* **2000**, *122*, 8075. (c) Paschetta, V.; Cordero, F. M.; Paugam, R.; Ollivier, J.; Brandi, A. and Salaün, J., *Synlett,* **2001**, 1233.
17. (a) Gensini, M.; Kozhushkov, S. I.; Frank, D.; Vidovic, D.; Brandi, A. and de Meijere, A., *Eur. J. Org. Chem*., **2003**, 2001. (b) Ferrara, M.; Cordero, F. M.; Goti, A.; Brandi, A.; Estieu, K.; Paugam, R.; Ollivier, J. and Salaün, J., *Eur. J. Org. Chem.,* **1999**, 2725. (c) Estieu, K.; Paugam, R.; Ollivier, J.; Salaün, J.; Cordero, F. M.; Goti, A. and Brandi, A., *J. Org. Chem.,* **1997**, *62*, 8276. (d) Anichini, A.; Goti, A.; Brandi, A.; Kozhushkov, S. I. and de Meijere, A., *J. Chem. Soc., Chem. Commun.,* **1997**, 261. (e) Machetti, F.; Cordero, F. M.; De Sarlo, F.; Guarna,A. and Brandi, A., *Tetrahedron Lett.,* **1996**, *37*, 4205. (f) Goti, A.; Cordero, F. M. and Brandi, A., *Top. Curr. Chem.,* **1996**, *178*, 1. (g) Goti, A.; Anichini, B.; Brandi, A.; de Meijere, A.; Citti, L. and Nevischi, S., *Tetrahedron Lett.,* **1995**, *36*, 5811. (h) Cordero, F. M. and Brandi A., *Tetrahedron Lett.,* **1995**, *36*, 1343. (i) Brandi, A.; Goti, A.; Kozhushkov, S. and de Meijere, A., *J. Chem. Soc., Chem. Commun.,* **1994**, 2185. (j) Goti, A.; Brandi, A.; De Sarlo, F. and Guarna, A., *Tetrahedron,* **1992**, *48*, 5283. (k) Brandi, A.; Garro, S.; Guarna, A.; Goti, A.; Cordero, F. and De Sarlo, F., *J. Org. Chem.,* **1988**, *53*, 2430.

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Breckpot β-Lactam Synthesis

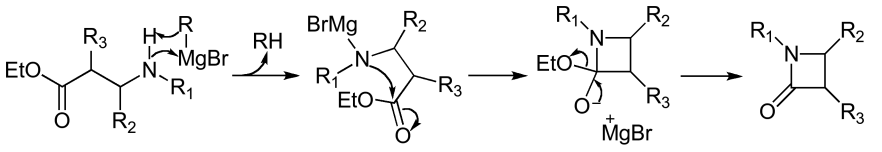
A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Breckpot in 1923.[1] It is the synthesis of β-lactam via the cyclization of esters of β-amino acids with Grignard reagent and is known as the Breckpot β-lactam synthesis.[2] This reaction has been modified to form β-lactam by the treatment of β-amino acid with Mukaiyama's reagent,[3] or the β-amino ester with *N*-methyl pyridinium salt.[4]

B. GENERAL REACTION SCHEME

C. PROPOSED MECHANISMS

A simple mechanism is displayed here.



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D. MODIFICATION

This reaction has been modified by using Mukaiyama's reagent[3] or *N*-methyl pyridinium salt[4] to convert the β-amino acids into β-lactams.

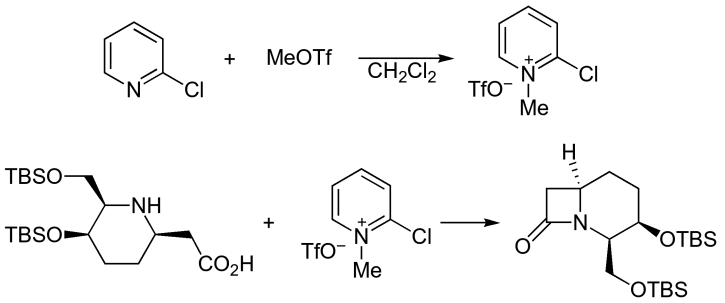
E. APPLICATIONS

This reaction has been used to synthesize β-lactams[5] such as azetidinone.

F. RELATED REACTIONS

Although there is no reaction directly related to the Breckpot β-actam synthesis, other methods of preparing β-lactams include the cycloaddition of imino compound with ketene,[6] the reaction between diazomethane and isocyanate,[7] and the use of bromomalonic ester and primary amine.[8]

G. CITED EXPERIMENTAL EXAMPLES



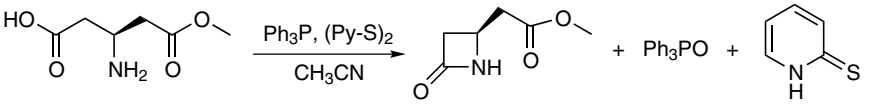
Reference 4.

Preparation of *N*-Methyl-2-Chloropyridinium Triflate

In a resealable tube was added 2.4 g 2-chloropyridine (2.0 mL, 21.1 mmol) and 3.5 mL CH_2Cl_2. The solution was degassed by three freeze–thaw cycles, and the tube was then purged with argon. The colorless solution was cooled to -78°C; and, with stirring, 3.48 g methyl trifluoromethanesulfonate (2.4 mL, 21.2 mmol) was added over 45 s, as a white precipitate began to form. The cooling bath was removed, the tube was closed under argon, and the cloudy mixture was stirred for 16 h. Then 20 mL toluene was added to the white mixture, and after stirring for additional 30 minutes, the precipitate slowly settled to the bottom of the tube, leaving a clear supernatant, which was removed via syringe. An additional 20 mL dry toluene was added to wash the precipitate, and the toluene was removed via syringe, with all operations being done under a stream of argon. The washed precipitate was dried under high vacuum for 48 h at room temperature to afford 5.5 g *N*-methyl-2-chloropyridinium triflate, in a yield of 94%, m.p. 162–164°C.

The Preparation of β-Lactam

To a solution of 1.08 g 2-chloro-1-methylpyridinium triflate (3.90 mmol) in 230 mL dry CH_3CN was added 1.48 g *N*,*N*-diisopropylethylamine (2.0 mL, 11.5 mmol). The colorless solution was heated at 65–70°C while a solution of 0.50 g amino acid (1.2 mmol) in 230 mL dry CH_3CN was slowly added via syringe pump over 4 h. After the addition was complete, the slightly yellow solution was heated at 65–70°C for 15 min more and then was stirred at room temperature for 12 h. The solution was diluted with 150 mL CH_2Cl_2 and concentrated to 5% of its original volume. An additional 200 mL CH_2Cl_2 was added, and the solution was concentrated to 10 mL and partitioned between 500 mL CH_2Cl_2 and 400 mL H_2O. The cloudy aqueous phase was extracted with CH_2Cl_2 (4 × 120 mL). The combined organic layer was washed with 100 mL brine, dried, and evaporated to a dark red oil, which was chromatographed on a 7 cm × 15 cm plug of SiO_2 using EtOAc/hexanes (1:3) as an eluent to give 433 mg (2*R*,3*R*,6*R*)-8-oxo-3-*tert*-butyldimethylsilyloxy-2-*tert*-butyldimethylsilyloxy-methyl-1-azabicyclo-[4.2.0]octane, in a yield of 90%, m.p. 58–59°C.



Reference 3.

At room temperature, to a 0.05 M acetonitrile solution of (S)-3-amino-4-(methoxycarbony1)butyric acid was added 1.2 eq. triphenylphosphine and 2-pyridine disulfide, respectively. Then the reaction mixture was heated to 55–60°C for 12 h with stirring, the homogeneity and a yellow color were seen at the end of the reaction. After removal of the solvent in vacuo, the product was separated from the triphenylphosphine oxide and thione by chromatography on silica gel using 1:l ethermethylene chloride for elution, and the fractions containing the desired β-lactam compound (TLC, $R_f = 0.20, CH_2Cl_2$-Et_2O, 1:1) were further purified by chromatography on silica gel, affording 84% (S)-4-[(methoxycarbony1)-methyl]-2-azetidinone, m.p. 67.5–68°C.

Other references related to the Breckpot β-lactam synthesis are cited in the literature. [9]

H. REFERENCES

1. Breckpot, R., *Bull. Soc. Chim. Belg.*, **1923**, 32, 412. *Chem. Abstr.,* **1924**, *18*, 1113.
2. Searles, S. and Wann, R. E., *Chem. Ind. (London),* **1964**, 2097.
3. Kobayashi, S.; Iimori, T.; Izawa, T. and Ohno, M., *J. Am. Chem. Soc.,* **1981**, *103*, 2406.
4. Folmer, J. J.; Acero, C.; Thai, D. L. and Rapoport, H., *J. Org. Chem.,* **1998**, *63*, 8170.
5. (a) Holley, R. W. and Holley, A. D., *J. Am. Chem. Soc.,* **1949**, *71*, 2124. (b) Holley, R. W. and Holley, A. D., *J. Am. Chem. Soc.,* **1949**, *71*, 2129.
6. Bose, A. K.; Manhas, M. S.; Vincent, J. E.; Gala, K. and Fernandez, I. F., *J. Org. Chem.,* **1982**, *47*, 4075.
7. Sheehan, J. C. and Izzo, P. T., *J. Am. Chem. Soc.,* **1948**, *70*, 1985.

8. (a) Chatterjee, B. G. and Moza, P. N., *J. Med. Chem.,* **1966**, *9*, 259. (b) Blicke, F. F. and Gould, W. A., *J. Org. Chem.,* **1958**, *23*, 1102. (c) Sheehan, J. C. and Bose, A. K., *J. Am. Chem. Soc.,* **1951**, *73*, 1761. (d) Sheehan, J. C. and Bose, A. K., *J. Am. Chem. Soc.,* **1950**, *72*, 5158.
9. (a) Miyata, O.; Namba, M.; Ueda, M. and Naito, T., *Org. Biomol. Chem.,* **2004**, *2*, 1274. (b) Shibuya, M.; Kuretani, M. and Kubota, S., *Tetrahedron Lett.,* **1981**, *22*, 4453. (c) Kametani, T.; Nagahara, T.; Suzuki, Y.; Yokohama, S.; Huang, S.-P. and Ihara, M., *Heterocycles,* **1980**, *14*, 403. (d) Tufariello, J. J.; Lee, G. E.; Senaratne, P. A. and Al-Nuri, M., *Tetrahedron Lett.,* **1979**, *20*, 4359. (e) Woodward, R. B.; Heusler, K.; Gosteil, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.; Ranganathan, S. and Vorbruggen, H., *J. Am. Chem. Soc.,* **1966**, *88*, 852. (f) Searles, S., and Wann, R. E. *Chem. Ind. (London),* **1964**, 2097.

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Bredt's Rule

A. GENERAL DESCRIPTION OF THE REACTION

This phenomenon was first reported by Bredt in 1902[1] and was summarized as Bredt's rule in 1924.[2] Bredt's rule[3] is an empirical formulation[4] that may be stated in qualitative terms: a double bond cannot be placed with one terminus at the bridgehead of a bridged ring system,[5] such as in $[x.y.z]$ bicyclic system ($x \geq y \geq z$, $z \neq 0$), unless the rings are large enough to accommodate the double bond without excessive strain (e.g., $S = x + y + z \geq 9$; for a tricyclic system, $S \geq 11$).[6] When the ring is big enough, the so called anti-Bredt' rule[7] molecules can be synthesized and isolated where the double bonds exist at the bridgehead carbon.[8] Bredt's rule is useful mainly as an exclusion criterion during the assignment of structures and the interpretation of reactions of bridged ring compounds.[5] Due to the nature of Bredt's rule, many organic reactions readily operating under regular conditions do not occur easily,[5] such as the dehydrohalogenation of halides, dehydration of alcohols, decarboxylation of β-keto acid (with a bridgehead carboxyl group), enolization of ketones, formation of anhydride, enol lactonization of γ- and δ-keto acids, and formation and reaction of lactams. In a bicyclic system that holds CH bonds perpendicular to the π orbitals, Bredt's rule provides powerful kinetic stabilization.[9]

B. GENERAL REACTION SCHEME

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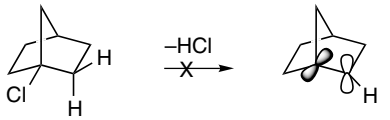
C. PROPOSED MECHANISMS

The excessive strain arising from the torsional forces on the double bond of the bicyclic system will twist the *p* orbital of doubly bonded carbon atoms away from the maximal overlap,[4] thus destabilizing the molecule, as illustrated below.



D. MODIFICATION

N/A

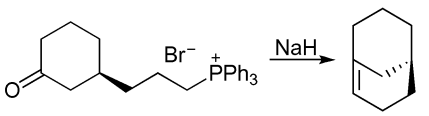
E. APPLICATIONS

Bredt's rule is used in the assignment of structures and interpretation of reactivity for bicyclic systems.

F. RELATED REACTIONS

N/A

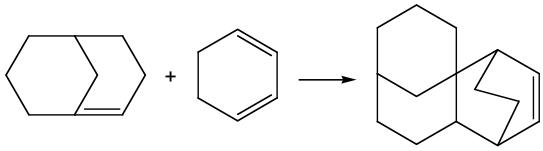
G. CITED EXPERIMENTAL EXAMPLES



Reference 8a.

Sodium hydride (1.05 g, 43.6 mmol), washed oil free with dry pentane, and 5.25 g (+)-3-(3-oxocyclohexyl)propyl-triphenylphosphonium bromide (10.9 mmol), were suspended in 40 mL dry tetraglyme containing 0.96 g 2-methyl-2-butanol under nitrogen. After the mixture was heated to 70°C for 30 min, the temperature was raised gradually to 120°C over 4 h, and the mixture was kept at this temperature for 20 min. Distillation in vacuo (120°C, 10 mmHg) removed low-boiling fractions, and the residue was vacuum distilled

(oil bath temperature 120–125°C, 5 mmHg) into a cold trap. The distillate was diluted with dry pentane, dried over anhydrous Na_2SO_4, and chromatographed on Florisil. Elution with dry pentane yielded 360 mg (-)-(S)-bicyclo[3.3.1]-1(2)-nonene as a colorless oil, in a yield of 27%.



Reference 10.

A solution of 122 mg bicyclo[3.3.1] non-1-ene (1.0 mmol) in 8 mL pentane was combined with a solution of 0.78 g 1,3-cyclohexadiene (9.72 mmol) at room temperature. After 48 h, analysis by TLC indicated 2% of the adduct had formed. The solution was sealed in a Carius tube and heated to 110°C for 42 h. After removal of the solvent, 150 mg of adduct was isolated by preparative TLC, in a yield of 74%.

Other references related to Bredt's rule are cited in the literature.[11]

H. REFERENCES

1. Bredt, J.; Houben, J. and Levy, P., *Ber*., **1902**, *36*, 1286.
2. Bredt, J.; Thouet, H. and Schmitz, J., *Ann.*, **1924**, *437*, 1, and references therein.
3. (a) Rong, G. B. and Zhao, Z. D., *Youji Huaxue*, **1992**, *12*, 139. (b) Buchanan, G. L., *J. Chem. Soc., Perkin Trans. I,* **1984**, 2669. (c) Anderson, D. W. and Buchanan, G. L., *Tetrahedron,* **1981**, *37*, 977. (d) Buchanan, G. L., *Org. Magnet. Reson.,* **1978**, *11*, 45. (e) Verbrugge, P. A., *Chem. Tech. (Amsterdam),* **1976**, *31*, 119. (f) Verbrugge, P. A., *Chem. Tech. (Amsterdam),* **1976**, *31*, 9. (g) Buchanan, G. L.; Kean, N. B. and Taylor, R., *Tetrahedron*, **1975**, *31*, 1583. (h) Duhamel, L.; Siret, P. and Mulot, F., *Compt. Rend.,* **1974**, *279*, 1159. (i) Koebrich, G., *Angew. Chem.,* **1973**, *85*, 494. (j) Chong, J. A. and Wiseman, J. R., *J. Am. Chem. Soc.,* **1972**, *94*, 8627. (k) Buchanan, G. L.; Kean, N. B. and Taylor, R., *J. Chem. Soc., Chem. Commun.,* **1972**, 201. (l) Koebrich, G. and Baumann, M., *Angew. Chem. Int. Ed. Engl.,* **1972**, *11*, 52. (m) Buchanan, G. L. and Jamieson, G., *Tetrahedron,* **1972**, *28*, 1123. (n) Buchanan, G. L. and Jamieson, G., *Tetrahedron,* **1972**, *28*, 1129. (o) Mehta, G., *Indian J. Chem. Edu.,* **1971**, *2*, 8. (p) Wiseman, J. R. and Chong, J. A., *J. Am. Chem. Soc.,* **1969**, *91*, 7775. (q) Carruthers, W. and Qureshi, M. I., *J. Chem. Soc. D,* **1969**, 832. (r) Grob, C. A. and Sieber, A., *Helv. Chim. Acta,* **1967**, *50*, 2531. (s) Lukes, R. and Ferles, M., *Coll. Czech. Chem. Commun.,* **1959**, *24*, 1297. (t) Chiurdoglu, G.; Goldenberg, C. and Geeraerts, J., *Bull. Soc. Chim. Belg.,* **1957**, *66*, 200. (u) Prelog, V.; Barman, P. and Zimmermann, M., *Helv. Chim. Acta,* **1949**, *32*, 1284. (v) Prelog, V.; Ruzicka, L.; Barman, P. and Frenkiel, L., *Helv. Chim. Acta,* **1948**, *31*, 92. (w) Lukes, R., *Coll. Czech. Chem. Commun.,* **1938**, *10*, 148. (x) Schonberg, A., *J. Chem. Soc.,* **1938**, 824. (y) Bredt, J., *J. Prakt. Chem.,* **1937**, *148*, 221. (z) Bredt, J., *J. Prakt. Chem.,* **1936**, *147*, 22.
4. Schaefer, J. P. and Lark, J. C., *J. Org. Chem.,* **1965**, *30*, 1337.
5. Wiseman, J. R., *J. Am. Chem. Soc.,* **1967**, *89*, 5966.
6. Fawcett, F. S., *Chem. Rev.,* **1950**, *47*, 219.
7. (a) Novak, I., *J. Chem. Inf. Model.,* **2005**, *45*, 334. (b) Iida, H.; Uekusa, H.; Ohashi, Y.; Hamana, H.; Machiguchi, T. and Matsumoto, K., *Heterocycles,* **2004**, *64*, 447. (c) Wijsman, G. W.; Iglesias,

G. A.; Beekman, M. C.; de Wolf, W. H.; Bickelhaupt, F.; Kooijman, H. and Spek, A. L., *J. Org. Chem.,* **2001**, *66*, 1216. (d) Matsumoto, K.; Iida, H.; Katsura, H.; Machiguchi, T.; Uekusa, H. and Ohashi, Y., *J. Chem. Soc., Perkin Trans. I,* **1996**, 2333. (e) Wijsman, G. W.; De Wolf, W. H.; Bickelhaupt, F.; Kooijman, H. and Spek, A. L., *J. Am. Chem. Soc.,* **1992**, *114*, 9191. (f) Shea, K. J.; Lease, T. G. and Ziller, J. W., *J. Am. Chem. Soc.,* **1990**, *112*, 8627. (g) Williams, R. M. and Lee, B. H., *J. Am. Chem. Soc.,* **1986**, *108*, 6431. (h) Hall, H. K. and El-Shekeil, A., *Chem. Rev.,* **1983**, *83*, 549. (i) Hall, H. K. and El-Shekeil, A., *Polymer Bull.,* **1980**, *3*, 233. (j) Hall, H. K. and El-Shekeil, A., *J. Org. Chem.,* **1980**, *45*, 5325. (k) Shiotani, S.; Kometani, T.; Kurobe, A. and Mitsuhashi, K., *J. Org. Chem.,* **1976**, *41*, 4106.

8. (a) Nakazaki, M.; Naemura, K. and Nakahara, S., *J. Org. Chem.,* **1979**, *44*, 2438. (b) Keese, R., *Angew. Chem. Int. Ed. Engl.,* **1975**, *14*, 528. (c) Buchanan, G. L., *Chem. Soc. Rev.,* **1974**, *3*, 41. (d) Köbrich, G., *Angew. Chem. Int. Ed. Engl.,* **1973**, *12*, 464.
9. (a) Nelsen, S. F. and Gannett, P. M., *J. Am. Chem. Soc.,* **1982**, *104*, 5292. (b) Nelsen, S. F.; Kessel, C. R.; Brien, D. J. and Weinhold, F., *J. Org. Chem.,* **1980**, *45*, 2116. (c) Nelsen, S. F.; Kessel, C. R. and Brien, D. J., *J. Am. Chem. Soc.,* **1980**, *102*, 702. (d) Nelsen, S. F. and Kessel, C. R., *J. Am. Chem. Soc.,* **1979**, *101*, 2503. (e) Nelsen, S. F. and Kessel, C. R., *J. Chem. Soc., Chem. Commun.,* **1977**, 490. (f) Nelsen, S. F. and Kessel, C. R., *J. Am. Chem. Soc.,* **1977**, *99*, 2392.
10. Wiseman, J. R. and Pletcher, W. A., *J. Am. Chem. Soc.*, **1970**, *92*, 956.
11. (a) Weedon, B. R.; Haddon, R. C.; Spielmann, H. P. and Meier, M. S., *J. Am. Chem. Soc.,* **1999**, *121*, 335. (b) Haddon, R. C. and Raghavachari, K., *Tertrahedron*, **1996**, *52*, 5207. (c) Diederich, F.; Isaacs, L. and Philp, D., *J. Chem. Soc., Perkin Trans. II,* **1994**, 391. (d) Hopf, H.; Laue, T. and Zander, M., *Angew. Chem. Int. Ed. Engl.,* **1991**, *30*, 432. (e) Krabbenhoft, H. O.; Wiseman, J. R. and Quinn, C. B., *J. Am. Chem. Soc.,* **1974**, *96*, 258. (f) Quinn, C. B.; Wiseman, J. R. and Calabrese, J. C., *J. Am. Chem. Soc.,* **1973**, *95*, 6121. (g) Quinn, C. B. and Wiseman, J. R., *J. Am. Chem. Soc.,* **1973**, *95*, 1342. (h) Quinn, C. B. and Wiseman, J. R., *J. Am. Chem. Soc.,* **1973**, *95*, 6120. (i) Wiseman, J. R.; Chan, H.-F. and Ahola, C. J., *J. Am. Chem. Soc.,* **1969**, *91*, 2812. (j) Marshall, J. A. and Faubl, H., *J. Am. Chem. Soc.,* **1967**, *89*, 5965. (k) Fort, R. C. and Schleyer, P. v. R., "Bridgehead Reactivity" in *Advances in Alicyclic Chemistry*, ed. Hart, H. and Karabatsos, G. J., Academic Press, New York, **1966**, 1, 283–370. (l) Ferris, J. P. and Miller, N. C., *J. Am. Chem. Soc.,* **1966**, *88*, 3522. (m) Schaefer, J. P. and Lark, J. C., *J. Org. Chem.,* **1965**, *30*, 1336. (n) Berson, J. A. and Willcott, M. R., *J. Org. Chem.,* **1965**, *30*, 3569. (o) Prelog, V., *J. Chem. Soc.,* **1950**, 420.

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Brook Rearrangement

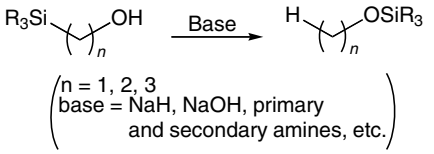
A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Brook in 1958.[1] It is a base-catalyzed intramolecular migration of a silyl group from a carbon atom to an oxygen anion via a mechanism involving a hypervalent pentacoordinate silicon species[2] with retention of the configuration at the silicon atom and inversion of the configuration at the carbon atom.[3] Therefore, this transformation is generally known as the Brook rearrangement.[4] However, it falls into two types: the normal Brook rearrangement and the radical Brook rearrangement.[5] When a hydroxyl group presents in silanes, the driving forces for such rearrangement during the treatment with base is the stronger Si–O bond over C–Si bond. Although the most common rearrangement is the [1,2] rearrangement (in α-silyl alcohols), the migration of the silyl group to a longer distance has also been reported, such as the [1,3] (in β-silyl alcohols),[6] [1,4] (in γ-silyl alcohols),[7] and [1,5] Brook rearrangement.[4b] In addition, protiodesilylation of a β-hydroxyalkylsilane under basic conditions in the presence of a proton source is known as a homo-Brook rearrangement.[4h,4r,8] The substituents on carbon that can delocalize a negative charge, such as the vinyl and aryl groups, can accelerate the rearrangement.[2] On the other hand, this rearrangement is reversible in some cases and requires an excess amount of base. The reverse rearrangement is called the *anti*-Brook rearrangement,[3,9] reverse Brook rearrangement,[3,4p,9,10] Wright-West rearrangement,[11] Wittig rearrangement,[2] or *retro*-Brook rearrangement.[7b,7c,12,13] The driving force for the reverse Brook rearrangement presumably is the stronger stability of alkoxide over carbanion.[3] It is found that the Brook rearrangement can even be initiated using a neutral base such as carbene[14] or by the addition of anion to the carbonyl group in ketones or lactones.[15] In addition, the silyl group can migrate not only to the oxygen atom but also to the nitrogen atom; the migration in latter case is called the *aza*-Brook rearrangement.[16] A similar migration tendency is also

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

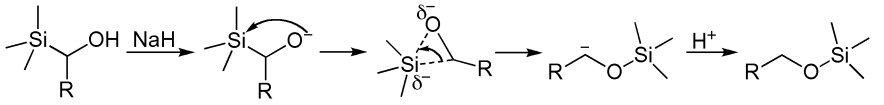
found in tin compounds, and the migration of stannyl group analogues to Brook rearrangement is called *stannyl*-Brook rearrangement,[12a,17] or the *stanna*-Brook rearrangement.[15a,18] Likewise, the similar rearrangement on sulfur-containing compounds is referred to as *thia*-Brook rearrangement.[19] This rearrangement has been applied to the preparation of a variety of building blocks[20] and complex natural products,[21] and has been extensively reviewed.[22]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The mechanism is illustrated by a simple [1,2]-Brook rearrangement.



D. MODIFICATION

The *aza*-Brook,[16] *stanna*-Brook,[12a,15a,17,18] and *thia*-Brook[19] rearrangements should be considered as modifications of the regular Brook rearrangement.

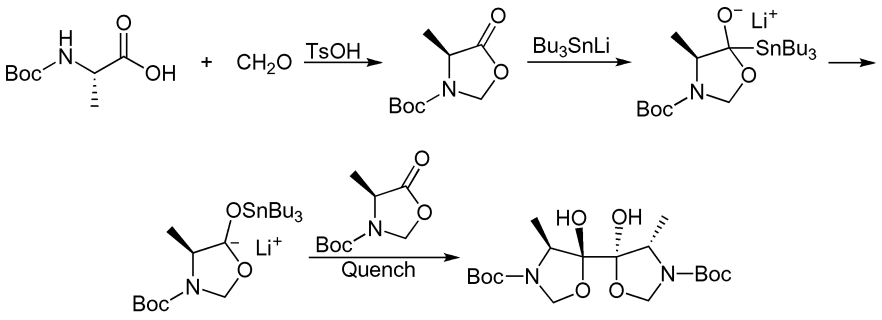
E. APPLICATIONS

This reaction has been used to synthesize different building blocks[20] and even complex natural products.[21]

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 15a.

General Procedure for the Preparation of *N*-Boc-Oxazolidines

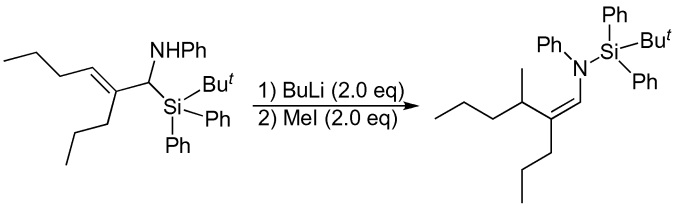
A mixture of *N*-Boc-protected amino acid (5 mmol), 195 mg paraformaldehyde (6.5 mmol), and 43 mg *p*-toluensulfonic acid (0.25 mmol) in 50 mL benzene was refluxed with the aid of a Dean-Stark trap, and heating was continued until no starting material was detected by TLC (1–3 h). The reaction mixture was cooled to room temperature, washed with 5% $KHCO_3$ (2 × 30 mL) and brine (30 mL), dried, and concentrated. The crude product was purified by column chromatography or by crystallization from suitable solvents. For (4*S*)-*N*-*tert*-butyloxycarbonyl-4-methyl-1,3-oxazolidin-5-one from *N*-Boc-analine, 825 mg was obtained by crystallization from CH_2Cl_2-hexane as white needles, in a yield of 82%, m.p. 66–67°C.

General Procedure for the Preparation of α-Amino Acids-Derived Dimers

Method A A 0°C solution of 220 μL diisopropylamine (1.6 mmol) in 5 mL THF was treated with 1.53 mmol *n*-BuLi and stirred for 15 min. Then 360 μL tributyltin hydride (1.35 mmol) was added and stirred for an additional 15 min. The solution of Bu_3SnLi thus prepared was cooled to −78°C and treated with 5 mL THF solution with oxazolidinone (0.9 mmol). The reaction mixture was stirred at −78°C for 3 h, quenched by addition of 2 mL phosphate buffer (pH = 7.0); and then partitioned between the phosphate buffer and EtOAc. The aqueous layer was extracted with 10 mL EtOAc, and the combined organic phase was washed with 15 mL brine, dried, filtered, and concentrated under reduced pressure to give a residue that was purified by column chromatography (SiO_2, EtOAc/Hexane = 1 : 3).

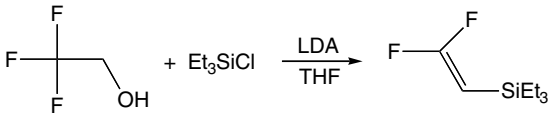
Method B A 0°C solution of 300 μL bis(tributyltin) (0.6 mmol) in 2 mL THF was treated with 0.6 mmol *n*-BuLi and stirred for 15 min. It was then cooled to −78°C, and treated via cannula with a solution of 0.4 mmol oxazolidinone in 4 mL THF. The resulting solution was stirred for 3.5 h. The rest of the procedure was similar to Method A. Using Method A, 115 mg di-*tert*-butyl (4*S*,4′*S*,5*S*,5′*S*) 5,5′-dihydroxy-4,4′-dimethyl-5,5′-bi-1,3-oxazolidine-3,3′-dicarboxylate was obtained from column chromatography (EtOAc/hexane = 1 : 8) as a white foam, in a yield of 63%.

To a stirred solution of 20.3 mg silyl amine (0.0446 mmol) in 1.7 mL THF was added 0.06 mL BuLi solution in hexane (1.59 M, 0.0954 mmol) at −78°C, and the



Reference 16d.

solution was stirred at the same temperature for 30 min. To this solution was added 0.2 mL HMPA and 0.008 mL methyl iodide (0.129 mmol) at −78°C, and the solution was stirred at the same temperature for 30 min. The solution was warmed to 0°C, and saturated NH_4Cl solution was added. The aqueous layer was extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed (hexane/EtOAc = 30:1) to afford 20.9 mg *N*-*t*-butyldiphenylsilyl-*N*-((*Z*)-3-methyl-2-propyl-2-hexenyl)aniline as a colorless oil, in a yield of 100%.



Reference 23.

To a 500-mL three-necked, round-bottom flask with a septum cap (flame dried) under an inert atmosphere was added 50 mL THF, 5.0 g trifluoroethanol (50 mmol), 50 mmol triethylsilyl chloride, and 5.0 mL HMPA in a dry ice bath. To this mixture was added 175 mmol LDA in 100 mL THF (3.5 eq.), and the solution was stirred at 0°C for 3 h or at −20°C for overnight. Then the solution was injected into 500 mL H_2O in a 1000-mL flask at room temperature via syringe with slow stirring. After being stirred for 10 min, 100 mL 5 M HF solution was added, and the solution was vigorously stirred for 30 min at room temperature to allow the conversion of the silanol to the corresponding fluorosilane, then 50 mL pentane was added, and the organic phase was separated, washed with aqueous $NaHCO_3$, and dried over anhydrous $MgSO_4$. After removal of the drying agent, the solvent was evaporated under gentle vacuum. The residue was subjected to distillation, and 60% of difluoroacetyltriethylsilane was obtained.

Other references related to the Brook rearrangement are cited in the literature.[24]

H. REFERENCES

1. Brook, A. G., *J. Am. Chem. Soc.,* **1958**, *80*, 1886.
2. Jung, M. E. and Nichols, C. J., *J. Org. Chem.,* **1996**, *61*, 9065.
3. Linderman, R. J. and Ghannam, A., *J. Am. Chem. Soc.,* **1990**, *112*, 2392.
4. (a) Nakai, Y.; Kawahata, M.; Yamaguchi, K. and Takeda, K., *J. Org. Chem.,* **2007**, *72*, 1379. (b) Smith, A. B.; Xian, M.; Kim, W.-S. and Kim, D.-S., *J. Am. Chem. Soc.,* **2006**, *128*, 12368. (c) Okugawa, S.; Masu, H.; Yamaguchi, K. and Takeda, K., *J. Org. Chem.,* **2005**, *70*, 10515.

(d) Unger, R.; Cohen, T. and Marek, I., *Org. Lett.,* **2005**, *7*, 5313. (e) Clayden, J.; Watson, D. W.; and Chambers, M., *Tetrahedron,* **2005**, *61*, 3195. (f) Tanaka, K. and Takeda, K., *Tetrahedron Lett.,* **2004**, *45*, 7859. (g) Fleming, I.; Lawrence, A. J.; Richardson, R. D.; Surry, D. S. and West, M. C., *Helv. Chim. Acta,* **2002**, *85*, 3349. (h) Naganuma, K.; Kawashima, T. and Okazaki, R., *Chem. Lett.,* **1999**, 1139. (i) Takeda, K. and Ohtani, Y., *Org. Lett.,* **1999**, *1*, 677. (j) Takeda, K.; Ubayama, H.; Sano, A.; Yoshii, E. and Koizumi, T., *Tetrahedron Lett.,* **1998**, *39*, 5243. (k) Smith, A. B. and Boldi, A. M., *J. Am. Chem. Soc.,* **1997**, *119*, 6925. (l) Jung, M. E. and Nichols, C. J., *J. Org. Chem.,* **1996**, *61*, 9065. (m) Wu, H.-J.; Yen, C.-H. and Chuang, C.-T., *Tetrahedron Lett.,* **1996**, *37*, 7395. (n) Fuerstner, A.; Seidel, G.; Gabor, B.; Kopiske, C.; Krueger, C. and Mynott, R., *Tetrahedron,* **1995**, *51*, 8875. (o) Kang, K. T.; Sung, T. M.; Lee, K. R.; Lee, J. G. and Jyung, K. K., *Bull. Korean Chem. Soc.,* **1993**, *14*, 757. (p) Boche, G.; Opel, A.; Marsch, M.; Harms, K.; Haller, F.; Lohrenz, J. C. W.; Thuemmler, C. and Koch, W., *Chem. Ber.,* **1992**, *125*, 2265. (q) Koreeda, M. and Koo, S., *Tetrahedron Lett.,* **1990**, *31*, 831. (r) Yamamoto, K.; Kimura, T. and Tomo, Y., *Tetrahedron Lett.,* **1985**, *26*, 4505.

5. (a) Huang, C.-H.; Chang, S.-Y.; Wang, N.-S. and Tsai, Y.-M., *J. Org. Chem.,* **2001**, *66*, 8983. (b) Paredes, M. D. and Alonso, R., *J. Org. Chem.,* **2000**, *65*, 2292. (c) Jiaang, W. T.; Lin, H. C.; Tang, K. H.; Chang, L. B. and Tsai, Y. M., *J. Org. Chem*., **1999**, *64*, 618. (d) Paredes, M. D. and Alonso, R., *Tetrahedron Lett.,* **1999**, *40*, 3973. (e) Schiesser, C. S. and Styles, M. L., *J. Chem. Soc., Perkin Trans. II,* **1997**, 2335. (f) Curran, D. P.; Diederichsen, U. and Palovich, M., *J. Am. Chem. Soc.,* **1997**, *119*, 4797. (g) Chang, S.-Y.; Jiaang, W.-T.; Cherng, C.-D.; Tang, K.-H.; Huang, C.-H. and Tsai, Y.-M., *J. Org. Chem.,* **1997**, *62*, 9089. (h) Robertson, J. and Burrows, J. N., *Tetrahedron Lett.,* **1994**, *35*, 3777. (i) Tsai, Y.-M. and Ke, B.-W., *J. Chin. Chem. Soc. (Taipei),* **1993**, *40*, 641. (j) Harris, J. M.; MacInnes, I.; Walton, J. C. and Maillard, B., *J. Organomet. Chem.,* **1991**, *403*, C25. (k) Tsai, Y.-M. and Cherng, C.-D., *Tetrahedron Lett.,* **1991**, *32*, 3515. (l) Dalton, J. C. and Bourque, R. A., *J. Am. Chem. Soc.,* **1981**, *103*, 699.
6. (a) He, H.-M.; Fanwick, P. E.; Wood, K. and Cushman, M., *J. Org. Chem.,* **1996**, *61*, 1554. (b) He, H.-M.; Fanwick, P. E.; Wood, K. and Cushman, M., *J. Org. Chem.,* **1995**, *60*, 5905.
7. (a) Lautens, M.; Delanghe, P. H. M.; Goh, J. B. and Zhang, C. H., *J. Org. Chem.,* **1995**, *60*, 4213. (b) Jiang, X.-L. and Bailey, W. F., O*rganometallics,* **1995**, *14*, 5704. (c) Hoffmann, R. and Brückner, R., *Ber.,* **1992**, *125*, 2731. (d) Evans, D. A.; Takacs, J. M. and Hurst, K. M., *J. Am. Chem. Soc.,* **1979**, *101*, 371.
8. (a) Kawashima, T.; Naganuma, K. and Okazaki, R., *Organometallics*, **1998**, *17*, 367. (b) Wilson, S. R. and Georgiadis, G. M., *J. Org. Chem.*, **1983**, *48*, 4143. (c) Hudrlik, P. F.; Hudrlik, A. M. and Kulkarni, A. K., *J. Am. Chem. Soc.,* **1982**, *104*, 6809.
9. Linderman, R. J. and Ghannam, A., *J. Org. Chem.,* **1988**, *53*, 2878.
10. (a) Sakaguchi, K.; Fujita, M.; Suzuki, H.; Higashino, M. and Ohfune, Y., *Tetrahedron Lett.,* **2000**, *41*, 6589. (b) Wang, Y. G. and Dolg, M., *Tetrahedron,* **1999**, *55*, 12751.
11. Yu, Y. M. and Feng, S. Y., *J. Phys. Chem. A,* **2004**, *108*, 7468.
12. (a) Simpkins, S. M. E.; Kariuki, B. M.; Aricó, C. S. and Cox, L. R., *Org. Lett.,* **2003**, *5*, 3971. (b) Gandon, V.; Bertus, P. and Szymoniak, J., *Tetrahedron Lett.,* **2000**, *41*, 3053. (c) Gandon, V.; Bertus, P. and Szymoniak, J., *Tetrahedron*, **2000**, *56*, 4465. (d) Shotwell, J. B.; Hu, S. J.; Medina, E.; Abe, M.; Cole, R.; Crews, C. M. and Wood, J. L., *Tetrahedron Lett.,* **2000**, *41*, 9639. (e) Gibson, C.; Buck, T.; Walker, M. and Brückner, R., *Synlett*, **1998**, 201. (f) Goeppel, D. and Brückner, R., *Tetrahedron Lett.,* **1997**, *38*, 2937. (g) Sammtleben, F.; Noltemeyer, M. and Brückner, R., *Tetrahedron Lett.,* **1997**, *38*, 3893. (h) Gibson, C.; Buck, T.; Noltemeyer, M. and Brückner, R., *Tetrahedron Lett.,* **1997**, *38*, 2933. (i) Behrens, K.; Kneisel, B.; Noltemeyer, M. and Brückner, R., *Liebigs Ann*., **1995**, 385. (j) Winter, E. and Brückner, R., *Synlett*, **1994**, 1049. (k) Hoffmann, R. and Brückner, R.,*Ber.,* **1992**, *125*, 1471.
13. (a) Haftbaradaran, F.; Mund, G.; Batchelor, R. J.; Britten, J. F. and Leznoff, D. B., *Dalton Trans.,* **2005**, 2343. (b) Bailey, W. F. and Jiang, X. L., *ARKIVOC*, **2005**, (*vi*), 25. (c) Nahm, M. R.; Xin,

L. H.; Potnick, J. R.; Yates, C. M.; White, P. S. and Johnson, J. S., *Angew. Chem. Int. Ed.,* **2005**, *44*, 2377. (d) Nelkenbaum, E.; Kapon, M. and Eisen, M. S., *J. Organomet. Chem.,* **2005**, *690*, 2297. (e) Gandon, V.; Bertus, P. and Szymoniak, J., *Tetrahedron,* **2000**, *56*, 4467. (f) Kleinfeld, S. H.; Wegelius, E. and Hoppe, D., *Helv. Chim. Acta,* **1999**, *82*, 2413. (g) Comanita, B. M.; Woo, S. and Fallis, A. G., *Tetrahedron Lett*., **1999**, *40*, 5283. (h) Bousbaa, J.; Ooms, F. and Krief, A., *Tetrahedron Lett*., **1997**, *38*, 7625.

14. Mattson, A. E.; Bharadwaj, A. R. and Scheidt, K. A., *J. Am. Chem. Soc.,* **2004**, *126*, 2314.
15. (a) Paleo, M. R.; Calaza, M. I.; Graña, P. and Sardina, F. J., *Org. Lett.,* **2004**, *6*, 1061. (b) Sasaki, M.; Kawanishi, E.; Nakai, Y.; Matsumoto, T.; Yamaguchi, K. and Takeda, K., *J. Org. Chem.,* **2003**, *68*, 9330. (c) Patrocínio, A. F. and Moran, P. J. S., *J. Braz. Chem. Soc*., **2001**, *12*, 7.
16. (a) Yagi, K.; Tsuritani, T.; Takami, K.; Shinokubo, H. and Oshima, K., *J. Am. Chem. Soc.,* **2004**, *126*, 8618. (b) Sieburth, S. M.; O'Hare, H. K.; Xu, J. Y.; Chen, Y. P. and Liu, G. D., *Org. Lett.,* **2003**, *5*, 1859. (c) Liu, G. D. and Sieburth, S. M., *Org. Lett.,* **2003**, *5*, 4677. (d) Honda, T. and Mori, M., *J. Org. Chem*., **1996**, *61*, 1196. (e) Lappert, M. F. and Liu, D.-S., *J. Organomet. Chem.,* **1995**, *500*, 203. (f) Cunico, R. F. and Kuan, C. P., *J. Org. Chem*., **1992**, *57*, 3331. (g) Bulman Page, P. C.; van Niel, M. B. and Westwood, D., *J. Chem. Soc., Perkin Trans. I,* **1988**, 269. (h) Fuji, K.; Ueda, M.; Sumi, K. and Fujita, E., *J. Org. Chem.,* **1985**, *50*, 662.
17. Fleming, I. and Mandal, A. K., *Chem. Commun.,* **1999**, 923.
18. Monje, P.; Grana, P.; Paleo, M. R. and Sardina, F. J., *Org. Lett.,* **2006**, *8*, 951.
19. Takeda, K.; Sumi, K. and Hagisawa, S., *J. Organomet. Chem.,* **2000**, *611*, 449.
20. (a) Takeda, K.; Sawada, Y. and Sumi, K., *Org. Lett*., **2002**, *4*, 1031. (b) Lighu, X.; Nicewicz, D. A. and Johnson, J. S., *Org. Lett*., **2002**, *4*, 2957.
21. (a) Hu, T. and Corey, E. J., *Org. Lett*., **2002**, *4*, 2441. (b) Zhang, J. and Corey, E. J., *Org. Lett*., **2001**, *3*, 3215. (c) Corey, E. J.; Luo, G. and Lin, L. S., *J. Am. Chem. Soc.,* **1997**, *119*, 9927.
22. (a) Moser, W. H., *Tetrahedron,* **2001**, *57*, 2065. (b) Brook, M. A., *Silicon in Organic, Organometallic, and Polymer Chemistry*, John Wiley & Sons, New York, **2000**. (c) Qi, H. and Curran, D. P., "Acyl Silicon, Germanium, or Boron Functions" in *Comprehensive Organic Functional Group Transformations*, ed. Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W. and Moody, C. J., Elsevier, Oxford, **1995**, pp. 409–431. (d) Cirillo, P. F. and Panek, J. S., *Org. Prep. Proc. Int.,* **1992**, *24*, 553. (e) Bulman Page, P. C.; Klair, S. S. and Rosenthal, S., *Chem. Soc. Rev*., **1990**, *19*, 147. (f) Colvin, E., *Silicon in Organic Synthesis*, Butterworth, London, **1981**. (g) Brook, A. G. and Bassindale, A. R., "Molecular Rearrangement of Organosilicon Compounds" in *Organic Chemistry*, *42* (*Rearrangements in Ground and Exited States, pt. 2*), ed. de Mayo, P., Academic Press, New York, **1980**, pp. 149–221. (h) Brook, A. G., *Acc. Chem. Res.,* **1974**, *7*, 77.
23. Higashiya, S.; Chung, W. J.; Lim, D. S.; Ngo, S. C.; Kelly, W. H.; Toscano, P. J. and Welch, J. T., *J. Org. Chem.,* **2004**, *69*, 6323.
24. (a) Baati, R.; Mioskowski, C.; Barma, D.; Kache, R. and Falck, J. R., *Org. Lett.,* **2006**, *8*, 2949. (b) Nakazaki, A.; Nakai, T. and Tomooka, K., *Angew. Chem. Int. Ed.,* **2006**, *45*, 2235. (c) Matsumoto, T.; Masu, H.; Yamaguchi, K. and Takeda, K., *Org. Lett.,* **2004**, *6*, 4367. (d) Okugawa, S. and Takeda, K., *Org. Lett.,* **2004**, *6*, 2973. (e) Sawada, Y.; Sasaki, M. and Takeda, K., *Org. Lett.,* **2004**, *6*, 2277. (f) Linghu, X.; Potnick, J. R. and Johnson, J. S., *J. Am. Chem. Soc.,* **2004**, *126*, 3070. (g) Nicewicz, D. A.; Yates, C. M. and Johnson, J. S., *J. Org. Chem.,* **2004**, *69*, 6548. (h) Nicewicz, D. A.; Yates, C. M. and Johnson, J. S., *Angew. Chem. Int. Ed*., **2004**, *43*, 2652. (i) Jankowski, P.; Pleœniak, K. and Wicha, J., *Org. Lett.,* **2003**, *5*, 2789. (j) Takeda, K.; Haraguchi, H. and Okamoto, Y., *Org. Lett.,* **2003**, *5*, 3705. (k) Buswell, M. and Fleming, I., *Chem. Commun.,* **2003**, 202. (l) Moser, W. H.; Zhang, J.; Lecher, C. S.; Frazier, T. L. and Pink, M., *Org. Lett.,* **2002**, *4*, 1981. (m) Tipparaju, S. K.; Mandal, S. K.; Sur, S.; Puranik, V. G. and Sarkar, A., *Chem. Commun.,* **2002**, 1924. (n) Takeda, K.; Kawanishi, E.; Sasaki, M.; Takahashi, Y. and Yamaguchi, K., *Org. Lett.,* **2002**, *4*, 1511. (o) Buswell, M. and Fleming, I., *ARKIVOC*, **2002**, 46. (p) Straub, T.; Haskel, A.; Neyroud, T. G.; Kapon, M.; Botoshansky, M.

and Eisen, M. S., *Organometallics,* **2001**, *20*, 5017. (q) Moser, W. H.; Endsley, K. E. and Colyer, J. T., *Org. Lett*., **2000**, *2*, 717. (r) Takeda, K. and Ohnishi, Y., *Tetrahedron Lett.,* **2000**, *41*, 4169. (s) Pezacki, J. P.; Loncke, P. G.; Ross, J. P.; Warkentin, J. and Gadosy, T. A., *Org. Lett.,* **2000**, *2*, 2733. (t) Takeda, K.; Nakane, D. and Takeda, M., *Org. Lett.,* **2000**, *2*, 1903. (u) Takeda, K. and Tanaka, T., *Synlett,* **1999**, 705. (v) Takeda, K.; Nakajima, A.; Takeda, M.; Okamoto, Y.; Sato, T.; Yoshii, E.; Koizumi, T. and Shiro, M., *J. Am. Chem. Soc.,* **1998**, *120*, 4947. (w) Wu, H.-J.; Yen, C.-H. and Chuang, C.-T., *J. Org. Chem.,* **1998**, *63*, 5064. (x) Taniguchi, Y.; Fujii, N.; Takaki, K. and Fujiwara, Y., *Appl. Organomet. Chem*., **1995**, *9*, 377. (y) Katritzky, A. R.; Hong, Q. and Yang, Z., *Organometallics,* **1995**, *14*, 734. (z) Bienz, S.; Enev, V. and Huber, P., *Tetrahedron Lett.,* **1994**, *35*, 1161. (aa) Murai, T.; Oda, T.; Kimura, F.; Onishi, H.; Kanda, T. and Kato, S., *J. Chem. Soc*., *Chem. Commun*., **1994**, 2143. (bb) Labrecque, D.; Nwe, K. T. and Chan, T. H., *Organometallics,* **1994**, *13*, 332. (cc) Sakuragi, A.; Shirai, N.; Sato, Y.; Kurono, Y. and Hatano, K., *J. Org. Chem*., **1994**, *59*, 148. (dd) Beak, P.; Kerrick, S. T.; Wu, S. and Chu, J., *J. Am. Chem. Soc*., **1994**, *116*, 3231. (ee) Takeda, K.; Nakatani, J.; Nakamura, H.; Sako, K.; Yoshii, E. and Yamaguchi, K., *Synlett*, **1993**, 841. (ff) Takeda, K.; Fujisawa, M.; Makino, T.; Yoshii, E. and Yamaguchi, K., *J. Am. Chem. Soc.,* **1993**, *115*, 9351. (gg) Linderman, R. J. and Chen, K., *Tetrahedron Lett*., **1992**, *33*, 6767. (hh) Reich, H. J.; Holtan, R. C. and Bolm, C., *J. Am. Chem. Soc.,* **1990**, *112*, 5609. (ii) Okazaki, S. and Sato, Y., *Synthesis,* **1990**, 36. (jj) Degl'Innocenti, A.; Ricci, A.; Mordini, A.; Reginato, G. and Colotta, V., *Gazz. Chim. Ital*., **1987**, *117*, 645. (kk) Brook, A. G. and Fieldhouse, S. A., *J. Organomet. Chem*., **1967**, *10*, 235. (ll) Brook, A. G., *J. Am. Chem. Soc.,* **1959**, *81*, 981.

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Brown Hydroboration

A. GENERAL DESCRIPTION OF THE REACTION

This reaction can be traced back to the doctoral dissertation of Brown at Chicago in 1939, when he first carried out a reaction of diborane with alkenes.[1] However, the real origin and extensive studies of hydroboration started in 1956 when Brown moved to Purdue.[2] It is the addition of boron hydrides to the less-substituted carbon atom of alkenes (*anti*-Markownikoff addition),[3] allenes, dienes, and alkynes to form organoboranes from the less hindered side in a *cis* fashion. The formed organoboranes can then be converted to a variety of compounds,[4] including acetylenes, acids,[5] alcohols,[6] aldehydes,[5] alkanes,[7] alkenes,[8] amines,[5] esters,[5] ketones[5] and nitriles. Therefore, this reaction is generally known as the Brown hydroboration.[9] When one or two hydrogen atoms in hydroborane are substituted by bulk groups, more valuable organoboranes are formed, which show dramatically improved regioselectivity and diastereoselectivity in hydroboration. These organoboranes are the volatile dimmer (B_2H_6), borabicyclo[3.3.1]nonane (9-BBN),[8,10] thexylborane ($ThxBH_2$),[11] thexyldialkylborane, thexylalkylchloroborane (ThBHCl),[12] disiamylborane (Sia_2BH), diisobutylene-2-borane ($DibBH_2$),[13] catecholborane (CBH),[14] pinacolborane (PBH),[15] *trans*-2,5-dimethylborolane,[16] dilongifolyborane (Lgf_2BH), LimBH,[17] diisopinocampheyl-borane (Ipc_2BH),[18] isopinocampheylboranes,[19] etc. As for the electron deficiency on the boron atom, boron hydride can form complex with Lewis bases (the borane carriers[20]) as well. The early studied boron hydride complexes are $BH_3{\cdot}THF$ and $BH_3{\cdot}Me_2S$, which can be added to alkenes rapidly and quantitatively to yield a wide variety of fully or partially substituted organoboranes.[21] The boron hydride complexes with Lewis bases fall into three categories: ether complex, thioether complex, and amine complex. The most common etheral hydroborate is $BH_3{\cdot}THF$;[21] the thioether hydroborates[20,22] include dimethyl

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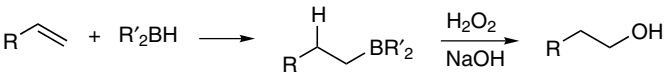
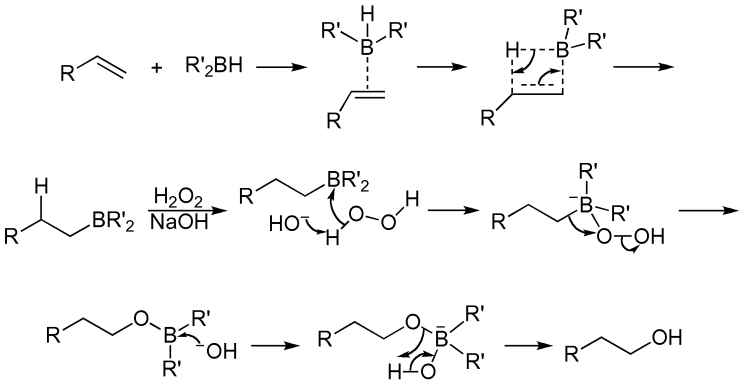
sulfide, 1,4-oxathiane, *tert*-butyl methyl sulfide, isoamyl methyl sulfide, ethyl isoamyl sulfide, *tert*-butyl isoamyl sulfide, diisoamyl sulfide, tetrahydrothiophene, tetrahydrothiopyran, thioanisole, 3-ethylthiotetrahydrofuran, bis(3-tetrahydrofuryl) sulfide, and bis(2-methoxyethyl) sulfide.[20] The amine hydroborates[23] include ethylenediamines[24] and tertiary amines,[25] (such as *N*,*N*-dialkyl-*tert*-alkylamines,[26] *tert*-butyldialkylamine,[27] *N*,*N*-dialkylanilines,[28] *N*-ethyl-*N*-isopropylaniline,[29] *N*,*N*-diisopropyl-*N*-isobutylamine,[30] and pyridine[31]). Different organoboranes might show different chemoselectivities. For example, the hydroborations of fluorinated terminal alkenes give 1- or 2-alcohol by using pinacolborane or catecholborane, respectively.[14] The new improvement in hydroboration is transition-metal promoted hydroboration,[32] which can alter the chemoselectivity and even the reaction mechanism. For instance, when the carbonyl group and alkene coexist in a molecule, catecholborane will add to the carbonyl group first, whereas in the presence of less than 1% of $Rh(PPh_3)_3Cl$, the hydroboration of alkene takes place preferentially.[33] As for the versatile applications of the Brown hydroboration, more than 500 research papers have been published in this area, and hydroboration itself has been extensively reviewed in the literature.[4,32,34]

B. GENERAL REACTION SCHEME

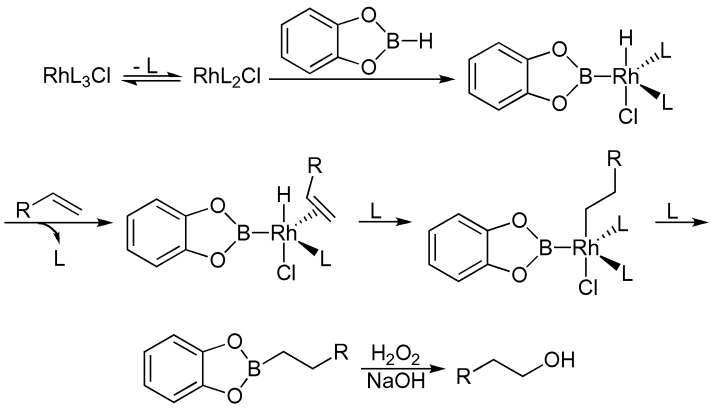


C. PROPOSED MECHANISMS

An exemplary mechanism of the regular hydroboration of alkenes is illustrated in Scheme 1. The mechanism for the transition-metal promoted hydroboration is shown in Scheme 2.[35]



SCHEME 1. *General mechanism of the hydroboration of olefin.*



SCHEME 2. *Mechanism of transition-metal promoted Brown hydroboration.*

D. MODIFICATION

The original hydroborane (B_2H_6) has been modified to different organoboranes for the enantioselective hydroboration, as shown in Figure 1.

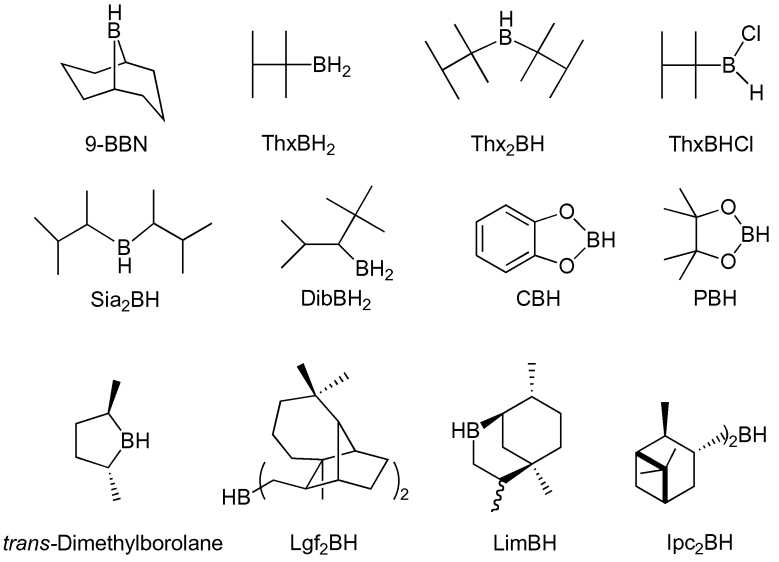


FIGURE 1. *Sterically hindered hydroboranes for enantioselective hydroboration.*

E. APPLICATIONS

The Brown hydroboration has wide applications in functional group transformations, as outlined in Figure 2.[36] The enantiopure boranes from α-pinene and their applications are given in Figure 3.[19]

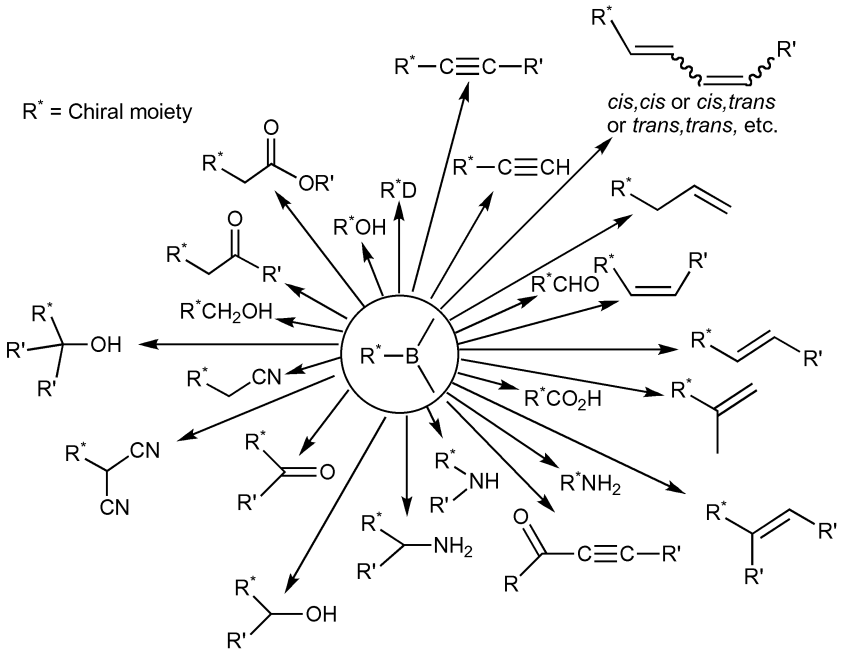


FIGURE 2. *Conversion of alkylborane into different functional groups.*

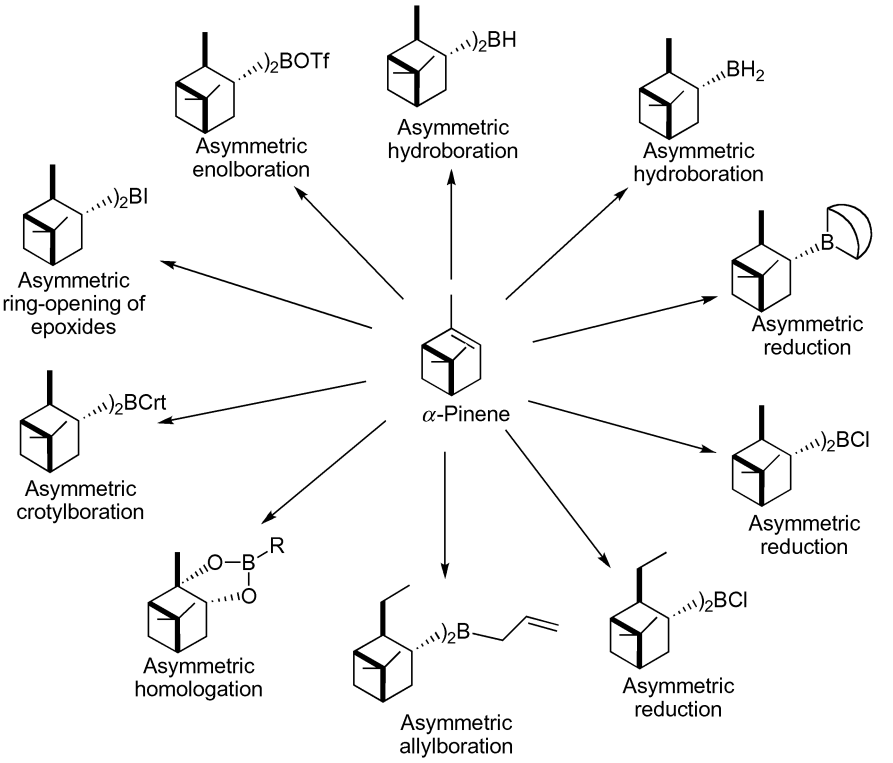
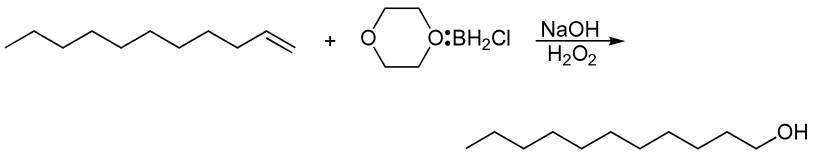


FIGURE 3. *Hydroboranes prepared from α-pinene.*

F. RELATED REACTIONS

This reaction is similar to the *Suzuki Coupling*.

G. CITED EXPERIMENTAL EXAMPLES

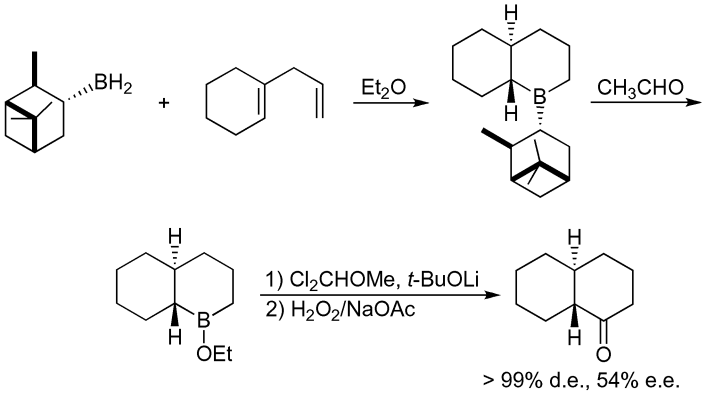


Reference 35.

Hydroboration of Representative Olefins using Dioxane-BH_2Cl

Hydroboration of representative olefins—such as 1-octene, 1-decene, styrene, α-methylstyrene, 2-methyl-1-pentene, *cis*-4-methyl-2-pentene, 2-methyl-2-butene, α-pinene, cyclohexene, 3-carene, 1-phenyl-2-methyl-1-propene, 2,3-dimethyl-2-butene and 1,2-dimethylcyclopentene—with dioxane-BH_2Cl was carried out in dioxane and dichloromethane solvents. The procedure followed for all the olefins in both the solvents are same. The procedure followed for 1-decene in dichloromethane is representative.

An oven-dried 50-mL round-bottomed flask provided with a septum inlet and stirring bar was cooled to 0°C under nitrogen. The flask was charged with 5 mmol dioxane-BH_2Cl in 8.7 mL dichloromethane. To this was added 1.4 g 1-decene (10 mmol). The final solution is 0.5 M for BH_2Cl and 1.0 M for 1-decene. The contents were further stirred at room temperature. The course of reaction was followed by ^{11}B NMR and hydride analysis of residual active hydride. Both these studies showed the completion of the reaction after 15 min. The reaction mixture was treated with the slow addition of water followed by the addition of 7.0 mL 3.0 M sodium hydroxide (21 mmol), then 3.0 mL methanol was added followed by the slow addition of 6 mmol hydrogen peroxide. The contents were further stirred at room temperature for 3 h and at 40°C for 1 h to ensure complete oxidation. The organic compound was extracted into diethyl ether. Drying and evaporation of the solvent provided essentially pure 1-decanol in 98% by GC, and 1.48 g 1-decanol was obtained, in a yield of 95%.



Reference 6a

A solution of $IpcBH_2$ (20 mmol) in 28.5 mL Et_2O was cooled to $-10^\circ C$, and HCl in Et_2O (20 mmol) was added to it dropwise with stirring. After the addition was complete, the ^{11}B NMR spectrum indicated the formation of a major amount of $IpcBHCl{\cdot}Et_2O$. In another flask, 2.68 g 1-allyl-1-cyclohexene (22 mmol) was dissolved in 10 mL Et_2O and cooled to $0^\circ C$. To it, preformed $IpcBHCl{\cdot}Et_2O$ solution was added dropwise, and the mixture was allowed to stir at $0^\circ C$ for 1 h. When the ^{11}B NMR spectrum indicated major formation of R_2-BCl (δ 74), the reaction mixture was cooled to $-20^\circ C$ (ice water bath), and 5.0 mL 1.0 M LAH (5 mmol) in Et_2O was added dropwise with stirring. The stirred mixture was allowed to warm to $24^\circ C$ (12 h). The ^{11}B NMR indicated the formation of clean trialkylborane (δ 81). The mixture was cooled to $0^\circ C$; and 2.5 mL acetaldehyde was added and stirred for 1 h, when the ^{11}B NMR spectrum indicated the formation of borinate ester (δ 52). The volatiles were removed by applying reduced pressure (10 mmHg, 30 min), the borinate ester was dissolved in 20 mL Et_2O, and the solution was cooled to $0^\circ C$. To it 2.7 mL α,α-dichloromethyl methyl ether (30 mmol) was added, followed by the dropwise addition of lithium *tert*-butoxide in *n*-hexanes (40 mmol, generated from *tert*-butyl alcohol and *n*-butyllithium) with stirring. The mixture was stirred at $0^\circ C$ for 1 h and then at $24^\circ C$ for 4 h. Water (10 mL) was added, and then the mixture was washed with water to pH = 7. Solvent was removed and 20 mL THF was added followed by the addition of 8.0 mL 3.0 M NaOAc and 8.0 mL 30% H_2O_2; the mixture was stirred at $24^\circ C$ for 1 h and then at 40–$50^\circ C$ for 1 h. The mixture was diluted with 40 mL Et_2O and then washed with water (4×10 mL), 10 mL brine, and dried over $MgSO_4$. The solvent was removed, and the residue was distilled at 64–$66^\circ C$ (0.5 mmHg) to afford 2.42 g the desired ketone in a yield of 76%, m.p., $38^\circ C$.

Other references related to the Brown hydroboration are cited in the literature.[37] Note that more than 500 references to this procedure can be found.

H. REFERENCES

1. Brown, H. C.; Schlesinger, H. I. and Burg, A. B., *J. Am. Chem. Soc.,* **1939**, *61*, 673.
2. (a) Brown, H. C., *J. Am. Chem. Soc.,* **1956**, *78*, 2583. (b) Brown, H. C. and Rao, B. C. S., *J. Am. Chem. Soc.,* **1956**, *78*, 5694.
3. Brown, H. C. and Rao, B. C. S., *J. Am. Chem. Soc.,* **1959**, *81*, 6423.
4. Brown, H. C. and Singaram, B., *Acc. Chem. Res.,* **1988**, *21*, 287.
5. Rangaishenvi, M. V.; Singaram, B. and Brown, H. C., *J. Org. Chem.,* **1991**, *56*, 3286.
6. (a) Dhokte, U. P.; Pathare, P. M.; Mahindroo, V. K. and Brown, H. C., *J. Org. Chem.,* **1998**, *63*, 8276. (b) Brown, H. C. and Rao, B. C. S., *J. Org. Chem.,* **1957**, *22*, 1135, 1136.
7. Brown, H. C.; Berbrugge, C. and Snyder, C. H., *J. Am. Chem. Soc.,* **1961**, *83*, 1001.
8. Singaram, B.; Rangaishenvi, M. V.; Brown, H. C.; Goralski, C. T. and Hasha, D. L., *J. Org. Chem.,* **1991**, *56*, 1543.
9. (a) Kanth, J. V. B., *Aldrichimica Acta*, **2002**, *35*, 57. (b) Brown, H. C., *Aldrichimica Acta*, **1974**, *7*, 43. (c) Nussium, M.; Mazur, Y. and Sondheimer, F., *J. Org. Chem.,* **1964**, *29*, 1131. (d) Nussium, M.; Mazur, Y. and Sondheimer, F., *J. Org. Chem.,* **1964**, *29*, 1120.
10. Vice, S.; Bara, T.; Bauer, A.; Evans, C. A.; Ford, J.; Josien, H.; McCombie, S.; Miller, M.; Nazareno, D.; Palani, A. and Tagat, J., *J. Org. Chem.*, **2001**, *66*, 2487.
11. (a) Negishi, E. and Brown, H. C., *Synthesis,* **1974**, *2*, 77. (b) Brown, H. C. and Negishi, E., *J. Am. Chem. Soc.,* **1967**, *89*, 5285.

12. Kulkarni, S. U.; Lee, H. D. and Brown, H. C., *J. Org. Chem.,* **1980**, *45*, 4542.
13. Schwier, J. R. and Brown, H. C., *J. Org. Chem.,* **1993**, *58*, 1546.
14. Ramachandran, P. V.; Jennings, M. P. and Brown, H. C., *Org. Lett.,* **1999**, *1*, 1399.
15. Pereira, S. and Srebnik, M., *J. Am. Chem. Soc*., **1996**, *118*, 909.
16. Masamune, S.; Kim, B. M.; Petersen, J. S.; Sato, T.; Veenstra, S. J. and Imai, T., *J. Am. Chem. Soc.,* **1985**, *107*, 4549.
17. Brown, H. C., *J. Organometal. Chem.,* **1995**, *500*, 1.
18. Brown, H. C. and Zweifel, G., *J. Am. Chem. Soc.,* **1961**, *83*, 486.
19. Dhokte, U. P. and Brown, H. C., *Organometallics,* **1996**, *15*, 3504.
20. Zaidlewicz, M.; Kanth, J. V. B. and Brown, H. C., *J. Org. Chem.,* **2000**, *65*, 6697.
21. Brown, H. C. and Mandal, A. K., *J. Org. Chem.,* **1992**, *57*, 4970.
22. (a) Brown, H. C.; Zaidlewicz, M.; Dalvi, P. V. and Biswas, G. K., *J. Org. Chem.,* **2001**, *66*, 4795. (b) Brown, H. C. and Ravindran, N., *Inorg. Chem.,* **1977**, *16*, 2938.
23. Brown, H. C. and Murray, L. T., *Inorg. Chem.,* **1984**, *23*, 2746.
24. (a) Brown, H. C. and Singaram, B., *Inorg. Chem.,* **1980**, *19*, 455. (b) Brown, H. C. and Singaram, B., *Inorg. Chem.,* **1979**, *18*, 53. (c) Brown, H. C.; Singaram, B. and Schwier, J. R., *Inorg. Chem.,* **1979**, *18*, 51.
25. Brown, H. C. and Kulkarni, S. U., *Inorg. Chem.,* **1977**, *16*, 3090.
26. Brown, H. C.; Kanth, J. V. B.; Dalvi, P. V. and Zaidlewicz, M., *J. Org. Chem.,* **2000**, *65*, 4655.
27. Brown, H. C.; Kanth, J. V. B.; Dalvi, P. V. and Zaidlewicz, M., *J. Org. Chem.,* **1999**, *64*, 6263.
28. Brown, H. C.; Zaidlewicz, M. and Dalvi, P. V., *Organometallics,* **1998**, *17*, 4202.
29. Brown, H. C.; Kanth, J. V. B. and Zaidlewicz, M., *J. Org. Chem.,* **1998**, *63*, 5154.
30. Brown, H. C.; Kanth, J. V. B. and Zaidlewicz, M., *Organometallics*, **1999**, *18*, 1310.
31. Brown, H. C. and Soderquist, J. A., *J. Org. Chem.,* **1980**, *45*, 846.
32. Burgess, K. and Ohlmeyer, M. J., *Chem. Rev.,* **1991**, *91*, 1179.
33. Mannig, D. and Noth, H., *Angew. Chem., Int. Ed. Eng.,* **1985**, *24*, 878.
34. (a) Crudden, C. M. and Edwards, D., *Eur. J. Org. Chem.,* **2003**, 4695. (b) Brown, H. C. and Ramachandran, P. V., "Asymmetric Catalysis Using Heterobimetallic Compounds" in *Advances in Asymmetric Synthesis*, ed. Hassner, A., JAI Press, Greenwich, Conn., **1995**, *1*, pp. 147–210. (c) Brown, H. C. and Ramachandran, P. V., *Pure & Appl. Chem.,* **1994**, *66*, 201. (d) Burgess, K. and Ohlmeyer, M. J., *Adv. Chem. Ser.,* **1992**, *230*, 163. (e) Brown, H. C. and Ramachandran, P. V., *Pure & Appl. Chem.,* **1991**, *63*, 307. (f) Smith, K. and Pelter, A., *Comp. Org. Syn.,* **1991**, *8*, 703–731. (g) Brown, H. C., *Tetrahedron,* **1981**, *37*, 3547. (h) Brown, H. C., *Synthesis via Boranes,* John Wiley & Sons, New York, **1975**. (i) House, H. O., *Modern Synthetic Reactions*, 2nd ed., W. A. Benjamin, Menlo Park, Calif., **1972**, pp. 106–130. (j) Brwon, H. C., *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, N.Y., **1972**. (k) Zweifel, G. and Brown, H. C., *Org. React.,* **1963**, *13*, 1–54.
35. Beletskaya, I. and Pelter, A., *Tetrahedron,* **1997**, *53*, 4957.
36. Kanth, J. V. B. and Brown, H. C., *J. Org. Chem.,* **2001**, *66*, 5359.
37. (a) Carter, K. D. and Panek, J. S., *Org. Lett.,* **2004**, *6*, 55. (b) Kezuka, S.; Ikeno, T. and Yamada, T., *Org. Lett.,* **2003**, *5*, 1841. (c) Bayer, M. J.; Pritzkow, H. and Siebert, W., *Z. Naturforsch.,* **2002**, *57b*, 295. (d) Laschober, G.; Zorzi, M. and Hodgetts, K. J., *Molecules,* **2001**, *6*, 244. (e) Kanth, J. V. B. and Brown, H. C., *Org. Lett.,* **1999**, *1*, 315. (f) Barrett, A. G.; Bennett, A. J.; Menzer, S.; Smith, M. L.; White, A. J. P. and Williams, D. J., *J. Org. Chem.,* **1999**, *64*, 162. (g) Dhokte, U. P. and Brown, H. C., *Organometallics,* **1998**, *17*, 2891. (h) Hanson, J. R.; Liman, M. D. and Nagaratnam, S., *J. Chem. Res. (S)*, **1997**, 282. (i) Parish, E. J.; Kizito, S. A. and Sun, H., *J. Chem. Res. (S)*, **1997**, 64. (j) Dhokte, U. P. and Brown, H. C., *J. Org. Chem.,* **1997**, *62*, 865.

(k) Dhokte, U. P.; Kulkarni, S. V. and Brown, H. C., *J. Org. Chem.,* **1996**, *61*, 5140. (l) Brown, H. C.; Mahindroo, V. K. and Dhokte, U. P., *J. Org. Chem.,* **1996**, *61*, 1906. (m) Gung, B. W.; Ohm, K. W. and Smith, D. T., *Synth. Commun.,* **1994**, *24*, 167. (n) Brown, H. C. and Dhokte, U. P., *J. Org. Chem.,* **1994**, *59*, 2025. (o) Brown, H. C. and Dhokte, U. P., *J. Org. Chem*., **1994**, *59*, 2365. (p) Brown, H. C. and Dhokte, U. P., *J. Org. Chem.,* **1994**, *59*, 5479. (q) Dhokte, U. P. and Brown, H. C., *Tetrahedron Lett.,* **1994**, *35*, 4715. (r) Srebnik, M.; Cole, T. E. and Brown, H. C., *J. Org. Chem*., **1990**, *55*, 5051. (s) Brown, H. C.; Weissman, S. A.; Perumal, P. T. and Dhokte, U. P., *J. Org. Chem.,* **1990**, *55*, 1217. (t) Brown, H. C.; Mandal, A. K.; Yoon, N. M.; Singaram, B.; Schwier, J. R. and Jadhav, P. K., *J. Org. Chem.,* **1982**, *47*, 5069. (u) Brown, H. C.; Jadhav, P. K.; Mandal, A. K., *J. Org. Chem.,* **1982**, *47*, 5074. (v) Brown, H. C. and Yoon, N. M., *J. Am. Chem. Soc.,* **1977**, *99*, 5514. (w) Pelter, A,; Smith, K.; Hutchings, M. G. and Rowe, K., *J . Chem. Soc*.,*Perkrn Trans. I,* **1975**, 129. (x) Brown, H. C.; Hamaoka, T. and Ravindran, N., *J. Am. Chem. Soc.,* **1973**, *95*, 5786. (y) Brown, H. C.; Gary, C. P. and Liu, K.-T., *J. Org. Chem*., **1971**, 36, 387. (z) Brown, H. C. and Rogic, M. M., *J. Am. Chem. Soc.,* **1969**, *91*, 2146. (aa) Brown, H. C. and Rathke, M. W., *J. Am. Chem. Soc.,* **1967**, *89*, 2737. (bb) Brown, H. C.; Ayyangar, N. R. and Zweifel, G., *J. Am. Chem. Soc.* **1964**, *86*, 397. (cc) Devaprabhakara, D. and Gardner, P. D*., J. Am. Chem. Soc.,* **1963**, *85*, 1458. (dd) Brown, H. C. and Gary, C. P., *J. Am. Chem. Soc*., **1961**, *83*, 2951, 2952. (ee) Brown, H. C. and Tsukamoto, A., *J. Am. Chem. Soc.,* **1960**, *82*, 746. (ff) Brown, H. C. and Zweifel, G., *J. Am. Chem. Soc.,* **1960**, *82*, 3223. (gg) Brown, H. C. and Zweifel, G., *J. Am. Chem. Soc*., **1959**, *81*, 247. (hh) Sondheimer, F. and Wolfe, S., *Can. J. Chem*., **1959**, *37*, 1870. (ii) Brown, H. C. and Zweifel, G., *J. Am. Chem. Soc.,* **1959**, *81*, 5832. (jj) Brown, H. C. and Murray, K., *J. Am. Chem. Soc.,* **1959**, *81*, 4108. (kk) Brown, H. C. and Rao, B. C. S., *J. Am. Chem. Soc.,* **1959**, *81*, 6428.

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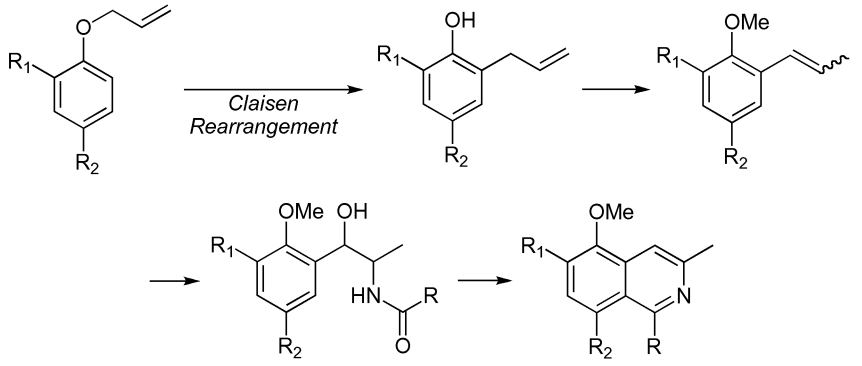
Bruckner Isoquinoline Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction may be traced back to 1935 when Bruckner reported the structure of 1,3-dimethyl-6,7-methylenedioxyisoquinoline.[1] The reaction is a unique method for synthesizing isoquinolines from allyl phenyl ether via the process of a *Claisen Rearrangement*, double-bond migration, amination, and cyclization.[2]

B. GENERAL REACTION SCHEME



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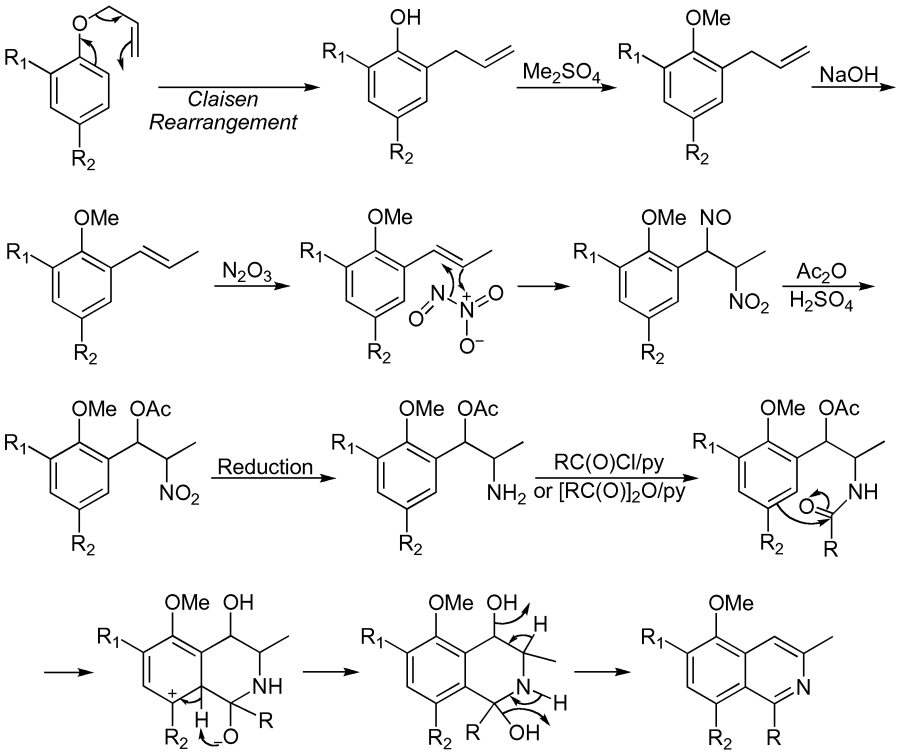
C. PROPOSED MECHANISMS

Displayed below is the reaction mechanism proposed by Govindachari and Pai.[2]



D. MODIFICATION

This reaction has been modified by using either phenyl oxazoline[3] or substituted benzaldehyde and nitroethane[4] as the starting materials for preparing isoquinoline.

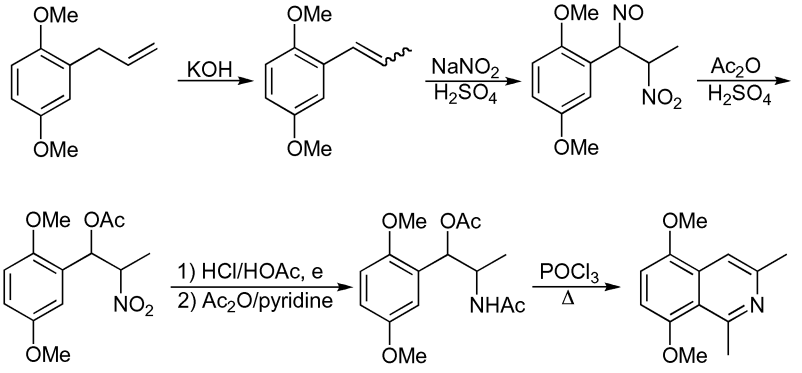
E. APPLICATIONS

This reaction can be used to synthesize the substituted isoquinolines.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 2.

Preparation of 2,5-Dimethoxypropenylbenzene

2,5-Dimethoxyallylbenzene was treated with a solution of potassium hydroxide in ethylene glycol at 170–175°C for 3 h to give 85% 2,5-dimethoxypropenylbenzene, b.p. 126°C (13 mmHg).

Preparation of 2,5-Dimethoxypropenylbenzene Pseudonitrosite

A solution of 1 g freshly distilled 2,5-dimethoxypropenylbenzene in 10 mL ether was treated with a solution of 21 g sodium nitrite in 8 mL water. Then 10 mL 4 N H_2SO_4 was added dropwise over 20 min. The solution turned green and then yellow, and a white crystalline solid appeared. It was left in an ice chest overnight, and the precipitate was filtered, washed with ether, then water, and dried in air. A total of 20 such experiments run simultaneously yielded 18 g 2,5-dimethoxypropenylbezneen pseudonitrosite, m.p. 130°C (dec.).

Formation of α-(2,5-Dirnethoxyphenyl)-β-Nitropropanol Acetate

A suspension of 7 g finely powdered pseudonitrosite in 20 mL acetic anhydride was cooled in ice and treated gradually, with good stirring, with 2 mL acetic anhydride containing a drop of concentrated sulfuric acid. The pseudonitrosite dissolved with evolution of nitrous fumes. After 2 h, the solution was poured onto ice water, the acetic anhydride was decomposed, and the emulsion was extracted with ether. The ether extract was dried and the ether extract was removed, yielding 7 g of a colorless syrupy oil, which could not be induced to crystallize. Attempts at purification by distillation in vacuo led to extensive decomposition.

Preparation of α-(2,5-Dimethoxyphenyl)-β-Acetylaminopropanol

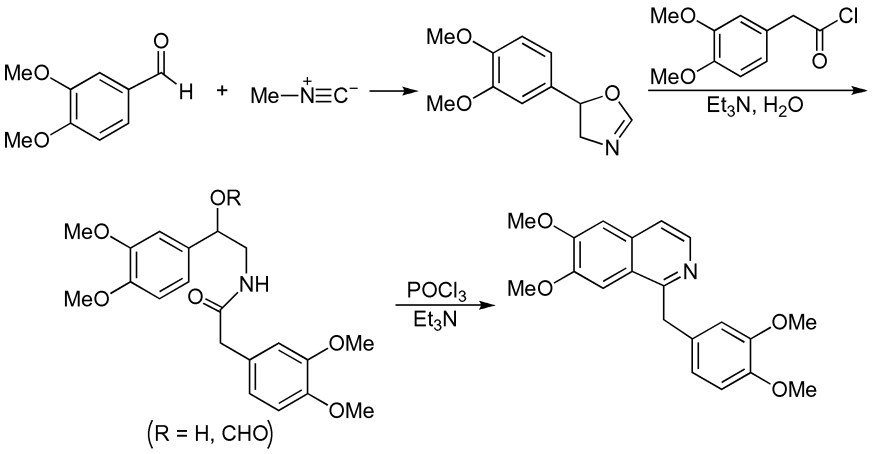
A solution of 7 g nitropropanol acetate in 100 mL alcohol, 50 mL glacial acetic acid, and 3 mL concentrated hydrochloric acid was reduced at a mercury cathode with the temperature kept below 60°C. At the end of the reduction, the solution was made neutral to Congo Red by the addition of sufficient sodium acetate and evaporated to dryness in vacuo at 50°C.

The residue was dissolved in 50 mL water and saturated with sodium bicarbonate. On standing in the ice chest overnight, the acetylamino compound separated. It was filtered, washed with a little water, and dried. Recrystallization from alcohol yielded 3.1 g α-(2,5-dimethoxyphenyl)-β-acetylaminopropanol, m.p. 156°C.

Acetylation of α-(2,5-dimethoxyphenyl)-β-acetylaminopropanol with acetic anhydride in pyridine at room temperature yielded α-(2,5-dimethoxyphenyl)-α-acetoxy-β-acetylaminopropane, melting at 98–100°C after recrystallization from benzene.

Formation of 1,3-Dimethyl-6,8-Dimethoxyisoquinoline

A solution of 1 g acetylamino compound in 10 mL dry toluene was treated with 3 mL phosphorus oxychloride and refluxed for 75 min, with exclusion of moisture. The solution was then poured into ice water, and the excess phosphorus oxychloride was decomposed by gentle warming on a water bath. A fluorescent orange-yellow solution was obtained, which was cooled strongly in ice and basified with sodium hydroxide solution. The isoquinoline was extracted with ether, and the ether extract was dried over potassium carbonate. Removal of the ether yielded 0.75 g of a thick oil, which was dissolved in dry benzene and passed through a column of 30 g alumina. On washing the column with benzene, a yellow zone moved rapidly into the filtrate. This fraction of the eluate on removal of benzene yielded 0.65 g of a pale yellow oil, which solidified on rubbing. Recrystallization from petroleum ether yielded pale yellow silky needles, melting at 70°C.



Reference 3.

n-BuLi (74.5 mmol) was added dropwise over 20 min to a -78°C solution of 75 mmol methyl isocyanidee in 200 mL anhydrous THF. After 40 min, 73.5 mmol veratraldehyde in 120 mL THF was slowly added to the yellow suspension of α-lithiomethyl isocyanide at such a rate that the temperature did not exceed −60°C. Stirring was continued for 30 min, then 2 mL MeOH was added, and the whole mixture was allowed to warm to room temperature. Extraction and crystallization in Et_2O yielded 13.0 g 5-(3,4-dimethoxyphenyl)-2-oxazoline in a yield of 85%, m.p. 49–50°C.

3,4-Dimethoxyphenyl acetyl chloride (414 mg, 1.93 mmol) in 18 mL dry CH_2Cl_2 was added dropwise to a solution of 400 mg 5-(3,4-dimethoxyphenyl)-2-oxazoline (1.93 mmol) in 20 mL dry CH_2Cl_2. After 30 min, 35 mg water (1 eq.) and 195 mg triethylamine (1 eq.) in

1.5 mL dry THF were added slowly. The hydrolysis products were extracted after 30 min, washed with brine, and evaporated. NMR analysis showed a 2.2:1 mixture of alcohol and ester that could be isolated via column chromatography. The ester melted at 166–167°C, and the alcohol melted at 126°C. The formate was hydrolyzed with $NaHCO_3$ in aqueous THF for 3 h.

$POCl_3$ (580 mg) was added dropwise to a refluxing solution of the above crude product of formate and alcohol in CH_3CN. After 1 h, the mixture was cooled, poured into ice water, washed with Et_2O, basified with 2 N NH_4OH, and extracted with EtOAc. Chromatography gave 371 mg papaverine, in a yield of 57% from oxazoline.

Other references related to the Bruckner isoquinoline synthesis are cited in the literature.[5]

H. REFERENCES

1. Bruckner, V. and Kardos, V., *Ann.,* **1935**, *518*, 226.
2. Govindachari, T. R. and Pai, B. R., *J. Org. Chem.,* **1953**, *18*, 1253.
3. Falck, J. R.; Manna, S. and Mioskowski, C., *J. Org. Chem.,* **1981**, *46*, 3742.
4. Shepard, E. R.; Noth, J. F.; Porter, H. D. and Simmans, C. K., *J. Am. Chem. Soc.,* **1952**, *74*, 4611.
5. (a) Fodor, G.; Bruckner, V.; Kiss, J. and Kovács, J., *J. Am. Chem. Soc.,* **1949**, *71*, 3694. (b) Bruckner, V.; Fodor, G.; Kovács, J. and Kiss, J., *J. Am. Chem. Soc.,* **1948**, *70*, 2697. (c) Bruckner, V.; Fodor, G.; Kiss, J. and Kovács, J., *J. Chem. Soc.,* **1948**, 885. (d) Govindachari, T. R.; Pai, B. R. and Rao, U. R., *Proc. Indian Acad. Sci., Sect. A,* **1958**, *48A*, 111. (e) Bruckner, V. and Fodor, G., *Ber.,* **1943**, *76*, 466. (f) Bruckner, V. and Fodor, G., *Ber.,* **1938**, *71*, 541. (g) Bruckner, V. and Fodor, G., *Ber.,* **1938**, *71*, 547. (h) Bruckner, V. and Krámli, A., *J. Prakt. Chem.,* **1936**, *145*, 291.

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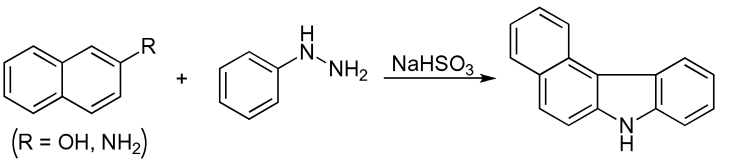
Bucherer Carbazole Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Bucherer in 1906.[1] It is the synthesis of carbazoles from aryl hydrazines, sodium bisulfite, and 1- or 2-naphthols (or 1- or 2-naphthylamines)[2] and is generally known as the Bucherer carbazole synthesis[3] or Bucherer reaction.[4] In addition, the reaction between 2-aminonaphthalene-1-sulfonic acid and phenylhydrazine also gives carbazole,[5] indicating that sulfonation of naphthylamine might be the early step in the reaction pathway. This reaction has been most commonly used hitherto for the preparation of dibenzocarboles.[6]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A tentative mechanism is proposed for this reaction.

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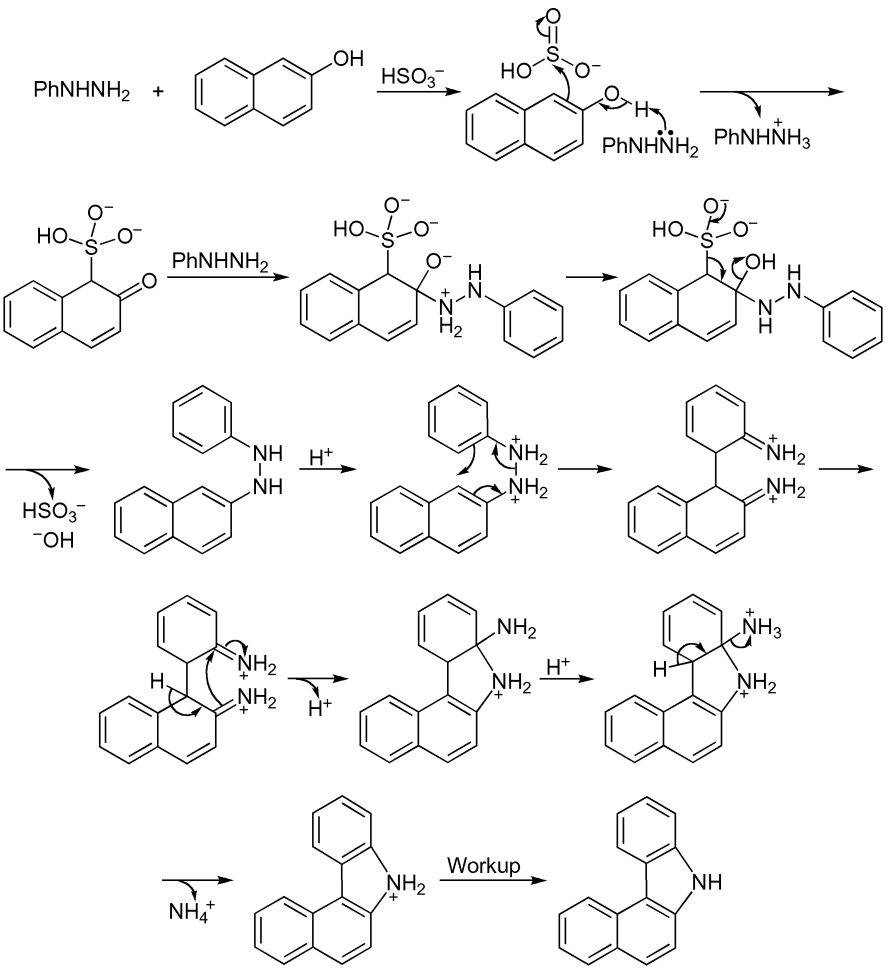


D. MODIFICATION

This reaction has been modified by using aryl hydrazine and tetralone in the presence of HCl to form carbazole.[6]

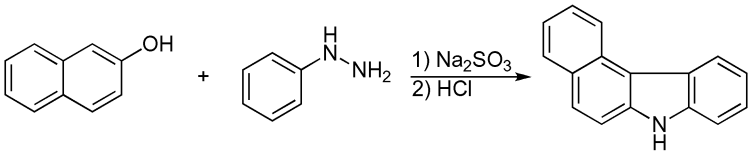
E. APPLICATIONS

This reaction is useful for the preparation of fused carbazole derivatives.

F. RELATED REACTIONS

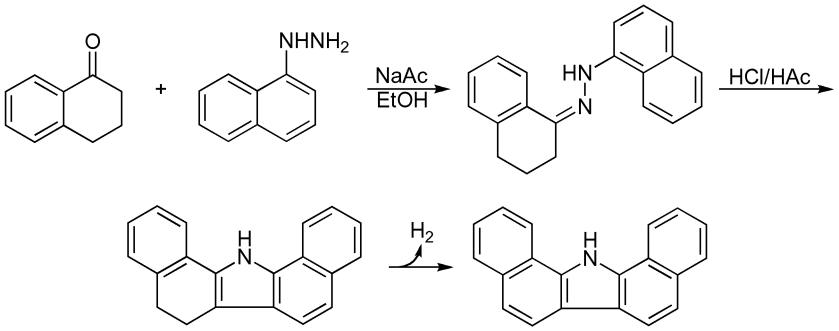
This reaction is related to the *Borsche-Drechsel Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

2-Naphthol (14.4 g, 0.10 mol) and 10.8 g phenylhydrazine (0.10 mol) were refluxed in 250 mL 36% sodium sulfite solution for 17 h. The reaction mixture was then treated with 200 mL concentrated hydrochloric acid under reflux for 2.5 h. The oily layer that separated was isolated by decanting the upper aqueous layer and was triturated with ether to give a red-brown solid. The solid was extracted with sodium hydroxide solution and filtered. The remaining yellow solid was dried and sublimed (100°C), and the sublimate was recrystallized from aqueous methanol to give 2.5 g 3,4-benzocarbazole as white needles (11.5 mmol), in a yield of 11.5%, m.p. 136–137°C.



Reference 6.

A mixture of 2.6 g α-tetralone, 4.0 g α-naphthylhydrazine hydrochloride, and 3.0 g sodium acetate was refluxed with 50 mL ethanol for 2 h. After cooling, an excess of water was added; the precipitate of the crude naphthylhydrazone was collected by suction, washed with water, and dissolved in 20 mL of the cyclization reagent (acetic acid and hydrogen chloride). After 5 min of heating on a water bath, the mixture was poured into water and the precipitate was washed thoroughly with water, dried, and crystallized from the mixture of benzene and ligroin to afford 2.5 g 3,4-dihydro-1,2,7,8-dibenzocarbazole, m.p., 178°C.

A mixture of 1.2 g 3,4-dihydro-1,2,7,8-dibenzocarbazole, 1.7 g chloranil, and 30 mL dry xylene was refluxed for 2 h. After cooling, the tetrachlorohydroquinone was filtered off by suction and washed with some xylene; the filtrate was shaken with a 10% aqueous solution of sodium hydroxide and then with water, and dried over calcium chloride. After the evaporation of xylene in a vacuum, the residue obtained was recrystallized twice from benzene, giving 1.0 g 1,2,7,8-dibenzocarbazole as pale yellowish needles, m.p. 212°C.

Other references related to the Bucherer carbazole synthesis are cited in the literature.[8]

H. REFERENCES

1. (a) Bucherer, H. T. and Grollé, A., *Ber.,* **1906**, *39*, 986. (b) Bucherer, H. T. and Seyde, F., *J. Prakt. Chem.,* **1908**, *77*, 403.
2. Robinson, B., *Chem. Rev.,* **1968**, *68*, 227.
3. Monatsber, H. S., *Monat. Deut. Akad. Wiss. Berlin*, **1961**, *3*, 48.
4. (a) Seeboth, H., *Angew. Chem. Int. Ed. Engl.,* **1967**, *6*, 307. (b) Seeboth, H.; Baerwolff, D. and Becker, B., *Ann.,* **1965**, *683*, 85. (c) Seeboth, H., *Monat. Deut. Akad. Wiss. Berlin,* **1964**, *6*, 268. (d) Rieche, A. and Seeboth, H., *Ann.,* **1960**, *638*, 81. (e) Fuchs, W. and Niszel, F., *Ber.,* **1927**, *60B*, 209.
5. Buu-Hoï, N. P.; Hoán, N. and Khoï, N. H., *J. Org. Chem.,* **1950**, *15*, 131.
6. Buu-Hoï, N. P.; Hoán, N. and Khoï, N. H., *J. Org. Chem.,* **1950**, *15*, 492.
7. Roberts, D. R. and White, E. H., *J. Am. Chem. Soc.,* **1970**, *92*, 4861.
8. (a) Allen, G. R.; Pidacks, C. and Weiss, M. J., *J. Am. Chem. Soc.,* **1966**, *88*, 2536. (b) Seeboth, H. and Rieche, A., *Ann.,* **1964**, *671*, 77. (c) Holt, P. F. and McNae, C. J., *J. Chem. Soc.,* **1964**, 1759. (d) Rieche, A. and Seeboth, H., *Ann.,* **1960**, *638*, 43. (e) Drake, N. L., *Org. React.*, **1942**, *1*, 114. (f) Fuchs, W. and Niszel, F., *Ber.,* **1927**, *60B*, 213. (g) Bucherer, H. T. and Sonnenburg, E. F., *J. Prakt. Chem.,* **1910**, *81*, 29. (h) Bucherer, H. T. and Sonnenburg, E. F., *J. Prakt. Chem.,* **1910**, *81*, 6.

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Bucherer Reaction

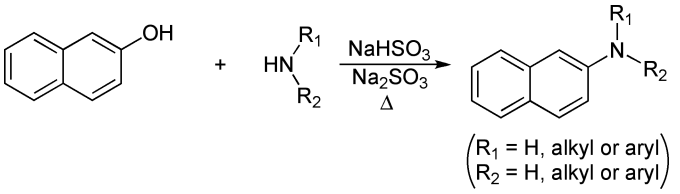
A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Bucherer in 1904.[1] It is a reaction for synthesizing β-naphthylamine from β-naphthol and aqueous ammonium sulfite or bisulfite via the formation of tetralone-sulfonic and tetralone-iminosulfonic acids and is generally known as the Bucherer reaction.[2] Although α-naphthylamine can also be prepared in a similar fashion, the corresponding reaction is much more difficult because of the steric interaction with *peri*-position.[3] It is know that the key step of this reaction is the ketonization of naphthol.[4] When 1,7-dihydroxynaphthalene is treated with a large excess of ammonia at 250°C, both aminonaphthol and diaminonaphthalene will form, but the major product is still the aminonaphthol;[5] however, the addition of sodium hydroxide into the solution will decrease the amount of diaminonaphthalene.[3] Only one hydroxyl group of binaphthol will be converted into an amino group to form NOBIN.[6] When primary or secondary amine is used in this reaction, *N*-substituted β-naphthylamine will form,[3,7] and α-amino acid can be readily linked to a naphthalene ring by the Bucherer reaction as well.[8] In contrast to this reaction, naphthol can also be converted into naphthylamine in a reaction with a complex of ammonia and Lewis acid, such as $CaCl_2$[9] or $ZnCl_2$.[10]

B. GENERAL REACTION SCHEME

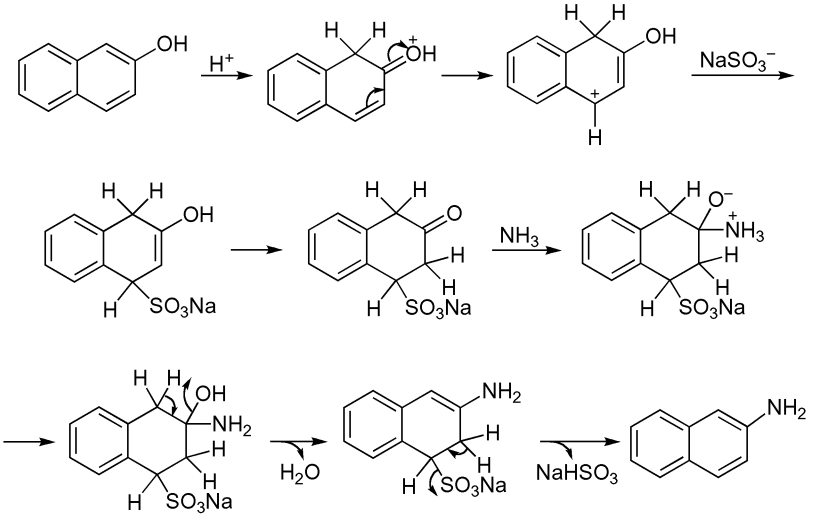
The general reaction is illustrated, including the reaction with ammonia and primary and secondary amines.

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang



C. PROPOSED MECHANISMS

Amination of β-naphthol with ammonia in the presence of sodium sulfite is shown below.



D. MODIFICATION

The amination of naphthalene using primary or secondary amines is one type of modification,[3,7] and the treatment of naphthol with a complex of Lewis acid and ammonia is another modification.[10] The latter was reported before the Bucherer reaction was published.

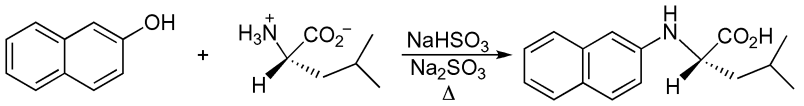
E. APPLICATIONS

This reaction is generally used to convert naphthols into naphthylamines.

F. RELATED REACTIONS

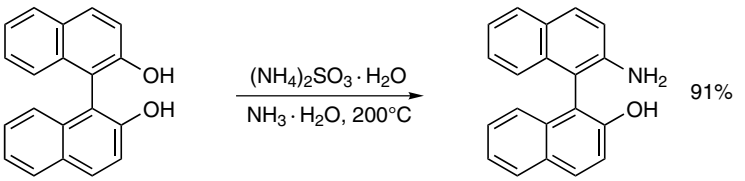
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 8.

A mixture of 10 g L-leucine (76 mmol), 11 g β-naphthol (76 mmol), and 9.6 g anhydrous Na_2SO_3 (76 mmol) was placed in a pressure vessel equipped with a magnetic stirring bar. Saturated $NaHSO_3$ solution (60 mL) was added; the bottle was sealed and heated slowly to 115°C while being stirred. After 1 day, two homogeneous layers formed. Heating and stirring were continued for 3 additional days. After being cooled, the bottle was emptied into a 1000-mL beaker and rinsed alternately with 5% $NaHCO_3$ and acetone. The combined washes and reaction mixture were diluted to 500 mL with water, the pH was adjusted to 8.5–9.0 with saturated Na_2CO_3 solution, and the mixture was washed twice with 60-mL portions of dichloromethane. The organic phase was back washed with two 60-mL portions of 5% $NaHCO_3$ solution, which were combined with the original aqueous phase. The 2-naphthol-containing organic phase may then be discarded or the unreacted 2-naphthol may be recovered. The aqueous phase was adjusted to pH 3 with 6 N hydrochloric acid (SO_2 and CO_2 were evolved). The resultant white precipitate was collected and washed with 50 mL ethyl acetate. The aqueous phase was extracted with two 50-mL portions of ethyl acetate and was then either discarded or evaporated to recover unreacted amino acid. The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The remaining solids were recrystallized from 95% ethanol to afford 4.8 g of (S)-(-)-α-*N*-(2-naphthyl)leucine as white crystals in a yield of 25%, m.p. 173°C.



Reference 6.

To a 125-mL Teflon-lined autoclave was added 5.0 g 1,1′-bi-2-naphthol (17.5 mmol), 23.5 g $(NH_4)_2SO_3 \cdot H_2O$ (175 mmol), and 65 mL of concentrated aqueous ammonia. The mixture was stirred at 200°C in an oil bath for 5 days. It was then cooled down to ambient temperature and filtered. The resulting solid was washed with water followed by recrystallization from benzene to afford 4.5 g pure 2-amino-2′-hydroxy-1,1′-binaphthyl, in a yield of 91%.

Other references related to the Bucherer reaction are cited in the literature.[11]

H. REFERENCES

1. Bucherer, H. T., *J. Prakt. Chem.,* **1904**, *69*, 49.
2. (a) Budzikiewicz, H., *Mini-Rev. Org. Chem.,* **2006**, *3*, 93. (b) Canete, A.; Melendrez, M. X.; Saitz, C. and Zanocco, A. L., *Synth. Commun.,* **2001**, *31*, 2143. (c) Kost, A. N.; Terenin, V. I. and Yudin,

L. G., *Khim. Geterotsiklicheskikh Soedinenii*, **1979**, 786. (d) Seeboth, H. and Becker, B., *Ann.,* **1966**, *693*, 201. (e) Seeboth, H.; Neumann, H. and Goersch, H., *Ann.,* **1965**, *683*, 93. (f) Seeboth, H.; Baerwolff, D. and Becker, B., *Ann.,* **1965**, *683*, 85. (g) Seeboth, H. and Rieche, A., *Ann.,* **1964**, *671*, 77. (h) Seeboth, H. and Rieche, A., *Ann.,* **1964**, *671*, 70. (i) Rieche, A. and Seeboth, H., *Ann.,* **1960**, *638*, 101. (j) Rieche, A. and Seeboth, H., *Ann.,* **1960**, *638*, 92. (k) Rieche, A. and Seeboth, H., *Ann.,* **1960**, *638*, 81. (l) Rieche, A. and Seeboth, H., *Ann.,* **1960**, *638*, 76. (m) Rieche, A. and Seeboth, H., *Ann.,* **1960**, *638*, 66. (n) Rieche, A. and Seeboth, H., *Ann.,* **1960**, *638*, 57. (o) Rieche, A. and Seeboth, H., *Ann.,* **1960**, *638*, 43. (p) Cowdrey, W. A., *J. Chem. Soc.,* **1946**, 1046. (q) Cowdrey, W. A., *J. Chem. Soc.,* **1946**, 1044. (r) Cowdrey, W. A., *J. Chem. Soc.,* **1946**, 1041.

3. Ross, D. L. and Chang, J. J., *J. Org. Chem.,* **1964**, *29*, 1180.
4. Balasubramaniyan, V., *Chem. Rev.,* **1966**, *66*, 567.
5. Kozlov, V. V. and Veselovskaya, I. K., *Zh. Obsh. Khim.,* **1961**, *31*, 3030. [*Chem. Abstr.,* **1962**, *57*, 739].
6. Körber, K.; Tang, W. J.; Hu, X. Q. and Zhang, X. M., *Tetrahedron Lett.,* **2002**, *43*, 7163.
7. Werbel, L. M.; Capps, D. B.; Elslager, E. F.; Pearlman, W.; Short, F. W.; Weinstein, E. A. and Worth, D. F., *J. Med. Chem.,* **1963**, *6*, 637.
8. Pirkle, W. H. and Pochapsky, T. C., *J. Org. Chem.,* **1986**, *51*, 102.
9. Leonard, N. J. and Hyson, A. M., *J. Am. Chem. Soc.,* **1949**, *71*, 1392.
10. (a) Phillis, J. P., *Chem. Rev.,* **1956**, *56*, 271. (b) Bedall, C. and Fischer, O., *Ber.,* **1881**, *14*, 2570.
11. (a) Kočovský, P.; Vyskočil, S. and Smrčina, M., *Chem. Rev.,* **2003**, *103*, 3213. (b) González, C. and Castedo, L., "Synthesis of Phenols" in *Chemistry of Phenols*, ed. Rappoport, Z., John Wiley & Sons, Chichester, **2003**, pp. 395–489. (c) Vyskočil, S.; Smrčina, M.; Lorenc, M.; Tišlerová, I.; Brooks, R. D.; Kulagowski, J. J.; Langer, V.; Farrugia, L. J. and Kočovský, P., *J. Org. Chem.,* **2001**, *66*, 1359. (d) Bendig, J.; Sauer, E.; Polz, K. and Schopf, G., *Tetrahedron,* **1992**, *48*, 9207. (e) Selvaraj, S.; Ramakrishnan, P. S. and Arumugam, N., *Recl. Trav. Chim. Pays-Bas,* **1989**, *108*, 36. (f) Gibson, M. S., "The Introduction of the Amino Group" in *The Chemistry of the Amino Group*, ed. Patai, S., Interscience, London, **1968**, p. 37. (g) Seeboth, H., *Angew. Chem. Int. Ed. Engl.,* **1967**, *6*, 307. (h) Allen, C. F. H. and Bell, A., *Org. Synth. Coll.,* **1966**, *3*, 78. (i) Newman, M. S. and Blum, J., *J. Am. Chem. Soc.,* **1964**, *86*, 503. (j) Karandasheva, N. N. and Bogdanov, S. V., *Zh. Obsh. Khim.,* **1955**, *25*, 1152. (k) Miller, L. E.; Hanneman, W. W.; St. John, W. L. and Smeby, R. R., *J. Am. Chem. Soc.,* **1954**, *76*, 296. (l) Corley, R. S. and Blout, E. R., *J. Am. Chem. Soc.,* **1947**, *69*, 755. (m) Hartshorn, E. B. and Baird, S. L., *J. Am. Chem. Soc.,* **1946**, *68*, 1562. (n) Johnson, W. S. and Matthews, F. J., *J. Am. Chem. Soc.,* **1944**, *66*, 210. (o) Drake, N. L., *Org. React.,* **1942**, *1*, 105. (p) Fieser, L. F.; Jacobsen, R. P. and Price, C. C., *J. Am. Chem. Soc.,* **1936**, *58*, 2163. (q) Fuchs, W., *Ber.,* **1926**, *59B*, 1411.

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Bucherer-Bergs Hydantoin Synthesis

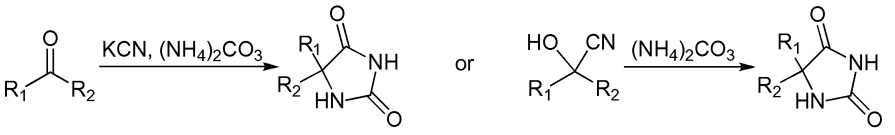
(Bucherer-Bergs Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first observed by Ciamician and Silber in 1905 who obtained 5,5-dimethylhydantoin from a mixture of acetone and hydrocyanic acid that had been exposed to sunlight for a period of 5–7 months.[1] Subsequently, Bergs reported the preparation of 5-substituted hydantoins from the corresponding aldehydes or ketones by treatment with potassium cyanide, ammonium carbonate, and carbon dioxide under several atmospheres of pressure at a temperature of 80°C for 4–6 h.[2] However, it was Bucherer who modified Bergs's procedure for synthesizing hydantoin from cyanohydrin and ammonium carbonate in an aqueous solution or benzene at temperatures below 60–70°C,[3] and studied the mechanism.[4] Therefore, this reaction is generally known as the Bucherer-Bergs reaction.[5] Occasionally, it is also referred to as the Bucherer-Bergs condition,[6] Bucherer-Bergs procedure,[7] Bucherer-Bergs method,[8] and Bucherer-Bergs hydantoin synthesis.[9] This reaction has been further modified by Henze.[10] So the Bucherer-Bergs hydantoin synthesis is the preparation of hydantoin from carbonyl compounds by treatment with 2 eq. potassium cyanide and 4 eq. ammonium carbonate[11] or from the corresponding cyanohydrin and ammonium carbonate. This reaction is one example of the multicomponent reactions (MCRs);[12] however, the carbonyl compounds—including formaldehyde, certain unsaturated aldehydes, certain hydroxy and nitroaryl aldehydes, bisdimethylaminoacetone, and pyruvic acid—are not suitable for this reaction.[11] The hydantoin itself not only demonstrates many biological activities, such as anticonvulsants,[13] antiarrhythmics,[14] antidiabetics,[15] serotonin, and fibrinogen receptor antagonists,[16] but is the starting material for preparing a variety of α-amino acids via hydrolysis.[14a,17]

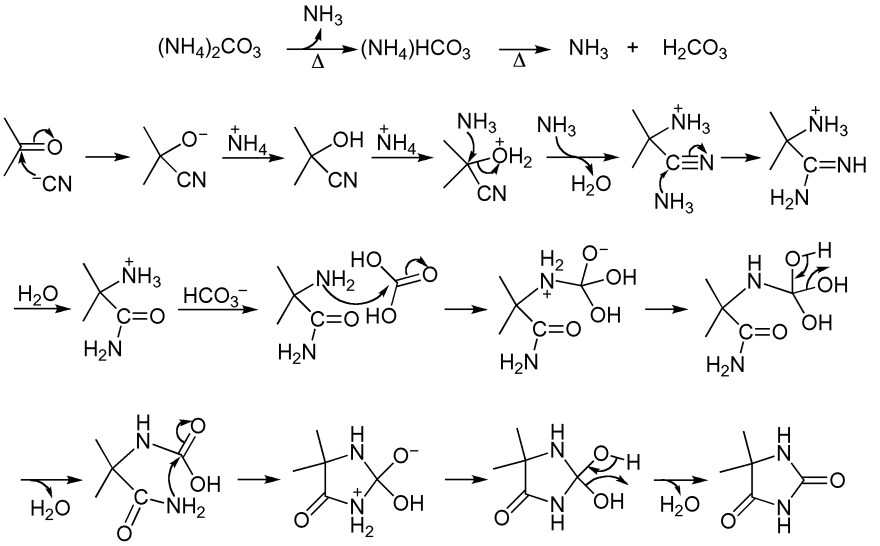
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Details of the reaction mechanism are tentatively shown below.



D. MODIFICATION

This reaction has been modified from acid-catalyzed cyclization of uredo acids;[18] from palladium catalyzed MCR among aldehydes, carbon monoxide, and ureas;[19] and from Ugi five-component condensation.[20] Alternatively, hydantoins can also be synthesized via other methods, such as the *1,3-Dipolar Cycloaddition* of 1-oxa-4-azabutadiene and aryl isocyanates[21] and the decomposition of barbituric acids in alcohol.[8]

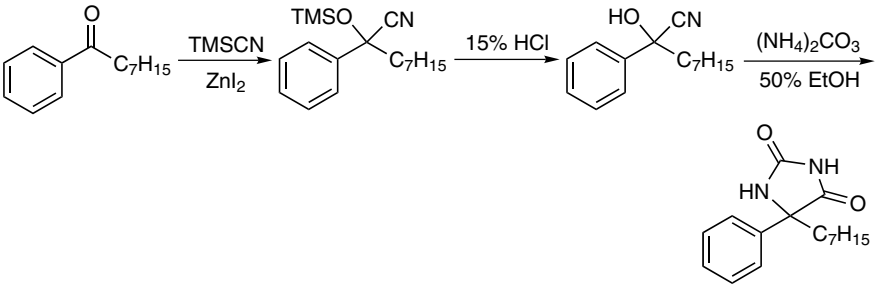
E. APPLICATIONS

This reaction is generally used for the synthesis of substituted hydantoins, which are further used to prepare different α-amino acids.

F. RELATED REACTIONS

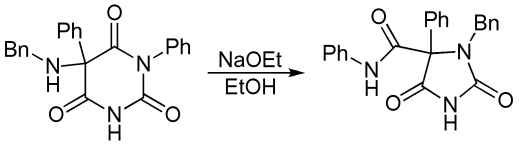
This reaction is related to the *Read Synthesis of Hydantoin* from amino acids and cyanate salts.[22]

G. CITED EXPERIMENTAL EXAMPLES



Reference 23.

A mixture of 1.5 g octanophenone (7.5 mmol), 0.70 g cyanotrimethylsilane (TMSCN) (7.5 mmol), and 5–10 mg ZnI_2 was stirred at room temperature under a nitrogen atmosphere. After 2 h, the TMS ether was hydrolyzed to the cyanohydrin by adding 10 mL ether and 10 mL 15% HCl; the resulting mixture was stirred vigorously for 1 h. The acidic layer was washed with ether (3 × 20 mL). The extracts were combined and evaporated to give 1.8 g cyanohydrin in a yield of 100%. This 1.8 g cyanohydrin (9.0 mmol) and 3.6 g $(NH_4)_2CO_3$ (3.6 mmol) were dissolved in 30 mL 50% ethanol while stirring under a nitrogen atmosphere. The mixture was heated slowly between 40° and 60°C for 12 h. The basic mixture was evaporated to half volume and cooled to room temperature. The precipitate was filtered and recrystallized from hot ethanol to give 0.5 g 5-heptyl-5-phenylhydantoin, in a yield of 21%, m.p. 124–126°C.



Reference 8.

To a solution of 0.18 g sodium (8 mmol) in 27 mL anhydrous ethanol was added 2 mmol 5-benzylamino-1,5-diphenylbarbituric acid. The mixture was refluxed for 3 h under an argon atmosphere. The solution was evaporated to dryness. The residue was taken up with a small amount of water, and insoluble material was removed by filtration. The filtrate was acidified with cold 1 N HCl. The precipitate was filtered off and dried under reduced pressure. If no crystallization was observed, the solution was extracted with ethyl acetate (4 × 5 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated to dryness. The crude oil was dissolved in mixture of ethanol–diethyl ether and cyclohexane. After the solution was cooled for at least 5 days, pure crystals were separated by suction filtration and dried to give 85% 1-benzyl-5-phenyl-5-phenylcarbamoylhydantoin, m.p. 185–195°C.

Other references related to the Bucherer-Bergs hydantoin synthesis are cited in the literature.[24]

H. REFERENCES

1. (a) Ciamician, G. and Silber, P., *Ber.,* **1905**, *38*, 1671. (b) Ciamician, G. and Silber, P., *Ber.,* **1914**, *47*, 1806.
2. Bergs, H., *German Pat*., **1932**, Dec. 14, 566,094 [*Chem. Abstr*., **1933**, *27*, 1001].
3. (a) Bucherer, H. T. and Fischbeck, H., *J. Prakt. Chem.,* **1934**, *140*, 69. (b) Bucherer, H. T. and Brandt, W., *J. Prakt. Chem.,* **1934**, *140*, 129. (c) Bucherer, H. T. and Barsch, H., *J. Prakt. Chem.,* **1934**, *140*, 151.
4. Bucherer, H. T. and Steiner, W., *J. Prakt. Chem.,* **1934**, *140*, 291.
5. (a) Montagne, C. and Shipman, M., *Synlett,* **2006**, 2203. (b) Wermuth, U. D.; Jenkins, I. D.; Bott, R. C.; Byriel, K. A. and Smith, G., *Aust. J. Chem.,* **2004**, *57*, 461. (c) Micova, J.; Steiner, B.; Koos, M.; Langer, V. and Gyepesova, D., *Carbohydr. Res.,* **2003**, *338*, 1917. (d) Mičová, J.; Steiner, B.; Koóš, M.; Langer, V. and Gyepesová, D., *Synlett,* **2002**, 1715. (e) Wyzlic, I. M.; Tjarks, W.; Soloway, A. H.; Perkins, D. J.; Burgos, M. and O'Reilly, K. P., *Inorg. Chem.,* **1996**, *35*, 4541. (f) Tanaka, K.-I.; Iwabuchi, H. and Sawanishi, H., *Tetrahedron: Asymmetry,* **1995**, *6*, 2271. (g) Chatterjie, N. and Alexander, G., *Res. Commun. Substances Abuse,* **1991**, *12*, 132. (h) Haroutounian, S. A.; Georgiadis, M. P. and Polissiou, M. G., *J. Heterocycl. Chem.,* **1989**, *26*, 1283. (i) Rizzi, J. P.; Schnur, R. C.; Hutson, N. J.; Kraus, K. G. and Kelbaugh, P. R., *J. Med. Chem.,* **1989**, *32*, 1208. (j) Taillades, J.; Rousset, A.; Lasperas, M. and Commeyras, A., *Bull. Soc. Chim. Fr.,* **1986**, 650. (k) Herdeis, C. and Gebhard, R., *Heterocycles,* **1986**, *24*, 1019. (l) Pedregal, C.; Trigo, G. G.; Espada, M.; Mathieu, D.; Phan Tan Luu, R.; Barcelo, C.; Lamarca, J. and Elguero, J., *J. Heterocycl. Chem.,* **1984**, *21*, 1527. (m) Sacripante, G. and Edward, J. T., *Can. J. Chem.,* **1982**, *60*, 1982. (n) Chubb, F. L.; Edward, J. T. and Wong, S. C., *J. Org. Chem.,* **1980**, *45*, 2315. (o) Ago, M. and Shimomura, K., *Nippon Kagaku Zasshi*, **1967**, *88*, 881. (p) Winstead, M. B.; Barr, D. E.; Hamel, C. R.; Renn, D. J.; Parker, H. I. and Neumann, R. M., *J. Med. Chem.,* **1965**, *8*, 117.
6. Sarges, R.; Goldstein, S. W.; Welch, W. M.; Swindell, A. C.; Siegel, T. W. and Beyer, T. A., *J. Med. Chem.,* **1990**, *33*, 1859.
7. Brown, M. L.; Brown, G. B. and Brouillette, W. J., *J. Med. Chem.,* **1997**, *40*, 602.
8. Meusel, M; Ambroźak, A.; Hecker, T. K. and Gütschow, M., *J. Org. Chem.,* **2003**, *68*, 4684.
9. Rousset, A.; Lasperas, M.; Taillades, J. and Commeyras, A.*, Tetrahedron*, **1980**, *36*, 2649.
10. (a) Henze, H. R. and Isbell, A. F., *J. Am. Chem. Soc.,* **1954**, *76*, 4152. (b) Henze, H. R. and Leslie, W. B., *J. Org. Chem.,* **1950**, *15*, 901. (c) Henze, H. R. and Craig, W. C., *J. Org. Chem.,* **1945**, *10*, 2. (d) Henze, H. R. and Speer, R. J., *J. Am. Chem. Soc.,* **1942**, *64*, 522. (e) Henze, H. R. and Magee, J. W., *J. Am. Chem. Soc.,* **1940**, *62*, 912. (f) Magee, J. W. and Henze, H. R., *J. Am. Chem. Soc.,* **1938**, *60*, 2148.
11. Ware, E., *Chem. Rev.,* **1950**, *46*, 403.
12. Ugi, I.; Werner, B. and Dömling, A., *Molecules,* **2003**, *8*, 53.
13. (a) Bazil, C. W. and Pedley, T. A., *Annu. Rev. Med*., **1998**, *49*, 135. (b) Luer, M. S., *Neurol. Res*., **1998**, *20*, 178.
14. (a) Knabe, J.; Baldauf, J. and Ahlhelm, A., *Pharmazie,* **1997**, *52*, 912. (b) Matsukura, M.; Daiku, Y.; Ueda, K.; Tanaka, S.; Igarashi, T. and Minami, N., *Chem. Pharm. Bull.,* **1992**, *40*, 1823.
15. (a) Somsák, L.; Kovács, L.; Tóth, M.; Ösz, E.; Szilágyi, L.; Györgydeák, Z.; Dinya, Z.; Docsa, T.; Tóth, B. and Gergely, P., *J. Med. Chem*., **2001**, *44*, 2843 (b) Sarges, R. and Oates, P. J., *Prog. Drug Res*., **1993**, *40*, 99.
16. (a) Byrtus, H.; Pawlowski, M.; Duszyńska, B.; Wesolowska, A.; Chojnacka-Wójcik, E. and Bojarski, A. J., *Pol. J. Pharmacol.,* **2001**, *53*, 395. (b) Peyman, A.; Wehner, V.; Knolle, J.; Stilz, H. U.; Breipohl, G.; Scheunemann, K.-H.; Carniato, D.; Ruxer, J.-M.; Gourvest, J.-F.; Gadek,

T. R. and Bodary, S., *Bioorg. Med. Chem. Lett*., **2000**, *10*, 179. (c) Moloney, G. P.; Martin, G. R.; Mathews, N.; Milne, A.; Hobbs, H.; Dodsworth, S.; Sang, P. Y.; Knight, C.; Williams, M.; Maxwell, M. and Glen, R. C., *J. Med. Chem.,* **1999**, *42*, 2504. (d) Moloney, G. P.; Robertson, A. D.; Martin, G. R.; MacLennan, S.; Mathews, N.; Dodsworth, S.; Sang, P. Y.; Knight, C. and Glen, R., *J. Med. Chem.,* **1997**, *40*, 2347. (e) Stilz, H. U.; Jablonka, B.; Just, M.; Knolle, J.; Paulus, E. F. and Zoller, G., *J. Med. Chem*., **1996**, *39*, 2118.

17. (a) Ugi, I.; Almstetter, M.; Bock, H.; Dömling, A.; Ebert, B.; Gruber, B.; Hanusch-Kompa, C.; Heck, S.; Kehagia-Drikos, K.; Lorenz, K.; Papathoma, S.; Raditschnig, R.; Schmid, T.; Werner, B. and von Zychlinski, A., *Croat. Chem. Acta,* **1998**, *71*, 527. (b) Domínguez, C.; Ezquerra, J.; Prieto, L.; Espada, M. and Pedregal, C., *Tetrahedron: Assymetry,* **1997**, *8*, 511. (c) Tanaka, K.-I. and Sawanishi, H., *Tetrahedron: Asymmetry,* **1995**, *6*, 1641. (d) Nagasawa, H. T.; Elberling, J. A. and Shirota, F. N., *J. Med. Chem*., **1973**, *16*, 823. (e) Pfeiffer, P. and Epler, H., *Ann.,* **1940**, *646*, 263. (f) Pfeiffer, P. and Diebold, A., *J. Prakt. Chem.,* **1937**, *148*, 24. (g) Pfeiffer, P. and Heinrich, E., *J. Prakt. Chem.,* **1936**, *146*, 105.
18. (a) Park, K.-H. and Kurth, M. J., *Tetrahedron Lett*., **2000**, *41*, 7409. (b) Boeijen, A.; Kruijtzer, J. A. W. and Liskamp, R. M. J., *Bioorg. Med. Chem. Lett*., **1998**, *8*, 2375. (c) DeWitt, S. H.; Kiely, J. S.; Stankovic, C. J.; Schroeder, M. C.; Cody, D. M. R. and Pavia, M. R., *Proc. Natl. Acad. Sci. USA,* **1993**, *90*, 6909. (d) Sarges, R.; Howard, H. R. and Kelbaugh, P. R., *J. Org. Chem*., **1982**, *47*, 4081.
19. Beller, M.; Eckert, M.; Moradi, W. A. and Neumann, H., *Angew. Chem. Int. Ed.,* **1999**, *38*, 1454.
20. (a) Moskal, J.; Moskal, A. and Milart, P., *Monatsh. Chem.,* **1984**, *115*, 187. (b) Moskal, J.; Moskal, A. and Milart, P., *Tetrahedron Lett.,* **1982**, *38*, 1787. (c) Moskal, J. and Moskal, A., *Synthesis,* **1979**, 794.
21. Hulme, C.; Ma, L.; Romano, J. J.; Morton, G.; Tang, S.-Y.; Cherrier, M.-P.; Choi, S.; Salvino, J. and Labaudiniere, R., *Tetrahedron Lett*., **2000**, *41*, 1889.
22. (a) López, C. A. and Trigo, G. G., *Adv. Heterocycl. Chem.,* **1985**, *38*, 177. (b) Read, W. T., *J. Am. Chem. Soc.*, **1922**, *44*, 1746.
23. Brown, M. L.; Zha, C. X. C.; van Dyke, C. C.; Brown, G. B. and Brouillette, W. J., *J. Med. Chem.,* **1999**, *42*, 1537.
24. (a) Mahmoodi, N. O. and Khodaee, Z., *Mendeleev Commun*., **2004**, 304. (b) Meusel, M. and Guetschow, M., *Org. Prep. Proc. Int.,* **2004**, *36*, 391. (c) Cui, Q.; Tang, K. and Ouyang, P. K., *Nanjing Huagong Xueyuan Xuebao*, **1995**, *17*, 125. (d) Brouillette, W. J.; Jestkov, V. P.; Brown, M. L.; Akhtar, M. S.; DeLorey, T. M. and Brown, G. B., *J. Med. Chem.,* **1994**, *37*, 3289. (e) Kwon, S. K. and Suh, J. J., *Yakhak Hoechi*, **1983**, *27*, 245. (f) Trigo, G. G.; Avendano, C.; Santos, E.; Edward, J. T. and Wong, S. C., *Can. J. Chem.,* **1979**, *57*, 1456. (g) Edward, J. T. and Jitrangsri, C., *Can. J. Chem.,* **1975**, *53*, 3339. (h) Shirai, T. and Takei, Y., *Yuki Gosei Kagaku Kyokaishi*, **1971**, *29*, 1135. (i) Shirai, T.; Sakurai, T. and Takei, Y., *Yuki Gosei Kagaku Kyokaishi*, **1971**, *29*, 1142. (j) Ugi, I., *Isonitrile Chemistry*, Academic Press, New York, vol. 20, **1971**. (k) Goodson, L. H.; Honigberg, I. L.; Lehman, J. J. and Burton, W. H., *J. Org. Chem.,* **1960**, *25*, 1920. (l) Hellmann, H. and Opitz, G., *a-Aminoalkylierung*, Verlag Chemie,Weinheim, **1960**.

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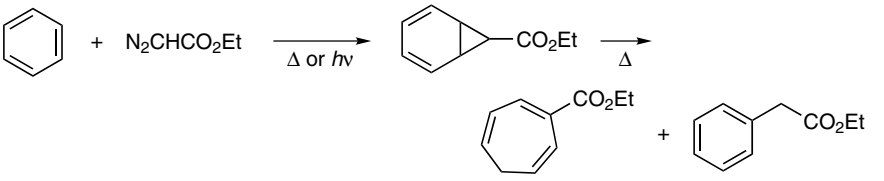
Büchner Ring Expansion
(Büchner Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Büchner et al. in 1885.[1] It is the synthesis of cycloheptatriene and phenylacetic acid derivatives through the rearrangement of norcaradiene carboxylates (i.e., the intermediate) generated from the reaction between aromatic compounds and carbene species, and this reaction is thus known as the Büchner reaction[2] or the Büchner ring expansion.[3] In this reaction, the carbene species can be generated from thermal or photolytical decomposition of diazoacetic acid esters. It is believed that an equilibrium exists between norcaradiene and cycloheptatriene derivatives in which the latter predominates in the equilibrium[4] according to the following experimental facts: (*a*) cycloheptatriene on hydrogenation gives cycloheptane,[5] whereas the addition of dienophiles usually gives products derived from norcaradiene[6] and (*b*) both the reaction of tropylium ion and cyanide ion followed by hydrolysis and the reaction of benzene and methyl diazoacetate followed by treatment with ammonia lead to the same substance.[4c] However, with two electron-withdrawing groups (e.g., CN) on the cyclopropyl ring, the 7,7-dicyano-norcaradiene is stable and can be isolated and subjected to other reactions.[7] Because the carbenes arising from the decomposition of diazo compounds are active, the normal Büchner ring expansion between these carbenes and aromatic compounds always afford a mixture of isomers.[8] However, when an rhodium complex [$Rh_2(OCOCF_3)_4$] is used, one major product will form with improved yield.[9] Other organometallic rhodium complexes might also be applicable for the Büchner ring expansion, such as the dirhodium tetraprolinate [Rh_2(S-DOSP)$_4$], which prefers the C-H insertion product,[10] and rhodium porphyrin complex, which shows competition between the addition and the C-H insertion.[11] Other organometallic complexes used in this reaction include copper complexes, such as Tp^{Br3}Cu(MeCN) and Tp^{Ms}Cu; the former gives predominately the addition products with monosubstituted benzenes, and the latter forms the α-C-H insertion product as the major product.[12]

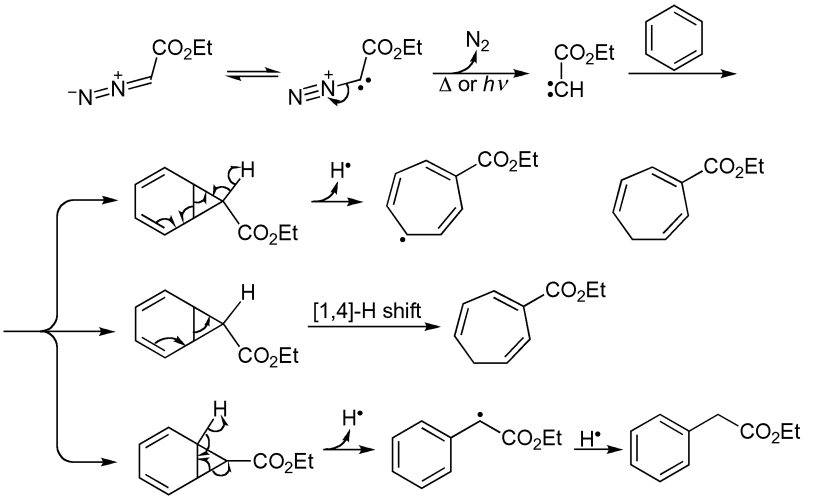
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A tentative mechanism is illustrated below.



D. MODIFICATION

This reaction has been modified for using organometallic carbene complexes to form either the addition or the C-H insertion products, depending on the catalyst used.[9–12]

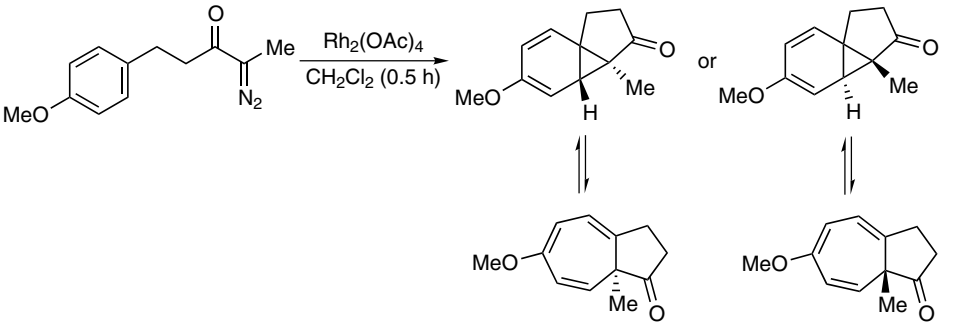
E. APPLICATIONS

Besides the general application in synthesis of cycloheptatrienes, different bicyclic products—for example, β-tetralones and azulenones—can be prepared via the intramolecular Büchner ring expansion.[12]

F. RELATED REACTIONS

This reaction is similar to the *Pfau-Plattner Azulene Synthesis*.

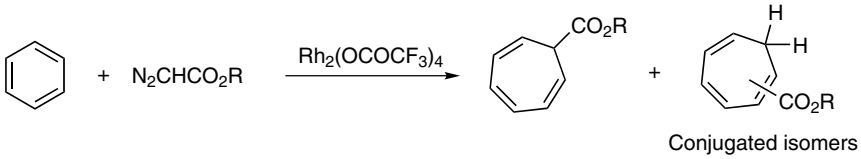
G. CITED EXPERIMENTAL EXAMPLES



Reference 13.

3-(4′-Methoxyphenyl)propanoyl chloride (0.44 g, 2.22 mmol)—prepared from 0.46 g 3-(4′-methoxyphenyl)propanoic acid (0.46 g, 2.55 mmol) and 15 mL freshly distilled thionyl chloride and purified by bulb-to-bulb distillation at 110°C (0.3 mmHg)—in 10 mL ether was added dropwise over 20 min to an ethereal diazoethane solution—prepared from 7.15 g *N*-ethyl-*N*-nitrosourea (61.1 mmol) at −20°C while stirring under nitrogen. The solution was allowed to slowly return to room temperature while being stirred for 3 h. The ether and residual diazoethane were evaporated under reduced pressure at room temperature, using a rotary evaporator fitted with an acetic acid trap. Purification by chromatography, using ethyl acetate/hexane (5:95) as the eluant, gave 0.42 g 2-diazo-5-(4′-methoxyphenyl)pentan-3-one as a yellow oil, in a yield of 75%.

2-Diazo-5-(4′-methoxyphenyl)pentan-3-one (100 mg, 0.459 mmol) in 100 mL CH_2Cl_2 was added dropwise over 1 h to a refluxing solution of 0.5 mg rhodium(II) acetate in 100 mL CH_2Cl_2. The reaction was monitored by TLC and was complete once the diazoketone had been added. Evaporation of the solvent at reduced pressure gave the crude product as a yellow oil. A ^{1}H NMR spectrum was recorded to determine the efficiency of the cyclization (88%) (percent of azulenone compared to aromatic by-products). Purification by flash chromatography, with gradient ethyl acetate–hexane as the eluant, gave 70 mg 3,8a-dihydro-6-methoxy-8a-methylazulen-1(2H)-one as a colorless oil, in a yield of 80%. No resolution of signals for enantiomers was seen in a ^{1}H NMR chiral shift study using (+)-Eu(hfc)$_3$. It was difficult to obtain this azulenone completely free of aromatic impurities.



Reference 9.

A diazo ester (5 mmol) was added with an automatic syringe (Sage Model 352) to the aromatic substrate (0.1 mol) containing the catalyst (0.02 mmol) within ∼ 2 h while the mixture was stirred magnetically at room temperature. After the decomposition of diazo ester, the reaction mixture was analyzed by VPC using an internal standerd (dimethyl fumarate

or diethyl phthalate). In preparative experiments, the mixture was distilled under vacuum (10^{-2}– 10^{-3} mmHg) to give alkyl cyclohepta-2,4,6-triene-1-carboxylate at a relatively low temperature so as to minimize the isomerization. For the reaction with benzene, the total yield of cycloheptatriene derivatives was 100%.

Other references related to the Büchner ring expansion are cited in the literature.[14]

H. REFERENCES

1. Büchner, E. and Curtius, T., *Ber.,* **1885**, *18*, 2377.
2. (a) Galan, B. R.; Gembicky, M.; Dominiak, P. M.; Keister, J. B. and Diver, S. T., *J. Am. Chem. Soc.,* **2005**, *127*, 15702. (b) Manitto, P.; Monti, D. and Speranza, G., *J. Org. Chem.,* **1995**, *60*, 484. (c) Kennedy, M.; McKervey, M. A.; Maguire, A. R.; Tuladhar, S. M. and Twohig, M. F., *J. Chem. Soc., Perkin Trans. I,* **1990**, 1047. (d) Duddeck, H.; Ferguson, G.; Kaitner, B.; Kennedy, M.; McKervey, M. A. and Maguire, A. R., *J. Chem. Soc., Perkin Trans. I,* **1990**, 1055.
3. Panne, P. and Fox, J. M., *J. Am. Chem. Soc.,* **2007**, *129*, 22.
4. (a) Ciganek, E., *J. Am. Chem. Soc.,* **1967**, *89*, 1454. (b) Ciganek, E., *J. Am. Chem. Soc.,* **1967**, *89*, 1458. (c) Doering, W. von E. and Knox, L. H., *J. Am. Chem. Soc.,* **1957**, *79*, 352.
5. Ciganek, E., *J. Am. Chem. Soc.,* **1965**, *87*, 1149.
6. (a) Alder, K.; Muders, R.; Krane, W. and Wirtz, P., *Ann.,* **1959**, *627*, 59. (b) Alder, K.; Jungen, H. and Rust, K., *Ann.,* **1957**, *602*, 94. (c) Alder, K.; Kaiser, K. and Schumacher, M., *Ann.,* **1957**, *602*, 80. (d) Doering, W. von E.; Laber, G.; Vonderwahl, R.; Chamberlain, N. F. and Williams, R. B., *J. Am. Chem. Soc.,* **1956**, *78*, 5448. (e) Alder, K. and Jacobs, G., *Ber.,* **1953**, *86*, 1528.
7. Ciganek, E., *J. Am. Chem. Soc.,* **1971**, *93*, 2207.
8. (a) Kirmse, W., *Carbene Chemistry*, Academic Press, New York, **1971**, p. 387. (b) Dave, V. and Warnhoff, E. W., *Org. React.,* **1970**, *17*, 239.
9. Anciaux, A. J.; Demonceau, A.; Noels, A. F.; Hubert, A. J.; Warin, R. and Teyssié, P., *J. Org. Chem.,* **1981**, *46*, 873.
10. Davies, H. M. L.; Jin, Q. H.; Ren, P. D. and Kovalevsky, A. Y., *J. Org. Chem.,* **2002**, *67*, 4165. and references cited therein.
11. Callot, H. J. and Metz, F., *Nov. J. Chem.,* **1985**, *9*, 167.
12. Morilla, M. E.; Díaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S. and Pérez, P. J., *Organometallics,* **2004,** *23*, 293.
13. Maguire, A. R.; O'Leary, P.; Harrington, F.; Lawrence, S. E. and Blake, A. J., *J. Org. Chem.,* **2001**, *66*, 7166.
14. (a) Im, C. Y.; Okuyama, T. and Sugimura, T., *Chem. Lett.,* **2007**, *36*, 314. (b) Ruedi, G. and Hansen, H.-J., *Helv. Chim. Acta,* **2001**, *84*, 1017. (c) Manitto, P.; Monti, D.; Zanzola, S. and Speranza, G., *Chem. Commun.,* **1999**, 543. (d) Maguire, A. R.; Buckley, N. R.; O'Leary, P. and Ferguson, G., *J. Chem. Soc., Perkin Trans. I,* **1998**, 4077. (e) Zhan, H.; Appels, D. C.; Hockless, D. C. R. and Mander, L. N., *Tetrahedron Lett.,* **1998**, *39*, 6577. (f) Morris, J. C.; Mander, L. N. and Hockless, D. C. R., *Synthesis,* **1998**, 455. (g) Manitto, P.; Monti, D.; Zanzola, S. and Speranza, G., *J. Org. Chem.,* **1997**, *62*, 6658. (h) Mander, L. N., *Synlett,* **1991**, 134. (i) Mander, L. N. and Wells, A. P., *Tetrahedron Lett.,* **1997**, *38*, 709. (j) Maguire, A. R.; Buckley, N. R.; O'Leary, P. and Ferguson, G., *Chem. Commun.,* **1996**, 2595. (k) Doyle, M. P.; Protopopova, M. N.; Peterson, C. S.; Vitale, J. P.; McKervey, M. A. and Fernandez Garcia, C., *J. Am. Chem. Soc.,* **1996**, *118*, 7865. (l) Pirrung, M. C. and Morehead, A. T., *J. Am. Chem. Soc.,* **1996**, *118*, 8162. (m) Matsumoto, M.; Shiono, T.; Mutoh, H.; Amano, M. and Arimitsu, S., *J. Chem. Soc., Chem. Commun.,* **1995**, 101. (n) Cordi,

A. A.; Lacoste, J.-M. and Hennig, P., *J. Chem. Soc., Perkin Trans. I,* **1993**, 3. (o) Kennedy, M.; McKervey, M. A.; Maguire, A. R.; Tuladhar, S. M. and Twohig, M. F., *J. Chem. Soc., Perkin Trans. I,* **1990**, 1047. (p) Garst, M. E. and Roberts, V. A., *J. Org. Chem.,* **1982**, *47*, 2188. (q) Ledon, H.; Linstrumelle, G. and Julia, S., *Tetrahedron,* **1973**, *29*, 3609. (r) Ledon, H.; Cannic, G.; Linstrumelle, G. and Julia, S., *Tetrahedron Lett.,* **1970**, 3971. (s) Corey, E. J.; Burke, H. J. and Remers, W. A., *J. Am. Chem. Soc.,* **1955**, *77*, 4941. (t) Dev, S., *J. Indian Chem. Soc.,* **1955**, *32*, 513. (u) Johns, R. B.; Johnson, A. W.; Langemann, A. and Murray, J., *J. Chem. Soc.,* **1955**, 309. (v) Johnson, A. W.; Langemann, A. and Murray, J., *J. Chem. Soc.,* **1953**, 2136. (w) Grundmann, C. and Ottmann, G., *Ann.,* **1953**, *582*, 163. (x) Büchner, E. and Schottenhammer, K., *Ber.,* **1920**, *53*, 865. (y) Büchner, E. and Hediger, S., *Ber.,* **1903**, *36*, 3502. (z) Büchner, E., *Ber.,* **1898**, *31*, 2241. (aa) Büchner, E., *Ber.,* **1897**, *30*, 632. (bb) Büchner, E., *Ber.,* **1896**, *29*, 106.

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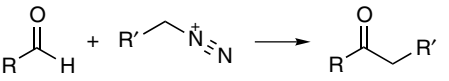
Büchner-Curtius-Schlotterbeck Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Büchner and Curtius in 1885[1] and subsequently by Schlotterbeck in 1907.[2] It is the reaction for forming ketones from aldehydes and aliphatic diazo compounds and is thus known as the Büchner-Curtius-Schlotterbeck reaction.[3] This reaction has been extended to synthesize β-keto esters from the condensation between diazo esters and aldehydes.[4] It should be pointed out that epoxides and aldehydes are also produced in this reaction, and the preparation of keto esters can also be performed in the presence of Lewis acids[5] or via a two-step process involving an *Aldol Reaction* of diazo ester and aldehyde followed by the oxidative elimination of nitrogen.[6]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A tentative mechanism is displayed here.

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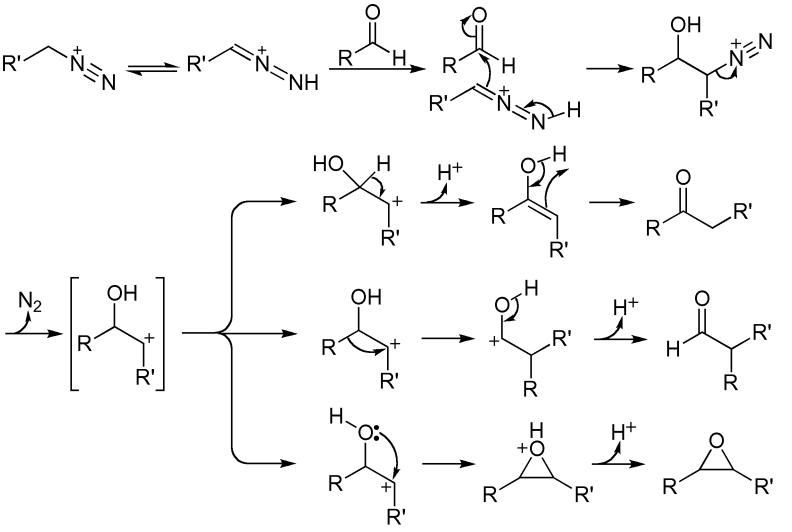


D. MODIFICATION

This reaction has been modified to undergo in the presence of Lewis acids.[5]

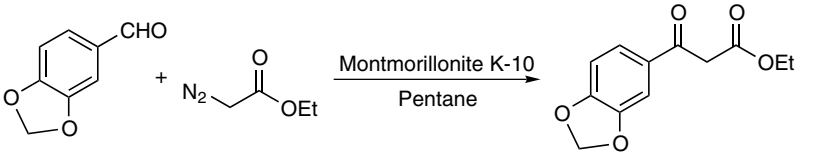
E. APPLICATIONS

This reaction has general application in the preparation of ketones and β-keto esters.[7]

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

A mixture of 5 mmol aldehyde, 7.5 mmol ethyl diazoacetate, and 100 mg montmorillonite K-10 in 10 mL pentane was stirred at room temperature for 6 h. After completion of the reaction (TLC), the catalyst was removed by filtration and washed with pentane (3 × 5 mL). The solvent was removed under reduced pressure to obtain the crude product, which was further purified by column chromatography on silica gel (ethyl acetate/light petroleum = 1:9) to give 69% β-keto ester, m.p. 41°C.

Other references related to the Büchner-Curtius-Schlotterbeck reaction are cited in the literature.[8]

H. REFERENCES

1. Büchner, E. and Curtius, T., *Ber.,* **1885**, *18*, 2371, 2373.
2. (a) Schlotterbeck, F., *Ber.,* **1907**, *40*, 479. (b) Schlotterbeck, F., *Ber.,* **1907**, *40*, 1826. (c) Schlotterbeck, F., *Ber.,* **1907**, *40*, 3000.
3. Bastus, J. B., *Tetrahedron Lett.,* **1963**, 955.
4. (a) Gutsche, C., *Org. React.,* **1954**, *8*, 364. (b) Dieckman, W., *Ber.,* **1910**, *43*, 1024.
5. (a) Holmquist, C. R. and Rosekamp, E. J., *J. Org. Chem.,* **1989**, *54*, 3258. (b) Fernandez, M. V.; Herera, F. J. G. and Perez, C. G., *Carbohydr. Res.,* **1983**, *124*, 333. (c) Aparicio, F. J.; Herrera, F. J. and Fernandez, M. V., *An Quim.,* **1978**, *74*, 1516.
6. (a) Pellicciari, R.; Natalini, B.; Fringuelli, R. and Ceccherelli, P., *J. Chem. Soc., Perkin Trans. I*, **1985**, 493. (b) Pellicciari, R.; Fringuelli, R.; Ceccherelli, P. and Sisani, E., *J. Chem. Soc., Chem. Commun.*, **1979**, 959. (c) Wenkert, E.; Ceccherelli, P. and Fugiel, R. A., *J. Org. Chem.*, **1978**, *43*, 3983. (d) Wenkert, E. and McPherson, A. J., *J. Am. Chem. Soc.*, **1954**, *76*, 8084.
7. Bandgar, B. P.; Pandit, S. S. and Sadavarte, V. S., *Green Chem.*, **2001**, *3*, 247.
8. (a) Eistert, B. and Langbein, A., *Ann.*, **1964**, *678*, 78. (b) Schlotterbeck, F., *Ber.,* **1909**, *42*, 2559. (c) Schlotterbeck, F., *Ber.,* **1909**, *42*, 2565. (d) Bertini, C., *Gazz. Chim. Ital.,* **1903**, *33*, 145.

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Buchwald Indoline Synthesis

(Buchwald Indole-Indoline Ring Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Buchwald in 1991.[1] It is a regiospecific synthesis of 3,4-disubstituted indoline and indole derivatives that involves the generation of a zirconocene-stabilized benzyne complex from *N*-allyl *o*-haloaniline, which undergoes intramolecular olefin insertion to a tricyclic indoline zirconacycle and then reacts with electrophiles or oxidating agents to give indoline derivatives.[1] Refluxing with ammonium formate in MeOH in the presence of Pd/C, the 3,4-disubstituted indoline derivatives are converted into indole derivatives, respectively;[2] alternatively, the intermediate *exo*-methylene indoline derivative can be transformed into indole via ene reaction.[1] This reaction is therefore referred to as the Buchwald indoline synthesis,[3] or the Buchwald indole-indoline ring synthesis.[3]

It should be pointed out that the 4-position of the indole ring systems is so electron deficient that the substituents are difficult to introduce at the 4-position by normal electrophilic substitution.[4] To circumvent this problem, two approaches have been developed: formation of the pyrrole ring using an annelation method onto an appropriately substituted aromatic precursor and direct introduction of the substituent into the 4-position of the existing indole framework.[4] Some known indole synthesis methods, including the *Batcho-Leimgruber Indole Synthesis*, *Bartoli Indole Synthesis, Fischer Indole Synthesis, Larock Indole Synthesis, Madelung Indole Synthesis*, and *Reissert Indole Synthesis*, belong to the annelation approaches, whereas only a few 4-substituted indole preparations are accomplished by the second approach, such as the application of chromium tricarbonyl complexs

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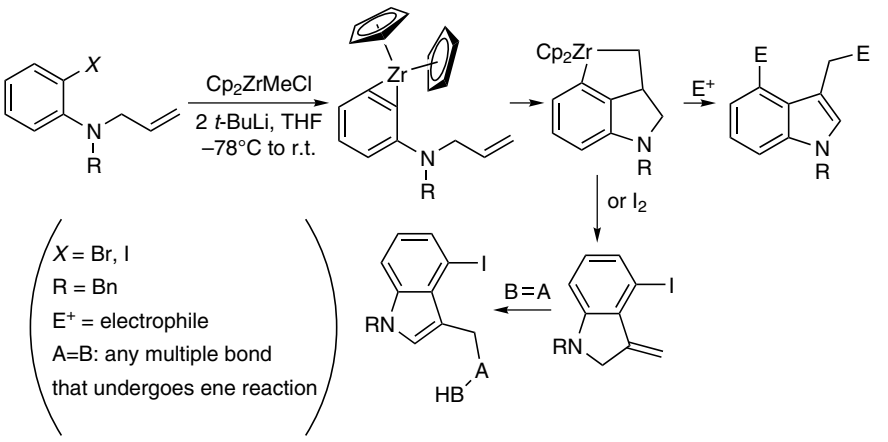
of indoles,[5] thallation/palladation,[6] and lithiation.[7] However, the first approach requires properly substituted starting materials, which can be expensive or not readily available, and the second approach uses toxic chromium complex.[4] In comparison, the Buchwald indoline synthesis requires only a catalytic amount of zirconocene and has been successfully applied to the synthesis of a variety of molecules containing indole or indoline scaffolds, such as tryptamine,[2,8] serotonin,[4] tryptophan[4] analogs, and some natural products (including makaluvamine C,[2] damirones A and B,[2] dehydrobufotenine,[2] clavicipitic acid,[9] and pharmacophore of CC-1065[4,9]).

On the other hand, the Buchwald indoline synthesis also holds some weakness, such as employing the air and moisture-sensitive zirconocene ($Cp_2Zr(Me)Cl$), the availability of *N*-allyl-*o*-bromoaniline, and the limited scope for indoles with substituents at both the 3- and 4-positions.[9] By applying the later-developed *Buchwald-Hartwig Amination*, Buchwald himself extended the indoline synthesis to other kinds of indoline and indole derivatives from an aryl Grignard reagent, an olefin, a primary amine, and the air-stable titanocene Cp_2TiCl_2.[9] In this modification, the aryl Grignard reagent is converted into a titanocene-stabilized benzyne complex, which intermolecularly inserts with olefin and then couples with amine to give indoline derivatives. In addition, 2-(*o*-halo-phenyl)ethylamine can be directly converted into indoline via the *Buchwald-Hartwig Coupling*;[2] likewise, *o*-bromobenzylic bromide can react with benzylamine to afford indoline by the *Buchwald-Hartwig Coupling*.[9] Even secondary amides and carbamates can be intramolecularly mounted onto aromatic nucleus, giving a variety of benzo-heterocycles.[10]

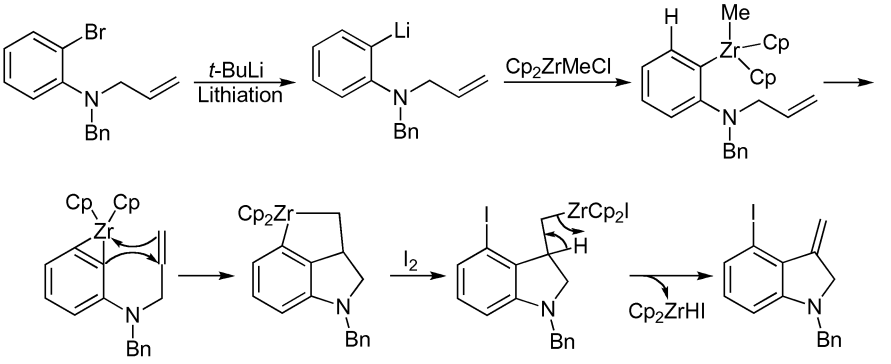
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

As described in the definition of Buchwald indoline synthesis, this reaction involves the formation of a zirconocene-stabilized benzyne complex that intramolecularly inserts to an *N*-allyl group to give a tricyclic indoline zirconacycle. In the presence of oxidating reagent or electrophiles, the indoline zirconacycle decomposes into indoline derivatives.[1]

Upon dehydrogenation, corresponding indole derivatives can be prepared. Displayed here is an illustration for the formation of *N*-benzyl-3-methylene-4-iodo-indoline.



D. MODIFICATION

The Buchwald indoline synthesis has been extended for preparing other kinds of indoline and indole derivatives not just 3,4-disubstituted indolines and indoles, starting from a readily available aromatic Grignard reagent, an olefin, a primary amine, and air-stable titanocene Cp_2TiCl_2.[9] In addition, the *Buchwald-Hartwig Coupling* has been used for the preparation of indoline and indole derivatives from readily available 2-(*o*-halo-phenyl)ethylamine[2] and 2-(*o*-halo-phenyl)ethylbromide and benzylamine.[9] Moreover, the *Buchwald-Hartwig Coupling* has also been used to modify the *Fischer Indole Synthesis* by coupling with aryl halide and hydrazone in the presence of methanesulfonic acid as the catalyst.[11]

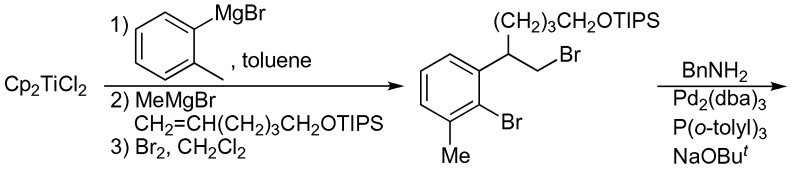
E. APPLICATIONS

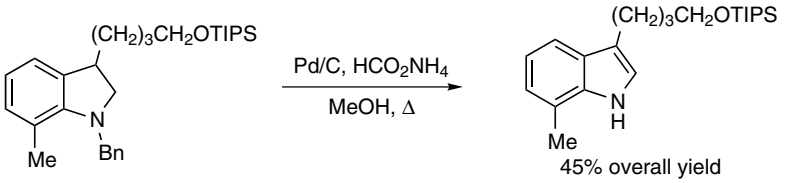
This reaction in combination with its modifications has broad application in the synthesis of polysubstituted indoline and indole derivatives.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



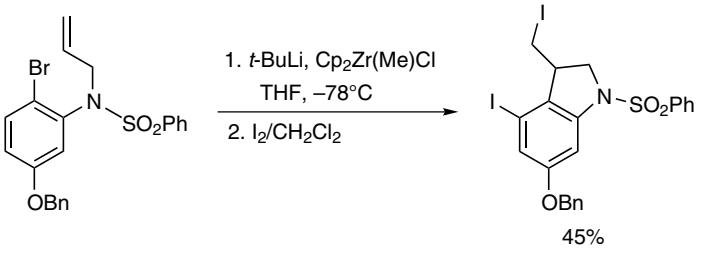


Reference 9.

To a solution of 0.08 M Cp_2TiCl_2 in toluene (2–4 mmol, 1.0 eq.) in a resealable Schlenk flask at room temperature was added 1.1 eq. of a THF solution of *o*-methylphenyl magnesium bromide under argon. After 1 h, 2.0 eq. of triisopropylsilyl hex-5-en-1-ol ether and a 1.0 eq. MeMgBr in Et_2O were added, then the flask was sealed and heated to 50°C for 4 h. After being cooled to room temperature, the solvent was removed in vacuo, and CH_2Cl_2 (12 mL/mmol Cp_2TiCl_2) was added. Then the solution was cooled to −78°C. A solution of 2.05 eq. Br_2 in CH_2Cl_2 at an appropriate concentration (6 mL/mmol Cp_2TiCl_2) at −78°C was added dropwise. The solution was warmed slowly to room temperature, then the solvent was removed in vacuo. *Caution:* Care should be used to ensure that the excess bromine has been destroyed. Hexane (30 mL/mmol Cp_2TiCl_2) was added; then the mixture was filtered through a pad of Celite, and the solvent was evaporated. The dibromide product was partially purified by flash chromatography, and a portion of the material (typically 25–50%) was used directly in the next step.

The appropriate amount of the above dibromide (1.0 eq.) was mixed with 4 mol % $Pd_2(dba)_3$, 16 mol % P(*o*-tolyl)$_3$, 4.0 eq. NaO-*t*-Bu, and 2.0 eq. benzylamine in toluene. The flask was sealed, then heated to 80°C for 16 h. Upon cooling to room temperature, the mixture was poured into a separatory funnel containing Et_2O and H_2O. The organic layer was washed with brine, dried over $MgSO_4$, and filtered and the solvent was evaporated. The indoline product was partially purified by flash chromatography, and a portion of the material (typically ∼50%) was used directly in the next step.

The indoline derivative (1.0 eq.) was treated with 10 mol % (by weight) Pd/C and 10.0 eq. ammonium formate in MeOH. The solution was refluxed for 1.5 h, then allowed to cool to room temperature and filtered through a short pad of Celite. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2. The organic layer was washed with H_2O, brine, dried over Na_2SO_4, and filtered, and the solvent was evaporated. The residue was purified by flash chromatography using hexane/CH_2Cl_2 (4:1 then 2:1) to afford 80 mg 3-[4-(triisopropylsilyl)oxy]butyl-7-methylindole as a colorless oil, in an overall yield of 45% from Cp_2TiCl_2.



Reference 12.

To a flame-dried Schlenk flask with a stir bar was charged 50 mL THF, 2.39 g zirconocene(methyl)chloride (8.8 mmol), 4.04 g *N*-allyl-*N*-(benzenesulfonyl)-5-(benzyloxy)-2-bromophenylamine (8.8 mmol), and 17.6 mmol *tert*-butyllithium in hexane at −78°C. After stirring at this temperature for 15 min, the solution was allowed to warm to 23°C and stirred for an additional 2 h. The THF was then removed in vacuo, and the residue was dissolved in 50 mL CH_2Cl_2. To this solution was added a suspension of 5.20 g iodine (20.5 mmol) in 50 mL CH_2Cl_2 at 0°C, and the mixture was stirred at 0°C for 4 h. After removal of CH_2Cl_2 in vacuo, the residue was dissolved in 100 mL Et_2O and washed with saturated aqueous Na_2SO_3 (3 × 100 mL) and water (3 × 100 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography using EtOAc/petroleum ether (1:10) as the eluent to afford 2.3 g (3*RS*)-1-(benzenesulfonyl)-6-(benzyloxy)-4-iodo-3-(iodomethyl)-2,3-dihydro-1*H*-indole as a yellow solid, in a yield of 45%, m.p. 49°C (Et_2O).

Other references related to the Buchwald indoline synthesis are cited in the literature.[13]

H. REFERENCES

1. Tidwell, J. H.; Senn, D. R. and Buchwald, S. L., *J. Am. Chem. Soc.,* **1991**, *113*, 4685.
2. Peat, A. J. and Buchwald, S. L., *J. Am. Chem. Soc.*, **1996**, *118*, 1028.
3. Gribble, G. W., *J. Chem. Soc*., *Perkin Trans. I*, **2000**, 1045.
4. Tidwell, J. H. and Buchwald, S. L., *J. Am. Chem. Soc.,* **1994**, *116*, 11797.
5. (a) Beswick, P. J.; Greenwood, C. S.; Mowlem, T. J.; Nechvatal, G. and Widdowson, D. A., *Tetrahedron,* **1988**, *44*, 7325. (b) Nechvatal, G.; Widdowson, D. A., *J. Chem. Soc., Chem. Commun.,* **1982**, 467. (c) Kozikowski, A. P. and Isobe, K., *J. Chem. Soc., Chem. Commun.,* **1978**, 1076.
6. (a) Somei, M.; Yamada, F. and Naka, K., *Chem. Pharm. Bull.,* **1987**, *35*, 1322. (b) Somei, M.; Saida, Y. and Komura, N., *Chem. Pharm. Bull.,* **1986**, *34*, 4116 and references cited therein.
7. Iwao, M., *Heterocycles,* **1993**, *36*, 29.
8. Tidwell, J. H. and Buchwald, S. L., J. *Org*. *Chem*., **1992**, *57*, 6380.
9. Aoki, K.; Peat, A. J. and Buchwald, S. L., *J. Am. Chem. Soc.*, **1998**, *120*, 3068.
10. Yang, B. H. and Buchwald, S. L., *Org. Lett.,* **1999**, *1*, 35.
11. Wagaw, S.; Yang, B. H. and Buchwald, S. L., *J. Am. Chem. Soc.,* **1998**, *120*, 6621.
12. Tietze, L. F. and Grote, T., *J. Org. Chem.,* **1994**, *59*, 192.
13. (a) Franz, A. K.; Dreyfuss, P. D. and Schreiber, S. L., *J. Am. Chem. Soc.,* **2007**, *129*, 1020. (b) Smith, A. B.; Kürti, L. and Davulcu, A. H., *Org. Lett.,* **2006**, *8*, 2167. (c) Fayol, A.; Fang, Y.-Q. and Lautens, M., *Org. Lett.,* **2006**, *8*, 4203. (d) Wolfe, J. P.; Rennels, R. A. and Buchwald, S. L., *Tetrahedron*, **1996**, *52*, 7525. (e) Tietze, L. F. and Buhr, W., *Angew. Chem. Int. Ed. Engl.,* **1995**, *34*, 1366. (f) Tidwell, J. H.; Peat, A. J. and Buchwald, S. L., *J. Org. Chem.*, **1994**, *59*, 7164.

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Buchwald-Hartwig Amination

(Buchwald-Hartwig Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction can be traced back to the original work of Migita in 1983,[1] and had been established gradually and concurrently from Buchwald[2] and Hartwig[3] since 1994. It is the transition metal (palladium) catalyzed cross-coupling between aryl halides or pseudohalides (triflates) and primary or secondary amines to form aromatic amines. Therefore, this reaction is generally known as the Buchwald-Hartwig amination.[4] In addition, this reaction has also been referred to as the Buchwald-Hartwig amidation,[5] Buchwald-Hartwig arylamination,[6] Buchwald-Hartwig C-N coupling,[7] Buchwald-Hartwig coupling,[8] Buchwald-Hartwig C-N cross coupling,[9] Buchwald-Hartwig reaction,[10] and in very rare cases as the Buchwald-Hartwig-Migita type coupling.[11] In this coupling reaction, the source of palladium is usually $Pd(OAc)_2$ or Pd_2dba_3 (tri(dibenzylideneacetone)dipalladium). While numerous ligands have been used to create the catalysts, it is found that when the strongly hindered phosphine ligands except for PPh_3[12] or very potent *N*-heterocyclic carbenes are applied as ligands, the coupling products are normally produced in high yields;[13] and among these ligands, the most common ones are DPPF(1,1′-bis-(diphenylphosphanyl)-ferrocene) and BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl).[4u,4v,14] In this coupling, once the chelated palladium catalyst forms, the oxidative addition of the aryl halide occurs; then the amine joins the complex, and the halide anion is removed from the complex by base, and finally the catalytic species is generated again via the reductive elimination of the product. It is found that $Pd(PPh_3)_4$ can be applied to the intramolecular version of such coupling (cyclization), and aryl iodides in this case are superior to corresponding bromides.[12a] In contrast, when aryl iodide are used in the intermolecular coupling, high yields can be achieved for those

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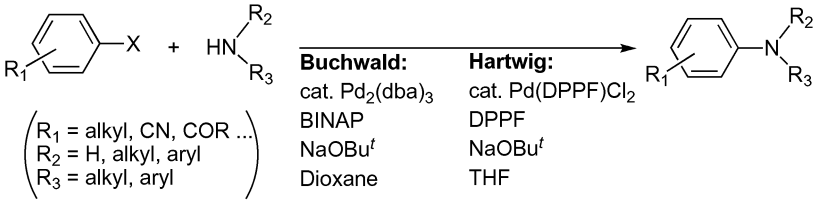
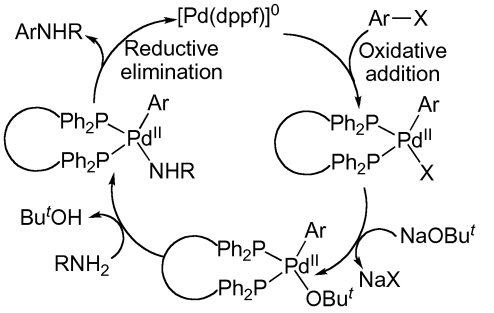
reactions between secondary amines in dioxane, whereas when primary amines are used, acceptable yields can be obtained for aryl iodides with an *ortho*-substituent.[15] However, when BINAP is used as ligand, it is not necessary to have an *ortho*-substituent adjacent to halide, and the loading amount of catalyst can be reduced.[14b] For comparison, DPPF is a good ligand for the coupling of electron-deficient aryl halide so that it is not necessary to use sterically encumbered phosphine as ligand. Under this condition, the reductive elimination over β-hydrogen is presumably due to the chelation and large bit angle of palladium, but not from steric effects.[16] On the other hand, it has been found that if $Pd(OAc)_2$ is used as a source of palladium, it must be premixed with BINAP before the addition of base, otherwise small number of catalyst can form, leading to a slow reaction in poor yield.[17] This reaction can be extended to synthesize aryl ethers by replacing primary or secondary amines with alcohols or phenols,[18] where palladium can be replaced by copper.[19] This reaction has found wide applications in the preparation of arylamines,[4r] nucleotide derivatives,[10h,20] tetracyclic systems,[10e] etc. Due to the versatility of this coupling, this relatively new reaction has already been reviewed many times.[4u,10e,11,12,14a,21,22]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The reaction mechanism is illustrated using DPPF as ligand as displayed below.[22,23]



D. MODIFICATION

This reaction has been modified to form aryl ethers from alcohols or phenols,[18] and to synthesize aryl amines using copper reagents.[19]

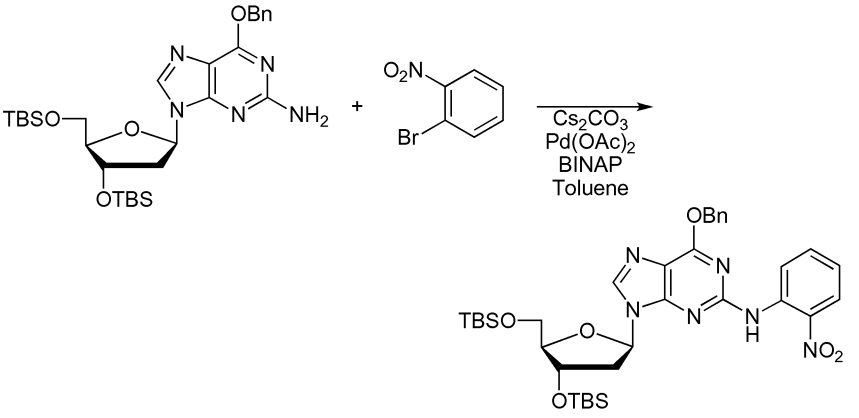
E. APPLICATIONS

This reaction has wide applications for the synthesis of aniline derivatives, indole alkaloids, pharmaceuticals, ligands, organic components and so on.[12a,14a,24]

F. RELATED REACTIONS

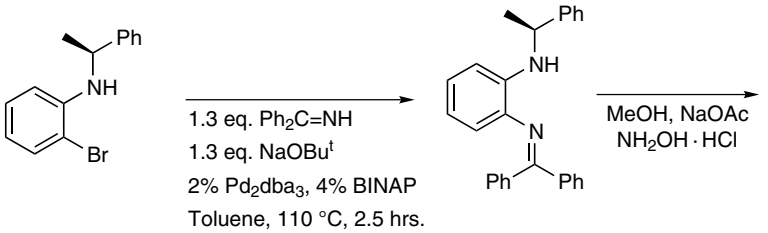
This reaction is related to many type of coupling reaction catalyzed by palladium complex, including the *Hiyama Coupling, Negishi Cross-Coupling, Sonogashira Coupling, Stille Coupling* and *Suzuki Coupling*.

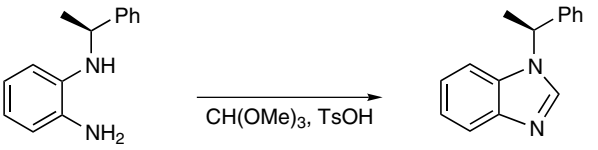
G. CITED EXPERIMENTAL EXAMPLES



Reference 10h.

An oven-dried reaction vial was charged with 0.100 g of nucleoside (0.171 mmol), 0.078 g of cesium carbonate (0.24 mmol, 1.4 equiv), 0.004 g of palladium acetate (0.017 mmol, 0.1 equiv), 0.016 g of BINAP (0.025 mmol, 0.15 equiv), 0.22 mmol of aryl bromide (1.3 equiv), and 1 mL of toluene. The vial was flushed with argon prior to sealing. The reaction mixture was stirred for 30 min at room temperature, heated at 80°C for 16 h, and then diluted with ethyl acetate. Centrifugation and concentration in a vacuum of the supernant liquid afforded a residue, which was purified by flash chromatography (silica gel, 10-30% ethyl acetate in hexane) to afford 0.116 g of N^2-(2-nitrophenyl)-O^6-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine as a yellow amorphous solid, in yield of 96%.





Reference 4r.

An oven-dried pressure tube equipped with magnetic stir bar and rubber septum was cooled under argon. The pressure tube was charged with 70.9 mg Pd_2dba_3 (0.0774 mmol, 2.0 mol %), 96.4 mg *rac*-BINAP (0.155 mmol, 4.0 mol %), and 15.0 mL toluene. The rubber septum was replaced with a Teflon screw cap, and the mixture was heated at 110°C in an oil bath for 30 min. The solution was then allowed to cool to room temperature, and 844 μL benzophenone imine (5.03 mmol, 1.30 equiv), 1.07 g bromoaniline (3.87 mmol, 1.00 equiv), and 483.4 mg sodium *tert*-butoxide (5.03 mmol, 1.30 equiv) were added. The pressure tube was sealed and heated in an oil bath at 110°C with stirring for 2.5 h. The solution was then allowed to cool to room temperature, diluted with diethyl ether, filtered through a pad of Celite, and concentrated via rotatory evaporator to give a crude dark brown-black oil which was purified by flash chromatography (gradient elution with 10% CH_2Cl_2/hexane to 50% CH_2Cl_2/hexane) to provide 1.44 g *N*-[(*S*)-1-phenylethyl]-*N*′-(diphenylmethylene)-1,2-benzenediamine as a yellow oil, in a yield of 99%. R_f = 0.14 (50% CH_2Cl_2/hexane).

To a 50 mL round-bottomed flask equipped with a magnetic stir bar were added 504.0 mg of above benzenediamine (1.34 mmol, 1.0 equiv), 30 mL methanol, 263.3 mg sodium acetate (3.21 mmol, 2.4 equiv), and 167.5 mg hydroxylamine hydrochloride (2.41 mmol, 1.8 equiv). The resulting solution was then stirred at room temperature for 1 hour. The solution was partitioned between 0.1 M NaOH and CH_2Cl_2, and the organic layer was dried over Na_2SO_4, filtered, and concentrated via rotatory evaporator. The resulting oil was purified by flash chromatography (elution with 6:1 hexane/EtOAc, then 4:1 hexane/EtOAc) to yield 268.8 mg *N*-[(*S*)-1-phenylethyl]-1,2-benzenediamine as a colorless oil that turned light red upon standing in solution or neat, in a yield of 95%, R_f= 0.21 (30% hexane/ethyl acetate).

To a 15 mL round-bottom flask equipped with magnetic stir bar was added 194.8 mg *N*-[(*S*)-1-phenylethyl]-1,2-benzenediamine (0.92 mmol, 1.0 equiv), 10.0 mL triethylorthoformate, and 17.5 mg *p*-toluenesulfonic acid monohydrate (0.092 mmol, 0.10 equiv), and the resulting solution was stirred for 8 h. The solution was then diluted with ethyl acetate and washed with $NaHCO_3$. The aqueous layer was back-extracted with ethyl acetate, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated via rotatory evaporator to give a brown oil. Purification by flash chromatography (elution with 1% MeOH/CH_2Cl_2) provided 185 mg 1-[(*S*)-1-phenylethyl]-1*H*-benzimidazole as a white solid, in a yield of 91%, m.p. 151–152°C, R_f = 0.26 (5% methanol/CH_2Cl_2).

Other references related to the Buchwald-Hartwig amination are collected in the literature.[25]

H. REFERENCES

1. Kosugi, M.; Kameyama, M. and Migita, T., *Chem. Lett.,* **1983**, 927.
2. Guram, A. S. and Buchwald, S. L., *J. Am. Chem. Soc.,* **1994**, *116*, 7901.

3. Paul, F.; Patt, J. and Hartwig, J. F., *J. Am. Chem. Soc.,* **1994**, *116*, 5969.
4. (a) Li, J. J.; Wang, Z. and Mitchell, L. H., *J. Org. Chem.,* **2007**, *72*, 3606. (b) McNulty, J.; Cheekoor, S.; Bender, T. P. and Coggan, J. A., *Eur. J. Org. Chem.,* **2007**, 1423. (c) Hesse, S. and Kirsch, G., *Synthesis,* **2007**, 1571. (d) Doherty, S.; Knight, J. G.; Smyth, C. H.; Sore, N. T.; Rath, R. K.; McFarlane, W.; Harrington, R. W. and Clegg, W., *Organometallics*, **2006**, *25*, 4341. (e) Christensen, H.; Kiil, S.; Dam-Johansen, K.; Nielsen, O. and Sommer, M. B., *Org. Proc. Res. Dev.,* **2006**, *10*, 762. (f) Zhang, W. and Nagashima, T., *J. Fluor. Chem.,* **2006**, *127*, 588. (g) Fayol, A.; Fang, Y.-Q. and Lautens, M., *Org. Lett.,* **2006**, *8*, 4203. (h) Kettler, P., *Speciality Chem. Mag.,* **2005**, *25*, 24. (i) Schlummer, B. and Scholz, U., *Speciality Chem. Mag.,* **2005**, *25*, 22. (j) Iyer, S.; Kulkarni, G. M.; Ramesh, C. and Sattar, A. K., *Indian J. Chem., Sect. B,* **2005**, *44B*, 1894. (k) Schlummer, B. and Scholz, U., *Chimica Oggi*, **2005**, *23*, 18. (l) Goossen, L. J.; Paetzold, J.; Briel, O.; Rivas-Nass, A.; Karch, R. and Kayser, B., *Synlett,* **2005**, 275. (m) Urgaonkar, S.; Xu, J.-H. and Verkade, J. G., *J. Org. Chem.,* **2004**, *69*, 9323. (n) Urgaonkar, S. and Verkade, J. G., *J. Org. Chem.,* **2004**, *69*, 9135. (o) Csuk, R.; Barthel, A. and Raschke, C., *Tetrahedron,* **2004**, *60*, 5737. (p) Meyers, C.; Maes, B. U. W.; Loones, K. T. J.; Bal, G.; Lemière, G. L. F. and Dommisse, R. A., *J. Org. Chem.,* **2004**, *69*, 6010. (q) Bedford, R. B.; Cazin, K. S. J.; Coles, S. J.; Gelbrich, T.; Horton, P. N.; Hursthouse, M. B. and Light, M. E., *Organometallics,* **2003**, *22*, 987. (r) Urgaonkar, S.; Xu, J. H. and Verkade, J. G., *J. Org. Chem.,* **2003**, *68*, 8416. (s) Ullrich, T. and Giraud, F., *Tetrahedron Lett*., 2003, *44*, 4207. (t) Rivas, F. M.; Giessert, A. J. and Diver, S. T., *J. Org. Chem.,* **2002**, *67*, 1708. (u) Rivas, F. M.; Riaz, U.; Giessert, A.; Smulik, J. A. and Diver, S. T., *Org. Lett.,* **2001**, *3*, 2673. (v) Kočovský, P.; Malkov, A. V.; Vyskočil, Š.; and Lloyd-Jones, G. C., *Pure & Appl. Chem.,* **1999**, *71*, 1425. (w) Kočovský, P.; Vyskočil, Š.; Císařová, I.; Sejbal, J.; Tišlerová, I.; Smrčina, M.; Lloyd-Jones, G. C.; Stephen, S. C.; Butts, C. P.; Murray, M. and Langer, V., *J. Am. Chem. Soc.,* **1999**, *121*, 7714.
5. (a) Bonnaterre, F.; Bois-Choussy, M. and Zhu, J. P., *Org. Lett.,* **2006**, *8*, 4351. (b) Cuny, G.; Bois-Choussy, M. and Zhu, J. P., *Angew. Chem. Int. Ed.,* **2003**, *42*, 4774.
6. (a) Begouin, A.; Hesse, S.; Queiroz, M.-J. R. P. and Kirsch, G., *Eur. J. Org. Chem.,* **2007**, 1678. (b) Takeji, T.-E.; Satoko, I.; Masataka, M. and Keiji, W., *Chem. Res. Toxicol.,* **2006,** *19*, 770. (c) Takamura-Enya, T.; Ishikawa, S.; Mochizuki, M. and Wakabayashi, K., *Nucleic Acids Res., Suppl.,* **2003**, 23.
7. (a) Balraju, V. and Iqbal, J., *J. Org. Chem.,* **2006**, *71*, 8954. (b) Shilova, E. A.; Moustrou, C. and Samat, A., *Tetrahedron Lett*., **2005**, *46*, 8857. (c) Ferreira, I. C. F. R.; Queiroz, M.-J. R. P. and Kirsch, G., *Tetrahedron*, **2003**, *59*, 975.
8. (a) Begouin, A.; Hesse, S.; Queiroz, M.-J. R. P. and Kirsch, G., *Eur. J. Org. Chem.,* **2007**, 1678. (b) Fleckenstein, C. A. and Plenio, H., *Chem. Eur. J.,* **2007**, *13*, 2701. (c) Begouin, A.; Hesse, S.; Queiroz, M.-J. R. P. and Kirsch, G., *Synthesis,* **2005**, 2373.
9. Queiroz, M.-J. R. P.; Ferreira, I. C. F. R.; Calhelha, R. C. and Estevinho, L. M., *Bioorg. Med. Chem.,* **2007**, *15*, 1788.
10. (a) Battistuzzi, G.; Bernini, R.; Cacchi, S.; De Salve, I. and Fabrizi, G., *Adv. Synth. Catal.,* **2007**, *349*, 297. (b) Marion, N.; Navarro, O.; Mei, J. G.; Stevens, E. D.; Scott, N. M. and Nolan, S. P., *J. Am. Chem. Soc.,* **2006**, *128*, 4101. (c) Al-Hussaini, A. S.; Klapper, M.; Pakula, T. and Müllen, K., *Macromolecules,* **2004**, *37*, 8269. (d) Kirsch, G.; Hesse, S. and Comel, A., *Curr. Org. Synth.,* **2004**, *1*, 47. (e) Olivera, R.; SanMartin, R.; Churruca, F. and Domïnguez, E., *J. Org. Chem.,* **2002**, *67*, 7215. (f) Johnson, F.; Bonala, R.; Tawde, D.; Torres, M. C. and Iden, C. R., *Chem. Res. Toxicol.,* **2002**, *15*, 1489. (g) Wang, Z. W. and Rizzo, C. J., *Org. Lett.,* **2001**, *3*, 565. (h) de Riccardis, F.; Bonala, R. R. and Johnson, F., *J. Am. Chem. Soc.,* **1999**, *121*, 10453.
11. Mulder, J. A.; Kurtz, K. C. M. and Hsung, R. P., *Synlett,* **2003**, 1379.
12. (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F. and Buchwald, S. L., *Acc. Chem. Res.,* **1998**, *31*, 805. (b) Hartwig, J. F., *Angew. Chem. Int. Ed.,* **1998**, *37*, 2046.

13. (a) Navarro, O.; Kaur, H.; Mahjoor, P. and Nolan, S. P., *J. Org. Chem.,* **2004**, *69*, 3173. (b) Herrmann, W. A., *Angew. Chem. Int. Ed. Engl.,* **2002**, *41*, 1290. (c) Grasa, G. A.; Viciu, M. S.; Huang, J. and Nolan, S. P., *J. Org. Chem.,* **2001**, *66*, 7729.
14. (a) Frost, C. G. and Mendonça, P., *J. Chem. Soc., Perkin Trans. I,* **1998**, 2615. (b) Wolfe, J. P.; Wagaw, S. and Buchwald, S. L., *J. Am. Chem. Soc.,* **1996**, *118*, 7215.
15. Wolfe, J. P. and Buchwald, S. L., *J. Org. Chem.,* **1996**, *61*, 1133.
16. Driver, M. S. and Hartwig, J. F., *J. Am. Chem. Soc.,* **1996**, *118*, 7217.
17. Wolfe, J. P. and Buchwald, S. L., *J. Org. Chem*., **2000**, *65*, 1144.
18. (a) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P. and Buchwald, S. L., *J. Am. Chem. Soc.,* **1999**, *121*, 4369. (b) Palucki, M.; Wolfe, J. P. and Buchwald, S. L., *J. Am. Chem. Soc.,* **1996**, *118*, 10333.
19. (a) Klapper, A.; Huang, X. and Buchwald, S. L., *J. Am. Chem. Soc.,* **2002**, *124*, 7421. (b) Kwong, F. Y.; Klapars, A. and Buchwald, S. L., *Org. Lett.,* **2002**, *4*, 581. (c) Shen, R. and Porco, J. A., *Org. Lett.,* **2002**, *2*, 1333. (d) Yamada, K.; Kubo, T.; Tokuyama, H. and Fukuyama, T., *Synlett,* **2002**, 231. (e) Klapars, A.; Antilla, J. C.; Huang, X. and Buchwald, S. L., *J. Am. Chem. Soc.,* **2001**, *123*, 7727. (f) Lam, P. Y. S.; Deudon, S.; Averill, K. M.; Li, R.; He, M. Y.; DeShong, P. and Clark, C. G., *J. Am. Chem. Soc.,* **2000**, *122*, 7600. (g) Kang, S.-K.; Lee, S.-H. and Lee, D., *Synlett,* **2000**, 1022. (h) Lindley, J., *Tetrahedron,* **1984**, *40*, 1433. (i) Yamamoto, T., *Synth. Commun.,* **1979**, *9*, 219.
20. Lakshman, M. K.; Keeler, J. C.; Hilmer, J. H. and Martin, J. Q., *J. Am. Chem. Soc.,* **1999**, *121*, 6090.
21. (a) Wolf, C. and Lerebours, R., *Org. Biomol. Chem.,* **2004**, *2*, 2161. (b) Muci, A. R. and Buchwald, S. L., *Top. Curr. Chem*., **2002**, *219*, 131. (c) Colacot, T. J., *Platinum Metals Rev.*, **2001**, *45*, 22. (d) Lipshutz, B. H., *Adv. Synth. Catal*., **2001**, *343*, 313. (e) Hartwig, J. F., *Pure & Appl. Chem*., **1999**, *71*, 1417.
22. Hartwig, J. F., *Synlett,* **1996**, 329.
23. Louie, J.; Paul, F. and Hartwig, J. F., *Organometallics,* **1996**, *15*, 2794.
24. (a) Kwit, M.; Kubicki, M.; Borowiak, T. and Gawronski, J., *Polish J. Chem.,* **2003**, *77*, 1669. (b) Yang, B. H. and Buchwald, S. L., *J. Organomet. Chem.,* **1999**, *576*, 125.
25. (a) Chakraborti, D.; Colis, L.; Schneider, R. and Basu, A. K., *Org. Lett*., **2003**, *5*, 2861. (b) Urgaonkar, S.; Nagarajan, M. and Verkade, J. G., *J. Org. Chem*., **2003**, *68*, 452. (c) Maes, B. U. W.; Jonkers, T. H. M.; Lemière, G. L. F.; Rombouts, G.; Pieters, L.; Haemers, A. and Domisse, R. A., *Synlett*, **2003**, 615. (d) Mukherjee, A. and Sarkar, A., *ARKIVOC*, **2003**, 87. (e) Gao, G. Y.; Colvin, A. J.; Chen, Y. and Zhang, X. P., *Org. Lett*., **2003**, *5*, 3261. (f) Nozaki, K.; Takahashi, K.; Nakano, K.; Tang, H-Z.; Fujiki, M.; Yamaguchi, S. and Tamao, K., *Angew. Chem. Int. Ed.,* **2003**, *42*, 2051. (g) Siemeling, U.; Auch, T.-C.; Kuhnert, O.; Malaun, M.; Kopacka, H. and Bildstein, B., *Z. Anorg. Allg. Chem*., **2003**, *629*, 1334. (h) Lopez, F.; Ohmura, T. and Hartwig, J. F., *J. Am. Chem. Soc*., **2003**, *125*, 3426. (i) Ohmura, T. and Hartwig, J. F., *J. Am. Chem. Soc*., **2002**, *124*, 15164. (j) Hartwig, J. F., In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, **2002**; p. 1051. (k) McManus, H. A. and Guiry, P. J., *J. Org. Chem*., **2002**, *67*, 8566. (l) Williams, B. S. and Goldberg, K. I., *J. Am. Chem. Soc.,* **2001**, *123*, 2576. (m) Ali, M. H. and Buchwald, S. L., *J. Org. Chem*., **2001**, *66*, 2560. (n) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J. and Buchwald, S. L., *J. Org. Chem*., **2000**, *65*, 1158. (o) Lipshutz, B. H. and Ueda, H., *Angew. Chem. Int. Ed*., **2000**, *39*, 4492. (p) Wentland, M. P.; Xu, G. Y.; Cio, C. L.; Ye, Y. C.; Duan, w. H.; Cohen, D. J.; Colasurdo, A. M. and Bidlack, J. M., *Bioorg. Med. Chem. Lett.,* **2000**, *10*, 183. (q) Frost, C. G. and Mendonça, P., *Tetrahedron: Asymmetry*, **1999**, *10*, 1831. (r) Kawatsura, M. and Hartwig, J. F., *J. Am. Chem. Soc*., **1999**, *121*, 1473. (s) Wolfe, J. P. and Buchwald, S. L., *Angew. Chem. Int. Ed*., **1999**, *38*, 2413. (t) Wolfe, J. P.; Singer, R. A.; Yang, B. H. and Buchwald, S. L., *J. Am. Chem. Soc*., **1999**, *121*, 9550. (u) Hartwig, J. F.; Kawatsura, M.; Hauck, S. H.; Shaughnessy, K. H. and Alcazar-Roman, L. M.,

J. Org. Chem., **1999**, *64*, 5575. (v) Mann, G.; Hartwig, J. F.; Driver, M. S. and Rivas, C. F., *J. Am. Chem. Soc*., **1998**, *120*, 827. (w) Old, D. W.; Wolfe, J. P. and Buchwald, S. L., *J. Am. Chem. Soc*., **1998**, *120*, 9722. (x) He, F.; Foxman, B. M. and Snider, B. B., *J. Am. Chem. Soc.,* **1998**, *120*, 6417. (y) McNeill, S.; Gray, M.; Briggs, L. E.; Li, J. J. and Snieckus, V., *Synlett*, **1998**, *4*, 419. (z) Ahman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M. and Buchwald, S. L., *J. Am. Chem. Soc*., **1998**, *120*, 1918. (aa) Wuellner, G.; Jaensch, H.; Kannenberg, S.; Schubert, F. and Boche, G., *Chem. Commun*., **1998**, 1509. (bb) Louie, J.; Hartwig, J. F. and Fry, A. J., *J. Am. Chem. Soc*., **1997**, *119*, 11695. (cc) Marcoux, J.; Wagaw, S. and Buchwald, S. L., *J. Org. Chem*., **1997**, *62*, 1568. (dd) Louie, J.; Driver, M. S.; Hamann, B. C. and Hartwig, J. F., *J. Org. Chem*., **1997**, *62*, 1268. (ee) Wolfe, J. P. and Buchwald, S. L., *J. Org. Chem.,* **1997**, *62*, 1264. (ff) Palucki, M. and Buchwald, S. L., *J. Am. Chem. Soc.,* **1997**, *119*, 11108. (gg) Hamann, B. C. and Hartwig, J. F., *J. Am. Chem. Soc.,* **1997**, *119*, 12382. (hh) Wolfe, J. P.; Rennels, R. A. and Buchwald, S. L., *Tetrahedron*, **1996**, 7525. (ii) Louie, J. and Hartwig, J. F., *Tetrahedron Lett*., **1995**, *36*, 3609. (jj) Guram, A. S.; Rennels, R. A. and Buchwald, S. L., *Angew. Chem. Int. Ed. Engl.,* **1995**, *34*, 1348.

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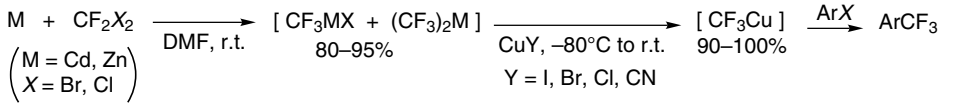
Burton Trifluoromethylation

A. GENERAL DESCRIPTION OF THE REACTION

Although many methods have been available for the introduction of trifluoromethyl group into aromatic compounds, the Burton trifluoromethylation, first reported in 1985,[1] is probably one of the most feasible methods for incorporating the CF_3 group directly into the molecules via *in situ* generation and coupling of CF_3Cu with aryl halide. All other earlier methods[2] had some drawbacks, including the application of expensive reagents (e.g., CF_3I, $(CF_3)_2Hg$) or requiring high temperatures or reducing aryl halides.[3] In contrast, trifluoromethyl copper is generated in the Burton trifluoromethylation via *in situ* metathesis of (trifluoromethyl)cadmium [CF_3CdX + $(CF_3)_2Cd$] or (trifluoromethyl)zinc [CF_3ZnX + $(CF_3)_2Zn$]; in addition, trifluoromethyl copper can also be generated *in situ* from cheap difluorodihalomethanes (Freon) precursors with soluble copper (I) salts, such as CuCl, CuBr, CuI, and CuCN. The metathesis reaction of copper (I) salts with [CF_3CdX] occurs rapidly even at –30°C, although the exchange between [CF_3ZnX] and CuBr is slow. One recent development of trifluoromethylation starts from CF_3SiMe_3.[4] It has been found that CF_3Cu is a versatile CF_2 transfer reagent, involving a selective C-F bond scission to form a difluorocarbene copper complex, and insertion of the CF_2 unit to the C-F bond of CF_3Cu provides a method for longer chain $CF_3(CF_2)_nCF_2$-Cu (n = 0–14) compounds.[5]

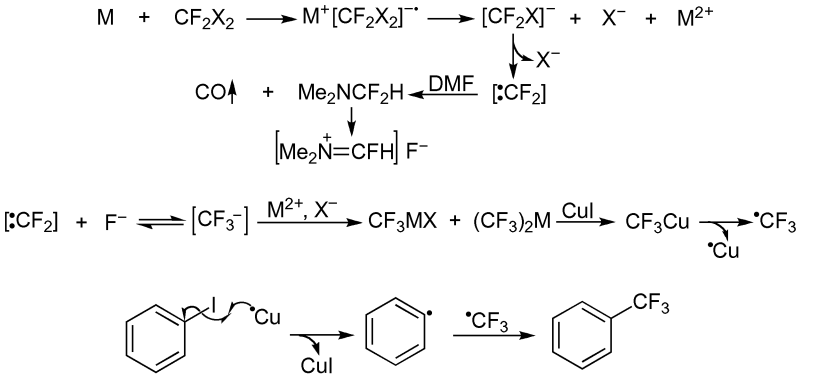
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

The mechanism shown here is according to Burton.[1]



D. MODIFICATION

N/A

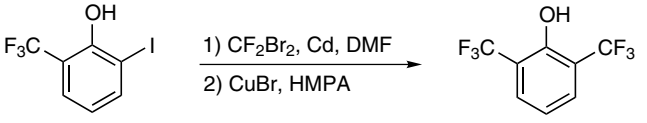
E. APPLICATIONS

This reaction can be used to incorporate the trifluoromethyl group into aromatic compounds.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 6.

A mixture of 21.0 g Cd powder (187 mmol) in 83 mL DMF was treated at 0°C with 11.5 mL CF_2Br_2 (125 mmol) at a rate that maintained the temperature below 40°C. The mixture was stirred at room temperature for an additional 30 min and was then diluted with 83 mL HMPA. The reaction mixture was cooled to 0°C, and to it was added 8.96 g CuBr (62.5 mmol), causing an exotherm to ~ 18°C. The mixture was then warmed to room temperature and stirred for 10 min. The resultant mixture of [CF_3Cu] was treated with 6.0 g 2-iodo-6-(trifluoromethyl)phenol (20.8 mmol) and then heated at 60°C for 90 min. The reaction mixture was cooled to room temperature and poured into a mixture of 3 N HCl and ether (200 mL each), and then the solids were removed from the mixture by filtration. The aqueous phase was extracted with ether, and the combined extract was washed with saturated NaCl and then dried over $MgSO_4$. The volatile was distilled from the crude product, which was then isolated by distillation to furnish 2.37g 2,6-bis(trifluoromethyl)phenol, in a yield of 47%, b.p. 70°C (30 mmHg).

Other references related to the Burton trifluoromethylation are cited in the literature.[7]

H. REFERENCES

1. Burton, D. J. and Wiemers, D. M., *J. Am. Chem. Soc.,* **1985**, *107*, 5014.
2. (a) Leroy, J.; Rubinstein, M. and Wakselman, C., *J. Fluor. Chem.,* **1985**, *27*, 291. (b) Suzuki, H.; Yoshida, Y. and Osuka, A., *Chem. Lett.,* **1982**, 135. (c) Matsui, K.; Tobita, E.; Ando, M. and Kondo, K., *Chem. Lett.,* **1981**, 1719. (d) Kobayashi, Y.; Yamamoto, K.; Asai, T.; Nakano, M. and Kumadaki, I., *J. Chem. Soc., Perkin Trans. I,* **1980**, 2755. (e) Kondratenko, N. V.; Vechirko, E. P. and Yagupolskii, L. M., *Synthesis,* **1980**, 932. (f) Kobayashi, Y. and Kumadaki, I., *J. Chem. Soc., Perkin Trans. I,* **1980**, 661. (g) McLoughlin, V. C. R. and Thrower, J., *Tetrahedron,* **1969**, *25*, 5921. (h) Kobayashi, Y.; Kumadaki, I., *Tetrahedron Lett.,* **1969**, 4095.
3. Wiemers, D. M. and Burton, D. J., *J. Am. Chem. Soc.,* **1986**, *108*, 832.
4. (a) Ramaiah, P.; Krishnamurti, R. and Prakash, G. K. S., *Org. Synth.,* **1995**, 232. (b) Krishnamurti, R.; Bellew, D. R. and Prakash, G. K. S., *J. Org. Chem.,* **1991**, *56*, 984. (c) Prakash, G. K. S.; Krishnamurti, R. and Olah, G. A., *J. Am. Chem. Soc.,* **1989**, *111*, 393.
5. Chiu, W.-Y. and Chiang, C.-M., *J. Phys. Chem. B,* **2003**, *107*, 6245.
6. Miller, J. A.; Coleman, M. C. and Matthews, R. S., *J. Org. Chem.,* **1993**, *58*, 2637.
7. (a) Yang, Z.-Y. and Burton, D. J., *J. Fluor. Chem.,* **2000**, *102*, 89. (b) McClinton, D. A., *Tetrahedron,* **1992**, *48*, 6555. (c) Yamazaki, T. and Kitazume, T., *Rev. Heteroat. Chem.,* **1992**, *7*, 132. (d) Burton, D. J. and Yan, Z. Y., *Tetrahedron,* **1992**, *48*, 189. (e) McClinton, M. A. and McClinton, D. A., *Tetrahedron,* **1992**, *48*, 6555. (f) Yang, Z.-Y.; Wiemers, D. M. and Burton, D. J., *J. Am. Chem. Soc.,* **1992**, *114*, 4402. (g) Van, P. L. and Wells, P. R., *Aust. J. Chem.,* **1992**, *45*, 1057. (h) Burton, D. J. and Yuang, Z. Y., *J. Fluor. Chem.,* **1989**, *44*, 339. (i) Clark, J. H.; McClinton, M. A.; Jones, C. W.; Landon, P.; Bishop, D. and Blade, R. J., *Tetrahedron Lett*., **1989**, *30*, 2133. (j) Clark, J. H.; McClinton, M. A. and Blade, R. J., *J. Chem. Soc., Chem. Commun.,* **1988**, 638.

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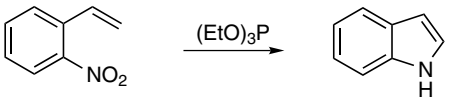
Cadogan-Sundberg Indole Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction can be traced back to the initial work of Cadogan for the preparation of carbazole by the reductive cyclization of aromatic nitro compounds with triethyl phosphite.[1] This reaction was then extended by Sundberg to the formation of indoles by the treatment of *o*-nitrostyrene with triethyl phosphite[2] or the formation of indolines from the *o*-alkyl nitrobenzenes.[3] Thus the formation of indole from the reduction of *o*-nitrostyrenes is referred to as the Cadogan-Sundberg indole synthesis.[4]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The Cadogan-Sundberg indole synthesis involves the insertion of phosphorus atom to the N=O double bond of the nitro group followed by the cleavage of triethyl phosphate to give *N*-hydroxyl indole. Subsequently, the *N*-hydroxyl indole was reduced by a second triethyl phosphite to afford indole as shown here.

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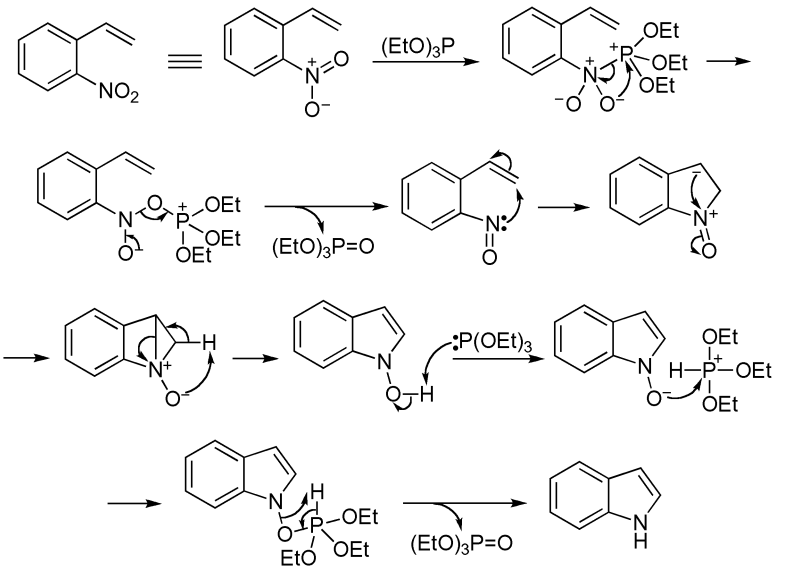


D. MODIFICATION

The reductive cyclization of *o*-nitrostryene (i.e., the Cadogan-Sundberg indole synthesis) has been improved by the transition metal catalyzation,[5] selenium-based reductive cyclization,[6] or hydrogen/Raney nickel reduced cyclization.[7]

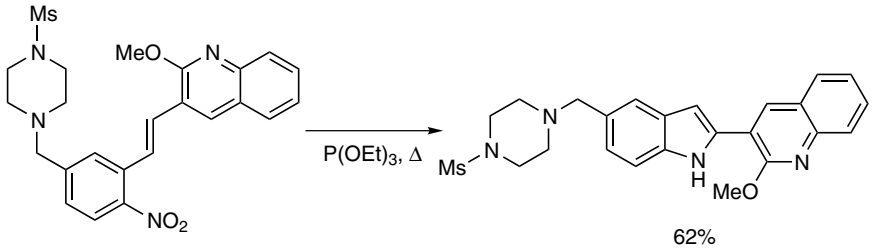
E. APPLICATIONS

This reaction is useful for the preparation of indole derivatives.

F. RELATED REACTIONS

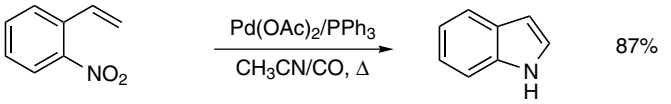
This reaction is related to the *Bartoli Indole Synthesis* from aromatic nitro compounds.

G. CITED EXPERIMENTAL EXAMPLES



Reference 8.

A solution 1.5 g *trans*-3-{2-[5-(4-methanesulfonylpiperazine-1-ylmethyl)-2-nitrophenyl]vinyl}-2-methoxyquinoline (3.10 mmol) in 15.5 mL $P(OEt)_3$ was heated to 155°C for 2 h and the solvent was removed under reduced pressure. The residue was purified by flash silica gel chromatography to give 908 mg 2-methoxy-3-[5-[[4-(methysulfonyl)-1-piperazinyl]methyl]-1*H*-indol-2-yl]quinoline as a light yellow solid, in a yield of 62%, m.p. 197–198°C.



Reference 5e.

To an oven-dried, threaded ACE glass pressure tube was added 298 mg 2-nitrostyrene (2.00 mmol), 26 mg palladium diacetate (0.12 mmol), 124 mg triphenylphosphine (0.48 mmol), and 4 mL CH_3CN. The tube was fitted with a pressure head, the solution was saturated with CO (4 cycles to 4 atm of CO), and the reaction mixture was heated to 70°C (oil bath temperature) under 4 atm of CO atmosphere until all starting material was consumed as judged by TLC ($\sim$ 15 h). The reaction mixture was diluted with 10 mL 10% aqueous HCl and extracted with Et_2O (3 $\times$ 10 mL). The combined organic phases were washed with 10 mL 10% HCl and dried over $MgSO_4$. Upon removal of the solvent, the residue was purified by chromatography using hexanes/EtOAc (9:1) to afford 203 mg indole as white crystals, in a yield of 87%.

Other references related to the Cadogan-Sundberg indole synthesis are cited in the literature.[9]

H. REFERENCES

1. (a) Cadogan, J. I. G. and Cameron-Wood, M., *Proc. Chem. Soc.,* **1962**, 361. (b) Cadogan, J. I. G.; Mackie, R. K. and Todd, M. J., *J. Chem. Soc., Chem. Commun.,* **1966**, 491.
2. (a) Sundberg, R. J., *J. Org. Chem.,* **1965**, *30*, 3604. (b) Sundberg, R. J. and Tamazaki, T., *J. Org. Chem.,* **1967**, *32*, 290.
3. Sundberg, R. J., *J. Am. Chem. Soc.,* **1966**, *88*, 3781.
4. (a) Ono, N., "Cadogan-Sundberg Indole Synthesis" in *The Nitro Group in Organic Synthesis*, Wiley-VCH, New York, **2001**. (b) Gribble, G. W., *J. Chem. Soc*., *Perkin Trans. I*, **2000**, 1045. (c) Gribble, G. W., *Contemp. Org. Synth.,* **1994**, *1*, 145.
5. (a) Dantale, S. W. and Söderberg, B. C. G., *Tetrahedron,* **2003**, *59*, 5507. (b) Scott, T. L. and Söderberg, B. C. G., *Tetrahedron Lett.,* **2002**, *43*, 1621. (c) Ragaini, F.; Sportiello, P. and Cenini, S., *J. Organomet. Chem.,* **1999**, *577*, 283. (d) Söderberg, B. C.; Rector, S. R. and O'Neil, S. N., *Tetrahedron Lett.,* **1999**, *40*, 3657. (e) Söderberg, B. C. and Shiver, J. A., *J. Org. Chem.,* **1997**, *62*, 5838.
6. Nishiyama, Y.; Maema, R.; Ohno, K.; Hirose, M. and Sonoda, N., *Tetrahedron Lett.*, **1999**, *40*, 5717.
7. Melhado, L. L. and Leonard, N. J., *J. Org. Chem.,* **1983**, *48*, 5130.
8. Kuethe, J. T.; Wong, A.; Qu, C. X.; Smitrovich, J.; Davies, I. W. and Hughes, D. L., *J. Org. Chem.,* **2005**, *70*, 2555.

9. (a) Dalpozzo, R. and Bartoli, G., *Curr. Org. Chem.,* **2005**, *9*, 163. (b) Kuethe, J. T.; Wong, A. and Davies, I. W., *Org. Lett.,* **2003**, *5*, 3721. (c) Kuethe, J. T., Wong, A. and Davies, I. W., *Org. Lett.,* **2003**, *5*, 3975. (d) Merlic, C. A.; You, Y.; McInnes, D. M.; Zechman, A. L.; Miller, M. M. and Deng, Q., *Tetrahedron,* **2001**, *57*, 5199. (e) Holzapfel, C. W. and Dwyer, C., *Heterocycles*, **1998**, *48*, 1513. (f) Jesudoss, K. and Srinivasan, P. C., *Synth. Commun.,* **1994**, *24*, 1701. (g) Cadogan, J. I. G. and Todd, M. J., *J. Chem. Soc.,* **1969**, 2808.

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Caglioti Reaction

(Caglioti Reduction, Caglioti Alkene Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Caglioti in 1962.[1] It is a conversion of a carbonyl group in either ketones or aldehydes into a methylene group or an olefinic moiety with vicinal carbon by treatment of the corresponding *p*-tosylhydroazones of the ketones or aldehydes with a hydride base, such as diborane (B_2H_6), lithium hydride (LiH), sodium borohydride ($NaBH_4$), lithium aluminum hydride ($LiAlH_4$), sodium cyanoborohydride ($NaBH_3CN$), and catecholborane. This reaction is thus generally known as the Caglioti reaction.[2] Occasionally, it is also referred to as the Caglioti reduction[3] and Caglioti alkene synthesis.[4]

In terms of conversion of carbonyls into methylene groups, the Caglioti reaction is an alternative to the normal *Wolff-Kishner Reduction*, *Huang-Minlon Modification*, and *Clemmensen Reduction*, but it is more closely related to *Bamford-Stevens Reaction*. When diborane is applied as a hydride source, the Caglioti reaction is often carried out for the reduction of α,β-unsaturated ketones in the presence of acetic anhydride.[2d] However, such conditions have been used only a few times due to the formation of diverse product, such as dienes and vicinal diacetates. It was found that when diborane is generated *in situ* from $NaBH_4$ and $BF_3{\cdot}Et_2O$ in diglyme while moisture and air are rigorously expelled from the reaction system, high yields of alkenes can be achieved from α,β-unsaturated ketones.[2d] The higher reactivity of diborane in diglyme rather than in THF is probably due to the formation of a stable complex between diborane and THF.[2d] When $LiAlH_4$ is applied as the hydride source,[2b,2e,5] mixture of hydrocarbons are obtained for the reduction of tosyl-

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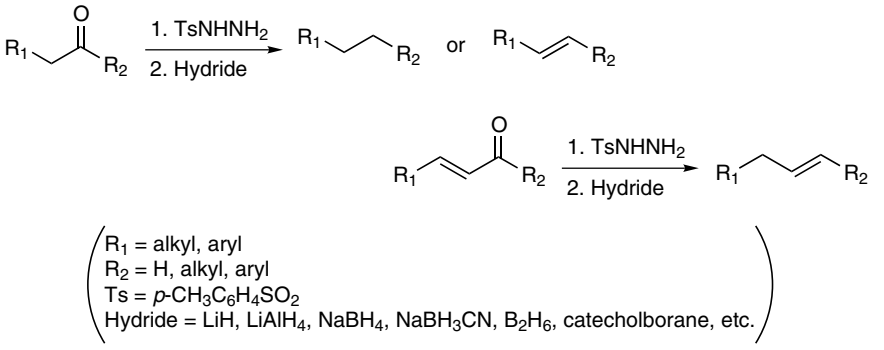
hydrazones of α,β-unsaturated ketones.[5a] Although $LiAlH_4$ is a strong hydride donor, it still fails to reduce the tosylhydrazone of 2,2-dimethyl-3,4-dien-hexaldehyde that has been successfully reduced by *Wolff-Kishner Reduction* in DMSO at 100°C by using $KOBu^t$ as the base.[5c] It is interesting that $LiAlH_4$ can simultaneously remove the α-nitro group and reduce the carbonyl group so that the *p*-tosylhydrazones of α-nitroketones in THF can be directly converted into saturated hydrocarbons.[2b] When $NaBH_4$ is applied for the reduction of *p*-tosylhydrazones of ketones, the reactions are often refluxed in methanol or dioxane.[6] However, the reaction often suffers from the relatively low selectivity at the reaction temperature.[6b,6c] As examples, the reaction might be accompanied by the concomitant reduction of the acetoxy group,[7] ester group,[8] and aromatic nitro group.[9] Even though lithium hydride (LiH) has been used in a few cases,[10] the low solubility of LiH may result in a sluggish reaction mixture.[10b] It was found that such difficulty can be overcome by the addition of a small amount of diglyme.[10b] Compared with the above hydride bases, sodium cyanoborohydride ($NaBH_3CN$) is a mild and highly selective reagent for reducing the tosylhydrazones of aliphatic ketones and aldehydes.[5a] The reduction can be carried out under acidic condition, such as in a 1:1 mixture of DMF and sulfolane containing *p*-toluenesulfonic acid at 100–105°C.[6c] Similar to the failure of $LiAlH_4$ in reduction of 2,2-dimethyl-3,4-dien-hexaldehyde with a carbonyl group adjacent to a tertiary carbon, $NaBH_3CN$ also fails to convert a β-tetralone with *spiro*-piperidine at the α-position; however, such type of carbonyl group can be converted by the *Huang-Minlon Modification*.[11] When catecholborane is used as the hydride source,[2b,12] the reduction occurs in mild conditions, such as at neutral pH, room temperature, and in an aprotic solvent; in addition, the reduction of the tosylhydrazones of ketones and aldehydes is also tolerated for most of functional groups and gives only a single hydrocarbon product.[12a]

It should be pointed out that from the known results, regardless of which hydride source (e.g., diborane,[2d] $NaBH_3CN$,[5a] and catecholborane[12b]) is applied for the reduction of α,β-unsaturated carbonyl molecules, the new formed carbon-carbon double bond will migrate to the original carbonyl location.

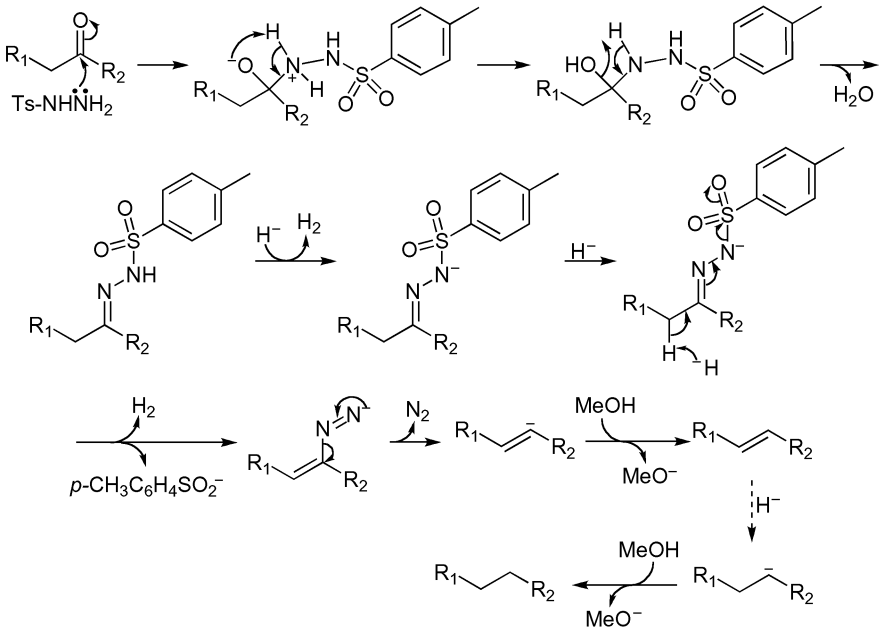
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It has been proposed that this reaction involves the initial reduction of tosylhydrazone to tosylhydrazine, followed by the elimination of *p*-toluenesulfinic acid and the decomposition

of the diimide intermediate to hydrocarbon.[6a,6c] However, because the sulfonamide proton is slightly acidic (pKa = 8.5),[5b] the initial reaction should remove such hydrogen atom. Upon the subsequent deprotonation of the α-proton and elimination of the *p*-toluenesulfinate, unsaturated diazo anion is formed, which decomposes to give an alkenyl anion. The abstraction of proton from solvent or any hydrogen source will give a neutral alkene. Furthermore, in the presence of an excess amount of hydride source, the addition of hydride to the olefinic double bond will afford a carbanion that can be simply quenched by solvent or a proton source. Provided here is an illustration of the reaction details.



D. MODIFICATION

The initial reaction condition has been extended to use catecholborane as the hydride source.[2b,12] In addition, optimal conditions when diborane is used as the hydride source have been developed using *in situ* generated diborane from $NaBH_4$ and $BF_3{\cdot}Et_2O$ in diglyme while rigorously removing moisture and air.[2d] Moreover, cyclic 1,3-diketones can be converted into cyclic 2-enones using a relatively weak base.[5b]

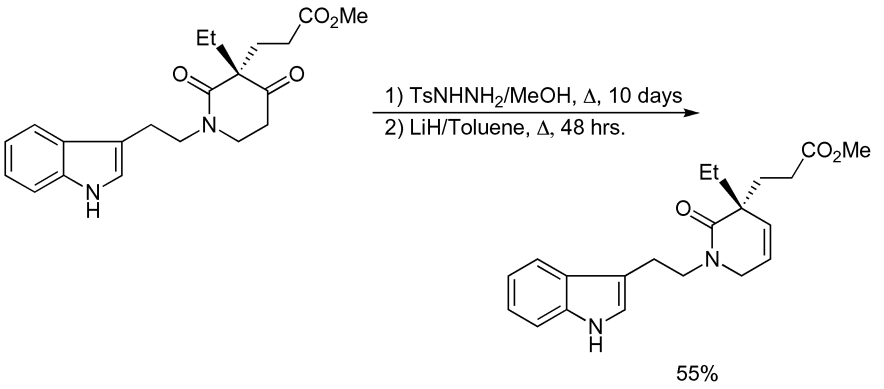
E. APPLICATIONS

Similar to the *Wolff-Kishner Reduction* and *Clemmensen Reduction*, this reaction is also useful for the conversion of carbonyl compounds into hydrocarbons and olefins.

F. RELATED REACTIONS

This reaction is closely related to the *Bamford-Stevens Reaction*.

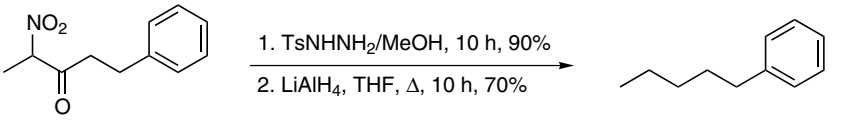
G. CITED EXPERIMENTAL EXAMPLES



Reference 10a.

A mixture of 2.0 g (*R*)-3-ethyl-1-[2-(1*H*-indol-3-yl)ethyl]-2,4-dioxo-3-piperidinepropanoic acid methyl ester (5.4 mmol) and 2.0 g (*p*-toluenesulfonyl)hydrazine (10.8 mmol) in 10 mL MeOH was refluxed for 2 days; then an additional 1.0 g (*p*-toluenesulfonyl)hydrazine (5.4 mmol) in 2.0 mL MeOH was added. The operation was repeated every 48 h over 10 days. The mixture was then concentrated under reduced pressure, and the residue was chromatographed on silica gel using hexane/EtOAc (1:1) to give 2.30 g pure (*R*)-3-ethyl-1-[2-(1*H*-indol-3-yl)ethyl]-2-oxo-4-[[(4-methylphenyl)sulfonyl]hydrazono]-3-piperidinepropanoic acid methyl ester as a yellow amorphous solid, in a yield of 80%.

To a suspension of 70 mg LiH (8.80 mmol) in 5 mL toluene was added 1.0 g above hydrazone (1.86 mmol). The mixture was refluxed for 48 h. After being cooled to 20°C, the above mixture was poured into crushed ice and extracted with CH_2Cl_2. The collected organic phases were washed with brine, dried, and concentrated in vacuo. Chromatography on silica gel using hexane/EtOAc (1:1) gave 362 mg (*R*)-3-ethyl-1-[2-(1*H*-indol-3-yl)ethyl]-2-oxo-1,2,3,6-tetrahydro-3-pyridinepropanoic acid methyl ester as a pale yellow oil, in a yield of 55%.



Reference 2b.

To a solution of 1.77 g 2-nitro-5-phenyl-3-pentanone (8.53 mmol) in 5 mL MeOH was added 10 mL MeOH solution of 1.65 g (*p*-tolylsulfony1)hydrazine (8.9 mmol); the mixture was stirred for 10 h, then water was added to precipitate 2-nitro-5-phenyl-3-pentanone (*p*-tolylsulfonyl)hydrazone, which was purified by recrystallization from MeOH/water, in a yield of 90%, m.p. 104–105°C.

To a solution of 0.3 g $LiAlH_4$ (7.92 mmol) in 30 mL dry THF at 0°C was added 0.99 g purified hydrazone (2.64 mmol) in 20 mL dry THF under a nitrogen atmosphere dropwise. The resulting mixture was stirred at 60°C for 10 h and cooled to room temperature. The

reaction mixture was treated with 20 mL cold water, acidified with 2 *N* HCl, and extracted with *n*-pentane (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated by distillation; the residue was purified by short silica gel chromatography using *n*-pentane as the eluent to give 70% of pentylbenzene, b.p. 115°C at 60 mmHg.

Other references related to the Caglioti reaction are cited in the literature.[13]

H. REFERENCES

1. (a) Caglioti, L.; Cainelli, G. and Selva, A., *Chim. Ind. (Milan),* **1962**, *44*, 36. (b) Caglioti, L.; Cainelli, G.; Maina, G. and Selva, A., *Gazz. Chim. Ital.,* **1962**, *92*, 309. (c) Caglioti, L. and Magi, M., *Tetrahedron Lett.,* **1962**, 1261.
2. (a) Camps, P.; Colet, G.; Segura, S. and Vázquez, S., *ARKIVOC,* **2007**, (*iv*) 8. (b) Ballini, R.; Petrini, M. and Rosini, G., *J. Org. Chem.,* **1990**, *55*, 5159. (c) Shoppee, C. W. and Hart, R. J., *J. Chem. Soc*., *Perkin Trans. I,* **1983**, 2369. (d) Cambie, R. C.; Rutledge, P. S.; Scott, D. W. and woodgate, P. D., *Aust. J. Chem.,* **1979**, *32*, 695. (e) Edamura, F. Y. and Nickon, A., *J. Org. Chem.,* **1970**, *35*, 1509.
3. Wenkert, E.; Wovkulich, P. M.; Pellicciari, R. and Ceccherelli, P., *J. Org. Chem.,* **1977**, *42*, 1105.
4. Lane, C. F., *Chem. Rev.,* **1976**, *76*, 773.
5. (a) Taylor, E. J. and Djerassi, C., *J. Am. Chem. Soc.,* **1976**, *98*, 2275. (b) Hiegel, G. A. and Burk, P., *J. Org. Chem.,* **1973**, *38*, 3637. (c) Jacobs, T. L.; Macomber, R. and Zunker, D., *J. Am. Chem. Soc.,* **1967**, *89*, 7001.
6. (a) Grandi, R.; Marchesini, A.; Pagnoni, U. M. and Trave, R., *J. Org. Chem.,* **1976**, *41*, 1755. (b) Hutchins, R. O.; Milewski, C. A. and Maryanoff, B. E., *J. Am. Chem. Soc.,* **1973**, *95*, 3662. (c) Hutchins, R. O.; Maryanoff, B. E. and Milewski, C. A., *J. Am. Chem. Soc.,* **1971**, *93*, 1793.
7. Caglioti, L., *Tetrahedron,* **1966**, *22*, 487.
8. (a) Takahashi, S. and Cohen, L. A., *J. Org. Chem.,* **1970**, *35*, 1505. (b) Brown, M. S. and Rapport, H., *J. Org. Chem.,* **1963**, *28*, 3261.
9. Hutchins, R. O.; Lamson, D.; Rua, L.; Milewski, C. and Maryanoff, B., *J. Org. Chem.,* **1971**, *36*, 803.
10. (a) Desmaële, D.; Mekouar, K. and d'Angelo, J., *J. Org. Chem.,* **1997**, *62*, 3890. (b) Trost, B. M. and Higuchi, R. I., *J. Am. Chem. Soc.,* **1996**, *118*, 10094. (c) Moriarty, R. M. and Paaren, H. E., *J. Org. Chem.,* **1981**, *46*, 970. (d) Dauben, W. G. and Fullerton, D. S., *J. Org. Chem.,* **1971**, *36*, 3277.
11. Chambers, M. S.; Baker, R.; Billington, D. C.; Knight, A. K.; Middlemiss, D. N. and Wong, E. H. F., *J. Med. Chem.,* **1992**, *35*, 2033.
12. (a) Kabalka, G. W. and Summers, S. T., *J. Org. Chem.,* **1981**, *46*, 1217. (b) Kabalka, G. W.; Yang, D. T. C. and Baker, J. D., *J. Org. Chem.,* **1976**, *41*, 574.
13. (a) Hong, S. and Corey, E. J., *J. Am. Chem. Soc.,* **2006**, *128*, 1346. (b) Campiani, G.; Butini, S.; Fattorusso, C.; Catalanotti, B.; Gemma, S.; Nacci, V.; Morelli, E.; Cagnotto, A.; Mereghetti, I.; Mennini, T.; Carli, M.; Minetti, P.; Di Cesare, M. A.; Mastroianni, D.; Scafetta, N.; Galletti, B.; Stasi, M. A.; Castorina, M.; Pacifici, L.; Vertechy, M.; Di Serio, S.; Ghirardi, O.; Tinti, O. and Carminati, P., *J. Med. Chem.,* **2004**, *47*, 143. (c) Kneubühler, S.; Testa, B.; Carta, V.; Altomare, C. and Carotti, A., *Helv. Chim. Acta,* **1993**, *76*, 1956. (d) Hoeve, W. T. and Wynberg, H., *J. Org. Chem.,* **1980**, *45*, 2925. (e) Natale, N. R. and Hutchins, R. O., *Org. Prep. Proced. Int.,* **1979**, *11*, 201. (f) Hutchins, R. O. and Natale, N. R., *J. Org. Chem.,* **1978**, *43*, 2299. (g) Kabalka, G. W.; Yang, D. T. C.; Chandler, J. H. and Baker, J. D., *Synthesis,* **1977**, 124. (h) Kabalka, G. W., *Org. Prep. Proced. Int.,* **1977**, *9*, 131. (i) Sasaki, T.; Eguchi, S. and Hirako, Y., *J. Org. Chem.,*

1977, *42*, 2981. (j) Wyllie, S. G.; Amos, B. A. and Tökés, L., *J. Org. Chem.,* **1977**, *42*, 725. (k) Kabalka, G. W. and Baker, J. D., *J. Org. Chem.,* **1975**, *40*, 1834. (l) Hutchins R. O.; Kacher, M. and Rua, L., *J. Org. Chem.,* **1975**, *40*, 923. (m) Cacchi, S.; Caglioti, L. and Paolucci, P., *Bull. Chem. Soc. Jpn.,* **1974**, *47*, 2323. (n) Midgley, I. and Djerassi, C., *Tetrahedron Lett.,* **1972**, 4673. (o) Caglioti, L., *Org. Synth.,* **1972**, *52*, 122. (p) Schmitz, F. J. and Peters, C. A., *J. Chem. Soc. C,* **1971**, 1905. (q) Chapman, N. B.; Sotheeswaran, S. and Toyne, K. J., *J. Org. Chem.,* **1970**, *35*, 917. (r) Tada, H. and Sawa, Y. K., *J. Org. Chem.,* **1968**, *33*, 3347. (s) White, J. D. and Gupta, D. N., *J. Am. Chem. Soc.,* **1968**, *90*, 6171. (t) Bailey, K. and Halsall, T. G., *J. Chem. Soc. C,* **1968**, 679. (u) Johnson, W. S., *Acc. Chem. Res.,* **1968**, *1*, 1. (v) Djerassi, C. and Tökés, L., *J. Am. Chem. Soc.,* **1966**, *88*, 536. (w) Cope, A. C.; Nealy, D. L.; Scheiner, P. and Wood, G., *J. Am. Chem. Soc.,* **1965**, *87*, 3130. (x) Fisher, M.; Pelah, Z.; Williams, D. H. and Djerassi, C., *Ber.,* **1965**, *98*, 3236. (y) Caglioti, L.; Cainelli, G.; Maina, G. and Selva, A., *Tetrahedron,* **1964**, *20*, 957. (z) Caglioti, L. and Grasselli, P., *Chem. Ind. (London),* **1964**, 153. (aa) Caglioti, L. and Magi, M., *Tetrahedron,* **1963**, *19*, 1127. (bb) Caglioti, L. and Casselli, P., *Chim. Ind. (Milan),* **1963**, 559.

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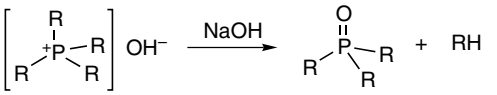
Cahours-Hofmann Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Cahours and Hofmann in 1857.[1] It is the degradation or decomposition of quaternary phosphonium hydroxides into hydrocarbons and trialkyl (or triaryl) phosphine oxides in the presence of bases such as NaOH. The trialkyl phosphine can be simply prepared by the interaction of phosphorus trichloride and zinc alkyls,[2] whereas the quaternary phosphonium hydroxides can be formed by the reaction between base and quaternary phosphonium halides, the latter come from the trialkyl (or triaryl) phosphine and alkyl halides. It is believed that this reaction involves the attack of hydroxide ion on a transient pentacovalent adduct arising from a phosphonium cation and a second hydroxide.[3] The decomposition or degradation of quaternary phosphonium hydroxide is in the following order, according to the alkyl or aryl groups attaching to the phosphorus atom: CH_2=CH-CH_2, $C_6H_5CH_2$ > C_6H_5 > CH_3 > $C_6H_5CH_2CH_2$ > C_2H_5 > C_3H_7. Similarly, tetrahydroxylmethyl phosphonium chloride decomposes in aqueous base to give trihydroxylmethyl phosphine oxide, hydrogen gas and formaldehyde.[4] In contrast to the formation of trialkyl phosphine oxide from this reaction, trialkyl phosphine sulfide can form directly from the reaction between trialkyl phosphine and sulfur.[5]

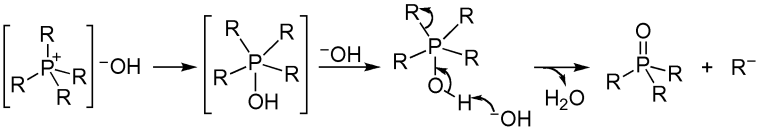
B. GENERAL REACTION SCHEME

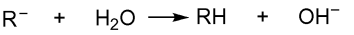


Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

It is believed that this reaction involves a transient pentacovalent phosphorus intermediate, as shown below.





D. MODIFICATION

The trialkyl phosphine oxide can be made from the oxidation of trialkyl phosphine by nitric acid.[4]

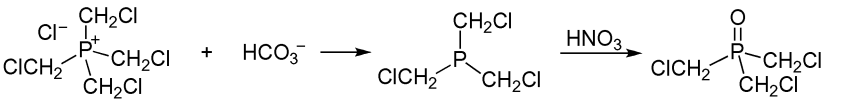
E. APPLICATIONS

This reaction can be used to synthesize different trialkyl- or triarylphosphine oxides.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



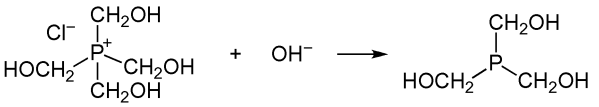
Reference 4.

Preparation of Tri-(Chloromethyl)phosphine

Tetra-(chloromethy1)-phosphonium chloride (5 g) in 20 mL water was treated with 8 g sodium bicarbonate. The solution became milky and gave a strong formaldehyde reaction with fusion reagent. The phosphine was shaken out with carbon bisulfide, dried over sodium sulfate, and distilled under diminished pressure; b.p. 100°C (7 mmHg). While heated at atmospheric pressure, tri-(chloromethyl)phosphine decomposes. It is a colorless, mobile liquid with a powerful, benumbing odor and with slight solubility in water.

Preparation of Tri-(Chloromethyl)phosphine Oxide

Tri-(chloromethyl)phosphine (0.75 g) was boiled for 1 h with 4 mL nitric acid. After evaporating on the water bath until the odor of nitric acid had disappeared, a syrup remained that crystallized on cooling to afford pure tri-(chloromethyl)phosphine oxide, m.p. 88–89°C, which is easily soluble in water and alcohol.



Reference 6.

Sodium hydroxide (1.6 g, 0.040 mol) in 25 mL water was added rapidly to 7.6 g tetra-(hydroxymethyl) phosphonium chloride (0.040 mol) in 50 mL water under nitrogen at room temperature in a closed system connected to a gas buret. No gas evolution was observed after stirring 20 h. The solvent was stripped at 50–60°C with water-pump vacuum, and 50 mL ethanol was added and the sodium chloride was filtered under nitrogen. Removal of ethanol in vacuum (45°C) gave 4.8 g tri-(hydroxymethyl) phosphine as clear viscous liquid, in a yield of 97%.

Other references related to the Cahours-Hofmann reaction are cited in the literature.[7]

H. REFERENCES

1. (a) Cahours, A. and Hofmann, A. W., *Ann.,* **1857**, *104*, 18. (b) Cahours, A. and Hofmann, A. W., *Ann.*, **1857**, *104*, 32.
2. (a) Cahours, A. and Hofmann, A. W., *Ann.*, **1857**, *104*, 1. (b) Cahours, A. and Hofmann, A. W., *Ann.*, **1857**, *104*, 29.
3. (a) Hoffmann, H., *Ann.,* **1960**, *634*, 1. (b) Zanger, M.; VanderWerf, C. A. and McEwen, W. E., *J. Am. Chem. Soc.,* **1959**, *81*, 3806. (c) Fenton, G. W. and Ingold, C. K., *J. Chem. Soc.,* **1929**, 2342.
4. Hoffman, A., *J. Am. Chem. Soc.,* **1930**, *52*, 2995.
5. Bartlett, P. D. and Meguerian, G., *J. Am. Chem. Soc.,* **1956**, *78*, 3710.
6. Grayson M., *J. Am. Chem. Soc.*, **1963**, *85*, 79.
7. (a) Frank, A. W., *Phosphorus, Sulfur & Related Elements,* **1978**, *5*, 19. (b) Vullo, W. J., *J. Org. Chem.,* **1968**, *33*, 3665. (c) Screttas, C. and Isbell, A. F., *J. Org. Chem.,* **1962**, *27*, 2573. (d) Hoffman, A., *J. Am. Chem. Soc.,* **1921**, *43*, 1684. (e) Renshaw, R. R. and Bell, F. K., *J. Am. Chem. Soc.,* **1921**, *43*, 916.

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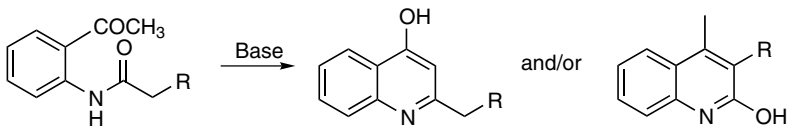
Camps Reaction
(Camps Quinoline Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially discovered by Guareschi in 1894 for the preparation of 2-hydroxy-3-cyano-4-methylquinoline by the condensation of *o*-aminoacetophenone with ethyl cyanoacetate,[1] which was subsequently extended by Camps.[2] It is a formation of hydroxyquinolines by means of the treatment of *N*-acyl *o*-acylanilines with a base in alcohol solution and is generally known as the Camps reaction.[3] Occasionally, it is also referred to as the Camps quinoline synthesis.[4] In this reaction, a variety of substituents can be introduced into position 3 and 4;[5] and *o*-amino derivatives of acetophenone, benzophenone, benzoylacetic ester, benzoylcarbinol, propiophenone,[6] etc. all undergo this reaction. When *o*-amino acetophenone reacts with esters of aliphatic acids, two isomers form simultaneously due to the subtle acidity difference between the methyl group (on acetyl group) and the methylene group (from acyl group on nitrogen). However, when an electron-withdrawing group, such as CN, $COCH_3$, COC_6H_5, CO_2Et, or C_6H_5, exists on the methylene group, only one product forms.[5]

B. GENERAL REACTION SCHEME



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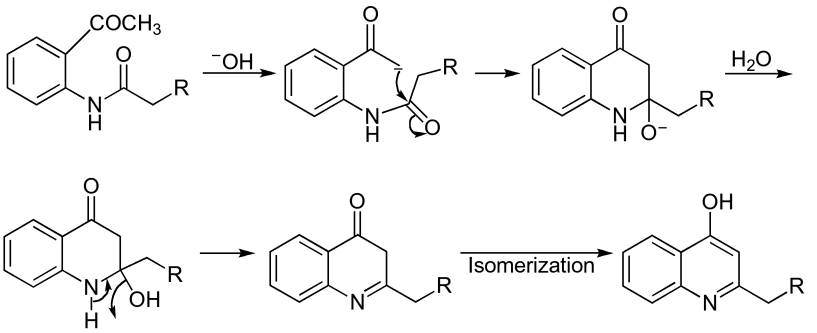
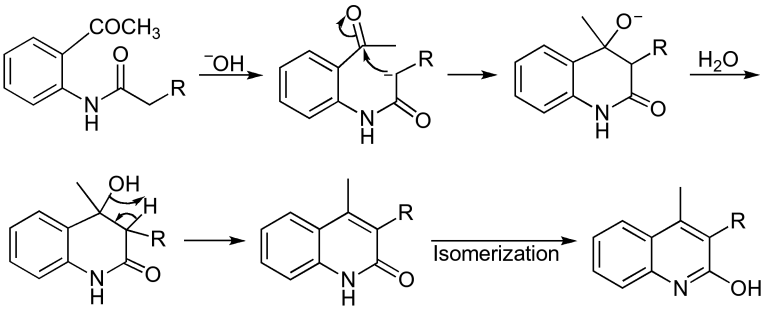
C. PROPOSED MECHANISMS

Displayed below is the formation of quinoline isomers arising from the deprotonation occurring at different positions (Schemes 1 and 2).



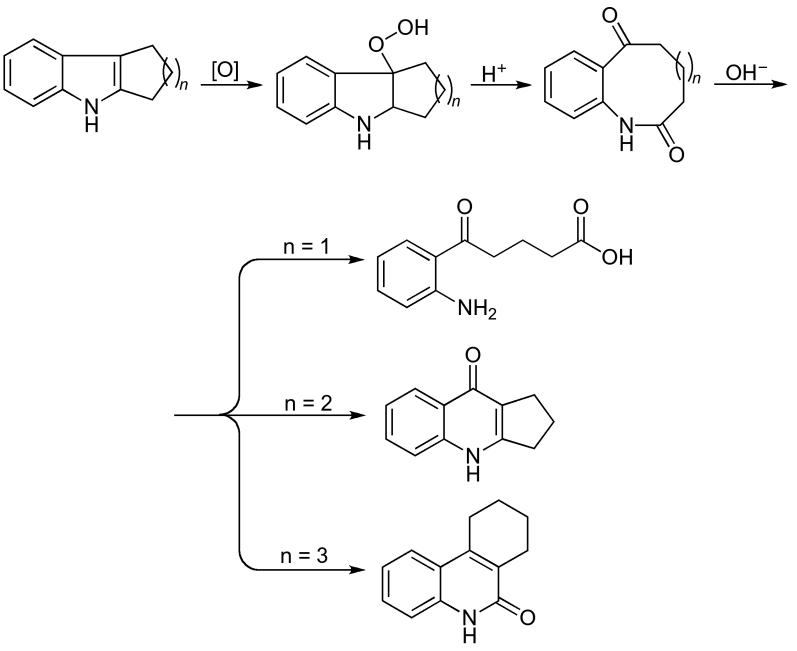
SCHEME 1. *Formation of 2-alkyl-4-hydroxyl quinoline.*



SCHEME 2. *Formation of 3,4-dialkyl-2-hydroxyl-quinoline.*

D. MODIFICATION

o-Amino phenylpropynic acid when treated with base also gives the corresponding substituted quinolines.[7] In addition, the Camps quinoline synthesis has been successfully adapted to fused indole systems. For example, 2,3-cyclopentenoindole, after converting to 1-*aza*-7,8-benzo-cyclooctane-2,6-dione via catalytic oxidation or autoxidation, gives 6-*o*-aminobenzoylbutyric acid when treated with base (or acid). The homologous lactam with base yields 2,3-cyclopenteno-4-quinolone, whereas the homologous 10-membered lactam undergoes an intramolecularly angular condensation to tetrahydrophenanthridone, as illustrated here.[3b]



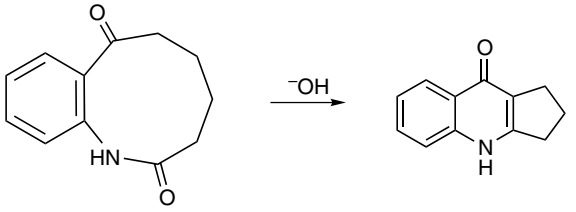
E. APPLICATIONS

This reaction is generally used to synthesize 3- and 4-substituted quinolines.

F. RELATED REACTIONS

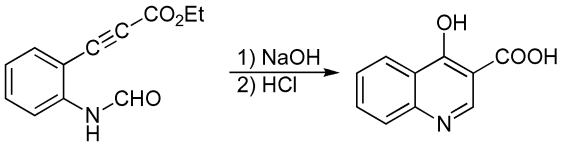
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3b.

When 50 mg 1-*aza*-8,9-benzcyclononene-2,7-dione was dissolved in cold 2 N sodium hydroxide, a yellow solution was obtained that, after a few seconds, warmed up slightly and became colorless. On neutralization, 2,3-cyclopenteno-4-quinolone was obtained as a colorless crystalline, which melted at 298°C under decomposition and progressive charring. On recrystallization from a mixture of benzene and ethanol, the crystals decomposed at 325–327°C. This compound in alcoholic solution gave a red-brown ferric chloride test.



Reference 7.

In a 1-L three-necked flask equipped with a stirrer, a condenser, and a dropping funnel was placed a solution of 4.0 g ethyl *o*-formamidophenylpropiolate (0.018 mol) in 71 mL absolute ethanol. The stirred, light green solution was warmed in an oil bath at 70°C, and 494 mL water was added dropwise over a 30-min period. During the addition, the temperature of the heating bath was raised gradually so that as the last the water was being added the solution was refluxing. Sodium hydroxide (8.24 g, 0.21 mol) in 82 mL water was added to the stirred, boiling solution, which thereupon displayed a strong, greenish blue fluorescence. After being heated under reflux for 2 h, the solution, which had turned light green, was cooled in an ice bath and freed of a small amount of flocculent material by filtration. The filtrate was made acidic to Congo Red with 20% hydrochloric acid. After refrigeration of this mixture, the product was collected by filtration, washed with a small volume of cold water, and dried at 100°C for 1 h. The cream-colored material weighed 2.2 g and yielded 1.1 g 4-hydroxy-3-quinolinecarboxylic acid as white needles after recrystallization from 500 mL absolute ethanol, in a yield of 32%, m.p. 263.0–263.5°C (dec.). The ethanolic mother liquor was saved.

Other references related to the Camps reaction are cited in the literature.[8]

H. REFERENCES

1. Guareschi, I., *Ann. Chim. Pharmac.,* **1894**, *19*, 339.
2. (a) Camps, R., *Arch. Pharm.,* **1902**, *240*, 135. (b) Camps, R., *Arch. Pharm.,* **1901**, *239*, 591. (c) Camps, R., *Ber.,* **1901**, *34*, 2703. (d) Camps, R., *Z. Physiol. Chem.,* **1901**, *33*, 390. (e) Camps, R., *Ber.,* **1899**, *32*, 3228. (f) Camps, R., *Arch. Pharm.,* **1899**, *237*, 659.
3. (a) Prezent, M. A. and Dorokhov, V. A., *Russ. Chem. Bull.,* **2003**, *52*, 2454. (b) Witkop, B.; Patrick, J. B. and Rosenblum, M., *J. Am. Chem. Soc.,* **1951**, *73*, 2641. (c) Koelsch, C. F. and Lucht, F. J., *J. Am. Chem. Soc.,* **1949**, *71*, 3556.
4. Yanagisawa, H.; Nakao, H. and Ando, A., *Chem. Pharm. Bull.,* **1973**, *21*, 1080.
5. Manske, R. H. F., *Chem. Rev.,* **1942**, *30*, 113.
6. Wohnlich, E., *Arch. Pharm.,* **1913**, *261*, 526.
7. Bornstein, J.; Reid, W. J. and Torres, D. J., *J. Am. Chem. Soc.,* **1954**, *76*, 2760.
8. (a) Yanagisawa, H.; Nakao, H. and Ando, A., *Chem. Pharm. Bull.,* **1973**, *21*, 1080. (b) Koetsch, C. F. and Lucht, F. J., *J. Am. Chem. Soc.* **1949**, *71*, 3556.

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Cannizzaro Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Cannizzaro in 1853.[1] It is the disproportionation of an aldehyde to an equimolar mixture of primary alcohol and carboxylic salt (i.e., with optimal yield of 50%) when treated with concentrated NaOH or other strong bases that is restricted to aldehydes without α-hydrogens to undergo *Aldol Condensation*. Therefore, it is generally known as the Cannizzaro reaction.[2] The reaction is found to be first order in base and second order in aldehyde; whereas at higher base concentrations, it is second order in both base and aldehyde.[3] In addition, the hydride transfer involved in this reaction takes place directly between aldehydes without intervention of reaction medium. For example, when the reaction is run in D_2O, the recovered alcohol contained no α-deuterium, indicating that the hydrogen comes from another mole of aldehyde and not from the medium.[4] It is interesting that benzyl benzoate can be prepared from the Cannizzaro reaction of benzladehyde.[5] The reaction in which the oxidant aldehyde differs from the reductant aldehyde is referred to as the cross (or crossed) Cannizzaro reaction.[6] The crossed Cannizzaro reaction is quite useful for synthesizing a high yield of alcohol. For example, in reactions of formaldehyde with any other aldehydes, formaldehyde is oxidized to formic acid,[7] especially when the reaction is catalyzed with $Ba(OH)_2 \cdot 8H_2O$ at 100–110°C in an oil bath or under microwave irradiation; under these conditions, more than 80–90% of the alcohol can form without any solvent.[8] For the crossed Cannizzaro reaction, an aldehyde bearing an electron-withdrawing substituent undergoes the reaction at a much faster rate than an aldehyde with an electron-donating group appended. When different aromatic aldehydes (rather than formaldehyde) are used, the aldehyde with an electron-donating group will be reduced, and the aldehyde with the electron-withdrawing group will be oxidized. For example, the following studied aldehydes are arranged in order of diminishing susceptibility to oxidation: *m*-nitrobenzaldehyde,

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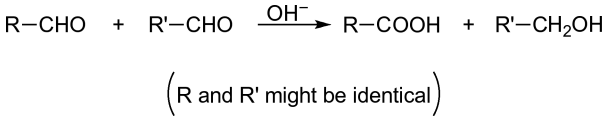
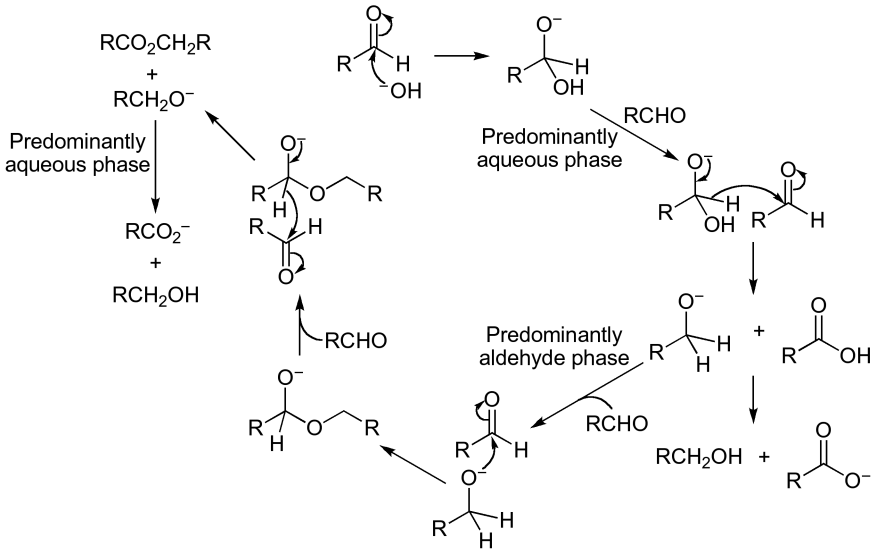
furfural, *p*-bromobenzaldehyde, benzaldehyde, and *p*-anisaldehyde.[9] This order correlates with the combined resonance and inductive influences of the substituent groups on the formyl group, contributing to the ease of (*a*) hydroxide ion attack and (*b*) hydride transfer. The reaction also takes place at high temperature and high pressure (HTHP, e.g., 250°C and 4 MPa) without any catalyst (base) to give more than 50% of methanol when formaldehyde is used.[10] In addition, the reaction also occurs on a solid surface (e.g., MgO[11] and TiO_2[12]) and in gas phase.[13]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Because organic aldehyde and aqueous base are not miscible, this reaction is actually a heterogenous reaction.[14] An illustrative mechanism is outlined here.



D. MODIFICATION

This reaction has been modified to occur at HTHP[10] and in solvent-free conditions using $Ba(OH)_2 \cdot 8H_2O$ under microwave irradiation.[8]

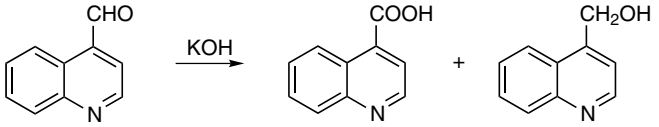
E. APPLICATIONS

This reaction has general application in the preparation of alcohols from aldehydes without α-hydrogens.

F. RELATED REACTIONS

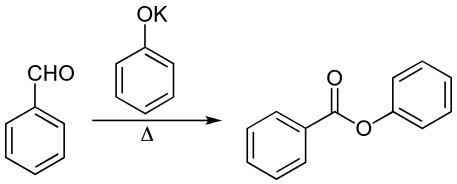
This reaction is related to the *Tishchenko Reaction*, *Meerwein-Ponndorf-Verlay Reduction*, and *Oppenauer Oxidation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 15.

A mixture of 0.01 mol cinchoninaldehyde and 0.01 mol potassium hydroxide was heated for 1–3 h on a steam bath; then the mixture was cooled and filtered to remove the insoluble by-product (which was purified by crystallization from aqueous pyridine and was proved to be hydrobenzoin from aldehyde). The aqueous alkaline filtrate was thoroughly extracted with ether to remove all the quinolyl-4-methanol formed. Finally, the aqueous solution left from the ether extraction was made neutral to Congo Red paper with hydrochloric acid and was chilled to precipitate, affording cinchoninic acid, which was crystallized from benzene as white crystals, m.p. 99–100°C.



Reference 14.

To a 50-mL flask was added 1.32 g anhydrous potassium phenolate (0.01 mol) and 50 g benzaldehyde (0.47 mol). The flask was sealed off and was then heated at 100°C for 18 h. The reaction mixture was filtered, and the filtrate was distilled in a Hickman still to remove residual salts. The distillate was redistilled through a Vigreaux distilling column at 10 mmHg to yield 15 g benzyl benzoate.

Other references related to the Cannizzaro reaction are collected in the literature.[16]

H. REFERENCES

1. Cannizzaro, S., *Ann.,* **1853**, *88*, 129.
2. (a) Chung, K.-H.; Moon, B.-C.; Lim, C. H.; Kim, J. P.; Lee, J. H. and Chi, D. Y., *Bull. Korean Chem. Soc.,* **2006**, *27*, 1203. (b) Liu, X.-L.; Zhu, B.-G. and Ge, D., *Wuran Fangzhi Jishu*, **2005**, *18*, 34. (c) Abaee, M. S.; Sharifi, R. and Mojtahedi, M. M., *Org. Lett.,* **2005**, *7*, 5893. (d) Curini, M.; Epifano, F.; Genovese, S.; Marcotullio, M. C. and Rosati, O., *Org. Lett.,* **2005**, *7*, 5747. (e) Wang, L.; Li, J.-T.; Wang, J.-S. and Xu, W.-Z., *Chemistry (Rajkot, India),* **2004**, *1*, 621. (f) Esteb, J. J.; Gligorich, K. M.; O'Reilly, S. A. and Richter, J. M., *J. Chem. Edu.,* **2004**, *81*, 1794. (g) Ishihara, K. and Yano, T., *Org. Lett.,* **2004**, *6*, 1983. (h) Tim, B. T.; Cho, C. S.; Kim, T.-J. and Shim, S. C.,

J. Chem. Res. (S), **2003**, 368. (i) Pourjavadi, A.; Soleimanzadeh, B. and Marandi, G. B., *Reactive & Functional Polymers,* **2002**, *51*, 49. (j) Yoshizawa, K.; Toyota, S. and Toda, F., *Tetrahedron Lett*., **2001**, *42*, 7983. (k) Sharifi, A.; Mojtahedi, M. M. and Saidi, M. R., *Tetrahedron Lett*., **1999**, *40*, 1179. (l) Sroubkova,L.; Horak, V. and Zahradnik, R., *Coll. Czech. Chem. Commun.,* **1997**, *62*, 147. (m) Polackova, V.; Tomova, V.; Elecko, P. and Toma, S., *Ultrason. Sonochem.,* **1996**, *3*, 15. (n) McKague, A. B.; Reeve, D. W.; Rettig, S. J. and Trotter, J., *Can. J. Chem.,* **1992**, *70*, 1706. (o) Bowden, K.; Butt, A. M. and Streater, M., *J. Chem. Soc., Perkin Trans. II,* **1992**, 567. (p) Mehta, G. and Padma, S., *J. Org. Chem.,* **1991**, *56*, 1298. (q) Anvia, F. and Bowden, K., *J. Chem. Soc., Perkin Trans. II,* **1990**, 2093. (r) Bowden, K.; El-Kaissi, F. A. and Ranson, R. J., *J. Chem. Soc., Perkin Trans. II,* **1990**, 2089. (s) Abbaszadeh, M. R. and Bowden, K., *J. Chem. Soc., Perkin Trans. II,* **1990**, 2081. (t) Ionescu, M.; Bota, T.; Manolache, M. and Ciobanu, M., *Revistade Chim. (Romania)*, **1988**, *39*, 1089. (u) Ando, T.; Clark, J. H.; Cork, D. G. and Kimura, T., *Chem. Lett.,* **1987**, 1315. (v) Ashby, E. C.; Coleman, D. and Gamasa, M., *J. Org. Chem.,* **1987**, *52*, 4079. (w) Rzepa, H. S. and Miller, J., *J. Chem. Soc., Perkin Trans. II,* **1985**, 717. (x) Ashby, E. C.; Coleman, D. T. and Gamasa, M. P., *Tetrahedron Lett*., **1983**, *24*, 851. (y) Bianchi, M.; Matteoli, U.; Menchi, G.; Frediani, P. and Piacenti, F., *J. Organomet. Chem.,* **1982**, *240*, 65. (z) Okuyama, T.; Kimura, K. and Fueno, T., *Bull. Chem. Soc. Jpn.,* **1982**, *55*, 2285. (aa) McDonald, R. S. and Sibley, C. E., *Can. J. Chem.,* **1981**, *59*, 1061. (bb) Bader, H. J. and Blume, R., *Praxis Naturwissen., Chem.,* **1978**, *27*, 267. (cc) Gokel, G. W.; Gerdes, H. M. and Rebert, N. W., *Tetrahedron Lett*., **1976**, 653.

3. (a) Hine, J., *Physical Organic Chemistry*, McGraw-Hill, New York, **1956**, p 259. (b) Lachowicz, D. R. and Gritter, R. J., *J. Org. Chem.,* **1953**, *28*, 106.
4. (a) Hauser, C. R.; Hamrick, P. J. and Stewart, A. F., *J. Org. Chem.,* **1956**, *21*, 260. (b) Fredenhagen, H. and Bonhoeffer, K. F., *Z. Phys. Chem.,* **1938**, *181A*, 379.
5. Lachman, A., *J. Am. Chem. Soc*., **1923**, *45*, 2356.
6. (a) Thakuria, J. A.; Baruah, M. and Sandhu, J. S., *Chem. Lett.,* **1999**, 995. (b) Sane, P. V. and Sharma, M. M., *Synth. Commun.,* **1987**, *17*, 1331. (c) Bikbaeva, G. G.; Kislina, I. S. and Vinnik, M. I., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1974**, 2440. (d) Bikbaeva, G. G.; Kislina, I. S. and Vinnik, M. I., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1974**, 2708.
7. Davidson, D. and Bogert, M. T., *J. Am. Chem. Soc.,* **1935**, *57*, 905.
8. Varma, R. S., *Green Chem.,* **1999**, 43.
9. Hazlet, S. E. and Stauffer, D. A., *J. Org. Chem.,* **1962**, *27*, 2021.
10. Tsujino, Y.; Wakai, C.; Matubayasi, N. and Nakahara, M., *ICR Annual Report,* **1998**, *5*,10.
11. Peng, X. D. and Barteau, M. A., *Langmuir,* **1989**, *5*, 1051.
12. Rekoske, J. E. and Barteau, M. A., *Langmuir,* **1999**, *15*, 2061.
13. Sheldon, J. C.; Bowie, J. H.; Dua, S.; Smith, J. D. and O'Hair, R. A. J., *J. Org. Chem.,* **1997**, *62*, 3931.
14. Kharasch, M. S. and Snyder, R. H., *J. Org. Chem.,* **1949**, *14*, 819.
15. Phillips, A. P., *J. Am. Chem. Soc.,* **1946**, *68*, 2568.
16. (a) Nguyen, R. and Huc, I., *Chem. Commun.,* **2003**, 942. (b) Varma, R. S.; Naicker, K. P. and Liesen, P. J., *Tetrahedron Lett.,* **1998**, *39*, 8437. (c) Gelebe, A. C. and Kaye, P. T., *South Afri. J. Chem.,* **1994**, *47*, 26. (d) Swain, C. G.; Powell, A. L.; Sheppard, W. A. and Morgan, C. R., *J. Am. Chem. Soc.*, **1979**, *101*, 3576. (e) Wiberg, K. B., *J. Am. Chem. Soc.,* **1954**, *76*, 5371. (f) Lachowicz, D. R. and Gritter, R. Y., *J. Org. Chem.,* **1953**, *28*, 106. (g) Pearl, I. A., *J. Org. Chem.,* **1947**, *12*, 89. (h) Phillips, A. P., *J. Am. Chem. Soc.,* **1946**, *68*, 2568. (i) Pearl, I. A., *J. Am. Chem. Soc.,* **1945**, *67*, 1628. (j) Geissman, T. A., *Org. React.*, **1944**, *2*, 94. (k) Hazlet, S. E. and Callison, R. B., *J. Am. Chem. Soc.,* **1944**, *66*, 1248.

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Carboni-Lindsey Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Carboni and Lindsey in 1959.[1] So far, more than 800 articles have been published on this topic,[2] including several reviews.[3] It is the reaction between tetrazines and a variety of unsaturated compounds, including dienes, acetylenes, and aliphatic and aromatic olefins, to yield 3,6-disubstituted pyridazines with the evolution of 1 equivalent of nitrogen,[1] and is generally known as the Carboni-Lindsey reaction.[2,4] This reaction apparently proceeds by the 1,4-addition of the -C–N-N–C- diene system of the tetrazine to an appropriate olefinic or acetylenic dienophile, followed by a rapid *retro-Diels-Alder Reaction*, leading to the final product accompanyed by the loss of nitrogen.[5] The Carboni-Lindsey reaction can be moderated by lowering the reaction temperature or by employing diluents such as ether or benzene.[1] Completion of the reaction is signaled by the disappearance of the characteristic red or violet-red tetrazine color and by the cessation of nitrogen evolution.[1] Because this reaction is dominated by a HOMO (dienophile)-LUMO (diene) interaction,[5a] the Carboni-Lindsey reaction takes place with a complementarily inverse electron demand of diene/dienophile substituent effects,[6] by which dienophiles containing electron-releasing substituents usually facilitate the reaction, and those with electron-attracting groups exhibit a retarding effect.[1]

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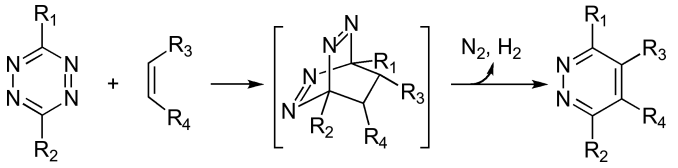
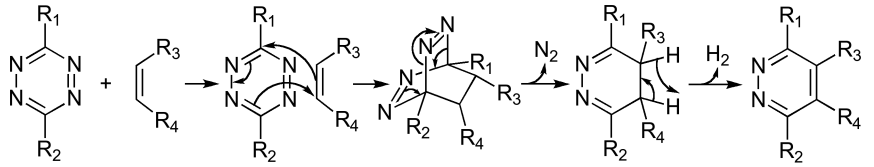
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Essentially, this reaction involves a *Diels-Alder Reaction* between tetrazine and a dienophile to form a bicyclic intermediate, which subsequently undergoes a *retro-Diels-Alder Reaction* accompanyed by the evolution of nitrogen to release the ring strain, as displayed below.[7]



D. MODIFICATION

The original reaction has been modified extensively using a variety of diene analogues to react with unsaturated compounds followed by the evolution of a volatile molecule, as reviewed in Ref. 3c.

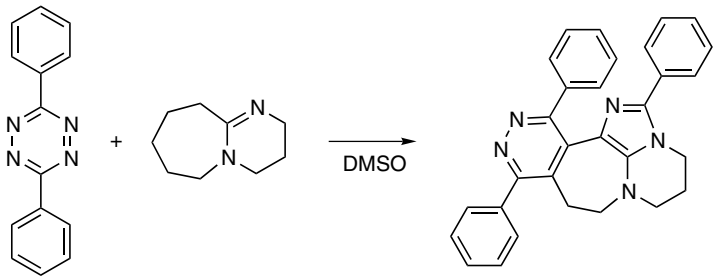
E. APPLICATIONS

This reaction has very broad application in the preparation of a variety of heterocycles.

F. RELATED REACTIONS

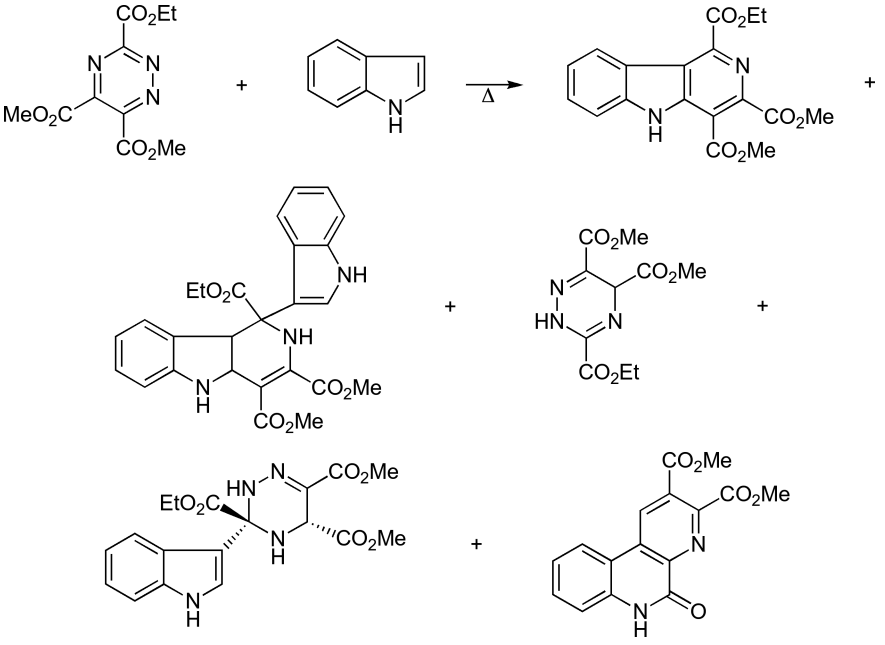
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 8.

To a solution of 1.68 g diphenyltetrazine (7.18 mmol) in 15 mL dimethyl sulfoxide was added 0.219 g DBU (1.44 mmol). This mixture was then heated at reflux under nitrogen for 2 h. The solution was cooled to room temperature, and 20 mL dichloromethane was added followed by 15 mL H_2O. The aqueous layer was removed, and the organic layer was washed twice with H_2O. The white precipitate, if any, was filtered and washed with several small amounts of dichloromethane. The concentrated organic layer was submitted to flash chromatography on silica gel with EtOAc followed by EtOAc:MeOH (9:1) to afford 0.295 g 2,8,11-triphenyl-3*H*,4*H*,5*H*,6*H*,7*H*-imidazo[4,5,1-*ef*][1,3]-diazaperhydroino[1,2-*f*] pyridazino[4,5-*d*]azepine as a yellow solid, m.p., 245–248°C (dec.).



Reference 9.

Preparation of Triazine

Ethyl oxalamidrazonate (7.5 mmol) was suspended in 50 mL anhydrous ethanol under argon with gentle heating. This suspension was then added dropwise with stirring to a solution of the dione (1 eq. unless otherwise noted) in 50 mL anhydrous ethanol also under argon at room temperature. After completion of the addition, stirring was continued at room temperature for 16 h, and the mixture was subsequently refluxed for 1 h. The solvent was removed in vacuo, and the crude product was purified by flash chromatography on silica gel to give corresponding triazine.

General Procedure for the Reaction of Indole with 1,2,4-Triazines and 1,2-Diazines

Indole (50 mg, 0.43 mmol), triazine or diazine, and the anhydrous solvent in appropriate amounts were placed in a reaction vessel consisting of a Pyrex glass tube (5 mm i.d. $\times$ 150 mm) sealed at one end. The vessel was capped with a septum and purged with argon. A balloon filled with argon on a syringe needle was inserted through the septum to maintain an argon atmosphere without allowing pressure build up during the reaction. The vessel was then placed in a sand bath pre-equilibrated to the desired temperature. For a representative reaction of indole (1.2 eq.) and 3-carbethoxy-5,6-dicarbomethoxy-1,2,4-triazine at 80°C for 48 h under argon, the following products were obtained after flash chromatography on silica gel and final centrifugal TLC purification, which are listed in the order of elution. (*a*) 1-Carbethoxy-3,4-dicarbomethoxy-γ-carboline (CH_2Cl_2/EtOAc = 9:1, 33% yield), yellow solid, m.p., 144–145°C; (*b*) l-carbethoxy-3,4-di-carbomethoxy-1-(3-indolyl)-2H-γ-carboline, mixture of tautomers eluted with CH_2Cl_2/EtOAc (9:l), in a yield of 21%; (*c*) 3-carbethoxy-5,6-dicarbomethoxy-2,5-dihydro-l,2,4-triazine was eluted and purified with CH_2Cl_2/EtOAc (4:l) as colorless oil, in a yield of 19%; (*d*) 3-carbethoxy-5,6-dicarbomet hoxy-3-(3-indolyl)-2,3,4,5-tetrahydro-l,2,4-triazine was eluted and purified with CH_2C1_2/EtOAc (4:1) as a white solid, in a yield of 6%, m.p. 217–218°C; (*e*) dimethyl 5-oxobenzo[f][1,7]naphthyridine-2,3-dicarboxylate was eluted and purified with CH_2Cl_2/MeOH (19:l) as a white solid, in a yield of 20%, m.p. 234–235°C.

Other references related to the Carboni-Lindsey reaction are cited in the literature.[10]

H. REFERENCES

1. Carboni, R. A.; Lindsey, R. V., J. *Am. Chem. Soc*., **1959**, *81*, 4342.
2. Zhou, X. J.; Kovalev, E. G.; Klug, J. T. and Khodorkovsky, V., *Org. Lett.,* **2001**, *3*, 1725.
3. (a) Sauer, J.; Heldmann, D. K.; Hetzenegger, J.; Krauthan, J.; Sichert, H. and Schuster, J., *Eur. J. Org. Chem*., **1998**, 2885. (b) Sauer, J., 1.2.4.5-Tetrazines in *Comprehensive Heterocyclic Chemistry II*, ed. Katritzky, A. R.; Rees, C. W. and Scriven, E. F. V., Pergamon Press, Oxford, **1996**, *6*, p. 901. (c) Boger, D. L. and Weinreb, S. N., *Hetero Diels-Alder Methodology in Organic Synthesis*, Academic Press, London, **1987**. (d) Boger, D. L., *Chem. Rev*., **1986**, *86*, 781.
4. (a) Seitz, G. and Gorge, L., *Chem. Ztg.*, **1984**, *108*, 331. (b) Kovalev, E. G.; Postovskii, I. Y.; Rusinov, G. L. and Shegal, I. L., *Khim. Geterotsiklicheskikh Soedinenii,* **1981**, 1462.

5. (a) Wijnen, J. W.; Zavarise, S.; Engberts, J. B. F. N. and Charton, M., *J. Org. Chem.,* **1996**, *61*, 2001. (b) Sauer, J.; Mielert, A.; Lang, D. and Peter, D., *Ber*., **1965**, *98*, 1435.
6. Sauer, J. and Wiest, H., *Angew. Chem. Int. Ed. Engl.,* **1962**, *1*, 269.
7. Oxley, J. C.; Smith, J. L. and Zhang, J., *J. Phys. Chem. A,* **2000**, *104*, 6764.
8. Sammelson, R. E.; Olmstead, M. M.; Haddadin, M. J. and Kurth, M. J., *J. Org. Chem.,* **2000**, *65*, 9265.
9. Benson, S. C.; Gross, J. L. and Snyder, J. K., *J. Org. Chem.,* **1990**, *55*, 3257.
10. (a) Rusinov, G. L.; Ishmetova, R. I.; Ganebnykh, I. N. and Chupakhin, O. N., *Heterocycl. Commun.,* **2006**, *12*, 99. (b) Sauer, J., *Eur. J. Org. Chem.,* **2002**, 791. (c) Bodwell, G. and Li, J., *Org. Lett.,* **2002**, *3*, 127. (d) Rusinov, G. L.; Ishmetova, R. I.; Latosh, N. I.; Ganebnych, I. N.; Chupakhin, O. N. and Potemkin, V. A., *Russ. Chem. Bull.,* **2000**, *49*, 355. (e) Sauer, J., *Bull. Soc. Chim. Belg*., **1992**, *101*, 521. (f) Frissen, A. E.; Geurtsen, G.; Marcelis, A. T. M. and van der Plas, H. C., *Tetrahedron,* **1990**, *46*, 595. (g) De Bie, D. A.; Ostrowicz, A.; Geurtsen, G. and van der Plas, H. C., *Tetrahedron,* **1988**, *44*, 2977. (h) Gleiter, R.; Schehlmann, V.; Spanget-Larsen, J.; Fischer, H. and Neugebauer, F. A., *J. Org. Chem.,* **1988**, *53*, 5756. (i) Boger, D. L. and Panek, J. S., *J. Org. Chem.,* **1981**, *46*, 2179. (j) Sauer, J. and Sustmann, R., *Angew. Chem. Int. Ed. Engl*., **1980**, *19*, 779. (k) Haddadin, M. J.; Firsan, S. J. and Nader, B. S., *J. Org. Chem.,* **1979**, *44*, 629. (l) Deyrup, J. A. and Gingrich, H. L., *Tetrahedron Lett.,* **1977**, *31*, 15. (m) Steglich, W.; Buschmann, E.; Gansen, G. and Wilschowitz, L., *Synthesis,* **1977**, 252. (n) Lang, S. A.; Johnson, B. D.; Cohen, E.; Sloboda, A. E. and Greenblatt, E., *J. Med. Chem.,* **1976**, *19*, 1404. (o) Seitz, G. and Kaempchen, T., *Arch. Pharm.*, **1976**, *309*, 679. (p) Jojima, T.; Takeshiba, H. and Kinoto, T., *Chem. Pharm. Bull.,* **1976**, *24*, 1581. (q) Anastassiou, A. G. and Reichmanis, E., *J. Chem. Soc., Chem. Commun.,* **1976**, 313. (r) Seitz, G. and Kaempchen, T., *Chem. Ztg*., **1975**, *99*, 503. (s) Warrener, R. N.; Elix, J. A. and Wilson, W. S., *Aust. J. Chem.,* **1973**, *26*, 389. (t) Steigel, A.; Sauer, J.; Kleier, D. A. and Binsch, G., *J. Am. Chem. Soc.,* **1972**, *94*, 2770. (u) Meresz, O. and Foster-Verner, P. A., *J. Chem. Soc., Chem. Commun.,* **1972**, 950. (v) Paquette, L. A.; Short, M. R and Kelly, J. F., *J. Am. Chem. Soc.,* **1971**, *93*, 7179. (w) Evnin, A. B.; Arnold, D. R.; Karnischky, L. A. and Strom, E., *J. Am. Chem. Soc.,* **1970**, *92*, 6218. (x) Steigel, A. and Sauer, J., *Tetrahedron Lett.,* **1970**, *38*, 3357. (y) Heinrichs, G.; Krapf, H.; Schroder, B.; Steigel, A.; Troll, T. and Sauer, J., *Angew. Chem. Int. Ed. Engl.,* **1970**, *9*, 1617. (z) Harder, R. J.; Carboni, R. A. and Castle, J. E., *J. Am. Chem. Soc.,* **1967**, *89*, 2643. (aa) Sauer, J., *Angew. Chem. Int. Ed. Engl.,* **1967**, *6*, 16. (bb) Sauer J. and Heinrichs G.,*Tetrahedron Lett.*, **1966**, 4979. (cc) Sauer, J. and Lang, D., *Angew. Chem.,* **1964**, *76*, 603. (dd) Avram, M.; Dinulescu, I. G.; Marica, E. and Nenitzescu, C. D., *Ber.,* **1962**, *95*, 2248. (ee) Allegretti, J.; Hancock, J. and Knutson, R. S., *J. Org. Chem.,* **1962**, *27*, 1463. (ff) Butte, W. A. and Cage, F. H., *J. Org. Chem.,* **1961**, *26*, 4690. (gg) Carboni, R. A. and Lindsey, R. V., *J. Am. Chem. Soc.,* **1958**, *80*, 5793.

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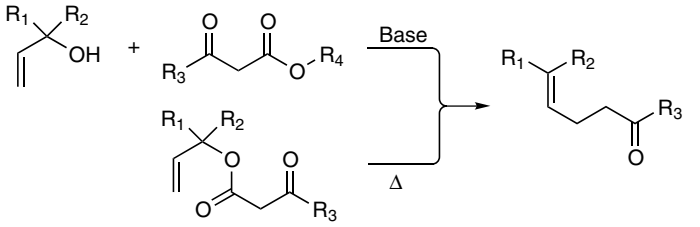
Carroll Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Carroll in 1940.[1] It is a well-established thermal rearrangement for preparing γ, δ-unsaturated ketones from allyl acetoacetates or base-catalyzed reactions between allyl alcohols and β-ketoesters. Therefore, it is generally known as the Carroll rearrangement.[2] This rearrangement in principle is a complement to the *Claisen Rearrangement*[3] and has not found widespread application in organic synthesis due to the harsh conditions[3,4] (temperatures of 130–220°C after *in situ* preparation of the β-ketoester) and lack of an efficient method for β-ketoesters.[3] However, when the formed β-ketoesters are treated with 2 eq. of base (e.g., LDA), the enolate form of the β-ketoesters can rearrange in much milder conditions.[3,5] It was found that the β-ketoesters from secondary or tertiary alcohols rearrange faster than those from primary alcohols.[4] On the other hand, the adsorption of the tertiary allylic acetoacetate on neutral alumina will also facilitate the Carroll rearrangement.[6] Recently, it was found that this rearrangement can be catalyzed by a ruthenium complex with high regioselectivity, but a lower regiospecificity compared to the uncatalyzed Carroll rearrangement.[7]

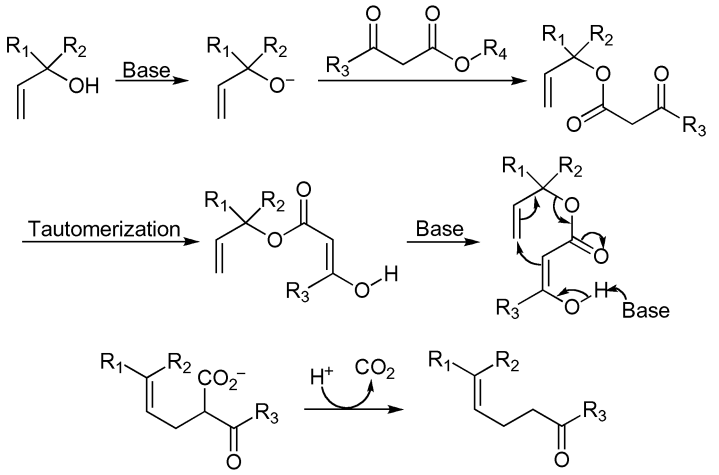
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The reaction mechanism is given here by showing the reaction between an allylic alcohol and a β-ketoester in the presence of a general base.



D. MODIFICATION

The rearrangement of allyl β-ketoesters absorbed on an alumina surface at 60°C is one of the modifications,[5] other modifications include a ruthenium complex catalyzed rearrangement.[6]

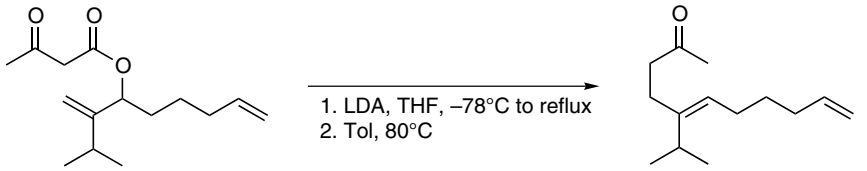
E. APPLICATIONS

This reaction has general application in the preparation of γ,δ-unsaturated ketones.

F. RELATED REACTIONS

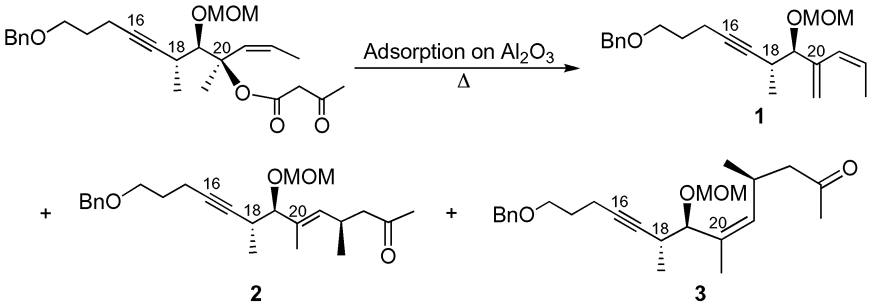
This reaction is related to the *Claisen Rearrangement*, *Ficini-Claisen Rearrangement*, and *Overman Rearrangement*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 8.

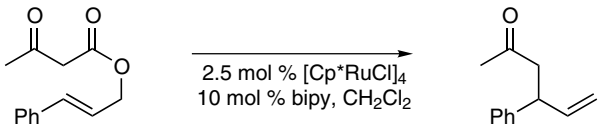
At 0°C, 21.14 mL *n*-BuLi (0.053 mol) was added to 53.0 mL THF containing 7.85 mL $(i\text{-Pr})_2NH$ (0.056 mol). The resulting solution was stirred for 30 min and then cooled to −78°C. Then 4.44 g 2-methyl-3-methylene-8-penten-4-yl acetoacetate (0.018 mol) in 20 mL THF was added dropwise to the LDA solution at −78°C. The reaction mixture was warmed to room temperature and stirred for 4 h followed by 1 h of refluxing, which was then cooled to room temperature, concentrated *without heating*, and taken up in water. The water layer was then washed with Et_2O. The Et_2O layer was further washed with 0.01 M NaOH. The combined aqueous layers were diluted with CH_2Cl_2. Then, 1 M HCl was added slowly to this H_2O/CH_2Cl_2 mixture with rapid stirring. Upon complete acidification, the two layers separated. The CH_2Cl_2 layer was separated, and the water layer was further extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were washed with brine, dried over Na_2SO_4, and concentrated *without heating*. The residue was dissolved in 20 mL toluene and heated at 80°C for 1 h. The solution was concentrated and purified by flash chromatography on silica gel (80:1 hexanes/EtOAc) to give 2.25 g 5-(1-methylethyl)-5E,10-undecadien-2-one with a yield greater than 75%.



Reference 6.

To a solution of 552 mg (1*R*,2*R*,3*R*)-8-benzyloxy-2-methoxymethoxy-1,3-dimethyl-1-((*Z*)-prop-1-enyl)oct-4-ynyl 2-oxobutanoate in 30 mL CH_2Cl_2 was added 17 g neutral alumina. The solvent was evaporated under reduced pressure, and the resulting dry powder was stirred at 60°C. After 12 h, the solid reaction mixture was suspended in EtOAc, filtered through Celite, and thoroughly washed with EtOAc. The filtrate was evaporated under reduced pressure, and analysis of the GC-MS and ^1H NMR spectra of the crude material indicated the formation of compounds (6*R*,7*R*,9*Z*)-1-benzyloxy-7-methoxymethoxy-6-methyl-8-methyleneundec-9-en-4-yne (**1**), (4*R*,5*E*,7*R*,8*R*)-13-benzyloxy-7-methoxymethoxy-4,6,8-trimethyltridec-5-en-9yn-2-one (**2**), and (4*S*,5*Z*,7*R*,8*R*)-13-benzyloxy-7-methoxymethoxy-4,6,8-trimethyltridec-5-en-9-yn-2-one

(**3**) in a 4:92:4 ratio. The crude material was purified by flash chromatography (petroleum ether/EtOAc gradient, 90:10 to 80:20) to afford 37 mg (9%) of **1**, R_f = 0.76 (petroleum ether/EtOAc, 70:30); 305 mg (61%) of **2** as colorless oils, R_f = 0.56 (petroleum ether/EtOAc, 70:30); and 17 mg (3%) of **3**, R_f = 0.50 (petroleum ether/EtOAc, 70:30).



Reference 7b.

In a Schlenk tube under argon, $[Cp^*RuCl]_4$ (2.5 mol %) and bipyridine (10 mol %) were dissolved in 2 mL methylene chloride. The resulting deep purple solution was allowed to stir briefly before the addition of 1 mmol of allyl-β-ketoester in 3 mL methylene chloride via cannula. The reaction was allowed to stir under argon until the resulting dark burnt orange solution returned to purple ($\sim$1.5 h). Following solvent evaporation, the crude product was purified via flash chromatography (SiO_2, 15% Et_2O/hexane), providing the products in a 94% yield as a pale yellow oil with >95% purity.

Other references related to Carroll Rearrangement are cited in the literature.[9]

H. REFERENCES

1. (a) Carroll, M. F., *J. Chem. Soc.,* **1940**, 704. (b) Carroll, M. F., *J. Chem. Soc.,* **1940**, 1226. (c) Carroll, M. F., *J. Chem. Soc.,* **1941**, 507.
2. (a) Constant, S.; Tortoioli, S.; Mueller, J. and Lacour, J., *Angew. Chem. Int. Ed.,* **2007**, *46*, 2082. (b) Kuwano, R.; Ishida, N. and Murakami, M., *Chem. Commun.,* **2005**, 3951. (c) Jung, M. E. and Duclos, B. A., *Tetrahedron Lett*., **2004**, *45*, 107. (d) Enders, D.; Knopp, M.; Runsink, J. and Raabe, G., *Liebigs Annalen,* **1996**, 1095. (e) Sorgi, K. L.; Scott, L.; Maryanoff, C. A., *Tetrahedron Lett.,* **1995**, *36*, 3597. (f) Ouvrard, N.; Baldy, A.; Rodriguez, J.; Santelli, M.; Feneau-Dupont, J. and Declercq, J. P., *Acta Crystallograph., Sect. C: Cryst. Struct. Commun.,* **1994**, *C50*, 624. (g) Wilson, S. R. and Augelli, C. E., *Org. Synth.,* **1990**, *68*, 210. (h) Smit, V. A.; Pogrebnoi, S. I.; Kal'yan, Yu. B. and Krimer, M. Z., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1987**, 959. (i) Podraza, K. F., *J. Heterocycl. Chem.,* **1986**, *23*, 581.
3. Wilson, S. R. and Price, M. F., *J. Org. Chem.,* **1984**, *49*, 722.
4. Castro, A. M. M., *Chem. Rev.,* **2004**, *104*, 2939.
5. (a) Hatcher, M. A. and Posner, G. H., *Tetrahedron Lett.,* **2002**, *43*, 5009. (b) Enders, D.; Knopp, M.; Runsink, J. and Raabe, G., *Angew. Chem. Int. Ed. Engl.,* **1995**, *34*, 2278. (c) Genus, J. F.; Peters, D. D.; Ding, J.-F. and Bryson, T. A., *Synlett,* **1994**, 209. (d) Ouvrard, N.; Rodriguez, J. and Santelli, M., *Tetrahedron Lett.,* **1993**, *34*, 1149. (e) Echavarren, A. M.; de Mendoza, J.; Prados, P. and Zapata, A., *Tetrahedron Lett.,* **1991**, *32*, 6421. (f) Snider, B. B. and Beal, R. B., *J. Org. Chem.,* **1988**, *53*, 4508. (g) Gilbert, J. C. and Kelly, T. A., *Tetrahedron,* **1988**, *44*, 7587.
6. Defosseux, M.; Blanchard, N.; Meyer, C. and Cossy, J., *J. Org. Chem.,* **2004**, 69, 4626.
7. (a) Burger, E. C. and Tunge, J. A., *Org. Lett.,* **2004**, *6*, 4113. (b) Burger, E. C. and Tunge, J. A., *Org. Lett.,* **2004**, *6*, 2603.
8. Shi, B.; Hawryluk, N. A. and Snider, B. B., *J. Org. Chem.,* **2003**, *68*, 1030.

9. (a) Defosseux, M.; Blanchard, N.; Meyer, C. and Cossy, J., *Org. Lett.,* **2003**, *5*, 4037. (b) Hong, S.-P.; Lindsay, H. A.; Yaramasu, T.; Zhang, X. W. and McIntosh, M. C., *J. Org. Chem.,* **2002**, *67*, 2042. (c) Nowicki, J., *Molecules,* **2000**, *5*, 1033. (d) Wilson, S. R. and Augelli, C. E., *Org. Synth. Coll.* **1993**, *8*, 235. (e) Tanabe, M. and Hayashi, K. *J. Org. Chem*., **1980**, *102*, 862. (f) Camps, F.; Canela, R.; Coll, J.; Meaaeguer, A, and Roca, A., *Tetrahedron,* **1978**, *34*, 2179. (g) Cookson, R. C. and Parsons, D. J., *J. Chem. Soc., Chem. Commun.,* **1976**, 990. (h) Narwid, T. A.; Cooney, K. E. and Uskokovic, M. R., *Helv. Chim. Acta,* **1974**, *57*, 771. (i) Hoffmann, W., *Chem. Ztg.,* **1973**, *97*, 23. (j) Kimel, W.; Sax, N. W.; Kaiser, S.; Eichmann, G. G.; Chase, G. O. and Ofner, A., J. *Org. Chem.,* **1958**, *23*, 153. (k) Dreux, J. and Cologne, J., *Bull. Soc., Chim. Fr.,* **1955**, 1312. (l) Kimel, W. and Cope, A. C., *J. Am. Chem. Soc.,* **1943**, *65*, 1992.

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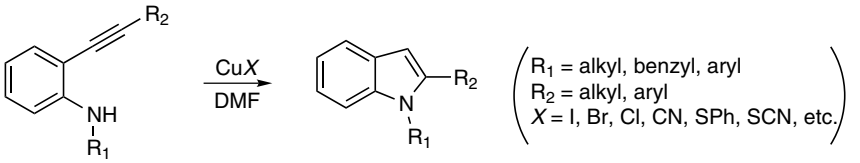
Castro Indole Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Castro in 1966.[1] It is the synthesis of indoles by cuprous halide catalyzed intramolecular cyclization of *o*-ethynylanilines or the coupling between *o*-haloaniline and cuprous mono-substituted acetylide and is generally known as the Castro indole synthesis.[2] In this reaction, the *o*-ethynylanilines are readily available by either *Castro-Stephens Coupling* or *Sonogashira Coupling* from *o*-haloanilines and acetylene or mono-substituted acetylenes. This reaction is especially suitable for the preparation of 2-substituted indoles and can be applied as an alternative for *Fischer Indole Synthesis*.[1] During the coupling, the reactivity of *o*-haloanilines are found to be on the order of I > Br > Cl >> fluorine, while the catalytic efficiency of cuprous salts varies along with the counteranions and decreases in the sequence of Cl > Br > I > CN > SPh > SCN.[1] In addition, this reaction is distinctly affected by the solvent effect. For example, (*o*-amino)phenylacetylide, slightly soluble in DMF at room temperature, cyclizes intramolecularly in DMF to give indole exclusively; however, the same starting material, soluble in warm pyridine, affords only either uncyclized acetylene or tolane (i.e., diphenylacetylene) in pyridine.[1] In addition, *o*-aminotolane will not cyclize in the presence of CuI or cuprous phenylacetylide in pyridine, but undergoes the cyclization smoothly when treated with CuI in DMF.[1] Therefore, indoles can be synthesized in two steps: *Castro-Stephens Coupling* in pyridine and Castro indole synthesis in DMF.[1]

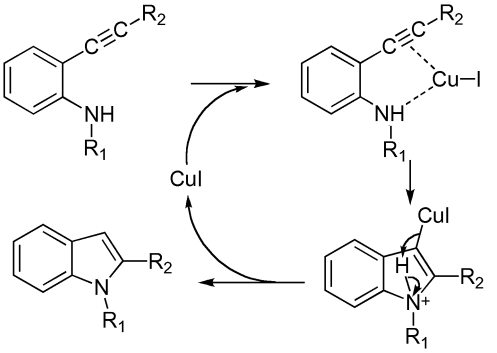
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Because no mechanism about Castro indole synthesis is available, a tentative illustration about the reaction mechanism is provided below.



D. MODIFICATION

This reaction has been modified by the treatment of *N*-benzyl (2-trimethylsilylethynyl)aniline in DMF with CuI and $CaCO_3$ to give *N*-benzylindole with concurrent elimination of the trimethylsilyl group.[2c]

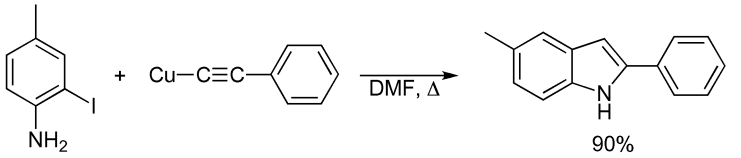
E. APPLICATIONS

This reaction has general applications in the preparation of indoles, especially the 2-substituted indoles.

F. RELATED REACTIONS

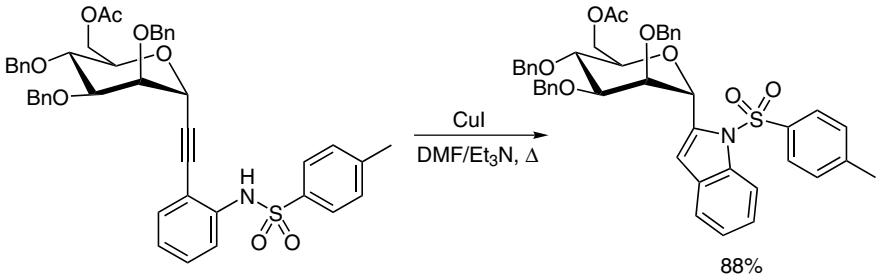
This reaction is related to the *Castro-Stephens Coupling*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 1.

To a 200-mL, three-necked flask equipped with a nitrogen inlet, a reflux condenser connected to a mercury trap, and a magnetic stirring bar was added 1.86 g cuprous phenylacetylide (0.011 mol) and 80 mL dimethylformamide (DMF). The flask and contents were thoroughly flushed with nitrogen with stirring. Under nitrogen 2.56 g 2-iodo-4-methylaniline (0.011 mol) in 20 mL DMF was added. The resulting mixture was stirred at 120°C for 22 h. The dark reaction mixture was filtered, and the filtrate was concentrated to dryness in vacuo in a rotary evaporator. The resulting residue was taken up in chloroform, filtered, added to petroleum ether (b.p. 60–70°C), and concentrated. The residue was purified by recrystallization from chloroform-petroleum ether to yield 2.04 g 5-methyl-2-phenylindole, in a yield of 90%, m.p. 214–214.5°C.



Reference 2a.

To a solution of 3.71 g 1-(6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-mannopyranosyl)-2-*o*-(*p*-toluenesulfoamidyl)phenylethyne (4.99 mmol) in 60 mL Et_3N and 30 mL DMF was added 187 mg CuI (0.98 mmol). After stirring at 80°C for 30 min, water was added. The mixture was extracted three times with EtOAc. The combined organic layer was subsequently washed with aqueous NH_4Cl solution, water, and brine each for two times. Upon removal of the solvent, the residue was purified by silica gel column chromatography using ether/hexanes (1:2) to give 3.28 g 2-(6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-mannopyranosyl)-1-(*p*-toluenesulfonyl) indole, in a yield of 88%.

Other references related to the Castro indole synthesis are cited in the literature.[3]

H. REFERENCES

1. Castro, C. E.; Gaughan, E. J. and Owsley, D. C., *J. Org. Chem.*, **1966**, *31*, 4071.
2. (a) Nishikawa, T.; Koide, Y.; Kajii, S.; Wada, K.; Ishikawa, M. and Isobe, M., *Org. Biomol. Chem.,* **2005**, *3*, 687. (b) Manabe, S. and Ito, Y., *Trends Glycosci Glycotechnol,* **2003**, *15*, 181. (c) Fujiwara, J.; Fukutani, Y.; Sano, H.; Maruoka, K. and Yamamoto, H., *J. Am. Chem. Soc.,* **1983**, *105*, 7177.
3. (a) Nishikawa, T.; Ishikawa, M.; Wada, K. and Isobe, M., *Synlett,* **2001**, *SI*, 945. (b) Nishikawa, T.; Ishikawa, M. and Isobe, M., *Synlett,* **1999**, 123. (c) Fujiwara, J.; Fukutani, Y; Sano, H.; Maruoka, K. and Yamamoto, H., *J. Am. Chem. Soc.*, **1983**, *105*, 7177.

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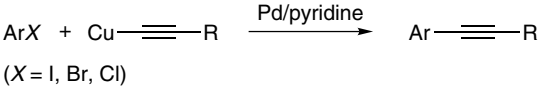
Castro-Stephens Coupling

(Stephens-Castro Coupling, Castro Coupling)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Castro and Stephens in 1963.[1] It is the preparation of arylacetylenes by the coupling of cuprous acetylides with aryl halides in boiling pyridines.[2] Therefore, this reaction is generally known as the Castro-Stephens coupling,[3] Stephens-Castro coupling,[4] or simply as the Castro coupling.[5] Currently, this coupling is one of the most commonly used methods for the synthesis of aryl acetylenes.[6] Moreover, under the Castro-Stephens coupling condition, acetylenes also couple with vinyl halides[7] or even allyl halides[8] and amines,[1] by which indoles are formed in the coupling with amines.[1,9] It is reported that the reactivity of vinyl halide in this coupling is in the order of I > Br > Cl,[10] and the reactivity order of aryl halides decreases in the sequence of I > Br > Cl >> F, while the efficacy of the cuprous species varied with the nature of the ligand in the sequence Cl> Br > I > CN > SPh > SCN. However, this coupling has also shown some limitations, including the poor coupling of terminal acetylenes with an electron-withdrawing group[11] and the coupling of acetylenes with an epoxide or quinone group.[12]

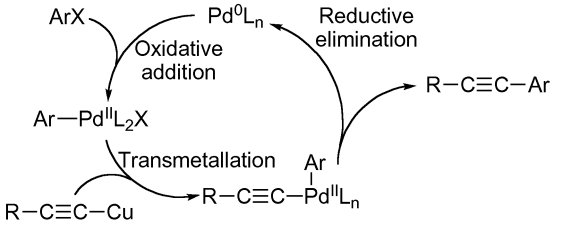
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

A mechanism similar to other alkynylative couplings is illustrated here.[3]



D. MODIFICATION

This coupling has been modified to undergo in the presence of cuprous iodide and triethylamine;[13] in the presence of bis(triphenylphosphine) palladium(II) chloride, cuprous iodide, and triethylamine;[14] or under the conditions of catalytic CuI, Ph_3P, K_2CO_3, and DMF at 120°C.[15]

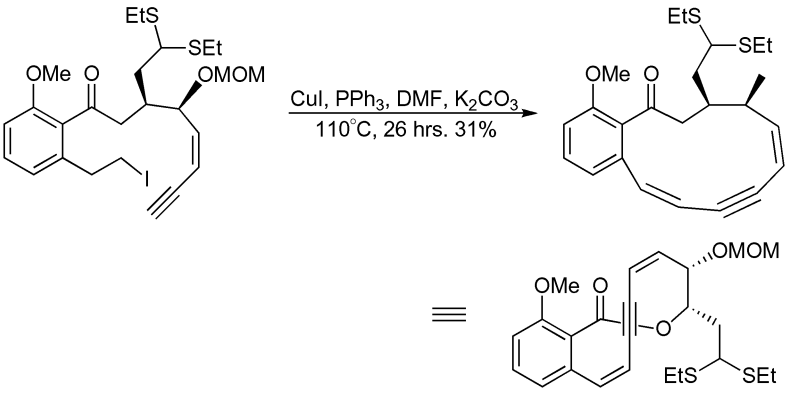
E. APPLICATIONS

This reaction has been widely used for the preparation of aryl acetylenes and vinyl acetylenes.

F. RELATED REACTIONS

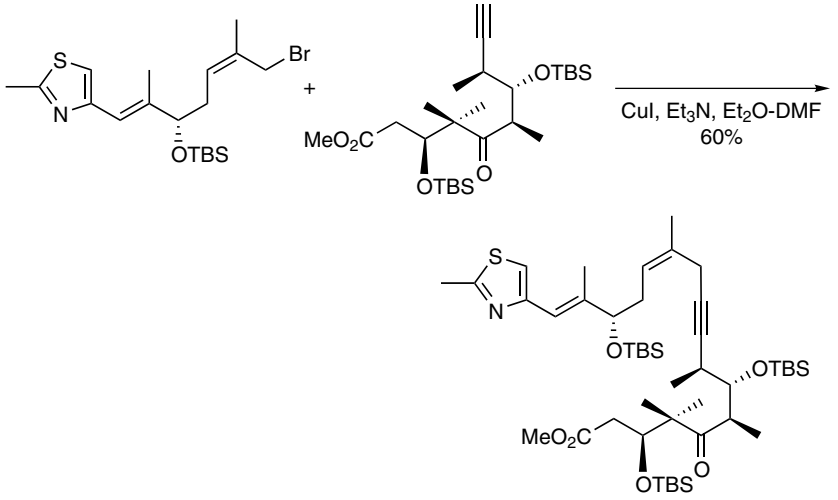
This reaction is closely related to the *Sonogashira Coupling*, which uses a catalytic amount of palladium and copper, whereas the Castro-Stephens coupling uses a stoichiometric amount of copper.[16]

G. CITED EXPERIMENTAL EXAMPLES



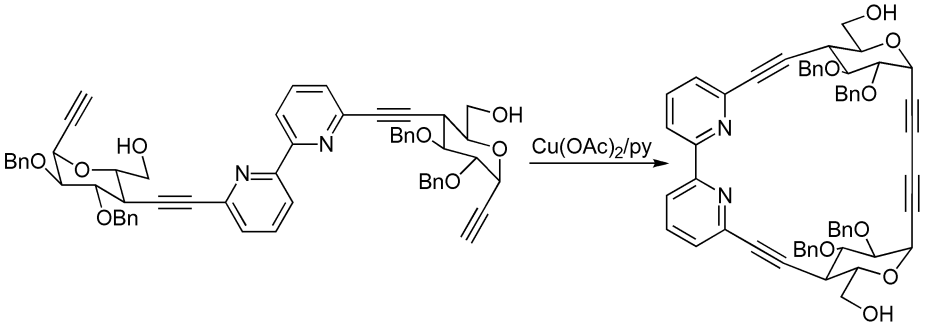
Reference 17.

A mixture of 54 mg (1*E*,3*Z*)-(1*S*,2*S*)-2-(2-iodovinyl)-6-methoxybenzoic acid 1-(2,2-bis-ethylsulfanylethyl)-2-methoxymethoxyhex-3-en-5-ynyl ester (91 μmol), 2 mg copper(I)-iodide (11 μmol), 6 mg triphenylphosphine (23 μmol), and 22 mg K_2CO_3 (159 μmol) in 20 mL dry DMF was heated at 110°C for 26 h. Extractive workup with ether and column chromatography (EtOAc/hexanes = 1:9) furnished 13 mg (1*Z*,9*Z*)-(7*S*,8*S*)-7-(2,2-bis-ethylsulfanylethyl)-4-methoxy-8-methoxymethoxy-8,9-dihydro-6-oxabenzocyclododeca-1,9-dien-11-ynone as a colorless oil, in a yield of 31%.



Reference 18.

To a stirred solution of acetylene (70.0 mg, 0.135 mmol) in 1.0 mL Et_2O and 0.4 mL DMF at room temperature were added 18.8 μL Et_3N (0.135 mmol) and 25.7 mg CuI (0.135 mmol). After the mixture became clear (~5 min), a solution of allyl bromide (29.1 mg, 0.068 mmol) in 1.0 mL Et_2O was added. The solution was stirred for 18 h, quenched with 5 mL saturated aqueous $Na_2S_2O_3$, and extracted with Et_2O (3 × 2 mL). The combined extracts were dried over $MgSO_4$ and concentrated in vacuo; the residue was purified by chromatography on silica gel, eluting with 50–60% CH_2Cl_2/hexane to give 35.6 mg of coupling compound as a colorless oil, in a yield of 60%.



Reference 19.

A degassed solution of 449 mg $Cu(OAc)_2$ (2.47 mmol) in 450 mL pyridine was treated at 50°C under nitrogen with a solution of 112 mg 3,3′-[(2,2′-bipyridine-6,6′-diyl)diethyne-2,1-diyl]-bis-[2,6-anhydro-4,5-di-*O*-benzyl-3-deoxy-D-glycero-D-gulo-oct-7-ynitol] (0.12 mmol) in 1 mL pyridine within 10 h, stirred for 20 h, and evaporated. The residue was dissolved in 20 mL CH_2Cl_2 and 7 mL saturated aqueous KCN solution and stirred for ~12 h. Extraction with CH_2Cl_2 and following double flash chromatography (CH_2Cl_2/MeOH, 49:1; and $CHCl_3$/AcOEt, 4:1) gave 66 mg 2,6:11,15-dianhydro-4,5,12,13-tetra-*O*-benzyl-3,14-C-[(2,2′-bipyridine-6,6′-diyl)diethyne-2,1-diyl]-3,7,8,9,10,14-hexadeoxy-D-erythro-l-ido-l-gulo-hexadeca-7,9-diynitol as a white solid, in a yield of 59%, $R_f = 0.26$ (EtOAc), m.p. 189–191°C (dec.).

Other references related to the Castro-Stephens coupling are cited in the literature.[20]

H. REFERENCES

1. (a) Castro, C. E. and Stephens, R. D., *J. Org. Chem.,* **1963**, *28*, 2163. (b) Castro, C. E. and Stephens, R. D., *J. Org. Chem.,* **1963**, *28*, 3313.
2. (a) Walker, W. H. and Rokita, S. E., *J. Org. Chem.,* **2003**, *68*, 1563. (b) Kang, S.-K.; Yoon, S.-K. and Kim, Y.-M., *Org. Lett.,* **2001**, *3*, 2697.
3. (a) Woon, E. C. Y.; Dhami, A.; Mahon, M. F. and Threadgill, M. D., *Tetrahedron,* **2007**, *63*, 4191. (b) Woon, E. C. Y.; Dhami, A.; Mahon, M. F. and Threadgill, M. D., *Tetrahedron,* **2006**, *62*, 4829.
4. (a) Kabbara, J.; Hoffmann, C. and Schinzer, D., *Synthesis,* **1995**, 299. (b) Staab, H. A. and Neunhoeffer, K., *Synthesis,* **1974**, 424.
5. Van Koten, G.; Ten Hoedt, R. W. M. and Noltes, J. G., *J. Org. Chem.,* **1977**, *42*, 2705.
6. Negishi, E.-I. and Anastasia, L., *Chem. Rev.,* **2003**, *103*, 1979.
7. Grissom, J. W.; Calkins, T. L and McMillen, H. A., *J. Org. Chem.,* **1993**, *58*, 6556.
8. White, J. D.; Sundermann, K. F. and Wartmann, M., *Org. Lett.,* **2002**, *4*, 995.
9. See *Castro Indole Synthesis* herein (P. 616).
10. (a) Rausch, M. D.; Siegel, A. and Kelmann, L. P., *J. Org. Chem.,* **1968**, *33*, 468. (b) Castro, C. E.; Gaughan, E. J. and Owsley, D. C., *J. Org. Chem.,* **1966**, *31*, 4071.
11. Sakamoto, T.; Shiga, F.; Yasuhara, A.; Uchiyama, D.; Kondo, Y. and Yamanaka, H., *Synthesis,* **1992**, 746.
12. Danishefsky, S. J. and Shair, M. D., *J. Org. Chem.,* **1996**, *61*, 16.
13. Mignani, G.; Chevalier, C.; Grass, F.; Allmang, G. and Morel, D., *Tetrahedron Lett.,* **1990**, *31*, 5161.
14. (a) Singh, R. and Just, G., *Tetrahedron Lett.,* **1990**, *31*, 185. (b) Guillerm, D. and Linstrumelle, G., *Tetrahedron Lett.,* **1985**, *26*, 3811.
15. Okuro, K.; Furuune, M.; Enna, M.; Miura, M. and Nomura, M., *J. Org. Chem.,* **1993**, *58*, 4716.
16. (a) Coleman, R. S. and Garg, R., *Org. Lett.,* **2001**, *3*, 3487. (b) Sonogashira, K., "Cross-Coupling Reactions to sp Carbon Atoms" in *Metal-Catalyzed Cross-Coupling Reactions*, ed. Diederich, F. and Stang, P., Wiley-VCH, New York, **1998**, pp. 203–229. (c) Sonogashira, K.; Tohda, Y. and Hagihara, N., *Tetrahedron Lett.,* **1975**, 4467.
17. Haack, T.; Kurtkaya, S.; Snyder, J. and Georg, G. I., *Org. Lett.,* **2003**, *5*, 5019.
18. White, J. D.; Carter, R. G.; Sundermann, K. F. and Wartmann, M., *J. Am. Chem. Soc.,* **2001**, *123*, 5407.
19. Bürli, R. and Vasella, A., *Helv. Chim. Acta,* **1999**, *82*, 485.

20. (a) Hudson, R. H. E. and Moszynski, J. M., *Synlett,* **2006**, 2997. (b) Alonso, F.; Beletskaya, I. P. and Yus, M., *Chem. Rev.,* **2004**, *104*, 3079. (c) Waters, M. S.; Cowen, J. A.; McWilliams, J. C.; Maligres, P. E. and Askin, D., *Tetrahedron Lett*., **2000**, *41*, 141. (d) Tan, D. S.; Foley, M. A.; Stockwell, B. R.; Shair, M. D. and Schreiber, S. L., *J. Am. Chem. Soc*., **1999**, *121*, 9073. (e) Yu, M. S.; Lopez, De Leon, L.; McGguire, M. A. and Botha, G., *Tetrahedron Lett.,* **1998**, *39*, 9347. (f) Hay, L. A.; Koenig, T. M.; Ginah, F. O.; Copp, J. D. and Mitchell, D., *J. Org. Chem.,* **1998**, *63*, 5050. (g) Dibowski, H. and Schimdtchen, F. P., *Tetrahedron Lett.,* **1998**, *39*, 525. (h) Dibowski, H. and Schimdtchen, F. P., *Angew. Chem. Int. Ed.,* **1998**, *37*, 476. (i) Grissom, J. W.; Klingberg, D.; Huang, D. H. and Slattery, B. J., *J. Org. Chem.,* **1997**, *62*, 603. (j) Hessler, A.; Stelzer, O.; Dibowski, H.; Worm, K. and Schmidtchen, F. P., *J. Org. Chem.,* **1997**, *62*, 2362. (k) Andrus, M. B. and Lepore, S. D., *J. Am. Chem. Soc.,* **1997**, *119*, 2327. (l) Padwa, A.; Kassir, J. M.; Semones, M. A. and Weingarten, M. D., *J. Org. Chem.,* **1995**, *60*, 53. (m) Padwa, A.; Austin, D. J.; Gareau, Y.; Kassir, J. M. and Xu, S. L., *J. Am. Chem. Soc*., **1993**, 115, *2631*. (n) Kinder, J. D.; Tessier, C. A. and Youngs, W. J., *Synlett,* **1993**, 149. (o) Padwa, A.; Chiacchiot, U.; Fairfax, D. J.; Kassir, J. M.; Litrico, A.; Semones, M. A. and Xu, S. L., *J. Org. Chem.,* **1993**, *58*, 6429. (p) Padwa, A.; Krumpe, K. E.; Gareau, Y. and Chiacchiot, U., *J. Org. Chem.,* **1991**, *56*, 2523. (q) Crevisy, C. and Beau, J.-M., *Tetrahedron Lett*., **1991**, *32*, 3171. (r) Guillerm, D. and Linstrumelle, G., *Tetrahedron Lett*., **1985**, *26*, 3811. (s) Heck, R. F., *Acc. Chem. Res.,* **1979**, *12*, 146. (t) Dieck, H. A. and Heck, R. F., J. *Organomet. Chem.,* **1975**, *93*, 259. (u) Castro, C. E.; Havlin, R.; Honwad, V. K.; Malte, A. and Moje, S., *J. Am. Chem. Soc.,* **1969**, *91*, 6464. (v) Castro, C. E.; Gaughan, E. J. and Owley, D. C., *J. Org. Chem.,* **1965**, *30*, 587.

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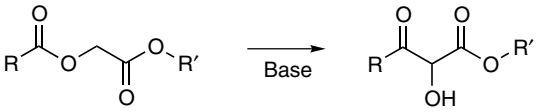
Chan Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Chan in 1984.[1] It is a base-induced rearrangement of α-acyloxy-acetates to α-hydroxy-β-keto-esters[2] and is thus known as the Chan rearrangement.[2,3] It should be pointed out that under similar conditions amino ketone can also be prepared.[4] The intermediate enediolate formed in the presence of an excess amount of base (usually LDA) can react with Me_3SiCl or Ac_2O to afford corresponding trimethylsilyl or acetyl derivatives.[1,2] This reaction is a convenient means for assembling an array of three contiguous oxygenated carbons[2] and has successfully been applied to the syntheses of some natural products, including the indole-bisoxazole fragment of diazonamide A,[4] (+)-aplasmomycin,[5] boromycin,[6] taxol,[7] and polyoxazole.[4]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

This reaction involves the deprotonation of α-(acyloxy) acetate, and the resulting carbanion adds to the carbonyl moiety of the α-acyloxy group to form an epoxide, which

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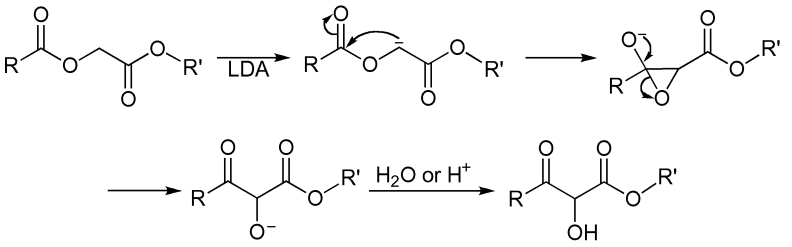
subsequently undergoes fragmentation to give the α-hydroxy-β-keto ester,[1,2] as displayed here.



D. MODIFICATION

N/A

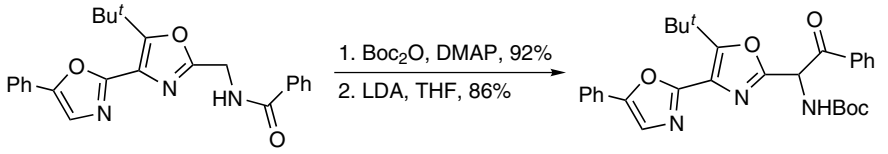
E. APPLICATIONS

This reaction has a general application in the synthesis of compounds containing three contiguous oxygenated carbons[2] and has been successfully applied to the preparation of diazonamide A,[4] aplasmomycin,[5] boromycin,[6] taxol,[7] etc.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES

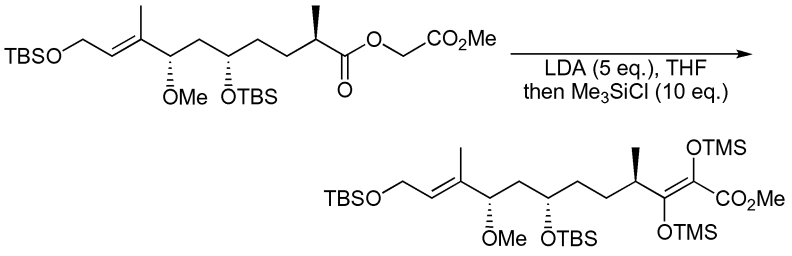


Reference 4.

A solution of 32 mg *N*-(5′-*tert*-butyl-5-phenyl-[2,4′]bioxazolyl-2′-ylmethyl)-benzamide (0.080 mmol) in 1 mL THF was treated with 10 mg DMAP (0.089 mmol) and 35 mg Boc_2O (0.16 mmol). The reaction mixture was stirred for 19 h, diluted with EtOAc, washed with 10% HCl, saturated $NaHCO_3$, and dried over $MgSO_4$. Upon filtration and concentration, the residue was purified by column chromatography on SiO_2 (EtOAc/hexanes, 1:19–1:9) to give 37 mg of the oily imide, in a yield of 92%. $R_f = 0.64$ (EtOAc/hexanes, 1:1).

A solution of 0.050 mL *i*-Pr_2NH (0.36 mmol) in 1 mL THF was treated with 0.2 mL 1.6 M BuLi in hexane (0.32 mmol) and cooled to –78°C. A solution of 35 mg above imide (0.070 mmol) in 1 mL THF was added, and the reaction mixture was stirred for above 30 min,

diluted with EtOAc, washed with 10% HCl, saturated $NaHCO_3$, and dried over Na_2SO_4. After filtration and evaporation, the residue was purified by column chromatography on SiO_2 (EtOAc/hexanes, 1:9–3:7) to give 30 mg of oily [1-(5′-*tert*-butyl-5-phenyl-[2,4′] bioxazolyl-2′-yl)-2-oxo-2-phenylethyl]-carbamic acid *tert*-butyl ester, in a yield of 86%. $R_f = 0.64$ (EtOAc/hexanes, 1:1).



Reference 2.

To a solution of LDA, prepared by the addition of 43 μL 1.6 M *n*-BuLi in hexane (0.072 mmol) to a solution of 9.4 μL diisopropylamine (0.072 mmol) in 0.2 mL THF at 0°C over 15 min was added a solution of 8 mg ester (0.014 mmol) in 0.15 mL THF. The mixture was stirred for 1 h and then cooled to –78°C; 13.5 μL TMSCl (0.11 mmol) was then added. After being stirred for 10 min, the solution was allowed to warm to 0°C and was stirred for an additional 15 min. The mixture was poured into hexane, and the resulting solution was washed with pH 7 phosphate buffer (3 × 5 mL). The extracts were combined, washed with brine, and dried over Na_2SO_4. Concentration gave 13 mg of crude product as a clear oil.

Other references related to the Chan rearrangement are cited in the literature.[8]

H. REFERENCES

1. Lee, S. D.; Chan, T. H. and Kwon, K. S., *Tetrahedron Lett.,* **1984**, *25*, 3399.
2. White, J. D. and Jeffrey, S. C., *J. Org. Chem.,* **1996**, *61*, 2600.
3. Yang, Y. and Wang, D., *Huaxue Tongbao*, **1997**, 30.
4. Wipf, P. and Methot, J.-L., *Org. Lett.,* **2001**, *3*, 1261.
5. White, J. D.; Vedananda, T. R.; Kang, M.-C.; Choudhry, S. C., *J. Am. Chem. Soc.,* **1986**, *108*, 8105.
6. White, J. D.; Avery, M. A.; Choudhry, S. C.; Dhingra, O. P.; Gray, B. D.; Kang, M.-C., Kuo, S.-C. and Whittle, A. J., *J. Am. Chem. Soc.,* **1989**, *111*, 790.
7. Holton, R. A.; Somoza, C.; Kim, H.-B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C. L.; Vu, P.; Tang, S. H.; Zhang, P. S.; Murthi, K. K.; Gentile, L. N. and Liu, J. H., *J. Am. Chem. Soc.,* **1994**, *116*, 1597.
8. (a) Wessjohann, L., *Angew. Chem. Int. Ed. Engl.,* **1994**, *33*, 959. (b) Holton, R. A., *J. Am. Chem. Soc.,* **1988**, *110*, 6558.

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Chapman Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Mumm and co-workers in 1915[1] and was extensively investigated by Chapman in 1920s and 1930s.[2] It is the thermal rearrangement of aryl imidates to *N*, *N*-diaryl amides, and is generally known as the Chapman rearrangement.[3] Occasionally, this reaction is also referred to as the Beckmann-Chapman rearrangement.[4] It was found that this rearrangement follows approximately a first-order kinetics[5] and proceeds readily with high yields in either polar or nonpolar solvents,[2e] but it is accelerated by polar solvents. In addition, this reaction can even take place in a solid state at one-fifteenth to one-fifth the rate of that estimated in solution.[4c] In fact, it is an intramolecular nucleophilic aromatic substitution that proceeds stereospecifically with migration of that aryl ring attached to oxygen, and the *ortho* substituents on the aryl ring connecting to oxygen atom have been shown to enhance the migration rate. This effect is known as steric acceleration due to the hindered rotation (SAHR) effect,[3l,3m] as the free rotation will restrict the formation of a four-membered ring in the transition state.[3l] Moreover, it is also found that a *para* electron-donating group also increases the migration rate, whereas a *para* electron-withdrawing group (Cl, NO_2, etc.) decreases the reaction rate.[4c] This rearrangement has been used for the preparation of substituted *N*-phenylanthranilic acids.[3r] It should be pointed out that if the migrating aryl moiety has an α-acidic hydrogen at the *ortho* position, then an "abnormal" Chapman Rearrangement also occurs.[3q]

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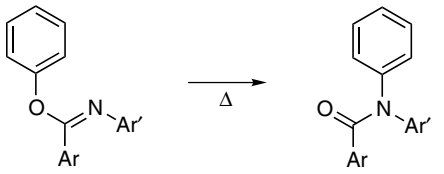
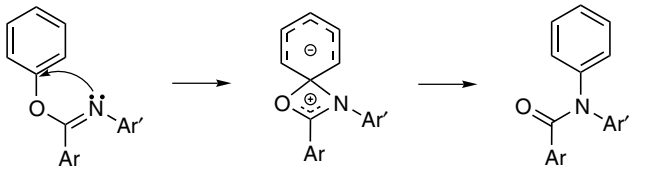
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The Chapman rearrangement involves the *ipso* attack of a nitrogen atom and the subsequent cleavage of the C–O bond, as displayed here.



D. MODIFICATION

N/A

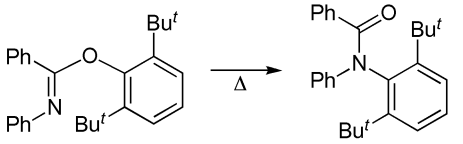
E. APPLICATIONS

This reaction has general application in the preparation of *N*-acyl anilines.

F. RELATED REACTIONS

This reaction is related to the *Newman-Kwart Rearrangement*.

G. CITED EXPERIMENTAL EXAMPLES



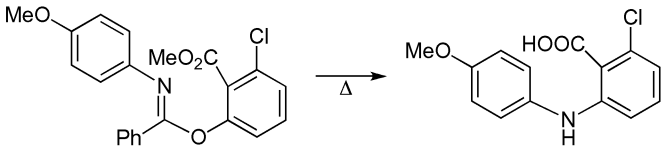
Reference 3m.

The Preparation of 2,6-di-*t*-Butylphenyl *N*-Phenylbenzimidate

Exactly 10.0 g 2,6-di-*t*-butylphenol (0.0486 mol) and 0.1 g triphenylmethane were dissolved in 150 mL tetrahydrofuran. While the solution was stirred under nitrogen, ~31 mL 1.6 *M* butyllithium in hexane was added, whereupon the red color of the triphenylmethyl carbanion just appeared. Then 10.47 g *N*-phenylbenzimidoyl chloride (0.0486 mol) in 75 mL tetrahydrofuran was added, and the system was stirred overnight at room temperature under nitrogen. After the reaction mixture was combined with 400 mL ethyl ether, it was extracted with water, dried with anhydrous magnesium sulfate, and freed of solvent on a rotary evaporator to give 19.35 g of a viscous red oil. Chromatography on 400 g alumina, using hexane as the elution solvent, afforded some 2,6-di-*t*-butylphenol and impure 2,6-disubstituted phenyl *N*-phenylbenzimidates. Two recrystallizations from methanol afforded 4.28 g imidate as colorless plates, in a yield of 23%, m.p. 127.5–128.5°C.

The Chapman Rearrangement

A 1.0 g 2,6-disubstituted phenyl *N*-phenylbenzimidate was sealed in a glass tube in air and heated at 305°C for 6 h. The resulting cooled mass was chromatographed to give *N*-(2,6-di-*t*-butylphenyl)benzanilide with a broad melting point of 129–133.5°C.



Reference 3r.

To a solution of NaOEt prepared from 0.11 g sodium (4.7 mmol) and 10 mL absolute ethanol, cooled in an ice bath, was added in rapid succession 0.88 g methyl 2-chloro-6-hydroxybenzoate (4.7 mmol) and a solution of 1.14 g *N*-4-methoxyphenylbenzimidyl chloride (4.7 mmol) in 30 mL dry ether. The reaction mixture was shaken vigorously, whereupon a precipitate of sodium chloride began to form. The mixture was allowed to stand at room temperature for 48 h, the solvent was evaporated, and the residue was diluted with water. The resulting oily solid was removed by extraction with ether, the ethereal solution was dried, and the ether was distilled. The crude imido ester was heated in a nitrogen atmosphere at 210–215°C for 70 min, then dissolved in 10.8 mL ethanol; the alcoholic solution was diluted with 5.4 mL water and 5.4 mL of a 1 *M* ethanolic sodium ethoxide. The solution was refluxed for 1.5 h, the alcohol was evaporated on a steam bath, and the aqueous solution was acidified with dilute HCl. The dark oil that formed was separated by decantation, and the crude benzoate of the substituted anthranilic acid was dissolved in 22 mL ethanol. A solution of 7.2 g sodium hydroxide in 7.2 mL water was added, and the mixture was refluxed for 1 h. The alcohol was evaporated, and the solution was then acidified. The brown solid was extracted *exhaustively* with boiling water to remove the benzoic acid, and the remaining brown solid was recrystallized from aqueous ethanol. The yellow needle-like crystals of *N*-(4′-methoxyphenyl)-6-chloroanthranilic acid, in a total amount of 0.36 g, was obtained, in a yield of 27.7%, m.p., 139.5–140.5°C (dec).

Other references related to the Chapman rearrangement are cited in the literature.[6]

H. REFERENCES

1. Mumm, O.; Hesse, H. and Volquartz, H., *Ber.,* **1915**, *48*, 379.
2. (a) Chapman, A. W., *J. Chem. Soc.,* **1925**, 1992. (b) Chapman, A. W., *J. Chem. Soc.*,**1927**, 1743. (c) Chapman, A. W., *J. Chem. Soc.,* **1929**, 569. (d) Chapman, A. W., *J. Chem. Soc.,* **1930**, 2462. (e) Chapman, A. W. and Howis, C. C., *J. Chem. Soc.,* **1933**, 806. (f) Chapman, A. W., *J. Chem. Soc.,* **1934**, 1550. (g) Chapman, A. W. and Fidler, F. A., *J. Chem. Soc.,* **1936**, 451.
3. (a) Noroozi-Pesyan, N., *Heterocycl. Commun.,* **2006**, *12*, 329. (b) Burdukovskii, V. F.; Mognonov, D. M.; Allayarov, S. R.; Botoeva, S. O. and Mazurevskaya, Z. P., *Russ. Chem. Bull.,* **2004**, *53*, 1773. (c) Wang, X. S.; Cai, Y. L. and Xu, Z. X., *Zhongguo Yaoxue Zazhi (Beijing)*, **1997**, *32*, 774. (d) Kimura, M.; Okabayashi, I. and Isogai, K., *J. Heterocycl. Chem.,* **1988**, *25*, 315. (e) Kimura, M., *J. Chem. Soc., Perkin Trans. II,* **1987**, 205. (f) Peterson, L. H.; Douglas, A. W. and Tolman, R. L., *J. Heterocycl. Chem.,* **1981**, *18*, 659. (g) Shawali, A. S.; Hassaneen, H. M. and Almousawi, S., *Bull. Chem. Soc. Jpn.,* **1978**, *51*, 512. (h) Ramirez, F.; Telefus, C. D. and Prasad, V. A. V., *Tetrahedron,* **1975**, *31*, 2007. (i) Goldberg, V. D. and Harris, M. M., *J. Chem. Soc., Perkin Trans. II,* **1973**, 1303. (j) Hegarty, A. F.; Kearney, J. A. and Scott, F. L., *J. Chem. Soc., Perkin Trans. II,* **1973**, 1422. (k) Wheeler, O. H.; Roman, F.; Santiago, M. V. and Quiles, F., *Can. J. Chem.,* **1969**, *47*, 503. (l) Relles, H. M. and Pizzolato, G., *J. Org. Chem.,* **1968**, *33*, 2249. (m) Relles, H. M., *J. Org. Chem.,* **1968**, *33*, 2245. (n) Bock, G., *Chem. Ber.,* **1967**, *100*, 2870. (o) Barclay, R., *Can. J. Chem.,* **1965**, *43*, 2125. (p) Schulenberg, J. W. and Archer, S., *Org. React.,* **1965**, *14*, 1. (q) Schulenberg, J. W. and Archer, S., *J. Am. Chem. Soc.,* **1960**, *82*, 2035. (r) Dauben, W. G. and Hodgson, R. L., *J. Am. Chem. Soc.,* **1950**, *72*, 3479.
4. (a) Snegirev, V. F.; Antipin, M. Y.; Khrustalev, V. N. and Struchkov, Y. T., *Izv. Akad. Nauk, Ser. Khim.,* **1994**, 1073. (b) Rozantsev, E. G.; Chudinov, A. V. and Sholle, V. D., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1980**, 2114. (c) McCullough, J. D.; Curtin, D. Y. and Paul, I. C., *J. Am. Chem. Soc.,* **1972**, *94*, 874. (d) Fischer, H. P. and Funk-Kretschmar, F., *Helv. Chim. Acta,* **1969**, *52*, 913.
5. Wiberg, K. B. and Rowland, B. I., *J. Am. Chem. Soc.,* **1955**, *77*, 2205.
6. (a) Dubau-Assibat, N.; Baceiredo, A.; Dahan, F. and Bertrand, G., *Bull. Soc. Chim. Fr.,* **1995**, *132*, 1139. (b) Dessolin, M.; Eisenstein, O.; Golfier, M.; Prange, T. and Sautet, P., *J. Chem. Soc., Chem. Commun.,* **1992**, 132. (c) Suttle, N. A. and Williams, A., *J. Chem. Soc., Perkin Trans. II,* **1983**, 1369. (d) Peterson, L. H.; Douglas, A. W. and Tolman, R. L., *J. Heterocyclic Chem.,* **1981**, *18*, 659. (e) Shawali, A. S. and Hassaneen, H. M., *Tetrahedron,* **1972**, *28*, 5903. (f) Schulenberg, J. W. and Archer, S., *Org. React.,* **1965**, *14*, 1. (g) Smith, P. A. S., "Chapter 8, Rearrangements Involving Migration to an Electron–Deficient Nitrogen or Oxygen" in *Molecular Rearrangements*, ed. de Mayo, P., Interscience, New York, 1963.

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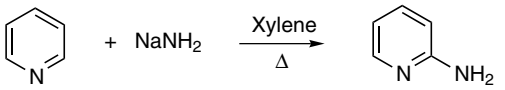
Chichibabin Amination

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Chichibabin in 1914.[1] It is the preparation of 2-aminopyridine from pyridine and sodium amide in boiling inert solvent (such as xylene, toluene, and benzene),[2] and is generally known as the Chichibabin amination[3] or Chichibabin reaction.[4] This reaction is a simple method of synthesizing 2-aminopyridine for which the traditional procedure for aromatic amines via nitration and subsequent reduction works poorly for pyridines. Strangely enough, it is found that the yield of 2-aminopyridine depends to a large extent on the condition of the sodium amide used in the synthesis.[5] For example, the purest sodium amide fails to react appreciably with pyridine, whereas less pure sodium amide (commercial product or standing in laboratory for some time) gives good yields. It is possible that the impurities in sodium amide may have the catalytic effect. In this reaction, if the amount of sodium amide is increased, then a second amino group might be introduced to the aromatic ring.[6] However, when both position 2 and 6 are blocked by substituents, the amino group will be introduced into position 4, though with a low yield. The source of amine in this reaction can be sodium amide ($NaNH_2$), potassium amide (KNH_2),[7] or even organic amide (KNHR).[8] In addition, if organic amine is connected to a pyridine ring, then cyclic amine will form under these conditions. Moreover, this reaction works not only for the pyridine series but also for other nitrogen-containing heterocycles, including purines,[7b] pyrazines,[9] naphthyridines,[10] triazine,[7] and pyrimidines.[7b] It is proposed that this reaction if carried out in liquid ammonia takes place at least partially via the S_N(ANRORC) mechanism.[7]

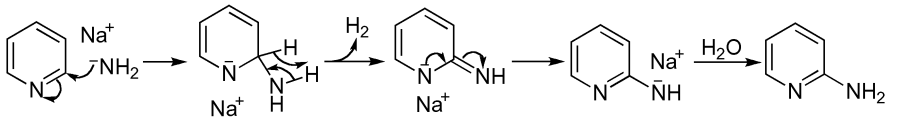
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME

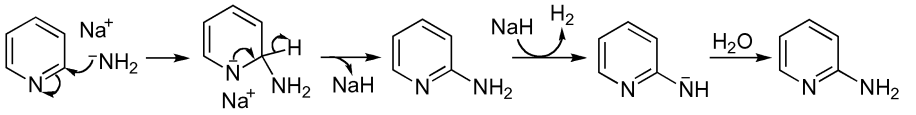


C. PROPOSED MECHANISMS

The reaction may involve the addition of an amide anion to the pyridine ring, followed by elimination of hydrogen and the formation of 2-aminopyridine upon hydrolysis (Scheme 1). More plausibly, the reaction may proceed via the addition of an amide anion to the pyridine ring, followed by the elimination of hydride, which then deprotonates at the amino group, as shown in Scheme 2.



Scheme 1.



Scheme 2.

D. MODIFICATION

N/A

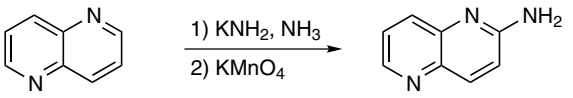
E. APPLICATIONS

This reaction has a general application in the preparation of nitrogen-containing aromatic amines, for which the traditional procedure via nitration followed by reduction works poorly or is not applicable.

F. RELATED REACTIONS

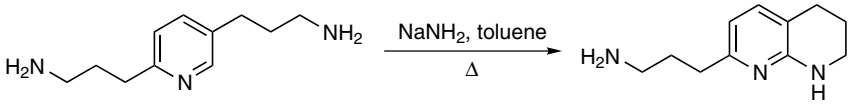
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3j.

To 15 mL liquid ammonia containing potassium amide, obtained by a reaction with 0.15 g potassium was added 0.20 g 1,5-naphthyridine. After the mixture was stirred for 10 min and 0.80 g $KMnO_4$ was added in small portions, the mixture was stirred for another 10 min. The potassium amide was then decomposed with $(NH_4)_2SO_4$. After evaporation of the ammonia, a concentrated aqueous solution of ammonia was added, and the mixture was continuously extracted with chloroform over 48 h. The residue obtained on evaporation of the chloroform was taken up in a minimum amount of methanol and developed by use of an Autoliner Desaga (model 121000) on a plate (20 × 40 cm) covered by a 2-mm layer of silica gel DFW and eluted with chloroform/ethanol (10:1) to give one band, which was extracted with methanol. Evaporation of methanol afforded 80 mg 2-amino-1,5-naphthyridine, in a yield of 36%, m.p., 203.5–205°C.



Reference 8.

To a solution of 233 g 3,3′-pyridine-2,5-diyldipropan-1-amine (1.21 mol) in 4 L toluene was added 255 g $NaNH_2$ (90 wt %, 5.88 mol); the mixture was heated to 90°C for 7 h. The reaction was monitored by HPLC and was considered complete when less than 1% of starting material was left. The mixture was cooled to 5°C, and 1 L 4.4 M NaCl was added at such a rate as to maintain the temperature at 10°C. When the addition was complete, the mixture was allowed to warm to 18–22°C and was stirred for 18 h. The layers were separated, and the aqueous phase was extracted with toluene. Water was added to the aqueous phase, and it was further extracted with toluene. The toluene extracts were combined to give 6.1 kg of solution. Evaporation of solvent afforded 207 g 3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propan-1-amine, in a yield of 90%.

Other references related to the Chichibabin amination are cited in the literature.[11]

H. REFERENCES

1. Chichibabin, A. E. and Seide, O. A., *J. Russ. Phys. Chem. Soc.,* **1914**, *46*, 1216 [*Chem. Abstr.,* **1915**, *9*, 1901].
2. Bergstrom, F. W. and Fernelius, W. C., *Chem. Rev.,* **1933**, *12*, 43.
3. (a) Kiselyov, A. S. and Strekowski, L., *Synth. Commun.,* **1994**, *24*, 2387. (b) Gulevskaya, A. V.; Pozharskii, A. F. and Lomachenkova, L. V., *Khim. Geterotsiklicheskikh Soedinenii,* **1990**, 1575. (c) Buurman, D. J. and van der Plas, H. C., *J. Heterocycl. Chem.,* **1987**, *24*, 1377. (d) van der, Plas H. C., *Khim. Geterotsiklicheskikh Soedinenii*, **1987**, 1011. (e) Breuker, K.; van der Plas, H. C.

and van Veldhuizen, A., *Isr. J. Chem.,* **1986**, *27*, 67. (f) Van der Plas, H. C. and Wozniak, M., *Croat. Chem. Acta,* **1986**, *59*, 33. (g) Rykowski, A. and van der Plas, H. C., *Synthesis,* **1985**, 884. (h) Tondys, H.; van der Plas, H. C. and Wozniak, M., *J. Heterocycl. Chem.,* **1985**, *22*, 353. (i) Breuker, J. and van der Plas, H. C., *Rec.: J. Royal Netherlands Chem. Soc.,* **1983**, *102*, 367. (j) Van den Haak, H. J. W.; van der Plas, H. C. and van Veldhuizen, B., *J. Org. Chem.,* **1981**, *46*, 2134.

4. (a) Varlamov, A. V.; Levov, A. N.; Toze, F.; Chernyshev, A. I.; Davydov, V. V.; Ryabov, M. A. and Egorova, O. A., *Chem. Heterocycl. Compd.,* **2002**, *38*, 1484. (b) Yao, Z. P.; Gao, X. and Ren, P. D., *Daxue Huaxue*, **2001**, *16*, 48. (c) McGill, C. K. and Rappa, A., *Adv. Heterocycl. Chem.,* **1988**, *44*, 1. (d) Doron'kin, V. N.; Pozharskii, A. F. and Kashparov, I. S., *Khim. Geterotsiklicheskikh Soedinenii*, **1979**, 257. (e) Simig, G. and van der Plas, H. C., *Rec. Trav. Chim. Pays-Bas,* **1976**, *95*, 125. (f) Rosowsky, A.; Papathanasopoulos, N. and Modest, E. J., *J. Heterocycl. Chem.,* **1972**, *9*, 1449.
5. Wibaut, J. P. and Dingemanse, E., *Rec. Trav. Chim. Pays-Bas Belg.,* **1923**, *42*, 240.
6. Chichibabin, A. E. and Seide, O. A., *J. Russ. Phys. Chem. Soc.,* **1920**, *50*, 522 [*Chem. Abstr.,* **1924**, *18*, 1496].
7. (a) Breuker, K. and van der Plas, H. C., *J. Org. Chem.,* **1979**, *44*, 4677. (b) Kos, N. J.; van der Plas, H. C. and van Veldhuizen, B., *J. Org. Chem.,* **1979**, *44*, 3140.
8. Hartner, F. W.; Hsiao, Y.; Eng, K. K.; Rivera, N. R.; Palucki, M.; Tan, L. S.; Yasuda, N.; Hughes, D. L.; Weissman, S.; Zewge, D.; King, T.; Tschaen, D. and Volante, R. P., *J. Org. Chem.,* **2004**, *69*, 8723.
9. Chichibabin, A. E. and Schukina, M. N., *J. Russ. Phys. Chem. Soc.,* **1930**, *62*, 1189; *Chem. Abstr.,* **1931**, *25*, 2728.
10. (a) Brown, E. V. and Plasz, A. C., *J. Heterocycl. Chem.,* **1970**, *7*, 593. (b) Paudler, W. W. and Kress, T. J., *J. Org. Chem.,* **1968**, *33*, 1384. (c) Hart, E. P., *J. Chem. Soc.,* **1954**, 1879.
11. (a) Krems, I. J. and Spoerri, P. E., *Chem. Rev.,* **1947**, *40*, 279. (b) Bergstrom, F. W., *Chem. Rev.,* **1944**, 35, 77. (c) Seide, O. A., *Ber.,* **1924**, 57*B*, 791. (d) Seide, O. A., *J. Russ. Phys. Chem. Soc.,* **1920**, *50*, 534; *Chem. Abstr.,* **1924**, *18*, 1497.

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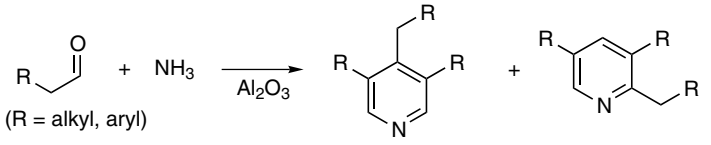
Chichibabin Pyridine Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Chichibabin in 1906.[1] It is the preparation of substituted pyridines by thermal cyclo-condensation of aldehydes and ammonia by passing aldehydes and ammonia over a contact catalyst such as alumina.[2] Therefore, this reaction is generally known as the Chichibabin pyridine synthesis[3] or Chichibabin synthesis.[4] In addition, this reaction is also referred to as the Chichibabin-Bayer reaction[5] or Chichibabin cyclotrimerization.[6] Besides aldehydes, ammonia gas also reacts with acetylene or acetonitrile over a heated contact catalyst to give pyridine derivatives;[3] in addition, the Chichibabin pyridine synthesis also takes place with aliphatic and aromatic ketones, α,β-unsaturated aldehyde, and keto acids. It is reported that when higher aliphatic aldehyde reacts with ammonia at high temperature, besides the expected pyridine product, the abnormal pyridine derivatives also form in which the higher aliphatic aldehyde breaks down in part to formaldehyde that cyclo-condenses with two molecules of the higher aldehyde and ammonia.[2e] Moreover, the yield of 3,5-diphenylpyridine from phenylacetaldehyde can be increased by a factor of about three by the addition of an equivalent amount of isobutyraldehyde, basic iron acetate, or methanolic formaldehyde.[7] It is proposed that this reaction proceeds through a series of *Aldol Condensations*, followed by a cyclization and dehydrogenation.[8] Currently, this reaction has been applied to the syntheses of pyridine and collidine derivatives.[9]

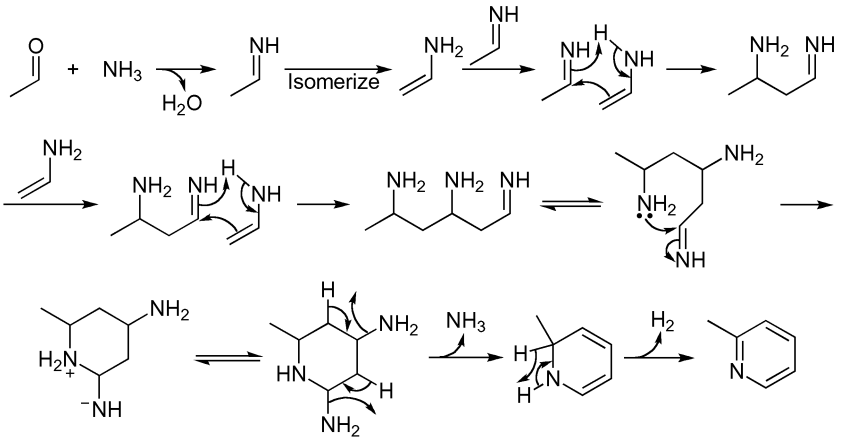
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The reaction mechanism is illustrated by the reaction between acetaldehyde and ammonia.



D. MODIFICATION

N/A

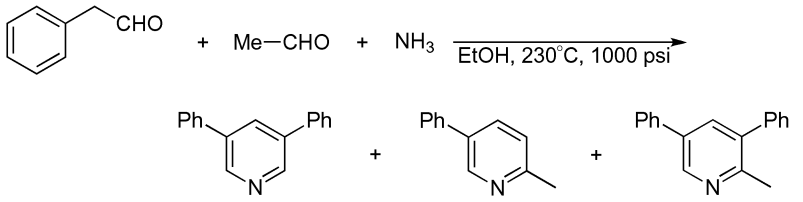
E. APPLICATIONS

This reaction has been used for the syntheses of pyridine and collidine derivatives.

F. RELATED REACTIONS

N/A

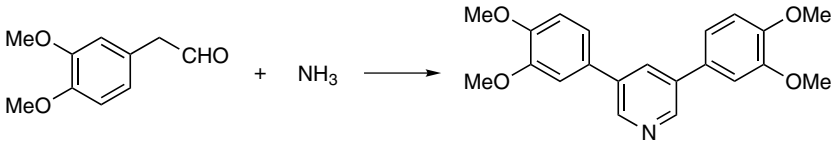
G. CITED EXPERIMENTAL EXAMPLES



Reference 10.

Phenylacetaldehyde (120 g, 1 mol) and 0.5 mol of another aldehyde component were dissolved in 350 mL saturated solution of ammonia in absolute ethanol. The solution was sealed in a 1-L stainless-steel bomb and heated at 225–230°C for 6 h with constant rocking. The pressure was ~1000 psi. The bomb was then cooled and opened; the contents was transferred to a distilling flask. As much ethanol as possible was distilled on the steam bath at atmospheric pressure. The residue was subjected to a preliminary distillation in which everything boiling up to ~280°C (1 mmHg) was collected; except in the case of the acetaldehyde condensation, in which a preliminary distillation with superheated steam at 200°C was resorted to (omission of this preliminary treatment led to difficulties in the subsequent extraction step). The distillate was taken up in ether and extracted 15 times with 2 *N* HCl. The residual ether layer was discarded, and the aqueous layer plus a third layer—which invariably formed—were made basic with an excess of concentrated ammonium hydroxide. The bases liberated were extracted with ether and dried over potassium carbonate; the solution was then concentrated.

For the case of the condensation among phenylacetaldehyde, acetaldehyde, and ammonia, 60.5 g of crude basic reaction product on standing overnight deposited 15.0 g 3,5-di-phenylpyridine, which was collected after diluting the mixture with 50 mL ligroin (b.p. 60–71°C). The material melted at 136–138°C. The remaining material was distilled to give three arbitrary fractions. The first fraction (b.p. up to 174°C, at 13 mmHg), weighed 3.9 g and was proved to be 2-methyl-5-phenylpyridine. The second fraction (b.p. 174–230°C, 13 mmHg), weighed 27.65 g and was proved to be 2-methyl-3,5-diphenylpyridine, with an actual of boiling point 226–228°C at 13 mmHg. The third fraction (b.p. 230–250°C, 13 mmHg), weighed 4.33 g and was proved to be 2-methyl-3,5-diphenylpyridine.



Reference 7.

A solution of 45.5 g homoveratric aldehyde in 250 mL freshly prepared absolute alcohol was boiled under reflux for 1 h while a current of dry ammonia gas was bubbled through it. The solvent and excess ammonia were then distilled at reduced pressure, and the spongy, apparently amorphous residue was heated with 100 mL 1 *N* HCl in anhydrous ethanol (or methanol). The excess ethanol and hydrogen chloride were then distilled (at atmospheric pressure or in vacuo) and the residue was slurried with acetone. Most

of the tarry material dissolved and light-colored crystals of the hydrochloride of 3,5-diveratrylpyridine remained. They were collected, washed with acetone until nearly colorless, and dissolved in 350 mL boiling 95% ethanol. The addition of 100 mL concentrated aqueous ammonia and 100 mL water to this solution led to the precipitation of 3,5-diveratrylpyridine in the form of shiny leaflets. The suspension was chilled, and 5.66 g of the crystals was collected. Recrystallization gave 4.44 g 3,5-diveratrylpyridine, m.p. 170–173°C.

Other references related to the Chichibabin pyridine synthesis are cited in the literature.[11]

H. REFERENCES

1. Chichibabin A. E., *ZhRFHO*, **1906**, *37*, 1229.
2. (a) Chichibabin, A. E. and Orochko, D. I., *J. Russ. Phys. Chem. Soc.,* **1930**, *62*, 1201 [*Chem. Abstr.* **1931**, *25*, 2725]. (b) Chichibabin, A. E. and Oparina, M. P., *Ber.,* **1927**, *60B*, 1877. (c) Chichibabin, A. E., *J. Prakt. Chem.,* **1924**, *107*, 129. (d) Chichibabin, A. E.; Moschkin, P. A. and Tyaschelova, L. S., *J. Prakt. Chem.,* **1924**, *107*, 132. (e) Chichibabin, A. E. and Oparina, M. P., *J. Prakt. Chem.,* **1924**, *107*, 145. (f) Chichibabin, A. E., *J. Russ. Phys. Chem. Soc.,* **1923**, *54*, 411; [*Chem. Abstr.,* **1924**, *18*, 2495]. (g) Chichibabin, A. E.; Moschkin, P. A. and Tyaschelova, L. S., *J. Russ. Phys. Chem. Soc.,* **1923**, *54*, 413 [*Chem. Abstr.,* **1924**, *18*, 2495]. (h) Chichibabin, A. E. and Oparina, M. P., *J. Russ. Phys. Chem. Soc.,* **1923**, *54*, 428 [*Chem. Abstr*., **1924**, *18*, 2495].
3. (a) Snider, B. B. and Neubert, B. J., *Org. Lett.,* **2005**, *7*, 2715. (b) Weiss, M., *J. Am. Chem. Soc.,* **1952**, *74*, 200.
4. (a) Sagitullin, R. S.; Shkil, G. P.; Nosonova, I. I. and Ferber, A. A., *Khim. Geterotsiklicheskikh Soedinenii*, **1996**, 147. (b) Frank, R. L. and Riener, E. F., *J. Am. Chem. Soc.,* **1950**, *72*, 4182. (c) Frank, R. L. and Seven, R. P., *J. Am. Chem. Soc.,* **1949**, *71*, 2629.
5. Panzella, L.; Di Donato, P.; Comes, S.; Napolitano, A.; Palumbo, A. and d'Ischia, M., *Tetrahedron Lett*., **2005**, *46*, 6457.
6. (a) Liepina, I.; Sile, M.; Karakhanov, R. A. and Avots, A., *Latvijas PSR Zinatnu Akademijas Vestis, Kimijas Serija*, **1989**, 433. (b) Liepina, I.; Slavinska, V.; Sile, M.; Avots, A. and Karakhanov, R. A., *Latvijas PSR Zinatnu Akademijas Vestis, Kimijas Serija*, **1989**, 339.
7. Eliel, E. L.; McBride, R. T. and Kaufmann, St., *J. Am. Chem. Soc.,* **1953**, *75*, 4291.
8. Strain, H. H., *J. Am. Chem. Soc.,* **1932**, *54*, 1221.
9. (a) Chichibabin, A. E., *Bull. Soc. Chim.,* **1937**, *4*, 1826 [*Chem. Abstr.,* **1938**, *32*, 1699]. (b) Chichibabin, A. E. and Oparina, M. P., *J. Prakt. Chem.,* **1924**, *107*, 138. (c) Chichibabin, A. E. and Oparina, M. P., *J. Russ. Phys. Chem. Soc.,* **1923**, *54*, 420 [*Chem. Abstr.,* **1924**, *18*, 2495].
10. Farley, C. P. and Eliel, E. L., *J. Am. Chem. Soc.,* **1956**, *78*, 3477.
11. (a) Donchak, L. N.; Zagoruiko, M. A. and Kaminskii, V. A., *Zh. Org. Khim.,* **1995**, *31*, 1872. (b) Liepina, I.; Slavinskaya, V. A.; Sile, M.; Avots, A. and Karakhanov, R. A., *Latvijas PSR Zinatnu Akademijas Vestis, Kimijas Serija*, **1989**, 334. (c) Soldatenkov, A. T.; Fedorov, V. O.; Chandra, R.; Polosin, V. M.; Mikaya, A. I. and Prostakov, N. S., *Zh. Org. Khim.,* **1980**, *16*, 188. (d) Kessar, S. V.; Nadir, U. K. and Singh, M., *Indian J. Chem.,* **1973**, *11*, 825. (e) Kametani T., Nemoto H., Takano S.,*Chem. Pharm. Bull.*, **1968**, *16*, 367. (f) Weiss, M., *J. Am. Chem. Soc.,* **1952**, *74*, 200. (g) Frank, R. L and Riener, E. P., *J. Am. Chem. Soc.,* **1950**, *72*, 4182. (h) Frank, R. L. and Seven, R. P., *J. Am. Chem. Soc.,* **1949**, *71*, 2629. (i) Krems, I. J and Spoerri, P. E., *Chem. Rev.,* **1947**, *40*, 279. (j) Bergstrom, F. W., *Chem. Rev.,* **1944**, *35*, 77. (k) Gautier, J. A. and Renault, J., *Bull. Soc. Chim. Fr.,* **1955**, 588.

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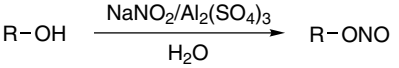
Chretien-Longi Reaction

A. GENERAL DESCRIPTION OF THE REACTION

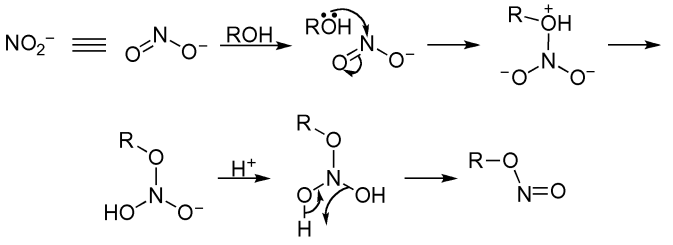
This reaction was first reported by Chretien and Longi in 1944.[1] It is a general preparation of nitrite ester by means of the treatment of alcohols with nitrous acid in aqueous acidic solution.[2] In the original protocol, alcohol was mixed with sodium nitrite followed by the addition of aluminum sulfate, which hydrolyzes to lower the pH.[1] This reaction has been modified to occur in acetic acid.[2]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A tentative mechanism is proposed here.



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D. MODIFICATION

The original procedure has been modified to take place in aqueous acetic acid solution.

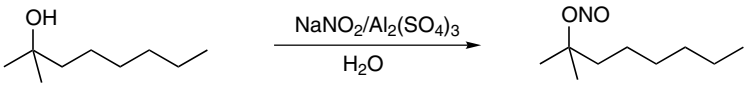
E. APPLICATIONS

This reaction is used for the preparation of nitrite esters.

F. RELATED REACTIONS

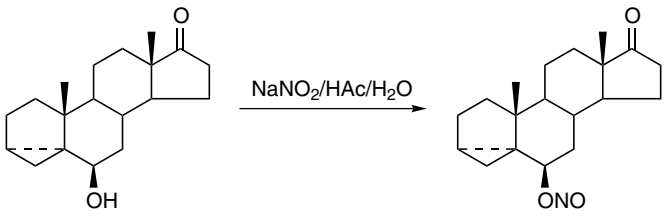
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3.

In a three-necked flask fitted with a stirrer and a dropping funnel were placed 43.2 g 2-methyl-2-octanol (0.3 mol) and 41.4 g sodium nitrite (0.6 mol) dissolved in a minimum amount of water. The mixture was cooled to 0°C and then, with continuous stirring, 71 g $Al_2(SO_4)_3 \cdot 18H_2O$ (0.12 mol) dissolved in sufficient water to give a 40% solution was added over a period of 1 h. After the addition was complete, the reaction mixture was stirred at ice temperatures for 2 h more and poured into a separatory funnel; the aqueous layer was removed, and the yellow organic layer was washed three times with water and dried over anhydrous sodium sulfate. Rectification gave 37.8 g 2-methyl-2-octyl nitrite, in a yield of 72%, b.p., 56°C (3 mmHg).



Reference 2.

6β-Hydroxy-3α,5α-cycloandrostan-l7-one (804 mg) was dissolved in 53 mL glacial acetic acid. A freshly prepared solution of 2.8 g sodium nitrite in 17.6 mL water was added, and the resulting solution was allowed to stand at room temperature for 15 min. The solution was then shaken with 200 mL ether and 500 mL water. The aqueous solution was separated and extracted with 200 mL ether. The ether solutions were combined and washed in series with three 100-mL portions of water, two 150-mL portions of 5% sodium

bicarbonate solution, and three 100-mL portions of water. The ether solutions were dried over anhydrous magnesium sulfate. The ether was evaporated, leaving 858 mg clear, orange viscous oil. This material was placed on a column of 80 g neutral activity III alumina in 10 mL ether solution. Elution with 1:23 ether/pentane solution yielded 503 mg of the nitrite ester of 6β-hydroxy-3α,5α-cycloandrostan-17-one as a pale green oil.

Other references related to the Chretien-Longi reaction are cited in the literature.[4]

H. REFERENCES

1. Chretien, A. and Longi, Y., *Compd. Rent.*, **1945**, *220*, 746.
2. Tadanier, J. and Cole, W., *J. Org. Chem.,* **1962**, *27*, 4615.
3. Kornblum, N.; Smiley, R. A.; Ungnade, H. E.; White, A. M.; Taub, B. and Herbert, S. A., *J. Am. Chem. Soc.,* **1955**, *77*, 5528.
4. (a) Bevilard P. and Choucroum J., *Bull. Soc. Chim. Fr.*, **1957**, 337. (b) Kornblum, N.; Taub, B. and Ungnade, H. E., *J. Am. Chem. Soc.,* **1954**, *76*, 3209.

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Chugaev Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Chugaev (Tschugaeff) in 1899.[1] It is the conversion of alcohols into olefins by the pyrolysis of the corresponding xanthate esters and is generally known as the Chugaev reaction;[2] in addition, this reaction is occasionally referred to as the Chugaev elimination,[3] Chugaev xanthate reaction[4] and Chugaev xanthic reaction.[5] This pyrolysis proceeds via an intramolecular *cis*-elimination without the rearrangement of the carbon skeleton, a phenomenon generally referred to as the Chugaev reaction rule.[6] This reaction is particularly useful for the conversion of secondary and tertiary alcohols into olefins[7] because the xanthate esters of primary alcohols have higher thermal stability and thus are relatively difficult to decompose during heating and can even be distilled in vacuo.[7] On the other hand, this reaction is reported to be first order in kinetics[8] via a concerted cyclic mechanism,[9] by which the eliminated groups are all in *cis*-configuration[8a,10] with only a few exceptions[2d,6,11] and the preference for hydrogen removal follows the order of $3^\circ > 2^\circ > 1^\circ$.[12] The unusual feature of this reaction is that no carbon skeleton rearrangements occur during pyrolysis, which are often encountered in the dehydration of certain alcohols by other methods.[10] However, the original procedure—in which the xanthate ester is prepared by reacting sodium or potassium (preferably the latter) with alcohol in an inert solvent (e.g., xylene) followed by the addition of carbon disulfide and then refluxing with methyl iodide or methyl sulfate (methyl ester affording the best yield)—is generally avoided because it is dangerous and inconvenient.[7] Therefore, it is modified to react alcohol with 1 eq. NaOH or KOH and CS_2 in a neutral solvent (e.g., Et_2O, CCl_4) to form xanthate in one step, followed by the reaction with methyl iodide. This modification is less hazardous and more practicable.[7] This reaction has been used for the preparation of a variety of

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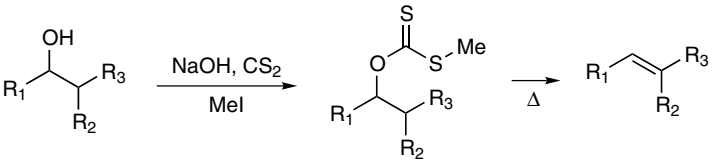
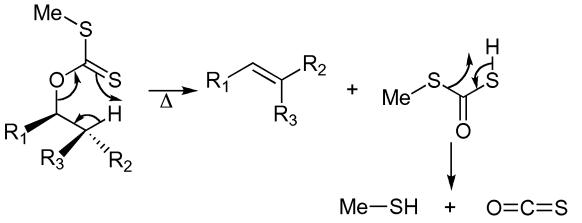
olefins, including benzylidene cyclohexane,[13] bornylene,[14] chlolesterylene,[14] guajene,[15] limonene,[14] menthene,[1] tetraphenylethylene,[13] and thujene.[14]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is believed that this reaction takes place via an intramolecular cyclic concerted process, as outlined here.[8a,10–12]



D. MODIFICATION

This reaction has been modified to generate xanthates in one step via the reaction of alcohols with CS_2 and NaOH (or KOH).[7]

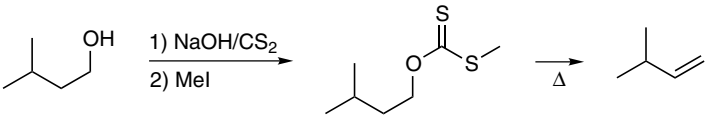
E. APPLICATIONS

This reaction has wide application in the synthesis of olefins.

F. RELATED REACTIONS

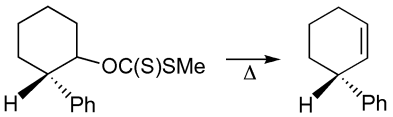
This reaction is related to the *Cope Elimination* and *Hofmann Elimination*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

In a 2-L flask were placed 40.5 g finely pulverized sodium hydroxide, 89 g isoamyl alcohol, 600 mL diethyl ether, and 50 mL carbon tetrachloride. The flask was attached to a trident fitted with a mechanical stirrer, a Pyrex reflux condenser, and a dropping funnel. The mixture was stirred for 0.5 h to dissolve part of the base and form a finely divided suspension of the remainder. Then 76 g carbon disulfide was added over 1 h, with the temperature below 30°C. After 3 h of stirring, 149 g methyl iodide was added dropwise, and the mixture was stirred and refluxed for 6 h. After filtering off the potassium iodide, the lower-boiling constituents were removed by distillation, and the residual xanthate was distilled at 10 mmHg through a 68 × 1.1-cm, indented, total-condensation column. The yellow distillate (b.p. l00–105°C) was further purified by one more distillation. Then the collected xanthate ester was heated in a 1-L flask under a partial reflux column for 7.5 h by a free flame, the distillate being condensed by a copper coil packed in an ice–salt mixture. The distillate was purified by three extractions with 40% potassium hydroxide solution and one treatment with 20 mL saturated mercuric chloride solution to remove the mercaptan; then it was dried over anhydrous sodium sulfate and distilled through the 68 × 1.1-cm column. The isopropylethylene collected boiled at 19–20°C (740 mmHg).



Reference 10.

To a 50-mL round-bottomed flask equipped with a Friedrich condenser was placed 5.0 g methyl *cis*-2-phenylcyclohexylxanthate. A gas bubbler was attached to the condenser so that the course of the decomposition could be followed. The flask was immersed in a Wood's metal bath, and the temperature was gradually increased. A slight decomposition began when the bath temperature reached 165°C. It was then raised to 210–215°C, maintained at that level for 40 min, and then it was increased to 235–240°C for 5 min. After cooling, the material in the flask was transferred to a 10-mL modified Claisen flask and distilled. 3-Phenyl-cyclohexene in two fractions, with a combined weight of 2.1 g (71%), came over at 70–71°C (2 mmHg).

Other references related to the Chugaev reaction are cited in the literature.[16]

H. REFERENCES

1. Chugaev, L., *Ber.,* **1899**, *32*, 3332.
2. (a) Kholodova, Yu. D., *Ukrain. Biokhim. Zh.,* **1988**, *60*, 88. (b) Kholodova, Yu. D., *Anal. Chem. Symp. Ser.,* **1982**, *10*, 519. (c) Kholodova, Yu. D., *Khim. Prirodnykh Soedinenii*, **1977**, 227. (d) Harano, K. and Taguchi, T., *Yakugaku Zasshi*, **1974**, *94*, 1495. (e) Jallageas, J. C. and Casadevall, E., *Compt. Rend.,* **1972**, *275*, 347. (f) Meurling, P.; Sjoberg, K. and Sjoberg, B., *Acta Chem. Scand.,* **1972**, *26*, 279. (g) Rutherford, K. G.; Ottenbrite, R. M. and Tang, B. K., *J. Chem. Soc. C,* **1971**, 582. (h) De Groot, A.; Evenhuis, B. and Wynberg, H., *J. Org. Chem.,* **1968**, *33*, 2214. (i) Nace, H. R., *Org. React.,* **1962**, 12, *57*. (j) Polyakov, A. V.; Rogovin, Z. A. and Derevitskaya, V. A., *Vysokomolekulyarnye Soedineniya*, **1962**, *5*, 161. (k) Bader, R. F. W. and Bourns, A. N., *Can. J. Chem.,* **1961**, *39*, 348. (l) Polyakov, A. I.; Derevitskaya, V. A. and

Rogovin, Z. A., *Vysokomolekulyarnye Soedineniya*, **1960**, *2*, 386. (m) Franzen, V. and Krauch, H., *Chemiker-Zeitung*, **1955**, *79*, 548. (n) Cram, D. J., *J. Am. Chem. Soc.,* **1949**, *71*, 3883.

3. Chande, M. S. and Pranjpe, S. D., *Indian J. Chem.,* **1973**, *11*, 1206.
4. Sysoeva, N. D., *Uspekhi Khimii*, **1951**, *20*, 498.
5. Sysoeva, N. D., *Trudy Uzbekskogo Inst. Narodnogo Khoz.*, **1940**, 59.
6. (a) Harano, K. and Taguchi, T., *Chem. Pharm. Bull.,* **1975**, *23*, 467. (b) Kawata, T.; Harano, K. and Taguchi, T., *Chem. Pharm. Bull.,* **1973**, *21*, 604. (c) Harano, K. and Taguchi, T., *Yakugaku Zasshi*, **1973**, *93*, 804. (d) Harano, K. and Taguchi, T., *Chem. Pharm. Bull.,* **1972**, *20*, 2348. (e) Harano, K. and Taguchi, T., *Chem. Pharm. Bull.,* **1972**, *20*, 2357. (f) Kawazoe, Y. and Taguchi, T., *Yakugaku Zasshi*, **1972**, *92*, 677. (g) Mori, M.; Kanayama, H.; Tabata, K. and Taguchi, T., *Yakugaku Zasshi*, **1969**, *89*, 1631. (h) Mori, M. and Taguchi, T., *Yakugaku Zasshi*, **1969**, *89*, 1496. (i) Yoshihira, K. and Taguchi, T., *Yakugaku Zasshi*, **1969**, *89*, 1225. (j) Taguchi, T.; Kawazoe, Y.; Yoshihira, K.; Kanayama, H.; Mori, M.; Tabata, K. and Harano, K., *Tetrahedron Lett*., **1965**, 2717.
7. Whitmore, F. C. and Simpson, C. T., *J. Am. Chem. Soc.,* **1933**, *55*, 3809.
8. (a) O'Conner, G. L. and Nace, H. R., *J. Am. Chem. Soc.,* **1952**, *74*, 5454. (b) O'Conner, G. L. and Nace, H. R., *J. Am. Chem. Soc.,* **1953**, *75*, 2118.
9. Stevens, P. G. and Richmond, J. H., *J. Am. Chem. Soc.,* **1941**, *63*, 3132.
10. Alexander, E. R. and Mudrak, A., *J. Am. Chem. Soc.,* **1950**, *72*, 1810.
11. Bordwell, F. G. and Landis, P. S., *J. Am. Chem. Soc.,* **1958**, *80*, 2450.
12. Benkeser, R. A. and Hazdra, J., *J. Am. Chem. Soc.,* **1959**, *81*, 228.
13. Kurssanoff*, Ber.,* **1931**, *64*, 2297.
14. (a) Chugaev, L. and Budrick, V., *Ann.,* **1912**, *388*, 280. (b) Chugaev, L. A. and Fomin, V., *Ber.,* **1912**, *45*, 1293. (c) Chugaev, L. and Fomin, V., *Ann.,* **1910**, *375*, 288. (d) Tschugaeff, L. and Gasteff (or spelled as Gustev), A., *Ber.,* **1909**, *42*, 4631. (e) Tschugaeff, L., *Ber.,* **1904**, *37*, 1479. (f) Tschugaeff, L., *Ber.,* **1901**, *34*, 2276. (g) Tschugaeff, L., *Ber.,* **1900**, *33*, 3118. (h) Chugaev, L., *Ber.,* **1900**, *33*, 735.
15. Gandurin, A., *Ber.,* **1909**, *41*, 4359.
16. (a) Nakagawa, H.; Sugahara, T. and Ogasawara, K., *Org. Lett.,* **2000**, *2*, 3181. (b) Ray, P. S. and Manning, M. J., *Heterocycles,* **1994**, *33*, 1361. (c) Fu, X. and Cook, J. M., *Tetrahedron Lett.,* **1990**, *31*, 3409. (d) Depuy, C. H. and King, R. W., *Chem. Rev.,* **1960**, *60*, 444. (e) Alexander, E. R. and Mudrak, A., *J. Am. Chem. Soc.,* **1950**, *72*, 3194.

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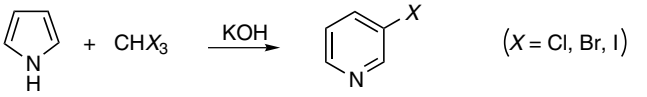
Ciamician-Dennstedt Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Ciamician and Dennstedt in 1881.[1] It is a transformation of pyrrole into 3-halopyridine by heating the mixture of pyrrole and haloform or methylene halides in alkaline solution. Therefore, this reaction is known as the Ciamician-Dennstedt reaction.[2] It is known that haloform, when treated with a base,[3] such as NaOH, KOH, will afford dihalocarbene; in addition, methylene halides when treated with a strong base,[4] such as NaOEt and NaOMe, will also form dihalocarbene. The generated dihalocarbene then electrophilically adds to pyrrole to form an unstable dihalocyclopropane, which then rearranges to a 3-halopyridine.[5] In most cases, haloform is used rather than methylene halides, and the *Reimer-Tiemann Reaction* always competes with this reaction when the dihalocarbene inserts into aromatic ring and forms aldehyde via hydrolysis.[6] Therefore, the yield of the Ciamician-Dennstedt reaction is always low, in the reported range of 1–30%.[4a,6] Similar to pyrrole, indene will be transformed to naphthalene,[7] and indole will be converted to quinoline.[8] It is reported that a chloro, bromo, carbethoxy, or phenyl group on indene will inhibit the addition of dichlorocarbene to the indene ring, while the electron-donating groups (e.g., methyl, isopropyl, and ethoxy) have no effect on the yield compared with indene itself.[9] It is interesting that more than 30% of pyridine can be obtained via vapor phase reaction between pyrrole and haloform, without the added base.[8]

B. GENERAL REACTION SCHEME



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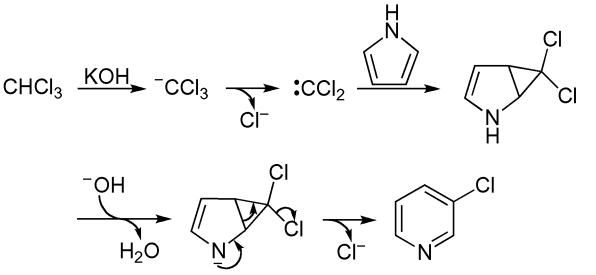
C. PROPOSED MECHANISMS

The reaction involves the generation of dihalocarbene from haloform and a base, e.g., KOH, which then inserts into the pyrrole ring. The subsequent ring enlargement affords the pyridine derivative, as illustrated by the reaction of chloroform and pyrrole.



D. MODIFICATION

The Ciamician-Dennstedt reaction has been modified to take place in a vapor phase via passing the mixture of pyrrole and chloroform (1:5 ratio) into a glass tube at 550°C to give 33% of pyridine derivative.

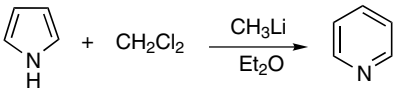
E. APPLICATIONS

This reaction can be used for the preparation of 3-halo pyridines, naphthalenes, and quinolines.

F. RELATED REACTIONS

N/A

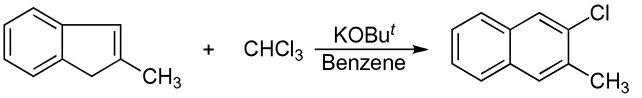
G. CITED EXPERIMENTAL EXAMPLES



Reference 5.

A solution of methyllithium (0.4 mol) in 235 mL diethyl ether was added with vigorous stirring to a solution of 7.0 g pyrrole (0.104 mol) in methylene chloride. The addition was carried out under a protective atmosphere of nitrogen, and the temperature was maintained at 25°C. After the addition was complete (2 h), the reaction mixture was hydrolyzed with ice water, and the polymeric material was removed by filtration over cellulose powder. The solution was acidified and nonbasic material was extracted with ether. The aqueous layer was then made basic, saturated with potassium carbonate, and exhaustively extracted with ether. The combined ether extracts were dried with potassium carbonate and the solvent was distilled off over a Vigreux column. The residue was distilled over a micro Vigreux

column. Pyridine (2.60 g, 0.033 mol) was collected between 114° and 114.5°C, in a yield of 32%.



Reference 9.

A solution of 15.6 g 2-methylindene (0.12 mol) in 15 mL dry thiophene-free benzene was added to dry pulverized potassium *t*-butoxide (maintained under dry oxygen-free nitrogen) prepared from 2.0 g potassium (0.051 mol) and *t*-butyl alcohol. The orange slurry was stirred vigorously, and cooled in an ice bath, while 4.8 g freshly distilled chloroform (0.040 mol) was added over a period of ~15 min. A static nitrogen atmosphere was maintained during the addition, and the mixture was then allowed to stand at room temperature overnight. The entire mixture was steam distilled from water containing 0.08 mol sodium carbonate. An undetermined amount of nonvolatile red tar remained in the flask. The distillate was extracted with petroleum ether (b.p. 60–68°C), and the condenser was washed with the same solvent. The organic washes and extracts were dried, filtered, and the solvent was removed by distillation. Fractional distillation of the residue afforded 9.6 g unreacted 2-methylindene (0.0727 mol). The light green residue, m.p. 113–120°C, was recrystallized once from ethanol, and 2.61 g 2-methyl-3-chloro-naphthalene was obtained as refractive pale green platelets, in a yield of 37%, m.p. 122.5–123°C.

Other references related to the Ciamician-Dennstedt reaction are cited in the literature.[10]

H. REFERENCES

1. Ciamician, G. L. and Dennstedt, M., *Ber.,* **1881**, *14*, 1153.
2. Krauch, H. and Kunz, W., *Chemiker-Zeitung,* **1959**, *83*, 815.
3. (a) Kirmse, W., *Angew. Chem.*, **1959**, *71*, 537. (b) Hine, J. and Dowell, M., *J. Am. Chem. Soc.,* **1954**, *76*, 2688. (c) Hine, J., *J. Am. Chem. Soc.,* **1950**, *72*, 2438.
4. (a) Alexander, E. R.; Herrick, A. B. and Roder, J. M., *J. Am. Chem. Soc.,* **1950**, *72*, 2760. (b) Ciamician, G. L., *Ber.,* **1904**, *37*, 4201. (c) Dennstedt, M. and Zimmerman, J., *Ber.,* **1885**, *18*, 3316.
5. Closs, G. L. and Schwartz, G. M., *J. Org. Chem.,* **1961**, *26*, 2609.
6. Wynberg, H., *Chem. Rev.,* **1960**, *60*, 169.
7. Parham, W. E.; Reiff, H. E. and Swartzdntruber, P., *J. Am. Chem. Soc.,* **1956**, *78*, 1437.
8. Rice, H. L. and Londergan, T. E., *J. Am. Chem. Soc.,* **1955**, *77*, 4678.
9. Parham, W. E. and Wright, C. D., *J. Org. Chem.,* **1957**, *22*, 1473.
10. (a) Rees, C. W. and Smithen, C. E., *J. Chem. Soc.*, **1964**, 928, 938. (b) Baltazzi, E. and Krimen, L. L., *Chem. Rev.,* **1963**, *63*, 525. (c) Vogel, E., *Angew. Chem.,* **1960**, *72*, 8. (d) Skell, P. S. and Sandler, R. S., *J. Am. Chem. Soc.,* **1958**, *80*, 2024. (e) Parham, W. E. and Reiff, H. E., *J. Am. Chem. Soc.,* **1955**, *77*, 1177. (f) Ellinger, A. and Flamand, C., *Ber.,* **1906**, *39*, 4388. (g) Madnanini, P. C., *Ber.,* **1887**, *20*, 2608. (h) Ciamician, G. L. and Silber, P., *Ber.,* **1885**, *18*, 721. (i) Dennstedt, M. and Zimmerman, J., *Ber.,* **1885**, *18*, 3316. (j) Ciamician, G. L. and Dennstedt, M., *Ber.,* **1882**, *15*, 1172.

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Claisen Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Ludwig Claisen in 1912.[1] It is initially defined as the thermal isomerization of an allyl vinyl ether or of its nitrogen- or sulfur-containing analogous derivatives to afford a bifunctionalized molecule in a $[\pi_{2a} + \sigma_{2s} + \pi_{2s}]$ process. In fact, the Claisen rearrangement[2] is a highly stereoselective [3,3]-sigmatropic rearrangement of allyl vinyl or allyl aryl ethers to yield γ,δ-unsaturated carbonyl compounds or *o*-allyl substituted phenols, respectively. This reaction can be chemoselective, regioselective, diastereoselective, and entantioselective and afford a variety of multifunctionalized molecules.[3] When allyl aryl ethers undergo this rearrangement, the resulting γ,δ-unsaturated carbonyl compound will transform into *o*-allyl phenols via re-aromatization; however, if the *ortho* position is blocked by other substituents rather than hydrogen, then the *Cope Rearrangement* occurs and the allyl group will migrate to the *para* position of the aromatic ring followed by enolization (*para* Claisen rearrangement).[3,4] In most cases, the reaction proceeds preferably via a chair-like transition state,[5] and chiral, enantiomerically enriched starting materials give products of highly optical purity. Occasionally, this reaction also takes a boat-like transition state.[6] So far, all the Claisen rearrangements, if not catalyzed, occur at a relatively high temperature, e.g., >100°C.[3,7] In addition, this rearrangement runs faster in a polar solvent,[8] and it is observed that the relative rate of the rearrangement for allyl vinyl ether decreases in the order of water > trifluoroacetic acid > methanol > ethanol > 2-propanol > acetonitrile > acetone ≈ benzene > cyclohexane.[9] Moreover, the microwave irradiation can also accelerate the reaction rate.[10] It is quite interesting that substituents on allyl vinyl ether play important roles on the reactivity of corresponding allyl vinyl ethers, and those substituent effects are summarized in Table 1.[3] It is clear that the introduction of those rate-enhancing groups will accelerate the respective rearrangement accordingly. As a result,

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the same reaction can take place at low temperature, and these modifications lead to more than 20 variations of the traditional Claisen rearrangement.[11] These modified Claisen rearrangements include the *Abnormal Claisen Rearrangement*,[12] acyl-Claisen rearrangement,[13] allene Claisen rearrangement,[14] allenoate-Claisen rearrangement,[11] aromatic amino-Claisen rearrangement,[15] *Aza-Claisen Rearrangement*,[16] *Carroll Rearrangement*,[17] chelate Claisen rearrangement,[18] C-O coupling-Claisen rearrangement,[19] 1,3-diaza-Claisen rearrangement,[20] diosphenol-Claisen rearrangement,[21] enzymatic Claisen rearrangement,[22] Eschenmoser-Claisen rearrangement,[23] Ficini-Claisen rearrangement,[24] Ireland-Claisen rearrangement,[25] Johnson-Claisen rearrangement[26] (also called Johnson ortho ester Claisen rearrangement[27]), Metalla-Claisen rearrangement,[28] photo-Claisen rearrangement,[29] propargyl Claisen rearrangement,[30] reductive Claisen rearrangement,[31] Reformatsky-Claisen rearrangement,[32] retro-Claisen rearrangement (or process),[33] ring-expansion Claisen rearrangement,[34] and thio-Claisen rearrangement.[6b,34] It should be noted here that *Aza-Claisen Rearrangement, Carroll Rearrangement*, Eschenmoser-Claisen rearrangement, Ireland-Claisen rearrangement and Johnson-Claisen rearrangement have gained much more attention than the others, though the other variations are gradually showing importance and versatility. The Ireland-Claisen rearrangement can set up two stereogenic centers with high levels of predictability through the judicious choice of solvent.[36] Among these variations, the *Abnormal Claisen Rearrangement*, *Aza-Claisen Rearrangement*, and *Carroll Rearrangement* have been described separately. Because of its versatility and importance, the Claisen rearrangement has been extensively reviewed.[3,37]

B. GENERAL REACTION SCHEME

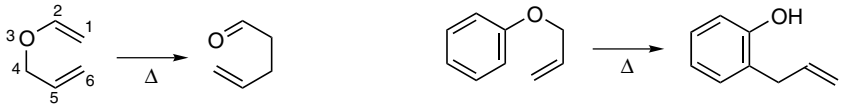
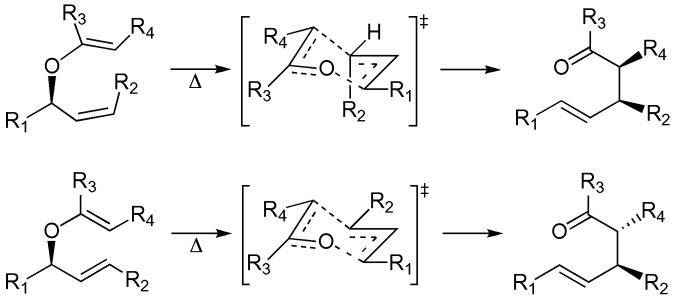


TABLE 1. The Position and Substituent Effect on Rearrangement Rate

Accelerating Groups		Decelerating Groups	
Electron-Donating Position 1,2,4,6	Electron-Withdrawing Position 2,4,5	Electron-Donating Position 5	Electron-Withdrawing Position 1,6

C. PROPOSED MECHANISMS

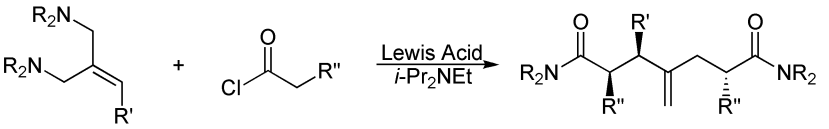
Most rearrangements take place via a chair-like concerted mechanism as outlined here.



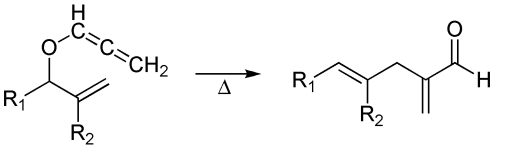
D. MODIFICATION

The most important modifications of the Claisen rearrangement are summarized here.

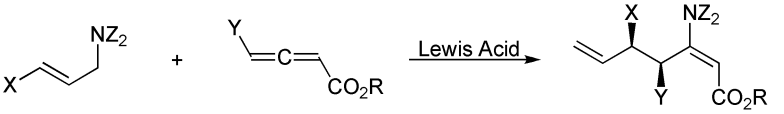
Acyl-Claisen rearrangement.



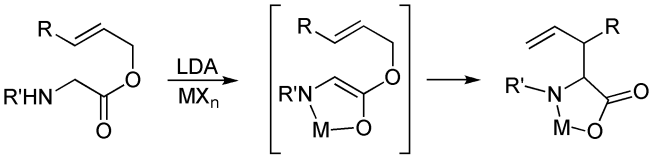
Allene Claisen rearrangement.



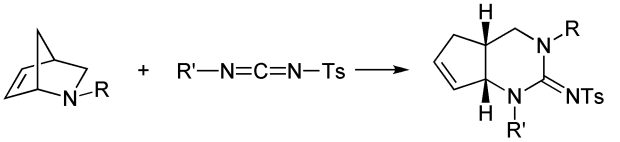
Allenoate-Claisen rearrangement.



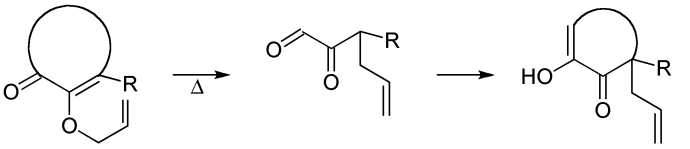
Chelate Claisen rearrangement.



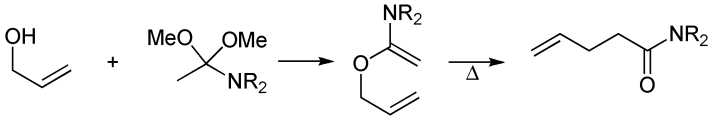
1,3-Diaza-Claisen rearrangement.



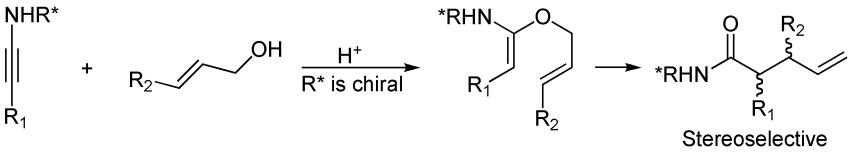
Diosphenol-Claisen rearrangement.



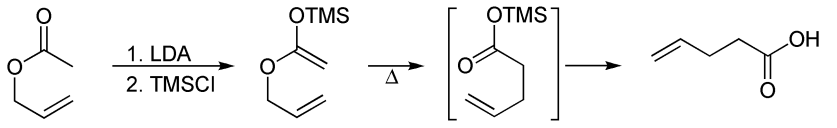
Eschenmoser-Claisen rearrangement.



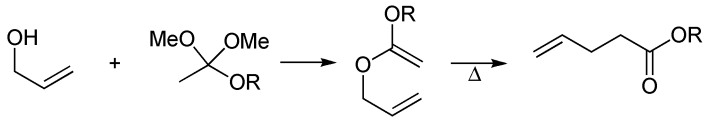
Ficini-Claisen rearrangement.



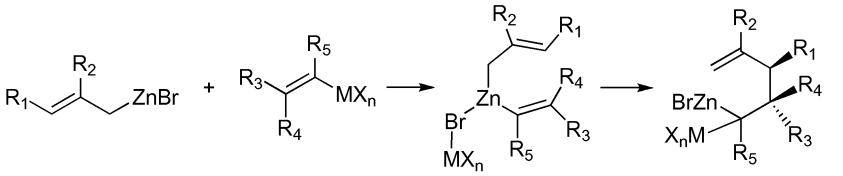
Ireland-Claisen rearrangement.



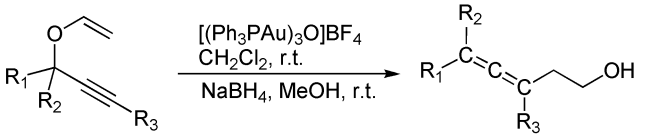
Johnson-Claisen rearrangement.



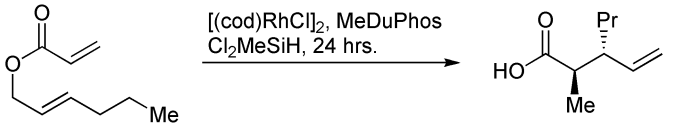
Metalla-Claisen rearrangement.



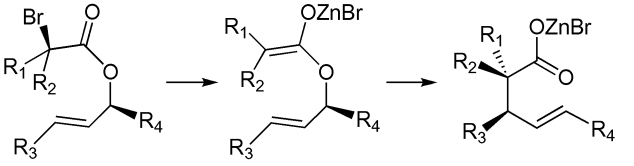
Propargyl Claisen rearrangement.



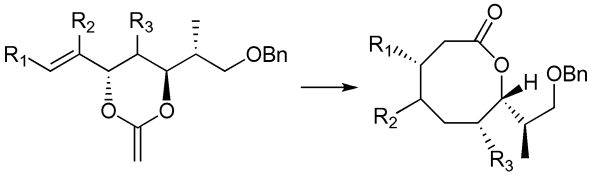
Reductive Claisen rearrangement.



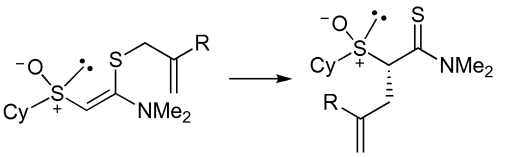
Reformatsky-Claisen rearrangement.



Ring-expansion Claisen rearrangement.



Thio-Claisen rearrangement.



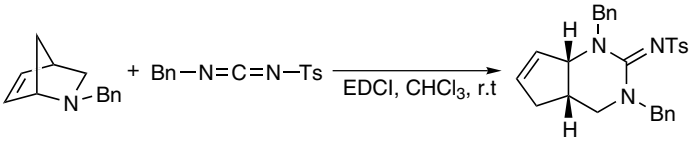
E. APPLICATIONS

This reaction, along with its various modifications have wide applications in organic synthesis, even in the formation of polymer.[38]

F. RELATED REACTIONS

This reaction is related to the *Cope Rearrangement* and *Overman Rearrangement*.

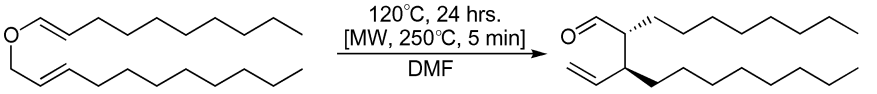
G. CITED EXPERIMENTAL EXAMPLES



Reference 20b.

2-Benzyl-2-*aza*-bicyclo[2.2.1]hept-5-ene (0.100 g, 0.538 mmol) and 0.094 mL DIEA (0.538 mmol) were added to a solution of 0.103 g EDCI (0.538 mmol) and 0.172 g *N*-tosyl-*N′*-benzyl thiourea (0.538 mmol) in 5 mL $CHCl_3$ at room temperature. The resulting solution was maintained at room temperature overnight. The reaction mixture was then poured into a mixture of 65 mL EtOAc and 65 mL 0.25M aqueous citric acid. The organic layer was washed with 65 mL 0.25M aqueous citric acid and 65 mL water (twice), dried over Na_2SO_4, and concentrated. Purification of the residue on silica gel, eluting with hexanes/EtOAc (2:3)

gave 0.170 g *N*-(1,3-dibenzyl-1,3,4,4a,5,7a-hexahydro-cyclopentapyrimidin-2-ylidene)-4-methylbenzene sulfonamide as a colorless oil, in a yield of 67%.



Reference 19.

Conventional Heating

A test tube was charged with 160 mg *E*-1-dec-1-enyl-*E*-undec-2-ene (519 μmol) and 500 μL DMF, evacuated, and backfilled with argon (flushing for 10 min). This was then sealed and heated at 120°C for 24 h. After cooling to room temperature, 20 mL Et_2O was added, and the solution was extracted with water (3 × 25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The product was obtained as a yellow oil without further purification (144 mg, 90% yield), dr = 94:6 (^{1}H NMR).

Microwave Heating

A microwave vial was charged with 76 mg *E*-1-dec-1-enyl-*E*−undec-2-ene (247 μmol) and 1 mL DMF. This was then sealed and heated at 250°C for 5 min in a microwave synthesizer. Et_2O was added (20 mL) and extracted with water (3 × 25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The product was obtained as a yellow oil without further purification (61 mg, 80% yield), dr = 91 : 9 (^{1}H NMR).

Other references related to the Claisen rearrangement are cited in the literature.[39]

H. REFERENCES

1. Claisen, L., *Ber.,* **1912**, *45* , 3157.
2. (a) Kotha, S.; Shah, V. R. and Mandal, K., *Adv. Synth. Catal,* **2007**, *349*, 1159. (b) Mukaide, M.; Urasaki, Y.; Takegoshi, K. and Kajimoto, O., *J. Supercritical Fluids,* **2007**, *42*, 104. (c) Majetich, G.; Yu, J. H.; Li, Y. and Allen, S. H., *Heterocycles,* **2007**, *72*, 157. (d) Kotha, S.; Mandal, K.; Tiwari, A. and Mobin, S. M., *Chem. Eur. J.,* **2006**, *12*, 8024. (e) Clark, D. A.; Kulkarni, A. A.; Kalbarczyk, K.; Schertzer, B. and Diver, S. T., *J. Am. Chem. Soc.,* **2006**, *128*, 15632. (f) Robertson, J. and Fowler, T. G., *Org. Biomol. Chem.,* **2006**, *4*, 4307. (g) Grison, C.; Olszewski, T. K.; Crauste, C.; Fruchier, A.; Didierjean, C. and Coutrot, P., *Tetrahedron Lett*., **2006**, *47*, 6583. (h) Juers, S. and Thiem, J., *Synthesis,* **2006**, 2117. (i) Majumdar, K. C. and Alam, S., *J. Chem. Res.,* **2006**, 281. (j) Nelson, S. G. and Wang, K., *J. Am. Chem. Soc.,* **2006**, *128*, 4232. (k) Majumdar, K. C.; Rahaman, H.; Islam, R. and Roy, B., *Tetrahedron Lett*., **2006**, *47*, 2111. (l) Juers, S. and Thiem, J., *Tetrahedron: Asymmetry*, **2005**, *16*, 1631. (m) Yoshida, H.; Kobayashi, Y.; Hiratani, K. and Saigo, K., *Tetrahedron Lett*., **2005**, 46, 3901. (n) Davis, C. J.; Hurst, T. E.; Jacob, A. M. and Moody, C. J.,

J. Org. Chem., **2005**, *70*, 4414. (o) Hong, S.-P.; Yoon, S.-J.; Yu, B.-C., *Tetrahedron Lett*., **2005**, *46*, 779. (p) Craig, D. and Grellepois, F., *Org. Lett.,* **2005**, *7*, 463. (q) Huang, K.-S. and Wang, E.-C., *J. Chinese Chem. Soc.,* **2004**, *51*, 383. (r) Schobert, R.; Gordon, G. J.; Mullen, G. and Stehle, R., *Tetrahedron Lett*., **2004**, *45*, 1121. (s) Brenna, E.; Fuganti, C.; Gatti, F. G.; Passoni, M. and Serra, S., *Tetrahedron: Asymmetry*, **2003**, 14, 2401. (t) Kawasaki, T.; Ogawa, A.; Takashima, Y. and Sakamoto, M., *Tetrahedron Lett*., **2003**, *44*, 1591. (u) Mohamed, M. and Brook, M. A., *Helv. Chim. Acta,* **2002**, *85*, 4165. (v) Wipf, P. and Rodriguez, S., *Adv. Synth. Catal.,* **2002**, *344*, 434. (w) Koyama, E.; Yang, G.; Tsuzuki, S. and Hiratani, K., *Eur. J. Org. Chem.,* **2002**, 1996. (x) Abraham, L.; Czerwonka, R. and Hiersemann, M., *Angew. Chem. Int. Ed.,* **2001**, *40*, 4700. (y) Tokuhisa, H.; Ogihara, T.; Nagawa, Y. and Hiratani, K., *J. Incl. Phenom. Macrocycl. Chem.,* **2001**, *39*, 347. (z) Koyama, E.; Yang, G. and Hiratani, K., *Tetrahedron Lett*., **2000**, *41*, 8111. (aa) Ley, S. V.; Gutteridge, C. E.; Pape, A. R.; Spilling, C. D. and Zumbrunn, C., *Synlett,* **1999**, 1295. (bb) Pettus, T. R. R.; Chen, X.-T. and Danishefsky, S. J., *J. Am. Chem. Soc.,* **1998**, *120*, 12684. (cc) Kazmaier, U. and Maier, S., *Chem. Commun.,* **1998**, 2535. (dd) Wang, J. S. and Gutsche, C. D., *J. Am. Chem. Soc.,* **1998**, *120*, 12226. (ee) Bernard, A. M. and Piras, P. P., *Synlett,* **1997**, 585. (ff) Gajewski, J. J., *Acc. Chem. Res.,* **1997**, *30*, 219. (gg) Kazmaier, U., *Tetrahedron Lett*., **1996**, *37*, 5351. (hh) Lai, G. F. and Anderson, W. K., *Synth. Commun.,* **1995**, *25*, 4087. (ii) Davidson, M. M.; Hillier, I. H. and Vincent, M. A., *Chem. Phys. Lett.,* **1995**, *246*, 536. (jj) Kazmaier, U., *Synlett,* **1995**, 1138. (kk) Murty, K. V. S. N.; Pal, R.; Datta, K. and Mal, D., *Synth. Commun.,* **1994**, *24*, 1287. (ll) Begue, J. P.; Bonnet-Delpon, D.; Wu, S. W. and M'Bida, A., *Tetrahedron Lett*., **1994**, *35*, 2907. (mm) Mukherjee, A.; Wu, Q. H. and le Noble, W. J., *J. Org. Chem.,* **1994**, *59*, 3270. (nn) Metz, P. and Linz, C., *Tetrahedron*, **1994**, *50*, 3951. (oo) Sugiyama, J.-i.; Tanikawa, K.; Okada, T.; Noguchi, K.; Ueda, M. and Endo, T., *Tetrahedron Lett*., **1994**, *35*, 3111. (pp) Dhanalekshmi, S.; Venkatachalam, C. S. and Balasubramanian, K. K., *J. Chem. Soc., Chem. Commun.,* **1994**, 511. (qq) Fukuyama, T.; Li, T. Q. and Peng, G., *Tetrahedron Lett*., **1994**, *35*, 2145. (rr) Augy-Dorey, S.; Barton, D. H. R.; Gero, S. D.; Quiclet-Sire, B. and Sagnard, I., *J. Chem. Soc., Chem. Commun.,* **1993**, 960. (ss) Balasubramanian, T. and Balasubramanian, K. K., *J. Chem. Soc., Chem. Commun.,* **1992**, 1760.

3. Castro, A. M. M., *Chem. Rev.,* **2004**, *104*, 2939.
4. Ryan, J. P. and O'Connor, P. R., *J. Am. Chem. Soc.,* **1952**, *74*, 5866.
5. (a) Kahn, S. D. and Hehre, W. J., *J. Org. Chem.,* **1988**, *53*, 301. (b) Vittorelli, P.; Hansen, H.-J. and Schmid, H., *Helv. Chim. Acta,* **1975**, *58*, 1293. (c) Frater, G.; Habich, A.; Hansen, H.-J. and Schmid, H., *Helv. Chim. Acta,* **1969**, *52*, 335. (d) Doering, W. V. E. and Roth, W. R., *Tetrahedron,* **1962**, *18*, 67.
6. (a) Khaledy, M. M.; Kalani, M. Y. S.; Khuong, K. S.; Houk, K. N.; Aviyente, V.; Neier, R.; Soldermann, N. and Velker, J., *J. Org. Chem.,* **2003**, *68*, 572. (b) Nowaczyk, S.; Alayrac, C.; Reboul, V.; Metzner, P. and Averbuch-Pouchot, M.-T., *J. Org. Chem.,* **2001**, 66,7841.
7. Cooper, J. A.; Olivares, C. M. and Sandford, G., *J. Org. Chem.,* **2001**, 66,4887.
8. (a) Coates, R. M.; Rogers, B. D.; Hobbs, S. J.; Peck, D. R. and Curran, D. P., *J. Am. Chem. Soc.,* **1987**, *109*, 1160. (b) White, W. N. and Wolfarth, E. F., *J. Org. Chem.,* **1970**, *35*, 3585. (c) Kincaid, J. F. and Tarbell, D. S., *J. Am. Chem. Soc.,* **1939**, *61*, 3085.
9. Brandes, E.; Grieco, P. A. and Gajewski, J. J., *J. Org. Chem.,* **1989**, *54*, 515.
10. (a) Durand-Reville, T.; Gobbi, L. B.; Gray, B. L.; Ley, S. V. and Scott, J. S., *Org. Lett.,* **2002**, *4*, 3847. (b) Daskiewicz, J.-B.; Bayet, C. and Barron, D., *Tetrahedron Lett.,* **2001**, *42*, 7241. (c) Kotha, S.; Sreenivasachary, N.; Brahmachary, E., *Tetrahedron,* **2001**, *57*, 6261. (d) Sampath Kumar, H. M.; Anjaneyulu, S.; Subba Reddy, B. V. and Yadav, J. S., *Synlett,* **2000**, 1129. (e) Madden, D.; Krchnak, V. and Lebl, M., *Persp. Drug Discov. Des.,* **1995**, *51*, 8135. (f) Gignere, R. J.; Bray, T. L.; Duncan, S. M. and Majetich, G., *Tetrahedron Lett.,* **1986**, *27*, 4945.
11. Lambett, T. H. and MacMillan, D. W. C., *J. Am. Chem. Soc.,* **2002**, *124*, 13646.

12. (a) Schobert, R.; Siegfried, S.; Gordon, G.; Mulholland, D.; Nieuwenhuyzen, M., *Tetrahedron Lett.,* **2001**, *42*, 4561. (b) Nakamura, S.; Ishihara, K.; Yamamoto, H., *J. Am. Chem. Soc.,* **2000**, *122*, 8131.

13. (a) Raubo, P.; Giuliano, C.; Hill, A. W.; Huscroft, I. T.; London, C.; Reeve, A.; Seward, E. M.; Swain, C. G. and Kulagowski, J. J., *Synlett,* **2006**, 600. (b) Dong, V. M. and MacMillan, D. W. C., *J. Am. Chem. Soc.,* **2001**, *123*, 2448. (c) Yoon, T. P. and MacMillan, D. W. C., *J. Am. Chem. Soc.,* **2001**, *123*, 2911.

14. (a) Parsons, P. J.; Thomson, P.; Taylor, A. and Sparks, T., *Org. Lett.,* **2000**, *2*, 571. (b) Dulcère, J.-P.; Crandall, J.; Faure, R.; Santelli, M.; Agati, V. and Mihoubi, M. N., *J. Org. Chem.,* **1993**, *58*, 5702. (c) Behrens, U.; Wolff, C. and Hoppe, D., *Synthesis,* **1991**, 644. (d) Egert, E.; Beck, H.; Schmidt, D.; Gonschorrek, C. and Hoppe, D., *Tetrahedron Lett*., **1987**, *28*, 789. (e) Hoppe, D.; Gonschorrek, C.; Egert, E. and Schmidt, D., *Angew. Chem.,* **1985**, *97*, 706.

15. (a) Shin, J.-H.; Park, J.; Lee, Y. and Lee, C. J., *Bull. Korean Chem. Soc.,* **2000**, *21*, 157. (b) Sreekumar, R. and Padmakumar, R., *Tetrahedron Lett.,* **1996**, *37*, 5281. (c) Lutz, R. P., *Chem. Rev*., **1984**, *84*, 205. (d) Rhoads, S. J. and Rautins, N. R., *Org. React*., **1975**, *22*, 1.

16. (a) Roe, J. M.; Webster, R. A. B. and Ganesan, A., *Org. Lett.,* **2003**, *5*, 2825. (b) Yoon, T. P.; Dong, V. M. and MacMillan, D. W. C., *J. Am. Chem. Soc.,* **1999**, *121*, 9726. (c) Ito, S. and Tsunoda, T., *Pure & Appl. Chem.,* **1994**, *66*, 2071. (d) Cid, M. M. and Pombo-Villar, E., *Helv. Chim. Acta,* **1993**, *76*, 1591. (e) Maurya, R.; Pittol, C. A.; Pryce, R. J.; Roberts, S. M.; Thomas, R. J. and Williams, J. O., *J. Chem. Soc., Perkin Trans. I,* **1992**, 1617. (f) Cid, M. M.; Eggnauer, U.; Weber, H. P. and Pombo-Villar, E., *Tetrahedron Lett.,* **1991**, *32*, 7233.

17. (a) Burger, E. C. and Tunge, J. A., *Org. Lett.,* **2004**, *6*, 4113. (b) Burger, E. C. and Tunge, J. A., *Org. Lett.,* **2004**, *6*, 2603. (c) Defosseux, M.; Blanchard, N.; Meyer, C. and Cossy, J., *J. Org. Chem.,* **2004**, *69*, 4626. (d) Shi, B.; Hawryluk, N. A. and Snider, B. B., *J. Org. Chem.,* **2003**, *68*, 1030.

18. (a) Kazmaier, U.; Mues, H. and Krebs, A., *Chem. Eur. J.,* **2002**, *8*, 1850. (b) Mues, H. and Kazmaier, U., *Synthesis,* **2001**, 487. (c) Maier, S. and Kazmaier, U., *Eur. J. Org. Chem.,* **2000**, 1241. (d) Kazmaier, U. and Krebs, A., *Tetrahedron Lett.,* **1999**, *40*, 479. (e) Krebs, A. and Kazmaier, U., *Tetrahedron Lett.,* **1996**, *37*, 7945. (f) Kazmaier, U., *Angew. Chem. Int. Ed. Engl.,* **1994**, *33*, 998.

19. Nordmann, G. and Buchwald, S. L, *J. Am. Chem. Soc.* **2003**, *125*, 4978.

20. (a) Bowser, A. M. and Madalengoitia, J. S., *Tetrahedron Lett*., **2005**, *46*, 2869. (b) Bowser, A. M. and Madalengoitia, J. S., *Org. Lett.,* **2004**, *6*, 3409.

21. (a) Ponaras, A. A., *Tetrahedron Lett.,* **1983**, *24*, 3. (b) Ponaras, A. A., *Tetrahedron Lett.,* **1980**, *21*, 4803.

22. Andrews, P. R.; Smith, G. D. and Young, I. G., *Biochemistry,* **1973**, *12*, 3492.

23. (a) Qu, H. C.; Gu, X. Y.; Min, B. J.; Liu, Z. H. and Hruby, V. J., *Org. Lett.,* **2006**, *8*, 4215. (b) Schepens, W.; Van Haver, D.; Vandewalle, M.; Bouillon, R.; Verstuyf, A. and De Clercq, P. J., *Org. Lett.,* **2006**, *8*, 4247. (c) Kuending, E. P.; Laxmisha, M. S.; Cannas, R.; Tchertchian, S. and Liu, R. G., *Helv. Chim. Acta,* **2005**, *88*, 1063. (d) Kuendig, E. P.; Cannas, R.; Fabritius, C.-H.; Grossheimann, G.; Kondratenko, M.; Laxmisha, M.; Pache, S.; Ratni, H.; Robvieux, F.; Romanens, P. and Tchertchian, S., *Pure & Appl. Chem.,* **2004**, *76*, 689. (e) Konno, T.; Nakano, H. and Kitazume, T., *J. Fluor. Chem.,* **1997**, *86*, 81. (f) Mulzer, J.; Bats, J. W.; List, B.; Opatz, T. and Trauner, D., *Synlett,* **1997**, 441. (g) Lautens, M.; Huboux, A. H.; Chin, B. and Downer, J., *Tetrahedron Lett.,* **1990**, *31*, 5829. (h) Coates, B.; Montgomery, D. and Stevenson, P. J., *Tetrahedron Lett.,* **1991**, *32*, 4199. (i) Wick, A. E.; Felix, D.; Gschwend-Steen, K. and Eschenmoser, A., *Helv. Chim. Acta,* **1969**, *52*, 1030. (j) Wick, A. E.; Felix, D.; Steen, K. and Eschenmoser, A., *Helv. Chim. Acta,* **1964**, *47*, 2425.

24. (a) Mulder, J. A.; Hsung, R. P.; Frederick, M. O.; Tracey, M. R. and Zificsak, C. A., *Org. Lett.,* **2002**, *4*, 1383. (b) Ficini, J.; Lumbroso-Bader, N. and Pouliquen, J., *Tetrahedron Lett.,* **1968**, *9*, 4139. (c) Ficini, J. and Barbara, C., *Tetrahedron Lett.,* **1966**, *7*, 6425.

25. (a) Soldermann, N.; Velker, J.; Neels, A.; Stoeckli-Evans, H. and Neier, R., *Synthesis,* **2007**, 2379. (b) Li, Y. X.; Goeke, A.; Wang, R. Y.; Wang, Q. R. and Frater, G., *Tetrahedron,* **2007**, *63*, 9605. (c) Li, Y. X.; Wang, Q. R.; Goeke, A. and Frater, G., *Synlett*, **2007**, 288. (d) Bunte, J. O.; Cuzzupe, A. N.; Daly, A. M. and Rizzacasa, M. A., *Angew. Chem. Int. Ed.,* **2006**, *45*, 6376. (e) Fujiwara, K.; Goto, A.; Sato, D.; Kawai, H. and Suzuki, T., *Tetrahedron Lett*., **2005**, *46*, 3465. (f) Calad, S. A. and Woerpel, K. A., *J. Am. Chem. Soc.,* **2005**, *127*, 2046. (g) Hoeck, S.; Koch, F. and Borschberg, H.-J., *Tetrahedron: Asymmetry*, **2004**, *15*, 1801. (h) Gilbert, J. C.; Yin, J. D.; Fakhreddine, F. H. and Karpinski, M. L., *Tetrahedron,* **2004**, *60*, 51. (i) Betson, M. S. and Fleming, I., *Org. Biomol. Chem.,* **2003**, *1*, 4005. (j) Churcher, I.; Williams, S.; Kerrad, S.; Harrison, T.; Castro, J. L.; Shearman, M. S.; Lewis, H. D.; Clarke, E. E.; Wrigley, J. D. J.; Beher, D.; Tang, Y. S. and Liu, W. S., *J. Med. Chem.,* **2003**, *46*, 2275. (k) Wang, X. D. J.; Hart, S. A.; Xu, B. L.; Mason, M. D.; Goodell, J. R. and Etzkorn, F. A., *J. Org. Chem.,* **2003**, *68*, 2343. (l) Yang, Y. H.; Petersen, J. L. and Wang, K. K., *J. Org. Chem.,* **2003**, *68*, 8545. (m) Hong, S.-P.; Lindsay, H. A.; Yaramasu, T.; Zhang, X. W. and McIntosh, M. C., *J. Org. Chem.,* **2002**, *67*, 2042. (n) Barrett, A. G. B.; Ahmed, M.; Baker, S. P.; Baugh, S. P. D.; Braddock, D. C.; Procopiou, P. A.; White, A. J. P. and Williams, D. J., *J. Org. Chem.,* **2000**, *65*, 3716. (o) Hattori, K. and Yamamoto, H., *Tetrahedron,* **1994**, *50*, 3099. (p) Corey, E. J. and Lee, D.-H., *J. Am. Chem. Soc.,* **1991**, *113*, 4026. (q) Ireland, R. E.; Wipf, P. and Armstrong, J. D., *J. Org. Chem.,* **1991**, *56*, 650. (r) Ireland, R. E.; Mueller, R. H. and Willard, A. K., *J. Am. Chem. Soc.,* **1976**, *98*, 2868. (s) Ireland, R. E. and Mueller, R. H., *J. Am. Chem. Soc.,* **1972**, *94*, 5897. (t) Konno, T.; Daitoh, T.; Ishihara, T. and Yamanaka, H.,*Tetrahedron: Asymmetry*, **2001**, *12*, 2743. (u) Soldermann, N.; Velker, J.; Vallat, O.; Stoeckli-Evans, H. and Neier, R., *Helv. Chim. Acta,* **2000**, *83*, 2266. (v) Khripach, V. A.; Zhabinskii, V. N.; Konstantinova, O. V. and Khripach, N. B., *Tetrahedron Lett*., **2000**, *41*, 5765. (w) Matsui, S.; Oka, N.; Hashimoto, Y. and Saigo, K., *Enantiomer,* **2000**, *5*, 105. (x) Velker, J.; Roblin, J.-P.; Neels, A.; Tesouro, A.; Stoeckli-Evans, H.; Klaerner, F.-G.; Gehrke, J.-S. and Neier, R., *Synlett,* **1999**, 925. (y) Magnus, P. and Westwood, N., *Tetrahedron Lett*., **1999**, *40*, 4659. (z) Moffatt, E.-M. and Thomas, E. J., *Tetrahedron*, **1999**, *55*, 3723. (aa) Dorling, E. K. and Thomas, E. J., *Tetrahedron Lett*., **1999**, *40*, 471. (bb) Zhang, X. W. and McIntosh, M. C., *Tetrahedron Lett*., **1998**, *39*, 7043. (cc) Pratt, L. M.; Beckett, R. P.; Bellamy, C. L.; Corkill, D. J.; Cossins, J.; Courtney, P. F.; Davies, S. J.; Davidson, A. H.; Drummond, A. H.; Helfrich, K.; Lewis, C. N.; Mangan, M.; Martin, F. M.; Miller, K.; Nayee, P.; Ricketts, M. L.; Thomas, W.; Todd, R. S. and Whittaker, M., *Bioorg. Med. Chem. Lett.,* **1998**, *8*, 1359. (dd) Pratt, L. M.; Bowles, S. A.; Courtney, S. F.; Hidden, C.; Lewis, C. N.; Martin, F. M. and Todd, R. S., *Synlett,* **1998**, 531. (ee) Hull, H. M. and Knight, D. W., *J. Chem. Soc., Perkin Trans. I,* **1997**, 857. (ff) Takai, K.; Ueda, T.; Kaihara, H.; Sunami, Y. and Moriwake, T., *J. Org. Chem.,* **1996**, *61*, 8728.

26. (a) Das, B.; Majhi, A.; Reddy, K. R. and Venkateswarlu, K., *J. Mol. Catal. A: Chem.,* **2007**, *263*, 273. (b) Markad, S. D.; Karanjule, N. S.; Sharma, T.; Sabharwal, S. G.; Puranik, V. G. and Dhavale, D. D., *Org. Biomol. Chem.,* **2006**, *4*, 2549. (c) Ozturk, C.; Aviyente, V. and Houk, K. N., *J. Org. Chem.,* **2005**, *70*, 7028. (d) Funabiki, K.; Hara, N.; Nagamori, M.; Shibata, K. and Matsui, M., *J. Fluor. Chem.,* **2003**, *122*, 237. (e) Kumareswaran, R.; Shahi, P. S.; Rani, S.; Gupta, A.; Madhusudanan, K. P. and Vankar, Y. D., *ARKIVOC,* **2002**, (*vii*), 126. (f) Butt, A. H.; Percy, J. M. and Spencer, N. S., *Chem. Commun.,* **2000**, 1691. (g) Schlama, T.; Baati, R.; Gouverneur, V.; Valleix, A.; Flack, J. R. and Mioskowski, C., *Angew. Chem. Int. Ed.,* **1998**, *37*, 2085. (h) Basavaiah, D.; Pandiaraju, S. and Krishnamacharyulu, M., *Synlett,* **1996**, 747. (i) Basavaiah, D. and Pandiaraju, S., *Tetrahedron Lett.,* **1995**, *36*, 757. (j) Elworthy, T. R.; Morgans, D. J.; Palmer, W. S.; Repke, D. B.; Smith, D. B. and Waltos, A. M., *Tetrahedron Lett*., **1994**, 35, 4951. (k) Bao, R.; Valverde, S. and Herradon, B., *Synlett,* **1992**, 217. (l) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brockson, T. J.; Li, T.; Faulkner, D. J. and Petersen, M. R., *J. Am. Chem. Soc.,* **1970**, *92*, 741.

27. Yadav, V. K.; Jeyaraj, D. A.; Parvez, M. and Yamdagni, R., *J. Org. Chem.,* **1999**, *64*, 2928.

28. (a) Hirai, A.; Nakamura, M. and Nakamura, E., *J. Am. Chem. Soc.,* **2000**, *122*, 11791. (b) Zhang, H.; Song, G.-Q.; Zhang, W.-H. and Zhong, J., *Jiangsu Shiyou Huagong Xueyuan Xuebao*, **2000**, *12*, 11. (c) Marek, I.; Lefrancois, J. M. and Normant, J. F., *Tetrahedron Lett*., **1991**, *32*, 5969.

(d) Marek, I. and Normant, J. F., *Tetrahedron Lett*., **1991**, *32*, 5973. (e) Normant, J. F.; Quirion, J. C.; Alexakis, A. and Masuda, Y., *Tetrahedron Lett.,* **1989**, *30*, 3955. (f) Normant, J. F.; Quirion, J. C., *Tetrahedron Lett.,* **1989**, *30*, 3959. (g) Knochel, P. and Normant, J. F., *Tetrahedron Lett.,* **1986**, *27*, 1039. (h) Knochel, P. and Normant, J. F., *Tetrahedron Lett.,* **1986**, *27*, 1043. (i) Knochel, P. and Normant, J. F., *Tetrahedron Lett.,* **1986**, *27*, 4427. (j) Knochel, P. and Normant, J. F., *Tetrahedron Lett.,* **1986**, *27*, 4431.

29. (a) Pincock, A. L.; Pincock, J. A. and Stefanova, R., *J. Am. Chem. Soc.,* **2002**, *124*, 9768. (b) Gu, W.; Warrier, M.; Schoon, B.; Ramamurthy, V. and Weiss, R. G., *Langmuir,* **2000**, *16*, 6977.
30. (a) Menz, H. and Kirsch, S. F., *Org. Lett.,* **2006**, *8*, 4795. (b) Sherry, B. D. and Toste, F. D., *J. Am. Chem. Soc.,* **2004**, *126*, 15978. (c) Otter, B. A.; Saluja, S. S. and Fox, J. J., *J. Org. Chem.,* **1972**, *37*, 2858.
31. (a) Miller, S. P. and Morken, J. P., *Org. Lett.,* **2002**, *4*, 2743. (b) Sharghi, H. and Aghapour, G., *J. Org. Chem.,* **2000**, *65*, 2813. (c) Cambie, R. C.; Milbank, J. B. J. and Rutledge, P. S., *Org. Prep. Proc. Int.,* **1997**, *29*, 365. (d) Harrington-Frost, N. M.; Milbank, J. B. J. and Rutledge, P. S., *Aust. J. Chem.,* **1997**, *50*, 379. (e) Cambie, R. C.; Milbank, J. B. J. and Rutledge, P. S., *Synth. Commun.,* **1996**, *26*, 715. (f) Khalafy, J. and Bruce, J. M., *J. Sci., Islamic Rep. Iran,* **1993**, *4*, 285. (g) Boddy, I. K.; Boniface, P. J.; Cambie, R. C.; Craw, P. A.; Huang, Z. D.; Larsen, D. S.; McDonald, H.; Rutledge, P. S. and Woodgate, P. D., *Aust. J. Chem.,* **1984**, *37*,1511. (h) Boddy, I. K.; Boniface, P. J.; Cambie, R. C.; Craw, P. A.; Larsen, D. S.; McDonald, H.; Rutledge, P. S. and Woodgate, P. D., *Tetrahedron Lett*., **1982**, *23*, 4407.
32. (a) Hill, E. A.; Link, D. C. and Donndelinger, P., *J. Org. Chem.,* **1981**, *46*, 1177. (b) Baldwin, J. E. and Walker, J. A., *J. Chem. Soc., Chem. Commun.,* **1973**, 117.
33. (a) Boeckman, R. K.; Zhang, J. and Reeder, M. R., *Org. Lett.,* **2002**, *4*, 3891. (b) Boeckman, R. K. Jr.; Flann, C. J. and Poss, K. M., *J. Am. Chem. Soc.,* **1985**, *107*, 4359. (c) Rhoads, S. J. and Cockroft, R. D., *J. Am. Chem. Soc.,* **1969**, *91*, 2815. (d) Rey, M. and Dreiding, A. S., *Helv. Chim. Acta,* **1965**, *48*, 1985.
34. (a) McErlean, C. S. P.; Proisy, N.; Davis, C. J.; Boland, N. A.; Sharp, S. Y.; Boxall, K.; Slawin, A. M. Z.; Workman, P. and Moody, C. J., *Org. Biomol. Chem.,* **2007**, *5*, 531. (b) Dimartino, G. and Percy, J. M., *Chem. Commun.*, **2000**, 2339. (c) Davidson, J. E. P.; Anderson, E. A.; Buhr, W.; Harrison, J. R.; O'Sullivan, P. T.; Collins, I.; Green, R. H. and Holmes, A. B., *Chem. Commun.*, **2000**, 629. (d) Harrison, J. R.; Holmes, A. B. and Collins, I., *Synlett*, **1999**, 972.
35. (a) Majumdar, K. C. and Pal, N., *Lett. Org. Chem.,* **2007**, *4*, 120. (b) Moghaddam, F.; Boeini, H. and Zargarani, D., *J. Sulfur Chem.,* **2005**, *26*, 331. (c) Mohan, C.; Singh, P. and Mahajan, M. P., *Tetrahedron,* **2005**, *61*, 10774. (d) Majumdar, K. C.; Saha, D. and Ghosh, M., *Synth. Commun.,* **2005**, *35*, 947. (e) Majumdar, K. C. and Biswas, A., *Monatsh. Chem.,* **2004**, *135*, 1001. (f) Mohan, C.; Kumar, V. and Mahajan, M. P., *Tetrahedron Lett*., **2004**, *45*, 6075. (g) Majumdar, K. C. and Bandyopadhyay, A., *Monatsh. Chem.,* **2004**, *135*, 581. (h) Majumdar, K. C.; Sarkar, S. and Ghosh, S., *Synth. Commun.,* **2004**, *34*, 1265. (i) Majumdar, K. C. and Ghosh, M., *J. Indian Chem. Soc.,* **2003**, *80*, 1077. (j) Majumdar, K. C.; Ghosh, S. and Ghosh, M., *Tetrahedron,* **2003**, *59*, 7251. (k) Novikov, A. V.; Kennedy, A. R. and Rainier, J. D., *J. Org. Chem.,* **2003**, *68*, 993. (l) He, S. W.; Kozmin, S. A. and Rawal, V. H., *J. Am. Chem. Soc.,* **2000**, *122*, 190. (m) Alayrac, C.; Fromont, C.; Metzner, P. and Anh, N. T., *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 371. (n) Jain, S.; Sinha, N.; Dikshit, D. K. and Anand, N., *Tetrahedron Lett.,* **1995**, *36*, 8467. (o) Reddy, K. V. and Rajappa, S., *Tetrahedron Lett.,* **1992**, *33*, 7957. (p) Metzner, P., *Synthesis,* **1992**, 1185. (q) Welch, J. T. and Eswarakrishnan, S., *J. Am. Chem. Soc.,* **1987**, *109*, 6716. (r) Tamaru, Y.; Furukawa, Y.; Mizutani, M.; Kitao, O. and Yoshida, Z., *J. Org. Chem.,* **1983**, *48*, 3631. (s) Takano, S.; Hirama, M. and Ogasawara, K., *Tetrahedron Lett.,* **1982**, *23*, 881. (t) Bycroft, B. W. and Landon, W., *J. Chem. Soc., Chem. Commun.,* **1970**, 168. (u) Bycroft, B. W. and Landon, W., *J. Chem. Soc., Chem. Commun.,* **1970**, 967. (v) Schuijl, P. J. W.and Brandsma, L., *Recl. Trav. Chim. Pays-Bas,* **1968**, *87*, 929.

36. (a) Ireland, R. E.; Wipf, P. and Xiang, J. N., *J. Org. Chem.,* **1991**, *56*, 3572. (b) Bartlett, P. A. and Barstow, J. F., *J. Org. Chem.,* **1982**, *47*, 3933.

37. (a) Hiersemann, M. and Abraham, L., *Eur. J. Org. Chem.,* **2002**, 1461. (b) Chai, Y.; Hong, S.; Lindsay, H. A.; McFarland, C. and McIntosh, M. C. *Tetrahedron* **2002**, *58*, 2905. (c) Nowicki, J., *Molecules,* **2000**, *5*, 1033 (d) Ito, H. and Taguchi, T., *Chem. Soc. Rev.,* **1999**, *28*, 43. (e) Enders, D.; Knopp, M. and Schiffers, R., *Tetrahedron: Asymmetry*, **1996**, *7*, 1847. (f) Pereira, S. and Srebnik, M., *Aldrichimica Acta,* **1993**, *26*, 17. (g) Wipf, P., "Sigmatropic Process" in *Comprehensive Organic Synthesis*; ed. Trost, B. M., Fleming, J. and Paquette, L. A., Pergamon Press. oxford, **1991**; *5*, p. 827. (h) Blechert, S., *Synthesis,* **1989**, 71. (i) Ziegler, F. E., *Chem. Rev.,* **1988**, *88*, 1423. (j) Ziegler, F. E., *Acc. Chem. Res.,* **1977**, *10*, 589. (k) Rhoads, S. J. and Raulins, N. R., *Org. React.,* **1975**, *22*, 1.

38. Yang, G.; Matsuzono, S.-i.; Koyama, E.; Tokuhisa, H. and Hiratani, K., *Macromolecules,* **2001**, *34*, 6545.

39. (a) Gozzo, F. C.; Fernades, S. A.; Rodrigues, D. C.; Eberlin, M. N. and Marsaioli, A. J., *J. Org. Chem.,* **2003**, *68*, 5493. (b) Nelson, S. G.; Bungard, C. J. and Wang, K., *J. Am. Chem. Soc.,* **2003**, *125*, 13000. (c) Hur, S. and Bruice, T. C., *J. Am. Chem. Soc.,* **2003**, *125*, 5964. (d) Repasky, M. P.; Guimarães, C. R. W.; Chandrasekhar, J.; Tirado-Rives, J. and Jorgensen, W. L., *J. Am. Chem. Soc.,* **2003**, *125*, 6663. (e) Majumdar, K. C.; Kundu, U. K. and Ghosh, S. K., *Org. Lett.,* **2002**, *4*, 2629. (f) May, J. A. and Stoltz, B. M., *J. Am. Chem. Soc.,* **2002**, *124*, 12426. (g) Hiersemann, M. and Abraham, L., *Org. Lett.,* **2001**, *3*, 49. (h) Wipf, P. and Ribe, S., *Org. Lett.,* **2001**, *3*, 1503. (i) Davies, H. M. L.; Ren, P. D. and Jin, Q. H., *Org. Lett.,* **2001**, *3*, 3587. (j) Hudlicky, T.; Oppong, K.; Duan, C.; Stanton, C.; Laufersweiler, M. J. and Natchus, M. G., *Bioorg. Med. Chem. Lett.,* **2001**, *11*, 627. (k) Ovaska, T. V. and Roses, J. B., *Org. Lett.,* **2000**, *2*, 2361. (l) Ito, H.; Sato, A.; Kobayashi, T. and Taguchi, T., *Chem. Commun.*, **1998**, 2441. (m) Hiratani, K.; Kasuga, K.; Goto, M. and Uzawa, H., *J. Am. Chem. Soc.,* **1997**, *119*, 12677. (n) Metzner, P., *Pure & Appl. Chem.,* **1996**, *68*, 863. (o) Claisen, L. and Tietze, E., *Ber.,* **1926**, *59*, 2344. (p) Claisen, L. and Tietze, E., *Ber.,* **1925**, *58*, 275.

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Claisen-Schmidt Condensation

(Claisen-Schmidt Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Claisen[1] and Schmidt[2] concurrently in 1881. It is the condensation of an aromatic aldehyde with an aliphatic aldehyde or ketone in the presence of a base or an acid to form an α,β-unsaturated aldehyde or ketone[3] with high chemoselectivity.[4] Therefore, this reaction is generally known as the Claisen-Schmidt condensation[5] and is occasionally referred to as the Claisen-Schmidt reaction.[6] In this reaction, the asymmetric ketones react with the aromatic aldehyde through the less substituted position (a methyl group) under basic conditions or through the more substituted position under acidic catalysis.[3] However, this reaction is often contaminated with some minor side reactions, including *bis*-condensation, aliphatic aldehyde dimerization,[7] and *Cannizzaro Reaction* or *Tischenko Reaction* of aromatic aldehydes.[8] It was reported that the reaction between arylaldehydes and cycloalkanones afford predominantly α,α'-diarylidenecycloalkanones instead of α-arylidenecycloalkanones.[8] The orientation of the generated exocyclic bonds is exclusively *trans* with respect to the aryl ring and the carbonyl group of the cycloalkanone.[9] So far, the Claisen-Schmidt condensation has been applied to the preparation of chalcone,[10] flavanone,[10c] 1,3-diarylpropane derivatives, and a new family of macrocycles in a single step.[8,11] This condensation can be accelerated by microwave activation either in a polar solvent (e.g., H_2O) or without solvent, starting from aldehydes or by means of acetals.[3] The benefits of using microwave irradiation in this reaction include the concomitant enhancement of reaction yield and the reduction in reaction time.[12] On the other hand, magnesium oxide crystal has been applied as catalyst for this condensation, in which the catalyst can be reused for five times without loss of activity and selectivity; in

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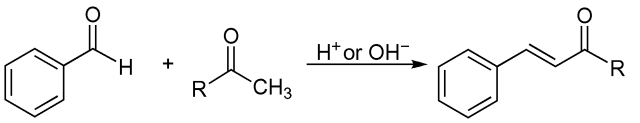
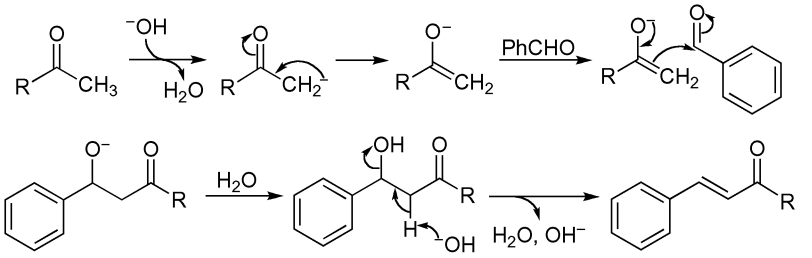
addition, it is observed that any of the reactants (benzaldehydes and acetopheones) with substituent groups in either of the two aromatic rings undergo the Claisen-Schmidt condensation at a slower rate than the unsubstituted reactants.[13] Recently, this condensation has been used to build a 644-member library of chalcones by parallel synthesis from substituted acetophenones and benzaldehydes.[10a]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Essentially, the Claisen-Schmidt condensation involves an *Aldol Condensation*,[3,10a] as illustrated by the reaction under basic condition.



D. MODIFICATION

Microwave irradiation has been introduced to accelerate the Claisen-Schmidt condensation;[3,12] in addition, magnesium oxide crystal has been applied as catalyst for this condensation.[13]

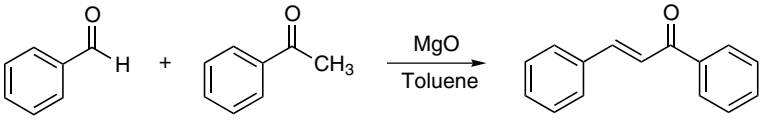
E. APPLICATIONS

This reaction has general application in the preparation of chalcones, flavanones, 1,3-diarypropanes, etc.

F. RELATED REACTIONS

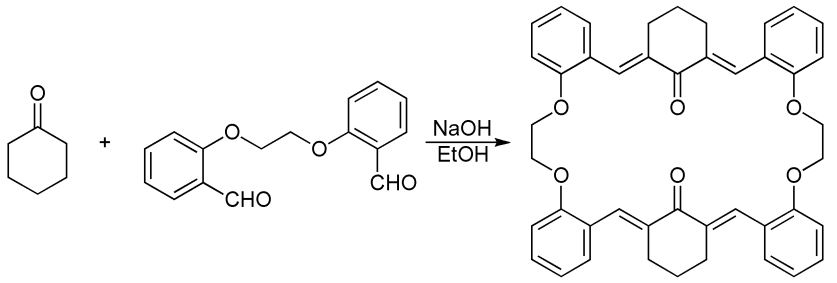
This reaction is related to the *Aldol Condensation.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 13.

A mixture of 0.35 mL acetophenone (3 mmol), 0.254 mL benzaldehyde (2.5 mmol), and 0.175 g magnesium oxide crystal was introduced into a 50-mL round-bottomed flask containing 10 mL dry toluene, which was stirred under reflux for 12 h under nitrogen atmosphere (to avoid the oxidation of benzaldehyde to benzoic acid). After completion of the reaction (as monitored by TLC), the reaction mixture was centrifuged to separate the catalyst and washed several times with ether. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. After purification by flash chromatography on silica gel using 5% ethyl acetate in petroleum ether, the chalcone was obtained in 98% yield.



Reference 8.

To an 1.83 L 95% ethanolic solution containing 10.1 g 1,2-bis(2-formylphenoxy)ethane (37.4 mmol) and 5.53 g cyclohexanone (56.3 mmol) was added aqueous NaOH solution (22.5 g/45 mL, 563 mmol) in one portion. After being stirred at room temperature for 6 days, a bright yellow precipitate was filtered from the reaction. The precipitate was washed thoroughly with 1.0 M HCl and water and dried in an oven (90°C) to constant weight (10.3 g). A portion of the precipitate (920 mg) was washed with hot chloroform to afford 380 mg 9,10:18,19:24,25-tetrabenzo-5,8,20,23-tetraoxa-tricyclo[25.3.1.$1^{12,16}$]-dotriaconta-1,3,9,11,16,18,24,26 -octaene-31,32-dione as a bright yellow powder, in a yield of 34%, m.p.: solid turns brown at 292–293°C and melts sharply at 297–298°C.

Other references related to the Claisen-Schmidt condensation are cited in the literature.[14]

H. REFERENCES

1. Claisen, L. and Claparède, A., *Ber.,* **1881**, *14*, 2460.
2. Schmidt, J. G., *Ber.,* **1881**, *14*, 1459.
3. Mestres, R., *Green Chem.,* **2004**, *6*, 583.
4. (a) Heathcock, C. H., "Catalyzed Additions of Nucleophilic Alkenes to C=X" in *Comprehensive Organic Synthesis*, ed. Trost, B. M.; Fleming, I. and Heathcock, C. H., Pergamon Press, Oxford, **1991**, p. 133. (b) Nielsen, A. T. and Houlihan, W. J., *Org. React.,* **1968**, *16*, 1.
5. (a) Wang, Y. C.; Ye, J. X. and Liang, X. M., *Adv. Synth. Catal.,* **2007**, *349*, 1033. (b) Calvino, V.; Picallo, M.; Lopez-Peinado, A. J.; Martin-Aranda, R. M. and Duran-Valle, C. J., *Appl. Surface Sci.,* **2006**, *252*, 6071. (c) Bhagat, S.; Sharma, R.; Sawant, D. M.; Sharma, L. and Chakraborti, A. K., *J. Mol. Cata. A: Chem.,* **2006**, *244*, 20. (d) Hargrove-Leak, S. C.; Lichtenberger, J. and Amiridis, M. D., *Chem. Ind.,* **2005**, *104*, 385. (e) Jhala, J. S.; Ranawat, P. S.; Dulawat, S. S. and Verma, B. L., *Indian J. Heterocycl. Chem.,* **2005**, *14*, 357. (f) Hatsuda, M.; Kuroda, T. and Seki, M., *Synth. Commun.,* **2003**, *33*, 427. (g) Mogilaiah, K. and Reddy, N. V., *Synth. Commun.,* **2003**, *33*, 73. (h) Zhu, Z.-Q.; Zeng, J.-Q.; Li, Y.-Q. and Liu, L.-M., *Youji Huaxue*, **2003**, *23*, 72. (i) Mogilaiah, K. and Kankaiah, G., *Indian J. Chem., Sect. B,* **2002**, *41B*, 2194. (j) Sebti, S.; Solhy, A.; Tahir, R. and Smahi, A., *Appl. Catal. A: Gen.,* **2002**, *235*, 273. (k) Sebti, S.; Saber, A.; Rhihil, A.; Nazih, R. and Tahir, R., *Appl. Catal. A: Gen.,* **2001**, *206*, 217. (l) Subbanwad, G. R.; Baseer, M. A. and Vibhute, Y. B., *Orient. J. Chem.,* **2000**, *16*, 567. (m) Cheng, M. S.; Li, R. S. and Kenyon, G., *Chinese Chem. Lett.,* **2000**, *11*, 851. (n) Mogilaiah, K. and Rao, R. B., *Indian J. Chem., Sect. B,* **1999**, 38*B*, 869. (o) Guida, A.; Lhouty, M. H.; Tichit, D.; Figueras, F. and Geneste, P., *Appl. Catal. A: Gen.,* **1997**, *164*, 251. (p) Kazantseva, V. M. and Korshunov, S. P., *Zh. Org. Khim.,* **1994**, *30*, 313. (q) Dominguez, C.; Plumet, J.; Gaset, A. and Rigal, L., *Can. J. Chem.,* **1992**, *70*, 2306. (r) Climent, M. J.; Garcia, H.; Primo, J. and Corma, A., *Catal. Lett.,* **1990**, *4*, 85. (s) Aguilera, A.; Alcantara, A. R.; Marinas, J. M. and Sinisterra, J. V., *Can. J. Chem.,* **1987**, *65*, 1165. (t) Garcia Raso, A.; Campaner, B.; Sinisterra, J. V. and Marinas, J. M., *Anal. Quim., Ser. C,* **1982**, *78*, 112. (u) Fine, S. A. and Pulaski, P. D., *J. Org. Chem.,* **1973**, *38*, 1747. (v) Uchida, A.; Saito, S. and Matsuda, S., *Bull. Chem. Soc. Jpn.,* **1969**, *42*, 2989.
6. (a) Mu, J.-X.; Yin, X.-F. and Wang, Y.-G., *Synlett,* **2005**, 3163. (b) Formentin, P.; Garcia, H. and Leyva, A., *J. Mol. Catal. A: Chem.,* **2004**, *214*, 137. (c) Gasull, E. I.; Silber, J. J.; Blanco, S. E.; Tomas, F. and Ferretti, F. H., *THEOCHEM,* **2000**, *503*, 131. (d) Sadvilkar, V. G.; Samant, S. D. and Gaikar, V. G., *J. Chem. Technol. Biotechnol.,* **1995**, *62*, 405. (e) Sinistierra, J. V.; Garcia-Raso, A.; Cabello, J. A. and Marinas, J. M., *Synthesis,* **1984**, 502.
7. Yanagisawa, A.; Goudu, R. and Arai, T., *Org. Lett.,* **2004**, *6*, 4281.
8. Higham, L. T.; Kreher, U. P.; Raston, C. L.; Scott, J. L. and Strauss, C. R., *Org. Lett.,* **2004**, *6*, 3257.
9. (a) Smith, P. J.; Dimmock, J. R. and Turner, W. A., *Can. J. Chem.,* **1973**, *51*, 1458. (b) Hassner, A. and Mead, T. C., *Tetrahedron,* **1964**, *20*, 2201. (c) Huitric, A. C. and Kumler, W. D., *J. Am. Chem. Soc.,* **1956**, *78*, 614.
10. (a) Lawrence, N. J.; Rennison, D.; McGown, A. T.; Ducki, S.; Gul, L. A.; Hadfield, J. A. and Khan, N., *J. Comb. Chem.,* **2001,** *3*, 421. (b) Babu, G. and Perumal, P. T., *Synth. Commun.,* **1997**, *27*, 3677. (c) Climent, M. J.; Corma, A.; Iborra, S. and Primo, J., *J. Catal.*, **1995**, *151*, 60.
11. (a) Rao, M. L. N.; Houjou, H. and Hiratani, K., *Tetrahedron Lett.,* **2001**, *42*, 8351. (b) Vogtle, F.; Mayenfels, P. and Luppertz, F., *Synthesis,* **1984**, 580.
12. Bowman, M. D.; Jeske, R. C. and Blackwell, H. E., *Org. Lett.,* **2004**, *6*, 2019.
13. Choudary, B. M.; Kantam, M. L.; Ranganath, K. V. S.; Mahendar, K. and Sreedhar, B., *J. Am. Chem. Soc.,* **2004**, *126*, 3396.

14. (a) Baell, J. B.; Gable, R. W.; Harvey, A. J.; Toovey, N.; Herzog, T.; Hänsel, W. and Wulff, H., *J. Med. Chem.,* **2004**, *47*, 2326. (b) Oyedapo, A. O.; Makanju, V. O.; Adewunmi, C. O.; Iwalewa, E. O. and Adenowo, T. K., *Afr. J. Trad. CAM,* **2004**, *1*, 55. (c) Nolen, S. A.; Liotta, C. L.; Eckert, C. A. and Gläser, R., *Green Chem.*, **2003**, *5*, 663. (d) Banwell, M. G., *Pure & Appl. Chem.,* **1996**, *68*, 539. (e) Larsen, R. D.; Corley, E. G.; King, A. O.; Carroll, J. D.; Davis, P.; Verhoeven, T. R.; Reider, P. J.; Labelle, M.; Gauthier, J. Y.; Xiang, Y. B. and Zamboni, R. J., *J. Org. Chem.,* **1996**, *61*, 3398. (f) Artico, M.; Santo, R. D.; Costi, R.; Massa, S.; Retico, A.; Artico, M.; Apuzzo, G.; Simonetti, G. and Strippoli, V., *J. Med. Chem.,* **1996**, *38*, 4223. (g) House, H. O., *Modern Synthetic Reactions*, 2nd ed., W. A. Benjamin, Menlo Park, Calif., **1972**, pp. 632–639. (h) Mahal H. S. and Venkataraman K., *Curr. Sci.*, **1933**, *4*, 214.

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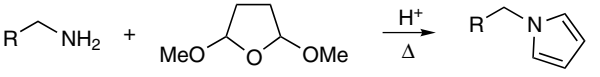
Clauson-Kaas Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Clauson-Kaas and Tyle in 1952.[1] It is a synthesis of pyrrole derivative from the condensation between a primary aliphatic or aromatic amine and 2,5-dimethoxy-tetrahydrofuran in the presence of an acid catalyst. Therefore, this reaction is generally known as the Clauson-Kaas reaction[2] or occasionally referred to as the Clauson-Kaas procedure.[3] The acid catalysts used in this reaction include acetic acid,[2d,3b,4] phosphorus pentoxide,[5] and 4-chloropyridinium hydrochloride.[6] This reaction opens a door to convert the primary amino group into a pyrrole group,[7] which has been used to prepare a variety of pyrrole derivatives containing different substituents,[8] especially for polycyclic structures containing pyrrole.[7] However, this reaction is not a good method for synthesizing pyrrole if the desired compound contains an acidic labile group—for example, in the presence of a imidazole group, this reaction either does not work[9] or give only poor yield.[2d] Alternatively, the pyrrole can be prepared from a primary amine and 1,4-dichloro-1,4-dimethoxybutane in the presence of an acid catalyst (e.g., Amberlyst A-21).[10]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A simple illustration of the reaction mechanism is provided here.

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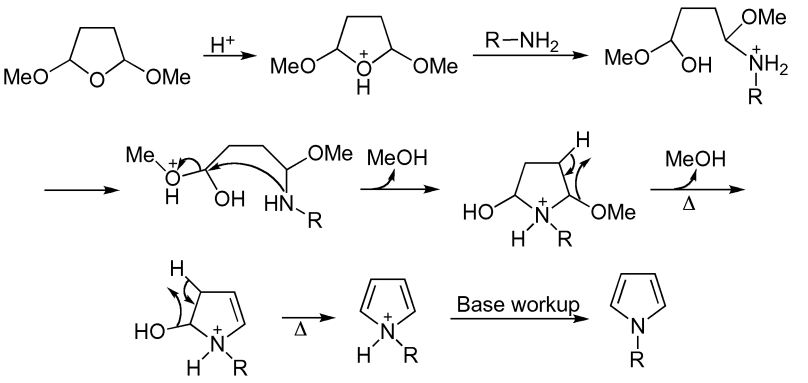


D. MODIFICATION

This reaction has been modified to start from 1,4-dichloro-1,4-dimethoxybutane and primary amine in the presence of an acid catalyst.[10]

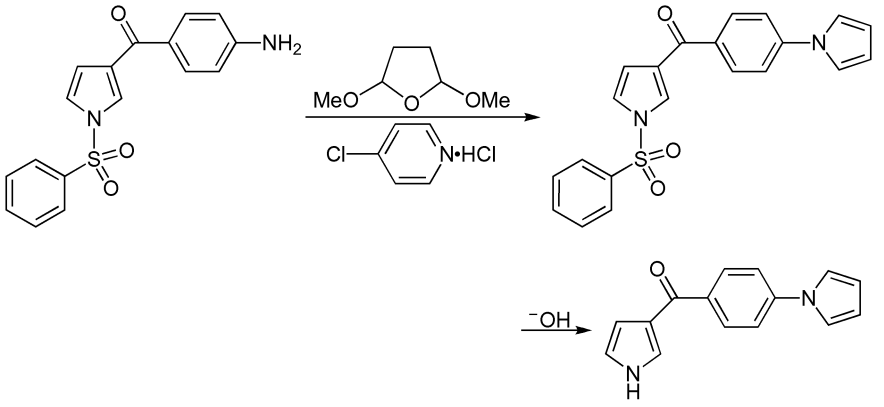
E. APPLICATIONS

This reaction has general application in the synthesis of pyrrole derivatives.

F. RELATED REACTIONS

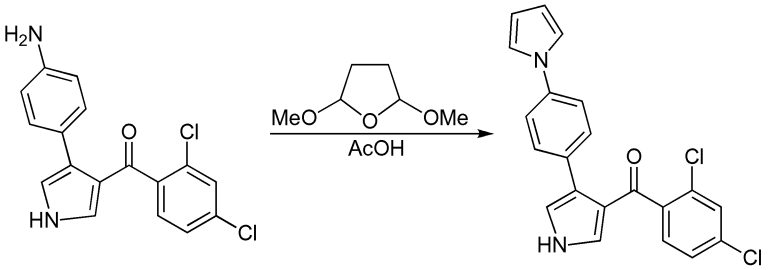
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 2c.

A mixture of 1.5 g crude 1-benzenesulfonyl-1*H*-pyrrol-3-yl-4-aminophenyl-methanone, 0.97 g 4-chloropyridine hydrochloride (6.47 mmol), and 0.88 g 2,5-dimethoxytetrahydrofuran (5.8 mmol) in 30 mL dioxane was refluxed for 3 h under a nitrogen atmosphere. The resulting solution was evaporated under reduced pressure, and the residue was dissolved in Et_2O, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was dissolved in 50 mL dioxane; to this solution, 50 mL 5 *N* NaOH solution was added. The reaction mixture was vigorously stirred at room temperature for 24 h. The organic layer was collected, and the aqueous solution was thoroughly extracted with EtOAc (2 × 50 mL). The combined organic layer and extracts were washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was flash chromatographed with EtOAc/petroleum ether (3:1) followed by recrystallization from toluene/petroleum ether to provide 0.26 g 1*H*-pyrrol-3-yl-4-pyrrol-1-ylphenyl-methanone, in a yield of 24%, m.p. 172–173°C.



Reference 11.

A solution of 1.0 g [4-(4-aminophenyl)-1*H*-pyrrol-3-yl]-(2,4-dichlorophenyl) methanone (3.0 mmol) and 410 mg 2,5-dimethoxytetrahydrofuran (3.1 mmol) in 20 mL acetic acid was refluxed for 30 min. After the mixture was cooled, the solvent was removed and the residue was chromatographed on aluminum oxide (EtOAc as the eluent) to give 810 mg pure (2,4-dichlorophenyl)-[4-[4-(1*H*-pyrrol-1-yl)phenyl]-1*H*pyrrol-3-yl]methanone, in a yield of 70%.

Other experimental details for the Clauson-Kaas reaction are available,[7,8,12] and additional references related to the Clauson-Kaas reaction are cited in the literature.[13]

H. REFERENCES

1. Clauson-Kaas, N. and Tyle, Z., *Acta Chem. Scand.*, **1952**, *6*, 667.
2. (a) Gourlay, B. S.; Molesworth, P. P.; Ryan, J. H. and Smith, J. A., *Tetrahedron Lett*., **2006**, *47*, 799. (b) Lellouche, J.-P.; Perlman, N.; Joseph, A.; Govindaraji, S.; Buzhansky, L.; Yakir, A. and Bruce, I., *Chem. Commun.,* **2004**, 560. (c) Nicolaou, I. and Demopoulos, V., *J. Med. Chem.,* **2003**, *46*, 417. (d) Enguehard, C.; Renou, J.-L.; Allouchi, H.; Leger, J.-M. and Gueiffier, A., *Chem. Pharm. Bull.,* **2000**, *48*, 935.
3. (a) Hrnèariková, K. and Végh, D., *Molecules,* **2003**, *8*, 536. (b) Artico, M.; Silvestri, R.; Massa, S.; Loi, A. G.; Corrias, S.; Piras, G. and Colla, P. L., *J. Med. Chem.,* **1996**, *39*, 522.
4. (a) Tembo, O. N.; Dallemagne, P.; Rault, S. and Robba, M., *Heterocycles,* **1993**, *36*, 2129. (b) Josey, A. D., *Org. Synth. Coll. V,* **1973**, 716.

5. (a) Leysen, F. Y. and Ottenheijm, H. C. J., *Synth. Commun*., **1995**, *25*, 1857. (b) Elming, N. and Clauson-Kass, N., *Acta Chem. Scand.,* **1952**, *6*, 867.
6. Cardinaud, I.; Gueiffier, A.; Debouzy, J-C.; Milhared, J-C. and Chapat, J-P., *Heterocycles,* **1993**, *36*, 2513.
7. Josey, A. D. and Jenner, E. L., *J. Org. Chem.,* **1962**, *27*, 2466.
8. Sircar, I.; Winters, R. T.; Quin, J.; Lu, G. H.; Major, T. C. and Panekt, R. L., *J. Med. Chem.,* **1993**, *36*, 1735.
9. Artico, M.; Santo, R. D.; Costi, R.; Massa, S.; Retico, A.; Artico, M.; Apuzzo, G.; Simonetti, G. and Strippoli, V., *J. Med. Chem.,* **1996**, *38*, 4223.
10. Chan, T. H. and Lee, S. D., *J. Org. Chem.,* **1983**, *48*, 3059.
11. Tafi, A.; Costi, R.; Botta, M.; Santo, R. D.; Corelli, F.; Massa, S.; Ciacci, A.; Manetti, F. and Artico, M., *J. Med. Chem.,* **2002**, *45*, 2720.
12. Seino, H.; Ishii, Y.; Sasagawa, T. and Hidai, M., *J. Am. Chem. Soc.,* **1995**, *117*, 12181.
13. (a) Govindaraji, S.; Nakache, P.; Marks, V.; Pomerantz, Z.; Zaban, A. and Lellouche, J.-P., *J. Org. Chem.,* **2006**, *71*, 9139. (b) Lichtenthaler, F. W., *Acc. Chem. Res*., **2002**, *35*, 728. (c) Périé, K.; Marks, R.; Szunerits, S. Cosnier, S. and Lellouche, J.-P., *Tetrahedron Lett*., **2000**, *41*, 3725. (d) Noble, C. O. and McCarley, R. L., *Org. Lett*., **1999**, *1*, 1021. (e) Dallemagne P., Sonnet P., Enguehard C. and Rault S., *J. Heterocyclic Chem*., **1996**, *33*, 1689. (f) Garcia, E. E.; Riley, J. G. and Fryer, R. I., *J. Org. Chem*., **1968**, *33*, 1359. (g) Patterson, J. M. and Burka, L. T., *J. Am. Chem. Soc.,* **1966**, *88*, 3671. (h) Elming, N. and Clauson-Kaas, N., *Acta Chem. Scand*., **1956**, *10*, 1603.

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Clay-Kinnear-Perren Condensation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Clay in 1951[1] and was subsequently extended by Kinnear and Perren in 1952.[2] It is the synthesis of alkylphosphonic dichlorides from alkyl chlorides, phosphorous trichloride and aluminum chloride and is known as the Clay-Kinnear-Perren condensation,[3] Kinnear-Perren-Clay reaction,[4] or simply the Kinnear-Perren reaction.[5] The resulting alkylphosphonic dichlorides can be further hydrolyzed to alkylphosphonic acids or subjected to the conditions to make other phosphorus-containing derivatives. As pointed out by Clay, the order of mixing reagents, control of reaction temperature, anhydrous conditions of the reagents and apparatus, and the final molar ratio of water to ionic complex in hydrolysis all have important effects on this reaction.[1] For example, no reaction takes place if $AlCl_3$ was dissolved in alkyl chloride before the addition of PCl_3 and the molar ratio of H_2O to complex being hydrolyzed must be within the limits of 7:1 to 11:1. It was also found that complex formed from alkyl chloride, PCl_3 and $AlCl_3$ has high thermal stability with a melting point $\sim$370°C; the solution of such a complex in nitromethane conducts an electric current, indicating an ionic nature of the structure $[RPCl_3]^+[AlCl_4]^-$.[1] In addition, Kinnear and Perren reported[2,6] that when propyl or higher primary or secondary alkyl chlorides are used, only rearranged products are formed (similar to the *Friedel-Crafts Alkylation*[5g]); in a special case, the elimination of the methyl group from *tert*-amyl chloride also occurs.[2] The tendency of such rearrangement limits the utility of this reaction.[7] Similarly, the molar ratio is also important in the alcoholysis of such complexes.[8] However, no rearrangement was found for the complex from chloromethyltrimethylsilane,[9] even though chloromethyltrimethylsilane undergoes a *Wagner-Meerwein Rearrangement* to chlorodimethylethylsilane when treated with $AlCl_3$;[10] this reaction does not apply to chlorosilane either.[9]

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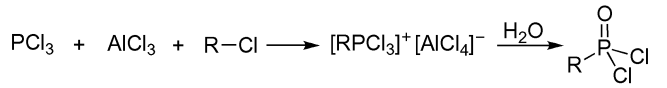
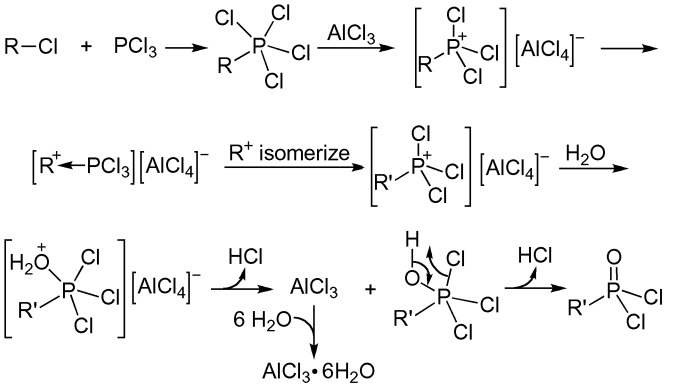
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A simple mechanism is displayed here.



D. MODIFICATION

N/A

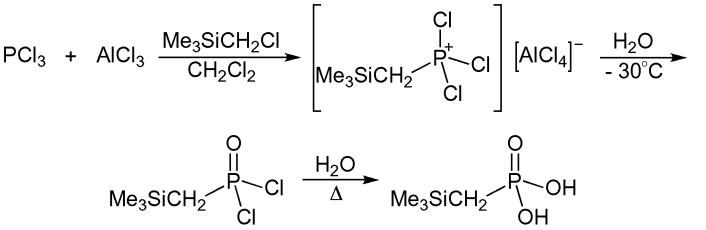
E. APPLICATIONS

This reaction provides a convenient method for preparing alkyl phosphonic chloride, which is an important intermediate for alkyl phosphonic acid and corresponding esters.

F. RELATED REACTIONS

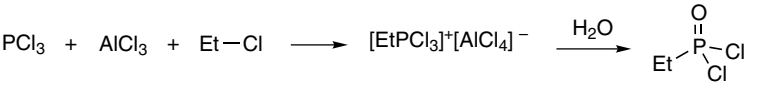
This reaction is related to the *Clayton-Jensen Reaction.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 9.

A mixture of 133.4 g anhydrous aluminum chloride (1.0 mol) and 137.4 g phosphorus trichloride (1.0 mol) in 300 mL methylene chloride was prepared under dry nitrogen. Chloromethyltrimethylsilane (122.7 g, 1.0 mol) was added dropwise with stirring over a 1-h period while the reaction temperature was maintained at 25–28°C by external cooling. The mixture was stirred for an additional hour at 25°C to give a clear solution of the complex salt. An equal volume of methylene chloride was added, and the solution was cooled to −30 in dry ice–acetone. Then 162 mL water was added dropwise with rapid stirring over a 1-h period. The temperature was kept below −20°C during hydrolysis of the complex to minimize the hydrolysis of the phosphonyl dichloride. Precipitated aluminum salt was removed on a filter and washed with methylene chloride. The filtrate was dried over calcium chloride at 0°C. After removal of the solvent, the crude product was distilled through an efficient column to give 64 g trimethylsilylmethylphosphonyl dichloride, b.p. 64°C (1.4 mmHg). Treatment of the distillation residue with boiling water gave 20 g of the corresponding phosphonic acid, m.p. 121°C from water.



Reference 1.

To a mixture of 13.3 g anhydrous $AlCl_3$ and 13.7 g PCl_3 was added 19.3 g ethyl chloride; the bottle was closed and placed in a shaking machine. (All reagents and the reaction bottle were cooled in a refrigerator at ∼ 4°C just before weighing and mixing). Up to the moment of closing the bottle, the temperature of the mixture had risen to 9°C. After 15 min of shaking, the temperature of the mixture had risen to 23°C. At this temperature, the solid $AlCl_3$ dissolved, accompanied by a sudden rise in temperature, which reached ∼35°C. The solution became pale yellow in color. After ∼12 min, the temperature dropped to 25°C, accompanied by the deposit of a white crystalline precipitate. The shaking of the mixture was continued for 1 h. The reaction bottle was then placed in a refrigerator at ∼4°C. After 24 h, the supernatant liquid was poured off, leaving 18 g dry crystalline material, m.p. 370°C (approximately). A solution of the complex in nitromethane was found to exhibit an electrical conductivity equivalent to that of a univalent salt in water.

This crystalline complex was dissolved in 200 mL methylene chloride, transferred to a three-necked 500-mL flask, cooled to 0°C, and hydrolyzed by adding dropwise (at the rate of 10 drops/min) 25.3 mL cold concentrated hydrochloric acid (4°C). The mixture was stirred for 2 h, beginning with the addition of the first drop of hydrochloric acid. The reaction flask was immersed in an ice water mixture which kept the temperature between 0° and 7°C throughout the hydrolysis. The cold mixture was filtered, and the filtrate was distilled to remove excess solvent, followed by vacuum distillation of the residue at 28 mmHg. The vacuum distillate yielded 7.6 g ethyl phosphonyl dichloride as a colorless liquid, b.p. 174.5°C.

Other references related to the Clay-Kinnear-Perren condensation are cited in the literature.[11]

H. REFERENCES

1. Clay, J. P., *J. Org. Chem.,* **1951**, *16*, 892.
2. Kinnear, A. M. and Perren, E. A., *J. Chem. Soc.,* **1952**, 3437.

3. Cade, J. A., *Tetrahedron*, **1958**, *2*, 322.
4. (a) Ilia, G.; Iliescu, S.; Dehelean, G.; Popa, A.; Pacureanu, L. and Macarie, L., *Revista Chim. (Romania),* **2001**, *52*, 101. (b) Chauzov, V. A.; Studnev, Y. N.; Rudnitskaya, L. S. and Fokin, A. V., *Zh. Obsh. Khim.,* **1987**, *57*, 2250.
5. (a) Plack, V.; Goerlich, J. R. and Schmutzler, R., *Z. Naturforsch., B: Chem. Sci.,* **1998**, *53*, 1265. (b) Boutevin, B.; Hervaud, Y. and Pietrasanta, Y., *Phosphorus & Sulfur & Related Elements,* **1981**, *11*, 373. (c) Bauer, G.; Haegele, G. and Sartori, P., *Phosphorus & Sulfur & Related Elements,* **1980**, *8*, 95. (d) Weiss, J. V. and Schmutzler, R., *J. Chem. Soc., Chem. Commun.,* **1976**, 643. (e) Harris, R. K.; Lewellyn, M.; Wazeer, M. I. M.; Woplin, J. R.; Dunmur, R. E.; Hewson, M. J. C. and Schmutzeer, R., *J. Chem. Soc., Dalton Trans.,* **1975**, 61. (f) Maier, L., *Helv. Chim. Acta,* **1969**, *52*, 1337. (g) Metzger, S. H.; Basedow, O. H. and Isbell, A. F., *J. Org. Chem.,* **1964**, *29*, 627.
6. Perren, E. A. and Kinnear, A. M., *Brit. Pat*., **1954**, Apr. 28, 707,961 [*Chem. Abstr.,* **1955**, *49*, 7588].
7. Freedman, L. D. and Doak, G. O., *Chem. Rev.,* **1957**, *57*, 479.
8. Hoffmann, F. W.; Simmons, T. C. and Glunz, L. J., *J. Am. Chem. Soc.,* **1957**, *79*, 3570.
9. Hartle, R. J., *J. Org. Chem.,* **1966**, *31*, 4288.
10. Whitmore, F. C.; Sommer, L. H. and Gold, J., *J. Am. Chem. Soc.,* **1947**, *69*, 1976.
11. (a) Savignac, P. and Iorga, B., *Modern Phosphonate Chemistry*, CRC Press, Boca Raton, **2003**. (b) Waschbüsch, R.; Carran, J.; Marinetti, A. and Savignac, P., *Synthesis*, **1997**, 727. (c) Gilyazov, M. M. and Levin, Ya. A., *Khim. Elementoorg. Soedin.*, **1976**, 213. (d) Pawar R. A., *J. Prakt. Chem.*, **1974**, *316*, 507. (e) Jungermann, E.; McBride, J. J.; Clutter, R. and Mais, A., *J. Org. Chem.,* **1962**, *27*, 606. (f) Clay, J. P., *U. S. Pat.,* **1956**, May, 01, 2,744,132. (g) Kennard, K. C. and Hamilton, C. S., *J. Am. Chem. Soc.,* **1955**, *77*, 1156. (h) Crofts, P. C. and Kosolapoff, G. M., *J. Am. Chem. Soc.,* **1953**, *75*, 3379.

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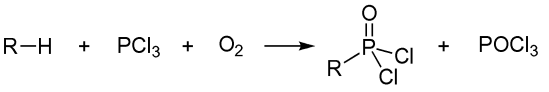
Clayton-Jensen Chlorophosphonation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially studied almost coincidently by three groups: Clayton and Jensen;[1] Soborovsky, Zinovyev, and Englin in the pre-Soviet Union;[2] and Graf in Germany.[3] However, Clayton and Jensen first reported this reaction in 1948,[1] although Graf might study this reaction first whereas had published his result last.[4] It is the direct chlorophosphonation of aliphatic hydrocarbons by treatment of the hydrocarbons with oxygen and phosphorus trichloride (benzene does not react[1]). Because this reaction is always contaminated by the oxidation of phosphorus trichloride to phosphorus oxychloride,[4] the yield of phosphonyl chloride is generally ~25% based on PCl_3 used.[1] Even though more than 16 catalysts have been tested for this reaction, no apparent catalytic effect of these substances has been clearly found;[5] in contrast, sulfuric acid,[1] iodine,[1] iron powder,[5] and boron trifluoride[5] actually inhibit this reaction. In addition, there is no appreciable influence of light on the yield.[1] In this reaction, the steric effect is obvious, for example, a 13% yield was obtained for the reaction of toluene, whereas a 2.3% yield was obtained from diphenylmethane, and no product at all was yielded from triphenylmethane.[6] In addition, this reaction works only for phosphorus trichloride, not for other phosphorus halides (PBr_3, PI_3, etc.).[1] It is interesting that, to an extent, a higher yield is obtained when more hydrocarbon is used—for example, the yield increases from 20.0% to 29.2% when the molar ratio of cyclohexane to PCl_3 increases from 0.5 to 2.0; however, a further increase in yield is not detectable when more cyclohexane is used.[5] It is reported that this reaction is not spontaneous when sufficient pure reagents are used; The apparently spontaneous nature of the reaction arises from the presence of trace amounts of an initiator in the hydrocarbon.[7] Accordingly, no effective change in yield was found when the reaction was carried out in a temperature range of -40° to 70°C.[5]

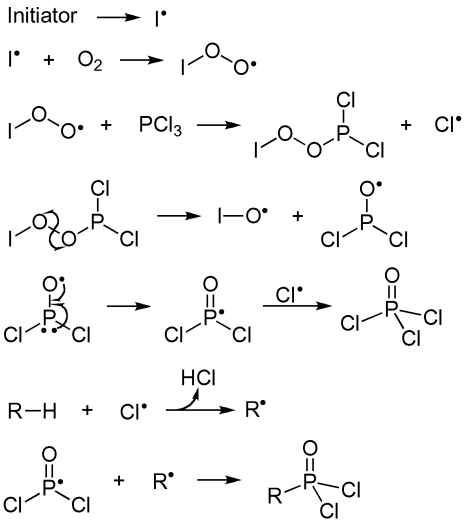
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Although extensively studies have been carried out by Flurry[7] and Mayo,[4] a new mechanism is proposed here to satisfy most of the experimental results.



D. MODIFICATION

N/A

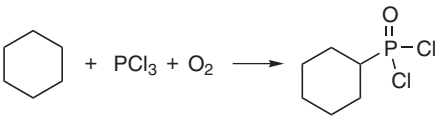
E. APPLICATIONS

This reaction has general application in the preparation of alkyl phosphonyl chlorides, which are the intermediates for alkyl phosphonic acid and corresponding esters.

F. RELATED REACTIONS

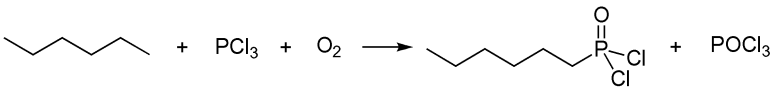
This reaction is related to the *Clay-Kinnear-Perren reaction.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 4.

To a flask equipped with an inlet tube, a thermometer and a cold finger condenser containing powdered dry ice was added 1 eq. cyclohexane and more than 4 eq. PCl_3. The flask was cooled by ice water bath; when the liquid temperature approached that of the bath (1–2°C), introduction of oxygen or air was begun. Reaction set in at once, as indicated by rapid rise in temperature. The rate was limited (in the absence of diluents and inhibitors) by the oxygen supply, usually so that the reaction temperature did not exceed 15°C. When the phosphorus trichloride was exhausted, or nearly so,the temperature of the reaction mixture quickly returned to 1–2°C. Stirring under oxygen was continued for 10–60 min more. The reaction mixture was then weighed and transferred to a Claisen distilling flask with a side arm like a Vigreux column and with thermometers to measure both liquid and vapor temperatures. The bulk of the cyclohexane and phosphorus oxychloride was distilled at atmospheric pressure up to a residue temperature of ~160°C. The residue was then transferred to a smaller flask, and removal of cyclohexane and phosphorus trichloride was continued up to a vapor temperature of 50°C at 20 mmHg pressure. Cyclohexylphosphonyl chloride, easily separated from other materials, was collected up to 135°C at 20 mmHg, or near 85°C at 0.3 mmHg. It was usually colorless, with a melting point in the range of 35–39°C (m.p. after recrystallization from petroleum ether, 39.5–40.5°C). The yield of cyclohexylphosphonyl chloride ($C_6H_{11}POCl_2$) and diphosphonyl chloride [$C_6H_{10}(POCl_2)_2$] was in the range of 70–90%.



Reference 1.

A total of 41 g 99% pure *n*-heptane (0.41 mol) was mixed with 224 g PCl_3 (1.64 mol) and bubbled, by means of a sintered glass plate, with oxygen at a slow rate for 5 h. The maximum temperature was kept below 60°C by means of a water bath. The light yellow liquid was distilled at 10 mmHg, phosphorus oxychloride boiling below 90°C was discarded, and the fraction boiling between 106° and 108°C was collected in a total amount of 28.1 g; in addition, ~16 g of residue was obtained. The narrow boiling fraction, which could not be made to crystallize, was analyzed for phosphorus and chlorine.

Other references related to the Clayton-Jensen chlorophosphonation are cited in the literature.[8]

H. REFERENCES

1. Clayton, J. O. and Jensen, W. L., *J. Am. Chem. Soc.,* **1948**, *70*, 3880.
2. Soborovsky, L. Z.; Zinovyev, Y. M. and Englin, M. A., *Dokl. Akad. Nauk SSSR,* **1949**, *67*, 293.
3. Graf, R., *Ber.,* **1952**, *55*, 9.
4. Mayo, F. R.; Durham, L. J. and Griggs, K. S., *J. Am. Chem. Soc.,* **1963**, *85*, 3156.
5. Isbell, A. F. and Wadsworth, F. T., *J. Am. Chem. Soc.,* **1956**, *78*, 6042.
6. Jensen, W. L. and Noller, C. R., *J. Am. Chem. Soc.,* **1949**, *71*, 2384.
7. Flurry, R. L. and Boozer, C. E., *J. Org. Chem.,* **1966**, *31*, 2076.

8. (a) Zinovyev, Y. M.; Kulakova, V. N. and Soborovsky, L. Z., *J. Gen. Chem. USSR,* **1958**, *28*, 1600. (b) Zinovyev, Y. M. and Soborovsky, L. Z., *J. Gen. Chem. USSR,* **1956**, *26*, 3375. (c) Zinovyev, Y. M.; Muler, L. I. and Soborovsky, L. Z., *J. Gen. Chem. USSR,* **1954**, *24*, 391. (d) Soborovsky, L. Z. and Zinovyev, Y. M., *J. Gen. Chem. USSR,* **1954**, *24*, 527. (e) Jensen, W. L. and Clayton, J. O., *U.S. Pat.,* **1954**, July 6, 2,683,168. (f) Soborovsky, L. Z.; Zinovyev, Y. M. and Englin, M. A., *Dokl. Akad. Nauk SSR,* **1950**, *73*, 333. (g) Lesfauries, P. and Rumpf, P., *Bull. Soc. Chim. Fr.,* **1950**, 542.

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Clemmensen Reduction

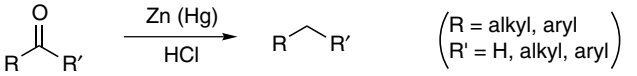
A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Clemmensen of Park Davis Co in 1913.[1] It is the reduction of carbonyl groups (in aldehydes and ketones) to methylene groups with zinc amalgam and hydrochloric acid, and is generally known as the Clemmensen reduction.[2] In some cases, mercury salt (e.g., $HgCl_2$) is not necessary; and the reaction is carried out in acetic acid with zinc and HCl.[3] This reduction is a complementary method for the *Wolff-Kishner Reduction* and *Minlong Huang Reduction* of carbonyl groups with some obvious advantages, such as the adaptability to base labile and acid stable compounds without the rearrangement that the *Wolff-Kishner Reduction* often bears.[4] Although the Clemmensen reduction generally converts carbonyl group into methylene group, it is important to be aware of a few circumstances in which abnormal reactions occur: (*a*) the hydroxyl aromatics (isomer of cyclic vinyl ketone) are not reduced; (*b*) the α-keto acids or α-keto esters are partially reduced to only α-hydroxyl acids or esters, respectively;[5] (*c*) the reduction of 1,3-diketones always involves the rearrangement via pinacol-type intermediate;[6] (*d*) the reduction of 2,2-diphenyl-l,3-indandione gives 2,2-diphenylindan and 1,2-diphenylindene (the latter is the major product) and the rearrangement of the phenyl group occurs when the 2 position of indanone is disubstituted;[7] (*e*) the reduction of β-keto esters affords pure hydrocarbon, which apparently involves both alcoholysis and decarboxylation[8] (it is reported that such event does not occur in absolute alcohol with HCl present[9]); (*f*) the reduction of butyroin gives only 4-octanone, which strangely reduces the hydroxyl group and leaves the carbonyl group untouched;[10] (*g*) the reduction of benzophenone is not successful, giving a resinous product;[11] (*h*) the reduction of acetophenone in dilute hydrochloric acid gives styrene instead of ethylbenzene;[1] (*i*) the reduction of 2-unsubstituted isoflavone gives mixtures of isoflavenes;[12] (*j*) the reduction of atom-bridged bicyclic α-aminoketones

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

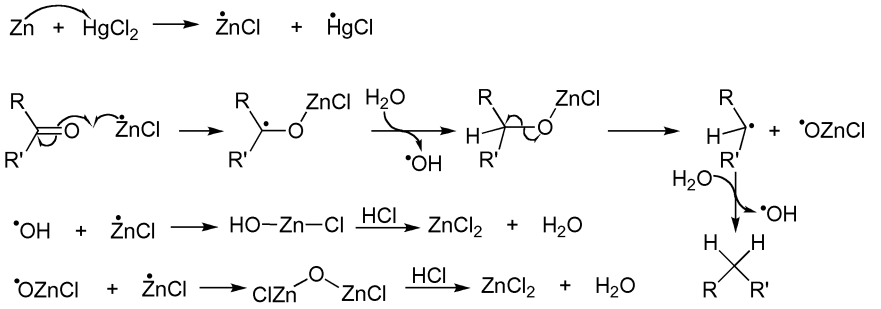
involves two competing reactions—the cleavage of the Cα-N bond and the conversion of CO to CH_2[13]—affording rearranged (ring-contraction) or ring-opening products;[14] (*k*) the reduction of cyclic thioketone affords ring-contraction product;[15] and (*l*) the reduction of ω-dimethylaminoacetophenone yields the cleavage product ethylbenzene.[16] It has been reported that alcohol is not the intermediate of the Clemmensen reduction, because under this condition, alcohol will not give hydrocarbon, except for allyl and benzyl alcohol, which change into chloride.[17] In contrast, it is believed that carbonium is involved in this reduction[3c,18] and reaction occurs at the zinc surface. For molecules that are not so soluble in these reaction conditions, such as keto acids, the addition of alcohol will improve the yield; however, the resulting acid might also be converted into ester. Under these conditions, the addition of toluene to the reaction solution will optimize the yield.[19]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is believed that the alcohol is not the intermediate in this reduction; therefore, the mechanism outlined here is similar to that described by di Vona and Rosnati,[17] although another mechanistic illustration was given by Nakabayashi.[18] In this reduction, radical HgCl· will react similarly, so its reaction path is not given. The new radical ·OHgCl can be reduced to mercury by zinc, and mercury will again participate in the reaction cycle, as shown below.



D. MODIFICATION

The addition of water-miscible solvent, such as alcohol, acetic acid, or dioxane, will facilitate the reduction of keto acids. In addition, transformation of the acid into low melting point ester and the addition of a certain amount of toluene to retain the ester in a clear surface layer can simplify the reduction and optimize the yield.[19]

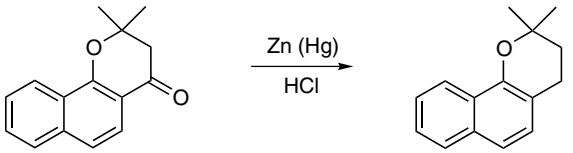
E. APPLICATIONS

This reaction has been widely used to convert a carbonyl group into a methylene group, with important applications in the preparation of polycyclic aromatics[20] and aromatics containing unbranched side hydrocarbon chains,[21] the latter is not attainable from the *Friedel-Crafts Alkylation*.

F. RELATED REACTIONS

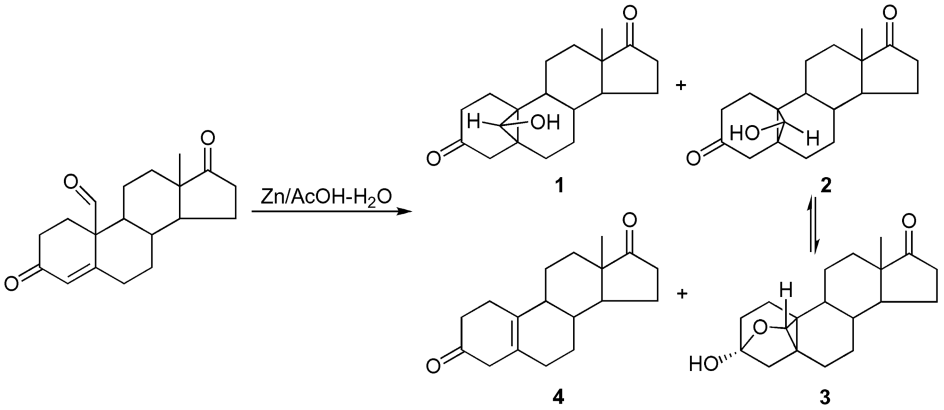
This reaction is a complementary reduction for the *Wolff-Kishner Reduction* and *Minlong Huang Reduction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 22.

To a mixture of 2.0 g zinc powder and 0.10 g $HgCl_2$ was added 20 mL water; the resulting slurry was shaken thoroughly for 5 min. To it was added 10 mL 18% HCl (1:1 mixture of H_2O and conc. HCl), and the mixture was again shaken vigorously when zinc amalgam was obtained. To this zinc amalgam was added 2.2 mmol γ-naphthopyrone and 25 mL HCl (4:1 mixture of conc. HCl and H_2O), and the contents were refluxed for 3 h. After completion of the reaction (monitored by TLC), the contents were extracted with diethyl ether. Workup of the organic layer provided a product that, on purification using column chromatography, yielded 80% of oily 3,4-dihydro-2,2-dimethylnaphthopyran.



Reference 3b.

To a solution of 8.0 g 19-formylandrost-4-ene-3,17-dione (26.5 mmol) in 160 mL 50% acetic acid was added 40.0 g zinc powder. The mixture was stirred for 1.5 h and was diluted with 500 mL CH_2Cl_2 and filtered. The filtrate was washed with water and aqueous $NaHCO_3$, dried, concentrated ($\sim$ 15 mL) and diluted with Et_2O to give 5.0 g (19*R*)-19-hydroxy-5β,19-cycloandrostane-3,17-dione (**1**), in a yield of 62.5%, m.p. 160–167°C, which on recrystallization from CH_2Cl_2–Et_2O gave an analytically pure sample, m.p. 169–179°C (dec.). A portion of the mother liquor (1 g) on flash column chromatography eluted with 80% Et_2O-LP gave 240 mg estra-5(10)-ene-3,17-dione (**4**) in a yield of 3.3%, m.p. 144–148°C, and 130 mg (19*R*)-19-hydroxy-5β,19-cycloandrostane-3,17-dione (**1**), m.p. 160–167°C, and 45 mg of a mixture of (19*S*)-19-hydroxy-5β,19-cycloandrostane-3,17-dione (**2**) and (19*S*)-3-hydroxy-3β,19-oxido-5β,19-cycloandrostan-17-one (**3**), in a yield of 0.56%, m.p. 160–165°C. The wide melting point range observed results from the thermal instability of the cyclopropanols.

Other references related to the Clemmensen reduction are cited in the literature.[23]

H. REFERENCES

1. Clemmensen, E., *Ber.,* **1913**, *46*, 1837.
2. (a) Alessandrini, L.; Ciuffreda, P.; Santaniello, E. and Terraneo, G., *Steroids,* **2004**, *69*, 789. (b) Palacios, J. C. and Cintas, P., *J. Chem. Edu.,* **1998**, *75*, 938. (c) Zakharkin, L. I.; Ol'shevskaya, V. A. and Vinogradova, L. E., *Russ. Chem. Bull.,* **1997**, *46*, 1158. (d) Davis, B. R. and Hinds, M. G., *Aust. J. Chem.,* **1997**, *50*, 309. (e) Xu, Z.-L. and Wong, H. N. C., *Youji Huaxue*, **1996**, *16*, 440. (f) Denifl, P.; Hradsky, A.; Bildstein, B. and Wurst, K., *J. Organomet. Chem.,* **1996**, *523*, 79. (g) Hiegel, G. A. and Carney, J. R., *Synth. Commun.,* **1996**, *26*, 2625. (h) Bailey, K. E. and Davis, B. R., *Aust. J. Chem.,* **1995**, *48*, 1827. (i) Ni, Y.; Kisic, A.; Wilson, W. K. and Schroepfer, G. J., *J. Lipid Res.,* **1994**, *35*, 546. (j) Ni, Y.; Kim, H. S.; Wilson, W. K.; Kisic, A. and Schroepfer, G. J., *Tetrahedron Lett*., **1993**, *34*, 3687. (k) Davis, B. R.; Hinds, M. G. and Ting, P. P. C., *Aust. J. Chem.,* **1992**, *45*, 865. (l) Martins, F. J. C.; Viljoen, A. M.; Coetzee, M.; Fourie, L. and Wessels, P. L., *Tetrahedron,* **1991**, *47*, 9215. (m) Di Vona, M. L.; Floris, B.; Luchetti, L. and Rosnati, V., *Tetrahedron Lett*., **1990**, *31*, 6081. (n) Talapatra, S. K.; Chakrabarti, S.; Mallik, A. K. and Talapatra, B., *Tetrahedron,* **1990**, *46*, 6047. (o) Martins, F. J. C.; Fourie, L.; Venter, H. J. and Wessels, P. L., *Tetrahedron*, **1990**, *46*, 623. (p) Clark, G. R.; Davis, B. R.; Hinds, M. G. and Rickard, C. E. F., *Aust. J. Chem.,* **1988**, *41*, 1191. (q) Banerjee, A. K.; Alvarez, G. J.; Santana, M. and Carrasco, M. C., *Tetrahedron*, **1986**, *42*, 6615. (r) Burdon, J. and Price, R. C., *J. Chem. Soc., Chem. Commun.,* **1986**, 893. (s) Elphimoff-Felkin, I. and Sarda, P., *Tetrahedron Lett*., **1983**, *24*, 4425. (t) Mirek, J.; Gaweda, M. and Kawalek, B., *Pol. J. Chem.,* **1981**, *55*, 987. (u) Buchanan, J. G. St. C.; Crump, D. R. and Davis, B. R., *J. Chem. Soc., Perkin Trans. I,* **1979**, 2826. (v) Horner, L. and Schmitt, E., *Ann.,* **1978**, 1617. (w) Jefford, C. W. and Boschung, A. F., *Helv. Chim. Acta,* **1976**, *59*, 962. (x) Vedejs, E., *Org. React.,* **1975**, *22*, 401. (y) Swisher, J. V. and Chen, H.-H., *J. Organomet. Chem.,* **1974**, *69*, 93. (z) Ison, R. R. and Hassan, M. M. A., *J. Pharm. Sci.,* **1973**, *62*, 1388. (aa) Toda, M.; Hayashi, M.; Hirata, Y. and Yamamura, S., *Bull. Chem. Soc. Jpn.,* **1972**, *45*, 264. (bb) Eisenbraun, E. J.; Duncan, W. P.; Russell, J. E.; Keen, G. W.; Flanagan P. W. and Hamming, M. C., *J. Org. Chem.,* **1972**, *37*, 142. (cc) Goldberg, S. I.; Bailey, W. D. and McGregor, M. L., *J. Org. Chem.,* **1971**, *36*, 761. (dd) Crump, D. R. and Davis, B. R., *J. Chem. Soc., Chem. Commun.,* **1970**, 768. (ee) Curphey, T. J. and McCartney, R. L., *J. Org. Chem.,* **1969**, *34*, 1964. (ff) Sheth, J. P. and Tolkachev, O. N., *Indian J. Appl. Chem.,* **1968**, *31*, 137. (gg) Rausch, M. D. and Adams, D. L., *J. Org. Chem.,* **1967**, *32*, 4144. (hh) Kaplan, M. L., *J. Org. Chem.,* **1967**,

32, 2346. (ii) Enzell, C., *Tetrahedron Lett*., **1966**, 1285. (jj) Wenkert, E. and Kariv, E., *Chem. Commun. (London),* **1965**, 570.

3. (a) Tisdale, E. J.; Vong, B. G.; Li, H. M.; Kim, S. H.; Chowdhury, C. and Theodorakis, E. A., *Tetrahedron,* **2003**, *59*, 6873. (b) Templeton, J. F.; Ling, Y. Z.; Lin, W. Y.; Majgier-Baranowska, H. and Marat, K., *J. Chem. Soc., Perkin Trans. I,* **1997**, 1895. (c) Thyagarajan, B. S., *Chem. Rev.,* **1954**, *54*, 1019.
4. Levin, M. D.; Kaszynski, P. and Michl, J., *Chem. Rev.,* **2000**, 100,169.
5. Martin, E. L., "*The Clemmensen Reduction*" in *Organic Reactions,* ed. Adams, R., John wiley & Sons, New York, 1942, 1, p. 159.
6. Cusack, N. J. and Davis, B. R., *J. Org. Chem.,* **1965**, *30*, 2062.
7. (a) Galton, S. A. and Abbas, R., *J. Org. Chem.,* **1973**, *38*, 2008. (b) Galton, S. A.; Kalafer, M. and Beringer, F. M., *J. Org. Chem.,* **1970**, *35*, 1.
8. Shirley, D. A. and Schmidt, G. A., *J. Am. Chem. Soc.,* **1951**, *73*, 5493.
9. Connor, R. and Adkins, H., *J. Am. Chem. Soc.,* **1932**, *54*, 3420.
10. Smith, W. T., *J. Am. Chem. Soc.,* **1951**, *73*, 1883.
11. Bradlow, H. L. and VanderWerf, C. A., *J. Am. Chem. Soc.,* **1947**, *69*, 1254.
12. Dudley, K. H.; Miller, H. W.; Corley, R. C. and Wall, M. E., *J. Org. Chem.,* **1967**, *32*, 2317.
13. Leonard, N. J.; Curry, J. W. and Sagura, J. J., *J. Am. Chem. Soc.,* **1953**, *75*, 6249.
14. (a) Leonard, N. J.; Sentz, R. C. and Middleton, W. J., *J. Am. Chem. Soc.,* **1953**, *75*, 1674. (b) Leonard, N. J.; Fuller, G. and Dryden, H. L., *J. Am. Chem. Soc.,* **1953**, *75*, 3727. (c) Leonard, N. J. and Sentz, R. C., *J. Am. Chem. Soc.,* **1952**, *74*, 1704. (d) Leonard, N. J. and Nicolaides, E. D., *J. Am. Chem. Soc.,* **1951**, *73*, 5210. (e) Leonard, N. J. and Barthel, E., *J. Am. Chem. Soc.,* **1950**, *72*, 3632. (f) Leonard, N. J. and Pines, S. H., *J. Am. Chem. Soc.,* **1950**, *72*, 4931. (g) Leonard, N. J. and Wildman, W. C., *J. Am. Chem. Soc.,* **1949**, *71*, 3089. (h) Leonard, N. J. and Ruyle, W. V., *J. Am. Chem. Soc.,* **1949**, *71*, 3094. (i) Leonard, N. J. and Barthel, E., *J. Am. Chem. Soc.,* **1949**, *71*, 3098. (j) Leonard, N. J. and Wildman, W. C., *J. Am. Chem. Soc.,* **1949**, *71*, 3100.
15. Leonard, N. J. and Figueras, J., *J. Am. Chem. Soc.,* **1952**, *74*, 917.
16. Von Braun, J. and Weissbach, *Ber.,* **1929**, *62*, 2416.
17. Di Vona, M. L. and Rosnati, V., *J. Org. Chem.,* **1991**, *56*, 4269.
18. Nakabayashi, T., *J. Am. Chem. Soc.,* **1960**, *82*, 3900.
19. Martin, E. L., *J. Am. Chem. Soc.,* **1936**, *58*, 1438.
20. Buess, C. M. and Lawson, D. D., *Chem. Rev.,* **1960**, *60*, 313.
21. Stevens, R., *Chem. Rev.,* **1966**, *66*, 19.
22. Paradkar, M. V.; Godbole, H. M.; Ranade, A. A. and Joseph, A. R., *J. Chem. Res. (S),* **1998**, 318.
23. (a) Li, W. D. Z. and Wang, Y.-Q., *Org. Lett.,* **2003**, *5*, 2931. (b) Bieniek, A.; Epsztajn, J. and Kulikiewicz, K. K., *Polish J. Chem*., **2003**, *77*, 1385. (c) Ishimoto, K.; Mitoma, Y.; Nagashima, S.; Tashiro, H.; Prakash, G. K. S.; Olah, G. A. and Tashiro, M., *Chem. Commun.,* **2003**, 514. (d) Bronger, R. P. J.; Silva, S. M.; Kamer, P. C. J. and Leeuwen, P. W. N. M., *Chem. Commun.,* **2002**, 3044. (e) Ashry, E. S. H. E.; Hamid, H. A.; Kassem, A. A. and Shoukry, M., *Molecules,* **2002**, *7*, 155. (f) Yamamura, S. and Nishiyama, S., *Comp. Org. Syn.,* **1991**, *8*, 309. (g) Hughes, I.; Nolan, W. P. and Raphael, R. A. *J. Chem. Soc., Perkin Trans. I,* **1990**, 2475. (h) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J. and Hudlicky, T., *Chem. Rev.,* **1989**, *89*, 165. (i) Hughes, I. and Raphael, R. A., *Tetrahedron Lett*., **1983**, *24*, 1441. (j) Minabe, M.; Yoshida, M.; Fujimoto, M. and Suzuki, K., *J. Org. Chem.,* **1976**, *41*, 1935. (k) Gibson, D. H. and DePuy, C. H., *Chem. Rev.,* **1974**, *74*, 605. (l) Topp, A.; Boldt, P. and Schmand, H., *Ann.,* **1974**, 1167. (m) Buchanan, J. G. St. C. and Woodgate, P. D., *Quart. Rev.,* **1969**, *23*, 522. (n) Weeks, D. P. and Cella, J., *J. Org. Chem.,* **1969**, *34*, 3713. (o) Muller, E.; Fiedler, G.; Huber, H.; Narr, B.; Suhr, H. and Witte, K., *Z. Naturforsch*., **1963**, *18B*, 5. (p) Bergmann, E. D. and Blum, J., *J. Org.*

Chem., **1962**, *27*, 527. (q) Kakabayashi, T., *J. Am. Chem. Soc.,* **1960**, *82*, 3906. (r) Kakabayashi, T., *J. Am. Chem. Soc.,* **1960**, *82*, 3909. (s) Straschewski, D., *Angew. Chem.,* **1959**, *71*, 726. (t) Poutsma, M. and Wolthuis, E., *J. Org. Chem.,* **1959**, *24*, 875. (u) Brewster, J. H., *J. Am. Chem. Soc.,* **1954**, *76*, 6364. (v) Brewster, J. H.; Patterson, J. and Fidler, D. A., *J. Am. Chem. Soc.,* **1954**, *76*, 6368. (w) Herzog, H. L. and Buchman, E. R., *J. Org. Chem.,* **1951**, *16*, 99. (x) Clemo, G. R.; Raper, R. and Vipond, H. J., *J. Chem. Soc.,* **1949**, 2095. (y) Sumpter, W. C., *Chem. Rev.,* **1945**, *37*, 443. (z) Jack, K. M. and Rule, H. G., *J. Chem. Soc.,* **1938**, 188. (aa) Ghigi, E., *Gazz. Chim. Ital.,* **1938**, *68*, 184. (bb) Goldestien, H. and Glauser, W., *Helv. Chim. Acta,* **1934**, *17*, 788. (cc) Sobotka, H., *Chem. Rev.,* **1934**, *15*, 311. (dd) Clemmensen, E., *Ber.,* **1914**, *47*, 51. (ee) Clemmensen, E., *Ber.,* **1914**, *47*, 681.

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Cohen Reductive Lithiation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was originally reported coincidently by Cohen[1] and Screttas[2] in 1978 but was extensively investigated by Cohen.[3] It is the formation of organic lithium compound by reductive lithiation of phenyl thioethers with aromatic radical anions, and the formed organic lithium compound can react with electrophiles to produce a variety of molecules. Currently, the aromatic radical anions used include lithium naphthalenide (LN),[4] lithium 1-(dimethylamino)-naphthalenide (LDMAN),[3s] lithium *p*,*p*′-di-*tert*-butylbiphenylide (LDBB)[3m] and lithium 2,6-di-*tert*-butylnaphthalenide (LDBN).[3b] Besides the phenyl-thioethers, the following molecules can also be reduced by the above aromatic radical anions: acetals,[5] allylic and benzylic ethers,[3m,6] amines,[7] carboxylic acids and esters,[8] epoxides,[3p,9] ketones,[10] nitriles,[11] organic halides,[12] selenides,[13] sulfates,[14] sulfides,[7] sulfones,[15] and tetrahydrofurans.[3m,16] In addition, the versatility of this method is also shown in the preparation of allylsilane,[17] 1,3-diol,[18] highly crowd amines (from α-amino nitriles),[19] butenyl alcohol (via sigmatropic [2,3] rearrangement),[4] and especially the five-membered carbocycles via the anionic cyclization with good stereoselectivity.[3a,4] Unfortunately, the aromatic radical anions involved in this reaction must be generated in tetrahydrofuran (THF), and no other solvent has been successful for the generation of such anions with lithium counterions, except for dimethyl ether (DME), which works for LDMAN.[3b] It was found that the reductive lithiuation of epoxides and oxetanes involves the transfer of an electron to an antibonding orbital (LUMO) of the corresponding heterocycle followed by a ring opening to an intermediate containing an oxyanion and a carbon radical. Two methodologies have been developed to stabilize both the LUMO and the

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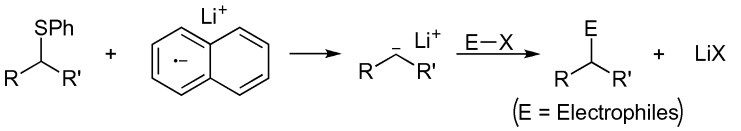
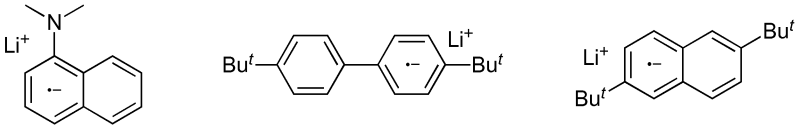
formed intermediates, the application of a Lewis acid (e.g., $BF_3{\cdot}Et_2O$) and the introduction of a vinyl group to the α-position of THF.[3m] It was reported that during the reductive lithiation of tetrahydrofurans and tetrahydropyrans, both the axial and the equatorial epimers predominantly give the axial lithio derivative.[3s]

B. GENERAL REACTION SCHEME



Other aromatic radical anions are also given here.



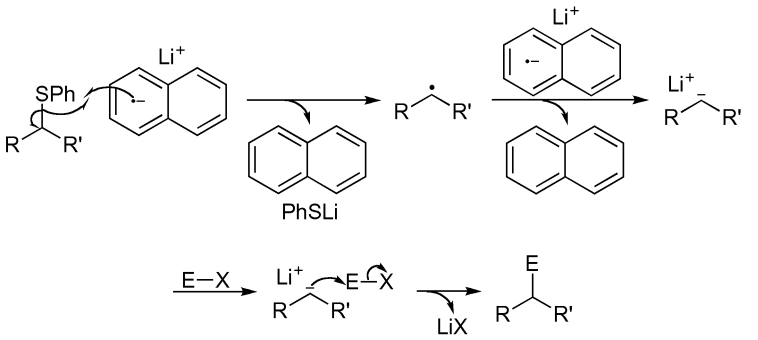
Lithium 1-(dimethylamino)-naphthalenide (LDMAN).

Lithium *p,p′*-di-*tert*-butylbiphenylide (LDBB).

Lithium 2,6-di-*tert*-butylnaphthalenide (LDBN).

C. PROPOSED MECHANISMS

This reaction involves single electron transfer process as displayed below.



D. MODIFICATION

N/A

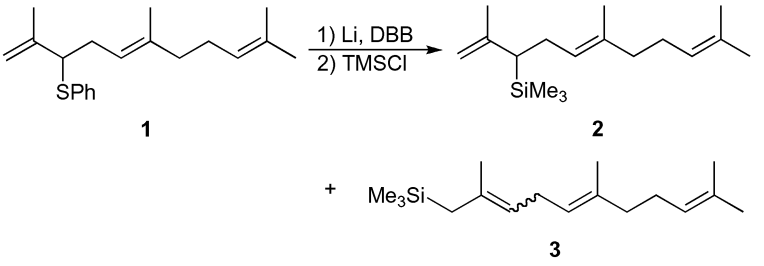
E. APPLICATIONS

This reaction has wide application in organic synthesis.

F. RELATED REACTIONS

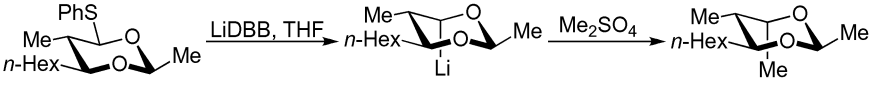
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 17.

To a two-necked, round-bottom flask equipped with an argon inlet were added 1.4 mL THF and 18 mg DBB (0.07 mmol, 0.1 eq.). Small lithium pieces (233 mg, 33.5 mmol, 50 eq.) were prepared and quickly added to the solution of DBB while the flask was rapidly purged with argon. The mixture was sonicated for 5 min, then cooled to −78°C. A solution of 200 mg allylthioether **1** (0.67 mmol, 1 eq.) in 1 mL THF was added to the preformed solution of LiDBB under argon, and the mixture was stirred until the original dark green color reappeared; then 146 mg TMSCl (1.34 mmol, 2 eq.) was added. The reaction was maintained at −78°C for an additional 5 min, and the resulting solution was filtered to remove the excess of lithium. The mixture was extracted three times with Et_2O. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated to dryness. Purification of the resulting yellow oily residue by chromatography (hexane) yielded 135 mg of a mixture of structures **2** and **3** in a 8:92 ratio as a colorless oil, in a total yield of 76%, R_f = 0.78 (hexane).



Reference 20.

A 0.2 M solution of LiDBB in dry THF was prepared according to the reported procedure.[3k] The phenylthioacetal (200 mg, 0.468 mmol) was dissolved in 4 mL dry THF, and to it was added a crystal of 1,10-phenanthroline. The solution was cooled under argon to −78°C, and then *n*-BuLi (2.0 M solution in hexanes) was added dropwise until a permanent red coloration just appeared (typically 50–100 mL was enough to quench any moisture in the reaction). The LiDBB solution (4.0 eq.) was added dropwise to the reaction mixture. Initially, an orange-red color appeared, and addition was continued until a permanent dark green color persisted. After 5 min, the green reaction mixture was treated with 492 mg Me_2SO_4 (370 mL, 3.90 mmol, 6.0 eq.), and then was stirred at −78°C for 1 h. The reaction

mixture was quenched with 10% NH_4OH/saturated NH_4Cl (1:1). The reaction mixture was extracted with CH_2Cl_2 (three times), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by chromatography (SiO_2). Initially, 20% CH_2Cl_2/hexanes was used as the eluent to remove thiophenol and di-*tert*-butylbiphenyl, followed by 3% *tert*-butylmethyl ether/hexanes to afford 106 mg (2*R*,4*S*,5*R*,6*S*)-2,4,5-trimethyl-6-hexyl-1,3-dioxane (0.494 mmol) as a pale yellow oil, in a yield of 76.5%.

Other references related to the Cohen reductive lithiation are cited in the literature.[20]

H. REFERENCES

1. Cohen, T.; Daniewski, W. M. and Weisenfeld, R. B., *Tetrahedron Lett.,* **1978**, 4665.
2. Screttas, C. G. and Micha-Screttas, M., *J. Org. Chem.,* **1978**, *43*, 1064.
3. (a) Deng, K.; Bensari, A. and Cohen, T., *J. Am. Chem. Soc.,* **2002**, *124*, 12106. (b) Cohen, T.; Kreethadumrongdat, T.; Liu, X. J. and Kulkarni, V., *J. Am. Chem. Soc.,* **2001**, *123*, 3478. (c) Cheng, D.; Zhu, S.; Liu, X.; Norton, S. H. and Cohen, T., *J. Am. Chem. Soc.,* **1999**, *121*, 10241. (d) Chen, F. P.; Mudryk, B. and Cohen, T., *Tetrahedron,* **1999**, *55*, 3291. (e) Liu, H.; Shook, C. A.; Thiruvazhi, M.; Jamison, J. A. and Cohen, T., *J. Am. Chem. Soc.,* **1998**, *120*, 605. (f) Cohen, T. and Zhu, S., *Tetrahedron,* **1997**, *53*, 17607. (g) Cohen, T. and Tong, S., *Tetrahedron,* **1997**, *53*, 9487. (h) Cohen, T.; Zhang, B. and Cherkauskas, J. P., *Tetrahedron,* **1994**, *50*, 11569. (i) Chen, F.; Mudryk, B. and Cohen, T., *Tetrahedron,* **1994**, *50*, 12793. (j) Mudryk, B. and Cohen, T., *J. Am. Chem. Soc.,* **1993**, *115*, 3855. (k) Mudryk, B. and Cohen, T., *Org. Synth.,* **1993**, *72*, 173. (l) Cherkauskas, J. P. and Cohen, T., *J. Org. Chem.,* **1992**, *57*, 6. (m) Mudryk, B. and Cohen, T., *J. Am. Chem. Soc.,* **1991**, *113*, 1866. (n) Mudryk, B. and Cohen, T., *J. Org. Chem.,* **1991**, *56*, 5760. (o) Cohen, T. and Doubleday, M. D., *J. Org. Chem.,* **1990**, *55*, 4784. (p) Cohen, T.; Jeong, I.-H.; Mudryk, B.; Bhupathy, M. and Awad, M. M. A., *J. Org. Chem.,* **1990**, *55*, 1528. (q) Mudryk, B. and Cohen, T., *J. Org. Chem.,* **1989**, *54*, 5657. (r) Cohen, T. and Bhupathy, M., *Acc. Chem. Res.,* **1989**, *22*, 152. (s) Cohen, T. and Lin, M.-T., *J. Am. Chem. Soc.,* **1984**, *106*, 1130. (t) Cohen, T. and Matz, J. R., *J. Am. Chem. Soc.,* **1980**, 102,6900. (u) Cohen, T. and Matz, J. R., *Synth. Commun.,* **1980**, *10*, 311. (v) Cohen, T. and Weisenfeld, R. B., *J. Org. Chem.,* **1979**, *4*4, 3601.
4. Broka, C. A. and Shen, T., *J. Am. Chem. Soc.,* **1989**, *111*, 2981.
5. Azzena, U.; Melloni, G.; Pisano, L. and Sechi, B., *Tetrahedron Lett.,* **1994**, *35*, 6759.
6. (a) Azzena, U.; Demartis, S.; Pilo, L. and Piras, E., *Tetrahedron,* **2000**, *56*, 8375. (b) Azzena, U.; Demartis, S. and Melloni, G., *J. Org. Chem.,* **1996**, *61*, 3. (c) Ireland, R. E. and Smith, M. G., *J. Am. Chem. Soc.,* **1988**, *110*, 854. (d) Lansbury, P. T. and Caridi, F. J., *J. Chem. Soc., Chem. Commun.,* **1970**, 714. (e) Eisch, J. J. and Jacobs, A. M., *J. Org. Chem.,* **1963**, *28*, 2145.
7. Block, E.; Guo, C.; Thiruvazhi, M. and Toscano, P. J., *J. Am. Chem. Soc.,* **1994**, 116, 9403
8. (a) Karaman, R. and Fry, J. L., *Tetrahedron Lett.,* **1989**, *30*, 6267. (b) Karaman, R. and Fry, J. L., *Tetrahedron Lett.,* **1989**, *30*, 4935.
9. (a) Behnke, D.; Hennig, L.; Findeisen, M.; Welzel, P.; Müller, D.; Thormann, M. and Hofmann, H.-J., *Tetrahedron,* **2000**, *56*, 1081. (b) Falvello, L. R.; Foubelo, F.; Soler, T. and Yus, M., *Tetrahedron: Asymmetry,* **2000**, *11*, 2063. (c) Bartmann, E., *Angew. Chem. Int. Ed. Engl.,* **1986**, *25*, 653.
10. Rawal, V. H.; Dufour, C. and Iwasa, S., *Tetrahedron Lett.,* **1995**, 19.
11. (a) Buckmelter, A. J.; Powers, J. P. and Rychnovsky, S. D., *J. Am. Chem. Soc.,* **1998**, 120, 5589. (b) Zeller, E.; Sajus, H. and Grierson, D. S., *Synlett,* **1991**, 44.

12. (a) Grieco, P. A. and Dai Y., *J. Am. Chem. Soc.,* **1998**, *120*, 5128. (b) Schultz, D. A.; Boal, A. K. and Farmer, G. T., *J. Org. Chem.,* **1998**, *63*, 9462. (c) Yanagisawa A.; Ogasawara K.; Yasue K. and Yamamoto H., *J. Chem. Soc., Chem. Commun.,* **1996**, *3*, 367. (d) Ley, S. V. and Mio, S., *Synlett,* **1996**, 789. (e) Tamao, K. and Kawachi, A., *Organometallics,* **1995**, *14*, 3108. (f) Kondo, Y.; Murata. N. and Sakamoto, T., *Heterocycles,* **1994**, *37*, 1467. (g) Lesimple, P. and Beau, J.-M., *Bioorg. Med. Chem.,* **1994**, *2*, 1319.

13. (a) Krief, A.; Nazih, A. and Hobe, M., *Tetrahedron Lett.,* **1995**, *36*, 8111. (b) Krief, A. and Nazih, A., *Tetrahedron Lett.,* **1995**, *36*, 8115. (c) Krief, A.; Hobe, M.; Badaoui, E.; Bousbaa, J.; Dumont, W. and Nazih, A., *Synlett,* **1993**, 707.

14. (a) Guijarro, D.; Guillena, G.; Mancheno, B. and Yus, M., *Tetrahedron,* **1994**, *50*, 3427. (b) Guijarry, D.; Mancheno, B. and Yus, M., *Tetrahedron Lett.,* **1992**, *33*, 5597.

15. (a) Norcross, R. D.; von Matt, P.; Kolb, H. C. and Bellus, D., *Tetrahedron,* **1997**, *53*, 10289. (b) Yu, J.; Cho, H.-S.; Chandrasekhar, S. and Falck, J. R., *Tetrahedron Lett.,* **1994**, *35*, 5437. (c) Yu, J.; Cho, H.-S. and Falck, J. R., *J. Org. Chem.,* **1993**, *58*, 5892. (d) Beau, J.-M. and Sinay, P., *Tetrahedron Lett.,* **1985**, *26*, 6185.

16. (a) Dvorak, C. A. and Rawal, V. H., *J. Chem. Soc., Chem. Commun.,* **1997**, 2381. (b) Oikawa, M.; Oikawa, H. and Ichihara, A., *Tetrahedron,* **1995**, *51*, 6237.

17. Streiff, S.; Ribeiro, N. and Désaubry, L., *J. Org. Chem.,* **2004**, *69*, 7592.

18. Rychnovsky, S. D.; Buckmelter, A. J.; Dahanukar, V. H. and Skalitzky, D. J., *J. Org. Chem.,* **1999**, *64*, 6849.

19. Wolckenhauer, S. A. and Rychnovsky, S. D., *Org. Lett.,* **2004**, *6*, 2745.

20. (a) Rychnovsky, S. D., *J. Org. Chem.,* **1989**, *54*, 4982. (b) Rychnovsky, S. D. and Mickus, D. E., *Tetrahedron Lett.,* **1989**, *30*, 3011. (c) Boeckman, R. K.; Enholm, E. J.; Demko, D. M. and Charette, A. B., *J. Org. Chem.,* **1986**, *51*, 4743.

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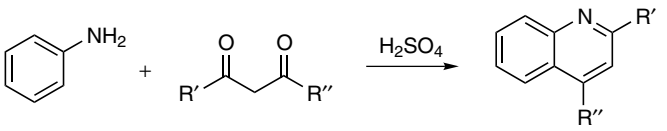
Combes Quinoline Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Combes in 1888.[1] It is the synthesis of quinolines by the condensation of primary aromatic amines with acetoacetone or other β-diketones followed by cyclization in the presence of sulfuric acid. This method provides a rapid access to the 2,4-substituted quinoline skeleton;[2] but, it suffers from low regioselectivity,[3] such as in the case of *meta*-substituted anilines with two different *ortho* positions for ring closure. It was found that polyphosphoric acid is a better catalyst than sulfuric acid for the cyclization,[4] and the factors that affect this reaction have been reviewed by Roberts and Turner.[5]

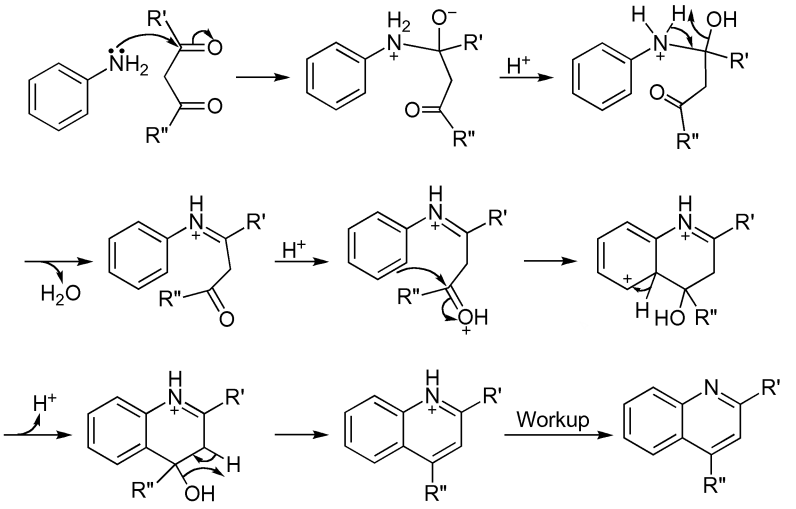
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

This reaction involves a condensation between aniline and β-diketone followed by an acid-catalyzed cyclization, as displayed here.

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang



D. MODIFICATION

This reaction has been modified to use polyphosphoric acid as the acidic catalyst to improve the overall yield.[4] In addition, Vilsmeier reagent can be applied to the cyclization step.[6]

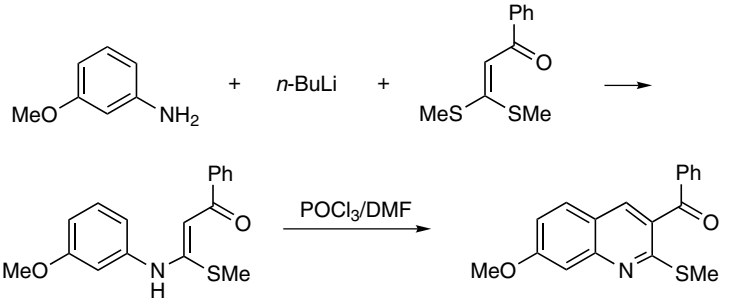
E. APPLICATIONS

This reaction has a general application in the preparation of quinoline derivatives, especially for those quinolines with substituents at position 2 and/or 5.

F. RELATED REACTIONS

This reaction is related to the *Camps Reaction, Conrad-Limpach Quinoline Synthesis, Doebner-Miller Reaction, Gould-Jacobs Quinoline Synthesis, Niementowski Reaction,* and *Skraup Reaction*.

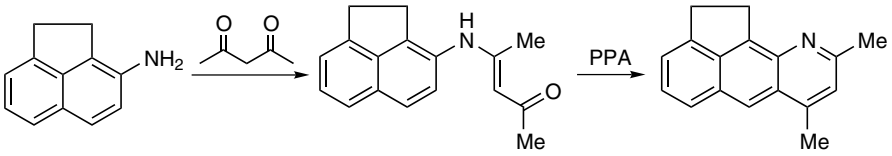
G. CITED EXPERIMENTAL EXAMPLES



Reference 6.

To a stirred solution of 10 mmol *m*-methoxyaniline in 50 mL dry THF was added 5.2 mL *n*-BuLi (12 mmol) under nitrogen atmosphere over a period of 10 min at −78°C. The reaction mixture was brought to room temperature and was further stirred for 45 min. A solution of 10 mmol α-oxoketene-*S*,*S*-acetal in 25 mL dry THF was added at 0°C, and the reaction mixture was further stirred at room temperature for 2 h. It was refluxed for 18–20 h to complete the reaction, then cooled, poured into 100 mL of saturated NH_4Cl solution, and extracted with $CHCl_3$ (2 × 50 mL). The combined extracts were washed with water (2 × 50 mL) and brine (50 mL), dried over Na_2SO_4, and evaporated to give crude 3-(3-methoxyanilino)-3-methylthio-1-phenylprop-2-en-1-one, which was purified by column chromatography over silica gel using hexanes/EtOAc as the eluent. A total of 2.45 g of product was obtained, in a yield of 82%. This compound can be further purified by recrystallization from $CHCl_3$/hexane to afford light yellow crystals, m.p. 75–76°C, $R_f = 0.59$ (9:1 hexanes/EtOAc).

A solution of 5 mmol α-oxoketene-*N*,*S*-acetal in 5 mL DMF (or DMA, $Cl_2CHCHCl_2$) was added dropwise at 0°C to a solution of Vilsmeier reagent prepared from 0.7 mL $POCl_3$ (7.5 mmol) and 7.5 mmol DMF or DMA at 0–5°C under nitrogen atmosphere. After further stirring for 5–6 h at room temperature, the reaction mixture was heated to 80–90°C for 3–4 h (monitored by TLC). It was then cooled, poured into 100 mL ice cold saturated $NaHCO_3$ solution, and extracted with chloroform (4 × 50 mL). The combined organic extracts were washed with water (3 × 50 mL) and 25 mL brine and dried over Na_2SO_4; the solvent was evaporated under reduced pressure to afford crude 3-benzoyl-7-methoxy-2-methylthioquinoline, which was purified by column chromatography over silica gel using hexanes/EtOAc as the eluent; 1.25 g quinoline was obtained, in a yield of 81%. This quinoline can be further purified by recrystallization from $CHCl_3$/hexane to afford a light yellow solid, m.p. 105–106°C, $R_f = 0.60$ (9:1 hexanes/EtOAc).



Reference 4.

3-Aminoacenaphthene (8.68 g, 51.3 mmol) and 13 mL 2,4-pentanedione (127 mmol) were mixed and heated for 16 h at 100°C. The mixture was cooled, and the product was recrystallized from benzene-hexanes to give 10.0 g 3-[(l-methyl-3-oxobut-l-enyl)amino]acenaphthene as light brown crystals (39.8 mmol), in a yield of 78%, m.p. 150–152°C.

The enamine (0.45 g, 1.79 mmol) was mixed in a Pyrex tube with 10 g polyphosphoric acid. The mixture was heated gradually to 160–170°C with stirring. After all of the solid had dissolved (∼ 2 h), the tube was cooled, water was added, and the reaction mixture was quenched with excess aqueous NaOH. The resulting mixture was extracted with 200 mL ether, and the extract was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave 0.42 g pure yellow-orange 7,9-dimethyl-l0-azaaceanthrene, in a yield of 100%, m.p. 164–166°C.

Other references related to the Combes quinoline synthesis are cited in the literature.[7]

H. REFERENCES

1. (a) Combes, A., *Compt. Rend.,* **1888**, *106*, 142. (b) Combes, A., *Compt. Rend.,* **1888**, *106*, 1536. (c) Combes, A., *Bull. Soc. Chim. Fr.,* **1888**, *49*, 89. (d) Combes, A., *Bull. Soc. Chim. Fr.,* **1888**, *49*, 91.
2. Misani, F. and Bogert, M. T., *J. Org. Chem.,* **1946**, 11, 458.
3. Jiang, B. and Si, Y.-G., *J. Org. Chem.,* **2002**, *67*, 9449.
4. West, A. P.; Engen, D. V. and Pascal, R. A., *J. Org. Chem.,* **1992**, *57*, 784.
5. (a) Roberts, E. and Turner, E. E., *J. Chem. Soc.,* **1927**, 1832. (b) Roberts, E. and Turner, E. E., *J. Chem. Soc.,* **1927**, 1840.
6. Mahata, P. K.; Venkatesh, C.; Syam Kumar, U. K.; Ila, H. and Junjappa, H., *J. Org. Chem.,* **2003**, *68*, 3966.
7. (a) Gilchrust, T. L., *Heterocyclic Chemistry*, 3rd ed., Addison-Wesley Longman, Essex, **1997**, pp. 158–164. (b) Jones, G., "Pyridines and their Benzo Derivatives: Synthesis" in *Comprehensive Heterocyclic Chemistry II,* ed. Katritzky, A. R.; Rees, C. W. and Scriven, E. F. V., Pergamon Press: Oxford, **1996**, *5*, p. 167. (c) Claret, P. A., *Quinolines*, in *Comprehensive Organic Chemistry, The Synthesis and Reactions of Organic Compounds,* ed. Sammes, P. G., Pergamon Press: Oxford, **1979**, *4*, pp. 155–203. (d) Born, J., *J. Org. Chem.,* **1972**, *37*, 3952. (e) Lloyd, D. and Gagen, J. M. F., *J. Chem. Soc.*, *C*, **1970**, 2488. (f) Johnson, W. S. and Matthews, F. J., *J. Am. Chem. Soc.,* **1944**, *66*, 210. (g) Bergstrom, F. W., *Chem. Rev.,* **1944**, *35*, 156. (h) Manske, R. H. F., *Chem. Rev.,* **1942**, *30*, 113. (i) Axe, W. N. and Bailey, J. R., *J. Am. Chem. Soc.,* **1938**, *60*, 3028. (j) Besthorn, E.; Banzhof, E. and Jaeglé, G., *Ber.,* **1894**, *27*, 3035. (k) Besthorn, E. and Jaeglé, G., *Ber.,* **1894**, *27*, 907.

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Conrad-Limpach Quinoline Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Conrad and Limpach in 1887.[1] It is the synthesis of 4-quinolones, which often isomerize (or aromatize) to 4-hydroxyquinolines through the thermal condensation of primary aromatic amines with the carbonyl group of β-ketoesters followed by the cyclization of Schiff base intermediates (alkyl β-arylaminocrotonates). Therefore, it is known as the Conrad-Limpach quinoline synthesis[2] or Conrad-Limpach synthesis.[3] However, during the condensation of primary aromatic amines with β-ketoesters, the amino group might also react at the ester group of β-ketoesters to form β-ketoacetamide intermediates (isomerize to ketoacetanilides), which cyclize to 2-hydroxyquinolines; this type of conversion was initially discovered on Knorr in 1886.[4] Therefore, the Conrad-Limpach quinoline synthesis sometimes is also referred to as Conrad-Limpach-Knorr quinolone synthesis,[5] Conrad-Limpach-Knorr reaction,[6] and Knorr-Conrad-Limpach method.[7] Nevertheless, there are still some distinctive differences between these two reactions. For example, β-ketoesters are used in Conrad-Limpach quinoline synthesis, whereas ethyl acetoacetate is mostly used in the *Knorr Quinoline Synthesis*, in addition, higher temperature of condensation results in the Knorr product, whereas moderate or lower temperatures lead to the Conrad-Limpach product.[6] Furthermore, the presence of iodine or an acidic catalyst is often necessary for the Conrad-Limpach quinoline synthesis.[6] In this reaction, the condensed intermediates have seldom been isolated and characterized because, in most cases, these intermediates are viscous oils that are directly subjected to thermal cyclization.[8] During the cyclization, the protonated carbonyl group will function as an electrophile, whereas the aromatic ring acts as a nucleophile;[9] if an

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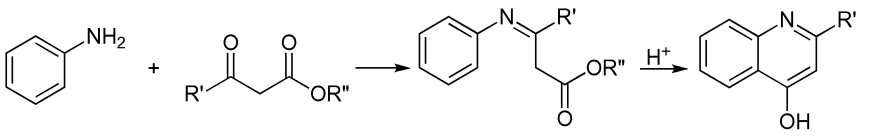
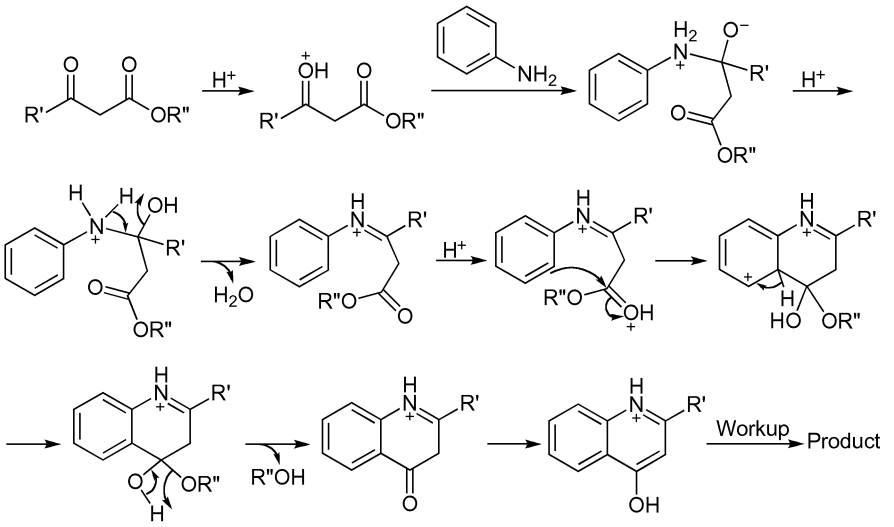
electron-withdrawing group exists on the aromatic ring, such as a nitro group, then the cyclization is difficult.[6,7,10] Similarly, as a poor nucleophile, 3-aminopyridine is difficult to react with β-ketoesters to form naphthyridine;[9] it is surprising, however, that 2,6-diaminopyridine reacts conveniently to afford naphthyridine even at room temperature,[11] this is likely attributed to the distribution of an electron cloud to the pyridyl ring from the two strong electron-donating amino groups.

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Displayed below is a general illustration of the reaction.



D. MODIFICATION

This reaction has been modified for the use of acetoacetonitriles[12] and Meldrum's acid[13] instead of β-ketoesters to afford 4-hydroxyquinolines.

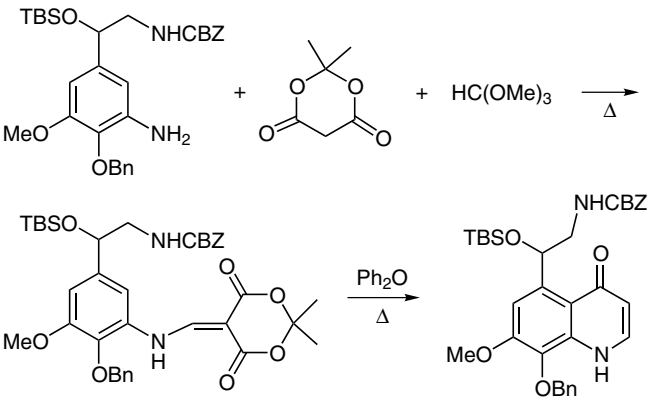
E. APPLICATIONS

This reaction is generally good for the synthesis of 4-hydroxyquinolines and 4-quinolones.

F. RELATED REACTIONS

This reaction is related to the *Camps Reaction, Combes Quinoline Synthesis, Doebner-Miller Reaction, Gould-Jacobs Quinoline Synthesis, Niementowski Reaction* and *Skraup Reaction*.

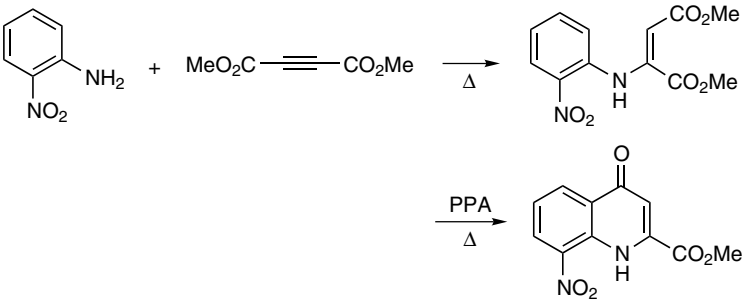
G. CITED EXPERIMENTAL EXAMPLES



Reference 13.

Meldrum's acid (0.413 g, 2.87 mmol) was refluxed under nitrogen in 35 mL trimethyl orthoformate for 2 h. *O*-Benzyl *N*-2-(5-amino-4-benzyloxy-3-methoxyphenyl)-2-(*tert*-butyldimethylsilyloxy)ethyl carbamate (1.14 g, 2.39 mmol) dissolved in 15 mL trimethyl orthoformate, was added to the solution of Meldrum's acid, and the mixture was refluxed for 4 h. The solvent was removed in vacuo and the residue was subjected to flash chromatography (2:1 hexane/EtOAc) to give 1.00 g 5-[5-[2-(benzyloxycarbonylamino)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2-benzyloxy-3-methoxyphenylaminomethylene]-2,2-dimethyl-1,3-dioxane-4,6-dione as a white solid, in a yield of 87%, m.p. 110–111°C after recrystallization from EtOAc/hexanes.

To a solution of 100 mL diphenyl ether was added 1.09 g 1,3-dioxane-4,6-dione (1.57 mmol). A stream of nitrogen was passed through the solution for 20 min and the flask was then lowered into a large silicone oil bath preheated to 240°C. The temperature of the bath dropped to 225°C and rose again to 240°C in 5–7 min. The solution was stirred in the bath for a total of 18 min, then removed and allowed to cool. The solvent was removed under vacuum (0.1 mmHg, 110°C). Flash chromatography (1:2 to 6:1 hexanes/EtOAc) gave 0.326 g *O*-benzyl *N*-2-(*tert*-butyldimethylsilyloxy)-2-[8-benzyloxy-7-methoxy-4(1*H*)-quinolinon-5-yl]ethyl carbamate as a tan solid, in a yield of 35%. An analytical sample, m.p. 63–65°C, was obtained by recrystallization from EtOAc/hexanes.



Reference 5.

An equal molar amount (0.02 mol) of *o*-nitroaniline and dimethyl acetylenedicarboxylate was mixed in 100 mL anhydrous methanol and refluxed for 24–48 h. The reaction mixture was cooled in ice, and the precipitated product was removed by filtration. Successive crystal crops were obtained by concentration in vacuo of the mother liquors to give 95% of a *Michael Addition* product, m.p. 130–131°C.

A paste, formed from intimately mixing 2–4 g Michael adduct with 20–30 g polyphosphoric acid, was heated with stirring at 140–180°C for 30 min. Considerable foaming resulted, and the mixture turned progressively darker. After cooling to 100°C, the viscous solution was poured into a mixture of chopped ice and water and scratched with a glass rod to induce crystallization. If allowed to stand at ice bath temperatures for 5–10 h before filtration, the filterability of the product was improved. The solid, removed by vacuum filtration, was air dried and recrystallized from methanol. The sample was purified by sublimation at 0.5 mmHg at 20°C under its melting point, the yield was 47%, m.p. 195°C.

Other references related to the Conrad-Limpach quinoline synthesis are cited in the literature.[14]

H. REFERENCES

1. (a) Conrad, M. and Limpach, L., *Ber.,* **1887**, *20*, 944. (b) Conrad, M. and Limpach, L., *Ber.,* **1887**, *20*, 948.
2. Kulkarni, S. A.; Thakor, V. M. and Shah, R. C., *J. Indian Chem. Soc.*, **1951**, *28*, 688.
3. (a) Egri, J.; Halmos, J. and Rakoczi, J., *Acta Chim. Acad. Sci. Hungaricae,* **1973**, *78*, 217. (b) Steck, E. A.; Hallock, L. L.; Holland, A. J. and Fletcher, L. T., *J. Am. Chem. Soc.,* **1948**, *70*, 1012.
4. (a) Knorr, L., *Ann.,* **1886**, *236*, 69. (b) Knorr, L., *Ann.,* **1888**, *245*, 357. (c) Knorr, L., *Ann.,* **1888**, *245*, 378.
5. Heindel, N. D.; Bechara, I. S.; Lemke, T. F. and Fish, V. B., *J. Org. Chem.,* **1967**, *32*, 4155.
6. Misani, F. and Bogert, M. T., *J. Org. Chem.,* **1945**, *10*, 347.
7. Carmack, M. and Von, I., *J. Am. Chem. Soc.,* **1946**, *68*, 1809.
8. Heindel, N. D.; Bechara, I. S.; Kennewell, P. D.; Molnar, J.; Ohnmacht, C. J.; Lemke, S. M. and Lemke, T. F., *J. Med. Chem.,* **1968**, *11*, 1218.
9. Hauser, C. R. and Reynolds, G. A., *J. Org. Chem.,* **1950**, *15*, 1224.
10. Coffey, S.; Thomson, J. K. and Wilson, E. J., *J. Chem. Soc.,* **1936**, 856.

11. Hauser, C. R. and Weiss, M. J., *J. Org. Chem.,* **1949**, *14*, 453.
12. Hauser, C. R. and Murray, J. G., *J. Am. Chem. Soc.,* **1955**, *77*, 2851.
13. Walz, A. J. and Sundberg, R. J., *J. Org. Chem.,* **2000**, *65*, 8001.
14. (a) Reddy, B. and Reddy, V., *Synth. Commun.,* **1999**, *29*, 2789. (b) Ouar, M. E.; Knouzi, N. and Hamelin, J., *J. Chem. Res. (S)*, **1998**, 92. (c) Cassis, R.; Tapia, R. and Valderrama, J. A., *Synth. Commun,.* **1985**, *15*, 125. (d) Moore, J. A. and Mitchell, T. D., *J. Polym. Chem.,* **1980**, *18*, 3029. (e) Jones, G., "Quinolines", in *The Chemistry of Heterocyclic Compounds,* ed. Jones, G., John Wiley & Sons, New York, **1977**, *32*, Part 1, pp. 137–151. (f) Perche, J.-C. and Saint-Ruf, G., *J. Heterocycl. Chem.* **1974**, *11*, 93. (g) Madhav, R.; Dufresne, R. and Southwick, P., *J. Heterocycl. Chem.,* **1973**, *10*, 225. (h) Werner, W., *Tetrahedron,* **1969**, *25*, 255. (i) Heidel N. D. and Ohnmacht C. J., *J. Heterocycl. Chem.*, **1968**, *5*, 869. (j) Reitsema, R. H., *Chem. Rev.,* **1948**, *43*, 43. (k) Manske, R. H. F., *Chem. Rev.* **1942**, *30*, 113. (l) Limpach, L., *Ber.,* **1931**, *64*, 970. (m) Conrad, M. and Limpach, L., *Ber.,* **1891**, *24*, 2990.

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Cope Elimination
(Cope Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Wolffenstein in 1898.[1] It is the synthesis of olefins from thermal decomposition (i.e., pyrolysis) of *N*-oxides of tertiary amines. However, this reaction did not drawn much attention until 1949, when Cope extensively explored its scope and mechanism.[2] Therefore, this reaction is referred to as the Cope-Mamlock-Wolffenstein hydroxylamine elimination,[3] but is more generally known as the Cope elimination[4] or Cope reaction.[3,5] On the other hand, the reversal process of this reaction (e.g., the addition of hydroxylamine to double bond) is generally referred to as the reverse Cope elimination[6] or *retro*-Cope elimination.[7] This reaction is cleanly first order in substrate,[4o] and undergoes an intramolecular five-membered cyclic synchronous transition state,[4g] in which hydrogen and nitrogen are coplanar.[4p] An isotopic labeling study indicates that both the C-H and the C-N bond cleavage may be well advanced at the transition state, with considerable development of double-bond character.[4m] The pyrolysis of tertiary amine oxides occurs in the temperature range of 120–150°C without any solvent present;[4o] however, this pyrolysis can occur under extremely mild conditions and even at room temperature when dimethyl sulfoxide is used as a solvent.[4o] The order of the eliminating alkyl group after correction for the number of available β-hydrogen atoms is *p*-phenylethyl >> *t*-butyl > isobutyl ~ isopropyl ~ *n*-decyl > *n*-butyl > isoamyl > ethyl > *n*-propyl.[2g] Of particular preparative importance is that this reaction is free from side reactions compared to other eliminations,[4p] and it produces medium-size *trans* olefins during the elimination[2i,2j] (with same exceptions[4m]), especially for the highly strained bridge double bond.[4l] However, the pyrolysis of allyldialkylamine oxides and benzyldimethylamine oxide at temperatures of 80–165°C, result in the migration of the allyl and benzyl groups from the nitrogen to the oxygen atom, instead of an elimination.[9] This reaction has also been studied theoretically.[4g,10]

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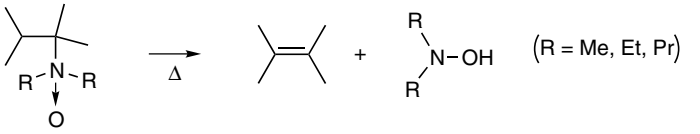
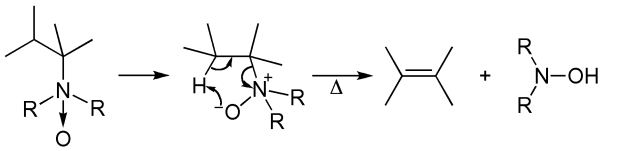
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

This reaction involves an intramolecular five-membered cyclic synchronous transition state, as displayed below.



D. MODIFICATION

This reaction has been modified to occur at extremely mild conditions in a solvent of DMSO.[4o] In addition, the *sila*-Cope elimination has recently been developed.[11]

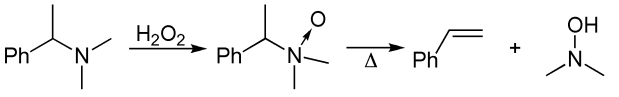
E. APPLICATIONS

This reaction has general application in the preparation of olefins.

F. RELATED REACTIONS

This reaction is related to the *Bamford-Stevens Reaction, Chugaev Reaction, Hofmann Elimination* and *Ramberg-Bäcklund Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



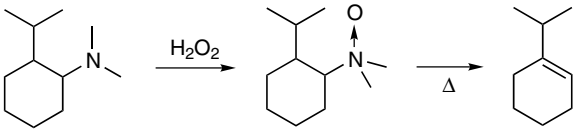
Reference 2k.

N,*N*-Dimethyl-(α-phenylethy1)-amine (11.0 g) was stirred with 18.3 g 35% aqueous hydrogen peroxide (150% excess) for 11 h at room temperature. The excess hydrogen peroxide was decomposed by stirring the mixture with 8 cm^2 of clean platinum foil until

the evolution of oxygen ceased. Most of the water was removed by distillation at 35 mmHg pressure and a bath temperature of 45–55°C; the distillate and material that condensed in a trap cooled with a mixture of dry ice and trichloroethylene in the vacuum line were saved. The residual syrup was diluted with 25 mL absolute ethanol and concentrated again under reduced pressure while nitrogen was admitted through a capillary ebulliator inlet. The process was repeated twice to remove as much water as possible. The amine oxide remained as a viscous syrup, which from its odor contained a small amount of styrene.

A 100-mL round-bottomed flask fitted with a capillary nitrogen inlet and containing the tertiary amine oxide was connected by a large-diameter tube to a condenser set for distillation, which led to two receivers in series cooled in a mixture of dry ice and trichloroethylene. The system was evacuated to 5 mmHg, and the flask was immersed in an oil bath at 85°C. The bath temperature was slowly raised to 115°C over 35 min, at which time almost all of the material had distilled. The bath temperature was raised to 150°C to complete the distillation; 0.35 g of a tarry residue remained. The distillate was combined with the distillate obtained in concentration of the amine oxide solution, pentane was added as a solvent, and the mixture was washed with dilute hydrochloric acid. The acid solution was extracted with pentane, and the pentane solutions were washed with water until neutral. The combined aqueous layers containing hydrochloric acid were concentrated under reduced pressure to a crystalline residue, which was dried by adding absolute alcohol, reconcentrating under reduced pressure, and placing in a vacuum desiccator over phosphorus pentoxide. The yield of *N*,*N*-dimethylhydroxylamine hydrochloride was 6.73 g (94%), m.p. 101–104°C (sealed capillary).

The pentane solution containing the neutral product was dried over magnesium sulfate and concentrated at atmospheric pressure, after the addition of a crystal of picric acid as a polymerization inhibitor. Distillation of the residue afforded 5.34 g styrene, in a yield of 70%, b.p. 82–83°C at 102 mmHg.



Reference 2d.

N,*N*-Dimethyl-D-neomenthylamine was oxidized, and the resulting amine oxide (5.85 g) was pyrolyzed in a round-bottomed flask equipped with a capillary nitrogen inlet and connected through a Vigreux column to two traps in series and cooled in a dry ice acetone mixture. The flask was heated to 90–130°C (7 mmHg) for 30 min and raised to 160°C. The contents of the traps were allowed to melt and then were combined and diluted with 40 mL pentane. The pentane solution was extracted with hydrochloric acid, which when treated with excess sodium hydroxide solution, gave 0.54 g *N*,*N*-dimethyl-D-neomenthylamine (9% recovered), b.p., 87–92°C (10 mmHg). After being washed and then evaporated, the pentane solution yielded 3.38 g menthene in a yield of 77%, b.p., 97–98°C (80 mmHg). (*Note*: The procedure was completely reorganized according to the described experiment.)

Other references related to the Cope elimination are cited in the literature.[12]

H. REFERENCES

1. (a) Wernick, W. and Wolffenstein, R., *Ber.,* **1898**, *31*, 1553. (b) Mamlock, L. and Wolffenstein, R., *Ber.,* **1900**, *33*, 159.
2. (a) Cope, A. C. and Trumbull, E. R., *Org. React.,* **1960**, *11*, 317. (b) Cope, A. C.; Ciganek, E.; Howell, C. F. and Schweizer, E.E., *J. Am. Chem. Soc.*, **1960**, *82*, 4663. (c) Cope, A. C. and LeBel, N. A., *J. Am. Chem. Soc.*, **1960**, *82*, 4656. (d) Cope, A. C. and Acton, E. M., *J. Am. Chem. Soc.*, **1958**, *80*, 355. (e) Cope, A. C. and Bumgardner, C. L., *J. Am. Chem. Soc.*, **1957**, *79*, 960. (f) Cope, A. C.; Bumgardner, C. L. and Schweizer, E. E., *J. Am. Chem. Soc.*, **1957**, *79*, 4729. (g) Cope, A. C.; Lebel, N. A.; Lee, H. H. and Moore, W. R., *J. Am. Chem. Soc.*, **1957**, *79*, 4720. (h) Cope, A. C. and Lee, H.-H., *J. Am. Chem. Soc.,* **1957**, *79*, 964. (i) Cope, A. C.; McLean, D. C. and Nelson, N. A., *J. Am. Chem. Soc.*, **1955**, *77*, 1628. (j) Cope, A. C.; Pike, R. A. and Spencer, C. F., *J. Am. Chem. Soc.*, **1953**, *75*, 3212. (k) Cope, A. C.; Foster, T. T. and Towle, P. H., *J. Am. Chem. Soc.*, **1949**, *71*, 3929.
3. Weller, S. W.; Choksi, B. C. and Sanyal, S. K., *Ind. Eng. Chem. Prod. Res. Dev.,* **1971**, *10*, 38.
4. (a) Ellis, G. L.; O'Neil, I. A.; Ramos, V. E.; Kalindjian, S. B.; Chorlton, A. P. and Tapolczay, D. J., *Tetrahedron Lett*., **2007**, *48*, 1687. (b) Acevedo, O. and Jorgensen, W. L., *J. Am. Chem. Soc.,* **2006**, *128*, 6141. (c) Griffin, R. J.; Henderson, A.; Curtin, N. J.; Echalier, A.; Endicott, J. A.; Hardcastle, I. R.; Newell, D. R.; Noble, M. E. M.; Wang, L.-Z. and Golding, B. T., *J. Am. Chem. Soc.,* **2006**, *128*, 6012. (d) O'Neil, I. A.; Ramos, V. E.; Ellis, G. L.; Cleator, E.; Chorlton, A. P.; Tapolczay, D. J. and Kalindjian, S. B., *Tetrahedron Lett*., **2004**, *45*, 3659. (e) Bagley, M. C. and Tovey, J., *Tetrahedron Lett*., **2001**, *42*, 351. (f) Clancy, S. F.; Thies, M.; Paradies, H.; Thies, M. and Paradies, H., *Chem. Commun.,* **1997**, 2035. (g) Komaromi, I. and Tronchet, J. M. J., *J. Phys. Chem. A,* **1997**, *101*, 3554. (h) Ciganek, E.; Read, J. M. and Calabrese, J. C., *J. Org. Chem.,* **1995**, *60*, 5795. (i) Woolhouse, A. D.; Gainsford, G. J. and Crump, D. R., *J. Heterocycl. Chem.,* **1993**, *30*, 873. (j) Leis, H. J. and Gleispach, H., *J. Chromatography,* **1989**, *494*, 324. (k) Sato, T.; Ito, O.; Mori, S. and Otsu, T., *J. Poly. Sci., Poly. Chem. Ed.,* **1984**, *22*, 1661. (l) Adams, B. L. and Kovacic, P., *J. Am. Chem. Soc.,* **1974**, *96*, 7014. (m) Bach, R. D.; Andrzejewski, D. and Dusold, L. R., *J. Org. Chem.,* **1973**, *38*, 1742. (n) Krupicka, J. and Zavada, J., *Coll. Czech. Chem. Commun.,* **1967**, *32*, 2797. (o) Cram, D. J.; Sahyun, M. R. V. and Knox, G. R., *J. Am. Chem. Soc.,* **1962**, *84*, 1734. (p) DePuy, C. H. and King, R. W., *Chem. Rev.,* **1960**, *60*, 431.
5. (a) Wright, D. R.; Sims, L. B. and Fry, A., *J. Am. Chem. Soc.,* **1983**, *105*, 3714. (b) Zavada, J.; Pankova, M. and Svoboda, M., *Coll. Czech. Chem. Commun.,* **1973**, *38*, 2102.
6. (a) Henry, N. and O'Neil, I. A., *Tetrahedron Lett*., **2007**, *48*, 1691. (b) Ellis, G. L.; O'Neil, I. A.; Ramos, V. E.; Cleator, E.; Kalindjian, S. B.; Chorlton, A. P. and Tapolczay, D. J., *Tetrahedron Lett*., **2007**, *48*, 1683. (c) O'Neil, I. A.; Cleator, E.; Elena Ramos, V.; Chorlton, A. P. and Tapolczay, D. J., *Tetrahedron Lett*., **2004**, *45*, 3655. (d) Dumez, E.; Faure, R. and Dulcere, J.-P., *Eur. J. Org. Chem.,* **2001**, 2577. (e) Gravestock, M. B.; Knight, D. W.; Malik, K. M. A. and Thornton, S. R., *J. Chem. Soc., Perkin Trans. I,* **2000**, 3292. (f) Alcaide, B. and Saez, E., *Tetrahedron Lett*., **2000**, *41*, 1647. (g) Knight, D. W. and Salter, R., *Tetrahedron Lett*., **1999**, *40*, 5915. (h) Hanrahan, J. R. and Knight, D. W., *Chem. Commun.,* **1998**, 2231. (i) Wheildon, A. R.; Knight, D. W. and Leese, M. P., *Tetrahedron Lett*., **1997**, *38*, 8553. (j) Gallagher, B. M. and Pearson, W. H., *Chemtracts: Org. Chem*., **1996**, *9*, 126. (k) Ciganek, E., *J. Org. Chem.,* **1995**, *60*, 5803. (l) Ciganek, E., *J. Org. Chem.,* **1990**, *55*, 3007.
7. Gravestock, M. B.; Knight, D. W. and Thornton, S. R., *J. Chem. Soc., Chem. Commun.,* **1993**, 169.
8. Adams, B. L. and Kovacic, P., *J. Am. Chem. Soc.,* **1974**, *96*, 7014.
9. Cope, A. C. and Towle, P. H., *J. Am. Chem. Soc.,* **1949**, *71*, 3423.
10. Bach, R. D.; Gonzales, C.; Andres, J. L. and Schlegel, H. B., *J. Org. Chem.,* **1995**, *60*, 4653.

11. (a) Vidal, T.; Magnier, E. and Langlois, Y., *Tetrahedron*, **1998**, *54*, 5959. (b) Langlois, Y.; Konopski, L.; Bac, N. V.; Chiaroni, A. and Riche, C., *Tetrahedron Lett*., **1990**, *31*, 1865. (c) Fall, Y.; Nguyen V. B. and Langlois, Y., *Tetrahedron Lett*., **1986**, *27*, 3611.

12. (a) Bach, R. D. and Braden, M. L., *J. Org. Chem.,* **1991**, *56*, 7194. (b) Astles, P. C.; Mortlock, S. V. and Thomas, E. J., "The Cope Elimination, Sulfoxide Elimination and Related Thermal Reactions" in *Comprehensive Organic Synthesis* ed. Trost, B. M. and Fleming, I., Pergamon Press: Oxford, **1991**, *6*, p. 1011. (c) Kwart, H. and Brechbiel, M., *J. Am. Chem. Soc.,* **1981**, *103*, 4650. (d) Chiao, W.-B. and Saunders, W. H., *J. Am. Chem. Soc.,* **1978**, *100*, 2802. (e) Siegl, W. O. and Johnson, C. R., *J. Org. Chem.*, **1970**, *35*, 3657. (f) Ohloff, G. and Lienhard, B., *Helv. Chim. Acta*, **1965**, *48*, 182. (g) Caserio, F. F.; Parker, S. H.; Piccolini, R. and Roberts, J. D., *J. Am. Chem. Soc.,* **1958**, *80*, 5507. (h) Cram, D. J. and McCarty, J. E., *J. Am. Chem. Soc.,* **1954**, *76*, 5740. (i) Jones, L. W., *J. Am. Chem. Soc.,* **1914**, *36*, 1268.

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Cope Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Cope and Hardy in 1940.[1] It is the thermal isomerization of a 1,5-diene through the highly stereoselective [3,3] sigmatropic rearrangement leading to a more stable 1,5-diene and is generally known as the Cope rearrangement.[2] From 1940, the Cope rearrangement and its variants have been extensively explored, and the comparable variants include the *amino*-Cope rearrangement,[3] *aza*-Cope rearrangement[4] (or *aza*-Cope reaction[5]), *diaza*-Cope rearrangement,[6] *oxaza*-Cope rearrangement,[7] *oxonia*-Cope rearrangement,[8] *oxy*-Cope rearrangement[9] (or *oxa*-Cope rearrangement[10]), *sila*-Cope rearrangement[11] (or *silyoxy*[12] or *silylox*-Cope rearrangement[13]), and *thio*-Cope rearrangement.[14] On the one hand, the Cope rearrangement can be either thermally[15] or photochemically[16] activated; on the other hand, it also can be catalyzed by acid,[8e,17] antibody,[18] and enzyme[19] or mediated via an indium atom.[9o] For this popular rearrangement, a few mechanisms have been proposed; a stepwise mechanism[20] (or two-step mechanism[20b,21]), a mechanism with a diradical character[22] (via dissociation into a pair of resonance stabilized allyl radicals followed by ring closure[21]), and a concerted mechanism.[8e,23] Much experimental evidence favors the concerted mechanism, and it has been reported that the stepwise mechanism occurs only in cases with strong radical stabilizing substituents at C2 and C5, such as the reaction of 2,5-diphenyl-1,5-hexadiene;[21] and the mechanism with the diradical character is even less popular.[21] In the Cope rearrangement via the concerted mechanism, the chair-like transition state is favored,[24] and the transition state is not polarized; as a result, no apparent solvent effect has been observed when decane and anisole are used as solvents.[23b] It should be pointed out that besides the reaction in the

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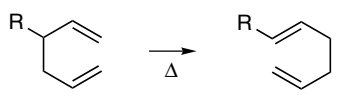
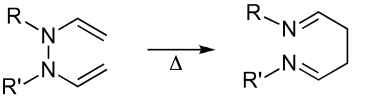
solution phase, the Cope rearrangement can also occur in a vapor phase.[16] Although most of the rearrangements involve the double allylic alternation, single *Allylic Rearrangement* has also been observed,[25] for which the term *oxy*-Cope rearrangement[9] has been proposed. Besides extensive experimental studies, comparable theoretical studies have been carried out.[21,22,26] It is important to note that when a hydroxyl group appears at position 3 of the 1,5-diene, the rearrangement rate is extremely accelerated, especially when such a molecule is treated with a strong base, such as potassium hydride (KH), the reaction rate can be 10^{10}–10^{17} faster than the normal Cope rearrangement.[27] This fast Cope rearrangement is known simply as the *oxy*-Cope rearrangement.[9,15,25] When two hydroxyl groups occur at positions 3 and 4, the rearrangement occurs at a temperature as low as –78°C.[28] The driving force for the neutral or anionic *oxy*-Cope rearrangement is to form an enol or enolate, which can irreversibly tautomerize to the corresponding carbonyl compound. It has been reported that the fast rate for the *oxy*-Cope rearrangement is due to the bond-weakening effect of the anionic alkoxy group on the adjacent C3-C4 bond;[29] as a result, the reaction runs faster when the alkoxy anion is more naked (modulated by the application of a larger counterion and crown ether).[30] In addition, when the unsaturation of 1,5-diene is extended (i.e., more double-bond conjugated to the 1,5-diene), the rearrangement is even faster.[9n] This reaction has been extensively reviewed.[31]

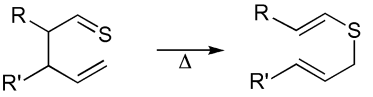
B. GENERAL REACTION SCHEME



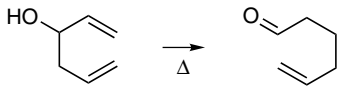
Cope rearrangement.



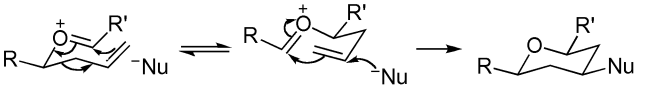
Diaza-Cope rearrangement.



Thia-Cope rearrangement.



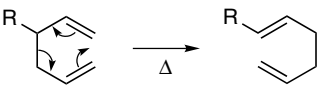
Oxy-Cope rearrangement.



Oxonia-Cope rearrangement.

C. PROPOSED MECHANISMS

In most cases, this reaction involves a concert mechanism, as simply displayed here.



D. MODIFICATION

This reaction is very popular and has been extensively studied and modified. The modifications include the different variants of the Cope rearrangements outlined earlier. In addition, this reaction has been modified to proceed by means of indium metal,[9o] acid,[8e,17] antibody,[18] and enzymes.[19]

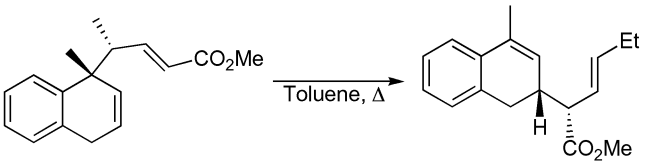
E. APPLICATIONS

This reaction has very broad applications in modern organic synthesis.

F. RELATED REACTIONS

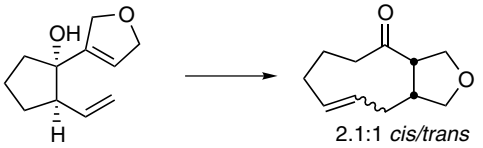
This reaction is related to the *Claisen Rearrangement* and its variants.

G. CITED EXPERIMENTAL EXAMPLES



Reference 32.

A solution of 74 mg (*R*, 2*E*)-methyl 4-((*S*)-1,4-dihydro-1-methylnaphthalen-1-yl)hex-2-enoate (98.4% e.e.) in 5 mL toluene was refluxed for 6 h. Toluene was evaporated, and the residue was purified by flash chromatography on silica gel (20:1 pentane/ether eluent) to provide 68 mg (*S*, 3*E*)-methyl 2-((*R*)-1,2-dihydro-4-methylnaphthalen-2-yl)hex-3-enoate as a colorless oil (98.0% e.e.), in a yield of 92%, R_f = 0.38 (10:1 pentane/ether).



Reference 9p.

To a solution of 80.0 mg 18-crown-6 in 5 mL THF was added 50 mg alcohol (0.277 mmol) by syringe. After being cooled to -40°C, 0.60 mL KHMDS solution in toluene (0.5 M, 0.30 mmol) was added dropwise, and the solution was stirred for 1 h. While still cold, the reaction mixture was poured into 30 mL 1 N HCl solution and extracted with EtOAc (2 × 30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The remaining residue was purified by chromatography (4:1 hexanes/ether) to give 27.0 mg *cis*-cyclic ketone (0.150 mmol, 54% yield) as the less polar product and 13.0 mg *trans*-cyclic ketone (0.072 mmol, 26% yield) as the more polar product.

Other references related to the Cope rearrangement and *oxy*-Cope rearrangement are cited in the literature.[33]

H. REFERENCES

1. Cope, A. C. and Hardy, E. M., *J. Am. Chem. Soc.,* **1940**, *62*, 441.
2. (a) Huang, J. S. and Kertesz, M., *J. Am. Chem. Soc.,* **2006**, *128*, 7277. (b) Pei, X.-Q.; Jia, J.-F. and Wu, H.-S., *Huaxue Xuebao*, **2007**, *65*, 579. (c) Miura, T.; Kiyota, K.; Kusama, H. and Iwasawa, N., *J. Organomet. Chem.,* **2007**, *692*, 562. (d) Su, K.-J.; Mieusset, J.-L.; Arion, V. B.; Brecker, L. and Brinker, U. H., *Org. Lett.,* **2007**, *9*, 113. (e) Kusama, H.; Onizawa, Y. and Iwasawa, N., *J. Am. Chem. Soc.,* **2006**, *128*, 16500. (f) Davies, H. M. L. and Dai, X., *Tetrahedron,* **2006**, *62*, 10477. (g) Polo, V. and Andres, J., *J. Comput. Chem.,* **2005**, *26*, 1427. (h) Zora, M., *J. Org. Chem.,* **2005**, *70*, 6018. (i) Duncan, J. A. and Spong, M. C., *J. Phys. Org. Chem.,* **2005**, *18*, 462. (j) McGuire, M. J. and Piecuch, P., *J. Am. Chem. Soc.,* **2005**, *127*, 2608. (k) Malachowski, W. P. and Banerji, M., *Tetrahedron Lett*., **2004**, *45*, 8183. (l) Singh, P. M. and Lyngdoh, R. H. D, *Indian J. Chem., Sect. B.,* **2004**, *43B*, 1958. (m) Shimizu, M.; Fujimoto, T.; Liu, X. Y. and Hiyama, T., *Chem. Lett.,* **2004**, *33*, 438. (n) Isobe, H.; Yamanaka, S. and Yamaguchi, K., *Int. J. Quantum Chem.,* **2003**, *95*, 532. (o) Sarpong, R.; Su, J. T. and Stoltz, B. M., *J. Am. Chem. Soc.,* **2003**, *125*, 13624. (p) Sakai, S., *THEOCHEM*, **2002**, *583*, 181. (q) Forgione, P.; Wilson, P. D.; Yap, G. P. A. and Fallis, A. G., *Synthesis*, **2000**, 921. (r) Hiersemann, M., *Synlett*, **2000**, 415. (s) Haeffner, F.; Houk, K. N.; Reddy, Y. R. and Paquette, L. A., *J. Am. Chem. Soc.,* **2000**, *122*, 3799. (t) Staroverov, V. N. and Davidson, E. R., *J. Am. Chem. Soc.,* **2000**, *122*, 7377. (u) Hrovat, D. A.; Chen, J. G.; Houk, K. N. and Borden, W. T., *J. Am. Chem. Soc.,* **2000**, *122*, 7456. (v) Corey, E. J. and Kania, R. S., *Tetrahedron Lett*., **1998**, *39*, 741. (w) Santora, V. J. and Moore, H. W., *J. Org. Chem.,* **1996**, *61*, 7976. (x) Greeves, N. and Vines, K. J., *Tetrahedron Lett*., **1994**, *35*, 7077. (y) Janardhanam, S. and Rajagopalan, K., *J. Chem. Soc., Perkin Trans. I,* **1992**, 2727.
3. (a) Allin, S. M.; Essat, M.; Pita, C. H.; Baird, R. D.; McKee, V.; Elsegood, M.; Edgar, M.; Andrews, D. M.; Shah, P. and Aspinall, I., *Org. Biomol. Chem.,* **2005**, *3*, 809. (b) Allin, S. M.; Baird, R. D. and Lins, R. J., *Tetrahedron Lett*., **2002**, *43*, 4195. (c) Allin, S. M. and Button, M. A. C., *Tetrahedron Lett*., **1999**, *40*, 3801. (d) Allin, S. M.; Button, M. A. C.; Baird, R. D., *Synlett*, **1998**, 1117. (e) Allin, S. M. and Button, M. A. C., *Tetrahedron Lett*., **1998**, *39*, 3345. (f) Allin, S. M.; Button, M. A. C. and Shuttleworth, S. J., *Synlett*, **1997**, 725.
4. (a) Johnson, B. F.; Marrero, E. L.; Turley, W. A. and Lindsay, H. A., *Synlett,* **2007**, 893. (b) Merino, P.; Tejero, T. and Mannucci, V., *Tetrahedron Lett*., **2007**, *48*, 3385. (c) Weston, M. H.; Nakajima, K.; Parvez, M. and Back, T. G., *Chem. Commun.,* **2006**, 3903. (d) Wittmann, U.; Tranel, F.; Froehlich, R. and Haufe, G., *Synthesis*, **2006**, 2085. (e) Aron, Z. D. and Overman, L. E., *Org. Lett.,* **2005**, *7*, 913. (f) Brummond, K. M. and Hong, S.-P., *J. Org. Chem.,* **2005**, *70*, 907. (g) Fiedler, D.; Bergman, R. G. and Raymond, K. N., *Angew. Chem. Int. Ed.,* **2004**, *43*, 6748. (h) Gomes, M. J. S.; Sharma, L.; Prabhakar, S.; Lobo, A. M. and Gloria, P. M. C., *Chem. Commun.,* **2002**, 746. (i) Cooke, A.; Bennett, J. and McDaid, E., *Tetrahedron Lett*., **2002**, *43*, 903. (j) Brummond, K. M. and Lu, J. L., *Org. Lett.,* **2001**, *3*, 1347. (k) Winter, R. F.; Klinkhammer, K.-W. and Zalis, S., *Organometallics,* **2001**, *20*, 1317. (l) McComsey, D. F. and Maryanoff, B. E., *J. Org. Chem.,* **2000**, *65*, 4938. (m) Yadav, J. S.; Reddy, B. V. S.; Rasheed, M. A. and Kumar, H. M. S., *Synlett,* **2000**, 487. (n) Obrecht, D.; Zumbrunn, C. and Mueller, K., *J. Org. Chem.,* **1999**, *64*, 6891. (o) Deloisy, S. and Kunz, H., *Tetrahedron Lett*., **1998**, *39*, 791. (p) Katritzky, A. R.; Feng, D. M.; Qi, M.; Lang, H. Y. and Steel, P. J., *Bull. Soc. Chim. Belg.,* **1997**, *106*, 419. (q) Sreekumar, R. and Padmakumar, R., *Tetrahedron Lett*., **1996**, *37*, 5281. (r) Deur, C.; Miller, M. and Hegedus, L. S., *J. Org. Chem.,* **1996**, *61*, 2871. (s) Walters, M. A., *Tetrahedron Lett*., **1995**, *36*, 7055. (t) Zakharkin, L. I. and Guseva, V. V., *Izv. Akad. Nauk, Ser. Khim.,* **1995**, 192. (u) Wang, M.-X. and Huang, Z.-T., *J. Org. Chem.,* **1995**, *60*, 2807. (v) Cook, G. R. and Stille, J.

R., *Tetrahedron*, **1994**, *50*, 4105. (w) Gilchrist, T. L.; Gonsalves, A. M. A. R. and Pinho e Melo, T. M. V. D., *Tetrahedron Lett*., **1993**, *34*, 6945. (x) Knight, S. D.; Overman, L. E. and Pairaudeau, G., *J. Am. Chem. Soc.,* **1993**, *115*, 9293. (y) Agami, C.; Couty, F.; Lin, J.; Mikaeloff, A. and Poursoulis, M., *Tetrahedron*, **1993**, *49*, 7239.

5. (a) Walters, M. A., *J. Org. Chem.,* **1996**, *61*, 978. (b) Walters, M. A.; Hoem, A. B. and McDonough, C. S., *J. Org. Chem.,* **1996**, *61*, 55.
6. (a) Kim, H.-J.; Kim, H.; Alhakimi, G.; Jeong, E. J.; Thavarajah, N.; Studnicki, L.; Koprianiuk, A.; Lough, A. J.; Suh, J. and Chin, J., *J. Am. Chem. Soc.,* **2005**, *127*, 16370. (b) Chin, J.; Mancin, F.; Thavarajah, N.; Lee, D.; Lough, A. and Chung, D. S., *J. Am. Chem. Soc.,* **2003**, *125*, 15276. (c) Voegtle, F. and Goldschmitt, E., *Chem. Ber.,* **1976**, *109*, 1. (d) Goldschmitt, E. and Voegtle, F., *ChED, Chemie: Experiment + Didaktik,* **1975**, *1*, 335. (e) Voegtle, F. and Goldschmitt, E., *Angew. Chem.,* **1974**, *86*, 520.
7. Zakarian, A. and Lu, C.-D., *J. Am. Chem. Soc.,* **2006**, *128*, 5356.
8. (a) Jasti, R. and Rychnovsky, S. D., *Org. Lett.,* **2006**, *8*, 2175. (b) Chen, Y.-H. and McDonald, F. E., *J. Am. Chem. Soc.,* **2006**, *128*, 4568. (c) Jasti, R.; Anderson, C. D. and Rychnovsky, S. D., *J. Am. Chem. Soc.,* **2005**, *127*, 9939. (d) Dalgard, J. E. and Rychnovsky, S. D., *J. Am. Chem. Soc.,* **2004**, *126*, 15662. (e) Loh, T.-P.; Hu, Q.-Y. and Ma, L.-T., *Org. Lett.,* **2002**, *4*, 2389. (f) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D. and Willis, C. L., *Org. Lett.,* **2002**, *4*, 577.
9. (a) Levina, I. S.; Kulikova, L. E.; Shashkov, A. S.; Galakhova, T. N. and Kamernitsky, A. V., *Russ. J. Bioorg. Chem.,* **2007**, *33*, 310. (b) Rasheeth, A. and Huq, C. A. M. A., *Synth. Commun.,* **2007**, *37*, 1557. (c) Hussaini, S. S.; Raj, A. R. N. and Huq, C. A. M. A., *Tetrahedron Lett.*, **2007**, *48*, 775. (d) Marti, S.; Andres, J.; Moliner, V.; Silla, E.; Tunon, I. and Bertran, J., *J. Phys. Chem. A,* **2006**, *110*, 726. (e) Bravo, J., *Revista Boliviana Quim.,* **2005**, *22*, 1. (f) Hua, Z. M.; Yu, W. S.; Su, M. and Jin, Z. D., *Org. Lett.,* **2005**, *7*, 1939. (g) Black, K. A.; Leach, A. G.; Kalani, M. Y. S. and Houk, K. N., *J. Am. Chem. Soc.,* **2004**, *126*, 9695. (h) Banwell, M. G.; Edwards, A. J.; McLeod, M. D. and Stewart, S. G., *Aust. J. Chem.,* **2004**, *57*, 641. (i) Woodland, C. A.; Crawley, G. C. and Hartley, R. C., *Tetrahedron Lett*., **2004**, *46*, 1227. (j) Pi, J.-H. and Huang, X., *Synlett,* **2003**, 2413. (k) DiMartino, G.; Hursthouse, M. B.; Light, M. E.; Percy, J. M.; Spencer, N. S. and Tolley, M., *Org. Biomol. Chem.,* **2003**, *1*, 4423. (l) Maurin, P.; Kim, S.-H.; Cho, S. Y. and Cha, J. K., *Angew. Chem. Int. Ed.,* **2003**, *42*, 5044. (m) Ogawa, Y.; Toyama, M.; Karikomi, M.; Seki, K.; Haga, K. and Uyehara, T., *Tetrahedron Lett*., **2003**, *44*, 2167. (n) Gentric, L.; Hanna, I.; Huboux, A. and Zaghdoudi, R., *Org. Lett.,* **2003**, *5*, 3631. (o) Villalva-Servin, N. P.; Melekov, A. and Fallis, A. G., *Synthesis*, **2003**, 790. (p) White, B. H. and Snapper, M. L., *J. Am. Chem. Soc.,* **2003**, *125*, 14901. (q) Asada, T.; Gouda, H. and Kollman, P. A., *J. Am. Chem. Soc.,* **2002**, *124*, 12535. (r) Chuard, R.; Giraud, A. and Renaud, P., *Angew. Chem. Int. Ed.,* **2002**, *41*, 4321. (s) Rahiman, A. K.; Hussaini, S. S. and Huq, C. A. M. A., *Curr. Sci.,* **2002**, *82*, 1138. (t) Dongol, K. G.; Wartchow, R. and Butenschon, H., *Eur. J. Org. Chem.,* **2002**, 1972. (u) Hashimoto, H.; Jin, T.; Karikomi, M.; Seki, K.; Haga, K. and Uyehara, T., *Tetrahedron Lett*., **2002**, *43*, 3633. (v) Schulze, S. M.; Santella, N.; Grabowski, J. J. and Lee, J. K., *J. Org. Chem.,* **2001**, *66*, 7247. (w) Voigt, B.; Wartchow, R. and Butenschon, H., *Eur. J. Org. Chem.,* **2001**, 2519. (x) Hiersemann, M., *Eur. J. Org. Chem.,* **2001**, 483. (y) Dimartino, G.; Gelbrich, T.; Hursthouse, M. B.; Light, M. E.; Percy, J. M and Spencer, N. S., *Chem. Commun.,* **1999**, 2535. (z) Lee, E.; Lee, Y. R.; Moon, B. J.; Kwon, O.; Shim, M. S. and Yun, J. S., *J. Org. Chem.,* **1994**, *59*, 1444. (aa) Berson, J. A. and Walsh, E. J., *J. Am. Chem. Soc.,* **1968**, *90*, 4732. (bb) Brown, E.; Leriverend, P. and Conia, J. M., *Tetrahedron Lett.,* **1966**, 6115. (cc) Viola, A. and Levasseur, L., *J. Am. Chem. Soc.,* **1965**, *87*, 1150.
10. (a) Ohshita, J.; Yoshimoto, K.; Iida, T. and Kunai, A., *J. Am. Chem. Soc.,* **2001**, *123*, 8400. (b) Schmidt, R. R.; Baer, T. and Wild, R., *Synthesis*, **1995**, 868. (c) Saczewski, F. and Debowski, T., *Tetrahedron Lett*., **1993**, *34*, 2843.

11. (a) Horino, Y.; Luzung, M. R. and Toste, F. D., *J. Am. Chem. Soc.,* **2006**, *128*, 11364. (b) Fall, Y.; Nguyen, V. B. and Langlois, Y., *Tetrahedron Lett*., **1986**, *27*, 3611.
12. Black, W. C.; Giroux, A. and Greidanus, G., *Tetrahedron Lett*., **1996**, *37*, 4471.
13. (a) Schneider, C. and Khaliel, S., *Synlett*, **2006**, 1413. (b) Schneider, C., *Synlett*, **2001**, 1079. (c) Bio, M. M. and Leighton, J. L., *J. Am. Chem. Soc.,* **1999**, *121*, 890. (d) Schneider, C., *Eur. J. Org. Chem.,* **1998**, 1661. (e) Schneider, C., *Synlett*, **1997**, 815. (f) Kato, N.; Takeshita, H.; Tanaka, S. and Kataoka, H., *J. Chem. Soc., Perkin Trans. I,* **1989**, 1833. (g) Kato, N.; Kataoka, H.; Ohbuchi, S.; Tanaka, S. and Takeshita, H., *J. Chem. Soc., Chem. Commun.,* **1988**, 354.
14. (a) Freeman, F.; Lee, M. Y.; Lu, H. Y.; Wang, X. J. and Rodriguez, E., *J. Org. Chem.,* **1994**, *59*, 3695. (b) Braverman, S. and Freund, M., *Tetrahedron,* **1990**, *46*, 5759. (c) Nicolaou, K. C. and Gronberg, R. D., *J. Am. Chem. Soc.,* **1990**, *112*, 4085. (d) Oshima, K.; Takahashi, H.; Yamamoto, H. and Nozaki, H., *J. Am. Chem. Soc.,* **1973**, *95*, 2693.
15. Berson, J. A. and Walsh, E. J., *J. Am. Chem. Soc.,* **1968**, *90*, 4729.
16. Ward, H. R. and Karafiath, E., *J. Am. Chem. Soc.,* **1969**, *91*, 522.
17. Miller, B., *J. Am. Chem. Soc.,* **1965**, *87*, 5115.
18. Braisted, A. C. and Schultz, P. G., *J. Am. Chem. Soc.,* **1994**, *116*, 2211.
19. (a) Marti, S.; Andrés, J.; Moliner, V.; Silla, E.; Tuñón, I and Bertrán, J., *J. Am. Chem. Soc.,* **2004**, *126*, 311. (b) Aemissegger, A.; Juan, B. and Hilvert, D., *J. Org. Chem.,* **2002**, *67*, 6725.
20. (a) Wessel, T. E. and Berson, J. A., *J. Am. Chem. Soc.,* **1994**, *116*, 495. (b) Gleiter, R. and Sigwart, C., *J. Org. Chem.,* **1994**, *59*, 1027. (c) Hammond, G. S. and DeBoer, C. D., *J. Am. Chem. Soc.,* **1964**, *86*, 899. (d) Berson, J. A. and Jones, M., *J. Am. Chem. Soc.,* **1964**, *86*, 5017.
21. Black, K. A.; Wilsey, S. and Houk, K. N., *J. Am. Chem. Soc.,* **2003**, *125*, 6715.
22. Blavins, J. J.; Cooper, D. L. and Karadakov, P. B., *J. Phys. Chem. A,* **2004**, *108*, 194.
23. (a) Doering, W. von E.; Birladeanu, L.; Sarma, K.; Teles, J. H.; Klärner, F.-G. and Gehrke, J.-S., *J. Am. Chem. Soc.,* **1994**, *116*, 4289. (b) Berndt, D. C., *J. Chem. Eng. Data,* **1969**, *14*, 112. (c) Doering, W. von E. and Roth, W. R., *Tetahedron,* **1962**, *18*, 67.
24. Evans, D. A. and Nelson, J. V., *J. Am. Chem. Soc.* **1980**, *102*, 774.
25. Berson, J. A. and Jones, M., *J. Am. Chem. Soc.,* **1964**, *86*, 5019.
26. (a) Bethke, S.; Hrovat, D. A.; Borden, W. T. and Gleiter, R., *J. Org. Chem.,* **2004**, *69*, 3294. (b) Ventura, E.; do Monte, S. A.; Dallos, M. and Lischka, H., *J. Phys. Chem. A*, **2003**, *107*, 1175. (c) Tantillo, D. J. and Hoffmann, R., *J. Org. Chem.,* **2002**, *67*, 1419. (d) Hrovat, D. A.; Chen, J.; Houk, K. N. and Borden, W. T., *J. Am. Chem. Soc.,* **2000**, *122*, 745. (e) Kozlowski, P. M.; Dupuis, M. and Davidson, E. R., *J. Am. Chem. Soc.,* **1995**, *117*, 774. (f) Hrovat, D. A.; Morokuma, K. and Borden, W. T., *J. Am. Chem. Soc.,* **1994**, *116*, 1072. (g) Wiest, O.; Black, K. A. and Houk, K. N., *J. Am. Chem. Soc.,* **1994**, *116*, 10336. (h) Simonetta, M.; Favini, G.; Mariani, C. and Gramaccioni, P.,*J. Am. Chem. Soc.,* **1968**, *90*, 1280.
27. Evans, D. A. and Golob, A. M., *J. Am. Chem. Soc.,* **1975**, *97*, 4765.
28. (a) Butenschön, H., *Pure & Appl. Chem.*, **2002**, *74*, 57. (b) Brands, M.; Wey, H. G.; Bruckmann, J.; Krüger, C. and Butenschön. H., *Chem. Eur. J.*, **1996**, *2*, 182. (c) Brands, M.; Goddard, R.; Wey, H. G. and Butenschön. H., *Angew. Chem.,* **1993**, *105*, 285.
29. (a) Evans, D. A. and Baillargeon, D. J., *Tetrahedron Lett.,* **1978**, 3315. (b) Evans, D. A. and Baillargeon, D. J., *Tetrahedron Lett.*, **1978**, 3319.
30. Bunnage, M. E. and Nicolaou, K. C., *Chem. Eur. J.,* **1997**, *3*, 187.
31. (a) Paquette, L.A., *Tetrahedron,* **1997**, *53*, 13971. (b) Durairaj, K., *Curr. Sci.,* **1994**, *66*, 917. (c) Wilson, S. R., *Org. React.,* **1993**, *43*, 93. (d) Hill, R.K., "Chapter 7.1, Cope, Oxy-Cope Rearrangements", in *Comprehensive Organic synthesis*, ed. Trost, B. M. and Fleming, I., Pergamon Press, Oxford, **1991**, *5*. (e) Paquette, L. A., *Angew. Chem. Int. Ed. Engl.,* **1990**, *29*, 609. (f) Blechert,

S., *Synthesis,* **1989**, 71. (g) Przheval'skii, N. M. and Grandberg, I. I., *Russ. Chem. Rev.,* **1987**, *56*, 477. (h) Lutz, R. P., *Chem. Rev.,* **1984**, *84*, 205. (i) Overman, L. E., *Angew. Chem. Int. Ed. Engl.,* **1984**, *23*, 579. (j) Heimgartner, H.; Hansen, H. and Schmid, H., *Adv. Org. Chem.,* **1979**, *9*(2), 655. (k) Rhodds, S. J. and Raulins, N. R., *Org. React.,* **1975**, *22*, 1.

32. Davies, H. M. L. and Jin, Q. H., *J. Am. Chem. Soc.,* **2004**, *126*, 10862.

33. (a) Davies, H. M. L. and Beckwith, R. E. J., *J. Org. Chem.,* **2004**, *69*, 9241. (b) Kawasaki, T.; Nonaka, Y.; Watanabe, K.; Ogawa, A.; Higuchi, K.; Terashima, R.; Masuda, K. and Sakamoto, M., *J. Org. Chem.,* **2001**, *66*, 1200. (c) Frauenfelder, C.; Schmid, G. A.; Vogelsang, T. and Borschberg, H.-J., *Chimia*, **2001**, *55*, 828. (d) Singh, V. and Iyer, S., *Chem. Commun.*, **2001**, 2578. (e) Nowicki, J., *Molecules,* **2000**, *5*, 1033. (f) Paquette, L. A.; Gao, Z.; Ni, Z. and Smith, G. F., *J. Am. Chem. Soc.,* **1998**, *120*, 2543. (g) Schneider, C., *Synlett,* **1997**, 815. (h) Barluenga, J., *Pure & Appl. Chem.,* **1996**, *68*, 543. (i) Iida, K-I. and Hirama, M., *J. Am. Chem. Soc.,* **1994**, *116*, 10310. (j) Lantos, I. and Zhang, W.-Y., *Tetrahedron Lett*., **1994**, *35*, 5977. (k) Wharton, P. S. and Kretchmer, R. A., *J. Org. Chem.,* **1968**, *33*, 4258. (l) Manning, D. T.; Coleman, H. A. and Langdale-Smith, R. A., *J. Org. Chem.,* **1968**, *33*, 4413. (m) Schroder, G.; Oth, J. F. M. and Mereny, R., *Angew. Chem. Int. Ed. Engl.,* **1965**, *4*, 752. (n) Miller, B., *J. Am. Chem. Soc.,* **1965**, *87*, 5515. (o) Gibson, D. H. and Pettit, R., *J. Am. Chem. Soc.,* **1965**, *87*, 2620. (p) Walling, C. and Naiman, M., *J. Am. Chem. Soc.,* **1962**, *84*, 2628.

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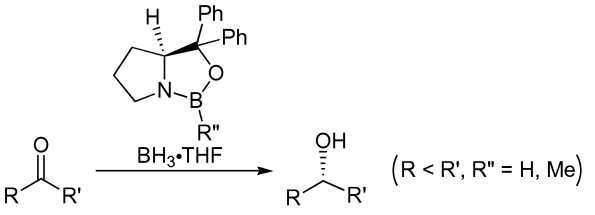
Corey-Bakshi-Shibata Reduction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Core, and co-workers in 1987.[1] It is a reduction of ketone by borane in the presence of a chiral oxazaborolidine catalyst, with excellent enantioselectivity, high chemical yield,[2] high turnover of the catalyst, and exceptional rate enhancement.[3] Therefore, this reaction is often known as the Corey-Bakshi-Shibata reduction,[4] or simply the CBS reduction.[5] Occasionally, this reaction is also referred to as the Corey-Bakshi-Shibata asymmetric reduction.[6] Likewise, the chiral oxazaborolidine, known as the Corey-Bakshi-Shibata catalyst[7] or the CBS catalyst,[2,7] is a small molecule with multifunctionality.[3] The endocyclic boron-methylated catalyst shows a superior air and moisture stability[5c,5d] that can be weighed in the open air.[3] It was proposed that this reduction undergoes a catalytic cycle in four principal steps: the coordination of the nitrogen atom of the Lewis base to borane, complexation of the ketone to the endocyclic boron (functioning as Lewis acid) via the Lewis acid–base interaction, hydride transfer from borane to the carbonyl carbon, and dissociation of the alkoxyborane moiety and regeneration of the catalyst.[5c] It is reported that up to two of the three hydrides of borane can be transferred for reduction.[8] On the one hand, this reaction has been extensively modified experimentally, including variations of the catalyst,[9] borane reagent,[10] order and rate of addition,[8c] solvent,[8c] and temperature.[8b] This reaction has also been investigated theoretically,[5c,11] especially from the work of Nevalainen.[12] This reaction has been reviewed several times.[13]

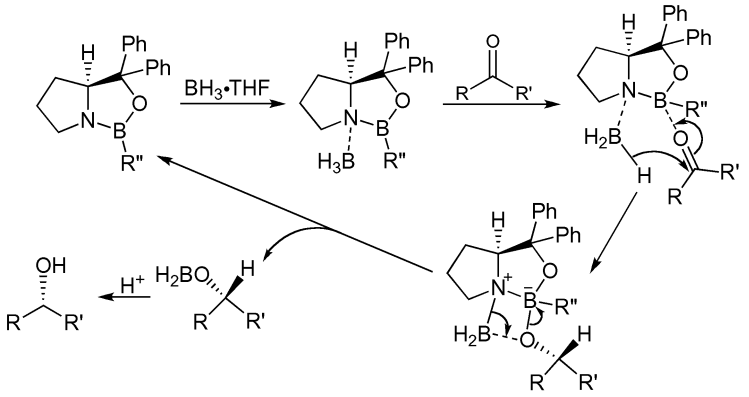
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The reaction involves the coordination of a nitrogen atom to borane, the carbonyl group to the endocyclic boron atom and subsequent hydride transfer and decomposition of the alkoxyborane intermediate to the chiral alcohol.



D. MODIFICATION

This reaction has been modified to have a methyl group attach to the endocyclic boron atom of the CBS catalyst.[3,5c,5d]

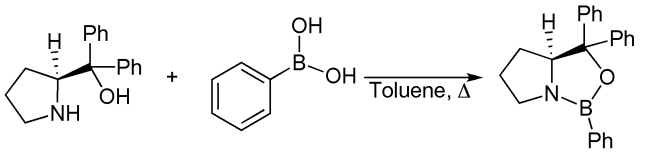
E. APPLICATIONS

This reaction has a general application in the stereospecific transformation of prochiral ketones into secondary alcohols.

F. RELATED REACTIONS

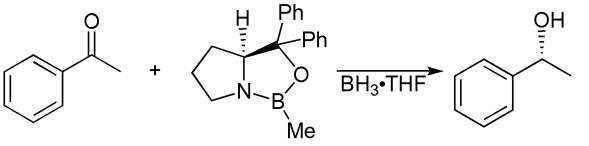
This reaction is related to the *Brown Hydroboration*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4e.

In a 100-mL dry Schlenk flask were added 2.0 mmol amino alcohol, 2.1 mmol phenylboronic acid, and 40 mL dry toluene. The suspension mixture was heated to reflux in an atmosphere of argon for 24 h with azeotropic removal of water, which was trapped by 10 g 4-Å molecular sieves placed in a pressure-equalizing dropping funnel between the flask and the condenser. The toluene was then removed in vacuo,and the residue was purified by Kugelrohr distillation (215–220°C, 0.5 mbar) to give 93% pure (*S*)-1,3,3-triphenylperhydropyrrolo[1,2-c][1,2,3]oxazaborole.



Reference 2.

To 20 mL of a 0.074 M solution of catalyst in THF at 0°C was added 1.77 mL 1 M BH_3·THF. This was followed quickly by the addition of 0.35 g acetophenone (2.94 mmol) in 0.5 mL THF. The solution was stirred for 30 min at room temperature, treated with 5 mL 0.5 M HCl, and stirred for an additional 10 min. The solution was extracted twice with Et_2O. The extracts were washed with brine, dried over Na_2SO_4, and concentrated. A GC analysis indicated a yield of 100% with 85.5% e.e.

Other references related to the Corey-Bakshi-Shibata reduction are cited in the literature.[14]

H. REFERENCES

1. Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P. and Singh, V. K., *J. Am. Chem. Soc.*, **1987**, *109*, 7925.
2. Price, M. D.; Sui, J. K.; Kurth, M. J. and Schore, N. E., *J. Org. Chem.,* **2002**, *67*, 8086.
3. Rowlands, G. J., *Tetrahedron,* **2001**, *57*, 1865.
4. (a) Bichlmaier, I.; Siiskonen, A.; Kurkela, M.; Finel, M. and Yli-Kauhaluoma, J., *Biol. Chem.,* **2006**, *387*, 407. (b) Bichlmaier, I.; Siiskonen, A.; Finel, M. and Yli-Kauhaluoma, J., *J. Med. Chem.,* **2006**, *49*, 1818. (c) Ghosh, A. K. and Swanson, L., *J. Org. Chem.,* **2003**, *68*, 9823. (d) de Koning, C. B.; Giles, R. G. F.; Green, I. R. and Jahed, N. M., *Tetrahedron Lett.*, **2002**, *43*, 4199. (e) Schmidt, R.; Jockel, H.; Schmalz, H.-G. and Jope, H., *J. Chem. Soc., Perkin Trans. II,* **1997** 2725.
5. (a) Nising, C. F.; Ohnemueller, U. K. and Braese, S., *Synthesis,* **2006**, 2643. (b) Yu, C.-M.; Kim, C. and Kweon, J.-H., *Chem. Commun.,* **2004**, 2494. (c) Alagona, G.; Ghio, C.; Persico, M. and

Tomasi, S., *J. Am. Chem. Soc.,* **2003**, *125*, 10027. (d) Ghosh, A. K. and Swanson, L., *J. Org. Chem.,* **2003**, *68*, 9823. (e) Garrett, C. E.; Prasad, K.; Repic, O. and Blacklock, T. J., *Tetrahedron: Asymmetry*, **2002**, *13*, 1347. (f) Chen, W.-Y.; Lu, J.; Zhang, Y.-W. and Shen, Z.-X., *Youji Huaxue*, **2002**, *22*, 42. (g) Chen, W.-Y.; Lu, J.; Zhang, Y.-W. and Shen, Z.-X., *Chinese Chem. Lett.,* **2001**, *12*, 1079. (h) Spivey, A. C.; Andrews, B. I.; Brown, A. D. and Frampton, C. S., *Chem. Commun.,* **1999**, 2523. (i) Spivey, A. C.; Andrews, B. I.; Brown, A. D. and Frampton, C. S., *Chem. Commun.*, **1999**, 2523. (j) Schwink, L. and Knochel, P., *Tetrahedron Lett*., **1996**, *37*, 25.

6. De Koning, C. B.; Giles, R. G. F.; Green, I. R. and Jahed, N. M., *Tetrahedron*, **2003**, *59*, 3175.
7. Harb, W.; Ruiz-López, M. F.; Coutrot, F.; Grison, C. and Coutrot, P., *J. Am. Chem. Soc.,* **2004**, *126*, 6996.
8. (a) Prasad, K. R. K. and Joshi, N. N., *Tetrahedron: Asymmetry,* **1996**, *7*, 3147. (b) Stone, G. B., *Tetrahedron: Asymmetry,* **1994**, *5*, 465. (c) Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Hoogsteen, K.; Carrol, J. D.; Corley, E. G. and Grabowski, E. J. J., *J. Org. Chem.,* **1993**, *58*, 2880. (d) Corey, E. J.; Shibata, S. and Bakshi, R. K., *J. Org. Chem.,* **1988**, *53*, 2861.
9. Quallich, J. G.; Blake, J. F. and Woodall, T. M., *J. Am. Chem. Soc.*, **1994**, *116*, 8516.
10. Franot, C.; Stone, G. B.; Engeli, P.; Spöndlin, C. and Waldvogel, E., *Tetrahedron: Asymmetry*, **1995**, *6*, 2755.
11. DiMare, M., *J. Org. Chem.,* **1996**, *61*, 8378.
12. (a) Nevalainen, V. *Tetrahedron: Asymmetry,* **1996**, *7*, 2655. (b) Nevalainen, V.; Uggla, R.; Sundberg, M. R., *Tetrahedron: Asymmetry,* **1995**, *6*, 1431. (c) Nevalainen, V., *Tetrahedron: Asymmetry,* **1994**, *5*, 903. (d) Nevalainen, V., *Tetrahedron: Asymmetry,* **1994**, *5*, 767. (e) Nevalainen, V., *Tetrahedron: Asymmetry,* **1994**, *5*, 395. (f) Nevalainen, V., *Tetrahedron: Asymmetry,* **1994**, *5*, 387. (g) Nevalainen, V., *Tetrahedron: Asymmetry,* **1994**, *5*, 289. (h) Nevalainen, V., *Tetrahedron: Asymmetry,* **1993**, *4*, 1597. (i) Nevalainen, V., *Tetrahedron: Asymmetry,* **1993**, *4*, 1569. (j) Nevalainen, V., *Tetrahedron: Asymmetry,* **1993**, *4*, 1565. (k) Nevalainen, V., *Tetrahedron: Asymmetry,* **1993**, *4*, 1505. (l) Nevalainen, V., *Tetrahedron: Asymmetry,* **1992**, *3*, 933. (m) Nevalainen, V., *Tetrahedron: Asymmetry,* **1992**, *3*, 921. (n) Nevalainen, V., *Tetrahedron: Asymmetry,* **1992**, *3*, 1441. (o) Nevalainen, V., *Tetrahedron: Asymmetry,* **1992**, *3*, 1563. (p) Nevalainen, V., *Tetrahedron: Asymmetry,* **1991**, *2*, 1133. (q) Nevalainen, V., *Tetrahedron: Asymmetry,* **1991**, *2*, 827. (r) Nevalainen, V., *Tetrahedron: Asymmetry,* **1991**, *2*, 429. (s) Nevalainen, V., *Tetrahedron: Asymmetry,* **1991**, *2*, 63.
13. (a) Corey, E. J. and Helal, C. J., *Angew. Chem. Int. Ed.,* **1998**, *37*, 1987 (b) Deloux, L. and Srebnik, M., *Chem. Rev.,* **1993**, *93*, 763. (c) Singh, V. K., *Synthesis,* **1992**, 605. (d) Wallbaum, S. and Martens, J., *Tetrahedron: Asymmetry,* **1992**, *3*, 1475.
14. (a) Della Monica, C.; Della Sala, G.; D'Urso, D.; Izzo, I. and Spinella, A., *Tetrahedron Lett*., **2005**, *46*, 4061. (b) Herzon, S. B. and Myers, A. G., *J. Am. Chem. Soc.,* **2005**, *127*, 5342. (c) Szpilman, A. M.; Korshin, E. E.; Rozenberg, H. and Bachi, M. D., *J. Org. Chem.,* **2005**, *70*, 3618. (d) Kuo, F. J.; Clodfelter, D. K. and Wheeler, W. J., *J. Labelled Compd. Radiopharm.,* **2004**, *47*, 615. (e) Joullié, M. M. and Richard, D. J., *Chem. Commun.,* **2004**, 2011. (f) Selkälä, S., *Total Synthesis of Amaminol A*., Ph.D. dissertation, Helsinki University of Technology, **2003**. (g) Fu, X. Y.; McAllister, T. L.; Thiruvengadam, T. K.; Tann, C.-H. and Su, D., *Tetrahedron Lett*., **2003**, *44*, 801. (h) Woodward, S., *Curr. Sci.,* **2000**, *78*, 1314. (i) Clark, W. M.; Tickner-Eldridge, A. M.; Huang, G. K.; Pridgen, L. N.; Olsen, M. A.; Mills, R. J.; Lantos, I. and Baine, N. H., *J. Am. Chem. Soc.*, **1998**, *120*, 4550. (j) Corey, E. J.; Guzman-Perez, A. and Lazerwith, S. E., *J. Am. Chem. Soc.* **1997**, *119*, 11769. (k) Rao, M. N.; McGuigan, M. A.; Zhang, X.; Shaked, Z.; Kinney, W. A.; Bulliard, M.; Laboue, B. and Lee, N. E., *J. Org. Chem.*, **1997**, *62*, 4541. (l) Ostendorf, M.; Romagnoli, R.; Pereiro, I. C.; Roos, E. C.; Moolenaar, M. J.; Speckamp, W. N. and Hiemstra, H., *Tetrahedron: Asymmetry*, **1997**, *8*, 1773. (m) Giles, R. G. F. and Green, I. R., *Synth. Commun.,* **1996**, *26*, 3161. (n) Corey, E. J. and Jardine, P. da S., *Tetrahedron Lett*., **1989**, *30*, 7297. (o) Corey, E. J.; Bakshi, R. K. and Shibata, S., *J. Am. Chem. Soc*. **1987**, *109*, 5551.

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Corey-Chaykovsky Epoxidation

(Corey-Chaykovsky Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

Although this reaction was first reported by Johnson in 1958,[1] it was Corey and Chaykovsky who extensively explored its scope in the 1960s.[2] It is the preparation of monosubstituted or geminally disubstituted epoxides from aldehydes or ketones with either methylsulfonium or methyloxosulfonium ylides. Therefore, it is often known as the Corey-Chaykovsky reaction;[3] and occasionally, it is also referred to as Corey-Chaykovsky epoxide synthesis,[4] Corey-Chaykovsky epoxidation,[5] or Corey-Chaykovsky oxiranylation.[6] Likewise, methylsulfonium or methyloxosulfonium ylide is known as the Corey-Chaykovsky reagent.[7] Traditionally, trimethylsulfoxonium ylide ($Me_2S{=}CH_2$) is prepared from trimethyl sulfoxonium iodide with NaH in DMSO that is stable at 0°C in an inert atmosphere and condenses with carbonyl compounds at 0–25°C.[4] Trimethyloxosulfonium ylide ($Me_2S(O){=}CH_2$) reacts at temperature of 50°C.[4] In this reaction, the ylide behaves as a nucleophile at the initial stage, and epoxide is formed from a backside attack of an oxido anion on the β-carbon.[3d] It has been reported that pentacoordinate 1,2λ^4-oxathietanes are intermediates in the addition step of this reaction.[3d] A few mechanisms have been proposed for this epoxidation, including the concerted mechanism, *anti*-addition, and torsional rotation pathways;[3b] however, it has been reported that the concerted mechanism is not favorable, and the *trans* epoxides are formed via the *anti*-addition pathway.[3b] This reaction has been modified to start from a dry mixture of trimethylsulfonium salt with potassium *tert*-butoxide and NaH, which remain stable, and the ylide is generated upon

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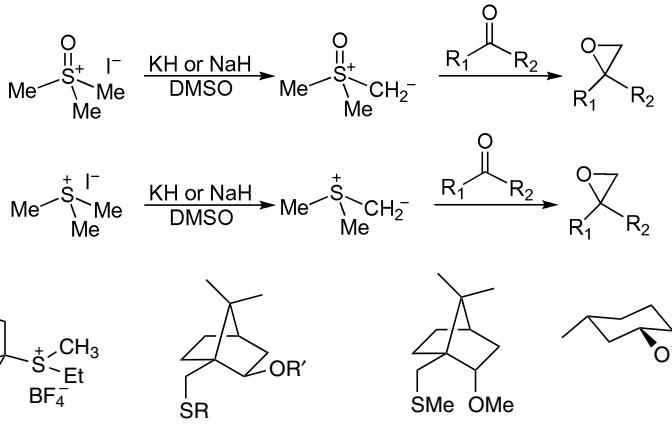
the addition of DMSO or a DMSO/THF solution of carbonyl compounds.[4] Similar to the *Wittig Reaction*, the Corey-Chaykovsky ylide leads to the formation of olefin,[8] as shown by the reaction with benzophenone at 75–100°C.[9] Furthermore, the ylide can add to alkene to form cyclopropane,[3c] imines to give aziridines,[10] etc. This reaction has been made catalytically in two phases.[11] It has been reported that if chiral sulfur ylides are used, optical active epoxides can be obtained from the achiral aldehydes and ketones.[12] So far, different chiral sulfur ylides have been designed as shown in reaction scheme.

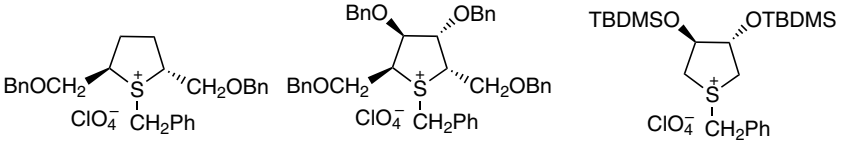
B. GENERAL REACTION SCHEME



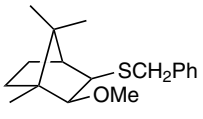
Trost[12a]

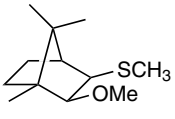
Furukawa[12b]

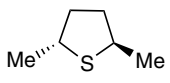
Solladié-Cavallo[12e–12j]

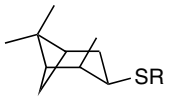


Durst[12c–12d]





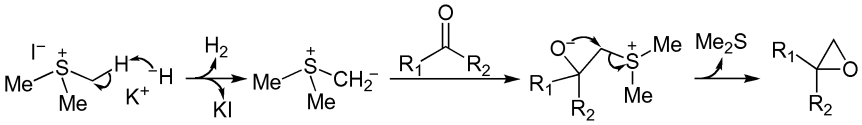




Dai[12k] Metzner[12l–12n] Aggarwal[12o]

C. PROPOSED MECHANISMS

The mechanism is demonstrated by the reaction between trimethylsulfoxonium ylide and a general ketone, as shown here.



D. MODIFICATION

N/A

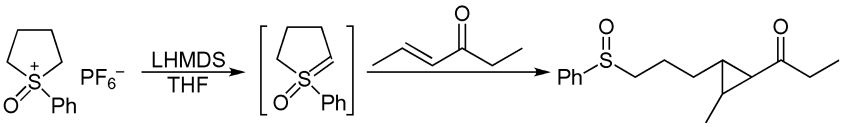
E. APPLICATIONS

N/A

F. RELATED REACTIONS

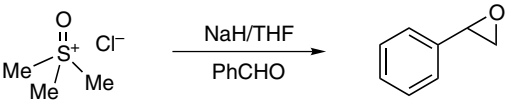
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3c.

To a solution of 0.10 g five-membered oxosulfonium salt (0.31 mmol) in 2 mL dry THF was added dropwise a solution of 0.32 mL 1 M lithium bis(trimethylsilyl)amide (0.32 mmol), and the mixture was stirred at room temperature for 10 min. A solution of 0.03 g 4-hexen-3-one (0.31 mmol) in 2 mL dry THF was then added dropwise to the mixture, and the resulting solution was stirred for 14 h. The mixture was quenched with water and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using EtOAc/$CHCl_3$ (1:1) as an eluent to give 98% of product as a colorless liquid.



Reference 2a.

The ylide was prepared by refluxing a mixture of 0.04 mol sodium hydride, 5.12 g (0.04 mol) trimethyloxosulfonium chloride, and 30 mL dry tetrahydrofuran under nitrogen until the evolution of hydrogen ceased (∼2 h). With the reaction mixture held at 55°C, a solution of 3.18 g (0.03 mol) benzaldehyde in 30 mL dry tetrahydrofuran was slowly added dropwise with stirring over a period of 1.5 h and the reaction mixture was then stirred at 55°C for an additional hour. The mixture was concentrated under reduced pressure (generated by a water aspirator) to a volume of ∼10 mL, then 50 mL water was added. The mixture was extracted with pentane (some resinous material remained in the aqueous phase). The combined pentane extracts were dried over anhydrous sodium sulfate and evaporated; the pale yellow residue was evaporatively distilled at 80°C (5.0 mmHg) to yield 2.0 g of colorless styrene oxide, in a yield of 55.6%.

Other references related to the Corey-Chaykovsky epoxidation are cited in the literature.[13]

H. REFERENCES

1. Johnson, A. W. and Lacount, R. B., *Chem. Ind. (London),* **1958**, 1440.
2. (a) Corey, E. J. and Chaykovsky, M., *J. Am. Chem. Soc.,* **1965**, *87*, 1353. (b) Corey, E. J. and Chaykovsky, M., *J. Am. Chem. Soc.,* **1964**, *86*, 1640. (c) Corey, E. J. and Chaykovsky, M., *J. Am. Chem. Soc.,* **1962**, *84*, 867. (d) Corey, E. J. and Chaykovsky, M., *J. Am. Chem. Soc.,* **1962**, *84*, 3782.
3. (a) Elliott, M. C., *J. Chem. Soc*., *Perkin Trans. 1*, **2000**, 1291. (b) Lindvall, M. K. and Koskinen, A. M. P., *J. Org. Chem.,* **1999**, *64*, 4596. (c) Akiyama, H.; Fujimoto, T.; Ohshima, K.; Hoshino, K.; Yamamoto, I and Iriye, R., *Org. Lett.,* **1999**, *1*, 427. (d) Ohno, F.; Kawashima, T. and Okazaki, R., *Chem. Commun*., **1997**, 1671. (e) Ohno, F.; Kawashima, T. and Okazaki, R., *J. Am. Chem. Soc.,* **1996**, *118*, 697.
4. Ciaccio, J. A.; Drahus, A. L.; Meis, R.; Tingle, C. T.; Smrtka, M. and Geneste, R., *Synth. Commun.,* **2003**, *33*, 2135.
5. (a) Edwards, D. R.; Du, J. and Crudden, C. M., *Org. Lett.,* **2007**, *9*, 2397. (b) Chandrasekhar, S.; Narasihmulu, Ch.; Jagadeshwar, V. and Venkatram Reddy, K., *Tetrahedron Lett*., **2003**, *44*, 3629. (c) Rowlands, G. J., *Tetrahedron,* **2001**, *57*, 1865.
6. Christian, C. and Robert, B., *Helv. Chim. Acta,* **1993**, *76*, 2070.
7. Ng, J. S., *Synth. Commun.,* **1990**, *20*, 1193.
8. Myllymäki, V., *Design, Synthesis and Testing of New Chiral Sulfide Catalyst for Corey-Chaykovsky Reaction*, dissertation, Oulu University, **2001**.
9. Chaykovsky, M. and Corey, E. J., *J. Org. Chem.,* **1963**, *28*, 254.
10. Morton, D.; Pearson, D.; Field, R. A. and Stockman, R. A., *Synlett,* **2003**, 1985.
11. Aggarwal, V. K., *Synlett*, **1998**, 329.
12. (a) Trost, B. M. and Hammen, R. F., *J. Am. Chem. Soc.,* **1973**, *95*, 962. (b) Furukawa, N.; Sugiara, Y. and Fujihara, H., *J. Org. Chem.,* **1989**, *54*, 4222. (c) Durst, T.; Breau, L. and Ben, R. N., *Phosphorus & Sulfur*, **1993**, *74*, 215. (d) Breau, L.; Ogilwie, W. W. and Durst, T., *Tetrahedron Lett.,* **1990**, *31*, 35. (e) Solladié-Cavallo, A. and Adib, A., *Tetrahedron,* **1992**, *48*, 2453. (f) Solladié-Cavallo, A.; Adib, A.; Schmitt, M.; Fischer, J. and DeCian, J., *Tetrahedron: Asymmetry,* **1992**, *3*, 1597. (g) Solladié-Cavallo, A. and Diep-Vohuule, A., *J. Org. Chem.,* **1995**, *60*, 3494. (h) Solladié-Cavallo, A.; Diep-Vohuule, A.; Sunjic, V. and Vinkovic, V., *Tetrahedron: Asymmetry,* **1996**, *7*, 1783. (i) Solladié-Cavallo, A.; Bouérat, L. and Roje, M., *Tetrahedron Lett.,* **2000**, *41*, 7309. (j) Solladié-Cavallo, A.; Roje, A.; Isarno, T.; Sunjic, V. and Vinkovic, V., *Eur. J. Org. Chem.,* **2000**, 1077. (k) Li, A.-H.; Dai, L.-X.; Hou, X.-L.; Huang, Y.-Z. and Li, F.-W., *J. Org. Chem.,* **1996**, *64*, 489. (l) Julienne, K.; Metzner, P.; Henryon, V. and Greiner, A., *J. Org. Chem.,* **1998**, *63*, 4532. (m) Julienne, K.; Metzner, P.; Greiner, A. and Henryon, V., *Phosphorus, Sulfur & Silicon & Related Elements,* **1999**, *153*, 341. (n) Julienne, K.; Metzner, P. and Henryon, V., *J. Chem. Soc., Perkin Trans. I,* **1999**, 731. (o) Aggarwal, V. K.; Kalomiri, M. and Thomas, A. P., *Tetrahedron: Asymmetry,* **1994**, *5*, 723.
13. (a) Peng, Y.; Yang, J.-H. and Li, W.-D. Z., *Tetrahedron*, **2006**, *62*, 1209. (b) Aggarwal, V. K.; Coogan, M. P.; Stenson, R. A.; Jones, R. V. H.; Fieldhouse, R. and Blacker, J., *Eur. J. Org. Chem.,* **2002**, 319. (c) Saito, T.; Akiba, D.; Sakairi, M. and Kanazawa, S., *Tetrahedron Lett*., **2001**, *42*, 57. (d) Moriarty, R. M.; Enache, L. A.; Gilardi, R.; Gould, G. L. and Wink, D. J., *Chem. Commun*., **1998**, 1155. (e) Koketsu, J.; Ninomiya, Y.; Suzuki, Y. and Koga, N., *Inorg. Chem.,* **1997**, *36*, 694. (f) Li, A.-H.; Dai, L.-X. and Aggarwal, V. K., *Chem. Rev.,* **1997**, *97*, 2341. (g) Volatron, F. and Eisenstein, O., *J. Am. Chem. Soc.,* **1987**, *109*, 1. (h) Johnson, A. W. and LaCount, R. B., *J. Am. Chem. Soc.,* **1961**, *83*, 417.

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Corey-Fuchs Reaction

(Corey-Fuchs Dibromoolefination, Corey-Fuchs Homologation, Corey-Fuchs Olefination)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Corey and Fuchs in 1972.[1] It is a two-step process to prepare a terminal alkyne with one-carbon homologation of an aldehyde or to prepare an alkyne derivative by the treatment of the alkynide intermediate with an electrophile before an aqueous workup. Therefore, it is generally known as the Corey-Fuchs reaction.[2] Occasionally, it is also referred to as the Corey-Fuchs dibromoolefination[3] and Corey-Fuchs homologation.[4] In this reaction, the first step is the reaction of an aldehyde with PPh_3 and carbon tetrahalide[1,5] or haloform[6] to form dihaloalkene, and the second step involves the treatment of dihaloalkene with a base (e.g., BuLi,[7] LDA,[5] or KO^tBu[6]) to generate a haloalkyne that undergoes metal-halogen exchange to give lithium alkynide. Aqueous workup of such lithium alkynide affords the corresponding terminal alkyne, whereas the treatment of this intermediate with an electrophile before workup generates alkyne derivatives.[8] Therefore, this reaction is also known as the Corey-Fuchs ethynylation.[9] In addition, because dihaloalkene is formed as a reaction intermediate that can be obtained before the treatment with a strong base, this reaction is also referred to as the Corey-Fuchs olefination.[10]

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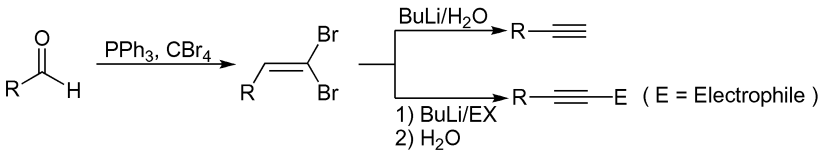
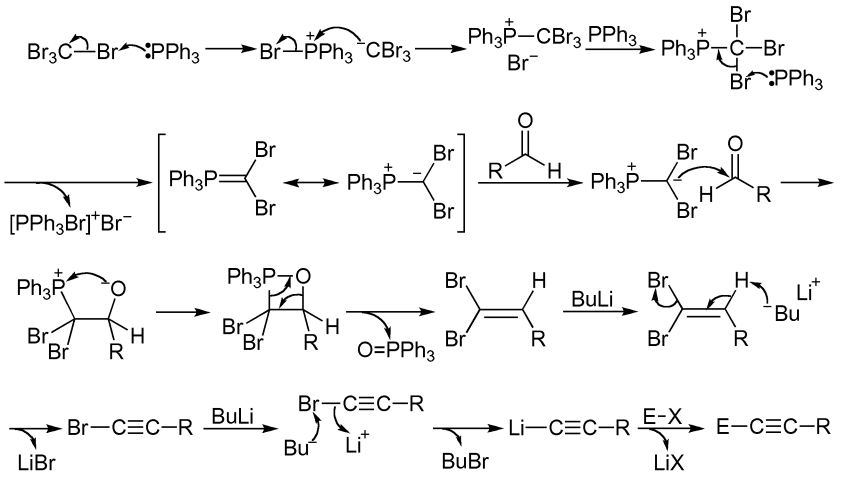
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Provided below is a simple illustration of the reaction mechanism.



D. MODIFICATION

Haloform has been applied to this reaction.[6] In addition, zinc dust has been added to the procedure to prepare dibromoalkene with an improved yield.[11]

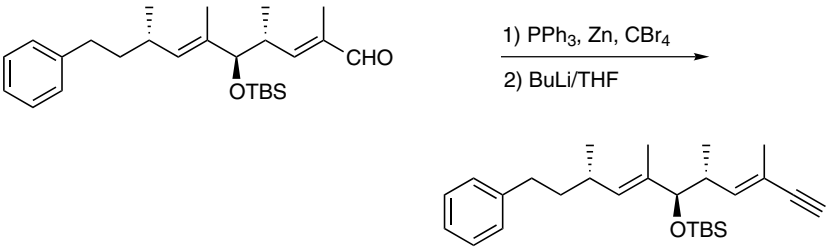
E. APPLICATIONS

This reaction has general application in the preparation of alkyne derivatives, especially for the terminal alkynes.

F. RELATED REACTIONS

This reaction is related to the *Wittig Reaction*.

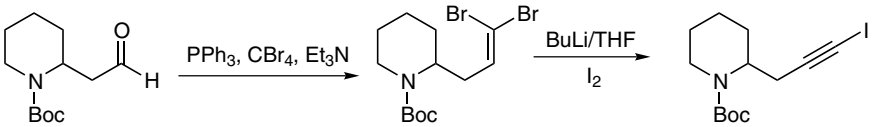
G. CITED EXPERIMENTAL EXAMPLES



Reference 11.

To a mixture of 1.45 g PPh_3 (5.51 mmol) and 0.36 g zinc dust (5.51 mmol) in 20 mL CH_2Cl_2 was added 1.83 g CBr_4 (5.51 mmol) at 0°C. The resultant yellow slurry was stirred at 0°C for 15 min and 23°C for 15 min. The solution of 1.14 g (2*E*,4*R*,5*R*,6*E*,8*S*)-2,4,6,8-tetramethyl-5-(*t*-butyldimethylsilyloxy)-10-phenyl-2,6-decadien-1-al (2.755 mmol) in 8 mL CH_2Cl_2 was then added via cannula. The resulting reaction mixture was stirred at 23°C for 6 h. Pentane (100 mL) was added, and the precipitates formed were filtered off through Celite. The solid residue was dissolved in 10 mL CH_2Cl_2, reprecipitated with 30 mL pentane, and filtered again. This process was repeated for a total of three times. The combined pentane filtrates were concentrated, and the resulting liquid was purified on silica gel (1% EtOAc/hexanes) to give 1.54 g (3*E*,5*R*,6*R*,7*E*,9*S*)-1,1-dibromo-3,5,7,9-tetramethyl-6-(*t*-butyldimethylsilyloxy)-11-phenyl-1,3,7-undecatriene as a colorless oil, in a yield of 98%.

To a stirring solution of 1.52 g (3*E*,5*R*,6*R*,7*E*,9*S*)-1,1-dibromo-3,5,7,9-tetramethyl-6-(*t*-butyldimethylsilyloxy)-11-phenyl-1,3,7-undecatriene (2.66 mmol) in 14 mL THF cooled to –78°C was added 2.23 mL 2.5 M *n*-BuLi in hexanes (5.59 mmol). The resulting yellow solution was stirred at −78°C for 15 min then warmed to 0°C and stirred at 0°C for 30 min. Saturated NH_4Cl solution was added. The mixture was diluted with ether and washed with brine until pH = 7. The combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography (silica gel, 1% EtOAc/hexanes) gave 1.01 g (3*E*,5*R*,6*R*,7*E*,9*S*)-3,5,7,9-tetramethyl-6-(*t*-butyldimethylsilyloxy)-11-phenyl-3,7-undecadien-1-yne as a colorless oil, in a yield of 92%.



Reference 10d.

To a cold (−40°C) solution of 8.87 g PPh_3 (33.82 mmol, 6.4 eq.) in 140 mL dry CH_2Cl_2 was slowly added 5.61 g CBr_4 (16.91 mmol, 3.2 eq.) in 20 mL CH_2Cl_2 under nitrogen. After 15 min of stirring, 15.5 mL NEt_3 (0.111 mol, 12.51 eq.) was added, and the flask was cooled to −78°C. Then, 1.2 g 2-(2-oxoethyl)-1-piperidinecarboxylic acid *tert*-butyl ester (5.28 mmol, 1 eq.) in 20 mL CH_2Cl_2 was added. The temperature reached 0°C over 2 h and the reaction mixture was quenched with water followed by the addition of 10 mL

30% H_2O_2. After being stirred for 15 min at room temperature, the product was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 19:1) to furnish 1.77 g 2-(3,3-dibromo-2-propenyl)-1-piperidinecarboxylic acid *tert*-butyl ester as a white solide, in a yield of 87%, m.p. 135°C.

n-BuLi (5.55 mL, 12.49 mmol, 2 eq.) was added dropwise under nitrogen to 30 mL THF solution containing 2.39 g dibromide (6.25 mmol, 1 eq.) at −78°C. After being stirred for 1 h, the solution was warmed to 0°C, and 2.38 g iodine (9.37 mmol, 1.5 eq.) in 20 mL THF was added. After being stirred overnight at room temperature, the reaction mixture was quenched with a saturated $Na_2S_2O_3$ solution. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated to give 2.16 g 2-(3-iodo-2-propynyl)-1-piperidinecarboxylic acid *tert*-butyl ester as a slightly yellow solid, in a yield of 99%, m.p.139°C.

Other references related to the Corey-Fuchs reaction are cited in the literature. [12]

H. REFERENCES

1. Corey, E. J. and Fuchs, P. L., *Tetrahedron Lett.,* **1972**, 3769.
2. (a) Sahu, B.; Muruganantham, R. and Namboothiri, I. N. N., *Eur. J. Org. Chem.,* **2007**, 2477. (b) Miao, Q.; Xie, X.-G.; Zhang, J.-Y.; She, X.-G. and Pan, X.-F., *J. Chinese Pharm. Sci.,* **2007**, *16*, 41. (c) Yadav, J. S.; Reddy, P. M. K. and Reddy, P. V., *Tetrahedron Lett*., **2007**, *48*, 1037. (d) Clement, S.; Guyard, L.; Knorr, M.; Dilsky, S.; Strohmann, C. and Arroyo, M., *J. Organomet. Chem.,* **2007**, *692*, 839. (e) Rosiak, A.; Frey, W. and Christoffers, J., *Eur. J. Org. Chem.,* **2006**, 4044. (f) Stepnicka, P. and Cisarova, I., *J. Organomet. Chem.,* **2006**, *691*, 2863. (g) Tanaka, K. and Shoji, T., *Org. Lett.,* **2005**, *7*, 3561. (h) Tanaka, K.; Nishida, G.; Ogino, M.; Hirano, M. and Noguchi, K., *Org. Lett.,* **2005**, *7*, 3119. (i) Mamane, V.; Hannen, P. and Fuerstner, A., *Chem. Eur. J.,* **2004**, *10*, 4556. (j) Pastine, S. J.; Youn, S. W. and Sames, D., *Tetrahedron*, **2003**, *59*, 8859. (k) Mainetti, E.; Fensterbank, L. and Malacria, M., *Synlett*, **2002**, 923. (l) Kaafarani, B. R.; Pinkerton, A. A. and Neckers, D. C., *Tetrahedron Lett*., **2001**, *42*, 8137.
3. (a) Bures, F.; Schweizer, W. B.; May, J.; Boudon, C.; Gisselbrecht, J.-P.; Gross, M.; Biaggio, I. and Diederich, F., *Chem. Eur. J.,* **2007**, *13*, 5378. (b) Nierengarten, J.-F.; Zhang, S.; Gegout, A.; Urbani, M.; Armaroli, N.; Marconi, G. and Rio, Y., *J. Org. Chem.,* **2005**, *70*, 7550. (c) Nierengarten, J.-F.; Gu, T.; Hadziioannou, G.; Tsamouras, D. and Krasnikov, V., *Helv. Chim. Acta,* **2004**, *87*, 2948. (d) Anthony, J.; Boldi, A. M.; Rubin, Y.; Hobi, M.; Gramlich, V.; Knobler, C. B.; Seiler, P. and Diederich, F., *Helv. Chim. Acta,* **1995**, *78*, 13.
4. (a) Riveiros, R.; Rumbo, A.; Sarandeses, L. A. and Mourino, A., *J. Org. Chem.,* **2007**, *72*, 5477. (b) Falomir, E.; Murga, J.; Carda, M. and Marco, J. A., *Tetrahedron Lett.,* **2003**, *44*, 539.
5. Gibtner, T.; Hampel, F.; Gisselbrecht, J.-P. and Hirsch, A., *Chem. Eur. J.,* **2002**, *68*, 408.
6. Michel, P. and Rassat, A., *Tetrahedron Lett.*, **1999**, *40*, 8579.
7. Gilbert, A. M.; Miller, R. and Wulff, W. D., *Tetrahedron*, **1999**, *55*, 1607.
8. Gosh, A. K. and Wang, Y., *J. Am. Chem. Soc.*, **2000**, *122*, 11027.
9. (a) Tobe, Y.; Nakanishi, H.; Sonoda, M.; Wakabayashi, T. and Achiba, Y., *Chem. Commun.*, **1999**, 1625. (b) Bridges, A. J.; Lee, A.; Schwartz, C. E.; Towle, M. J. and Littlefield, B. A., *Bioorg. Med. Chem.,* **1993**, *1*, 403.
10. (a) Poupon, J.-C.; Boezio, A. A. and Charette, A. B., *Angew. Chem. Int. Ed.,* **2006**, *45*, 1415. (b) Arefolov, A. and Panek, J. S., *J. Am. Chem. Soc.,* **2005**, *127*, 5596. (c) Auffrant, A.; Diederich,

F.; Boudon, C.; Gisselbrecht, J.-P. and Gross, M., *Helv. Chim. Acta,* **2004**, *87*, 3085. (d) Rouden, J.; Seitz, T.; Lemoucheux, L. and Lasne, M.-C., *J. Org. Chem.,* **2004**, *69*, 3787. (e) Donovan, P. M. and Scott, L. T., *J. Am. Chem. Soc.,* **2004**, *126*, 3108. (f) Giacobbe, S. A.; Di Fabio, R.; Baraldi, D.; Cugola, A. and Donati, D., *Synth. Commun.,* **1999**, *29*, 3125. (g) Polin, J.; Schmohel, E. and Balzani, V., *Synthesis*, **1998**, 321.

11. Zeng, X. Z.; Zeng, F. X. and Negishi, E.-i., *Org. Lett.,* **2004**, *6*, 3245.

12. (a) Chalifoux, W. A. and Tykwinski, R. R., *Chemical Record,* **2006**, *6*, 169. (b) Raw, S. A.; Reid, M.; Roman, E. and Taylor, R. J. K., *Synlett,* **2004**, 819. (c) Kraemer, C. S. and Mueller, T. J. J., *Eur. J. Org. Chem.,* **2003**, 3534. (d) Evans, D. A. and Starr, J. T., *Angew. Chem. Int. Ed*., **2002**, *41*, 1787. (e) Okamura, W. H.; Zhu, G.-D.; Hill, D. K.; Thomas, R. J.; Ringe, K.; Borchardt, D. B.; Norman, A. W. and Mueller, L. J., *J. Org. Chem.,* **2002**, *67*, 1637. (f) Fürstner, A.; Mathes, C. and Grela, K., *Chem. Commun.*, **2001**, 1057. (g) Guanti, G. and Riva, R., *Chem. Commun.,* **2000**, 1171. (h) Scheidt, K. A.; Tasaka, A.; Bannister, T. D.; Wendt, M. D. and Roush, W. R., *Angew. Chem. Int. Ed.,* **1999**, *38*, 1652. (i) Chatgilialoglu, C.; Gimisis, T. and Spada, G. P., *Chem. Eur. J.,* **1999**, *5*, 2866. (j) Alzeer, J.; Cai, C. and Vasella, A., *Helv. Chim. Acta,* **1995**, *78*, 242. (k) Grandjean, D.; Pale, D. and Chuche, J., *Tetrahedron Lett.,* **1994**, *35*, 3529.

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Corey-Gilman-Ganem Oxidation

(Corey-Ganem Oxidation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Corey and co-workers in 1968.[1] It is an efficient synthesis of α,β-unsaturated esters by treatment of α,β-unsaturated aldehydes (or allyl alcohols) with manganese dioxide and potassium cyanide in a proper alcohol. This reaction is thus known as the Corey-Gilman-Ganem oxidation[2] in general or simply the Corey-Ganem oxidatin.[3]

It should be pointed out that manganese dioxide is a mild oxidant that usually converts primary allylic alcohols into conjugated aldehydes without significant further oxidation to carboxylic acids.[4,5] However, in the presence of HCN and cyanide, the α,β-unsaturated aldehydes could be converted into cyanohydrins, which are susceptible to the oxidation of MnO_2 to acyl cyanides. In the presence of an alcohol, the α,β-unsaturated esters are obtained.[1] It should be emphasized that this reaction works only for α,β-unsaturated aldehydes and will not cause any *cis-trans* isomerization for the α,β-unsaturated double bond.[1] For example, benzaldehyde (> 95%), cinnamaldehyde (> 95%), furfural (> 95%), geranial (85–95%), and farnesal (> 95%) have all been transformed into the corresponding methyl esters.[1]

For comparison, silver oxide (Ag_2O) is usually applied to convert a saturated aldehyde into a carboxylic acid; when it is used for α,β-unsaturated aldehydes, it usually causes an undesired *cis-trans* isomerization for the α,β-unsaturated bond as well as other base-induced side reactions.[1] However, in the presence of potassium cyanide, the more powerful oxidant of

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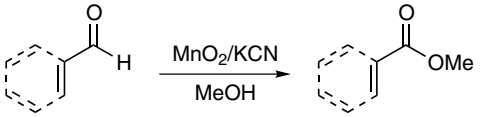
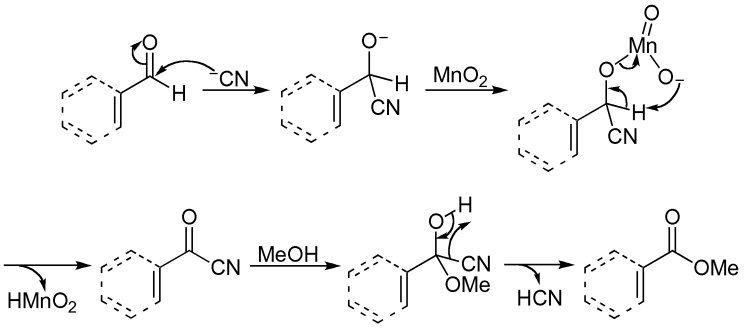
argentic oxide (AgO) oxidizes the α,β-unsaturated aldehydes only into the corresponding carboxylic acids. Therefore, either methyl ester (with active MnO_2) or carboxylic acid (with AgO) could be obtained as expected.[1] Unfortunately, this reaction fails to oxidize piperonal[2] and allyl alcohols with extended conjugation;[6] in addition, this reaction may have the potential problem of the conjugate addition from cyanide ion.

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is believed that this reaction involves the formation of cyanohydrins, which are then converted into the corresponding acyl cyanides; the acyl cyanides are subsequently transformed to either acids or esters in the presence of appropriate solvents, such as acetic acid or methanol.[1,6,7] A tentative illustration of the mechanism for the Corey-Gilman-Ganem oxidation is thus given here.



D. MODIFICATION

This reaction has been improved by the treatment of aldehydes with trimethylsilyl cyanide to give trimethylsilyl cyanohydrins, which are subsequently hydrolyzed to cyanohydrins under weakly acidic conditions and oxidized by MnO_2 to acyl cyanides. Such improvement works under the condition that the original reaction protocol fails.[6] In addition, MnO_2 has been implemented to a tandem oxidation process (TOP) recently because of its mild oxidation ability.[5a]

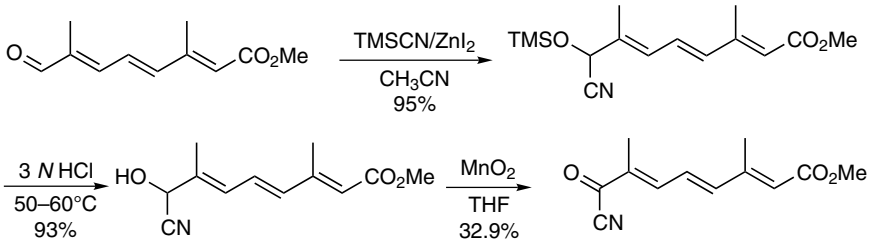
E. APPLICATIONS

This reaction has certain application in the preparation of α,β-unsaturated esters.

F. RELATED REACTIONS

This reaction is related to the *Ball-Goodwin-Morton Oxidation*.

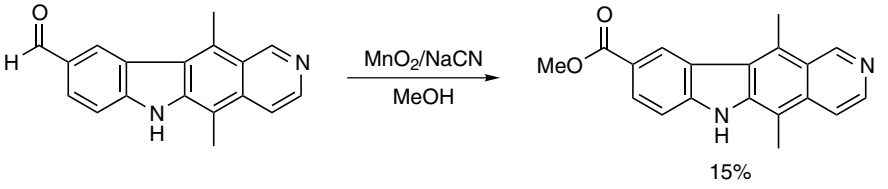
G. CITED EXPERIMENTAL EXAMPLES



Reference 6.

To a solution of 5.3 g methyl 7-formyl-3,7-dimethyl-2,4,6-octatrienoate (27.0 mmol) in 50 mL dry CH_3CN containing a few milligrams of ZnI_2 was added 3.65 mL trimethylsilyl cyanide (27.0 mmol), and the resulting solution was stirred under an atmosphere of nitrogen at room temperature for 2.5 h. The reaction mixture was then treated with charcoal, filtered through Celite, and concentrated to a syrup that was dried in vacuo to afford 7.6 g methyl 8-cyano-8-(trimethylsilyloxy)-3,7-dimethyl-2,4,6-octatrienoate, in a yield of 95%. After that, 6.0 g of this intermediate (20.4 mmol) was suspended in 80 mL 3 *N* HCl, and the mixture was stirred under a nitrogen atmosphere for 2 h at 50–60°C. After cooling, a pale yellow solid was collected by filtration, washed with water, and dried in vacuo to yield 4.2 g methyl 8-cyano-8-hydroxy-3,7-dimethyl-2,4,6-octatrienoate, in a yield of 93%.

To a solution of 2.3 g cyanohydrin (10.4 mmol) in 100 mL THF was added 7.5 g activated MnO_2; the mixture was stirred under a nitrogen atmosphere for 2.5 h at room temperature. The MnO_2 was then removed by filtration and washed with THF. The filtrate, including washings, was concentrated under reduced pressure to a syrup that crystallized to 2.2 g of a solid, which was taken up in CH_2Cl_2 and further purified by flash chromatography to give 750 mg methyl 7-(cyanocarbonyl)-3,7-dimethyl-2,4,6-octatrienoate, in a yield of 32.9% (isolated and pure), m.p. 91–92°C.



Reference 8.

A mixture of 40 mg 9-formylellipticine (0.144 mmol), 200 mg MnO_2 and 200 mg NaCN in 50 mL MeOH was stirred under refluxing for 96 h. The TLC on silica gel ($CHCl_3$/MeOH/NH_4OH, 90:9:1) showed the disappearance of the starting material at $R_f =$ 0.77 and the formation of a major spot at R_f = 0.81. The reaction mixture was cooled to

room temperature and filtered through Celite, and the remaining on Celite was washed with 20 mL MeOH. The combined filtrates were evaporated under reduced pressure to dryness, and the residue was stirred in 12 mL water, of which the pH was adjusted to 8 with the dropwise addition of acetic acid. This suspension was stored at 5°C for 18 h and filtered. The residue was washed well with water, air-dried, and flash chromatographed on silica gel using a gradient of 2–8% MeOH in $CHCl_3$. Appropriate fractions were pooled and evaporated to afford a residue that was dissolved in glacial acetic acid and filtered. This solution was evaporated to dryness under reduced pressure, and the residue was dissolved in hot EtOAc and left at 0°C for 72 h. The deposited solid was filtered and dried to afford 6 mg ellipticine-9-carboxylic acid methyl ester as a yellow solid, in a yield of 15%, m.p. 272–274°C (dec.), R_f = 0.24 (benzene/EtOH = 9:1). (*Note:* Be aware that the yield might vary owing to the loss of any small amount of material in such a small reaction scale.)

Other references related to the Corey-Gilman-Ganem oxidation are cited in the literature.[9]

H. REFERENCES

1. Corey, E. J.; Gilman, N. W. and Ganem, B. E., *J. Am. Chem. Soc.,* **1968**, *90*, 5616.
2. (a) Rinner, U. and Hudlicky, T., *Synlett,* **2005**, 365. (b) Keck, G. E.; Wagner, T. T. and Rodriquez, J. F. D., *J. Am. Chem. Soc.,* **1999**, *121*, 5176.
3. Coleman, R. S.; Walczak, M. C. and Campbell, E. L., *J. Am. Chem. Soc.,* **2005**, *127*, 16038.
4. See *Ball-Goodwin-Morton Oxidation* herein (P. 173).
5. (a) Taylor, R. J. K.; Reid, M.; Foot, J. and Raw, S. A., *Acc. Chem. Res.,* **2005**, *38*, 851. (b) Fieser, L. F. and Fieser, M., *Reagents for Organic Synthesis,* John Wiley & Sons., New York, **1967**, pp. 637–643.
6. Shealy, Y. F.; Riordan, J. M.; Frye, J. L.; Simpson-Herren, L.; Sani, B. P. and Hill, D. L., *J. Med. Chem.,* **2003**, *46*, 1931.
7. George, M. V. and Balachandran, K. S., *Chem. Rev.,* **1975**, *75*, 491.
8. Devraj, R.; Barrett, J. F.; Fernandez, J. A.; Katzenellenbogen, J. A. and Cushman, M., *J. Med. Chem.,* **1996**, *39*, 3367.
9. (a) Foot, J. S.; Kanno, H.; Giblin, G. M. P. and Taylor, R. J. K., *Synthesis,* **2003**, 1055. (b) Foot, J. S.; Kanno, H.; Giblin, G. M. P. and Taylor, R. J. K., *Synlett,* **2002**, 1293. (c) Yamamoto, H. and Oritani, T., *Tetrahedron Lett.,* **1995**, *36*, 5797. (d) Baciocchi, E.; Muraglia, E. and Sleiter, G., *J. Org. Chem.,* **1992**, *57*, 2486. (e) Fisher, M. J.; Chow, K.; Villalobos, A. and Danishefsky, S. J., *J. Org. Chem.,* **1991**, *56*, 2900. (f) Schlessinger, R. H.; Iwanowicz, E. J. and Springer, J. P., *J. Org. Chem.,* **1986**, *51*, 3070. (g) Kondo, K.; Negishi, A.; Matsui, K.; Tunemoto, D. and Masamune, S., *J. Chem. Soc., Chem. Commun.,* **1972**, 1311. (h) Corey, E. J.; Katzenellenbogen, J. A.; Gilman, N. W.; Roman, S. A. and Erickson, B. W., *J. Am. Chem. Soc.,* **1968**, *90*, 5618.

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Corey-Kim Oxidation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Corey and Kim in 1972.[1] It is the preparation of aldehydes and ketones from the oxidation of primary and secondary alcohols via their dimethylalkoxysulfonium salts. Therefore, this reaction is generally known as the Corey-Kim oxidation[2] or simply the Corey-Kim reaction.[3] This reaction is operationally simple, highly selective, and efficient.[1] On large reaction scale, the dimethylalkoxysulfonium salt of alcohols are formed with dimethylsulfide and chlorine;[1] whereas on a laboratory scale, the dimethylchlorosulfonium salt can be generated more conveniently from *N*-succinimide chloride (or *N*-chlorosuccinimide, NCS) and dimethylsulfide, by which the formation of hydrogen chloride is avoided.[1] The combination of *N*-succinimide chloride and dimethylsulfide is therefore called the Corey-Kim reagent[4] which offers a milder oxidation condition and cleaner products.[1] Upon treatment with the base, the dimethylchlorosulfonium salt cleaves intramolecularly to give aldehydes and ketones. The application of 6-morpholinohexan-1-thiol ether[2b] or dodecyl methyl sulfide[2d] as the substitute for dimethylsulfide results in an odorless oxidation condition. In addition, the Corey-Kim reagent provides a new methylation of an unsaturated bond from the nucleophilic addition of carbanion followed by the treatment with Raney nickle.[4a]

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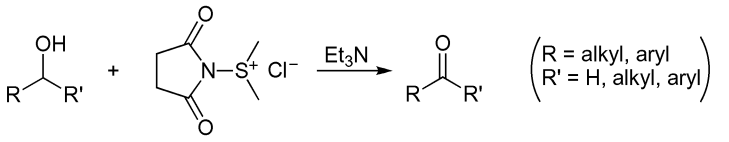
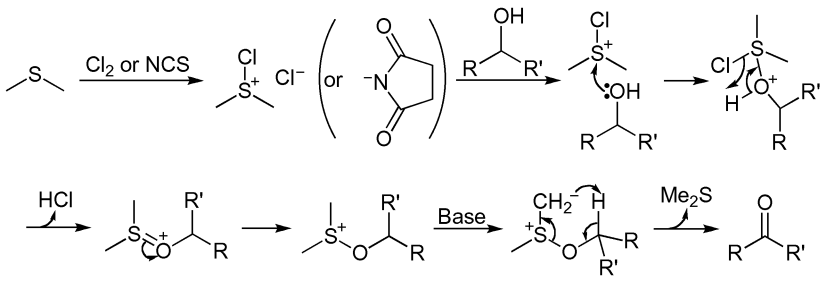
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Displayed below is a simple illustration of the reaction mechanism.



D. MODIFICATION

The nonvolatile thioethers have been substituted for the dimethyl sulfide to provide an odorless oxidation condition.[2b−2d]

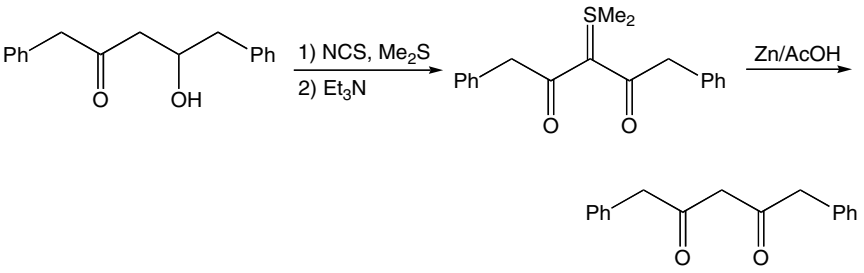
E. APPLICATIONS

This reaction has general applications in the conversion of primary and secondary alcohols into aldehydes and ketones, respectively.

F. RELATED REACTIONS

This reaction is related to the *Dess-Martin Oxidation, Swern Oxidation*, and *Pfitzner-Moffatt Oxidation*.

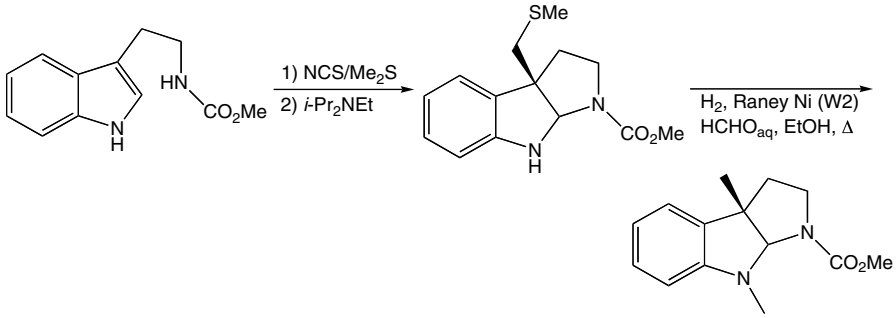
G. CITED EXPERIMENTAL EXAMPLES



Reference 4b.

To a stirred suspension of 20 mmol NCS in 60 mL anhydrous CH_2Cl_2 was added dropwise 40 mmol dimethyl sulfide at –70°C under argon, and stirring was continued for 1 h. Then a solution of 4.0 mmol 4-hydroxy-1,5-diphenyl-pentan-2-one in 6 mL CH_2Cl_2 was added; at the same temperature, the solution was stirred for 1 h. Triethylamine (60 mmol) was then added, and after 1 h the reaction mixture was treated with 20 mL saturated brine. This mixture was extracted with ether, and the organic layer was washed with saturated brine and evaporated. The residue was purified by column chromatography using 95:5 chloroform/acetone as an eluent to give 80% dimethylsulfonium 1-(phenylacetyl)-2-oxo-3-phenylpropylide as a pale yellow viscous oil.

To a stirred suspension of 1.5 mmol of the ylide and 30 mmol zinc powder in 25 mL CH_2Cl_2 was added 30 mmol acetic acid at 0°C, and stirring was continued at room temperature overnight. The mixture was filtered through Celite, and the filtrate was washed with saturated $NaHCO_3$ and water, eluted with CH_2Cl_2 through a short column of Florisil (100–200 mesh), and evaporated. The crude product was crystallized from methanol to give 88% 1,5-diphenyl-2,4-pentanedione, m.p. 64–65°C.



Reference 4a.

To a solution of *N*-chlorosuccinimide (133 mg, 1.0 mmol) in CH_2Cl_2 was added 75 mg dimethyl sulfide (1.2 mmol) at –78°C, and the mixture was stirred for 1 h. To this reaction mixture, was added a solution of 109 mg indole derivative (0.5 mmol) in CH_2Cl_2 and 155 mg diisipropylethylamine (1.2 mmol); the whole mixture was stirred for 2 h at –78°C. The mixture was treated with cooled brine and extracted with CH_2Cl_2. The combined organic layers were washed and dried over $MgSO_4$. After evaporation of the solvent,

a residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane 1:5 to1:2) and afforded 139 mg 3a-methylthiomethyl-1-methoxycarbonyl-8-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole in a yield of 92%, m.p. 86.5–87.5°C (white powder was recrystallized from Et_2O). (*Note:* The procedure for the second step is not provided in the original literature.)

Other references related to the Corey-Kim oxidation are cited in the literature. [5]

H. REFERENCES

1. Corey, E. J. and Kim, C. U., *J. Am. Chem. Soc*., **1972**, *94*, 7586.
2. (a) Schilling, G., *GIT Labor-Fachzeitschrift*, **2005**, *49*, 154. (b) Nishide, K.; Patra, P. K.; Matoba, M.; Shanmugasundaram, K. and Node, M., *Green Chem.,* **2004**, *6*, 142. (c) Ohsugi, S.-I.; Nishide, K.; Oono, K.; Okuyama, K.; Fudesaka, M.; Kodama, S. and Node, M., *Tetrahedron*, **2003**, *59*, 8393. (d) Nishide, K.; Ohsugi, S.-I.; Fudesaka, M.; Kodama, S. and Node, M., *Tetrahedron Lett*., **2002**, *43*, 5177.
3. Crich, D. and Neelamkavil, S., *Tetrahedron*, **2002**, *58*, 3865.
4. (a) Kawahara, M.; Nishida, A. and Nakagawa, M., *Org. Lett.,* **2000**, *2*, 675. (b) Pulkkinen, J. T. and Vepsäläinen, J. J., *J. Org. Chem.,* **1996**, *61*, 8604. (c) Katayama, S.; Fukuda, K.; Watanabe, T. and Yamauchi, M., *Synthesis,* **1988**, 178.
5. (a) Ohsugi, S.-I.; Nishide, K.; Oono, K.; Okuyama, K.; Fudesaka, M.; Kodama, S. and Node, M., T*etrahedron*, **2003**, *59*, 8393. (b) Katayama, S.; Watanabe, T. and Yamauchi, M., *Chem. Pharm. Bull*., **1992**, *40*, 2836. (c) Corey, E. J. and Kim, C. U., *Tetrahedron Lett.,* **1974**, 287. (d) Corey, E. J. and Kim, C. U., *J. Org. Chem.,* **1973**, *38*, 1233.

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Corey-Kwiatkowski Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Corey and Kwiatkowski in 1966.[1] It is the preparation of olefins from the reaction between aldehydes or ketones and lithium alkylphosphonamides followed by the decomposition of β-hydroxyphosphonamide intermediates in refluxing benzene or toluene.[1] Therefore, it is known as the Corey-Kwiatkowski reaction.[2] The direct addition product (i.e., the lithio derivative) is quite stable even at 0°C in THF under nitrogen.[1] The hydroxyphosphonamides from ketones generally decompose faster than those from aldehydes, and the ones with α-substituent(s) decompose even faster.[3] This method is good for a wide variety of olefins, including the mono-, di-, tri- and tetra-substituted olefins.[1,3] Compared to the *Wittig Reaction*, this method of olefination has following obvious advantages:[1] (*a*) the absence of triphenylphosphine oxide, which can complicate the isolation of olefin; (*b*) the possibility of purification at the stage of β-hydroxyphosphonamide; (*c*) relatively easy control of stereochemistry of the olefins (to form either *cis*- or *trans*-olefin); and (*d*) availability and potential low cost of the phosphonamides, which can be prepared from phosphonyl dichlorides and dimethylamine[3] or cyclic diamines[4] (phosphonyl dichloride can be synthesized by alkylation of phosphorus trichloride with alkyl chloride and $AlCl_3$).[3] In addition, the alkyl phosphonamides can be replaced by alkyl phosophonothiate where the formed β-hydroxyphosphonothiate can decompose at low temperature (e.g., room temperature), and silver salt can be applied as catalyst.[5] The lithio derivatives of both phosphonamides and phosphonothiates can be derivatized via alkylation with alkyl halides.[1,3,5] The reaction between lithium phosphonamide or phosphonate and

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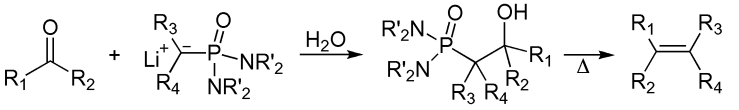
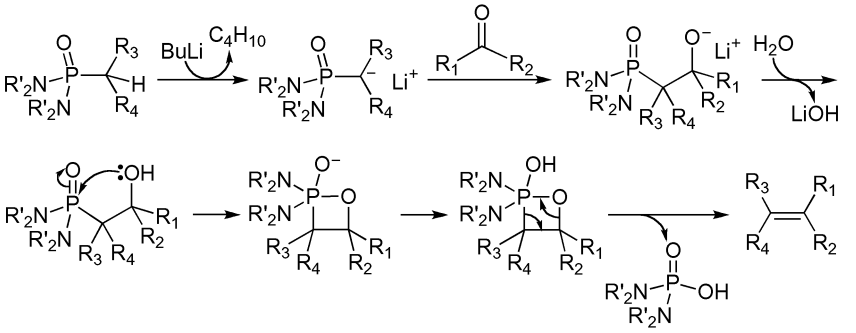
ester to give β-keto phosphonamide or phosphonate is called the Corey-Kwiatkowski condensation.[6]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Displayed below is a simple illustration of the reaction mechanism.



D. MODIFICATION

This reaction has been modified to start with cyclic phosphonamides via the reaction between phosphonyl dichloride with diamines.[4]

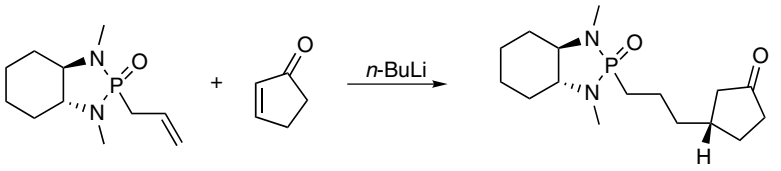
E. APPLICATIONS

This reaction has general application in the synthesis of multisubstituted olefins.

F. RELATED REACTIONS

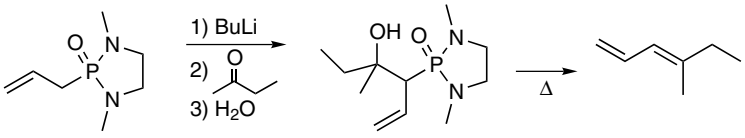
This reaction is related to the *Wittig Reaction* and *Emmons-Horner Reaction.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 4a.

To a solution of 1 mmol allyl phosphonamide in 10 mL THF was added 1.2 mmol of *n*-BuLi (1.6 or 2.5 M solution in hexane) at −78°C under argon. A solution of 1.2 mmol α,β-unsaturated-cyclopentanone in 5 mL THF at −78°C was added immediately via cannula. The reaction mixture was stirred at −78°C for 30 min, slowly quenched with saturated aqueous NH_4Cl (or with MeI (10 eq.), with BnBr (5 eq.), and with allyl bromide (5 eq.)) to form further alkylated products and allowed to warm to ambient temperature. The mixture was diluted with 50 mL EtOAc and washed with 20 mL brine and 20 mL water. The organic layer was separated, dried over $MgSO_4$, and concentrated in vacuo. The resulting crude product was purified by column chromatography (EtOAc/MeOH) to give 88% of 1,4-addition product, with R:S ratio of 93:7.



Reference 4c.

To a stirred solution of 0.628 g cyclic allyl phosphonamide (3.61 mmol) in 10 mL tetrahydrofuran was added 2.4 mL 1.6 M *n*-butyllithium (3.84 mmol) at –78°C under argon. After 0.5 h, 0.285 g methyl ethyl ketone (4.18 mmol) was added. Water (0.2 mL) was added after an additional 10 min, and the solution was allowed to warm to room temperature, whereupon the reaction mixture was diluted with 100 mL methylene chloride and filtered through a glass wool plug. The solution was dried over sodium sulfate and filtered, and the solvent was evaporated under vacuum at room temperature to yield 0.816 g of a sticky yellow syrup containing some residual methylene chloride.

A suspension of 0.389 g of the sticky syrup (1.58 mmol, containing some methylene chloride) in 0.5 mL Nujol along with 0.4 g anhydrous calcium carbonate was degassed and then heated to 133°C for 2 h under vacuum, the volatile products were collected in a trap and held at –196°C. The trapped material was distilled into a tared flask to yield 0.175 g *cis*- and *trans*-mixture of 4-methyl 1,3-hexadienes, in a yield of 90% after correction of CH_2Cl_2.

Other references related to the Corey-Kwiatkowski olefination are cited in the literature.[7]

H. REFERENCES

1. Corey, E. J. and Kwiatkowski, G. T., *J. Am. Chem. Soc.,* **1966**, *88*, 5652.
2. Mulzer, J.; Martin, H. J. and List, B., *Tetrahedron Lett*., **1996**, *37*, 9177.
3. Corey, E. J. and Kwiatkowski, G. T., *J. Am. Chem. Soc.,* **1968**, *90*, 6816.
4. (a) Hanessian, S.; Gomtsyan, A. and Malek, N., *J. Org. Chem.,* **2000**, *65*, 5623. (b) Hanessian, S.; Delorme, D.; Beaudoin, S. and Leblanc, Y., *J. Am. Chem. Soc.,* **1984**, *106*, 5154. (c) Corey, E. J. and Cane, D. E., Corey, E. J. and Cane, D. E., *J. Org. Chem.,* **1969**, *34*, 3053.
5. Corey, E. J. and Kwiatkowski, G. T., *J. Am. Chem. Soc.,* **1966**, *88*, 5654.
6. Ciufolini, M. A. and Roschangar, F., *Angew. Chem. Int. Ed. Engl.,* **1996**, *35*, 1692.
7. (a) Reichwein, J. F. and Pagenkopf, B. L., *J. Am. Chem. Soc.,* **2003**, *125*, 1821. (b) Corey, E. J. and Kwiatkowski, G. T., *J. Am. Chem. Soc.,* **1966**, *88*, 5653.

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Corey-Link Reaction

(Corey-Link Amino Acid Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Corey and Link in 1992.[1] It is an enantioselective synthesis of α-amino acids by means of the asymmetric reduction of trichloromethyl ketones from catecholborane in the presence of either (*R*)- or (*S*)-oxazaborolidine, followed by the treatment of the resulting alcohols with base and sodium azide and subsequently the reductive conversion of the azido group into an amino group. Therefore, this reaction is generally known as the Corey-Link reaction.[2] Occasionally, it is also referred to as the Corey-Link amino acid synthesis,[2e,3] Corey-Link procedure,[2e] etc.

In this reaction, the trichloromethyl ketones can be prepared either from the nucleophilic addition of trichloromethide to aldehydes followed by oxidation or from acylation of carbon nucleophile by trichloroacetyl chloride.[1] It has been found that in the presence of catalytic amount of either (*R*)- or (*S*)-oxazaborolidine, the reduction of the corresponding trichloromethyl ketones by catecholborane usually gives high selectivity, e.g., with greater than 97:3 of enantioselectivity.[1] Upon treatment of 2 eq. sodium azide and 4 eq. NaOH in aqueous dimethyl glycol, the trichloromethyl carbinol is smoothly converted into α-azido acid with inversion of the configuration.[1] Then the α-azido acids can be reduced by palladium-catalyzed hydrogenation,[1] zinc in acetic acid,[4] or possibly by the *Staudinger Reaction* to give α-amino acids. Due to the nature of this reaction, the Corey-Link reaction is useful for the preparation of α-azido esters, α-azido acids, and α-amino acids with desired stereochemistry by the correctly chosen chiral catalyst.[1]

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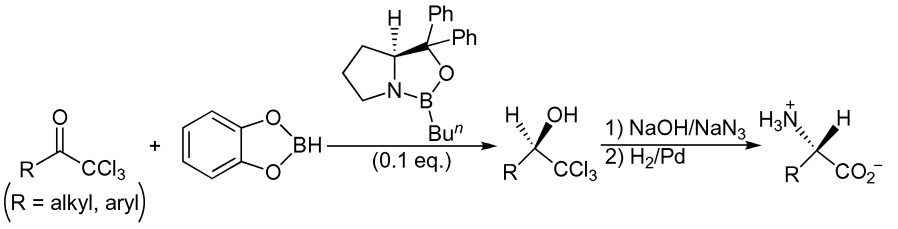
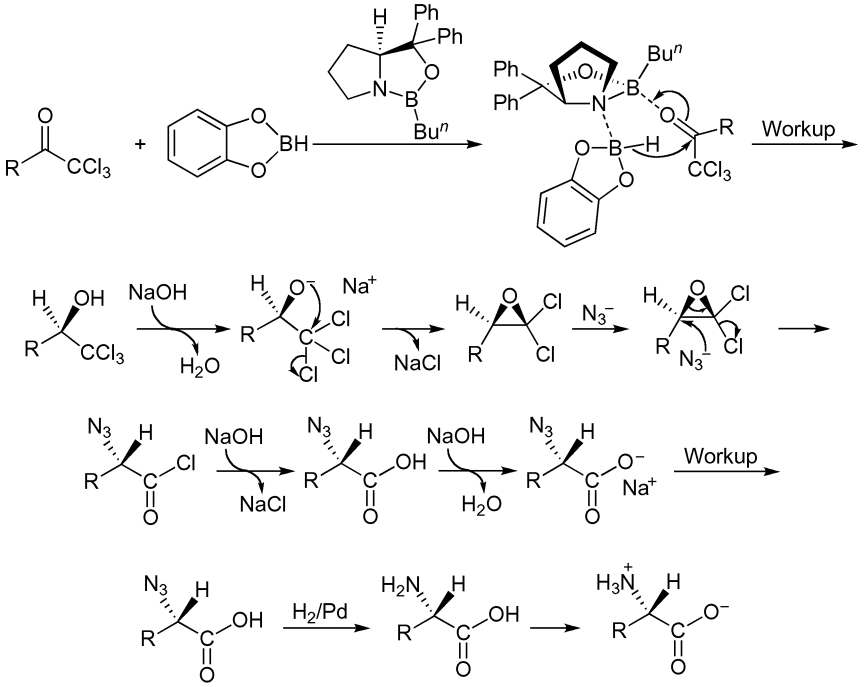
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The high enantioselectivity for the reduction of trichloromethyl ketones by catecholborane is due to the directive effect of (*R*)- or (*S*)-oxazaborolidine.[5] After deprotonation by base, the trichloromethyl carbinol forms alkoxide and attacks the adjacent trichloromethyl group intramolecularly to form *gem*-dichlorooxirane or *gem*-dichloroepoxide, which is highly reactive toward nucleophilic attack by azide anion and proceeds a S_N2 substitution with exclusive inversion of the configuration accompanied by concerted ring opening to give α-azido acid.[1] Finally, the resulting α-azido acid can be simply converted into α-amino acid. The detail of this reaction is displayed below.



D. MODIFICATION

This reaction has been modified by treatment of *gem*-trichloromethyl-substituted tertiary alcohols (generated from the nucleophilic addition of trichloromethide), e.g., $CHCl_3$ + LHMDS) by sodium azide and an organic base (e.g., DBU) in alcohol to form α-azido ester in a one-pot manner.[2,6] The resulting α-azido ester can then be selectively converted into α-azido alcohol with cold $NaBH_4$.[7]

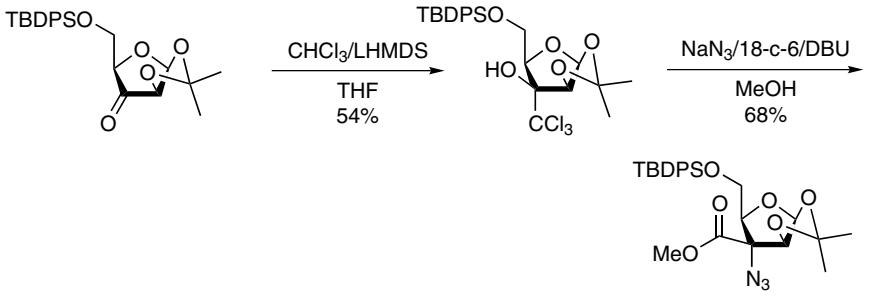
E. APPLICATIONS

This reaction has general applications in the preparation of α-amino acids of determined stereochemistry.

F. RELATED REACTIONS

This reaction is related to the *Corey-Bakshi-Shibata Reduction* and *Strecker Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2e.

To a solution of 15 mL anhydrous pyridine (187 mmol) in 150 mL anhydrous CH_2Cl_2 was added 9.4 g CrO_3 (94 mmol), and the mixture was stirred for 15 min. After the mixture was cooled to 0°C, a solution of 10.0 g 5-*O*-*tert*-butyldiphenylsilyl-1,2-*O*-isopropylidene-β-D-arabinofuranose (23.0 mmol) in 70 mL CH_2Cl_2 was added dropwise. Acetic anhydride (9.0 mL, 94 mmol) was added, and the mixture was stirred for 30 min. The whole mass was poured into a 500-mL 1:4 mixture of toluene and EtOAc. After being stirred for 20 min, the mixture was filtered through a layer of silica, and the silica gel was rinsed three times with EtOAc. The combined filtrate was evaporated under reduced pressure to give 8.70 g 5-*O*-*tert*-butyldiphenylsilyl-1,2-*O*-isopropylidene-β-D-arabinofuran-3-ulose as an oil, in a yield of 90%.

To a solution of 2.6 mL $CHCl_3$ (32 mmol) in 25 mL anhydrous THF was added 2.5 g 5-*O*-*tert*-butyldiphenylsilyl-1,2-*O*-isopropylidene-β-D-arabinofuran-3-ulose (5.9 mmol). After the solution was cooled to –78°C, 21.3 mL 1.0 M LiHMDS solution in THF (21.3 mmol)

was added slowly. The solution was stirred at –78°C for 3 h, and the reaction mixture was then poured into an ice cold saturated aqueous $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2, and the combined organic phases were dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using hexanes/EtOAc (9:1) as the eluent to afford 1.72 g 5-*O*-*tert*-butyldiphenylsilyl-3-*C*-trichloromethyl-1,2-*O*-isopropylidene-β-D-lyxofuranose as an oil, in a yield of 54%.

To 25 mL anhydrous MeOH was added 2.9 g tertiary alcohol (5.3 mmol), then 1.04 g NaN_3 (16.0 mmol) and 15.0 mg 18-crown-6 (0.057 mmol) were added. Then 4.0 mL DBU (26.7 mmo) was added dropwise, the resulting mixture was stirred at 50°C for 1 h and poured into 50 mL saturated aqueous NH_4Cl solution. The mixture was extracted with ether, the combined organic extracts were dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using hexanes/EtOAc (9:1) as the eluent to afford 1.83 g 3-*C*-azido-5-*O*-*tert*-butyldiphenylsilyl-1,2-*O*-isopropylidene-3-*C*-methoxycarbonyl-β-D-arabinofuranose as an oil, in a yield of 68%.

Other references related to the Corey-Link reaction are cited in the literature.[8]

H. REFERENCES

1. Corey, E. J. and Link, J. O., *J. Am. Chem. Soc.,* **1992**, *114*, 1906.
2. (a) Schafmeister, C. E., *U.S. Pat*., Sept. 28, **2006**, 20060217534A1. (b) Scaffidi, A.; Skelton, B. W.; Stick, R. V. and White, A. H., *Aust. J. Chem.,* **2006**, *59*, 426. (c) Scaffidi, A.; Skelton, B. W.; Stick, R. V. and White, A. H., *Aust. J. Chem.,* 2004, *57*, 723. (d) Forman, G. S.; Scaffidi, A. and Stick, R. V., *Aust. J. Chem.,* **2004**, *57*, 25. (e) Sørensen, M. H.; Nielsen, C. and Nielsen, P., *J. Org. Chem.,* **2001**, *66*, 4878. (f) Dominguez, C.; Ezquerra, J.; Baker, S. R.; Borrelly, S.; Prieto, L.; Espada, M. and Pedregal, C., *Tetrahedron Lett.*, **1998**, *39*, 9305.
3. (a) Barrett, G. C., "Amino Acids" in *Amino Acids, Peptides and Proteins, vol. 32*, ed. Davies, J. S., The Royal Society of Chemistry, Cambridge, UK, **2001**, pp. 1–160. (b) Baker, S. R. and Hancox, T. C., *Tetrahedron Lett.,* **1999**, *40*, 781.
4. Habay, S. A., "The Synthesis and Characterization of Water Soluble Hydroindole-Based Nanostructures of Designed Three-Dimensional Architectures" Doctoral Dissertation, University of Pittsburgh, **2005**.
5. Nicolaou, K. C.; Sorensen, E. J. and Winssinger, N., *J. Chem. Edu.,* **1998**, *75*, 1225.
6. Pedregal, C. and Prowse, W., *Bioorg. Med. Chem.*, **2002**, *10*, 433.
7. Mori, K. and Kinsho, T., *Liebigs Ann.,* **1991**, 1309.
8. (a) Anwar, M.; Bailey, J. H.; Dickinson, L. C.; Edwards, H. J.; Goswami, R. and Moloney, M. G., *Org. Biomol. Chem.,* **2003**, *1*, 2364. (b) Pedregal, C. and Prowse, W., *Bioorg. Med. Chem.,* **2002**, *10*, 433.

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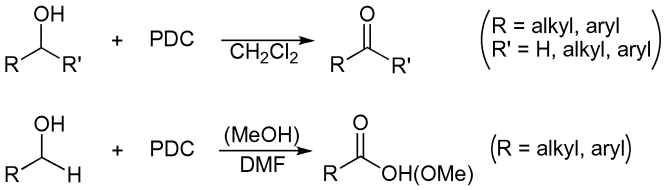
Corey-Schmidt Oxidation
(PDC Oxidation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Corey and Schmidt in 1979.[1] It is the oxidation of an organic compound using pyridinium dichromate (PDC) and is simply known as the PDC oxidation.[2] PDC is a stable, bright orange solid prepared by dissolving CrO_3 in a minimal volume of water followed by precipitation after the addition of pyridine. PDC is less acidic than PCC but more acidic than the Collins reagent. In this reaction, primary alcohols can be oxidized to either aldehydes[3] or carboxylic acids[4] or even esters,[5] depending on the substrate and solvent. Normally, the suspension of PDC in dichloromethane oxidizes primary alcohols to the corresponding aldehydes,[3] whereas PDC in DMF oxidizes primary alcohols into either carboxylic acids[4] or methyl esters (in the presence of methanol for latter case[5]). Similarly, PDC can also oxidize the aldehyde group into a carboxylic group in a solvent of DMF.[6] The oxidation of alcohols to other esters are not successful. On the other hand, secondary alcohols can be oxidized to ketones too.[7] In addition, pyridinium dichromate can also oxidize the active methylene group (either allylic or benzylic) into a carbonyl group in the presence of *t*-butyl hydroperoxide,[8] whereas PDC alone will not affect the benzyl ethers of alcohols.[9] This oxidation has shown some advantages over other chromium-based oxidations (e.g., Jones, Fieser, CrO_3/AcOH, and pyridinium chlorochromate) in the oxidation of diols into diketones, and the rest of the chromium-based oxidations are reported to give lower yields accompanyed by other oxidized products when compared to the Corey-Schmidt oxidation.[7] It has been reported that when a methylamino group is present in the substrate alcohol, the oxidation using PDC does not succeed.[10] This oxidation has been reviewed.[11]

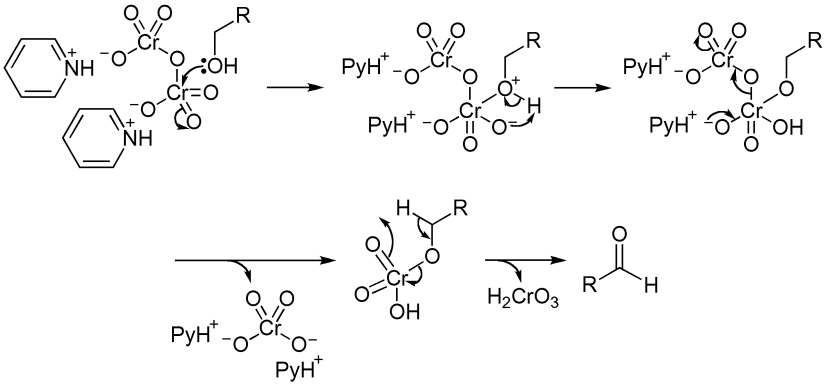
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

PDC was originally prepared by Corey and co-workers by adding 1 eq. pyridine to a solution of chromium (VI) trioxide and concentrated hydrochloric acid, which precipitated as pyridinium dichromate salt. In the PDC oxidation, the six-valent chromium atom is reduced to only four valents, as displayed here.



D. MODIFICATION

N/A

E. APPLICATIONS

This reaction has wide application for the oxidation of alcohols.

F. RELATED REACTIONS

This reaction is related to the *Corey-Suggs Oxidation*.

G. CITED EXPERIMENTAL EXAMPLES

Reference 12.

Pyridinium dichromate (15.64 g, 41.6 mmol) was suspended in a mixture of 320 mL dry CH_2Cl_2 and 11.8 mL acetic anhydride (124.8 mmol). A solution of 11.11 g 1-*O*-methyl-3,5-di-*O*-benzyl-α,β-D-ribofuranose-3,4,5,5′-$^2H_4$ (32.0 mmol) in dry CH_2Cl_2 was added to the suspension, and the reaction mixture was refluxed at ~80°C for 3 h. After the dilution with EtOAc, a precipitate was formed, and the solution was filtered through silica gel using EtOAc as the eluent. The solvents were evaporated, and the residue was co-evaporated with toluene to give 7.93 g 1-*O*-methyl-3,5-di-*O*-benzyl-α,β-D-ribofuranose-2-ulose-3,4,5,5′-$^2H_4$ as an oily product (23.0 mmol, 72%), which was taken to the next step without further purification.

Reference 4a.

(*R*)-2-Hydroxy-1-*tert*-butoxycarbonylaminoethylcarbamic acid benzyl ester (1.0 g, 3.22 mmol) was dissolved in 3.2 mL DMF. Solid PDC (3.64 g, 9.67 mmol) was then added, and the reaction mixture was stirred for 20 h at room temperature. The reaction mixture was then poured into 100 mL water, acidified to pH 3, and extracted with EtOAc (4 × 30 mL). The organic phase was washed with water. Upon the addition of saturated $NaHCO_3$ solution (3 × 30 mL), the product transferred to the aqueous phase, which was washed once with EtOAc and then acidified with solid $NaHSO_4$ to pH 3. The precipitated product was then extracted with EtOAc (3 × 30 mL), and the combined extracts were washed with water, dried over anhydrous $MgSO_4$, and evaporated to yield 596 mg (*R*)-benzyloxycarbonylamino-*tert*-butoxycarbonylaminoacetic acid, [(*R*)-Boc-(Cbz)-Agl-OH], in a yield of 59%, m.p. 149–150°C.

Other references related to the Corey-Schmidt oxidation are cited in the literature.[13]

H. REFERENCES

1. Corey, E. J. and Schmidt, G., *Tetrahedron Lett.,* **1979**, 399.
2. (a) Xu, G.; Hou, A.-J.; Wang, R.-R.; Liang, G.-Y.; Zheng, Y.-T.; Liu, Z.-Y.; Li, X.-L.; Zhao, Y.; Huang, S.-X.; Peng, L.-Y. and Zhao, Q.-S., *Org. Lett.,* **2006**, *8*, 4453. (b) Nakamura, M.; Inoue, J. and Yamada, T., *Bioorg. Med. Chem. Lett.,* **2000**, *10*, 2807.
3. (a) Rusterholz, D. B.; Gorman, D. B. and Gassman, P. G., *Molecules,* **1997**, *2*, 80. (b) de Montellano, P. R. O. and Grab, L. A., *Biochemistry,* **1987**, *26*, 5310. (c) Terpstra, J. W. and van Leusen, A. M., *J. Org. Chem.,* **1986**, *51*, 230.

4. (a) Sypniewski, M.; Penke, B.; Simon, L. and Rivier, J., *J. Org. Chem.,* **2000**, *65*, 6595. (b) Berkowitz, D. B.; Eggen, M. J.; Shen, Q. R. and Shoemaker, R. K., *J. Org. Chem.,* **1996**, *61*, 4666. (c) Kawabata, T.; Kimura, Y.; Ito, Y. and Terashima, S., *Tetrahedron,* **1988**, *44*, 2149. (d) Schreiber, S. L. and Wang, Z. Y., *J. Am. Chem. Soc.,* **1985**, *107*, 5303.
5. (a) Garegg, P. J.; Olsson, L. and Oscarson, S., *J. Org. Chem.,* **1995**, *60*, 2200. (b) O'Connor, B. and Just, G., *Tetrahedron Lett.,* **1987**, *28*, 3235.
6. Mazur, P. and Nakanishi, K., *J. Org. Chem.,* **1992**, *57*, 1047.
7. Zalikowski, J. A.; Gilbert, K. E. and Borden, W. T., *J. Org. Chem.,* **1980**, *45*, 346.
8. Chidambaram, N. and Chandrasekaran, S., *J. Org. Chem.,* **1987**, *52*, 5048.
9. Bal, B. S.; Kochhar, K. S. and Pinnick, H. W., *J. Org. Chem.,* **1981**, *46*, 1492.
10. Jiang, S. D.; McCullough, K. J.; Mekki, B.; Singh, G. and Wightman, R. H., *J. Chem. Soc., Perkin Trans. I,* **1997**, 1805.
11. Ley, S. V.; Madin, A., "Chapter 2.7, Oxidation Adjacent to Oxygen of Alcohols by Chromium Reagents" in *Comprehensive Organic Synthesis*, ed. Trost, B. M. and Fleming, I., Pergamon Press, Oxford, **1991**, *7*.
12. Földesi, A.; Trifonova, A.; Dinya, Z. and Chattopadhyaya, J., *J. Org. Chem.,* **2001**, *66*, 6560.
13. (a) Hu, X.-D.; Fan, C.-A.; Zhang, F.-M. and Tu, Y. Q., *Angew. Chem. Int. Ed.,* **2004**, *43*, 1702. (b) Kabilan, S.; Girija, R.; Reis, J. C. R.; Segurado, M. A. P. and Gomes, de Oliveira, J. D., *J. Chem. Soc., Perkin Trans. II*, **2002**, 1151. (c) Evans, L. D. B.; Roszak, A. W.; Noble, L. J.; Robinson, D. A.; Chalk, P. A.; Mattews, J. L.; Coggins, J. R.; Price, N. C. and Lapthorn, A. J., *FEBS Letters,* **2002**, *530*, 24. (d) Cha, J. S. and Chun, J. H., *Bull. Korean Chem. Soc*., **2000**, *21*, 375. (e) Hrebabecky, H. and Holy, A., *Coll. Czech. Chem. Commun.,* **1997**, *62*, 1128. (f) Furuyoshi, S.; Shi, Y.-Q. and Rando, R. R., *Biochemistry,* **1993**, *32*, 5425. (g) Muzart, J., *Chem. Rev.,* **1992**, *92*, 113. (h) Rosini, G.; Galarini, R.; Marotta, E. and Righi, P., *J. Org. Chem.,* **1990**, *55*, 781. (i) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pilli, R. and Badertscher, U., *J. Org. Chem.,* **1985**, *50*, 2095.

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Corey-Suggs Oxidation
(PCC Oxidation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Corey and Suggs in 1975.[1] It is the oxidation of primary and secondary alcohols into carbonyl compounds using pyridinium chlorochromate (PCC) commonly in a solvent of dichloromethane. Therefore, this reaction is known as the Corey-Suggs oxidation[2] but more generally referred to as PCC oxidation.[3] Likewise, PCC is usually called the Corey-Suggs reagent.[2,3g] This reaction was originally reported as using 1:1.5 ratio of substrate to PCC for a complete oxidation; however, it was subsequently reported that the Corey-Suggs oxidation involves only two electrons, and a 1:1 ratio of substrate to PCC is enough for the complete conversion of alcohols into carbonyl compounds.[4] The Corey-Suggs oxidation has become a popular method in organic synthesis because of its commercial availability, efficiency, shelf-stability, and versatility.[2] Since PCC is very acidic, a tautomerization is always accompanied after the generation of the carbonyl group, leading to the isomerization of product.[5] However, it has been reported that a peroxide bond can sustain under such acidic oxidation conditions,[6] and cyclic acetal will be converted into lactone.[7] On the other hand, when different hydroxyl groups are present, the allylic or benzylic alcohol will be oxidized before the oxidation of the regular alcohol groups;[8] this preference of selectivity is enhanced when PCC is used in conjunction with dimethylamino pyridine (DMAP).[8c,8d] In addition, the oxidation from poly[vinylpyridinium] chlorochromate (PVPCC) is much faster than normal PCC.[9] Using PCC as oxidizing reagent, cyclic allyl alcohols can be transformed into α,β-unsaturated cycloketones,[8a,8b] in which the C=C double bond can sit at a different ring of the cyclic compound.[8a] However, the oxidation of a tertiary cyclic allyl alcohol leads to a rearrangement involving the migration of double bond.[10] The substitution of PCC with *n*-butylammonium chlorochromate (BACC) makes

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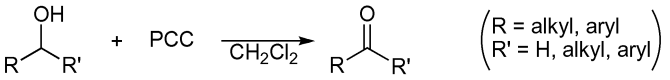
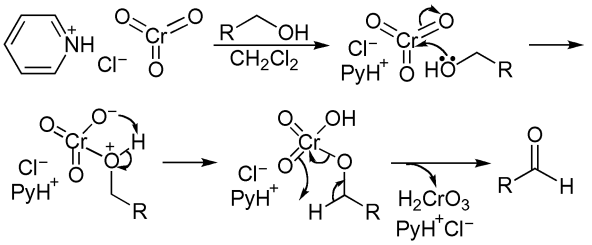
this oxidation homogeneous when 18-crown-6 is present.[11] The Corey-Suggs oxidation can also be improved using ultrasound agitation.[2] It has been reported that under the Corey-Suggs oxidation conditions, a substrate with a double bond of 5 carbons from the hydroxyl group might form cyclic ketone via tandem oxidation-cyclizationoxidation.[12]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A mechanism similar to the *Corey-Schmidt Oxidation* is displayed here.



D. MODIFICATION

This reaction has been widely modified, including the substitution of PCC with PVPCC[9] or BACC[11] and the absorbing of PCC with silica gel accompanied by ultrasound agitation.[2]

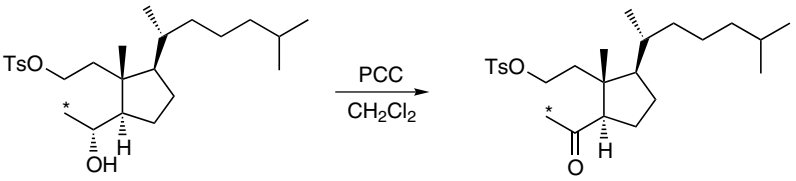
E. APPLICATIONS

Similar to the *Corey-Schmidt Oxidation*, the Corey-Suggs oxidation also has general application in the oxidation of alcohols.

F. RELATED REACTIONS

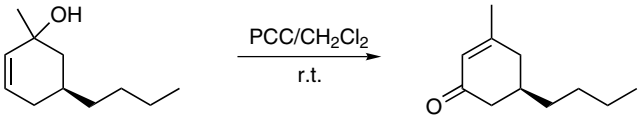
This reaction is related to the *Corey-Schmidt Oxidation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 13.

To a solution of 980 mg [9-^{13}C]-11-tosyloxy-9,11-seco-de-A,B-cholestan-8α-ol (2.23 mmol) in 30 mL CH_2Cl_2 was added 960 mg pyridinium chlorochromate (4.46 mmol) at room temperature. The dark brown mixture was stirred at room temperature for 15 h and was then directly loaded onto a short silica gel column and eluted with EtOAc/hexane (1:4.5). Further purification by HPLC (1:4 EtOAc/hexane) afforded 860 mg [9-^{13}C]-9,11-seco-11-tosyloxy-de-A,B-cholestan-8-one as a liquid, in a yield of 88%.



Reference 10.

To a solution of 205 mg PCC (pyridinium chlorochromate, 0.95 mmol) in 2 mL CH_2Cl_2 was added 80 mg (1*RS*,5*S*)-1-hydroxy-1-methyl-5-butyl-2-cyclohexene (0.48 mmol) in 0.2 mL CH_2Cl_2 dropwise. The resulting dark brown mixture was stirred at room temperature for 2 h, quenched with water, and extracted with Et_2O. Drying over $MgSO_4$, and concentration in vacuo gave an oil that was purified by flash chromatography (SiO_2, hexanes/Et_2O) to yield 66 mg (*R*)-3-methyl-5-butyl-2-cyclohexenone as a colorless oil, in a yield of 83% (97.9% e.e.).

Other references related to the Corey-Suggs oxidation are cited in the literature.[14]

H. REFERENCES

1. Corey, E. J. and Suggs, J. W., *Tetrahedron Lett.,* **1975**, 2647.
2. Adams, L. L. and Luzzio, F. A., *J. Org. Chem.,* **1989**, *54*, 5387.
3. (a) Srikanth, G. S. C.; Krishna, U. M.; Trivedi, G. K. and Cannon, J. F., *Tetrahedron,* **2006**, *62*, 11165. (b) Beihoffer, L. A.; Craven, R. A.; Knight, K. S.; Sisson, C. R. and Waddell, T. G., *Trans. Metal Chem.,* **2005**, *30*, 582. (c) Bressette, A. R. and Glover, L. C., *Synlett*, **2004**, 738. (d) Liang, T. and Kuwahara, S., *Biosci. Biotech. Biochem.,* **2002**, *66*, 2501. (e) Dhillon, R. S.; Kaur, A. P. and Kaur, G., *J. Indian Chem. Soc.,* **2000**, *77*, 453. (f) de Costa, B. R.; Bowen, W. D.; Hellewell, S. B.; George, C.; Rothman, R. B.; Reid, A. A.; Walker, J. M.; Jacobson, A. E. and Rice, K. C., *J. Med. Chem.,* **1989**, *32*, 1996. (g) Marshall, J. A. and Black, T. H., *J. Am. Chem. Soc.,* **1980**, *102*, 7581.
4. Brown, H. C.; Rao, C. G. and Kulkarni, S. U., *J. Org. Chem.,* **1979**, *44*, 2809.

5. Dieks, H.; Senge, M. O.; Kirste, B. and Kurreck, H., *J. Org. Chem.,* **1997**, *62*, 8666.
6. Adam, W.; Balci, M. and Kilic, H., *J. Org. Chem.,* **2000**, *65*, 5926.
7. Sabes, S. E.; Urbanek, R. A. and Forsyth, C. J., *J. Am. Chem. Soc.,* **1998**, *120*, 2534.
8. (a) Bonini, C.; Iavarone, C.; Trogolo, C. and Di Fabio, R., *J. Org. Chem.,* **1985**, *50*, 958. (b) Bonadies, F.; Di Fabio, R. and Bonini, C., *J. Org. Chem.,* **1984**, *49*, 1647. (c) Parish, E. J. and Scott, A. D., *J. Org. Chem.,* **1983**, *48*, 4766. (d) Guziec, F. S. and Luzzio, F. A., *J. Org. Chem.,* **1982**, *47*, 1787.
9. Frechet, J. M. J.; Warnock, J. and Farrall, M. J., *J. Org. Chem.,* **1978**, *43*, 2618.
10. Hareau, G. P.-J.; Koiwa, M.; Hikichi, S. and Sato, F., *J. Am. Chem. Soc.,* **1999**, *121*, 3640.
11. Kasmai, H. S.; Mischke, S. G. and Blake, T. J., *J. Org. Chem.,* **1995**, *60*, 2267.
12. Bahia, P. S. and Snaith, J. S., *J. Org. Chem.,* **2004**, *69*, 3226.
13. Okamura, W. H.; Zhu, G. D.; Hill, D. K.; Thomas, R. J.; Ringe, K.; Borchardt, D. B.; Norman, A. W. and Mueller, L. J., *J. Org. Chem.,* **2002**, *67*, 1637.
14. (a) Sannigrahi, M.; Mayhew, D. L. and Clive, D. L. J., *J. Org. Chem.,* **1999**, *64*, 2776. (b) Li, A.-H.; Moro, S.; Forsyth, N.; Melman, N.; Ji, X.-D. and Jacobson, K. A., *J. Med. Chem.,* **1999**, *42*, 706. (c) Piancatelli, G.; Scettri, A. and Dauria, M., *Synthesis,* **1982**, 245. (d) Willis, J. P.; Gogins, K. A. Z. and Miller, L. L., *J. Org. Chem.,* **1981**, *46*, 3215.

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Corey-Winter Olefination

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Corey and Winter in 1963.[1] It is the transformation of 1,2-diols into alkenes via the *cis*- (or *syn*-) elimination of cyclic thionocarbonate in the presence of trimethyl- or triethylphosphite. The intermediate cyclic thionocarbonate is prepared from the reaction of 1,2-diols with either thiophosgene[2] or thiocarbonyldiimidazole,[3] or by the treatment of 1,2-diols with *n*-BuLi followed by the addition of CS_2 and methyl iodide.[1] Therefore, this reaction is known as the Corey-Winter olefination,[2e,4] Corey-Winter olefination reaction,[5] Corey-Winter reaction,[2a,6] Corey-Winter alkene synthesis,[3a,7] Corey-Winter *cis*-deoxygenation,[8] and Corey olefin synthesis.[2h] A similar preparation of olefins was again reported by Corey and Hopkins in 1982,[9] and the reaction under this condition is referred to as Corey-Hopkins methodology[10] or Corey-Hopkins protocol.[2c] On the one hand, it is assumed that the Corey-Winter olefination proceeds via the attack of phosphite on sulfur, leading to an unstable carbene, which reacts with another phosphite to exclude carbon dioxide and produce the olefin.[1,7] On the other hand, the reaction has also been claimed to undergo a concerted, cyclo-elimination mechanism for the product-forming step.[7] This reaction has been proved to be a position-specific (i.e., regiospecific) and stereospecific reaction for synthesizing olefin,[1,2f] which is also good for the highly substituted[1] or highly strained olefins.[7] In addition, this reaction has been successfully applied to the preparation of sugar derivatives.[7]

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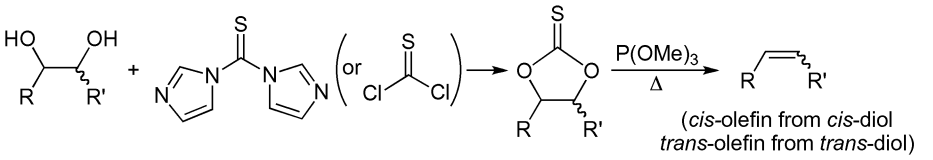
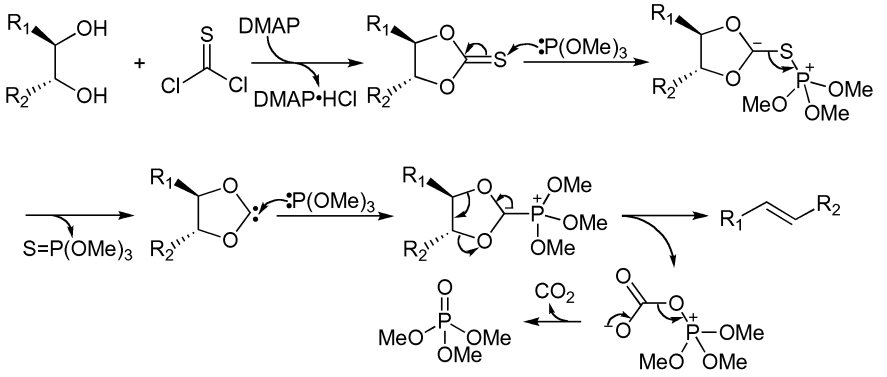
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Provided here is a simple illustration of the reaction mechanism using thiophosgene and trimethyl phosphite.



D. MODIFICATION

N/A

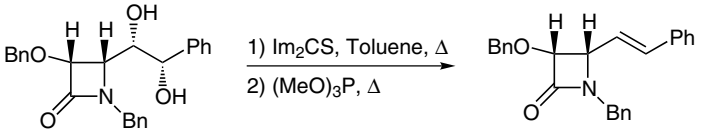
E. APPLICATIONS

This reaction has general application in the preparation of stereospecific olefins and even highly strained olefins.

F. RELATED REACTIONS

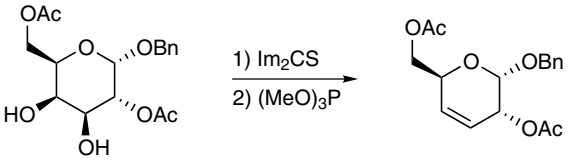
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3a.

A mixture of 1 mmol diol, 0.24 g 1,1′-thiocarbonyldiimidazole (1.2 mmol), and 5 mL toluene was heated at 100°C until the starting diol disappeared as monitored by TLC (typically 16 h). The reaction mixture was then cooled to room temperature, diluted with CH_2Cl_2, and washed with 0.1 N HCl and a saturated solution of $NaHCO_3$. After drying over $MgSO_4$, the solvent was evaporated under reduced pressure to give the corresponding crude thiocarbonate. The obtained crude thiocarbonate was dissolved in 4 mL $P(OMe)_3$, and the resulting solution was kept at reflux until the intermediate thiocarbonate was consumed (typically 16 h). Then, the mixture was cooled to 40°C, and the solvent was removed under vaccum to give the alkene, which was purified by flash column chromatography (0.199 g, 54%), m.p. 75–78°C.



Reference 11.

To a solution of 1.71 g diol (4.83 mmol) in 28 mL dry acetonitrile was added under nitrogen 2.58 g 1,1′-thiocarbonyldiimidazole (14.5 mmol), and the solution was stirred at room temperature for 5 h. The reaction mixture was then poured into brine and extracted with $CHCl_3$. The organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Dry column chromatography of the residue (hexanes/EtOAc, 75:25 → 35:65) gave 1.72 g benzyl 2,6-di-*O*-acetyl-3,4-*O*-thiocarbonyl-α-D-galactopyranoside (4.34 mmol, 90%) and 280 mg benzyl 2,6-di-*O*-acetyl-3,4-di-*O*-(1′*H*-imidazol-1′-ylthiocarbonyl)-α-D-galactopyranoside (0.488 mmol, 10%).

A solution of 1.63 g thiocarbonate (4.12 mmol) in 100 mL trimethyl phosphite was refluxed for 4.5 h. The reaction mixture was then concentrated under high vacuum (1 mmHg), and the residue was purified by dry column chromatography (hexanes/EtOAc, 85:15) to give 1.05 g benzyl 2,6-di-*O*-acetyl-3,4-dideoxy-α-D-*erythro*-hex-3-enopyranoside (3.28 mmol), in a yield of 80%.

Other references related to the Corey-Winter olefination are cited in the literature.[12]

H. REFERENCES

1. Corey, E. J. and Winter, R. A. E., *J. Am. Chem. Soc.*, **1963**, *85*, 2677.
2. (a) Brüggemann, M.; McDonald, A. I.; Overman, L. E.; Rosen, M. D.; Schwink, L. and Scott, J. P., *J. Am. Chem. Soc.,* **2003**, *125*, 15284. (b) Araki, H.; Inoue, M. and Katoh, T., *Org. Chem.,*

2003, *5*, 3903. (c) Martín, R.; Alcón, M.; Pericàs, M. A. and Riera, A., *J. Org. Chem.,* **2002**, *67*, 6896. (d) Wagaman, M. W.; Bellmann, E.; Cucullu, M. and Grubbs, R. H., *J. Org. Chem.,* **1997**, *62*, 9076. (e) Geokjian, P. G.; Wu, T.-C.; Kang, H.-Y. and Kishi, Y., *J. Org. Chem.,* **1991**, *56*, 6422. (f) Shull, B. K. and Koreeda, M., *J. Org. Chem.,* **1990**, *55*, 99. (g) Jones, F. N. and Andreades, S., *J. Org. Chem.,* **1969**, *34*, 3011. (h) Applequist, D. E.; Lintner, M. A. and Searle, R., *J. Org. Chem.,* **1968**, *33*, 254. (i) Hunter, D. H. and Cram, D. J., *J. Am. Chem. Soc.,* **1966**, *88*, 5765.

3. (a) Palomo, C.; Oiarbide, M.; Landa, A.; Esnal, A. and Linden, A., *J. Org. Chem.,* **2001**, *66*, 4180. (b) Alcaide, B.; Polanco, C. and Sierra, M. A., *J. Org. Chem.,* **1998**, *63*, 6786. (c) Maeba, I.; Morishita, N.; Francom, P. and Robins, M. J., *J. Org. Chem.,* **1998**, *63*, 7539. (d) Yamazaki, N. and Kibayashi, C., *J. Am. Chem. Soc.,* **1989**, *111*, 1396. (e) Bien, S. and Segal, J., *J. Org. Chem.,* **1977**, *42*, 3983.
4. (a) Grayson, J. I.,*Org. Proc. Res. Dev.,* **1997**, *1*, 240. (b) Jahnisch, K., *Liebigs Annalen/Recueil*, **1997**, 757. (c) Li, L. P.; Thomas, S. A.; Klein, L. L.; Yeung, C. M.; Maring, C. J.; Grampovnik, D. J.; Lartey, P. A. and Plattner, J. J., *J. Med. Chem.,* **1994**, *37*, 2655. (d) Dyong, I.; Jersch, N. and Lam-Chi, Q., *Chem. Ber.,* **1979**, *112*, 1859.
5. Banwell, M. G.; Edwards, A. J. and Loong, D. T. J., *ARKIVOC*, **2004**, 53.
6. (a) Chasey, K. L.; Paquette, L. A. and Blount, J. F., *J. Org. Chem.,* **1982**, *47*, 5262. (b) Greenhouse, R.; Borden, W. T.; Ravindranathan, T.; Hirotsu, K. and Clardy, J., *J. Am. Chem. Soc.,* **1977**, *99*, 6955.
7. Horton, D. and Tindall, C. G., *J. Org. Chem.,* **1970**, *35*, 3558.
8. Kiddle, J. J., *Chem. Rev.,* **1995**, *95*, 2189.
9. Corey, E. J. and Hopkins, P. B., *Tetrahedron Lett.,* **1982**, *23*, 1979.
10. Dressel, J.; Chasey, K. L. and Paquette, L. A., *J. Am. Chem. Soc.*, **1988**, *110*, 5479.
11. Dorta, R. L.; Martín, A.; Salazar, J. A.; Suárez, E. and Prange, T., *J. Org. Chem.,* **1998**, *63*, 2251.
12. (a) Dorta, R. L.; Martín, A.; Salazar, J. A.; Suárez, E. and Prange, T., *J. Org. Chem.,* **1998**, *63*, 2251. (b) Semmelhack, M. F. and Gallagher, J., *Tetrahedron Lett.,* **1993**, *34*, 4121. (c) Groneberg, R. D.; Miyazaki, T.; Stylianides, N. A.; Schulze, T. J.; Stahl, W.; Schreiner, E. P.; Suzuki, T.; Iwabuchi, Y.; Smith, A. L. and Nicolaou, K. C., *J. Am. Chem. Soc.,* **1993**, *115*, 7593. (d) Dudycz, L. W., *Nucleosides & Nucleotides,* **1989**, *8*, 35. (e) Chu, C. K.; Bhadti, V. S.; Doboszewski, B.; Gu, Z. P.; Kosugi, Y.; Pullaiah, K. C. and van Roey, P., *J. Org. Chem.,* **1989**, *54*, 2217. (f) Corey, E. J. and Hopkins, P. B., *Tetrahedron Lett*., **1982**, *23*, 1979. (g) Paquette, L. A.; Micheli, R. P. and Photis, J. M., *J. Am. Chem. Soc.,* **1977**, *99*, 7911. (h) Koreeda, M.; Koizumi, N. and Teicher, B. A., *J. Chem. Soc., Chem. Commun.,* **1976**, 1036. (i) McGahren, W. J.; Ellestad, G. A.; Morton, G. O.; Kunstmann, M. P. and Mullen, P., *J. Org. Chem.,* **1973**, *38*, 3542. (j) Tichy, M. and Sicher, J., *Tetrahedron Lett.,* **1969**, 4609. (k) Horton, D. and Turner, W. N., *Carbohydr. Res.,* **1966**, *1*, 444. (l) Corey, E. J.; Carey, F. A. and Winter, R. A. E., *J. Am. Chem. Soc*., **1965**, *87*, 934.

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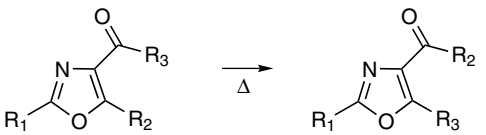
Cornforth Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Cornforth in 1949.[1] It is the thermal rearrangement of 4-carbonyl substituted oxazoles to their isomeric oxazoles[2] through a ring-opening process to form a zwitterionic dicarbonyl nitrile ylides followed by a ring closure (i.e., 1,5-dipolar cyclization[2a]). Therefore, this reaction is generally known as the Cornforth rearrangement.[2b,3] Although this rearrangement is a special type of heterocyclic ring transformation (HRT) which has been found for "almost all heterocycles of any ring size and any type, number or distribution of heteroatoms,"[4] it has been applied to the syntheses of 5-alkyl-,[2a] 5-amino-,[1,2b,3d] 5-aryl-,[2a] 5-(arylthio)-,[3d] and 5-halo-oxazoles.[2a] More importantly, this reaction provides a method for synthesizing the substituted amino acids.[5] Comparably, 1-acylaziridines can rearrange into 2-alkyloxazolines by thermal inducement or triggering by a strong acid or nucleophilic reagent.[6]

B. GENERAL REACTION SCHEME



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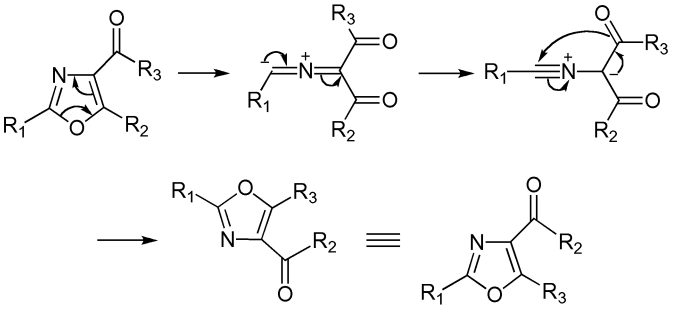
C. PROPOSED MECHANISMS

This reaction involves an intermediate of zwitterionic dicarbonyl nitrile ylides, which cyclizes to the oxazole isomer, as shown here.



D. MODIFICATION

N/A

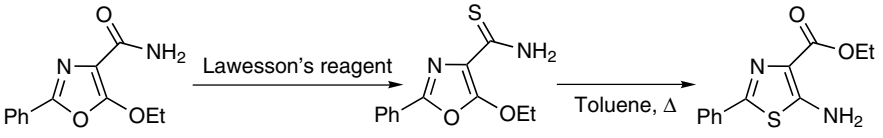
E. APPLICATIONS

This reaction can be used for the preparation of substituted oxazoles and amino acid and even imidazole[3d] and oxazolo[4,5-d]pyrimidin-7-one.[7]

F. RELATED REACTIONS

This reaction is related to the *ANRORC Rearrangement* and the *Boulton-Katritzky Rearrangement*.

G. CITED EXPERIMENTAL EXAMPLES

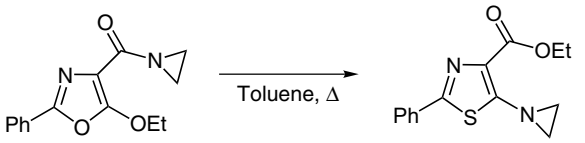


Reference 2a.

A mixture of 4.64 g 2-phenyl-4-(aminocarbonyl)-5-ethoxyoxazole (2.0 mmol) and 8.09 g 2,4-bis(methoxyphenyl)-l,3-dithia-2,4-diphosphetane 2,4-disulfide (*Lawesson's Reagent*) (2.0 mmol) in 50 mL tetrahydrofuran was refluxed for 2 h. The solvent was removed under reduced pressure. Flash chromatography of the residue on silica gel (hexane/EtOAc, 4:1) afforded 3.27 g 2-phenyl-4-(aminothiocarbonyl)-5-ethoxyoxazole as an oil that solidified

under vacuum, in a yield of 66%. Pure sample can be obtained via recrystallization from cyclohexane, m.p. 117–119°C.

A solution of 1.0 mmol 2-phenyl-4-(aminothiocarbonyl)-5-ethoxyoxazole in 50 mL toluene was refluxed for 17 h. The solvent was removed under reduced pressure, and the residue was recrystallized from cyclohexane to give 87% of 2-phenyl-4-(ethoxycarbonyl)-5-aminothiazole, m.p. 134–135°C.



Reference 3d.

A solution of 5 mmol 2-phenyl-5-ethoxyoxazole-4-carboxylic acid chloride in 20 mL benzene was added to a solution of 5 mmol aziridine and 0.5 g triethylamine (5 mmol) in 40 mL benzene at 0°C. The mixture was then stirred for 3 h at room temperature, filtered, washed with water, and dried over $MgSO_4$. Upon removal of benzene by evaporation, the resulting amides were recrystallized several times from petroleum ether (b.p. 60–70°C) to give 80% of 2-phenyl-5-ethoxyoxazole-4-carboxy-aziridine amide, m.p. 82–83°C.

This amide was refluxed in dry toluene for 17 h. The solvent was then removed and the residue was recrystallized from petroleum ether. More than 90% of pure ethyl 2-phenyl-5-aziridinoxazole-4-carboxylate was obtained, m.p. 118–119°C.

Other references related to the Cornforth rearrangement are cited in the literature. [8]

H. REFERENCES

1. Cornforth, J. W., *The Chemistry of Penicillin,* Princeton University Press, Princeton, N.J., **1949**, p. 700.
2. (a) Corrao, S. L.; Macielag, M. J. and Turchi, I. J., *J. Org. Chem.,* **1990**, *55*, 4484. (b) Dewar, M. J. S. and Turchi, I. J., *J. Am. Chem. Soc.,* **1974**, *96*, 6148. (c) Padwa, A. and Chen, E., *J. Org. Chem.,* **1974**, *39*, 1976.
3. (a) Nolt, M. B.; Smiley, M. A.; Varga, S. L.; McClain, R. T.; Wolkenberg, S. E. and Lindsley, C. W., *Tetrahedron*, **2006**, *62*, 4698. (b) Williams, D. R. and McClymont, E. L., *Tetrahedron Lett.*, **1993**, *34*, 7705. (c) Dewar, M. J. S. and Turchi, I. J., *J. Chem. Soc., Perkin Trans. II,* **1977**, 724. (d) Dewar, M. J. S. and Turchi, I. J., *J. Org. Chem.,* **1975**, *40*, 1521. (e) Dewar, M. J. S.; Spanninger, P. A. and Turchi, I. J., *J. Chem. Soc., Chem. Commun.,* **1973**, 925.
4. Babaev, E. V.; Lushnikov, D. E. and Zefirov, N. S., *J. Am. Chem. Soc.,* **1993**, *115*, 2416.
5. (a) Steglich, W. and Hofle, G., *Ber.,* **1971**, *104*, 1408. (b) Steglich, W. and Hofle, G., *Tetrahedron Lett.,* **1970**, 4727. (c) Steglich, W. and Hofle, G., *Ber.,* **1969**, *102*, 883, 899.
6. (a) Pyttman, C. U. and McManus, S. P., *J. Org. Chem.,* **1970**, *35*, 1187. (b) Heine, H. W., *Angew. Chem. Int. Ed. Engl.,* **1962**, *1*, 528. (c) Pittman, A. G. and Lundin, R. E., *J. Polymer Sci.,* **1964**, *2A*, 3803.
7. Turchi, I. J. and Maryanoff, C. A., *Synthesis,* **1983**, 837.
8. (a) L'abbe, G.; Ilisiu, A. M.; Dehaen, W. and Toppet, S., *J. Chem. Soc., Perkin Trans. I,* **1993**, 2259. (b) L'abbe, G., *J. Heterocycl. Chem.,* **1984**, *21*, 627.

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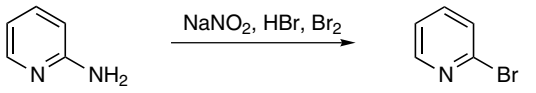
Craig 2-Bromo-Pyridine Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

The preparation of 2-bromopyridine from 2-aminopyridine was first reported by Chichibabin and Ryasanjev in 1915,[1] however, the yield was low.[2] In 1934, Craig reported a modified method for preparing 2-bromo-pyridine in high yield from 2-amino-pyridine,[2] therefore, this reaction is called Craig 2-bromo-pyridine synthesis. In this reaction, a concentrated aqueous solution of sodium nitrite and 2-amino-pyridine was added to a concentrated hydrobromic acid saturated with bromine. It was found that 2 mole of bromine and at least 2.5 mol of sodium nitrite are necessary to obtain an optimal yield of 2-bromo-pyridine.[2] This method has been used to prepare 2-bromo-pyrimidines.[3]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Because no mechanistic detail has been reported for this reaction in the literature, a tentative mechanism is proposed here according to the experimental fact that 2 mol of bromine and sodium nitrite are necessary for the best results.[2]

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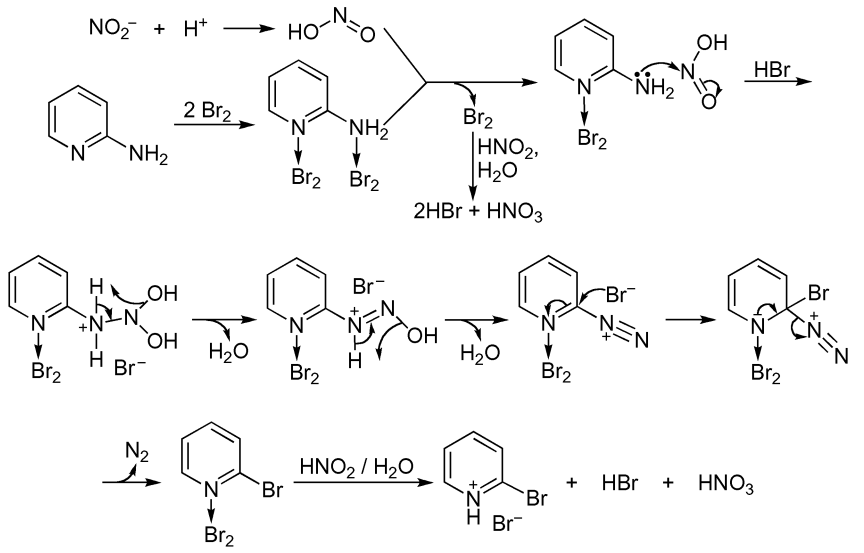


D. MODIFICATION

N/A

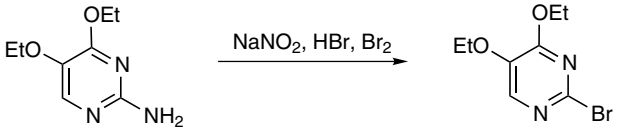
E. APPLICATIONS

This reaction has been used for the preparation of 2-bromo-pyridine and 2-bromo-pyrimidine.

F. RELATED REACTIONS

N/A

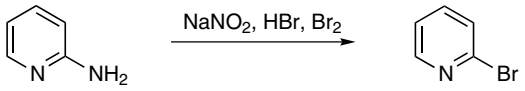
G. CITED EXPERIMENTAL EXAMPLES



Reference 3.

To a suspension of 20.2 g 2-amino-4,5-diethoxypyrimidine (0.11 mol) in 55 mL 48% hydrobromic acid, 16.9 mL bromine (0.32 mol) was added at 0°C with stirring, over a period of 45 min. During this addition, the mixture became very thick but subsequently thinned out again. A solution of 19.4 g sodium nitrite (0.28 mol) in 28 mL water was added,

still at 0°C,over a 30-min period, and the stirring was continued for an additional 30 min. The resulting dark solution was cooled to −10°C, and 200 mL 20% solution of sodium hydroxide was added until a permanent basic reaction was produced. Filtration yielded 21.5 g 2-bromo-4,5-diethoxypyrimidine as a pale yellow solid, m.p. 49°C, in a yield of 79.0%.



Reference 4.

In a 5-L, three-necked flask fitted with a mechanical stirrer, a dropping funnel, and a thermometer for reading low temperatures was placed 790 mL 48% hydrobromic acid (7 mol). The flask and contents were cooled to 10–20°C in an ice salt bath, and 150 g 2-amino-pyridine (1.59 mol) was added over a period of ∼10 min. While the temperature was kept at 0°C or lower, 240 mL bromine (4.7 mol) was added dropwise. A solution of 275 g sodium nitrite (4 mol) in 400 mL water was added dropwise over a period of 2 h, the temperature being carefully maintained at 0°C or lower. After an additional 30 min of stirring, a solution of 600 g sodium hydroxide (15 mol) in 600 mL water was added at such a rate that the temperature did not rise above 20–25°C. The nearly colorless reaction mixture was extracted with four 250-mL portions of ether. The extract was dried for 1 h over 100 g solid KOH and was then distilled through a Vigreux column (15 cm in length). 2-Bromo-pyridine distils was collected at 74–75°C (13 mmHg), and 216–230 g product was obtained, in a yield of 86–92%.

Other references related to the Craig 2-bromo-pyridine synthesis are cited in the literature.[5]

H. REFERENCES

1. Chichibabin, A. E. and Ryasanjev, M. D., *J. Russ. Phys. Chem. Soc.,* **1915**, *47*, 1571.
2. Craig, L. M., *J. Am. Chem. Soc.,* **1934**, *56*, 231.
3. Bader, H. and Spiere, N., *J. Org. Chem.,* **1963**, *28*, 2155.
4. (a) Allen, C. F. H. and Thirtle, J. R., *Org. Synth. Coll. III,* **1955**, 136. (b) Allen, C. F. H. and Thirtle, J. R., *Org. Synth.,* **1946**, *26*, 16.
5. (a) Young, T. E. and Amstutz, E. D., *J. Am. Chem. Soc.,* **1951**, *73*, 4773. (b) Ellingson, R. C. and Henry, R. L., *J. Am. Chem. Soc.,* **1949**, *71*, 2798. (c) Case, F. H., *J. Am. Chem. Soc.,* **1946**, *68*, 2574. (d) Bergstrom, F. W., *Chem. Rev.,* **1944**, *35*, 77. (e) Craig, L. C., *J. Am. Chem. Soc.,* **1934**, *56*, 1144.

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Criegee Glycol Oxidation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Criegee in 1931.[1] It is an oxidation of 1,2-diols (or glycols) to aldehydes or ketones with lead tetraacetate [$Pb(OAc)_4$, LTA] via the cleavage of C-C bond between the hydroxyl-carrying carbon atoms. This oxidation takes place almost quantitatively at room temperature, and the oxidation rate depends greatly on the structure of glycol and corresponding solvent.[2] Originally, this reaction was reported to occur only in anhydrous organic solvent,[3] and much of the efforts are focused on the drying of the solvent;[2] however, this reaction was proved to be feasible in organic solvent with moisture or even in aqueous solution if the oxidation is faster than the hydrolysis of lead tetraacetate,[2,4] as shown in the oxidation of monosaccharides such as glucose and mannose.[2] In addition, lead tetraacetate can oxidize not only 1,2-diols but also α-amino alcohols,[5] α-hydroxyl carbonyl compounds,[6] and α-keto acids.[6b] In this oxidation, the configuration or even conformation of diol plays an important role, and it is found that the oxidation of *cis*-diol is faster than *trans*-diol, especially when *cis*-diol forms a five-membered ring structure. As a result, the amount of *cis*-diol on a five-membered ring can be titrated regardless the presence of *trans*-diol on a five membered ring, or *cis*-diol or *trans*-diol on a six-membered ring.[7] However, when *cis*-diol on pyranoside exists in the boat conformation, the oxidation of such diol with lead tetraacetate might proceed fast compared to the *cis*-diol in a five-membered ring. In addition, this reaction can also be carried out in solvents such as acetic acid, benzene, chloroform, nitrobenzene, and tetrachloroethane.[2] During the oxidation of sugars, it was found that glucose, glycerol, mannitol, and xylose are oxidized readily in aqueous solution, whereas sucrose cannot be oxidized under a similar condition.[4a] Interestingly, it was found that the oxidation of α-hydroxyl tertiary amine is different from a similar oxidation on α-hydroxyl primary or secondary amine, by which the oxidation of the former gives a secondary amine

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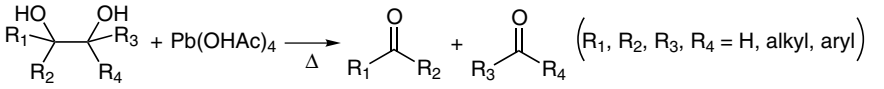
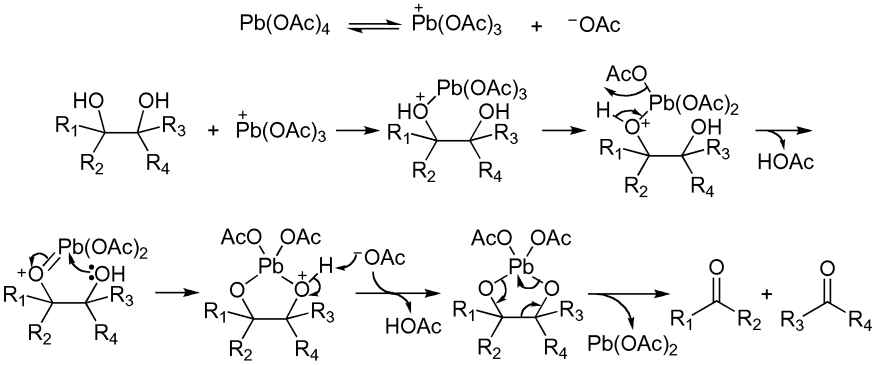
and aldehyde involving the cleavage of a C-N bond, whereas the latter involves the cleavage of a C-C bond.[5] The Criegee glycol oxidation is similar to the oxidation of diols using periodate in aqueous solution, i.e., the *Malaprade Reaction*; however, during the oxidation of 1,2,3-triols, the extensive periodate oxidation gives only aldehydes or ketones as well as formic acid.[8] The oxidation from excess lead tetraacetate gives aldehydes or ketones and carbon dioxide (from the middle hydroxyl group) as well.[4b] It was found that the decomposition of lead tetraacetate holds an ionic mechanism.[9] Other oxidations using lead tetraacetate include the oxidation of alcohols (to ketones),[9b] conjugated dienes (to esters of *cis*- or *trans*-glycol),[10] olefin (to glycol acetate or allylic acetate),[10a,11] cyclooctanol (to ether-containing tetrahydrofuran rings),[10a] thioether (to sulfone),[12] sugars,[4,12,13] and amines.[5]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

According to the fact that the decomposition of lead tetraacetate involves a cationic mechanism, the Griegee glycol oxidation mechanism is outlined tentatively.



D. MODIFICATION

N/A

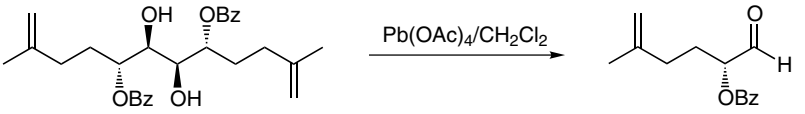
E. APPLICATIONS

This reaction has wide application in the analysis of carbohydrate structures and the cleavage of adjacent diols, α-keto alcohols, α-keto acids, and hydroxyamines. In addition, this oxidation also renders a method for preparing aldehydes and ketones.

F. RELATED REACTIONS

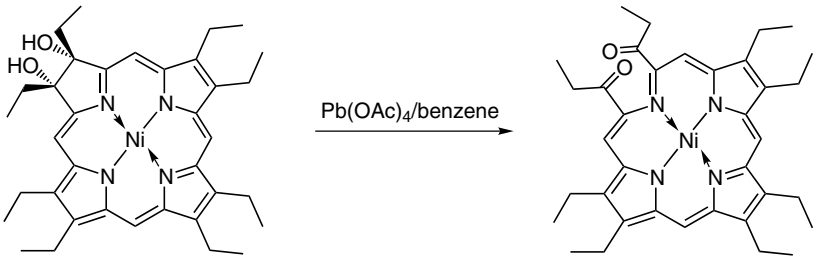
This reaction is related to the *Malaprade Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 14.

A solution of 190 mg lead tetraacetate in 10 mL CH_2Cl_2 was cooled to $-20°C$ and 115 mg (5*R*,6*R*,7*R*,8*R*)-2,11-dimethyl-5,8-bis(benzoyloxy)-6,7-dihydroxydodeca-1,11-diene (0.50 mmol) was added. After stirring for 1 h at this temperature, the reaction mixture was warmed to room temperature and quenched with 0.5 mL ethylene glycol. The upper phase was separated, and the residue was washed with CH_2Cl_2. The combined organic solution was washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was then purified by flash column chromatography on silica gel (5% ethyl acetate in hexane) to give 105 mg (2*R*)-2-benzoyloxy-5-methylhex-5-enal, in a yield of 91%.



Reference 15.

Nickel(II) *cis*-diol (75 mg) dissolved in 8 mL anhydrous benzene was stirred with 54 mg freshly crystallized (from HOAc), dried (over KOH pellets in vacuo, dark) lead tetraacetate (in excess) for 15 min at room temperature. Ethylene glycol (0.5 mL) was added, and stirring was continued for 2 min. Chloroform (50 mL) was added, and the mixture was washed with water (2 × 25 mL) and the combined organic phases were dried over Na_2SO_4, filtered, and taken to dryness. The residue was chromatographed on silica gel 60 (12 cm × 3 cm) with chloroform. The leaf green fraction was collected, evaporated, and crystallized from dichloromethane-methanol to give 57 mg (2,3,7,8,12,13,17,18-octaethyl-2,3-dioxo-2,3-secochlorinato)-nickel(II) as small green needles, in a yield of 76%, m.p. 180–185°C, $R_f = 0.48$ ($CHCl_3$).

Other references related to the Criegee glycol oxidation are cited in the literature.[16]

H. REFERENCES

1. Criegee, R., *Ber.,* **1931**, *64*, 260.
2. Baer, E.; Grosheintz, J. M. and Fischer, H. O. L., *J. Am. Chem. Soc.,* **1939**, *61*, 2607.
3. Criegee, R., *Angew. Chem.,* **1937**, *50*, 153.
4. (a) Hockett, R. C. and Zief, M., *J. Am. Chem. Soc.,* **1950**, *72*, 2130. (b) Abraham, S., *J. Am. Chem. Soc.,* **1950**, *72*, 4050.
5. Leonard, N. J. and Rebenstorf, M. A., *J. Am. Chem. Soc.,* **1945**, *67*, 49.
6. (a) Evans, D. A.; Bender, S. L. and Morris, J., *J. Am. Chem. Soc.,* **1988**, *110*, 2506. (b) Baer, E., *J. Am. Chem. Soc.,* **1942**, *64*, 1416.
7. Reeves, R. E., *Anal. Chem.,* **1949**, *21*, 751.
8. Hurd, C. D.; Baker, P. J.; Holysz, R. P. and Saunders, W. H., *J. Org. Chem.,* **1953**, *18*, 186.
9. (a) Cope, A. C.; Gordon, M.; Moon, S. and Park, C. H., *J. Am. Chem. Soc.,* **1965**, *87*, 3119. (b) Mosher, W. A.; Kehr, C. L. and Wright, L. W., *J. Org. Chem.,* **1961**, *26*, 1044. (c) Brutcher, F. V. and Vara, F. J., *J. Am. Chem. Soc.,* **1956**, *78*, 5695. (d) Mosher, W. A. and Kehr, C. L., *J. Am. Chem. Soc.,* **1953**, *75*, 3172.
10. (a) Criegee, R., *Ann.,* **1930**, *481*, 263. (b) Criegee, R. and Beuker, H., *Ann.,* **1939**, *541*, 218.
11. (a) Alkonyi, I., *Ber.,* **1963**, *96*, 1873. (b) Anderson, C. B. and Winstein, S., *J. Org. Chem.,* **1963**, *28*, 605. (c) Kabbe, H. J., *Ann.,* **1962**, *656*, 204. (d) Whitham, G. H., *J. Chem. Soc.,* **1961**, 2232.
12. Baker, S. B., *J. Am. Chem. Soc.,* **1952**, *74*, 827.
13. (a) Hockett, R. C.; Dienes, M. T.; Fletcher, H. G. and Ramsden, H. E., *J. Am. Chem. Soc.,* **1944**, *66*, 467. (b) Hockett, R. C. and Fletcher, H. G., *J. Am. Chem. Soc.,* **1944**, *66*, 469. (c) Hockett, R. C.; Nickerson, M. H. and Reeder, W. H., *J. Am. Chem. Soc.,* **1944**, *66*, 472. (d) Hockett, R. C. and Mowery, D. F., *J. Am. Chem. Soc.,* **1943**, *65*, 403. (e) Hockett, R. C.; Dienes, M. T. and Ramdsen, H. E., *J. Am. Chem. Soc.,* **1943**, *65*, 1474. (f) McClenahan, W. S. and Hockett, R. C., *J. Am. Chem. Soc.,* **1938**, *60*, 2061.
14. Yu, L. B.; Zhang, R. Z. and Wang, Z. Q., *J. Chem. Soc*., *Perkin Trans. I,* **2001**, 2958.
15. Adams, K. R.; Bonnett, R.; Burke, P. J.; Salgado, A. and Vallés, M. A., *J. Chem. Soc., Perkin Trans. I,* **1997**, 1769.
16. (a) Glaudemans, C. P. J., *Makromol. Chem.,* **2003**, *47*, 1. (b) Khripach, V. A.; Zhabinskii, V. N.; Kotyatkina, A. I.; Fando, G. P.; Zhiburtovich, Y. Y.; Lyakhov, A. S.; Ashry, E. S. H. E.; Hamid, H. A.; Kassem, A. A. and Shoukry, M, *Molecules,* **2002**, *7*, 155. (c) Unaleroglu, C.; Aviyente, V. and Arseniyadis, S., *J. Org. Chem.,* **2002**, *67*, 2447. (d) Govorova, A. A.; Groen, M. B.; van der Louw, J. and de Groot, A., *Coll. Czech. Chem. Commun.,* **2001**, *66*, 1764. (e) Chandrasekhar, S. and Roy, C. D., *J. Chem. Soc., Perkin Trans. II,* **1994**, 2141. (f) House, H. O., *Modern Synthetic Reactions*, 2nd ed., W. A. Benjamin, Menlo Park, Calif., **1972**, pp. 359–387. (g) Whelan, W. J., *Ann. Rev. Biochem.,* **1960**, *29*, 105. (h) Bell, R. P.; Rivlin, V. G. and Waters, W. A., *J. Chem. Soc.,* **1958**, 1696. (i) Criegee, R.; Hoger, E.; Huber, G.; Kruck, P.; Marktscheffel, F. and Schellenberger, H., *Ann.,* **1956**, *599*, 81. (j) Criegee, R.; Hoger, E.; Huber, G.; Kruck, P.; Marktscheffel, F. and Schellenberger, H., *Ann.,* **1956**, *599*, 81. (k) Djerassi, C. and Ehrlich, R., *J. Org. Chem.,* **1954**, *19*, 1351. (l) Criegee, R., in *Newer Methods of Preparative Organic Chemistry*, ed. Foerst, W. Interscience, New York, **1948**, p. 12. (m) Kato, H., *Nippon Kagaku Kaishi*, **1938**, *59*, 817. (n) Viebock, F., *Ber.,* **1934**, *67B*, 197.

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Criegee Ozonolysis

A. GENERAL DESCRIPTION OF THE REACTION

It was Schönbein who studied the ozonolysis first;[1] however, it was Criegee who initially investigated the mechanism of ozonolysis beginning in the 1950s.[2] Therefore, Criegee was considered the "father of modern ozone organic chemistry,"[1] and the reaction between olefins and ozone to form aldehydes, ketones, carboxylic acids, etc. is known as the Criegee ozonolysis[3] or Criegee reaction.[4] This reaction occurs in three steps: formation of primary ozonides, splitting of primary ozonides, and formation of secondary ozonides.[5] In this reaction, ozone as an electrophile,[6] adds to the C=C double bond of olefin via a concerted *1,3-Dipolar Cycloaddition*, a symmetry allowed ($4_s + 2_s$) cycloaddition,[5] to form vibrationally excited primary ozonide[7] (POZ, the 1,2,3-trioxolane,[8] or the so-called molozonide[1]) in a *syn*- or an *anti*-form,[5] which quickly splits to an excited carbonyl oxide (Criegee intermediate, CI[5,7–9]) and a carbonyl compound, which in turn couple stereospecifically into the secondary ozonide[5] (SOZ, the 1,2,4-trioxolane,[8,10] or the so-called true ozonide[1]) via retrocycloaddition. Then the secondary ozonide is reduced to aldehyde or ketone via a variety of reducing reagents, including Zn/AcOH, Me_2S, Ph_3P, Me_3P, and $(NC)_2C{=}C(CN)_2$. This reaction is usually carried out in a suitable solvent (AcOH, CCl_4, $CHCl_3$, hexane, EtOAc, CH_2Cl_2, etc.) at low temperature by passing a stream of dry ozonized oxygen (1–15% O_3) until the disappearance of the olefins. In addition, a unified concept[11] was proposed for this reaction, which differs from the Criegee mechanism in the prediction of the position of a labeled oxygen atom when the primary ozonide reacts with a labeled aldehyde in a crossover experiment.[12] It was found that the electron-donating groups accelerate the reaction, and the electron-withdrawing groups decrease the reaction rate.[6] This reaction is frequently

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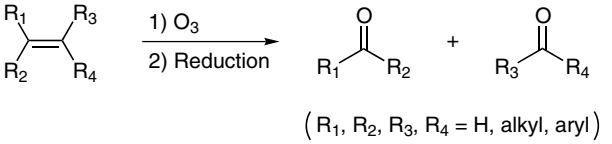
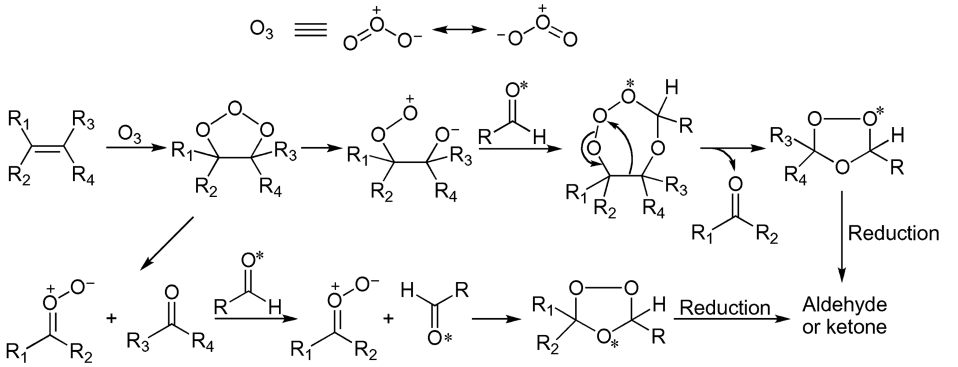
used for structure determination as well as synthetic purposes. Sometimes, ammonia and primary amines are added during the ozonolyses of olefins as the participating solvents, and "amozonolysis" is used for this reaction condition.[13] Tertiary amines are formed as reductive amination products in high yield when secondary amines are added to the solution of mono- or 1,1-disubstituted olefins during ozonolysis.[14] It has been reported that the ozonolysis of olefins is one of the major methods of forming aerosol.[15] On the other hand, this reaction has also been studied extensively in theory.[16]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A mechanism of the unified concept is demonstrated here.[12]



D. MODIFICATION

This reaction has been modified for synthesizing tertiary amines via reductive amination by the addition of secondary amines during the ozonolysis.[13]

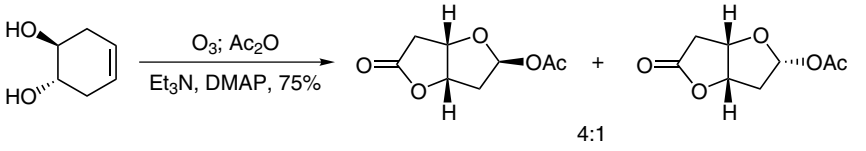
E. APPLICATIONS

This reaction has general application in the determination of the structure of molecules containing C=C double bonds as well as in the preparation of aldehydes and ketones.

F. RELATED REACTIONS

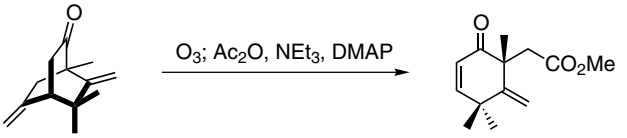
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3a.

A solution of 0.44 g cyclohexenyl diol (3.8 mmol) in 190 mL EtOAc at −78°C was purged with ozone until the solution turned blue. The system was then purged with N_2 for approximately 10 min or until the blue color disappeared. To this solution were added slowly (∼30 min each) via syringe pump 2.36 g Ac_2O (23.2 mmol) and 3.8 g Et_3N (38.0 mmol), and stirring was continued at −78°C for 10 min before the addition of 0.2 g DMAP (1.8 mmol). The reaction mixture was allowed to warm to room temperature and stir overnight. It was then quenched with $NaHCO_3$ and extracted with EtOAc (3 × 100 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography with Et_2O furnished 0.52 g lactone as crystalline solids, in a yield of 75% with a diastereomeric ratio of 4:1.



Reference 17.

Precooled dry ozone in oxygen gas was passed through a cold (−70°C) suspension of 200 mg (-)-(1*R*,4*S*)-1,5,5-trimethyl-6,8-bis(methylene)bicyclo-[2.2.2]octan-2-one (1.05 mmol) and 10 mg $NaHCO_3$ in 5 mL MeOH-CH_2Cl_2 (1:4) for 5 min. Excess ozone was flushed off with oxygen. The solvent was evaporated in vacuo, and the residue was dissolved in 2 mL dry benzene. To this mixture were added 1 mL acetic anhydride (10.5 mmol), 0.7 mL triethylamine (5.2 mmol), and a catalytic amount of DMAP; the resulting mixture was stirred at room temperature for 15 min and then refluxed for 6 h. The reaction mixture was diluted with water and extracted with ether. The ethereal extract was washed with 3 *N* aqueous HCl and water. Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc/hexane (1:50) as the eluent furnished 80 mg unreacted starting material. Further elution of the column with EtOAc/hexane (1:20 to 1:10) as the eluent furnished 93 mg (+)-methyl (1*R*)-1,5,5-trimethyl-6-methylenecyclohex-3-en-2-one-1-acetate as an oil, in a yield of 67% based on the consumed starting material.

Other references related to the Criegee ozonolysis are cited in the literature.[18]

H. REFERENCES

1. Bailey, P. S. "Ozonation in Organic Chemistry" in *Vol. 1*, *Olefinic Compounds in Organic Chemistry* that is, *Vol. 39* of *Organic Chemistry: A Series of Monographs*, ed. Blomquist, A. T. and Wasserman, H. H., Academic Press, New York, **1978**, *39–1*, pp. 1–24.
2. Criegee, R., *Angew. Chem. Int. Ed. Engl.,* **1975**, *14*, 745.
3. (a) Jiang, L.; Martinelli, J. R. and Burke, S. D., *J. Org. Chem.,* **2003**, *68*, 1150. (b) Bailey, P. S. and Ferrell, T. M., *J. Am. Chem. Soc.,* **1978**, *100*, 899.
4. (a) Wojciechowski, B. J.; Pearson, W. H. and Kuczkowski, R. L., *J. Org. Chem.,* **1989**, *54*, 115. (b) Choe, J. I.; Painter, M. K. and Kuczkowski, R. L., *J. Am. Chem. Soc.,* **1984**, *106*, 2891.
5. Ponec, R.; Yuzhakov, G.; Haas, Y. and Samuni, U., *J. Org. Chem.,* **1997,** *62*, 2757.
6. Carles, J. and Fliszár, S., *Adv. Chem. Ser.,* **1972**, *112*, 35.
7. Chuong, B.; Zhang, J. Y. and Donahue, N. M, *J. Am. Chem. Soc.,* **2004**, *126*, 12363.
8. Clark, R. J. H. and Foley, L. J., *J. Phys. Chem. A,* **2002**, *106*, 3356.
9. (a) Johnson, D.; Lewin, A. G. and Marston, G., *J. Phys. Chem. A,* **2001**, *105*, 2933. (b) Tobias, H. J. and Ziemann, P. J., *J. Phys. Chem. A,* **2001**, *105*, 6129.
10. Aplincourt, P. and Ruiz-López, M. F., *J. Am. Chem. Soc.,* **2000**, *122*, 8990.
11. (a) Story, P. R.; Alford, J. A.; Burgess, J. R. and Ray, W. C., *J. Am. Chem. Soc.,* **1971**, *93*, 3041. (b) Story, P. R.; Alford, J. A.; Burgess, J. R. and Ray, W. C., *J. Am. Chem. Soc.,* **1971**, *93*, 3044. (c) Story, P. R.; Bishop, C. E. and Burgess, J. R., *J. Am. Chem. Soc.,* **1968**, *90*, 1907. (d) Murray, R. W.; Youssefye, R. D. and Story, P. R., *J. Am. Chem. Soc.,* **1966**, *88*, 3143. (e) Story, P. R.; Murrary, R. W. and Youssefye, R. D., *J. Am. Chem. Soc.,* **1966**, *88*, 3144.
12. Geletneky, C. and Berger, S., *Eur. J. Org. Chem.,* **1998**, 1625.
13. Fremery, M. I. and Fields, E. K., *J. Org. Chem.*, **1964**, *29*, 2240.
14. Hon, Y. S.; Lin, S. W.; Lu, L. and Chen, Y. J., *Tetrahedron,* **1995**, *51*, 5019.
15. (a) Hearn, J. D. and Smith, G. D., *J. Phys. Chem. A,* **2004**, *108*, 10019. (b) Ziemann, P. J., *J. Phys. Chem. A,* **2002**, *106*, 4390. (c) Bonn, B.; Schuster, G. and Moortgat, G. K., *J. Phys. Chem. A,* **2002**, *106*, 2869. (d) Tobias, H. J. and Ziemann, P. J., *Environ. Sci. Technol.,* **2000**, *34*, 2105. (e) Tobias, H. J.; Docherty, K. S.; Beving, D. E. and Ziemann, P. J., *Environ. Sci. Technol.,* **2000**, *34*, 2116. (f) Kalberer, M.; Yu, J.; Cocker, D. R.; Flagan, R. C. and Seinfeld, J. H., *Environ. Sci. Technol.,* **2000**, *34*, 4894. (g) Yu, J.; Cocker, D. R., III; Griffin, R. J.; Flagan, R. and Seinfeld, J. H., *J. Atmos. Chem.,* **1999**, *34*, 207. (h) Hoffman, T.; Odum, J. R.; Bowman, F.; Collins, D.; Klockow, D.; Flagan, R. C. and Seinfeld, J. H., *J. Atmos. Chem.,* **1997**, *26*, 189. (i) Pandis, S.; Paulson, S.; Seinfeld, J. and Flagan, R., *Atmos. Environ.,* **1992**, *26A*, 2266. (j) Hatakeyama, S.; Izumi, K.; Fukuyama, T. and Akimoto, H., *J. Geophys. Res.,* **1989**, *94*, 13013. (k) Hatakeyama, S.; Ohno, M.; Weng, J.-H.; Takagi, H. and Akimoto, H., *Environ. Sci. Technol.,* **1987**, *21*, 52. (l) Hatakeyama, S.; Tanonaka, T.; Weng, J.; Bandow, H.; Takagi, H. and Akimoto, H., *Environ. Sci. Technol.,* **1985**, *19*, 935. (m) Yokouchi, Y. and Ambe, Y., *Atmos. Environ.,* **1985**, *19*, 1271.
16. (a) Hasson, A. S.; Chung, M. Y.; Kuwata, K. T.; Converse, A. D.; Krohn, D. and Paulson, S. E., *J. Phys. Chem. A,* **2003**, *107*, 6176. (b) Olzmann, M.; Kraka, E.; Cremer, D.; Gutbrod, R. and Andersson, S., *J. Phys. Chem. A,* **1997**, *101*, 9421. (c) Hiberty, P. C., *J. Am. Chem. Soc.,* **1976**, *98*, 6088. (d) Wadt, W. R. and Goddard, W. A., *J. Am. Chem. Soc.,* **1975**, *97*, 3004.
17. Srikrishna, A. and Anebouselvy, K., *J. Org. Chem.,* **2001**, *66*, 7102.
18. (a) Presto, A. A. and Donahue, N. M., *J. Phys. Chem. A,* **2004**, *108*, 9096. (b) Mvula, E. and von Sonntag, C., *Org. Biomol. Chem.*, **2003**, *1*, 1749. (c) Paryzek, Z.; Koenig, H.; Skiera, I. and Rychlewska, U., *Polish J. Chem.,* **2002**, *76*, 921. (d) Johnson, D.; Lewin, A. G. and Marston, G., *J. Phys. Chem. A,* **2001**, *105*, 2933. (e) Tobias, H. J. and Ziemann, P. J., *J. Phys. Chem. A,*

2001, *105*, 6129. (f) Jung, M. E. and Davidov, P., *Org. Lett.,* **2001**, *3*, 627. (g) Fenske, J. D.; Hasson, A. S.; Ho, A. W. and Paulson, S. E., *J. Phys. Chem. A,* **2000**, *104*, 9921. (h) Neeb, P. and Moortgat, G. K., *J. Phys. Chem. A,* **1999**, *103*, 9003. (i) Neeb, P.; Horie, O. and Moortgat, G. K., *J. Phys. Chem. A,* **1998**, *102*, 6778. (j) Manoilova, O. V.; Lavalley, J. C.; Tsyganenko, N. M. and Tsyganenko, A. A., *Langmuir,* **1998**, *14*, 5813. (k) Aurell, M. J.; Ceita, L.; Mestres, R. and Tortajada, A., *Tetrahedron*, **1997**, *53*, 10883. (l) Klopman, G. and Joiner, C. M., *J. Am. Chem. Soc.,* **1975**, *97*, 5287.

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Criegee Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Criegee in 1944.[1] It is the rearrangement of peroxy ester into ketone, ester, or carbonate and alcohol via oxygen insertion or consecutive oxygen insertion. Therefore, it is generally known as the Criegee rearrangement.[2] The peroxy ester is primarily formed from the reaction between peracid and tertiary alcohol. In addition, the peroxy ester can also be prepared from the reaction between ketone and peracid (i.e., the *Baeyer-Villiger Oxidation*), and the additional product of peracid to ketone is often referred to as the Criegee intermediate.[2e,3] From this point of view, the *Baeyer-Villiger Oxidation* is a subset of the Criegee rearrangement.[2e] In this reaction, the often-used peracids include *p*-nitroperbenzoic acid[2f] and trifluoroperacetic acid[2c,2d,4] because they are strong enough and give good leaving groups. It is widely assumed that the migrating group rearranges from a position *anti*-periplanar to the dissociating oxygen-oxygen bond of the peroxy ester.[5] During the rearrangement, the electron-donating ability of the migrating group will facilitate such movement,[2i,6] whereas the electron-withdrawing or electron-deficient group will not migrate.[7] This reaction has been proven to occur via an ionic mechanism,[1] but the second step of migration is believed to be concerted.[3a] For this reaction, allylic hydroperoxides will yield cyclic or acyclic enol ethers,[2f] and the isopropenyl group can be easily removed.[8] The major differences between the Criegee rearrangement and the *Baeyer-Villiger Oxidation* include (*a*) a consecutive oxygen insertion occurs in former, but no oxygen insertion has been reported for ketones and aldehdyes;[5] and (*b*) the starting material is tertiary alcohols in the Criegee rearrangement, but ketones are used in the *Baeyer-Villiger Oxidation*.

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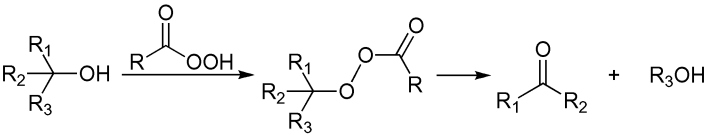
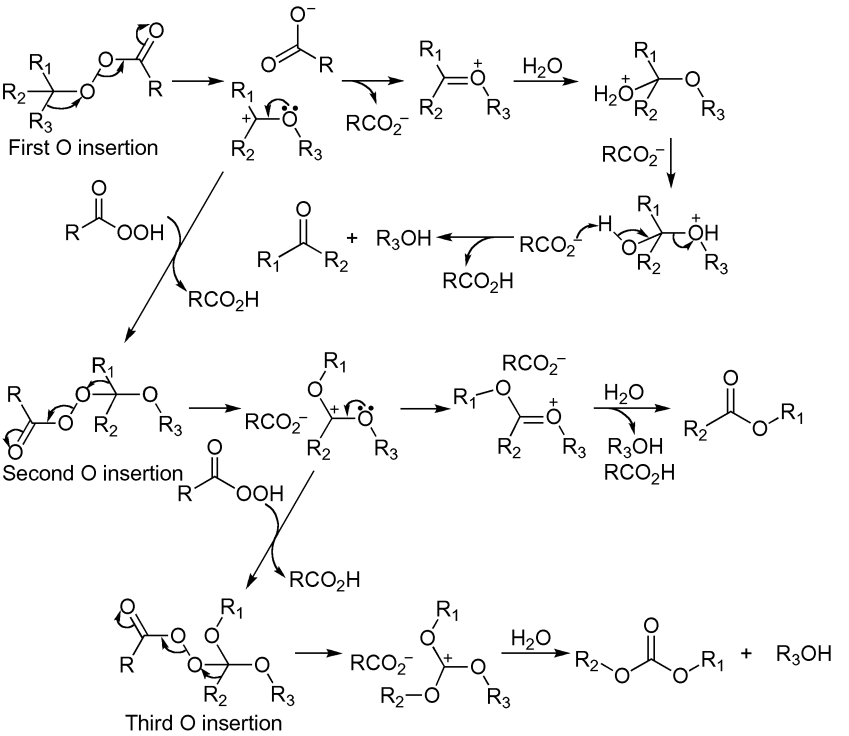
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Displayed below is the reaction mechanism, including the formation of ketone, ester, and orthoester via oxygen insertion.



D. MODIFICATION

N/A

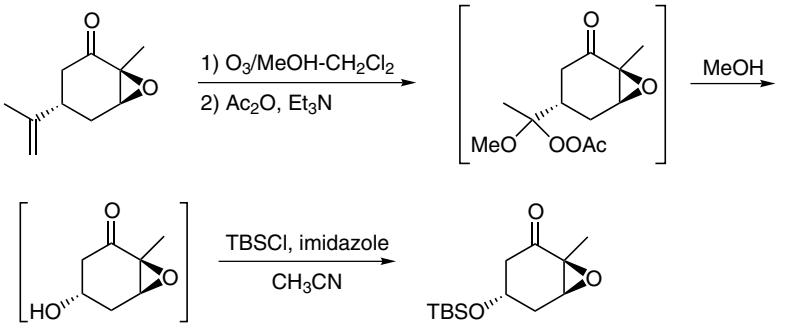
E. APPLICATIONS

This reaction is useful for the removal of the isopropenyl group and conversion of tertiary alcohols into ketones and aldehydes.

F. RELATED REACTIONS

This reaction is related to the *Baeyer-Villiger Oxidation*.

G. CITED EXPERIMENTAL EXAMPLES

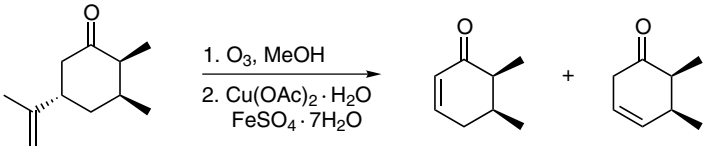


Reference 8a.

A solution of 20 g (1*S*,4*S*,6*S*)-1-methyl-4-(1-methylethenyl)-7-oxabicyclo-[4.1.0]-heptan-2-one (120 mmol) and 20 mL methanol (494 mmol) in 200 mL dichloromethane was cooled with a dry ice–acetone bath; the nitrogen inlet tube was replaced with a gas dispersion tube, and the gas outlet tube was connected to a trap through a wide 4-mm i.d. tube immersed in a 2 L 1 M KI solution. Then ozonized air (4 L/min) was continuously passed through the reaction mixture at $-68 \pm 3^{\circ}$C. The reaction turned pale blue after 65 min, indicating the completion of the reaction. Then excess ozone was removed by purging with nitrogen (4 L/min) for 30 min, and the mixture was allowed to warm to 14°C over 40 min to ensure complete conversion of the initially formed ozonide to the desired hydroperoxide. Then the mixture was cooled to -25°C, and 117 mL triethylamine (839 mmol) was added over 5 min while maintaining the temperature of the mixture below -25°C. Then 2.0 g DMAP (16.4 mmol) was added in one portion, followed by the slow addition of 79.6 mL acetic anhydride (843 mmol) over 10 min while maintaining the reaction temperature between -25° and -38°C. The mixture was allowed to warm to -8°C over 30 min and stirred at $-7 \pm 1^{\circ}$C for 1.5 h. TLC analysis indicated a complete reaction. The reaction was quenched by the slow addition of 33 mL methanol, while maintaining the temperature of the mixture below 10°C (over 7 min). After being stirred at 5°C for 5 min, the mixture was diluted with 220 mL hexane, washed consecutively with 10% aqueous citric acid (2×150 mL) and saturated aqueous $KHCO_3$ (2×80 mL), dried over Na_2SO_4, and concentrated to dryness at 30°C under reduced pressure to give 38.2 g crude (1*S*,4*S*, 6*S*)-4-(1-acetylhydroperoxy-1-methoxyethyl)-1-methyl-7-oxabicyclo[4.1.0]heptan-2-one as a yellow oil. This material was relatively unstable and was immediately used in the next step without further purification.

A mixture of the crude product (120 mmol in theory) and 2.0 g NaOAc (24.4 mmol) in 245 mL methanol was stirred at 37°C overnight. TLC analysis indicated a complete reaction. Then the mixture was concentrated to dryness at 39°C, and the residue (29 g) was dissolved in 40 mL acetonitrile. The resulting solution was concentrated to dryness at

35°C under reduced pressure, and additional 40 mL acetonitrile was added. The resulting solution was again concentrated to dryness at 35°C under reduced pressure, and then 35 mL acetonitrile and 29.5 g imidazole (433 mmol) were added. After the mixture was cooled with an ice water bath, *tert*-butylchlorodimethylsilane (32.6 g, 217 mmol) was added. The cold bath was removed, and the mixture was stirred at room temperature for 4 h. The reaction was quenched by the addition of 10 mL methanol. After the mixture was stirred for 5 min, 55 mL ice water was added, and the mixture was extracted with hexanes (2 × 50 mL). The combined organic extracts were washed with 50 mL 2:3 v/v mixture of methanol and water, dried over Na_2SO_4, and concentrated to dryness at 40°C under reduced pressure. Further drying of the residue at 46°C and 0.4 mmHg for 1 h gave 25.2 g crude (1*S*,4*S*,6*S*)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-methyl-7-oxabicyclo[4.1.0]heptan-2-one as a pale yellow oil, with a 81.7% yield on the basis of the initial starting material used.



Reference 8b.

Ozone was passed through a solution of 6.62 g (*S*,*S*,*S*)-2,3-dimethyl-5-(2-propen-2-yl)-cyclohexanone (39.8 mmol) in 100 mL dry methanol for 1.5 h while cooling between −10° and −40°C. The slightly blue solution was then purged with argon for 10 min, and 16.0 g $Cu(OAc)_2{\cdot}H_2O$ (80.0 mmol) was added while stirring at −20°C. After 15 min, 13.3 g $FeSO_4{\cdot}7H_2O$ (48.0 mmol) was added, and the mixture was warmed slowly to room temperature. After being stirred for 18 h, water was added and the mixture was washed five times with diethyl ether. The combined organic phases were washed with a saturated $NaHCO_3$ solution, brine and water, and dried over $MgSO_4$. After the removal of the solvent in vacuo, the crude product was purified by column chromatography (SiO_2, petroleum ether/*tert*-butyl methyl ether, 10:1), providing 2.11 g (*S*,*S*)-5,6-dimethyl-2-cyclohexenone (43% yield) and 0.62 g (*S*,*S*)-5,6-dimethyl-3-cyclohexenone (13% yield) as colorless liquids.

Other references related to the Criegee rearrangement are cited in the literature.[9]

H. REFERENCES

1. Criegee, R., *Ber.,* **1944**, *77*, 722.
2. (a) Krasutsky, P. A. and Kolomitsyn, I. V., *ARKIVOC,* **2005**, (*iv*) 151. (b) Zhang, Y.; Zeng, Z.-H.; Liu, Y.-Y.; Cheng, X.-X.; Wang, X.-S. and Zhang, B.-W., *Chem. Lett.,* **2005**, *34*, 368. (c) Krasutsky, P. A.; Kolomitsyn, I. V.; Kiprof, P.; Carlson, R. M.; Sydorenko, N. A. and Fokin, A. A., *J. Org. Chem.,* **2001**, *66*, 1701. (d) Krasutsky, P. A.; Kolomitsyn, I. V.; Kiprof, P.; Carlson, R. M. and Fokin, A. A., *J. Org. Chem.,* **2000**, *65*, 3926. (e) Goodman, R. M. and Kishi, Y., *J. Am. Chem. Soc.,* **1998**, *120*, 9392. (f) Goodman, R. M. and Kishi, Y., *J. Org. Chem.,* **1994**, *59*, 5125. (g) Menges, M. and Brueckner, R., *Synlett*, **1993**, 901. (h) Taljaard, B.; Goosen, A. and McCleland, C. W., *J. Chem. Soc., Perkin Trans. I,* **1989**, 931. (i) Schreiber, S. L. and Liew, W. F., *Tetrahedron Lett*., **1983**, *24*, 2363. (j) Wistuba, E. and Ruechardt, C., *Tetrahedron Lett*, **1981**, *22*, 3389. (k) Muto, S. and Bruice, T. C., *J. Am. Chem. Soc.,* **1980**, *102*, 7379. (l) Kropf, H. and

Bernert, C. R., *Ann.,* **1971**, *751*, 109. (m) Kropf, H. and Bernert, C. R., *Ann.,* **1971**, *751*, 121. (n) Schoellner, R.; Weiland, J. and Muehlstaedt, M., *Zeitsch. Chem.,* **1963**, *3*, 390.

3. (a) Sever, R. R. and Root, T. W., *J. Phys. Chem. B,* **2003**, *107*, 10848. (b) Crudden, C. M.; Chen, A. C. and Calhoun, L. A., *Angew. Chem. Int. Ed.,* **2000**, *39*, 2852.
4. Krasutsky, P. A.; Kolomitsyn, I. V.; Krasutsky, S. G. and Kiprof, P., *Org. Lett.,* **2004**, *6*, 2539.
5. (a) Noyori, R.; Sato, T. and Kobayashi, H., *Bull. Chem. Soc. Jpn.,* **1983**, *56*, 2661. (b) Noyori, R.; Sato, T. and Kobayashi, H., *Tetrahedron Lett*., **1980**, *21*, 2569. (c) Hawthorne, M. F.; Emmons, W. D. and McCallum, K. S., *J. Am. Chem. Soc.,* **1958**, *80*, 6393.
6. (a) Schenck, G. O. and Schulte-Elte, K.-H., *Liebigs Ann. Chem.,* **1958**, *618*, 185. (b) Treibs, W. and Heyner, E., *Ber.,* **1957**, *90*, 2285.
7. Porter, N. A.; Caldwell, S. E. and Lowe, J. R., *J. Org. Chem.,* **1998**, *63*, 5547.
8. (a) Daniewski, A. R.; Garofalo, L. M.; Hutchings, S. D.; Kabat, M. M.; Liu, W.; Okabe, M.; Radinov, R. and Yiannikouros, G. P., *J. Org. Chem.,* **2002**, *67*, 1580. (b) Ebert, S. and Krause, N., *Eur. J. Org. Chem.,* **2001**, 3831. (c) de Groot, A.; Jansen, B. J. M.; Verstegen-Haaksma, A. A.; Swarts, H. J.; Orru, R. V. A.; Stork, G. A. and Wijnberg, J. B. P. A., *Pure & Appl. Chem.,* **1994**, *66*, 2053.
9. (a) Straganz, G. D.; Hofer, H.; Steiner, W. and Nidetzky, B., *J. Am. Chem. Soc.,* **2004**, *126*, 12202. (b) Kizil, M.; Yilmaz, E. I.; Pirinççioğlu, N. and Aytekin, Ç., *Turk. J. Chem.,* **2003**, *27*, 539. (c) Marchand, A. P.; Kumar, V. S. and Hariprakasha, H. K., *J. Org. Chem.,* **2001**, *66*, 2072. (d) Pettus, T. R. R.; Chen, X.-T. and Danishefsky, S. J., *J. Am. Chem. Soc.,* **1998**, *120*, 12684. (e) Grammer, J. C.; Loo, J. A.; Edmonds, C. G.; Cremo, C. R. and Yount, R. G., *Biochemistry,* **1996**, *35*, 15582. (f) Muto, S. and Bruice, T. C., *J. Am. Chem. Soc.,* **1980**, *102*, 7379. (g) Criegee, R., *Angew. Chem. Int. Ed. Engl.,* **1975**, *14*, 745. (h) Cope, A. C. and Holzman, G., *J. Am. Chem. Soc.,* **1960**, *72*, 3062. (i) Criegee, R. and Kaspar, R., *Ann. Chem*., **1948**, *560*, 127.

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Crum-Brown-Gibson Substitution Rule

A. GENERAL DESCRIPTION OF THE REACTION

This is one of the many rules guiding the position of the incoming electrophile on an aromatic ring, primarily in the substituted benzene ring, in electrophilic aromatic substitution. The Crum-Brown-Gibson rule,[1] proposed by Crum-Brown and Gibson in 1892,[2] is the best known rule for the directive influence[3] for electrophilic aromatic substitution, although several investigators had proposed similar rules before Crum-Brown and Gibson, including Körner in 1874,[4] Hübner in 1875,[5] Nölting in 1876,[6] and Armstrong in 1887.[7] In addition, a few other investigators also proposed explanations for electrophilic aromatic substitution after 1892, including Flürscheim in 1902,[8] Vörlander in 1902,[9] Fry in 1911,[10] Stieglitz in 1922,[11] and Prins in 1925.[12] The rules from Körner, Hübner, and Nölting are also combined as the Hübner-Nölting-Körner rule.[13] The original Crum-Brown-Gibson rule stated that the substituent already present on the benzene ring is considered to be linked to hydrogen (i.e., the benzene ring can be replaced by a hydrogen atom), and if the corresponding compound can be directly oxidized, then the second incoming group will take up the position *meta* to the existing substituent; otherwise, the incoming group would enter the position either *para* or *ortho* to the existing substituent. For example, if the existing substituent is Cl, the corresponding compound is HCl, which cannot be oxidized directly to HClO, then, Cl is a *para*- and *ortho*-directing group.[13] It should be pointed out that the Crum-Brown-Gibson rule and the other rules listed earlier all are empirical generalizations of experimental results and do not provide information about the reaction mechanism.[14] In addition, most of the rules cover only the majority of experimental results with a few exceptions.[3]

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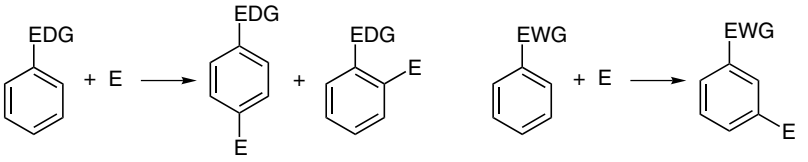
The advanced knowledge about the electrophilic aromatic substitution is generally summarized here. The existing substituent on the aromatic ring (e.g., benzene) has a twofold effect on such substitution: the effect on determining the location of incoming electrophilic group and the effect on the substitution reaction rate. Basically, this substitution is a two-step process: the addition of an electrophile to the C=C double bond on the aromatic ring and the elimination of a hydrogen atom from the attacking position. The existing substituent on the aromatic ring can be the electron-donating group or the electron-withdrawing group, which affect the reaction quite differently. If such an effect is not counted, (i.e., regardless of the electronic character of substituent), then *para*- or *ortho*-substitution is favored. This is because a carbocation intermediate is formed in the first step by the addition of an electrophile, and this carbocation intermediate can isomerize to three other resonance structures, as illustrated later. If the incoming electrophile attacks at either the *para*- or *ortho*-position, the resonance structures of the resulting carbocation intermediate include two secondary carbocations and one tertiary carbocation, and normally tertiary carbocation is much more stable than the secondary carbocation. In contrast, if the incoming electrophile enters at the position *meta* to the existing group, then the formed carbocation intermediate contains only three resonance structures of secondary carbocations, indicating the preferred position would be either the *para*- or *ortho*-position. Considering the steric hindrance from the existing substituent and incoming electrophile, the *para*-substitution is the most favored. However, compared to hydrogen, all the substituents on the aromatic ring can be divided into either electron-donating groups or electron-withdrawing groups. For the case of halogens and the electron-donating groups (either contributing a lone electron pair such as OR or NR_2 or donating a certain electron cloud via superconjugation such as alkyl), they can further stabilize all the formed carbocation intermediates, but stabilize the formed carbocation intermediates only when the incoming electrophile primarily enters at either the *ortho*- or the *para*-position of the existing substituent, and yield the *ortho*- and *para*-substituted products. This is because the electron-donating group is either directly linked to the formed carbocation or in conjugation with the carbocation. Therefore, these substituents are called *ortho*/*para* directors.[15] For comparison, if the existing group is an electron-withdrawing substituent excluding halogen (e.g., NO_2, CN), it will destabilize all the resonance structures of the carbocation intermediate but destabilize the carbocation intermediate formed primarily from *ortho*- or *para*-incoming electrophile, because the electron-withdrawing group is either directly connected to carbocation or in conjugation with carbocation. Therefore, only the carbocation intermediate from the *meta*-attacking electrophile can productively form the final *meta*-substituted product. Thus the electron-withdrawing groups are also called *meta* directors.[15]

Accordingly, the substituent favoring the *ortho*- or *para*-substitution (i.e., electron-donating group) is called the *ortho*/*para* director; in addition, because all these groups stabilize the formed carbocation intermediates and facilitate the substitution, these groups are also called activators. On the other hand, the electron-withdrawing group, which disfavors the formation of the carbocation intermediate, will slow down the reaction rate compared to benzene; thus the electron-withdrawing groups are also called deactivators.

The substituents on the polycyclic aromatic compounds, such as naphthalene, phenanthrene, fluoranthrene, and pyrene, are much more complicated; however, the substitution positions are still determined by the relative stabilities of the formed carbocation intermediates.[16]

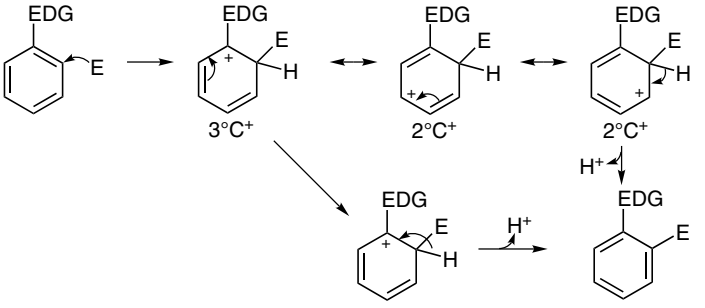
B. GENERAL REACTION SCHEME



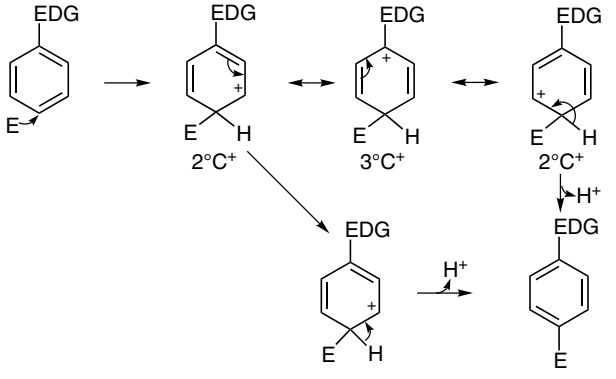
(*EDG*, electron-donating group; *E*, electrophile; *EWG*, electron-withdrawing group)

C. PROPOSED MECHANISMS

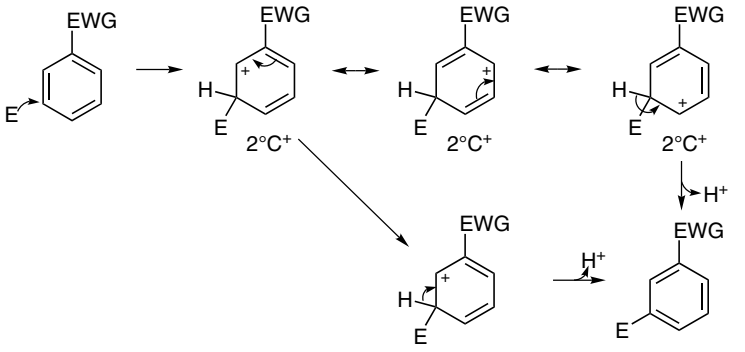
In the case of *ortho*-substitution.



In the case of *para*-substitution.



In the case of *meta*-substitution.



D. MODIFICATION

N/A

E. APPLICATIONS

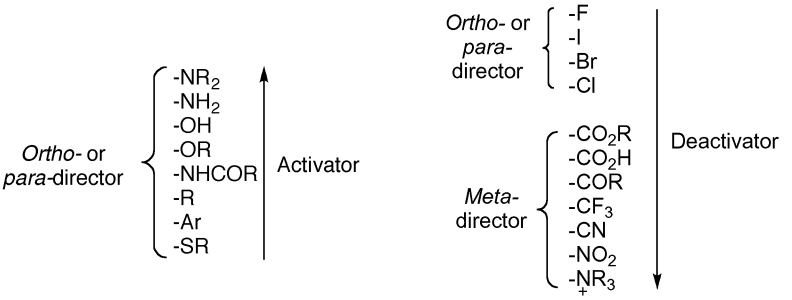
This rule is very useful for the design of organic synthesis routes.

F. RELATED REACTIONS

This rule is related to the rules mentioned in Section A.[4–12]

G. CITED EXPERIMENTAL EXAMPLES

Because so many reactions are available from textbooks and journals, no experimental details are provided here; however, some relevant experiments are given in the discussion of the *Friedel-Crafts Alkylation* and *Friedel-Crafts Acylation*. Listed here are some common electron-donating groups and electron-withdrawing groups. The characteristics and of other substituents are given by Hansch and co-workers.[17]



Other references related to the Crum-Brown-Gibson substitution rule are cited in the literature.[18]

H. REFERENCES

1. Fry, H. S., *Z. Physik. Chem*., **1911**, *76*, 385.
2. Crum Brown, A. and Gibson, J., *J. Chem. Soc.,* **1892**, *61*, 367.
3. Francis, A. W., *Chem. Rev.,* **1926**, *3*, 257.
4. Körner, W., *Gazz. Chim. Ital.,* **1874**, *4*, 305, 446.
5. Hübner, H. *Ber.,* **1875**, *8*, 873.
6. Nölting, E., *Ber.,* **1876**, *9*, 1797.
7. Armstrong, H. E., *J. Chem. Soc.,* **1887**, *51*, 258.
8. (a) Flürscheim, B., *J. Prakt. Chem.,* **1902**, *66*, 321. (b) Flürscheim, B., *J. Prakt. Chem.,* **1905**, *71*, 497. (c) Flürscheim, B., *Ber.,* **1906**, *39*, 2015.
9. Vörlander, D., *Ann.,* **1902**, *320*, 122.
10. (a) Fry, H. S., *J. Am. Chem. Soc.,* **1914**, *36*, 248, (b) Fry, H. S., *J. Am. Chem. Soc.,* **1915**, *37*, 855.
11. (a) Stieglitz, J., *J. Am. Chem. Soc.,* **1922**, *44*, 729. (b) Stieglitz, J., *J. Am. Chem. Soc.,* **1922**, *44*, 1293.
12. Prins, H. J., *Rec. Trav. Chim. Pays-Bas Belg.,* **1925**, *44*, 169.
13. Holleman, A. F., *Chem. Rev.,* **1924**, *1*, 187.
14. Krarasch, M. S. and Chalkley, L., *J. Am. Chem. Soc.,* **1921**, *43*, 607.
15. Daley, R. F. and Daley, S. J., *Organic Chemistry,* William C. Brown Publishers, Dubique, Iowa, **1996**, ch. 18.
16. Wang, D. Z. R. and Streitwieser, A., *Theoretical Chemcal Account,* **1999**, *102*, 78.
17. Hansch, C.; Leo, A. and Taft, R. W., *Chem. Rev.,* **1991**, *91*, 165.
18. (a) Stevenson, C. D.; Wagner, E. P. and Reiter, R. C., *J. Phys. Chem*., **1993**, *97*, 10585. (b) Hazlet, S.; Alliger, G. and Tiede, R., *J. Am. Chem. Soc.,* **1939**, *61*, 1447. (c) Fry, H. S., *Chem. Rev.,* **1929**, *5*, 557. (d) Waters, W. A., *Chem. Rev.,* **1930**, *7*, 407. (e) Krarasch, M. S. and Jacobsohn, I. M., *J. Am. Chem. Soc.,* **1921**, *43*, 1894. (f) Fry, H. S., *J. Am. Chem. Soc.,* **1914**, *36*, 248. (g) Blanksma, J. J., *Rec. Trav. Chim. Pays-Bas Belg.,* **1904**, *23*, 202.

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Curtius Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Curtius in 1890.[1] It is the formation of isocyanate by thermal decomposition of acyl azides prepared from acyl halide and sodium azide and is generally known as the Curtius rearrangement.[2] Although this reaction is thought to proceed via a concerted mechanism[3] and form carbonyl nitrene intermediate,[3a,3b,3g,4] from which the R group migrates to the nitrogen atom to give isocyanate, some evidence supporting the stepwise mechanism has also been reported.[3a] Nevertheless, the Curtius rearrangement occurs with complete retention of configuration at the migrating carbon,[5] and the migration from the carbon to the nitrogen atom is an irreversible intramolecular reaction in first-order kinetics.[6] Because it is an intramolecular rearrangement, a solvent or salt effect is not evident.[6] The intermediate isocyanate can be isolated or subjected to subsequent reaction directly—for example, isocyanate reacts with water to form an unstable carbamic acid, which undergoes spontaneous decarboxylation to produce amine with one fewer carbon unit. This special reaction is referred to as the Curtius reaction.[7] In addition, the Curtius rearrangement is also known as the Curtius-type reaction,[7b] Curtius degradation,[8] Hofmann-Beckmann-Curtius-Lossen rearrangement,[9] and Curtius-type rearrangement.[10] On the one hand, the Curtius rearrangement has been used with great success for the preparation of non-commercially available isocyantes from a diverse assortment of carboxylic acids, including aliphatic,[11] aromatic,[12] heterocyclic,[13] unsaturated,[14] and chiral acids.[15] In addition, this rearrangement is good for the preparation of tetrazoles,[16] cyanamides,[16] oxazolidones,[17] amino alcohol,[18] furano carbamate,[7a] etc. On the other hand, the pyrolysis of acyl azides can also be carried out photolytically,[3b,3g,4,19] via a concerted mechanism.[3b] When acyl

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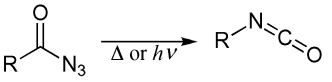
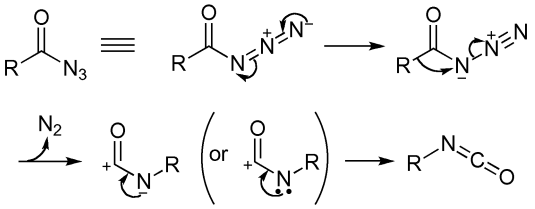
azide contains a halogen or hydroxyl group at the α-position, an aldehyde or ketone forms.[7c] It should be pointed out that benzenesulfonyl azide also undergoes a similar rearrangement and gives a sulfurylaniline intermediate.[10d] Recently, the Curtius rearrangement was carried out under microwave irradiation[20] and was modified using phase-transfer catalysis;[21] however, the most important modification of the Curtius rearrangement is to use the Shiori reagent[18]—that is, diphenylphosphoryl azide (DPPA).[22]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A simple mechanism involving a nitrene intermediate is displayed here.



D. MODIFICATION

This rearrangement has been modified to use the Shiori reagent as the azide source;[22] in addition, this reaction has been extended to proceed under photo [3b,3g,4,19] or microwave[20] irradiation.

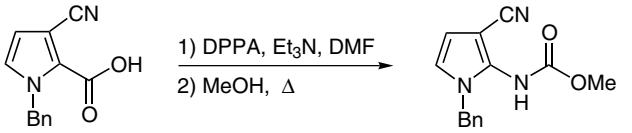
E. APPLICATIONS

The major applications of this rearrangement are the preparation of a variety of isocyanates and amines. In addition, this reaction is also valuable for the preparation of tetrazoles,[16] cyanamides,[16] oxazolidones,[17] amino alcohol,[18] and furano carbamate.[7a]

F. RELATED REACTIONS

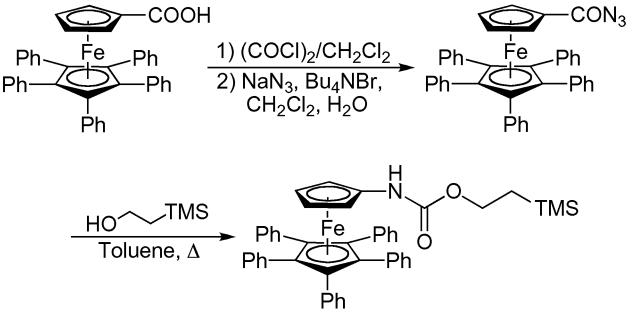
This reaction is related to the *Hofmann Degradation*, *Lossen Rearrangement*, and *Schmidt Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 22b.

To a solution of 7.04 g 1-benzyl-3-cyanopyrrole-2-carboxylic acid (31.12 mmol) in 75 mL *N,N*-dimethylformamide at 0°C was added 7.65 mL diphenylphosphoryl azide (DPPA, 9.72 g, 35.30 mmol, 1.1 eq.) and 4.75 mL triethylamine (3.42 g, 33.80 mmol, 1.1 eq.). The solution was allowed to stir at room temperature for 6 h. Methanol (7 mL) was added, and the reaction mixture was heated at 65°C for 8 h. The solvents were evaporated in vacuo, and the resulting residue was dissolved in 140 mL EtOAc. The solution was then extracted with 1 N aqueous HCl solution (3 × 80 mL), washed with saturated aqueous $NaHCO_3$ solution (3 × 80 mL), dried over anhydrous $MgSO_4$, and concentrated to dryness. The residue was recrystallized from ethanol to give 4.695 g 1-benzyl-2-methoxycarbonylamino-3-cyanopyrrole, in a yield of 59%, m.p. 140–142°C.



Reference 23.

1,2,3,4,5-Pentaphenylferrocene-1′-carboxylic acid (2.00 g, 3.3 mmol) was suspended in 20 mL CH_2Cl_2. Oxalyl chloride (0.84 g, 0.58mL, 6.6 mmol) was added followed by a drop of DMF. The mixture was stirred at room temperature for 3 h, after which the solvent and residual oxalyl chloride were removed in vacuo. The red solid thus obtained was taken up in 20 mL CH_2Cl_2. Tetrabutylammonium bromide (0.004 g, 0.01 mmol) was added, followed by a solution of 0.32 g NaN_3 (4.9 mmol) in 4 mL H_2O, and the mixture was stirred rapidly at room temperature for 18 h. An additional 50 mL water was added to the mixture, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), the combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo. Column chromatography (1:1 CH_2Cl_2/petroleum ether) gave 1.69 g 1,2,3,4,5-pentaphenyl-1′-acylazidoferrocene as a red solid, in a yield of 81%, m.p. 250°C (dec).

1,2,3,4,5-Pentaphenyl-1′-acylazideferrocene (1.48 g, 2.3 mmol) was dissolved in 15 mL toluene; the solution was heated to 105°C, and 0.67 mL of 2-(trimethylsilyl)ethanol (4.7 mmol) was added in a single portion. The red solution obtained was stirred at this temperature for 3 h, by which time the color had changed to dark orange. The mixture was cooled to room temperature, 50 mL 1 M NaOH was added, and the solution was stirred for

5 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo to give an orange solid. Chromatography (1:1 CH_2Cl_2/petroleum ether) gave 1.61 g 1,2,3,4,5-pentaphenylferrocene-1′-(2-trimethylsilyl)-ethyl carbamate as an orange solid, in a yield of 95%, m.p.132–134°C.

Other references related to the Curtius rearrangement are cited in the literature.[24]

H. REFERENCES

1. Curtius, T., *Ber.,* **1890**, *23*, 3023.
2. (a) Zabalov, M. V. and Tiger, R. P., *Russ. Chem. Bull.,* **2007**, *56*, 7. (b) Davis, M. C., *Synth. Commun.,* **2007**, *37*, 1457. (c) Sawada, D.; Sasayama, S.; Takahashi, H. and Ikegami, S., *Eur. J. Org. Chem.,* **2007**, 1064. (d) Tada, T.; Ishida, Y. and Saigo, K., *Synlett,* **2007**, 235. (e) Yamatsugu, K.; Kamijo, S.; Suto, Y.; Kanai, M. and Shibasaki, M., *Tetrahedron Lett*., **2007**, *48*, 1403. (f) Lebel, H. and Leogane, O., *Org. Lett.,* **2006**, *8*, 5717. (g) Sawada, D.; Sasayama, S.; Takahashi, H. and Ikegami, S., *Tetrahedron Lett*., **2006**, *47*, 7219. (h) Jung, D. Y.; Kang, S.; Chang, S. and Kim, Y. H., *Synlett,* **2006**, 86. (i) Zabalov, M. V. and Tiger, R. P., *Russ. Chem. Bull.,* **2005**, *54*, 2270. (j) Lebel, H. and Leogane, O., *Org. Lett.,* **2005**, *7*, 4107. (k) Babu, V. V. S.; Kantharaju; T. and Subramanyam, J., *Int. J. Peptide Res. Therap.,* **2005**, *11*, 131. (l) Gomez-Sanchez, E. and Marco-Contelles, J., *Tetrahedron*, **2005**, *61*, 1207. (m) Dussault, P. H. and Xu, C. P., *Tetrahedron Lett*., **2004**, *45*, 7455. (n) Moore, J. D.; Sprott, K. T. and Hanson, P. R., *J. Org. Chem.,* **2002**, *67*, 8123. (o) Braibante, M. E. F.; Braibante, H. S. and Costenaro, E. R., *Synthesis,* **1999**, 943. (p) Sunami, S.; Sagara, T.; Ohkubo, M. and Morishima, H., *Tetrahedron Lett*., **1999**, *40*, 1721. (q) Am Ende, D. J.; DeVries, K. M.; Clifford, P. J. and Brenek, S. J., *Org. Proc. Res. Dev.,* **1998**, *2*, 382. (r) Khoukhi, M.; Vaultier, M.; Benalil, A. and Carboni, B., *Synthesis*, **1996**, 483. (s) Batori, S.; Messmer, A. and Timpe, H. J., *Heterocycles,* **1991**, *32*, 649. (t) Okada, Y.; Tsuda, Y. and Yagyu, M., *Chem. Pharm. Bull.,* **1980**, *28*, 2254. (u) Saikachi, H. and Kitagawa, T., *Chem. Pharm. Bull.,* **1978**, *26*, 1054. (v) Brandstrom, A.; Lamm, B. and Palmertz, I., *Acta Chem. Scand., Ser. B,* **1974**, *28*, 699. (w) Washburne, S. S. and Peterson, W. R., *J. Am. Oil Chem. Soc.,* **1972**, *49*, 694. (x) Wilds, A. L.; Woolsey, N. F.; Berghe, J. V. D. and Winestock, C. H., *Tetrahedron Lett*., **1965**, 4841. (y) Stolle, R. and Merkle, N., *J. Prakt. Chem.,* **1928**, *119*, 275.
3. (a) Liu, J.; Mandel, S.; Hadad, C. M. and Platz, M. S., *J. Org. Chem.,* **2004**, *69*, 8583. (b) Lwowski, W.; de Mauriac, R. A.;Thompson, M.; Wilde, R. E. and Chen, S.-Y., *J. Org. Chem.,* **1975**, *40*, 2608. (c) Eibler, E. and Sauer, J., *Tetrahedron Lett.,* **1974**, 2569. (d) Hayashi, Y. and Swern, D., *J. Am. Chem. Soc.,* **1973**, *95*, 5205. (e) Lwowski, W., "Carbonylnitrenes" in "*Nitrenes*", ed. Lwowski, W., Wiley-Interscience, New York, **1970**, pp. 185–224. (f) Boyer, J. H., "Rearrangements Involving Nitrene Intermediates" in "*Mechanisms of Molecular Migration*", ed. Thyagarajan, B. S., Wiley-Interscience, New York, **1969**, *2*, pp. 267–318. (g) Linke, S.; Tisue, G. T. and Lwowski, W., *J. Am. Chem. Soc.,* **1967**, *89*, 6308.
4. Denmark, S. E. and Dorow, R. L., *J. Org. Chem.,* **1989**, *54*, 5.
5. (a) Hibbs, D. E.; Hursthouse, M. B.; Jones, I. G.; Jones, W.; Malik, K. M. A. and North, M., *J. Org. Chem.,* **1998**, *63*, 1496. (b) Ghosh, A. K. and Fidanze, S., *J. Org. Chem.,* **1998**, *63*, 6146. (c) Ghosh, A. K. and Liu, W. M., *J. Org. Chem.,* **1996**, *61*, 6175. (d) Grunewald, G. L. and Ye, Q., *J. Org. Chem.,* **1988**, *53*, 4021. (e) Glass, R. S.; McConnell, W. W. and Andruski, S. P., *J. Org. Chem.,* **1986**, *51*, 5123. (f) Smith, P. A. S., *Derivatives of Hydrazine and other Hydronitrogens Having N-N Bonds*, Benjamin, Reading, **1983**, pp. 272–273. (g) Shioiri, T.; Ninomiya, K. and Yamada, S., *J. Am. Chem. Soc.,* **1972**, *94*, 6203. (h) Banthorpe, D. V., "Rearrangements Involving

Azido Groups" in *The Chemistry of Azide Group*, ed. Patai, S., Interscience, New York, **1971**, pp. 397–440. (i) Forster, M. O., *J. Chem. Soc.,* **1909**, *95*, 433.

6. Newman, M. S.; Lee, S. H. and Garrett, A. B., *J. Am. Chem. Soc.,* **1947**, *69*, 113.
7. (a) Kedrowski, B. L., *J. Org. Chem.,* **2003**, *68*, 5403. (b) de Kimpe, N.; Boeykens, M. and Tehrani, K. A., *J. Org. Chem.,* **1994**, *59*, 8215. (c) Zook, H. D.; Ream, M. and Delchamps, E. W., *J. Am. Chem. Soc.,* **1953**, *75*, 5590.
8. Mason, C. D. and Nord, F. F., *J. Org. Chem.,* **1951**, *16*, 1869.
9. Franklin, E. C., *Chem. Rev.,* **1934**, *12*, 219.
10. (a) Kumar, N. S.; Kumar, K. P.; Kumar, K. V. P. P.; Kommana, P.; Vittal, J. J. and Swamy, K. C. K., *J. Org. Chem.,* **2004**, *69*, 1880. (b) Baceiredo, A.; Bertrand, G.; Majoral, J.-P.; Anba, F. E. and Manuel, G., *J. Am. Chem. Soc.,* **1985**, *107*, 3945. (c) Baceiredo, A.; Bertrand, G.; Majoral, J.-P.; Wermuth, U. and Schmutzler, R., *J. Am. Chem. Soc.,* **1984**, *106*, 7065. (d) Abramovitch, R. A. and Holcomb, W. D., *J. Chem. Soc. D,* **1969**, 1298. e) Lwowski, A. and Scheiffele, E., *J. Am. Chem. Soc.,* **1965**, *87*, 4359.
11. Guan, H.-P.; Ksebati, M. B.; Cheng, Y.-C.; Drach, J. C.; Kern, E. R. and Zemlicka, J., *J. Org. Chem.,* **2000**, *65*, 1280.
12. Hitotsuyanagi, Y.; Kobayashi, M.; Morita, H.; Itokawa, H. and Takeya, K., *Tetrahedron Lett.,* **1999**, *40*, 9107.
13. Arranz, M. E.; Diaz, J. A.; Ingate, S. T.; Witvrouw, M.; Pannecouque, C.; Balzarini, J.; De Clercq, E. and Vega, S., *Bioorg. Med. Chem.,* **1999**, *7*, 2811.
14. Pais, G. C. G. and Maier, M. E., *J. Org. Chem.,* **1999**, *64*, 4551.
15. Wiberg, K. B. and Oesterle, C., *J. Org. Chem*., **1999**, *64*, 7763.
16. Imhof, R.; Ladner, D. W. and Muchowski, J. M., *J. Org. Chem.,* **1977**, *42*, 3709.
17. Vaughan, W. R. and Spencer, J. L., *J. Org. Chem.,* **1960**, *25*, 1077.
18. Sasmal, S.; Geyer, A. and Maier, M. E., *J. Org. Chem.,* **2002**, *67*, 6260.
19. Chehade, K. A. H. and Spielmann, H. P., *J. Org. Chem.,* **2000**, *65*, 4949.
20. Patil, B. S.; Vasanthakumar, G.-R. and Babu, V. V. S., *J. Org. Chem.,* **2003**, *68*, 7274.
21. Groszek, G., *Org. Proc. Res. Dev.,* **2002**, *6*, 759.
22. (a) Spino, C.; Tremblay, M.-C. and Gobdout, C., *Org. Lett.,* **2004**, *6*, 2801. (b) Chien, T.-C.; Meade, E. A.; Hinkley, J. M. and Townsend, L. B., *Org. Lett.,* **2004**, *6*, 2857. (c) Spino, C. and Gobdout, C., *J. Am. Chem. Soc.,* **2003**, *125*, 12106. (d) Ecija, M.; Diez, A.; Rubiralta, M.; Casamitjana, N.; Kogan, M. J. and Giralt, E., *J. Org. Chem.,* **2003**, *68*, 9541. (e) Armstrong, A. and Scutt, J. N., *Org. Lett.,* **2003**, *5*, 2331. (f) Ghosh, A. K.; Bischoff, A. and Cappiello, J., *Org. Lett.,* **2001**, *3*, 2677. (g) Back, T. G. and Nakajima, K., *J. Org. Chem.,* **1998**, *63*, 6566. (h) Jacobi, P. A.; Murphree, S.; Rupprecht, F. and Zheng, W. J., *J. Org. Chem.,* **1996**, *61*, 2413.
23. Butler, D. C. D. and Richards, C. J., *Organometallics,* **2002**, *21*, 5433.
24. (a) Miller, J. A. and Nguyen, S. T., *Mini-Rev. Org. Chem.*, **2005**, *2*, 39. (b) Englund, E. A.; Gopi, H. N. and Appella, D. H., *Org. Lett.,* **2004**, *6*, 213. (c) Marinescu, L.; Thinggaard, J.; Thomsen, I. B. and Bols, M., *J. Org. Chem.,* **2003**, *68*, 9453. (d) Nettekoven, M. and Jenny, C., *Org. Proc. Res. Dev.,* **2003**, *7*, 38. (e) Smith, A. B.; Safonov, I. G. and Corbett, R. M., *J. Am. Chem. Soc.,* **2002**, *124*, 11102. (f) Okaniwa, M.; Takeuchi, K.; Asai, M. and Ueda, M., *Macromolecules,* **2002**, *35*, 6224. (g) Okaniwa, M.; Takeuchi, K.; Asai, M. and Ueda, M., *Macromolecules,* **2002**, *35*, 6232. (h) Govindan, C. K., *Org. Proc. Res. Dev.,* **2002**, *6*, 74. (i) Sibi, M. P. and Deshpande, P. K., *J. Chem. Soc*., *Perkin Trans. 1*, **2000**, 1461. (j) Migawa, M. T. and Swayze, E. E., *Org. Lett.,* **2000**, *2*, 3309. (k) Padwa, A. and Wu, T. H., *ARKIVOC,* **2000**, (i), 193. (l) Zhang, C. Y. and Tour, J. M., *J. Am. Chem. Soc.,* **1999**, *121*, 8783. (m) Padwa, A.; Brodney, M. A.; Liu, B.; Satake, K. and Wu, T. H., *J. Org. Chem.,* **1999**, *64*, 3595. (n) Evans, D. A.; Wu, L. D.; Wiener, J. J. M.; Johnson, J. S.; Ripin, D. H. B. and Tedrow, J. S., *J. Org. Chem.,* **1999**, *64*, 6411. (o) Yao, Y. X.; Lamba, J. J.

S. and Tour, J. M., *J. Am. Chem. Soc.,* **1998**, *120*, 2805. (p) Broggini, G.; Garanti, L.; Molteni, G. and Zecchi, G., *J. Chem. Res (S).,* **1998**, 688. (q) Zhang, C.; Lomenzo, S. A.; Ballay, C. J.; Trudell, M. L., *J. Org. Chem.,* **1997**, *62*, 7888. (r) Sibi, M. P.; Lu, J. L. and Edwards, J., *J. Org. Chem.,* **1997**, *62*, 5864. (s) Olsen, R. K.; Hennen, W. J. and Wardle, R. B., *J. Org. Chem.,* **1982**, *47*, 4605. (t) Brower, K. R., *J. Am. Chem. Soc.,* **1961**, *83*, 4370. (u) Yukawa, Y. and Tsuno, Y., *J. Am. Chem. Soc.,* **1959**, *81*, 2007. (v) Yukawa, Y. and Tsuno, Y., *J. Am. Chem. Soc.,* **1958**, *80*, 6346. (w) Yukawa, Y. and Tsuno, Y., *J. Am. Chem. Soc.,* **1957**, *79*, 5530. (x) Bothnerby, A. A. and Friendman, L., *J. Am. Chem. Soc.,* **1951**, *73*, 5391. (y) Hauser, C. R. and Kantor, S. W., *J. Am. Chem. Soc.,* **1950**, *72*, 4284. (z) Saunders, J. H. and Slocombe, R. J., *Chem. Rev.,* **1948**, *43*, 205. (aa) Newman, M. S. and Gildenhorn, H. L., *J. Am. Chem. Soc.,* **1948**, *70*, 317. (bb) Smith, P. A. S., *Org. React.,* **1946**, *3*, 337.

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[m+n(+. . .)] Cycloaddition

A. GENERAL DESCRIPTION OF THE REACTION

Modern organic synthesis with its increasing ecological concerns demands a highly efficient process to transform simple starting materials rapidly into complex building blocks, from which the desired products can be formed.[1] One of the best ways to address this challenge relies on the application of a cycloaddition reaction, in which two or more molecules can combine and form new ring structures, along with the formation of multiple bonds and multiple stereogenic centers in a single step.[2] In addition, cycloadditions are also considered the right choice when high regioselectivities, chemoselectivities and stereoselectivities are concerned.[3] Except for the famous *Diels-Alder Reaction*, *1,3-Dipolar Cycloaddition*, and *[2+2] Cycloaddition* (including a special case of *Paterno-Buchi Reaction*), which are described separately, many types of cycloadditions currently used in organic syntheses are summarized in this chapter of cycloaddition, including [2+1], [2+2+1], [2+2+2], [2+2+2+1], [3+2+1], [3+2+2], [3+2+2+2], [3+3], [4+1], [4+2+1], [4+2+2], [4+3], [4+4], [5+1], [5+1+2+1], [5+2], [5+2+1], [5+3], [5+4], [6+2], [6+3], [6+4], [6+6], and [8+2] cycloadditions. Each of these cycloadditions can be treated as an individual reaction like the other named reactions discussed in this book; therefore, for each type of cycloaddition I have provided one experimental example accompanied along with related references.

B. REFERENCES

1. (a) Rodríguez, J. R.; Rumbo, A.; Castedo, L. and Mascareñas, J. L., *J. Org. Chem.,* **1999**, *64*, 966. (b) Rodríguez, J. R.; Rumbo, A.; Castedo, L. and Mascareñas, J. L., *J. Org. Chem.,* **1999**, *64*, 4560.
2. Sieburth, S. McN.; Lin, C.-H. and Rucando, D., *J. Org. Chem.,* **1999**, *64*, 950.

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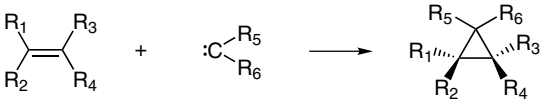
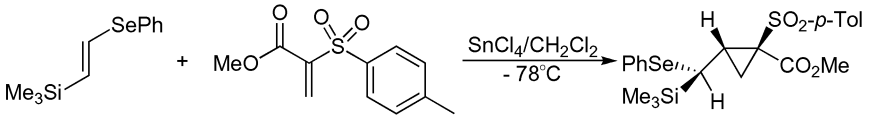
3. (a) Slowinski, F.; Aubert, C. and Malacria, M., *J. Org. Chem.,* **2003**, *68*, 378. (b) Sieburth, S. McN.; Rucando, D. and Lin, C.-H., *J. Org. Chem.,* **1999**, *64*, 954.

[2+1] Cycloaddition

A. GENERAL REACTION SCHEME



B. CITED EXPERIMENTAL EXAMPLES



Reference 1.

To a solution of 250 mg 1-phenylseleno-2-trimethylsilylethene (1.0 mmol) in 2.4 mL dichloromethane was added 0.173 mL $SnCl_4$ (391 mg, 1.5 mmol) followed by 312 mg 2-*p*-toluenesulfonylacrylate (1.3 mmol) at −78°C. The mixture was stirred at −78°C for 3 h. The reaction mixture was quenched by 0.32 mL triethylamine (230 mg, 2.3 mmol) and then with saturated aqueous $NaHCO_3$. The mixture was extracted with dichloromethane, and the organic phase was washed with water, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography over silica gel eluting with hexane/ether (2:1) to give 278 mg methyl *R*-1-(*p*-toluenesulfonyl)-*c*-2-[(phenylseleno)-(trimethylsilyl)methyl]-1-cyclopropanecarboxylate, in a yield of 56%. An analytically pure sample was recrystallized from hexanes/ether as colorless crystals, m.p. 117–119°C.

Other references related to [2 + 1] cycloaddition are cited in the literature.[2]

C. REFERENCES

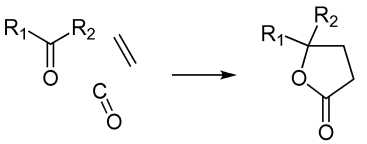
1. Yamazaki, S.; Yanase, Y.; Tanigawa, E.; Yamabe, S. and Tamura, H., *J. Org. Chem.,* **1999**, *64*, 9521.
2. (a) Han, J. L. and Ong, C. W., *Tetrahedron*, **2005**, *61*, 1501. (b) Nomura, K.; Oshima, K. and Matsubara, S., *Tetrahedron Lett*., **2004**, *45*, 5957. (c) Holzinger, M.; Steinmetz, J.; Samaille, D.; Glerup, M.; Paillet, M.; Bernier, P.; Ley, L. and Graupner, R., *Carbon*, **2004**, *42*, 941.

(d) Knorr, R., *Chem. Rev*., **2004**, *104*, 3795. (e) Gehrhus, B. and Hitchcock, P. B., *Organometallics*, **2004**, *23*, 2848. (f) Lou, Y.; Horikawa, M.; Kloster, R. A.; Hawryluk, N. A. and Corey, E. J., *J. Am. Chem. Soc*., **2004**, *126*, 8916. (g) Lu, X.; Tian, F. and Zhang, Q., *J. Phys. Chem. B*., **2003**, *107*, 8388. (h) Matsubara, S.; Ukai, K.; Fushimi, H.; Yokota, Y.; Yoshino, H.; Oshima, K.; Omoto, K.; Ogawa, A.; Hioki, Y. and Fujimoto, H., *Tetrahedron*, **2002**, *58*, 8255. (i) Barluenga, J.; Fernández-Rodríguez, M. A.; Andina, F. and Aguilar, E., *J. Am. Chem. Soc*., **2002**, *124*, 10978. (j) Yamazaki, S.; Yanase, Y.; Kamimoto, K.; Yamada, K. and Yamamoto, K., *J. Org. Chem*., **2001**, *66*, 5915. (k) Nguyen, L. T.; Proft, F. D.; Nguyen, M. T. and Geerlings, P., *J. Org. Chem*., **2001**, *66*, 4316. (l) Nguyen, L. T.; De Proft, F.; Nguyen, M. T. and Geerlings, P., *J. Org. Chem*., **2001**, *66*, 4316. (m) Chowdhury, S. K.; Amarasinghe, K. K.; Heeg, M. J. and Montgomery, J., *J. Am. Chem. Soc*., **2000**, *122*, 6775. (n) Ukai, K.; Oshima, K. and matsubara, S., *J. Am. Chem. Soc.,* **2000**, *122*, 12047. (o) Nguyen, L. T.; Le, T. N.; De Proft, F.; Chandra, A. K.; Langenaeker, W.; Nguyen, M. T. and Geerlings, P., *J. Am. Chem. Soc*., **1999**, *121*, 5992. (p) Yamazaki, S.; Takada, T.; Imanishi, T.; Moriguchi, Y. and Yamabe, S., *J. Org. Chem*., **1998**, *63*, 5919. (q) Nguyen, L. T.; Le, T. N.; Proft, F. D.; Chandra, A. K.; Langenaeker, W.; Nguyen, M. T. and Geerlings, P., *J. Am. Chem. Soc*., **1999**, *121*, 5992. (r) Yamazaki, S.; Inoue, T.; Hamada, T. and Takada, T., *J. Org. Chem*., **1999**, *64*, 282. (s) Yamazaki, S.; Kataoka, H. and Yamabe, S., *J. Org. Chem*., **1999**, *64*, 2367.

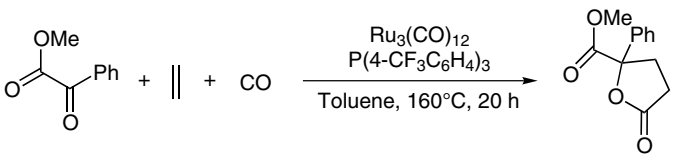
[2+2+1] Cycloaddition

A. GENERAL REACTION SCHEME

In this reaction, the π-bond of the ketone or aldehyde, the π-bond of the alkene, and the carbon atom of CO are integrated into compounds with a five-membered ring, such as γ-butyrolactones.[1]



B. CITED EXPERIMENTAL EXAMPLES



Reference 1.

A 50-mL stainless autoclave were charged with 328 mg methyl benzoylformate (2 mmol), 70 mg P(4-$CF_3C_6H_4)_3$ (0.15 mmol), 6 mL toluene, and 32 mg $Ru_3(CO)_{12}$ (0.05 mmol). After the system was flushed with 10 atm ethylene three times, it was pressurized with ethylene to 3 atm and then with carbon monoxide to additional 5 atm. Then the autoclave was immersed in an oil bath at 160°C. After 20 h, it was removed from the oil bath and allowed to cool for ∼1 h. The gases were then released. The contents were transferred to a round-bottomed flask with toluene, and the volatiles were removed in vacuo. The residue was subjected to column chromatography on a silica gel (eluent, hexane/EtOAc, 5:1) to give 413 mg tetrahydro-5-oxo-2-phenyl-2-furancarboxylic acid methyl ester as a colorless solid, in a yield of 94%. Purification by bulb-to-bulb distillation afforded the analytically pure product, m.p. 54–56°C, $R_f = 0.34$ (hexane/EtOAc, 5:1).

Other references related to [2+2+1] cycloaddition are cited in the literature.[2]

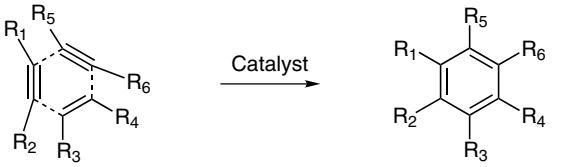
C. REFERENCES

1. Chatani, N.; Tobisu, M.; Asaumi, T.; Fukumoto, Y. and Murai, S., *J. Am. Chem. Soc.,* **1999,** *121*, 7160.
2. (a) Manku, S. and Curran, D. P., *J. Comb. Chem.,* **2005**, *7*, 63. (b) Wender, P. A.; Croatt, M. P. and Deschamps, N. M., *J. Am. Chem. Soc.,* **2004**, *126*, 5948. (c) Odedra, A.; Wu, C.-J.; Madhushaw, R. J.; Wang, S.-L. and Liu, R.-S., *J. Am. Chem. Soc.,* **2003**, *125*, 9610. (d) Odedra, A.; Wu, C.-J.; Madhushaw, R. J.; Wang, S.-L. and Liu, R.-S., *J. Am. Chem. Soc.,* **2003**, *125*, 9610. (e) Imbriglio, J. E. and Rainier, J. D., *Tetrahedron Lett.,* **2001**, *42*, 6987. (f) Ishikawa, T.; Shimizu, K.; Ishii, H.; Ikeda, S. and Saito, S., *J. Org. Chem.,* **2001**, *66*, 3834. (g) Knölker, H.-J. and Cämmerer, S., *Tetrahedron Lett.,* **2000**, *41*, 5035. (h) Brummond, K. M. and Kent, J. L., *Tetrahedron,* **2000**, *56*, 3263. (i) Son, S. U.; Choi, D. S.; Chung, Y. K. and Lee, S.-G., *Org. Lett.,* **2000**, *2*, 2097. (j) Tobisu, M.; Chatani, N.; Asaumi, T.; Amako, K.; Ie, Y.; Fukumoto, Y. and Murai, S., *J. Am. Chem. Soc.,* **2000**, *122*, 12663. (k) Mahuteau-Betzer, F. and Ghosez, L., *Tetrahedron Lett.,* **1999**, *40*, 5183. (l) Knölker, H.-J.; Braier, A.; Bröcher, D. J.; Jones, P. G. and Piotrowski, H., *Tetrahedron Lett.,* **1999**, *40*, 8075. (m) Brummond, K. M.; Wan, H. and Kent, J. L., *J. Org. Chem.,* **1998**, *63*, 6535.

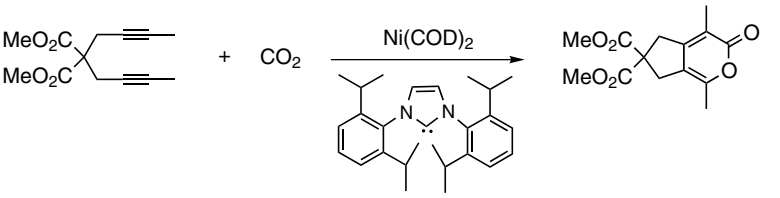
[2+2+2] Cycloaddition

A. GENERAL REACTION SCHEME

The [2+2+2] cycloaddition reaction of three unsaturated partners provides a powerful tool to form three carbon-carbon bonds in a single chemical transformation,[1] especially for the formation of polycyclic compounds via intramolecular cyclization with high regio-, chemo- and stereoselectivities.



B. CITED EXPERIMENTAL EXAMPLES



Reference 1.

An oven-dried two-neck round-bottomed flask equipped with a magnetic stir bar, septum, gas adapter, and balloon was evacuated and filled with CO_2. A solution of 200 mg 2,2-di-but-2-ynyl-malonic acid dimethyl ester (0.85 mmol) was added, and the flask was submerged into a 60°C oil bath. To the stirring solution, 3 mL toluene solution containing 12 mg $Ni(COD)_2$ (0.04 mmol) and 31 mg IPr (0.08 mmol) was added. The dark greenish black reaction mixture was then heated for 2 h (or until complete consumption of the starting material was observed as judged by GC), cooled to ambient temperature, concentrated, and purified by recrystallization in CH_2Cl_2 and hexanes to afford 228 mg 1,4-dimethyl-3-oxo-3,5-dihydro-7H-cyclopenta[c]pyran-6,6-dicarboxylic acid dimethyl ester as a white solid, in a yield of 96%.

Other references related to [2+2+2] cycloaddition are cited in the literature.[3,4]

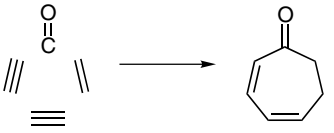
C. REFERENCES

1. Slowinski, F.; Aubert, C. and Malacria, M., *J. Org. Chem.,* **2003**, *68*, 378.
2. Louie, J.; Gibby, J. E.; Farnworth, M. V. and Tekavec, T. N., *J. Am. Chem. Soc.,* **2002**, *124*, 15188.
3. (a) Heller, B.; Sundermann, B.; Buschmann, H.; Drexler, H.-J.; You, J. S.; Holzgrabe, U.; Heller, E. and Oehmer, G., *J. Org. Chem.,* **2002**, *67*, 4414. (b) Shanmugasundaram, M.; Wu, M. S.; Jeganmohan, M.; Huang, C.-W. and Cheng, C.-H., *J. Org. Chem.,* **2002**, *67*, 7724. (c) Yamamoto, Y.; Takagishi, H. and Itoh, K., *J. Am. Chem. Soc.,* **2002**, *124*, 28. (d) Yamamoto, Y.; Takagishi, H. and Itoh, K., *J. Am. Chem. Soc.,* **2002**, *124*, 6844. (e) Gevorgyan, V.; Radhakrishnan, U.; Takeda, A.; Rubina, M.; Rubin, M. and Yamamoto, Y., *J. Org. Chem.,* **2001**, *66*, 2835. (f) Yamamoto, Y.; Ogawa, R. and Ithoh, K., *J. Am. Chem. Soc.,* **2001**, *123*, 6189. (g) Eichberg, M. J.; Dorta, R. L.; Grotjahn, D. B.; Lamottke, K.; Schmidt, M. and Vollhardt, K. P. C., *J. Am. Chem. Soc.,* **2001**, *123*, 9324. (h) Ozerov, O. V.; Patrick, B. O. and Ladipo, F. T., *J. Am. Chem. Soc.,* **2000**, *122*, 6423. (i) Fletcher, J. T. and Therien, M. J., *J. Am. Chem. Soc.,* **2000**, *122*, 12393. (j) Eichberg, M. J.; Dorta, R. L.; Lamottke, K. and Vollhardt, K. P. C., *Org. Lett.,* **2000**, *2*, 2479. (k) Seo, J.; Chui, H. M. P.; Heeg, M. J. and Montgomery, J., *J. Am. Chem. Soc.,* **1999**, *121*, 476. (l) Varela, J. A.; Castedo, L.; Saá, C., *Org. Lett.,* **1999**, *1*, 2141.

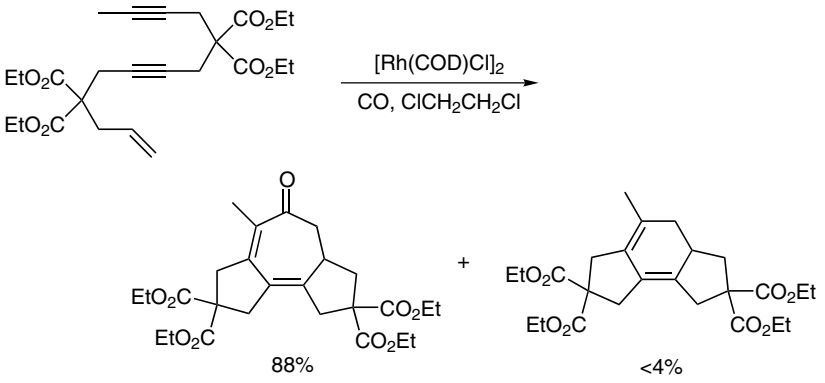
4. (a) Shibata, T.; Fujimoto, T.; Yokota, K. and Takagi, K., *J. Am. Chem. Soc.,* **2004**, *126*, 8382. (b) Ura, Y.; Sato, Y.; Shiotsuki, M.; Kondo, T. and Mitsudo, T.-A., *J. Mol. Catal. A: Chemical,* **2004**, *209*, 35. (c) Yamamoto, Y.; Kitahara, H.; Hattori, R. and Itoh, K., *Organometallics,* **1998**, *17*, 1910. (d) Takeuchi, R. and Nakaya, Y., *Org. Lett.,* **2003**, *5*, 3659. (e) Bonaga, L. V. R.; Zhang, H.-C.; Gauthier, D. A.; Reddy, I. and Maryanoff, B. E.; *Org. Lett.,* **2003**, *5*, 4537. (f) Takeuchi, R. and Nakaya, Y., *Org. Lett.,* **2003**, 5, 3659. (g) Turek, P.; Kotora, M.; Hocek, M. and Císaïová, I., *Tetrahedron Lett.,* **2003**, *44*, 785. (h) Kotha, S. and Brahmachary, E., *Bioorg. Med. Chem.,* **2002**, *10*, 2291. (i) Shanmugasundaram, M.; Wu, M.-S.; Jeganmohan, M.; Huang, C.-W. and Cheng, C.-H., *J. Org. Chem.,* **2002**, *67*, 7724. (j) Su, Q.; Zhou, X. M.; Islam, K. and Kyle, D. J., *Tetrahedron Lett.,* **2001**, *42*, 6495. (k) Takeuchi, R.; Tanaka, S. and Nakaya, Y., *Tetrahedron Lett.,* **2001**, *42*, 2991. (l) Grigg, R.; Sridharan, V.; Wang, J. and Xu, J., *Tetrahedron,* **2000**, *56*, 8967. (m) Kotha, S. and Sreenivasachary,N., *Bioorg. Med. Chem.,* **2000**, *10*, 1413. (n) Pardigon, O.; Tenaglia, A. and Buono, G., *Tetrahedron Lett.,* **2000**, *41*, 4089. (o) Son, S. U.; Choi, D. S.; Chung, Y. K. and Lee, S.-G., *Org. Lett.,* **2000**, *2*, 2097. (p) Grigg, R.; Savic, V. and Tambyrajah, V., *Tetrahedron Lett.,* **2000**, *41*, 3003. (q) Slowinski, F.; Aubert, C. and Malacria, M., *Tetrahedron Lett.,* **1999**, *40*, 707. (r) Slowinski, F.; Aubert, C. and Malacria, M., *Tetrahedron Lett.,* **1999**, *40*, 5849. (s) Sato, Y.; Ohashi, K. and Mori, M., *Tetrahedron Lett.,* **1999**, *40*, 5231. (t) Yamamoto, Y.; Nagata, A. and Itoh, K., *Tetrahedron Lett.,* **1999**, *40*, 5035. (u) Chowdhury, F. A.; Nishino, H. and Kurosawa, K., *Tetrahedron Lett.,* **1998**, *39*, 7931. (v) Llerena, D.; Buisine, O.; Aubert, C. and Malacria, M., *Tetrahedron,* **1998**, *54*, 9373. (w) Ikeda, S.-i.; Watanabe, H. and Sato, Y., *J. Org. Chem.,* **1998**, *63*, 7026. (x) Varela, J. A.; Castedo, L. and Saa, C., *J. Am. Chem. Soc.,* **1998**, *120*, 12147. (y) Kotha, S. and Brahmachary, E., *Tetrahedron Lett.,* **1997**, *38*, 3561. (z) Aubert, C.; Llerena, D. and Malacria, M., *Tetrahedron Lett.,* **1994**, *35*, 2341 (aa) Vanossi, M.; mella, M. and Albini, A., *J. Am. Chem. Soc.,* **1994**, *116*, 10070. (bb) Gleiter, R. and Schehlmann, V., *Tetrahedron Lett.,* **1989**, *30*, 2893. (cc) Gotteland, J.-P.and Malacria, M., *Tetrahedron Lett.,* **1989**, *30*, 2541. (dd) Neeson, S. J. and Stevenson, P. J., *Tetrahedron Lett.,* **1988**, *29*, 813. (ee) Yoshida, J.-i.; Sakaguchi, K.; Isoe, S. and Hirotsu, K., *Tetrahedron Lett.,* **1987**, *28*, 667. (ff) Trah, S.; Weidmann, K.; Fritz, H. and Prinzbach, H., *Tetrahedron Lett.,* **1987**, *28*, 4403. (gg) Dower, W. V.; Peter, K. and Vollhardt, C., *Tetrahedron,* **1986**, *42*, 1873. (hh) Borrini, A.; Diviersi, P.; Ingrosso, G.; Lucherini, A. and Serra, G., *J. Mol. Catal.,* **1985**, *30*, 181. (ii) Papadopoulos, M. and Jnenerrk, G., *Tetrahedron Lett.,* **1985**, *26*, 3335. (jj) Hoberg, H. and Oster, B. W., *J. Organomet. Chem.,* **1983**, *252*, 359. (kk) Hoberg, H. and Schaefer, D., *J. Organomet. Chem.,* **1982**, *238*, 383. (ll) Grigg, R.; Scott, R. and Stevenson, P., *Tetrahedron Lett.,* **1982**, *23*, 2691.

[2+2+2+1] Cycloaddition

A. GENERAL REACTION SCHEME



B. CITED EXPERIMENTAL EXAMPLES



Reference 1.

4,4,9,9-Tetra(carbethoxy)tridec-1-ene-6,11-diyne (100 mg, 0.216 mmol) was introduced to a Schlenck tube, followed by 2.16 mL $Cl(CH_2)_2Cl$ under argon, and then CO was bubbled into the solution at room temperature. After 15 min 5.3 mg $[Rh(COD)Cl]_2$ (0.0108 mmol, 5 mol %) was added under CO, and the resulting mixture was stirred at room temperature for an additional 5 min. Then the reaction mixture was heated to 50ºC with stirring and kept for 16 h under CO (ambient pressure, bubbled into the solution). All volatiles were removed from the reaction mixture under reduced pressure, and the crude product was purified by flash chromatography on silica gel (EtOAc/hexanes, 1:9 to 3:7) affording 93 mg 6-methyl-2,2,8,8-tetra(carbethoxy)-5-oxo-1,3a,4,5,7,9-hexahydro-3H-cyclopenta[e]azulene as a light yellow oil, in a yield of 92.5% (88% isolated yield, R_f = 0.30, EtOAc/hexanes, 1:4), and <4 mg 5-methyl-2,2,7,7-tetra(carbethoxy)-1,3,3a,4,6,8-hexahydro-as-indacene as a colorless oil, in 5.5% yield (<4% isolated yield, R_f = 0.56, EtOAc/hexanes, 1:4).

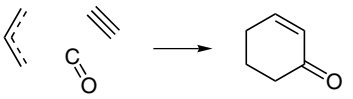
No other references related to [2+2+2+1] cycloaddition are found in the available literature.

C. REFERENCES

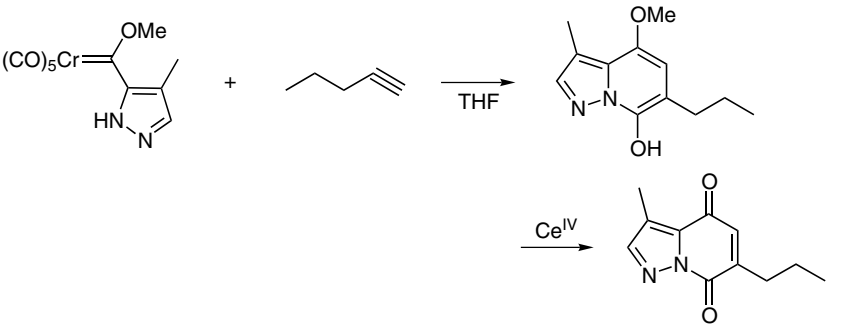
1. Bennacer, B.; Fujiwara, M. and Ojima, I., *Org. Lett.,* **2004**, *6*, 3589.

[3+2+1] Cycloaddition

A. GENERAL REACTION SCHEME



B. CITED EXPERIMENTAL EXAMPLES



Reference 1.

A 3.2 mL THF solution of 102 mg chromium complex (0.32 mmol) and 0.05 mL 1-pentyne (0.49 mmol) was deoxygenated by the freeze-thaw method (−196→25°C, three cycles) in a 25-mL pear-shaped flask that had the 14/20 joint replaced by an 8-mm threaded high-vacuum stopcock. The solution was then heated under argon at 45°C for 18 h and then diluted with 10 mL ether and oxidized by being poured into 5 mL 0.5 M aqueous cerric ammonium nitrate solution and being stirred at room temperature for 30 min. The organic layer was washed with water and brine and dried over $MgSO_4$. After the removal of solvents, the residue was flash chromatographed with an eluent mixture of CH_2C1_2/ether/hexanes (1:1:4) to provide 20 mg quinone as a pale yellow solid, in a yield of 31%, m.p. 129.5–130.5°C.

Other references related to [3+2+1] cycloaddition are cited in the literature.[2]

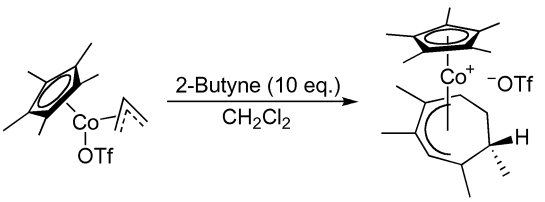
C. REFERENCES

1. Chan, K. S. and Wulff, W. D., *J. Am. Chem. Soc.,* **1986**, *108*, 5229.
2. Lee, S. I.; Park, J. H.; Chung, Y. K. and Lee, S.-G., *J. Am. Chem. Soc.,* **2004**, *126*, 2714.

[3+2+2] Cycloaddition

A. GENERAL REACTION SCHEME

B. CITED EXPERIMENTAL EXAMPLES



Reference 1.

To a drybox, was placed 315.5 mg $(C_5Me_5)Co(\eta^3\text{-}C_3H_5)(OTf)$ (0.820 mmol) in a flask equipped with a Kontes valve. This flask was removed to the Schlenk line, and 10 mL dichloromethane was added. On the high vacuum line, 0.44 g 2-butyne (8.2 mmol) was added by vacuum transfer. The solution was cooled to -78°C and then allowed to warm slowly to room temperature while being stirred overnight. The solvent was evaporated, the residue was washed with diethyl ether and then dissolved in dichloromethane and filtered through Celite. Evaporation gave 327.3 mg of a red, somewhat impure solid, in a yield of 81%. The material could be partially purified by being dissolved in a minimal amount of dichloromethane and added dropwise to an excess of rapidly stirring diethyl ether.

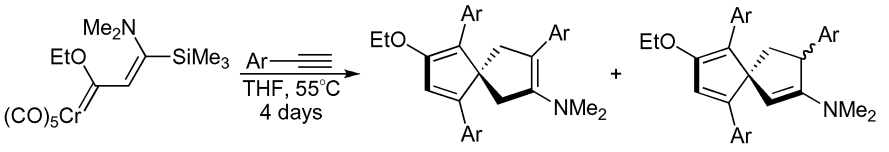
Other references related to [3+2+2] cycloaddition are cited in the literature.[2]

C. REFERENCES

1. Dzwiniel, T. L.; Etkin, N. and Stryker, J. M., *J. Am. Chem. Soc.,* **1999,** 121,10640.
2. (a) Etkin, N.; Dzwiniel, T. L.; Schweibert, K. E. and Stryker, J. M., *J. Am. Chem. Soc.,* **1998**, *120*, 9702. (b) Schwiebert, K. E. and Stryker, J. M., *J. Am. Chem. Soc.,* **1995**, *117*, 8275. (c) Sugimoto, T.; Nojima, M.; Kusabayashi, S. and McCullough, K. J., *J. Am. Chem. Soc.,* **1990**, *112*, 3690.

[3+2+2+2] Cycloaddition

A. GENERAL REACTION SCHEME



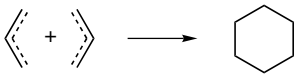
No experimental procedure is given for this reaction.[1] Other references related to [3+2+2+2] cycloaddition are cited in the literature.[2]

B. REFERENCES

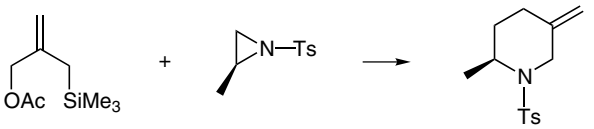
1. Schirmer, H.; Duetsch, M.; Stein, F.; Labahn, T.; Knieriem, B. and de Meijere, A., *Angew. Chem. Int. Ed.,* **1999**, *38*, 1285.
2. Schirmer, H.; Duetsch, M.; Stein, F.; Labahn, T.; Knieriem, B. and de Meijere, A., *Angew. Chem.,* **1999**, *111*, 1369.

[3+3] Cycloaddition

A. GENERAL REACTION SCHEME



B. CITED EXPERIMENTAL EXAMPLES



Reference 1.

To a suspension of 50 mg $Pd(OAc)_2$ (0.22 mmol, 1 eq.) in 1.6 mL THF was added 0.33 mg $P(O\text{-}i\text{-}Pr)_3$ (1.34 mmol, 6 eq.) and then 0.18 mL 2.5 M *n*-BuLi in hexanes (0.45 mmol, 2 eq.); the resultant yellow solution (0.14 M palladium catalyst) was stirred for 15 min before use.

A solution of 150 mg tosyl aziridine (0.71 mmol, 1.5 eq.) in 3 mL THF was treated with 0.34 mL freshly prepared 0.14 M palladium catalyst solution (0.05 mmol, 10 mol %) and 0.10 mL alkene (0.47 mmol, 1 eq.); the reaction mixture was refluxed for 16 h. Solvent was removed in vacuo and the residue was purified by flash chromatography to yield 102 mg (*S*)-2-methyl-5-methylene-1-(toluene-4-sulfonyl)-piperidine as a white solid, in a yield of 82%, m.p. 68–69°C.

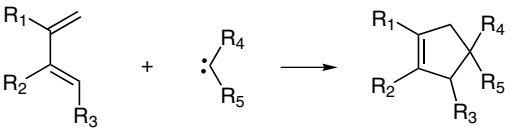
Other references related to [3+3] cycloaddition are cited in the literature.[2,3]

C. REFERENCES

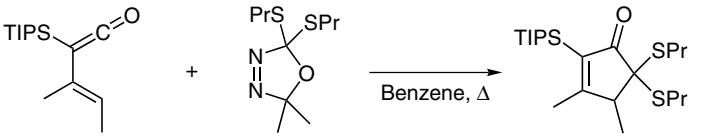
1. Hedley, S. J.; Moran, W. J.; Price, D. A. and Harrity, J. P. A., *J. Org. Chem.,* **2003**, *68*, 4286.
2. (a) Shen, H. C.; Wnag, J. S.; Cole, K. P.; McLaughlin, M. J.; Morgan, C. D.; Douglas, C. J.; Hsung, R. P.; Coverdale, H. A.; Gerasyuto, A. I.; Hahn, J. M.; Liu, J.; Sklenicka, H. M.; Wei, L.-L.; Zehnder, L. R. and Zificsak, C. A., *J. Org. Chem.,* **2003**, *68*, 1729. (b) Sklenicka, H. M.; Hsung, R. P.; McLaughlin, M. J.; Wei, L.-L.; Gerasyuto, A. I. and Brennessel, W. B., *J. Am. Chem. Soc.,* **2002**, *124*, 10435. (c) Shen, K.-H.; Lush, S.-F.; Chen, T.-L. and Liu, R.-S., *J. Org. Chem.,* **2001**, *66*, 8106. (d) Zehnder, L. R.; Wei, L.-L.; Hsung, R. P.; Cole, K. P.; McLaughlin, M. J.; Shen, H. C.; Sklenicka, H. M.; Wang, J. S. and Zificsak, C. A., *Org. Lett.,* **2001**, *3*, 2141. (e) Madhushaw, R. J.; Li, C.-L.; Shen, K.-H.; Hu, C.-C. and Liu, R.-S., *J. Am. Chem. Soc.,* **2001**, *123*, 7427. (f) Sklenicka, H. M.; Hsung, R. P.; Wie, L.-L.; McLaughlin, M. J.; gerasyuto, A. I. and Degen, S. J., *Org. Lett.,* **2000**, *2*, 1161. (g) Hsung, R. P.; Shen, H. C.; Douglas, C. J.; Morgan, C. D.; Degen, S. J. and Yao, L. J., *J. Org. Chem.,* **1999**, *64*, 690.
3. (a) Luo, S.; Zhao, J. and Zhai, H., *J. Org. Chem.,* **2004**, *69*, 4548. (b) Sydorenko, N.; Hsung, R. P.; Darwish, O. S.; Hahn, J. M. and Liu, J., *J. Org. Chem.,* **2004**, *69*, 6732. (c) Cole, K. P. and Hsung, R. P., *Org. Lett.,* **2003**, *5*, 4843. (d) Kurdyumov, A. V.; Hsung, R. P.; Ihlen, K. and Wang, J., *Org. Lett.,* **2003**, *5*, 3935. (e) Luo, S.; Zificsak, C. A. and Hsung, R. P., *Org. Lett.,* **2003**, *5*, 4709. (f) McLaughlin, M. J.; Shen, H. C. and Hsung, R. P., *Tetrahedron Lett.,* **2001**, *42*, 609. (g) Pearson, W. H.; Fang, W. and Kampf, J. W., *J. Org. Chem.,* **1994**, *59*, 2682. (h) Angle, S. R. and Boyce, J. P., *Tetrahedron Lett.,* **1994**, *35*, 6461. (i) Mori, M.; Sugiyama, T.; Nojima, M.; Kusabayashi, S. and McCullough, K. J., *J. Org. Chem.,* **1992**, *57*, 2285. (j) Bambal, R. B. and Kemmitt, R. D. W., *J. Organomet. Chem.,* **1989**, *362*, C18. (k) Leung, T. W.; Christoph, G. G. and Wojcicki, A., *Inorg. Chim. Acta,* **1983**, *76*, L281.

[4+1] Cycloaddition

A. GENERAL REACTION SCHEME



B. CITED EXPERIMENTAL EXAMPLES



Reference 1.

A benzene solution of 0.05 M vinylketene (1 eq.) and 2 eq. of bis(propylthio)carbene precursor was refluxed until the completion of the reaction (typically 1–2 h). The resulting solution was cooled down to room temperature and directly chromatographed on silica gel (hexane, then EtOAc/hexane) to give 96% of product as a colorless oil.

Other references related to [4+1] cycloaddition are cited in the literature.[2,3]

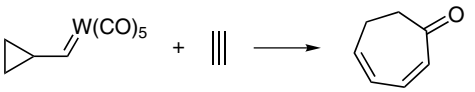
C. REFERENCES

1. Rigby, J. H. and Wang, Z. Q., *Org. Lett.,* **2003**, *5*, 263.
2. (a) Rigby, J. H. and Wang, Z. Q., *Org. Lett.,* **2002**, *4*, 4289. (b) Maestri, A. G.; Cherry, K. S.; Toboni, J. J. and Brown, S. N., *J. Am. Chem. Soc.,* **2001**, *123*, 7459. (c) Morimoto, T.; Chatani, N. and Murai, S., *J. Am. Chem. Soc.,* **1999**, *121*, 1758. (d) Murakami, M.; Itami, K. and Ito, Y., *Organometallics,* **1999**, *18*, 1326. (e) Murakami, M.; Itami, K. and Ito, Y., *J. Am. Chem. Soc.,* **1999**, *121*, 4130.
3. (a) Oshita, M.; Yamashita, K.; Tobisu, M. and Chatani, N., *J. Am. Chem. Soc.,* **2005**, *127*, 761. (b) Wu, Y.; Xu, K. L. and Xie, D. Q., *Tetrahedron,* **2005**, *61*, 507. (c) Spino, C.; Rezaei, H.; Dupont-Gaudet, K. and Belanger, F., *J. Am. Chem. Soc.,* **2004**, *126*, 9926. (d) Lu, X.; Petersen, J. L. and Wang, K. K., *Org. Lett.,* **2003**, *5*, 3277. (e) Chatani, N.; Oshita, M.; Tobisu, M.; Ishii, Y. and Murai, S., *J. Am. Chem. Soc.,* **2003**, *125*, 7812. (f) Nair, V.; Menon, R. S.;Vinod, A. U. and Viji, S., *Tetrahedron Lett.,* **2002**, *43*, 2293. (g) Rigby, J. H. and Dong,W., *Org. Lett.,* **2000**, *2*, 1673. (h) Murakami, M.; Itami, K. and Ito, Y., *Organometallics*, **1999**, *18*, 1326. (i) Loebach, J. L.; Bennett, D. M. and Danheiser, R. L., *J. Am. Chem. Soc.,* **1998,** *120*, 9690. (j) Abele, H.; Haas, A.; Lieb, M. and Schelvis, M., *J. Fluor. Chem.,* **1997**, *84*, 75. (k) Murakami, M.; Itami, K. and Ito, Y., *J. Am. Chem. Soc.,* **1997**, *119*, 2950. (l) Sigman, M. S. and Eaton, B. E., *J. Am. Chem. Soc.,*

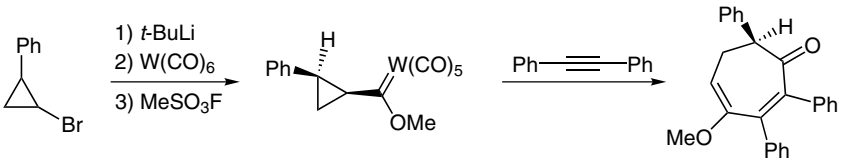
1996, *118*, 11783. (m) Colomvakos, J. D.; Egle, I.; Ma, J.; Pole, D. L.; Tidwell, T. T. and Warkentin, J., *J. Org. Chem.,* **1996**, *61*, 9522. (n) Sigman, M. S. and Eaton, B. E., *J. Org. Chem.,* **1994**, *59*, 7488. (o) Sierra, M. A.; Soderberg, B.; Lander, P. A. and Hegedus, L. S., *Organometallics,* **1993**, *12*, 3769. (p) Rigby, J. H. and Qabar, M., *J. Am. Chem. Soc.,* **1991**, *113*, 8975. (q) Evanseck, J. D.; Mareda, J. and Houk, K. N., *J. Am. Chem. Soc.,* **1990**, *112*, 73. (r) Krageloh, K.; Anderson, G. H. and Stang, P. J., *J. Am. Chem. Soc.,* **1984**, *106*, 6015. (s) Houk, K. N.; Rondan, N. G.; Paddon-Row, M. N.; Jefford, C. W.; Huy, P. T.; Burrow, P. D. and Jordan, K. D., *J. Am. Chem. Soc.,* **1983**, *105*, 5563. (t) Swenton, J. S. and Bartlett, P. D., *J. Am. Chem. Soc.,* **1968**, *90*, 2056.

[4+2+1] Cycloaddition

A. GENERAL REACTION SCHEME



B. CITED EXPERIMENTAL EXAMPLES



Reference 1.

To a solution of 1.10 g 1-bromo-2-phenyl cyclopropane (5.7 mmol) in 25 mL diethyl ether at –78°C under nitrogen was added via syringe 6.7 mL 1.7 M *t*-butyllithium (10.5 mmol) in pentane. The mixture was stirred for 30 min at –78°C, and then transferred via cannula to a suspension of 2.0 g tungsten hexacarbonyl (5.7 mmol) in 100 mL diethyl ether at 0°C. The mixture was warmed to room temperature, and then stirred for 1 h. The mixture was cooled to 0°C, and 1.4 mL methyl fluorosulfonate (17.7 mmol) was added, and the mixture was stirred at room temperature for 30 min. The reaction mixture was poured into saturated $NaHCO_3$ solution in a separatory funnel and then extracted with hexane. The hexane layer was washed three times with water and then brine, dried over $MgSO_4$, and concentrated. The residue was purified via column chromatography using pure hexane as the eluent to give two fractions. The first fraction (0.804 g, 29%) was identified as the *cis* isomer complex that is used in the highlighted reaction example. The second fraction (0.536 g, 20%) was the *trans* isomer.

To 20 mL refluxing xylene under nitrogen was added a solution of 0.1 g carbene complex (0.207 mmol), 0.060 g diphenylacetylene (0.330 mmol), and 0.090 g 1,2-(bis)-diphenylphosphinobenzene (0.20 mmol) in 30 mL xylene over a period of 6 h. Then the solution was refluxed for an additional 10 h. The mixture was cooled to 25°C, and the solvent was removed on a rotary evaporator. The residue was dissolved in 1:1 hexane/EtOAc and then filtered through celite. After the removal of the solvent on a rotary evaporator, final purification was achieved by flash chromatography using hexane/EtOAc (9:1 to 4:1) as the eluent, to give 0.040 g cycloheptadienone, in a yield of 53%.

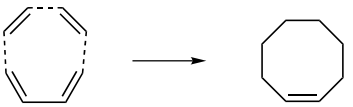
No other references related to [4+2+1] cycloaddition are found in the available literature.

C. REFERENCES

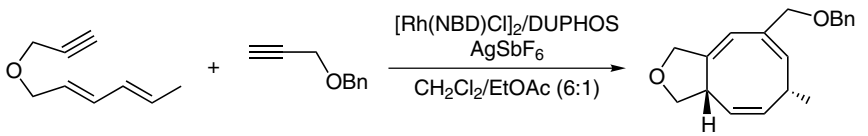
1. Herndon, J. W.; Chatterjee, G.; Patel, P. P.; Matasi, J. J.; Tumer, S. U.; Harp, J. J. and Reid, M. D., *J. Am. Chem. Soc.,* **1991**, *113*, 7808.

[4+2+2] Cycloaddition

A. GENERAL REACTION SCHEME



B. CITED EXPERIMENTAL EXAMPLES



Reference 1.

Preparation of Catalyst

To a vial containing 75 mg $[Rh(NBD)Cl]_2$ (0.16 mmol) was added 2 mL THF. After being stirred for 15 min, this orange solution was quickly transferred via cannula to a vial with 2 mL THF solution containing 98 mg (S,S)-Me-DuPHOS (0.32 mmol). After being stirred for 15 min, this red solution was transferred via cannula to a vial containing a

solution of 56 mg $AgSbF_6$ (0.16 mmol) in 2 mL THF. After 15 min, this dark suspension was transferred to a tarred vial using a syringe fitted with a filter. The cherry red filtrate was concentrated in vacuo and kept under vacuum (< 1 mmHg) overnight to remove all solvent, and 211 mg of an orange-red solid was collected. This catalyst can be stored under nitrogen at 0°C for a short period of time.

Cycloaddition Procedure

To a clean, dry 15-mL Schlenk tube was added 30 mg catalyst in 2 mL CH_2Cl_2. Hydrogen was gently bubbled through the orange-red solution for 3 min causing it to become dark and cloudy. Then 0.5 mL EtOAc was added, followed by sparging with nitrogen for 3 min. The terminal alkyne (1.9 mmol) was added along with 0.5 mL CH_2Cl_2, and the reaction was stirred to ensure homogeneity. Finally, the dienyne (0.38 mmol) was added along with 0.5 mL CH_2Cl_2. The reaction was freeze-pump-thawed three times, back-filled with nitrogen, and stirred overnight in a 60°C oil bath. Flash chromatography with 5% or 10% EtOAc in hexanes yields 73% of the pure product.

Other references related to [4+2+2] cycloaddition are cited in the literature.[2]

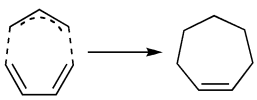
C. REFERENCES

1. Gilbertson, G. R. and DeBoef, B., *J. Am. Chem. Soc.,* **2002**, *124*, 8784.
2. (a) Varela, J. A.; Castedo, L. and Saa, C., *Org. Lett.,* **2003**, *5*, 2841. (b) Ma, B. and Snyder, J. K., *Organometallics,* **2002,** *21*, 4688. (c) Evans, P. A.; Robinson, J. E.; Baum, E. W. and Fazal, A. N., *J. Am. Chem. Soc.,* **2002**, *124*, 8782. (d) Chen, Y.; Kiattansakul, R.; Ma, B. and Snyder, J. K., *J. Org. Chem.,* **2001,** *66*, 6932. (e) Chen, Y.; Kiattansakul, R.; Ma, B. and Snyder, J. K., *J. Org. Chem.,* **2001**, *66*, 6932. (f) Kiattansakul, R. and Snyder, J. K., *Tetrahedron Lett.,* **1999**, *40*, 1079. (g) Chen, Y. and Snyder, J. K., *J. Org. Chem.,* **1998**, *63*, 2060.

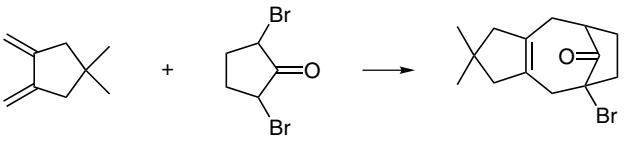
[4+3] Cycloaddition

A. GENERAL REACTION SCHEME

The cycloaddition between dienes and allylic cations provides a convenient method for forming complex seven-membered rings from simple starting materials.[1]



B. CITED EXPERIMENTAL EXAMPLES



Reference 2.

To a 35 mL trifluoroethanol solution of 2.05 g dibromocyclopentanone (8.47 mmol, 1.2 eq.) was added under dry nitrogen a solution of 862 mg 1,1-dimethyl-3,4-dimethylene-cyclopentane (7.06 mmol, 1.0 eq.) in 35 mL toluene. The resulting solution was cooled down to –23°C via a dry ice-carbon tetrachloride bath while vigorously stirring. Then 2.57 g triethylamine (25.4 mmol, 3.6 eq.) was added dropwise. After 40 min, the reaction was quenched with water and allowed to warm to room temperature. The reaction mixture was diluted with ether, washed with water and brine, and dried over magnesium sulfate. Flash chromotagraphy, and drying under vacuum afforded 1.059g (3R, 6R)-6-bromo-10,10-dimethyltricyclo[6.3.1^{3,6}.0]-undec-1(8)-ene-12-one, in a yield of 53%.

Other references related to [4+3] cycloaddition are cited in the literature,[3,4] and reviews for [4+3] cycloaddition are available.[1,5]

C. REFERENCES

1. Harmata, M., *Acc. Chem. Res*., **2001**, *34*, 595.
2. Harmata, M. and Bohnert, G. J., *Org. Lett.,* **2003**, *5*, 59.
3. (a) Wang, Y.; Schill, B. D.; Arif, A. M. and West, F. G., *Org. Lett.,* **2003**, *5*, 2747. (b) Harmata, M.; Ghosh, S. K.; Hong, X. C.; Wacharasindhu, S. and Kirchhoefer, P., *J. Am. Chem. Soc.,* **2003**, *125*, 2058. (c) Meilert, K. T.; Schwenter, M.-E.; Shatz, Y.; Dubbaka, S. R. and Vogel, P., *J. Org. Chem.,* **2003**, *68*, 2964. (d) Carreaux, F.; Possémé, F.; Carboni, B.; Arrieta, A.; Lecea, B. and Cossío, F. P., *J. Org. Chem.,* **2002**, *67*, 9153. (e) Barluenga, J.; Martínez, S.; Suárez-Sobrino, A. L. and Tomás, M., *J. Am. Chem. Soc.,* **2002**, *124*, 5948. (f)Aungst, R. A. and Funk, R. L., *Org. Lett.,* **2001**, *3*, 3553. (g) Xiong, H.; Hsung, R. P.; Berry, C. R. and Rameshkumar, C., *J. Am. Chem. Soc.,* 2001, *123*, 7174. (h) Cramer, C. J.; Harmata, M. and Rashatasakhon, P., *J. Org. Chem.,* **2001**, *66*, 5641. (i) Harmata, M. and Rashatasakhon, P., *Org. Lett.,* **2001**, *3*, 2533. (j) Kumar, K.; Kapoor, R.; Kapur, A. and Ishar, M. P. S., *Org. Lett.,* **2000**, *2*, 2023. (k) Beck, H.; Stark, C. B. W. and Hoffmann, H. M. R., *Org. Lett.,* **2000**, *2*, 883. (l) Harmata, M. and Rashatasakhon, P., *Org. Lett.,* **2000**, *2*, 2913. (m) Wang, Y.; Arif, A. M. and West, F. G., *J. Am. Chem. Soc.,* **1999**, *121*, 876. (n) Cho, S. Y.; Lee, J. C. and Cha, J. K., *J. Org. Chem.,* **1999**, *64*, 3394. (o) Barluenga, J.; Tomás, M.; Rubio, E.; López-Pelegrín, J.; García-Granda, S. and Priede, M. P., *J. Am. Chem. Soc.,* **1999**, *121*, 3065.
4. (a) Huang, J. and Hsung, R. P., *J. Am. Chem. Soc.,* **2005**, *127*, 50. (b) Davies, H. M. L. and Dai, X., *J. Am. Chem. Soc.,* **2004**, *126*, 2692. (c) Harmata, M.; Ghosh, S. K.; Hong, X.; Wacharasindhu, S. and Kirchhoefer, P., *J. Am. Chem. Soc.,* **2003**, *125*, 2058. (d)Grainger, R. S.; Owoare, R. B.; Tisselli, P. and Steed, J. W., *J. Org. Chem.,* **2003**, *68*, 7899. (e) Saez, J. A.; Arno, M. and Domingo, L. R., *Org. Lett.,* **2003**, *5*, 4117. (f) Xiong, H.; Huang, J.; Ghosh, S. K. and Hsung, R. P., *J. Am. Chem. Soc.,* **2003**, *125*, 12694. (g) Xiong, H.; Hsung, R. P.; Shen, L. C. and Hahn, J. M., *Tetrahedron Lett.,* **2002**, *43*, 4449. (h) Avenoza, A.; Busto, J. H.; Cativiela, C. and

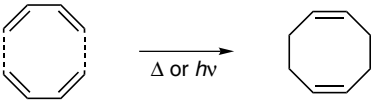
Peregrina, J. M., *Tetrahedron Lett.,* **2002**, *43*, 4167. (i) Russu, W. A.; Villalon, V. P.; Wang, V. R.; Miranda, J. A. and Little, R. D., *Tetrahedron Lett.,* **2002**, *43*, 8459. (j) Harmata, M.; Bohnert, G.; Kürti, L. and Barnes, C. L., *Tetrahedron Lett.,* **2002**, *43*, 2347. (k) Montaña, A. M. and Grima, P. M., *Tetrahedron Lett.,* **2002**, *43*, 2017. (l) Montaña, A. M. and Grima, P. M., *Tetrahedron Lett.,* **2001**, *42*, 7809. (m) Harmata, M. and Rashatasakhon, P., *Tetrahedron Lett.,* **2001**, *42*, 5593. (n) Hartama, M.; Bohnert, G. and Barnes, C. L., *Tetrahedron Lett.,* **2001**, *42*, 149. (o) Cho, S. Y.; Lee, H. I. and Cha, J. K., *Org. Lett.,* **2001**, *3*, 2891. (p) Harmata, M. and Schreiner, P. R., *Org. Lett.,* **2001**, *3*, 3663. (q) Lee, J. C. and Cha, J. K., *Tetrahedron,* **2000**, *56*, 10175. (r) Kreiselmeier, G. and Föhlisch, B., *Tetrahedron Lett.,* **2000**, *41*, 1375. (s) Ou, L. G.; Hu, Y. H.; Song, G. Q. and Bai, D. L., *Tetrahedron,* **1999**, *55*, 13999. (t) Hu, Y. H.; Ou, L. G. and Bai, D. L., *Tetrahedron Lett.,* **1999**, *40*, 545. (u) Harmata, M.; Shao, L. X.; Kürti, L. and Abeywardane, A., *Tetrahedron Lett.,* **1999**, *40*, 1075. (v) Harmata, M.; Jones, D. E.; Kahraman, M.; Sharma, U. and Barnes, C. L., *Tetrahedron Lett.,* **1999**, *40*, 1831. (w) Montaña, Á. M. and Fernández, D., *Tetrahedron Lett.,* **1999**, *40*, 6499. (x) Lee, K. and Cha, J. K., *Org. Lett.,* **1999**, *1*, 523. (y) Lee, J. C.; Jin, S.-J. and Cha, J. K., *J. Org. Chem.,* **1998**, *63*, 2804. (z) Föhlisch, B. and Radl, A., *J. Fluor. Chem.,* **1998**, *90*, 23. (aa) Harmata, M. and Kahraman, M., *Tetrahedron Lett.,* **1998**, *39*, 3421. (bb) Harmata, M. and Carter, K. W., *Tetrahedron Lett.,* **1997**, *38*, 7985. (cc) Lubineau, A. and Bouchain, G., *Tetrahedron Lett.,* **1997**, *38*, 8031. (dd) Harmata, M. and Jones, D. E., *Tetrahedron Lett.,* **1997**, *38*, 3861. (ee) Kende, A. S. and Huang, H., *Tetrahedron Lett.,* **1997**, *38*, 3353. (ff) Harmata, M. and Jones, D. E., *J. Org. Chem.,* **1997**, *62*, 1578. (gg) Harmata, M.; Herron, B. F.; Kahraman, M. and Barnes, C. L., *J. Org. Chem.,* **1997**, *62*, 6051. (hh) Lautens, M.; Aspiotis, R. and Colucci, J., *J. Am. Chem. Soc.,* **1996**, *118*, 10930. (ii) Harmata, M.; Elomari, S. and Barnes, C. L., *J. Am. Chem. Soc.,* **1996**, *118*, 2860. (jj) Harmata, M. and Jones, D. E., *Tetrahedron Lett.,* **1996**, *37*, 783. (kk) Harmata, M.; Elahmad, S. and Barnes, C. L., *Tetrahedron Lett.,* **1995**, *36*, 7158. (ll) Harmata, M.; Elahmad, S. and Barnes, C. L., *Tetrahedron Lett.,* **1995**, *36*, 1397. (mm) Jin, S.-J.; Choi, J.-R.; Oh, J. H.; Lee, D. H. and Cha, J. K., *J. Am. Chem. Soc.,* **1995**, *117*, 10914. (nn) Kim, H. J.; Ziani-Cherif, C.; Oh, J. H. and Cha, J. K., *J. Org. Chem.,* **1995**, *60*, 792. (oo) Harmata, M.; Gamlath, C. B.; Barnes, C. L. and Jones, D. E., *J. Org. Chem.,* **1995**, *60*, 5077. (pp) Harmata, M.; Elahmad, S. and Barnes, C. L., *J. Org. Chem.,* **1994**, *59*, 1241. (qq) Trost, B. M. and Marrs, C. M., *J. Am. Chem. Soc.,* **1993**, *115*, 6636. (rr) West, F. G.; Hartke-Karger, C.; Koch, D. J.; Kuehn, C. E. and Arif, A. M., *J. Org. Chem.,* **1993**, *58*, 6795. (ss) Harmata, M. and Herron, B. F., *J. Org. Chem.,* **1993**, *58*, 7393. (tt) Harmata, M. and Elahmad, S., *Tetrahedron Lett.,* **1993**, *34*, 789. (uu) Harmata, M.; Gamlath, C. B. and Barnes, C. L., *Tetrahedron Lett.,* **1993**, *34*, 265. (vv) Harmata, M. and Herron, B. F., *Tetrahedron Lett.,* **1993**, *34*, 5381. (ww) Singleton, D. A., *J. Am. Chem. Soc.,* **1992**, *114*, 6563. (xx) Harmata, M.; Fletcher, V. R. and Claassen,R. J., *J. Am. Chem. Soc.,* **1991**, *113*, 9861. (yy) Harmata, M.; Fletcher, V. R. and Claassen, R. J., *J. Am. Chem. Soc.,* **1991**, *113*, 9861. (zz) Ohno, M.; Mori, K.; Hattori, T. and Eguchi, S., *J. Org. Chem.,* **1990**, *55*, 7086. (aaa) Harmata, M.; Gamlath, C. B. and Barnes, C. L., *Tetrahedron Lett.,* **1990**, *31*, 5981. (bbb) Harmata, M. and Gamlath, C. B., *J. Org. Chem.,* **1988**, *53*, 6154. (ccc) Baran, J. and Mayr, H., *J. Am. Chem. Soc.,* **1987**, *109*, 6519. (ddd) Baran, J. and Mayr, H., *J. Am. Chem. Soc.,* **1987**, *109*, 6519. (eee) Trost, B. M. and MacPherson, D. T., *J. Am. Chem. Soc.,* **1987**, *109*, 3483. (fff) Trost, B. M. and MacPherson, D. T., *J. Am. Chem. Soc.,* **1987**, *109*, 3483. (ggg) Paquette, L. A.; Hathaway, S. J.; Kravetz, T. M. and Hsu, L. Y., *J. Am. Chem. Soc.,* **1984**, *106*, 5741.

5. (a) Cha, J. K. and Oh, J., *Curr. Org. Chem*., **1998**, *2*, 217. (b) Rigby, J. H. and Pigge, F. C., *Org. React*., **1997**, *51*, 351. (c) Harmata, M., *Adv. Cycloaddit*., **1997**, *4*, 41. (d) Harmata, M., *Recent Res. Dev. Org. Chem*., **1997**, *1*, 523. (e) Harmata, M., *Tetrahedron,* **1997**, *53*, 6235. (f) Hosomi, A. and Tominaga, Y., "[4+3] Cycloadditions" in *Comprehensive Organic Synthesis,* ed. Trost, B. M. and Fleming, I., Pergamon, Oxford, **1991,** pp. 593–615. (g) Mann, J., *Tetrahedron,* **1986**, *42*, 4611. (h) Hoffman, H. M. R., *Angew. Chem. Int. Ed. Engl.,* **1984**, *23*, 1. (i) Noyori, R. and Hayakawa, Y., *Org. React.,* **1983**, *29*, 163.

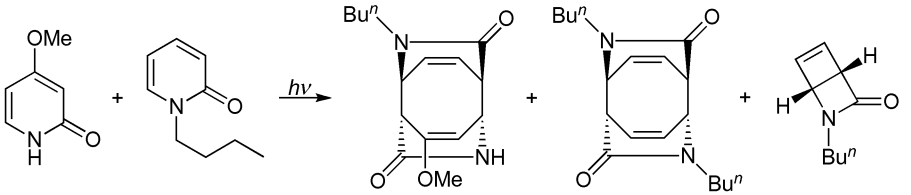
[4+4] Cycloaddition

A. GENERAL REACTION SCHEME

The [4 + 4] cycloadditions is a versatile method for the preparation of 1,5-cyclooctadiene, especially under photochemical reaction condition.[1]



B. CITED EXPERIMENTAL EXAMPLES



Reference 2.

A stream of dry nitrogen was passed through a solution of 454 mg 4-methoxy-2-pyridone (3.62 mmol) and 77 mg *N*-butyl-2-pyridone (0.51 mmol) in 8.3 mL methanol in a Pyrex test tube for several minutes, and the test tube was then sealed with a septum and fitted with a nitrogen balloon. This tube was taped to the side of a water-cooled quartz cooling jacket surrounding a 450-W medium-pressure mercury lamp inside of a Pyrex filter and irradiated for a total of 72 h. The methanol was removed in vacuo, and the residue was taken up in acetonitrile. On standing, 4-methoxy-2-pyridone crystallized from solution. The mother liquor was concentrated and chromatographed. A gradient of hexane and ethyl acetate (1:1 hexane/ethyl acetate to 100% ethyl acetate) led to the isolation of Dewar pyridone (2-butyl-2-azabicyclo[2.2.0]hex-5-en-3-one) in a 5% yield, $R_f = 0.70$ (3:2, hexane/EtOAc), 8% (1α,2β,5β,6α)-3,7-dibutyl-3,7-diazatricyclo[4.2.2.2^{2,5}]-dodeca-9,11-diene-4,8-dione, R_f = 0.17 (1:1, hexane/EtOAc), and 51% (1α,2β,5β,6α)-3-butyl-9-methoxy-3,7-diazatricyclo-[4.2.2.2^{2,5}]dodeca-9,11-diene-4,8-dione using isopropanol/acetonitrile (1:9) as the eluent, $R_f = 0.25$ (1:9, isopropanol/acetonitrile), m.p. 179°C.

Other references related to [4+4] cycloaddition are cited in the literature.[3]

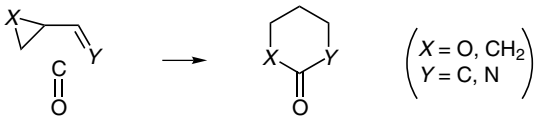
C. REFERENCES

1. Sieburth, S. M., "The Inter- and Intramolecular [4 + 4] Photocycloaddition of 2-Pyridones and Its Application to Natural Product Synthesis" in *Advances in Cycloaddition,* ed. Harmata, M., JAI: Greenwich, Conn., **1999**, *5*, pp. 85–118.

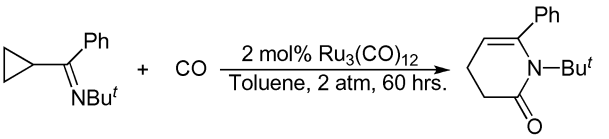
2. Sieburth, S. McN.; Lin, C.-H. and Rucando, D., *J. Org. Chem.,* **1999**, *64*, 950.
3. (a) Zhang, Y.; Wang, L.; Zhang, M.; Fun, H.-K. and Xu, J.-H., *Org. Lett.,* **2004**, *6*, 4893. (b) Sieburth, S. M.; Madsen-Duggan, C. B. and Zhang, F. N., *Tetrahedron Lett.,* **2001**, *42*, 5155. (c) Ader, T. A.; Champey, C. A.; Kuznetsova, L. V.; Li, T.; Lim, Y.-H.; Rucando, D. and Sieburth, S. M., *Org. Lett.,* **2001**, *3*, 2165. (d) Sieburth, S. M.; McGee, K. F. and Al-Tel, T. H., *Tetrahedron Lett.,* **1999**, *40*, 4007. (e) Sieburth, S. M.; Rucando, D. and Lin, C.-H., *J. Org. Chem.,* **1999**, *64*, 954. (f) Sieburth, S. McN. and McGee, K. F., *Org. Lett.,* **1999**, *1*, 1775. (g) Sieburth, S. M.; McGee, K. F. and Al-Tel, T. H., *J. Am. Chem. Soc.,* **1998**, *120*, 587. (h) Deumal, M.; Bearpark, M. J.; Smith, B. R.; Olivucci, M.; Bernardi, F. and Robb, M. A., *J. Org. Chem.,* **1998**, *63*, 4594. (i) Sieburth, S. M.; Al-Tel, T. H. and Rucando, D., *Tetrahedron Lett.,* **1997**, *38*, 8433. (j) Bearpark, M. J.; Deumal, M.; Robb, M. A.; Vreven,T.; Yamamoto, N.; Olivucci, M. and Bernardi, F., *J. Am. Chem. Soc.,* **1997**, *119*, 709. (k) Wender, P. A.; Nuss, J. M.; Smith, D. B.; Suarez-Sobrino A, Vågberg, J.; Decosta, D. and Bordner, J., *J. Org. Chem.,* **1997**, *62*, 4908. (l) Sieburth, S. M. and Cunard, N. T., *Tetrahedron,* **1996**, *52*, 6251. (m) Sieburth, S. M. and Lin, C.-H., *J. Org. Chem.,* **1994**, *59*, 3597. (n) Wender, P. A. and Tebbe, M. J., *Synthesis,* **1991**, 1089. (o) Wender P. A.; Ihle, N. C. and Correia, C. R. D., *J. Am. Chem. Soc.,* **1988**, *110*, 5904. (p) Wender, P. A. and Ihle, N. C., *Tetrahedron Lett.,* **1987**, *28*, 2451. (q) Wender, P. A. and Ihle, N. C., *J. Am. Chem. Soc.,* **1986**, *108*, 4678. (r) Wender, P. A. and Ihle, N. C., *J. Am. Chem. Soc.,* **1986**, *108*, 4678. (s) Taylor, E. C. and Paudler, W. W., *Tetrahedron Lett.,* **1960**, 1.

[5+1] Cycloaddition

A. GENERAL REACTION SCHEME



B. CITED EXPERIMENTAL EXAMPLES



Reference 1.

A 50-mL stainless autoclave was charged with 201 mg cyclopropyl phenyl *N*-(1,1-dimethylethyl) ketimine (1 mmol), 3 mL toluene, and 13 mg $Ru_3(CO)_{12}$ (0.02 mmol). The system was flushed with 10 atm of CO three times, after which it was pressurized to 2 atm

and immersed in an oil bath at 160°C. After 60 h the autoclave was removed from the oil bath and cooled for 1 h, followed by release of the CO. The contents were transferred to a round-bottomed flask with ether, and the volatiles were removed in vacuo. The residue was subjected to column chromatography on silica gel with an eluent of hexane/Et_2O (3:1) to give 175 mg 3,4-dihydro-1-(1,1-dimethylethyl)-6-phenyl-2(1*H*)-pyridinone as a white solid, in a yield of 76%.

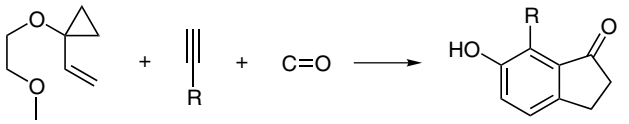
Other references related to [5+1] cycloaddition are cited in the literature.[2]

C. REFERENCES

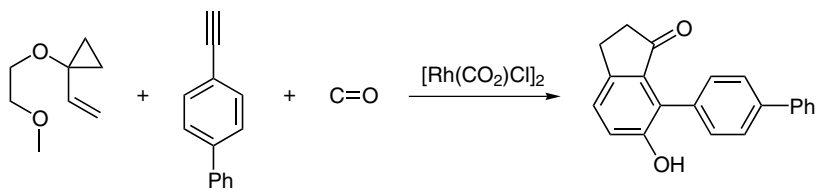
1. Kamitani, A.; Chatani, N.; Morimoto, T. and Murai, S., *J. Org. Chem.,* **2000**, *65*, 9230.
2. (a) Odedra, A.; Wu, C.-J.; Madhushaw, R. J.; Wang, S.-L. and Liu, R.-S., *J. Am. Chem. Soc.,* **2003**, *125*, 9610. (b) Murakami, M.; Itami, K.; Ubukata, M.; Tsuji, I. and Ito, Y., *J. Org. Chem.,* **1998**, *63*, 4.

[5+1+2+1] Cycloaddition

A. GENERAL REACTION SCHEME



B. CITED EXPERIMENTAL EXAMPLES



Reference 1.

In an oven-dried, borosilicate glass test tube, capped with a rubber septum and dried under a CO atmosphere from a balloon, was added 4 mg $[Rh(CO)_2Cl]_2$ (0.010 mmol) in

4.0 mL toluene. A 25-G needle outlet was added, and the atmosphere of the test tube was sparged with CO from the balloon for 15 min. During this time, 114 mg vinylcyclopropane (0.80 mmol) and 70 mg biphenylacetylene (0.40 mmol) were added sequentially. After sparging was completed, the reaction was heated in a 60°C, thermostat-controlled oil bath under a CO atmosphere (balloon). The reaction was monitored using TLC. After 30 h, the reaction was cooled to room temperature, and the crude reaction mixture was then purified directly by flash column chromatography (silica gel, dichloromethane) to afford 112 mg cycloadduct as an off-white solid, in a yield of 93%.

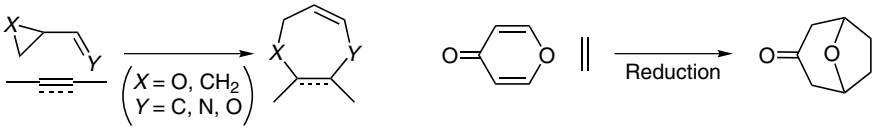
No other references related to [5+1+2+1] cycloaddition are found in the available literature.

C. REFERENCES

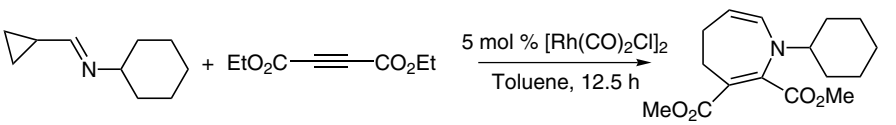
1. Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Pham, S. M. and Zhang, L., *J. Am. Chem. Soc.,* **2005**, *127*, 2836.

[5+2] Cycloaddition

A. GENERAL REACTION SCHEME



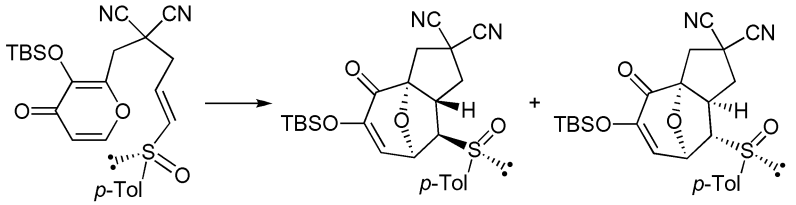
B. CITED EXPERIMENTAL EXAMPLES



Reference 1.

An oven-dried, 50-mL reaction flask, under a positive pressure of dry nitrogen, was charged with 2.0 mmol cyclohexamine and 15 mL toluene. Hexadecane (100 μL) was added

as an internal standard to determine conversion and GC yields. Cyclopropyl formaldehyde (170 μL, 2.2 mmol) was then added, and the reaction quickly turned cloudy. A Dean-Stark trap with a 5-mL hold-up volume was attached to the reaction setup. The reaction was allowed to stir at room temperature for 1 h, and then heated to reflux for 1 h with azeotropic removal of the water. The reaction was then cooled to 60°C, and 38.9 mg $[Rh(CO)_2Cl]_2$ (0.1 mmol) was added. A 10 mL toluene solution containing 0.49 mL DMAD (3.99 mmol) was added by syringe pump over 12.5 h. The reaction was cooled to room temperature and filtered through a short pad of silica gel using Et_2O as the eluant and concentrated in vacuo. The residue was purified by flash column chromatography (Et_2O/petroleum ether as the eluant) to give 1-cyclohexyl-4,5-dihydro-1*H*-azepine-2,3-dicarboxylic acid dimethyl ester in 85% isolated yield.



Reference 2.

A 10 mL toluene solution of 100 mg 2-[(3-*t*-butyldimethylsilyloxy-4-oxo-4*H*-2-pyranyl)methyl]-2-[(2*E*,R_S)-3-*p*-tolylsulfinyl-2-propenyl]malononitrile (0.21 mmol) was refluxed for 10 h. The solvent was evaporated and the crude product was purified by flash chromatography (25–50%, EtOAc/hexanes) to afford a 91:9 ratio of diastereoisomers of (1*R*,5*S*,6*R*,7*R*,R_S)-9-*t*-butyldimethylsilyloxy-6-[*p*-tolylsulfinyl-10-oxo-11-oxatricyclo[5.3.1.$0^{1,5}$]undec-8-ene-3,3-dicarbonitrile (R_f = 0.54; hexane/EtOAc,1:1) and (1*S*,5*R*,6*S*,7*S*,R_S)-9-*t*-butyldimethylsilyloxy-6-[*p*-tolylsulfinyl-10-oxa-11-oxatricyclo-[5.3.1.$0^{1,5}$]undec-8-en-3,3-dicarbonitrile (R_f = 0.70; hexane/EtOAc, 1:1) as colorless oils, in a yield of 98%.

Other references related to [5+2] cycloaddition are cited in the literature. [3–7]

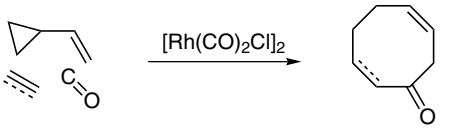
C. REFERENCES

1. Wender, P. A.; Pedersen, T. M. and Scanio, M. J. C., *J. Am. Chem. Soc.,* **2002**, *124*, 15154.
2. López, F.; Castedo, L. and Mascareñas, J. L., *Org. Lett.,* **2000**, *2*, 1005.
3. For intramolecular [5 + 2] cycloadditions with alkyne: (a) Trost, B. M.; Toste, F. D. and Shen, H., *J. Am. Chem. Soc.,* **2000**, *122*, 2379. (b) Wender, P. A.; Dyckman, A. J.; Husfeld, C. O.; Kadereit, D.; Love, J. A. and Rieck, H., *J. Am. Chem. Soc.,* **1999**, *121*, 10442. (c) Wender, P. A. and Dyckman, A. J., *Org. Lett.,* **1999**, *1*, 2089. (d) Wender, P. A.; Takahashi, H. and Witulski, B., *J. Am. Chem. Soc,* **1995**, *117*, 4720.
4. For intermolecular [5 + 2] cycloadditions with alkynes: (a) Wender, P. A.; Dyckman, A. J.; Husfeld, C. O. and Scanio, M. J. C., *Org. Lett.,* **2000**, *2*, 1609. (b) Wender, P. A.; Rieck, H. and Fuji, M., *J. Am. Chem. Soc.,* **1998**, *120*, 10976.
5. For intramolecular [5 + 2] cycloadditions with alkenes: (a) Wender, P. A.; Husfeld, C. O.; Langkopf, E. and Love, J. A., *J. Am. Chem. Soc.,* **1998**, *120*, 1940. (b) Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A. and Pleuss, N., *Tetrahedron,* **1998**, *54*, 7203.

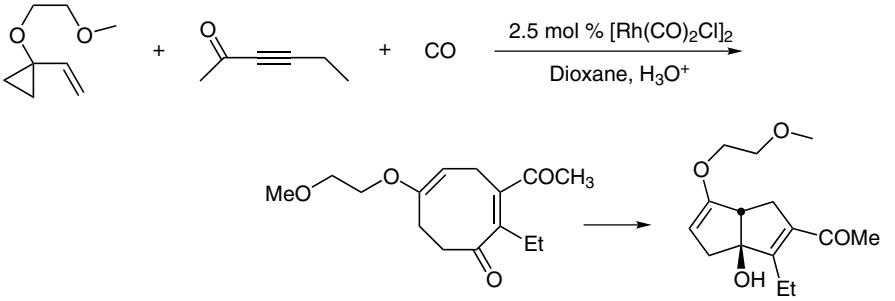
6. For intramolecular [5 + 2] cycloadditions with allenes: (a) Wender, P. A.; Glorius, F.; Husfeld, C. O.; Langkopf, E. and Love, J. A., *J. Am. Chem. Soc.,* **1999**, *121*, 5348. (b) Wender, P. A.; Fuji, M.; Husfeld, C. O. and Love, J. A., *Org. Lett.,* **1999**, *1*, 137.
7. (a) Celanire, S.; Marlin, F.; Baldwin, J. E. and Adlington, R. M., *Tetrahedron,* **2005**, *61*, 3025. (b) Krishna, U. M.; Deodhar, K. D. and Trivedi, G. K., *Tetrahedron*, **2004**, *60*, 4829. (c) Krishna, U. M. and Trivedi, G. K., *Tetrahedron Lett.,* **2004**, *45*, 257. (d) Baldwin, J. E.; Wayweg, A. V. W.; Pritchard, G. J.and Adlington, R. M., *Tetrahedron Lett.,* **2003**, *44*, 4543. (e) Trost, B. M.; Shen, H. C.; Schulz, T.; Koradin, C. and Schirok, H., *Org. Lett.,* **2003**, *5*, 4149. (f) Tanino, K.; Kondo, F.; Shimizu, T. and Miyashita, M., *Org. Lett.,* **2002**, *4*, 2217. (g) Wender, P. A.; Bi, F. C.; Brodney, M. A. and Gosselin, F., *Org. Lett.,* **2001**, *3*, 2105. (h) López, F.; Castedo, L. and Mascareñas, J. L., *Org. Lett.,* **2001**, *3*, 623. (i) Wender, P. A.; Barzilay, C. M. and Dyckman, A. J., *J. Am. Chem. Soc.,* **2001,** *123*, 179. (j) Lopez, F.; Castedo, L. and Mascareñas, J. L., *Org. Lett.,* **2001**, *3*, 623. (k) Wender, P. A.; Bi, F. C.; Brodney, M. A. and Gosselin, F., *Org. Lett.,* **2001**,*3*, 2105. (l) Wender, P. A.; Barzilay, C. M. and Dyckman, A. J., *J. Am. Chem. Soc.,* **2001**,*123*, 179. (m) Wender, P. A.; Gamber, G. G. and Scanio, M. J. A., *Angew. Chem. Int. Ed.,* **2001**, *40*, 3895. (n) Magnus, P.; Waring, M. J.; Ollivier, C. and Lynch, V., *Tetrahedron Lett.,* **2001**, *42*, 4947. (o) Domingo, L. R. and Zaragozá, R. J., *Tetrahedron,* **2001**, *57*, 5597. (p) Lee, H.-Y.; Sohn, J.-H. and Kim, H. Y., *Tetrahedron Lett.,* **2001**, *42*, 1695. (q) Wang, B.; C. P. and Zhang, X. M., *Tetrahedron Lett.,* **2000**, *41*, 8041. (r) Tanino, K.; Shimizu, T.; Miyama, M. and Kuwajima, I., *J. Am. Chem. Soc.,* **2000**, *122*, 6116. (s) Wender, P. A. and Zhang, L., *Org. Lett.,* **2000**, *2*, 2323. (t) Trost, B. M. and Shen, H. C., *Org. Lett.,* **2000**, *2*, 2523. (u) Tanino, K.; Shimuzu, T.; Miyama, M. and Kuwajima, I., *J. Am. Chem. Soc.,* **2000,** *122*, 6116. (v) Malinakova, H. C. and Liebeskind, L. S., *Org. Lett.,* **2000**, *2*, 3909. (w) Malinakova, H. C. and Liebeskind, L. S., *Org. Lett.,* **2000**, *2*, 4083. (x) Malinakova, H. C. and Liebeskind, L. S., *Org. Lett.,* **2000**, *2*, 3909. (y) Trost, B. M.; Toste, F. D. and Shen, H., *J. Am. Chem. Soc.,* **2000**, *122*, 2379. (z) Yin, J. and Liebeskind, L. S., *J. Am. Chem. Soc.,* **1999**, *121*, 5811. (aa) Rodríguez, J. R.; Rumbo, A.; Castedo, L. and Mascareñas, J. L., *J. Org. Chem.,* **1999,** *64*, 966. (bb) Rodríguez, J. R.; Rumbo, A.; Castedo, L. and Mascareñas, J. L., *J. Org. Chem.,* **1999,** *64*, 4560. (cc) Yin, J. J. and Liebeskind, L. S., *J. Am. Chem. Soc.,* **1999,** *121*, 5811. (dd) Wender, P. A.; Husfeld, C. O.; Langkopf, E. and Love, J. A., *J. Am. Chem. Soc.,* **1998**, *120*, 1940. (ee) Wender, P. A. and Sperandio, D., *J. Org. Chem.*, **1998**, *63*, 4164. (ff) Takakura, H. and Yamamura, S., *Tetrahedron Lett.,* **1998**, *39*, 3717. (gg) Grieco, P. A. and Walker, J. K, *Tetrahedron,* **1997**, *53*, 8975. (hh) Collins, J. L.; Crieco, P. A. and Walker, J. K, *Tetrahedron Lett.,* **1997**, *38*, 1321. (ii) Barluenga, J.; Tomás, M.; Bieger, K.; García-Granda, S. and Santiago-García, R., *J. Organomet. Chem.,* **1997**, *529*, 233. (jj) Wender, P. A.; Rice, K. D. and Schnute, M. E., *J. Am. Chem. Soc.,* **1997**, *119*, 7897. (kk) Engler, T. A.; Scheibe, C. and Iyengar, R., *J. Org. Chem.,* **1997**, *62*, 8274. (ll) Wender, P. A.; Jesudason, C. D.; Nakahira, H.; Tamura, N.; Tebbe, A. L. and Ueno, Y., *J. Am. Chem. Soc.,* **1997**, *119*, 12976. (mm) Wender, P. A. and Mascareñas, J. L., *Tetrahedron Lett.,* **1997**, *33*, 2115. (nn) Chen, W.; Chung, H.-J.; Wang, C.; Sheridan, J. B.; Cote, M. L. and Lalancette, R. A., *Organometallics,* **1996**, *15*, 3337. (oo) Yueh, T.-C.; Lush, S.-F.; Lee, G.-H.; Peng, S.-M. and Liu, R.-S., *Organometallics*, **1996**, *15*, 5669. (pp) Chung, H.-J.; Sheridan, J. B.; Cote, M. L. and Lalancette, R. A., *Organometallics,* **1996**, *15*, 4575. (qq) Kreiter, C. G.; Fiedler, C.; Frank, W. and Reiβ, G. J., *J. Organomet. Chem.,* **1995**, *490*, 133. (rr) Kreiter, C. G.; Koch, E.-C.; Frank, W. and Reiβ, G., *Inorg. Chimica Acta,* **1994**, *220*, 77. (ss) Rumbo, A.; Castedo, L.; Mourino, A. and Mascareñas, J. L., *J. Org. Chem.,* **1993**, *58*, 5585. (tt) Wender, P. A. and Mascareñas, J. A., *J. Org. Chem.,* **1991**, *56*, 6267. (uu) Lee, T. V. and Cregg, C., *Synlett,* **1990**, 317. (vv) Engler, T. A.; Letavic, M. A.; Combrink, K. D. and Takusagawa, F., *J. Org. Chem.,* **1990**, *55*, 5810. (ww) Lee, T. V.; Boucher, R. J.; Porter, J. R. and Rockell, C. J. M. *Tetrahedron,* **1989**, *45*, 5887. (xx) Wender, P. A.; Kogen, H.; Lee, H. Y.; Munger, J. D. Jr.; Wilhelm, R. S. and Williams, P. D., *J. Am. Chem. Soc.,* **1989**, *111*, 8957. (yy) Wender, P. A.; Lee, H. Y.; Wilhelm, R. S. and Williams, P. D., *J. Am. Chem. Soc.,* **1989**, *111*, 8954. (zz) Lee, T. V.; Boucher, R. J. and Rockell, C. J. M., *Tetrahedron Lett.,* **1988**, *29*, 689. (aaa) Heilmann, W.; Koschinsky, R. and Mayr, H., *J. Org. Chem.,* **1987**, *52*, 1989.

[5+2+1] Cycloaddition

A. GENERAL REACTION SCHEME



B. CITED EXPERIMENTAL EXAMPLES



Reference 1.

To an oven-dried, septum-capped test tube were added 0.025 mmol $[Rh(CO)_2Cl]_2$ and 2.0 mL 1,4-dioxane, followed by 1.0 mmol vinylcyclopropane via syringe. The reaction mixture was purged with a stream of CO from a balloon for 15 min. The alkyne (1.2 mmol) was added via syringe. The septum was pierced with a needle, and the test tube was placed in an autoclave, pressurized to 2 atm, and heated to 60°C in a thermostat-controlled oil bath (for 1 atm reactions, the test tube was heated directly in an oil bath under a balloon of CO). The reaction was monitored by TLC or GC, and upon completion the reaction was cooled to room temperature. Water (200 mL) and 1% HCl in ethanol (25 mL) were added, and the hydrolysis was monitored by TLC (24 h). After hydrolysis, the reaction was concentrated in vacuo. Purification by flash chromatography (silica gel; 1:1, EtOAc/pentane) afforded 97% 5-acetyl-4-ethyl-3α-hydroxy-3,3α,6,6α-tetrahydro-2*H*-pentalen-1-one.

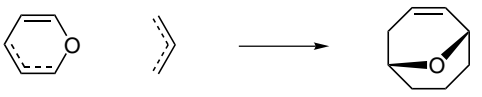
No other references related to [5+2+1] cycloaddition are found in the literature.

C. REFERENCES

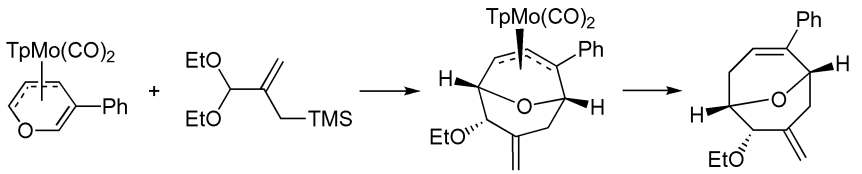
1. Wender, P. A.; Gamber, G. G.; Hubbard, R. D. and Zhang, L., *J. Am. Chem. Soc.,* **2002**, *124*, 2876.

[5+3] Cycloaddition

A. GENERAL REACTION SCHEME



B. CITED EXPERIMENTAL EXAMPLES



Reference 1.

To a solution of 180 mg molybdenum complex (0.34 mmol) and 298 mg allylic acetal (1.38 mmol) in 3.4 mL dry CH_2Cl_2 was added 17.0 mg $Sc(OTf)_3$ (0.034 mmol, 10 mol %) at –78°C under an argon atmosphere. The mixture was stirred at –78°C for 1 h. After the reaction was complete, the mixture was passed through a short pad of silica gel with 9:1 CH_2Cl_2/EtOAc. The filtrate was concentrated under vacuum and the residue was purified by flash chromatography using *n*-hexanes/CH_2Cl_2 as the eluent to afford 170.8 mg pure (+)-dicarbonyl[hydridotris(1-pyrazolyl)borato]{η-(2,3,4)-(1*S*,2*R*,5*S*,6*S*)-6-ethoxy-7-methylen-2-phenyl-9-oxabicyclo[3.3.1]non-3-en-2-yl}molybdenum in 98% e.e. as a red crystalline solid, in a yield of 80%. Recrystallization from *n*-hexanes/CH_2Cl_2 afforded 116 mg product in 99.5% e.e. with a 55% yield. $R_f = 0.25$ (*n*-hexanes/EtOAc, 7:1), m.p. > 200°C.

To a solution of 125 mg of the molybdenum complex (0.20 mmol) in 3.2 mL CH_2Cl_2 was added at room temperature 495 μL 37% aqueous HCl (6.0 mmol) dropwise over 2 min. The mixture was stirred at room temperature for 20 min and 30 mL EtOAc and 30 mL water were then added. The organic layer was washed with 30 mL saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (2:1, *n*-hexanes/CH_2Cl_2) to afford 41.4 mg (+)-(1*S*,5*S*,6*S*)-6-ethoxy-7-methylen-2-phenyl-9-oxabicyclo[3.3.1]non-2-ene, with 99.5% e.e. as a white solid, in a yield of 80%. $R_f = 0.08$ (2:1, *n*-hexane/CH_2Cl_2), m.p. 42–43°C.

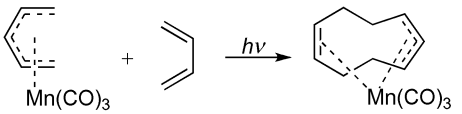
Other references related to [5 + 3] cycloaddition are cited in the literature.[2]

C. REFERENCES

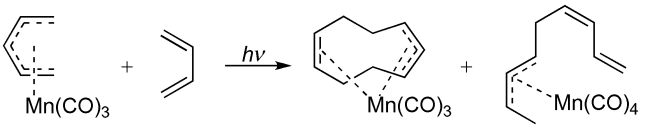
1. Arrayas, R. G. and Liebeskind, L. S., *J. Am. Chem. Soc.,* **2003**, *125*, 9026.
2. (a) Krishna, U. M.; Deodhar, K. D.; Trivedi, G. K. and Mobin, S. M., *J. Org. Chem.,* **2004**, *69*, 967. (b) El-Essawy, F. A. G.; Yassin, S. M.; El-Sakka, I. A.; Khattab, A. F.; Sotofte, I.; Madsen, J. O. and Senning, A., *J. Org. Chem.,* **1998**, *63*, 9840.

[5+4] Cycloaddition

A. GENERAL REACTION SCHEME



B. CITED EXPERIMENTAL EXAMPLES



Reference 1.

A mixture of 300 mg [$Mn(CO)_3(\eta^5\text{-}C_5H_7)$] (1.46 mmol) and ~5 mL 1,3-butadiene in *n*-hexane was irradiated by UV light at 235K. During the reaction, a large amount of pale brown decomposition product formed, which further turned into orange and finally faint yellow. After 1 h, the starting materials were completely consumed. Upon warming to room temperature, the reaction mixture was purified by HPLC using *n*-hexane as the eluent, and two fractions were obtained: tetracarbonyl-η^3-Z,E,Z-3,6,8-nonatrien-3-yl-mangan (60 mg, yellow oil, in a yield of 14%) and tricarbonyl-$\eta^{3:2}$-2,6-cyclononadien-1-yl-mangan (90 mg, yellow crystal, in a yield of 24%). (*Note:* this summary was translated from the original German article.)

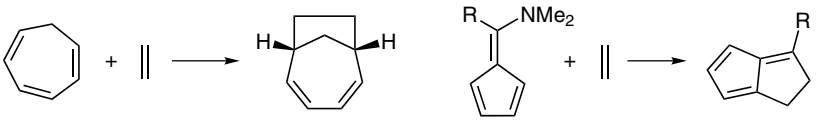
No other references are found related to [5 + 4] cycloaddition are found in the literature.

C. REFERENCES

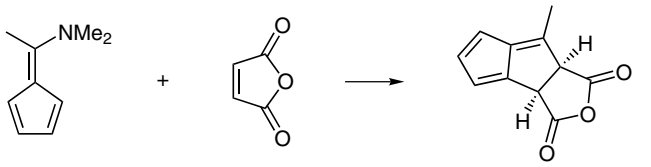
1. Kreiter, C. G. and Lehr, K., *J. Organomet. Chem.,* **1991**, *406*, 159.

[6+2] Cycloaddition

A. GENERAL REACTION SCHEME

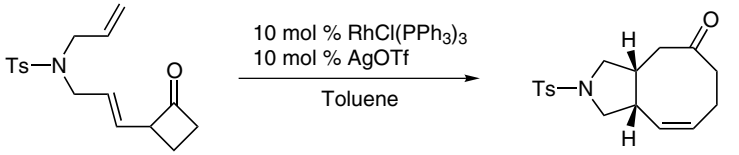


B. CITED EXPERIMENTAL EXAMPLES



Reference 1.

A benzene solution (10 mL) containing 270 mg 6-methyl-6-dimethylaminolfulvene (2 mmol) and 215 mg maleic anhydride (2.2 mmol) was stirred at 25ºC for 30 min. The solution was concentrated in vacuo to give a brown oil. The crude product was purified by flash column chromatography (silica gel) with 10% EtOAc/hexane to give 305 mg adduct, in a yield of 81%, $R_f = 0.35$ (15% EtOAc/hexane), m.p., 57–58ºC.



Reference 2.

To a base-washed, oven-dried Schlenk flask was added a solution of the substrate in toluene (0.014 M). Argon was bubbled through the solution for 10 min, followed by the addition of 10 mol % $RhCl(PPh_3)_3$ and 10 mol % AgOTf; then argon was bubbled again through the solution for 10 min. The mixture was stirred at 100ºC for 3 h. After being cooled to room temperature, the mixture was concentrated, and the residue was purified by flash column chromatography with silica to give 95% of the cycloaddition product. Other catalytic systems suitable for this cycloaddition include $[RhCl(CO)_2]_2$, $RhCl(CO)(PPh_3)_2$, $[RhCl(CO)_2]_2$ + n-Bu_3P, and $[RhCl(CO)_2]_2$ + PPh_3.

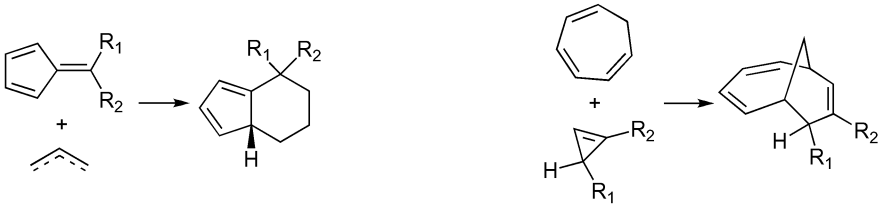
Other references related to [6+2] cycloaddition are cited in the literature.[3]

C. REFERENCES

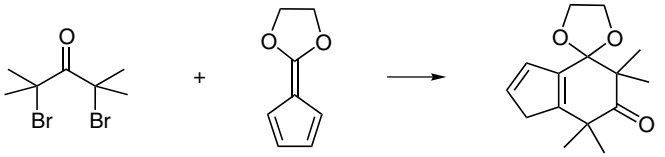
1. Hong, B.-C.; Shr, Y.-J.; Wu, J.-L.; Gupta, A. K. and Lin, K.-J., *Org. Lett.,* **2002**, *4*, 2249.
2. Wender, P. A.; Correa, A. G.; Sato, Y. and Sun, R., *J. Am. Chem. Soc.,* **2000**, *122*, 7815.
3. (a) Sugimura, T.; Im, C. Y. and Okuyama, T., *Tetrahedron Lett.,* **2004**, *45*, 1519. (b) Rigby, J. H.; Kondratenko, M. A. and Fiedler, C., *Org. Lett.,* **2000**, *2*, 3917. (c) Chen, W.; Chaffee, K.; Chung, H.-J. and Sheridan, J. B., *J. Am. Chem. Soc.,* **1996**, *118*, 9980. (d) Chaffee, K.; Huo, P.; Sheridan, J. B.; Barbieri, A.; Aistars, A.; Lalancette, R. A.; Ostrander, R. L. and Rheingold, A. L., *J. Am. Chem. Soc.,* **1995**, *117*, 1900. (e) Schmidt, T.; Bienewald, F. and Goddard, R., *J. Chem. Soc., Chem. Commun.,* **1994**, 1857. (f) Rigby, J. H.; Pigge, F. C. and Ferguson, M. D., *Tetrahedron Lett.,* **1994**, *35*, 8131. (g) Rigby, J. H.; Ateeq, H. S.; Charles, N. R.; Henshilwood, J. A.; Short, K. M. and Sugathapala, P. M., *Tetrahedron,* **1993**, *49*, 5495. (h) Chaffee, K.; Sheridan, J. B. and Aistars, A., *Organometallics,* **1992**, *11*, 18. (i) Fischler, I.; Grevels, F. W.; Leitich, J. and Ozkar, S., *Ber.,* **1991**, *124*, 2857. (j) Wu, T. C. and Houk, K. N., *J. Am. Chem. Soc.,* **1985**, *107*, 5308. (k) Mach, K.; Antropiusová, H.; Petrusová, L.; Hanuš, V.; Tureček, F. and Sedmera, P., *Tetrahedron,* **1984**, *40*, 3295. (l) Kumagai, T.; Tokida, A.; Kidoura, K.; Seshimoto, O. and Mukai, T., *Tetrahedron Lett.,* **1982**, *23*, 873. (m) Scott, L. T.; Erden, I.; Brunsvold, W. R.; Schultz, T. H.; Houk, K. N. and Paddon-Row, M. N., *J. Am. Chem. Soc.,* **1982**, *104*, 3659. (n) Kushner, A. S., *Tetrahedron Lett.,* **1971**, *12*, 3275.

[6+3] Cycloaddition

A. GENERAL REACTION SCHEME



B. CITED EXPERIMENTAL EXAMPLES



Reference 1.

To a mixture of 370 mg 2-cyclopenta-2,4-dienylidene-1,3-dioxolane (2.7 mmol) and 1.49 g $Fe_2(CO)_9$ (4.1 mmol) in 80 mL dry benzene was added 1.12 g 2,4-dibromo-2,4-dimethylpentan-3-one (4.1 mmol). The suspension was vigorously stirred for 2 h at 25°C and filtered. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography with 3% EtOAc/hexane to give 580 mg 1′,7′-dihydro-5′,5′,7′,7′-tetramethylspiro[1,3-dioxolane-2,4′-[4H]inden]-6′(5′H)-one as a colorless oil, in a yield of 86%, $R_f = 0.68$ (EtOAc/hexane = 1:10).

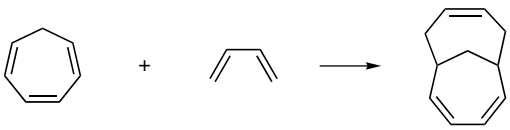
Other references related to [6+3] cycloaddition are cited in the literature.[2]

C. REFERENCES

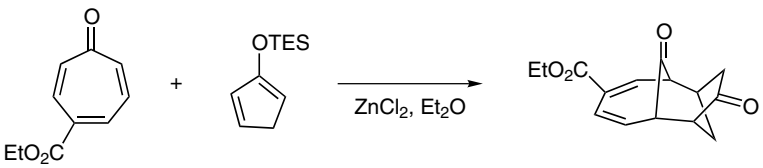
1. Hong, B.-C.; Sun, S.-S. and Tsai, Y.-C., *J. Org. Chem.,* **1997**, *62*, 7717.
2. (a) Hong, B.-C.; Gupta, A. K.; Wu, M.-F. and Liao, J.-H., *Tetrahedron Lett.,* **2004**, *45*, 1663. (b) Hong, B.-C.; Gupta, A. K.; Wu, M.-F.; Liao, J.-H. and Lee, G.-H., *Org. Lett.,* **2003**, *5*, 1689. (c) Barluenga, J.; Martínez, S.; Suárez-Sobrino, A. L. and Tomás, M., *J. Am. Chem. Soc.,* **2001**, *123*, 11113. (d) Hong, B.-C. and Sun, S.-S, *Tetrahedron Lett.,* **1996**, *37*, 659. (e) Chaffee, K.; Morcos, H.and Sheridan, J. B., *Tetrahedron Lett.,* **1995**, *36*, 1577. (f) Trost, B. M. and Seoane, P. R., *J. Am. Chem. Soc.,* **1987**, *109*, 615.

[6+4] Cycloaddition

A. GENERAL REACTION SCHEME



B. CITED EXPERIMENTAL EXAMPLES



Reference 1.

A solution of 71 mg 4-carboethoxy tropone (0.40 mmol, 1 eq.) in 3 mL dry ether was cannulated into a round-bottomed flask containing 6 mg freshly fused $ZnCl_2$ (0.04 mmol, 0.1 eq.). A solution of 235 mg 2-triethylsilyloxycyclopentadiene (1.20 mmol, 3 eq.) in 3 mL ether was then added to the reaction mixture via cannula. The reaction mixture was allowed to stir at room temperature for 5 min and then it was quenched by the addition of 5 mL 1M HCl solution and 5 mL THF. After being stirred overnight, the layers were separated, and the aqueous layer was then extracted with 5 mL EtOAc. The combined organic layers were washed with 5 mL saturated $NaHCO_3$ solution, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 40% EtOAc in hexanes to afford 91 mg 3,11-dioxo-tricyclo[4.4.1.$1^{2,5}$]dodeca-7,9-diene-8-carboxylic acid ethyl ester, in a yield of 88%.

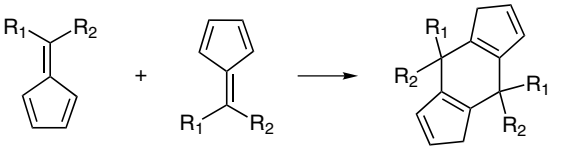
Other references related to [6+4] cycloaddition are cited in the literature.[2]

C. REFERENCES

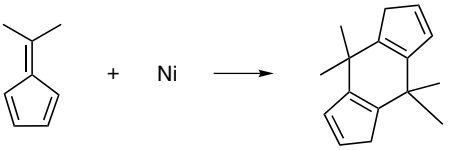
1. Isakovic, L.; Ashenhurst, J. A. and Gleason, J. L., *Org. Lett.,* **2001**, *3*, 4189.
2. (a) Rigby, K. H. and Fleming, M., *Tetrahedron Lett.,* **2002**, *43*, 8643. (b) Hong, B.-C.; Jiang, Y.-F. and Kumar, E. S., *Bioorg. Med. Chem. Lett.,* **2001**, *11*, 1981. (c) Rigby, J. H. and Fiedler, C., *J. Org. Chem.,* **1997**, *62*, 6106. (d) Kreiter, C. G.; Eckert, R.; Frank, W. and Reib, G. J., *Inorg. Chimica Acta,* **1996**, *251*, 95. (e) Keil, J.-M.; Massa, W.; Riedel, R.; Seitz, G. and Wocadlo, S., *Tetrahedron Lett.,* **1994**, *35*, 7923. (f) Gupta, Y. N.; Patterson, R. T.; Bimanand, A. Z. and Kouk, K. N., *Tetrahedron Lett.,* **1986**, *27*, 295. (g) Funk, R. L. and Bolton, G. L., *J. Am. Chem. Soc.,* **1986**, *108*, 4655. (h) Rigby, J. H.; Moore, T. L. and Rege, S., *J. Org. Chem.,* **1986**, *51*, 2398. (i) Kreiter, C. G.; Michels, E. and Kaub, J., *J. Organomet. Chem.,* **1986**, *312*, 221. (j) Garst, M. E.; Roberts, V. A.; Houk, K. N. and Rondan, N. G., *J. Am. Chem. Soc.,* **1984**, *106*, 3882. (k) Paquette, L. A.; Hathaway, S. J.; Kravetz, T. M. and Hsu, L. Y., *J. Am. Chem. Soc.,* **1984**, *106*, 5741. (l) Wu, T. C.; Mareda, J.; Gupta, Y. N. and Houk, K. N., *J. Am. Chem. Soc.,* **1983**, *105*, 6996. (m) Gupta, Y. N.; Doa, M. J. and Houk, K. N., *J. Am. Chem. Soc.,* **1982**, *104*, 7336. (n) Harano, K.; Ban, T.; Yasuda, M. and Kanematsu, K., *Tetrahedron Lett.,* **1979**, *20*, 1599. (o) Houk, K. N. and Luskus, L. J., *Tetrahedron Lett.,* **1979**, *11*, 4029. (p) Mukherjee, D.; Dunn, L. C. and Houk, K. N., *J. Am. Chem. Soc.,* **1979**, *101*, 251. (q) Dunn,L. C. and Houk, K. N., *Tetrahedron Lett.,* **1978**, *19*, 3411. (r) Mukherjee, D.; Watts, C. R. and Houk, K. N., *J. Org. Chem.,* **1978**, *43*, 817. (s) Reiter, S. E.; Dunn, L. C. and Houk, K. N., *J. Am. Chem. Soc.,* **1977**, *99*, 4199. (t) Dunn, L. C.; Chang, Y.-M. and Houk, K. N., *J. Am. Chem. Soc.,* **1976**, *98*, 7095. (u) Noble, W. J. Le and Ojosipe, B. A., *J. Am. Chem. Soc.,* **1975**, *97*, 5939. (v) Houk, K. N.; Luskus, L. J. and Bhacca, N. S., *Tetrahedron Lett.,* **1972**, *13*, 2297. (w) Houk, K. N. and Watts, C. R., *Tetrahedron Lett.,* **1970**, *11*, 4025. (x) Houk, K. N.; Luskus, L. J. and Bhacca, N. S., *J. Am. Chem. Soc.,* **1970**, *92*, 6392.

[6+6] Cycloaddition

A. GENERAL REACTION SCHEME



B. CITED EXPERIMENTAL EXAMPLES



Reference 1.

6,6-Dimethylfulvene and 250 mg nickel vapor were co-deposited at −196°C in a conventional metal atom reactor, and 130 mg of 6,6-dimethylfulvene dimmer was isolated upon sublimation of the residue.

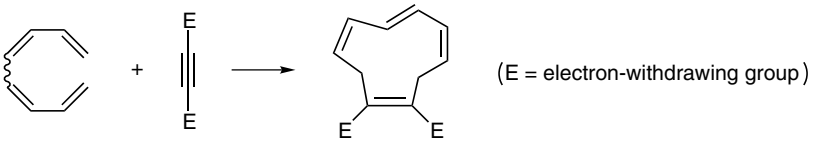
Other references related to [6+6] cycloaddition are cited in the literature.[2]

C. REFERENCES

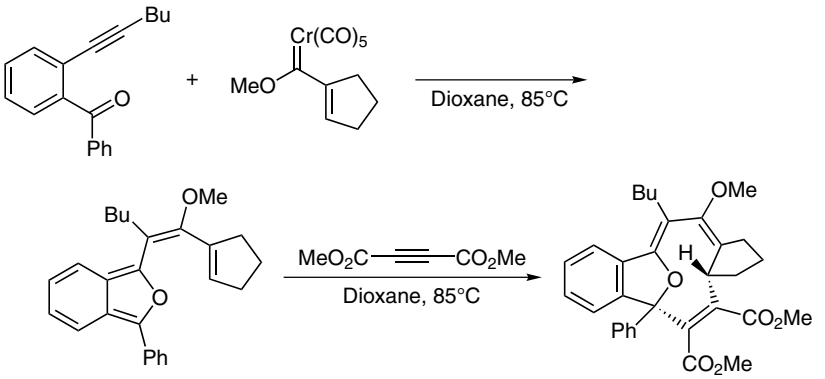
1. Hao, N.; Saywer, J. F.; Sayer, b. G. and McClinchey, M. J., *J. Am. Chem. Soc.,* **1979**, *101*, 2203.
2. (a) Mathew, T.; Keller, M.; Hunkler, D., and Prinzbach, H., *Tetrahedron Lett.,* **1996**, *37*, 4491. (b) Keil, J.-M.; Massa, W.; Riedel, R.; Seitz, G. and Wocadlo, S., *Tetrahedron Lett.,* **1994**, *35*, 7923. (c) Sedelmeier, G.; Fessner, H.-D.; Grund, C.; Spurr,P. R.; Fritz, H. and Prinzbach, H., *Tetrahedron Lett.,* **1986**, *27*, 1277. (d) Mukai, T.; Tezuka, T. and Akasaki, Y., *J. Am. Chem. Soc.,* **1966**, *88*, 5025.

[8+2] Cycloaddition

A. GENERAL REACTION SCHEME



B. CITED EXPERIMENTAL EXAMPLES



Reference 1.

To a solution of 0.242 g carbene complex (0.80 mmol) in 50 mL dioxane was added 0.157 g alkyne (0.60 mmol); the solution was heated to 85°C. Once the coupling reaction was complete (disappearance of alkyne by TLC analysis), dimethyl acetylenedicarboxylate (DMAD, 0.20 mL, 1.63 mmol) was added immediately at the same temperature, and the reaction was continued for 2 h. The solvent was removed on a rotary evaporator, and the residue was purified by flash column chromatography on silica gel using EtOAc/hexanes (1:10) as an eluent, to give 0.235 g of final [8+2] cycloaddition product, in a yield of 76%; and 10 mg of [4+2] cycloaddition product (3% yield).

Other references related to [8+2] cycloaddition are cited in the literature.[2]

C. REFERENCES

1. Luo, Y.; Herndon, J. W. and Cervantes-Lee, F., *J. Am. Chem. Soc.*, **2003**, *125*, 12720.
2. (a) Morita, N.; Yokoyama, R.; Asao, T.; Kurita, M.; Kikuchi, S. and Ito, S., *J. Organomet. Chem.,* **2002**, *642*, 80. (b) Pham, W.; Weissleder, R. and Tung, C.-H., *Tetrahedron Lett.,* **2002**, *43*, 19.

(c) Nair, V.; Anilkumar, G.; Nandakumar, M. V.; Mathew, B. and Rath, N. P., *Tetrahedron Lett.,* **1997**, *38*, 6441. (d) Yamabe, S.; Kawajiri, S.; Minato, T. and Machiguchi, T., *J. Org. Chem.,* **1993**, *58*, 1122. (e) Machiguchi, T. and Yamabe, S., *Tetrahedron Lett.,* **1990**, *31*, 4169. (f) Liu, C.-Y. and Houk, K. N., *Tetrahedron Lett.,* **1987**, *28*, 1367. (g) Liu, C.-Y. and Houk, K. N., *Tetrahedron Lett.,* **1987**, *28*, 1371. (h) Liu, C. Y.; Mareda, J.; Houk, K. N. and Fronczek, F. R., *J. Am. Chem. Soc.,* **1983**, *105*, 6714. (i) Cantrell, T. S., *J. Am. Chem. Soc.,* **1971**, *93*, 2540. (j) Farrant, G. C. and Feldmann, R., *Tetrahedron Lett.,* **1970**, *11*, 4979.

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[2+2] Cycloaddition

A. GENERAL DESCRIPTION OF THE REACTION

Any process involving the breakage of two π bonds and the formation of two σ bonds to form a four-membered ring structure in general should belong to [2+2] cycloaddition. Among the [2+2] cycloadditions, the reaction between a carbonyl compound and an alkene to form oxetane is known as the *Paterno-Büchi Reaction*, while the [2+2] cycloaddition of ketenes and imines to give 2-azetidinones (i.e., β-lactams) is referred to as the *Staudinger [2+2] Cycloaddition* and the [2+2] photocycloaddition between an enol of a 1,3-dicarbonyl compound (β-diketone, β-dialdehyde, or β-ketoaldehyde) and an olefin to form a cyclobutanol intermediate followed by a retro aldol condensation to 1,5-dicarbonyl compound is named the *de Mayo Reaction*. These reactions are discussed in their own chapters; therefore, this chapter will focus primarily on the formation of the four-membered ring of the carbon skeleton.

According to the Woodward-Hofmann rule, a concerted [2+2] cycloaddition of regular olefins at ground states is thermodynamically prohibited, whereas the olefins at excited states activated by UV irradiation is allowed.[1] Thus the normal cycloaddition of olefins under photochemical conditions are known as photochemical [2+2] cycloaddition,[2] [2+2] photocycloaddition,[3] and [2π+2π] photocycloaddition.[4] On the other hand, the reversion of [2+2] cycloaddition could also occur under UV irradiation, according to Woodward-Hofmann rule; and such a process is referred to as [2+2] photocycloreversion.[5] However, it should be pointed out that not all the [2+2] cycloadditions occur and under photochemical conditions, some unstable olefins—due to high electron deficiency or high ring strain (typically confined to ketenes, allenes, ketenimines and multifluorinated olefins)—can also

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

undergo the thermal [2+2] cycloadditions, with or without the help of Lewis acids or transition metal complexes via stepwise biradical or zwitterionic intermediates. In addition, most of reported [2+2] cycloadditions are intramolecular cycloadditions, due to a better defined regioselectivity, rate enhancement, and the ability to construct a polycyclic structure in one step.[6]

The first photochemical [2+2] cycloaddition was probably reported by Ciamician and Silber in 1908 for the synthesis of camphorcarvone,[7] which was confirmed by Büchi and Goldman in 1957.[8] Under photoirradiation, most of olefins undergo [2+2] cycloaddition. For example, norbornadiene (bicyclo[2.2.1]hepta-2,5-diene) with two ethylenic units fixed in space gives quadricyclane (tetracyclo[3.2.0.0^{2,7}.0^{4,6}]heptane) as the dominant photoproduct;[9] acetylene[2c] or 1,2-dichloroethylene[10] reacts with chiral 2(5*H*)-furanones (α,β-unsaturated lactones) to afford cyclobutene-fused lactones. In addition, acetylene also cyclizes with benzothiophene photochemically to form naphthalothiophene[3a] with an intramolecular enone moiety.[11] While acenaphthylene undergoes dimerization on irradiation into two isomeric dimmers,[12] 1,1-diethoxyethylene cyclizes with chiral polyfunctional 2-cyclohexenones to give only identified head-to-tail regioisomers, which are controlled by the rate of 1,4-biradical formation.[13] In addition, the photochemical [2+2] cycloaddition even occurs for olefins with certain steric hindrance. For example, *trans*-2-cyclooctenone reacts with dimethoxyethylene in a stepwise manner to give [2+2] cycloadduct;[14] singlet exciplex of *trans*-stilbene reacts with olefins properly,[15] and the olefin tethered with benzene undergoes *ortho* [2+2] cycloaddition.[16] In addition, benzyne, *N*,*N*-diethylpropynylamine (ynamine),[17] and enynamine[18] cyclize with C_{60}; and even *m*-phenylenebis(arylmethanofullerene) undergoes photochemical [2+2] cycloaddition to form the dimerized fullerene structure.[19] The rare occurring steric hindrance in photochemical [2+2] cycloaddition is attributed to the large number of mechanisms by which excited-state energy can be dissipated.[20] However, in a few cases, the extreme steric hindrance does burden the photochemical [2+2] cycloaddition. For instance, although 1,2-diphenylcyclobutene reacts with 2,5-dimethyl-2,4-hexadiene and itself, it does not undergo reaction with tetramethylethylene; moreover, 1,2-diphenylcyclopentene and 1,2-diphenylcyclohexene are unreactive in photochemical [2+2] cycloaddition,[3] and the methyl groups in 1,2-diphenyl-3,3,4,4-tetramethylcyclobutene effectively inhibit the possible [2+2] reaction with tetrachloroethylene.[20] Another example is the intramolecular cyclization of bis(1-methylethenyl-cyclopentadienyl)zirconium complex to form the catalyst for *ansa*-metallocene polymerization. While the 1-cyclohexylethenyl series cyclizes in a quantitative yield of complex, the 1-phenylethenyl series affords only 5% of corresponding product.[21]

In addition, molecules with olefinic structure can undergo photochemical [2+2] cycloaddition even in solid states. For example, cinnamic acid stacking in head-to-tail and head-to-head conformations in α- and β-crystalline shapes proceed photochemical [2+2] cycloaddition to afford α- and β-truxinic acids respectively,[22] while 1,4-bis(β-pyridyl-2-vinyl)benzene on Au(111) in solution dimerizes when irradiated by longer wavelength UV light ($\lambda > 400$ nm) but polymerizes under a shorter UV light ($\lambda < 400$ nm).[23] Producing the necessary unpaired electrons, the [2+2] cycloaddition is attributed to the origin of the magnetism in polymerized-C_{60} materials.[24] Although the only conjugated triene or higher polyene reported to undergo photochemical [2+2] cycloaddition is all-*trans*-hexatriene-1,6-dicarboxylic acid,[25] the [2+2] cycloaddition and photocycloreversion are responsible for the healing of the polymer.[3b] Moreover, coumarin is reported to undergo a thermal [2+2] cycloaddition in crystalline inclusion complexes under high vacuum conditions.[26]

It should be pointed out that in singlet [2+2] photocycloaddition, the regioselectivity and stereoselectivity are determined by the pericyclic minimum and exciple (or excimer) minimum, and the energy barrier between these two minima. As a result, HOMO-HOMO and LUMO-LUMO interactions favor the head-to-head regiochemistry and *syn*- or *cis*- stereochemistry in an excimer.[27] In contrast, the Rydberg-like excited singlet state is responsible for the [2+2] photocycloreversion.[5] Moreover, for the intramolecular [2+2] cycloaddition of hexa-1,5-dienes, the cycloaddition generally follows the rule of five, i.e., forming a five-membered ring rather than a six-membered ring via the 1,5-closure[28] due to the kinetic preference,[3a] as shown in the cyclization of 2-acyl-1,5-hexadienes[29] and even in the case of *o*-bisvinylbenzene in which the two vinyl groups are isolated by *o*-phenylene.[30] However, due to steric hindrance, the rule of five is dissipated in a few cyclizations. For example, in the cyclization of 1,5-hexadien-3-ones and 1-acyl-1,5-hexadienes, the substitution at C(s) results in a shift from a 1,5-closure to a 1,6-cyclization; the greater the substituent, the larger extent for this shift.[29] In addition, the existence of a bulky group between the two isolated alkene moieties or an electron-withdrawing group (e.g., ester) at the terminal of alkene also causes a violation of the rule of five.[31] Moreover, the rule of five is not followed when the 1,5-hexadiene systems undergo electron-transfer-induced rearrangements via a bifunctional 1,4-cyclohexanediyl radical cation intermediate.[32] In all these circumstances, when six-membered structures are formed, the reaction is known as the straight mode.[29,31]

On the other hand, allenes are a type of molecule with unsaturated carbon skeletons, which can undergo [2+2] cycloadditions under thermal conditions or photochemical initiation, or by Lewis acids or transition metal complex promotion. The reported cycloaddition between allene and enone is an example of cycloaddition under photochemical conditions,[33] while the intramolecular *gem*-difluoroallene-alkyne cycloaddition in the presence of either a stiochiometric or a catalytic amount of molybdenum hexacarbonyl [$Mo(CO)_6$] is an example of [2+2] cycloaddtion promoted by a transition metal complex.[34] Another transition metal complex is the imidotitanium complex.[35] Even though allenes are an inherently strained species[6] and can undergo thermal [2+2] cycloadditions, the strictly thermal reactions generally incur the drawbacks of high reaction temperatures, affording a mixture of chemoisomeric, regioisomeric, and stereoisomeric products in moderate or low yields.[36] For example, difluoroallene reacts with dichlorodifluoroethlene at 135°C to give a mixture of two isomers, the ratio of which varies along with the reaction time and with an overall preference of *exo*-difluoromethylene moiety. The reaction of difluoroallene with methylacrylonitrile at 100°C gives 39% isolated products in favor of different isomers.[37] However, [2+2] cycloaddition of alkynyl allene under microwave irradiation affords bicyclomethylenecyclobutenes with complete regioselectivity.[38] In addition, the strained 4-ethenylidene-1,3-oxazolidin-2-ones have been found to undergo a facile [2+2] cycloaddition with either alkenes or alkynes to furnish methylenecyclobutane and methylenecyclobutene derivatives.[36] In these reactions of allenes, the geometry of olefins can be completely transferred to the cycloadducts, whereas the cycloaddition of internal allenes with axial chirality might afford diastereomeric mixture of products.[39]

Ketenes are another type of unsaturated molecules of high electron deficiency and structural strains; therefore, they are very reactive for the [2+2] cycloaddition. The most common [2+2] cycloaddition involving ketenes are *Staudinger [2+2] Cycloadditions* to form β-lactones, initially reported in 1911, and the dimerization of ketenes.[40] Besides the easy cycloaddition with imine, as shown in the *Staudinger [2+2] Cycloaddition*, ketenes can also react with aldehydes to afford β-lactones. It has been found that high diastereoselectivity can

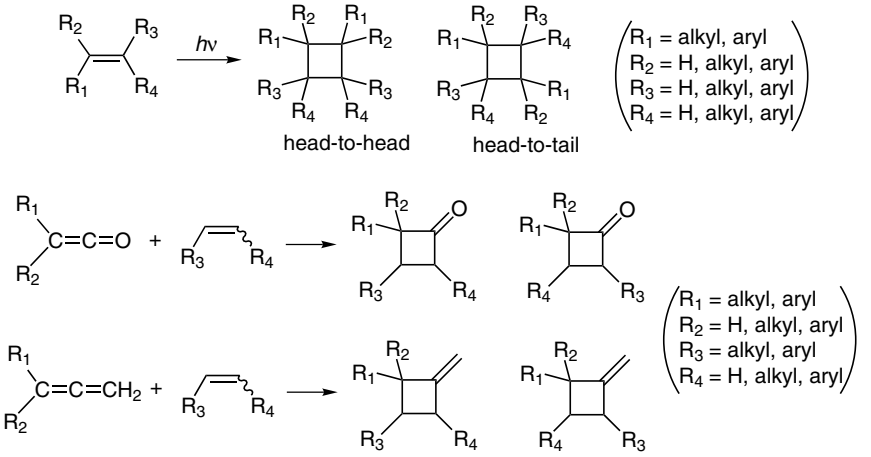
be reached for the reaction between trimethylsilkylketene and aldehydes when bulky, achiral Lewis acids are applied,[41] and the use of chiral Lewis acids leads to the optically active β-lactones.[42] For example, TADDOL-$TiCl_2$ catalyzed cycloaddition of trimethylsilylketene and aldehydes affords predominantly *cis* α-silylated β-lactones with moderate enantiomeric excesses,[43] and Cu(II)-bis(oxazoline) complexes mediate a highly enantioselective cycloaddition between (silyl)ketenes and chelating carbonyl compounds.[42a] Some other Lewis acids, including $BF_3{\cdot}OEt_2$[44] and a Me_3Al complex of axially chiral 1,1-binaphthalene-2,2-diol,[45] are also used for the cycloaddition of ketenes. In reactions with unactivated alkenes, the cycloaddition is often complicated by the dimerization of ketene itself; however, ketenes react with activated alkenes (e.g., vinyl ethers) more readily.[46] In this reaction, both C=O and C=C bond of ketene could be involved in the cycloaddition, although in preference with alkenes across the C=C bond;[46] therefore, the ketenes are often converted into the corresponding ketene silyl acetal,[47] ketene aminal[48] or ketene dimethyldithioacetal[49] to proceed the [2+2] cycloaddition. For example, the threefold [2+2] cycloaddition of benzyne and ketene silyl acetals gives polyoxygenated tricyclobutabenzenes,[47b] while squaric acid can be simply prepared from the [2+2] cycloaddition between tetraalkoxyethylenes and oxyketenes.[50] One of the most interesting [2+2] cycloadditions related to ketene is probably the recently reported one-pot process in which the nucelophilic catalyst serves up to four discrete roles: catalytic dehydrohalogenation of acid chlorides to form ketenes, catalytic dehydrohalogenation of α-chloroamines to form the corresponding imines, catalyst for the [2+2] cycloaddition to β-lactams, and reagent for the nucleophilic ring opening of β-lactams to afford β-substituted aspartic acids of high enantioselectivity and diastereoselectivity.[51] The cycloaddition of ketenes with alkenes can also be promoted by transition metal complexes, including the chromium[52] and titanium complexes.[51] Certainly, ketenes also react with allenes[53] and carbodiimides.[54] It is interesting that the intramolecular cycloaddition between the ketene and the alkene moiety with an aryl group also follows the rule of five.[55] In addition, such reactions have been measured to have a Hammett constant (F) of -1.39, a quantified indication of a modest charge development at the transition state that would be stabilized by an electron-donating group of styrene, and the cycloaddition is accelerated by the said electron-donating groups.[55]

As an substitute for ketenes, keteniminium cations can also react with imines to afford β-lactams.[56] It has been found that ketoketenes give better yields of cycloadducts than do ketene iminium salts, whereas aldoketene iminium salts prevail in corresponding aldoketenes in respective reactions.[57] In addition, ketenimines bearing an electron-withdrawing group (e.g., tosyl, cyano) on the nitrogen atom can react with imines to furnish azetidin-2-imines.[56]

Furthermore, for cyclic olefins, as the size of carbocyclic ring decreases, double bonds are more bent and twisted, thus the cyclic olefins show increased reactivity and can undergo the [2+2] cycloaddition thermally.[29] In parallel, the highly strained *anti*-Bredt rule olefins also readily undergo [2+2] cycloaddition. For example, 1-tricyclo[3.3.1.$1^{3,7}$]decene (adamantene) dimerizes to give both head-to-head and head-to-tail cycloadducts in a 1:2 ratio.[29] On the other hand, the thermal [2+2] cycloaddition also proceeds readily for the olefins of strong electron-withdrawing substituents, such as multifluorinated alkenes. For example, α,β,β-trifluorostyrenes bearing three fluorine atoms on the vinyl moiety readily dimerizes at temperatures ranging from 80° to 160°C via biradical intermediates.[58] On the basis of this reaction, a set of radical substituent constants has been established.[58b,58c] Likewise, 1,1-dichloro-2,2-difluoroethylene reacts with 1,3-dienes smoothly at 80°C.[59] In contrast, the Lewis acid can also promot the thermal cycloaddition of olefins, as indicated

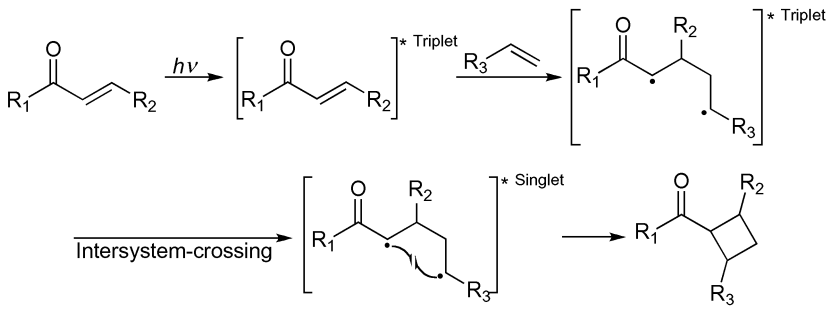
by the cyclodimerization of *trans*-anethole by $Fe(ClO_4)_3$[60] and the cycloaddition between 2-phenylselenyl propene and 3-buten-2-one by $EtAlCl_2$.[61]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The photochemical [2+2] cycloaddition between olefins generally proceeds through the excited state, while the reaction between alkenes and α,β-unsaturated carbonyl compounds involves the attack of an alkene to the triplet (π–π^*)-excited enone, forming an 1,4-biradical intermediate, which, after intersystem crossing to the singlet ground-state potential energy surface, cyclizes to cyclobutane derivatives.[2a] While the photosensitized dimerization of conjugated dienes proceeds via the attack of a triplet diene on an unactivated diene, forming a stable biradical intermediate that then cyclizes to cyclobutane derivatives,[59] the reaction between alkene and ketenes involves sequential nucleophilic additions via a zwitterionic intermediate or an antarafacial concerted process, depending on the nature of alkene.[55] The reaction between alkyl-substituted allenes and 1,1-dichloro-2,2-difluoroethene proceeds via a two-step, diradical intermediate process, as supported by the stereochemical characters and kinetic isotope effects.[55] A general illustration of [2+2] photocycloaddition between alkenes and α,β-unsaturated carbonyl compounds is provided below; the mechanisms for other types of cycloadditions outlined here can be found in corresponding references.



D. MODIFICATION

Because there are so many different types of [2+2] cycloadditions known to date, it is difficult to classify them.

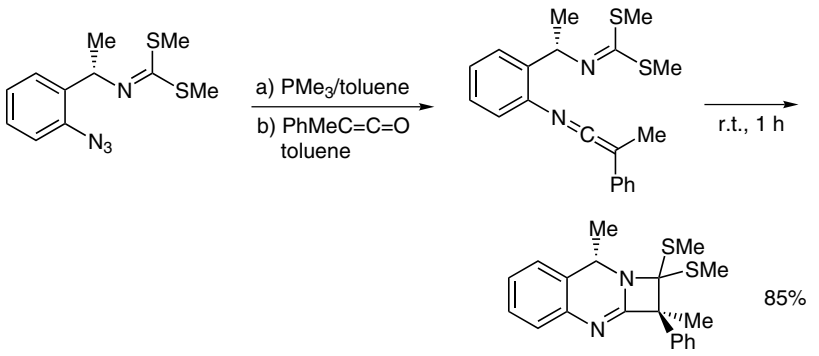
E. APPLICATIONS

This reaction has been extensively used in organic synthesis, as discussed above.

F. RELATED REACTIONS

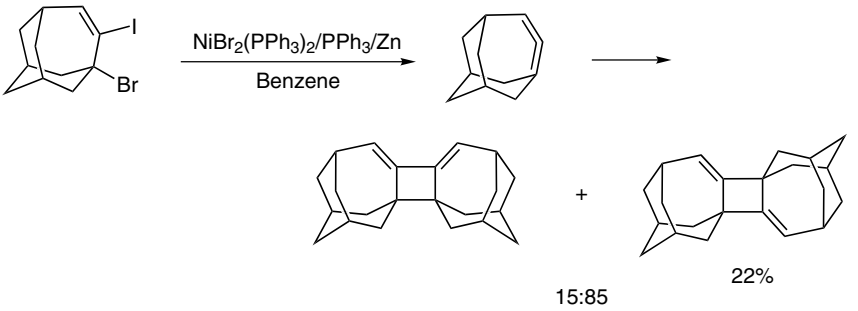
This reaction is related to the *Diels-Alder Reaction, de Mayo Reaction, Paterno-Büchi Reaction*, and *Staudinger [2+2] Cycloaddition*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 63.

To a solution of 0.8 g dimethyl *N*-[1-(2-azidophenyl)ethyl]dithiocarbonimidate (3 mmol) in 15 mL dry toluene, was added 3 mL 1 M trimethylphosphane in toluene (3 mmol), and the mixture was stirred at room temperature until the evolution of nitrogen ceased (15–30 min). Then, 0.40 g methyl phenyl ketene (3 mmol) was added, and the reaction mixture was stirred at room temperature until the ketenimine band $\sim$2000 cm^{-1} was not observed by IR spectroscopy (3–4 h). Upon removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography using hexanes/EtOAc (4:1 v/v) as the eluent to afford 0.90 g *trans*-2,8-dimethyl-1,1-bis(methylthio)-2-phenyl-1,2-dihydroazeto[2,1-*b*]quinazoline as colorless prisms (Et_2O), in a yield of 85%, m.p. 141–142°C.



Reference 29.

A suspension of 221 mg $NiBr_2(PPh_3)_2$ (0.30 mmol), 155 mg PPh_3 (0.59 mmol), and 155 mg activated zinc (2.4 mmol) in 1.8 mL dry benzene (1.8 mL) was heated to 50°C under argon atmosphere. After 15 min, the mixture became a dark red suspension. To this mixture was added dropwise a solution of 208 mg 3-bromo-4-iodo-4-homoadamantene (0.59 mmol) in 1.5 mL dry benzene at ambient temperature. The mixture was stirred for 1.3 h, and then filtered through neutral Al_2O_3 with benzene. Removal of the solvent afforded a 15:85 mixture of head-to-head and head-to-tail [2+2] cycloadducts as dark black crystals, whose recycling GPC separation and MPLC (SiO_2) and recrystallization from ethanol gave head-to-tail [2+2] cycloadduct as colorless crystals in a 22% yield, m.p. 264.0–264.5°C.

Other references related to [2+2] cycloaddition are cited in the literature.[64–67]

H. REFERENCES

1. Woodward, R. B. and Hoffmann, R., *Angew. Chem. Int. Ed. Engl.*, **1969**, *8*, 781.
2. (a) De Proft, F.; Fias, S.; van Alsenoy, C. and Geerlings, P., *J. Phys. Chem. A,* **2005**, *109*, 6335. (b) Chen, L. Y.; Nie, W.-L.; Paradies, J.; Kehr, G.; Fröhlich, R.; Wedeking, K. and Erker, G., *Organometallics,* **2006**, *25*, 5333. (c) Alibés, R.; de March, P.; Figueredo, M.; Fond, J.; Fu, X. L.; Racamonde, M.; Álvarez-Larena, Á. and Piniella, J. F., *J. Org. Chem.,* **2003**, *68*, 1283.
3. (a) Matlin, A. R.; Brinton, K. F. and Nivaggioli, B. T., *J. Phys. Org. Chem.,* **2007**, *20*, 83. (b) Chung, C.-M.; Roh, Y.-S.; Cho, S.-Y. and Kim, J.-G., *Chem. Mater.,* **2004**, *16*, 3982. (c) Skoric, I., Hutinec, A.; Marinic, Z. and Sindler-Kulyk, M., *ARKIVOC,* **2003**, (*xiv*), 87. (d) Hue, B. T. B.; Dijkink, J.; Kuiper, S.; Larson, K. K.; Guziec, F. S.; Goubitz, K.; Fraanje, J.; Schenk, H.; van Maarseveen, J. H. and Hiemstra, H., *Org. Biomol. Chem.,* **2003**, *1*, 4364. (e) Blaauw, R. H.; Brière, J.-F.; de Jong, R.; Benningshof, J. C. J.; van Ginkel, A. E.; Fraanje, J.; Goubitz, K.; Schenk, H.; Rutjes, F. P. J. T. and Hiemstra, H., *J. Org. Chem.,* **2001**, *66*, 233. (f) Mehta, G. and Nandakumar, J., *Tetrahedron Lett.,* **2001**, *42*, 7667. (g) Penn, J. H.; Gan, L.-X.; Eaton, T. A.; Chan, E. Y. and Lin, Z., *J. Org. Chem.,* **1988**, *53*, 1519. (h) Schreiber, S. L., *Science,* **1985**, *227*, 857.
4. (a) Wex, B.; Kaafarani, B. R.; Oliver, A. G.; Bauer, J. A. K. and Neckers, D. C., *J. Org. Chem.,* **2003**, *68*, 8258. (b) Silva, M. T.; Braz-Filho, R. and Netto-Ferreira, J. C., *J. Braz. Chem. Soc.,* **2000**, *11*, 479.
5. Leigh, W. J. and Postigo, J. A., *J. Am. Chem. Soc.,* **1995**, *117*, 1688.
6. Padwa, A.; Lipka, H.; Watterson, S. H. and Murphree, S. S., *J. Org. Chem.,* **2003**, *68*, 6238.
7. Ciamician, G. and Silber, P., *Ber.*, **1908**, *41*, 1928.
8. Büchi, G. and Goldman, I. M., *J. Am. Chem. Soc.,* **1957**, *79*, 4741.

9. Fuβ, W.; Pushpa, K. K.; Schmid, W. E. and Trushin, S. A., *Photochem. Photobiol. Sci.*, **2002**, *1*, 60.
10. Alibés, R.; de March, P.; Figueredo, M.; Font, J.; Racamonde, M. and Parella, T., *Org. Lett.,* **2004**, *6*, 1449.
11. Koft, E. R. and Smith, A. B., *J. Org. Chem.,* **1984**, *49*, 832.
12. Haga, N.; Nakajima, H.; Takayanagi, H. and Tokumaru, K., *J. Org. Chem.,* **1998**, *63*, 5372.
13. García-Expósito, E.; Álvarez-Larena, Á.; Branchadell, V. and Ortuño, R. M., *J. Org. Chem.,* **2004**, *69*, 1120.
14. (a) Eaton, P. E. and Lin, K., *J. Am. Chem. Soc.,* **1965**, *87*, 2052. (b) Corey, E. J.; Masaru, M. T.; LeMahieu, R. and Libit, L., *J. Am. Chem. Soc.,* **1965**, *87*, 2051. (c) Eaton, P. E. and Lin, K., *J. Am. Chem. Soc.,* **1964**, *86*, 2087. (d) Corey, E. J.; Bass, J. D.; LeMathieu, R. and Mitra, R. B., *J. Am. Chem. Soc.,* **1964**, *86*, 5570.
15. Shim, S. C.; Chae, J. S. and Choi, J. H., *J. Org. Chem.,* **1983**, *48*, 417.
16. Wagner, P. J., *Acc. Chem. Res.,* **2001**, *34*, 1.
17. (a) Wilson, S. R.; Kaprinidis, N.; Wu, Y. and Schuster, D. I., *J. Am. Chem. Soc.,* **1993**, *115*, 8495. (b) Wilson, S. R.; Wu, Y.; Kaprinidis, N. A.; Schuster, D. I. and Welch, C. J., *J. Org. Chem.,* **1993**, *58*, 6548. (c) Zhang, X.; Romero, A. and Foote, C. S., *J. Am. Chem. Soc.,* **1993**, *115*, 11924.
18. Zhang, X. J.; Fan, A. and Foote, C. S., *J. Org. Chem.,* **1996**, *61*, 5456.
19. Knol, J. and Hummelen, J. C., *J. Am. Chem. Soc.,* **2000**, *122*, 3226.
20. Penn, J. H.; Gan, L.-X.; Chan, E. Y.; Loesel, P. D. and Hohlneicher, G., *J. Org. Chem.,* **1989**, *54*, 601.
21. Erker, G.; Wilker, S.; Krüger, C. and Nolte, M., *Organometallics,* **1993**, *12*, 2140.
22. Bosch, E.; Hubig, S. M.; Lindeman, S. V. and Kochi, J. K., *J. Org. Chem.,* **1998**, *63*, 592.
23. Yang, G.-Z.; Wan, L.-J.; Zeng, Q.-D. and Bai, C.-L., *J. Phys. Chem. B,* **2003**, *107*, 5116.
24. Andriotis, A. N.; Sheetz, R. M. and Menon, M., *J. Phys.: Condens. Matter,* **2005**, *17*, L35.
25. Morgan, C. G.; Hudson, B. and Wolber, P. K., *Proc. Natl. Acad. Sci. USA,* **1980**, *77*, 26.
26. Wen, Y. Q.; Song, Y. L.; Zhao, D. B.; Ding, K. L.; Bian, J.; Zhang, X.; Wang, J. X.; Liu, Y.; Jiang, L. and Zhu, D. B., *Chem. Commun.,* **2005**, 2732.
27. Bentzien, J. and Klessinger, M., *J. Org. Chem.,* **1994**, *59*, 4887.
28. Roth, H. D.; Weng, H. X.; Zhou, D. H. and Herbertz, T., *Pure & Appl. Chem.,* **1997**, *69*, 809.
29. Agosta, W. C. and Wolff, S., *Pure & Appl. Chem.,* **1982**, *54*, 1579.
30. Basaric, N.; Marinic, Z. and Sindler-Kulyk, M., *J. Org. Chem.,* **2003**, *68*, 7524.
31. Blaauw, R. H.; Brière, J.-F.; de Jong, R.; Benningshof, J. C. J.; van Ginkel, A. E.; Rutjes, F. P. J. T.; Fraanje, J.; Goubitz, K.; Schenk, H. and Hiemstra, H., *Chem. Commun.,* **2000**, 1463.
32. Miyashi, T.; Konno, A. and Takahashi, Y., *J. Am. Chem. Soc.,* **1988**, *110*, 3676.
33. (a) Lupi, A.; Patamia, M. and Marini Bettolo, R., *Helv. Chim. Acta,* **1988**, *71*, 872. (b) Bettolo, R.; Tagliatesta, P.; Lupi, A. and Bravetti, D., *Helv. Chim. Acta,* **1983**, *66*, 1922.
34. Shen, Q. L. and Hammond, G. B., *J. Am. Chem. Soc.,* **2002**, *124*, 6534.
35. Trösch, D. J. M.; Collier, P. E.; Bashall, A.; Gade, L. H.; McPartlin, M.; Mountford, P. and Radojevic, S., *Organometallics,* **2001**, *20*, 3308.
36. Kimura, M.; Horino, Y.; Wakamiya, Y.; Okajima, T. and Tamaru, Y., *J. Am. Chem. Soc.,* **1997**, *119*, 10869.
37. Dolbier, W. R. and Burkholder, C. R., *J. Org. Chem.,* **1984**, *49*, 2381.
38. Brummond, K. M. and Chen, D. T., *Org. Lett.,* **2005**, *7*, 3473.
39. Ohno, H.; Mizutani, T.; Kadoh, Y.; Aso, A.; Miyamura, K.; Fujii, N. and Tanaka, T., *J. Org. Chem.,* **2007**, *72*, 4378.

40. Huisgen, R. and Otto, P., *J. Am. Chem. Soc.,* **1968**, *90*, 5342.
41. Maruoka, K.; Concepcion, A. B. and Yamamoto, H., *Synlett,* **1992**, 31.
42. (a) Evans, D. A. and Janey, J. M., *Org. Lett.,* **2001**, 3, 2125. (b) Nelson, S. G.; Peelen, T. J. and Wan, Z., *J. Am. Chem. Soc.,* **1999**, *121*, 9742.
43. Singleton, D. A.; Wang, Y. C.; Yang, H. W. and Romo, D., *Angew. Chem. Int. Ed.,* **2002**, *41*, 1572.
44. Romo, D.; Harrison, P. H. M.; Jenkins, S. I.; Riddoch, R. W.; Park, K.; Yang, H. W.; Zhao, C. X. and Wright, G. D., *Bioorg. Med. Chem.,* **1998**, *6*, 1255.
45. Tamai, Y.; Someya, M.; Fukumoto, J. and Miyano, S., *J. Chem. Soc., Perkin Trans. I,* **1994**, 1549.
46. Machiguchi, T.; Okamoto, J.; Takachi, J.; Hasegawa, T.; Yamabe, S. and Minato, T., *J. Am. Chem. Soc.,* **2003**, *125*, 14446.
47. (a) Hamura, T.; Ibusuki, Y.; Uekusa, H.; Matsumoto, T.; Siegel, J. S.; Baldridge, K. K. and Suzuki, K., *J. Am. Chem. Soc.,* **2006**, *128*, 10032. (b) Hamura, T.; Ibusuki, Y.; Uekusa, H.; Matsumoto, T. and Suzuku, K., *J. Am. Chem. Soc.,* **2006**, *128*, 3534. (c) Suzuki, K., *Pure & Appl. Chem.,* **2000**, *72*, 1783.
48. Xu, Y. L. and Dolbier, W. R., *J. Org. Chem.,* **1997**, *62*, 6503.
49. Narasaka, K., *Pure & Appl. Chem.,* **1992**, *64*, 1889.
50. Bellus, D., *J. Org. Chem.,* **1979**, *44*, 1208.
51. Dudding, T.; Hafez, A. M.; Taggi, A. E.; Wagerle, T. R. and Lectka, T., *Org. Lett.,* **2002**, *4*, 387.
52. Kim, O. K.; Wulff, W. D.; Jiang, W. Q. and Ball, R. G., *J. Org. Chem.,* **1993**, *58*, 5571.
53. McCaleb, K. L. and Halcomb, R. L., *Org. Lett.,* **2000**, *2*, 2631.
54. Kappe, C. O.; Färber, G.; Wentrup, C. and Kollenz, G., *J. Org. Chem.,* **1992**, *57*, 7078.
55. Bélanger, G.; Lévesque, F.; Pâquet, J. and Barbe, G., *J. Org. Chem.,* **2005**, *70*, 291.
56. Cossío, F. P.; Arrieta, A.; Lecea, B.; Alajarín, M.; Vidal, A. and Tovar, F., *J. Org. Chem.,* **2000**, *65*, 3633.
57. Brady, W. T.; Giang, Y.-S. F.; Weng, L. L. and Dad, M. M., *J. Org. Chem.,* **1987**, *52*, 2216.
58. (a) Jiang, X.-K.; Ji, G.-Z. and Wang, D. Z.-R., *J. Fluor. Chem.,* **1996**, *79*, 173. (b) Jiang, X.-K.; Ji, G.-Z. and Wang, Z.-R., *J. Fluor. Chem.,* **1994**, *66*, 187. (c) Jiang, X.-K. and Ji, G.-Z., *J. Org. Chem.,* **1992**, *57*, 6051.
59. Turro, N. J. and Bartlett, P. D., *J. Org. Chem.,* **1965**, *30*, 1849.
60. Ohara, H.; Itoh, T.; Nakamura, M. and Nakamura, E., *Chem. Lett.,* **2001**, *7*, 624.
61. Yamazaki, S.; Fujitsuka, H.; Takara, F. and Inoue, T., *J. Chem. Soc., Perkin Trans. I,* **1994**, 695.
62. Pasto, D. J. and Sugi, K. D., *J. Org. Chem.,* **1991**, *56*, 3795.
63. Alajarín, M.; Vidal, A.; Tovar, F.; de Arellano, M. C. R.; Cossío, F. P.; Arrieta, A and Lecea, B., *J. Org. Chem.,* **2000**, *65*, 7512.
64. For photochemical [2+2] cycloaddition of olefins: (a) Paradies, J.; Kehr, G.; Fröhlich, R. and Erker, G., *Proc. Natl. Acad. Sci. USA,* **2006**, *103*, 15333. (b) Zeidan, T. A.; Kovalenko, S. V.; Manoharan, M.; Clark, R. J.; Ghiviriga, I. and Alabugin, I. V., *J. Am. Chem. Soc.,* **2005**, *127*, 4270. (c) Skoric, I.; Marinic, Z. and Sindler-Kulyk, M., *Croat. Chem. Acta,* **2004**, *77*, 161. (d) Padwa, A.; Jacquez, M. N. and Schmidt, A., *J. Org. Chem.,* **2004**, *69*, 33. (e) Iwama, N.; Kato, T. and Sugano, T., *Organometallics,* **2004**, *23*, 5813. (f) Mislin, G. L. and Miesch, M., *J. Org. Chem.,* **2003**, *68*, 433. (g) Gromov, S. P.; Ushakov, E. N.; Fedorova, O. A.; Baskin, I. I.; Buevich, A. V.; Andryukhina, E. N.; Alfimov, M. V.; Johnels, D.; Edlund, U. G.; Whitesell, J. K. and Fox, M. A., *J. Org. Chem.,* **2003**, *68*, 6115. (h) García-Expósito, E.; Bearpark, M. J.; Ortuño, R. M.; Robb, M. A. and Branchadell, V., *J. Org. Chem.,* **2002**, *67*, 6070. (i) Xue, J.; Xu, J.-W.; Yang, L. and Xu, J.-H., *J. Org. Chem.,* **2000**, *65*, 30. (j) Matlin, A. R.; Lahti, P. M.; Appella, D.; Straumanis, A.; Lin, S.; Patel, H.; Jin, K.; Schreiber, K. P.; Pauls, J. and Raulerson, P., *J. Am. Chem. Soc.,* **1999**, *121*, 2164. (k) Sapich, B.; Stumpe, J.; Krawinkel, T. and Kricheldorf, H. R., *Macromolecules,* **1998**, *31*, 1016.

(l) Kobertz, W. R. and Essigmann, J. M., *J. Am. Chem. Soc.,* **1996**, *118*, 7101. (m) Crimmins, M. T., *Chem. Rev.*, **1988**, *88*, 1453. (n) Becker, D. and Haddad, N., *Tetrahedron Lett.*, **1986**, *27*, 6393. (o) Musser, A. K. and Fuchs, P. L., *J. Org. Chem.,* **1982**, *47*, 3121. (p) Wolff, S. and Agosta, W. C., *J. Org. Chem.,* **1980**, *45*, 3139. (q) Schell, F. M.; Cook, P. M.; Hawkinson, S. W.; Cassady, R. E. and Thiessen, W. E., *J. Org. Chem.,* **1979**, *44*, 1380. (r) Tamura, Y.; Ishibashi, H.; Hirai, M.; Kita, Y. and Ikeda, M., *J. Org. Chem.,* **1975**, *40*, 2702. (s) Srivivasan, R. and Carlough, K. H., *J. Am. Chem. Soc.,* **1967**, *89*, 4932.

65. For the [2+2] cycloaddition involving allenes: (a) Odedra, A.; Lush, S.-F. and Liu, R.-S., *J. Org. Chem.,* **2007**, *72*, 567. (b) Padwa, A.; Ni, Z. J. and Watterson, S. H., *Pure & Appl. Chem.,* **1996**, *68*, 831. (c) Pasto, D. J. and Sugi, K. D., *J. Org. Chem.,* **1992**, *57*, 12. (d) Pasto, D. J.; Sugi, K. D. and Alonso, D. E., *J. Org. Chem.,* **1992**, *57*, 1146. (e) Pasto, D. J. and Sugi, K. D., *J. Org. Chem.,* **1991**, 56, 6216. (f) Pasto, D. J. and Yang, S. H., *J. Org. Chem.,* **1986**, *51*, 3611.

66. For the [2+2] cycloaddition involving ketenes: (a) Barluenga, J. and Martínez, *ARKIVOC,* **2006,** (*vii*), 129. (b) Koch, R. and Wentrup, C., *Org. Biomol. Chem.,* **2004**, *2*, 195. (c) Molander, G. A.; St. Jean, D. J. and Haas, J., *J. Am. Chem. Soc.,* **2004**, *126*, 1642. (d) Zhu, C.; Shen, X. Q. and Nelson, S. G., *J. Am. Chem. Soc.,* **2004**, *126*, 5352. (e) Zhou, C. and Birney, D. M., *J. Am. Chem. Soc.,* **2002**, *124*, 5231. (f) Singh, J.; Bisacchi, G. S.; Ahmad, S.; Godfrey, J. D.; Kissick, T. P.; Mitt, T.; Kocy, O.; Vu, T.; Papaioannou, C. G.; Wong, M. K.; Heikes, J. E.; Zahler, R. and Mueller, R. H., *Org. Proc. Res. Dev.,* **1998**, *2*, 393. (g) Bao, J. M.; Wulff, W. D.; Dominy, J. B.; Fumo, M. J.; Grant, E. B.; Rob, A. C.; Whitcomb, M. C.; Yeung, S.-M.; Ostrander, R. L. and Rheingold, A. L., *J. Am. Chem. Soc.,* **1996**, *118*, 3392. (h) Salzner, U. and Bachrach, S. M., *J. Org. Chem.,* **1996**, *61*, 237. (i) Brady, W. T. and Gu, Y.-Q., *J. Org. Chem.,* **1988**, *53*, 1353. (j) Brady, W. T.; Giang, Y.-S. F.; Marchand, A. P. and Wu, A.-H., *J. Org. Chem.,* **1987**, *52*, 3457. (k) Brady, W. T. and Giang, Y. F., *J. Org. Chem.,* **1986**, *51*, 2145. (l) Kulkarni, Y. S. and Snider, B. B., *J. Org. Chem.,* **1985**, *50*, 2809. (m) Scheeren, H. W.; Aben, R. W. M.; Ooms, P. H. J. and Nivard, R. J. F., *J. Org. Chem.,* **1977**, *42*, 3128.

67. For the [2+2] cycloadditions involving ketenimines: (a) Alajarín, M.; Sánchez-Andrada, P.; Vidal, A. and Tovar, F., *J. Org. Chem.,* **2005**, *70*, 1340. (b) Fabian, W. M. F. and Janoschek, R., *J. Am. Chem. Soc.,* **1997**, *119*, 4253.

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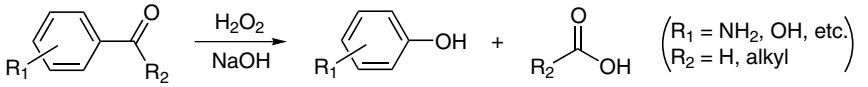
Dakin Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Dakin in 1909.[1] It is the preparation of phenols from aryl aldehydes or aryl ketones involving the oxidation of corresponding aromatic compounds by hydrogen peroxide in the presence of a base and subsequent hydrolysis of the aryl formate or alkylcarboxylate intermediates. Therefore, this reaction is generally known as the Dakin reaction.[2] It has been reported that the *para*- or *ortho*- substituents (such as OH, NH_2) on aryl aldehydes or aryl ketones will facilitate this reaction,[2l] especially for the ortho OH group, which accelerates the reaction via the formation of an intramolecular hydrogen bonding.[3]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Provided here is a tentative mechanism that reflects the effect of *para*- or *ortho*-OH to accelerate the reaction rate.

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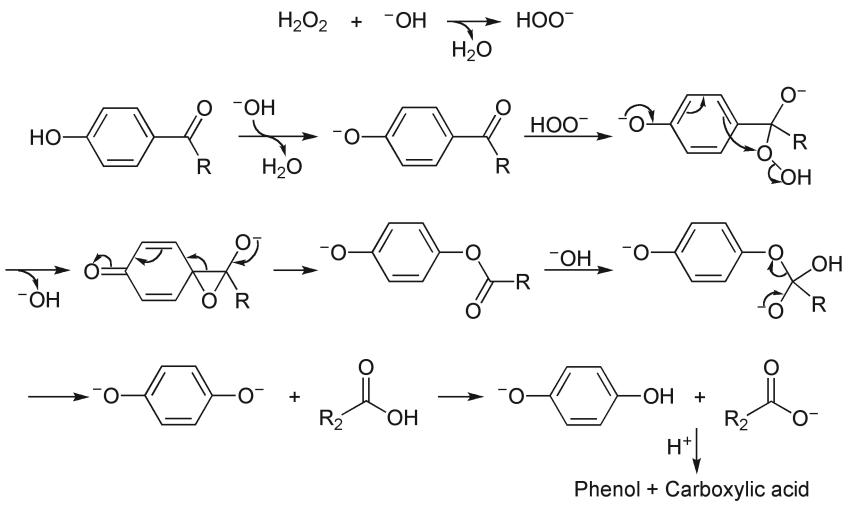


D. MODIFICATION

This reaction has been modified by using sodium percarbonate[2e] and urea-hydrogen peroxide complex[2b] as the oxidant. In addition, this reaction has been efficiently carried out in liquid ionic solvent.[2a]

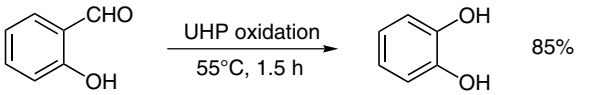
E. APPLICATIONS

This reaction has general applications in the synthesis of phenols from aryl aldehydes or aryl ketones.

F. RELATED REACTIONS

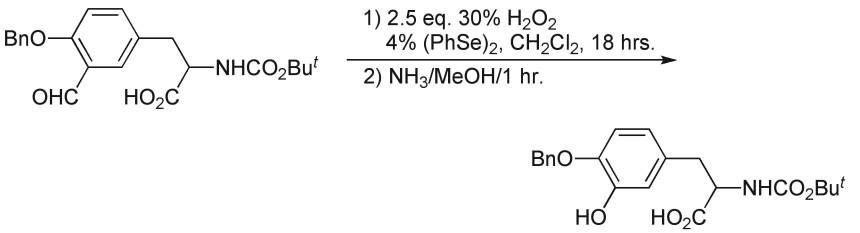
This reaction is related to the *Baeyer-Villiger Oxidation* and *Criegee Rearrangement*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2b.

To a glass test tube containing 376 mg finely powdered urea-hydrogen peroxide (UHP) adduct (4 mmol) was added 2 mmol *o*-hydroxy-benzaldehyde, and the reaction mixture was placed in an oil bath at 55°C for 1.5 h. After completion of the reaction, as monitored by TLC (8:2 v/v, hexane/EtOAc), the reaction mixture was extracted into EtOAc, and the combined extracts were washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to afford the crude product, which was purified by chromatography to give 85% catechol.



Reference 2c.

To a solution of 0.096 g 3-formyl-4-(benzyloxy)-*N*-Boc-L-tyrosine (0.24 mmol) in 3 mL dichloromethane were added 0.003 g diphenyl diselenide (0.01 mmol) and 0.062 mL 30% aqueous hydrogen peroxide (0.614 mmol). The reaction mixture was stirred at ambient temperature for 18 h. The mixture was then diluted with water and EtOAc, washed with brine, dried over $MgSO_4$, and concentrated on a rotary evaporator. The residue was dissolved in 3 mL methanol, and gaseous ammonia was bubbled through the solution for 20 min. The reaction mixture was then stirred at ambient temperature for 1 h. The mixture was then concentrated, and the residue was redissolved in water. The aqueous solution was acidified to pH 1 with 1 N HCl and back extracted with EtOAc. The organic extracts were washed with brine, dried over $MgSO_4$, and concentrated to give 0.073 g *N*-[(1,1-dimethylethoxy)carbonyl]-3-[3-hydroxy-4-(phenylmethoxy)phenyl]-L-alanine as a white foam, in a total yield of 78% for the two steps.

Other references related to the Dakin reaction are cited in the literature.[4]

H. REFERENCES

1. Dakin, H. D., *Am. Chem. J.*, **1909**, *42*, 477.
2. (a) Zambrano, J. L. and Dorta, R., *Synlett,* **2003**, 1545. (b) Varma, R. S. and Naicker, K. P., *Org. Lett.,* **1999**, *1*, 189. (c) Jung, M. E. and Lazarova, T. I., *J. Org. Chem.,* **1997**, *62*, 1553. (d) Evans, T.; Yamazaki, F. and Yang, D. T. C., *Proc. Arkansas Adad. Sci.,* **1993**, *47*, 139. (e) Kabalka, G. W.; Reddy, N. K. and Narayana, C., *Tetrahedron Lett*., **1992**, *33*, 865. (f) Belen'kaya, I. A.; Krokhina, G. P.; Sirik, S. A. and Andronati, S. A., *Khim. Geterotsiklicheskikh Soedinenii,* **1987**, 1683. (g) Xie, R. G.; Chen, Y. Q.; Yuang, D. Q. and Jin, H. Q., *Youji Huaxue*, **1984**, 297. (h) Chatterjee, A.; Biswas, G. K. and Kundu, A. B., *J. Indian Chem. Soc.,* **1969**, *46*, 429. (i) Fuks, R. and Chiurdoglu, G., *Bull. Soc. Chim. Belg.,* **1967**, *76*, 244. (j) Chiurdoglu, G. and Fuks, R., *Tetrahedron Lett*., **1963**, 1715. (k) Nikoforov, G. A. and Ershov, V. V., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1964**, 176. (l) Rosenblatt, D. H. and Rosenthal, R. W., *J. Am. Chem. Soc.,* **1953**, *75*, 4607.
3. Hocking, M. B. and Ong, J. H., *Can. J. Chem.,* **1977**, *55*, 102.
4. (a) Bodwell, G. J.; Hawco, K. M. and Satou, T., *Synlett*, **2003**, 879. (b) Coumbaros, J. C.; Kirkbride, K. P. and Klass, G., *J. Forensic Sci.,* **1999**, 1237. (c) Hocking, M. B.; Bhandari, K.; Shell, B. and Smyth, T. A., *J. Org. Chem.,* **1982**, *47*, 4208. (d) Ahluwalia, V. K.; Ghazanfari, F. A. and Rani, N., *Indian J. Chem., Sect. B,* **1981**, *20B*, 106. (e) Hocking, M. B.; Ko, M. and Smyth, T. A., *Can. J. Chem.,* **1978**, *56*, 2646. (f) Seshardri, T. R. and Venkatasubramanian, G. B., *J. Chem. Soc.,* **1959**, 1660. (g) Leffler, J. E., *Chem. Rev.,* **1949**, *45*, 385.

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Dakin-West Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Dakin and West in 1928.[1] It is the preparation of α-acetamido alkyl methyl ketones via the intermediate of azlactone by the treatment of α-amino acids with acetic anhydride in the presence of a base, such as pyridine. Therefore, this reaction is generally known as the Dakin-West reaction.[2] It was found that high temperature is usually necessary for this reaction when pyridine is used as solvent;[3] however, the addition of small amount of DMAP enables the reaction to occur at ambient temperatures with higher yield.[3,4] Many mechanisms have been proposed for this reaction, and the most probable one involves the acetylation of the amino group, followed by the cyclization to azlactone intermediate, which forms a stable carbanion when treated with a base; the acetylation of such carbanion leads to the formation of an azlactone of an α-acetamido-β-keto acid, which subsequently converts to α-acetamido alkyl methyl ketone upon decarboxylation.[5] It is such decarboxylation evolving 1 eq. CO_2 that makes this reaction difficult to control for scaling up during manufacturing.[6] Therefore, this reaction has been modified to use DMAP and triethylamine with additional acetic acid to provide water to promote the hydrolysis of azlactone; at the same time, alanine is added to control the CO_2 evolution.[6] Other studies of this reaction indicate that this reaction is generally applicable to acyclic alkyl and aryl acid anhydrides, including propionic, butyric, methoxyacetic, and benzoic anhydrides;[5b] however, only those α-amino acids and their derivatives that are able to form azlactones with an active α-hydrogen will undergo the Dakin-West reaction.[5b] Besides the use of anhydride in this reaction, benzoyl fluoride has also been found to react with α-amino acids in the presence of pyridine.[5b] It is interesting that treatment of *N*-acyl-*N*-alkyl α-amino

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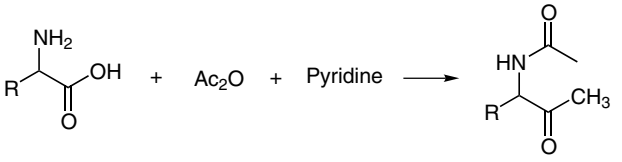
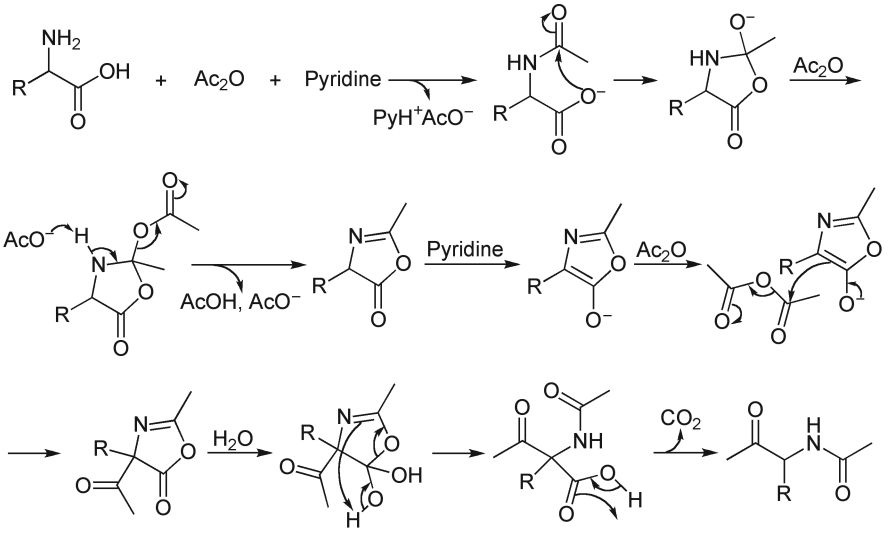
acids with trifluoroacetic anhydride under these reaction conditions leads to the formation of trifluoromethyl-substituted oxazole, acyloins, or morpholines, depending on the nature of substituents on the amino acid and/or the reaction conditions.[7]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

This reaction involves the acetylation of the amino group, formation of azlactone, deprotonation by a base, and additional acetylation and hydrolysis, as displayed here.



D. MODIFICATION

This reaction has been modified to use DMAP and triethylamine with additional acetic acid to control the evolution of carbon dioxide.[6]

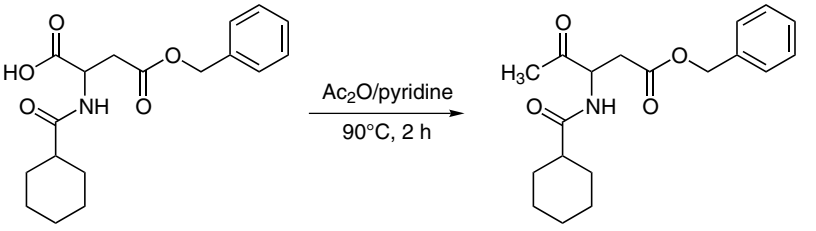
E. APPLICATIONS

This reaction is generally used in the synthesis of α-amino ketones.

F. RELATED REACTIONS

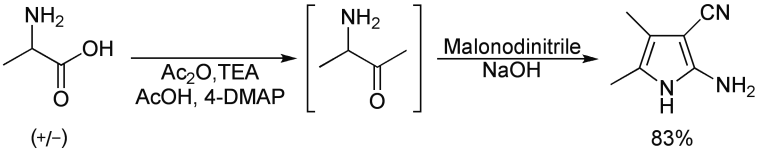
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 8.

A mixture of 1.72 g 2-(cyclohexanecarbonylamino)-succinic acid 4-benzyl ester (5.16 mmol), 5 mL pyridine, and 3 mL acetic anhydride was heated at 90°C for 2 h. Excess acid anhydride and pyridine were removed under reduced pressure, and the residue was then diluted with 150 mL ether. The organic phase was then washed successively with 50 mL 1.0 *N* HCl and 50 mL water, then dried over solid sodium sulfate, decanted, and concentrated under reduced pressure to yield an oil. The residue was purified by column chromatography (EtOAc/hexanes) to provide 1.16 g 3-(cyclohexanecarbonyl-amino)-4-oxo-pentanoic acid benzyl ester as a pale yellow oil, in a yield of 68%.



Reference 6.

A mixture of 338.5 g acetic anhydride (3.3 mol), 45 g acetic acid (0.75 mol), 379.5 g triethylamine (3.75 mol), and 1.83 g 4-(dimethylamino)-pyridine (0.015 mol) in a reaction vessel was heated to 50°C. Then 135 g racemic alanine (1.5 mol) was added as a solid over 6 h thereby maintaining the reaction temperature at 45–55°C. After completion of the alanine addition, the reaction mixture was stirred at 50°C for an additional 8 h. Acetic anhydride, triethylamine, and acetic acid were distilled off by vacuum distillation (10–15 mbar), while gradually raising the jacket temperature to a maximum of 100°C. The residue (GC assay > 95% acylaminoketone intermediate) was cooled to room temperature and diluted with 815 mL water. Malonodinitrile (94.5 g, 1.425 mol) was added, and this mixture was slowly added to 500 g aqueous sodium hydroxide solution (30%). The speed of addition was adjusted so that the reaction temperature did not exceed 60°C. The resulting suspension was cooled to 0°C, filtered, washed with water, and dried in vacuum at 55°C to yield 168 g 2-amino-3-cyano-4,5-dimethylpyrrole, in a yield of 83% for the total of the two steps, m.p. (DSC) 172°C.

Other references related to the Dakin-West reaction are cited in the literature.[9]

H. REFERENCES

1. (a) Dakin, H. D. and West, R., *J. Biol. Chem.,* **1928**, *78*, 91. (b) Dakin, H. D. and West, R., *J. Biol. Chem.,* **1928**, *78*, 745. (c) Dakin, H. D. and West, R., *J. Biol. Chem.,* **1928**, *78*, 757.
2. (a) Heravi, M. M.; Ranjbar, L.; Derikvand, F. and Bamoharram, F. F., *J. Mol. Catal. A: Chem.,* **2007**, *271*, 28. (b) Rafiee, E.; Tork, F. and Joshaghani, M., *Bioorg. Med. Chem. Lett.,* **2006**, *16*, 1221. (c) Rafiee, E.; Shahbazi, F.; Joshaghani, M. and Tork, F., *J. Mol. Catal. A: Chem.,* **2005**, *242*, 129. (d) Khodaei, M. M.; Khosropour, A. R. and Fattahpour, P., *Tetrahedron Lett*., **2005**, *46*, 2105. (e) Kawase, M.; Hirabayashi, M. and Saito, S., *Recent Res. Dev. Org. Chem.,* **2000**, *4*, 283. (f) Casimir, J. R.; Ettouati, L. and Paris, J., *Lett. Peptide Sci.,* **1998**, *5*, 13. (g) Kawase, M.; Okada, Y. and Miyamae, H., *Heterocycles,* **1998**, *48*, 285. (h) Kawase, M.; Hirabayashi, M.; Koiwai, H.; Yamamoto, K. and Miyamae, H., *Chem. Commun.,* **1998**, 641. (i) Kawasi, M.; Miyamae, H.; Narita, M. and Kurihara, T., *Tetrahedron Lett*., **1993**, *34*, 859. (j) Kawase, M., *J. Chem. Soc., Chem. Commun.,* **1992**, 1076. (k) Xue, T. H. and Liang, X. T., *Huaxue Xuebao*, **1986**, *44*, 1129. (l) Cleland, G. H. and Bennett, F. S., *Synthesis,* **1985**, 681. (m) Zhao, Z. Z.; Wang, L.; Lu, F. X. and Liang, X. T., *Huaxue Xuebao*, **1981**, *39*, 811. (n) Charles, I.; Latham, D. W. S.; Hartley, D.; Oxford, A. W. and Scopes, D. I. C., *J. Chem. Soc., Perkin Trans. I,* **1980**, 1139. (o) Krasovskii, A. N.; Grins, N.; Sheinkman, A. K.; Klyuev, N. A. and Belikov, A. B., *Khim. Geterotsiklicheskikh Soedinenii*, **1978**, 476. (p) Zav'yalov, S. I. and Budkova, T. K., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1977**, 1660. (q) Zav'yalov, S. I. and Ezhova, G. I., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1977**, 219. (r) Lepschy, J.; Hoefle, G.; Wilschowitz, L. and Steglich, W., *Ann.,* **1974**, 1753. (s) Yang, C.-Y., *Huaxue*, **1971**, 133. (t) Knorr, R. and Staudinger, G. K., *Chem. Ber.,* **1971**, *104*, 3621. (u) Knorr, R., *Chem. Ber.,* **1971**, *104*, 3633. (v) Aronova, N. I.; Makhova, N. N. and Zav'yalov, S. I., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1970**, 1835. (w) Zav'yalov, S. I.; Aronova, N. I.; Makhova, N. N.; Gunar, V. I.; Ovechkina, L. F.; Rodionova, N. A. and Gracheva, E. P., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1970**, 1119. (x) Gerencevic, N. and Prostenik, M., *Bull. Sci., Sect. A: Sci. Nat. Tech. Med.,* **1970**, *15*, 158. (y) Steglich, W. and Hoefle, G., *Chem. Ber.,* **1969**, *102*, 883. (z) Aronova, N. I.; Makhova, N. N.; Unanyan, M. P.; Kondrat'eva, G. V.; Rodionova, N. A. and Zav'yalov, S. I., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1968**, 2571. (aa) Steglich, W. and Hoefle, G., *Tetrahedron Lett*., **1968**, 1619. (bb) Kornhauser, A. and Keglevic, D., *Croat. Chem. Acta,* **1967**, *39*, 285. (cc) Prostenik, M.; Gerencevic, N.; Pluscec, J. and Sateva, M., *Naturwissenschaften*, **1960**, *47*, 496. (dd) Otvos, L.; Marton, J. and Meisel-Agoston, J., *Acta Chim. Acad. Sci. Hungaricae,* **1960**, *24*, 327. (ee) Otvos, L.; Marton, J. and Meisel-Agoston, J., *Acta Chim. Acad. Sci. Hungaricae,* **1960**, *24*, 321. (ff) Buchanan, B. L.; Reid, S. T.; Thomson, R. E. S. and Wood, E. G., *J. Chem. Soc.,* **1957**, 4427. (gg) Cornforth, J. W. and Elliott, D. F., *Science,* **1950**, *112*, 534.
3. Hoefle, G.; Steglich, W. and Vorbrueggen, H., *Angew. Chem. Int. Ed. Engl.,* **1978**, *17*, 569.
4. Redeker, U.; Engel, N. and Steglich, W., *Tetrahedron Lett.,* **1981**, 4263.
5. (a) Iwakura, Y.; Toda, F. and Suzuki, H., *J. Org. Chem.,* **1967**, *32*, 440. (b) Cleland, G. H. and Niemann, C., *J. Am. Chem. Soc.,* **1949**, *71*, 841.
6. Fischer, R. W. and Misun, M., *Org. Proc. Res. Dev.,* **2001**, *5*, 581.
7. Kawase, M.; Hirabayashi, M.; Kumakura, H.; Saito, S. and Yamamoto, K., *Chem. Pharm. Bull.,* **2000**, *48*, 114.
8. Godfrey, A. G.; Brooks, D. A.; Hay, L. A.; Peters, M.; McCarthy, J. R. and Mitchell, D., *J. Org. Chem.,* **2003**, *68*, 2623.
9. (a) Casimir, J. R., Turetta, C.; Ettouati, L. and Paris, J., *Tetrahedron Lett.,* **1995**, *36*, 4797. (b) Curran, T. T., *J. Fluor. Chem.,* **1995**, *74*, 107. (c) Peet, N. P.; Burkhart, J. P.; Angelastro, M. R.; Giroux, E. L.; Mehdi, S.; Bey, P.; Kolb, M.; Neises, B. and Schirlin, D., *J. Med. Chem.,* **1990**, *33*, 394. (d) Buchanan, G. L., *Chem. Soc. Rev.,* **1988**, *17*, 91. (e) Kolb, M.; Barth, J. and Neises, B., *Tetrahedron Lett.*, **1986**, *27*, 1579. (f) Kolb, M. and Neises, B., *Tetrahedron Lett.,*

1986, *27*, 4437. (g) Krasovskii, A. N.; Grin, N. P.; Sheinkman, A. K.; Klyuev, N. A. and Belikov, A. B., *Chem. Heterocycl. Comp.,* **1978**, *14*, 388. (h) Allinger, N. L.; Wang, G. L. and Dewhurst, B. B., *J. Org. Chem.,* **1974**, *39*, 1730. (i) Höfle, G.; Prox, A. and Steglich, W., *Ber.,* **1972**, *105*, 1718. (j) Steglich, W. and Hoefle, G., *Ber.,* **1971**, *104*, 3644. (k) Knorr, R. and Huisgen, R., *Ber.,* **1970**, *103*, 2598. (l) Dyer, E. and Minnier, C. E., *J. Org. Chem.,* **1968**, *33*, 880. (m) Singh, G. and Singh, S., *Tetrahedron Lett.,* **1964**, 3789. (n) King, J. A. and McMillan, F. H. *J. Am. Chem. Soc.* **1955**, *77*, 2814. (o) Attenburrow, J.; Elliott, D. F. and Penny, G. F., *J. Chem. Soc*., **1948**, 310. (p) Wiley, R. H. and Borum, O. H., *J. Am. Chem. Soc.,* **1948**, *70*, 2005. (q) Wiley, R. H., *J. Org. Chem.,* **1947**, *12*, 43.

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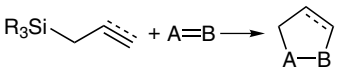
Danheiser Annulation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Danheiser and co-workers in 1981.[1] It is the synthesis of five-membered carbocycles[1,2] and heterocycles (including dihydrofurans,[3] pyrrolines,[3] isoxazoles,[4] azulenes,[5] and furans[6]) from organosilanes and electron-deficient compounds via a [3+2] annulation,[7] by which organosilanes serve as three-carbon components (such as allenylsilanes,[1] propargylsilanes,[7b] and allylsilanes)[7] and electron-deficient compounds (such as α,β-unsaturated compounds[7]). Thus this reaction is referred to as the Danheiser annulation.[8] It should be pointed out that this reaction can be promoted by strong Lewis acids such as $TiCl_4$.[9] In addition, when allylsilane and propargylsilanes are used as a three-carbon component source, a large trialkylsilyl group will facilitate this annulation and suppress the normal desilylation, leading to the formation of allenes.[7b] Moreover, allylstannanes are also found to undergo this reaction.[10]

B. GENERAL REACTION SCHEME



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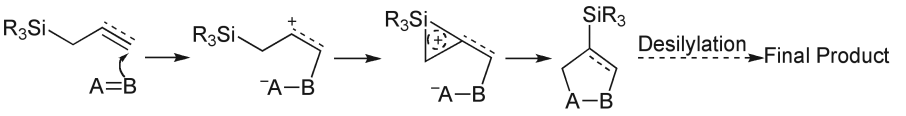
C. PROPOSED MECHANISMS

A tentative mechanism is proposed below.



D. MODIFICATION

N/A

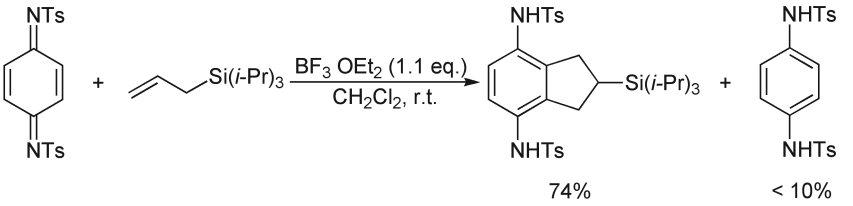
E. APPLICATIONS

This reaction has general application in the synthesis of five-membered carbocycles and heterocycles.

F. RELATED REACTIONS

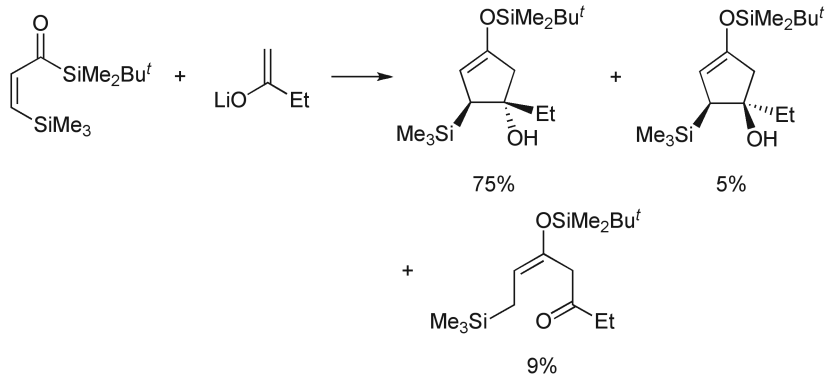
This reaction is related to *1,3-Dipolar Cycloaddition*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 7a.

To a cold solution (at 0°C) of 8 mL dichloromethane containing 96 mg allyltriisopropylsilane (0.48 mmol) and 83 mg quinoneimide (0.20 mmol) was added 1.1 eq. $BF_3{\cdot}OEt_2$. The reaction was allowed to attain room temperature gradually and was stirred at that temperature for 72 h and then quenched by ice cold water. The mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layer was washed with water, brine, and water (10 mL each) and dried over anhydrous Na_2SO_4. Upon removal of solvent, the residue was purified by column chromatography to give 74% of product, m.p., 238–239°C.



Reference 11.

To a cooled (–80°C) solution of LDA, prepared from 199 μL diisopropylamine (1.42 mmol) and 971 μL 1.44 M *n*-BuLi in hexane (1.40 mmol) in 1.4 mL THF was added dropwise a solution of 125 μL 2-butanone (1.4 mmol) in 1.4 mL THF. After being stirred at –80°C for 15 min, the solution was added dropwise via a cannula to 58 mL cooled (–80°C) THF solution containing 300 mg cis-α,β-unsaturated ketone (1.24 mmol). The reaction mixture was allowed to warm to 0°C over 30 min, and quenched by 81 μL AcOH (1.42 mmol) in 0.5 mL THF. The mixture was diluted with 30 mL saturated aqueous NH_4Cl and extracted with Et_2O (30 mL × 3). The combined organic phases were washed with 50 mL saturated brine, dried, and concentrated. The residual oil was subjected to column chromatography (silica gel, 40 g; elution with 12:1 hexane/Et_2O) to give 294 mg annulation product, in a yield of 75%, plus 109 mg of two other products as mixture that could be separated by MPLC (10 mM silica gel, elution with 40:1 haxane/Et_2O).

Other references related to the Danheiser annulation are cited in the literature.[12]

H. REFERENCES

1. Danheiser, R. L.; Carini, D. J. and Basak, A., *J. Am. Chem. Soc.,* **1981**, *103*, 1604.
2. (a) Danheiser, R. L.; Fink, D. M. and Tsai, Y.-M., *Org. Synth. Coll. Vol. VIII,* **1993**, 347. (b) Danheiser, R. L. and Fink, D. M., *Tetrahedron Lett.,* **1985**, *26*, 2513. (c) Danheiser, R. L.; Carini, D. J.; Fink, D. M. and Basak, A., *Tetrahedron,* **1983**, *39*, 935.
3. Danheiser, R. L.; Kwasigroch, C. A. and Tsai, Y.-M., *J. Am. Chem. Soc.,* **1985**, *107*, 7233.
4. Danheiser, R. L. and Becker, D. A., *Heterocycles,* **1987**, *25*, 277.
5. Becker, D. A. and Danheiser, R. L., *J. Am. Chem. Soc.,* **1989**, *111*, 389.
6. Danheiser, R. L.; Stoner, E. J.; Koyama, H.; Yamashita, D. S. and Klade, C. A., *J. Am. Chem. Soc.,* **1989**, *111*, 4407.
7. (a) Nair, V.; Rajesh, C.; Dhanya, R. and Rath, N. P., *Org. Lett.,* **2002**, *4*, 953. (b) Danheiser, R. L.; Dixon, B. R. and Gleason, R. W., *J. Org. Chem.,* **1992**, *57*, 6094.
8. (a) Smith, A. B.; Adams, C. M.; Kozmin, S. A. and Paone, D. V., *J. Am. Chem. Soc.,* **2001**, *123*, 5925. (b) Smith, A. B.; Kozmin, S. A.; Adams, C. M. and Paone, D. V., *J. Am. Chem. Soc.,* **2000**, *122*, 4984.
9. Panek, J. S. and Jain, N. F., *J. Org. Chem.,* **1993**, *58*, 2345.

10. Herndon, J. W.; Wu, C.; Harp, J. J. and Kreutzer, K. A., *Synlett,* **1991**, 1.

11. Takeda, K.; Yamawaki, K. and Hatakeyama, N., *J. Org. Chem.*, **2002**, *67*, 1786.

12. (a) Peng, Z.-H. and Woerpel, K. A., *Org. Lett.,* **2001**, *3*, 675. (b) Peng, Z.-H. and Woerpel, K. A., *Org. Lett.,* **2000**, *2*, 1379. (c) Organ, M. G.; Dragan, V.; Miller, M.; Froese, R. D. and Goddard, J. D., *J. Org. Chem.*, **2000**, *65*, 3666. (d) Roberson, C. W. and Woerpel, K. A., *J. Org. Chem.*, **1999**, *64*, 1434. (e) Masuya, K.; Domon, K.; Tanino, K. and Kuwajima, I., *J. Am. Chem. Soc.*, **1998**, *120*, 1724. (f) Brengel, G. P. and Meyers, A. I., *J. Org. Chem.*, **1996**, *61*, 3230. (g) Panek, J. S. and Beresis, R. T., *J. Am. Chem. Soc.,* **1993**, *115*, 7898. (h) Takeda, K.; Fujisawa, M.; Makino, T.; Yoshii, E. and Yamaguchi, K., *J. Am. Chem. Soc.,* **1993**, *115*, 9351. (i) Danheiser, R. L.; Takahashi, T.; Bertók, B. and Dixon, B. R., *Tetrahedron Lett.*, **1993**, *34*, 3845. (j) Panek, J. S., "Silicon Stabilization" in *Comprenhensive Organic Synthesis*, ed. Trost, B. M. and Fleming, I., Pergamon Press, Oxford, **1991**, *1*, pp. 579–627. (k) Curran, D. P.; Chen, M.-H.; Spletzer, E.; Seong, C. M. and Chang, C.-T., *J. Am. Chem. Soc.,* **1989**, *111*, 8872. (l) Danheiser, R. L.; Gee, S. K. and Sard, H., *J. Am. Chem. Soc.,* **1982**, *104*, 7670.

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Darzens Condensation

A. GENERAL DESCRIPTION OF THE REACTION

Although this reaction was initially reported by Erlenmeyer in 1892,[1] it is often known as the Darzens condensation,[2] Darzens glycidic ester condensation[2ee,2ww,3] or Darzens reaction,[3c,3d,4] after Darzens's work in the 1900s.[5] Other names used for this condensation include Darzens-type condensation,[4f] Darzens synthesis,[6] and Darzens glycidic ester synthesis.[2yy,7] This reaction is the synthesis of glycidic esters from the condensation between aldehydes or ketones and esters of α-halo-carboxylic acids. Currently, besides the α-halogenated carboxylic esters, this type of condensation has been extended to α-halogenated nitriles,[8] sulfoxides,[9] sulfones,[10] sulfoximines,[11] carboxylic amides,[4f] etc. Therefore, a rather general definition of the Darzens condensation is accepted,[2aaa] including all the base-catalyzed condensations between carbonyl compounds and molecules carrying activated protons at the α-halogenated position, which results in the formation of an oxirane ring and the release of a halide ion. A special case is the reaction between carbonyl compounds and α-halogenated ketimine, which is also referred to as the *aza*-Darzens reaction.[4f] Normally, this reaction would be carried out in an anhydrous aprotic nonpolar solvent (e.g. benzene, ethyl ether) at low temperature,[3c] although ethanol and even aqueous dioxane have also been used as a solvent.[2aaa] Specifically, this reaction has been modified to occur in the solid-liquid two-phase system using a solid base and catalyst at temperatures higher than 100°C.[3c] The catalysts often used are crown ethers and quaternary salt, and their catalytic efficiences are found in the following order: 18-C-6 > DC-18-C-6 > DB-18-C-6 > $Bu_4P^+Br^-$ > $PhCH_2N^+Et_3Br^-$.[3c] This reaction has been proven to undergo a

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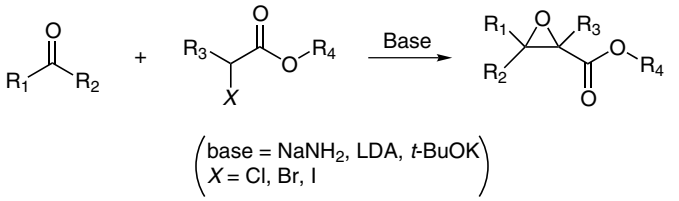
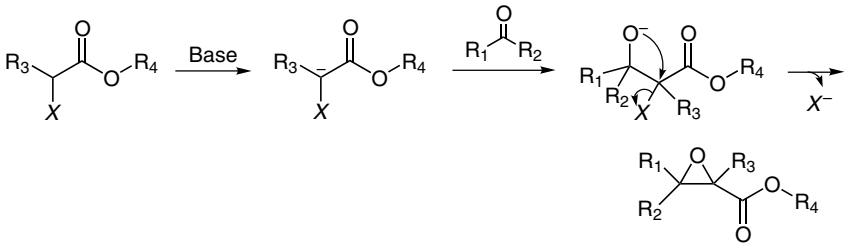
carbanion mechanism, instead of a carbenoid[3f] or divalent radical mechanism,[2zz] and normally produces more stable erythro diastereomers.[12]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified to occur in solid-liquid two-phase systems in the presence of crown-ether or quaternary salt as the catalyst.[3c]

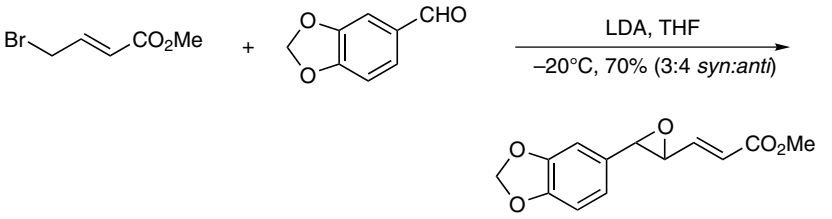
E. APPLICATIONS

This reaction has general applications in the synthesis of epoxide (or oxirane) and glycidic esters.

F. RELATED REACTIONS

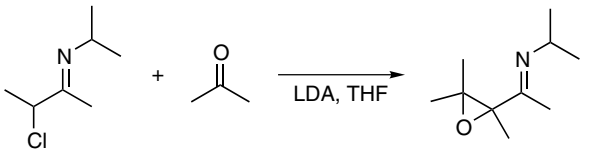
This reaction is related to the *Aldol Condensation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 21.

An LDA (34 mmol) solution [generated by the addition of 23.4 mL of 1.6 M *n*-BuLi (37.4 mmol) to a solution of 4.75 mL diisopropylamine (34 mmol) in 40 mL THF at −20°C under nitrogen] was added dropwise to a stirred solution of 10.2 g piperonal (68 mmol) and 2 mL methyl 4-bromocrotonate (17 mmol) in 60 mL THF under nitrogen at −20°C. Typically, the transfer lasts 1 h for 20 mmol crotonate. The reaction was stirred for 2 h at −20°C and then quenched with 40 mL saturated aqueous NH_4Cl. The layers were separated, and the aqueous layer was extracted with ether (3 × 20 mL). The combined, organic layers were then washed with saturated aqueous $NaHSO_3$ (from 40 g $NaHSO_3$ solid), 20 mL saturated aqueous $NaHCO_3$, and brine (3 × 30 mL). They were then dried over $MgSO_4$ and concentrated. Purification by flash chromatography (ether/petroleum ether, 1 : 3) afforded 2.95 g methyl 4,5-epoxy-5-[3′,4′-methylenedioxypehnyl]pent-2-enoate as 43:57 of *syn* to *anti* mixture, in a yield of 70%.



Reference 4f.

To a solution of lithium diisopropylamide (LDA, 0.105–0.150 mol) at 0°C in 150 mL THF (prepared from 0.105–0.150 mol *n*-BuLi and 0.2 mol diisopropylamine) was added a solution of 0.1 mol α-chloro ketimine in 20 mL THF. The deprotonation was complete after 2 h at 0°C, then 0.1–0.2 mol acetone was added dropwise to the solution of 3-chloro-1-aza-allylic anion. After the addition, the reaction mixture was stirred for 10 h at room temperature. The reaction mixture was then poured into water and extracted with ether (3×100 mL). The combined extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The product was purified via vacuum distillation between 50°C and 60°C at 13 mmHg.

Other references related to the Darzens condensation are cited in the literature.[13]

H. REFERENCES

1. (a) Erlenmeyer E., *Ann.*, **1892**, *271*, 137. (b) Erlenmeyer, E., *Ber.*, **1900**, *33*, 3001.
2. (a) Achard, T. J. R.; Belokon, Y. N.; Ilyin, M.; Moskalenko, M.; North, M. and Pizzato, F., *Tetrahedron Lett*., **2007**, *48*, 2965. (b) Achard, T. J. R.; Belokon, Y. N.; Hunt, J.; North, M. and Pizzato, F., *Tetrahedron Lett*., **2007**, *48*, 2961. (c) Li, L.; Ren, Z.-J.; Cao, W.-G.; Huang, P.-G. and Zhu, H., *Youji Huaxue*, **2007**, *27*, 120. (d) Mamedov, V. A.; Berdnikov, E. A.; Tsuboi, S.; Hamamoto, H.; Komiyama, T.; Gorbunova, E. A.; Gubaidullin, A. T. and Litvinov, I. A., *Russ. Chem. Bull.,* **2006**, *55*, 1455. (e) Wang, Z.-T.; Xu, L.-W.; Xia, C.-G. and Wang, H.-Q., *Helv. Chim. Acta,* **2004**, *87*, 1958. (f) Wang, Z. T.; Xu, L. W.; Mu, Z. G.; Xia, C. G. and Wang, H. Q., *J. Mol. Catal. A: Chem.,* **2004**, *218*, 157. (g) Crouch, R. D.; Holden, M. S. and Romany, C. A., *J. Chem. Edu.,* **2004**, *81*, 711. (h) Ghosh, A. K. and Kim, J.-H., *Org. Lett.,* **2004**, *6*, 2725. (i) Shi, D.-Q.; Zhang, S.; Zhuang, Q.-Y.; Wang, X.-S.; Tu, S.-J. and Hu, H.-W., *Chinese J. Chem.,* **2003**, *21*, 680. (j) Mamaghani, M.; Tabatabaeian, K.; Ghanadzadeh, A. and Habibi, F., *Tetrahedron Lett*., **2003**, *44*, 4775. (k) Rekhter, M. A., *Russ. J. Org. Chem.,* **2002**, *38*, 141. (l) Aldous, D. J.; Dalençon,A. J. and Steel, P. G., *Org. Lett.,* **2002**, *4*, 1159. (m) Shinohara, Y.; Ohba, Y.; Takagi, R.; Kojima, S. and Ohkata, K., *Heterocycles*, **2001**,

55, 9. (n) Huang, G. B.; Cao, G. F.; Wu, K. M. and Huang, L., *Chinese Chem. Lett.,* **1999**, *10*, 441. (o) Arai, S. and Shioiri, T., *Tetrahedron Lett*., **1998**, *39*, 2145. (p) Mamedov, V. A.; Gazizova, L. Kh.; Nurkhametova, I. Z.; Gubaidullin, A. T.; Litvinov, I. A.; Tsuboi, S. and Levin, Y. A., *Chem. Lett.,* **1998**, 243. (q) Takagi, R.; Kimura, J.; Shinohara, Y.; Ohba, Y.; Takezono, K.; Hiraga, Y.; Kojima, S. and Ohkata, K., *J. Chem. Soc., Perkin Trans. I,* **1998**, 689. (r) Bako, P.; Szollosy, A.; Bombicz, P. and Toke, L., *Synlett,* **1997**, 291. (s) Ohkata, K.; Kimura, J.; Shinohara, Y.; Takagi, R. and Hiraga, Y., *Chem. Commun.,* **1996**, 2411. (t) You, J. M.; Ding, Y. J.; Zhou, L. J. and Sun, X. J., *Huaxue Shijie*, **1995**, *36*, 318. (u) Berdnikov, E. A. and Mamedov, V. A., *Izv. Akad. Nauk, Ser. Khim.,* **1995**, 1544. (v) Bandsal, R. K. and Sharma, V. K., *Indian J. Chem., Sect. B,* **1992**, 31*B*, 521. (w) Mamedov, V. A.; Polushina, V. L.; Mertsalova, F. F. and Nuretdinov, I. A., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1992**, 204. (x) Baldoli, C.; Del Buttero, P. and Maiorana, S., *Tetrahedron*, **1990**, *46*, 7823. (y) Wassef, W. N. and El-Barky, M. M., *J. Chem. Res. (S),* **1990**, 402. (z) Andre-Barres, C.; Langlois, Y. and Gomez-Pacios, M., *Tetrahedron: Asymmetry,* **1990**, *1*, 571. (aa) Kitazume, T. and Ikeya, T., *Chem. Express,* **1989**, *4*, 81. (bb) Kou, F. Q.; Yang, G. H. and Li, Y. J., *Yiyao Gongye,* **1986**, *17*, 83. (cc) Annunziata, R.; Banfi, S. and Colonna, S., *Tetrahedron Lett*., **1985**, *26*, 2471. (dd) Makosza, M.; Golinski, J.; Baran, J. and Dziewonska-Baran, D., *Chem. Lett.,* **1984**, 1619. (ee) Bauman, J. G.; Hawley, R. C. and Rapoport, H., *J. Org. Chem.,* **1984**, *49*, 3791. (ff) Akabori, S.; Ohtomi, M. and Yatabe, S., *Bull. Chem. Soc. Jpn.,* **1980**, *53*, 1463. (gg) Jonczyk, A.; Kwast, A. and Makosza, M., *J. Chem. Soc., Chem. Commun.,* **1977**, 902. (hh) Wartski, L., *J. Chem. Soc., Chem. Commun.,* **1977**, 602. (ii) Sipos, G.; Schobel, G. and Sirokman, F., *J. Chem. Soc., Perkin Trans. II,* **1975**, 805. (jj) Cacchi, S. and Paolucci, G., *Chim. Ind. (Milan),* **1974**, *56*, 198. (kk) Elkik, E. and Francesch, C., *Bull. Soc. Chim. Fr.,* **1973**, 1277. (ll) Elkik, E. and Francesch, C., *Bull. Soc. Chim. Fr.,* **1973**, 1281. (mm) Woolsey, N. F. and Khalil, M. H., *J. Org. Chem.,* **1973**, *38*, 4216. (nn) Sipos, G.; Schobel, G. and Balaspiri, L., *Acta Chim. Acad. Sci. Hungaricae,* **1971**, *68*, 149. (oo) Vogt, P. F. and Tavares, D. F., *Can. J. Chem.,* **1969**, *47*, 2875. (pp) Shaikh, A. A. and Thaker, K. A., *J. Indian Chem. Soc.,* **1968**, *45*, 185. (qq) Sipos, G. and Sirokman, F., *Nature,* **1964**, *202*, 898. (rr) McDonald, R. N. and Schwab, P. A., *J. Org. Chem.,* **1964**, *31*, 2459. (ss) Sipos, G.; Czukor, B. and Dobo, I., *Acta Phys. Chem.,* **1963**, *9*, 48. (tt)Tung, C. C.; Speziale, A. J. and Frazier, H. W., *J. Org. Chem.,* **1963**, *28*, 1514. (uu) Sipos, I. G. and Szabo, M. R., *Acta Phys. Chem.,* **1962**, *8*, 84. (vv) Barnes, R. A.; Manganelli, M. A. and Damle, S. S., *Chem. Ind. (London),* **1962**, 511. (ww) Reeve, W. and Compere, E. L., *J. Am. Chem. Soc.,* **1961**, *83*, 2755. (xx) Speziale, A. J. and Frazier, H. W., *J. Org. Chem.,* **1961**, *26*, 3176. (yy) Clement, R. A. and Shieh, T.-C., *J. Org. Chem.,* **1960**, *25*, 1850. (zz) Ballester, M. and Pérez-Blanco, D., *J. Org. Chem.,* **1958**, *23*, 652. (aaa) Ballester, M., *Chem. Rev.,* **1955**, *55*, 283. (bbb) Ballester, M. and Bartlett, P. D., *J. Am. Chem. Soc.,* **1953**, *75*, 2042.

3. (a) Devarajan, R.; Arunachalam, V.; Kumaraswamy, M. D. K.; Tajuddin, I. and Joghee, T., *J. Appl. Poly. Sci.,* **1992**, *44*, 1473. (b) Abdel-Magid, A.; Pridgen, L. N.; Eggleston, D. S. and Lantos, I., *J. Am. Chem. Soc.,* **1986**, *108*, 4595. (c) Kimura, C.; Kashiwaya, K.; Mural, K. and Katada, H., *Ind. Eng. Chem. Prod. Res. Dev.,* **1983**, *22*, 118. (d) Johnson, C. R. and Bade, T. R., *J. Org. Chem.,* **1982**, *47*, 1205. (e) Kavadias, G. and Velkof, S., *Can. J. Chem.,* **1978**, *56*, 730. (f) Bachelor, F. W. and Bansal, R. K., *J. Org. Chem.,* **1969**, *34*, 3600. (g) Munch-Petersen, J., *Acta Chem. Scand.,* **1953**, *7*, 1041.
4. (a) Sharifi, A.; Salimi, R.; Mirzaei, M. and Abaee, M. S., *Synth. Commun.,* **2007**, *37*, 1825. (b) Wedler, C.; Kunath, A. and Schick, H., *Angew. Chem. Int. Ed. Engl.,* **1995**, *34*, 2028. (c) Mamedov, V. A. and Nuretdinov, I. A., *Izv. Akad. Nauk, Ser. Khim.,* **1992**, 2159. (d) Mamedov, V. A.; Malaev, V. G.; Sibgatullina, F. G.; Nuretdinov, I. A. and Kitaev, Yu. P., *Izv. Akad. Nauk, Ser. Khim.,* **1992**, 438. (e) Svoboda, J.; Nic, M. and Palecek, J., *Coll. Czech. Chem. Commun.,* **1992**, *57*, 119. (f) Sulmon, P.; de Kimpe, N.; Schamp, N.; Declercq, J.-P. and Tinant, B., *J. Org. Chem.,* **1988**, *53*, 4457. (g) Awad, W. I.; Awad, B. M.; Guirguis, N. R.

and Wassef, W. N., *Egypt. J. Chem.,* **1980**, *23*, 293. (h) Koppel, G. A., *Tetrahedron Lett*., **1972**, 1507. (i) Dormidonov, I. A.; Martynov, V. F. and Timofeev, V. E., *Zh. Obsh. Khim.,* **1972**, *42*, 479. (j) White, J. D.; Bremner, J. B.; Dimsdale, M. J. and Garcea, R. L., *J. Am. Chem. Soc.,* **1971**, *93*, 281. (k) Karaulov, E. S.; Chuguev, Yu. P. and Tilichenko, M. N., *Zh. Org. Khim.,* **1969**, *5*, 1512. (l) Zimmerman, H. E. and Ahramjian, L., *J. Am. Chem. Soc.,* **1959**, *81*, 2086. (m) Berson, J. A., *J. Am. Chem. Soc.,* **1952**, *74*, 5175.

5. (a) Darzens, G., *Compt. Rend.,* **1904**, *139*, 1214. (b) Darzens, G., *Compt. Rend.,* **1906**, *141*, 766.
6. Ogata, Y.; Kawasaki, A. and Hirata, H., *J. Org. Chem.,* **1970**, *35*, 2203.
7. Dahn, H. and Loewe, I., *Chimia*, **1957**, *11*, 98.
8. (a) Althoff, W. and Tinapp, P., *Arch. Pharm.,* **1982**, *315*, 284. (b) Coutrot, P., *Bull. Soc. Chim. Fr.,* **1974**, 1965.
9. (a) Satoh, T.; Itoh, M.; Ohara, T. and Yamakawa, K., *Bull. Chem. Soc. Jpn.,* **1987**, *60*, 1839. (b) Satoh, T.; Kaneko, Y.; Sakata, K. and Yamakawa, K., *Bull. Chem. Soc. Jpn.,* **1986**, *59*, 457. (c) Satoh, T.; Kumagawa, T. and Yamakawa, K., *Bull. Chem. Soc. Jpn.,* **1985**, *58*, 2849. (d) Reutrakul, V. and Kanghae, W., *Tetrahedron Lett.,* **1977**, 1377. (e) Durst, T. and Tin, K.-C., *Tetrahedron Lett.,* **1970**, 2369. (f) Taverses, D. F.; Estep, R. E. and Blezard, M., *Tetrahedron Lett.,* **1970**, 2373.
10. Adamczyk, M.; Dolence, E. K.; Watt, D. S.; Christi, M. R.; Reibenspies, J. H. and Anderson, O. P., *J. Org. Chem.,* **1984**, *49*, 1878.
11. Corkins, H. G.; Veenstra, L. and Johnson, C. R., *J. Org. Chem.,* **1978**, *43*, 4233.
12. (a) Kwart, H. and Kirt, L., *J. Org. Chem*., **1957**, *22*, 116. (b) Cromwell, N. H. and Setterquist, R. A., *J. Am. Chem. Soc*., **1954**, *76*, 5752.
13. (a) Tanaka, K. and Shiraishi, R., *Green Chem.,* **2001**, *3*, 135. (b) Martin, S. F., *Synthesis,* **1979**, 633. (c) Dagli, D. J.; Yu, P.-S. and Wemple, J., *J. Org. Chem.,* **1975**, *40*, 3173. (d) Akira, T.; Sadao, T. and Toru, H., *Bull. Chem. Soc. Jpn.*, **1973**, *46*, 1844. (e) Deschamps B. and Seyden-Penne, J., *Tetrahedron*, **1971**, *27*, 3959. (f) Sipos G., Schoebel G. and Balaspizi L., *J. Chem. Soc. Ser. C*, **1970**, 1154. (g) Sisido, K.; Nakanisi, O. and Nozaki, H., *J. Org. Chem.,* **1961**, *26*, 4878. (h) Field, L. and Carlile, C. G., *J. Org. Chem.,* **1961**, *26*, 3170. (i) Zimmerman, H. E. and Ahramjian, L., *J. Am. Chem. Soc.,* **1960**, *82*, 5459. (j) Johnson, W. S.; Belew, J. S.; Chinn, L. J. and Hunt, R. H., *J. Am. Chem. Soc.,* **1953**, *75*, 4995. (k) Newman, M. S. and Magerlein, B. J., *Org. React.,* **1949**, *5*, 413. (l) Yarnall, W. A. and Wallis, E. S., *J. Am. Chem. Soc.,* **1937**, *59*, 951. (m) Claisen L., *Ber.*, **1905**, *38*, 693.

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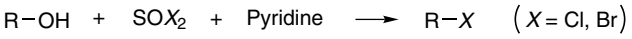
Darzens Halogenation

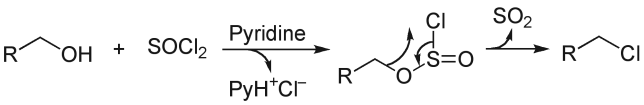
A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Darzens in 1911.[1] It is the synthesis of alkyl halide from alcohols via the treatment of thionyl chloride or bromide in the presence of small amounts of tertiary amines such as pyridine. This is a general method with good yields for the preparation of alkyl halides,[2] without the disadvantage of using halogen derivatives of phosphorus that might cause the isomerization, polymerization,[1] and the *Walden Inversion* of certain optically active alcohols.[3] It is reported that when alcohols are treated with equivalent amounts of thionyl chloride in the presence of pyridine, it results in no chlorination[4] or yields the alkyl sulfite instead of the alkyl halide.[5] However, in a large excess of thionyl halide and a small amount of pyridine, alkyl halides will form upon reflux.[2] In a special case, alkyl halide can form in high yield even without a base in presence.[2]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



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D. MODIFICATION

N/A

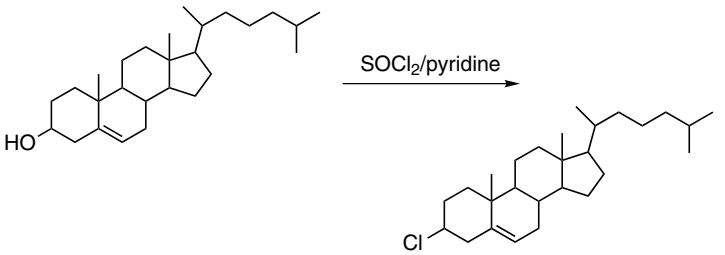
E. APPLICATIONS

This reaction has general application in the conversion of alcohols into alkyl halides.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 2.

To a mixture of 5 g cholesterol and 1 mL pyridine was added 10 mL thionyl chloride rapidly. The reaction mixture was kept cool with running water and was refluxed for 1 h. Sulfur dioxide was liberated. The mixture was cooled, poured into water, and then extracted with ether. The ethereal solution was dried over anhydrous sodium carbonate. When the solvent was removed under reduced pressure a semicrystalline product remained. This was recrystallized from alcohol and identified as cholesteryl chloride; m.p. 95–96°C. The reaction was repeated without the addition of pyridine with identical results. The yield was almost quantitative.

Other references related to the Darzens halogenation are cited in the literature.[6]

H. REFERENCES

1. Darzens, G., *Compt. Rend.*, **1911**, *152*, 1314.
2. Daughenbaugh, P. J. and Allison, J. B., *J. Am. Chem. Soc.,* **1929**, *51*, 3665.
3. McKenzie, A. and Clough, G. W., *J. Chem. Soc.,* **1913**, *103*, 687.
4. Whitmore, F. C. and Rothrock, H. S., *J. Am. Chem. Soc.,* **1932**, *54*, 3431.
5. (a) Ruzicka, L. and Liebl, Fr., *Helv. Chim. Acta,* **1923**, *6*, 278. (b) Richter, M. M., *Ber.,* **1916**, *49*, 2339.
6. (a) Gerrard, W. and Hudson, H. R., *J. Chem. Soc.,* **1963**, 1059. (b) Newman, M. S. and Wotiz, J. H., *J. Am. Chem. Soc.,* **1949**, *71*, 1292.

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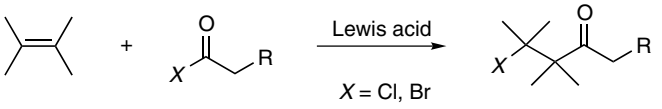
Darzens Olefin Acylation
(Kondakov Acylation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Kondakov in 1892.[1] It is the preparation of β-haloketones via the direct condensation of acyl halides or acyl anhydride[2] and olefins in the presence of Lewis acid. Therefore, it is generally known as the Kondakov acylation[3] or Kondakov reaction.[4] However, this reaction is also known as the Darzens acylation of olefin[5] or the Darzens reaction[5] after Darzens's work in 1910.[6] The Lewis acid catalysts suitable for this condensation include $SnCl_4$, $AlCl_3$, $TiCl_4$, and BF_3. However, a subtle difference does exist between the Kondakov acylation and the original Darzens reaction condition in which acyl halides react with alicyclic olefins in the presence of $AlCl_3$ for the latter case. Different from the *Fridel-Crafts Acylation* in which the carbocation from acyl addition can be stabilized and the recurring of aromaticity leads to a high yield of acylation products, the Darzens olefin acylation, often fails due to the formation of various unstable intermediates from electrophilic addition, elimination, and isomerization.[7] In particular, the acylation of olefins from chloroformates fail almost exclusively,[7] except one example in which unexpected regiochemistry was obtained.[8] It is reported that in the presence of a base with low nucleophilicity, both α,β-unsaturated and β,γ-unsaturated ketones might form.[7]

B. GENERAL REACTION SCHEME



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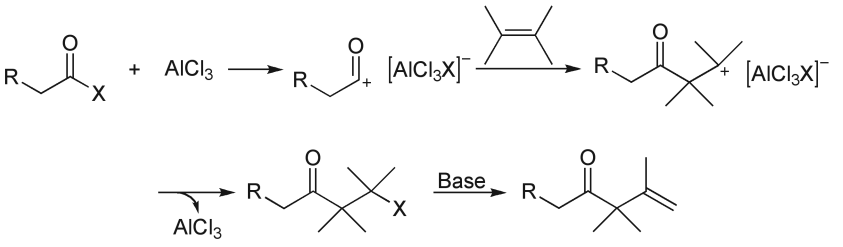
C. PROPOSED MECHANISMS



D. MODIFICATION

The addition of non-nucleophilic base will result in the formation of α,β- or β,γ-unsaturated ketones.

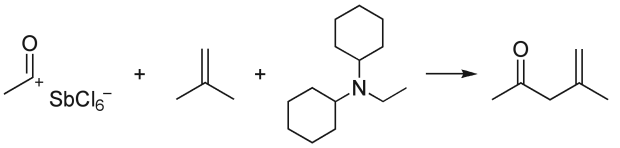
E. APPLICATIONS

This reaction has applications in the preparation of β-halo ketones and α,β- or β,γ-unsaturated ketones.

F. RELATED REACTIONS

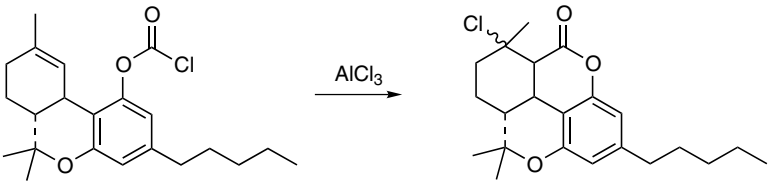
This reaction is related to the *Fridel-Crafts Acylation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

Equimolar amounts of isobutene (5 mmol) and dicyclohexylethylamine (5 mmol), each dissolved in 5 mL CH_2C1_2, were mixed and quickly added to the partially dissolved acetyl hexachloroantimonate ($CH_3CO^+SbCl_6^-$) in 20 mL CH_2Cl_2 under vigorous stirring at –50°C. The temperature was kept at –50°C for 1 h. After the reaction was completed, the dark brown reaction mixture was immediately poured into 200 mL *n*-pentane containing 3 mL water to decompose any remaining acetyl hexachloroantimonate and shaken for 1 min, and the precipitate was removed by filtration. The precipitate was washed twice with *n*-pentane, and the combined organic layers were washed with water, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oily product. The acetylated products were purified by preparative GLC in a yield of 90%.



Reference 5.

A solution of 16.5 Δ^9-tetrahydrocannabinol (Δ^9-THC) chloroformate (43.9 mmol) in 72 mL CH_2Cl_2 was added in one portion to a stirring suspension of 17.5 g $AlCl_3$ (132 mmol) in 231 mL dry CH_2Cl_2 under nitrogen. The reaction mixture turned dark red, and nearly all the $AlCl_3$ appeared to dissolve. After 40 min the reaction was quenched by the rapid addition of 36.4 g K_2CO_3 (264 mmol) in 35 mL H_2O with vigorous stirring. After the boiling subsided, the granular precipitate was filtered through a coarse fritted filter. The amount of H_2O employed in the quenching process was limited to avoid the formation of a difficult to filter pasty solid. The resin obtained after removing the solvent in vacuo was eluted from 600 g silica gel with 40% CH_2C1_2/hexane to yield 8.47 g 6-chloro-5a,7,8,8a,9,10c-hexahydro-6,9,9-trimethyl-2-pentyl-5H,6H-[2]benzopyrano[5,4,3-cde][1]benzopyran-5-one, in a yield of 51%.

Other references related to the Darzens olefin acylation are cited in the literature.[9]

H. REFERENCES

1. (a) Kondakov, I. L., *Zh. Russ. Fiz-Khim. O-va.,* **1892**, *24*, 309. (b) Kondakov, I. L., *Bull. Soc. Chim. Fr.,* **1892**, *7*, 576. (c) Kondakov, I. L., *J. Prakt. Chem.*, **1893**, *48*, 467.
2. Groves, J. K., *Chem. Soc. Rev.,* **1972**, *1*, 73.
3. Dalavoy, V. S.; Deodhar, V. B. and Nayak, U. R., *Indian J. Chem., Sect. B,* **1982**, *21B*, 907.
4. (a) Verghese, J., *Indian Perfumer,* **1984**, *28*, 156. (b) Belov, V. N. and Rudol'fi, T. A., *Sbornik Statei Obshchei Khim., Akad. Nauk S.S.S.R.*, **1953**, *1*, 266.
5. Seltzman, H. H.; Hsieh, Y.-A.; Pitt, C. G. and Reggio, P. H., *J. Org. Chem.,* **1991**, *56*, 1549.
6. Darzens, G., *Compt. Rend.,* **1910**, *150*, 707.
7. Hoffmann, H. M. R. and Tsushima, T., *J. Am. Chem. Soc.,* **1977**, *99*, 6008.
8. (a) Nenitzescu, C. D. and Balaban, A. T., "*Dehydrogenating Condensations of Aromatics (Scholl and Related Reactions)*" in *Friedel Crafts and Related Reactions,* ed. Olah, G. A., Wiley-Interscience, New York, **1964**, *2*, pp. 979–1047. (b) Izard, E. F., *U.S. Pat*., **1935**, Nov. 2, 2,020,685 [*Chem. Abstr*. **1936**, *30*, 485].
9. (a) Ibragimov, I. I.; Mamedov, E. I.; Aliev, A. G.; Mekhtieva, T. S.; Mekhtieva, Sh. Z.; Guseinov, S. A. and Abdullaeva, T. I., *Zh. Org. Khim.,* **1990**, *26*, 1654. (b) Klein, E. and Rojahn, W., *Tetrahedron Lett.*, **1971**, *39*, 3607. (c) Hanuise, J. and Smolders, R. R., *Bull. Soc. Chim. Fr.*, **1967**, 2139.

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Darzens-Nenitzescu Reaction

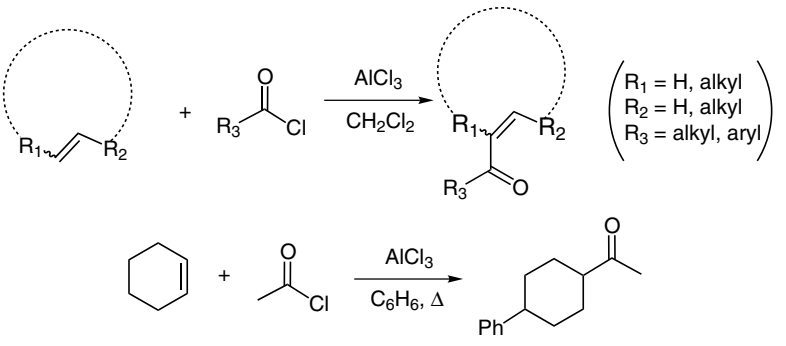
(Nenitzescu Acylation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Nenitzescu in 1931.[1] It is the formation of an α,β-unsaturated ketone directly by aluminum chloride–promoted acylation of alkenes with acyl halides. Therefore, it is known as the Darzens-Nenitzescu reaction (or Nenitzescu reductive acylation),[2] or Nenitzescu acylation.[3] Under such reaction conditions, Nenitzescu prepared 2-butenyl methyl ketone from acetyl chloride and 1-butene[4] and dimethylacetylcyclohexene from acetyl chloride and cyclooctene.[5] However, in the presence of benzene or hexane, the saturated ketones are often resolved, as supported by the preparation of 4-phenyl cyclohexyl methyl ketone from the reaction of cyclohexene and acetyl chloride in benzene,[6] and the synthesis of 3- or 4-methylcyclohexyl methyl ketone by refluxing the mixture of cycloheptene and acetyl chloride in cyclohexane or isopentane.[5b,7] This is probably caused by the intermolecular hydrogen transfer from the solvent.[8] In addition, owing to its intrinsic strain, cyclopropyl group reacts in a manner similar to an olefinic functionality so that it can be readily acylated.[9] It should be pointed out that under various reaction conditions, the Darzens-Nenitzescu reaction is often complicated by the formation of β-halo ketones, β,γ-enones, or β-acyloxy ketones.[8,10] This complication can be overcome by an aluminum chloride–promoted acylation with vinyl mercuric chloride, resulting in a high purity of stereochemistry.[11]

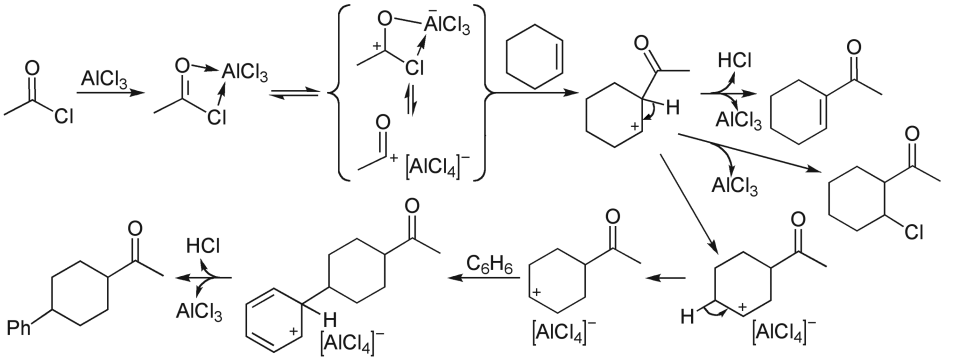
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Although the mechanism for the formation of acetylcyclohexane is known,[3] an alternative mechanism is proposed here for the acylation of cyclohexene with acetyl chloride. In this reaction, after the acyl cation adds to double bond, the elimination of the α-proton gives an α,β-unsaturated ketone, whereas the attack of chloride produces a β-chloroketone. Since acetyl is an electron-withdrawing group, it is plausible that the positive charge migrates to form a more stable carbocation, which electrophilically alkylates with benzene.



D. MODIFICATION

The formation of α,β-unsaturated ketones has been modified by the acylation of vinyl mercuric chloride.[11] In addition, this reaction has been extended to the acylation of alkynes[10] and a zinc chloride-promoted acylation of olefins.[12]

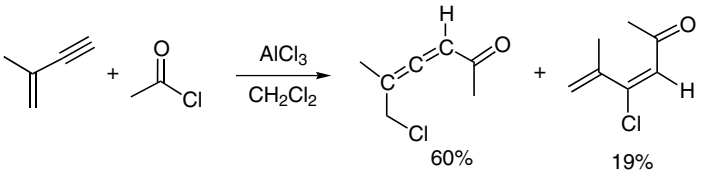
E. APPLICATIONS

This reaction has general application in the preparation of α,β-unsaturated ketones.

F. RELATED REACTIONS

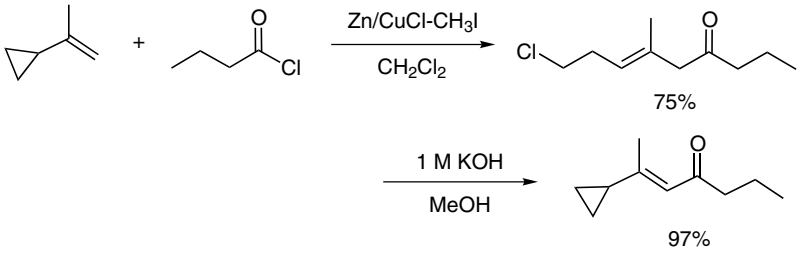
This reaction is related to the *Friedel-Crafts Acylation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 10.

A mixture of 3.33 g $AlCl_3$ (25 mmol), 1.96 mL acetyl chloride (27.5 mmol, 1.1 eq.), and 45 mL anhydrous CH_2Cl_2 was stirred until dissolution. The resulting solution was stirred for 3 min at 20 mmHg and cooled to –90°C; then 2.86 mL 2-methyl-1-buten-3-yne (30 mmol, 1.2 eq.) in 30 mL anhydrous CH_2Cl_2 was slowly added over 2 h. The solution was allowed to warm to –60°C, the mixture was stirred until the completion of reaction, as monitored by TLC, and then transferred to a vigorously stirring mixture of crushed ice and Et_2O. The organic layer was quickly stirred with a saturated solution of $NaHCO_3$ and dried using $MgSO_4$ and stored in a refrigerator. After filtration and concentration in vacuo at room temperature, the crude product was quickly flash chromatographed on silica gel, eluting with a gradient of pentane/ether to afford 60% 5-methyl-6-chloro-3,4-hexadien-2-one and 19% 5-methyl-4-chloro-3,5-hexadien-2-one, which were stored in refrigerator.



Reference 12.

A mixture of 6.54 g zinc dust (0.10 mol) and 0.99 g cuprous chloride (0.01 mol) in 30 mL CH_2Cl_2 was refluxed with stirring under nitrogen for 30 min. After the mixture was cooled to room temperature, 7.1 g iodomethane (0.05 mol) was added, and the mixture was then refluxed for an additional 1 h. Into the solution of the freshly prepared active zinc compounds was added 4.11 g 2-cyclopropyl-propene (0.05 mol) in 10 mL CH_2Cl_2 at 0–5°C under nitrogen with stirring. After a short period, 1.07 g butyryl chloride (0.010 mol) in 10 mL CH_2Cl_2 was added dropwise into the above stirred mixture in 15 min at 15–20°C with external cooling. An exothermic reaction took place, and the mixture gradually turned red-brown. The reaction mixture was stirred at room temperature for 2 h and then was refluxed for another 2 h. After that, 30 mL 10% H_2SO_4 was carefully added into the mixture under

cooling with an ice water bath. The reaction mixture was filtered with suction and extracted with ether (3×50 mL). The combined ethereal solution was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated to give a mixture of products, which was purified to give 75% 9-chloro-6-methyl-6-en-4-nanone. This product, upon treatment with 1 M KOH in methanol, gives 97% 1-cyclopropyl-2-en-hept-4-one.

Other references related to the Darzens-Nenitzescu reaction are cited in the literature.[13]

H. REFERENCES

1. Nenitzescu, C. D. and Ionescu, C. N., *Ann.,* **1931**, *491*, 189.
2. Otvos, L.; Tudos, H. and Szabolcs, A., *Acta Chim. Acad. Sci. Hungaricae,* **1972**, *71*, 193.
3. Patrick, J. B. and Saunders, E. K., *Tetrahedron Lett*., **1979**, 4009.
4. Nenitzescu, C. D. and Gavat, I. G., *Ann.,* **1935**, *519*, 260.
5. (a) Nenitzescu, C. D., in *Friedel-Crafts and Related Reactions*, ed. Olah, G. A., Interscience Publishers, New York, **1964**, *III*, p. 1125. (b) Nenitzescu, C. D., Pogany, I. and Mihai, G., *Acad. Rep. Populare Romine, Studii Cercetari Chim.,* **1958**, *6*, 375. [*Chem. Abstr.,* **1950**, *53*, 18885o].
6. Johnson, W. S. and Offenhauer, R. D., *J. Am. Chem. Soc.,* **1945**, *67*, 1045.
7. Friess, S. L. and Pinson, R., *J. Am. Chem. Soc.,* **1951**, *73*, 3512.
8. Rand, L. and Dolinski, R. J., *J. Org. Chem.,* **1966**, *31*, 3063.
9. Doyle, M. P.; Elliott, R. C. and Dellaria, J. F., *J. Org. Chem.,* **1978**, *43*, 4459.
10. Santelli-Rouvier, C.; Lefrère, S. and Santelli, M., *J. Org. Chem.,* **1996**, *61*, 6678.
11. Larock, R. C. and Bernhardt, J. C., *J. Org. Chem.,* **1978**, *43*, 710.
12. Shono, T.; Nishiguchi, I.; Sasaki, M.; Ikeda, H. and Kurita, M., *J. Org. Chem.,* **1983**, *48*, 2503.
13. (a) Morel-Fourrier, C.; Dulcere, J.-P. and Santelli, M., *J. Am. Chem. Soc.,* **1991**, *113*, 8062. (b) Snider, B. B. and Jackson, A. C., *J. Org. Chem.,* **1982**, *47*, 5393. (c) Hoffmann, H. M. R. and Tsushima, T., *J. Am. Chem. Soc.,* **1977**, *99*, 6008. (d) Cantrell, T. S., *J. Org. Chem.,* **1967**, *32*, 1669. (e) Rand, L. and Dolinski, R. J., *J. Org. Chem.,* **1966**, *31*, 4061. (f) Stevens, C. L. and Farkas, E., *J. Am. Chem. Soc.,* **1953**, *75*, 3306. (g) Nenitzescu, C. D. and Gavat, I. G., *Ber.,* **1937**, *70*, 1883. (h) Nenitzescu, C. D. and Cioranescu, E., *Ber.,* **1936**, *69*, 1820. (i) Nenitzescu, C. D. and Chicos, I., *Ber.,* **1935**, *68*, 1584. (j) Nenitzescu, C. D. and Cantuniari, I. P., *Ann.,* **1934**, *510*, 269.

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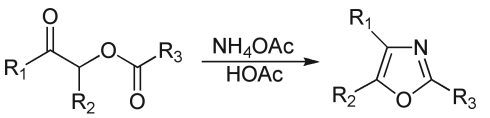
Davidson Oxazole Cyclization

(Davidson Cyclization)

A. GENERAL DESCRIPTION OF THE REACTION

Although this reaction had been investigated by Japp in the early stage of its development,[1] it was Davidson and co-workers who studied both the mechanism and method of formulating a general procedure for the preparation of substituted oxazoles.[2] Therefore, this reaction is known as the Davidson cyclization[3] or Davidson oxazole cyclization.[3] It is the preparation of substituted oxazole by condensation of *O*-acylacylion with ammonia or ammonium acetate. The *O*-acylacyloin or *O*-acyl benzoin can be prepared from the reaction between acyloin or benzoin with carboxylic acid in the presence of DCC,[4] or from the reaction between α-haloketone with carboxylic acid under basic conditions.[5] It has been found that the cyclization to form oxazole does not occur when ammonia or ammonium acetate is replaced by organic amines.[6] This reaction is best for 2,4,5-trisubstituted oxazole or oxazoles with an aromatic substituent at C-5,[7] whereas it works poorly for the preparation of 2,4-disubstituted or monosubstituted oxazoles.[3]

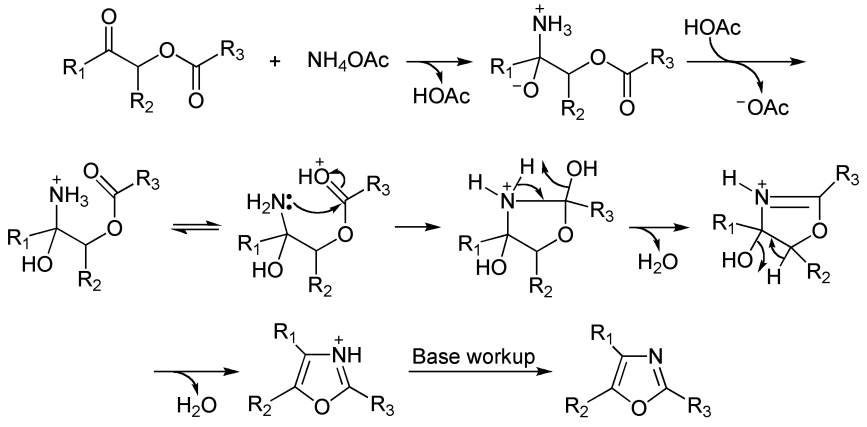
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

The early mechanisms from both Japp[1] and Davidson[2] are not clear and an updated new mechanism is proposed here.



D. MODIFICATION

This reaction has been modified to generate *O*-acylacyloin via the reaction of α-haloketone with carboxylic acid under basic conditions.[5]

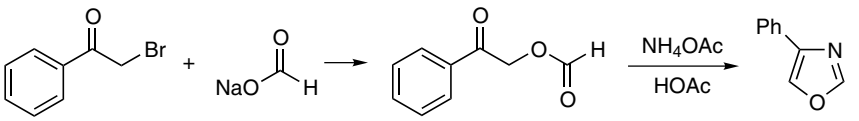
E. APPLICATIONS

This reaction has general application in the preparation of 2,4,5-trisubstituted oxazoles.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 5.

A mixture of 20.0 g bromoacetophenone (0.100 mol) and 8.84 g sodium formate (0.13 mol) in 200 mL DMF was stirred for 12 h. The solution was then poured into 800 mL water and extracted with CH_2Cl_2 until the aqueous layer was colorless. The organic phase was washed with saturated brine, dried over Na_2SO_4, and evaporated. Residual DMF was removed by vacuum distillation, leaving 13.6 g α-(formy1oxy)acetophenone as a yellow oil, in a yield of 83%.

A mixture of 10.4 g of this crude α-(formyloxy) acetophenone (63.4 mmol) and 24.3 g ammonium acetate (315 mmol) in 125 mL acetic acid was refluxed for 1.5 h. After cooling, it was added to 500 mL water and extracted with CH_2Cl_2. The organic phase was neutralized by careful addition (foaming) of saturated $NaHCO_3$ solution, washed with brine, dried over Na_2SO_4, evaporated, and distilled to yield 4.52 g 2-phenyl-oxazole in a yield of 49.5%, b.p. 60–61°C (at 0.1 mmHg).

Other references related to the Davidson oxazole cyclization are cited in the literature.[8]

H. REFERENCES

1. (a) Japp, F. R., *Ber.,* **1883**, *16*, 2636. (b) Japp, F. R., *J. Chem. Soc.,* **1883**, *43*, 9.
2. (a) Davidson, D.; Weiss, M. and Jelling, M., *J. Org. Chem.,* **1937**, *2*, 319. (b) Davidson, D.; Weiss, M. and Jelling, M., *J. Org. Chem.,* **1937**, *2*, 328.
3. Smith, A. B.; Friestad, G. K.; Barbosa, J.; Bertounesque, E.; Duan, J. J.-W.; Hull, K. G.; Iwashima, M.; Qiu, Y. P.; Spoor, P. G. and Salvatore, B. A., *J. Am. Chem. Soc.,* **1999**, *121*, 10478.
4. Wasserman, H. H.; McCarthy, K. E. and Prowse, K. S., *Chem. Rev.,* **1986**, *86*, 845.
5. Whitney, S. E.; Winter, M. and Rickborn, B., *J. Org. Chem.,* **1990**, *55*, 929.
6. Wiley, R. H., *Chem. Rev.,* **1945**, *37*, 401.
7. Theilig, G., *Ber.,* **1953**, *86*, 96.
8. (a) Hashimoto, H.; Imamura, K.; Haruta, J.-I. and Wakitani, K., *J. Med. Chem.*, **2002**, *45*, 1511. (b) Whitney, S. E. and Rickborn, B., *J. Org. Chem.,* **1991**, *56*, 3058. (c) Lipshutz, B. H. and Hungate, R. W., *J. Org. Chem.,* **1981**, *46*, 1410. (d) Turchi, I. J., *Ind. Eng. Chem. Prod. Res. Dev.,* **1981**, *20*, 32. (e) Strazybny, P. P. E.; van Es, T. and Backeberg, O. G., *J. Org. Chem.,* **1963**, *28*, 3381. (f) Aldous, D. L.; Riebsomer, J. L. and Castle, R. N., *J. Org. Chem.,* **1960**, *25*, 1151. (g) Selwitz, C. M. and Kosak, A. I., *J. Am. Chem. Soc.,* **1955**, *77*, 5370. (h) Kreps, S. I. and Day, A. R., *J. Org. Chem.,* **1941**, *6*, 140. (i) Sircar, A. C. and Sircar, G. C., *J. Chem. Soc.,* **1923**, *123*, 1559.

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de Mayo Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by de Mayo in 1962.[1] It is a two-step process involving the [2+2] photocycloaddition of an enol of a 1,3-dicarbonyl compound (e.g., β-diketone,[1,2] β-dialdehyde,[3] or β-ketoaldehyde[4]) with an olefin to form a cyclobutanol intermediate and the *retro* aldol condensation of such a cyclobutanol to give 1,5-dicarbonyl compounds. Therefore, this reaction is generally known as the de Mayo reaction.[5] Occasionally, it is also referred to as the de Mayo photocycloaddition.[6] In this reaction, it is known that in the absence of extreme steric hindrance, the regiochemistry of cycloaddition is predictable,[7] and such regioselectivity will also be affected by a solvent.[8] When an electron-deficient, polarized olefin (CH_2=CHR, R = CN, Cl, $COCH_3$, CO_2CH_3, etc) is subjected to the [2+2] photocycloaddition with enol of 1,3-dicarbonyl compound, the so-called head-to-tail regioisomer with *exo*-orientation of R on such an olefin is the favored product.[9] However, in the case of unsymmetrical 1,3-dicarbonyl compound, regioselectivity of the enolization will result in a significant problem, and the original reaction pattern would be modified using β-keto esters.[5i] In addition, dioxolenones are used as a covalently locked enol form of a β-keto ester to avoid the competing *Paterno-Büchi Reaction* that forms oxetanes.[10] It should be pointed out that the cyclobutanol intermediate from cyclic 1,3-dicarbonyl compound can be transformed into either cyclooctanedione[5e] or cyclohexenone (via an *Aldol Reaction*).[9]

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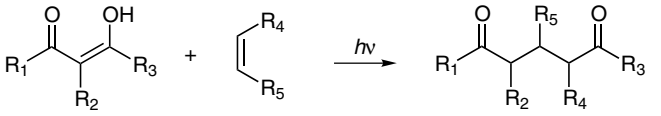
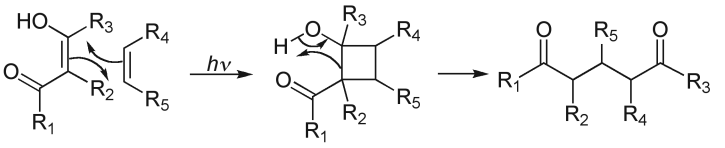
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified to form enols from β-keto esters.[5i,10]

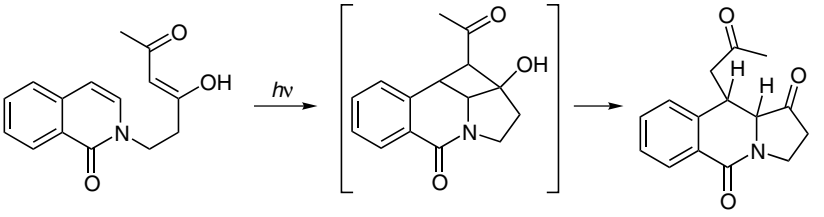
E. APPLICATIONS

This reaction has a wide range of application in the preparation of 1,5-dicarbonyl compounds, especially in regard to the synthesis of the smallest known bicyclic compound ([4.3.1] undecane) with *trans* bridgehead hydrogen.[10b]

F. RELATED REACTIONS

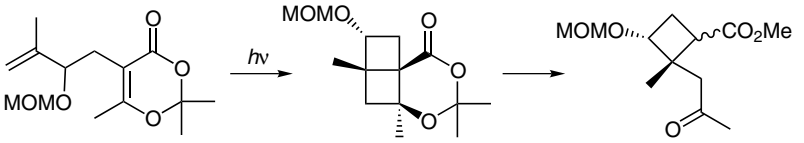
This reaction is related to *[2+2] Cycloaddition* and *Aldol Condensation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 9.

A solution containing 101 mg 2-(3,5-dioxo-1-hexyl)isoquinolin-1(2*H*)-one (0.39 mmol) in 10 mL acetonitrile was purged with nitrogen for 15 min before irradiation through a Pyrex filter at ambient temperature for 1.5 h. The reaction mixture was concentrated under reduced pressure by rotary evaporation. Flash chromatography (silica, EtOAc/hexane, 2:1) gave 72.3 mg 10-(2-oxopropyl)-2,3,10,10a-tetrahydropyrrolo[1,2-*b*]-isoquinolin-1,5-dione as a white crystalline solid, in a yield of 71.6%, m.p. 184–185°C.



Reference 10a.

Irradiation of a solution of 277 mg 5-(2-methoxymethoxy-3-methylbut-3-enyl)-2,2,6-trimethyl-[1,3]dioxin-4-one (1.03 mmol) in 50 mL acetonitrile/acetone mixture (9:1 v/v) for 2–3 h afforded 130 mg 3-methoxymethoxy-4,6,8,8-tetramethyl-7,9-dioxatricyclo[4.4.0.0^{1,4}]decan-10-one as a colorless oil after purification (EtOAc/petroleum ether, 1:3, R_f = 0.24), in a yield of 47%. When 81 mg this photo-cycloadduct (0.3 mmol) was treated with base in refluxing THF for 30 min, 56 mg of a 30:70 mixture of 3-methoxymethoxy-2-methyl-2-(2-oxopropyl)cyclobutanecarboxylic acid methyl ester of diastereomers was obtained as a colorless oil after column chromatography (Et_2O/petroleum ether, 1:4), in a yield of 77%. Both isomers were separated by further chromatography.

Other references related to the de Mayo reaction are cited in the literature.[11]

H. REFERENCES

1. de Mayo, P.; Takashita, H. and Satter, A. B. M. A., *Proc. Chem. Soc.,* **1962**, 119.
2. de Mayo, P. and Takeshita, H., *Can. J. Chem.,* **1963**, *41*, 440.
3. (a) Partridge, J. J.; Chadha, N. K. and Uskokovic, M. R., *J. Am. Chem. Soc.,* **1973**, *95*, 532. (b) Buchi, G.; Carlson, J. A.; Powell, J. E. and Tietze, L.-F., *J. Am. Chem. Soc.,* **1970**, *92*, 2165.
4. (a) Baldwin, S. W.; Gawley, R. E.; Doll, R. J. and Leung, K. H., *J. Org. Chem.,* **1975**, *40*, 1865. (b) Baldwin, S. W. and Gawley, R. E., *Tetrahedron Lett.,* **1975**, 3969.
5. (a) Sato, M.; Sunami, S.; Kogawa, T. and Kaneko, C., *Chem. Lett.,* **1994**, 2191. (b) Sato, M.; Abe, Y.; Takayama, K.; Sekiguchi, K.; Kaneko, C.; Inoue, N.; Furuya, T. and Inukai, N., *J. Heterocycl. Chem.,* **1991**, *28*, 241. (c) Sato, M.; Takayama, K.; Sekiguchi, K.; Abe, Y.; Furuya, T.; Inukai, N. and Kaneko, C., *Chem. Lett.,* **1989**, 1925. (d) Barone, R.; Arbelot, M. and Chanon, M., *Tetrahedron Computer Methodology*, **1988**, *1*, 3. (e) Disanayaka, B. W. and Weedon, A. C., *J. Org. Chem.,* **1987**, *52*, 2905. (f) Disanayaka, B. W. and Weedon, A. C., *J. Chem. Soc., Chem. Commun.,* **1985**, 1282. (g) Oppolzer, W. and Godel, T., *Helv. Chim. Acta,* **1984**, *67*, 1154. (h) Barker, A. J. and Pattenden, G., *J. Chem. Soc., Perkin Trans. I,* **1983**, 1901. (i) Pearlman, B. A., *J. Am. Chem. Soc.,* **1979**, *101*, 6398. (j) Oppolzer, W. and Bird, T. G. C., *Helv. Chim. Acta,* **1979**, *62*, 1199.
6. (a) Wang, J.-J.; Ji, J.-Y. and Mori, A., *Youji Huaxue,* **2006**, *26*, 653. (b) Wang, J.-J.; Yin, J.-G.; Wu, X.-R.; Zhao, Y.; Mori, A.; Hatsui, T. and Takeshita, H., *Youji Huaxue*, **2003**, *23*, 1120.
7. Corey, E. J.; Bass, J. D.; LeMahieu, R. and Mitra, R. B., *J. Am. Chem. Soc.,* **1964**, *86*, 5570.

8. (a) Berenjian, N.; de Mayo, P.; Sturgeon, M.-E.; Syndes, L. K. and Weedon, A. C., *Can. J. Chem.,* **1982**, *60*, 425. (b) Challand, B. D. and de Mayo, P., *J. Chem. Soc., Chem. Commun.,* **1968**, 982.
9. Minter, D. E. and Winslow, C. D., *J. Org. Chem.,* **2004**, *69*, 1603.
10. (a) Blaauw, R. H.; Brière, J.-F.; de Jong, R.; Benningshof, J. C. J.; van Ginkel, A. E.; Fraanje, J.; Goubitz, K.; Schenk, H.; Rutjes, F. P. J. T. and Hiemstra, H., *J. Org. Chem.,* **2001**, *66*, 233. (b) Winkler, J. D. and Hey, J. P., *Tetrahedron Lett.,* 1988, *29*, 4691. (c) Baldwin, S. and Wilkinson, J., *J. Am. Chem. Soc.,* **1980**, *102*, 3634.
11. (a) Winkler, J. D.; Rouse, M. B.; Greaney, M. F.; Harrison, S. J. and Jeon, Y. T., *J. Am. Chem. Soc.,* **2002**, *124*, 9726. (b) Jensen, A. W.; Khong, A.; Saunders, M.; Wilson, S. and Schuster, D. I., *J. Am. Chem. Soc.,* **1997**, *119*, 7303. (c) Mal, J.; Nath, A. and Venkateswaran, R. V., *J. Org. Chem.,* **1996**, *61*, 9164. (d) Quevillon, T. M. and Weedon, A. C., *Tetrahedron Lett.,* **1996**, *37*, 3939. (e) Galatsis, P. and Manwell, J. J., *Tetrahedron,* **1995**, *51*, 665. (f) Weedon, A. C., "[2 + 2]-Photocycloaddition Reactions of Enolized 1,3-Diketones and 1,2-Diketones with Alkenes: The de Mayo Reaction" in *CRC Handbook of Organic Photochemistery and Photobiology*, ed. Horspool, W. M. and Song, P.-S., CRC Press, Boca Raton, **1995**, chapter 54. (g) Weedon, A. C., "Enone Photochemical Cycloaddition in Organic Synthesis" in *Synthetic Organic Photochemistry*, ed. Horspool, W. M., Plenum, New York, **1984**, pp. 61–148. (h) Oppolzer, W., *Pure & Appl. Chem.,* **1981**, *53*, 1189. (i) Barker, A. J. and Pattenden, G., *Tetrahedron Lett.,* **1980**, *21*, 3513. (j) de Mayo, P., *Acc. Chem. Res.,* **1971**, *4*, 41. (k) de Mayo, P., *Pure & Appl. Chem.,* **1964**, *9*, 597.

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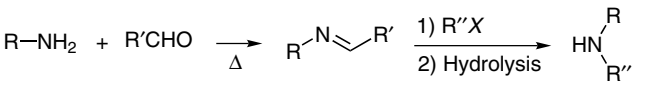
Decker-Becker Secondary Amine Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

Although Forster initially reported this reaction,[1] it was Decker and Becker who investigated it in more depth and made this reaction an applicable route for the preparation of secondary amines.[2] Therefore, this reaction is known as the Decker-Becker method[3] or Forster reaction,[4] but it is named the Decker-Becker secondary amine synthesis in this book. It is the synthesis of secondary amine by the condensation of primary amines with aldehydes to form an imine intermediate, which then reacts with alkyl halides via alkylation to finally afford secondary amines after hydrolysis. This reaction gives good results when methyl halides are used but works poorly and unstably when larger alkyl halides are applied.[5]

B. GENERAL REACTION SCHEME



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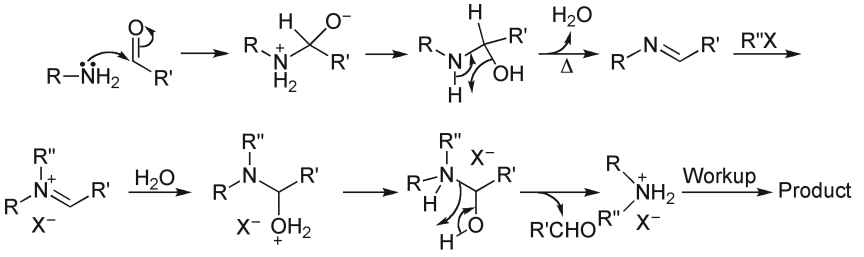
C. PROPOSED MECHANISMS



D. MODIFICATION

N/A

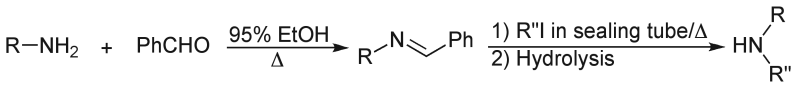
E. APPLICATIONS

This reaction has general application in the preparation of secondary amines, especially for the alkyl (aryl) methyl amines.

F. RELATED REACTIONS

This reaction is related to the *Leuckart Reaction* and *Eschweiler-Clarke Methylation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 5.

General Method for Preparation of Schiff Base

After the mixture of equal amounts of primary amines and benzaldehyde in 95% ethanol was refluxed for 30 min, the solvent was removed and the Schiff base was obtained in roughly 95% via vacuum distillation. These Schiff bases were mostly yellow oils and were used directly without further purification.

Alkylation and Hydrolysis

To a thoroughly dried Carius tube were added equal amounts of Schiff base and the appropriate alkyl iodide. After sealing, the tube was heated at 100°C by steam for 4–24 h, the longer time being used for the higher halides. The reaction was considered complete

when the whole contents of the tube upon cooling was a red to orange viscous oil or a partially crystalline mass. A layer of mobile liquid above the viscous mass showed the reaction to be incomplete. After opening, the contents of the tube were washed out with an alcohol—methyl alcohol for the methylated product and ethyl alcohol for the higher alkylated product—to which had been added one eighth its volume of water. The mixture was refluxed for 30 min then the mixture was poured into an equal volume of water and boiled until the odor of benzaldehyde had disappeared. The solution was made weakly acid with acetic acid and extracted three times with ether. After basification with 30% sodium hydroxide, the amine was extracted with ether, the ethereal solution was dried with anhydrous magnesium sulfate, and after removal of the solvent, the residue was distilled in vacuo.The hydrochlorides of these secondary amines were prepared from an anhydrous ether solution by the addition of gaseous hydrogen chloride and were recrystallized from ether-alcohol mixtures. The yields vary from 29% to 93%.

Other references related to the Decker-Becker secondary amine synthesis are cited in the literature.[6]

H. REFERENCES

1. Forster, M. O., *J. Chem. Soc.*, **1899**, *75*, 934.
2. (a) Decker, H. and Becker, P., *Ber.,* **1912**, *45*, 2404. (b) Decker, H. and Becker, P., *Ber.,* **1912**, *45*, 2407. (c) Decker, H. and Becker P., *Ann.*, **1913**, *395*, 328. (d) Decker, H. and Becker P., *Ann.*, **1913**, *395*, 342. (e) Decker, H. and Becker P., *Ann.*, **1913**, *395*, 362.
3. Zenitz, B. L.; Macks, E. B. and Moore, M. L., *J. Am. Chem. Soc.,* **1948**, *70*, 955.
4. (a) Lawrence, S. A., *Amines: Synthesis, Properties and Applications*, Cambridge University Press, Cambridge, **2004**. (b) Làbbé, G.; D'hooge, B. and Dehaen, W., *Molecules,* **1997**, *1*, 190.
5. Woodruff, E. H.; Lambooy, J. P. and Burt, W. E., *J. Am. Chem. Soc.,* **1940**, *62*, 922.
6. (a) Zenitz, B. L.; Macks, E. B. and Moore, M. L., *J. Am. Chem. Soc.,* **1948**, *70*, 955. (b) Zenitz, B. L.; Macks, E. B. and Moore, M. L., *J. Am. Chem. Soc.,* **1947**, *69*, 1117. (c) Baltzly, R. and Buck, J. S., *J. Am. Chem. Soc.,* **1940**, *62*, 161. (d) Späth, E. and Bruck, J., *Ber.,* **1937**, *70*, 2446. (e) Buck, J. S., *J. Am. Chem. Soc.,* **1932**, *54*, 3661. (f) Shepard, N. A. and Ticknor, A. A., *J. Am. Chem. Soc.,* **1916**, *38*, 381.

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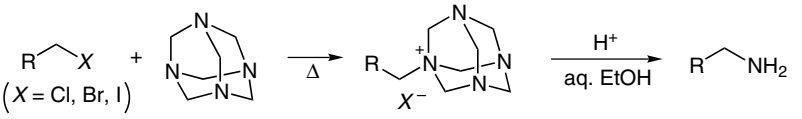
Delépine Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Delépine in 1895.[1] It is the preparation of primary aliphatic amines by acidic hydrolysis of quaternary amines formed from alkyl halides and urotropine (i.e., hexamethylene tetramine).[2] Therefore, this reaction is generally known as the Delépine reaction.[3]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A tentative mechanism is displayed here.

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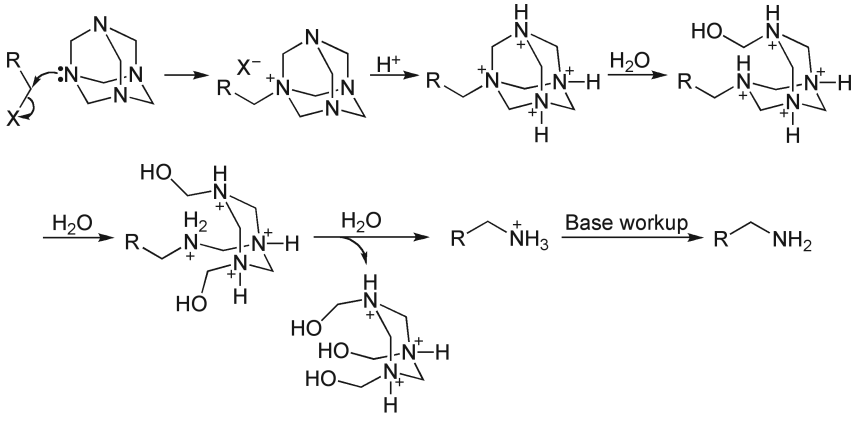


D. MODIFICATION

N/A

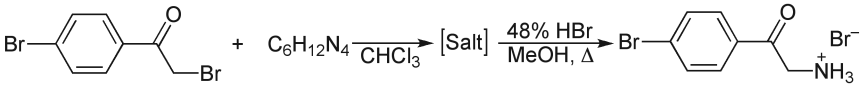
E. APPLICATIONS

This reaction has general applications in the conversion of alkyl halides into primary amines.

F. RELATED REACTIONS

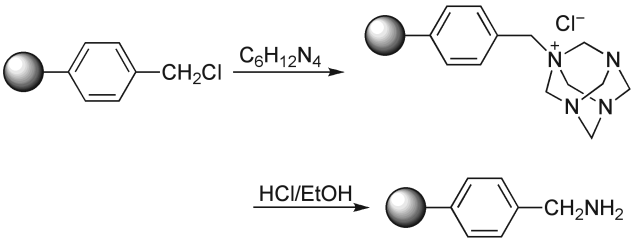
This reaction is related to the *Gabriel Primary Amine Synthesis* and *Sommelet Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4.

Hexamethylene tetramine (49.2 g, 0.350 mol) was dissolved in 750 mL chloroform, then 97.4 g 2,4′-dibromo-acetophenone (7.4 g, 0.350 mol) was added all at once; the suspension was stirred overnight and the quaternary salt was collected, washed with 750 mL chloroform, and dried at 60°C under reduced pressure (20 mmHg) for 4 h. The product was treated with 900 mL methanol and 120 mL 48% hydrobromic acid at 20°C for 2 days. Solid was always present, so 600 mL methanol was added, and the suspension was heated at 50°C overnight and then at reflux for 1.5 h, cooled to 20°C, and evaporated at a bath temperature of 50°C to obtain a mushy solid, which was recrystallized from 700 mL water to give 84.4 g 4-bromobenzoylmethylammonium bromide dihydrate, in a yield of 73%, m.p. 273–277°C (dec.)



Reference 3.

A tube containing 300 mg monolithic VBC/DVB PolyHIPE (1.23 mmol of chloromethyl groups) was set in an Argonaut Quest 210 apparatus and a 240 mL ethanol solution of reagents (hexamethylenetetramine and sodium iodide, five times excess relative to chloromethyl groups) was passed through at a flow rate of 20 mL/h and at 60°C. The product was washed with EtOH, EtOH/water (1:1), and water; subsequently, a solution of 240 mL conc. HCl/EtOH (1:15) was passed through at a flow rate of 20 mL/h and at 75°C. The product was washed with EtOH, EtOH/water (1:1), MeOH, NEt_3, and MeOH and dried at 50°C (10 mbar, 48 h).

Other references related to the Delépine reaction are cited in the literature.[5]

H. REFERENCES

1. Delépine M., *Compt. Rend.,* **1895**, *120*, 501.
2. Blaevic, N.; Kolbah, D.; Belin, B.; Sunjic, V. and Kajfe, F., *Synthesis,* **1979**, 161.
3. (a) Krajnc, P.; Brown, J. F. and Cameron, N. R., *Org. Lett.,* **2002**, *4*, 2497. (b) Ergozhin, E. E.; Zimanov, M. S.; Tastanov, K. Kh. and Khalikova, V. K., *Izv. Akad. Nauk Kazakhskoi SSR, Ser. Khim.,* **1990**, 50. (c) Brandänge, S. and Rodriguez, B., *Synthesis,* **1988**, 347. (d) Quessy, S. N.; Williams, L. R. and Baddeley, V. G., *J. Chem. Soc., Perkin Trans. I,* **1979**, 512. (e) Quessy, S. N.; Williams, L. R. and Baddeley, V. G., *Synth. Commun.,* **1978**, *8*, 45.
4. Kauffman, J. M. and Moyna, G., *J. Org. Chem.,* **2003**, *68*, 839.
5. (a) Gomez, L.; Gellibert, F.; Wagner, A. and Mioskowski, C., *J. Comb. Chem.,* **2000**, *2*, 75. (b) Ahlbrecht, H.; Schmitt, C. and Kornetzky, D., *Synthesis,* **1991**, 637. (c) Henry, R. A.; Hollins, R. A.; Lowe-Ma, C.; Moore, D. W. and Nissan, R. A., *J. Org. Chem.,* **1990**, *55*, 1796. (d) Ahlbrecht, H. and Kornetzki, D., *Synthesis,* **1988**, 775. (e) Szafranck, J.; Blotny, G. and Vouros, P. *Tetrahedron,* **1978**, *34*, 2763. (f) Basace, Y.; Marszak-Fleury, A. and Marszak, I., *Bull. Soc. Chim. Fr.,* **1971**, 1468. (g) Prainov, L., *Arch. Pharm.*, **1970**, *303*, 134. (h) Marzsak, I. and Koulkes, M., *Bull. Soc. Chim. Fr.*, **1956**, 93. (i) Angyal, S. J., *Org. React.,* **1954**, *8*, 197. (j) Delépine, M., *Bull. Soc. Chim. Fr.,* **1902**, *27*, 812. (k) Delépine, M., *Bull. Soc. Chim. Fr.,* **1898**, *19*, 270. (l) Delépine M., *Compt. Rend.,* **1897**, *124*, 292.

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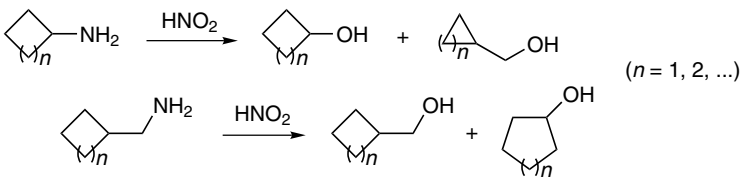
Demjanov Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Demjanov (sometimes spelled Demjanow or Dem'yanov) in 1903.[1] It is the conversion of primary amines into alcohols by means of the diazotization of those amines with nitrous acid, accompanying the migration of the carbon atom when the primary amino groups are on the ring or at the α-position of the side chain. Therefore, this reaction is generally known as the Demjanov rearrangement[2] or Demjanov reaction.[3] In the case of cyclic aliphatic amines, alcohols with enlarged or contracted rings are formed, depending on the position of the amino group. If an amino group is directly attached to the ring, then ring contraction occurs;[4] in the case of primary amines, when the amino group is connected to the cyclic ring via a methylene group, the ring expands after diazotization.[2g,5] The Demjanov rearrangement under this condition is also referred to as the Demjanov ring expansion.[5a,6] If an aromatic group is attached to the same position where an aminomethylene sits, phenyl migration happens without ring enlargement.[2f]

B. GENERAL REACTION SCHEME



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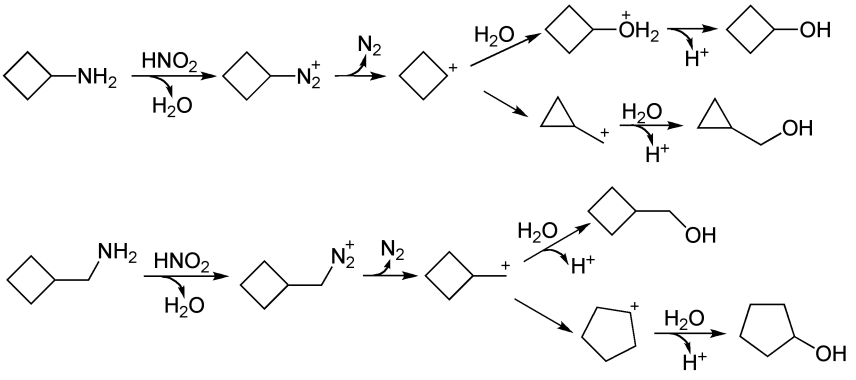
C. PROPOSED MECHANISMS



D. MODIFICATION

N/A

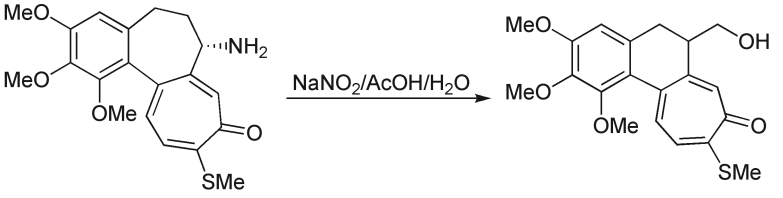
E. APPLICATIONS

This reaction has general application in the preparation of cyclic compounds with different sizes.

F. RELATED REACTIONS

This reaction is related to the *Tiffeneau-Demjanov Rearrangement* and *Wagner-Meerwein Rearrangement*, both involve carbocation intermediates.

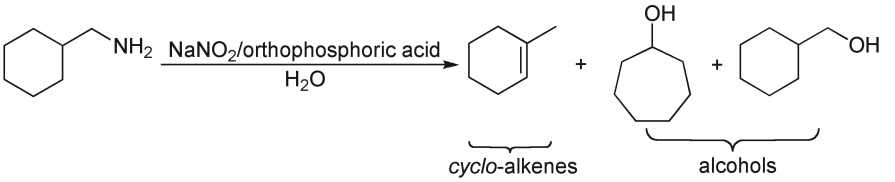
G. CITED EXPERIMENTAL EXAMPLES



Reference 4.

To a solution of 42.7 mg deacetylthiocolchicine (0.11 mmol) in 4 mL water was added 10.9 mg sodium nitrite in 1 mL water containing two drops of acetic acid. The reaction mixture was stirred at room temperature for 24 h and extracted with $CHCl_3$ (30 mL × 3). The extract was washed with 5% $NaHCO_3$ solution, water, and brine until pH = 7. It was dried over anhydrous Na_2SO_4 and concentrated. Purification of the residue by preparative TLC plates with $CHC1_3$/MeOH (95:5) as the eluant furnished 18.1 mg

pure 5,6-dihydro-6(*S*)-(hydroxymethyl)-1,2,3-trimethoxy-9-(methylthio)-8*H*-cyclohepta [a]naphthalene-8-one. Crystallization from CH_2Cl_2-Et_2O afforded yellow crystals, in a yield of 42%, m.p. 201–203°C.



Reference 2e.

Cyclohexanemethylamine (45.2 g, 0.4 mol) was treated with $NaNO_2$ in dilute aqueous orthophosphoric acid at room temperature for 1 h and then at 95°C for 1 h. Fractional distillation of the crude product gave 9.4 g cycloalkene mixtures (b.p. 90–115°C) and 26.6 g alcohol mixtures (b.p. 50–95°C at 20 mmHg).

Other references related to the Demjanov rearrangement are cited in the literature.[7]

H. REFERENCES

1. Demjanov, N. J. and Lushnikov, M., *J. Russ. Phys. Chem. Soc.,* **1903**, *35*, 26.
2. (a) Nikishova, N. G. and Bundel, Yu. G., *Vestnik Moskovskogo Universiteta, Ser. 2: Khim.,* **1985**, *26*, 486. (b) Novikov, G. P. and Bundel, Yu. G., *Dokl. Akad. Nauk SSSR,* **1985**, *280*, 1366. (c) Hass, E. C. and Plath, P. J., *Bremer Briefe Chem.,* **1977**, *1*, 6. (d) Bundel, Y. G.; Funtova, S. M. and Reutov, O. A., *Dokl. Akad. Nauk SSSR,* **1971**, *200*, 107. (e) Kotani, R., *J. Chem. Eng. Data,* **1966**, *11*, 248. (f) Diamond, J.; Bruce, W. F. and Tyson, F. T., *J. Org. Chem.,* **1965**, *30*, 1840. (g) Kotani, R., *J. Org. Chem.,* **1965**, *30*, 350.
3. (a) Dmitriev, L. B.; Grandberg, I. I. and Moskalenko, V. A., *Khim. Geterotsiklicheskikh Soedinenii*, **1970**, 1654. (b) Reutov, O. A. and Shatkina, T. N., *Dokl. Akad. Nauk SSSR,* **1962**, *142*, 835.
4. Sun, L.; McPhail, A. T.; Hamel, E.; Lin, C. M.; Hastie, S. B.; Chang, J.-J. and Lee, K.-H., *J. Med. Chem.,* **1993**, *36*, 544.
5. (a) Nakazaki, M.; Naemura, K. and Hashimoto, M., *J. Org. Chem.,* **1983**, *48*, 2289. (b) Hall, H. K., *J. Am. Chem. Soc.,* **1960**, *82*, 1209. (c) Hall, H. K., *J. Org. Chem.,* **1960**, *25*, 42.
6. Bundel, Y. G.; Prokhorenko, I. R. and Reutov, O. A., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1972**, 707.
7. (a) Fattori, D.; Henry, S. and Vogel, P., *Tetrahedron,* **1993**, *49*, 1649. (b) Nakazaki, M.; Naemura, K.; Chikamutsu, H.; Iwasaki, M. and Hashimoto, M., *J. Org. Chem.,* **1981**, *46*, 2300. (c) Nakazaki, M.; Naemura, K.; Chikamatsu, H.; Iwasaki, M.; Hashimoto, M., *Chem. Lett.,* **1980**, 1571. (d) Dave, V.; Stothers, J. B. and Warnhoff, E. W., *Can. J. Chem.*, **1979**, *57*, 1557. (e) Murray, R. K. and Ford, T. M., *J. Org. Chem.,* **1979**, *44*, 3504. (f) Bundel, Yu. G.; Funtova, S. M. and Reutov, O. A., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1972**, 935. (g) Dmitriev, L. B.; Grandberg, I. I. and Moskalenko, V. A., *Chem. Heterocycl. Compds.,* **1970**, *6*, 1544. (h) Stetter, H. and Goebel, P., *Ber.,* **1963**, *96*, 550. (i) Smith, P. A. S. and Baer, D. R., *Org. React.,* **1960**, *11*, 157. (j) Alder, K. and Reubke, R., *Ber.,* **1958**, *91*, 1525. (k) Ruzicka, L. and Brugger, W., *Helv. Chim. Acta,* **1926**, *9*, 339. (l) Wallach, O., *Ann.,* **1907**, *353*, 318. (m) Demjanov, N. J. and Dojarenko, M., *Ber.,* **1909**, *41*, 43. (n) Demjanov, N. J., *Ber.,* **1907**, *40*, 4393, 4961. (o) Demjanov, N. J., *J. Russ. Phys. Chem. Soc.*, **1904**, *36*, 186.

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Dess-Martin Periodinane Oxidation

(Dess-Martin Oxidation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Dess and Martin in 1983.[1] It is the conversion of primary and secondary alcohols into carbonyl compounds (aldehydes and ketones) by means of the oxidation with a hypervalent iodine compound (i.e., 12-I-5 triacetoxyperiodinane).[2] Therefore, this reaction is generally known as the Dess-Martin periodinane oxidation[3] or simply referred to as the Dess-Martin oxidation.[4] On the other hand, the hypervalent iodine compound is called the Dess-Martin periodinane (DMP),[2,5] Dess-Martin reagent,[6] Dess-Martin Periodinane reagent,[7] or Dess-Martin oxidant,[8] which tolerates a variety of functional groups.[2,5u,9] The actual oxidation condition is mild and normally completes within 2 h at room temperature and in a solvent with either slightly acidic or neutral pH.[5v] This oxidation normally gives high yields of products without overoxidation and can be easily worked up.[10] Therefore, this oxidation is suitable for the oxidation of substrates containing sensitive functionalities.[5v] The reaction has been carried out in different solvents but often in dichloromethane or chloroform. It was found that DMP might not be the actual oxidation reagent, while the substituted periodinane (the replacement of one or two acetyl groups by hydroxyl or ethoxy) oxidizes the alcohols faster than DMP. Therefore, addition of certain amounts of water to the reaction solution can accelerate the oxidation.[4c] It has been found that the oxidation of alcohols using DMP is faster in ionic liquids (either hydrophilic or hydrophobic) than in conventional solvents (e.g., DMSO, DMF, and EtOAc) and gives excellent yields with high selectivity.[11] Unfortunately, it is difficult to prepare

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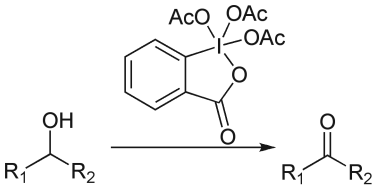
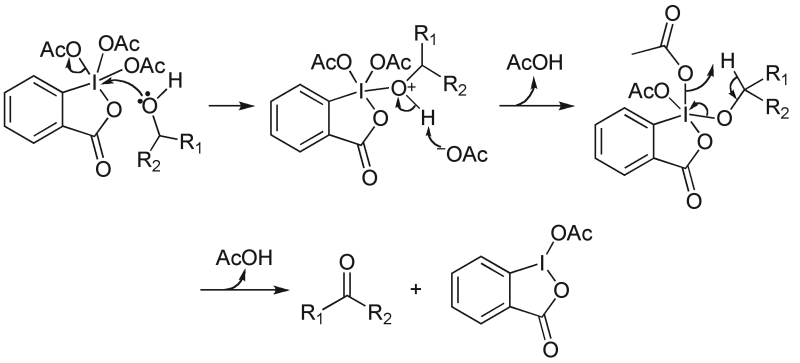
DMP with high purity by the original procedure;[5v,12] therefore, a few modifications have been suggested.[4c,5v,6b,13] In addition, DMP has been successfully used in the syntheses of polycyclic heterocycles[14] and in the removal of thioketals and thioacetals.[15] It should be mentioned that other hypervalent iodine compounds can be used as oxidants as well,[2] especially for the *o*-iodoxybenzoic acid (IBX), the precursor to DMP, which can oxidize tertiary cyclic allyl alcohol into α,β-unsaturated cyclic ketones[16] and secondary amines into imines[17] and can convert epoxides or aziridines into corresponding α-hydroxy ketones or α-amino ketones.[18]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

The preparation of DMP has been modified by substituting acetic acid with only a catalytic amount of TsOH during the acetylation step. By this modification, pure DMP can be easily obtained on a 100-g scale with an isolated yield of $> 90\%$.[5v] In addition, the oxidation itself has been accelerated by the addition of water to the reaction solution.[4c]

E. APPLICATIONS

N/A

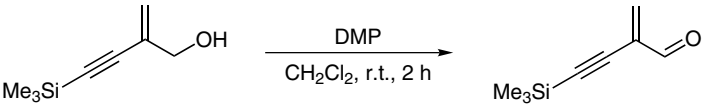
F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES

Reference 19.

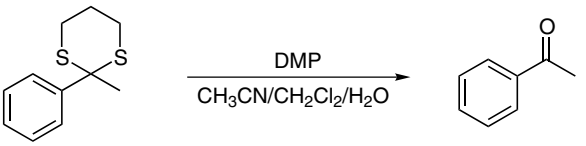
To a solution of 3 mL CH_2Cl_2 containing 111.4 mg forocidin (0.2 mmol) was added 101.8 mg Dess-Martin periodinane (0.24 mmol). After being stirred for 30 min at room temperature, a solution of 10 μL H_2O in 10 mL CH_2Cl_2 was added slowly via a dropping funnel. The pale yellow solution was stirred for 2–3 h until formation of a noticeable precipitate, then concentrated under reduced pressure; the residue was taken up in 30 mL ether. It was washed with 15 mL 10% $Na_2S_2O_3$/saturated aqueous $NaHCO_3$ (v/v 1:1), followed by 10 mL H_2O and 10 mL brine. The combined aqueous layers were extracted with $CHCl_3$ (3×10 mL). The combined organic layers were dried with Na_2SO_4 and concentrated. Column chromatography ($CHCl_3/CH_3OH$, v/v 9:1, 1% NH_3) of the residue afforded 61% of ketone as a pale yellow solid.



Reference 20.

A 50-mL, two-necked, pear-shaped flask fitted with an argon inlet adapter and a rubber septum was charged with a solution of 30 mL dichloromethane containing 0.942 g of the allylic alcohol (6.11 mmol). After the solution was cooled to 0°C, 2.856 g Dess-Martin periodinane (6.73 mmol) was added in one portion. The heterogeneous reaction mixture was stirred at 0°C for 5 min and then allowed to warm to room temperature. After 20 min, the reaction mixture was cooled to –78°C and diluted with 30 mL pentane, followed by the addition of 3.227 g poly(4-vinylpyridine) (30.69 mmol) in one portion. The resulting mixture was stirred at –78°C for 25 min. A 2.5-cm diameter jacketed column fitted with a rubber septum at the top and a short needle at the bottom was charged with a 6-cm plug of silica gel, which was cooled at –78°C by filling the jacket with dry ice acetone. The reaction mixture was transferred into the column by cannula and filtered through the silica gel under a positive pressure of argon into a 200-mL recovery flask fitted with a rubber septum with a short needle as a vent. The reaction flask and the column were rinsed with four 15-mL

portions of 4:1 pentane/ether. The filtrate was concentrated by rotary evaporation at 25°C (20 mmHg) to a volume of ∼3 mL and this solution was then cooled to –78°C and diluted with 5 mL toluene. The resulting solution was concentrated by rotary evaporation at 25°C to a volume of ∼3 mL. The resulting pale yellow solution was cooled to –78°C and further concentrated at 0.05 mmHg (∼15 min) to furnish 2-methylene-4-trimethylsilyl-but-3-ynal as a yellow oil, in a yield of 53%.



Reference 15.

To a sample of 210 mg 2-methyl-2-phenyl-1,3-dithiane (1.0 mmol) in 5.0 mL 8:1:1 $MeCN/CH_2Cl_2/H_2O$ (0.2 M) was added 424 mg Dess-Martin periodinane (2.0 mmol) in one portion. The reaction mixture was stirred at room temperature, and exposed to air for 2 h until the complete consumption of starting material as observed by TLC. The reaction was quenched with 20 mL 50% aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted three times into 50 mL CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (silica, 5% EtOAc/hexanes) afforded 112 mg (92%) of the desired acetophenone.

Other references related to the Dess-Martin periodinane oxidation are cited in the literature.[21]

H. REFERENCES

1. Dess, D. B. and Martin, J. C., *J. Org. Chem.,* **1983**, *48*, 4155.
2. Dess, D. B. and Martin, J. C., *J. Am. Chem. Soc.,* **1991**, *113*, 7277.
3. (a) Reed, N. A.; Rapp, R. D.; Hamann, C. S. and Artz, P. G., *J. Chem. Edu.,* **2005**, *82*, 1053. (b) Barrett, A. G. M.; Hamprecht, D. and Ohkubo, M., *J. Org. Chem.,* **1997**, *62*, 9376.
4. (a) Li, C.; Twamley, B. and Natale, N. R., *Acta Crystallograph., Sect. E: Struct. Rept. Online,* **2006**, *E62*, o854. (b) Bach, T. and Kirsch, S., *Synlett,* **2001**, 1974. (c) Meyer, S. D. and Schreiber, S. L., *J. Org. Chem.,* **1994**, *59*, 7549.
5. (a) Moorthy, J. N.; Singhal, N. and Senapati, K., *Org. Biomol. Chem.,* **2007**, *5*, 767. (b) Bandgar, S. B.; Bandgar, B. P.; Korbad, B. L. and Sawant, S. S., *Tetrahedron Lett.*, **2007**, *48*, 1287. (c) Heggelund, A. and Undheim, K., *Kjemi,* **2006**, *66*, 10. (d) Nicolaou, K. C. and Mathison, C. J. N., *Angew. Chem. Int. Ed.,* **2005**, *44*, 5992. (e) Heravi, M. M.; Dirkwand, F.; Oskooie, H. A. and Ghassemzadeh, M., *Heterocycl. Commun.,* **2005**, *11*, 75. (f) Oskooie, S. H. A.; Heravi, M. M.; Sarmad, N.; Saednia, A. and Ghassemzadeh, M., *Indian J. Chem., Sect. B,* **2003**, *42B*, 2890. (g) Luo, H. B. and Xie, Y. Y., *Chinese Chem. Lett.,* **2003**, *14*, 555. (h) Heravi, M. M.; Sangsefidi, L.; Oskooie, H. A.; Ghassemzadeh, M. and Tabar-Hydar, K., *Phosphorus, Sulfur & Silicon and Related Elements,* **2003**, *178*, 707. (i) Bose, D. S. and Reddy, A. V. N., *Tetrahedron Lett.*, **2003**, *44*, 3543. (j) Schilling, G., *GIT Labor-Fachzeitschrift*, **2002**, *46*, 84. (k) Wavrin, L. and Viala, J., *Synthesis,* **2002**, 326. (l) Boeckman, R. K.; Shao, P. C. and Mullins, J. J., *Org. Synth.,* **2000**, *77*, 141. (m) Roels, J. and Metz, P., *Synlett*, **2001**, 789. (n) Candela Lena, J. I.; Martin Hernando, J.

I.; Rico Ferreira, M. del R.; Altinel, E. and Arseniyadis, S., *Synlett,* **2001**, 597. (o) Oskooie, H. A.; Khalilpoor, M.; Saednia, A.; Sarmad, N. and Heravi, M. M., *Phosphorus, Sulfur & Silicon and Related Elements,* **2000**, *166*, 197. (p) Jenkins, N. E.; Ware, R. W.; Atkinson, R. N. and King, S. B., *Synth. Commun.,* **2000**, *30*, 947. (q) Nicolaou, K. C.; Zhong, Y.-L. and Baran, P. S., *Angew. Chem. Int. Ed.,* **2000**, *39*, 622. (r) Chaudhari, S. S. and Akamanchi, K. G., *Synthesis*, **1999**, 760. (s) Speicher, A.; Bomm, V. and Eicher, T., *J. Prakt. Chem.,* **1996**, *338*, 588. (t) Shiraki, R.; Sumino, A.; Tadano, K.-I and Ogawa, S., *J. Org. Chem.,* **1996**, *61*, 2845. (u) Meyer, S. D. and Schreiber, S. L., *J. Org. Chem.,* **1994**, *59*, 7549. (v) Ireland, R. E. and Liu, L. B., *J. Org. Chem.,* **1993**, *58*, 2899.

6. (a) Commeiras, L.; Valls, R.; Santelli, M. and Parrain, J.-L., *Synlett*, **2003**, 1719. (b) Niu, C. S.; Pettersson, T. and Miller, M. J., *J. Org. Chem.,* **1996**, *61*, 1014. (c) Batchelor, M. J.; Gillespie, R. J.; Golec, J. M. C. and Hedgecock, C. J. R., *Tetrahedron Lett.,* **1993**, *34*, 167. (d) Linderman, R. J. and Graves, D. M., *J. Org. Chem.,* **1989**, *54*, 661. (e) Schwarz, M.; Waters, R. M. and Graminski, G. F., *Chem. Ind. (London),* **1986**, 789.
7. (a) Zhang, Q.-S.; Huang, X.-G. and Li, A. Y., *Huaxue Shiji*, **2005**, *27*, 401. (b) Wnuk, S. F.; Yuan, C.-S.; Borchardt, R. T.; Balzarini, J.; de Clercq, E. and Robins, M. J., *J. Med. Chem.,* **1997**, *40*, 1608. (c) Marshall, J. A. and Sehon, C. A., *J. Org. Chem.,* **1997**, *62*, 4313. (d) Harry-O'Kuru, R. E.; Smith, J. and Wolfe, M. S., *J. Org. Chem.,* **1997**, *62*, 1754. (e) Burkhart, J. P.; Peet, N. P. and Bey, P., *Tetrahedron Lett.,* **1988**, *29*, 3433.
8. Lawrence, N. J.; Grump, J. P.; McGown, A. T. and Hadfield, J. A., *Tetrahedron Lett.,* **2001**, *42*, 3939.
9. Zhdankin, V. V. and Stang, P. J., *Chem. Rev.,* **2002**, *102*, 2523.
10. Chaudhari, S. S., *Synlett,* **2000**, 278.
11. Yadav, J. S.; Reddy, B. V. S.; Basak, A. K. and Narsaiah, A. V., *Tetrahedron,* **2004**, *60*, 2131.
12. Kim, G.; Lee, D. G. and Chang, S., *Bull. Korean Chem. Soc.,* **2001**, *22*, 943.
13. (a) Boeckman, R. K.; Shao, P. C. and Mullins, J. J., *Org. Syn. Coll.,* **2004**, *10*, 696. (b) Boeckman, R. K.; Shao, P. C. and Mullins, J. J., *Org. Synth. Coll.,* **2004**, *10*, 696.
14. (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L. and Sugita, K., *J. Am. Chem. Soc.,* **2002**, *124*, 2212. (b) Nicolaou, K. C.; Sugita, K.; Baran, P. S. and Zhong, Y.-L., *J. Am. Chem. Soc.,* **2002**, *124*, 2221.
15. Langille, N. F.; Dakin, L. A. and Panek, J. S., *Org. Lett.,* **2003**, *5*, 575.
16. Shibuya, M.; Ito, S.; Takahashi, M. and Iwabuchi, Y., *Org. Lett.,* **2004**, *6*, 4303.
17. Nicolaou, K. C.; Mathison, C. J. N. and Montagnon, T., *Angew. Chem.*, **2003**, *115*, 4211.
18. Surendra, K.; Krishnaveni, N. S.; Reddy, M. A.; Nageswar, Y. V. D. and Rao, K. R., *J. Org. Chem.,* **2003**, *68*, 9119.
19. Zöllner, T.; Gebhardt, P.; Beckert, R. and Hertweck, C., *J. Nat. Prod.,* **2005**, *68*, 112.
20. Thongsornkleeb, C. and Danheiser, R. L., *J. Org. Chem.,* **2005**, *70*, 2364.
21. (a) Deng, L.-H.; Wu, H.; Yu, B.; Jiang, M.-R. and Wu, J.-R., *Chin. J. Chem.*, **2004**, *22*, 994. (b) Tohma, H. and Kita, Y., *Adv. Synth. Catal.,* **2004**, *346*, 111. (c) Kikuchi, H.; Tasaka, H.; Hirai, S.; Takaya, Y.; Iwabuchi, Y.; Ooi, H.; Hatakeyama, S.; Kim, H.-S.; Wataya, Y. and Oshima, Y., *J. Med. Chem.,* **2002**, *45*, 2563. (d) Constantino, M. G.; de Souza, A. X. and da Silva, G. V. J., *Molecules,* **2002**, *7*, 475. (e) Caddick, S.; Cheung, S.; Doyle, V. E.; Frost, L. M.; Soscia, M. G.; Delisser, V. M.; Williams, M. R. V.; Etheridge, Z. C.; Khan, S.; Hitchcock, P. B.; Pairaudeau, G. and Vile, S., *Tetrahedron*, **2001**, *57*, 6295. (f) Yu, C. Z. and Hu, L. Q., *Tetrahedron Lett.,* **2001**, *42*, 5167. (g) Paulvannan, K.; Hale, R.; Sedehi, D. and Chen, T., *Tetrahedron,* **2001**, *57*, 9677. (h) Nicolau, K. C.; Xu, J.; Murphy, F.; Barluenga, S.; Baudoin, O.; Wei, H.-X.; Gray, D. L. F. and Oshima, T., *Angew. Chem. Int. Ed.,* **1999**, *38*, 2447. (i) Tückmantel, W.; Kozikowski, A. P. and Romanczyk, L. J., *J. Am. Chem. Soc.,* **1999**, *121*, 12073. (j) Deng, S.; Yu, B.; Lou, Y. and Hui, Y., *J. Org. Chem.,* **1999**, *64*, 202. (k) Matsushima, T.; Mori, M.; Zheng, B.-Z.; Maeda, H.;

Nakajima, N.; Uenishi, J.-I. and Yonemitsu, O., *Chem. Pharm. Bull.,* **1999**, *47*, 308. (l) Bell, T. W.; Cragg, P. J.; Firestone, A.; Kwok, A. D-I.; Liu, J.; Ludwig, R. and Sodoma, A., *J. Org. Chem.,* **1998**, *63*, 2232. (m) Chaudhari, S. S. and Akamanchi, K. G., *Tetrahedron Lett.,* **1998**, *39*, 3209. (n) Hu, T.; Schaus, J. V.; Lam, K.; Palfreyman, M. G.; Wuonola, M.; Gustafson, G. and Panek, J. S., *J. Org. Chem.,* **1998**, *63*, 2401. (o) Carreira, E. M. and Ledford, B. E., *J. Braz. Chem. Soc.,* **1998**, *9*, 405. (p) Sato, Y.; Takimoto, M. and Mori, M., *Synlett,* **1997**, 734. (q) Kende, A. S., *Pure & Appl. Chem.,* **1997**, *69*, 407. (r) Bastiaans, H. M. M.; van der Baan, J. L. and Ottenheijm, H. C. J., *J. Org. Chem.,* **1997**, *62*, 3880. (s) Comins, D. L.; LaMunyon, D. H. and Chen, X. H., *J. Org. Chem.,* **1997**, *62*, 8182. (t) De Munari, S.; Firgerio, M. and Santagostino, M., *J. Org. Chem.,* **1996**, *61*, 9272. (u) Cox, R. J.; Sherwin, W. A.; Lam, L. K. P. and Vederas, J. C., *J. Am. Chem. Soc.,* **1996**, *118*, 7449. (v) Pandit, U. K.; Borer, B. C.; Bieräugel, H. and Deerenberg, S., *Pure & Appl. Chem.,* **1994**, *66*, 2131. (w) Cook, G. P. and Greenberg, M. M., *J. Org. Chem.,* **1994**, *59*, 4704. (x) Wipf, P. and Miller, C. P., *J. Org. Chem.,* **1993**, *58*, 3604. (y) Samano, V. and Robins, M. J., *J. Org. Chem.,* **1990**, *55*, 5186.

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D-Homo Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This rearrangement can be traced back to 1938 when 17β-hydroxy-20-ketosteroid was treated with a base to give a ring-enlarged ketone.[1] As this rearrangement occurs at the D-ring of steroids without the loss of a carbon, it is known as D-homo rearrangement or D-homo annulation.[2] In this rearrangement, when 17-hydroxy-20-ketosteroids are treated with either bases or acids (Lewis acids), they will rearrange and give six-membered D-rings; the products resulting from the base treatment differ greatly from those caused by the acid treatment, showing characteristic stereospecificity.[2b,2j,2l] Explicitly, the 17α-hydroxy-20-ketosteroids will form products with 17aβ-hydroxy configurations when treated with base, and 17β-hydroxy compounds give 17aα-hydroxy-D-homo derivatives. In contrast, when 17aα-hydroxy compounds are treated with Lewis acids, the 17aα-hydroxy-D-homo derivatives form, and 17β-hydroxy compounds give corresponding 17aβ-derivatives.[2b,2j,2l] The Lewis acids or the combinations of acids tested for this rearrangement include $MgBr_2$, $BF_3/Ac_2O/AcOH$, $AlCl_3/Ac_2O/AcOH$, $ZnCl_2/Ac_2O/AcOH$, and $SnCl_4/Ac_2O/AcOH$. However, the stereospecificity might not hold in the presence of a proton donor when Lewis acid is used.[2l] The rearrangement also occurs when a carbocation forms at position 20 without a carbonyl group.[3]

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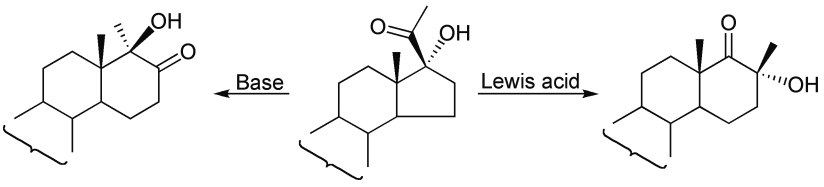
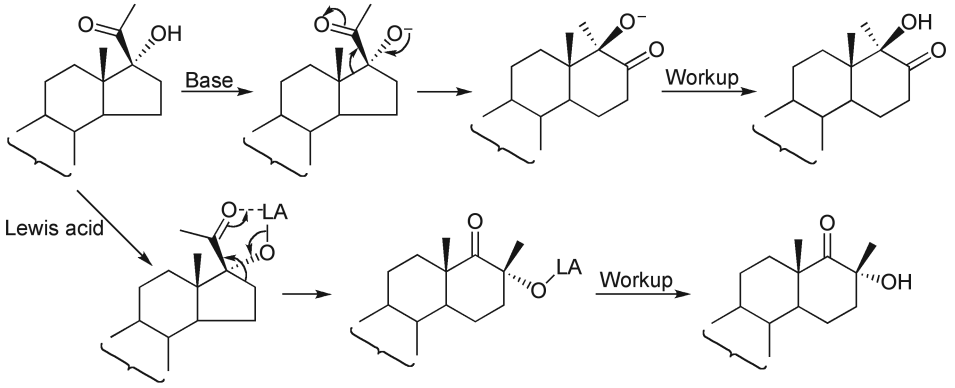
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is proposed that when 17α-hydroxy-20-ketosteroids are treated with a base, the oxygen atom on the carbonyl group will stay away from the oxygen anion originated from the hydroxy group; the migration will give a 17aβ-hydroxy derivative. In contrast, when the same molecule is treated with a Lewis acid, both oxygen atoms on the carbonyl and hydroxyl group will coordinate with the Lewis acid, and the migration of alkyl group results in a D-homo derivative with complete conservation of steric configuration, as illustrated here.



D. MODIFICATION

N/A

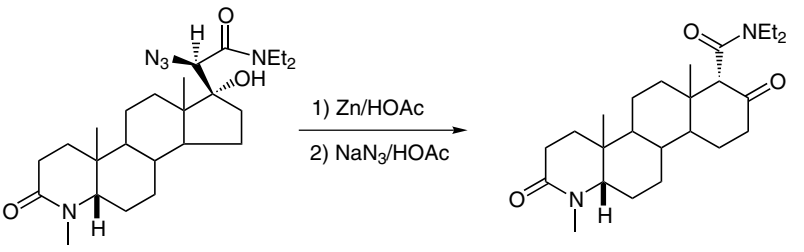
E. APPLICATIONS

This rearrangement has been used for the preparation of a series of steroid derivatives.

F. RELATED REACTIONS

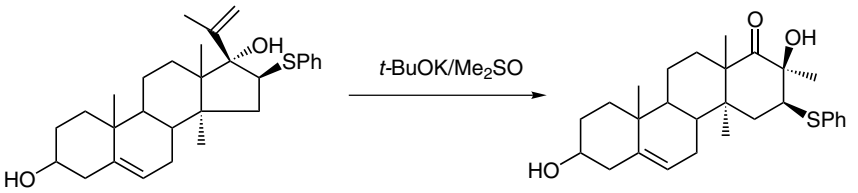
This reaction is related to the *Pinacol Rearrangement*.[2j]

G. CITED EXPERIMENTAL EXAMPLES



Reference 3.

To a solution of 1.37 g *N*,*N*-diethyl-4-methyl-3-oxo-17α-hydroxy-20α-azido-4-aza-5α-pregnane-21-carboxyamide in 35.0 mL acetic acid was added 1.37 g zinc powder in small portions over a period of 45 min at 20°C. The reaction mixture was stirred for 2 h at room temperature, after which gas evolution had ceased. The reaction mixture was filtered through Supercel and the excess of zinc was thoroughly washed with 27.8 mL of water containing 12.0 mL of acetic acid. The combined filtrates were diluted with 100 mL water and extracted with EtOAc. The extract was washed twice with water, and these washings were added to the acid layer. The latter was cooled in ice, and the pH was adjusted to 3–4; then 1.3 g sodium nitrite was added in portions. The diazotization was allowed to proceed overnight at 0–5°C with constant stirring. The reaction mixture was extracted four times with EtOAc, and the organic layers were combined and washed with water and brine, dried over $MgSO_4$, then filtered, and concentrated to give 1.07 g of a pale yellow oil. This oily material was then chromatographed on 60.0 g of EM silica gel with 3:2 acetone/hexane to give 683.0 mg 17α-(diethylcarbamoyl)-4-methyl-D-homo-4-aza-5α-androstane-3,17-dione as an amorphous material and 153.0 mg of a polar material as foam. Further purification of the former on HPLC followed by recrystallization afforded pure compound with melting point at 159–160°C.



Reference 2b.

To a solution of 196 mg 3β,17α-dihydroxy-16β-(phenylthio)pregn-5-en-20-one in 2 mL dry DMSO was added 2.6 mL 0.035 M *t*-BuOK in DMSO. After being stirred for 2 min at room temperature, the reaction mixture was quenched with concentrated HCl and worked up. After removal of the solvent, 200 mg 3β,17β-dihydroxy-17α-methyl-16β-(phenylthio)-D-homo-androst-5-en-17a-one was obtained. Recrystallization from ether afford pure product with melting point at 131–133°C.

Other references related to the D-homo rearrangement are cited in the literature.[4]

H. REFERENCES

1. Ruzicka, L. and Meldahl, H., *Helv. Chim. Acta,* **1938**, *21*, 1760.
2. (a) Schor, L.; Gros, E. G. and Seldes, A. M., *J. Chem. Soc., Perkin Trans. I,* **1992**, 453. (b) Bischofberger, N. and Walker, K. A. M., *J. Org. Chem.,* **1985**, *50*, 3604. (c) Rabinovich, D.; Shakked, Z.; Kirson, I.; Guenzberg, G. and Glotter, E., *J. Chem. Soc., Chem. Commun.,* **1976**, 461. (d) Lukacs, G.; Cloarec, L.; Lacombe, L. and Lusinchi, X., *Bull. Soc. Chim. Fr.,* **1972**, 180. (e) Mitsuhashi, H.; Shimizu, Y. and Kawahara, N., *Tetrahedron,* **1968**, *24*, 2789. (f) Elphimoff-Felkin, I., *Experientia,* **1959**, *15*, 447. (g) Wendler, N. L.; Taub, D. and Firestone, R., *Experientia,* **1959**, *15*, 237. (h) Wendler, N. L. and Taub, D., *J. Am. Chem. Soc.,* **1958**, *80*, 3402. (i) Oliveto, E. P.; Gerold, C.; Rausser, R. and Hershberg, E. B., *J. Am. Chem. Soc.,* **1957**, *79*, 3594. (j) Fukushima, D. K.; Dobriner, S.; Heffler, M. S.; Kritchevsky, T. H.; Herling, F. and Roberts, G., *J. Am. Chem. Soc.,* **1955**, *77*, 6585. (k) Georgian, V. and Kunder, N., *Chem. & Ind. (London),* **1954**, 431. (l) Turner, R. B., *J. Am. Chem. Soc.,* **1953**, *75*, 3484.
3. Steinberg, N. G.; Rasmusson, G. H.; Reynolds, G. F.; Hirshfield, J. H. and Arison, B. H., *J. Org. Chem.,* **1984**, *49*, 4731.
4. (a) Hanson, J. R., *Nat. Prod. Rep.*, **2004**, *21*, 386. (b) Schor, L.; Gros, E. G. and Seldes, A. M., *J. Chem. Soc., Perkin Trans. I,* **1992**, 453. (c) Schor, L.; Seldes, A. M. and Gros, E. G., *J. Chem. Soc., Perkin Trans. I,* **1990**, 163. (d) Rabinovich, D.; Shakked, Z.; Kirson, I.; Guenzberg, G. and Glotter, E., *J. Chem. Soc., Chem. Commun.,* **1976**, 461. (e) Deshmane, S. S. and Hirschmann, H., *J. Org. Chem.,* **1975**, *40*, 3470. (f) Hirschmann, F. B. and Hrischmann, H., *J. Org. Chem.,* **1973**, *38*, 1270. (g) Harper, I. T.; Tinsley, K. and Levine, S. D., *J. Org. Chem.,* **1971**, *36*, 59. (h) Lee, H. and Wolff, M. E., *J. Org. Chem.,* **1967**, *32*, 192. (i) Morrow, D. F.; Brokke, M. E.; Moersch, G. W.; Butler, M. E.; Klein, C. F.; Neuklis, W. A., and Huang, E. C. Y., *J. Org. Chem.,* **1965**, *30*, 212. (j) Wendler, N. L., "Rearrangements in Steroids" in *Molecular Rearrangements*, part 2, ed. de Mayo, P., Wiley-Interscience, New York, **1964**, pp. 1114–1138. (k) Wendler, N. L.; Taub, D. and Walker, R. W., *Tetrahedron,* **1960**, *11*, 163. (l) Wendler, N. L. and Taub, D., *J. Am. Chem. Soc.,* **1958**, *80*, 3402. (m) Oliveto, E. P.; Gerold, C.; Rausser, R. and Hershberg, E. B., *J. Am. Chem. Soc.,* **1957**, *79*, 3594. (n) Wendler, N. L. and Taub, *Chem. & Ind. (London),* **1957**, 822. (o) Wendler, N. L.; Taub, D.; Dobriner, S. and Fukushima, D. K., *J. Am. Chem. Soc.,* **1956**, *78*, 5027. (p) Hiskey, C. F.; Hirschmann, R. and Wendler, N. L., *J. Am. Chem. Soc.,* **1953**, *75*, 5135. (q) Shoppee, C. W. and Prins, D. A., *Helv. Chim. Acta,* **1943**, *26*, 201. (r) Ruzicka, L. and Meldahl, H. F., *Helv. Chim. Acta,* **1940**, *23*, 364. (s) Ruzicka, L. and Meldahl, H., *Helv. Chim. Acta,* **1939**, *22*, 421. (t) Ruzicka, L.; Gatzi, K. and Reichstein, T., *Helv. Chim. Acta,* **1939**, *22*, 626.

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Dieckmann Condensation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Dieckmann in 1894.[1] It is a base-promoted intramolecular condensation of α,ω-diesters to form cyclic β-ketoesters that can be further transformed into cyclic ketone upon hydrolysis and decarboxylation. Therefore, it is generally known as the Dieckmann condensation.[2] In addition, this reaction is often referred to as the Dieckmann reaction[3] or Dieckmann cyclization.[4] Occasionally, it is called Dieckmann ring closure.[5] It should be pointed out that this reaction is not only good for the preparation of 5- or 6-membered cyclic β-keto esters[1,6] but also an important tool for synthesizing even larger cyclic ketones.[7] Examples include the cyclization of various aminodiesters to 10-membered cyclic aminoketones and 16- and 20-membered cyclic diaminodiketones.[8] The formation of 5- to 6-membered cyclic β-keto esters is usually carried out in an alcoholic solvent by the treatment of sodium alkoxide; whereas the formation of large cyclic ketones take places in an aprotic solvent (e.g., xylene) under high dilution conditions when diesters are treated with potassium *t*-butoxide under nitrogen atmosphere,[7a] such as the formation of metacyclophanes from methyl esters of *meta*-benzenedialkanoic acids with carbonyl groups at the centers of the *meta*-bridges.[9] The importance of this reaction has been evidenced in the preparation of complicated cyclic compounds in a series of tandem reactions, as shown in the tandem [2+2] cycloaddition-Dieckmann condensation[10] and tandem conjugate addition- (or *Michael Addition*)-Dieckmann condensation.[11] Theoretically, the Dieckmann condensation is a special case of *Claisen Condensation*, and its mechanism is also similar to the *Claisen Condensation*. It has been proved that the Dieckmann con-

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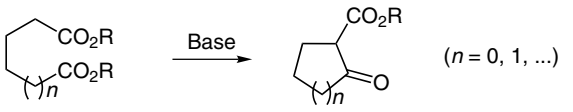
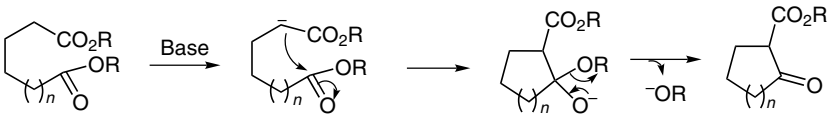
densation also occurs in the gas phase, with a mechanism analogous to the solution phase condensation.[12] However, the carbanion formed from proton abstraction in the solution phase is the actual intermediate for condensation, while the carbanion generated similarly in the gas phase may not necessarily be the intermediate of condensation.[12]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

N/A

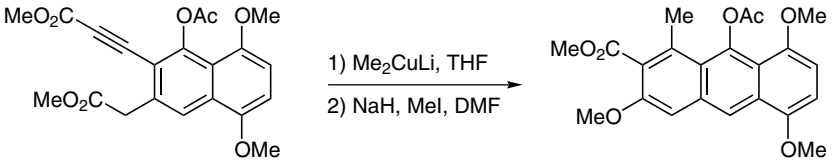
E. APPLICATIONS

This reaction has general application in the synthesis of cyclic ketones.

F. RELATED REACTIONS

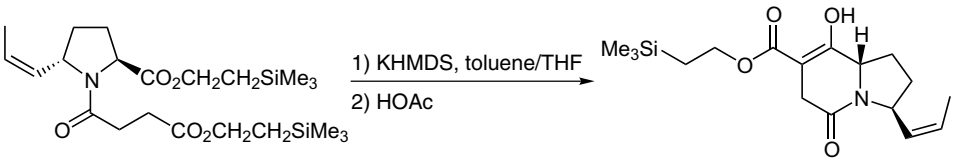
This reaction is related to the *Claisen Condensation.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 13.

To an ice-cooled suspension of CuI (119 mg, 0.627 mmol) in 2 mL THF was added 0.78 mL 1.6 M ether solution of MeLi (1.255 mmol) during stirring. The mixture was stirred for 10 min, then 200 mg 3-(1-acetoxy-5,8-dimethoxy-3-methoxycarbonylmethyl-naphthalen-2-yl)-propynoic acid methyl ester (0.502 mmol) in 4 mL THF was introduced via cannulation. The reaction mixture was allowed to warm up to room temperature and then stirred overnight. Then it was quenched with 10% HCl, and the product was extracted with EtOAc. Organic layers were combined and washed with water, dried over Na_2SO_4, and concentrated in vacuo. The crude yellow product (160 mg, 84% crude yield) was used in the next step without purification. To a solution of crude phenol (160 mg, 0.41 mmol) in 2 mL DMF at room temperature was added 160 mg K_2CO_3 (1.16 mmol) followed by 0.05 mL MeI (0.8 mmol). The resulting suspension was stirred overnight; and then diluted with water. The product was extracted with EtOAc, and the combined organic layers were washed with water, dried over Na_2SO_4, and concentrated in vacuo. Silica gel chromatography (CH_2Cl_2) yielded 120 mg 9-acetoxy-3,5,8-trimethoxy-1-methyl-anthracene-2-carboxylic acid methyl ester as a yellow solid, in a yield of 60% over two steps, m.p. 227–228°C.



Reference 4d.

To a solution of 0.486 g (2*S*,5*S*)-5-*cis*-propenyl-1-[3-(2-trimethylsilanylethoxy-carbonyl)propionyl]pyrrolidine-2-carboxylic acid 2-trimethylsilanylethyl ester (1.07 mmol) in 100 mL THF at –78°C under argon was slowly added 3.21 mL 0.5 M potassium bis(trimethylsilyl)amide in toluene (1.61 mmol). A pale orange solution was formed, which was allowed to warm to room temperature over 2 h. The reaction was then quenched with 0.31 mL glacial acetic acid (5.5 mmol), and the solvent was evaporated. The residue was triturated with Et_2O and filtered, and the filtrate was dried over sodium sulfate and evaporated to yield an orange oil, which was purified by column chromatography (EtOAc/hexanes, 1:4) to yield 0.188 g (3*S*,9*R*)-8-hydroxy-5-oxo-3-*cis*-propenyl-1,2,3,5,6,8a-hexahydroindolizine-7-carboxylic acid 2-trimethylsilanylethyl ester as an unstable colorless solid, in a yield of 52%.

Other references related to the Dieckmann condensation are cited in the literature.[13]

H. REFERENCES

1. (a) Dieckmann, W., *Ber.*, **1894**, *27*, 102. b) Dieckmann, W., *Ber.*, **1894**, *27*, 965.
2. (a) Nagase, R.; Gotoh, H.; Katayama, M.; Manta, N. and Tanabe, Y., *Heterocycles,* **2007**, *72*, 697. (b) Boehme, R.; Jung, G. and Breitmaier, E., *Helv. Chim. Acta,* **2005**, *88*, 2837. (c) Tanabe, Y.; Manta, N.; Nagase, R.; Misaki, T.; Nishii, Y.; Sunagawa, M. and Sasaki, A., *Adv. Synth. Catal.,* **2003**, *345*, 967. (d) Shinohara, I.; Okue, M.; Yamada, Y. and Nagaoka, H., *Tetrahedron Lett*., **2003**, *44*, 4649. (e) Tanabe, Y.; Makita, A.; Funakoshi, S.; Hamasaki, R. and Kawakusu,

T., *Adv. Synth. Catal.,* **2002**, *344*, 507. (f) Deville, J. P. and Behar, V., *Org. Lett.,* **2002**, *4*, 1403. (g) Rabiczko, J.; Urbanczyk-Lipkowska, Z. and Chmielewski, M., *Tetrahedron*, **2002**, *58*, 1433. (h) Balo, C.; Fernandez, F.; Garcia-Mera, X. and Lopez, C., *Org. Prep. Proc. Int.,* **2000**, *32*, 563. (i) Toda, F.; Suzuki, T. and Higa, S., *J. Chem. Soc., Perkin Trans. I,* **1998**, 3521. (j) Kulkarni, B. A. and Ganesan, A., *Angew. Chem. Int. Ed. Engl.,* **1997**, *36*, 2454. (k) Nishimura, T.; Sunagawa, M.; Okajima, T. and Fukazawa, Y., *Tetrahedron Lett*., **1997**, *38*, 7063. (l) Kanemasa, S.; Yamamoto, H. and Kobayashi, S., *Tetrahedron Lett*., **1996**, *37*, 8505. (m) Sieburth, S. McN. and Chen, C.-A., *Synlett,* **1995**, 928. (n) Boger, D. L. and Nishi, T., *Bioorg. Med. Chem.,* **1995**, *3*, 67. (o) Honda, T. and Mori, M., *Chem. Lett.,* **1994**, 1013. (p) Ukrainets, I. V.; Taran, S. G.; Bezugly, P. A. and Evtifeeva, O. A., *Khim. Geterotsiklicheskikh Soedinenii*, **1993**, 1219. (q) Christl, M.; Lanzendoerfer, U.; Groetsch, M. M.; Hegmann, J.; Ditterich, E.; Huettner, G.; Peters, E. M.; Peters, K. and von Schnering, H. G., *Chem. Ber.,* **1993**, *126*, 797. (r) Patek, M., *Coll. Czech. Chem. Commun.,* **1990**, *55*, 1223. (s) Patek, M. and Hampl, F., *Coll. Czech. Chem. Commun.,* **1989**, *54*, 3267. (t) Raftery, M. J. and Bowie, J. H., *Org. Mass Spect.,* **1988**, *23*, 719. (u) Kodpinid, M. and Thebtaranonth, Y., *Tetrahedron Lett*., **1984**, *25*, 2509. (v) Nomura, K.; Suda, S.; Takeuchi, M.; Adachi, J. and Masuda, K., *Heterocycles*, **1983**, *20*, 2051. (w) Nesmeyanov, A. N.; Yur'eva, L. P.; Zaitseva, N. N. and Vasyukova, N. I., *J. Organomet. Chem.,* **1978**, *153*, 341.

3. (a) Cuny, G. D.; Lee, K. and Choi, S. W., *Lett. Org. Chem.,* **2006**, *3*, 68. (b) Wang, Y. and Ma, D., *Tetrahedron: Asymmetry*, **2001**, *12*, 725. (c) Pinto, A. C.; Abdala, R. V. and Costa, P. R. R., *Tetrahedron: Asymmetry*, **2000**, *11*, 4239. (d) Jackson, B. G.; Gardner, J. P. and Heath, P. C., *Tetrahedron Lett*., **1990**, *31*, 6317. (e) Unangst, P. C.; Connor, D. T.; Stabler, S. R. and Weikert, R. J., *J. Heterocycl. Chem.,* **1987**, *24*, 811. (f) De Vries, J. G.; Hauser, G. and Sigmund, G., *Heterocycles*, **1985**, *23*, 1081. (g) Hurd, R. N. and Shah, D. H., *J. Org. Chem.,* **1973**, *38*, 390.
4. (a) Groth, U.; Kesenheimer, C. and Kreye, P., *Synlett,* **2006**, 2223. (b) Covarrubias-Zuniga, A.; San German-Sanchez, L.; Maldonado, L. A.; Romero-Ortega, M. and Avila-Zarraga, J. G., *Synthesis*, **2005**, 2293. (c) Groth, U.; Halfbrodt, W.; Kalogerakis, A.; Koehler, T. and Kreye, P., *Synlett*, **2004**, 291. (d) Hanessian, S.; Sailes, H.; Munro, A. and Therrien, E., *J. Org. Chem.,* **2003**, *68*, 7219. (e) Andrews, M. D.; Brewster, A. G.; Crapnell, K. M.; Ibbett, A. J.; Jones, T.; Moloney, M. G.; Prout, K. and Watkin, D., *J. Chem. Soc., Perkin Trans. I,* **1998**, 223. (f) Pecanha, E. P.; Barreiro, E. J. and Fraga, C. A. M., *Quim. Nova*, **1997**, *20*, 435. (g) Groth, U.; Halfbrodt, W.; Koehler, T. and Kreye, P., *Liebigs Annalen Chem.*, **1994**, 885. (h) Poncet, J.; Jouin, P.; Castro, B.; Nicolas, L.; Boutar, M. and Gaudemer, A., *J. Chem. Soc., Perkin Trans. I,* **1990**, 611. (i) Bonjoch, J.; Serret, I. and Bosch, J., *Tetrahedron,* **1984**, *40*, 2505. (j) Crowley, J. I. and Rapoport, H., *J. Org. Chem.,* **1980**, *45*, 3215. (k) Nee, G. and Tchoubar, B., *Tetrahedron Lett*., **1979**, 3717.
5. Totton, E. L.; Kilpatrick, G. R.; Horton, N. and Blakeney, S. A., *J. Org. Chem.,* **1965**, *30*, 1647.
6. Dieckmann, W., *Ann.,* **1901**, *317*, 27.
7. (a) Leonard, N. J. and Schimelpfenig, C. W., *J. Org. Chem.,* **1958**, *23*, 1708. (b) Ziegler, K.; Eberle, H. and Ohlinger, H., *Ann.,* **1933**, *504*, 94.
8. (a) Leonard, N. J.; Õki, M. and Chiavarelli, S., *J. Am. Chem. Soc.,* **1955**, *77*, 6234. (b) Leonard, N. J. and Õki, M., *J. Am. Chem. Soc.,* **1955**, *77*, 6241. (c) Leonard, N. J. and Õki, M., *J. Am. Chem. Soc.,* **1955**, *77*, 6245.
9. Schimelpfenig, C. W., *J. Org. Chem.,* **1975**, *40*, 1493.
10. (a) Shindo, M.; Sato, Y. and Shishido, K., *J. Org. Chem.,* **2001**, *66*, 7818. (b) Shindo, M.; Sato, Y. and Shishido, K., *J. Am. Chem. Soc.*, **1999**, *121*, 6507.
11. (a) Tatsuta, K.; Yamazaki, T.; Mase, T. and Yoshimoto, T., *Tetrahedron Lett*., **1998**, *39*, 1771. (b) Kobayashi, K.; Maeda, K.; Uneda, T.; Morikawa, O. and Konishi, H., *J. Chem. Soc., Perkin Trans. I*, **1997**, 443. (c) Maiti, S.; Bhaduri, S.; Achari, B.; Banerjee, A. K.; Nayak, N. P. and Mukherjee, A. K., *Tetrahedron Lett*., **1996**, *44*, 8061. (d) Bunce, R. A. and Harris, C. R., *J. Org. Chem.,* **1992**, *57*, 6981.
12. Burinsky, D. J. and Cooks, R. G., *J. Org. Chem.,* **1982**, *47*, 4864.

13. Kozhinov, D. V. and Behar, V., *J. Org. Chem.*, **2004**, *69*, 1378.

14. (a) Martinez, A. D.; Deville, J. P.; Stevens, J. L and Behar, V., *J. Org. Chem.*, **2004**, *69*, 991. (b) Vedejs, E. and Zajac, M. A., *Org. Lett.,* **2001**, *3*, 2451. (c) Sano, S.; Ushirogochi, H.; Morimoto, K.; Tamai, S. and Nagao, Y., *Chem. Commun.,* **1996**, 1775. (d) Sibi, M. P.; Christensen, J. W.; Kim, S.-G.; Eggen, M.; Stessman, C. and Oien, L., *Tetrahedron Lett*., **1995**, *36*, 6209. (e) Neyer, G. and Ugi, I., *Synthesis*, **1991**, 743. (f) Davis, D. R. and Garratt, P. J., "Acylation of Esters, Ketones and Nitriles" in *Comprehensive Organic Synthesis*, ed. Trost, B. M. and Fleming, I., Pergamon, Oxford, **1991**, *2*, pp. 795–863. (g) Chakravarti, R. N. and Dutta, N., *J. Ind. Chem. Soc.*, **1974**, *51*, 239. (h) Bagavant, G.; Thaoker, M. R. and Raich, N. K., *Curr. Sci.,* **1974**, *43*, 248. (i) Nace, H. R. and Smith, A. H., *J. Org. Chem.,* **1973**, *38*, 1941. (j) Ginsburg, D., *Acc. Chem. Res.,* **1969**, *2*, 121. (k) Thaoker, M. R. and Bagavant, G., *J. Ind. Chem. Soc.*, **1968**, *45*, 885. (l) Schaefer, J. P. and Bloomfield, J. J., *Org. React.,* **1967**, *15*, 1. (m) Totton, E. L.; Camp, N. C.; Cooper, G. M.; Haywood, B. D. and Lewis, D. P., *J. Org. Chem.,* **1967**, *32*, 2033. (n) House, H. O. and Babad, H., *J. Org. Chem.*, **1963**, *28*, 90. (o) Totton, E. L.; Freeman, R. C.; Powell, H. and Yarboro, T., *J. Org. Chem.,* **1961**, *26*, 343. (p) Kline, G. B., *J. Am. Chem. Soc.,* **1959**, *81*, 2251. (q) Carrick, W. L. and Fry, A., *J. Am. Chem. Soc.,* **1955**, *77*, 4381. (r) Dieckmann, W. and Groeneveld, A., *Ann.,* **1901**, *317*, 27. (s) Dieckmann, W. and Groeneveld, A., *Ber.,* **1900**, *33*, 595. (t) Dieckmann, W., *Ber.,* **1900**, *33*, 2670.

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Diels-Alder Reaction
(Diels-Alder Condensation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Diels and Alder in 1928.[1] It is an electrocyclic [4+2]-cycloaddition between a conjugated diene and a dienophile (either alkene or alkyne) for the synthesis of an unsaturated six-membered ring. Therefore, it is generally known as the Diels-Alder reaction[2] or Diels-Alder cycloaddition.[3] However, it was also referred to as the Diels-Alder diene synthesis,[4] and the Diels-Alder synthesis[5] during the early development stage of this reaction. The products from this reaction are called cycloadducts. As numerous publications on Diels-Alder reaction appear each year, it is impossible to review all of them.[6] For example, the Diels-Alder reaction probably is one of the most commonly applied reactions in organic synthesis, as indicated by the 637 papers published from 1990 to 2000 on ACS. In addition, there are many monographs (or books[7]) and reviews[2l-2p,3m,4-6,8] available for the Diels-Alder reaction. In this reaction, the substituents on diene and dienophile both play very important roles, as they all affect the electron densities and orbital energy of the reactants. Generally speaking, a diene can react with a dienophile using diene's HOMO (highest occupied molecular orbital) and dienophile's LUMO (lowest unoccupied molecular orbital) or vice versa. According to the Woodward-Hofman's rule[9] and Fukui's frontier molecular orbital theory (FMO),[10] the Diels-Alder reaction can be divided into three types: the normal Diels-Alder reaction ($HOMO_{diene}$+ $LUMO_{dienophile}$), the inverse electron demand Diels-Alder reaction or simply the inverse Diels-Alder reaction ($LUMO_{diene}$+ $HOMO_{dienophile}$), and the neutral Diels-Alder reaction.[8n] The reaction rate is related to the magnitude of the lowest HOMO–LUMO energy separation attainable by the diene-dienophile components. For the normal Diels-Alder reaction, electron-donating groups on dienes will level up the HOMO energy of dienes, and the electron-withdrawing group will lower the LUMO energy of dienophile; as a result, the magnitude between the HOMO–LUMO gaps is reduced, and the Diels-Alder reaction is

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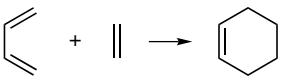
accelerated. Similarly, the electron demanding will be reversed on dienes and dienophiles in the inverse electron demand Diels-Alder reaction. For the neutral Diels-Alder reaction, the energy gap between $HOMO_{diene}$- $LUMO_{dienophile}$ and $LUMO_{diene}$ - $HOMO_{dienophile}$ does not differ too much, and either combination will lead to the formation of product, as in the case of ethylene and 1,3-butadiene.[11]

It is important to note that the Diels-Alder reaction shows high regioselectivity, diastereoselectivity and enantioselectivity, which are controlled by the compatibility between the HOMO–LUMO pairs of dienes and dienophiles. During the cycloaddition, dienes can take s-*cis* or s-*trans* conformation (*cisoid* or *transoid*); however, only the s-*cis* conformation can participate in the cycloaddition.[8s,12] If dienes are restricted to s-*trans* conformation, almost no Diels-Alder reactions occur from these dienes.[13] The small cyclic dienes have been forced to take the s-*cis* conformation (e.g., cyclopentadienes and cyclohexadienes); they are very good candidates for such reaction.[14] For the case of dienophiles, *cis*-dienophiles give *cis*-substitution, and *trans*-dienophiles result in *trans*-substitution in the cycloadducts. The major product for cyclic diene is an *endo* product, in which the electron-withdrawing groups will be on the same side as the double bond of the bicyclic ring, because it is favored by secondary orbital interactions via kinetic control.[15] Overall, the product formed from the suprafacial–suprafacial interaction with the *endo* approach will be the most favored product.[2m]

The introduction of an atom other than carbon to either dienes or dienophiles will result in the hetero-Diels-Alder reaction.[16] Owing to the nature (steric effect, electronic effect, etc.) of substituents on dienes and dienophiles, the Diels-Alder reaction might occur through a synchronous concerted, an asynchronous concerted, or a stepwise reaction mechanism.[17] The stepwise and asynchronous concerted Diels-Alder reactions proceed via diradical intermediates,[18] whereas the synchronous concerted mechanisms does not. It should be pointed out that most of the Diels-Alder reactions are concerted; as a result, both the rate constants and the stereoselectivities of Diels-Alder reaction are only moderately sensitive to the changes in the nature of organic solvents.[8i] However, it has been clearly shown that the applications of water to the reaction system can greatly accelerate such reactions.[19] Other modifications on this reactions include the application of high pressure,[2e] Lewis acid,[20] and ultrasound radiation.[8i] More information about this reaction can be easily attained from reviews and relevant books.

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Provided here is a simple illustration for the Diels-Alder reaction proceeding through a synchronous concerted mechanism.

D. MODIFICATION

There are many modifications on this reaction, including the application of Lewis acids, aqueous media, high pressure, and ultrasonic radiation.

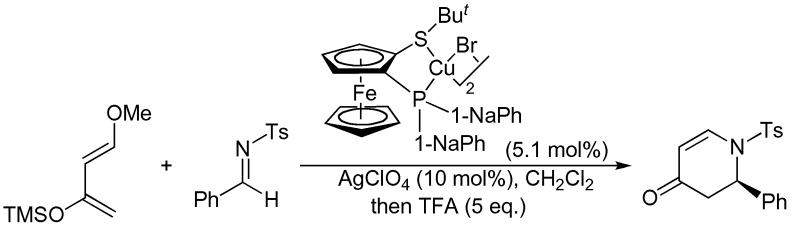
E. APPLICATIONS

This reaction has very broad application in organic synthesis, regarding the preparation of cyclic compounds.

F. RELATED REACTIONS

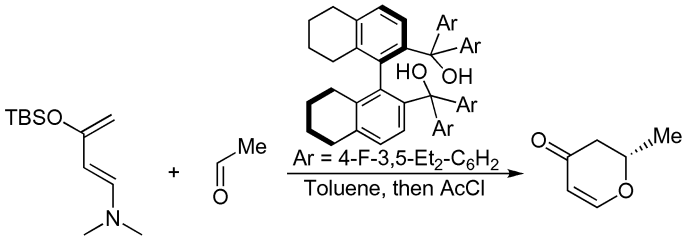
This reaction is related to *Retro-Diels-Alder Reaction.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 21.

A solution of 0.0056 mmol ferrocene catalyst and 0.011 mmol $AgClO_4$ in 0.6 mL CH_2Cl_2 was stirred in the dark at room temperature under argon for 2 h and treated with a solution of 0.11 mmol imine in 1 mL CH_2Cl_2. The reaction mixture was stirred at room temperature for 5 min before it was treated with 0.15 mmol diene at room temperature. Once the starting material was consumed, 0.1–0.2 mL TFA was added, and the mixture was stirred at room temperature for 30–60 min. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, dried over $MgSO_4$ and filtered. After evaporation of the solvent, the residue was purified by flash chromatography (*n*-hexane/EtOAc, 4:1) to give (*R*)-2-phenyl-1-(*p*-tolylsulfonyl)-2,3-dihydro-4-1*H*-pyridone [(*R*)-5a] as a white solide, in a yield of 87%, 97% e.e., m.p., 122–123°C (CH_2Cl_2/*n*-hexane).



Reference 22.

To a solution of 1.0 mmol aldehyde and 0.1 mmol diol in 0.5 mL toluene at –40°C (temperature of the cooling bath) was added 0.5 mmol (*E*)-1-dimethylamino-3-*tert*-butyldimethylsiloxy-1,3-butadiene dropwise (5–10 s). The reaction was maintained at the temperature for 1 day. The reaction was then brought to –78°C (dry ice/acetone) before dilution with 1.0 mL CH_2Cl_2 and subsequent addition of 1.0 mmol acetyl chloride. This was allowed to stir for 30 min at –78°C before the crude mixture was transferred directly on top of a silica gel column and eluted with hexanes/EtOAc to afford 75% 2,3-dihydro-2-methyl-4*H*-pyran-4-one as a pale yellow oil, with 97% e.e.

Other references related to the Diels-Alder reactions are cited in the literature.[23]

H. REFERENCES

1. Diels, O. and Alder, K., *Ann.,* **1928**, *460*, 98.
2. (a) Heredia-Moya, J.; Krohn, K.; Florke, U.; Pessoa-Mahana, H.; Weiss-Lopez, B.; Estevez-Braun, A. and Araya-Maturana, R., *Heterocycles*, **2007**, *71*, 1327. (b) Iida, K.; Mitani, M. and Kuroda, C., *Bull. Chem. Soc. Jpn.,* **2007**, *80*, 966. (c) Motoyoshiya, J.; Masue, Y.; Nishi, Y. and Aoyama, H., *Nat. Prod. Commun.,* **2007**, *2*, 67.(d) Mohan, C.; Bhargava, G.; Pannu, A. P. S. and Mahajan, M. P., *Tetrahedron Lett*., **2007**, *48*, 1711. (e) Ilyin, A.; Kysil, V.; Krasavin, M.; Kurashvili, I. and Ivachtchenko, A. V., *J. Org. Chem.,* **2006**, *71*, 9544. (f) Keiko, N. A.; Kuznetsova, T. A.; Larina, L. I.; Chuvashev, Yu. A.; Klepikova, T. A. and Sherstyannikova, L. V., *Russ. J. Org. Chem.,* **2006**, *42*, 1421. (g) Fu, A. P. and Thiel, W., *THEOCHEM*, **2006**, *765*, 45. (h) Yamashita, Y.; Salter, M. M.; Aoyama, K. and Kobayashi, S., *Angew. Chem. Int. Ed.,* **2006**, *45*, 3816. (i) He, M.; Struble, J. R. and Bode, J. W., *J. Am. Chem. Soc.,* **2006**, *128*, 8418. (j) Brel, V. K., *Synthesis*, **2006**, 339. (k) Girotti, R.; Marrocchi, A.; Minuti, L.; Piermatti, O.; Pizzo, F. and Vaccaro, L., *J. Org. Chem.,* **2006**, *71*, 70. (l) Mehta, G. and Uma, R., *Acc. Chem. Res.,* **2000**, *33*, 278. (m) Kagan, H. B. and Riant, O., *Chem. Rev.,* **1992**, *92*, 1007. (n) Thomas, E. J., *Acc. Chem. Res.,* **1991**, *24*, 229. (o) Brieger, G. and Bennett, J. N., *Chem. Rev.,* **1980**, *80*, 63. (p) McCabe, J. R. and Eckert, C. A., *Acc. Chem. Res.,* **1974**, *7*, 251.
3. (a) Songis, O.; Didierjean, C.; Laurent, C.; Martinez, J. and Calmes, M., *Eur. J. Org. Chem.,* **2007**, 3166. (b) Timko, M. T.; Allen, A. J.; Danheiser, R. L.; Steinfeld, J. I.; Smith, K. A. and Tester, J. W., *Ind. Eng. Chem. Res.,* **2006**, *45*, 1594. (c) Fuwa, H. and Sasaki, M., *Chem. Commun.,* **2007**, 2876. (d) Patrick, T. B.; Gorrell, K. and Rogers, J., *J. Fluor. Chem.,* **2007**, *128*, 710. (e) Borthakur, S. K.; Boruah, P. and Goswami, B. N., *J. Chem. Res.,* **2007**, 127. (f) Shin, I.-J.; Choi, E.-S. and Cho, C.-G., *Angew. Chem. Int. Ed.,* **2007**, *46*, 2303. (g) Alvarez-Manzaneda, E. J.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidour, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Hmamouchi, M. and Bouanou, H., *J. Org. Chem.,* **2007**, *72*, 3332. (h) Gu, S.-Y.; Sheu, J.-H. and Su, M.-D., *Inorg. Chem.,* **2007**, *46*, 2028. (i) Stumpe, K.; Komber, H. and Voit, B. I., *Macromol. Chem. Phys.,* **2006**, *207*, 1825. (j) Diaz-Ortiz, A.; De Cozar, A.; Prieto, P.; De la Hoz, A. and Moreno, A., *Tetrahedron Lett*., **2006**, *47*, 8761. (k) Menard-Moyon, C.; Dumas, F.; Doris, E. and Mioskowski, C., *J. Am. Chem. Soc.,* **2006**, *128*, 14764. (l) Ostrowski, S. and Wyrebek, P., *Tetrahedron Lett*., **2006**, *47*, 8437. (m) Weinreb, S. M., *Acc. Chem. Res.,* **1985**, *18*, 16.
4. Norton, J. A., *Chem. Rev.,* **1942**, *31*, 319.
5. Needleman, S. B. and Kuo, M. C. C., *Chem. Rev.,* **1962**, *62*, 405.
6. Kumar, A., *Chem. Rev.,* **2001**, *101*, 1.
7. (a) Fringuelli, F. and Taticchi, A., *The Diels-Alder Reaction: Selected Practical Methods*, John Wiley & Sons, Chichester, **2002**. (b) Fringuelli, F. and Taticchi, A., *Dienes in the Diels-Alder Reaction*, Wiley-Interscience, New York, **1990**. (c) Boger, D. L. and Weinreb, S. M., *Hetero*

Diels-Alder Methodology in Organic Synthesis, Academic Press, San Diego, **1987**. (d) Taber, D. F., *Intramolecular Diels-Alder and Alder Ene Reactions*, Springer-Verlag, Berlin, **1984**. (e) Hamer, J., *1,4-Cycloaddition Reactions, the Diels-Alder Reaction in Heterocyclic Syntheses*, Academic Press, New York, **1967**. (f) Wassermann, A., *Diels-Alder Reactions; Organic Background and Physicochemical Aspects*, Elsevier Publications, Amsterdam, **1965**.

8. (a) Notz, W.; Tanaka, F. and Barbas, C. F., *Acc. Chem. Res.,* **2004**, *37*, 580. (b) Klunder, A. J. H.; Zhu, J. and Zwanenburg, B., *Chem. Rev.,* **1999**, *99*, 1163. (c) Winklerm, J. D., *Chem. Rev.,* **1996**, *96*, 167. (d) Houk, K. N.; Gonzàlez, J. and Li, Y., *Acc. Chem. Res.,* **1995**, *28*, 81. (e) Streith, J. and DeFoin, A., *Synthesis,* **1994**, 1107. (f) Oh, T. and Reilly, M., *Org. Prep. Proceed. Int.,* **1994**, *26*, 131. (g) Waldmann, H., *Synthesis,* **1994**, 535. (h) Boger, D. L., *Synthesis,* **1994**, 451. (i) Pindur, U.; Lutz, G. and Otto, C., *Chem. Rev.,* **1993**, *93*, 741. (j) Oppolzer, W., *Comp. Org. Syn.,* **1991**, *5*, 315. (k) Rousch, W. R., *Comp. Org. Syn.,* **1991**, *5*, 513. (l) Weinreb, S. M., *Comp. Org. Syn.,* **1991**, *5*, 401. (m) Schmidt, R. R., *Acc. Chem. Res.,* **1986**, *19*, 250. (n) Boger, D. L., *Chem. Rev.,* **1986**, *86*, 781. (o) Ciganek, E., *Org. React.,* **1984**, *32*, 1. (p) Oppolzer, W., *Angew. Chem. Int. Ed. Engl.,* **1977**, *16*, 10. (q) Houk, K. N., *Acc. Chem. Res.,* **1975**, *8*, 363. (r) Carlson, R. G., *Annu. Rep. Med. Chem.,* **1974**, *9*, 270. (s) Hill, R. K., *Chem. Rev.,* **1961**, 537. (t) Butz, L. W. and Rytina, A. W., *Org. React.,* **1949**, *5*, 136. (u) Kloetzel, M. C., *Org. React.,* **1948**, *4*, 1. (v) Holmes, H. L., *Org. React.,* **1948**, *4*, 60. (w) Kwart, H. and King, K., *Chem. Rev.,* **1968**, *68*, 415.
9. (a) Woodward, R. B. and Hoffman, R., *J. Am. Chem. Soc.,* **1965**, *87*, 2511. (b) Woodward, R. B. and Hoffman, R., *J. Am. Chem. Soc.,* **1965**, *87*, 395. (c) Woodward, R. B., *J. Am. Chem. Soc.,* **1942**, *64*, 3058.
10. Fukui, A., *Acc. Chem. Res.*, **1971**, *4*, 57.
11. (a) Berski, S.; Andrés, J.; Silvi, B. and Domingo, L. R., *J. Phys. Chem. A,* **2003**, *107*, 6014. (b) Dinadayalane, T. C.; Vijaya, R.; Smitha, A. and Sastry G. N., *J. Phys. Chem. A,* **2002**, *106*, 1627. (c) Goldstein, E.; Beno, B. and Houk, K. N., *J. Am. Chem. Soc.,* **1996**, *118*, 6036. (d) Dewar, M. J. S.; Olivella, S. and Stewart, J. J. P., *J. Am. Chem. Soc.,* **1986**, *108*, 5771.
12. (a) Lin, Y.-S.; Chang, S.-Y.; Yang, M.-S.; Rao, Ch. P.; Peddinti, R. K.; Tsai, Y.-F. and Liao, C.-C., *J. Org. Chem.,* **2004**, *69*, 447. (b) Robiette, R.; Cheboub-Benchaba, K.; Peeters, D. and Marchand-Brynaert, J., *J. Org. Chem.,* **2003**, *68*, 9809.
13. Saito, A.; Ito, H. and Taguchi, T., *Org. Lett.,* **2002**, *4*, 4619.
14. Ohkata, K.; Tamura, Y.; Shetuni, B. B.; Takagi, R.; Miyanaga, W.; Kojima, S. and Paquette, L. A., *J. Am. Chem. Soc.,* **2004**, *126*, 16783.
15. (a) Arrieta, A.; Cossio, F. P. and Lecea, B., *J. Org. Chem.,* **2001**, *66*, 6178. (b) Apeloig, Y. and Matzner, E., *J. Am. Chem. Soc.,* **1995**, *117*, 5375. (c) Fox, M. A.; Cardona, R. and Kiwiet, N. J., *J. Org. Chem.,* **1987**, *52*, 1469. (d) Alston, P. V.; Gordon, M. D.; Ottenbrite, R. M. and Cohen, T., *J. Org. Chem.,* **1983**, *48*, 5051. (e) Alston, P.; Ottenbrite, R. and Cohen, T., *J. Org. Chem.,* **1979**, *44*, 3739. (f) Alston, P. V.; Ottenbrite, R. M. and Cohen, T., *J. Org. Chem.,* **1978**, *43*, 1864. (g) Eckroth, D. R., *J. Org. Chem.,* **1976**, *41*, 394.
16. (a) Amos, D. T.; Renslo, A. R. and Danheiser, R. L., *J. Am. Chem. Soc.,* **2003**, *125*, 4970. (b) Chavez, D. E. and Jacobsen, E. N., *Org. Lett.,* **2003**, *5*, 2563. (c) Huang, Y. and Rawal, V. H., *J. Am. Chem. Soc.,* **2002**, *124*, 9662. (d) Bear, B. R. and Shea, K. J., *Org. Lett.,* **2001**, *3*, 723.
17. (a) Minary, P. and Tuckerman, M. E., *J. Am. Chem. Soc.,* **2004**, *126*, 13920. (b) Chronakis, N. and Orfanopoulos, M., *Org. Lett.,* **2001**, *3*, 545. (c) Orlova, G. and Goddard, J. D., *J. Org. Chem.,* **2001**, *66*, 4026. (d) Sakai, S., *J. Phys. Chem. A.,* **2000**, *104*, 922. (e) Chen, J. S.; Houk, K. N. and Foote, C. S., *J. Am. Chem. Soc.,* **1998**, *120*, 12303.(f) Houk, K. N.; Lin, Y. T. and Brown, F. K., *J. Am. Chem. Soc.,* **1986**, *108*, 554.
18. Branchadell, V.; Font, J.; Moglioni, A. G.; Ochoa de Echaguen, C.; Oliva, A.; Ortuno, R. M.; Veciana, J. and Vidal-Gancedo, J., *J. Am. Chem. Soc.,* **1997**, *119*, 9992.

19. Breslow, R., *Acc. Chem. Res.,* **1991**, *24*, 150.

20. (a) Davies, H. M. L. and Dai, X., *J. Am. Chem. Soc.,* **2004**, *126*, 2692. (b) Mori, K.; Hara, T.; Mizugaki, T.; Ebitani, K. and Kaneda, K., *J. Am. Chem. Soc.,* **2003**, *125*, 11460. (c) Doyle, M. P.; Phillips, I. M. and Hu, W., *J. Am. Chem. Soc.,* **2001**, *123*, 5366.

21. Mancheño, O. G.; Arrayás, R. G. and Carretero, J. C., *J. Am. Chem. Soc.,* **2004**, *126*, 456.

22. Unni, A. K.; Takenaka, N.; Yamamoto, H. and Rawal, V. H., *J. Am. Chem. Soc.,* **2005**, *127*, 1336.

23. (a) Kelleher, S.; Muldoon, J.; Mueller-Bunz, H. and Evans, P., *Tetrahedron Lett*., **2007**, *48*, 4733. (b) Yoshizawa, M.; Tamura, M. and Fujita, M., *Science,* **2006**, *312*, 251. (c) Ishihara, K. and Fushimi, M., *Org. Lett.,* **2006**, *8*, 1921.

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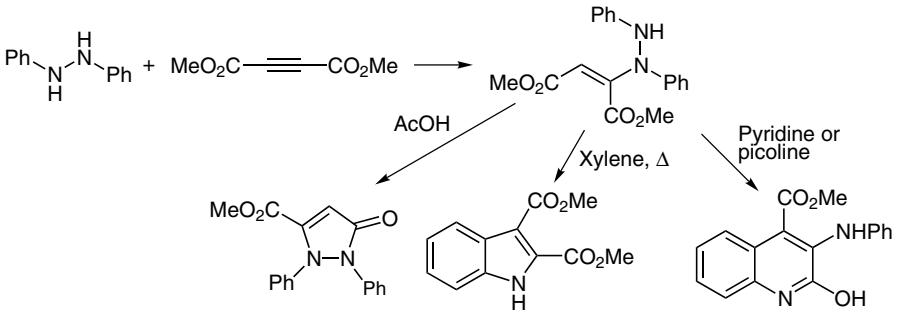
Diels-Reese Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Diels and Reese in 1934.[1] It is the conjugate addition between hydroazobenzene and dimethyl acetylene-dicarboxylate. The resulting adduct can be transformed into three different heterocyclic compounds under various experimental conditions (i.e., pyrazolones with acid, indoles upon heating in xylene, and quinolones with base[2]). For example, 1,2-diphenyl-3-carbomethoxy-5-pyrazolone will be generated from the adduct in acetic acid (acidic condition), whereas dimethyl indole-2,3-dicarboxylate is produced in xylene (neutral condition) and 2-hydroxy-3-anilino-4-carbomethoxy-quinoline is yielded in pyridine (basic condition).[1,3] The latter can be further converted into 2,3-dihydroquinoline upon decarboxylation and hydrolysis.[4] This reaction has been extended to heat the 1:1 adduct in picoline.[3]

B. GENERAL REACTION SCHEME



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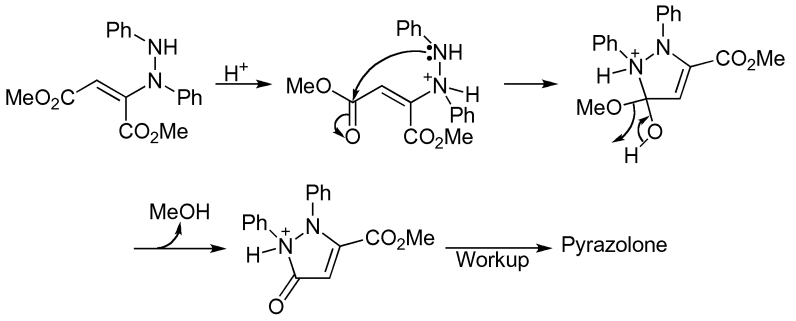
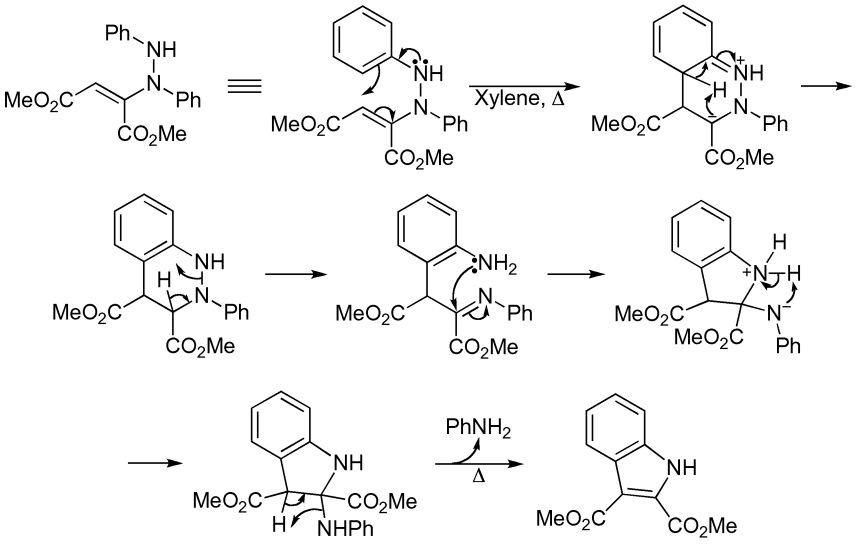
C. PROPOSED MECHANISMS

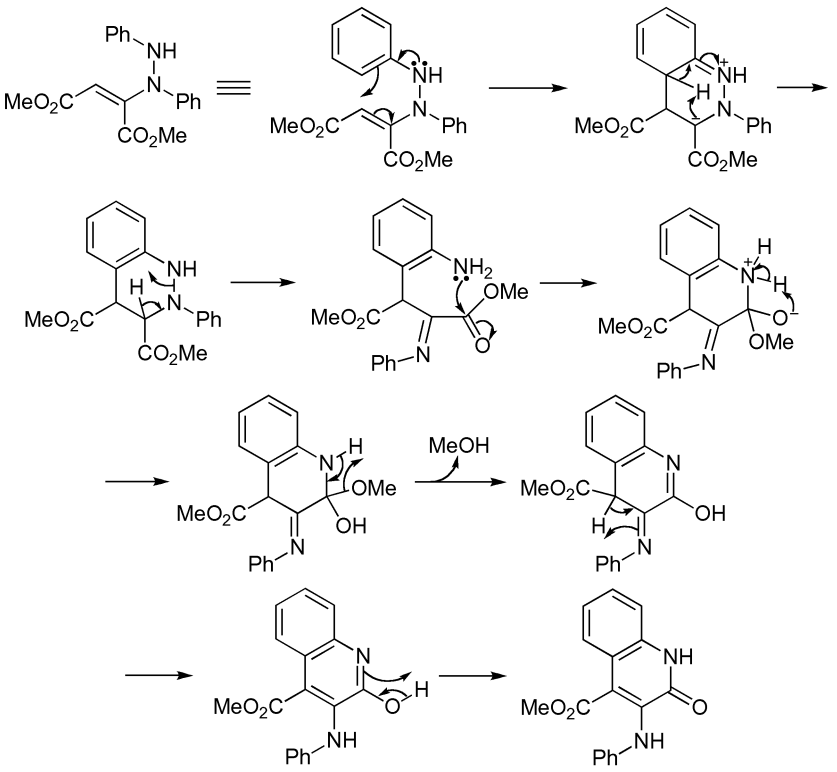
Because no mechanistic information about this reaction is available, the routes to form the three different products are tentatively outlined (Schemes 1–3.)



SCHEME 1. *Formation of pyrazolone by the Diels-Reese reaction.*



SCHEME 2. *Formation of indole derivative in xylene.*



SCHEME 3. *Formation of quinolone derivative.*

D. MODIFICATION

The refluxing of the adduct in α-picoline provides a higher yield of quinoline than that in pyridine.[3]

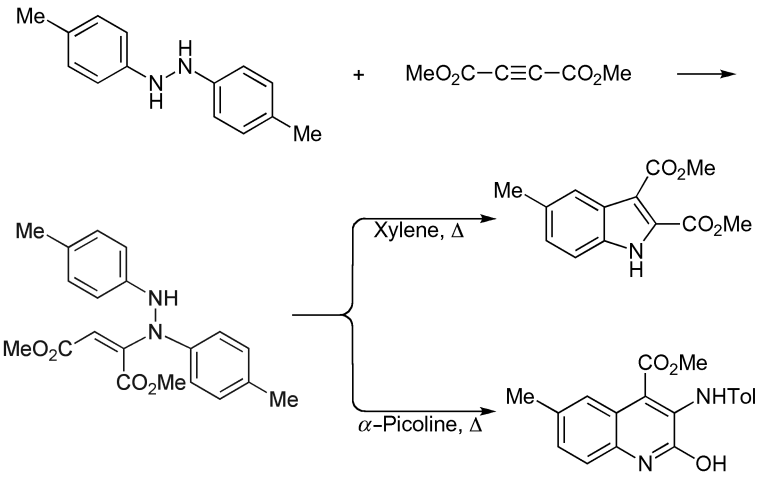
E. APPLICATIONS

This reaction can be used for the preparation of pyrazolones, indoles, and quinolines.

F. RELATED REACTIONS

This reaction is related to the *Fischer Indole Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 3.

Preparation of Adducts

A mixture of 6.5 g freshly prepared 4,4-dimethylhydrazobenzene (0.031 mol), 20 mL methanol and 5.5 g dimethyl acetylenedicarboxylate (0.038 mol) was refluxed. Within 1 min, the solid dissolved to form an orange-red solution that boiled spontaneously for 4 min. The mixture was refluxed for an additional 90 min. After standing in the ice-box overnight, the mixture had set to a yellow mash, which was filtered and washed with 5 mL cold ether to afford 7.1 g light yellow powder after dryness, in a yield of 66%. The adduct was pure enough for further reaction, m.p. 138–140°C (dec.)

Preparation of Quinoline

A solution of 10.0 g of the adduct (0.028 mol) in 20 mL α-picoline was refluxed for 1 h. The excess picoline was evaporated at room temperature. The brown residue, which was permeated with crystals, was stirred with 10 mL methanol, filtered, and washed with a little methanol. After drying under vacuum, 5.5 g 2-hydroxy-3-(p-toluino)-4-carbomethoxy-6-methylquinoline was obtained, in a yield of 61%, m.p. 236–237°C. Gold yellow needles can form after recrystallization in acetic acid, with a melting point of 237–238°C.

Preparation of Indole

A suspension of 2.0 g adduct (0.057 mol) in 4 mL xylene was refluxed for 1 h. The brown solution on cooling deposited a yellow solid, which was filtered and washed with methanol to give 1.1 g dimethyl 5-methylindole-2,3-dicarboxylate, in a yield of 66%. Recrystallization from acetic acid gave small golden yellow needles, melting at 236–237°C.

No other references for the Diels-Reese reaction are found from available literature sources.

H. REFERENCES

1. Diels, O. and Reese, J., *Ann.,* **1934**, *511*, 168.
2. Rapoport, H. and Tretter, J. R., *J. Am. Chem. Soc.,* **1958**, *80*, 5574.
3. Huntress, E. H.; Bornstein, J. and Hearon, W. M., *J. Am. Chem. Soc.,* **1956**, *78*, 2225.
4. Diels, O. and Reese, J., *Ann.,* **1935**, *519*, 147.

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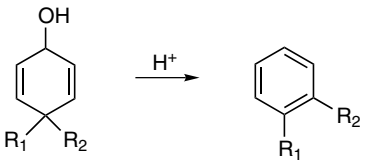
Dienol-Benzene Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction can be traced back to 1956.[1] It is an acid-promoted conversion of 4,4-disubstituted cyclohex-2,5-dienol into substituted benzene and is generally known as the dienol-benzene rearrangement.[2] It has been clearly shown that both the transition state and intermediate in this rearrangement have substantial carbonium ion characters.[2c] However, this reaction is catalyzed only by H^+ in acetate, formate, and phosphate buffers. In aqueous solution of $HClO_4$ and H_2SO_4, the rearrangement has been found to be first-order kinetics for 4-methyl-4-trichloromethyl cyclohex-2,5-dienol. In addition, the rearrangement of 4,4-dimethyl cyclohex-2,5-dienol is complicated with the isomerization to 6,6-dimethylcyclohex-2,4-dienol, leading to *o*-xylene.[2c] This reaction is useful for introducing aromaticity into the A-ring of steroids.[2m]

B. GENERAL REACTION SCHEME



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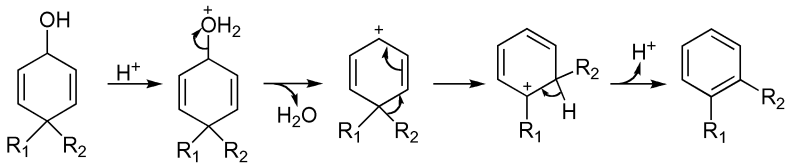
C. PROPOSED MECHANISMS



D. MODIFICATION

N/A

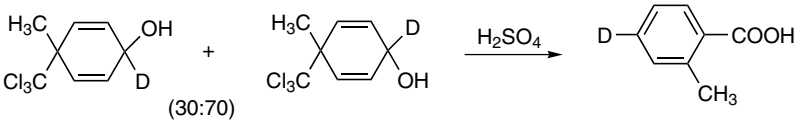
E. APPLICATIONS

This reaction has general application in the conversion of 4,4-disubstituted cyclohex-2,5-dienol (or dienone) into aromatic compounds.

F. RELATED REACTIONS

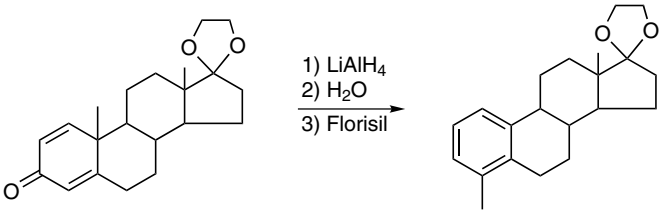
This reaction is closely related to the *Dienone-Phenol Rearrangement* but is not as common.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2c.

A sample of 200 mg 1-D-4-methyl-4′-trichloromethyl-cyclohex-2,5-dienol (30:70 ratio) was treated with 1 mL conc. H_2SO_4 at 0°C for 25 min. The addition of ice gave 4-D-*o*-toluic acid, m.p. 96–100°C.



Reference 2m.

To a mixture of 1.0 g 1,4-androstadiene-3,17-dione-17-ethylene ketal and 1.0 g $LiAlH_4$ was added slowly 100 mL dry ether, while the temperature was maintained at 0–5°C under mechanical agitation. The reaction mixture was then refluxed for 2 h, cooled again to 0–5°C and 10 mL acetone was added cautiously with agitation. Then 10 mL water was added dropwise under stirring. The mixture was filtered, and the hydrated alumina was washed with ether. The combined filtrates were washed with water, dried over Na_2SO_4, and concentrated to give 990 mg of a colorless oil. The oil was taken up in hexane and chromatographed on 15 g Florisil. The hexane fractions were pooled and crystallized from hexane at –78°C to afford 250 mg 4-methylestra-1,3,5(10)-triene-17-one 17 ethylene ketal, m.p. 115–116.5°C.

Other references related to the dienol-benzene rearrangement are cited in the literature.[3]

H. REFERENCES

1. Plieninger, H. and Keilich, G., *Angew. Chem.,* **1956**, *68*, 618.
2. (a) Hanson, J. R., *J. Chem. Res.,* **2005**, 141. (b) Summematter, W. and Heimgartner, H., *Helv. Chim. Acta,* **1984**, *67*, 1298. (c) Vitullo, V. P.; Cashen, M. J.; Marx, J. N.; Caudle, L. J. and Fritz, J. R., *J. Am. Chem. Soc.,* **1978**, *100*, 1205. (d) Vitullo, V. P. and Cashen, M. J., *Tetrahedron Lett*., **1973**, 4823. (e) Grueter, H.; Hansen, H. J. and Schmid, H., *Helv. Chim. Acta,* **1973**, *56*, 2479. (f) Heimgartner, H.; Zsindely, J.; Hansen, H. J. and Schmid, H., *Helv. Chim. Acta,* **1972**, *55*, 1113. (g) Hansen, H. J.; Sutter, B. and Schmid, H., *Helv. Chim. Acta,* **1968**, *51*, 828. (h) Caspi, E.; Piatak, D. M. and Grover, P. K., *J. Chem. Soc. C,* **1966**, 1034. (i) Caspi, E. and Grover, P. K., *Steroids*, **1963**, *1*, 39. (j) Plieninger, H.; Ege, G. and Ullah, M. I., *Chem. Ber.,* **1963**, *96*, 1610. (k) Dannenberg, H. and Hans-Guenter, N., *Ann.,* **1961**, *646*, 148. (l) Plieninger, H. and Keilich, G., *Chem. Ber.,* **1958**, *91*, 1891. (m) Gentles, M. J.; Moss, J. B.; Herzog, H. L. and Hershberg, E. B., *J. Am. Chem. Soc.,* **1958**, *80*, 3702.
3. (a) Fujita, S., *J. Chem. Inf. Comput. Sci.,* **1987**, *27*, 115. (b) Hey, D. H.; Jones, G. H. and Perkins, M. J., *J. Chem. Soc., Perkin Trans. I,* **1972**, 1162. (c) Klemm, L. H. and Taylor, D. R., *J. Org. Chem.,* **1970**, *35*, 3216. (d) Dannenberg, H.; von Dresler, D. D. and Koehler, T., *Ber.,* **1960**, *93*, 1989.

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Dienone-Phenol Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Auwers and Ziegler in 1921.[1] In most cases, it is the transformation of 4,4-disubstituted cyclohexadienone into a 3,4-disubstituted phenol upon treatment of acid; however, 2,2-disubstituted cyclohexadienone[2] and cyclohexadienone with exocyclic double bond[3] can also be converted into the corresponding disubstituted phenol under similar conditions. Therefore, this kind of transformation is generally known as the dienone-phenol rearrangement.[4] It is interesting that the rearrangement of endocyclic cyclohexadienone to its phenolic derivative is spontaneous[3] unless a dichloromethyl group presents at position 4[5] or the process is blocked in some manner,[3] such as by the presence of a bulky substituent (e.g., *tert*-butyl) at both positions 2 and 6 for cyclohexa-2,5-dienones[6] or position 6 for cyclohexa-3,5-dienones.[7] In these cases, the elimination of the bulky group is also accompanied by the migration of the alkyl group,[6,7] and the alkyl group might rearrange to position 6 for cyclohexa-3,5-dienone.[7] It has been shown that the driving force for all of these rearrangements is aromatization.[8] For the acid-promoted dienone-phenol rearrangement, the reaction media used are either aqueous mineral acids or anhydrous media[9] (e.g., acetic anhydride or ether[10]) with an acid catalyst. It has been found that the reaction media have strong effects on the rearrangement;[11] however, for one case of santonin, a general acid-catalyzed reaction holds, as the same product was formed from both media.[9] Because this reaction occurs via a carbocation transition state, it has been clearly shown that the regioselectivity is completely controlled by the electronic factors, not the steric

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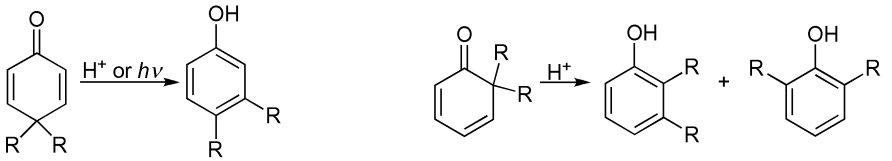
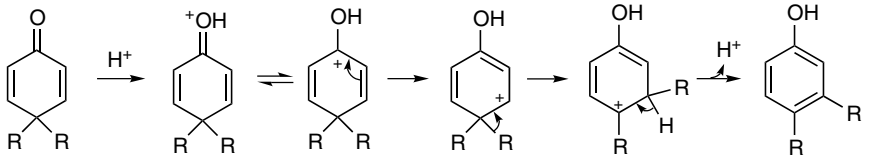
hindrance;[12] in addition, the stability of the final carbocation is the determining mechanistic element in such rearrangement.[13] Therefore, the migration tendency for two different groups at either 4,4 position or 2,2 position can be determined by comparing the relative stability of the carbocation formed via rearrangement. Under acid-promoted conditions, a few migration tendencies include CO_2Et > Ph (or alkyl),[13] Ph > Me,[14] vinyl > Me,[8] Me > OR,[15] and OR > Ph.[16] For the special cases of allyl and benzyl group, the actual rearrangement might undergo through the *Cope Rearrangement*.[7,17] Two successive *Allylic Rearrangements* are found for the rearrangement of quinamines.[18] Besides the acid promotion, the dienone-phenol rearrangement can also be catalyzed by base (NaOH for conversion phenol to dienone[19] and ammonia, primary, secondary, and tertiary amines for dienone to phenol[20]) or promoted photochemically.[21] Overall, the dienone-phenol rearrangement has proven valuable in the syntheses of steroids,[22] anthracene,[3] phenanthrene,[23] and a variety of phenols.

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The mechanism is illustrated by the rearrangement of 4,4-disubstituted cyclohexadienones to 3,4-disubstituted phenols, as displayed here.



D. MODIFICATION

The original rearrangement pattern has been modified by promoting the reaction photochemically[20] or by initializing the reaction via base.[19]

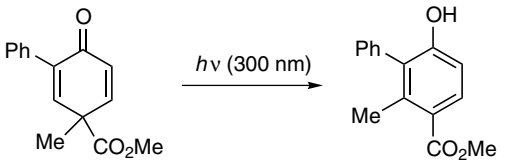
E. APPLICATIONS

This reaction has wide applications in the preparation of a variety of phenols; more important, this rearrangement has other uses in the syntheses of steroids, anthracene, and phenanthrene.

F. RELATED REACTIONS

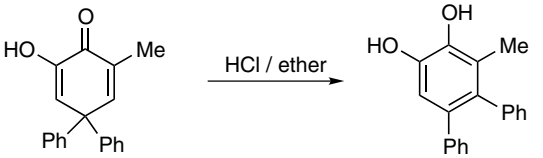
This reaction is related to the *Dienol-Benzene Rearrangement*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 21a.

A 0.06–0.08 M solution of 1-methyl-4-oxo-3-phenyl-cyclohexa-2,5-dienecarboxylic acid methyl ester in benzene was degassed by bubbling argon through the solution for 15 min. Irradiation through uranyl or Pyrex glass was carried out, and the final product of 6-hydroxy-2-methyl-biphenyl-3-carboxylic acid methyl ester was separated from chromatography on silica gel (4:1, hexane/EtOAc), in a yield of 85%.



Reference 12.

A 10-mL round-bottomed flask was fitted with a magnetic stirrer and charged with 0.7 mmol of 2-hydroxy-6-methyl-4,4-diphenylcyclohexa-2,5-dienone, 5 mL ether, and 2 mL conc. HCl. The mixture was stirred for 29 h, neutralized with a saturated $NaHCO_3$ solution, washed with water, and dried over $MgSO_4$. Upon removal of solvent, the residue was purified on preparative TLC and finally recrystallized from acetone/hexane to give white crystals, in a yield of 93%, m.p. 147–148°C, $R_f = 0.24$ (acetone/hexane, 1:4).

Other references related to the dienone-phenol rearrangement are cited in the literature.[24]

H. REFERENCES

1. Von Auwers, K. and Ziegler, K., *Ann.,* **1921**, *425*, 217.
2. (a) Miller, B. and Baghdadchi, J., *J. Org. Chem.,* **1987**, *52*, 3390. (b) Marvell, E. N. and Magoon, E., *J. Am. Chem. Soc.,* **1954**, *76*, 5118.
3. Marvell, E. N. and Geiszler, A. O., *J. Am. Chem. Soc.,* **1952**, *74*, 1259.
4. (a) Chen, J. C.; Zhou, G.; Li, W. D. and Li, Y. L, *Chinese Chem. Lett.,* **2003**, *14*, 689. (b) Bohn, M. L.; Justribo, V.; Testero, S. A.; Colombo, M. I.; Pellegrinet, S. C. and Ruveda, E. A., *J. Undergrad. Chem. Res.,* **2002**, *1*, 33. (c) Fu, L. H.; Xia, Y. M.; Cui, S. Z. and Zhu, C. F., *Daxue*

Huaxue, **2000**, *15*, 46. (d) Oshima, T.; Nakajima, Y.-I. and Nagai, T., *Heterocycles*, **1996**, *43*, 619. (e) Jiang, Y.; Maher, J. and Bassett, D., *Poly. Mater. Sci. Eng.,* **1995**, *72*, 259. (f) Hart, D. J.; Kim, A.; Krishnamurthy, R.; Merriman, G. H. and Waltos, A. M., *Tetrahedron,* **1992**, *48*, 8179. (g) Schultz, A. G. and Green, N. J., *J. Am. Chem. Soc.,* **1992**, *114*, 1824. (h) Kikugbawa, Y.; Kitamura, T. and Kawase, M., *J. Chem. Soc., Chem. Commun.,* **1989**, 525. (i) Hahn, Y. S. P., *Bull. Korean Chem. Soc.,* **1989**, *10*, 151. (j) Shi, X. L.; Day, R. and Miller, B., *J. Chem. Soc., Perkin Trans. I,* **1989**, 1166. (k) Goycoolea, C.; Santos, J. G. and Valderrama, J. A., *J. Chem. Soc., Perkin Trans. II,* **1988**, 1135. (l) Cassis, R.; Scholz, M.; Tapia, R. and Valderrama, J. A., *J. Chem. Soc., Perkin Trans. I,* **1987**, 2855. (m) Planas, A.; Tomas, J. and Bonet, J. J., *Tetrahedron Lett*., **1987**, *28*, 471. (n) Satoh, J. Y.; Haruta, A. M.; Satoh, T.; Satoh, K. and Takahashi, T. T., *J. Chem. Soc., Chem. Commun.,* **1986**, 1765. (o) Oda, T.; Yamaguchi, Y. and Sato, Y., *Chem. Pharm. Bull.,* **1986**, *34*, 858. (p) Cassis, R.; Scholz, M.; Tapia, R. and Valderrama, J. A., *Tetrahedron Lett*., **1985**, *26*, 6281. (q) Avent, A. G.; Hanson, J. R.; Ling, Y. Z. and Sadler, I. H., *J. Chem. Soc., Perkin Trans. I,* **1985**, 2129. (r) Fischer, A. and Henderson, G. N., *Can. J. Chem.,* **1983**, *61*, 1045. (s) Volod'kin, A. A.; Malysheva, R. D. and Ershov, V. V., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1982**, 715. (t) Hanson, J. R.; Raines, D. and Knights, S. G., *J. Chem. Soc., Perkin Trans. I,* **1980**, 1311. (u) Koptyug, V. A. and Buraev, V. I., *Zh. Org. Khim.,* **1980**, *16*, 1882. (v) Kokocinska, H. and Zalewski, R. I., *Bull. Acad. Polonaise Sci., Ser. Sci. Chim.,* **1979**, *27*, 575. (w) Fischer, A. and Henderson, G. N., *J. Chem. Soc., Chem. Commun.,* **1979**, 279. (x) Moore, G. G. I. and Kirk, A. R., *J. Org. Chem.,* **1979**, *44*, 925. (y) Pilkington, J. W. and Waring, A. J., *J. Chem. Soc., Perkin Trans. II,* **1976**, 1349. (z) Vitullo, V. P. and Logue, E. A., *J. Am. Chem. Soc.,* **1976**, *98*, 5906. (aa) Takeda, K.; Tanida, H. and Horiki, K., *Chem. Pharm. Bull.,* **1975**, *23*, 2711. (bb) Waring, A. J. , *Tetrahedron Lett*., **1975**, 171. (cc) Hughes, M. J. and Waring, A. J., *J. Chem. Soc., Perkin Trans. II,* **1974**, 1043. (dd) Miki, T.; Hiraga, K.; Masuya, H.; Asako, T.; Fujii, S.; Kawai, K.; Kikuchi, K.; Shintani, S. and Yamazaki, M., *Chem. Pharm. Bull.,* **1974**, *22*, 1439. (ee) Vitullo, V. P. and Logue, E. A., *J. Chem. Soc., Chem. Commun.,* **1974**, 228. (ff) Flynn, R. G. A. and Woodgate, P. D., *J. Chem. Soc., Perkin Trans. I,* **1974**, 964. (gg) Budzikiewicz, H. and Gunawan, J., *Monatsh. Chem.*, **1973**, *104*, 876. (hh) Widmer, U.; Zsindely, J.; Hansen, H. J. and Schmid, H., *Helv. Chim. Acta,* **1973**, *56*, 75. (ii) Cook, K. L. and Waring, A. J., *J. Chem. Soc., Perkin Trans. II,* **1973**, 88. (jj) Ter-Gabrielyan, E. G.; Gambaryan, N. P. and Knunyants, I. L., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1972**, 2107. (kk) Vitullo, V. P. and Grossman, N., *J. Am. Chem. Soc.,* **1972**, *94*, 3844. (ll) Bell, K. H., *Aust. J. Chem.,* **1972**, *25*, 1117. (mm) Kametani, T.; Fukumoto, K. and Fujihara, M., *J. Chem. Soc., Perkin Trans. I,* **1972**, 394. (nn) Takani, M. and Takahashi, K., *Chem. Pharm. Bull.,* **1971**, *19*, 2072. (oo) Vitullo, V. P., *J. Org. Chem.,* **1970**, *35*, 3976. (pp) Wolff, T. and Dannenberg, H., *Chem. Ber.,* **1970**, *103*, 917. (qq) Miller, B., *J. Am. Chem. Soc.,* **1969**, *91*, 2170.

5. Miller, T. G., *J. Org. Chem.,* **1962**, *29*, 1549.
6. Miller, B. and Margulies, H., *J. Am. Chem. Soc.,* **1965**, *87*, 5106.
7. Miller, B., *J. Am. Chem. Soc.,* **1970**, *92*, 432.
8. Marx, J. N. and Hahn, Y.-S. P., *J. Org. Chem.,* **1988**, *53*, 2866.
9. Dreiding, A. S.; Pummer, W. J. and Tomasewski, A. J., *J. Am. Chem. Soc.,* **1953**, *75*, 3159.
10. Goodwin, S. and Witkop, B., *J. Am. Chem. Soc.,* **1957**, *79*, 179.
11. Shine, H. J. and Schoening, C. E., *J. Org. Chem.,* **1972**, *37*, 2899.
12. Frimer, A. A.; Marks, V.; Sprecher, M. and Gilinsky-Sharon, P., *J. Org. Chem.,* **1994**, *59*, 1831.
13. Kagan, J.; Agdeppa, D. A.; Singh, S. P.; Mayers, D. A.; Boyajian, C.; Poorker, C. and Firth, B. E., *J. Am. Chem. Soc.,* **1976**, *98*, 4581.
14. Arnold, R. T. and Buckley, J. S., *J. Am. Chem. Soc.,* **1949**, *71*, 1781.
15. (a) Vitullo, V. P. and Logue, E. A., *J. Org. Chem.,* **1973**, *38*, 2265. (b) Vitullo, V. P. and Logue, E. A., *J. Org. Chem.,* **1972**, *37*, 3339.
16. Budzikjewicz, H. and Metlesics, W., *J. Org. Chem.,* **1959**, *24*, 1125.

17. Miller, B., *J. Am. Chem. Soc.,* **1965**, *87*, 5115.
18. (a) Miller, B., *J. Am. Chem. Soc.,* **1964**, *86*, 1127. (b) Miller, B., *J. Am. Chem. Soc.,* **1964**, *86*, 1135.
19. Takeya, T.; Kajiyama, M.; Nakamura, C. and Tobinaga, S., *Chem. Pharm. Bull.,* **1999**, *47*, 209.
20. Becker, A. R.; Richardson, D. J. and Bruice, T. C., *J. Am. Chem. Soc.,* **1977**, *99*, 5058.
21. (a) Guo, Z. H. and Schultz, A. G., *Org. Lett.,* **2001**, *3*, 1177. (b) Schultz, A. G. and Antoulinakis, E. G., *J. Org. Chem.,* **1996**, *61*, 4555. (c) Schultz, A. G. and Hardinger, S. A., *J. Org. Chem.,* **1991**, *56*, 1105. (d) Kropp, P. J., *J. Am. Chem. Soc.,* **1963**, *85*, 3779. (e) Zimmerman, H. E. and Schuster, D. I., *J. Am. Chem. Soc.,* **1962**, *84*, 4527.
22. (a) Draper, R. W.; Puar, M. S.; Vater, E. J. and McPhail, A. T., *Steroids,* **1998**, *63*, 135. (b) Al-Zamil, I. Z. and Waring, A. J., *Steroids,* **1989**, *53*, 663. (c) Kaufmann, S., *J. Org. Chem.,* **1963**, *28*, 1390. (d) Djerassi, C. and Grossnickle, T. T., *J. Am. Chem. Soc.,* **1954**, *76*, 1741. (e) Djerassi, C.; Rosenkranz, G.; Romo, J.; Pataki, J. and Kaufmann, S., *J. Am. Chem. Soc.,* **1950**, *72*, 4540. (f) Djerassi, C. and Scholz, C. R., *J. Am. Chem. Soc.,* **1948**, *70*, 1911. (g) Wilds, A. L. and Djerassi, C., *J. Am. Chem. Soc.,* **1946**, *68*, 1712. (h) Wilds, A. L. and Djerassi, C., *J. Am. Chem. Soc.,* **1946**, *68*, 1715.
23. Arnold, R. T.; Buckley, J. S. and Dodson, R. M., *J. Am. Chem. Soc.,* **1950**, *72*, 3153.
24. (a) Awale, S.; Tezuka, Y.; Wang, S. M. and Kadota, S., *Org. Lett.,* **2002**, *4*, 1707. (b) Colombo, M. I.; Testero, S. A.; Pellegrinet, S. C.; Bohn, M. L. and Rúveda, E. A., *Chem. Educator,* **2001**, *6*, 350. (c) Miller, B. and Shi, X. L., *J. Org. Chem.,* **1992**, *57*, 1677. (d) Goodyear, G. and Waring, A. J., *J. Chem. Soc., Perkin Trans. II,* **1990**, 103. (e) Dodge, J. A. and Chamberlin, A. R., *Tetrahedron Lett*., **1988**, *29*, 4827. (f) Miller, B. and Saidi, M. R., *J. Am. Chem. Soc.,* **1976**, *98*, 2227. (g) Miller, B., *Acc. Chem. Res.,* **1975**, *8*, 277. (h) Marx, J. N.; Argyle, J. C. and Norman, L. R., *J. Am. Chem. Soc.,* **1974**, *96*, 2121. (i) Widmer, U.; Hansen, H.-J. and Schmid, H., *Helv. Chim. Acta,* **1973**, *56*, 1895. (j) Waring, A. J., *Adv. Alicyclic Chem.,* **1967**, *1*, 207. (k) Collins, C. J. and Eastham, J. F.,"Rearrangements Involving the Carbonyl Group," in *The Chemistry of the Carbonyl Group*, ed. Patai, S., Wiley-Interscience, New York, **1966**, p. 775. (l) Miller, B. and Margulies, H., *Tetrahedron Lett.,* **1965**, 1727. (m) Miller, B., *J. Am. Chem. Soc.,* **1965**, *87*, 5111. (n) Hopff, W. H. and Dreiding, A. S., *Angew. Chem. Int. Ed. Engl.*, **1965**, *4*, 690. (o) Huffman, J. W. and Bethea, T. W., *J. Org. Chem.,* **1965**, *30*, 2956. (p) Bordwell, F. G. and Wellman, K. M., *J. Org. Chem.,* **1964**, *29*, 509. (q) Kropp, P. J., *J. Am. Chem. Soc.,* **1963**, *85*, 3280. (r) Metlesics, W.; Wessely, F. and Budzikiewicz, H., *Tetrahedron,* **1959**, *6*, 345. (s) Bloom, S. M., *J. Am. Chem. Soc.,* **1959**, *81*, 4728. (t) Gentles, M. J.; Moss, J. B.; Herzog, H. L. and Hershberg, E. B., *J. Am. Chem. Soc.,* **1958**, *80*, 3702. (u) Bloom, S. M., *J. Am. Chem. Soc.,* **1958**, *80*, 6280. (v) Dutler, H.; Bossard, H. and Jeger, O., *Helv. Chim. Acta,* **1957**, *40*, 494. (w) Marvell, E. N. and Magoon, E., *J. Am. Chem. Soc.,* **1955**, *77*, 2542. (x) Marvell, E. N. and Stephenson, J. L., *J. Am. Chem. Soc.,* **1955**, *77*, 5177. (y) Fenton, S. W.; Arnold, R. T. and Fritz, H. E., *J. Am. Chem. Soc.,* **1955**, *77*, 5983. (z) Sandoval, A.; Miramontes, L.; Rosenkranz, G. and Djerassi, C., *J. Am. Chem. Soc.,* **1951**, *73*, 990. (aa) Arnold, R. T.; Buckley, J. S. and Richter, J., *J. Am. Chem. Soc.,* **1947**, *69*, 2322. (bb) Clemo, G. R.; Haworth, R. D. and Walton, E., *J. Chem. Soc.,* **1930**, 1110.

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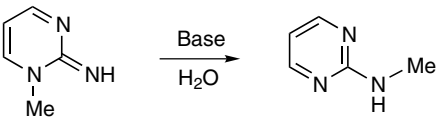
Dimroth Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

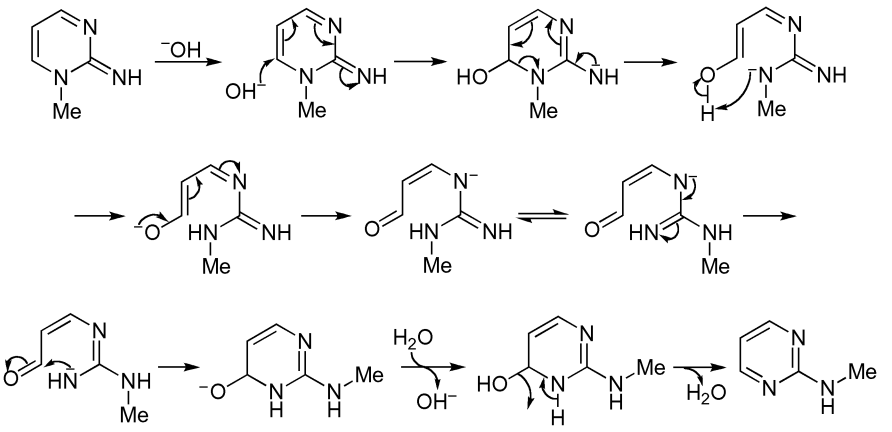
This reaction was first reported by Dimroth in 1909.[1] It is the base-catalyzed rearrangement or translocation of *exo*- and *endo*-cyclic heteroatoms on a heterocyclic ring and is generally known as the Dimroth rearrangement.[2] In quite a few cases, it is also referred to as the Dimroth-type rearrangement[3] or Dimroth reaction.[4] This type of rearrangement often occurs on a six-membered ring[5] but is also possible for five-membered rings.[6] Many Dimroth rearrangements involve 1H-1,2,3-triazoles.[6] In fact, this rearrangement undergoes a ring opening followed by a ring reclosure along with the translocation of heteroatoms.[5a] In most cases, the heteroatom is nitrogen, as indicated in the Section G.

B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS



D. MODIFICATION

N/A

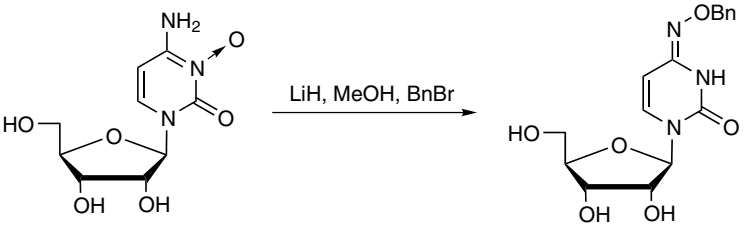
E. APPLICATIONS

This reaction can be generally used for the preparation of a variety of heterocycles.

F. RELATED REACTIONS

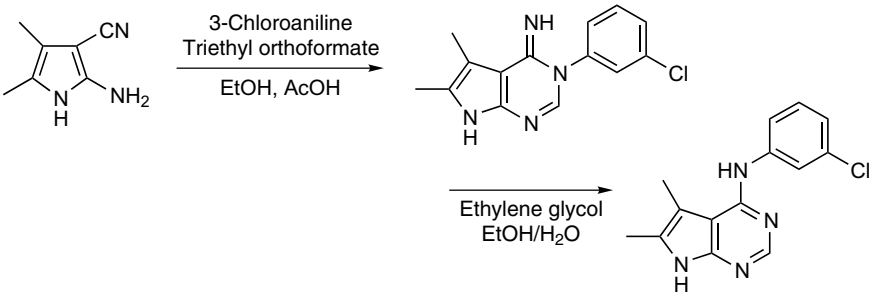
This reaction is related to the *ANRORC Rearrangement*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

To a suspension of 77.7 mg 4-amino-1-(3,4-dihydroxy-5-hydroxymethyltetrahydrofuran-2-yl)-1*H*-pyrimidin-2-one 3-oxide (cytidine N^3-oxide, 0.30 mmol) and 12.6 mg 95% pure lithium hydride (1.5 mmol) in 5 mL dry methanol was added 40 μL 98% pure benzyl bromide (0.33 mmol); the mixture was stirred at 37°C for 1 day under an argon atmosphere. TLC analysis of the reaction mixtures with chloroform/methanol/acetic acid (16:6:3) and chloroform/methanol (10:1) as the developing solvents showed complete consumption of the starting material for almost quantitative conversion to a less polar compound. After being neutralized with 1 N HCl solution and subsequent removal of the solvent under reduced pressure, the resulting residue was subjected to a short silica gel column by eluting with chloroform/methanol (20:1) to isolate 99.5 mg 1-(3,4-dihydroxy-5-hydroxymethyltetrahydrofuran-2-yl)-1*H*-pyrimidin-2,4-dione 4-*O*-benzyloxime (uridine 4-*O*-benzyloxime) as a colorless amorphous powder, in a yield of 95%, m.p. 123–125°C (from methanol).



Reference 8.

The mixture of 204.5 g triethyl orthoformate (1.35 mol), 700 mL absolute ethanol, and 222.0 g 3-chloroaniline (1.72 mol) was charged in a reaction vessel, and the pH was adjusted to 5–5.5 by addition of 6.65 g acetic acid (0.11 mol). The mixture was warmed to 50°C and stirred for 1 h. Then 166.0 g 2-amino-3-cyano-4,5-dimethylpyrrole (1.23 mol) was added as a solid over 6 h, while maintaining the temperature at 45–50°C. After completion of the addition, the mixture was kept at 50°C for additional 4 h and then for another 8 h at room temperature. After the addition of 100 mL water, the mixture was cooled to 0°C, and this temperature was maintained for 30 min. The resulting suspension was filtered, washed with ethanol/water (4:1), and dried in a vacuum at 50°C to yield 261 g 3-(3-chlorophenyl)-5,6-dimethyl-4H-pyrrolo[2,3-*d*]pyrimidine-4-imine, in a yield of 78%, m.p. > 150°C (dec).

A suspension of 300.0 g pyrrolopyrimidine (1.1 mmol) in 750 mL water, 750 mL absolute ethanol, and 1500 mL ethylene glycol was heated to 95°C for 4 h. The mixture was cooled to room temperature within 90 min. After the temperature was maintained at room temperature for an additional 1 h, the suspension was filtered, washed with water, and dried under vacuum at 50°C to yield 277 g 4-(3-chlorophenylamino)-5,6-dimethyl-7H-pyrrolo-[2,3-*d*]pyrimidine in a yield of 92%, m.p., 240–255°C.

Other references related to the Dimroth rearrangement are cited in the literature.[9]

H. REFERENCES

1. Dimroth, O., *Ann.,* **1909**, *364*, 183.
2. (a) Timofeev, E. N.; Mikhailov, S. N.; Zuev, A. N.; Efimtseva, E. V.; Herdewijn, P.; Somers, R. L. and Lemaitre, M. M., *Helv. Chim. Acta,* **2007**, *90*, 928. (b) Geide, I. V.; Glukhareva, T. V.; Matern, A. I. and Morzherin, Y. Y., *Chem. Heterocycl. Compd.,* **2006**, *42*, 121. (c) Glasnov, T. N.; Vugts, D. J.; Koningstein, M. M.; Desai, B.; Fabian, W. M. F.; Orru, R. V. A. and Kappe, C. O., *QSAR & Comb. Sci.,* **2005**, *25*, 509. (d) Nagamatsu, T. and Ahmed, S., *Heterocycles*, **2005**, *65*, 2683. (e) Subbotina, J. O.; Fabian, W. M. F.; Tarasov, E. V.; Volkova, N. N. and Bakulev, V. A., *Eur. J. Org. Chem.,* **2005**, 2914. (f) Morzerin, Y. Y.; Pospelova, T. A.; Gluhareva, T. V. and Matern, A. I., *ARKIVOC,* **2004**, (*xi*), 31. (g) Atanassov, P. K.; Linden, A. and Heimgartner, H., *Helv. Chim. Acta,* **2004**, *87*, 1873. (h) Rozhkov, V. Yu.; Batog, L. V.; Shevtsova, E. K. and Struchkova, M. I., *Mendeleev Commun*., **2004**, 76. (i) Nair, V.; Mathen, J. S.; Vinod, A. U. and Varma, R. L., *Chem. Lett.,* **2001**, 738. (j) Sangapure, S. S. and Mulagi, S. M., *Indian J. Heterocycl. Chem.,* **2000**, *10*, 27. (k) El Ashry, E. S. H.; El Kilany, Y.; Rashed, N. and Assafir, H., *Adv. Heterocycl. Chem.,* **1999**, *75*, 79. (l) Danagulyan, G. G., *Chem. Heterocycl. Compd.,* **1999**, *35*, 378. (m) Loakes, D.; Brown, D. M. and Salisbury, S. A., *J. Chem. Soc., Perkin Trans. I,* **1999**, 1333. (n) Nandeeshaiah, S. K. and Ambekar, S. Y., *Indian J. Chem., Sect. B,* **1998**, *37B*, 995. (o) El Ashry, E. S. H.; El Kilany, Y.; Rashed, N.; Mousaad, A. and Assafir, H., *Z. Naturforsch.,* **1998**, *53B*, 1203. (p) Barlow, T.; Takeshita, J. and Dipple, A., *Chem. Res. Toxicol.,* **1998**, *11*, 838. (q) Fleming, P. E.; Daikh, B. E. and Finke, R. G., *J. Inorg. Biochem.,* **1998**, *69*, 45. (r) Pagano, A. R.; Zhao, H.; Shallop, A. and Jones, R. A., *J. Org. Chem.,* **1998**, *63*, 3213. (s) Fujii, T. and Itaya, T., *Heterocycles,* **1998**, *48*, 359. (t) Itaya, T.; Ito, N.; Kanai, T. and Fujii, T., *Chem. Pharm. Bull.,* **1997**, *45*, 832. (u) Belik, A. V. and Igoshina, E. V., *Zh. Org. Khim.,* **1996**, *32*, 1742. (v) Deng, H. F.; Jiang, Y. Z. and Zhao, Z. Z., *Chinese Chem. Lett.,* **1994**, *5*, 271. (w) Fujii, T.; Saito, T.; Ii, R. and Suzuki, T., *Chem. Pharm. Bull.,* **1994**, *42*, 382. (x) Danagulyan, G. G.; Saakyan, L. G.; Panosyan, G. A.; Bulakhov, G. A.; Terentyev, P. B. and Zalinyan, M. G., *Khim. Geterotsiklicheskikh Soedinenii,* **1993**, 1545. (y) Stevens, M. F. G.; Chui, W. K. and Castro, M. A., *J. Heterocycl. Chem.,* **1993**, *30*, 849. (z) Saito, T.; Kanai, T. and Fujii, T., *Chem. Pharm. Bull.,* **1993**, *41*, 1850. (aa) Riemer, B.; Hassoun, A.; Liebscher, J.; Jones, P. G. and Chrapkowski, A., *J. Heterocycl. Chem.,* **1993**, *30*, 1607. (bb) Hirota, K.; Ni, P. Z.; Suzuki, A.; Takasu, H.; Kitade, Y. and Maki, Y., *Chem. Pharm. Bull.,* **1992**, *40*, 2839. (cc) Vaughan, K.; LaFrance, R. J.; Tang, Y. and Hooper, D. L., *J. Heterocycl. Chem.,* **1991**, *28*, 1709. (dd) Tittelbach, F., *J. Prakt. Chem.,* **1991**, *333*, 107. (ee) Fujii, T.; Saito, T.; Hisata, H. and Shinbo, K., *Chem. Pharm. Bull.,* **1990**, *38*, 3326. (ff) Fujii, T.; Saito, T. and Sori, S., *Chem. Pharm. Bull.,* **1990**, *38*, 2591. (gg) Leistner, S.; Guetschow, M. and Stach, J., *Arch. Pharm.,* **1990**, *323*, 857. (hh) Liebscher, J.; Hassoun, A.; van der Plas, H. and Stam, C., *J. Heterocycl. Chem.,* **1990**, *27*, 1441.
3. (a) Alberola, A.; Calvo, L. A.; Ortega, A. G.; Ruiz, M. C. S.; Yustos, P.; Granda, S. G. and Garcia-Rodriguez, E., *J. Org. Chem.,* **1999**, *64*, 9493. (b) Yamamoto, H.; Ohira, C.; Aso, T. and Pfleiderer, Wolfgang., *Bull. Chem. Soc. Jpn.,* **1987**, *60*, 4115. (c) DeMilo, A. B.; Oliver, J. E. and Gilardi, R. D., *J. Heterocycl. Chem.,* **1973**, *10*, 231. (d) Guerret, P.; Jacquier, R. and Maury, G., *J. Heterocycl. Chem.,* **1971**, *8*, 643.
4. (a) Schweiger, K., *Monatsh. Chem.,* **1983**, *114*, 581. (b) L'Abbe, G., *Ind. Chim. Belg.,* **1971**, *36*, 3.
5. (a) Kim, H.-Y. H.; Finneman, J. I.; Harris, C. M. and Harris, T. M., *Chem. Res. Toxicol.,* **2000**, *13*, 625. (b) Segal, A.; Mate, U. and Solomon, J. J., *Chem. Biol. Interact.,* **1979**, *28*, 333.
6. Katritzky, A. R.; Ji, F.-B.; Fan, W.-Q.; Gallos, J. K.; Greenhill, J. V.; King, R. W. and Steel, P. J., *J. Org. Chem.,* **1992**, *57*, 190.
7. Sako, M. and Kawada, H., *J. Org. Chem.,* **2004**, *69*, 8148.
8. Fischer, R. W. and Misun, M., *Org. Proc. Res. Dev.,* **2001**, *5*, 581.

9. (a) Morzerin, Y. Y.; Pospelova, T. A.; Gluhareva, T. V. and Matern, A. I., *ARKIVOC*, **2004**, 31. (b) Florea-Wang, D.; Haapala, E.; Mattinen, J.; Hakala, K.; Vilpo, J. and Hovinen, J., *Chem. Res. Toxicol.,* **2003**, *16*, 403. (c) Kanuri, M.; Nechev, L. V.; Tamura, P. J.; Harris, C. M.; Harris, T. M. and Lloyd, R. S., *Chem. Res. Toxicol.,* **2002**, *15*, 1572. (d) Munter, T.; Cottrell, L.; Hill, S.; Kronberg, L.; Watson, W. P. and Golding, B. T., *Chem. Res. Toxicol.,* **2002**, *15*, 1549. (e) Ostrowski, S., *Polish J. Chem*., **2001**, *75*, 1661. (f) Veldhuyzen, W. F.; Shallop, A. J.; Jones, R. A. and Rokita, S. E., *J. Am. Chem. Soc.,* **2001**, *123*, 11126. (g) Šibor, J. and Pazdera, P., *Chem. Papers,* **2000**, *54*, 28. (h) Chezal, J. M.; Delmas, G.; Mavel, S.; Elakmaoui, H.; Métin, J.; Diez, A.; Blache, Y.; Gueiffier, A.; Rubiralta, M.; Teulade, J. C. and Chavignon, O., *J. Org. Chem.,* **1997**, *62*, 4085. (i) Selzer, R. R. and Elfarra, A. A., *Chem. Res. Toxicol.,* **1996**, *9*, 875. (j) Laskos, E.; Lianis, P. S.; Rodios, N. A.; Terzis, A. and Raptopoulou, C. P., *Tetrahedron Lett*., **1995**, *36*, 5637. (k) Pazdera, P. and Pichler, J., *Chem. Papers,* **1991**, *45*, 517. (l) Fanghaenel, E.; Kordts, B.; Richter, A. M. and Dutschmann, K., *J. Prakt. Chem.,* **1990**, *332*, 387. (m) Raj, T. T. and Ambekar, S. Y., *J. Indian Chem. Soc.,* **1990**, *67*, 260. (n) Moderhack, D.; Goos, K. H. and Preu, L., *Chem. Ber.,* **1990**, *123*, 1575. (o) L'Abbe, G. and Vanderstede, E., *J. Heterocycl. Chem.,* **1989**, *26*, 1811. (p) Wamhoff, H. and Wambach, W., *Chem.-Zeitung,* **1989**, *113*, 11. (q) Spitzner, R.; Andersch, J. and Schroth, W., *Liebigs Annalen Chem.*, **1989**, 931. (r) L'Abbe, G.; Meutermans, W.; Van Meervelt, L.; King, G. S. D. and Lenstra, A. T. H., *Bull. Soc. Chim. Belg.,* **1988**, *97*, 179. (s) Bischoff, C. and Schroeder, E., *J. Prakt. Chem.,* **1988**, *330*, 289. (t) Dzurilla, M.; Kutschy, P. and Koscik, D., *Coll. Czech. Chem. Commun.,* **1987**, *52*, 2260. (u) Fujii, T.; Saito, T. and Terahara, N., *Chem. Pharm. Bull.,* **1986**, *34*, 1094. (v) Leiby, R. W.; Corley, E. G. and Heindel, N. D., *J. Org. Chem.,* **1978**, *43*, 3427. (w) Brown, D. J. and Lenega, K., *J. Chem. Soc., Perkin Trans. I,* **1974**, 372. (x) Gilchrist, T. L. and Gymer, G. E., *Adv. Heterocycl. Chem.,* **1974**, *16*, 33. (y) Potos, K. T. and Kane, J., *J. Org. Chem.,* **1974**, *39*, 3783. (z) Begtrup, M., *Acta Chem. Scand.,* **1972**, *26*, 1243. (aa) Wahren, M., *Z. Chem.,* **1969**, *9*, 241. (bb) Macon, J. B. and Wolfenden, R., *Biochemistry,* **1968**, *7*, 3453. (cc) Goerdeler, J. and Gnad, G., *Ber.,* **1966**, *99*, 1618. (dd) Brown, d. J. and Harper, J. S., *J. Chem. Soc.,* **1963**, 1276. (ee) Grout, R. J. and Partridge, M. W., *J. Chem. Soc.,* **1960**, 3540. (ff) Dimroth, O., *Ann.,* **1927**, *459*, 39.

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Di-Π-Methane Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This rearrangement was initially investigated by Zimmerman in 1966.[1] It is a photochemical reaction of a molecular entity comprising two π-systems separated by a saturated carbon atom (a sp^3 carbon, e.g., a methylene group) involving the migration of one π-moiety bonded to the saturated carbon to other π moiety accompanied by the concomitant formation of a cyclopropane ring from the remaining π-moiety and methylene group.[2] Therefore, this reaction is known as the Zimmerman rearrangement,[3] di-π-methane rearrangement,[4] di-π-methane photorearrangement,[5] or simply the di-π-methane reaction.[6] Currently, this rearrangement has at least six versions: the divinylmethane variant,[7] the arylvinylmethane variant,[8] the *oxa*-di-π-methane rearrangement[9] (or ODPM rearrangement[10]), the *aza*-di-π-methane rearrangement,[11]and two less common variants, (barrelene di-π-methane rearrangement[12] and metalla di-π-methane rearrangement[13]). The *oxa*-di-π-methane rearrangement is the photochemical reaction of a β,γ-unsaturated ketone to an α-cyclopropyl ketone via a 1,2-acyl shift.[14] All these variants differ from each other. For example, the divinylmethane and arylvinylmethane rearrangement involves both singlets and triplets[2] and are favored from the triplet state for bicyclic molecules and the excited singlet for acyclic compounds,[16] whereas the *oxa*-di-π-methane rearrangement occurs solely through triplets,[2] with only a few exceptions.[9j] In addition, the divinylmethane rearrangement readily occurs when the sp^3 carbon between the vinyls is substituted, but the arylvinyl methane rearrangement does not have such a requirement. The di-π-methane rearrangement has high regiospecificity, with a strong preference for migration of the less conjugated π-moiety to the more conjugated one,[16] which contains two important stages as a "bridge"

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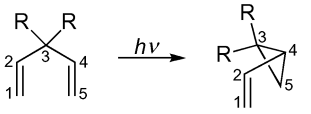
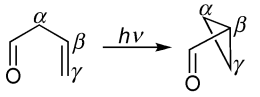
step and a "break" step.[17] It should be pointed out that the di-π-methane rearrangement can also be promoted by the application of plasma;[18] under certain conditions, the di-π-methane rearrangement is reversible.[19]

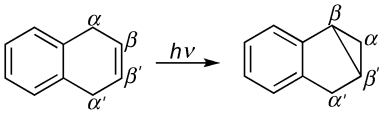
B. GENERAL REACTION SCHEME



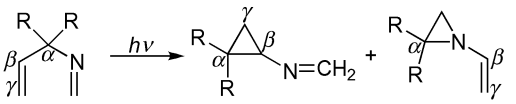
Divinyl type di-π-methane rearrangement.



Oxa-di-π-methane rearrangement.



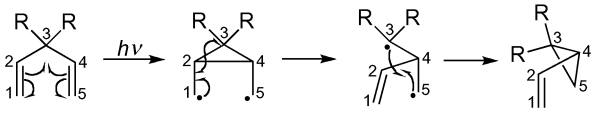
Arylvinyl type di-π-methane rearrangement.



Aza-di-π-methane rearrangement.

C. PROPOSED MECHANISMS

It is proposed that this rearrangement proceeds via the formation of the cyclopropane ring along with the generation of a biradical, followed by the ring opening of cyclopropane and the ring closure to form a new cyclopropane ring,[2,15] as illustrated here.



D. MODIFICATION

The original di-π-methane rearrangement has been modified to *oxa*-di-π-methane and *aza*-di-π-methane rearrangements.

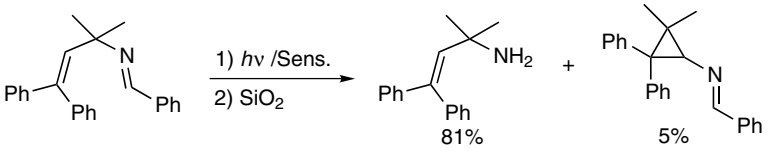
E. APPLICATIONS

This reaction can be used for the preparation of substituted cyclopropanes.

F. RELATED REACTIONS

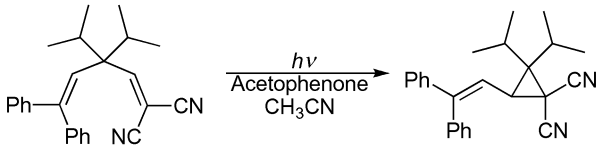
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 11b.

A mixture of 250 mg 3,3-dimethyl-1,5,5-triphenyl-2-aza-1,4-pentadiene (0.80 mmol), 550 mg *m*-methoxyacetophenone (3.7 mmol) and 450 mL dry *t*-BuOH was put into a quartz immersion well apparatus with a Pyrex filter. The solution was purged with argon for 1 h and was irradiated with a 400-W medium-pressure mercury arc lamp for 6 h. After completion of the irradiation, the solvent and the sensitizer were removed under reduced pressure, the residue was chromatographed with hexane/Et_2O (99:1) as an eluent to afford 65.0 mg benzaldehyde, and 13.0 mg of cyclopropylimine as a colorless oil, in a yield of 5%. Further elution with Et_2O yielded 25 mg of a highly polar material. Final elution with EtOH afforded 148 mg 1,1-dimethyl-3,3-diphenyl-2-propenylamine, in a yield of 81%.



Reference 20.

A solution of 51.0 mg 1,l-dicyano-5,5-diphenyl-3,3-diisopropyl-1,4-pentadiene (0.144 mmol) and 10 mL acetophenone (86 mmol) in 170 mL acetonitrile was irradiated with a 405-W Hanovia for 10 min after being purged with argon for 10 min. Concentration in vacuo and removal of acetophenone by bulb-to-bulb distillation (40°C at 0.1 mmHg) gave 56.2 mg of a pale yellow oil, which was further purified on HPLC. Elution with 1% ether in hexane gave 31.6 mg of starting material as fraction 1 and 17.8 mg 1,1-dicyano-2-(2,2-diphenylvinyl)-3,3-diisopropylcyclopropane as a colorless oil, which was recrystallized from pentane to give 9.3 mg of pure product, m.p. 76–77°C.

Other references related to the di-π-methane rearrangement are cited in the literature.[21]

H. REFERENCES

1. Zimmerman, H. E. and Grunewald, G. L., *J. Am. Chem. Soc.,* **1966**, *88*, 183.
2. Hixson, S. S.; Mariano, P. S. and Zimmerman, H. E., *Chem. Rev.,* **1973**, *73*, 531.
3. (a) Janssen, R. A. J.; Hummelen, J. C. and Wudl, F., *J. Am. Chem. Soc.,* **1995**, *117*, 544. (b) Adam, W.; Dörr, M.; Kron, J. and Rosenthal, R. J., *J. Am. Chem. Soc.,* **1987**, *109*, 7074.
4. (a) Benitez, M.; Bringmann, G.; Dreyer, M.; Garcia, H.; Ihmels, H.; Waidelich, M. and Wissel, K., *J. Org. Chem.,* **2005**, *70*, 5350. (b) Benitez, M.; Bringmann, G.; Dreyer, M.; Garcia, H.; Ihmels, H.; Waidelich, M. and Wissel, K., *J. Org. Chem.,* **2005**, *70*, 2315. (c) Armesto, D.; Ortiz, M.

J. and Agarrabeitia, A. R., *Mol. Supramol. Photochem.,* **2005**, *12*, 161. (d) Tanifuji, N.; Huang, H. H.; Shinagawa, Y. and Kobayashi, K., *Tetrahedron Lett*., **2003**, *44*, 751. (e) Zimmerman, H. E. and Chen, W. S., *Org. Lett.,* **2002**, *4*, 1155. (f) Unaldi, N. S. and Balci, M., *Tetrahedron Lett*., **2001**, *42*, 8365. (g) Da Silva, F. A.; Ferreira, A. B. B. and Neumann, M. G., *J. Braz. Chem. Soc.,* **1999**, *10*, 375. (h) Altundas, A.; Akbulut, N. and Balci, M., *Helv. Chim. Acta,* **1998**, *81*, 828. (i) Nair, V.; Anilkumar, G.; Prabhakaran, J.; Maliakal, D.; Eigendorf, G. K. and Williard, P. G., *J. Photochem. Photobiol., A: Chem.,* **1997**, *111*, 57. (j) Zimmerman, H. E. and Armesto, D., *Chem. Rev.,* **1996**, *96*, 3065. (k) Dura, R. D. and Paquette, L. A., *J. Org. Chem.,* **1996**, *71*, 2456. (l) Muraoka, O.; Tanabe, G.; Higashiura, M.; Minematsu, T. and Momose, T., *J. Chem. Soc., Perkin Trans. I,* **1995**, 1437. (m) Su, M.-D., *Chem. Phys. Lett.,* **1995**, *237*, 317. (n) Roughton, A. L.; Pieper, W.; Muneer, M. and Demuth, M., *J. Information Record. Mater.,* **1994**, *21*, 707. (o) Reguero, M.; Bernardi, F.; Jones, H.; Olivucci, M.; Ragazos, I. N. and Robb, M. A., *J. Am. Chem. Soc.,* **1993**, *115*, 2073. (p) Momose, T.; Tanabe, G.; Tsujimori, H. and Muraoka, O., *Chem. Pharm. Bull.,* **1992**, *40*, 2525. (q) Zimmerman, H. E.; King, R. K. and Meinhardt, M. B., *J. Org. Chem.,* **1992**, *57*, 5484. (r) Zimmerman, H. E., *Org. Photochem.,* **1991**, *11*, 1. (s) Hemetsberger, H. and Nobbe, M., *Tetrahedron*, **1988**, *44*, 67.

5. (a) Altundas, R.; Dastan, A.; Unaldi, N. S.; Guven, K.; Uzun, O. and Balci, M., *Eur. J. Org. Chem.,* **2002**, 526. (b) Jimenez, M. C.; Miranda, M. A. and Tormos, R., *Chem. Commun.,* **2000**, 2341. (c) Garcia-Garibay, M. A.; Scheffer, J. R. and Watson, D. G., *J. Org. Chem.,* **1992**, *57*, 241.
6. Lewis, F. D.; Zuo, X. B.; Kalgutkar, R. S.; Miranda, M. A.; Font-Sanchis, E. and Perez-Prieto, J., *J. Am. Chem. Soc.,* **2000**, *122*, 8571.
7. Hixon, S. S., and Culter, T. P., *J. Am Chem. Soc.* **1973**, *95*, 3031.
8. Zimmerman H. E. and swafford, R. L., *J. Org. Chem.*, **1984**, *49*, 3069.
9. (a) Rao, V. J. and Griesbeck, A. G., *Mol. Supramol. Photochem.,* **2005**, *12*, 189. (b) Singh, V.; Vedantham, P. and Sahu, P. K., *Tetrahedron,* **2004**, *60*, 8161. (c) Corbett, R. M.; Lee, C.-S.; Sulikowski, M. M.; Reibenspies, J. and Sulikowski, G. A., *Tetrahedron,* **1997**, *53*, 11099. (d) Singh, V. and Jagadish, B., *Indian J. Chem., Sect. B,* **1996**, *35B*, 401. (e) Armesto, D.; Ortiz, M. J. and Ramano, S., *Tetrahedron Lett.,* **1995**, *36*, 965. (f) Singh, V. K.; Deota, P. T. and Bedekar, A. V., *J. Chem. Soc., Perkin Trans. I,* **1992**, 903. (g) Mehta, G. and Subrahmanyam, D., *J. Chem. Soc., Perkin Trans. I,* **1991**, 2289. (h) Mehta, G. and Subrahmanyam, D., *J. Chem. Soc., Perkin Trans. I,* **1991**, 395. (i) Zimmerman, H. E.; Gannett, T. P. and Keck, G. E., *J. Am. Chem. Soc.,* **1978**, *100*, 323. (j) Eckersley, T.; Parker, S. D. and Rogers, N. A. J., *Tetrahedron Lett.,* **1976**, *17*, 4393. (k) Murray, R. K. and Babiak, K. A., *Tetrahedron Lett.,* **1974**, *15*, 319. (l) Seeman, J. I. and Ziffer, H., *Tetrahedron Lett.,* **1973**, *14*, 4413. (m) Dauben, W. G.; Kellog, M. S.; Seeman, J. I. and Spitzer, W. A., *J. Am. Chem. Soc.,* **1970**, *92*, 1786.
10. (a) Armesto, D.; Ortiz M. J.; Romano, S,; Agrrabeitia, A. R.; Gallego, M. G. and Ramos , A., *J. Org Chem.*, **1996**, *61*, 1459. (b) Maiti, B. C.; Singh, R. and Lahiri, S., *J. Phtochem. Phtobiol., A Chem.,* **1995**, *91*, 27. (c) Coffin, R. L.; Cox, W. W.; Carlson, R. G. and Givens, R. S., *J. Am. Chem. Soc.,* **1979**, *101*, 3261.
11. (a) Lin, S.-Y.; Hsieh, H.-P.; Peddinti, R. K. and Liao, C.-C., *Tetrahedron Lett.,* **2003**, *44*, 8761. (b) Armesto, D.; Caballero, O.; Ortiz, M. J.; Agarrabeitia, A. R.; Martin-Fontecha, M. and Torres, M. R., *J. Org. Chem.,* **2003**, *68*, 6661. (c) Ortiz, M. J.; Agarrabeitia, A. R.; Aparicio-Lara, S. and Armesto, D., *Tetrahedron Lett.,* **1999**, *40*, 1759. (d) Armesto, D.; Gallego, M. G.; Horspool, W. M. and Agarrabeitia, A. R., *Tetrahedron*, **1995**, *51*, 9223. (e) Armesto, D.; Ramos, A. and Mayoral, E. P., *Tetrahedron Lett.,* **1994**, *35*, 3785. (f) Armesto, D. and Ramos, A., *Tetrahedron,* **1993**, *49*, 7159. (g) Armesto, D.; Gallego, M. G. and Horspool, W. M., *Tetrahedron Lett.,* **1990**, *31*, 2475. (h) Armesto, D.; Gallego, M. G. and Horspool, W. M., *Tetrahedron Lett.,* **1990**, *46*, 6185. (i) Armesto, D.; Horspool, W. M.; Mancheno, M. J. and Ortiz, M. J., *J. Chem. Soc., Perkin Trans. I,* **1990**, 2348. (j) Armesto, D.; Martin, J. A. F.; Pérez-Ossorio, R. and Horspool, W. M., *Tetrahedron Lett.,* **1982**, *23*, 2149.

12. Frutos, L. M.; Sancho, U. and Castano, O., *Org. Lett.,* **2004**, *6*, 1229.
13. Uenaldi, S.; Aumann, R. and Froehlich, R., *Chem. Eur. J.,* **2003**, *9*, 3300.
14. McClure, C. K.; Kiessling, A. J. and Link, J. S., *Org. Lett.,* **2003**, *5*, 3811.
15. Quenemoen, K.; Borden, W. T.; Davidson, E. R. and Faller, D., *J. Am. Chem. Soc.,* **1985**, *107*, 5054.
16. (a) Zimmerman, H. E. and Pratt, A. C., *J. Am. Chem. Soc.,* **1970**, *92*, 6259. (b) Zimmerman, H. E. and Mariano, P. S., *J. Am. Chem. Soc.,* **1969**, *91*, 1718.
17. Hahn, R. C. and Johnson, R. P., *J. Am. Chem. Soc.,* **1977**, *99*, 1508.
18. Mizobuchi, Y. and Miller, L., *J. Org. Chem.,* **1985**, *50*, 318.
19. (a) Lamberts, J. J. M. and Laarhoven, W. H., *J. Org. Chem.,* **1983**, *48*, 2202. (b) Rich, J. D.; Drahnak, T. J.; West, R. and Michl, J., *J. Organomet. Chem.,* **1981**, *212*, C1.
20. Zimmerman, H. E. and Cassel, J. M., *J. Org. Chem.,* **1989**, *54*, 3800.
21. (a) Ünaldi, N. S. and Balci, M., *Tetrahedron Lett.,* **2001**, *42*, 8365. (b) Janz, K. M. and Scheffer, J. R., *Tetrahedron Lett.,* **1999**, *40*, 8725. (c) Rattray, G.; Yang, J.; Gudmundsdottir, A. D. and Scheffer, J. R., *Tetrahedron Lett.,* **1993**, *34*, 35. (d) Roughton, A.; Muneer, M.; Klopp, I.; Krüger, C. and Demuth, M., *J. Am. Chem. Soc.*, **1993**, *115*, 2085. (e) Reguero, M.; Bernardi, F.; Jones, H.; Olivucci, M.; Ragazos, I. N. and Robb, M. A., *J. Am. Chem. Soc.,* **1993**, *115*, 2073. (f) Chen, J. X.; Pokkuluri, P. R.; Scheffer, J. R. and Trotter, J., *Tetrahedron Lett.,* **1992**, *33*, 1535. (g) Hemetsberger, H. and Nispel, F., *Tetrahedron,* **1990**, *46*, 3823. (h) Wan, P.; Budac, D.; Earle, M. and Shukla, D., *J. Am. Chem. Soc.,* **1990**, *112*, 8048. (i) Adam, W.; de Lucchi, O. and Dörr, M., *J. Am. Chem. Soc.,* **1989**, *111*, 5209. (j) Zimmerman, H. E.; Nuss, J. M. and Tantillo, A. W., *J. Org. Chem.,* **1988**, *53*, 3792. (k) Adam, W.; Berkessel, A. and Krimm, S., *J. Am. Chem. Soc.,* **1986**, *108*, 4556. (l) Zimmerman, H. E. and Schissel, D. N., *J. Org. Chem.,* **1986**, *51*, 196. (m) Adam, W.; Berkessel, A.; Hildenbrand, K.; Peters, E.-M.; Peters, K. and von Schnering, H. G., *J. Org. Chem.,* **1985**, *50*, 4899. (n) Lamberts, J. J. M. and Laarhoven, W. H., *J. Am. Chem. Soc.,* **1984**, *106*, 1736. (o) Look, S. A.; Fenical, W.; Engen, D. V. and Clardy, J., *J. Am. Chem. Soc.,* **1984**, *106*, 5026. (p) Paquette, L. A. and Bay, E., *J. Am. Chem. Soc.,* **1984**, *106*, 6693. (q) Cristol, S. J. and Hager, J. W., *J. Org. Chem.,* **1983**, *48*, 2005. (r) Kuzuya, M.; Adachi, M.; Noguchi, A. and Okuda, T., *Tetrahedron Lett.,* **1983**, *24*, 2271. (s) Hassner, A.; Middlemiss, D.; Murray-Rust, J. and Murray-Rust, P., *Tetrahedron,* **1982**, *38*, 2539. (t) Hemetsberger, H. and Holstein, W., *Tetrahedron,* **1982**, *38*, 3309. (u) Tokuda, M.; Suginome, H. and Miller, L. L., *Tetrahedron Lett.,* **1982**, *23*, 4573. (v) Scott, L. T. and Erden, I., *J. Am. Chem. Soc.,* **1982**, *104*, 1147. (w) Adam, W.; de Lucchi, O.; Peters, K.; Peters, E.-M. and von Schnering, H. G., *J. Am. Chem. Soc.,* **1982**, *104*, 5747. (x) Luibrand, R. T.; Broline, B. M.; Charles, K. A. and Drues, R. W., *J. Org. Chem.,* **1981**, *46*, 1874. (y) Adam, W. and de Lucchi, O., *J. Org. Chem.,* **1981**, *46*, 4133. (z) Zimmerman, H. E. and Factor, R. E., *Tetrahedron,* **1981**, *37*, 125. (aa) Kuzuya, M.; Mano, E.; Ishikawa, M.; Okuda, T. and Hart, H., *Tetrahedron Lett.,* **1981**, *22*, 1613. (bb) Schaffner, K. and Demuth, M., *Chimia*, **1980**, *34*, 184. (cc) Demuth, M.; Lemmer, D. and Schaffner, K., *J. Am. Chem. Soc.,* **1980**, *102*, 5407. (dd) Adam, W.; Carballeira, N. and de Lucchi, O., *J. Am. Chem. Soc.,* **1980**, *102*, 2107. (ee) Luibrand, R. T. and Fujinari, E. M., *J. Org. Chem.,* **1980**, *45*, 958. (ff) Zimmerman, H. E. and Factor, R. E., *J. Am. Chem. Soc.,* **1980**, *102*, 3538. (gg) Paquette, L. A.; Ku, A. Y.; Santiago, C.; Rozeboom, M. D. and Houk, K. N., *J. Am. Chem. Soc.,* **1979**, *101*, 5972. (hh) Demuth, M.; Burger, U.; Müller, H.W. and Schaffner, K., *J. Am. Chem. Soc.*, **1979**, *101*, 6763. (ii) Ku, A. Y.; Paquette, L. A.; Rozeboom, M. D. and Houk, K. N., *J. Am. Chem. Soc.,* **1979**, *101*, 5981. (jj) Goldschmidt, Z. and Shefi, M., *J. Org. Chem.,* **1979**, *44*, 1604. (kk) Zimmerman, H. E.; Gannett, T. P. and Keck, G. E., *J. Org. Chem.,* **1979**, *44*, 1982. (ll) Padwa, A. and Brookhart, T., *J. Org. Chem.,* **1979**, *44*, 4021. (mm) Kuzuya, M.; Mano, E.; Ishikawa, M.; Okuda, T. and Hart, H., *Tetrahedron Lett.,* **1979**, *20*, 523. (nn) Sato, T. and Ito, S., *Tetrahedron Lett.,* **1979**, *20*, 1051. (oo) Sasaki, t.; Eguchi, S.; Ohno, M. and Umemura, T., *Tetrahedron Lett.,* **1979**, *11*, 3895. (pp) Zimmerman, H. E. and Klun, R. T., *Tetrahedron,* **1978**, *34*, 1775.

(qq) Baeckström, P., *Tetrahedron,* **1978**, *34*, 3331. (rr) Zimmerman, H. E. and Welter, T. R., *J. Am. Chem. Soc.,* **1978**, *100*, 4131. (ss) Zimmerman, H. E. and Gruenbaum, W. T., *J. Org. Chem.,* **1978**, *43*, 1997. (tt) Zimmerman, H. E.; Steinmetz, M. G. and Kreil, C. L., *J. Am. Chem. Soc.,* **1978**, *100*, 4146. (uu) Stantiago, C.; McAlduff, E. J.; Houk, K. N.; Snow, R. A. and Paquette, L. A., *J. Am. Chem. Soc.,* **1978**, *100*, 6149. (vv) Mariano, P. S.; Watson, D. G. and Bay, E., *Tetrahedron,* **1977**, *33*, 11. (ww) van Noort, P. C. M. and Cerfontain, H., *Tetrahedron Lett.,* **1977**, *18*, 3899. (xx) Santiago, C. and Houk, K. N., *J. Am. Chem. Soc.,* **1976**, *98*, 3380. (yy) Zimmerman, H. E.; Boettcher, R. J.; Buehler, N. E.; Keck, G. E. and Steinmetz, M. G., *J. Am. Chem. Soc.,* **1976**, *98*, 7680. (zz) Zimmerman, H. E. and Samuel, C. J., *J. Am. Chem. Soc.,* **1975**, *97*, 448. (aaa) Lankin, D. C.; Chihal, D. M.; Bhacca, N. S. and Griffin, G. W., *J. Am. Chem. Soc.,* **1975**, *97*, 7133. (bbb) Mariano, P. S. and Watson, D. G., *Tetrahedron Lett.,* **1975**, *16*, 3439. (ccc) Goldschmidt, Z. and Gutman, U., *Tetrahedron,* **1974**, *30*, 3327. (ddd) Zimmerman, H. E. and Cotter, B. R., *J. Am. Chem. Soc.,* **1974**, *96*, 7445. (eee) Zimmerman, H. E.; Werthemann, D. P. and Kamm, K. S., *J. Am. Chem. Soc.,* **1974**, *96*, 439. (fff) Zimmerman, H. E.; Baeckstrom, P.; Johnson, T. and Kurtz, D. W., *J. Am. Chem. Soc.,* **1974**, *96*, 1459. (ggg) Zimmerman, H. E.; Robbins, J. D.; McKelvey, R. D.; Samuel, C. J. and Sousa, L. R., *J. Am. Chem. Soc.,* **1974**, *96*, 1974. (hhh) Zimmerman, H. E.; Robbins, J. D.; McKelvey, R. D.; Samuel, C. J. and Sousa, L. R., *J. Am. Chem. Soc.,* **1974**, *96*, 4630. (iii) Zimmerman, H. E. and Little, R. D., *J. Am. Chem. Soc.,* **1974**, *96*, 5143. (jjj) Lankin, D. C.; Chihal, D. M.; Griffin, G. W. and Bhacca, N. S., *Tetrahedron Lett.,* **1973**, *14*, 4009. (kkk) Zimmerman, H. E. and Viriot-Villaume, M.-L., *J. Am. Chem. Soc.,* **1973**, *95*, 1274. (lll) Zimmerman, H. E. and Pincock, J. A., *J. Am. Chem. Soc.,* **1973**, *95*, 2957. (mmm) Perreten, J.; Chihal, D. M.; Griffin, G. W.; Bhacca, N. S., *J. Am. Chem. Soc.,* **1973**, *95*, 3427. (nnn) Düurr, H.; Kober, H.; Halberstadt, I.; Neu, U.; Coburn, T. T.; Mitsuhashi, T. and Jones, W. M., *J. Am. Chem. Soc.,* **1973**, *95*, 3818. (ooo) Zimmerman, H. E.; Werthemann, D. P. and Kamm, K. S., *J. Am. Chem. Soc.,* **1973**, *95*, 5094. (ppp) Mariano, P. S. and Ko, J.-K., *J. Am. Chem. Soc.,* **1973**, *95*, 8670. (qqq) Mariano, P. S. and Ko, J.-K., *J. Am. Chem. Soc.,* **1972**, *94*, 1766. (rrr) Hixson, S. S., *J. Am. Chem. Soc.,* **1972**, *94*, 2507. (sss) Zimmerman, H. E. and Little, R. D., *J. Am. Chem. Soc.,* **1972**, *94*, 8256. (ttt) Zimmerman, H. E.; Baeckstrom, P.; Johnson, T. and Kurtz, D. W., *J. Am. Chem. Soc.,* **1972**, *94*, 5504. (uuu) Zimmerman, H. E. and Pincock, J. A., *J. Am. Chem. Soc.,* **1972**, *94*, 6208. (vvv) Zimmerman, H. E. and Baum, A. A., *J. Am. Chem. Soc.,* **1971**, *93*, 3646. (www) Dauben, W. G.; Spitzer, W. A. and Boden, R. M., *J. Org. Chem.,* **1971**, *36*, 2384. (xxx) Zimmerman, H. E.; Hackett, P.; Juers, D. F.; McCall, J. M. and Schröder, B., *J. Am. Chem. Soc.,* **1971**, *93*, 3653. (yyy) Goldschmidt, Z. and Kende, A. S., *Tetrahedron Lett.,* **1971**, *12*, 4625. (zzz) Paquette, L. A. and Meisinger, R. H., *Tetrahedron Lett.,* **1970**, *11*, 1479. (aaaa) Zimmerman, H. E. and Pratt, A. C., *J. Am. Chem. Soc.,* **1970**, *92*, 1407. (bbbb) Zimmerman, H. E. and Pratt, A. C., *J. Am. Chem. Soc.,* **1970**, *92*, 1409. (cccc) Zimmerman, H. E. and Epling, G. A., *J. Am. Chem. Soc.,* **1970**, *92*, 1411. (dddd) Zimmerman, H. E. and Bender, C. O., *J. Am. Chem. Soc.,* **1970**, *92*, 4366. (eeee) Dauben, W. G. and Spitzer, W. A., *J. Am. Chem. Soc.,* **1970**, *92*, 5817. (ffff) Zimmerman, H. E. and Pratt, A. C., *J. Am. Chem. Soc.,* **1970**, *92*, 6267. (gggg) Zimmerman, H. E. and Samuelson, G. E., *J. Am. Chem. Soc.,* **1969**, *91*, 5307. (hhhh) Zimmerman, H. E. and Bender, C. O., *J. Am. Chem. Soc.,* **1969**, *91*, 7516.

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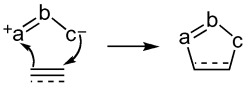
1,3-Dipolar Cycloaddition

A. GENERAL DESCRIPTION OF THE REACTION

The 1,3-dipolar cycloaddition[1] is a kind of cycloaddition reaction that involves the 1,3-dipolar molecules (called 1,3-dipoles) and dipolarophiles in analogues to the diene and dienophiles in *Diels-Alder Cycloadditions*. This reaction was first explored by Huisgen in 1960s[2,3] and was then extensively studied by Huisgen, Padwa,[4] Zecchi,[5] etc. Generally, the 1,3-dipolar molecules come from the combinations of carbon, nitrogen, and oxygen and can be divided into two categories: the propargyl-allenyl type and the allyl type, which are shown in Section B. The dipolarophiles can be either alkenes or alkynes. The outcome of this reaction will be a variety of five-membered heterocyclic molecules, which have been widely applied in medicinal/pharmaceutical chemistry.

B. GENERAL REACTION SCHEME

For the reaction of the allyl-type 1,3-dipoles, the reaction scheme can be generally presented as shown in Figure 1.



(a, b, c = N, O, C)

FIGURE 1. *Allyl type 1,3-Dipolar Cycloaddition.*

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Whereas in the propargyl-allenyl type 1,3-dipoles, with the existence of *sp* orbital, the reaction scheme will be generally shown in Figure 2.

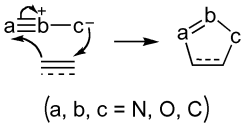
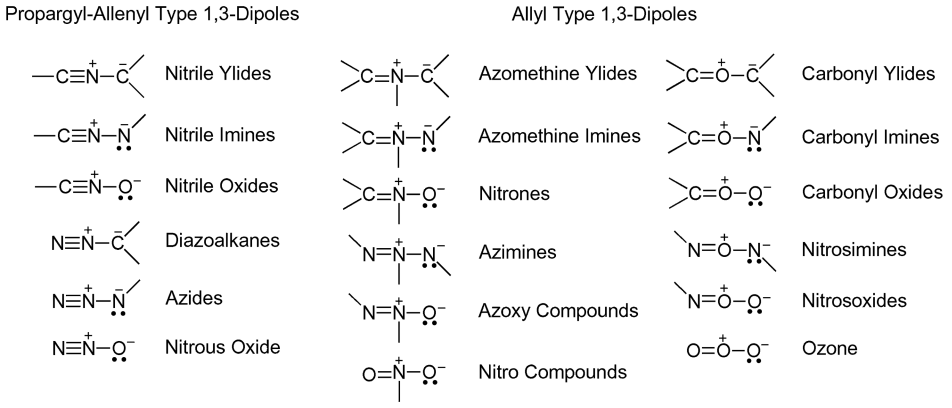


FIGURE 2. *Propargyl-allenyl type 1,3-Dipolar Cycloaddition.*

All the possible 1,3-dipolar molecules coming from carbon, nitrogen, and oxygen are summarized in Table 1.[3b] Sustmann presented a historical account for the 1,3-dipolar cycloaddition.[6] Other reviews about 1,3-dipolar cycloaddition are also available in the literature.[7]



C. PROPOSED MECHANISMS

Although only five atoms participate in the 1,3-dipolar cycloaddition, there are still six electrons ($4\pi + 2\pi$) involved in this reaction to form two new σ-bonds, similar to that in the *Diels-Alder Cycloaddition*. Mechanistically, most of the 1,3-dipolar cycloadditions are thought to undergo a concerted one-step process via a cyclic mechanism, as shown earlier. Although the transition state of 1,3-dipolar cycloaddition is more polar than that of the *Diels-Alder Cycloaddition*, the symmetry of the frontier orbitals is similar.

D. MODIFICATION

N/A

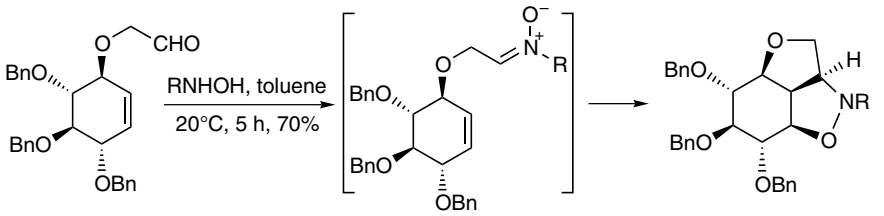
E. APPLICATIONS

This reaction has broad application in the preparation of a variety of five-membered heterocycles, by means of the combination of different dipolar molecules summarized earlier with either alkenes or alkynes.

F. RELATED REACTIONS

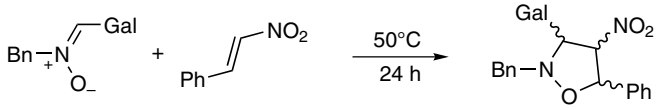
Besides 1,3-dipolar cycloaddition, there are many other types of cycloadditions. One of the most important cycloadditions is the *Diels-Alder Cycloaddition*, which gives six-membered cyclic compounds, in either heterocyclic or homocyclic. Two other important cycloadditions are *[2+2] Cycloaddition* and *Paterno-Büchi Reaction*. In addition, there are many other types of cycloadditions, such as [2+1], [2+2+1], [2+2+2], [2+2+2+1], [3+2+1], [3+2+2], [3+2+2+2], [3+3], [4+1], [4+2+1], [4+2+2], [4+3], [4+4], [5+1], [5+1+2+1], [5+2], [5+2+1], [5+3], [5+4], [6+2], [6+3], [6+4], [6+6] and [8+2] cycloadditions, which are summarized as a general *[m+n(+...)] Cycloaddition*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 8.

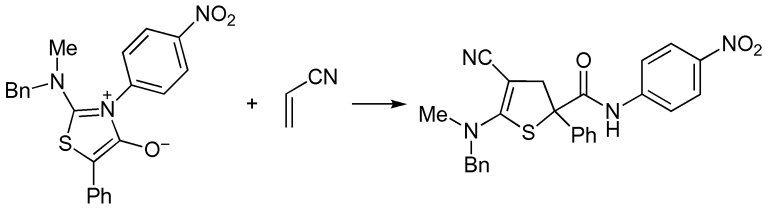
To a solution 0.46 g 2-[(1S,4S,5R,6S)-4,5,6-tris(benzyloxy)cyclohex-2-enyloxy]-acetaldehyde (1 mmol) in 5 mL anhydrous toluene was added a solution of 0.12 g *N*-benzyl-hydroxylamine (1.1 mmol, prepared from the hydrochloride acid with 0.1 mL triethylamine) in 2 mL anhydrous dichloromethane. The reaction mixture was stirred at 20°C for 2 h. Removal of the solvents under reduced pressure furnished a residue, which was chromatographed to give 0.4 g (2*aS*,4*a*S,5S,6S,7R,7*a*R,7*b*R)-2-benzyl-5,6,7-tris(benzyl-oxy)octa-hydro-2H-furo[4,3,2-c,d][1,2]benzisoxazole as a colorless wax, in a yield of 70%. $R_f = 0.45$ (toluene/ethyl acetate, 5:1). $[\alpha]_D^{22} = 86.14$ ($c = 1.0$, $CHCl_3$).



Reference 9.

A solution of 0.235 g (*Z*)-*N*-benzyl-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-ylidene)amine *N*-oxide (0.65 mmol) and 0.385 g β-nitrostyrene (2.60 mmol) in 0.5 mL toluene was stirred at 50°C. After 24 h, the conversion was complete, as indicated by

^{1}H NMR, which showed the formation of two diastereomers of 2-benzyl-3-(1,2:3,4-di-*O*-isopropylidene-α-D-galacto-pentopyranos-5-yl)-4-nitro-5-phenylisoxazolidines(65:35).



Reference 10.

To a solution of 0.84 g thioisomünchnones (2.0 mmol) in 10 mL dry CH_2Cl_2 was added 0.11 g acrylonitrile (2.0 mmol) and the reaction mixture was stirred at room temperature for 24 h. The solvent was then evaporated under reduced pressure, and the residue was treated with EtOAc to give 0.55 g 5-[benzyl-(methyl)amino]-4-cyano-N-(4-nitrophenyl)-2-phenyl-2,3-dihydrothiophene-2-carboxamide as crystals, in a yield of 58%, m.p. 167–169°C.

Other references related to 1,3-dipolar cycloaddition are cited in the literature.[11]

H. REFERENCES

1. (a) Stecko, S.; Pasniczek, K.; Jurczak, M.; Urbanczyk-Lipkowska, Z. and Chmielewski, M., *Tetrahedron: Asymmetry*, **2007**, *18*, 1085. (b) Boruah, M.; Konwar, D. and Das Sharma, S., *Tetrahedron Lett*., **2007**, *48*, 4535. (c) Cabrera, S.; Arrayas, R. G.; Martin-Matute, B.; Cossio, F. P. and Carretero, J. C., *Tetrahedron,* **2007**, *63*, 6587. (d) Deng, L. P. and Hu, Y. Z., *J. Heterocycl. Chem.,* **2007**, *44*, 597. (e) Azzouzi, S.; Jalal, R.; El Messaoudi, M.; Domingo, L. R.; Esseffar, M. and Aurell, M. J., *J. Phys. Org. Chem.,* **2007**, *20*, 245. (f) Llamas, T.; Arrayas, R. G. and Carretero, J. C., *Synthesis,* **2007**, 950. (g) Jin, T. N. and Yamamoto, Y., *Angew. Chem. Int. Ed.,* **2007**, *46*, 3323. (h) Sirion, U.; Kim, H. J.; Lee, J. H.; Seo, J. W.; Lee, B. S.; Lee, S. J.; Oh, S. J. and Chi, D. Y., *Tetrahedron Lett*., **2007**, *48*, 3953. (i) Cheng, S. L.; Wu, H. M. and Hu, X. M., *Synth. Commun.,* **2007**, *37*, 297. (j) Babu, A. R. S. and Raghunathan, R., *Synth. Commun.,* **2007**, *37*, 451. (k) Dedola, S.; Nepogodiev, S. A. and Field, R. A., *Org. Biomol. Chem.,* **2007**, *5*, 1006. (l) Liu, L.-P.; Lu, J.-M. and Shi, M., *Org. Lett.,* **2007**, *9*, 1303. (m) Dijkgraaf, I.; Rijnders, A. Y.; Soede, A.; Dechesne, A. C.; Van Esse, G. W.; Brouwer, A. J.; Corstens, F. H. M.; Boerman, O. C.; Rijkers, D. T. S. and Liskamp, R. M. J., *Org. Biomol. Chem.,* **2007**, *5*, 935. (n) Akao, A.; Tsuritani, T.; Kii, S.; Sato, K.; Nonoyama, N.; Mase, T. and Yasuda, N., *Synlett,* **2007**, 31. (o) Kobayashi, K.; Igura, Y.; Imachi, S.; Masui, Y. and Onaka, M., *Chem. Lett.,* **2007**, *36*, 60. (p) Belanger, G.; April, M.; Dauphin, E. and Roy, S., *J. Org. Chem.,* **2007**, *72*, 1104.
2. (a) Huisgen, R.; Fleischmann, R. and Eckell, A., *Tetrahedron Lett.,* **1960**, 1. (b) Huisgen, R. and Eckell, A., *Tetrahedron Lett*., **1960**, 5. (c) Grashey, R.; Huisgen, R. and Leitermann, H., *Tetrahedron Lett*., **1960**, 9.
3. (a) Huisgen, R., *J. Org. Chem*., **1976**, *41*, 403. (b) Huisgen, R., *Angew. Chem. Int. Ed. Engl.,* **1963**, *2*, 633. (c) Huisgen, R., *Angew. Chem. Int. Ed. Engl.,* **1963**, *2*, 565. (d) Huisgen, R., Seidel, M., Wallbillich, G. and Knupfer, H., *Tetrahedron*, **1962**, *17*, 3. (e) Huisgen, R., "1,3-Dipolar Cycloadditions—Introduction, Survey, Mechanism" in *1,3-Dipolar Cycloaddition Chemistry*, Vol. 1, ed. Padwa, A. [General Heterocyclic Chemistry Series, ed. Talyor, E. C. and Weissgberger, A.], John Wiley & Sons, New York, **1984**, pp. 1–176.
4. (a) Padwa, A. and Pearson, W ., eds., *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*, John Wiley & Sons, New York, **2002**. (b) Padwa,

A., ed., *1,3-Dipolar Cycloaddition Chemistry*, Vols. 1 and 2 [General Heterocyclic Chemistry Series, ed. Talyor, E. C. and Weissgberger, A.], John Wiley & Sons, New York, **1984**.

5. (a) Garanti, L.; Molteni, G. and Zecchi, G., *Heterocycles*, **1995**, *40*, 777. (b) Broggini, G.; Garanti, L.; Molteni, G. and Zecchi, G., *Tetrahedron*, **1998**, *54*, 2843. (c) Garanti, L.; Sala, A. and Zecchi, G., *Synthesis*, **1975**, 666.
6. Sustmann, R., *Heterocycles*, **1995**, *40*, 1.
7. (a) Gothelf, K. V. and Jørgensen, K. A., *Chem. Commun*., **2000**, 1449. (b) Raimondi, L. and Benaglia, M., *Eur. J. Org. Chem.,* **2001**, 1033. (c) Gothelf, K. V. and Jørgensen, K. A., *Chem. Rev.,* **1998**, *98*, 863.
8. Lalk, M.; Reinke, H. and Peseke, K., *Eur. J. Org. Chem.,* **2001**, 759.
9. Borrachero, P.; Cabrera, F.; Diánez, M. J.; Estrada, M. D.; Gómez-Guillén, M.; López-Castro, A.; Moreno, J. M.; de Paz, J. L., and Pérez-Garrido, S., *Tetrahedron*: *Asymmetry*, **1999**,10, 77.
10. Areces, P.; Avalos, M.; Babiano, R.; Cintas, P.; Gonzalez, L.; Hursthouse, M. B.; Jimenez, J. L.; Light, M. E.; Lopez, I.; Palacios, J. C. and Silvero, G., *Eur. J. Org. Chem.,* **2001**, 2135.
11. (a) Aggarwal, V. K.; Vicente, J. and Bonnert, R. V., *J. Org. Chem.,* **2003**, *68*, 5381. (b) Lolber, S.; Rodriguez-Loaiza, P. and Gmeiner, P., *Org. Lett.,* **2003**, *5*, 1753. (c) Bokach, N. A.; Khripoun, A. V.; Kukushkin, V. Y.; Haukka, M. and Pombeiro, A. J. L., *Inorg. Chem.,* **2003**, *42*, 896. (d) Blazey, C. M. and Heathcock, C. H., *J. Org. Chem.,* **2002**, *67*, 298. (e) Suga, H.; Inoue, K.; Inoue, S. and Kakehi, A., *J. Am. Chem. Soc.,* **2002**, *124*, 14836. (f) Savinov, S. N. and Austin, D. J., *Org. Lett.,* **2002**, *4*, 1415. (g) Sammelson, R. E.; Gurusinghe, C. D.; Kurth, J. M.; Olmstead, M. M. and Kurth, M. J., *J. Org. Chem.,* **2002**, *67*, 876. (h) Viton, F.; Bernardinelli, G.; Kündig, E. P., *J. Am. Chem. Soc.,* **2002**, *124*, 4968. (i) Lu, X.; Xu, X.; Wang, N. Q. and Zhang, Q. E., *J. Org. Chem.,* **2002**, *67*, 515. (j) Wilkie, G. D.; Elliott, G. I.; Blagg, B. S. J.; Wolkenberg, S. E.; Soenen, D. R.; Miller, M. M.; Pollack, S. and Boger, D. L., *J. Am. Chem. Soc.,* **2002**, *124*, 11292. (k) Zhou, C.-Y.; Yu, W.-Y. and Che, C.-M., *Org. Lett.,* **2002**, *4*, 3235. (l) Silva, A. M. G.; Tomé, A. C.; Neves, M. G. P. M. S.; Silva, A. M. S. and Cavaleiro, J. A. S., *J. Org. Chem.,* **2002**, *67*, 726. (m) Mita, T.; Ohtsuki, N.; Ikeno, T. and Yamada, T., *Org. Lett.,* **2002**, *4*, 2457. (n) Katritzky, A. R. and Singh, S. K., *J. Org. Chem.,* **2002**, *67*, 9077. (o) Shindo, M.; Itoh, K.; Tsuchiya, C. and Shishido, K., *Org. Lett.,* **2002**, *4*, 3119. (p) Nguyen, M. T.; Chandra, A. K.; Uchimaru, T. and Sakai, S., *J. Phys. Chem. A,* **2001**, *105*, 10943. (q) Kambe, M.; Arai, E.; Suzuki, M.; Tokuyama, H. and Fukuyama, T., *Org. Lett.,* **2001**, *3*, 2575. (r) Kostik, E. I.; Abiko, A. and Oku, A., *J. Org. Chem.,* **2001**, *66*, 1638. (s) Liu, F. and Austin, D. J., *Org. Lett.,* **2001**, *3*, 2273. (t) Hoveyda, H. R. and Hall, D. G., *Org. Lett.,* **2001**, *3*, 3491. (u) Carey, J. S., *J. Org. Chem.,* **2001**, *66*, 2526. (v) Scholz, J.; Görls, H.; Schumann, H. and Weimann, R., *Organometallics,* **2001**, *20*, 4394. (w) Huang, K. S.-L., Lee, E. H.; Olmstead, M. M. and Kurth, M. J., *J. Org. Chem.,* **2000**, *65*, 499. (x) Jen, W. S.; Wiener, J. J. M. and MacMillan, D. W. C., *J. Am. Chem. Soc.,* **2000**, *122*, 9874. (y) Suga, H.; Kakehi, A.; Ito, S.; Inoue, K.; Ishida, H. and Ibata, T., *Org. Lett.,* **2000**, *2*, 3145. (z) Toker, J. D.; Wentworth, P.; Hu, Y. F.; Houk, K. N. and Janda, K. D., *J. Am. Chem. Soc.,* **2000**, *122*, 3244. (aa) Tamura, O.; Gotanda, K.; Yoshino, J.; Morita, Y.; Terashima, R.; Kikuchi, M.; Miyawaki, T.; Mita, N.; Yamashita, M.; Ishibashi, H. and Sakamoto, M., *J. Org. Chem.,* **2000**, *65*, 8544. (bb) Kanemasa, S. and Kanai, T., *J. Am. Chem. Soc.,* **2000**, *122*, 10710. (cc) Sakata, K., *J. Phys. Chem. A,* **2000**, *104*, 10001. (dd) Jensen, K. B.; Roberson, M. and Jørgensen, K. A., *J. Org. Chem.,* **2000**, *65*, 9080. (ee) Calvo-Flores, F. G.; Isac-Garcia, J.; Hernández-Mateo, F.; Pérez-Balderas, F.; Calvo-Asin, J. A.; Sanchéz-Vaquero, E. and Santoyo-González, F., *Org. Lett.,* **2000**, *2*, 2499. (ff) Warrener, R. N.; Margetic, D.; Amarasekara, A. S. and Russell, R. A., *Org. Lett.,* **1999**, *1*, 203. (gg) Rifé, J.; Ortuño, R. M. and Lajoie, g. A., *J. Org. Chem.,* **1999**, *64*, 8958. (hh) Nguyen, M. T.; Chandra, A. K.; Sakai, S. and Morokuma, K., *J. Org. Chem.,* **1999**, *64*, 65. (ii) Hori, K.; Kodama, H.; Ohta, T. and Furukawa, I., *J. Org. Chem.,* **1999**, *64*, 5017. (jj) Yip, C.; Handerson, S.; Jordan, R. and Tam, W., *Org. Lett.,* **1999**, *1*, 791. (kk) Domingo, L. R., *J. Org. Chem.,* **1999**, *64*, 3922. (ll) Kitagaki, S.; Anada, M.; Kataoka, O.; Matsuno, K.; Umeda, C.; Watanabe, N. and Hashimoto, S.-I., *J. Am. Chem. Soc.,* **1999**, *121*, 1417.

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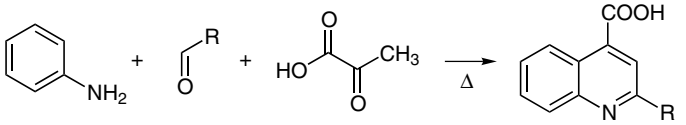
Doebner Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Doebner in 1887.[1] It is the synthesis of cinchoninic acid[2] (or quinolinic acid[3]) derivatives from the reaction of aromatic amines, aldehydes, and pyruvic acid, involving the removal of hydrogen from the aromatic ring.[3] However, the Doebner reaction failed when 2-chloro-5-aminopyridine,[3] 3-aminopyridine,[3] and 2-aminopyridine[4] were applied as the aromatic amines.

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

This reaction may involve an *Aldol Condensation* between the aldehyde and pyruvic acid to afford a β,γ-unsaturated α-keto acid that then undergoes the *Michael Addition* with aniline, as shown in Scheme 1.

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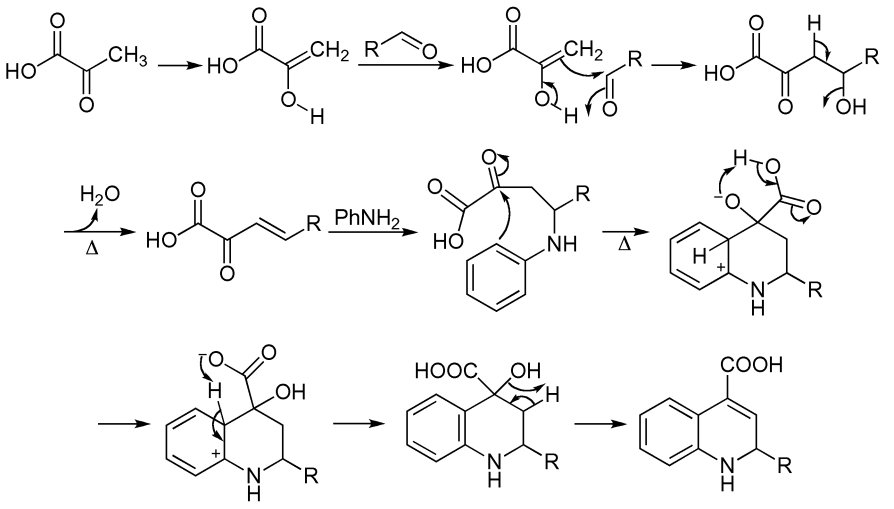
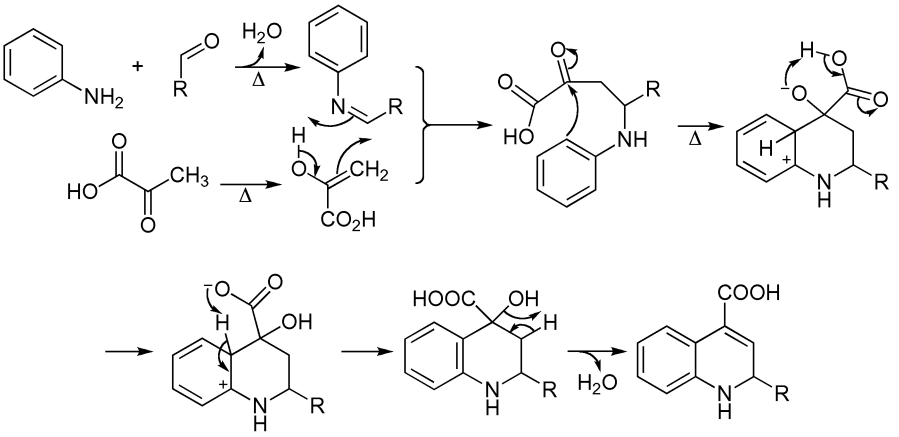


SCHEME 1. *Doebner reaction via aldol condensation.*

Alternatively, this reaction might involve the formation of a Schiff base between aniline and aldehyde, which then couples with pyruvic acid, as illustrated in Scheme 2.



SCHEME 2. *Doebner reaction involving Schiff base intermediate.*

D. MODIFICATION

N/A

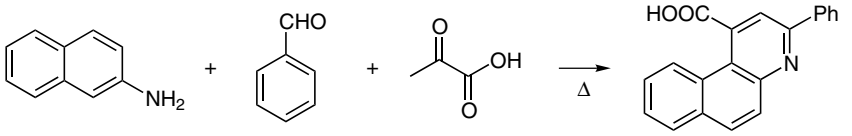
E. APPLICATIONS

This reaction has been applied to the synthesis of quinolinic acids and cinchoninic acids.

F. RELATED REACTIONS

The reaction is related to the *Combes Quinoline Synthesis* and *Conrad-Limpach Quinoline Synthesis.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 2.

The anil was first prepared from the reaction between benzaldehyde and 2-naphthylamine. Then the suspension of 0.2 mol anil and 0.1 mol pyruvic acid in 250 mL 95% ethanol was refluxed for 4 h. The benzocinchoninic acid separated as a crystalline insoluble precipitate, which was filtered out of the hot mixture, washed thoroughly with alcohol and ether, and dried to give 40% of product. The compound was a pale yellow solid that decomposed at 247°C.

Other references related to the Doebner reaction are cited in the literature.[5]

H. REFERENCES

1. (a) Doebner, O., *Ann.,* **1887**, *242*, 265. (b) Doebner, O., *Ber.,* **1887**, *20*, 277.
2. Robinson, E. A. and Bogert, M. T., *J. Org. Chem.,* **1936**, *1*, 65.
3. Weiss, M. J. and Hauser, C. R., *J. Am. Chem. Soc.,* **1946**, *68*, 722.
4. (a) Allen, C. F. H.; Spangler, F. W. and Webster, E. R., *J. Org. Chem.,* **1951**, *16*, 17. (b) Lappin, G. R.; Petersen, Q. R. and Wheeler, C. E., *J. Org. Chem.,* **1950**, *15*, 377. (c) Lappin, G. R., *J. Am. Chem. Soc.,* **1948**, *70*, 3348.
5. (a) Gream, G. E. and Serelis, A. K., *Aust. J. Chem.,* **1978**, *31*, 863. (b) Bergström, F. W., *Chem. Rev.,* **1944**, *35*, 156. (c) Doebner, O., *Ber.,* **1894**, *27*, 352. (d) Doebner, O., *Ber.,* **1894**, *27*, 2020.

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Doebner-Miller Reaction

(Doebner-Miller Synthesis, Doebner-von Miller Quinoline Synthesis, Skraup-Doebner-von Miller Quinoline Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Doebner and von Miller in 1881[1] as a modification of the original *Skraup Reaction*, and it was subsequently modified by Beyer in 1886.[2] It is an acidic condensation between primary aromatic amines (e.g., anilines) and α,β-unsaturated carbonyl compounds (mostly α,β-unsaturated aldehydes) to give 2,3-disubstituted quinolines. Therefore, this reaction is generally known as the Doebner-Miller reaction,[3] or Doebner-Miller synthesis.[4] In addition, this reaction is also referred to as the Doebner-von Miller quinoline synthesis,[5] Skraup-Doebner-von Miller reaction,[6] Skraup-Doebner-von Miller quinoline synthesis,[7] Doebner-Miller condensation,[8] and Doebner-Miller Quinaldine Synthesis.[9] For comparison, the modification from Beyer, known as the Beyer method[10] for quinoline, is an acidic condensation between anilines and α,β-unsaturated carbonyl compounds generated *in situ* from aldehyde or aldehyde and methyl ketone to afford 2,4-disubstituted quinolines.[11] The optimal condition of this reaction is to heat the mixture of aniline/aldehyde (1:2) at 100°C for 6 h with hydrochloric acid and zinc chloride; in addition, an oxidizing reagent is also needed in this reaction, such as nitrobenzene.[12] However, it has been reported that *N*-alkylanilines are also formed in this reaction.[13] The nature and

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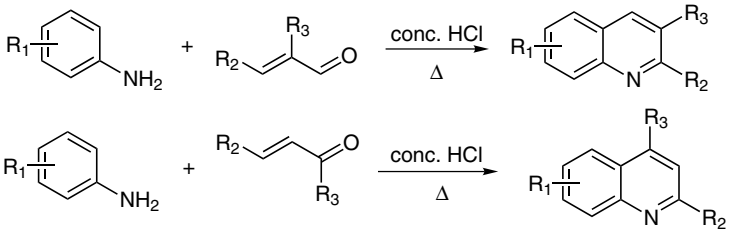
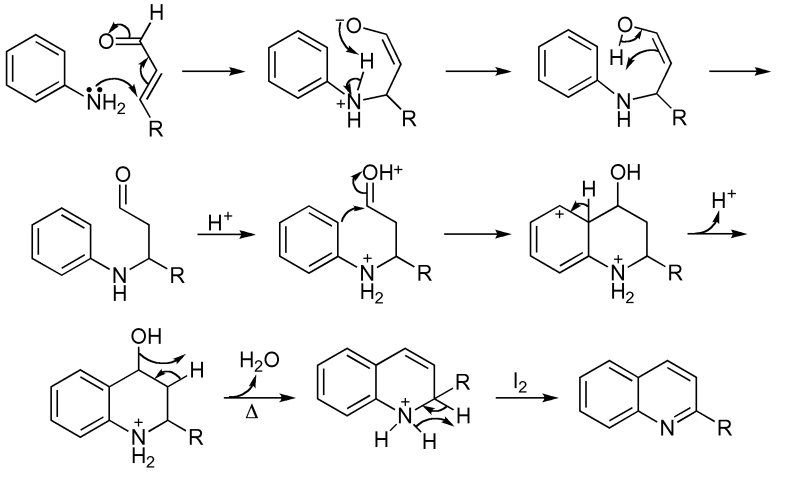
positions of substituents in anilines were found to have a sufficient effect on the reaction direction and quinoline yields, which the anilines with electron-donating groups normally afford higher yields of quinolines, whereas those with electron-withdrawing groups impede product formation.[14] For example, *o*- and *p*-substituted anilines form six- and eight-substituted quinolines,[15] respectively, *m*-substituted anilines (with *ortho-para* directing substituents) give a hardly separated mixture of five- and seven-substituted quinolines in low yields,[16] and *o*-nitro-*p*-methoxyaniline leads to no ring closure.[17] The generation of seven-substituted quinolines in high yields was observed in the application of (Pr^{+3}–PPh_3–DMF) as a catalyst in this reaction.[16] This reaction has been extensively reviewed.[18]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is evident that the condensation of aniline with a substituted acrolein to yield quinoline involves the loss not only of water but of two hydrogen atoms as well.[19] Therefore, the illustrative mechanism is proposed here for the reaction between a simple aniline and acrolein using iodine as an oxidizing reagent.



D. MODIFICATION

A catalytic amount of iodine is applied as a condensation reagent to form α,β-unsaturated carbonyl compound *in situ* in the formation of benzopyrano[3,4-f]quinolines.[20] In addition, the fume sulfuric acid is also a good reagent for this reaction, together with $FeSO_4$ and H_3BO_3.[21]

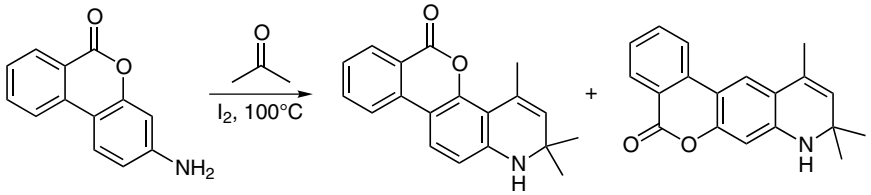
E. APPLICATIONS

This reaction is generally used for the synthesis of quinolines with substituents on the pyridinoid ring.

F. RELATED REACTIONS

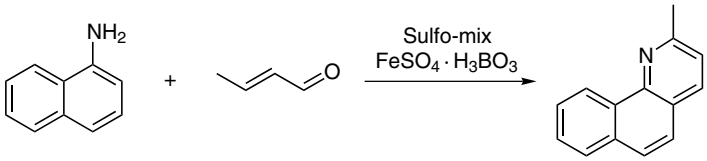
This reaction is related to the *Skraup Reaction*, but is used for the synthesis of quinolines bearing substitutents in the pyridinoid ring. This reaction is also related to the *Gould-Jacobs Quinoline Synthesis* and *Knorr Quinoline Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 20c

A solution of 185 mg 3-amino-6*H*-dibenzo[*b*,*d*]-pyran-6-one (0.87 mmol) and 25 mg iodine (0.10 mmol, 11 mol %) in 20 mL acetone was heated at 100°C in a sealed tube for 15 h. The mixture was concentrated and chromatographed (30–150 mm column, hexane/EtOAc, 10:1 to 2:1 gradient) to afford 150 mg 1,2-dihydro-2,2,4-trimethyl-10-isocoumarino[3,4-*f*]quinoline (60% yield, m.p. 197–199°C) and 75 mg 1,2-dihydro-2,2,4-trimethyl-10-isocoumarino-[4,3-*g*]quinoline (30% yield, m.p. 246–248°C).



Reference 21

To a warmed (110°C), homogeneous mixture of 58.5 g sulfo-mix [prepared from 48.0 g $H_2SO_4 \bullet SO_3$ (20%) and 10.5 g nitrogenzene], 1.4 g $FeSO_4 \cdot 7H_2O$, 2.4 g H_3BO_3, 25 mL water, and 5.72 g 1-naphthylamine (0.04 mol), was added dropwise over 30 min 3.5 g crotonaldehyde (0.05 mol). The bath temperature was raised to 130°C, and the reaction mixture was stirred for 5 h. The cooled solution was made basic with aqueous 20% NaOH and extracted with four 100-mL portions of $CHCl_3$. The combined $CHC1_3$ extracts were washed with water, dried over $MgSO_4$, and evaporated to dryness. The brown liquid residue was chromatographed on 100 g alumina. The elution with benzene was evaporated to give a yellow oil. Distillation gave 2.8 g 2-methylbenzo[h]quinoline as a pale yellow liquid, in a yield of 36%, b.p. 322–324°C.

Other references related to the Doebner-Miller reaction are cited in the literature.[22]

H. REFERENCES

1. (a) Doebner, O. and von Miller, W., *Ber.,* **1881**, *14*, 2812. (b) Doebner, O. and von Miller, W., *Ber.,* **1883**, *16*, 1664. (c) Doebner, O. and von Miller, W., *Ber.,* **1883**, *16*, 2464. (d) Doebner, O. and von Miller, W., *Ber.,* **1884**, *17*, 1698. (e) Doebner, O. and von Miller, W., *Ber.,* **1884**, *17*, 1712. (f) Doebner, O. and von Miller, W., *Ber.,* **1884**, *17*, 1718.
2. Beyer, C., *J. Prakt. Chem.* **1886**, *33*, 393.
3. (a) Chelucci, G. and Thummel, R. P., *Chem. Rev.,* **2002**, *102*, 3129. (b) Bordunov, A. V.; Bradshaw, J. S.; Zhang, X. X.; Dalley, N. K.; Kou, X. L. and Izatt, R. M., *Inorg. Chem.,* **1996**, *35*, 7229. (c) Barbieri, W.; Bernardi, L.; Colo, V. and Patelli, B., *Chim. Ind. (Milan),* **1972**, *54*, 786. (d) Phillips, J. P.; Emery, J. F. and Price, H. P., *Anal. Chem.*, **1952**, *24*, 1033. (e) Weizmann, M. and Bograchov, E., *J. Am. Chem. Soc.,* **1947**, *69*, 1222, (f) Campbell, K. N. and Schaffner, I. J., *J. Am. Chem. Soc.,* **1945**, *67*, 86.
4. (a) Matsugi, M.; Tabusa, F. and Minamikawa, J.-I., *Tetrahedron Lett.,* **2000**, *41*, 8523. (b) Saggiomo, A. J.; Kato, K. and Kaiya, T., *J. Med. Chem.,* **1968**, *11*, 277. (c) Atkinson, E. R. and Puttick, A. J., *J. Med. Chem.,* **1968**, *11*, 1223. (d) Campbell, K. N.; Tipson, R. S.; Elderfield, R. C.; Campbell, B. K.; Clapp, M. A.; Gensler, W. J.; Morrison, D. and Moran, W. J., *J. Org. Chem.,* **1947**, *12*, 803. (e) Kharasch, M. S.; Richlin, I. and Mayo, F. R., *J. Am. Chem. Soc.,* **1940**, *62*, 494. (f) Poth, E. J.; Schulze, W. A.; King, W. A.; Thompson, W. C.; Slagle, W. M.; Floyd, W. W. and Bailey, J. R., *J. Am. Chem. Soc.,* **1930**, *52*, 1239.
5. (a) Zhang, Z. P.; Tillekeratne, L. M. V. and Hudson, R. A., *Tetrahedron Lett*., **1998**, *39*, 5133. (b) Eisch, J. J. and Dluzniewski, T., *J. Org. Chem.,* **1989**, *54*, 1269. (c) Schindler, O. and Michaelis, W., *Helv. Chim. Acta,* **1970**, *53*, 776.
6. Dumitrescu, C., *Ind. Chim. Belg.,* **1967**, *32*, 117.
7. (a) Wu, Y.-C.; Liu, L.; Li, H.-J.; Wang, D. and Chen, Y.-J., *J. Org. Chem.,* **2006**, *71*, 6592. (b) Denmark, S. E. and Venkatraman, S., *J. Org. Chem.,* **2006**, *71*, 1668.
8. Atwell, G. J.; Baguley, B. C. and Denny, W. A., *J. Med. Chem.,* **1989**, *32*, 396.
9. (a) Leir, C. M., *J. Org. Chem.,* **1977**, *42*, 911. (b) Wagner, E. C., *J. Org. Chem.,* **1954**, *19*, 1862. (c) Gutekunst, G. O. and Gray, H. L., *J. Am. Chem. Soc.,* **1922**, *44*, 1741.
10. (a) Rogovik, L. I.; Chernyuk, I. N. and Pridan, V. E., *Zh. Org. Khim.,* **1979**, *15*, 637. (b) Chernyuk, I. N.; Rogovik, L. I.; Voloshenyuk, T. N. and Pilyugin, G. T., *Zh. Obsh. Khim.,* **1975**, *45*, 672. (c) Roberts, E. and Turnur, E. E., *J. Chem. Soc.,* **1927**, 1832.
11. Rohde, G., *Ber.,* **1887**, *20*, 1911.
12. Dzhemilev, U. M.; Selimov, F.A. and Khusnutdinov, R. A., *Izv. AN SSSR, Ser. Khim*., **1990**, 2447.

13. Carrigan, C. N.; Esslinger, C. S.; Bartlett, R. D.; Bridges, R. J. and Thompson, C. M., *Bioorg. Med. Chem. Lett*., **1999**, *9*, 2607.
14. Dzhemilev, U. M.; Selimov, F. A. and Tolstikov, G. A., *ARKIVOC*, **2001**, (*ix*), 85.
15. Dzhemilev, U. M.; Selimov, F. A.; Khusnutdinov, R. A.; Fatykhov, A. A.; Khalilov, L. M. and Tolstikov, G. A.*, Izv. AN SSSR, Ser. Khim*. **1991**, 1407.
16. Campbell, K. N.; Sommers, A. H.; Kerwin, J. F. and Campbell, B. K., *J. Am. Chem. Soc.,* **1968**, *46*, 1556.
17. (a) Utermohlen, W. P., *J. Org. Chem.,* **1943**, *8*, 544. (b) Bartow, E. and McCollum, E. V., *J. Am. Chem. Soc.,* **1904**, *26*, 700.
18. (a) Barton, D. and Ollis, G., eds., *Comprehensive Organic Chemistry*, vol. 4, Pergamon Press, New York, **1979**. (b) Claret, P. A., "Quinolines" in *Comprehensive Organic Chemistry, The Synthesis and Reactions of Organic Compounds*, ed., Sammes, P. G., Pergamon Press, Oxford, **1979**, *4*, pp. 155–203. (c) Jones, G., "Synthesis of the Quinoline Ring System," in *The Chemistry of Heterocyclic Compounds,* ed. Weissberger, A. and Taylor, E. C., John Wiley & Sons, London, **1977**, *32*, pp. 93–318. (d) Campbell, N., "*Bicyclic Compounds Containing a Pyridine Ring: Quinoline and Its Derivatives*" in *Rodd's Chemistry of Carbon Compounds*, ed. Coffey, S., 2nd. ed., Elsevier Scientific Publishing, Amsterdam, **1976**, *4F*, pp. 231–356. (e) Manske, R. H. F. and Kulka, M., *Org. React.,* **1953**, *7*, 59.
19. Manske, R. H. F., *Chem. Rev.,* **1942**, *30*, 113.
20. (a) Kym, P. R.; Kort, M. E.; Coghlan, M. J.; Moore, J. L.; Tang, R.; Ratajczyk, J. D.; Larson, D. P.; Elmore, S. W.; Pratt, J. K.; Stashko, M. A.; Falls, H. D.; Lin, C. W.; Nakane, M.; Miller, L.; Tyree, C. M.; Miner, J. N.; Jacobson, P. B.; Wilcox, D. M.; Nguyen, P. and Lane, B. C., *J. Med. Chem.* **2003**, *46*, 1016. (b) Coghlan, M. J.; Kym, P. R.; Elmore, S. W.; Wang, A. X.; Luly, J. R.; Wilcox, D.; Stashko, M.; Lin, C. W.; Miner, J.; Tyree, C.; Nakane, M.; Jacobson, P. and Lane, B. C., *J. Med. Chem.* **2001**, *44*, 2879. (c) Zhi, L.; Tegley, C. M.; Kallel, E. A.; Marschke, K. B.; Mais, D. E.; Gottardis, M. M. and Jones, T. K., *J. Med. Chem.* **1998**, *41*, 291. (d) Hamann, L. G.; Higuchi, R. I.; Zhi, L.; Edwards, J. P.; Wang, X. N.; Marschke, K. B.; Kong, J. W.; Farmer, L. J. and Jones, T. K., *J. Med. Chem.* **1998**, *41*, 623.
21. Hamada, Y. and Takeuchi, I., *J. Org. Chem.,* **1977**, *42*, 4209.
22. (a) Yamashkin, S. A. and Oreshkina, E. A., *Chem. Heterocycl. Compd.,* **2006**, *42*, 701. (b) Clavier, S.; Rist, Ø.; Hansen, S.; Gerlach, L.-O.; Högberg, T. and Bergman, J., *Org. Biomol. Chem.,* **2003**, *1*, 4248. (c) Schoffers, E., *Euro. J. Org. Chem.,* **2003**, 1145. (d) Matsugi, M.; Tabusa, F. and Minamikawa, J.-I., *Tetrahedron Lett.,* **2000**, *41*, 8525. (e) Outt, P. E.; Ares, J. J.; Roberts, G. E. Wang, X. D.; Cupps, T. L. and Wireko, F. C., *J. Org. Chem.* **1998**, *63*, 5762. (f) Dzhemilev, U. M.; Selimov, F.A.; Khusnutdinov, R. A.; Fatykhov, A. A.; Andreikov, E. I. and Obamin, G. A., *Izv. Akad. Nauk, Ser. Khim*., **1992**, 1139. (g) Nawrocka, W. and Zimecki, M., *Arch. Pharm.,* **1999**, *331*, 249. (h) Corey, E. J.; Tramontano, A. *J. Am. Chem. Soc*. **1981**, *103*, 5600. (i) Allinger N. L., Wang G. L. and Dewhurst B. B., *J. Org. Chem.*, **1974**, *12*, 1730. (j) Dauphinee, G. A. and Forrest, T. P. *J. Chem. Soc. D*, **1969**, 327. (k) Pilyugin G. T. and Guculyak B. M., *Usp. Himii*, **1963**, *32*, 389. (l) Badger, G. M., Crocker, H. P., Ennis, B. C., Tayler, J. A., Matthews, W. E., Raper, W. G. C., Samuel, E., L. and Spotswood, I. M., *Aust. J. Chem*. **1963**, *16*, 814. (m) Fiedler H., *J. Prakt. Chem.*, **1961**, *13*, 86. (n) Ardashev, B. I., *Uspekhi Khimii*, **1954**, *23*, 45. (o) Campbell, K. N.; Helbing, C. H. and Kerwin, J. F., *J. Am. Chem. Soc.,* **1946**, *68*, 1840. (p) Prices, C. C and Roberts, R. M., *J. Org. Chem.* **1946**, *11*, 463. (q) Steck, E. A.; Hallock, L. L. and Holland, A. J., *J. Am. Chem. Soc.,* **1946**, *68*, 380. Bergström, F. W., *Chem. Rev.* **1944**, *35*, 153. (r) Manske, R. H., *Chem. Rev.,* **1942**, *30* 113. (s) Charriou, A., *Bull. Soc. Encour. Ind. Nation.,* **1935**, *134*, 153. (t) Phillips, M. and Goss, M. J., *J. Am. Chem. Soc.,* **1926**, *48*, 823. (u) Braunholz, W. T. K., *J. Chem. Soc.,* **1922**, *121*, 169. (v) Braunholz, W. T. K., *J. Am. Chem. Soc.,* **1922**, *44*, 2967. (w) Mans, F. G., *J. Chem. Soc.,* **1922**, *121*, 2178. (x) Ciusa, R., *Gazz. Chim. Ital.,* **1922**, *62*, *(II),* 43. (y) Mills, W. H.; Harris, J. E. G.; Lambourne, H. *J. Chem. Soc.* **1921**, *119*, 1294. (z) Ciusa, R. and

Zerbini, G., *Gazz. Chim. Ital.*, **1920**, *60, (II),* 317. (aa) Edwards, M. G.; Garrod, R. E. and Jokes, H. O., *J. Chem. Soc.,* **1912**, *101*, 1376. (bb) Garrod, R. E.; Jones, H. D. and Evans, P. E., *J. Chem. Soc.,* **1912**, *101*, 1389. (cc) Jones, H. D. and Evans, P. E., *J. Chem. Soc.,* **1911**, *99*, 334. (dd) Blaise, E. E.; Maire, M. *Bull. Soc. Chim*. **1908**, *3*, 667. (ee) Simon, L. J. and Mauguin, C., *Compt. Rend.,* **1907**, *144*, 1275. (ff) Eibker, A., *Ann.,* **1901**, *318*, 58. (gg) von Miller, W. and Plochl, J., *Ber.,* **1896**, *29*, 1462. (hh) Berend, L. and Thomas, E., *Ber.,* **1892**, *26*, 2548. (ii) Busch, A. and Koenings, W., *Ber.,* **1891**, *24*, 3962. (jj) von Miller, W. and Kinkelin, F., *Ber.,* **1887**, *20*, 1916. (kk) Pictet, A. and Duparc, L., *Ber.,* **1887**, *20*, 3415. (ll) Doebner, O., *Ber.,* **1887**, *20*, 277. (mm) von Miller, W. and Kinkelin, F., *Ber.,* **1886**, *19*, 535. (nn) Doebner, O. and von Miller, W., *Ber.,* **1885**, *18*, 1645.

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Doering-Moore-Skattebøl Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Doering and LaFlamme in 1958[1] but subsequently improved by both Moore in 1960[2] and Skettebøl in 1961.[3] It is a two-step preparation of allene via the addition of dibromocarbene to olefin,[4] followed by the treatment of the corresponding geminal cyclopropyl dibromide with alkyllithium under low temperature.[2,3] Therefore, this reaction is called the Doering-Moore-Skettebøl reaction,[5] Doering-Moore-Skettebøl-like reaction,[6] Doering-Moore-Skettebøl procedure,[5c] or Doering-Moore-Skettebøl method.[7] However, the original Doering method is to treat the geminal cyclopropyl dibromide with magnesium to give pure allene in a 16–35% yield or with high-surface sodium to give a high yield of allene but complicated with different isomers.[1] It was found that the alkyllithiums, including butyllithium and methyllithium, work equally well in the preparation of internal allenes without either cyclic or acyclic isomerization.[8] It has been proven that this reaction involves a carbene-like intermediate (a carbenoid) or a free carbene (cyclopropylidene).[5c] The transient carbenes can undergo either ring opening to allenes[9] or possibly a specific C-H bond insertion.[7,10] A potential side product of this reaction is the alkylation product from 1-halo-1-lithiocyclopropane when carried out at very low temperatures.[11] It is interesting that the conversion from anti-substituted cyclopropylidenes proceeds with a high degree of stereospecificity, whereas the *syn*-substituted cyclopropylidenes retain very low stereoselectivity in this process.[12]

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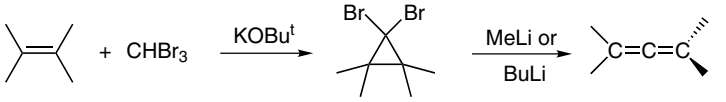
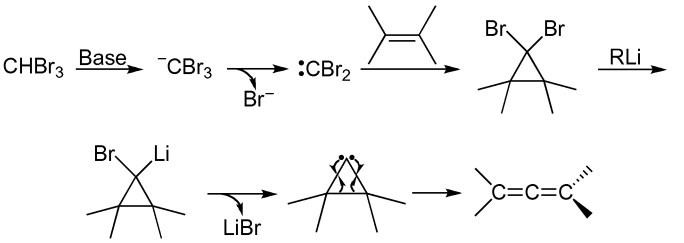
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

The original procedure of Doering and LaFlamme was modified and improved by Moore and Skattebøl.

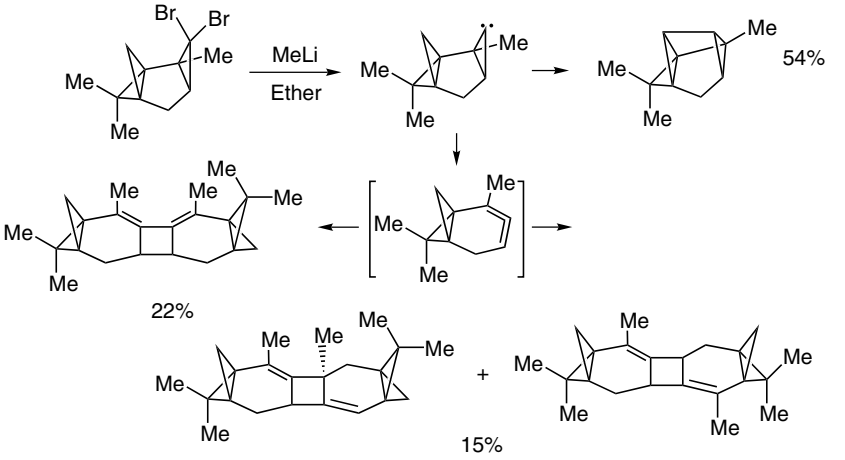
E. APPLICATIONS

This reaction has become a general method for the preparation of allene derivatives.

F. RELATED REACTIONS

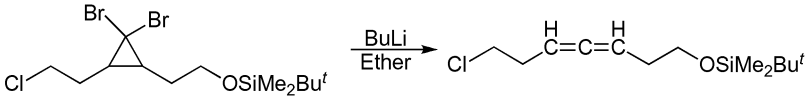
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

To a solution of 15.40 g 3,3-dibromo-2,7,7-trimethyl-tricyclo[4.1.1.$0^{2,4}$]octane (50.0 mmol) in 100 mL dry ether was added dropwise 37.5 mL 1.6 M MeLi in ether (60 mmol) at room temperature, and the resulting solution was stirred for 2 h. The reaction mixture was quenched with water. The mixture was extracted with ether, and the organic layer was washed with saturated NaCl and dried over $MgSO_4$. After the removal of the solvent (20°C, 15 mmHg), the product mixture (8.77 g) was distilled at 38°C (5 mmHg) to provide 4.04 g the insertion product 3,7,7-trimethyltetracyclo[4.2.0.0^{2,4}.0^{3,8}]octane as a colorless liquid, in a yield of 54%. The residue was passed through silica gel (70 g), eluting with hexane to yield the head-to-head allene dimer 1*R*,6*R*,8*S*,10*R*,11*R*,13*S*-2,5,7,7,14,14-hexamethylpentacyclo [11.1.1.1^{6,8}.0^{3,11}.0^{4,10}]hexadeca-2,4-diene, which was further purified by recrystallization from ethanol to yield 1.62 g of colorless crystals in a yield of 22%, m.p., 122.5–123.0°C. The oily second fraction was 1.19 g of a diastereomeric mixture of the head-to-tail dimer 7,7,9,11,14,14-hexamethylpentacyclo-[11.1.1.1^{6,8}.0^{3,11}.0^{4,10}]hexadeca-2,9-diene and head-to-head allene dimer 2,7,7,9,14,14-hexamethylpentacyclo-[11.1.1.1^{6,8}.0^{3,11}.0^{4,10}]hexadeca-2,9-diene, in a yield of 15%.



Reference 13.

A solution of 21.14 g dibromocyclopropane (50 mmol) in 80 mL ether was cooled to –70°C in a three-necked flask equipped with a mechanical stirrer and then treated with 33.4 mL 1.5 N *n*-butyllithium (50 mmol) over 25 min. The reaction mixture was stirred at –70°C for another 60 min and then poured into ice water and extracted with ether. The ethereal solution was washed with brine, dried over K_2CO_3, and concentrated. The residue was distilled to give 11.02 g 7-chlorohepta-3,4-diene-1-yl *tert*-butyldimethylsilyl ether in a yield of 84%, b.p., 80°C at 0.5 mmHg.

Other references related to the Doering-Moore-Skattebøl reaction are cited in the literature.[14]

H. REFERENCES

1. Doering, W. von E. and LaFlamme, P. M., *Tetrahedron,* **1958**, *2*, 75.
2. Moore, W. R. and Ward, H. R., *J. Org. Chem*., **1960**, *25*, 2073.
3. Skattebøl, L., *Tetrahedron Lett*., **1961**, 167.
4. Doering, W. von E. and Hoffmann, A. K., *J. Am. Chem. Soc.,* **1954**, *76*, 6162.
5. (a) Christl, M.; Braun, M.; Fischer, H.; Groetsch, S.; Mueller, G.; Leusser, D.; Deuerlein, S.; Stalke, D.; Arnone, M. and Engels, B., *Eur. J. Org. Chem.,* **2006**, 5045. (b) Janssen, C. E. and Krause, N., *Eur. J. Org. Chem.,* **2005**, 2322. (c) Sydnes, L. K., *Chem. Rev.,* **2003**, *103*, 1133. (d) Satoh, T.; Kurihara, T. and Fujita, K., *Tetrahedron*, **2001**, *57*, 5369. (e) Christl, M.; Braun, M.; Wolz, E. and Wagner, W., *Chem. Ber.,* **1994**, *127*, 1137.
6. Hashmi, A. S. K., *J. Prakt. Chem.,* **1996**, *338*, 491.
7. Azizoglu, A.; Özen, R.; Hökelek, T. and Balci, M., *J. Org. Chem.,* **2004**, *69*, 1202.
8. Moore, W. R. and Ward, H. R., *J. Org. Chem.,* **1962**, *27*, 4179.

9. (a) Baird, M. S.; Nizovtsev, A. V. and Bolesov, I. G., *Tetrahedron,* **2002**, *58*, 1581. (b) Dillon, P. W. and Underwood, G. R., *J. Am. Chem. Soc.,* **1977**, *99*, 2435. (c) Kleveland, K. and Skattebøl, L., *Acta Chem. Scand., Ser. B.,* **1975**, *B29*, 191. (d) Baird, M. S., *J. Chem. Soc., Chem. Commun.,* **1971**, 1145.

10. (a) Paquette, L. A.; Zon, G. and Taylor, R. T., *J. Org. Chem.,* **1974**, *39*, 2677. (b) Hammon, D. P. G. and Trenerry, V. C., *Tetrahedron Lett.,* **1974**, 1371. (c) Reinarz, R. B. and Fonken, G. J., *Tetrahedron Lett.,* **1974**, 441. (d) Brown, D. W.; Hendrick, M. E. and Jones, M., *Tetrahedron Lett.,* **1973**, 3951. (e) Moore, W. R.; Taylor, K. G.; Müller, P.; Hall, S. S.; Gaibel, Z. L. F., *Tetrahedron Lett.,* **1970**, 2365. (f) Moore, W. R. and Hill, J. B., *Tetrahedron Lett.,* **1970**, 4553. (g) Skattebøl, L., *Tetrahedron,* **1967**, *23*, 1107. (h) Skattebøl, L., *Acta Chem. Scand.,* **1963**, *17*, 1683. (i) Skattebøl, L., *Chem. Ind. (London),* **1962**, 2146.

11. (a) Kitatani, K.; Hiyama, T. and Nozaki, H., *J. Am. Chem. Soc.,* **1975**, *97*, 949. (b) Lambert, R. L. and Seyferth, D., *J. Am. Chem. Soc.,* **1972**, *94*, 9248. (c) Corey, E. J. and Posner, G. H., *J. Am. Chem. Soc.,* **1968**, *90*, 5615.

12. Rauk, A.; Bouma, W. J. and Radom, L., *J. Am. Chem. Soc.,* **1985**, *107*, 3780.

13. Patterson, J. W.; Pfister, J. R.; Wagner, P. J. and Murthy, D. V. K., *J. Org. Chem.,* **1983**, *48*, 2572.

14. (a) Bettinger, H. F.; Schleyer, P. V. R.; Schreiner, P. R. and Schaefer, H. F., *J. Org. Chem.,* **1997**, *62*, 9267. (b) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J. and Hudlicky, T., *Chem. Rev.,* **1989**, *89*, 165. (c) Sueiras, J. and Okamura, W. H., *J. Am. Chem. Soc.,* **1980**, *102*, 6255. (d) Waali, E. E. and Allison, N. T., *J. Org. Chem.,* **1979**, *44*, 3266. (e) Heldeweg, R. F. and Hogeveen, H., *J. Org. Chem.,* **1978**, *43*, 1916. (f) Carlton, J. B.; Levin, R. H. and Clardy, J., *J. Am. Chem. Soc.,* **1976**, *98*, 6068. (g) Loozen, H. J.; Castenmiller, W. A.; Buter, E. J. M. and Buck, H. M., *J. Org. Chem.,* **1976**, *41*, 2965. (h) Lilje, K. C. and Macomber, R. S., *J. Org. Chem.,* **1974**, *39*, 3600. (i) Taylor, D. R., *Chem. Rev.,* **1967**, *67*, 317. (j) Skattebøl, L., *J. Org. Chem.,* **1966**, *31*, 1554. (k) Skattebøl, L., *J. Org. Chem.,* **1966**, *31*, 2789. (l) Chinoporos, E., *Chem. Rev.,* **1963**, *63*, 235. (m) Jones, W. M.; Grasley, M. H. and Brey, W. S., *J. Am. Chem. Soc.,* **1963**, *85*, 2754.

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Dötz Benzannulation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Dötz in 1975.[1] It is a thermal reaction for preparing phenol derivatives from an aromatic or vinylic alkoxy pentacarbonyl chromium carbene complex (often called a Fischer carbene complex[2] or chromium carbene complex[3]) and an alkyne. It is known that this reaction involves the initial insertion of an alkyne to the Fischer carbene complex to form a dienylcarbene complex intermediate (called metallahexatrienes),[4] the carbon monoxide insertion to give vinylketene, and a final electrocyclization.[5] Therefore, this reaction is generally known as the Dötz benzannulation.[5,6] In addition, this reaction is also referred to as the Dötz reaction,[4,5,7] Dötz annulation,[8] Dötz annulation process,[6j] and Dötz chromium carbene benzannulation.[9] The Fischer chromium carbene complex can be easily prepared from chromium hexacarbonyl and organolithium reagent, followed by the *O*-alkylation.[3b,10] It has been found that this reaction is optimal with neutral alkynes (neutral alkynes > electron-deficient alkynes),[11] by which the isomers of the alkyne insertion intermediates form an equilibrium.[12] However, the isomer, of which the larger substituent on alkynes is *ortho* to the phenolic group, predominates in the equilibrium.[5,11] Because there are many possible branching points for the side reactions, twelve[13] to twenty-one[7e] distinct types of products (depending on the reaction conditions and substituents) have been identified, including indenes,[14] furans,[15] and cyclopentenones.[16] It has been reported that the optimal condition of this reaction is to perform the reaction in heptane instead of ethereal solvents (Et_2O, THF) at a chromium carbene complex concentration of 0.3 M, with a slight excess of alkyne (1.0–1.5 eq.).[11] On the other hand, a reaction involving the cleavage of the vinylic carbon-carbon bond in original Fischer carbene complex is also known.[17] In addition, transition metals other than chromium

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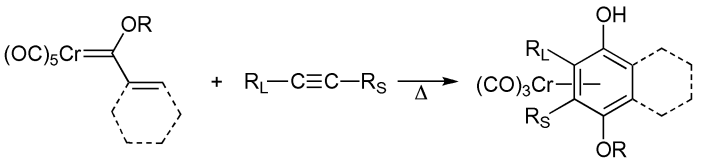
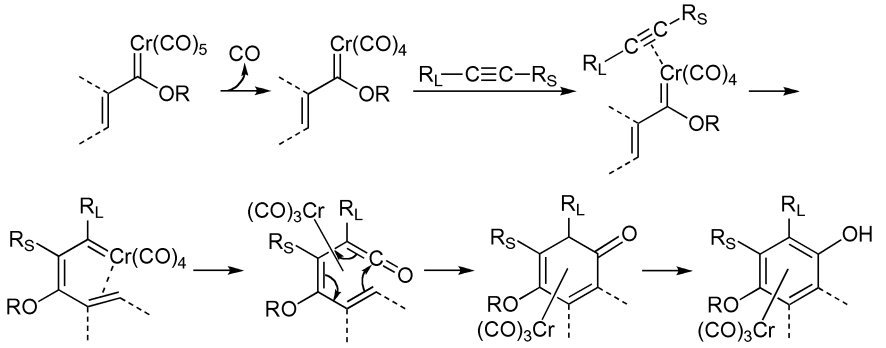
have also been found to undergo a similar reaction, such as manganese.[18] This reaction has been used for the preparation of biaryls,[2b] with central-to-central,[19] central-to-planar,[20] planar-to-axial,[21] and central-to-axial chirality transfer.[22]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

The chromium has been replaced by other transition metals, such as manganese.[18]

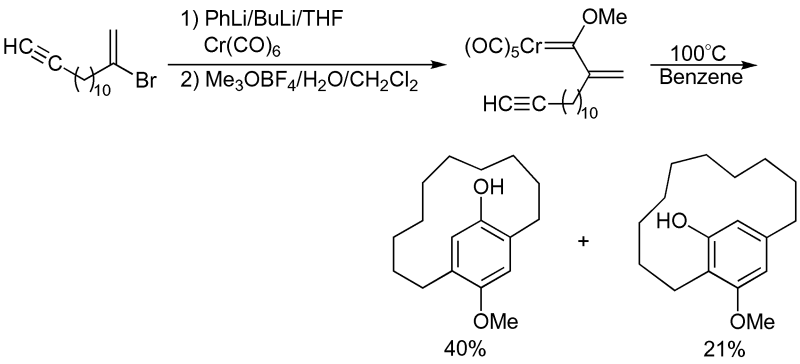
E. APPLICATIONS

This reaction has general application in the preparation of phenol derivatives; in addition, other types of molecules (indenes, furans, cyclopentenones, etc.) can be prepared.

F. RELATED REACTIONS

This reaction is related to the *Fischer Carbene Complexes*.

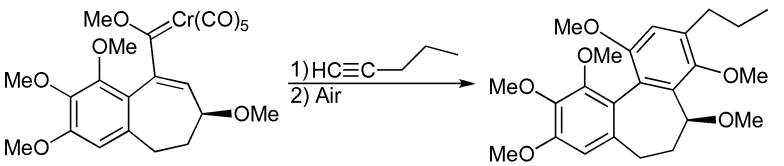
G. CITED EXPERIMENTAL EXAMPLES



Reference 17.

2-Bromo-1-decen-9-yne (167.3 mg, 0.778 mmol) was dissolved in 18 mL THF and cooled to −78°C. PhLi (0.782 mmol) was added dropwise, and the mixture was stirred at −78°C for 1.5 h. Then 1.57 mmol *t*-BuLi was added; the resultant solution turned yellow immediately and then green. The reaction mixture was stirred at –78°C for 30 min and then was transferred to 35 mL THF at –78°C containing 172.2 mg $Cr(CO)_6$ (0.782 mmol). This reaction mixture was warmed to room temperature and stirred for 2 h. The solvent was removed, and the residue was dried on high vacuum for 40 min and then taken up in H_2O/CH_2Cl_2 (10 mL/10 mL). Me_3OBF_4 (230 mg, 1.55 mmol) was added, and the yellow suspension turned orange immediately. The mixture was stirred at room temperature for 80 min and quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with ether, and the organic layer was washed with brine, dried over $MgSO_4$, concentrated, and chromatographed (pentane) to give 128.5 mg pentacarbonyl (1-methoxy-2-methylene-9-decynylidene) chromium(0) as a red oil, in a yield of 44%, R_f = 0.14 (hexanes).

Alkenyl carbene complex was dissolved in benzene at a concentration of 0.002 M. The red solution was deoxygenated by the freeze-pump-thaw method (four cycles) and heated in an oil bath to 100°C. The solution turned from red to yellow during the reaction. After the completion of the reaction, the solvent was removed, and the residue was taken up in CH_2Cl_2/ether, and stirred in air overnight. The mixture was then loaded on silica gel and chromatographed to give 40% of *p*-methoxy phenol derivative and 21% of *m*-methoxy phenol derivative.



Reference 22.

To an approximately 0.33 M solution of the carbene complex in dry benzene was added a threefold excess of 1-pentyne. The resulting solution was deoxygenated by the freeze-pump-thaw method (–196°C/25°C, three cycles). The flask was back-filled with argon at

room temperature, sealed, and then heated at 55–58°C for 36 h. The red clear solution gradually changed to a dark mixture. The reaction mixture was opened to air and stirred in the open flask for 12 h. The solvent was removed in vacuo, and the crude product was diluted with 50% EtOAc in hexane and filtered through a layer of silica gel. The crude product was purified by flash chromatography on silica gel (15–25% gradient of EtOAc in hexane) to give 40% of yellowish crystal as the only diastereomer, m.p. 148–148.5°C.

Other references related to the Dötz benzannulation are cited in the literature.[23,24]

H. REFERENCES

1. Dötz, K. H., *Angew. Chem. Int. Ed. Engl*., **1975**, *14*, 644.
2. (a) Barluenga, J.; Aznar, F.; Palomero, M. A. and Barluenga, S., *Org. Lett*., **1999**, *1*, 541. (b) Bao, J. M.; Wulff, W. D.; Fumo, M. J.; Grant, E. G.; Heller, D. P.; Whitcomb, M. C. and Yeung, S.-M., *J. Am. Chem. Soc.*, **1996**, *118*, 2166.
3. (a) Gleichmann, M. M.; Dötz, K. H. and Hess, B. A., *J. Am. Chem. Soc*., **1996**, *118*, 10551. (b) Hafner, A.; Hegedus, L. S.; de Weck, G.; Hawkins, B. and Dötz, K. H., *J. Am. Chem. Soc*., **1988**, *110*, 8413.
4. Barluenga, J.; Aznar, F. and Palomero, M. Á., *J. Org. Chem*., **2003**, *68*, 537.
5. Moser, W. H.; Sun, L. D. and Huffman, J. C., *Org. Lett*., **2001**, *3*, 3389.
6. (a) Gupta, A.; Sen, S.; Harmata, M. and Pulley, S. R., *J. Org. Chem.,* **2005**, *70*, 7422. (b) Pulley, S. R. and Czako, B., *Tetrahedron Lett*., **2004**, *45*, 5511. (c) Anderson, J. C.; Denton, R. M.; Hickin, H. G. and Wilson, C., *Tetrahedron*, **2004**, *60*, 2327. (d) Anderson, J. C.; Cran, J. W. and King, N. P., *Tetrahedron Lett*., **2003**, *44*, 7771. (e) Hutchinson, E. J.; Kerr, W. J. and Magennis, E. J., *Chem. Commun*., **2002**, 2262. (f) Anderson, J. C.; Cran, J. W. and King, N. P., *Tetrahedron Lett*., **2002**, *43*, 3849. (g) Caldwell, J. J.; Colman, R.; Kerr, W. J. and Magennis, E. J., *Synlett*, **2001**, 1428. (h) Barluenga, J.; López, L. A.; Martínez, S. and Tomás, M., *J. Org. Chem*., **1998**, *63*, 7588. (i) Painter, J. E.; Quayle, P. and Patel, P., *Tetrahedron Lett*., **1995**, *36*, 8089. (j) Merino, I. and Hegedus, L. S., *Organometallics*, **1995**, *14*, 2522.
7. (a) Sola, M.; Duran, M. and Torrent, M., *Catal. Metal Complex,* **2002**, *25*, 269. (b) Torrent, M.; Duran, M. and Solà, M., *J. Am. Chem. Soc*., **1999**, *121*, 1309. (c) Pulley, S. R. and Carey, J. P., *J. Org. Chem*., **1998**, *63*, 5275. (d) Torrent, M.; Duran, M. and Solà, M., *Organometallics*, **1998**, *17*, 1492. (e) de Meijere, A., *Pure & Appl. Chem*., **1996**, *68*, 61. (f) Hemdon, J. W. and Hayford, A., *Organometallics*, **1995**, *14*, 1556.
8. Davies, M. W.; Johnson, C. N. and Harrity, J. P. A., *J. Org. Chem.,* **2001**, *66*, 3525.
9. Parker, K. A. and Coburn, C. A., *J. Org. Chem*., **1991**, *56*, 1666.
10. Fischer, E. O.; Krieter, C. G.; Kollmeier, H. J.; Muller, J. and Fischer, R. D., *J. Organomet. Chem*., **1971**, *28*, 237.
11. Boger, D. L. and Jacobson, I. C., *J. Org. Chem*., **1990**, *55*, 1919.
12. Waters, M. L.; Bos, M. E. and Wulff, W. D., *J. Am. Chem. Soc*., **1999**, *121*, 6403.
13. Gross, M. F. and Finn, M. G., *J. Am. Chem. Soc*., **1994**, *116*, 10921.
14. (a) Dötz, K. H.; Dietz, R. E.; Kappenstein, C.; Neugebauer, D. and Schubert, U., *Ber*., **1979**, *112*, 3682. (b) Dötz, K. H.; Neugebauer, D., *Angew. Chem. Int. Ed. Engl*., **1978**, *17*, 851.
15. (a) Wulff, W. and Kaesler, R. W., *Organometallics*, **1985**, *4*, 1416. (b) Dötz, K. H., *J. Organomet. Chem*., **1977**, *140*, 177.
16. (a) Herndon, J. W.; Tumer, S. U. and Schnatter, W. F., *J. Am. Chem. Soc*., **1988**, *110*, 3334. (b) Dötz, K. H.; Trenkle, B. and Schubert, U., *Angew. Chem. Int. Ed. Engl*., **1981**, *20*, 287.

17. Wang, H.; Huang, J.; Wulff, W. D. and Rheingold, A. L., *J. Am. Chem. Soc*., **2003**, *125*, 8980.
18. (a) Balzer, B. L.; Cazanoue, M. and Finn, M. G., *J. Am. Chem. Soc*., **1992**, *114*, 8135. (b) Balzer, B. L.; Cazanoue, M.; Sabat, M. and Finn, M. G., *Organometallics*, **1992**, *11*, 1759.
19. (a) Hsung, R. P.; Quinn, J. F.; Weisenberg, B. A.; Wulff, W. D.; Yap, G. P. A. and Rheingold, A. L., *J. Chem. Soc., Chem. Commun*., **1997**, 615. (b) Quinn, J. F.; Powers, T. S.; Wulff, W. D.; Yap, G. P. A. and Rheingold, A. L., *Organometallics*, **1997**, *16*, 4945.
20. (a) Dötz, K. H. and Stinner, C., *Tetrahedron: Asymmetry*, **1997**, *8*, 1751. (b) Beddoes, R. L.; King, J. D. and Quayle, P., *Tetrahedron Lett*., **1995**, *36*, 3027. (c) Neidlein, R.; Gürtler, S. and Krieger, C., *Helv. Chim Acta*, **1994**, *77*, 2303.
21. Fogel, L.; Hsung, R. P.; Wulff, W. D.; Sommer, R. D. and Rheingold, A. L., *J. Am. Chem. Soc*., **2001**, *123*, 5580.
22. Vorogushin, A. V.; Wulff, W. D. and Hansen, H.-J., *J. Am. Chem. Soc*., **2002**, *124*, 6512.
23. (a) Martínez-Álvarez, R.; Gómez-Gallego, M.; Fernández, I.; Mancheño, M. J. and Sierra, M. A., *Organometallics*, **2004**, *23*, 4647. (b) Wang, H.; Wulff, W. D. and Rheingold, A. L., *J. Am. Chem. Soc*., **2000**, *122*, 9862. (c) Quast, L.; Nieger, M. and Dötz, K. H., *Organometallics*, **2000**, *19*, 2179. (d) Pulley, S. R.; Sen, S.; Vorogushin, A. and Swanson, E., *Org. Lett*., **1999**, *1*, 1721. (e) Longen, A.; Nieger, M.; Airola, K. and Dötz, K. H., *Organometallics*, **1998**, *17*, 1538. (f) Su, J.; Wulff, W. D. and Ball, R. G., *J. Org. Chem*., **1998**, *63*, 8440. (g) Kretschik, O.; Nieger, M. and Dötz, K. H., *Organometallics*, **1996**, *15*, 3625. (h) Semmelback, M. F.; Ho, Z.; Cohen, D.; Steigerwald, M.; Lee, M. C.; Lee, G.; Gilbert, A. M.; Wulff, W. D. and Ball, R. G., *J. Am. Chem. Soc*., **1994**, *116*, 7108. (i) Chamberlin, S.; Waters, M. L. and Wulff, W. D., *J. Am. Chem. Soc*., **1994**, *116*, 3113. (j) Chamberlin, S. and Wulff, W. D., *J. Org. Chem*., **1994**, *49*, 3047. (k) Chamberlin, S.; Wulff, W. D. and Bax, B., *Tetrahedron*, **1993**, *49*, 5531. (l) Chamberlin, S. and Wulff, W. D., *J. Am. Chem. Soc*., **1992**, *114*, 10667. (m) Gordon, D. M.; Danishefsky, S. J. and Schulte, G. K., *J. Org. Chem*., **1992**, *57*, 7052. (n) Boger, D. L. and Jacobson, I. C., *J. Org. Chem.,* **1991**, *56*, 2115. (o) Yamashita, A.; Schaub, R. G.; Bach, M. K.; White, G. J.; Toy, A.; Ghazal, N. B.; Burdick, M. D.; Brashler, J. R. and Holm, M. S., *J. Med. Chem*., **1990**, *33*, 775. (p) Schore, N. E., *Chem. Rev*., **1988**, *88*, 1081. (q) Wulff, W. D. and Xu, Y.-C., *J. Am. Chem. Soc*., **1988**, *110*, 2312. (r) Chan, K. S.; Peterson, G. A.; Brandvold, T. A.; Faron, K. L.; Challener, C. A.; Hyldahl, C. and Wulff, W. D., *J. Organometal. Chem.*, **1987**, *334*, 9. (s) Posner, G. H., *Chem. Rev*., **1986**, *86*, 831. (t) Wulff, W. D.; Chan, K.-S. and Tang, P.-C., *J. Org. Chem*., **1984**, *49*, 2293.
24. (a) Zaragoza Dörwald, F., *Metal Carbenes in Organic Synthesis*, Wiley-VCH, Weinheim **1999**. (b) Dötz, K. H. and Tomuschat, P., *Chem. Soc. Rev*., **1999**, *28*, 187. (c) Harvey, D. F. and Sigano, D. M., *Chem. Rev*., **1996**, *96*, 271. (d) Dötz, K. H., *New J. Chem*., **1990**, *14*, 433. (e) Wulff, W. D., "*Transition Metal-Carbene Complexes in Organic Synthesis*" in *Advances in Metal-Organic Chemistry*, ed. Liebeskind, L. S., JAI Press Inc., Greenwich, Conn., **1989**, *1*, pp. 209–393. (f) Dötz, K. H.; Fischer, H.; Hofmann, P.; Kreissel, F. R.; Schubert, U. and Weiss, K., *Transition Metal Carbene Complexes*, Verlag Chemie, Deerfield Beach, Fla., **1984**. (g) Dötz, K. H., *Angew. Chem. Int. Ed. Engl*., **1984**, *23*, 587.

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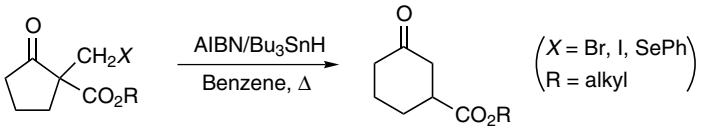
Dowd-Beckwith Ring Expansion

A. GENERAL DESCRIPTION OF THE REACTION

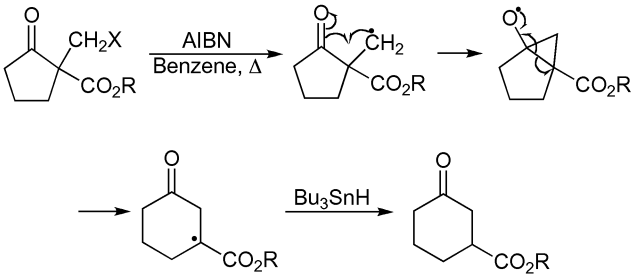
This reaction was first reported by Dowd[1] and Beckwith[2] concurrently in 1987. It is a general method for one-carbon ring expansion of cycloketone via the introduction of a halomethyl group to cyclic β-keto esters followed by radical dehalogenation (e.g., through the addition of a mixture of tributyltin hydride and AIBN in refluxing benzene solution). After radical dehalogenation, the carbon radical adds to the neighboring carbonyl group, leading to a cyclopropyloxy radical that is unstable and forces the cyclopropyl ring to break and form a larger cycloketone. Therefore, this reaction is generally known as the Dowd-Beckwith ring expansion.[3] In addition, it is also referred to as the Dowd-Beckwith type ring expansion,[4] Beckwith-Dowd type rearrangement,[5] Beckwith-Dowd expansion,[5] Dowd-Beckwith rearrangement,[4] Beckwith-Dowd ring expansion,[5,6] and Beckwith-Dowd ring enlargement.[7] It is proposed that the ester group in the cyclic β-keto ester can facilitate the alkylation, activate the radical addition to carbonyl group, and assist the ring opening of the cyclopropyloxy radical.[8] It has been found that the acyl radical cyclization is irreversible on any kinetically significant time scale;[5] however, the radical cyclization to the carbonyl group may fail if a highly congested transition state is involved.[4] This reaction has been studied extensively[8] and extended for preparing middle-size cycloketones via four-carbon ring expansion by Dowd.[9]

B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS



D. MODIFICATION

Tributyltin hydride has been replaced by the silylated cyclohexadienes as the proton source.[7] In addition, zinc and indium have been applied to initiate similar ring-expansion reactions.[10]

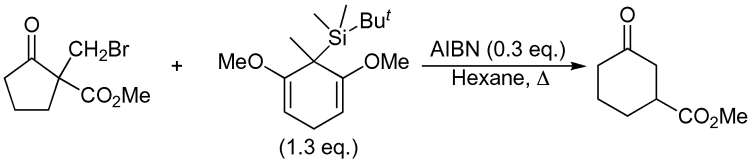
E. APPLICATIONS

This reaction has been widely used for the preparation of cyclic ketones.

F. RELATED REACTIONS

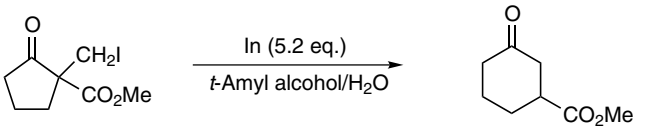
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

Methyl 1-bromomethyl-2-oxo-cyclopentanoate (235 mg, 1 mmol), 349 mg silylated cyclohexadiene (1.3 mmol), and 50 mg AIBN (0.3 mmol) were dissolved in 5 mL hexane under argon. The reaction mixture was refluxed for 7 h. Removal of the solvent in vacuo and purification by flash chromatography (Et_2O/pentane, 3:8) afforded 76 mg methyl 3-oxo-cyclohexane-1-carboxylate as a colorless oil, in a yield of 49%.



Reference 10.

Indium powder (2.08 mmol) was added to a refluxing solution of 0.4 mmol α-iodomethyl cyclic β-keto ester in a mixed solvent of 2 mL *tert*-amyl alcohol and 1 mL water under an argon atmosphere. The mixture was refluxed for 2 h under stirring. After the reaction, the mixture was filtered through Celite, then the solvent was removed, and the residue was purified by silica gel column chromatography to afford 59% methyl 3-oxo-cyclohexane-1-carboxylate as a colorless oil.

Other references related to the Dowd-Beckwith ring expansion are cited in the literature.[11]

H. REFERENCES

1. Dowd, P. and Choi, S.-C., *J. Am. Chem. Soc.,* **1987**, *109*, 3493.
2. Beckwith, A. L. J.; O'Shea, D. M.; Gerba, S. and Westwood, S. W., *J. Chem. Soc., Chem. Commun.,* **1987**, 666.
3. (a) Ardura, D. and Sordo, T. L., *J. Org. Chem.,* **2005**, *70*, 9417. (b) Ardura, D. and Sordo, T. L., *Tetrahedron Lett*., **2004**, *45*, 8691.
4. Crimmins, M. T.; Wang, Z. and McKerlie, L. A., *J. Am. Chem. Soc.,* **1998**, *120*, 1747.
5. Chatgilialoglu, C.; Crich, D.; Komatsu, M. and Ryu, I., *Chem. Rev.,* **1999**, *99*, 1991.
6. Rodríguez, J. R.; Castedo, L. and Mascareñas, J. L., *Org. Lett.,* **2001**, *3*, 1181.
7. Studer, A.; Amrein, S.; Schleth, F.; Schulte, T. and Walton, J. C., *J. Am. Chem. Soc.,* **2003**, *125*, 5726.
8. Dowd, P. and Zhang, W., *Chem. Rev.,* **1993**, *93*, 2091.
9. (a) Dowd, P. and Zhang, W., *J. Am. Chem. Soc.,* **1992**, *114*, 10084. (b) Dowd, P. and Zhang, W., *J. Am. Chem. Soc.,* **1991**, *113*, 9875. (c) Dowd, P. and Choi, S.-C., *J. Am. Chem. Soc.,* **1987**, *109*, 6548.
10. Sugi, M.; Sakuma, D. and Togo, H., *J. Org. Chem.,* **2003**, *68*, 7629.
11. (a) Zhang, W., *Curr. Org. Chem.,* **2002**, *6*, 1015. (b) Wilsey, S.; Dowd, P. and Houk, K. N., *J. Org. Chem.,* **1999**, *64*, 8801. (c) Mehta, G. and Singh, V., *Chem. Rev.,* **1999**, *99*, 881. (d) Chatgilialoglu, C.; Timokhin, V. I. and Ballestri, M., *J. Org. Chem.,* **1998**, *63*, 1327. (e) Wang, C.; Gu, X.; Yu, M. S. and Curran, D. P., *Tetrahedron,* **1998**, *54*, 8355. (f) Banwell, M. G. and Cameron, J. M., *Tetrahedron Lett.,* **1996**, *37*, 525. (g) Parsons, P. J.; Penkett, C. S. and Shell, A. J., *Chem. Rev.,* **1996**, *96*, 195. (h) Dowd, P. and Zhang, W., *Tetrahedron Lett.,* **1996**, *37*, 957. (i) Rawal, V. H.; Dufour, C. and Iwasa, S. *Tetrahedron Lett.,* **1995**, *36*, 19. (j) Zheng, W.; Collins, M. R.; Mahmood, K. and Dowd, P., *Tetrahedron Lett.,* **1995**, *36*, 2729. (k) Kim, S.; Joe, G. H. and Do, J. Y., *J. Am. Chem. Soc.,* **1993**, *115*, 3328. (l) Galatsis, P.; Millan, S. D. and Faber, T., *J. Org. Chem.,* **1993**, *58*, 1215. (m) Dowd, P. and Zhang, W., *J. Org. Chem.,* **1992**, *57*, 7163. (n) Zhang, W. and Dowd, P., *Tetrahedron Lett.,* **1992**, *33*, 3285. (o) Dowd, P. and Zhang, W., *Tetrahedron Lett.,* **1992**, *33*, 7307. (p) Dowd, P. and Choi, S.-C., *Tetrahedron,* **1989**, 45, 77. (q) Beckwith, A. L. J.; O'Shea, D. M. and Westwood, S. W., *J. Am. Chem. Soc.,* **1988**, *110*, 2565. (r) Baldwin, J. E.; Adlington, R. M. and Robertson, J., *J. Chem. Soc., Chem. Commun.,* **1988**, 1404.

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Duff Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Duff and Bills in 1932.[1] It is the formylation of phenols or aromatic amines in a mixture of hexamethylenetetramine, boric acid, and glycerol. Therefore, it is generally known as the Duff reaction.[2] In a few cases, it is also referred to as the Duff formylation[3] and Duff synthesis.[4] This reaction is normally very fast and usually gives only *ortho*-formylated (or a small amounts of *ortho*, *para*-disubstituted) product[5] (e.g., in the case of phenols); however, this procedure gives *para*-products in the case of anilines. It is found that electron-withdrawing groups hinder or prevent the reaction from taking place;[5] therefore, hydroxypyridines and hydroxyquinolines cannot be formylated.[5] Though they do not work with glycerol/boric acid, the *N*,*N*-dialkylanilines can be formylated in a mixture of formic acid and acetic acid but not in either one alone.[5] Further modification of this reaction by conducting the reaction in anhydrous trifluoroacetic acid results in a milder reaction condition,[2q,6] with a high yield and no detectable isomer or dialdehydes.[2q] This modification gives a high order of *para*-formylation product; even simple hydrocarbons can be converted to imine products, which are transformed to aryl aldehydes on hydrolysis.[2q] However, this modification may also give *ortho*-formylated products,[2l] and a dimmer of aniline in cyclic form may result instead of the normal formylation.[2g] In addition, reactions in a mixed solvent of THF/HMPA also provide relatively high yield.[2h]

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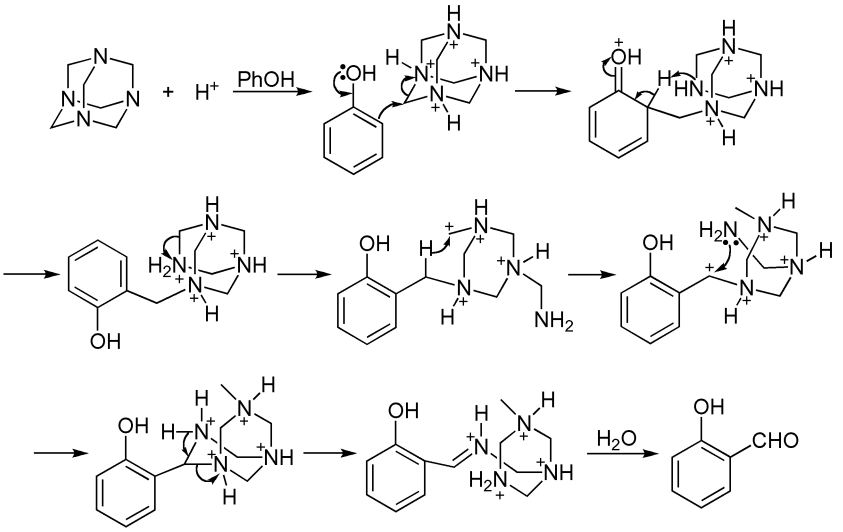
B. GENERAL REACTION SCHEME

C. PROPOSED MECHANISMS

A tentative mechanism is proposed below, although no mechanistic details are available from the cited literature.



D. MODIFICATION

The original Duff reaction condition has been modified to run in trifluoroacetic acid.

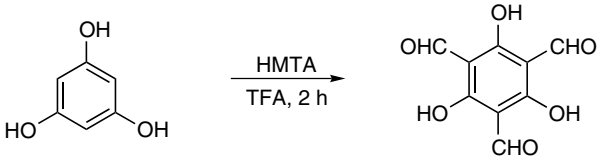
E. APPLICATIONS

This reaction has general applications in the formylation of aromatic compounds.

F. RELATED REACTIONS

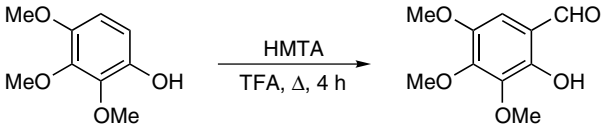
This reaction is related to the *Reimer-Tiemann Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 3a.

To a mixture of 15.098 g hexamethylenetetramine (108 mmol) and 6.014 g dried phloroglucinol (49 mmol) under nitrogen was added 90 mL trifluoroacetic acid. The solution was heated at 100°C for ∼2.5 h. Approximately 150 mL 3 M HCl was added, and the solution was heated at 100°C for 1 h. After cooling to room temperature, the solution was filtered through Celite, extracted with ∼350 mL dichloromethane, dried over magnesium sulfate, and filtered. Rotary evaporation of the solution afforded 1.48 g triformylphloroglucinol as an off-white powder, in a yield of 14% with 99% purity by ^{1}H NMR. Further purification has been conducted by sublimation.



Reference 2c.

A solution of 100 mg 2,3,4-trimethoxyphenol (0.54 mmol) and 75.7 mg hexamethylenetetramine (0.54 mmol) in 0.5 mL trifluoroacetic acid was refluxed for 4 h. After the reaction was quenched with the addition of ice, the resulting mixture was further stirred for 15 min and extracted with ether. The combined organic extracts were washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (benzene/acetone, 10:1) of the residue gave 79.4 mg 2-hydroxyl-3,4,5-trimethoxy benzaldehyde as a powder, in a yield of 69%, m.p.: 41–43°C (recrystallized from hexane).

Other references related to the Duff reaction are cited in the literature.[7]

H. REFERENCES

1. Duff, J. C. and Bills, E. J., *J. Chem. Soc.,* **1932**, 1987.
2. (a) Belostotskaya, I. S.; Komissarova, N. L.; Prokof'eva, T. I.; Kurkovskaya, L. N. and Vol'eva, V. B., *Russ. J. Org. Chem.,* **2005**, *41*, 703. (b) Meutermans, W. D. F.; Golding, S. W.; Bourne, G. T.; Miranda, L. P.; Dooley, M. J.; Alewood, P. F. and Smythe, M. L., *J. Am. Chem. Soc.,* **1999**, *121*, 9790. (c) Fukuda,Y.; Furuta, H.; Kusama, Y.; Ebisu, H.; Oomori, Y. and Terashima, S., *J. Med. Chem.,* **1999**, *42*, 1448. (d) Lindoy, L. F.; Meehan, G. V. and Svenstrup, N., *Synthesis*, **1998**, 1029. (e) Sedishev, I. P.; Kutin, A. A. and Zhulin, V. M., *Izv. Akad. Nauk, Ser. Khim.,* **1995**, 319. (f) Sedishev, I. P.; Agafonov, N. E.; Kutin, A. A. and Zhulin, V. M., *Izv. Akad. Nauk, Ser. Khim.,* **1995**, 2221. (g) Johnson, R. A.; Gorman, R. R.; Wnuk, R. J.; Crittenden, N. J. and Aiken, J. W., *J. Med. Chem.,* **1993**, *36*, 3202. (h) Garcia, B.; Lee,

C.-H.; Blaskó, A. and Bruice, T. C., *J. Am. Chem. Soc.,* **1991**, *113*, 8118. (i) Ishibashi, F.; Miyoshi, N.; Okahashi, H.; Mizuno, M.; Yamada, M. and Katagiri, M., *Chem. Express,* **1991**, *6*, 37. (j) Komissarova, N. L.; Belostotskaya, I. S.; Shubina, O. V.; Ershov, V. V.; Voznesenskii, V. N. and Chervin, I. I., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1988**, 2186. (k) Mathew, T. V. and Chauhan, V. S., *Indian J. Chem., Sect. B,* **1987**, *26B*, 1071. (l) Johnson, r. A.; Nidy, E. G.; Aiken, J. W.; Crittenden, N. J. and Gorman, R. R., *J. Med. Chem.,* **1986**, *29*, 1461. (m) Mohan, S. B. and Murti, V. V. S., *Indian J. Chem., Sect. B,* **1982**, *21B*, 887. (n) Solimabi; K. S. P. and Paknikar, S. K., *Indian J. Chem., Sect. B,* **1981**, *20B*, 244. (o) Kostova, I. N.; Pardeshi, N.; Rangaswami, S. and Lee, Y.-W., *Indian J. Chem., Sect. B,* **1980**, *19B*, 859. (p) Chatterjee, A. and Biswas, K. M., *J. Org. Chem.,* **1973**, *38*, 4002. (q) Smith, W. E., *J. Org. Chem.,* **1972**, *37*, 3972.

3. (a) Chong, J. H.; Sauer, M.; Patrick, B. O. and MacLachlan, M. J., *Org. Lett.,* **2003**, *5*, 3823. (b) Tanoue, Y.; Terada, A. and Matsumoto, Y., *Bull. Chem. Soc. Jpn.,* **1989**, *62*, 2736. (c) Florvall, L.; Ask, A.-L.; Ögren, S.-O. and Ross, S. B., *J. Med. Chem.,* **1978**, *21*, 56. (d) Feigl, F. and Jungreis, E., *Analyst,* **1958**, *83*, 666.
4. Snyder, H. R.; Swaminathan, S. and Sims, H. J., *J. Am. Chem. Soc.,* **1952**, *74*, 5110.
5. Ferguson, L. N., *Chem. Rev.,* **1946**, *38*, 227.
6. Clark, M. T. and Miller, D. D., *J. Org. Chem.,* **1986**, *51*, 4072.
7. (a) Song, Y. M.; Yao, X. Q.; Chen, H. L.; Pan, G. Z.; Hu, X. Q. and Zheng, Z., *J. Chem. Soc., Perkin Trans. 1*, **2002**, 870. (b) Miranda, L. P.; Meutermans, W. D. F.; Smythe, M. and Alewood, P. F., *J. Org. Chem.,* **2000**, *65*, 5460. (c) Anderson, A. A.; Goetzen, T.; Shackelford, S. A. and Tsank, S., *Synth. Commun.,* **2000**, *30*, 3227. (d) Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y. P.; Nie, X. Y. and Zepp, C. M., *J. Org. Chem.,* **1994**, *59*, 1939. (e) Harayami, T.; Nakatsuka, K.; Nishioka, H.; Murakami, K.; Ohmori, Y.; Takeuchi, Y.; Ishii, H. and Kenmotsu, K., *Heterocycles,* **1994**, *38*, 2729. (f) Nussbaumer, P.; Dorfstätter, G.; Grassberger, M. A.; Leitner, I.; Meingassner, J. G.; Thirring, K. and Stütz, A., *J. Med. Chem.,* **1993**, *36*, 2115. (g) Wada, F.; Hirayama, H.; Namiki, H.; Kikukawa, K. and Matsuda, T., *Bull. Chem. Soc. Jpn.,* **1980**, *53*, 1473. (h) Ogata, Y. and Sugiura, F., *Tetrahedron,* **1968**, *24*, 5001. (i) Ramachandran, P. K.; Tefteller, A. T.; Paulson, G. O.; Cheng, T.; Lin, C. T. and Horton, W. J., *J. Org. Chem.,* **1963**, *28*, 398. (j) Browne, M. F. and Shriner, R. L., *J. Org. Chem.,* **1957**, *22*, 1320. (k) Duff, J. C. and Furness, V., *J. Chem. Soc.,* **1951**, 1512. (l) Duff, J. C., *J. Chem. Soc.,* **1945**, 276. (m) Duff, J. C., *J. Chem. Soc.,* **1941**, 547. (n) Duff, J. C. and Bills, E. J., *J. Chem. Soc.,* **1934**, 1305.

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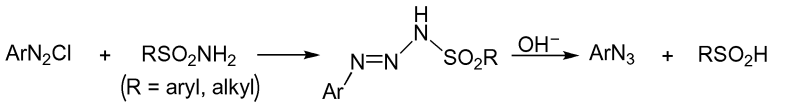
Dutt-Wormall Reaction

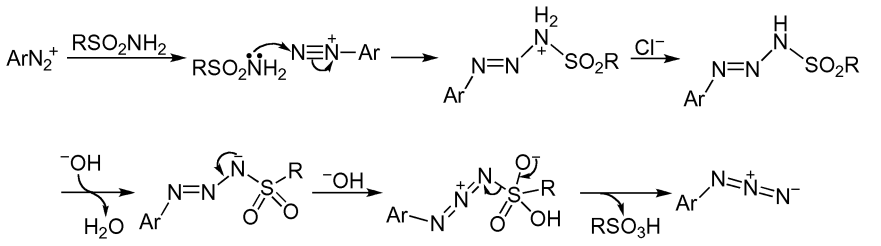
A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Dutt, Whitehead, and Wormall in 1921.[1] It is the preparation of aromatic azide via the basic hydrolysis of aromatic diazoaminosulfinate that can be easily synthesized from aromatic diazonium salt and arylsulfonamide or alkylsulfonamide. Therefore, this reaction is known as the Dutt-Wormall reaction.[2] Similarly, azides can be prepared via the cleavage of compounds from diazonium salt with ammonia,[3] hydrazine,[4] hydroxylamine,[4c,4d,5] etc.

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



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D. MODIFICATION

N/A

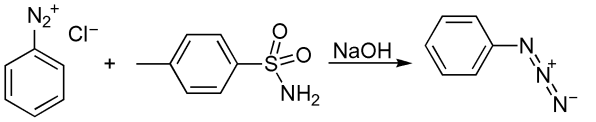
E. APPLICATIONS

This reaction has been used for the preparation of aromatic azides.

F. RELATED REACTIONS

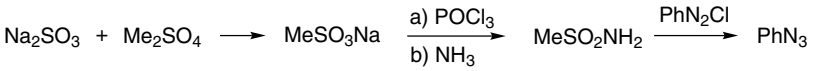
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 1.

Benzenediazonium chloride (made from 9.3 g aniline) was slowly added to a solution of 17 g *p*-toluenesulfonamide and 15 g NaOH in 350 mL water. In this case no precipitate was formed, but an orange, opalescent liquid was obtained that smelled strongly of phenylazoimide. A drop of the liquid produced a deep red coloration on β-naphthol test paper. The mixture was kept overnight in the ice box, and a considerable amount of oil had accumulated at the bottom of the vessel, but the liquid still gave the red coloration with β-naphthol test paper. Sodium hydroxide (15 g) was then added, and the mixture was stirred until no color reaction was obtained with β-naphthol test paper. It was then extracted with ether, the ether was distilled off, and the residue was distilled in steam. The steam distillate was again extracted with ether, and the extract was dried over $CaCl_2$ and distilled in a vacuum from a water bath. The yield of phenylazoimide was 9 g, and the calculated yield was 11.9 g. It was a clear yellow liquid, with a characteristic, penetrating, but not unpleasant smell. It exploded when heated in a test tube over a Bensen flame but distilled at 81°C at 44 mmHg.



Reference 6.

Preparation of Methanesulfonamide

Methyl sulfate (100 g) was slowly dropped over 1 h into a mixture of 300 g Na_2SO_3, 375 mL water, and 125 mL MeOH, while boiling under reflux. The solid residue obtained by evaporation of the filtered solution was extracted with 80% alcohol and crystallized. The yield of sodium methanesulfonate, which contained a small proportion of sodium methyl

sulfate was ~94%. The sulfonyl chloride was prepared by heating 100 g sulfonate and 200 g phosphoryl chloride (phosphorus pentachloride may be used, but the reaction is rather vigorous) at 130–150°C for 2 h. The liquid was purified by fractional distillation and the portion that had a boiling point between 152° and 159°C was collected, in amount of 60 g. The methanesulfonamide was prepared by saturating a cold benzene solution of the methanesulfonyl chloride with dry ammonia gas. The mixture was finally warmed and filtered and the solvent was distilled off. The residue was crystallized from benzene/alcohol as colorless, monoclinic plates, m.p. 84–85°C.

Preparation of Phenylazide

To a mixture of 19 g methanesulfonamide, 16 g NaOH, and 400 mL water was added slowly a benzenediazonium chloride prepared by mixing a solution of 18.6 g aniline, 60 mL of concentrated HCl and 100 mL water with 14 g $NaNO_2$ in 60 mL water. The yellow solid that first appeared soon decomposed, and the phenylazide thereby produced was extracted with ether and purified in the usual way, in amount of 19.0 g.

Other references related to the Dutt-Wormall reaction are cited in the literature.[7]

H. REFERENCES

1. Dutt, P. K.; Whitehead, H. R. and Wormall, A., *J. Chem. Soc.,* **1921**, *119*, 2088.
2. Bretschneider, H. and Rager, H., *Monatsh. Chem.,* **1950**, *81*, 970.
3. (a) Griess, P., *Ber.,* **1869**, *2*, 370. (b) Griess, P., *J. Prakt. Chem.,* **1867**, *101*, 74. (c) Griess, P., *Ann.,* **1866**, *137*, 39. (d) Griess, P., *Ann.,* **1865**, *135*, 121.
4. (a) Wohl, A. and Schiff, H., *Ber.,* **1900**, *33*, 2741. (b) Curtius, T., *Ber.,* **1893**, *26*, 1263. (c) Fischer, E., *Ann.,* **1878**, *190*, 67, 94, 96, 145. (d) Fischer, E., *Ber.,* **1877**, *10*, 1334.
5. (a) Bresler, H. W.; Friedman, W. H. and Mai, J., *Ber.,* **1905**, *39*, 876. (b) Mai, J., *Ber.,* **1893**, *26*, 1271. (c) Mai, J., *Ber.,* **1892**, *25*, 372. (d) Mai, J., *Ber.,* **1892**, *25*, 1685. (e) Mai, J., *Ber.,* **1891**, *24*, 3418.
6. Dutt, P. K., *J. Chem. Soc.,* **1924**, *125*, 1463.
7. (a) Boyer, J. H. and Canter, F. C., *Chem. Rev.,* **1954**, *54*, 1. (b) Key, A. and Dutt, P. V., *J. Chem. Soc.,* **1928**, 2035. (c) Dutt, P. K., *J. Chem. Soc.,* **1923**, *123*, 269.

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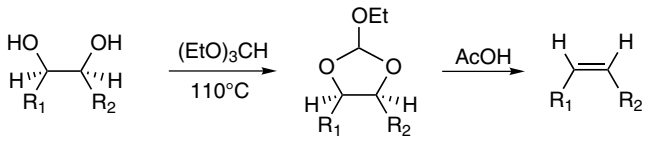
Eastwood Olefination

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Grank and Eastwood in 1964.[1] It is the stereospecific preparation of olefin from vicinal diol by means of the thermal decomposition of a five-membered cyclic orthoformate of the diol in the presence of a catalytic amount of acid (e.g., acetic acid). Therefore, this reaction is known as the Eastwood procedure[2] or Eastwood deoxygenation procedure,[2,3] but is called Eastwood Olefination in this book. It has been reported that using acetic anhydride as a solvent, the cyclic orthoformate can be converted into olefin in a high yield.[4] This improvement is referred to as Ando's modification.[3b] The Eastwood olefination is especially good in the preparation of dideoxy nucleosides and nucleotides.[5] Because acetic anhydride might cause the cleavage of the *N*-glycosyl bond,[5] dideoxy thymidine has been prepared using hydrous zirconium oxide as the catalyst and tributylamine as the stabilizer.[3b]

B. GENERAL REACTION SCHEME



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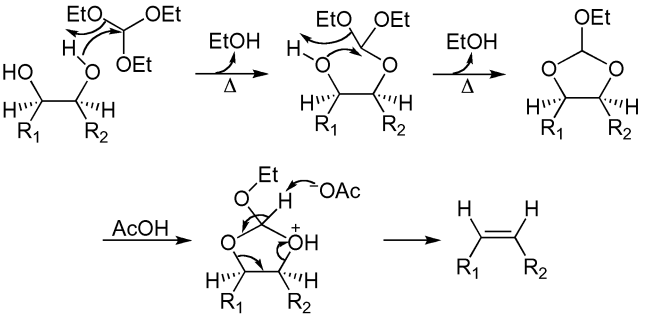
C. PROPOSED MECHANISMS



D. MODIFICATION

The decomposition of cyclic orthoformate of vicinal diol has been carried out in acetic anhydride.[4]

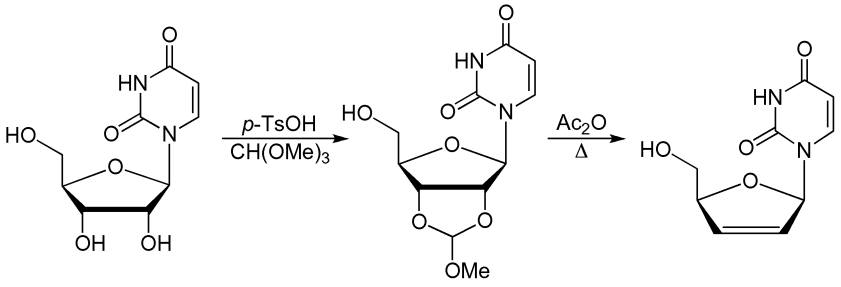
E. APPLICATIONS

This reaction has been applied in the preparation of olefin, dideoxy nucleosides, and nucleotides.

F. RELATED REACTIONS

This reaction is related to the *Corey-Winter Olefination*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 5.

To a solution of 100 g uridine (410 mmol) in 250 mL trimethyl orthoformate was added 3.0 g *p*-toluenesulfonic acid monohydrate (15.8 mmol). The solution was stirred at room temperature for l6 h and then cooled to 10°C. Sodium methoxide in methanol (28%, 3.39 g,

17.6 mmol) and 100 mL toluene was added, and the resulting mixture was stirred for 1 h at 10°C. The reaction mixture was filtered, and the separated crystal was washed with 100 mL toluene and dried to yield 113.6 g 2′,3′-*O*-(methoxymethylene) uridine as a white crystal, in a yield of 96%. $R_f = 0.34$ ($CHCl_3$/MeOH = 10/1).

A solution of 5.0 g 2′,3′-*O*-(methoxymethylene) uridine (17.5 mmol) in 50 mL acetic anhydride was stirred for 3 h at 132°C. The reaction mixture was cooled to room temperature and evaporated. Chloroform (50 mL) was added, and the mixture was washed with 50 mL aqueous $NaHCO_3$. Aqueous layer was extracted with 50 mL $CHCl_3$, and the combined organic layers were dried over Na_2SO_4, concentrated, and purified by silica gel column chromatography ($CHCl_3$/MeOH, 10:1) to give 1.87 g 1-(5-*O*-acetyl-2′,3′-dideoxy)-β-D-glycero-pent-2-enofuranosyl)uracil, in a yield of 42%, m.p. 128–128.5°C (recrystallized from EtOH).

Other references related to the Eastwood olefination are cited in the literature.[6]

H. REFERENCES

1. Grank, G. and Eastwood, F. W., *Aust. J. Chem.,* **1964**, *17*, 1392.
2. Mansuri, M. M.; Starrett, J. E.; Wos, J. A.; Tortolani, D. R.; Brodfuehrer, P. R.; Howell, H. G. and Martin, J. C., *J. Org. Chem.,* **1989**, *54*, 4780.
3. (a) Gavriliu, D.; Fossey, C.; Ciurea, A.; Delbederi, Z.; Sugeac, E.; Ladurée, D.; Schmidt, S.; Laumond, G. and Aubertin, A. M., *Nucleosides, Nucleotides & Nucleic Acids,* **2002**, *21*, 505. (b) Huryn, D. M. and Okabe, M., *Chem. Rev.,* **1992**, *92*, 1745.
4. Ando, M.; Ohhara, H. and Takase, K., *Chem. Lett.,* **1986**, 879.
5. Shiragami, H.; Irie, Y.; Shirae, H.; Yokozeki, K. and Yasuda, N., *J. Org. Chem.,* **1988**, *53*, 5170.
6. (a) Horton, D.; Thomson, J. K. and Tindall, C. G., *Methods Carbohydr. Chem.,* **1994**, *6*, 297. (b) Shiragami, H.; Shirae, H.; Irie, Y.; Yokozeki, K. and Yasuda, N., *Nucleic Acids Symposium Ser.,* **1988**, *20*, 17. (c) Block, E., *Org. React.,* **1984**, *30*, 478. (d) Eastwood, F. W.; Harrington, K. J.; Josan, J. S. and Pura, J. L., *Tetrahedron Lett.,* **1970**, 5223. (e) Josan, J. S. and Eastwood, F. W., *Aust. J. Chem.,* **1968**, *21*, 2013. (f) Josan, J. S. and Eastwood, F. W., *Carbohydr. Res.,* **1968**, *7*, 161.

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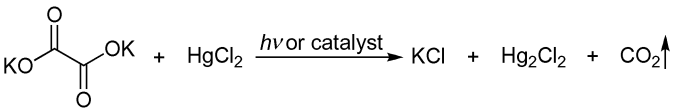
Eder Reaction

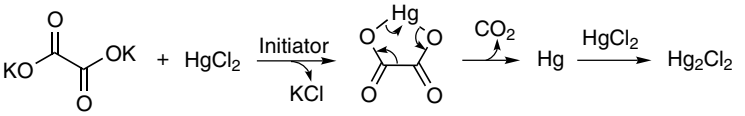
A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Eder in 1880.[1] It is the photochemical reduction of mercuric chloride to calomel by oxalates and is generally known as the Eder reaction.[2] This reaction has been proved to be a chain reaction[3] of great energy efficiency,[3] with a chain length of nearly 1,000,000,[4] so that it is often used in actinometry, including x-ray actinometry.[5] This reaction can be induced at room temperature[2d] by illumination,[2d] oxidizing reagents (e.g., $KMnO_4$, MnO_2),[2d,6] and reducing reagents;[4] however, it can also be inhibited by a few substances, including oxygen,[3,6,7] phenols,[2e] and other inorganic chlorides.[8] Some fluorescent dyes,[7b] potassium trioxalatocobaltiate,[7a] quinine,[4] and $FeCl_3$[4] function as photochemical sensitizers.

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



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D. MODIFICATION

N/A

E. APPLICATIONS

This reaction has been used in actinometry but not in actual organic synthesis as yet.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES

No experimental procedure has been cited for this reaction.

Other references related to the Eder reaction are cited in the literature.[9]

H. REFERENCES

1. Eder, J. M., *Ber.,* **1880**, *13*, 166.
2. (a) Sakuraba, S. and Ikeya, S., *Bull. Chem. Soc. Jpn.,* **1957**, *30*, 662. (b) Murty, K. S. and Rao, G. G., *Z. Physik. Chem.,* **1957**, *207*, 168. (c) Kornfeld, G., *Sci. Ind. Photograph.,* **1952**, *23*, 377. (d) Cartledge, G. H., *J. Am. Chem. Soc.,* **1941**, *63*, 906. (e) Weber, K., *Z. Physik. Chem*., **1934**, *A169*, 224. (f) Bekhterev, P., *J. Russ. Phys.-Chem. Soc.*, **1925**, *57*, 161.
3. Roseveare, W. E., *J. Am. Chem. Soc.,* **1930**, *52*, 2612.
4. Hausman, E. A. and Davis, T. W., *J. Am. Chem. Soc.,* **1954**, *76*, 5341.
5. (a) Woodard, H. Q.; Quimby, E. H. and Downes, H. R., *Am. J. Roentgenol. Radium Therapy,* **1933**, *29*, 308. (b) Quimby, E. H. and Downes, H. R., *Radiology*, **1930**, *14*, 468. (c) Wyckoff, R. W. G. and Baker, L. E., *Am. J. Roentgenol. Radium Therapy,* **1929**, *22*, 551.
6. Cartledge, G. H. and Djang, T. G., *J. Am. Chem. Soc.,* **1933**, *55*, 3214.
7. (a) Roseveare, W. E. and Olson, A. R., *J. Am. Chem. Soc.,* **1929**, *51*, 1716. (b) Jodlbauer, A. and von Tappeiner, H., *Ber.,* **1905**, *38*, 2602.
8. Berger, G., *Rec. Trav. Chim.,* **1921**, *40*, 387.
9. (a) Sakurab, S. and Ikeya, S., *Bull. Chem. Soc. Jpn.,* **1957**, *30*, 748. (b) Kornfeld, G., *Sci. Ind. Photograph*., **1952**, *23*, 377. (c) Cartledge, G. H. and Goldheim, S. L., *J. Am. Chem. Soc.,* **1933**, *55*, 3583.

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Edman Degradation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Edman in 1949.[1] It is the reaction between phenyl isothiocyanate and the free amino group of the *N*-terminal amino acid within a polypeptide to generate a thiourea, which upon the intramolecular cyclization via the nucleophilic addition of the amino group to adjacent amide carbonyl cleaves the *N*-terminal amino acids as a phenylthiohydantoin derivative and leaves the second amino acid as the *N*-terminus again.[2] Therefore, this reaction is generally known as the Edman degradation.[3] The cleaved phenylthiohydantoin derivatives of the amino acids can be identified by using chromatography.[4] This process can be repeated many times until the whole sequence of the peptide is determined. The advantages of this method include well-characterized conditions for the derivatization and cleavage reactions, high stepwise yields, and simple identification of the cleaved phenylthiohydantoin derivative by chromatography.[4] However, this method does have a few disadvantages, including the difficult separation of the phenylthiohydantoin derivative from the residual peptide segment in the solution phase during the sequencing of a small peptide,[5] low sensitivity,[4] the need for highly purified samples,[4] the long cycle times[4,6] and the high cost.[6] To overcome these weaknesses, the reaction can be carried out by means of solid-phase support synthesis (SPSS), so that a small protein or peptide can be sequenced automatically. However, providing that each cycle of the Edman degradation is 99% complete, this reaction is good for identifying only the first 50 amino acids in a sequence. Considering the degradative nature of this reaction, the Edman degradation has not often been adapted for normal organic synthesis.[2] Further development has made this degradation useful for sequencing the C-terminal segments of hydroxyethylamine-derived peptides[7] and an efficient method for the synthesis of 2-iminohydantoins.[2]

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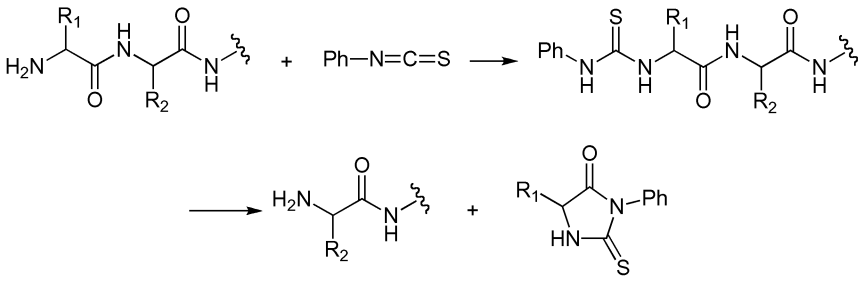
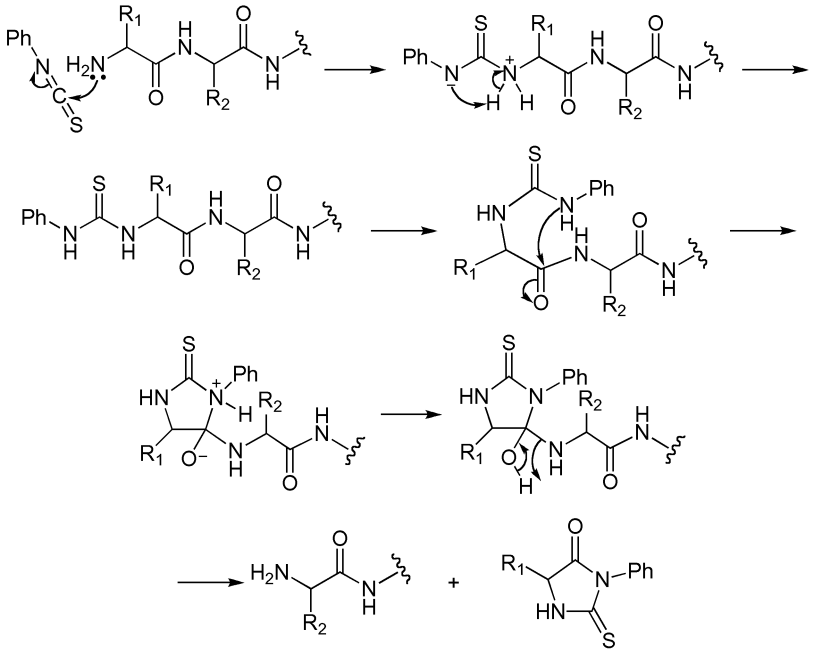
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified to a solid-state reaction, and polypeptides can be sequenced automatically.[5] In addition, this degradation can be used to sequence C-terminal segments of hydroxyethylamine-derived peptides[7] and for the preparation of 2-iminohydantoins.[2]

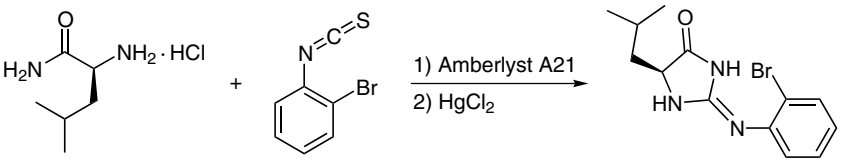
E. APPLICATIONS

This reaction has general application in protein sequencing.

F. RELATED REACTIONS

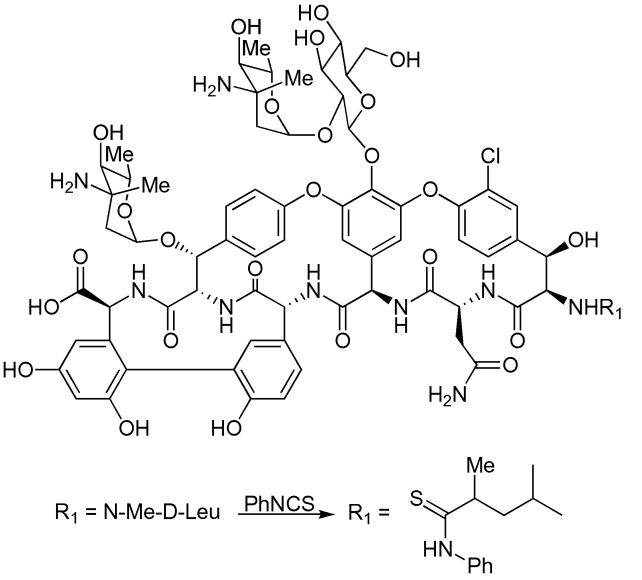
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 2.

To a mixture of 0.38 mmol of L-leucine amide and 0.5 g weakly basic amberlyst-A21 ion-exchange resin in 2.0 mL MeCN was added 0.38 mmol 2-bromophenyl isothiocyanate; the mixture was stirred at room temperature for 1 h. To the reaction mixture was added 0.42 mmol $HgCl_2$, and the mixture was then stirred overnight. The reaction mixture was diluted with 2.0 mL EtOAc and filtered through a pre-packed Celite column, using 4 mL EtOAc to remove the amberlyst-A21 resin and HgS by-product. The solution was added to the Celite column and allowed to sit in the column for 1 min before suction was applied to the column. After column chromatography, 99% yield of iminohydantoin with 98% of purity was obtained.



Reference 8.

Duolite basic anion-exchanger A 30 (OH^- form) was added to a solution of 500 mg eremomycin sulfate (0.3 mmol) in 100 mL water, and the mixture was left at room temperature for 3 h. Eremomycin base solution was filtered off and concentrated in vacuo with the addition of *n*-BuOH; then 50 mL acetone was added to give a precipitate. The latter was filtered off, washed with acetone, and dried in vacuo to give 410 mg eremomycin base (0.26 mmol). It was dissolved in 5 mL of a pyridine/water (1:1) mixture, and 0.02 mL PhNCS (0.2 mmol) was added under argon. The reaction mixture was stirred at room temperature for 16 h, concentrated in vacuo with the addition of *n*-BuOH, and applied to a column with silanized silica gel (2 × 100 mL), previously equilibrated with 0.001 M acetic acid. Acetic acid solution (0.001 M) was used for elution to give fractions containing nonreacted eremomycin. A mixture of MeOH/0.001 M AcOH (2:8) at a rate of 30 mL/h was used to give fractions containing *N*-phenylaminothiocarbonyleremomycin. The fractions were pooled and concentrated with the addition of *n*-BuOH in vacuo, and 50 mL acetone was added to yield the precipitate, which was filtered off, washed with acetone, and dried to yield 303 mg *N*-phenylaminothiocarbonyleremomycin, in a yield of 68%.

Other references related to the Edman degradation are cited in the literature.[9]

H. REFERENCES

1. Edman, P., *Arch. Biochem. Biophys*., **1949**, *22*, 475.
2. Evindar, G. and Batey, R. A., *Org. Lett.,* **2003**, *5*, 1201.
3. (a) Chen, W. Z.; Yin, X. F.; Mu, J. X. and Yin, Y., *Chem. Commun.,* **2007**, 2488. (b) Joo, S. H.; Xiao, Q.; Ling, Y.; Gopishetty, B. and Pei, D. H., *J. Am. Chem. Soc.,* **2006**, *128*, 13000. (c) Thakkar, A.; Wavreille, A.-S. and Pei, D. H., *Anal. Chem.,* **2006**, *78*, 5935. (d) Miyashita, M., *Nature Rev. Mol. Cell Biology,* **2001**, *2*, 325. (e) Boeijen, A. and Liskamp, R. M. J., *Tetrahedron Lett*., **1998**, *39*, 3589. (f) Gheorghe, M. T.; Jornvall, H. and Bergman, T., *Anal. Biochem.,* **1997**, *254*, 119. (g) Pauwels, W.; Farmer, P.B.; Osterman-Golkar, S.; Severi, M.; Cordero, R.; Bailey, E. and Veulemans, H., *J. Chromatography, B: Biomed. Sci. & Appl.,* **1997**, *702*, 77. (h) Meyer, H. E.; Heber, M.; Eisermann, B.; Korte, H.; Metzger, J. W. and Jung, G., *Anal. Biochem.,* **1994**, *223*, 185. (i) Gooley, A. A.; Pisano, A.; Packer, N. H.; Ball, M.; Jones, A.; Alewood, P. F.; Redmond, J. W. and Williams, K. L., *Glycoconjugate J.,* **1994**, *11*, 180. (j) McBroom, T.; Stubbs, H. J.; Wadhwa, M. S.; Thomas, V. H. and Rice, K. G., *Anal. Biochem.,* **1994**, *222*, 243. (k) Caporale, C.; Carrano, L.; Nitti, G.; Poerio, E.; Pucci, P. and Buonocore, V., *Protein Sequences & Data Analysis.,* **1991**, *4*, 3.
4. Reid, g. E.; Tichy, S. E.; Pérez, J.; O'Hair, R. A. J.; Simpson, R. J. and Kenttämaa, H. I., *J. Am. Chem. Soc.,* **2001**, *123*, 1184.
5. Laursen, R. A., *J. Am. Chem. Soc.,* **1966**, *88*, 5344.
6. (a) Hoffmann, C.; Blechschmidt, D.; Krüger, R.; Karas, M. and Griesinger, C., *J. Comb. Chem.,* **2002**, *4*, 79. (b) Wang, P.; Arabaci, G. and Pei, D. H., *J. Comb. Chem.,* **2001**, *3*, 251.
7. Brewer, M.; Oost, T.; Sukonpan, C.; Pereckas, M. and Rich, D. H., *Org. Lett.,* **2002**, *4*, 3469.
8. Printsevskaya, S. S.; Pavlov, A. Y.; Olsufyeva, E. N.; Mirchink, E. P.; Isakova, E. B.; Reznikova, M. I.; Goldman, R. C.; Branstrom, A. A.; Baizman, E. R.; Longley, C. B.; Sztarieskai, F.; Batta, G. and Preobrazhenskaya, M. N., *J. Med. Chem.,* **2002**, *45*, 1340.
9. (a) Sweeney, M. C. and Pei, D. H., *J. Comb. Chem.,* **2003**, *5*, 218. (b) Opatz, T. and Liskamp, R. M. J., *J. Comb. Chem.,* **2002**, *4*, 275. (c) Liu, R. W.; Marik, J. and Lam, K. S., *J. Am. Chem. Soc.,* **2002**, *124*, 7678. (d) Hallock, Y. F.; Sowder, R. C.; Pannell, L. K.; Hughes, C. B.; Johnson, D. G.; Gulakowski, R.; Cardellina, J. H. and Boyd, M. R., *J. Org. Chem.,* **2000**, *65*, 124. (e) Peterson, J. J.

and Meares, C. F., *Bioconjugate Chem*., **1998**, *9*, 618. (f) Corey, E. J.; Cheng, H. M.; Baker, C. H.; Matsuda, S. P. T.; Li, D. and Song, X. L., *J. Am. Chem. Soc.,* **1997**, *119*, 1289. (g) Cheung, Y. W.; Abell, C. and Balasubramanian, S., *J. Am. Chem. Soc.,* **1997**, *119*, 9568. (h) Muller, K.; Gombert, F. O.; Manning, U.; Grossmuller, F.; Graff, P.; Zaegel, H.; Zuber, J. F.; Freuler, F.; Tschopp, C. and Baumann, G., *J. Biol. Chem.,* **1996**, *271*, 16500. (i) Malabarba, A.; Ciabatti, R.; Maggini, M.; Ferrari, P.; Colombo, L. and Denaro, M., *J. Org. Chem.,* **1996**, *61*, 2151. (j) Bösze, S.; Mak, M.; Medzihradszky-Schweiger, H. and Hudecz, F., *J. Chromatog., A,* **1994**, *668*, 345. (k) Wu, J.; Ma, Q. N. and Lam, K. S., *Biochemistry,* **1994**, *33*, 14825. (l) Chen, J. K.; Lane, W. S.; Brauer, A. W.; Tanaka, A. and Schreiber, S. L., *J. Am. Chem. Soc.,* **1993**, *115*, 12591. (m) Songyang, Z.; Shoelson, S. E.; Chaudhuri, M.; Gish, G.; Pawson, T.; Haser, W. G.; King, F.; Roberts, T.; Ratnofsky, S.; Lechleider, R. J.; Neel, B. G.; Birge, R. B.; Fajardo, J. E.; Chou, M. M.; Hanafusa, H.; Schaffhausen, B. and Cantley, L. C., *Cell,* **1993**, *72*, 767. (n) Fields, C. G.; VanDrisse, V. L. and Fields, G. B., *Peptide Res.,* **1993**, *6*, 39. (o) Lam, K. S.; Salmon, S. E.; Hersh, E. M.; Hruby, V. J.; Kazmierski, W. M. and Knapp, R. J., *Nature,* **1991**, *354*, 82. (p) Han, K.-K.; Belaiche, D.; Moreau, O. and Briand, G., *Int. J. Biochem.,* **1985**, *17*, 429. (q) Heinrikson, L., "The Edman Degradation in Protein Sequence Analysis" in *Biochemical and Biophysical Studies of Proteins and Nucleic Acids,* ed. Lo, T.-B., Elsevier, New York, **1984**, pp. 285–302. (r) Laursen, R. A. and Machleidt, W., *Methods Biochem. Anal.,* **1980**, *26*, 201. (s) Edman, P., *Acta Chem. Scand.,* **1950**, *4*, 283.

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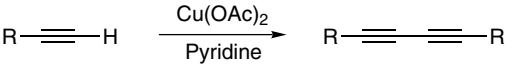
Eglinton Coupling

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Eglinton in 1956.[1] It is an oxidative coupling of terminal alkynes[2] by means of the treatment of the alkynes with a stoichiometric amounts of copper (II) acetate [$Cu(OAc)_2$] in pyridine.[1,3] Therefore, this reaction is generally known as the Eglinton coupling.[3,4] In addition, this reaction is also referred to as the Eglinton method,[5] Eglinton methodology,[2a] Eglinton coupling reaction,[3] Eglinton oxidative coupling,[2c,6] Eglinton-Glaser reaction,[7] Eglinton reaction,[2a,8] and Eglinton condition.[9] It can be homogenous when the reaction is carried out in methanolic pyridine.[10] This reaction is especially useful for the preparation of linearly conjugated all-carbon chains (polyacetylenes)[11] or cyclic dimmer, trimer, tetramer and even pentamer of compounds with two terminal alkynyl groups.[2a] It is interesting that the homocoupling of 3,6-di-(*t*-butyl)-3,6-dihydroxyl-1,4,7-octa-triynes with $Cu(OAc)_2$ gives cyclic dimmer in pyridine, whereas the solid state reaction with $Cu(OAc)_2 \cdot 2Py$ affords linear coupling product.[12]

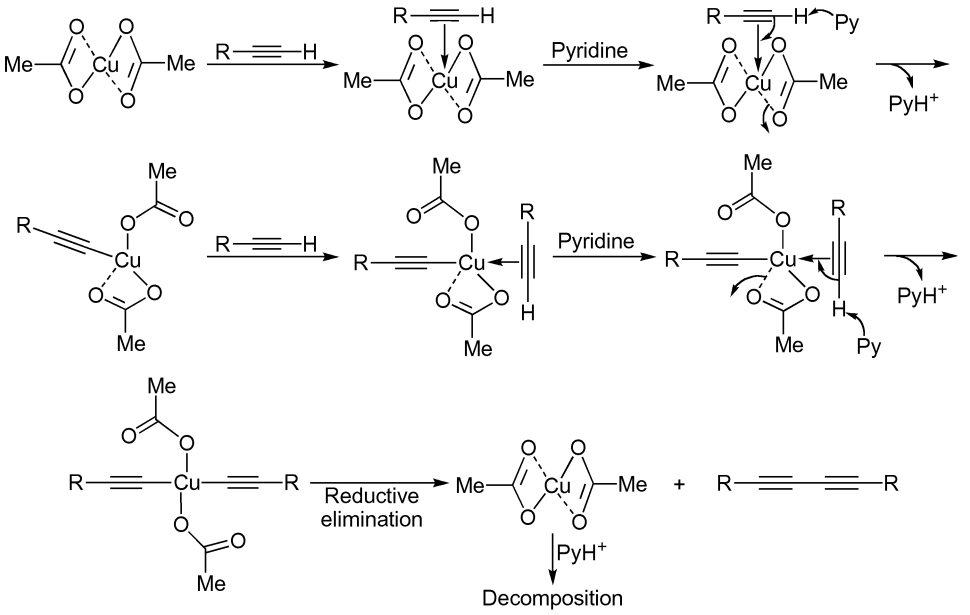
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

As no mechanism can be found for this reaction, a tentative mechanism is provided here. It is known that Cu(II) will form square-pyramidal geometry, whereas Cu(I) forms tetrahedral geometry.[13] In $Cu(OAc)_2$, copper (II) has nine out-shell electrons and can form five coordination bonds, like that in $CuSO_4 \cdot 5H_2O$.



D. MODIFICATION

This reaction has been modified to use a mixture of $Cu_2Cl_2/CuCl_2$ in pyridine for the coupling.[14] In addition, terminal alkynes protected by trimethylsilyl group can also couple under this reaction conditions via prior deprotection by K_2CO_3.[5a]

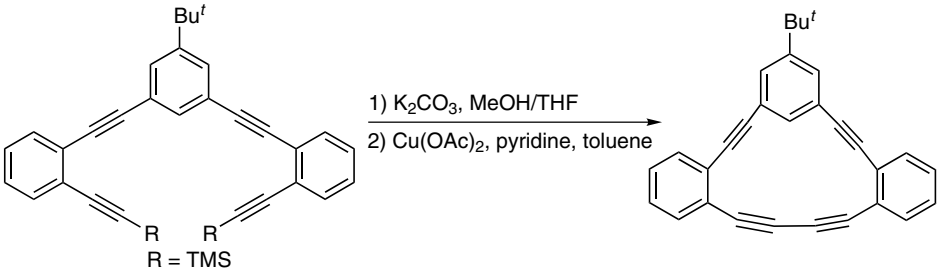
E. APPLICATIONS

This reaction has wide application in coupling terminal alkynes, especially in the formation of cyclic alkynes.

F. RELATED REACTIONS

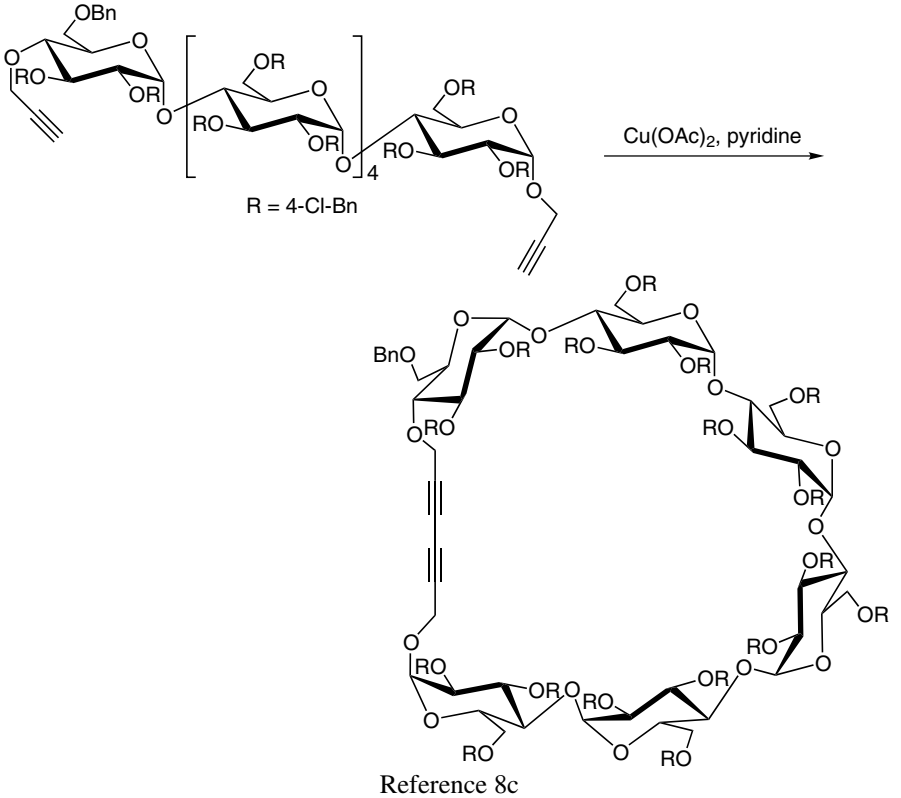
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 5a

A total of 158 mg TMS-protected alkynes (0.30 mmol) in 20 mL methanol/THF mixture (1:1) was treated with 83 mg K_2CO_3 (0.60 mmol). After TMS was deprotected, the solvent was evaporated on a rotatory evaporator, and 100 mL toluene was added to dissolve the residue. To an another flask charged with 5.45 g $Cu(OAc)_2$ (30.0 mmol), 450 mL pyridine, and 100 mL toluene under a nitrogen atmosphere was added dropwise 100 mL toluene containing the alkyne through a Hershberg dropping funnel at room temperature over 32 h, and the mixture was stirred for additional 10 h. During the reaction, the flask was wrapped with aluminum foil to protect the product from light. After removal of the solvent in vacuo, the residue was purified by flash chromatography followed by preparative HPLC to give 95 mg dibenzo[12]metacyclophanetetrayne as a colorless solid in a yield of 83%, m.p., $>220^\circ$C (dec).



Reference 8c

A solution of 110 mg $Cu(OAc)_2$ (0.611 mmol) in 110 mL pyridine was added at 60°C under argon to a solution of 200 mg 6-*O*-benzyl-2,3-*bis*-*O*-(4-chlorobenzyl)-4-*O*-(prop-2-yn-1-yl)-α-D-glucopyranosyl-[(1→4)-2,3,6-*tris*-*O*-(4-chlorobenzyl)-α-D-glucopyranosyl]$_4$-(1→4)-2,3,6-*tris*-*O*-(4-chlorobenzyl)-α-D-glucopyranoside (0.061 mmol) in 12 mL pyridine within 3 h. The mixture was then stirred for an additional hour and evaporated. The residue was dissolved in 80 mL EtOAc and washed with an aqueous solution of Na_4TMEDA (367 μL, 2.44 mmol), 40 mL water, and 40 mL brine and dried over $MgSO_4$. Evaporation and flash chromatography (toluene/EtOAc, 40:1 → 20:1) gave 166 mg 6-*O*-benzyl-2,3-*bis*-*O*-(4-chlorobenzyl)-α-D-glucopyranosyl-[(1→4)-2,3,6-*tris*-*O*-(4-chlorobenzyl)-α-D-glucopyranosyl]$_4$-(1→4)-2,3,6-*tris*-*O*-(4-chlorobenzyl)-α-D-glucopyranoside 6:4^{VI}-anhydride as a white foam, in a yield of 83%, R_f = 0.41 (toluene/EtOAc, 9:1), m.p. 55–58°C.

Other references related to the Eglinton coupling are cited in the literature.[15]

H. REFERENCES

1. Eglinton, G. and Galbraith, A. R., *Chem. & Ind. (London),* **1956**, 737.
2. (a) García-Frutos, E. M.; Fernández-Lázaro, F.; Maya, E. M.; Vázquez, P. and Torres, T., *J. Org. Chem.,* **2000**, *65*, 6841. (b) Iyer, R. S. and Selegue, J. P., *J. Am. Chem. Soc.,* **1987**, *109*, 910. (c) Ghosal, S.; Luke, G. P. and Kyler, K. S., *J. Org. Chem.,* **1987**, *52*, 4296.
3. Inouchi, K.; Kobashi, S.; Takimiya, K.; Aso, Y. and Otsubo, T., *Org. Lett.,* **2002**, *4*, 2533.
4. (a) Miljanic, O. S.; Dichtel, W. R.; Khan, S. I.; Mortezaei, S.; Heath, J. R. and Stoddart, J. F., *J. Am. Chem. Soc.,* **2007**, *129*, 8236. (b) Miljanic, O. S.; Dichtel, W. R.; Mortezaei, S. and Stoddart, J. F., *Org. Lett.,* **2006**, *8*, 4835. (c) Setaka, W.; Kanai, S.; Kabuto, C. and Kira, M., *Chem. Lett.,* **2006**, *35*, 1364. (d) Elwahy, A. H. M. and Hafner, K., *Eur. J. Org. Chem.,* **2006**, 3910. (e) Goichi, M.; Miyahara, H. and Toyota, S., *Chem. Lett.,* **2006**, *35*, 920. (f) Haino, T.; Fukunaga, C. and Fukazawa, Y., *Org. Lett.,* **2006**, *8*, 3545. (g) Fabian, K. H. H.; Elwahy, A. H. M. and Hafner, K., *Eur. J. Org. Chem.,* **2006**, 791. (h) Stichler-Bonaparte, J. and Vasella, A., *Helv. Chim. Acta,* **2001**, *84*, 2355. (i) Fabian, K. H. H.; Lindner, H.-J.; Nimmerfroh, N. and Hafner, K., *Angew. Chem. Int. Ed.,* **2001**, *40*, 3402. (j) Tobe, Y.; Utsumi, N.; Nagano, A.; Sonoda, M. and Naemura, K., *Tetrahedron*, **2001**, *57*, 8075. (k) Sumi, N.; Nakanishi, H.; Ueno, S.; Takimiya, K.; Aso, Y. and Otsubo, T., *Bull. Chem. Soc. Jpn.,* **2001**, *74*, 979. (l) Markl, G.; Zollitsch, T.; Kreitmeier, P.; Prinzhorn, M.; Reithinger, S. and Eibler, E., *Chem. Eur. J.,* **2000**, *6*, 3806. (m) Krämer, C. S.; Zeitler, K. and Muller, T. J. J., *Org. Lett.,* **2000**, *2*, 3723. (n) Nakanishi, H.; Sumi, N.; Aso, Y. and Otsubo, T., *J. Org. Chem.,* **1998**, *63*, 8632. (o) Haley, M. M. and Langsdorf, B. L., *Chem. Commun.,* **1997**, 1121. (p) Srinivasan, R.; Devan, B.; Shanmugam, P. and Rajagopalan, K., *Indian J. Chem., Sect. B,* **1997**, *36B*, 123. (q) Bunz, U. H. F., *Angew. Chem. Int. Ed. Engl.,* **1996**, *35*, 969. (r) Awaji, H.; Sugimoto, T. and Yoshida, Z.-I., *J. Phys. Org. Chem.,* **1988**, 1, 47. (s) Domnin, I. N.; Ivanov, A. L. and Favorskaya, I. A., *Zh. Org. Khim.,* **1986**, *22*, 1780. (t) Akiyama, S.; Misumi, S. and Nakagawa, M., *Bull. Chem. Soc. Jpn.,* **1960**, *33*, 1293.
5. (a) Tobe, Y.; Kishi, J.-Y.; Ohki, I. and Sonoda, M., *J. Org. Chem.,* **2003**, *68*, 3330. (b) Tobe, Y.; Utsumi, N.; Kawabata, K.; Nagano, A.; Adachi, K.; Araki, S.; Sonoda, M.; Hirose, K. and Naemura, K., *J. Am. Chem. Soc.,* **2002**, *124*, 5350.
6. (a) Akiyama, S.; Ogura, F. and Nakagawa, M., *Bull. Chem. Soc. Jpn.,* **1971**, *44*, 3443. (b) Fukui, K.; Okamoto, T. and Nakagawa, M., *Tetrahedron Lett*., **1971**, 3121. (c) Ando, T. and Nakagawa, M., *Tetrahedron Lett*., **1966**, 4437.
7. Rodríguez, J. G.; Esquivias, J.; Lafuente, A. and Díaz, C., *J. Org. Chem.,* **2003**, *68*, 8120.

8. (a) Sato, R.; Hamasaka, G.; Yamamoto, T.; Muraoka, H.; Nakajo, S. and Ogawa, S., *Bull. Chem. Soc. Jpn.,* **2007**, *80*, 768. (b) Quach, T. D. and Batey, R. A., *Org. Lett.,* **2003**, *5*, 1381. (c) Hoffmann, B.; Bernet, B. and Vasella, A., *Helv. Chim. Acta,* **2002**, *85*, 265. (d) Berscheid, R. and Voegtle, F., *Synthesis*, **1992**, 58.
9. (a) Xu, G.-L.; Zou, G.; Ni, Y.-H.; DeRose, M. C.; Crutchley, R. J. and Ren, T., *J. Am. Chem. Soc.,* **2003**, *125*, 10057. (b) Nishinaga, T.; Kawamura, T. and Komatsu, K., *J. Org. Chem.,* **1997**, *62*, 5354. (c) Barrett, A. G. M.; Boys, M. L. and Boehm, T. L., *J. Org. Chem.,* **1996**, *61*, 685.
10. Hay, A. S., *J. Org. Chem.,* **1960**, *25*, 1275.
11. Jones, E. R. H.; Lee, H. H. and Whiting, M. C., *J. Chem. Soc*., **1960**, 3483.
12. Toda, F. and Tokumaru, Y., *Chem. Lett*., **1990**, 987.
13. Lu, J.; Paliwala, T.; Lim, S. C.; Yu, C.; Niu, T. Y. and Jacobson, A. J., *Inorg. Chem.,* **1997**, *36*, 923.
14. Bunz, U. H. F.; Roidl, G.; Altmann, M.; Enkelmann, V. and Shimizu, K. D., *J. Am. Chem. Soc.,* **1999**, *121*, 10719.
15. (a) Sharman, W. M. and van Lier, J. E., *J. Porphyrins & Phthalocyanines,* **2000**, *4*, 441. (b) Bunz, U. H. F. and Enkelmann, V., *Chem. Eur. J.,* **1999**, *5*, 263. (c) Nishinaga, T.; Nakayama, H.; Nodera, H. and Komatsu, K., *Tetrahedron Lett.,* **1998**, *39*, 7139. (d) Bürli, R. and Vasella, A., *Helv. Chim. Acta,* **1997**, *80*, 2215. (e) Haley, M. M.; Bell, M. L.; Brand, S. C.; Kimball, D. B.; Pak, J. J. and Wan, W. B., *Tetrahedron Lett.,* **1997**, *38*, 7483. (f) Hébert, N.; Beck, A.; Lennox, R. B. and Just, G., *J. Org. Chem.,* **1992**, *57*, 1777. (g) Wolovsky, R. and Sondheimer, F., *J. Am. Chem. Soc.,* **1966**, *88*, 1525. (h) Campbell, I. D.; Eglinton, G.; Henderson, W. and Raphael, R. A., *J. Chem. Soc.*, *Chem. Commun*., **1966**, 87. (i) Campbell, I. D. and Eglinton, G., *J. Chem. Soc.,* **1964**, 1158. (j) Bohlmann, F.; Schonowsky, H.; Inhoffen, E. and Grau, G., *Ber.,* **1964**, *97*, 794. (k) Eglinton, G. and McCrae, W., eds., *Advances in Organic Chemistry,* Interscience, New York, **1963**, *4*, pp. 225–328. (l) Sondheimer, F. and Wolovsky, R., *J. Am. Chem. Soc.,* **1962**, *84*, 260. (m) Hay, A. S., *J. Org. Chem.,* **1962**, *27*, 3320. (n) Behr, O. M.; Eglinton, G.; Galbraith, A. R. and Raphael, R. A., *J. Chem. Soc.,* **1960**, 3614. (o) Sondheimer, F.; Wolovsky, R. and Gaoni, Y., *J. Am. Chem. Soc.,* **1960**, *32*, 755. (p) Eglinton, G. and Galbraith, A. R., *J. Chem. Soc.,* **1959**, 889. (q) Behr, O. M.; Eglinton, G. and Raphael, R. A., *Chem. Ind. (London),* **1959**, 699. (r) Eglinton, G. and Galbraith, A. R., *Proc. Chem. Soc.,* **1957**, 350.

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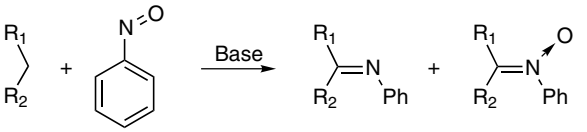
Ehrlich-Sachs Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Ehrlich and Sachs in 1899.[1] It is the condensation between compounds of active methylene groups and aromatic nitroso molecules and is generally known as the Ehrlich-Sachs reaction.[2] This reaction can be initiated by base, acid, or simply heating,[3] but in most cases, it is triggered by a base. In this reaction, two competing products are formed[4]—the dehydrate azomethine derivative (or Schiff base) and the oxidized nitrone derivative. As the actual reaction mechanism has not been well understood, it is difficult to predict which product will eventually form. However, it is known that the reaction condition, the acidity of the methylene group, and the structure of compounds with the methylene group all affect the reaction outcome.[4] It is plausible that the reaction of the base-generated enolate from 1,3-dicarbonyl compound or aryl alkyl ketones predominantly gives the azomethine derivatives[5] with a few exceptions.[6] The base applicable for this reaction can be as weak as sodium carbonate.[7]

B. GENERAL REACTION SCHEME



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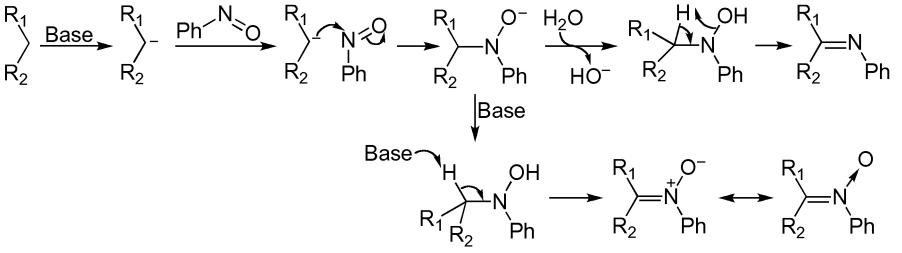
C. PROPOSED MECHANISMS

Because the mechanism of this reaction is not quite clear, a tentative mechanism is outlined here.



D. MODIFICATION

N/A

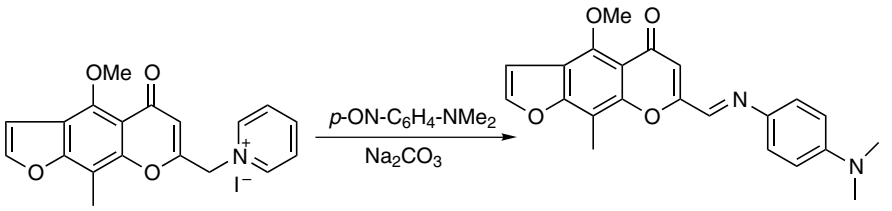
E. APPLICATIONS

This reaction is generally used in the preparation of azomethine derivatives, which are used in the dye and drug industry.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

To a solution of 7.0 g 1-(4-oxo-1,4H-5,8-dimethoxyfuro-4′,5′,6,7-chromene-2-ylmethyl)pyridinium iodide in 240 mL aqueous ethanol (50%) at 40°C was added a solution of 2.8 g *p*-nitrosodimethylaniline hydrochloride in 50 mL water. The reaction mixture was

then treated dropwise, while stirring, with a solution of 2.0 g Na_2CO_3 in 20 mL water over 15 min; then the solution was kept aside at room temperature for 4 h. The solid separated. On addition of 400 mL water, the reaction mixture was extracted with $CHCl_3$ and washed with dilute H_2SO_4 (1%) and finally with water. The organic layer was dried and concentrated to afford a solid that was crystallized from 2.5 L ethanol to give 2.5 g of 5,8-dimethoxyfuro-4′,5′,6,7-chromone-2-*p*-dimethylamino-phenylazomethine as golden yellow needles, m.p. 212°C (dec.).

Other references related to the Ehrlich-Sachs reaction are cited in the literature.[8]

H. REFERENCES

1. Ehrlich, P. and Sachs, F., *Ber.,* **1899**, *32*, 2341.
2. (a) Laskar, D. D.; Prajapati, D. and Sandhu, J. S., *Synth. Commun.,* **2001**, *31*, 1427. (b) Millich, F. and El-Shoubary, M. T., *Org. Prep. Proc. Int.,* **1996**, *28*, 366. (c) Belousova, S. P.; Vasil'ev, N. V.; Kolomiets, A. F.; Nikolaev, K. M.; Sokol'skii, G. A. and Fokin, A. V., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1984**, 1198. (d) Anderson, D. M. W. and Duncan, J. L., *J. Chem. Soc.,* **1961**, 1631. (e) Anderson, D. M. W. and Bell, F., *J. Chem. Soc.,* **1959**, 3708. (f) Bell, F., *J. Chem. Soc.,* **1957**, 516. (g) McGookin, A., *J. Appl. Chem.,* **1955**, *5*, 65. (h) Barrow, F. and Thorneycroft, F. J., *J. Chem. Soc.,* **1939**, 769.
3. Adam, W. and Krebs, O., *Chem. Rev.,* **2003**, *103*, 4131.
4. Zuman, P. and Shah, B., *Chem. Rev.,* **1994**, *94*, 1621.
5. (a) Markov, V. I.; Prosyanik, A. V.; Fedoseenko, D. V.; Loban, S. V. and Starovoitov, V. V., *Zh. Org. Khim.,* **1984**, *20*, 2424. (b) Hepfinger, N. F.; Griffin, N. F. and Shapiro, B. L., *Tetrahedron lett.*, **1963**, 1365. (c) Nohira, H.; Sato, K. and Mukaiyama, T., *Bull. Chem. Soc. Jpn.,* **1963**, *36*, 870. (d) Pfeiffer, P. and Böttcher, H., *J. Prakt. Chem.,* **1937**, *148*, 126.
6. (a) Schönberg, A. and Azzem, R. C., *J. Chem. Soc.,* **1939**, 1428. (b) Schönberg, A., *Nature,* **1938**, *142*, 997.
7. Mustafa, A.; Starkovsky, N. A. and Salama, T. I., *J. Org. Chem.,* **1961**, *26*, 886.
8. (a) Salgado-Zamora, H. and Taylor, E. C., *Heterocycl. Commun.,* **2006**, *12*, 307. (b) De, S. K.; Dhara, M. G. and Mallik, A. K., *Can. J. Chem.,* **1998**, *76*, 199. (c) Mustafa, A.; Starkovsky, N. A. and Salama, T. I., *J. Org. Chem.,* **1961**, *26*, 886. (d) Allen, C. F. H.; Allan, J. V. and Wilson, C. V., *J. Am. Chem. Soc.,* **1944**, *66*, 1805.

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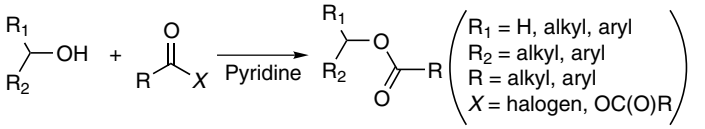
Einhorn Acylation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Einhorn and Hollandt in 1898.[1] It is the acylation of alcohols using anhydride or acyl halide in a tertiary amine such as pyridine. Therefore, this reaction is known as the Einhorn acylation,[2] Einhorn reaction,[3] and Deninger-Einhorn method.[4] The function of tertiary amines in this reaction have been identified as both nucleophilic acylation catalyst[5] and acid scavenger.[6] The solid evidence of nucleophilic catalyst is to record the UV spectrum of the intermediate acetylpyridinium salt in water.[7] Subsequently, a number of highly nucleophilic tertiary amines have been employed for the acylation of alcohols. These tertiary amines include triethylamine,[8] 4-(dimethylamino)pyridine (DMAP),[9] 1,4-diazabicyclo[2.2.2]octane (DABCO),[3b,3c,10] and 1,2,2,6,6-pentamethylpiperidine (PMP).[11] In addition, when chiral tertiary amines are used as catalysts, secondary alcohols can be selectively acylated to afford the chiral ester.[2]

B. GENERAL REACTION SCHEME



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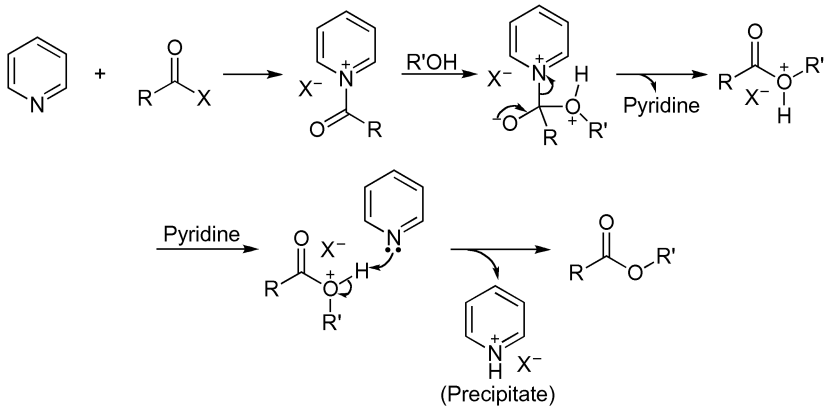
C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified by adding 4-(dimethylamino)pyridine (DMAP) as a catalyst during the acylation in pyridine.[3c]

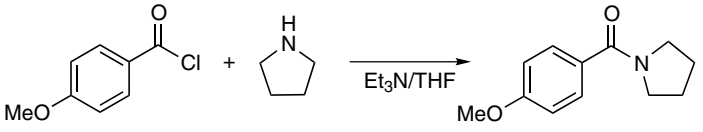
E. APPLICATIONS

This reaction has wide application in the preparation of esters from alcohols and acylation reagents (e.g., acyl halides and anhydrides).

F. RELATED REACTIONS

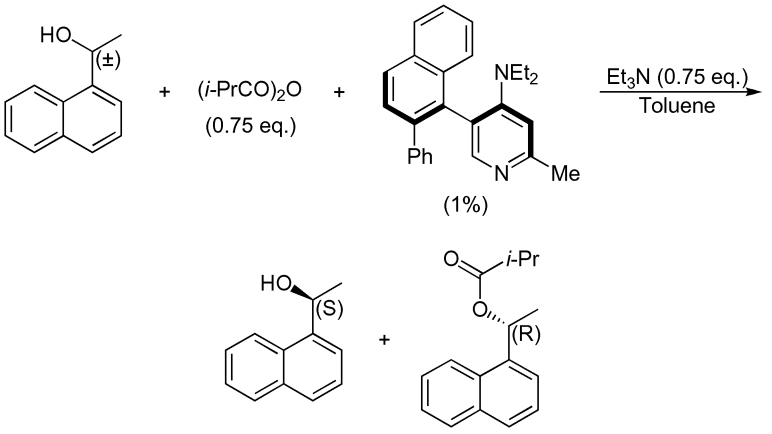
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3a.

To the solution of 4.20 g 4-methoxybenzoyl chloride (24.0 mmol) and 32 mL Et_3N in 30 mL THF was added a solution of 2 mL pyrrolidine (24 mmol) in 5 mL THF. The mixture was refluxed for 1 h. After cooling to ambient temperature, the solution was filtered and the filtrate was concentrated. The crude product was purified by column chromatography (CH_2Cl_2) to afford 75% of 1-(4-methoxybenzoyl)pyrrolidine.



Reference 2.

A solution of 172.0 mg (±)-1-(1-naphthyl)ethanol (1.00 mmol), 104 mL Et_3N (0.75 mmol), and 3.7 mg of the catalyst (10 μmol, > 99.9% e.e.) in 2.0 mL toluene was cooled to 0°C. Under vigorous stirring, 331 μL $(i\text{-PrCO})_2O$ (2.00 mmol) was added dropwise. After 24 h at 0°C, the reaction was quenched by 10 mL MeOH at 0°C. The mixture was allowed to warm to room temperature over 15 min, and the solvents were evaporated in vacuo. 1-(1-Naphthyl)ethanol and its isobutyric ester were separated by flash chromatography (petroleum ether/CH_2Cl_2 from 1:1 to pure CH_2Cl_2) to give 35.9% e.e. of (S)-ester.

Other references related to the Einhorn acylation are cited in the literature.[12]

H. REFERENCES

1. Einhorn, A. and Hollandt, F., *Ann.,* **1898**, *301*, 95.
2. Spivey, A. C.; Maddaford, A.; Leese, D. P. and Redgrave, A. J., *J. Chem. Soc*., *Perkin Trans. I*, **2001**, 1785.
3. (a) Sasse, A.; Sadek, B.; Ligneau, X.; Elz, S.; Pertz, H. H.; Luger, P.; Ganellin, C. R.; Arrang, J.-M.; Schwartz, J.-C.; Schunack, W. and Stark, H., *J. Med. Chem.,* **2000**, *43*, 3335. (b) Pertz, H. H.; Milhahn, H.-C. and Eich, E., *J. Med. Chem.,* **1999**, *42*, 659. (c) Stark, H.; Purand, K.; Hüls, A.; Ligneau, X.; Garbarg, M.; Schwartz, J.-C. and Schunack, W., *J. Med. Chem.,* **1996**, *39*, 1220.
4. Ogura, H., *J. Org. Chem.,* **1960**, *25*, 679.
5. (a) Cherkasova, E. M.; Bogatkov, S. V. and Golovina, Z. P., *Russ. Chem. Rev.,* **1977**, *46*, 246. (b) Butler, A. R. and Gold, V., *J. Chem. Soc.,* **1961**, 4362. (c) Bender, M. L., *Chem. Rev.,* **1960**, *60*, 53. (d) Gold, V. and Jefferson, E. G., *J. Chem. Soc.,* **1953**, 1416. (e) Gold, V. and Jefferson, E. G., *J. Chem. Soc.,* **1953**, 1409. (f) Bafna, S. L. and Gold, V., *J. Chem. Soc.,* **1953**, 1406.
6. Iqbal, J. and Srivastava, R. R., *J. Org. Chem.,* **1992**, *57*, 2001.
7. (a) Sheinkman, A. K.; Suminov, S. I. and Kost, A. N., *Russ. Chem. Rev.,* **1973**, *42*, 642. (b) Fersht, A. R. and Jencks, W. P., *J. Am. Chem. Soc.,* **1970**, *92*, 5442. (c) Fersht, A. R. and Jencks, W. P., *J. Am. Chem. Soc.,* **1970**, *92*, 5432.
8. Krause, M.; Rouleau, A.; Stark, H.; Luger, P.; Lipp, R.; Garbarg, M.; Schwartz, J.-C. and Schunack, W., *J. Med. Chem.,* **1995**, *38*, 4070.

9. (a) Ragnarsson, U. and Grehn, L., *Acc. Chem. Res.,* **1998**, *31*, 494. (b) Scriven, F. V., *Chem. Soc. Rev.,* **1983**, *12*, 129. (c) Höfle, G.; Steglich, W. and Vorbruggen, H., *Angew. Chem. Int. Ed. Engl.,* **1978**, *17*, 569. (d) Hassner, A.; Krepski, L. R. and Alexanian, V., *Tetrahedron,* **1978**, *34*, 2069. (e) Steglich, W. and Höfle, G., *Angew. Chem. Int. Ed. Engl.,* **1969**, *8*, 981.
10. (a) Mallavadhani, U. V., in *Encyclopedia of Reagents for Organic Synthesis,* ed. Paquette, L. A., John Wiley & Sons, New York, **1995**, *2*, pp. 1494–1497. (b) Litvinenko, L. M.; Savelova, V. A.; Solomoichenko, T. N.; Zaslavskij, V. G. and Ved, T. V., *Organic Reactivity (Tartu),* **1985**, *22*, 176. (c) Schenk, G. H.; Wines, P. and Mojzis, C., *Anal. Chem.,* **1964**, *36*, 914.
11. (a) Schyja, W.; Petersen, S. and Luning, U., *Liebigs Ann.,* **1996**, 2099. (b) Ishihara, K.; Kurihara, H. and Yamamoto, H., *J. Org. Chem.,* **1993**, *58*, 3791.
12. (a) Olah, G. A. and Szilagyi, P. J., *J. Am. Chem. Soc.,* **1969**, *91*, 2949. (b) Klages, F. and Zange, E., *Ann.,* **1957**, *607*, 35. (c) Doering, W. V. E. and McEwen, W. E., *J. Am. Chem. Soc.,* **1951**, *73*, 2104. (d) Raiford, L. C. and Dudley, J. R., *Proc. Iowa Acad. Sci.,* **1944**, *51*, 313. (e) Raiford, L. C. and Shelton, J. R., *J. Org. Chem.,* **1939**, *4*, 207. (f) Muller, A., *Ber.,* **1932**, *65B*, 1055. (g) Nelson, R. E. and Rothrock, H. S., *J. Am. Chem. Soc.,* **1929**, *51*, 2761. (h) Raiford, L. C. and Mortensen, F. C., *J. Am. Chem. Soc.,* **1928**, *50*, 1201. (i) Raiford, L. C. and Lankelma, H. P., *J. Am. Chem. Soc.,* **1925**, *47*, 1111. (j) Raiford, L. C. and Greider, C. E., *J. Am. Chem. Soc.,* **1924**, *46*, 430. (k) Raiford, L. C. and Couture, J. R., *J. Am. Chem. Soc.,* **1924**, *46*, 2305.

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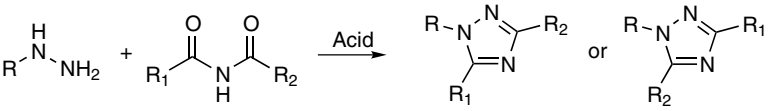
Einhorn-Brunner Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Einhorn in 1905[1] and was extended by Brunner in 1914,[2] therefore, it is known as the Einhorn-Brunner reaction.[3] It is the synthesis of 1,2,4-triazoles by acid-catalyzed condensation between hydrazines (or semicarbazides) and diacylamines. It should be pointed out when two side chains in diacylamine are different, two isomeric triazoles will form. It was found that the substituent in the diacylamine derived from the stronger acid would appear in position 3 of the resulting triazole,[3e] indicating that the reaction is initiated by the attack of the free amino group of hydrazine on the more electrophilic carbonyl group of the stronger acid moiety.[3c]

B. GENERAL REACTION SCHEME



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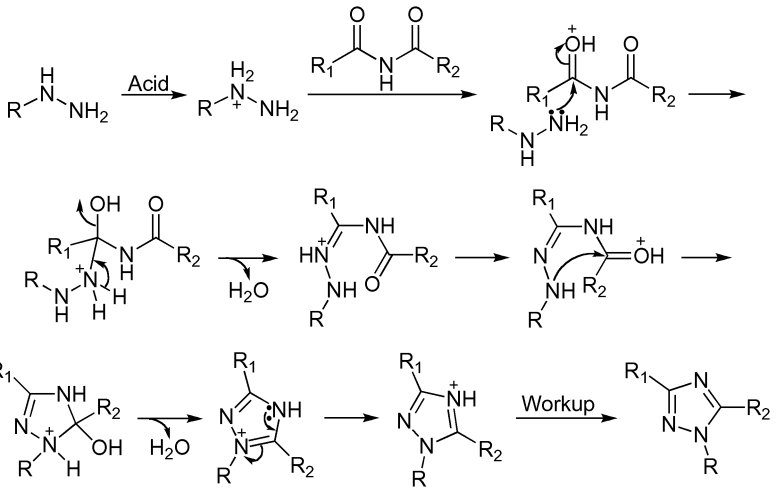
C. PROPOSED MECHANISMS



D. MODIFICATION

A new preparation of 1,2,4-triazoles has been developed using tosylmethyl isocyanide and a diazonium salt.[3b]

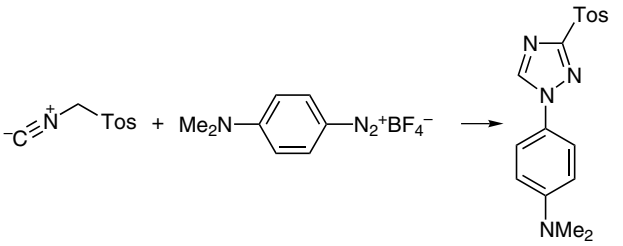
E. APPLICATIONS

This reaction has been used in the preparation of 1,2,4-triazoles (the most successful method[3c]).

F. RELATED REACTIONS

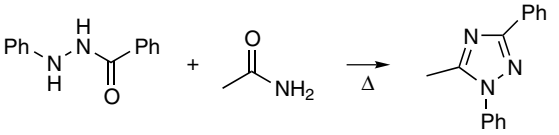
This reaction is related to the *Pellizzari Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 3b.

A solution of 9.75 g tosyl methyl isocynide (50 mmol) and 23.5 g *p*-dimethylaminobenzenediazonium tetrafluoroborate (100 mmol) in a mixture of 200 mL Me_2SO, 160 mL MeOH, and 80 mL H_2O was cooled in ice salt. To the stirred solution was added over 45 min a solution of 10.5 g K_2CO_3 in 100 mL cold water. After being stirred for another 10 min, the reaction mixture was poured in 4 L ice water that was almost saturated with NaCl. The precipitate was collected, washed with water and dried. Column chromatography (alumina, CH_2C1_2/THF, 3:2) gave 16.0 g 1-*p*-dimethylaminophenyl-3-tosyl-1,2,4-triazole, in a yield of 94%, m.p. 172–175°C. An analytically pure sample was obtained by preparative TLC (alumina, CH_2Cl_2) followed by crystallization from hot ethanol, with a melting point of 177–178.5°C.



Reference 3e.

1-Benzoyl-2-phenylhydrazine (6.0 g) and 15.0 g dry, freshly distilled acetamide were refluxed in an oil bath at 250°C for 4 h. The acetamide was distilled off at atmospheric pressure, and the residue was extracted with ether (2 × 50 mL), leaving 2.1 g undissolved 1-benzoyl-2-phenylhydrazine (m.p. 166°C). The crude triazole extract (3.8 g) was fractionated to give the main fraction as a pale yellow oil, b.p. 210–215°C (25 mmHg), which solidified after several months (2.1 g). Recrystallization from light petroleum (b.p. 40–60°C) removed 1-acetyl-2-phenylhydrazine (0.08 g, m.p. 129°C). The petroleum extract was sublimed at 40°C (2 mmHg) to afford oily crystals, m.p. 80–85°C. The compound was identified as 5-methyl-1,3-diphenyl-1,2,4-triazole.

Other references related to the Einhorn-Brunner reaction are cited in the literature.[4]

H. REFERENCES

1. (a) Einhorn, A., *Ann.,* **1905**, *343*, 207. (b) Einhorn, A.; Bischkopff, E. and Szelinski, B., *Ann.,* **1905**, *343*, 223.
2. (a) Brunner, K., *Ber.,* **1914**, *47*, 2671. (b) Brunner, K., *Monatsh.,* **1915**, *36*, 509. (c) Brunner, K., *Monatsh.,* **1915**, *36*, 530.
3. (a) Lin, Y.-I; Lang, S. A.; Lovell, M. F. and Perkinson, N. A., *J. Org. Chem.,* **1979**, *44*, 4160. (b) Van Leusen, A. M.; Hoogenboom, B. E. and Houwing, H. A., *J. Org. Chem.,* **1976**, *41*, 711. (c) Potts, K. T., *Chem. Rev.,* **1961**, *61*, 87. (d) Atkinson, M. R.; Parkes, E. A. and Polya, J. B., *J. Chem. Soc.,* **1954**, 4256. (e) Atkinson, M. R. and Polya, J. B., *J. Chem. Soc.,* **1952**, 3418.
4. (a) Hu, K.; Bradshaw, J. S.; Pastushok, V. N.; Krakowiak, K. E.; Dalley, N. K.; Zhang, X. X. and Izatt, R. M., *J. Org. Chem.,* **1998**, *63*, 4786. (b) Lee, L. A.; Evans, R. and Wheeler, J. W., *J. Org. Chem.,* **1972**, *37*, 343. (c) Boyer, H. J., *The Structure and Reactions of Organic Compounds*, ed. Elderfield, R. C., John Wiley & Sons, New York, **1961**, *7*, p. 438. (d) Atkinson, M. R. and Polya, J. B., *J. Chem. Soc.,* **1954**, 141. (e) Atkinson, M. R. and Polya, J. B., *J. Chem. Soc.,* **1954**, 3319. (f) Atkinson, M. R.; Komzak, A. A.; Parkes, E. A. and Polya, J. B., *J. Chem. Soc.,* **1954**, 4508. (g) Hernler, F., *Monatsh.,* **1929**, *51*, 269. (h) Grüner, R. and Brunner, K., *Monatsh.,* **1927**, *48*, 43. (i) Gabel, W. and Schmidegg, O., *Monatsh.,* **1926**, *47*, 747. (j) Hernles, F. and Matthes, F., *Monatsh.,* **1926**, *47*, 797. (k) Wolchowe, H., *Monatsh.,* **1916**, *37*, 479.

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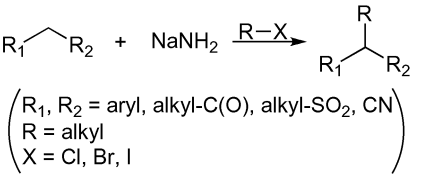
Eisleb Alkylation

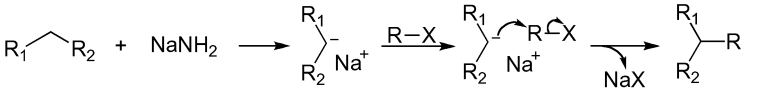
A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Eisleb in 1941.[1] It is the alkylation of compounds of active hydrogen with alkyl halide via the treatment of sodium amide. The compounds with active hydrogens include deoxybenzoin,[1a] diphenylmethane,[2] phenylacetonitrile,[3] fluorene,[2,4] benzyl phenyl sulfone,[5] and 2-pyridyl acetonitrile.[6] This reaction normally gives a satisfactory yield of introducing *N*,*N*-dialkylamino alkyl group to compounds with an active proton.[4]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



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D. MODIFICATION

N/A

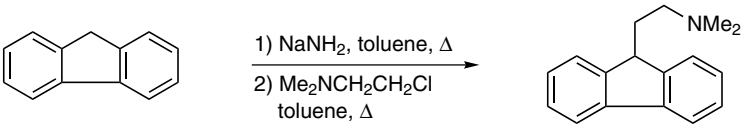
E. APPLICATIONS

This reaction is used for the alkylation of compounds with active hydrogens.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 4a.

A solution of 120 g fluorene (0.72 mol) in 250 mL toluene was refluxed with 15 g sodium amide (0.575 mol) for 1.5 h, then a solution of β-dimethylaminoethyl chloride in toluene (base liberated from 57.0 g β-dimethylaminoethyl chloride hydrochloride in 150 mL toluene) was added. The mixture was refluxed for another 4 h, then cooled and decomposed with sufficient 4 *N* HCl to render it acid to Congo red. The organic layer was washed twice with dilute hydrochloric acid and evaporated to leave about 50 g unreacted fluorene. The aqueous acidic layers were combined, made alkaline, and extracted with ether. Fractional distillation of the dried ethereal extract gave 44.2 g crude 9-(β-dimethylaminoethyl)-fluorene, in a yield of 41%, b.p, 156–165°C (at 2 mmHg). This product was further purified by the following process. The product, dissolved in 200 mL warm alcohol, was treated with 400 mL hot 5% $HClO_4$ solution; the perchlorate was purified by recrystallization from water, m.p. 206–208°C. The recrystallized perchlorate was dispersed in a mixture of 300 mL hot water and 100 mL hot benzene, the mixture was basified and vigorously mixed, and the benzene layer was separated. The aqueous layer was extracted with hot benzene again, and the benzene layers were combined,and distilled to give 28.0 g pure 9-(β-dimethaminoethyl)-fluorene, in an overall yield of 34%, b.p. 153–154°C (1.7 mmHg).

Other references related to the Eisleb alkylation are cited in the literature.[7]

H. REFERENCES

1. (a) Eisleb, O., *Ber.,* **1941**, *74B*, 1433. (b) Eisleb, O., *Ger. Pat.,* Aug. 20, **1940**, 695,216. (*Chem. Abstr.,* **1941**, *35*, 5646).
2. Ruddy, A. W. and Buckley, J. S., *J. Am. Chem. Soc.,* **1950**, *72*, 718.

3. Levine, R. and Fernelius, W. C., *Chem. Rev.,* **1954**, *54*, 449.
4. (a) King, J. A.; Meltzer, R. I. and Doczi, J., *J. Am. Chem. Soc.,* **1955**, *77*, 2217. (b) Cavallito, C. J.; Gray, A. P. and Spinner, E. E., *J. Am. Chem. Soc.,* **1954**, *76*, 1862.
5. Klenk, M. M.; Suter, C. M. and Archer, S., *J. Am. Chem. Soc.,* **1948**, *70*, 3846.
6. Dummel, R. J.; Wrinkle, W. and Mosher, H. S., *J. Am. Chem. Soc.,* **1956**, *78*, 1936.
7. Eisleb, O., *Ger. Pat.*, June 11, **1943**, 735,866. (*Chem. Abstr.* **1944**, *38*, 4101).

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Elbs Persulfate Oxidation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Elbs in 1893.[1] It is the oxidative hydroxylation of aromatic compounds via the treatment of persulfate salt in the presence of alkali. Therefore, this reaction is generally known as the Elbs persulfate oxidation.[2] Occasionally, this reaction is also referred to as the Elbs alkaline persulfate oxidation,[3] Elbs oxidation,[4] Elbs peroxydisulfate oxidation,[5] Elbs persulphate oxidation,[6] Elbs reaction[2l,7] or Elbs-Seshadri persulfate oxidation.[8] In this oxidation, a hydroxyl group is mounted onto an aromatic ring predominantly in the *para*-position of a preexisting group;[3,5b] however, if the *para*-position has already been blocked, then hydroxylation at *ortho*-position occurs with much lower yield;[2s] no *meta*- hydroxylation has been reported yet.[5b] The persulfate is also called peroxydisulfate or peroxodisulfate.[5b] The persulfate salts suitable for this reaction include ammonium persulfate[2s] and potassium persulfate;[2s] all of them give similar results,[2s] indicating that the actual component in this oxidation is the persulfate ion. Although the yield of this oxidation is generally low, it normally affords a product with high purity.[2s] It has been reported that the yield can be improved by carrying out the oxidation in a solution saturated with NaCl or Na_2SO_4[2s] or when oxygen is purged off by nitrogen.[9] The aromatics suitable for this reaction include phenols, naphthols, coumarins, and flavones.[2s] It is assumed that this reaction occurs through a radical mechanism,[2h,2s,2w,3] because ammonium persulfate often initiates a radical reaction in aqueous solution; however, some evidence indicates that this oxidation predominantly involves the ionic nucleophilic substitution,[5] in which the electron-donating group facilitates the reaction and the electron-withdrawing group retards the reaction. In addition, it was found that the oxidation of phenol from the mixture of

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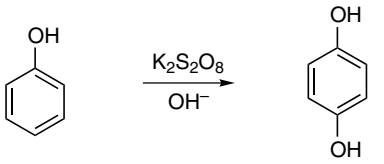
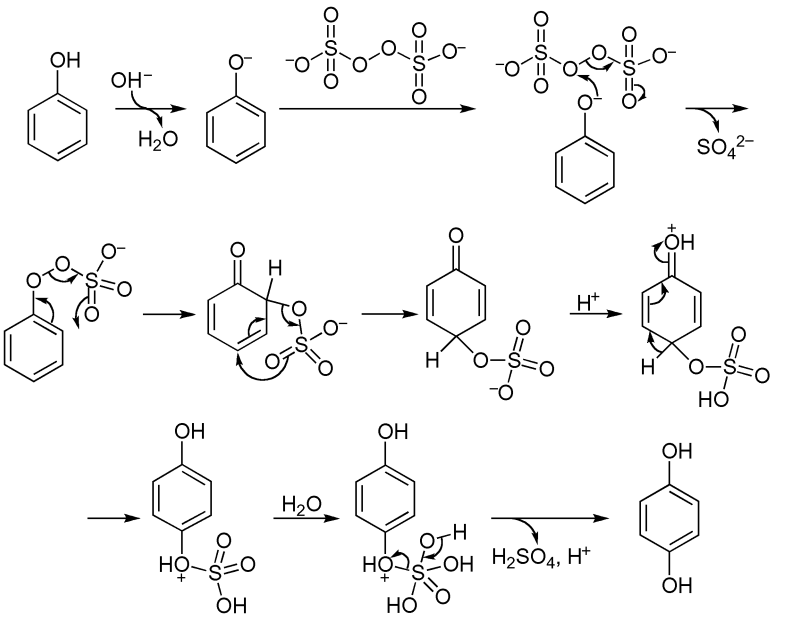
$KHSO_5$-$KHSO_4$-K_2SO_4 gives similar results to those from potassium persulfate.[2h] This reaction has been modified as oxidation from hydrogen peroxide in the presence of alkali.[10] Another modification is the application of a quaternary ammonium hydroxide as the base, such as tetramethylammonium hydroxide or tetraethylammonium hydroxide; the later gives a better yield.[9] Overall, this reaction is often used for the preparation of the aromatics with alkoxy groups by the alkylation after the hydroxylation.[2f,7a,11]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Because both radical and ionic mechanisms have been proposed for this reaction and no mechanistic detail has been given in the literature, a new ionic mechanism similar to the *Abnormal Claisen Rearrangement* is proposed and outlined here.



D. MODIFICATION

This reaction has been modified to oxidize the aromatics using hydrogen peroxide in the presence of an alkali.[2s] Other modifications include the application of tetramethylammonium hydroxide or tetraethylammonium hydroxide as a base during the oxidation.[9]

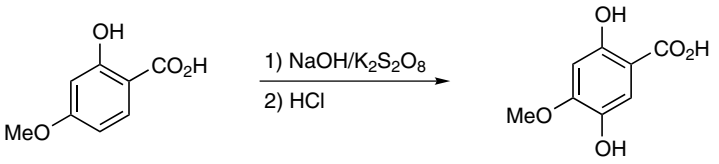
E. APPLICATIONS

This reaction has been widely applied in the preparation of hydroxyl aromatics and alkoxylated aromatics.

F. RELATED REACTIONS

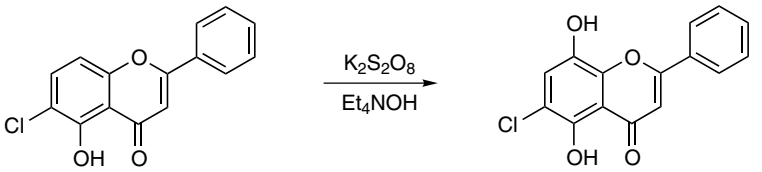
This reaction is related to the *Boyland-Sims Oxidation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2d.

To a solution of 10.0 g 2-hydroxy-4-methoxybenzoic acid (59.5 mmol) and 8.0 g NaOH (200 mmol) in 90 mL water at 10°C was added a solution of 17.0 g potassium persulfate (62.9 mmol) in 300 mL water over a 4-h period. The reaction mixture was then allowed to warm to room temperature and was stirred for 24 h, resulting in a purple solution. The mixture was neutralized with 1 N hydrochloric acid and extracted with ether (3 × 150 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$. Concentration and recrystallization from ethanol and water afforded 3.21 g 2,5-dihydroxy-4-methoxybenzoic acid as colorless rectangular rods, in a yield of 30%, m.p. 200–202°C (dec).



Reference 9.

To a 1-L, three-necked flask equipped with dropping funnel, stirrer, and fritted-glass gas dispersion rod was added 4.0 g 6-chloro-5-hydroxyflavone dissolved in 280 mL of a 10% aqueous solution of tetraethylammonium hydroxide and 9 mL pyridine. The resulting solution was purged with nitrogen for 1.5 h at 30–35°C. Then followed the dropwise addition to the stirred solution of 6.85 g potassium peroxydisulfate in 150 mL oxygen-free water over a 4-h period. An additional 9 mL pyridine was added after 2 h to maintain a homogeneous mixture. The reaction mixture was stirred for an additional 20 h at 30–35°C and filtered to give 1.25 g potassium salt of 6-chloro-5-hydroxyflavone; the filtrate was acidified with concentrated HCl to Congo red. The filtrate was neutralized with very dilute sodium hydroxide (∼1%), and the resulting 3.4 g of tan precipitate was collected by filtration. The

tan precipitate was dissolved in 40 mL cold 5% NaOH and filtered; ~200 mg of dark solid was collected and discarded. The filtrate was acidified to Congo red with concentrated HC1, and the resulting tan precipitate was collected and dried. The tan material then was placed in 80 mL hot water, and the pH was adjusted to 7.5–8.0 with 1% sodium hydroxide solution. The resulting mixture was stirred for 15 min and filtered, and the dark brown precipitate was discarded. To the filtrate was added 25 mL concentrated HC1, and the acidified filtrate was heated 2 h on a steam bath. 6-Chloro-5,8-dihydroxyflavone was obtained as a yellow powder and collected by filtration in a yield of 1.02 g (34% based on 2.84 g of starting material), m.p. 244–247°C. One crystallization from ethanol gave the pure substance (mp. 248–249°C). The filtrate from the original crude product isolation was acidified with 25 mL concentrated HCl and heated on a steam bath; and 360 mg crude substance was collected. Chromatography of the latter on a column of Florex/Celite (5:l wt.) with EtOAc as the solvent, gave an additional 30 mg 6-chloro-5,8-dihydroxyflavone, thus making the total yield 1.05 g.

Other references related to the Elbs persulfate oxidation are cited in the literature.[12]

H. REFERENCES

1. Elbs, K., *J. Prakt. Chem.,* **1893**, *48*, 179.
2. (a) Watson, K. G. and Serban, A., *Aust. J. Chem.,* **1995**, *48*, 1503. (b) Singh, U. S.; Scannell, R. T.; An, H. Y.; Carter, B. J. and Hecht, S. M., *J. Am. Chem. Soc.,* **1995**, *117*, 12691. (c) Ng, S. C.; Sim, K. Y. and Loh, S. E., *Bull. Singapore Nat. Inst. Chem.,* **1992**, *20*, 193. (d) Evans, J. C.; Klix, R. C. and Bach, R. D., *J. Org. Chem.,* **1988**, *53*, 5519. (e) Hurst, D. T., *Aust. J. Chem.,* **1983**, *36*, 1285. (f) Glennon, R. A.; Liebowitz, S. M. and Anderson, G. M., *J. Med. Chem.,* **1980**, *23*, 294. (g) Jerina, D.; Daly, J.; Landis, W.; Witkop, B. and Udenfriend, S., *J. Am. Chem. Soc.,* **1967**, *89*, 3347. (h) Kennedy, R. J. and Stock, A. M., *J. Org. Chem.,* **1960**, *25*, 1901. (i) Lele, S. S. and Sethna, S., *J. Org. Chem.,* **1958**, *23*, 1731. (j) Desai, N. J. and Sethna, S., *J. Org. Chem.,* **1957**, *22*, 388. (k) Naik, R. M. and Thakor, V. M., *J. Org. Chem.,* **1957**, *22*, 1696. (l) Kharasch, N.; Kalfayan, S. H. and Arterberry, J. D., *J. Org. Chem.,* **1956**, *21*, 925. (m) Rao, K. B. and Rao, N. V. S., *J. Sci. Ind. Res.,* **1956**, *15B*, 14. (n) Bacon, R. G. R., *Sci. Proc. Roy. Dublin Soc.*, **1956**, *27*, 177. (o) Rao, K. B. and Rao, N. V. S., *J. Sci. Ind. Res.,* **1955**, *14B*, 130. (p) Oliverio, A.; Schiavello, A. and Sebastiani, C., *Annali Chim. (Italy),* **1952**, *42*, 75. (q) Dalvi, V. J.; Desai, R. B. and Sethna, S., *J. Indian Chem. Soc.*, **1951**, *28*, 366. (r) Desai, R. B. and Sethna, S., *J. Indian Chem. Soc.*, **1951**, *28*, 213. (s) Sethna, S. M., *Chem. Rev.,* **1951**, *49*, 91. (t) Parikh, R. J. and Sethna, S., *J. Indian Chem. Soc.,* **1950**, *27*, 369. (u) Forrest, J. and Petrow, V., *J. Chem. Soc.,* **1950**, 2340. (v) Allen, C. F. H. and van Allan, J. A., *J. Org. Chem.,* **1949**, *14*, 798. (w) Baker, W. and Brown, N. C., *J. Chem. Soc.,* **1948**, 2303.
3. Dermer, O. C. and Edmison, M. T., *Chem. Rev.,* **1957**, *57*, 77.
4. (a) Behrman, E. J., *J. Org. Chem.,* **1992**, *57*, 2266. (b) Ogata, Y. and Akada, T., *Kagaku no Ryoiki*, **1971**, *25*, 489. (c) Rauhut, M. M.; Semsel, A. M. and Roberts, B. G., *J. Org. Chem.,* **1966**, *31*, 2431.
5. (a) Behrman, E. J., *J. Am. Chem. Soc.,* **1963**, *85*, 3478. (b) Behrman, E. J. and Walker, P. P., *J. Am. Chem. Soc.,* **1962**, *84*, 3454.
6. Naik, R. M. and Thakor, V. M., *J. Org. Chem.,* **1957**, *22*, 1630.
7. (a) Beutler, J. A.; Hamel, E.; Vlietinck, A. J.; Haemers, A.; Rajan, P.; Roitman, J. N.; Cardellina, J. H. and Boyd, M. R., *J. Med. Chem.,* **1998**, *41*, 2333. (b) Cass, M. W.; Rapaport, E. and White, E. H., *J. Am. Chem. Soc.,* **1972**, *94*, 3168.

8. Kane, V. V.; Kulkarni, A. B. and Shah, R. C., *J. Sci. Ind. Res.,* **1959**, *18B*, 75.
9. Looker, J. H.; Edman, J. R. and Kingsbury, C. A., *J. Org. Chem.,* **1984**, *49*, 645.
10. (a) Roberts, J. C., *Chem. Rev.,* **1961**, *61*, 592. (b) Naik, R. M. and Thakor, V. M., *J. Org. Chem.,* **1957**, *22*, 1626.
11. Bunnett, J. F. and Jenvey, J., *J. Org. Chem.,* **1996**, *61*, 8069.
12. (a) Behrman, E. J., *Org. React.,* **1988**, *35*, 421. (b) Parker, K. A.; Spero, D. M. and Koziski, K. A., *J. Org. Chem.,* **1987**, *52*, 183. (c) Feiring, A. E. and Sheppard, W. A., *J. Org. Chem.,* **1975**, *40*, 2543. (d) Becker, H.-D., *J. Org. Chem.,* **1969**, *34*, 2026. (e) Lee, J. B.; Uff, B. C., *Quart. Rev.,* **1967**, *21*, 453. (f) Ramirez, F.; Chen, E. H. and Dershowitz, S., *J. Am. Chem. Soc.,* **1959**, *81*, 4338. (g) Behrman, E. J. and Pitt, B. M., *J. Am. Chem. Soc.,* **1958**, *80*, 3717. (h) Dermer, O. C. and Edmison, M. T., *Chem. Rev.,* **1957**, *57*, 103. (i) Hull, R., *J. Chem. Soc.,* **1956**, 2033. (j) Phillips, J. P., *Chem. Rev.,* **1956**, *56*, 271. (k) Seikel, M. K.; Haines, A. L. and Thompson, H. D., *J. Am. Chem. Soc.,* **1955**, *77*, 1196. (l) Schock, R. U. and Tabern, D. L., *J. Org. Chem.,* **1951**, *16*, 1772. (m) Kolthoff, I. M. and Miller, I. K., *J. Am. Chem. Soc.,* **1951**, *73*, 3055. (n) Seshadri, T. R., *Proc. Indian Acad. Sci. Sect. A,* **1947**, *25A*, 417. (o) Baker, W.; Brown, N. C. and Scott, J. A., *J. Chem. Soc.,* **1939**, 1922.

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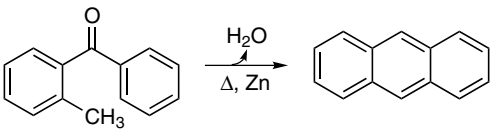
Elbs Reaction

A. GENERAL DESCRIPTION OF THE REACTION

Although the thermal decomposition of *o*-methylbenzophenones had been studied by Behr and van Dorp in 1873[1] and Ador and Rilliet in 1878,[2] it was Elbs who extensively investigated this reaction beginning in 1884.[3] Therefore, it is generally referred to as the Elbs reaction[4] or Elbs pyrolysis.[5] This reaction is the preparation of polyaromatics (especially anthracene) by intramolecular condensation of diaryl ketones containing a methyl or methylene substituent *ortho* to the carbonyl group. This reaction is usually carried out by means of high-temperature pyrolysis in the absence of a solvent or catalyst.[4a,4c] In some cases, it is accompanied by the elimination of substituents before the pyrolysis, such as fluoro,[4b,6] methyl,[4b] and methoxy.[4b] As a result, the Elbs reaction is not a perfect method for the preparation of polyaromatics with substituents,[7] although it is by far the most rapid and economical method for the synthesis of parent polyaromatics.[7] It has been proposed that hydrogen transfer is involved in this reaction.[4b] In addition, the yield of the Elbs reaction can be improved by removing the formed anthracene derivatives at intervals from the reaction zone.[8]

B. GENERAL REACTION SCHEME



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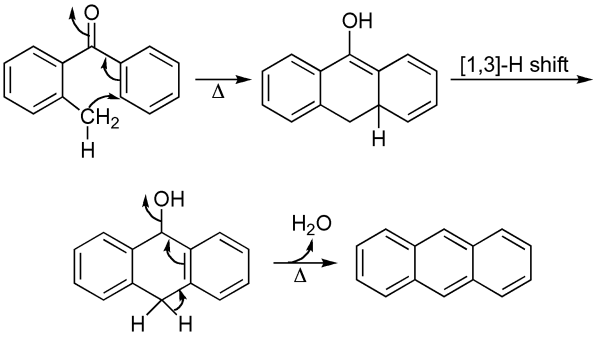
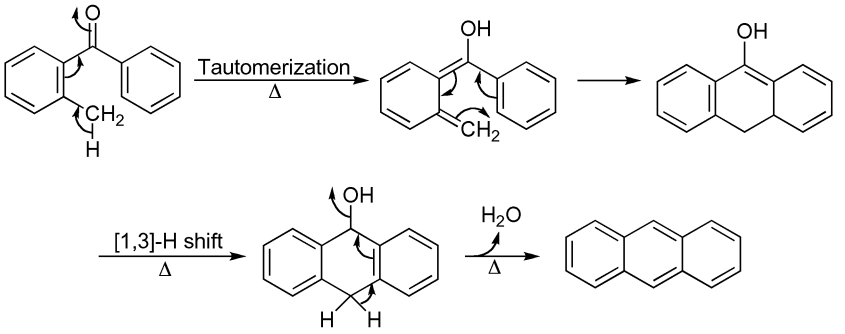
C. PROPOSED MECHANISMS

At least three different mechanisms have been proposed for this reaction. Displayed here are two of the most plausible mechanisms from Fieser and Cook.

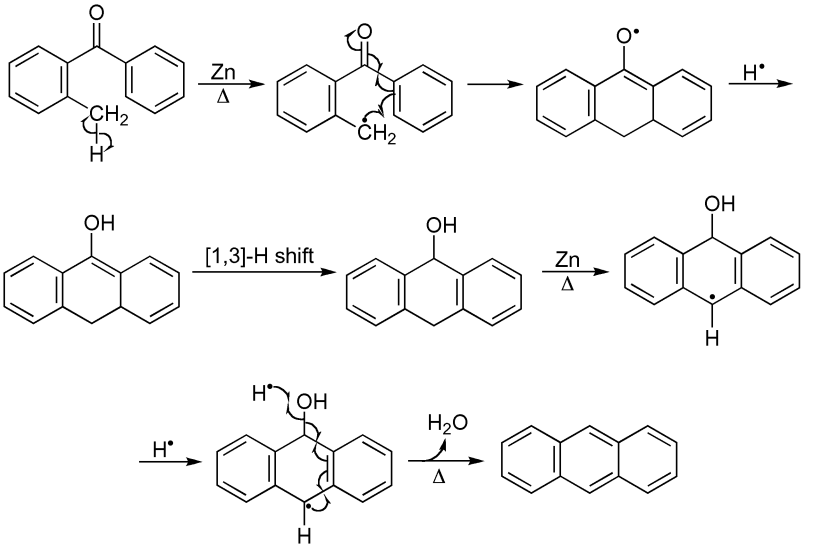
Fieser's mechanism.[9]



Cook's mechanism:[10]



In addition, an alternative mechanism is proposed here involving the generation of radical by high-temperature pyrolysis, as illustrated below.



D. MODIFICATION

N/A

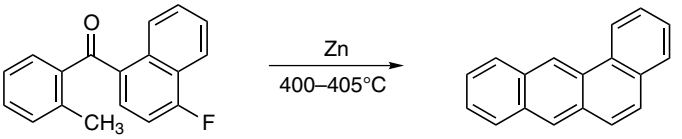
E. APPLICATIONS

This reaction has been widely used in the preparation of polyaromatic compounds.

F. RELATED REACTIONS

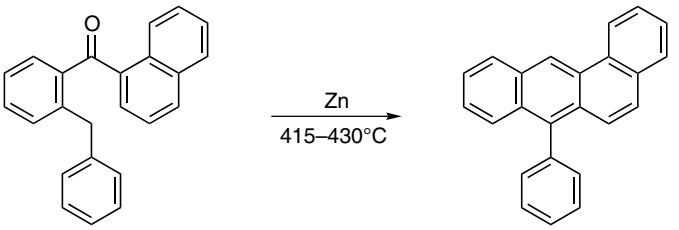
This reaction is related to the *Bradsher Cyclization*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4c.

A mixture of 4.0 g 1-fluoro-4-(*o*-toluoyl)naphthalene and 2.0 g zinc dust was heated at 400–405°C for 2 h and flash distilled under 1 mmHg. The distillate was brought to crystallization by treatment with a mixture of ethanol and benzene, and the product was chromatographed on alumina (benzene/petroleum ether, 3:1) to afford 1.1 g 1,2-benzanthracene, in a yield of 32%, m.p. 160°C.



Reference 4b.

A mixture of 3.0 g of 2-benzylphenyl 1-naphthyl ketone and 1.0 g powdered zinc was heated at 415–430°C for 3 hours in an atmosphere of nitrogen. The product was flash-distilled under vacuum and purified by chromatography on alumina with petroleum ether, and 0.9 g 7-phenylbenz[a]anthracene was obtained, in a yield of 32%, m.p. 182–183°C. No other products were isolated.

Other references related to the Elbs reaction are cited in the literature.[11]

H. REFERENCES

1. (a) Behr, A. and van Dorp, W. A., *Ber.,* **1873**, *6*, 753. (b) Behr, A. and van Dorp, W. A., *Ber.,* **1874**, *7*, 16.
2. Ador, E. and Rilliet, A., *Ber.,* **1878**, *11*, 399.
3. (a) Elbs, K. and Larsen, E., *Ber.,* **1884**, *17*, 2847. (b) Elbs, K. and Larsen, E., *Ber.,* **1885**, *18*, 1797. (c) Elbs, K. and Olberg, G., *Ber.,* **1886**, *19*, 408. (d) Elbs, K., *J. Prakt. Chem.,* **1886**, *33*, 180. (e) Elbs, K., *J. Prakt. Chem.,* **1887**, *35*, 465. (f) Elbs, K., *J. Prakt. Chem.,* **1890**, *41*, 1. (g) Elbs, K., *J. Prakt. Chem.,* **1890**, *41*, 121.
4. (a) Buu-Hoi, N. P.; Marie, C. and Jacquignon, P., *Bull. Soc. Chim. Fr.,* **1970**, 1873. (b) Vingiello, F. A. and Thornton, J. R., *J. Org. Chem.,* **1966**, *31*, 659. (c) Bergmann, E. D. and Blum, J., *J. Org. Chem.,* **1961**, *26*, 3214. (d) Vingiello, F. A.; Borkovec, A. and Zajac, W., *J. Am. Chem. Soc.,* **1958**, *80*, 1714. (e) Buu-Hoi, N. P.; Lavit, D. and Jacquignon, P., *Rec. Trav. Chim. Pays-Bas Belg.,* **1957**, *76*, 962. (f) Hurd, C. D. and Azorlosa, J., *J. Am. Chem. Soc.,* **1951**, *73*, 37.
5. Moriconi, E. J.; Rakoczy, B. and O'Connor, W. F., *J. Org. Chem.,* **1962**, *27*, 3618.
6. Bergmann, E. D. and Blum, J., *J. Org. Chem.,* **1960**, *25*, 474.
7. Vingiello, F. A. and Henson, P. D., *J. Org. Chem.,* **1965**, *30*, 2842.
8. (a) Morgan, G. T. and Coulson, E. A., *J. Chem. Soc.,* **1929**, 2551. (b) Morgan, G. T. and Coulson, E. A., *J. Chem. Soc.,* **1929**, 2203.
9. (a) Fieser, L. F., *Org. React.,* **1942**, *1*, 129. (b) Fieser, L. F. and Seligman, A. M., *J. Am. Chem. Soc.,* **1935**, *57*, 228. (c) Fieser, L. F. and Seligman, A. M., *J. Am. Chem. Soc.,* **1935**, *57*, 942. (d) Fieser, L. F. and Dietz, E. M., *Ber.,* **1929**, *62B*, 1827.
10. (a) Cook, J. W., *J. Chem. Soc.,* **1932**, 456. (b) Cook, J. W., *J. Chem. Soc.,* **1931**, 487.
11. (a) Newman, M. S. and Khanna, V. K., *J. Org. Chem.,* **1980**, *45*, 4507. (b) Buu-Hoï, N. P.; Marie, C. and Jacquignon, P., *J. Chem. Soc.,* **1971**, 431. (c) Mabille, P. and Buu-Hoï, N. P., *J. Org. Chem.,* **1960**, *25*, 1094. (d) Buu-Hoï, N. P. and Lavit, D., *Rec. Trav. Chim.,* **1957**, *76*, 419. (e) Badger, G. N. and Christie, B. J., *J. Chem. Soc.,* **1956**, 3435. (f) Carruthers, W., *J. Chem. Soc.,* **1956**, 603. (g) Lambert, P. and Martin, R. H., *Bull. Soc. Chim. Belg.,* **1952**, *61*, 124. (h) Bachmann, W. E., *J. Org. Chem.,* **1937**, *2*, 347. (i) Clar, E. and John, F., *Ber.,* **1930**, *63B*, 2967. (j) Clar, E., *Ber.,* **1929**, *62B*, 350. (k) Clar, E. and John, F., *Ber.,* **1929**, *62B*, 3021. (l) Elbs, K., *J. Prakt. Chem.,* **1891**, *44*, 467. (m) Elbs, K., *J. Prakt. Chem.,* **1890**, *41*, 7.

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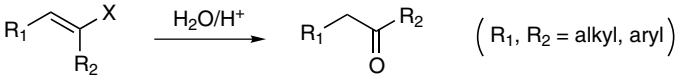
Eltekoff Hydrolysis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Eltekoff in 1873.[1] It is the hydrolysis of olefinic halides in aqueous alkali solution to generate glycol that further forms carbonyl compounds (aldehyde or ketone). In the original procedure,[2] Eltekoff heated the olefinic halides with lead oxide and water to 140–150°C and obtained acetaldehyde and ethylene glycol from ethylene bromide (or chloride), acetone and propionaldehyde from the propylene halides, etc. At the same time, Eltekoff found that the yield of the carbonyl compound was directly related to the reaction time—that is, the longer the halide was heated with lead oxide and water, the higher the yield of carbonyl compounds and the lower the amount of glycol formed.[3] This result indicates that the carbonyl compounds were generated from the dehydration of glycols in the slightly acidic solution. However, it was found that lead oxide or a high temperature was unnecessary for this reaction,[4] and olefinic halides could be easily hydrolyzed to glycols[3,5] but not directly to carbonyl compounds when treated with the aqueous alkali solution. If the alkali is omitted, then the glycols might rearrange into carbonyl compounds[6] (a kind of *Pinacol Rearrangement* in a slightly acidic solution). It is assumed that this reaction under acidic condition occurs via an $A_{SE}2$ mechanism.[7] This reaction has become one of the most convenient methods for the production of ketones.[3]

B. GENERAL REACTION SCHEME



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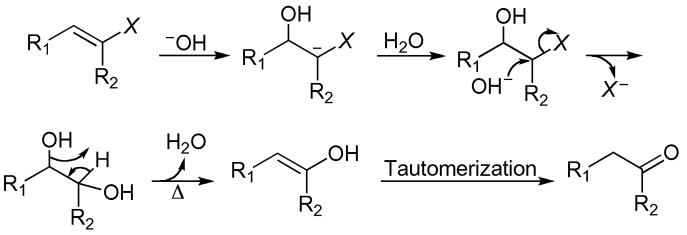
C. PROPOSED MECHANISMS

In slightly acidic conditions, the hydration of olefin gives halo-alcohol, which decomposes to carbonyl compound, as outlined below.[7]



D. MODIFICATION

This reaction has been modified for treating vicinal dihalides with an aqueous alkali solution to produce glycols and carbonyl compounds.

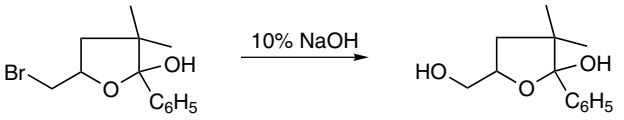
E. APPLICATIONS

This reaction has been used to prepare glycols, aldehydes, and ketones.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 6a.

A mixture of 1.5 g 5-bromomethyl-3,3-dimethyl-2-phenyltetrahydro-2-furanol ("bromohydrin"), 2.5 mL 10% NaOH, and 50 mL dioxane was stirred and refluxed for 4 h and then poured into 1 L water. The mixture was extracted with four 200-mL portions of ether. The organic layers were combined and washed with 100 mL water (five times) and 40 mL brine (three times). Removal of the ether at room temperature left 1.22 g orange oil, which was chromatogrphed from petroleum ether on 37.0 g alumina. Elution with petroleum ether and 10:1 petroleum ether/ether gave 0.75 g of a white solid (the starting material) and 0.36 g 2-hydroxy-5-hydroxymethyl-3,3-dimethyl-2-phenyltetrahydrofuran as a white solid, in a yield of 30%.

Other references related to the Eltekoff hydrolysis are cited in the literature.[8]

H. REFERENCES

1. Eltekoff, A., *Ber.,* **1873**, *6*, 558.
2. (a) Eltekoff, A., *Ber.,* **1878**, *11*, 989. (b) Eltekoff, A., *Ber.,* **1878**, *11*, 990. (c) Eltekoff, A., *J. Russ. Phys. Chem. Soc.,* **1878**, *10*, 215.
3. Suter, C. M. and Zook, H. D., *J. Am. Chem. Soc.,* **1944**, *66*, 738.
4. Whitmore, F. C. and Evers, W. L., *J. Am. Chem. Soc.,* **1933**, *55*, 812.
5. Dolgorukova-Dobryanska, N. I., *J. Russ. Phys. Chem. Soc.,* **1925**, *57*, 283 [*Chem. Abstr.,* **1926**, *20*, 2311].
6. (a) Holum, J. R.; Jorenby, D. and Mattison, P., *J. Org. Chem.,* **1964**, *29*, 769. (b) Evers, W. L.; Rothrock, H. S.; Woodburn, H. M.; Stahly, E. E. and Whitmore, F. C., *J. Am. Chem. Soc.,* **1933**, *55*, 1136. (c) Krassuski, K., *J. Russ. Phys. Chem. Soc.,* **1902**, *33*, 791. (d) Froebe, W. and Hochstetter, A., *Monatsh.,* **1902**, *23*, 1075. (e) Ipatieff, W., *J. Prakt. Chem.,* **1891**, *53*, 257.
7. Chwang, W. K.; Knittel, P.; Koshy, K. M. and Tidwell, T. T., *J. Am. Chem. Soc.,* **1977**, *99*, 3395.
8. (a) Suter, C. M. and Milne, H. B., *J. Am. Chem. Soc.,* **1940**, *62*, 3473. (b) Bartlett, P. D. and Bavley, A., *J. Am. Chem. Soc.,* **1938**, *60*, 2416. (c) Bartlett, P. D. and Pöckel, I., *J. Am. Chem. Soc.,* **1937**, *59*, 820. (d) Michael, A., *J. Am. Chem. Soc.,* **1920**, *42*, 787.

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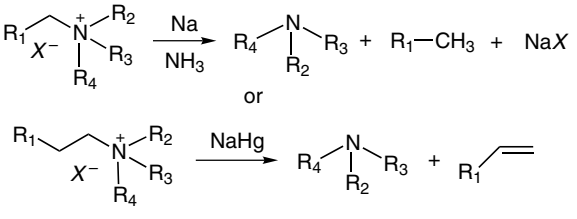
Emde Degradation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Emde in 1906.[1] It is the reductive cleavage of quaternary ammonium salt of nitrogen-containing compounds (especially in heterocyclic forms) by means of the treatment with an excess of sodium amalgam in an alcoholic or aqueous solution.[2] In fact, this reaction is the modification of *Hofmann Degradation*; therefore, it is sometimes known as the Hofmann and Emde degradation[3] or the Emde-Birch fission.[4] However, this reaction is generally referred to as the Emde degradation[5,6] or Emde reduction,[5a,5b,5e,5f,7] and the corresponding products are called the Emde products.[5d,5e] The order of groups to be cleaved was found to be: $RC(O)CH_2$, $PhCH{=}CHCH_2$ > benzyl > allyl > phenyl > methyl.[2] It was found that the position of the scission for the nitrogenous heterocyclic ring depended on the reaction condition,[7c] affording one product[7f] or two products.[5a] This reaction has been modified to treat the quaternary ammonium salt with sodium/dry ammonia,[5f,7g] sodium/ammonia/0.5% water,[8] or by electrolytic reduction in dry ammonia (or with 0.5% water present)[9] or to degrade the ammonium salt by photo irradiation.[10]

B. GENERAL REACTION SCHEME



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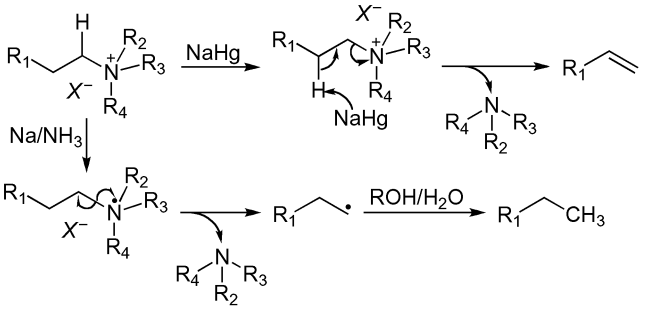
C. PROPOSED MECHANISMS

Because not much mechanistic information is available for this reaction, a tentative mechanism is outlined here to indicate the formation of different types of products (e.g., alkenes and alkanes).



D. MODIFICATION

This reaction has been modified to occur in liquid ammonia by treatment of sodium alone.[5f,7g] In addition, a photo-Edme degradation has been developed.[10]

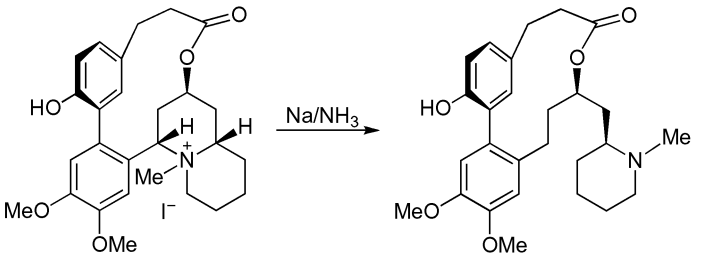
E. APPLICATIONS

This reaction has been successfully applied in the degradation of nitrogenous heterocyclic compounds and the elucidation of many alkaloids structures.

F. RELATED REACTIONS

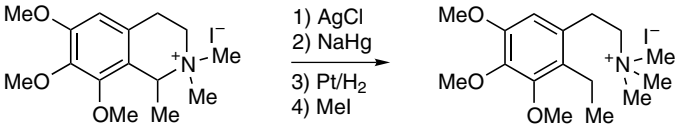
This reaction is related to the *Hofmann Degradation* and *von Braun Degradation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 5b.

To a solution of 2.05 g decinine methiodide (3.55 mmol) in 175 mL liquid ammonia was added 0.29 g sodium. When the blue color had disappeared, the ammonia was allowed to evaporate. The residue was dissolved in water, the pH was adjusted to 10, and the mixture was extracted with chloroform. The chloroform extract was dried and diluted with 95% ethanol, and the volume was reduced until crystallization ensued. A yield of 1.19 g *N*-methyldihydrodecinine was obtained, in a yield of 74%, m.p. 230–231°C.



Reference 7d.

To 10 mL hot water containing 460 mg *O*,*N*-dimethyl-DL-anhalonidine methiodide was added 0.5 g freshly precipitated silver chloride (from 0.5 g silver nitrate). After being shaken in the dark for 30 min, the mixture was filtered, and 20 g 3% sodium amalgam was added. After being heats on a steam bath for 18 h, the oil floating on the surface was extracted with ether. The dried ether extract was evaporated, and the residue was dissolved in 30 mL ethanol. Then 40 mg of platinum oxide was added, and the mixture was hydrogenated for 12 h at 30 psi. The residue obtained on evaporation of the filtered solution was dissolved in 30 mL methanol, and 0.3 mL methyl iodide was added. After standing overnight, the solution was evaporated to small bulk, and EtOAc was added when colorless needles of 2-ethyl-3,4,5-trimethoxy-phenylethyltrimethylammonium iodide was obtained (84 mg), m.p., 216–218°C. Fine needles (m.p. 218–219°C) were obtained on recrystallization from ethanol.

Other references related to the Emde degradation are cited in the literature.[11]

H. REFERENCES

1. Emde, H., *Arch. Pharm.,* **1906**, *244*, 289.
2. Grovenstein, E.; Blanchard, E. P.; Gordon, D. A. Stevenson, R. W., *J. Am. Chem. Soc.,* **1959**, *81*, 4842.
3. (a) Cannon, J. G.; Khonje, P. R.; Long, J. P., *J. Med. Chem.,* **1975**, *18*, 110. (b) Cannon, J. G.; Borgman, R. J.; Aleem, M. A. and Long, J. P., *J. Med. Chem.,* **1973**, *16*, 219. (c) Fales, H. M. and Wildman, W. C., *J. Am. Chem. Soc.,* **1956**, *78*, 4151. (d) Thyagarajan, B. S., *Chem. Rev.,* **1954**, *54* 1019. (e) Folkers, K.; Koniuszy, F. and Shavel, J., *J. Am. Chem. Soc.,* **1951**, *73*, 589. (f) Folkers, K.; Koniuszy, F. and Shavel, J., *J. Am. Chem. Soc.,* **1942**, *64*, 2146.
4. Floss, H. G.; Hornemann, U.; Schilling, N.; Kelley, K.; Groeger, D. and Erge, D., *J. Am. Chem. Soc.,* **1968**, *90*, 6500.
5. (a) Parry, R. J.; Chang, M. N. T.; Schwab, J. M. and Foxman, B. M., *J. Am. Chem. Soc.,* **1980**, *100*, 1099. (b) Ferris, J. P.; Boyce, C. B. and Briner, R. C., *J. Am. Chem. Soc.,* **1971**, *93*, 2942. (c) Ferris, J. P.; Boyce, C. B.; Briner, R. C.; Weiss, U.; Qureshi, I. H. and Sharpless, N. E., *J. Am. Chem. Soc.,* **1971**, *93*, 2963. (d) Bartlett, M. F.; Korzun, B.; Sklar, R.; Smith, A. F. and Taylor, W. I., *J. Org. Chem.,* **1963**, *28*, 1445. (e) Boekelheide, V.; Ceder, O.; Matsume, M. and Zürcher, A., *J. Am. Chem. Soc.,* **1959**, *81*, 2256. (f) Conroy, H.; Brook, P. R.; Rout, M. K. and Silverman, N., *J. Am. Chem. Soc.,* **1958**, *80*, 5178. (g) Witkop, B. and Goodwin, S., *J. Am. Chem. Soc.,*

1953, *75*, 3371. (h) Mosettig, E. and Krueger, J. W., *J. Org. Chem.,* **1939**, *4*, 317. (i) Mosettig, E. and Krueger, J. W., *J. Am. Chem. Soc.,* **1936**, *58*, 1311. (j) Mosettig, E. and Robinson, R. A., *J. Am. Chem. Soc.,* **1935**, *57*, 902.

6. (a) Simanek, V.; Hruban, L.; Preininger, V.; Nemeckova, A. and Klasek, A., *Coll. Czech. Chem. Commun.,* **1975**, *40*, 705. (b) Simanek, V.; Klasek, A.; Hruban, L.; Preininger, V. and Santavy, F., *Tetrahedron Lett*., **1974**, 2171. (c) Simanek, V.; Klasek, A. and Santavy, F., *Tetrahedron Lett*., **1973**, 1779. (d) Sugasawa, S. and Matsuo, H., *Chem. Pharm. Bull.,* **1958**, *6*, 601. (e) Irie, H.; Tsuda, Y. and Uyeo, S., *J. Chem. Soc.,* **1959**, 1446. (f) Sugasawa, S. and Matsuo, H., *Chem. Pharm. Bull.,* **1956**, *4*, 142.
7. (a) Leete, E. and Bodem, G. B., *J. Am. Chem. Soc.,* **1976**, *98*, 6321. (b) Kapadia, G. J.; Rao, G. S.; Leete, E.; Fayez, M. B. E.; Vaishnav, Y. N. and Fales, H. M., *J. Am. Chem. Soc.,* **1970**, *92*, 6943. (c) Robinson, B., *Chem. Rev.,* **1969**, *69*, 785. (d) Leete, E., *J. Am. Chem. Soc.,* **1966**, *88*, 4218. (e) Leete, E.; Ahmad, A. and Kompis, I., *J. Am. Chem. Soc.,* **1965**, *87*, 4168. (f) Leete, E. and Friedman, A. R., *J. Am. Chem. Soc.,* **1964**, *86*, 1224. (g) Leete, E., *J. Am. Chem. Soc.,* **1960**, *82*, 6338.
8. Wrobél, J. T.; Bién, A. S. and Pazdo, K. M., *Chem. Ind. (London),* **1966**, 1759.
9. Wrobél, J. T.; Pazdo, K. M. and Bién, A. S., *Chem. Ind. (London),* **1966**, 1760.
10. Partali, V.; Jolidon, S. and Hansen, H.-J., *Helv. Chim. Acta,* **1985**, *68*, 1952.
11. (a) Baudoin, O.; Guenard, D. and Gueritte, F., *Mini-Rev. Org. Chem.,* **2004**, *1*, 333. (b) Lévy, J.; Soufyane, M.; Mirand, C.; Doe de Maindreville, M. and Royer, D., *Tetrahedron: Asymmetry,* **1997**, *8*, 4127. (c) Gaskell, A. J. and Joule, J. A., *Tetrahedron,* **1968**, *24*, 5115. (d) Dolby, L. J. and Gribble, G. W., *J. Org. Chem.,* **1967**, *32*, 1391. (e) Kutney, J. P.; Abdurahman, N.; LeQuesne, P.; Piers, E. and Vlattas, I., *J. Am. Chem. Soc.,* **1966**, *88*, 3656. (f) Herbst, D.; Rees, R.; Hughes, G. A. and Smith, H., *J. Med. Chem.,* **1966**, *9*, 864. (g) Harley-Mason, J.; Rahman, A. and Beisler, J. A., *J. Chem. Soc., Chem. Commun.,* **1966**, 743. (h) Wenkert, E.; Garrett, S. and Dove, K. G., *Can. J. Chem.,* **1964**, *42*, 482. (i) Hesse, M.; von Philipsborn, W.; Schumann, D.; Spiteller, G.; Spiteller-Friedmann, M.; Taylor, W. I.; Schmid, H. and Karrer, P., *Helv. Chim. Acta,* **1964**, *47*, 878. (j) Mishima, H.; Kurabayashi, M. and Iwai, I., *J. Org. Chem.,* **1963**, *28*, 2621. (k) Saito, S. and May, E. L., *J. Org. Chem.,* **1962**, *27*, 1087. (l) Leete, E., *Chem. Ind. (London),* **1960**, 692. (m) Humber, L. G.; Kondo, H.; Kotera, K.; Takagi, S.; Takeda, K.; Taylor, W. I.; Thomas, B. R.; Tsuda, Y.; Tsuka, K.; Uyeo, S.; Yajima, H. and Yanaihara, N., *J. Chem. Soc.,* **1954**, 4622. (n) Birch, A., *Org. React.,* **1953**, *7*, 143. (o) Fuson, R. C.; Jackson, H. L. and Grieshaber, E. W., *J. Org. Chem.,* **1952**, *7*, 1529. (p) Wieland, H. and Weisskopf, W., *Ann.,* **1943**, *555*, 1. (q) Wieland, H. and Müller, O., *Ann.,* **1940**, *545*, 66. (r) Emde, H. and Kull, H., *Arch. Pharm.,* **1934**, *272*, 469. (s) Emde, H., *Helv. Chim. Acta,* **1932**, *15*, 1330. (t) Robinson, R. and Sugasawa, S., *J. Chem. Soc.,* **1932**, 789. (u) Schöpf, C. and Braun, W., *Ann.,* **1928**, *465*, 138. (v) Faltis, F. and Krausz, M., *Monatsh. Chem.,* **1922**, *42*, 377. (w) Emde, H., *Ann.,* **1912**, *391*, 88. (x) Emde, H., *Ber.,* **1909**, *42*, 2590.

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Emmert Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Emmert and Asendorf in 1939.[1] It is the formation of pyridylalkyl or pyridyldialkyl carbinols by condensation of pyridine (or its analogues) with aldehydes or ketones in the presence of aluminum or magnesium amalgam. Therefore, it is generally known as the Emmert reaction.[2] Pyridine and its analogues are assumed nonreactive toward alkylation or acylation, due to the C=N bond in pyridine ring.[3] However, the alkylation of pyridine can occur when aldehyes or ketones are treated with aluminum or magnesium, mercuric chloride, and iodine[4] or treated with very small amounts of mercuric chloride with few drops of mercury.[4] It was found that other metals with low reduction potentials do not work in this reaction, and the metals of high reduction potentials and poor coordinating power do not offer the alkylation product but the pinacols of ketones.[2e] It is magnesium or aluminum that combines both characters of high reduction potential (2.4 V and 1.7 V, respectively) and coordinating power functions well for this reaction.[2e] Beryllium (1.69 V) functions similarly, but gives very poor yields.[2e] In this reaction, pyridine might react with dialkyl, diaryl, alkyl aryl, and cyclic ketones, while steric effects from *ortho* substituent on pyridine might inhibit the reaction between such pyridine and aryl ketones.[2e] Although the exact function of the metal is not quite clear,[2f] it is assumed that the metal supplies two electrons to the carbonyl compound, resulting in a carbanion that attacks the pyridine ring.[2e] Therefore, the electron-donating group on ketones can increase the negativity of a carbanion to facilitate the addition to the pyridine ring; likewise, ketone gives a better yield than aldehyde as of the hyperconjugation of alkyl group on ketone.[2e] In this reaction, moisture will inhibit the reaction, and solvents such as carboxylic acids and

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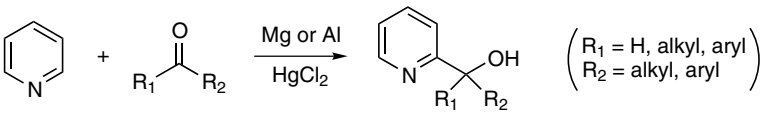
alcohols that donate a proton through ionization are not feasible for this reaction either.[2e] Under reductive conditions, no hydrogenated pyridines are formed, indicating that air is the oxidizing agent.[2e] Other nitrogenous heterocycles, including picolines, can be similarly alkylated.[2f] Although both magnesium and aluminum work for this reaction, there exist some subtle differences between magnesium and aluminum. For example, when magnesium is used in the absence of mercuric chloride, the reaction is very slow and any variation of the reactants ratio gives a low yield of the desired product;[4] however, when aluminum is used, increasing the proportions of pyridine or aluminum increases the yields of the desired product.[4] In addition, aluminum may give 4-alkylated pyridyl carbinol, as larger aluminum might form a transannular bridge between the nitrogen atom and the 4-position of pyridine.[2e]

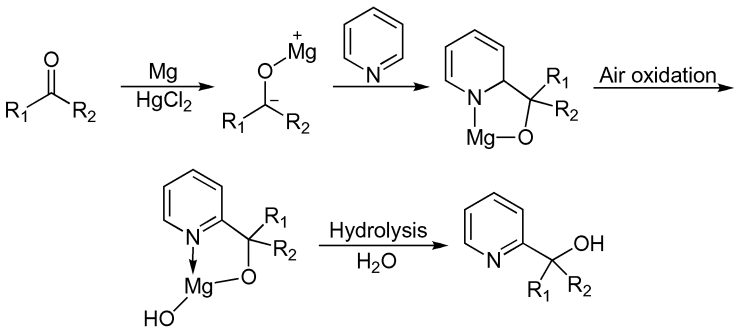
Moreover, magnesium and aluminum can also be applied for the acylation of pyridine derivatives with acid esters via a similar mechanism, involving a two-electron transfer process, with the activity order of Al > Mg > Be.[5] Other acid derivatives (e.g., *N*,*N*-dialkylamides and nitriles) also react with pyridines in lower yields; however, the low-boiling acid derivatives may give low yields too, as the reaction is normally carried out at 100°C.[5] In general, aromatic esters afford higher yields than aliphatic esters, because the carbanion intermediates can be stabilized via resonance.[5]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is assumed that the metal donates two electrons at a time to form the carbanion, which adds to pyridine ring,[2e] as illustrated by the reaction of Mg.



D. MODIFICATION

This reaction has been modified to form acylated pyridine derivatives.[5]

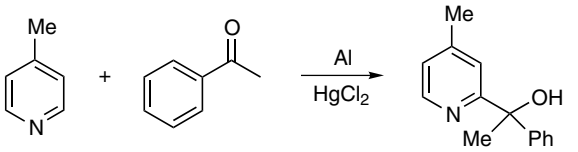
E. APPLICATIONS

This reaction is very useful in the preparation of 2-alkylated or 2-acylated pyridine derivatives as well as picoline and quinoline derivatives.

F. RELATED REACTIONS

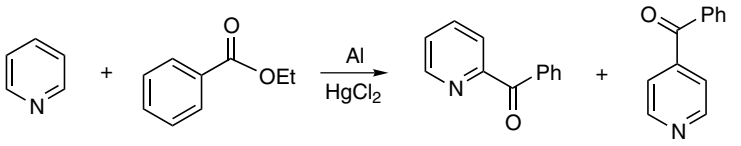
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 2e.

Granular (30-mesh) aluminum (27 g, 1 mol), 0.5 g mercuric chloride, and a few drops of mercury were preheated together for 30 min at 100°C in a 1-L, three-necked flask fitted with a dropping funnel, condenser, and mercury sealed stirrer. A mixture of 25 g each 4-picoline and acetophenone was added in one portion and stirred until the reaction began. The beginning of the reaction was accompanied by an evolution of heat and a color change to dark green. The remaining picoline (290 g, 3.5 mol total) was added in one portion, and 185 g acetophenone (1.75 mol total) was added dropwise under vigorous stirring within 5.5 h. The temperature was kept at 130°C during the addition with the aid of a heating mantle. After that, the mixture was stirred for additional 3.5 h at 130°C, and then cooled and decomposed by being poured into 1 L 3 N NaOH solution. The separating oil was extracted successively with 200-mL portions of 6 N HCl. The acid extract was made basic with a NaOH solution. The organic layer was dried over $CaSO_4$ and distilled. The fraction boiling at 130–135°C (0.8 mmHg) was collected in a total amount of 85 g and in a yield of 30%; it was recrystallized from petroleum ether to yield a colorless solid, m.p. 69.5 −70°C.



Reference 5.

Granular (30-mesh) aluminum (27 g, 1 mol), 5 g mercuric chloride, and several drops of mercury were preheated together for 2 h at 100°C in a 1-L, three-necked flask fitted with a dropping funnel, condenser, and stirrer. Ethyl benzoate (25 g) and 25 g pyridine were added to the metallic mixture to initiate the reaction. A green color developed immediately and turned to a muddy brown within a few minutes. Then 250 g pyridine (3.5 mol total) was added dropwise over a period of 2 h during refluxing. At the end of this addition

the reaction mixture was dark colored. Ethyl benzoate (425 g, 3.0 mol total) was added dropwise to the reaction mixture over a period of 24 h at which time all of the aluminum metal had reacted. The cooled reaction mixture was stripped of unreacted pyridine using an aspirator and mild heating, and then the remaining viscous oil (350–400 mL) was poured into 1500 mL petroleum ether (90–100°C). This addition resulted in the precipitation of a brown solid (286 g), which could be filtered, dried, and allowed to stand in the presence of air without any noticeable decomposition. This complex was hydrolyzed with 6 N HCl, the oil layer was distilled under vacuum through a 30-cm glass helix–packed column, and the following fractions were collected: 2-benzoylpyridine (87.0 g, 32.5%, 124–126°C at 1.5 mmHg), 4-benzoylpyridine (19.4 g, 7.1%, 126–146°C at 1.9 mmHg, m.p.,72.5–73°C), and mixture of benzil and benzoin (26.7 g, 12.7%).

Other references related to the Emmert reaction are cited in the literature.[6]

H. REFERENCES

1. Emmert, B. and Asendorf, E., *Ber.,* **1939**, *72*, 1188.
2. (a) Sheinkman, A. K.; Nelin, E. N.; Luk'yanenko, L. V. and Klyuev, N. A., *Zh. Org. Khim.,* **1978**, *14*, 2542. (b) Tschesche, R. and Fuehrer, W., *Chem. Ber.,* **1978**, *111*, 3502. (c) Sheinkman, A. K.; Potashnikova, S. G. and Baranov, S. N., *Zh. Org. Khim.,* **1971**, *7*, 1550. (d) Russell, C. A.; Crawforth, C. E. and Meth-Cohn, O., *J. Chem. Soc. D,* **1970**, 1406. (e) Bachman, G. B.; Hamer, M.; Dunning, E. and Schisla, R. M., *J. Org. Chem.,* **1957**, *22*, 1296. (f) Lochte, H. L.; Kruse, P. F. and Wheeler, E. N., *J. Am. Chem. Soc.,* **1953**, *75*, 4477.
3. Abramovitch, R. A.; Smith, E. M.; Knaus, E. E. and Saha, M., *J. Org. Chem.,* **1972**, *37*, 1690.
4. Tilford, C. H.; Shelton, R. S. and Campen, M. G. V., *J. Am. Chem. Soc.,* **1948**, *70*, 4001.
5. Bachman, G. B. and Schisla, R. M., *J. Org. Chem.,* **1957**, *22*, 1302.
6. (a) Chiron, J. and Galy, J.-P., *Synthesis*, **2004**, 313. (b) Lawrence, S. A., *Amines: Synthesis, Properties and Applications*, Cambridge University Press, Cambridge **2004**. (c) Noyce, D. S.; Virgilio, J. A. and Bartman, B., *J. Org. Chem.,* **1973**, *38*, 2657. (d) Abramovitch, R. A.; Coutts, R. T. and Smith, E. M., *J. Org. Chem.,* **1972**, *37*, 3584. (e) Abramovitch, R. and Vinutha, A. R., *J. Chem. Soc*. **1969**, *C*, 2104. (f) Abramovitch, R. A. and Saha, J. G., *Adv. Heterocycl. Chem.,* **1966**, *6*, 229. (g) McCarty, F. J.; Tilford, C. H. and Campen, M. G. V., *J. Am. Chem. Soc.,* **1957**, *79*, 472. (h) Tilford, C. H. and Campen, M. G. V., *J. Am. Chem. Soc.,* **1954**, *76*, 2431. (i) Lochte, H. L.; Kruse, P. F. and Wheeler, E. N., *J. Am. Chem. Soc.,* **1953**, *75*, 4472. (j) Nunn, A. J. and Schofield, K., *J. Chem. Soc.,* **1952**, 586. (k) Bachman, G. B. and Micucci, D. D., *J. Am. Chem. Soc.,* **1948**, *70*, 2381. (l) Lochte, H. L.; Thomas, E. D. and Truitt, P., *J. Am. Chem. Soc.,* **1944**, *66*, 550. (m) Emmert, B. and Pirot, E., *Ber.,* **1941**, *74*, 714.

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Erlenmeyer-Plöchl Azlactone Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

The condensation between aromatic aldehydes and hippuric acid in the presence of acetic anhydride was initially reported by Plöchl in 1883[1] and was studied extensively by Erlenmeyer in 1892.[2] In addition, Erlenmeyer corrected the original assigned structure of a product containing a three-membered ring and coined the word *azlactone* for the formed product.[3] Therefore, this reaction is known as the Plöchl-Erlenmeyer reaction,[4] Erlenmeyer-Plöchl reaction,[5] Erlenmeyer-Plöchl synthesis,[6] Erlenmeyer-Plöchl oxazolone synthesis,[7] Erlenmeyer-Plöchl method,[8] Erlenmeyer synthesis,[9] and Erlenmeyer azlactone synthesis.[10] In detail, the Erlenmeyer-Plöchl azlactone synthesis is the preparation of azlactones (also called oxazolones[11]) in a *Z* configuration (originally assigned to the *E* configuration)[10b] by condensation of aromatic aldehydes with hippuric acid (the benzoyl glycine derivatives[12]) in the presence of acetic anhydride. The formed azlactones have found many applications in organic synthesis, especially for α-ketos, α-amino acids[2c,2d] and peptides.[13] This reaction normally gives one product: the thermodynamically stable one;[10b] however, two products are also formed in some cases.[7] In addition, transacylation often occurs in this reaction, especially when the reaction mixture is refluxed.[5b,6] Thus the yields of desired products are not very high, and extensive purification of crude azlactones should be avoided to generate higher yields.[5b]

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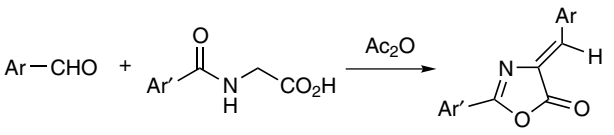
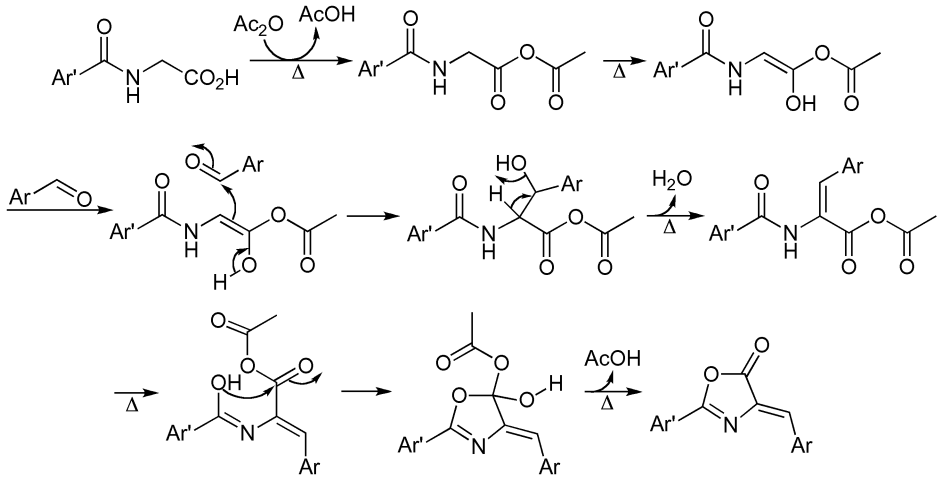
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified to occur in polyphosphoric acid (PPA) to form the azlactones in the *E* configuration.[10b]

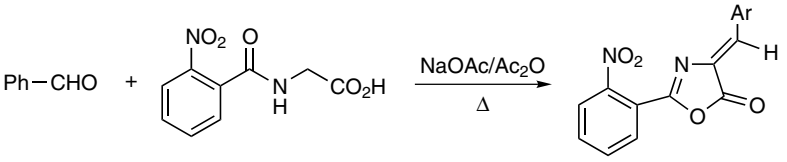
E. APPLICATIONS

This reaction has been used for the synthesis of α-keto, α-amino acids,[2c,2d] and peptides.[13]

F. RELATED REACTIONS

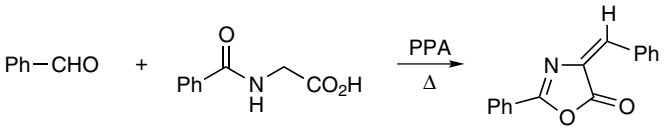
This reaction is related to the *Bergmann-Stern Azlactone Synthesis*, *Claisen Condensation*, and *Perkin Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4b.

To a flask equipped with a condenser, were added 1.07 mmol *ortho*-nitrobenzoylglycine, 0.96 mmol benzaldehyde, 0.96 mmol fused NaOAc, and 3 mmol acetic anhydride. The mixture was heated in a boiling water bath for 1 h. After cooling, 2 mL 95% ethanol was added to the flask, and the mixture was left at 5°C for 4–6 h. The precipitate formed was filtered and washed with cold ethanol, then with boiling water, and again with cold ethanol. The dried precipitate was recrystallized to a constant melting point in acetic acid to give 57% product as yellow needles, m.p. 210°C.



Reference 10b.

To a sample of polyphosphoric acid prepared from 20 mL phosphoric acid and 32 g phosphoric anhydride was added 5.3 g benzaldehyde (50 mmol) and 8.95 g hippuric acid (50 mmol). The mixture was then heated on a steam bath (80–95°C) for 90 min and then poured into water. The resultant solid product was collected and repeatedly washed with water. Finally, 12.0 g 2-phenyl-4-phenylmethylene-2-oxazolin-5-one was recrystallized from a mixture of benzene-Skellysolve B, in a yield of 90%, m.p. 146–147°C.

Other references related to the Erlenmeyer-Plöchel azlactone synthesis are cited in the literature.[14]

H. REFERENCES

1. Plöchl, J., *Ber.,* **1883**, *16*, 2815.
2. (a) Erlenmeyer, E., *Ann.,* **1892**, *271*, 167. (b) Erlenmeyer, E., *Ann.,* **1893**, *275*, 1. (c) Erlenmeyer, E., *Ber.,* **1900**, *33*, 2036. (d) Erlenmeyer, E., *Ber.,* **1902**, *35*, 243. (e) Erlenmeyer, E., *Ann.,* **1904**, *337*, 265.
3. Cooper, A. J. L.; Ginos, J. Z. and Meister, A., *Chem. Rev.,* **1983**, *83*, 321.
4. (a) Ivanova, G., *Tetrahedron*, **1992**, *48*, 177. (b) Bassi, D. A.; Deulofeu, V. and Ortega, F. A. F., *J. Am. Chem. Soc.,* **1953**, *75*, 171.
5. (a) Zavyalov, S. I.; Dorofeyeva, O. V. and Rumyantseva, Y. Y., *Khim.-Farmatsevticheskii Zh.,* **1993**, *27*, 76. (b) Bennett, E. L. and Niemann, C., *J. Am. Chem. Soc.,* **1950**, *72*, 1803.
6. Bennett, E. L. and Hoerger, E., *J. Am. Chem. Soc.,* **1952**, *74*, 5975.

7. Pages, R. A. and Burger, A., *J. Med. Chem.,* **1966**, *9*, 766.
8. Mosberg, H. I.; Sobczyk-Kojiro, K.; Subramanian, P.; Crippen, G. M.; Ramalingam, K. and Woodard, R. W., *J. Am. Chem. Soc.,* **1990**, *112*, 822.
9. (a) Yu, C. M.; Zhou, B. C.; Su, W. K. and Xu, Z. Y., *Synth. Commun.,* **2006**, *36*, 3447. (b) Chandrasekhar, S. and Karri, P., *Tetrahedron Lett*., **2006**, *47*, 5763. (c) Karade, N. N.; Shirodkar, S. G.; Dhoot, B. M. and Waghmare, P. B., *J. Chem. Res.,* **2005**, *46*. (d) Mogilaiah, K.; Prashanthi, M. and Reddy, C. S., *Indian J. Chem., Sect. B,* **2003**, *42B*, 2126.
10. (a) Chandrasekhar, S. and Karri, P., *Tetrahedron Lett*., **2007**, *48*, 785. (b) Rao, Y. S., *J. Org. Chem.,* **1976**, *41*, 722. (c) Boekelheide, V. and Schramm, L. M., *J. Org. Chem.,* **1949**, *14*, 298.
11. Kobayashi, S.; Bryant, L. L.; Tsukamoto, Y. and Saegusa, T., *Macromolecules,* **1986**, *19*, 1547.
12. Henze, H. R.; Whitney, W. B. and Eppright, M. A., *J. Am. Chem. Soc.,* **1940**, *62*, 565.
13. (a) Leplawy, M. T.; Jones, D. S.; Kenner, G. W. and Sheppard, R. C., *Tetrahedron,* **1960**, *11*, 39. (b) Bergmann, M.; Stern, F. and Witte, C., *Ann.,* **1926**, *449*, 277.
14. (a) Palcut, M., *J. Chem. Res.,* **2005**, 766. (b) Schumacher, M.; Miesch, L. and Franck-Neumann, M., *Tetrahedron Lett*., **2003**, *44*, 5393. (c) Konkel, J. T.; Fan, J. F.; Jayachandran, B. and Kirk, K. L., *J. Fluor. Chem.,* **2002**, *115*, 27. (d) Combs, A. P. and Armstrong, R. W., *Tetrahedron Lett.,* **1992**, *33*, 6419. (e) Cornforth, J.; Ming-Hui, D., *J. Chem. Soc., Perkin Trans. I,* **1991**, 2183. (f) Moriya, T.; Yoneda, N.; Miyoshi, M. and Matsumoto, K., *J. Org. Chem.,* **1982**, *47*, 94. (g) Kriby, G. W. and Varley, M. J., *J. Chem. Soc., Chem. Commun.,* **1974**, 833. (h) Steglich, W., *Fortsch. Chem. Forsch.,* **1969**, *12*, 84. (i) Muxfeldt, H.; Behling, J.; Grethe, G. and Rogalski, W., *J. Am. Chem. Soc.,* **1967**, *89*, 4991. (j) Filler, R.; Rao, K. B. and Rao, Y. S., *J. Org. Chem.,* **1962**, *27*, 1110. (k) Crawford, M. and Little, W. T., *J. Chem. Soc.,* **1959**, 729. (l) Shaw, K. N. F.; McMillan, A.; Gudmundson, A. G. and Armstrong, M. D., *J. Org. Chem.,* **1958**, *23*, 1171. (m) Stefanovic, G. and Stefanovic, M., *J. Org. Chem.,* **1956**, *21*, 161. (n) Buckles, R. E.; Filler, R. and Hilfman, L., *J. Org. Chem.,* **1952**, *17*, 233. (o) Carter, H. E., *Org. React.,* **1946**, *3*, 198. (p) Raiford, L. C. and Buurman, C. H., *J. Org. Chem.,* **1944**, *9*, 466. (q) Carter, H. E. and Risser, W. C., *J. Biol. Chem.,* **1941**, *139*, 255. (r) Plöchl, J., *Ber.,* **1884**, *17*, 1616.

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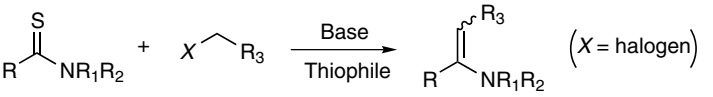
Eschenmoser Coupling

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Fischli and Eschenmoser in 1967 during the synthesis of vitamin B_{12}.[1] It is the formation of vinylogous amides and urethanes by alkylation of secondary or tertiary thioamides with an electrophilic reagent followed by the extrusion of sulfur. Therefore, it is known as the Eschenmoser coupling,[2] Eschenmoser coupling reaction,[3] Eschenmoser's method,[4] Eschenmoser sulfide contraction,[5] Eschenmoser sulfide contraction methodology,[6] or Eschenmoser sulfide reaction.[7] Essentially, this reaction is analogous to the *aza Claisen-Schmidt Condensation*;[5c] however, it is not well suited for introducing the *meso* substituents.[8]

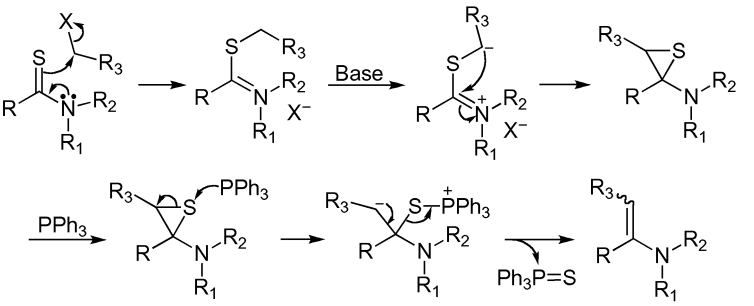
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Provided here is a tentative mechanism for the Eschenmoser coupling.

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang



D. MODIFICATION

This reaction has been modified to form vinyl thioether through peroxide initiation.[5c]

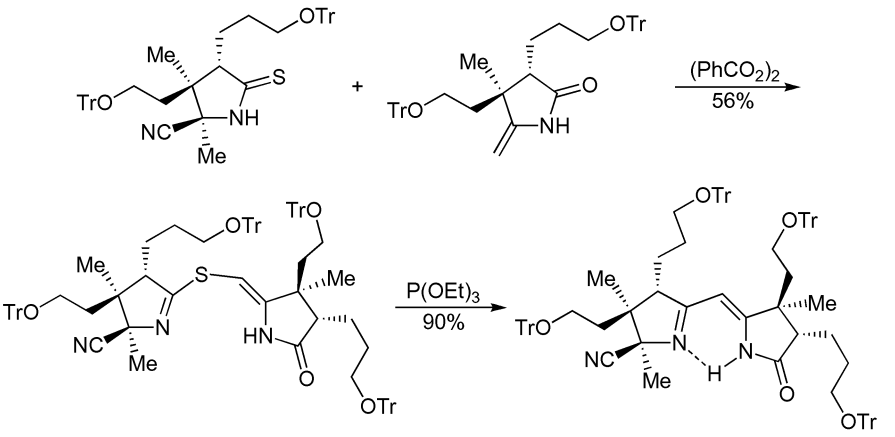
E. APPLICATIONS

This reaction has general application in the preparation of vinylogous amides, especially for vitamin B_{12}.

F. RELATED REACTIONS

This reaction is related to the *Claisen-Schmidt Condensation*.

G. CITED EXPERIMENTAL EXAMPLES

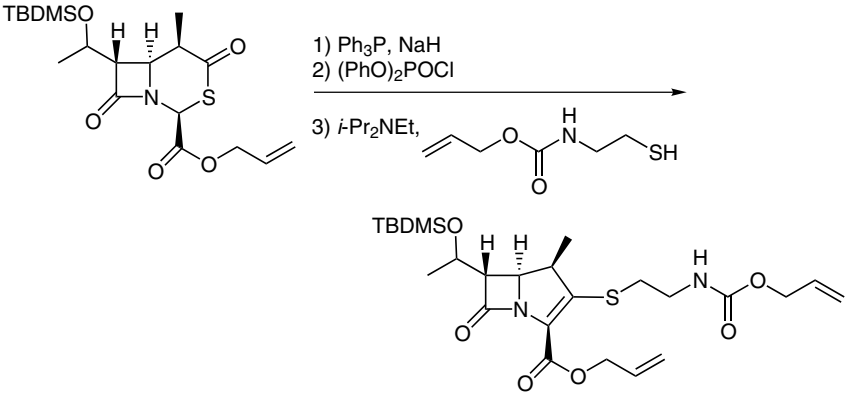


Reference 5c.

A solution of 1.74 g (2R,3S,4S)-2,3-dimethyl-5-thioxo-3-(2-(trityloxy)ethyl)-4-(3-(trityloxy)propyl)pyrrolidine-2-carbonitrile (1.00 mmol) in 5 mL dry benzene was added to freshly prepared (3S,4S)-4-methyl-5-methylene-4-(2-(trityloxy)ethyl)-3-(3-(trityloxy)-

propyl)pyrrolidin-2-one (1.50 mmol, 1.047 g). At 0°C, benzoyl peroxide (415 mg, 1.20 mmol) was added. The mixture was stirred in the dark and under argon for 24 h and poured into a mixture of diethyl ether and saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated. Purification by silica gel chromatography (linear gradient of 10–20% EtOAc/hexane) afforded 804 mg [2*R*, 3*S*,4*S*,5(2*Z*,3*S*,4*S*)]-2,3-dimethyl-5-[(3-methyl-5-oxo-3-(2-(trityloxy)-ethyl)-4-(3-(trityloxy)propyl)pyrrolidin-2-ylidene)methanesulfonyl]-3-(2-(trityloxy)ethyl)-4-(3-(trityloxy)propyl)-3,4-dihydro-2*H*-pyrrole-2-carbonitrile, in a yield of 56%.

A solution of 200 mg sulfide (139 μmol) and 0.148 mL triethyl phosphite (142 mg, 850 μmol) in 2 mL dry benzene was degassed and heated to 120 °C for 72 h in a sealed tube. The mixture was concentrated and chromatographed on aluminium oxide (activity III–IV, linear gradient of 10–20% EtOAc/hexane) to give 177 mg [2*R*,3*S*,4*S*,5(2*Z*,3*S*,4*S*)]-2,3-dimethyl-5-[(3-methyl-5-oxo-3-(2-(trityloxy)ethyl)-4-(3-(trityloxy)propyl)pyrrolidin-2-ylidene)methyl]-3-(2-(trityloxy)ethyl)-4-(3-(trityloxy)-propyl)-3,4-dihydro-2*H*-pyrrole-2-carbonitrile as a mixture of diastereoisomers (~36:6:6:1), in a yield of 90%. Diastereomerically pure material was obtained by HPLC (Nuc 50–10, 10:1:2 hexane/MeOAc/diethyl ether, +20% hexane, 10 mL/min) to give 130 mg pure A-B-semicorrin as an amorphous solid, in a yield of 67%.



Reference 4.

To a stirred solution of 300 mg allyl (2*S*,5*R*,6*S*,7*S*)-7-[(1*R*)-1-[(*tert*-butyldimethylsilyl)-oxy]ethyl]-5-methyl-4,8-dioxo-1-aza-3-thiabicyclo[4.2.0]-octane-2-carboxylate (0.726 mmol) and 186 mg Ph_3P (0.726 mmol) in 6 mL DMF at −20°C under nitrogen was added 32 mg 60% NaH (0.798 mmol). After the reaction mixture was stirred for 2 h, 0.165 mL $(PhO)_2POCl$ (0.709 mmol) and 9 mg DMAP (0.07 mmol) were added to the mixture, and the stirring was continued at 0°C for 2 h. *N*-[(Allyloxy)carbonyl]cysteamine (152 mg, 0.944 mmol) and 0.165 mL *i*-Pr_2NEt (0.944 mmol) were added to the mixture, which was allowed to stand at 0°C in the refrigerator for 3 days. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried, and evaporated. The residue was purified by silica gel column chromatography (elution with *n*-hexane/EtOAc, 3:1) to afford 250 mg allyl (1*R*,5*S*, 6*S*)-6-[(1*R*)-1-[(*tert*-butyldimethylsilyl)-oxy]ethyl]-2-[[[2-[(allyloxy)-carbonyl]amino]-ethyl]thio]-1-methylcarbapen-2-em-3-carboxylate as a yellowish syrup, in a yield of 66%.

Other references related to the Eschenmoser coupling are cited in the literature.[9]

H. REFERENCES

1. (a) Fischli, A. and Eschenmoser, A., *Angew. Chem. Int. Ed. Engl.,* **1967**, *6*, 866. (b) Fischli, A. and Eschenmoser, A., *Angew. Chem.,* **1967**, *79*, 865.
2. (a) Russowsky, D. and Amaro da Silveira Neto, B., *Tetrahedron Lett*., **2004**, *45*, 1437. (b) Hashimoto, M.; Matsumoto, M. and Terashima, S., *Tetrahedron,* **2003**, *59*, 3041.
3. Shiosaki, K., "The Eschenmoser Coupling Reaction," in *Comprehensive Organic Synthesis*, ed. Trost, B. M. and Fleming, I., vol. ed.; Heathcock, C. H. Pergamon, Oxford, **1991**, *2*, pp. 865–894.
4. Sakurai, O.; Ogiku, T.; Takahashi, M.; Hayashi, M.; Yamanaka, T.; Horikawa, H. and Iwasaki, T., *J. Org. Chem.,* **1996**, *61*, 7889.
5. (a) Hashimoto, M.; Matsumoto, M. and Terashima, S., *Tetrahedron,* **2003**, *59*, 3019. (b) Gurjar, M. K. and Lalitha, S. V. S., *Pure & Appl. Chem.,* **1998**, *70*, 303. (c) Mulzer, J.; List, B. and Bats, J. W., *J. Am. Chem. Soc.,* **1997**, *119*, 5512. (d) Ha, J. D.; Lee, D. H. and Cha, J. K., *J. Org. Chem.,* **1997**, *62*, 4550. (e) Nair, V.; Turner, G. A. and Chamberlain, S. D., *J. Am. Chem. Soc.,* **1987**, *109*, 1223.
6. Jacobi, P. A. and Liu, H., *J. Org. Chem.,* **2000**, *65*, 7676.
7. Bellec, C. and Gaurat, O., *Can. J. Chem.,* **2004**, *82*, 1289.
8. Jacobi, P. A. and Liu, H., *Org. Lett.,* **1999**, *1*, 341.
9. (a) Jacobi, P. A. and Li, Y. K., *Org. Lett.,* **2003**, *5*, 701. (b) Ha, J. D. and Cha, J. K., *J. Am. Chem. Soc.,* **1999**, *121*, 10012. (c) Minehan, T. G. and Kishi, Y., *Tetrahedron Lett.,* **1997**, *38*, 6811. (d) Levillain, J. and Vazeux, M., *Synthesis,* **1995**, 56. (e) Montforts, F.-P.; Gerlach, B. and Höper, F., *Chem. Rev.,* **1994**, *94*, 327. (f) Kim, G.; Chu-Moyer, M. Y.; Danishefsky, S. J. and Schulte, G. K., *J. Am. Chem. Soc.,* **1993**, *115*, 30. (g) Bishop, J. E.; O'Connell, J. F. and Rapoport, H., *J. Org. Chem.,* **1991**, *56*, 5079. (h) Arnott, D. M.; Harrison, P. J.; Henderson, G. B.; Sheng, Z.-C.; Leeper, F. J. and Battersby, A. R., *J. Chem. Soc., Perkin Trans. I,* **1989**, 265. (i) Gugelchuk, M. M.; Hart, D. J. and Tsai, Y.-M., *J. Org. Chem.,* **1981**, *46*, 3671. (j) Eschenmoser, A. and Winter, C. E., *Science,* **1977**, *196*, 1410. (k) Vorbruggen, H. and Krolikiewicz, K., *Angew. Chem. Int. Ed. Engl.,* **1976**, *15*, 689. (l) Götschi, E.; Hunkeler, W.; Wild, H. J.; Schneider, P.; Fuhrer, W.; Gleason, J. and Eschenmoser, A., *Angew. Chem. Int. Ed. Engl.,* **1973**, *12*, 910. (m) Roth, M.; Dubs, P.; Götschi, E. and Eschenmoser, A., *Helv. Chim. Acta,* **1971**, *54*, 710. (n) Eschenmoser, A., *Pure & Appl. Chem. Suppl.,* **1971**, *2*, 69. (o) Woodward, R. B., *Pure & Appl. Chem.,* **1968**, *17*, 519.

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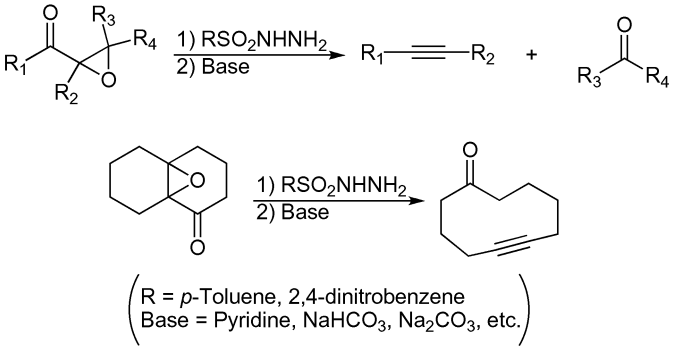
Eschenmoser Fragmentation

A. GENERAL DESCRIPTION OF THE REACTION

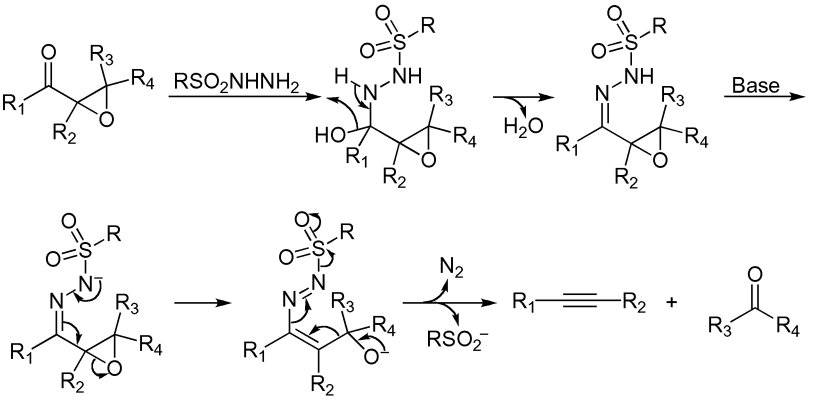
This reaction was initially reported concurrently by Eschenmoser[1] and Tanabe[2] in 1967. It is the cleavage of α,β-epoxyketones under mild conditions to acetylenic aldehydes or ketones with *p*-toluenesulfonylhydrazine using pyridine, $NaHCO_3$, or Na_2CO_3 as a catalyst.[3] Therefore, this reaction is generally known as the Eschenmoser fragmentation.[4] Occasionally, it is also referred to as the Eschenmoser-Tanabe Fragmentation[5] or α,β-epoxy ketone cleavage reaction.[3] It is interesting that more and more experimental evidence indicates that *p*-toluenesulfonylhydrazine is not a satisfactory reagent for the cleavage of α,β-epoxy ketones,[3,4a] thus alternative sulfonylhydrazines are applied to this reaction, including *p*-nitrobenzenesulfonylhydrazine.[4a] This reaction provides an alternative and spectacular type of ring expansion for the cyclic ketones.[4c] The driving force of this reaction arises from both enthalpic and entropic contributions, due to the formation of toluene sulfinate and the evolution of nitrogen gas, respectively. This reaction is assumed to proceed via a concerted mechanism.[5b]

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

p-Nitrobenzenesulfonylhydrazine[3] and mesitylene-sulfonylhydrazine[4c] have been substituted for *p*-toluenesulfonylhydrazine for the Eschenmoser fragmentation.

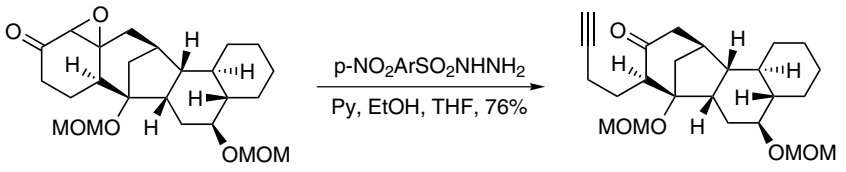
E. APPLICATIONS

This reaction has been used in the preparation of acetylenic aldehydes and ketones; in addition, it has been used to synthesize middle-size cyclic ketones.

F. RELATED REACTIONS

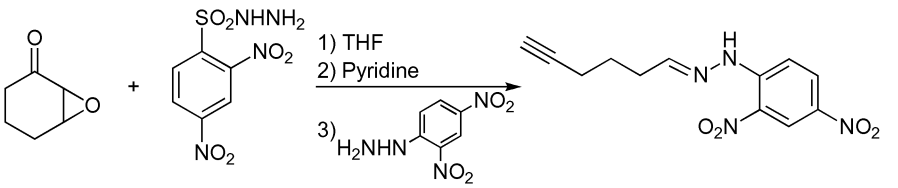
This reaction is related to the *Bamford-Stevens Reaction*, *Grob Fragmentation* and *Wharton Rearrangement*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4a.

(4a*SR*,5*SR*,6a*SR*,7*SR*,7a*RS*,13*RS*,13a*RS*,13b*RS*)-1,2,3,4,4a,5,6,6a,7,7a,8,9,11,11a,12,13,13a,13b–Octadecahydro-11,11a-epoxy-5,7-bismethoxymethoxy-7,13-methano-10*H*-benzo[4,5]cyclohepta[1,2-a]-naphthalen-10-one(60 mg, 0.14 mmol) was dissolved in a mixture of 2 mL THF and 5 mL ethanol, and the solution was cooled to −78°C. 4-Nitrobenzenesulfonyl hydrazide (34 mg, 0.16 mmol) was dissolved in 2 mL THF, and this solution was added to the cooled solution. The resulting solution was placed in an ice bath and stirred for 1 h. After which, 14 mg pyridine (0.18 mmol) was added, and the solution was allowed to warm to room temperature and the stirring was continued for a further 8 h. The resulting yellow solution was diluted with 10 mL 1 M NaOH and then extracted with EtOAc (3 × 15 mL). The organic layers were combined and washed with water (2 × 25 mL) and then brine (25 mL), and dried and evaporated in vacuo to give the crude alkynyl ketone. The crude product was purified by column chromatography (EtOAc/petroleum spirit, 1:3) to give 44 mg (4a*SR*,5*SR*,6a*SR*,7*SR*,8*RS*,11*SR*,11a*RS*,11b*RS*)-1,2,3,4,4a,5,6,6a,7,8,10,11,11a,11b-tetradecahydro-8-(but-3′-ynyl)-5,7-bismethoxymethoxy-7,11-methano-9*H*-cyclohepta[a]naphthalen-9-one as a clear oil that solidified on standing, in a yield of 76%, $R_f = 0.50$ (EtOAc/petroleum spirit 1:3).



Reference 3.

To a solution of 0.576 g 2,4-dinitrophenylsulfonylhydrazine (2.2 mmol) in 20 mL THF cooled to −25°C was added 0.224 g 2,3-epoxy cyclohexan-1-one (2 mmol). The reaction mixture was kept at −25 to −30°C for 30 min and then at −10°C for 30 min. The mixture was allowed to warm to 0°C, dried at this temperature over anhydrous magnesium sulfate for 20 min, and filtered below 0°C. After being stirred for 1 min a drop of pyridine was added and the stirring was continued. The mixture was taken out of the ice bath, and after 2 min another drop of pyridine was added. This caused an extensive effervescence, and the mixture turned deep orange in color. After 2 min, more pyridine (a total of 0.16 g, 2 mmol) was added, and the stirring was continued for 5 min. The mixture was filtered through Celite 545, and the filtrate was stirred with 1 g powdered $CuSO_4 \cdot 5H_2O$ for 25 min. It was filtered, and the volatile substances from the filtrate were transferred under vacuum (0.03 mmHg) at ambient temperature into a receiver containing 0.792 g 2,4-dinitrophenylhydrazine (4 mmol) in 75 mL THF. The mixture was stored at 25–30°C for 48 h. The solvent was removed by

rotary evaporation, and the residue was purified by preparative TLC on silica gel (methylene chloride, $R_f = 0.8$) to give 342 mg of the orange crystalline 2,4-dinitrophenylhydrazone of 5-hexynal, in a yield of 62%, m.p. 90–9l°C.

Other references related to the Eschenmoser fragmentation are cited in the literature.[6]

H. REFERENCES

1. (a) Eschenmoser, A.; Felix, D. and Ohloff, G., *Helv. Chim. Acta,* **1967**, *50*, 708. (b) Schreiber, D.; Felix, D.; Eschenmoser, A.; Winter, M.; Fautschi, F.; Schulte-Elte, K. H.; Sundt, E.; Ohloff, G.; Kalvoda, J.; Kaufmann, H.; Wieland, P. and Anner, G., *Helv. Chim. Acta,* **1967**, *50*, 2101. (c) Schreiber, J.; Felix, D.; Eschenmoser, A.; Winter, M.; Gautschi, F.; Schulte-Elte, K. H.; Sundt, E.; Ohloff, G.; Kalvoda, J.; Kaufmann, H.; Wieland, P. and Anner, G., *Helv. Chim. Acta,* **1967**, *50*, 2108.
2. (a) Tanabe, M.; Crowe, D. R.; Dehn, R. L. and Detre, G., *Tetrahedron Lett.,* **1967**, 3739. (b) Tanabe, M.; Crowe, D. F. and Dehn, R. L., *Tetrahedron Lett.,* **1967**, 3943.
3. Corey, E. J. and Sachdev, H. S., *J. Org. Chem.,* **1975**, *40*, 579.
4. (a) Murakami, Y.; Shindo, M. and Shishido, K., *Synlett,* **2005**, 664. (b) Constantieux, T. and Rodriguez, J., *Science of Synthesis,* **2004**, *26*, 413. (c) Mander, L. N. and McLachlan, M. M., *J. Am. Chem. Soc.,* **2003**, *125*, 2400. (d) Von Zezschwitz, P.; Petry, F. and de Meijere, A., *Chem. Eur. J.,* **2001**, *7*, 4035. (e) Yamamoto, K. and Heathcock, C. H., *Org. Lett.,* **2000**, *2*, 1709. (f) Abad, A.; Arno, M.; Agullo, C.; Cunat, A. C.; Meseguer, B. and Zaragoza, R. J., *J. Nat. Prod.,* **1993**, *56*, 2133. (g) Pradhan, S. K. and Sitabkhan, S., *Tetrahedron Lett*., **1993**, *34*, 5615. (h) Trost, B. M. and Chang, V. K., *Synthesis*, **1993**, 824. (i) Marples, B. A. and Spilling, C. D., *Tetrahedron*, **1992**, *48*, 4017. (j) Gordon, D. M.; Danishefsky, S. J. and Schulte, G. K., *J. Org. Chem.,* **1992**, *57*, 7052. (k) Leone, C. L. and Chamberlin, A. R., *Tetrahedron Lett*., **1991**, *32*, 1691. (l) Jung, M. E. and Hatfield, G. L., *Tetrahedron Lett*., **1983**, *24*, 3175. (m) Flynn, G. A., *J. Org. Chem.,* **1983**, *48*, 4125. (n) Marshall, J. A. and Flynn, K. E., *J. Am. Chem. Soc.,* **1982**, *104*, 7430. (o) Kane, V. V. and Doyle, D. L., *Tetrahedron Lett*., **1981**, *22*, 3027. (p) Reese, C. B. and Sanders, H. P., *Synthesis,* **1981**, 276. (q) Batzold, F. H. and Robinson, C. H., *J. Org. Chem.,* **1976**, *41*, 313. (r) Pradhan, S. K. and Girijavallabhan, V. M., *Steroids*, **1969**, *13*, 11.
5. (a) Kamijo, S. and Dudley, G. B., *J. Am. Chem. Soc.,* **2005**, *127*, 5028. (b) Mück-Lichtenfeld, C., *J. Org. Chem.,* **2000**, *65*, 1366.
6. (a) Herges, R., *Angew. Chem.,* **1994**, *106*, 261. (b) Dai, W. and Katzenellenbogen, J. A., *J. Org. Chem.,* **1993**, *58*, 1900. (c) Weyerstahl, P. and Marschall, H., Fragmentation Reactions in *Comprehensive Organic Synthesis*, ed. Trost, B. M. and Fleming, I., Pergamon Press, Elmsford, N.Y., **1991**, *6*, pp. 1041–1070. (d) Abad, A.; Agullo, C.; Arno, M.; Cunat, A. C. and Zaragoza, R. J., *Synlett,* **1991**, 787. (e) Welch, S. C. and Kabay, M. C., *J. Org. Chem.,* **1985**, *50*, 136. (f) Williams, D. R. and Grote, J., *J. Org. Chem.,* **1983**, *48*, 134. (g) Felix, D.; Müller, R. K.; Horn, U.; Joos, R.; Schreiber, J. and Eschenmoser, A., *Helv. Chim. Acta,* **1972**, *55*, 1276. (h) Foster, A. M. and Agosta, W. C., *J. Org. Chem.,* **1972**, *37*, 61. (i) Felix, D.; Schreiber, J.; Ohloff, G. and Eschenmoser, A., *Helv. Chim. Acta,* **1971**, *54*, 2896. (j) Müller, R. K.; Felix, D.; Schreiber, J. and Eschenmoser, A., *Helv. Chim. Acta,* **1970**, *53*, 1479. (k) Felix, D.; Schreiber, J.; Piers, K.; Horn, U. and Eschenmoser, A., *Helv. Chim. Acta,* **1968**, *51*, 1461. (l) Borrevang, P.; Hjort, J.; Rapala, R. T. and Edie, R., *Tetrahedron Lett.,* **1968**, 4905.

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Eschweiler-Clarke Methylation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Eschweiler in 1905,[1] and subsequently by Clarke and co-workers in 1933.[2] It is the preparation of tertiary methylamines from primary or secondary amines by means of the treatment of those amines with an excess amount of aqueous formaldehyde and formic acid. Therefore, it is generally known as the Eschweiler-Clarke methylation.[3] In addition, this reaction is also referred to as the Eschweiler-Clarke condition,[4] Eschweiler-Clarke *N*-methylation,[5] Eschweiler-Clarke procedure,[3j,6] Eschweiler-Clarke reaction,[3d,3g,3j,7] Eschweiler-Clarke reductive methylation,[8] Eschweiler-Clarke reductive *N*-methylation,[9] Clarke-Eschweiler methylation,[10] Clarke-Eschweiler reaction,[10b,10c,11] or Clarke-Eschweiler procedure.[11] In this reaction, the formate anion donates its proton to reduce the imine or iminium salt, so that carbon dioxide is evolved. Thus the whole process is a reductive amination of formaldehyde. This reaction is very useful for the reductive amination, without the application of hydrogen gas, catalyst (e.g., Pd/C), and high-pressure apparatus and has been widely applied to alkaloid chemistry. A special case of such reductive amination that occurs on phenylethylamine and results in the formation of tetrahydroisoquinolines is also referred to as the Clarke-Eschweiler cyclization.[7d,10b,10c] In a few cases, the methylation also occurs on an aromatic ring during the reductive amination.[3j]

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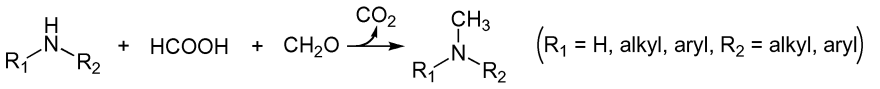
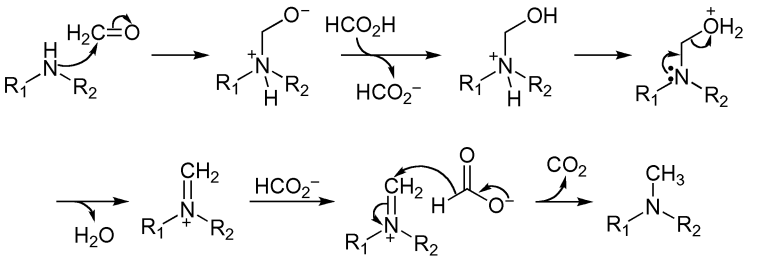
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

N/A

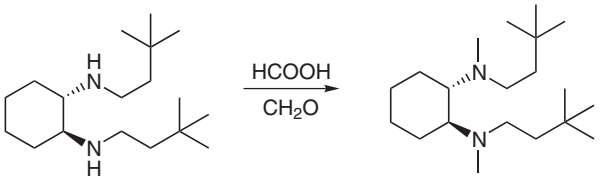
E. APPLICATIONS

This reaction has wide application in the methylation of primary and secondary amines.

F. RELATED REACTIONS

This reaction is related to the *Leuckart Reaction*.

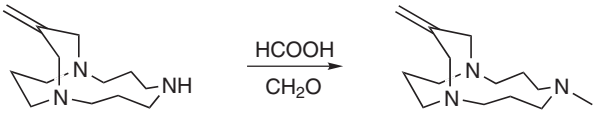
G. CITED EXPERIMENTAL EXAMPLES



Reference 3a.

Formic acid (96% aqueous solution, 0.69 mL, 17.5 mmol, 5 eq.) was cooled to 0°C in an ice water bath, and 0.99 g (1*S*,2*S*)-(+)-*N*,*N*′-bis(3,3-dimethylbutyl)-1,2-cyclohexanediamine (3.5 mmol, 1 eq.) was added slowly. A 37% aqueous formaldehyde

solution (7.7 mmol) was then added in one portion, and the solution was heated until carbon dioxide evolution began, at which time heating was discontinued. Once the formation of gas was no longer apparent, heating was resumed for 14–22 h. The cooled reaction mixture was then poured onto ice-cooled 10% aqueous hydrochloric acid (3.85 mmol, 1.1 eq.) and washed with four portions of diethyl ether. The pH of the aqueous phase was adjusted to 10 by the addition of solid NaOH pellets, and the solution was extracted with two portions of diethyl ether. The combined organic portions were dried over a potassium hydroxide-sodium sulfate mixture and concentrated by rotary evaporation. Rigorous drying of the product by heating with sodium metal and subsequent Kugelrohr distillation from fresh sodium provided 0.75 g (1*S*,2*S*)-(+)-*N*,*N*′-bis(3,3-dimethylbutyl)-*N*,*N*′-dimethyl-1,2-diaminocyclohexane as a clear, colorless oil, in a yield of 68%, b.p., 140–145°C (5 mmHg).



Reference 3d.

A mixture of 0.14 g 11-methylene-1,5,9-triazabicyclo[7.3.3]pentadecane (0.63 mmol), 78 μL 90% formic acid (1.5 mmol), and 54 μL 37% aqueous formaldehyde (0.66 mmol) was heated in an oil bath at 120°C for 16 h. The reaction mixture was basified with 10 M aqueous KOH solution and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated by rotary evaporation and dried under vacuum. The crude oily product was distilled from powdered KOH, yielding 65 mg 5-methyl-11-methylene-1,5,9-triazabicyclo[7.3.3]pentadecane as a colorless oil, in a yield of 43%, b.p. 100–110°C (0.3 mmHg).

Other references related to the Eschweiler-Clarke methylation are cited in the literature.[12]

H. REFERENCES

1. Eschweiler, W., *Ber.,* **1905**, *38*, 880.
2. (a) Clarke, H. T.; Gillespie, H. B. and Weisshaus, S. Z., *J. Am. Chem. Soc.*, **1933**, *55*, 4531. (b) Clarke H. T.; Gillesoie H. B. and Weishauss S. Z.,*J. Am. Chem. Soc.*, **1933**, *55*, 4571.
3. (a) Mealy, M. J.; Luderer, M. R.; Bailey, W. F. and Sommer, M. B., *J. Org. Chem.,* **2004**, *69*, 6042. (b) Chen, F.-L. and Sung, K. S., *J. Heterocycl. Chem.,* **2004**, *41*, 697. (c) Kočovský, P.; Vyskočil, Š. and Smrčina, M., *Chem. Rev.,* **2003**, *103*, 3213. (d) Bell, T. W.; Choi, H.-J.; Harte, W. and Drew, M. G. B., *J. Am. Chem. Soc.,* **2003**, *125*, 12196. (e) Tumiatti, V.; Rosini, M.; Bartolini, M.; Cavalli, A.; Marucci, G.; Andrisano, V.; Angeli, P.; Banzi, R.; Minarini, A.; Recanatini, M. and Melchiorre, C., *J. Med. Chem.,* **2003,** *46*, 954. (f) Rosenau, T.; Potthast, A.; Röhrling, J.; Hofinger, A.; Sixta, H. and Kosma, P., *Synth. Commun.,* **2002**, *32*, 457. (g) Harding, J. R.; Jones, J. R.; Lu, S.-Y. and Wood, R., *Tetrahedron Lett.,* **2002**, *43*, 9487. (h) Rahal, S. and Badache, L., *J. Soc. Algerienne Chim.,* **1994**, *4*, 75. (i) Alder, R. W.; Colclough, D. and Mowlam, R. W., *Tetrahedron Lett*., **1991**, *32*, 7755. (j) Bobowski, G., *J. Org. Chem.,* **1985**, *50*, 929. (k) Pine, S. H., *J. Chem. Edu.,* **1968**, *45*, 118. (l) Kametani, T. and Ogasawara, *J. Chem. Soc.,* **1964**, 4142.
4. (a) Al-Rawi, S.; Ahlborn, C. and Richert, C., *Org. Lett.,* **2005**, *7*, 1569. (b) Felpin, F.-X. and Lebreton, J., *Tetrahedron,* **2004**, *60*, 10127.

5. Spring, D. R.; Krishnan, S.; Blackwell, H. E. and Schreiber, S. L., *J. Am. Chem. Soc.,* **2002**, *124*, 1354.
6. (a) Englert, U.; Hu, C. H.; Salzer, A. and Alberico, E., *Organometallics,* **2004**, *23*, 5419. (b) Kitbunnadaj, R.; Hashimoto, T.; Poli, E.; Zuiderveld, O. P.; Menozzi, A.; Hidaka, R.; de Esch, I. J. P.; Bakker, R. A.; Menge, W. M. P. B.; Yamatodani, A.; Coruzzi, G.; Timmerman, H. and Leurs, R., *J. Med. Chem.,* **2004**, *47*, 2414. (c) Bruce, J. I.; Dickins, R. S.; Govenlock, L. J.; Gunnlaugsson, T.; Lopinski, S.; Lowe, M. P.; Parker, D.; Peacock, R. D.; Perry, J. J. B.; Aime, S. and Botta, M., *J. Am. Chem. Soc.,* **2000**, *122*, 9674.
7. (a) Dollé, V.; Nguyen, C. H.; Legraverend, M.; Aubertin, A.-M.; Kirn, A.; Andreola, M. L.; Ventura, M.; Tarrago-Litvak, L. and Bisagni, E., *J. Med. Chem.,* **2000**, *43*, 3949. (b) Bernet, B.; Piantini, U. and Vasella, A., *Carbohydr. Res.,* **1990**, *204*, 11. (c) Lindeke, B.; Anderson, E. and Jenden, D. J., *Biomed. Mass Spectrom.,* **1976**, *3*, 257. (d) Castrillón, J. A., *J. Am. Chem. Soc.,* **1952**, *74*, 558.
8. Hurley, C. A.; Wong, J. B.; Hailes, H. C. and Tabor, A. B., *J. Org. Chem.,* **2004**, *69*, 980.
9. Lee, S.-S.; Wu, W.-N.; Wilton, J. H.; Beal, J. L. and Doskotch, R. W., *J. Nat. Prod.,* **1999**, *62*, 1410.
10. (a) Snider, B. B. and Gu, Y. H., *Org. Lett.,* **2001**, *3*, 1761. (b) Cope, A. C. and Burrows, W. D., *J. Org. Chem.,* **1966**, *31*, 3099. (c) Cope, A. C. and Burrows, W. D., *J. Org. Chem.,* **1965**, *30*, 2163.
11. Baltzly, R., *J. Am. Chem. Soc.,* **1953**, *75*, 6038.
12. (a) Kitbunnadaj, R.; Hashimoto, T.; Poli, E.; Zuiderveld, O. P.; Menozzi, A.; Hidaka, R.; de Esch, I. J. P.; Bakker, R. A.; Menge, W. M. P. B.; Yamatodani, A.; Coruzzi, G.; Timmerman, H. and Leurs, R., *J. Med. Chem.,* **2005,** *48*, 2100. (b) Fraenkel, G. and Liu, H., *J. Am. Chem. Soc.,* **2004**, *126*, 5202. (c) Wijtmans, M.; Pratt, D. A.; Brinkhorst, J.; Serwa, R.; Valgimigli, L.; Pedulli, G. F. and Porter, N. A., *J. Org. Chem.,* **2004**, *69*, 9215. (d) Boros, E. E.; Samano, V.; Ray, J. A.; Thompson, J. B.; Jung, D. K.; Kaldor, I.; Koble, C. S.; Martin, M. T.; Styles, V. L.; Mook, R. A.; Feldman, P. L.; Savarese, J. J.; Belmont, M. R.; Bigham, E. C.; Boswell, G. E.; Hashim, M. A.; Patel, S. S.; Wisowaty, J. C.; Bowers, G. D.; Moseley, C. L.; Walsh, J. S.; Reese, M. J.; Rutkowske, R. D.; Sefler, A. M. and Spitzer, T. D., *J. Med. Chem.,* **2003,** *46*, 2502. (e) Selva, M.; Tundo, P. and Perosa, A., *J. Org. Chem.,* **2003**, *68*, 7374. (f) Debremaeker, D.; Visky, D.; Chepkwony, H. K.; van Schepdael, A.; Roets, E. and Hoogmartens, J., *Rapid Commun. Mass Spect.,* **2003**, *17*, 342. (g) Binet, J.; Thomas, D.; Benmbarek, A.; de Fornel, D. and Renaut, P., *Chem. Pharm. Bull.,* **2002**, *50*, 316. (h) Wikening, R. R.; Ratcliffe, R. W.; Doss, G. A.; Mosley, R. T. and Ball, R. G., *Tetrahedron,* **1997**, *53*, 16923. (i) Xu, J. and Yadan, J. C., *J. Org. Chem.,* **1995**, *60*, 6296. (j) Casanova, J. and Devi, P., *Synth. Commun.,* **1993**, *23*, 245. (k) Farkas, E. and Sunman, C. J., *J. Org. Chem.,* **1985**, *50*, 1110. (l) Takemura, H.; Suenaga, M.; Sakai, K.; Kawachi, H.; Shinmyozu, T.; Miyahara, Y. and Inazu, T., *J. Incl. Phenom. Macrocycl. Chem.,* **1984**, *2*, 207. (m) Cannon, J. G. and Milne, L. D., *J. Heterocycl. Chem.,* **1976**, *13*, 685. (n) Tichy, M. and Vasickova, S., *Coll. Czech. Chem. Commun.,* **1974**, *39*, 555. (o) Pine, S. H. and Sanchez, B. L., *J. Org. Chem.,* **1971**, *36*, 829. (p) Mathison, W.; Beasley, J. G.; Fowler, K. C. and Peters, E. R., *J. Med. Chem.,* **1969**, *12*, 928. (q) Kametani, T.; Noguchi, I. and Saito, K., *J. Heterocycl. Chem.,* **1969**, *6*, 869. (r) Nelson, W. L., *J. Heterocycl. Chem.,* **1968**, *5*, 231. (s) Reinhold, V. N.; Ishikawa, Y. and Melville, D. B., *J. Med. Chem.,* **1968**, *11*, 258. (t) Newman, M. S. and Lloyd, H. A., *J. Am. Chem. Soc.,* **1952**, *74*, 2672. (u) Moore, M. L., "The Leuckart Reaction" in *Organic Reactions*, ed. Adams, R., John Wiley & Sons, New York, **1949**, *5*, pp. 301–330. (v) Icke, R. N. and Wisegarver, B. B., *Org. Synth.,* **1946**, *25*, 89. (w) Icke, R. N. and Wisegarver, B. B., *Org. Synth.,* **1946**, *25*, 89. (x) Wagner, E. C., *J. Am. Chem. Soc.,* **1933**, *55*, 724. (y) Werner, E. A., *J. Chem. Soc.,* **1917**, *111*, 844. (z) Decker, H. and Becker, P., *Ann.*, **1913**, *395*, 343. (aa) Decker, H. and Becker, P., *Ber.,* **1912**, *45*, 2404.

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Ester Pyrolysis

A. GENERAL DESCRIPTION OF THE REACTION

It is said that this reaction was initially observed by Smith in 1842[1] or Heintz in 1854.[2] It is the unimolecular thermal cleavage of esters that hold β-hydrogen(s) on the alcoholic moiety via *cis*-elimination to form olefins without a carbon skeleton isomerization or double bond shift.[2b] Carboxylic acids are the by-products in this reaction. This reaction is good for esters containing volatile components of either acid or alcohol.[1b] It is assumed that the major controlling factor in ester pyrolysis is the difficulty to form a p-π conjugation between carbonyl oxygen and β-hydrogen in the ground state of the ester, that is, the stronger the conjugation (in the manner of semipolar six-membered cyclic ring), the easier for the pyrolysis to occur.[3] Therefore, it is found that γ-lactones are stable at 600°C, whereas larger lactones that can form a transient six-membered ring decompose at 500°C.[4] Although this reaction was thought to be concerted initially,[5] more experimental evidence indicates that it occurs via a semipolar six-membered transition state, with a partial negative charge on the departing oxygen atom.[6] It was found that the *Hofmann Rule* is followed in pyrolysis of the esters with aliphatic alcohols, in which the olefinic mixtures show a similar ratio of available β-hydrogens in the alcoholic component.[2b,7] As a result, the more primary protons, the easier for the pyrolysis; to an extreme extent, even *tert*-butyl acetate pyrolyzes at 360°C.[5b] For the case of *tert*-butyl esters, the pyrolysis rate is linear to the pKa of the corresponding

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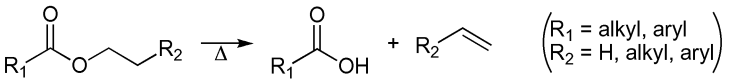
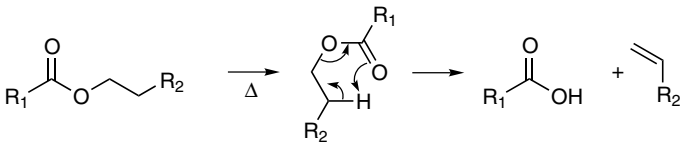
acids;[8] in contrast, the pyrolysis rate of isopropyl α-haloacetates is on the order of I > Br > Cl > F.[8] It was reported that when the acyl portion is varied within a series of esters, the pyrolysis temperature decreases in a zigzag fashion, by which the esters from acids with an even number of carbon atoms are slightly more stable than their neighboring analogues.[9] This reaction is especially important in thermal modification, recycling, and degradation of polyesters (poly ε-caprolactone)[10] and the synthesis of olefins that are difficult to obtain,[2b] such as the highly unsaturated compounds (e.g., 2-vinylbutadiene).[11] A few examples of ester pyrolysis that give special products are the formation of methylenecyclobutenone from the flash vacuum pyrolysis of furfuryl benzoate,[12] alkyl or aryl phenyl 2-methylene-1,3-diones from 3-phenylpropargyl esters,[13] and cyclic ethers containing three- to six-membered rings from cyclic carbonates with one or two hydroxyl groups.[14]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

N/A

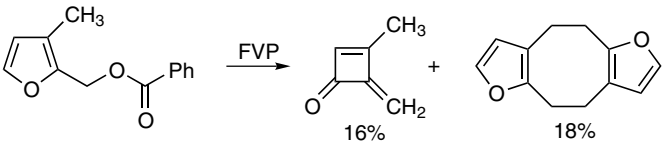
E. APPLICATIONS

This reaction has been widely applied to the synthesis of a variety of olefins and other special compounds (e.g., cyclic ethers).

F. RELATED REACTIONS

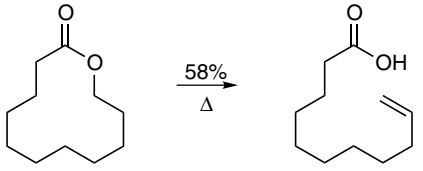
This reaction is related to the *Chugaev Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 12.

A 2.0 g 3-methylfurfuryl benzoate (9.25 mmol) was flash vacuum pyrolyzed at 630°C in the normal manner. A quantitative ^{1}H NMR analysis of the pyrolysate indicated the presence of 3-methyl-4-methylenecyclobutenone in a 21% yield and its dimmer in a 24% yield. Thick layer chromatography on silica gel plates (2000 μ) using two elutions with 20% EtOAc in hexanes afforded two major bands. The upper band consisted of 0.313 g 4*H*,5*H*,9*H*,10*H*-cycloocta[1,2-b:6,5-b′]difuran, in a yield of 18%, m.p. 49–52°C. The lower band was concentrated to give 0.139 g 3-methyl-4-methylenecyclobutenone, in a yield of 16%.



Reference 15.

A pyrolysis tube packed with Vycor Raschig rings was used in the standard pyrolysis apparatus, and 7.59 g 11-hydroxyhendecanoic acid lactone (41.2 mmol) was dropped through the pyrolysis tube at 520°C at a rate of 0.95 g/min to yield 6.87 g pale yellow liquid pyrolysate. A small amount of carbon was deposited in the pyrolysis tube. Titration at 0°C of a small portion of the pyrolysate dissolved in 95% ethanol indicated that the pyrolysate contained 86% of hendecenoic acid. The acid was separated from the lactone by 0.5 N sodium bicarbonate solution, then 0.5 N HCl and ether. The solvent was removed from the final ether extracts by distillation under reduced pressure, and the residue was dried in a vacuum desiccator to give 3.98 g 10-hendecenoic acid, in a yield of 58% (based on the weight of the pyrolysate), m.p. 17–19.6°C.

Other references related to the ester pyrolysis are cited in the literature.[16]

H. REFERENCES

1. (a) Smith, L., *Ann. Chim. Phys.* **1842**, *6*, 40. (b) Bailey, W. J. and Hewitt, J. J., *J. Org. Chem.,* **1956**, *21*, 543.
2. (a) Heintz, W., *Pogg. Ann.,* **1854**, *93*, 519. (b) Smith, G. G. and Wetzel, W. H., *J. Am. Chem. Soc.,* **1957**, *79*, 875.
3. Lee, I.; Cha, O. J. and Lee, B.-S., *J. Phys. Chem.,* **1990**, *94*, 3926.
4. Bailey, W. J. and Baylouny, R. A., *J. Am. Chem. Soc.,* **1959**, *81*, 2126.

5. (a) Tinkelenberg, A.; Kooyman, E. C. and Louw, R., *Recl. Trav. Chim. Pays-Bas,* **1972**, *91*, 3. (b) Hurd, C. D. and Blunk, F. H., *J. Am. Chem. Soc.,* **1938**, *60*, 2419.
6. (a) Chuchanl, G.; Martin, I.; Hernández, A. J. A.; Roilnov, A.; Fraile, G. and Bigiey, D. B., *J. Phys. Chem.,* **1980**, *84*, 944. (b) Amin, H. B. and Taylor, R., *J. Chem. Soc., Perkin Trans. II,* **1978**, 1091. (c) Kramer, D. J. and Smith, G. G., *Int. J. Chem. Kinet.,* **1974**, *6*, 849. (d) Taylor, R., *J. Chem. Soc., Perkin Trans. II,* **1972**, 165. (e) Smith, G. G. and Kelly, F. W., *Prog. React. Kinet.,* **1971**, *8*, 75.
7. (a) Bailey, W. J. and Hale, W. F., *J. Am. Chem. Soc.,* **1959**, *81*, 647. (b) Bailey, W. J. and King, C., *J. Org. Chem.,* **1956**, *21*, 858. (c) Bailey, W. J. and King, C., *J. Org. Chem.,* **1956**, *21*, 854. (d) Bailey, W. J. and King, C., *J. Org. Chem.,* **1956**, *21*, 648. (e) Bailey, W. J.; Hewitt, J. J. and King, C., *J. Am. Chem. Soc.,* **1955**, *77*, 357.
8. de Sarmlento, M. A. G.; Domínguez, R. M. and Chuchanl, G., *J. Phys. Chem.,* **1980**, *84*, 2531.
9. Smith, G. G. and Bagley, F. D., *J. Org. Chem.,* **1959**, *24*, 128.
10. (a) Young, S. K.; Gemeinhardt, G. C.; Sherman, J. W.; Storey, R. F.; Mauritz, K. A.; Schiraldi, D. A.; Polyakova, A.; Hiltner, A. and Baer, E., *Polymer,* **2002**, *43*, 6101. (b) Persenaire, O.; Alexandre, M.; Degée, P. and Dubois, P., *Biomacromolecules,* **2001**, *2*, 288.
11. Bailey, W. J. and Economy, J., *J. Am. Chem. Soc.,* **1955**, *77*, 1133.
12. Trahanovsky, W. S.; Cassady, T. J. and Woods, T. L., *J. Am. Chem. Soc.,* **1981**, *103*, 6691.
13. (a) Trahanovsky, W. S. and Emeis, S. L., *J. Am. Chem. Soc.,* **1975**, *97*, 3773. (b) Trahanovsky, W. S. and Mullen, P. W., *J. Am. Chem. Soc.,* **1972**, *94*, 5086.
14. Pattison, D. B., *J. Am. Chem. Soc.,* **1957**, *79*, 3455.
15. Bailey, W. J. and Bird, C. N., *J. Org. Chem.,* **1977**, *42*, 3895.
16. (a) Smith, G. G.; Mutter, L. and Todd, C. P., *J. Org. Chem.,* **1977**, *42*, 44. (b) Roach, L. C. and Daly, W. H., *J. Chem. Soc. D,* **1970**, 606. (c) Bailey, W. J. and Carpenter, W. G., *J. Org. Chem.,* **1964**, *29*, 1252. (d) Bailey, W. J.; Hudson, R. L. and Yates, E. T., *J. Org. Chem.,* **1963**, *28*, 828. (e) Bailey, W. J.; Barclay, R. and Baylouny, R. A., *J. Org. Chem.,* **1962**, *27*, 1851. (f) Bailey, W. J.; Carpenter, W. G. and Hermes, M. E., *J. Org. Chem.,* **1962**, *27*, 1975. (g) Bailey, W. J. and Hermes, M. E., *J. Org. Chem.,* **1962**, *27*, 2732. (h) Bailey, W. J. and Nielsen, N. A., *J. Org. Chem.,* **1962**, *27*, 3088. (i) Cope, A. C. and Youngquist, M. J., *J. Am. Chem. Soc.,* **1962**, *84*, 2411. (j) Baumgartner, G. J. and Wilson, C. L., *J. Am. Chem. Soc.,* **1959**, *81*, 2440. (k) Bailey, W. J. and Hale, W. F., *J. Am. Chem. Soc.,* **1959**, *81*, 651. (l) Bailey, W. J. and Economy, J., *J. Org. Chem.,* **1958**, *23*, 1002. (m) Royals, E. E., *J. Org. Chem.,* **1958**, *23*, 1822. (n) Bailey, W. J. and Barclay, R., *J. Org. Chem.,* **1956**, *21*, 328. (o) Bailey, W. J.; Cunov, C. H. and Nicholas, L, *J. Am. Chem. Soc.,* **1955**, *77*, 2787. (p) Bailey, W. J. and King, C., *J. Am. Chem. Soc.,* **1955**, *77*, 75. (q) Arnold, R. T.; Smith, G. G. and Dodson, R. M., *J. Org. Chem.,* **1951**, *16*, 1256. (r) Filachione, E. M.; Lengel, J. H. and Ratchford, W. P., *J. Am. Chem. Soc.,* **1950**, *72*, 839. (s) Rehberg, C. E. and Fisher, C. H., *J. Am. Chem. Soc.,* **1945**, *67*, 56. (t) Ratchford, W. P.; Rehberg, C. E. and Fisher, C. H., *J. Am. Chem. Soc.,* **1944**, *66*, 1864. (u) Bilger, E. M. and Hibbert, H., *J. Am. Chem. Soc.,* **1936**, *58*, 823.

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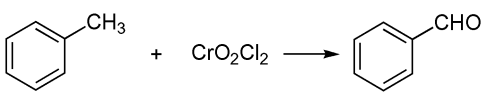
Étard Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Étard in 1880.[1] It is the oxidation of hydrocarbons by hexavalent chromium compounds (chromyl chloride,[2] i.e., chromatic acid chloride) to form a mixture of alcohol, carbonyl compounds (aldehyde or ketones), chloro-ketones, or aldehydes and the starting material.[3] Therefore, this reaction is generally known as the Étard reaction.[2,4] In this reaction, a highly hygroscopic brown powder forms[3b] which is called the Étard Complex[3a,3b,5] and is a heterogenous, oligomeric material[3a] containing carbonyl compounds and at least 2 equivences of chromium atom in a valence of IV and VI.[4i,6] It was found that the carbonyl compound functions as a ligand in the Étard complex[3a,3b] and can be displaced by other coordinating solvents, such as acetonitrile, acetone, and water.[3b] The wide distribution of products[3] (alcohols, ketones, chloroketones, and even epoxides[7]) and the lack of specificity[8] at the reaction site reduce the yields of the desired compounds.[9] As a result, this reaction is almost useless for organic synthesis, and the corresponding reaction mechanism is not clear either.[8] However, the oxidation of methylated homologs of benzene using chromyl chloride is an effective method for preparing aromatic aldehydes.[6,9,10]

B. GENERAL REACTION SCHEME



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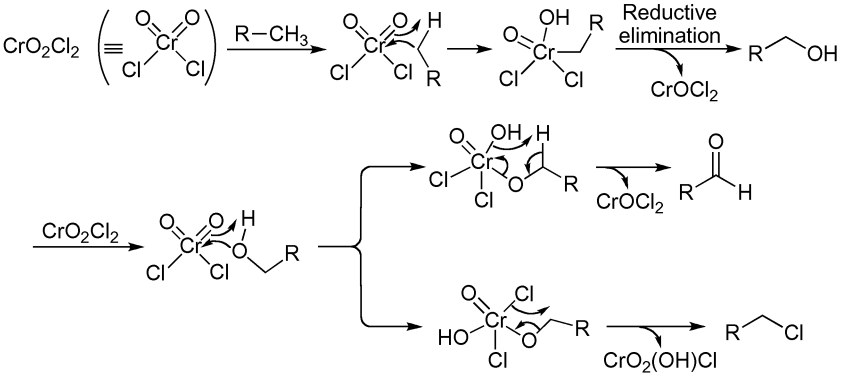
C. PROPOSED MECHANISMS

It is assumed that chromium (VI) is reduced by hydrocarbons via the formation of a Cr-C bond in the Étard reaction,[8] as outlined below.



D. MODIFICATION

N/A

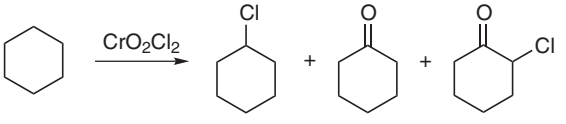
E. APPLICATIONS

This reaction has been used to prepare aromatic aldehydes.

F. RELATED REACTIONS

This reaction is related to the *Corey-Schmidt Oxidation* and *Corey-Suggs Oxidation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 3b.

The setup of thus reaction was done inside a glove box. To a greaseless Pyrex reaction vessel with small stir bar sealed with a Teflon valve with a ground, glass joint attachment was added 1 mL purified cyclohexane using a volumetric flask. Into the flask was syringed 20.0 ± 0.3 μL of CrO_2Cl_2 (0.247 mmol). The needle valve on the reaction flask was quickly closed, and the reaction vessel was removed from the glove box. The flask was then placed in a light-free, temperature-controlled circulating water bath at 80°C, and the reaction

mixture was set stirring. Over approximately 8 h, a brown solid formed on the bottom of the reaction vessel, while the solution turned from clear red to colorless. The reaction vessel was removed from the hot water and immediately frozen in a dry ice–acetone bath followed by the addition of 1.5 mL 0.1 M $Na_2S_2O_3$, yielding a clear green aqueous layer and a colorless organic phase. Chloroform (4 mL) and 10.0 $\pm$ 0.3 μL of *n*-heptane standard were added. After being stirred for 10–15 min, a 1 mL aliquot of the organic layer was pipetted into a vial followed by 30 mL TMEDA. The resulting solution was analyzed by GC/FID and GC/MS, indicating 10% chlorocyclohexane, 8.0% cyclohexanone, and 2.5% chlorocyclohexanone.

Other references related to the Étard reaction are cited in the literature.[11]

H. REFERENCES

1. (a) Étard, A. L., *Compt. Rend.,* **1880**, *90*, 534. (b) Étard, A. L., *Ann. Chim. Phys.,* **1881**, *22*, 218.
2. (a) Schiketanz, I. I.; Badea, F.; Hanes, A. and Necsoiu, I., *Rev. Roumaine Chim.,* **1984**, *29*, 353. (b) Schiketanz, I. I.; Hanes, A. and Necsoiu, I., *Rev. Roumaine Chim.,* **1977**, *22*, 1097. (c) Psemetchi, V.; Necsoiu, I.; Rentea, M. and Nenitzescu, C. D., *Rev. Roumaine Chim.,* **1969**, *14*, 1567. (d) Ghenciulescu, A.; Necsoiu, I. and Nenitzescu, C. D., *Rev. Roumaine Chim.,* **1969**, *14*, 1553. (e) Ghenciulescu, A.; Necsoiu, I.; Rentea, M. and Nenitzsecu, C. D., *Rev. Romaine Chim.,* **1969**, *14*, 1543. (f) Schiketanz, I.; Necsoiu, I.; Rentea, M. and Nenitzescu, C. D., *Rev. Roumaine Chim.,* **1968**, *13*, 1385. (g) Rentea, C. N.; Rentea, M.; Necsoiu, I. and Nenitzescu, C. D., *Tetrahedron*, **1968**, *24*, 4667. (h) Necsoiu, I.; Ghenciulescu, A.; Rentea, M.; Rentea, C. N. and Nenitzescu, C. D., *Rev. Roumaine Chim.,* **1967**, *12*, 1503. (i) Rentea, C. N.; Rentea, M.; Necsoiu, I. and Nenitzescu, C. D., *Rev. Roumaine Chim.,* **1967**, *12*, 1495. (j) Rentea, C. N.; Necsoiu, I.; Rentea, M.; Ghenciulescu, A. and Nenitzescu, C. D., *Tetrahedron*, **1966**, *22*, 3501. (k) Necsoiu, I.; Przemetchi, V.; Ghenciulescu, A.; Rentea, C. N. and Nenitzescu, C. D., *Tetrahedron*, **1966**, *22*, 3037.
3. (a) Cook, G. K. and Mayer, J. M., *J. Am. Chem. Soc.,* **1995**, *117*, 7139. (b) Cook, G. K. and Mayer, J. M., *J. Am. Chem. Soc.,* **1994**, *116*, 1855. (c) Freeman, F. and Yamachika, N. J., *J. Am. Chem. Soc.,* **1970**, *92*, 3730.
4. (a) Schildknecht, H. and Reichel, F., *Chem.-Zeitung, Chem. Apparatur,* **1970**, *94*, 165. (b) Gragerov, I. P. and Ponomarchuk, M. P., *Zh. Org. Khim.,* **1969**, *5*, 1145. (c) Duffin, H. C. and Tucker, R. B., *Tetrahedron*, **1968**, *24*, 6999. (d) Nenitzescu, C. D., *Bull. Soc. Chim. Fr.,* **1968**, 1349. (e) Schildknecht, H. and Hatzmann, G., *Angew. Chem. Int. Ed. Engl.,* **1968**, *7*, 293. (f) Makhija, R. C. and Stairs, R. A., *Can. J. Chem.,* **1968**, *46*, 1255. (g) Wheeler, O. H., *Can. J. Chem.,* **1964**, *42*, 706. (h) Stairs, R. A., *Can. J. Chem.,* **1964**, *42*, 550. (i) Necsoiu, I.; Balaban, A. T.; Pascaru, I.; Sliam, E.; Elian, M. and Nenitzescu, C. D., *Tetrahedron*, **1963**, *19*, 1133. (j) Schildknecht, H. and Foettinger, W., *Ann.,* **1962**, *659*, 20. (k) Gragerov, I. P. and Ponomarchuk, M. P., *Zh. Obsh. Khim.,* **1962**, *32*, 3568. (l) Stairs, R. A., *Can. J. Chem.,* **1962**, *40*, 1655. (m) Wiberg, K. B.; Marshall, B. and Foster, G., *Tetrahedron Lett*., **1962**, 345. (n) Stairs, R. A. and Burns, J. W., *Can. J. Chem.,* **1961**, *39*, 960. (o) Wheeler, O. H., *Can. J. Chem.,* **1960**, *38*, 2137. (p) Wheeler, O. H., *Can. J. Chem.,* **1958**, *36*, 949.
5. Limberg, C. and Köppe, R., *Inorg. Chem.,* **1999**, *38*, 2106.
6. Chien, J. C. W. and Kiang, J. K. Y., *Macromolecules,* **1980**, *13*, 280.
7. Mosher, W. A.; Steefgen, F. W. and Lansbury, P. T., *J. Org. Chem.,* **1961**, *26*, 670.
8. Rappé, A. K. and Goddard, W. A., *J. Am. Chem. Soc.,* **1982**, *104*, 3287.
9. Delatour, T.; Gremaud, E.; Mottier, P.; Richoz, J.; Vera, F. A. and Stadler, R. H., *J. Agric. Food Chem.,* **2003,** *51,* 6371.

10. (a) Laird, R. M. and Parker, R. E., *J. Am. Chem. Soc.,* **1961**, *83*, 4277. (b) Westheimer, F. H., *Chem. Rev.,* **1949**, *45,* 419.

11. (a) Limberg, C. and Doz, P., *Chem. Eur. J.,* **2000**, *6*, 2083. (b) Luzzio, F. A. and Moore, W. J., *J. Org. Chem.,* **1993**, *58*, 512. (c) Glemser, O. and Holznagel, W., *Angew. Chem. Int. Ed. Engl.,* **1962**, *1*, 220. (d) Sulima, L. V. and Gragerov, I. P., *J. Gen. Chem. USSR*, **1959**, *29*, 3787. (e) Wheeler, O. H., *Can. J. Chem.,* **1958**, *36*, 667. (f) Hartford, W. H. and Darrin, M., *Chem. Rev.,* **1958**, *58*, 1. (g) Hobbs, C. C. and Houston, B., *J. Am. Chem. Soc.,* **1954**, *76*, 1254. (h) Tillotson, A. and Houston, B., *J. Am. Chem. Soc.,* **1951**, *73*, 221. (i) Ferguson, L. N., *Chem. Rev.,* **1946**, *38*, 237.

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Evans Aldol Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Evans and co-workers in 1979.[1] It is the diastereoselective addition of the dibutylboryl enolate of chiral *N*-acyl-oxazolidone to aldehydes. In this reaction, the chiral auxiliary will help the generated enolate from the acyl part to take different conformations, depending on the presence or absence of oxophilic metal, to form the chelated coordination between the metal cation and the oxygens of two carbonyl groups.[2] The chiral *N*-acyl-oxazolidone is called the Evans reagent.[2] Because this reaction provides the most reliable means for controlling the vicinal *syn* stereogenic centers (especially for the case of propionate, with a diastereoselectivity of $> 140{:}1$ to $500{:}1$[3]), irrespective of the absolute configuration of α-branched aldehydes (i.e., a tolerance for a broad range of aldehydes, either alkyl or aryl, hindered or unhindered),[4] it has been successfully applied to the syntheses of many natural products (e.g., phyllanthocin,[5] and tautomycin[6]), especially the macrolides (amphidinolide B1,[7] tedanolide,[8] (+)-rhizoxin D,[9] altohyrtin A,[10] salicylihalamides,[11] bafilomycin A1,[12] aplyronine A,[13] etc.). It has been modified extensively to different variations, including the application of Lewis acid,[2,14] the modification of chiral auxiliaries (e.g., replacement of oxazolidone with 3,4,5,6-tetrahydro-2H-1,3,4-oxadiazin-2-ones (oxadiazinones)[15] or thiazolidinethione[14]), the application of different chelating metals.[16] Because of these modifications, this reaction gradually gained different names, including the Evans asymmetric aldol reaction,[2,17] Evans aldol condensation,[9,18] Evans aldol methodology,[19] Evans aldol process,[19] Evans aldol reaction,[4,5,9,11,13,20] Evans catalytic asymmetric aldol reaction,[21] Evans *syn*-aldol addition,[14] Evans-Tischenko reaction,[22] and Tischenko-Evans reaction.[23] For the special

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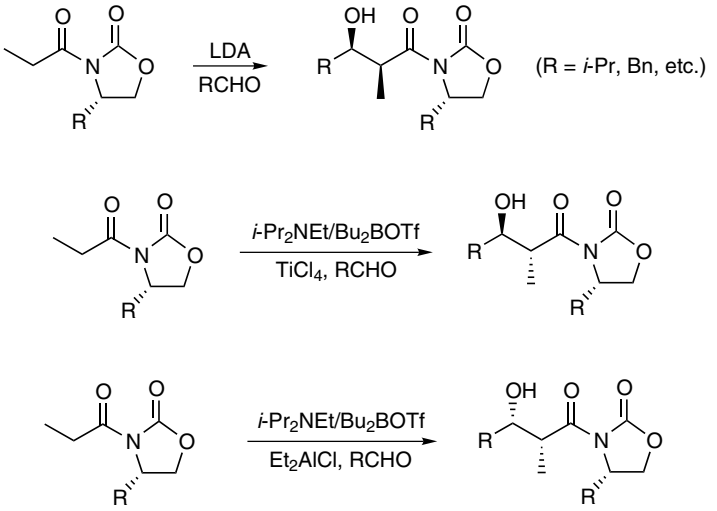
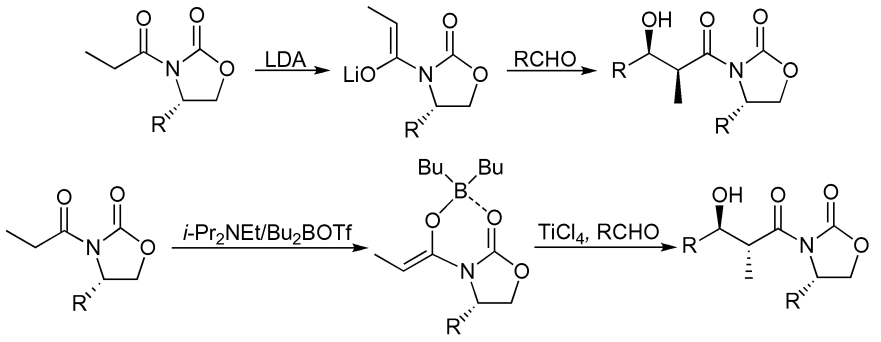
case of an aldol reaction in the presence of a Lewis acid, both "non-Evans" *syn*- and *anti*-aldol products can be generated, depending on the size of the applied Lewis acid (e.g., $TiCl_4$ and Et_2AlCl) or the experimental procedure (slow addition of $SnCl_4$ or $TiCl_4$).[2] The non-Evans *anti*-aldol product predominates if a large Lewis acid is used, such as Et_2AlCl, or the formation of a reactive 2:1 complex via the slow addition of $TiCl_4$; the non-Evans *syn*-aldol product will be formed favorably if a small Lewis acid such as $SnCl_4$ is applied. Coupling with the original Evans condition, three out of four aldol products can be produced selectively. Although the diastereoselectivity is not perfect, a product with high enantiomeric purity can be easily purified via crystallization.[2]

In addition, under the help of a chiral auxiliary group, the generated enolate can also react with electrophiles to form α-alkylated ketones,[4] and this specific reaction is called Evans alkylation[24] (such as in the case for the preparation of discodermolide[4]).

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

As for the characteristic controlling of stereochemistry during aldol reaction, the Evans aldol reaction has been extensively modified through the application of Lewis acids,[2,14] chiral auxiliaries (e.g., oxazolidone,[1,2] oxadiazinones,[15] thiazolidinethione[14]), chelating metals,[16] etc.

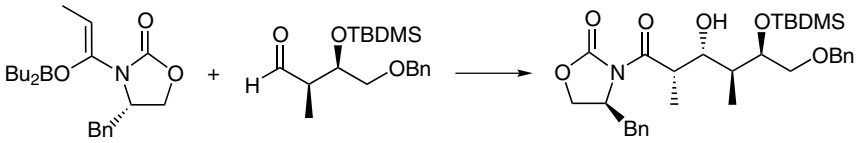
E. APPLICATIONS

This reaction is very useful for the preparation of the compounds with specific vicinal stereogenic centers.

F. RELATED REACTIONS

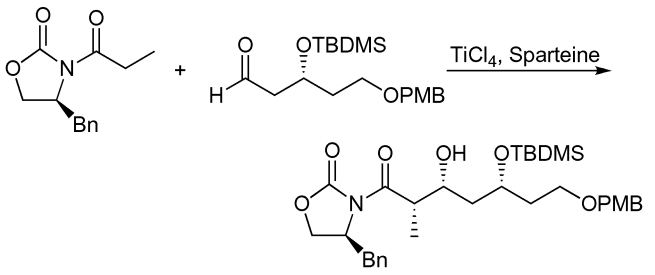
This reaction is related to the *Aldol Reaction*, *Mukaiyama Aldol Reaction,* and *Tischenko Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 12.

To a solution of 0.160 g propionyl (5*S*)-5-benzyl oxazolidinone (0.688 mmol) in 1.5 mL CH_2Cl_2 at 0°C were added dropwise 0.206 mL Bu_2BOTf (0.812 mmol, 1.18 eq.) and 0.125 mL Et_3N (0.908 mmol, 1.32 eq.). After 20 min, the reaction mixture was cooled to −78°C, and 0.246 g (-)-phenyl (2*R*,3*R*)-4-benzyloxy-3-(tert-butyldimethylsiloxy)-2-methylbutyrate (0.764 mmol, 1.1 eq.) in 0.3 mL CH_2Cl_2 was added dropwise. After 1 h at −78°C and 2 h at 0°C, 0.756 mL of a buffered phosphate solution (pH = 7) was added followed by the addition of 2.27 mL MeOH and a mixture of 30% H_2O_2/MeOH (2:1 ratio). After 1 h at 0°C, the reaction mixture was concentrated under vacuum, and ether was added followed by a saturated aqueous $Na_2S_2O_4$ solution. The aqueous solution was extracted with ether (four times), and the organic phases were washed with a saturated aqueous $NaHCO_3$ solution and then with brine. The resulting solution was dried over $MgSO_4$, filtered, and evaporated and the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 4:1) to give 0.305 g (+)-(4*S*)-3-[(2*S*,3*R*,4*S*,5*R*)-6-benzyloxy-5-(*tert*-butyldimethylsiloxy)-3-hydroxy-2,4-dimethyl-hexanoyl]-4-benzyloxalidin-2-one as a colorless oil, in a yield of 80%, $R_f = 0.33$ (petroleum ether/EtOAc, 4:1).



Reference 11.

To a stirred, cooled (0°C) solution of 2.86 g (4*S*)-4-(phenylmethyl)-3-propanoyl-1,3-oxazolidin-2-one (12.3 mmol) in 100 mL CH_2Cl_2 was added dropwise 1.42 mL titanium(IV) chloride (2.44 g, 12.9 mmol); the mixture was allowed to stir for 5 min. Subsequently, 7.04 mL (-)-sparteine (7.19 g, 30.7 mmol) was added to the yellow slurry. The dark red enolate solution was stirred for 20 min at 0°C before a solution of 4.76 g (3*R*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-5-[(4-methoxy-benzyl)oxy]pentanal (13.5 mmol) in 50 mL CH_2Cl_2 was added dropwise, and the mixture was stirred for 1 h at 0°C. The reaction was quenched with 20 mL half-saturated ammonium chloride. After separation of the layers, the organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography afforded 5.67 g (4*R*)-4-benzyl-3-{(2*R*,3*R*,5*R*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-3-hydroxy-7-[(4-methoxybenzyl)oxy]-2-methylheptanoyl}-1,3-oxazolidin-2-one as a colorless oil, in a yield of 79%. $R_f = 0.33$ (petroleum ether/Et_2O, 2:3).

Other references related to the Evans aldol reaction are cited in the literature.[25]

H. REFERENCES

1. Evans, D. A., Vogel, E. and Nelson, J. V., *J. Am. Chem. Soc.,* **1979**, *101*, 6120.
2. Walker, M. A. and Heathcock, C. H., *J. Org. Chem.,* **1991**, *56*, 5747.
3. Evans, D. A.; Bartroli, J. and Shih, T. L., *J. Am. Chem. Soc.,* **1981**, *103*, 2127.
4. Nakamura, S.; Inagaki, J.; Kitaguchi, J.; Tatani, K. and Hashimoto, S. H., *Chem. Pharm. Bull.,* **1999**, *47*, 1330.
5. Smith, A. B. and Empfield, J. R., *Chem. Pharm. Bull.,* **1999**, *47*, 1671.
6. Sheppeck, J. E.; Liu, W. and Chamberlin, A. R., *J. Org. Chem.,* **1997**, *62*, 387.
7. Zhang, W.; Carter, R. G. and Yokochi, A. F. T., *J. Org. Chem.,* **2004**, *69*, 2569.
8. Smith, A. B. and Lodise, S. A., *Org. Lett.,* **1999**, *1*, 1249.
9. Jiang, Y. H.; Hong, J. and Burke, S. D., *Org. Lett.,* **2004**, *6*, 1445.
10. Claffey, M. M.; Hayes, C. J. and Heathcock, C. H., *J. Org. Chem.,* **1999**, *64*, 8267.
11. Herb, C. and Maier, M. E., *J. Org. Chem.,* **2003**, *68*, 8129.
12. Eustache, F.; Dalko, P. I. and Cossy, J., *J. Org. Chem.,* **2003**, *68*, 9994.
13. Kogoshi, H.; Suenaga, K.; Mutou, T.; Ishigaki, T.; Atsumi, T.; Ishiwata, H.; Sakakura, A.; Ogawa, T.; Ojika, M. and Yamada, K., *J. Org. Chem.,* **1996**, *61*, 5326.
14. Crimmins, M. T.; King, B. W.; Tabet, E. A. and Chaudhary, K., *J. Org. Chem.,* **2001**, *66*, 894.

15. (a) Hitchcock, S. R.; Casper, D. M.; Vaughn, J. F.; Finefield, J. M.; Ferrence, G. M. and Esken, J. M., *J. Org. Chem.,* **2004**, *69*, 714. (b) Burgeson, J. R.; Renner, M. K.; Hardt, I.; Ferrence, G. M.; Standard, J. M. and Hitchcock, S. R., *J. Org. Chem.,* **2004**, *69*, 727.

16. Bartroli, J.; Turmo, E.; Belloc, J. and Forn, J., *J. Org. Chem.,* **1995**, *60*, 3000.

17. (a) Dias, L. C.; de Oliveira, L. G. and de Sousa, M. A., *Org. Lett.,* **2003**, *5*, 265. (b) Trotter, N. S.; Takahashi, S. and Nakata, T., *Org. Lett.,* **1999**, *1*, 957. (c) Maioli, A. T.; Civiello, R. L.; Foxman, B. M. and Gordon, D. M., *J. Org. Chem.,* **1997**, *62*, 7413.

18. Picoul, W.; Bedel, O.; Haudrechy, A. and Langlois, Y., *Pure & Appl. Chem.,* **2003**, *75*, 235.

19. Williams, D. R.; Patnaik, S. and Clark, M. P., *J. Org. Chem.,* **2001**, *66*, 8463.

20. (a) Shimada, T.; Yoshioka, M.; Konno, T. and Ishihara, T., *Org. Lett.,* **2006**, *8*, 1129. (b) Kadota, I.; Hu, Y. Q.; Packard, G. K. and Rychnovsky, S. D., *Proc. Nat. Acad. Sci. USA,* **2004**, *101*, 11992. (c) Fleming, K. N. and Taylor, R. E., *Angew. Chem. Int. Ed. Engl.,* **2004**, *43*, 1728. (d) Burke, M. D.; Berger, E. M. and Schreiber, S. L., *Science,* **2003**, *302*, 613. (e) Gabriel, T. and Wessjohann, L., *Tetrahedron Lett*., **1997**, *38*, 4387. (f) Iseki, K.; Oishi, S. and Kobayashi, Y., *Tetrahedron*, **1996**, *52*, 71. (g) Makino, Y.; Iseki, K.; Fujii, K.; Oishi, S.; Hirano, T. and Kobayashi, Y., *Tetrahedron Lett*., **1995**, *36*, 6527. (h) Hayashi, K.; Hamada, Y. and Shioiri, T., *Tetrahedron Lett*., **1991**, *32*, 7287.

21. DeRoy, P. L. and Charette, A. B., *Org. Lett.,* **2003**, *5*, 4163.

22. Lu, L.; Chang, H.-Y. and Fang, J.-M., *J. Org. Chem.,* **1999**, *64*, 843.

23. Keck, G. E. and Lundquist, G. D., *J. Org. Chem.,* **1999**, *64*, 4482.

24. (a) Crimmins, M. T.; Emmitte, K. A. and Katz, J. D., *Org. Lett.,* **2000**, *2*, 2165. (b) Andrus, M. B. and Lepore, S. D., *J. Am. Chem. Soc.,* **1997**, *119*, 2327. (c) Decicco, C. P. and Grover, P., *J. Am. Chem. Soc.,* **1996**, *61*, 3534. (d) Williams, D. R. and McGill, J. M., *J. Org. Chem.,* **1990**, *55*, 3457. (e) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S. and Bilodeau, M. T., *J. Am. Chem. Soc.,* **1990**, *112*, 8215. (f) Evans, D. A.; Ennis, M. D. and Le, T., *J. Am. Chem. Soc.,* **1984**, *106*, 1154. (g) Evans, D. A.; Ennis, M. D. and Mathre, D. J., *J. Am. Chem. Soc*., **1982**, *104*, 1737.

25. (a) Mahrwald, R., *Modern Aldol Reactions*, Gebunden, Wiley-VCH, Weinheim, **2004**. (b) Mickel, S. J.; Sedelmeier, G. H.; Niederer, D.; Daeffler, R.; Osmani, A.; Schreiner, K.; Seeger-Weibel, M.; Berod, B.; Schaer, K. and Gamboni, R., *Org. Proc. Res. Dev.,* **2004**, *8*, 92. (c) Tanaka, H.; Sawayama, A. M. and Wandless, T. J., *J. Am. Chem. Soc.,* **2003**, *125*, 6864. (d) Li, G. G.; Xu, X.; Chen, D. J.; Timmons, C.; Carducci, M. D. and Headley, A. D., *Org. Lett.,* **2003**, *5,* 329. (e) Wu, Y. K.; Shen, X.; Tang, C.-J.; Chen, Z.-L.; Hu, Q. and Shi, W., *J. Org. Chem.,* **2002**, *67*, 3802. (f) Shotwell, J. B, Krygowski, E. S.; Hines, J.; Koh, B.; Hungtsman, E. W. D.; Choi, H. W.; Schneekloth, J. S.; Wood, J. L. and Crews, C. M., *Org. Lett.,* **2002**, *4*, 3087. (g) Casper, D. M.; Burgeson, J. R.; Esken, J. M.; Ferrence, G. M. and Hitchcock, S. R., *Org. Lett.,* **2002**, *4*, 3739. (h) Crimmins, M. T. and Chaudhary, K., *Org. Lett.,* **2000**, *2*, 775. (i) Arya, P. and Qin, H. P., *Tetrahedron,* **2000**, *56*, 917. (j) Mapp, A. K. and Heathcock, C. H., *J. Org. Chem.,* **1999**, *64,* 23. (k) Pearson, C.; Rinehart, K. L. and Sugano, M., *Tetrahedron Lett.,* **1999**, *40*, 411. (l) Phoon, C. W. and Abell, C., *Tetrahedron Lett.,* **1998**, *39*, 2655. (m) Cowden, C. J. and Paterson, I., "Asymmetric Aldol Reactions using Boron Enolates" in *Organic Reactions*, ed. Paquette, L. A., John Wiley & Sons, New York, **1997**, *51*, pp. 1–200. (n) Galatsis, P.; Millan, S. D. and Ferguson, G., *J. Org. Chem.,* **1997**, *62*, 5048. (o) Ager, D. J.; Prakash, I. and Schaad, D. R., *Aldrichimica Acta,* **1997**, *30*, 3. (p) Sibi, M. P.; Lu, J. L. and Edwards, J., *J. Org. Chem.,* **1997**, *62,* 5864. (q) Franklin, A. S. and Paterson, I., *Contemp. Org. Synth.,* **1994**, *1*, 317. (r) Iseki, K.; Oishi, S.; Taguchi, T. and Kobayashi, Y., *Tetrahedron Lett.,* **1993**, *34*, 8147. (s) Gage, J. R. and Evans, D. A., *Org. Synth*., **1990**, *68*, 83. (t) Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N. and Mandel, G., *J. Am. Chem. Soc*., **1984**, *106*, 1154. (u) Evans, D. A., *Aldrichimica Acta,* **1982**, *15*, 23. (v) Evans, D. A., Nelson, J. V.; Vogel, E. and Taber, T. R., *J. Am. Chem. Soc.,* **1981**, *103*, 3099.

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Favorskii Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Favorskii in 1894.[1] It is a base-induced rearrangement of α-halo ketones to the corresponding carboxylic acid derivatives (e.g., acids, esters, and amides) with the same number of carbon atoms in the skeletons; and the bases can be hydroxide, alkoxide, or amines.[2] Therefore, it is generally known as the Favorskii rearrangement.[3] Occasionally, it is also referred to as the Favorskii reaction.[4]

There have been at least six different mechanisms proposed for this rearrangement: (*a*) the addition of alkoxide to the carbonyl group with the concomitant extrusion of a halide ion to form a final product via the intermediate of epoxide;[5] (*b*) the reaction of a nucleophile with a ketene generated by the base-induced elimination of hydrogen halide;[6] (*c*) the addition of alkoxide to the carbonyl group followed by the 1,2-migration of an alkyl group (similar to the *Benzilic Acid Rearrangement*; therefore, it is also called the semibenzilic acid mechanism[7] or abnormal or quasi-Favorskii rearrangement[8]); (*d*) the unimolecular dissociation of an α-halo ketone to a carbonium ion, which tautomerizes to isomeric carbonium then rearranges to product;[9] (*e*) the generation of a carbanion by deprotonation of α'-hydrogen followed by a nucleophilic substitution to form cyclopropanone, which undergoes rearrangement to a final product during alkoxide attacks[10] (this mechanism is also called the Loftfield mechanism[11] or cyclopropanone mechanism[12]); and (*f*) the formation of an oxyallylic anion that undergoes [4+3] cycloaddition.[13] Among these mechanisms, the semibenzilic acid mechanism and cyclopropanone mechanisms are most plausible.[7b,12a] When α'-hydrogens are available, the cyclopropanone mechanism is preferred,[10–12] whereas semibenzilic acid mechanism comes into play in the absence of

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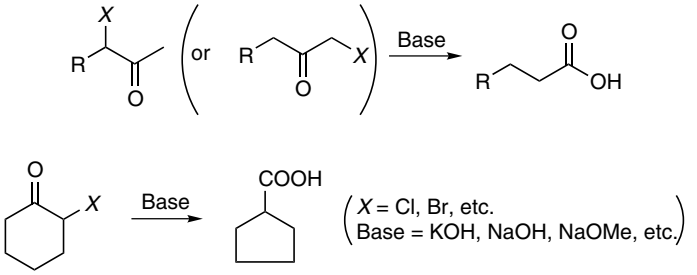
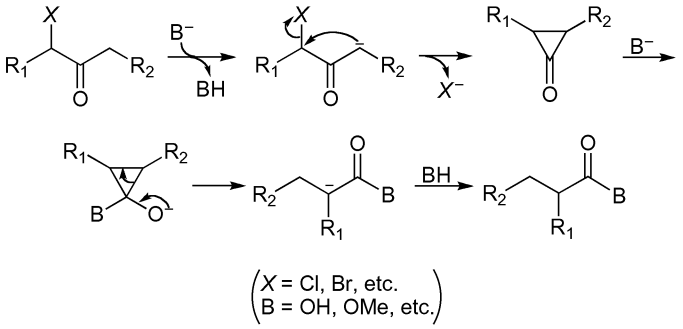
α'-hydrogens (e.g., in nonenolizable ketones[7b,14a]) or when the formation of cyclopropanone is prevented.[14] However, it has been reported that in the gas phase the semibenzilic acid mechanism is more favorable,[7b,12a] and the oxyallylic mechanism can be limited using a non-nucleophilic solvent such as trifluoroethanol.[13a] Similarly, many experimental results have shown that the actual reaction mechanisms depend on the reaction conditions.[15] Even the cyclopropanone mechanism can be concerted or unconcerted.[16] In this reaction, the deprotonation is the rate-limiting step, followed by a quick halo extrusion.[17] In the case of cyclic α-halo ketones, ring contraction occurs.[13b,18] A similar reaction occurs on β-halo ketones via the elimination of a hydrogen halide to cyclobutanone followed by the scission of cyclobutanone, known as the homo-Favorskii rearrangement.[11,19] This reaction has been proved to be a useful tool for synthesizing the highly strained esters, bicyclic esters,[13b] and some steroids,[20] norsteriods,[21] etc. In addition, this reaction has been successfully applied to the synthesis of saturated pyrollidine derivatives.[18a] Similarly, the base-induced rearrangement of ketimines will afford imidates or amides.[12b] More details about this reaction are described in reviews.[22]

B. GENERAL REACTION SCHEME

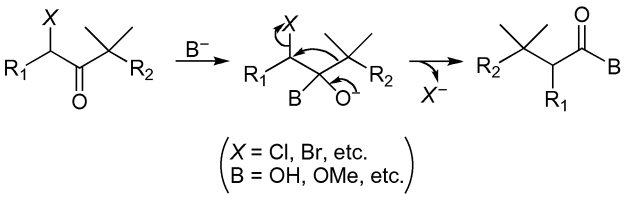


C. PROPOSED MECHANISMS

Although several mechanisms have been proposed for this reaction, only cyclopropanone mechanism (Scheme 1) and benzilic acid mechanism (Scheme 2) are displayed here.



SCHEME 1. *Favorskii rearrangement via cyclopropanone mechanism.*



SCHEME 2. *Favorskii rearrangement occurring a benzilic acid mechanism.*

D. MODIFICATION

N/A

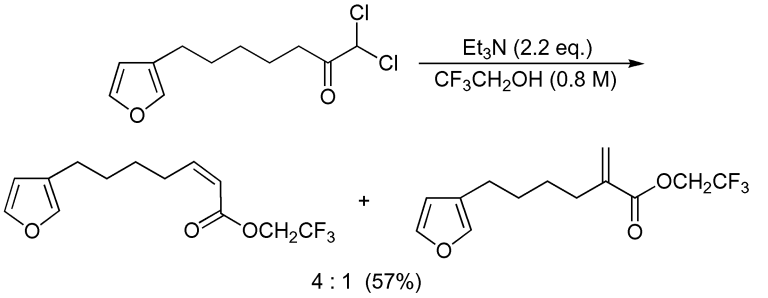
E. APPLICATIONS

This reaction has been successfully used to prepare bicyclic esters, steroids, norsteroids, pyrollidine, etc.

F. RELATED REACTIONS

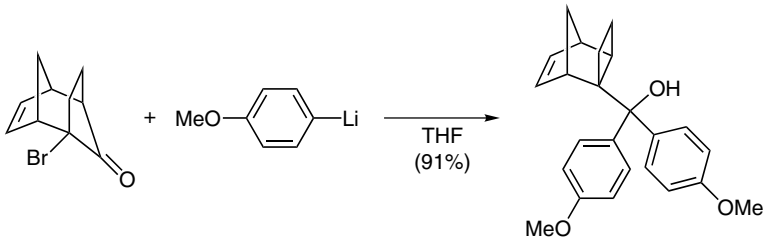
This reaction is related to *Benzilic Acid Rearrangement*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 13a.

To a solution of 50 mg 1,1-dichloro-7-furan-3′-yl-heptan-2-one (0.20 mmol) in 0.25 mL 1,1,1-trifluoroethanol (0.8 M) was added 60 μL triethylamine (0.44 mmol) at room temperature. The reaction mixture was heated at 50°C (oil bath) for 24 h before quenching with water and extracting with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated to give a residue that was purified by column chromatography (5:1, hexane/EtOAc) to give 31.3 mg an inseparable mixture of trifluoroethyl acrylic esters in a 4:1 ratio, in a yield of 57%, $R_f = 0.68$ (hexane/EtOAc, 5:1).



Reference 8a.

To a cooled solution of 100 mg bromoketone (0.44 mmol) in 4.4 mL THF at −78°C was added 2.2 eq. of 4-methoxyphenyl lithium solution dropwise. After being stirred at −78°C for 1 h, the reaction mixture was warmed to room temperature over 2 h and then stirred for an additional 4 h. It was quenched with distilled water, extracted by ether (3 × 10 mL), washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography with 5% EtOAc in hexane to yield 91% of bis(4-methoxyphenyl)tricyclo[4.2.1.$0^{2,5}$]non-7-en-2-ylmethanol as an oil.

Other references related to the Favorskii rearrangement are cited in the literature.[23]

H. REFERENCES

1. Favorskii, A. E., *J. Russ. Phys. Chem. Soc.,* **1894**, *26*, 559.
2. Castillo, R.; Andrés, J. and Moliner, V., *J. Phys. Chem. B,* **2001**, *105*, 2453.
3. (a) Miura, M.; Toriyama, M. and Motohashi, S., *Synth. Commun.,* **2006**, *36*, 259. (b) Foehlisch, B.; Franz, T. and Kreiselmeier, G., *Eur. J. Org. Chem.,* **2005**, 4687. (c) Guijarro, D. and Yus, M., *Curr. Org. Chem.,* **2005**, *9*, 1713. (d) Iglesias-Arteaga, M. A. and Velazquez-Huerta, G. A., *Tetrahedron Lett*., **2005**, *46*, 6897. (e) Elinson, M. N.; Feducovich, S. K.; Zaimovskaya, T. A.; Dorofeev, A. S.; Vereshchagin, A. N. and Nikishin, G. I., *Russ. Chem. Bull.,* **2003**, *52*, 998. (f) Elinson, M. N.; Feducovich, S. K.; Dorofeev, A. S.; Vereshchagin, A. N. and Nikishin, G. I., *Russ. Chem. Bull.,* **2003**, *52*, 228. (g) Muldgaard, L.; Thomsen, I. B.; Hazell, R. G. and Bols, M., *J. Chem. Soc., Perkin Trans. I,* **2002**, 1297. (h) Makarova, N. V.; Moiseev, I. K. and Zemtsova, M. N., *Russ. J. Gen. Chem.,* **2002**, *72*, 95. (i) Castillo, R.; Moliner, V.; Safont, V. S.; Oliva, M. and Andres, J., *THEOCHEM*, **1998**, *426*, 299. (j) Inesi, A.; Rossi, L.; Feroci, M. and Rizzuto, M., *New J. Chem.,* **1998**, *22*, 57. (k) Quan, B. and Dong, H. S., *Huaxue Yanjiu Yu Yingyong*, **1997**, *9*, 555. (l) Lee, E.; Yoon, C. H.; Lee, Y. J. and Kim, H. J., *Bull. Korean Chem. Soc.,* **1997**, *18*, 1247. (m) Krinitskaya, L. A., *Russ. Chem. Bull.,* **1997**, *46*, 1140. (n) El-Wareth, A.; Sarhan, A. O. and Hoffmann, H. M. R., *J. Prakt. Chem./Chem.-Zeit.,* **1997**, *339*, 390. (o) Mathew, F. and Myrboh, B., *Synth. Commun.,* **1996**, *26*, 1097. (p) De Angelis, F.; Feroci, M. and Inesi, A., *Bull. Soc. Chim. Fr.,* **1993**, *130*, 712. (q) Satoh, T.; Motohashi, S.; Kimura, S.; Tokutake, N. and Yamakawa, K., *Tetrahedron Lett*., **1993**, *34*, 4823. (r) Satoh, T.; Oguro, K.; Shishikura, J.; Kanetaka, N.; Okada, R. and Yamakawa, K., *Bull. Chem. Soc. Jpn.,* **1993**, *66*, 2339. (s) Satoh, T.; Oguro, K.; Shishikura, J.; Kanetaka, N.; Okada, R. and Yamakawa, K., *Tetrahedron Lett*., **1992**, *33*, 1455. (t) De Kimpe, N.; D'Hondt, L. and Moens, L., *Tetrahedron*, **1992**, *48*, 3183. (u) Carelli, I.; Curulli, A.; Inesi, A. and Zeuli, E., *J. Chem. Res. (S),* **1991**, 10. (v) Elinson, M. N.; Makhova, I. V. and Nikishin, G. I., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1989**, 1208. (w) Donskaya, N. A.; Bessmertnykh, A. G. and Shabarov, Yu. S., *Zh. Org. Khim.,* **1989**, *25*, 332. (x) Johnson, D. W. and Poulos, A., *Biomed. Environ. Mass Spect.,* **1988**, *18*, 603. (y) De Kimpe, N.; Stanoeva, E. and Schamp, N., *Tetrahedron Lett*., **1988**, *29*, 589. (z) Sakai, T.; Amano, E.; Miyata, K.; Utaka,

M. and Takeda, A., *Bull. Chem. Soc. Jpn.,* **1987**, *60*, 1945. (aa) Sakai, T.; Ishikawa, M.; Amano, E.; Utaka, M. and Takeda, A., *Bull. Chem. Soc. Jpn.,* **1987**, *60*, 2295. (bb) Sakai, T.; Yamawaki, A.; Katayama, T.; Okada, H.; Utaka, M. and Takeda, A., *Bull. Chem. Soc. Jpn.,* **1987**, *60*, 1067. (cc) Tsuboi, S.; Nagae, H.; Yamato, H. and Takeda, A., *Bull. Chem. Soc. Jpn.,* **1987**, *60*, 836. (dd) Kulinkovich, O. G.; Tishchenko, I. G. and Sviridov, S. V., *Zh. Org. Khim.,* **1986**, 22, 1416. (ee) Engler, T. A. and Falter, W., *Tetrahedron Lett*., **1986**, *27*, 4115. (ff) Engler, T. A. and Falter, W., *Tetrahedron Lett*., **1986**, *27*, 4119. (gg) Abad, A.; Arno, M.; Pedro, J. R. and Seoane, E., *J. Chem. Soc., Perkin Trans. I,* **1983**, 2471. (hh) Cambie, R. C.; Robertson, J. D.; Rutledge, P. S. and Woodgate, P. D., *Aust. J. Chem.,* **1982**, *35*, 183. (ii) Greuter, H.; Dingwall, J.; Martin, P. and Bellus, D., *Helv. Chim. Acta,* **1981**, *64*, 2812.

4. (a) Isaev, S. D.; Novikova, M. I.; Chizhov, O. S.; Shchrbakov, M. V.; Shishkin, O. V. and Yurchenko, A. G., *Ukrainskii Khim. Zh.,* **1999**, *65*, 137. (b) Kurzer, F. and Patel, J. N., *Monatsh. Chem.,* **1987**, *118*, 1363. (c) Itooka, T.; Matoba, K.; Yamazaki, T.; Muraoka, O. and Momose, T., *Chem. Pharm. Bull.,* **1986**, *34*, 2391. (d) Daum, S. J., *Tetrahedron Lett*., **1984**, *25*, 4725. (e) Martin, P., *Helv. Chim. Acta,* **1983**, *66*, 1189.
5. (a) Aston, E. A., *J. Am. Chem. Soc.,* **1940**, *62*, 2590. (b) Favorskii, A. E., *J. Prakt. Chem.,* **1913**, *88,* 641.
6. Richard, G., *Compt. Rend.,* **1933**, *197*, 1943.
7. (a) Harmata, M. and Rashatasakhon, P., *Org. Lett.,* **2001**, *3*, 2533. (b) Lu, T.-J.; Liu, S.-W. and Wang, S.-H., *J. Org. Chem.,* **1993**, *58*, 7945. (c) Tchoubar, B. and Sackur, O., *Compt. Rend.,* **1939**, *208*, 1020.
8. (a) Harmata, M. and Wacharasindhu, S., *J. Org. Chem.,* **2005**, *70*, 725. (b) Harmata, M. and Bohnert, G. J., *Org. Lett.,* **2003**, *5*, 59. (c) Gambacorta, A.; Turchetta, S, S.; Bovicelli, P. and Botta, M., *Tetrahedron,* **1991**, *47*, 9097. (d) Kraus, G. A. and Shi, J., *J. Org. Chem*., **1991**, *56*, 4147. (e) Kraus, G. A. and Shi, J., *J. Org. Chem*., **1990**, *56*, 5424. (f) Stevens, C. L.; Pillai, P. M. and Taylor, K. G., *J. Org. Chem.,* **1974**, *39*, 3158. (g) Smissman, E. E. and Diebold, J. L., *J. Org. Chem.,* **1965**, *30*, 4005. (h) Smissman, E. E. and Hite, G., *J. Am. Chem. Soc.,* **1960**, *82*, 3375.
9. (a) McPhee, W. and Klingsberg, E., *J. Am. Chem. Soc.,* **1944**, *66*, 1132. (b) Richard, G., *Compt. Rend.,* **1935**, *200*, 1944.
10. (a) Loftfield, R. B., *J. Am. Chem. Soc.,* **1951**, *73*, 4707. (b) Loftfield, R. B., *J. Am. Chem. Soc.,* **1950**, *72*, 632.
11. Zhang, L. M. and Koreeda, M., *Org. Lett.,* **2002**, *4*, 3755.
12. (a) Moliner, V.; Castillo, R.; Safont, V. S.; Oliva, M.; Bohn, S.; Tunon, I. and Andres, J., *J. Am. Chem. Soc.,* **1997**, *119*, 1941. (b) Kimpe, N. D.; Sulmon, P.; Moens, L.; Schamp, N.; Declercq, J.-P. and Meerssche, M. V., *J. Org. Chem.,* **1986**, *51*, 3839. (c) Rappe, C.; Knufsson, L.; Turro, N. J. and Gagosiad, R. B., *J. Am. Chem. Soc.,* **1970**, *92,* 2032.
13. (a) Grainger, R. S.; Owoare, R. B.; Tisselli, P. and Steed, J. W., *J. Org. Chem.,* **2003**, *68*, 7899. (b) Bai, D. L.; Xu, R.; Chu, G. H. and Zhu, X. Z., *J. Org. Chem.,* **1996**, *61,* 4600. (c) Bordwell, F. G. and Scamehorn, R. G., *J. Am. Chem. Soc.,* **1971**, *93*, 3410. (d) Bordwell, F. G. and Carlson, M. W., *J. Am. Chem. Soc.,* **1970**, *92*, 3377. (e) Turro, N. J., *Acc. Chem. Res.,* **1969**, *2*, 25. (f) Aston, J. G. and Newkirk, J. D., *J. Am. Chem. Soc.,* **1951**, *73*, 3900.
14. (a) Harmata, M.; Bohnert, G.; Kurti, L. and Barnes, C. L., *Tetrahedron Lett.,* **2002**, *43*, 2347. (b) Selman, S. and Eastham, J. F., *Quart. Rev. (London),* **1960**, *14*, 221.
15. (a) Erian, A. W.; Sherif, S. M. and Gaber, H. M., *Molecules,* **2003**, *8*, 793. (b) Turro, N. J. and Hammond, W. B., *J. Am. Chem. Soc.,* **1965**, *87*, 3258. (c) House, H. O. and Frank, G. A., *J. Org. Chem.,* **1965**, *30*, 2948.
16. Engel, C. R.; Mérand, Y. and Côté, J., *J. Org. Chem.,* **1982**, *47*, 4485.
17. (a) Myers, A. G. and Barbay, J. K., *Org. Lett.,* **2001**, *3*, 425. (b) Bordwell, F. G.; Frame, R. R.; Scamehorn, R. G.; Strong, J. G. and Meyerson, S., *J. Am. Chem. Soc.,* **1967**, *89*, 6704.

18. (a) Sosnovsky, G. and Cai, Z.-W., *J. Org. Chem.,* **1995**, *60*, 3414. (b) Lee, E. and Yoon, C. H., *J. Chem. Soc., Chem. Commun.,* **1994**, *4*, 479. (c) Brik, M. E., *Synth. Commun.,* **1990**, *20*, 1487. (d) Llera, J. M. and Fraser-Reid, B., *J. Org. Chem.,* **1989**, *54*, 5544. (e) Paquette, L. A.; Farkas, E. and Galemmo, R., *J. Org. Chem.,* **1981**, *46*, 5434. (f) Buchi, G. and Ecceiz, B., *J. Org. Chem.,* **1971**, *36*, 2021. (g) Wolinsky, J. and Chan, D., *J. Org. Chem.,* **1965**, *30*, 41.

19. (a) Ceccherelli, P.; Curini, M.; Pellicciari, R. and Wenkert, E., *J. Org. Chem.,* **1982**, *47*, 3172. (b) Bisceglia, R. H. and Cheer, C. J., *J. Chem. Soc., Chem. Comm*., **1973**, 165. (c) Wolff, S. and Agosta, W. C., *J. Chem. Soc., Chem. Comm*., **1973**, 771. (d) Tsuda, Y.; Tanno, T.; Ukai, A. and Isobe, K., *Tetrahedron Lett*., **1971**, 2009. (e) Wenkert, E.; Bakuzis, P.; Baumgarten, R. J.; Leicht, C. L. and Schenk, H. P., *J. Am. Chem. Soc.,* **1971**, *93*, 3208.

20. Romo, J. and de Vivar, A. R., *J. Am. Chem. Soc.,* **1957**, *79*, 1118.

21. (a) Nace, H. R. and Olsen, B. A., *J. Org. Chem.,* **1967**, *32*, 3438. (b) Smith, B. B. and Nace, H. R., *J. Am. Chem. Soc.,* **1954**, *76*, 6119.

22. (a) Baretta, A. and Waegill, B., "A Survey of Favorskii Rearrangement Mechanisms," in *Reactive Intermediates,* ed. Abramovitch, R. A., Plenum Press, New York, **1982**, pp. 527–585. (b) Chenier, P. J., *J. Chem. Edu.,* **1978**, *55*, 286. (c) Akhrem, A. A.; Ustynyuk, T. K. and Titov, Y. A., *Russ. Chem. Rev.,* **1970**, *39*, 732. (d) Kende, A. S., *Org. React.*, **1960**, *11*, 261. (e) Jacquier, R., *Bull. Soc. Chim. Fr.,* **1950**, *17*, 35.

23. (a) Harmata, M. and Wacharasindhu, S., *Org. Lett.,* **2005**, *7*, 2563. (b) Harmata, M.; Bohnert, G.; Kurti, L. and Barnes, C. L., *Tetrahedron Lett*., **2002**, *43*, 2347. (c) Xiang, L. K.; Kalaitzis, J. A.; Nilsen, G.; Chen, L. and Moore, B. S., *Org. Lett.,* **2002**, *4*, 957. (d) Feroci, M.; Inesi, A.; Rossi, L. and Sotgiu, G., *Eur. J. Org. Chem.,* **2001**, 2765. (e) Dhavale, D. D.; Mali, V. P.; Sudrik, S. G. and Sonawane, H. R., *Tetrahedron*, **1997**, *53*, 16789. (f) Rodios, N. A.; Bojilova, A.; Terzis, A. and Raptopoulou, C. P., *J. Heterocycl. Chem.,* **1994**, *31*, 1129. (g) Barbee, T. R.; Guy, H.; Heeg, M. J. and Albizati, K. F., *J. Org. Chem.,* **1991**, *56*, 6773. (h) Abad, A.; Agulló, C.; Arnó, M. and Seoane, F., *Tetrahedron,* **1986**, *42*, 2429. (i) Sakai, T.; Tabata, H. and Takeda, A., *J. Org. Chem.,* **1983**, *48*, 4618. (j) Schaad, L. J.; Hem, B. A. and Zahradnlk, R., *J. Org. Chem.,* **1981**, *46*, 1909. (k) Sakai, T.; Katayama, T. and Takeda, A., *J. Org. Chem.,* **1981**, *46*, 2924. (l) Sakai, T.; Amano, E.; Kawabata, A. and Takeda, A., *J. Org. Chem.,* **1980**, *45*, 43. (m) Galons, H.; Girardeau, J. F. and Combet-Farnoux, C., *Bull. Soc. Chim. Fr*., **1977**, 936. (n) Chenier, P. J. and Kao, J. C., *J. Org. Chem.,* **1976**, *41*, 3730. (o) Vickers, S. and Smissman, E. E., *J. Org. Chem.,* **1975**, *40*, 749. (p) Koutek, B.; Pavlickova, L. and Soucek, M., *Collect. Czech. Chem. Commun.,* **1973**, *38*, 3872. (q) Müller, H., *Angew. Chem. Int. Ed. Eng.,* **1971**, *10*, 652. (r) Bordwell, F. G. and Carlson, M. W., *J. Am. Chem. Soc.,* **1970**, *92*, 3370. (s) Bordwell, F. G.; Scamehorn, R. G. and Springer, W. R., *J. Am. Chem. Soc.,* **1969**, *81*, 2087. (t) Bordwell, F. G.; Carlson, M. W. and Knipe, A. C., *J. Am. Chem. Soc.,* **1969**, *91*, 3949. (u) Bordwell, F. G. and Almy, J., *J. Org. Chem.,* **1973**, *38*, 571. (v) Bordwell, F. G. and Strong, J., *J. Org. Chem.,* **1973**, *38*, 579. (w) Bordwell, F. G. and Almy, J., *J. Org. Chem.,* **1973**, *38*, 575. (x) Wolinsky, J. and Hutchins, R. O., *J. Org. Chem.,* **1972**, *37*, 3294. (y) Wolinsky, J.; Hutchins, R. O. and Gibson, T. W., *J. Org. Chem.,* **1968**, *33*, 407. (z) House, H. O. and Richey, F. A., *J. Org. Chem.,* **1967**, *32*, 2151. (aa) Smissman, E. E.; Lemke, T. L. and Kristiansen, O., *J. Am. Chem. Soc.,* **1966**, *88*, 334. (bb) Goheen, D. W. and Vaughan, W. R., *Org. Syn. Coll.* **1963**, *4*, 594. (cc) Fort, A. W., *J. Am. Chem. Soc.,* **1962**, *84*, 4979. (dd) Fort, A. W., *J. Am. Chem. Soc.,* **1962**, *84*, 2620. (ee) Fort, A. W., *J. Am. Chem. Soc.,* **1962**, *84*, 2625. (ff) House, H. O. and Gilmore, W. F., *J. Am. Chem. Soc.,* **1961**, *83*, 3980. (gg) Stork, G. and Borowitz, I. J., *J. Am. Chem. Soc.,* **1960**, *82*, 4307. (hh) Pappas, N. and Nace, H. R., *J. Am. Chem. Soc.,* **1959**, *81*, 4556. (ii) Hesse, G. and Urbanek, F., *Ber.,* **1958**, *91*, 2733. (jj) Tchoubar, B., *Bull. Soc. Chim. Fr.,* **1955**, *22*, 1363. (kk) Favorskii, A. E. and Bozhovskii, V. N., *J. Russ. Phys. Chem. Soc.,* **1914**, *46*, 1097. (ll) Favorskii, A. E., *J. Prakt. Chem.,* **1913**, *88*, 658.

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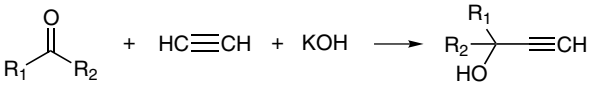
Favorskii-Babayan Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Favorskii in 1905[1] and subsequently extended by Babayan in 1939.[2] It is a base-promoted or -catalyzed ethynylation of aldehydes and ketones to produce secondary or tertiary acetylenic alcohols or glycols using anhydrous KOH or NaOH.[3] Therefore, it is generally known as the Favorskii-Babayan reaction[4] or Favorskii reaction.[5] Although it has been proposed that this reaction might involve a reaction between acetylene and the adduct from the ketone and KOH[1] or a coupling of potassium acetylide with the carbonyl compounds,[6] the most recent experimental results indicate that potassium hydroxide and acetylene first form a complex, rather than potassium acetylide in liquid ammonia, which then reacts with carbonyl compounds to form the acetylenic alcohols, where ammonia functions as a co-catalyst.[3] The experimental evidence includes (*a*) the loss of acetylene by the thermal decomposition of the formed dry complex at 1 mmHg and 100˚C within 4 h, whereas almost no decomposition occurs on potassium acetylide; (*b*) no stretch peak of the carbon-carbon triple bond and C−H bond on infrared spectra, indicating the contribution of the carbon-carbon triple bond and acetylic proton into the complex; and (*c*) strong association of the complex with an electron-donating solvent, such as ammonia or diisopropyl ether, and a part of the solvent remains after prolonged vacuum drying for the solvent-associated complex. The formed acetylenic alcohols can be used as nonionic surfactants.[7] It has been reported that NaOH also works for this reaction, although it is not as effective as KOH; moreover, LiOH is almost inert for this reaction.[3] It should be pointed out that the Favorskii-Babayan reaction also occurs in the presence of a catalytic amount of KOH.[8]

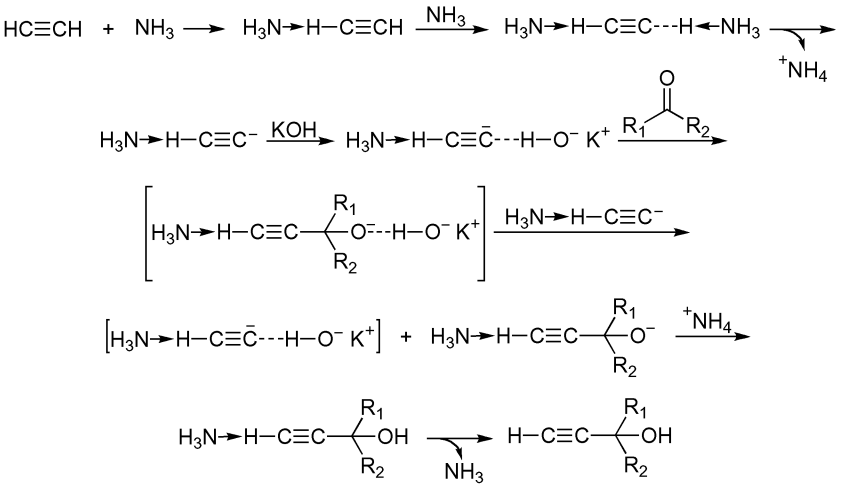
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Displayed below is the reaction mechanism modified from Tedschi's work.[3]



D. MODIFICATION

This reaction has been modified by using a catalytic amount of KOH.[8]

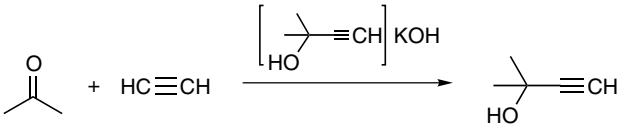
E. APPLICATIONS

This reaction has been used in the preparation of acetylenic alcohols that are used for nonionic surfactants.[7]

F. RELATED REACTIONS

This reaction is related to the *Arens-van Dorp Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 3.

Note: The preparation of methylbutynol-KOH adduct is written according to the preparation of the corresponding sodium adduct. Into a 1-L stainless-steel autoclave liner, under anhydrous conditions, was weighed 16.8 g finely ground potassium hydroxide (0.30 mol). The tightly sealed liner was quickly transferred to a standard 1-L stirred autoclave under a positive flow of dry nitrogen. To the sealed autoclave then was added 320 mL liquid ammonia followed by 40 g methylbutynol (0.48 mol) at a temperature of 14–20°C. The reaction mixture was stirred for 3.5 h and isolated in the usual manner using hexane as the inert diluent. The isolated adduct was dried under vacuum to constant weight.

To a 1-L stirred autoclave was added 0.10 mol methylbutynol-KOH adduct, 1.6 mol acetylene, and 200 mL liquid ammonia. Then 1.6 mol acetone was introduced into the autoclave within 30 min at 30–32°C. The total pressure in the autoclave averaged 160–185 psi. After 1.5 h, ammonia was vented, and dry CO_2 gas was introduced into autoclave to neutralize the catalyst complex to $KHCO_3$ and methylbutynol. The total conversion to methylbutynol before distillation was 97%, the catalytic conversion was 1170%, and the conversion to pure methylbutynol was 88%, b.p., 103–104°C.

Other references related to the Favorskii-Babayan reaction are cited in the literature.[9]

H. REFERENCES

1. (a) Favorskii, A. E., *J. Russ. Phys. Chem. Soc.,* **1905**, 37,643. (b) Favorskii, A. E., *Chem. Zentr.,* **1905**, 2, 1018.
2. Babayan, A.; Akopyan, B. and Gyuli-Kevhyan, R., *J. Gen. Chem. USSR*, **1939**, 9, 1631 [*Chem. Abstr.,* **1940**, 34, 2788].
3. Tedeschi, R. J., *J. Org. Chem.,* **1965**, 30, 3045.
4. (a) Petrov, A. D. and Mitrofanova, E. V., *Zh. Obsh. Khim.,* **1950**, 20, 289. (b) Petrov, A. D. and Mitrofanova, E. V., *Zh. Obsh. Khim.,* **1950**, 20, 271. (c) Petrov, A. D. and Mitrofanova, E. V., *Dokl. Akad. Nauk SSSR,* **1948**, 60, 1003.
5. (a) Shostakovskii, M. F.; Vlasov, V. M.; Kuznetsova, T. S.; Medvedeva, A. S. and Bestsennaya, N. V., *Zh. Org. Khim.,* **1968**, 4, 1747. (b) Favorskaya, I. A.; Shevchenko, Z. A. and Koshkina, I. M., *Zh. Org. Khim.,* **1967**, 3, 2075.
6. Bergmann, E. D., *The Chemistry of Acetylene and Related Compounds*, Interscience Publishers, New York, **1948**, pp. 50–51.
7. Leeds, M. W.; Tedeschi, R. J.; Dumovich, S. J. and Casey, A. W., *I & EC Prod. Res. Dev.,* **1965**, 4, 237.
8. Tedeschi, R. J.; Casey, A. W.; Clark, G. S.; Huckel, R. W.; Kindley, L. M. and Russel, J. P., *J. Org. Chem.,* **1963**, 28, 1740.

9. (a) Vilenchik, Ya. M.; Soshin, V. A.; Zayakina, L. P. and Kharchenko, A. P., *Zh. Org. Khim.,* **1978**, 14, 447. (b) Glazunova, E. M.; Sarkisov, Yu. E.; Grigina, I. N. and Sabirov, S. S.,, *Zh. Org. Khim.,* **1976**, 12, 516. (c) Shchelkunov, A. V.; Muldakhmetov, Z. M.; Rakhimzhanova, N. A. and Favorskaya, T. A., *Zh. Org. Khim.,* **1970**, 6, 930. (d) Shostakovskii, M. F.; Vlasov, V. M.; Kuznetsova, T. S.; Medvedeva, A. S. and Bestsennaya, N. V., *Zh. Org. Khim.,* **1968**, 4, 1747. (e) Tedeschi, R. J.; Wilson, M. F.; Scanlon, J.; Pawlak, M. and Cunicella, V., *J. Org. Chem.,* **1963**, 28, 2480. (f) Schachat, N. and Bagnell, J. J., *J. Org. Chem.,* **1962**, 27, 1498. (g) Raphael, R. A., *Acetylenic Compounds in Organic Synthesis*, Academic Press, New York, **1955**, pp. 10–12. (h) McKinnis, A. C., *Ind. Eng. Chem.,* **1955**, 47, 850.

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Feist-Bénary Reaction

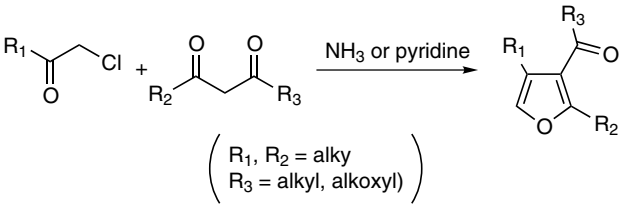
(Feist-Bénary Furan Synthesis, Feist-Bénary Condensation)

A. GENERAL DESCRIPTION OF THE REACTION

It was first reported by Feist in 1901[1] for preparing furan derivatives via the base-promoted condensation of β-dicarbonyl compounds with α-haloketones, and subsequently extended by Bénary in 1911 using 1,2-dichloroethyl ether and acetoacetic acid esters.[2] Therefore, the synthesis of furan derivatives by treatment of an α-halo ketone and β-dicarbonyl compound with a base is known as the Feist-Bénary condensation,[3] Feist-Bénary furan synthesis,[4] Feist-Bénary cyclocondensation,[5] or Feist-Bénary reaction.[6] The bases used are normally ammonia and pyridine, however, it was found advantageous to use aqueous pyridine to effect this reaction instead of ammonia, because the production of pyrrole derivative is obviated and the yield of the furan derivative is increased.[7] It was found that the first step is an *Aldol Condensation*,[6e] and the regioselectivity could be inverted if the alkylation of β-keto esters is carried out followed by the acid treatment.[8] In addition, the intermediate dihydrofuran can be isolated with good diastereoselectivity under mild conditions, and normally *cis* isomer is yielded when moderately acidic nucleophiles are used, whereas *trans*-isomers will be generated when highly acidic dicarbonyl compounds are used as nucleophiles.[5c,5d] This reaction has been extended to prepare furan from α,β-dichloroethyl ether and β-ketoester in aqueous pyridine solution to reduce the formation of pyrrole.[7,9]

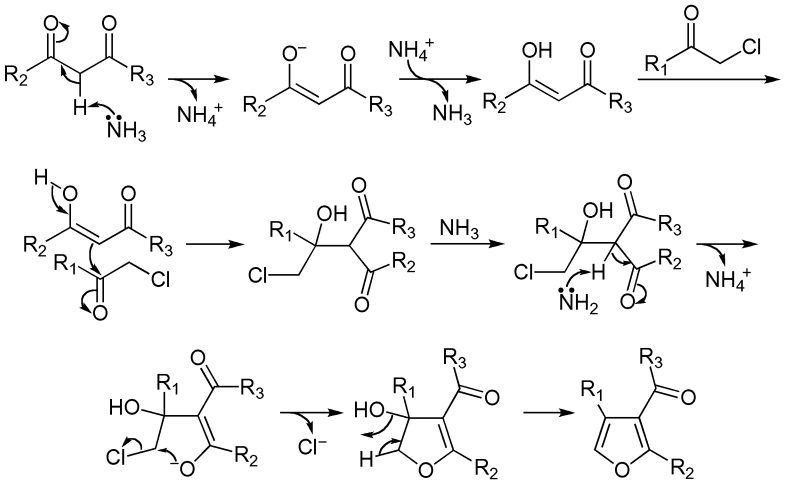
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Displayed below is the reaction mechanism using ammonia as the base.



D. MODIFICATION

This reaction has been modified by temporarily terminating the reaction to obtain the dihydrofuran derivatives.[6c,6d] In addition, this reaction has been carried out under an acidic conditions, such as in the presence of TFA,[5e] and by using 10% Et_3N as the base.[6d] Moreover, α,β-dichloroethyl ether has been used to substitute for the α-halo ketones.[7,9] Other modifications include the reaction of dicarbonyl compounds with acetylenes[10] and aldehydes.[11] Furthermore, a general preparation of five-membered heterocycles, including furans—although not related to the Feist-Bénary reaction—is also considered as a relevant modification.[3a]

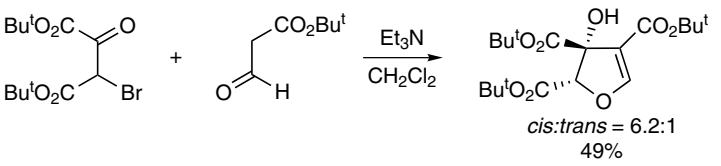
E. APPLICATIONS

This reaction has general applications in the preparation of furan derivatives.

F. RELATED REACTIONS

This reaction is related to the *Hantzsch Pyrrole Synthesis*.

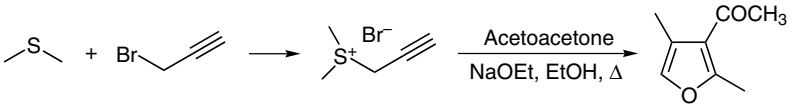
G. CITED EXPERIMENTAL EXAMPLES



Reference 6c.

To a solution of 6.59 g di-*t*-butyl oxalacetate (27.0 mmol) and 2.66 g NaOAc (27.0 mmol) in 40 mL acetic acid at room temperature was added slowly a solution of 1.38 mL Br_2 (4.31g, 27.0 mmol) in 14 mL acetic acid by cannula over 10 min. After being stirred at room temperature for 30 min, the reaction mixture was diluted with 150 mL water and extracted with CH_2Cl_2 (100 mL, 50 mL, 50 mL). The combined organic layers were washed with 150 mL saturated $NaHCO_3$. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 8.64 g unpurified α-bromo di-*t*-butyl oxalacetate as a yellow oil, in a yield of 99%. This product was used directly for the next step reaction without further purification.

To a solution 6.61 g formyl Meldrum's acids (38.4 mmol) in 77 mL benzene was added 3.62 mL (2.85g, 38.4 mmol) of *tert*-butanol. The reaction mixture was refluxed for 30 min and then cooled to room temperature. The resulting unpurified *tert*-butyl formylacetate solution was transferred via cannula to 8.63 g of the prepared α-bromo di-*t*-butyl oxalacetate (26.7 mmol). The resulting solution was cooled to 0°C, and then treated with 3.72 mL (2.70 g, 26.7 mmol) of Et_3N. After being stirred at 0°C for 14 h, the reaction was quenched by the addition of 80 mL Et_2O and 40 mL brine. The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 80 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residue by column chromatography (9:1 then 6:1 hexane/EtOAc) gave 5.08 g [2*S**,3*R**]-2,3-dihydro-3-hydroxy-2,3,4-furantricarboxylic acid tri-*t*-butyl ester as a mixture of two diastereomers in ratio of 6.2:1. The mixture was a pale yellow oil; crystallization from hexane at −20°C afforded 2.72 g of such product as a white powder, m.p. 97–98.5°C.



Reference 10.

Caution! These reactions should be performed in a hood because of the noxious odors. A mixture of 6.2 g dimethyl sulfide (0.10 mol), 11.9 g 3-bromopropyne (0.10 mol), and 10 mL acetonitrile was stirred magnetically for 20 h in a darkened, 100-mL round-bottomed

flask fitted with a calcium chloride drying tube. The resulting white, crystalline mass was filtered with suction and washed with three 50-mL portions of dry diethyl ether, giving 16.4 g sulfonium salt (in a yield of 90%, m.p. 105–106°C). This material may be used in the next step without purification but, if desired, it may be recrystallized from ethanol-ether with minimal loss, m.p. 109–110°C.

To a solution of 8.7 g acetylacetone (0.087 mol) in 175 mL 0.5 *M* ethanolic sodium ethoxide (0.087 mol), contained in a 500-mL, round-bottomed flask fitted with a condenser topped with a calcium chloride drying tube, was added a solution of 15.75 g dimethyl-2-propynylsulfonium bromide (0.087 mol) in 150 mL ethanol. The mixture was refluxed until the odor of dimethyl sulfide was no longer appreciable. The reaction flask was then fitted with a 30-cm, helix-packed column; by heating the flask with a water bath, ethanol was distilled through the column. The residue was treated with 200 mL ether, and the suspension was filtered. Ether was distilled from the filtrate at atmospheric pressure, and the residue was distilled, giving 9.7 g 3-acetyl-2,4-dimethylfuran, in a yield of 81%, b.p., 90–95°C (12 mmHg).

Other references related to the Feist-Bénary reaction are cited in the literature.[12]

H. REFERENCES

1. Feist, F., *Ber.,* **1901**, *34*, 1992.
2. (a) Bénary, F., *Ber.,* **1911**, *44*, 489. (b) Bénary, F., *Ber.,* **1911**, *44*, 493.
3. (a) Wipf, P.; Rahman, L. T. and Rector, S. R., *J. Org. Chem.,* **1998**, *63,* 7132. (b) Cambie, R. C.; Moratti, S. C.; Rutledge, P. S. and Woodgate, P. D., *Synth. Commun.,* **1990**, *20*, 1923.
4. Carson, J. R. and Wong, S., *J. Med. Chem.,* **1973**, *16*, 172.
5. (a) Mross, G.; Holtz, E. and Langer, P., *J. Org. Chem.,* **2006**, *71*, 8045. (b) Holtz, E. and Langer, P., *Synlett*, **2004**, 1805.
6. (a) Jin, Y.; Liu, X. Y.; Jing, L. L.; He, W.; Sun, X. L. and Zhang, S. Y., *Chirality*, **2007**, *19*, 386. (b) Calter, M. A.; Phillips, R. M. and Flaschenriem, C., *J. Am. Chem. Soc.,* **2005**, *127*, 14566. (c) Calter, M. A. and Zhu, C., *Org. Lett.,* **2002**, *4*, 205. (d) Calter, M. A.; Zhu, C. and Lachicotte, R. J., *Org. Lett.,* **2002**, *4*, 209. (e) Stauffer, F. and Neier, R., *Org. Lett.,* **2000**, *2*, 3535. (f) Bisagni, E.; Marquet, J. P.; Andre-Louisfert, J.; Cheutin, A. and Feinte, F., *Bull. Soc. Chim. Fr.,* **1967**, 2796.
7. Scott, E. W. and Johnson, J. R., *J. Am. Chem. Soc.,* **1932**, *54*, 2549.
8. Bambury, R. E.; Yaktin, H. K. and Wyckoff, K. K., *J. Heterocycl. Chem.,* **1968**, *5*, 95.
9. Blomquist, A. T. and Stevenson, H. B., *J. Am. Chem. Soc.,* **1934**, *56*, 146.
10. Howes, P. D. and Stirling, C. J. M., *Org. Syn. Coll.* **1988**, *6*, 31.
11. Kretchmer, R. A. and Laitar, R. A., *J. Org. Chem.,* **1978**, *43*, 4596.
12. (a) Lavoisier-Gallo, T. and Rodriguez, J., *J. Org. Chem.,* **1997**, *62*, 3787. (b) Friedrichsen, W., *Furans and their Benzo Derivatives: Synthesis,* in *Comprehensive Heterocyclic Chemistry*, ed. Katritzky, A. R.; Rees, C. W. and Scriven, E. F. V., Elsevier, Oxford, **1996**, 2, pp. 351–393. (c) Kochhar, K. S. and Pinnick, H. W., *J. Org. Chem.,* **1984**, *49*, 3222. (d) Kagan, J. and Mattes, K. C., *J. Org. Chem.,* **1980**, *45*, 1524. (e) Tsuboi, S.; Uno, T. and Takeda, A., *Chem. Lett.,* **1978**, 1325. (f) Batty, J. W.; Howes, P. D. and Stirling, C. J. M., *J. Chem. Soc., Perkin Trans. I*, **1973**, 65. (g) Bisagni, E.; Marquet, J. P.; Borzat, J. D.; Pepin, J. J. and André-Loursfert, J., *Bull. Soc. Chim. Fr.,* **1971**, 4042. (h) Bambury, R. E. and Miller, L. F., *J. Heterocycl. Chem.,* **1970**, *7,* 269. (i) McKinnon, D. M., *Can. J. Chem.,* **1965**, *43*, 2628. (j) Schulte, K. E.; Reisch, J. and Mock,

A., *Arch. Pharm. Ber. Deut. Pharm. Gesell.*, **1962**, *295*, 627. (k) Elderfield, R. C., *Heterocyclic Compounds,* John Wiley & Sons, New York, **1950**, *1*, pp. 132–134. (l) Wright, G. F. and Gilman, H., *Ind. Eng. Chem.,* **1948**, *40*, 1517. (m) Johnson, R. W., *J. Chem. Soc.,* **1946**, 895. (n) Bergstrom, F. W., *Chem. Rev.,* **1944**, *35*, 77. (o) Scott, E. W. and Johnson, J. R., *J. Am. Chem. Soc.,* **1933**, *55*, 2552. (p) Reichstein, T. and Zschokke, H., *Helv. Chim. Acta,* **1932**, *15*, 268. (q) Reichstein, T. and Zschokke, H., *Helv. Chim. Acta,* **1932**, *15*, 1105. (r) Reichstein, T. and Zschokke, H., *Helv. Chim. Acta,* **1932**, *15*, 1112. (s) Reichstein, T. and Zschokke, H., *Helv. Chim. Acta,* **1931**, *14*, 1270. (t) Bénary, E. and Konrad, R., *Ber.,* **1923**, *56*, 44. (u) Bénary, E., *Ber.,* **1918**, *51*, 567. (v) Bénary, E. and Silberman, B., *Ber.,* **1913**, *46*, 1363. (w) Feist, F., *Ber.,* **1902**, *35*, 1550. (x) Feist, F., *Ber.,* **1902**, *35*, 1537. (y) Feist, F., *Ber.,* **1902**, *35*, 1547**.**

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Fenton Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Fenton in 1893.[1] It is the generation of a hydroxyl radical by the decomposition of hydrogen peroxide in the presence of ferrous salt and is generally known as the Fenton reaction.[2] Although the Fenton reaction itself cannot be considered as a real organic reaction, it has found a wide application in organic, bio-organic, and environmental chemistry. It was found that the hydroxyl radical can be quickly generated[3] at the initial stage of the reaction,[4] which is very reactive[5] with a high oxidation potential.[5c] Many organic molecules can be oxidized using the hydroxyl radicals–for example, oxidation of α-hydroxy acids to α-keto acids and benzene to phenol and biphenyl,[6] the formation of methane and ethane by proton abstraction from DMSO,[3] and the degradation of single-stranded and double-stranded DNA.[7] Especially important is the application of this reaction in the degradation of organic pollutants (including Orange II,[8] 2,4,6-trinitrotoluene (TNT),[9] pentachlorophenol (PCP),[5a] and aniline[5c,10]) in groundwater and soils. In addition, the photo induced reaction called the photo-Fenton reaction[11] has been reported to enhance the iron cycling and degradation of contaminants.[11b] It was found that the oxidation of malachite green can be catalyzed by various aromatic additives, which can be transformed into hydroquinone-like structures; the reaction order follows hydroquinone > salicyclic acid > *p*-hydroxybenzoic acid > *m*-hydroxybenzoic acid > *p*-benzoquinone > carboxylic aromatics > amindo aromatics.[12] In addition, it was also found that other additives can also enhance such reactions—for example, the strong bidentate or tridentate ligands, such as bis(picolinate), ethylenediamine-*N*,*N*′-diacetate, and nitrilotriacetate.[13] Even the substitution of phosphate buffer by sodium trifluoroacetate will increase the amount of trapped

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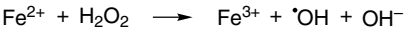
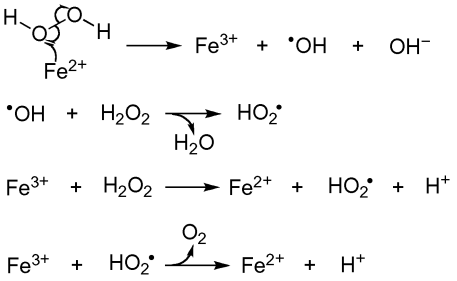
hydroxyl radical $\sim$ 300 times.[14] Similarly, ADP and ATP show a similar effect on this reaction.[15] It was found that the metallic Fenton reaction was more effective than the classical one,[5a] and other metal ions that function in the same manner are called Fenton-like reagents, including V^{4+}, Ti^{3+}, and Cr^{2+}.[16] This reaction is sometimes called the *Haber-Weiss Reaction*.[5b,17]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It has been proved that this reaction involves both hydroxyl and hydroperoxyl radicals,[18] with a pH usually less than 3.[9] Displayed below is the reaction mechanism.



D. MODIFICATION

This reaction has been modified to occur at a neutral pH using chelating agents.[9] Other modifications include the photo-Fenton reaction[11] and the initiation by other metal cations (e.g., Cr^{2+} and V^{4+}).[16]

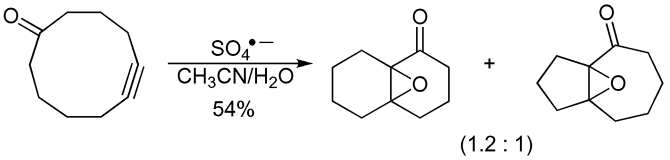
E. APPLICATIONS

This reaction has wide application in the degradation of organic waste in soil and groundwater.

F. RELATED REACTIONS

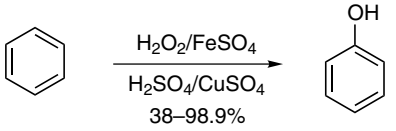
This reaction is related to the *Haber-Weiss Reaction.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 19.

To 30 mL CH_3CN solution containing 1 mmol 5-cyclodecynone was added 3 mmol persulfate dissolved in 10 mL water. To this heterogeneous reaction mixture, 3 mmol $Fe(EDTA)(SO_4)_2 \cdot 4H_2O$ in 30 mL water was quickly added under vigorous stirring through a dropping funnel. The reaction completed after $\sim$ 15 min (monitored by TLC), and the mixture was dilutes with water and extracted with EtOAc. The combined organic fractions were dried and evaporated. The residue was purified by chromatography (diethyl ether/pentane, 1:2) to afford 52% α,β-epoxy ketones in a ratio of 1.2:1. (*Note*: The molecular formula of $Fe(EDTA)(SO_4)_2 \cdot 4H_2O$ cannot be balanced by charge).



Reference 6.

Into a 100-mL Erlenmeyer flask with a rubber stopper equipped with four glass tubings was placed 25 mL of a solution that contained 50 mM H_2SO_4, 10 mM $FeSO_4$, and 30 mM $CuSO_4$. After air was purged from the flask with nitrogen through two glass tubings fitted to the rubber stopper, 0.75 mL benzene (8.4 mmol) was added through the third tubing using a microfeeder. Under magnetic stirring, a solution containing 100 mM H_2O_2 and 50 mM H_2SO_4 was added dropwise using another microfeeder at a rate of 0.2759 mL/min. After the addition of the precalculated amount of H_2O_2 at 25°C, the reaction mixture was allowed to stand for 30 min with stirring. After the remaining benzene was evaporated with a stream of nitrogen, 5 mL of the reaction mixture was diluted to 50 mL with 25 mM EDTA, and the yield of phenol, which varied from 38% to 98.9%, was analyzed using HPLC.

Other references related to the Fenton reaction are cited in the literature.[20]

H. REFERENCES

1. Fenton, H. J. H., *Proc. Chem. Soc.,* **1893**, *9*, 113.
2. (a) Evgenidou, E.; Konstantinou, I.; Fytianos, K. and Poulios, I., *Water Res*., **2007**, *41*, 2015. (b) Liu, H.; Li, X. Z.; Leng, Y. J. and Wang, C., *Water Res*., **2007**, *41*, 1161. (c) Liang, M. M. and Guo, L.-H., *Environ. Sci. Technol.*, **2007**, *41*, 658. (d) Jiang, C. C.; Pang, S. Y.; Ma, J.; Xie, W. P. and Zou, Y., *Zhongguo Jishui Paishui,* **2006**, *22*, 88. (e) Barros, J. A. G.; Fechine, G. J. M.; Alcantara, M. R. and Catalani, L. H., *Polymer*, **2006**, *47*, 8414. (f) Andrews, J. P.; Asaadi, M.; Clarke, B. and Ouki, S., *Water Sci. & Technol*., **2006**, *54*, 197. (g) Dalla Villa, R. and Pupo Nogueira, R. F., *Sci. Total Environ.,* **2006**, *371*, 11. (h) Palmroth, M. R. T.; Langwaldt, J. H.;

Aunola, T. A.; Goi, A.; Puhakka, J. A. and Tuhkanen, T. A., *J. Chem. Technol. Biotechnol.,* **2006**, *81*, 598. (i) Li, Y. C.; Bachas, L. G. and Bhattacharyya, D., *Environ. Eng. Sci.,* **2005**, *22*, 756. (j) Lin, J. Q.; Long, M. C.; Wu, B. L. and Xu, Q. Q., *Huaqiao Daxue Xuebao, Ziran Kexueban*, **2005**, *26*, 299. (k) Rachmilovich-Calis, S.; Masarwa, A.; Meyerstein, N. and Meyerstein, D., *Eur. J. Inorg. Chem.,* **2005**, 2875. (l) Goodell, B.; Qian, Y. H.; Jellison, J. and Richard, M., *Water Environ. Res*., **2004**, *76*, 2703. (m) Derbalah, A. S.; Nakatani, N. and Sakugawa, H., *Chemosphere*, **2004**, *57*, 635. (n) Teranishi, H.; Honda, Y.; Kuwahara, M. and Watanabe, T., *Wood Res*., **2003**, *90*, 13.

3. Eberhardt, M. K. and Colina, R., *J. Org. Chem.,* **1988**, *53*, 1071.
4. MacFaul, P. A.; Wayner, D. D. M. and Ingold, K. U., *Acc. Chem. Res.,* **1988**, *31*, 159.
5. (a) Lin, H. K. and Luong, H. V., *J. Minerals Mater. Charact. Eng.,* **2004**, *3*, 33. (b) Byrne, J. A.; Grieve, D. J.; Cave, A. C. and Shah, A. M., *Arch. Maladies Coeur Deasi Ssveaux,* **2003**, *96*, 214. (c) Hawkins, S. and Waguespack, Y., *J. Undergrad. Chem. Res.,* **2003**, *2*, 51.
6. Ito, S.; Mitarai, A.; Hikino, K.; Hirama, M. and Sasaki, K., *J. Org. Chem.,* **1992**, *57*, 6937.
7. Lloyd, D. R.; Carmichael, P. L and Phillips, D. H., *Chem. Res. Toxicol.,* **1998**, *11*, 420.
8. Bandeara, J.; Marrison, C.; Kiwi, J.; Plugarin, C. and Pevinger, P., *J. Photochem. Photobiol. A: Chemistry,* **1996**, *99*, 57.
9. Hur, J.-W.; Seo, S.-W.; Kim, M.-K. and Kong, S.-H., *Korean Chem. Eng. Res.,* **2005**, *43*, 153.
10. Fukushima, M.; Tataumi, K. and Morimoto, K. *Environ. Sci. Technol.,* **2000**, *34*, 2006.
11. (a) Feng, J. Y.; Hu, X. J. and Yue, P. L., *Environ. Sci. Technol.,* **2004**, *38*, 269. (b) Watts, R. J.; Bottenberg, B.; Hess, T. F.; Jensen, M. D. and Teel, A. L., *Environ. Sci. Technol.,* **1999**, *33*, 3432.
12. Chen, F.; Ma, W. H.; He, J. J. and Zhao, J. C., *J. Phys. Chem. A,* **2002**, *106,* 9485.
13. (a) Sawyer, D. T.; Sobkowiak, A. and Matsushita, T., *Acc. Chem. Res.,* **1996**, *29*, 409. (b) Sheu, C.; Sobkowiak, A.; Li, Z.; Ozbalik, N.; Barton, D. H. R. and Sawyer, D. T., *J. Am. Chem. Soc.,* **1989**, *111*, 8030. (c) Rush, J. D. and Koppenol, W. H., *J. Am. Chem. Soc.,* **1988**, *110*, 4957.
14. Li, L. X.; Abe, Y.; Mashino, T.; Mochizuki, M. and Miyata, N., *Anal. Sci.,* **2003**, *19*, 1083.
15. Aoyagi, S.; Yamazaki, M.; Miyasaka, T. and Sakai, K., *J. Chem. Eng. Jpn.,* **2001**, *34*, 956.
16. Czapski, G.; Samuni, A. and Meisel, D., *J. Phys. Chem.,* **1971**, *75*, 3271.
17. Buettner, G. R.; Doherty, T. P. and Patterson, L. K., *FEBS*, **1983**, *158*, 143.
18. (a) Zepp, R. G.; Faust, B. C. and Hoigue, J., *Environ. Sci. Technol.,* **1992**, *26*, 313. (b) Walling, C., *Acc. Chem. Res.,* **1975**, *8*, 125. (c) Barb, W. G.; Baxendale, J. H.; George, P. and Hargrave, K. R., *Trans. Faraday Soc.,* **1951**, *47*, 591.
19. Willie, U., *Org. Lett.,* **2000**, *2*, 3485.
20. (a) Liu, Q.; Berchner-Pfannschmidt, U.; Möller, U.; Brecht, M.; Wotzlaw, C.; Acker, H.; Jungermann, K. and Kietzman, T., *Proc. Nat. Acad. Sci. USA,* **2004**, *101*, 4302. (b) Frelon, S.; Douki, T.; Favier, A. and Cadet, J., *J. Chem. Soc., Perkin Trans. 1*, **2002**, 2866. (c) Joseph, J. M.; Destaillats, H.; Hung, H.-M. and Hoffmann, M. R., *J. Phys. Chem. A,* **2000**, *104,* 301. (d) Goldstein, S. and Meyerstein, D., *Acc. Chem. Res.,* **1999**, *32*, 547. (e) Benitez, F. J.; Beltran-Heredia, J.; Acero, J. L. and Rubio, F. J., *Ind. Eng. Chem. Res.*, **1999**, *38*, 1341. (f) Walling, C., *Acc. Chem. Res.*, **1998**, *31*, 155. (g) Taatjes, D. J.; Gaudiano, G.; Resing, K. and Koch, T. H., *J. Med. Chem.,* **1997**, *40,* 1276. (h) Pezzella, A.; d'Ischia, M.; Napolitano, A.; Misuraca, G. and Prota, G., *J. Med. Chem.,* **1997**, *40,* 2211. (i) Yoshimura, Y.; Iijima, T.; Watanabe, T. and Nakazawa, H., *J. Agric. Food Chem.,* **1997**, *45*, 4106. (j) Chen, R. and Pignatello, J. J., *Environ. Sci. Technol.,* **1997**, *31*, 2399. (k) Voelker, B. M. and Sulzberger, B., *Environ. Sci. Technol.,* **1996**, *30*, 1106. (l) Pignatello, J. J., *Environ. Sci. Technol.,* **1992**, *26*, 944. (m) Kanner, J. and Rosenthal, I., *Pure & Appl. Chem.,* **1992**, *64*, 1959. (n) Barbeni, M., Minero, C. and Pelizzetti, E., *Chemosphere,* **1987**, *16*, 2225. (o) Floyd, R. A.; Watson, J. J. and Wong, P. K., *J. Biochem. Biophys. Methods,* **1984**, *10*, 221. (p) Walling, C. and Amarnath, K., *J. Am. Chem. Soc.,* **1982**, *104*, 1185. (q) Tezuka, T.; Narita, N.; Ando, W. and Oae, S., *J. Am. Chem. Soc.,* **1981**, *103,* 3045. (r) Sosnovsky, G. and Rawlinson,

D., "Metal Ion-Catalyzed Reactions of Peroxyesters" in *Organic Peroxides*, ed. Swern, D., Interscience, New York, **1970**, pp. 269–336. (s) Norman, R. O. C., *Adv. Phys. Org. Chem*., **1967**, *5*, 53. (t) Brown, R. F.; Jamison, S. E.; Pandit, U. K.; Pinkus, J.; White, G. R. and Braendlin, H. P., *J. Org. Chem.,* **1964**, *29*, 146. (u) Moody, G. J., *Tetrahedron,* **1963**, *19*, 1705. (v) Dixon, W. T. and Norman, R. O. C. *Nature (London),* **1962**, *196*, 891. (w) Bray, W. G. and Gorin, M., *J. Am. Chem. Soc.,* **1932**, *54,* 2134. (x) Fenton, H. J. H. and Jackson, H., *J. Chem. Soc.,* **1899**, *75*, 1. (y) Fenton, H. J. H., *J. Chem. Soc.,* **1895**, *67*, 774. (z) Fenton, H. J. H., *J. Chem. Soc.,* **1894**, *65*, 899.

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Ferrier Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Ferrier and co-workers in 1962.[1] It is an acid-catalyzed or induced rearrangement of glycals[2] in the presence of different nucleophiles (or aglycons).[3] The acids used in this reaction include the protic acids[4] such as methanolic hydrochloric acid,[5] sulfuric acid,[6] and Lewis acids such as $SnBr_4$,[4,7] $EtAlCl_2$,[4,8] $SnCl_4$,[9] $Pd(CH_3CN)_2Cl_2$,[10] $NbCl_5$,[11] $ZnCl_2$,[12] $InCl_3$,[13] $Er(OTf)_3$,[14] $Bi(OTf)_3$,[15] $ZrCl_4$,[16] $Sc(OTf)_3$,[17] $LiBF_4$,[18] iodine,[4,19] and the most often used $BF_3{\cdot}Et_2O$.[2a,4,20] As for the acidic nature of this reaction, substrates sensitive to acidic conditions are precluded;[21] therefore, some neutral catalysts have been developed for this reaction, including iodonium dicollidinium perchlorate,[22] 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ),[23] and montmorillonite K-10 (a clay catalyst).[24] Among these catalysts, it has been found that $InCl_3$ has a superior catalytic activity relative to many other Lewis acid catalysts[9] and can be recovered without loss of any activity;[13a] however, $InCl_3$ should be used in combination with TMSCl, otherwise a stoichiometric amount of $InCl_3$ is needed.[13a] The nucleophiles in this reaction could be alcohols (to form alkyl glycosides),[2a] thio-alcohols (for thio-glycosides),[25] amino acids (for *O*- or *S*-glycopeptides),[3] monosaccharides (for disaccharide)[9] and even carbo-nucleophiles (to form allylic *C*-glycosides).[13b,26] Overall, this reaction has become an important synthetic tool,[27] which predominantly produces α-anomer[3,13a] in good to excellent yield.[9,13a] Although the mechanism of this reaction is still unclear,[4] an allylic isomerization of the glycal to a 2,3-dideoxy sugar followed by a S_N1-type reaction[4] through a cyclic allylic oxocarbenium ion in quasi-axial orientation is proposed.[28] Similarly, the *Allylic Rearrangement* also occurs on *exo*-rings,[29] and even works for 1,2-cyclopropanated

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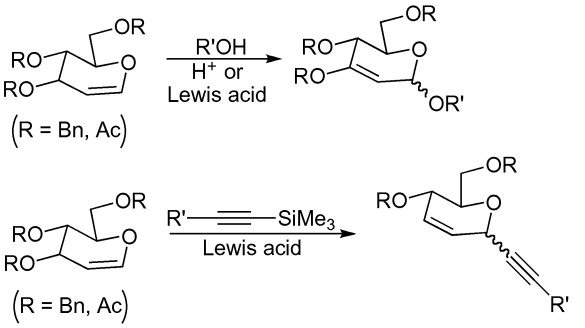
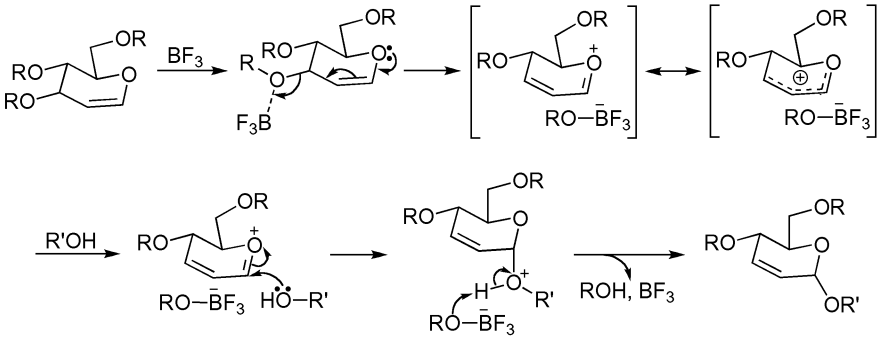
sugars.[10b] This reaction is most commonly cited as the Ferrier rearrangement,[2,4,10b,13a,21,30] Ferrier-type rearrangement,[2a,4,10b] or Ferrier reaction,[2a,3,26b,27,30d,31] but is called the Ferrier reaction in this book to differentiate it from another type of rearrangement also developed by Ferrier and co-workers.

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is believed that this reaction occurs via the intermediacy of a cyclic allylic oxocarbenium ion, as outlined here.



D. MODIFICATION

This reaction has been modified extensively by using different acids as catalyst, as described earlier. In addition, this reaction has been extended to the preparation of *C*-glycosides.

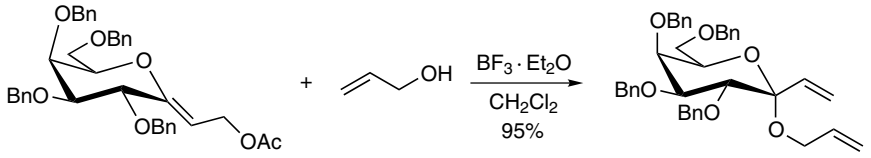
E. APPLICATIONS

This reaction has general applications in carbohydrate transformation.

F. RELATED REACTIONS

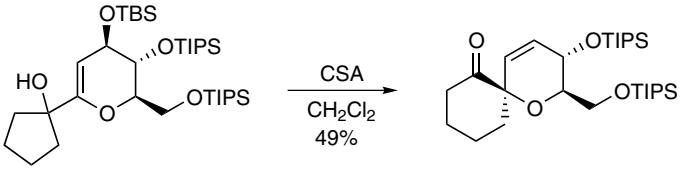
N/A

G. CITED EXPERIMENTAL EXAMPLES



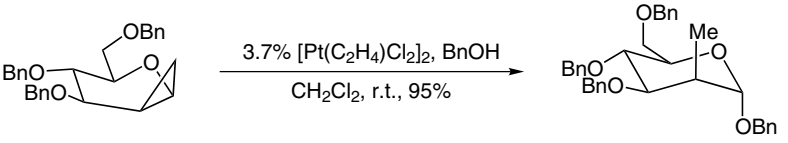
Reference 29.

To a stirred solution of an *exo*-glycal (1.0 eq.) and allyl alcohol (2.0 eq.) in anhydrous CH_2Cl_2 at 0°C was added 1.0 eq. $BF_3{\cdot}Et_2O$ dropwise in the presence of 4-Å molecular sieves. The reaction was usually complete within 1 h. The reaction mixture was quenched by the addition of saturated $NaHCO_3$ and extracted with CH_2Cl_2 (three times). The collected organic layers were washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The resulting residue was subjected to silica gel chromatography (with hexanes and EtOAc) to afford 95% of the listed product.



Reference 32.

A solution of 60 mg 1,5-anhydro-2-deoxy-1-*C*-(1-hydroxycyclopentyl)-3,4,6-tris-*O*-(triisopropylsilyl)-D-*arabino*-hex-1-enitol (0.09 mmol) in 40 mL dry CH_2Cl_2 was stirred in the presence of a catalytic quantity of camphorsulfonic acid for 1 h. Following the addition of 25 mL saturated $NaHCO_3$ solution, the aqueous phase was extracted with CH_2Cl_2 (3×50 mL), and the combined organic layers were dried and evaporated. The crude product was purified by flash chromatography on silica gel (elution with 2% EtOAc in hexanes) to give 22 mg of the listed product as a colorless oil, in a yield of 49%.



Reference 10b.

Zeise's dimmer ($[Pt(C_2H_4)Cl_2]_2$ (21.5 mg, 0.0366 mmol) was dissolved in 5 mL CH_2Cl_2 under an atmosphere of nitrogen. The solution was then transferred by syringe to a flask containing 1.0 mmol cyclopropane ring-fused sugar and 2.0 mmol benzyl alcohol. The

mixture was stirred under nitrogen at room temperature for 15 h. After removal of the solvent in vacuo, the crude mixture was purified by flash chromatography to give 95% benzyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-methyl-D-mannopyranoside with α:β anomeric ratio of 12:1.

Other references related to the Ferrier reaction are cited in the literature.[33]

H. REFERENCES

1. Ferrier, R. J.; Overend, W. G. and Ryan, A. E., *J. Chem. Soc. C*, **1962**, 3667.
2. (a) López, J. C.; Gómez, A. M.; Valverde, S. and Fraser-Reid, B., *J. Org. Chem.,* **1995**, *60*, 3851. (b) Kozikowski, A. P. and Park, P.-U., *J. Org. Chem.,* **1984**, *49*, 1674.
3. Liberek, B. and Smiatacz, Z., *Pol. J. Chem.,* **2000**, *74*, 989.
4. Banik, B. K.; Manhas, M. S. and Base, A. K., *J. Org. Chem.,* **1994**, *59*, 4714.
5. Herscovici, J.; Muleka, K.; Boumaiza, L. and Antonakis, K., *J. Chem. Soc., Perkin Trans. I,* **1990**, 1995.
6. Hadfield, A. F. and Sartorelli, A. C., *Carbohydr. Res.,* **1982**, *101*, 240.
7. Descotes, G. and Martin, J. C., *Carbohydr. Res.,* **1977**, *56*, 1680.
8. Lundt, I. and Pederson, C., *Acta Chem. Scand.,* **1970**, *24*, 240.
9. Frost, C. G. and Hartley, J. P., *Mini-Rev. Org. Chem.,* **2004**, *1*, 1.
10. (a) Zamojski, A., *Pol. J. Chem.,* **2002**, *76*, 1053. (b) Beyer, J.; Skaanderup, P. R. and Madsen, R., *J. Am. Chem. Soc.,* **2000,** *122*, 9575.
11. Hotha, S. and Tripathi, A., *Tetrahedron Lett*., **2005**, *46*, 4555.
12. Bettadaiah, B. K. and Srinivas, P., *Tetrahedron Lett*., **2003**, *44*, 7257.
13. (a) Ghosh, R.; Chakraborty, A. and Maiti, S., *ARKIVOC*, **2004**, 1. (b) Yadav, J. S. and Reddy, B. V. S., *Synthesis,* **2002**, 511. (c) Babu, B. S. and Balasubramanian, K. K., *Tetrahedron Lett.,* **2000**, *41*, 1271.
14. Procopio, A.; Dalpozzo, R.; De Nino, A.; Nardi, M.; Oliverio, M. and Russo, B., *Synthesis*, **2006**, 2608.
15. Babu, J. L.; Khare, A. and Vankar, Y. D., *Molecules*, **2005**, *10*, 884.
16. Swamy, N. R.; Srinivasulu, M.; Reddy, T. S.; Goud, T. V. and Venkateswarlu, Y., *J. Carbohydr. Chem.,* **2004**, *23*, 435.
17. Yadav, J. S.; Reddy, B. V. S.; Murthy, C. V. S. R. and Kumar, G. M., *Synlett*, **2000**, 1450.
18. (a) Babu, B. S. and Balasubramanian, K. K., *Synth. Commun.,* **1999**, *29*, 4299. (b) Babu, B. S. and Balasubramanian, K. K., *Synlett*, **1999**, 1261.
19. Koreeda, M.; Houston, T. A.; Shull, B. K.; Klemke, E. and Tuinman, R. J., *Synlett,* **1995**, 90.
20. (a) Hanna, I. and Wlodyka, P., *J. Org. Chem.,* **1997**, *62*, 6985. (b) Grynkiewicz, G.; Priebe, W. and Zamojski, A., *Carbohydr. Res.,* **1979**, *68*, 33.
21. Boga, S. B. and Balasubramanian, K. K., *ARKIVOC*, **2004**, 87.
22. Lopez, J. C. and Fraser-Reid, B., *J. Chem. Soc., Chem. Commun.,* **1992**, 94.
23. (a) Toshima, K. and Tatsuta, K., *Chem. Rev*., **1993**, *93*, 1503. (b) Toshima, K.; Ishizuka, T.; Matsuo, G.; Nakata, M. and Kinoshito, M., *J. Chem. Soc., Chem. Commun*., **1993**, 704.
24. (a) Toshima, K.; Miyamoto, N.; Matsuo, G.; Nakata, M. and Matsumura, S., *J. Chem. Soc., Chem. Commun*., **1996**, 1379. (b) Toshima, K.; Ishizuka, T.; Matsuo, G. and Nakata, M., S*ynlett*, **1995**, 306. (c) Toshima, K.; Ishizuka, T.; Matsuo, G. and Nakata, M., *J. Chem. Soc., Chem. Commun*., **1995**, 306.

25. (a) Valverde, S. and Garcia-Ochoa, S., *J. Carbohydr. Chem.,* **1989**, *9*, 553. (b) Valverde, S.; Garcia-Ochoa, S. and Martin-Lomas, M., *J. Chem. Soc., Chem. Commun.,* **1987**, 383. (c) Priebe, W. and Zamojski, A., *Tetrahedron,* **1980**, *36*, 287.

26. (a) Gemmell, N.; Meo, P. and Osborn, H. M. I., *Org. Lett.,* **2003**, *5*, 1649. (b) Yadav, J. S.; Reddy, B. V. S.; Krishnam Raju, A.; Venkateswara Rao, C. *Tetrahedron Lett.,* **2002**, *43*, 5437. (c) Danishefsky, S. and kerwin, J. F., *J. Org. Chem.,* **1982**, *47*, 3803. (d) Dawe, R. D. and Fraser-Reid, B., *J. Chem. Soc., Chem. Commun.,* **1981**, 1180.

27. Zhang, Y. D.; Reynolds, N. T.; Manju, K. and Rovis, T., *J. Am. Chem. Soc.,* **2002**, *124*, 9720.

28. (a) López, J. C.; Gómez, A. M.; Valverde, S. and Fraser-Reid, B., *J. Org. Chem.,* **1995**, *60*, 3851. (b) Ferrier, R. J., *J. Chem. Soc.,* **1964**, 5443.

29. Lin, H.-C.; Yang, W.-B.; Gu, Y.-F.; Chen, C.-Y.; Wu, C.-Y. and Lin, C.-H., *Org. Lett.,* **2003**, *5*, 1087.

30. (a) Swamy, N. R.; Srinivasulu, M.; Reddy, T. S.; Goud, T. V. and Venkateswarlu, Y., *J. Carbohydr. Chem.,* **2004**, *23*, 435. (b) Franz, A. H.; Samoshin, V. V.; Myers, C.; Hunter, A. D. and Gross, P. H., *Carbohydr. Res.,* **2003**, *338*, 851. (c) Filho, J. R. de F.; Srivastava, R. M.; Soro, Y.; Cottier, L. and Descotes, G., *J. Carbohydr. Chem.,* **2001**, *20*, 561. (d) Konstantinov, S.; Predojev, J.; Gojkov, S.; Pavlov, V. and Csanad, J., *J. Serb. Chem. Soc.,* **2001**, *66*, 499. (e) Estevez, V. A. and Prestwich, G. D., *J. Am. Chem. Soc.,* **1991**, *113*, 9885. (f) Kozikowski, A. P. and Park, P.-U., *J. Am. Chem. Soc.,* **1985**, *107*, 1763.

31. (a) Du, W. T. and Hu, Y. Z., *Synth. Commun.,* **2006**, *36*, 2035. (b) Inui, M.; Hosokawa, S.; Nakazaki, A. and Kobayashi, S., *Tetrahedron Lett*., **2005**, *46*, 3245. (c) Bolitt, V.; Mioskowski, C.; Lee, S.-G. and Falck, J. R., *J. Org. Chem.,* **1990**, *55*, 5812.

32. Paquette, L. A.; Kinney, M. J. and Dullweber, U., *J. Org. Chem.,* **1997**, *62*, 1713.

33. (a) Moilanen, S. B. and Tan, D. S., *Org. Biomol. Chem.*, **2005**, *3*, 798. (b) Donohoe, T. J.; Logan, J. G. and Laffan, D. D. P., *Org. Lett.,* **2003**, *5*, 4995. (c) Kubota, H.; Lim, J. W.; Depew, K. M. and Schreiber, S. L., *Chem. Biol.*, **2002**, *9*, 265. (d) Hudlicky, T., *Chem. Rev.,* **1996**, *96*, 3. (e) Danishefsky, S. J.; DeNinno, S. and Lartey, P., *J. Am. Chem. Soc*., **1987**, *109*, 2082. (f) Ferrier, R. J., *Methods Carbohydr. Chem.* **1972**, *6*, 307. (g) Ferrier, R. J. and Prasad, N., *J. Chem. Soc.,* **1969**, 570. (h) Ferrier, R. J. and Prasad, N., *J. Chem. Soc.,* **1969**, 575. (i) Ferrier, R. J., *Adv. Carbohydr. Chem. Biochem.,* **1969**, *24*, 199. (j) Ferrier, R. J., *Adv. Carbohydr. Chem. Biochem.,* **1965**, *20*, 67.

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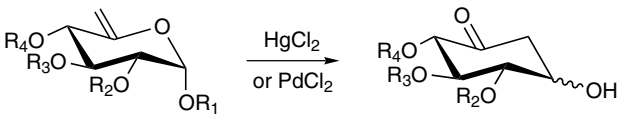
Ferrier-II Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Ferrier in 1979.[1] It is a mercury (II) salt[2]-induced or promoted conversion of 5-enopyranosides into cyclohexanones[3] with stereochemical control, by which substituents at positions 3 and 5 are predominantly in a *trans* relationship. To differentiate from another reaction also discovered by Ferrier (called the *Ferrier Reaction)*, this reaction is known as the Ferrier-II rearrangement,[3,4] Ferrier-II carbocyclization,[3,5] Ferrier carbocyclization,[6] or Ferrier-II reaction.[7] Occasionally, it is also referred to as the *Ferrier Reaction*.[8] Therefore, it is called the Ferrier-II rearrangement in this book. It is useful in the conversion of carbohydrates into carbosugars,[2a] *myo*-inositols,[9] and other natural products.[10]

B. GENERAL REACTION SCHEME



(R_1, R_2, R_3, R_4 = alkyl, benzyl, etc.)

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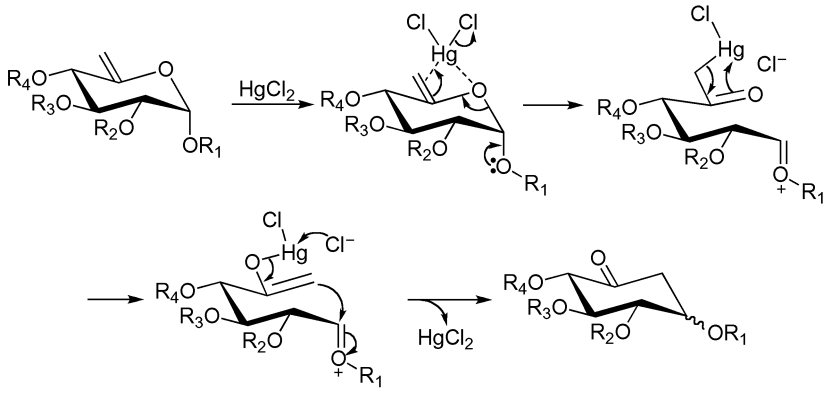
C. PROPOSED MECHANISMS

A simple mechanism is illustrated here.[11]



D. MODIFICATION

This reaction has been modified to occur under microwave irradiation[2a] and using palladium dichloride as a catalyst.[2a,3,4]

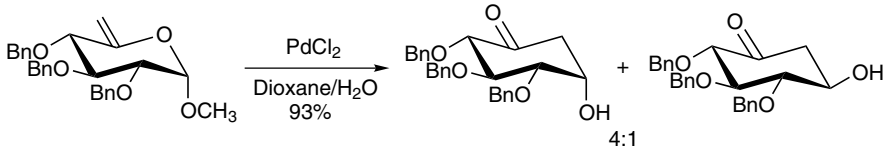
E. APPLICATIONS

This reaction has wide and important applications in the preparation of carbosugars and inositols.

F. RELATED REACTIONS

This reaction is related to the *Petasis-Ferrier Rearrangement*.

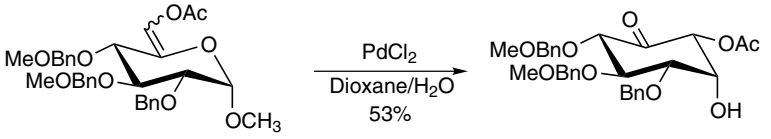
G. CITED EXPERIMENTAL EXAMPLES



Reference 2a.

To a solution of 2.3 g methyl-6-deoxy-2,3,4-tri-*O*-benzyl-α-D-hex-5-enopyranose (5.2 mmol) in 20 mL 1,4-dioxane and 10 mL water was added 0.37 g $PdCl_2$ (2.0 mmol) at room temperature. The mixture was stirred at 60°C with 300-W power in the microwave

for 5 min. The mixture was diluted with 60 mL EtOAc and washed with saturated aqueous $NaHCO_3$ (2 × 50 mL) and water (2 × 50 mL). The organic solvent was removed under reduced pressure. The product was purified by silica gel column chromatography (EtOAc/hexane, 2:3) to afford a 93% yield of α/β mixtures of 2,3,4-tri-*O*-benzyl-D-cyclohexanones, where the α-anomer is 1.7 g [3.8 mmol, 80% of the mixture, white solid, $R_f = 0.27$ (EtOAc/hexane, 3:7)] and the β-anomer is 0.41 g (0.95 mmol, 20% of the mixture).



Reference 3.

A mixture of 96.5 mg (*E*)-methyl 6-*O*-acetyl-2-*O*-benzyl-3,4-*O*-di-methoxybenzyl-α-D-*gluco*-hex-5-enopyranoside and (*Z*)-methyl 6-*O*-acetyl-2-*O*-benzyl-3,4-*O*-dimethoxybenzyl-α-D-*gluco*-hex-5-enopyranoside (0.171 mmol) and 3.0 mg $PdCl_2$ (0.017 mmol) in 3.3 mL of a dioxane-water mixture (2:1) was stirred at 60°C for 8 h. After the reaction was finished, water was added, and the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to dryness. Chromatography using EtOAc/hexane (1:2) gave 49.9 mg (1*R*,2*R*,3*S*,4*R*,5*S*)-3-benzyloxy-2-hydroxy-4,5-bis(4-methoxybenzyloxy)-6-oxocyclohexyl acetate as a solid (0.091 mmol), in a yield of 53.0%, $R_f = 0.33$ (EtOAc/hexane, 1:1).

Other references related to the Ferrier Rearrangement are cited in the literature.[12]

H. REFERENCES

1. Ferrier, R. J., *J. Chem. Soc., Perkin Trans. I*, **1979**, 1455.
2. (a) Ko, K.-S.; Zea, C. J. and Pohl, N. L., *J. Am. Chem. Soc*., **2004**, *126*, 13188. (b) Chida, N.; Ohtsuka, M.; Ogura, K. and Ogawa, S., *Bull. Chem. Soc. Jpn*., **1991**, *64*, 2118. (c) Machado, A. S.; Olesker, A. and Lukacs, G., *Carbohydr. Res*., **1985**, *135*, 231.
3. Takahashi, H.; Kittaka, H. and Ikegami, S., *J. Org. Chem*., **2001**, *66*, 2705.
4. Takahashi, H. and Ikegami, S., *Molecules,* **2005**, *10*, 901.
5. Takahashi, H.; Kittaka, H. and Ikegami, S., *Yuki Gosei Kagaku Kyokaishi,* **2000**, *58*, 120.
6. Taillefumier, C. and Chapleur, Y., *Can. J. Chem.,* **2000**, *78*, 708.
7. Takahashi, H.; Kittaka, H. and Ikegami, S., *Tetrahedron Lett*., **1998**, *39*, 9703.
8. (a) Hladezuk, I.; Olesker, A.; Tchertanov, L. and Cleophax, J., *Carbohydr. Res.,* **2001**, *330*, 257. (b) Yamauchi, N.; Terachi, T.; Eguchi, T. and Kakinuma, K., *Tetrahedron*, **1994**, *50*, 4125. (c) Machado, A. S.; Dubreuil, D.; Cleophax, J.; Gero, S. D. and Thomas, N. F., *Carbohydr. Res.,* **1992**, *233*, C5.
9. (a) Peng, J. A. and Prestwich, G. D., *Tetrahedron Lett.,* **1998**, *39*, 3965. (b) Prestwich, G. D., *Acc. Chem. Res*., **1996**, *29*, 503. (c) Chen, J.; Dormán, G. and Prestwich, G. D., *J. Org. Chem*., **1996**, *61*, 393. (d) Ferrier, R. and Middleton, S., *Chem. Rev.,* **1993**, *93*, 2779. (e) Estevez, V. A. and Prestwich, G. D., *J. Am. Chem. Soc*., **1991**, *113*, 9885. (f) Bender, S. L. and Budhu, R. J., *J. Am. Chem. Soc*., **1991**, *113*, 9883.

10. (a) Boyer, F. D. and Lallemand, F. D., *Tetrahedron*, **1994**, *50*, 10443. (b) Sato, K.; Bokura, M.; Moriyama, H.; Igarashi, T., *Chem. Lett.,* **1994**, *37*, 40.

11. (a) Chen, J.; Feng, L. and Prestwich, G. D., *J. Org. Chem*., **1998**, *63*, 6511. (b) Chen, J.; Profit, A. A. and Prestwich, G. D., *J. Org. Chem.*, **1996**, *61*, 6305.

12. (a) Yu, S.-H. and Chung, S.-K., *Tetrahedron: Asymmetry*, **2004**, *15*, 581. (b) Chen, J. J. and Deshpande, S. V., *Tetrahedron Lett.*, **2003**, *44*, 8873. (c) Lin, H.-C.; Yang, W.-B.; Gu, Y.-F.; Chen, C.-Y.; Wu, C.-Y. and Lin, C.-H., *Org. Lett.,* **2003**, *5*, 1087. (d) Dalko, P. I. and Sinay, P., *Angew. Chem. Int. Ed.,* **1999**, *38*, 773. (e) Imori, T.; Takahashi, H. and Ikegami, S., *Tetrahedron Lett*., **1995**, *31*, 649. (f) Ermolenko, M. S.; Olesker, A. and Lukacs, G., *Tetrahedron Lett*., **1994**, *35*, 711. (g) Sato, K.; Bokura, M.; Moriyama, H. and Igarashi, T., *Chem. Lett.,* **1994**, 37. (h) Boyer, F. D. and Lallemand, J. Y., *Tetrahedron*, **1994**, *50*, 10443. (i) Chida, N.; Ohtsuka, M. and Ogawa, S., *J. Org. Chem*., **1993**, *58*, 4441. (j) Chretien, F.; Wolf, R. and Chapleur, Y., *Nat. Prod. Lett.*, **1993**, *2,* 69. (k) Chida, N.; Ohtsuka, M.; Nakazawa, K. and Ogawa, S., *J. Org. Chem*., **1991**, *56*, 2976. (l) Bender, S. L. and Budhu, R. J., *J. Am. Chem. Soc*., **1991**, *113*, 9883. (m) Estevez, V. A. and Prestwich, G. D., *J. Am. Chem. Soc.* **1991**, *113*, 9885. (n) Barton, D. H. R.; Augy-Dorey, S.; Camara, J.; Dalko, P.; Delaumeny, J. M.; Gero, S. D.; Quiclet-Sire, B. and Stuetz, P., *Tetrahedron*, **1990**, *46,* 215. (o) Barton, D. H. R.; Camara, J.; Dalko, P.; Gero, S. D.; Quiclet-Sire, B. and Stuetz, P., *J. Org. Chem.,* **1989**, *54*, 3764. (p) Blattner, R. and Ferrier, R. J., *J. Chem. Soc., Chem. Commun*., **1987**, 1008. (q) Danishefsky, S. J.; DeNinno, S. and Lartey, P., *J. Am. Chem. Soc*., **1987**, *109*, 2082. (r) Machado, A. S.; Olesker, A. and Lukacs, G., *Carbohydr. Res.,* **1985**, *135*, 231. (s) Madi-Puskas, M.; Pelyvas, I. and Bognar, R., *J. Carbohydr. Chem.,* **1985**, *4*, 323. (t) Danishefsky, S. J. and Kerwin, J. F., *J. Org. Chem*., **1982**, *47*, 3803.

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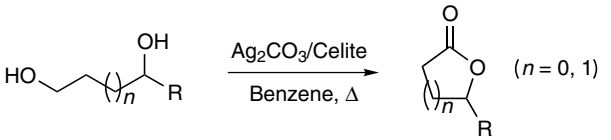
Fétizon Oxidation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Fétizon and Golfier in 1968.[1] It is a mild oxidation of alcohols into carbonyl compounds in refluxing benzene using silver carbonate absorbed on Celite as the oxidant. Therefore, it is known as the Fétizon oxidation,[2] and the silver carbonate on Celite is often called Fétizon's reagent.[2c,3] Fétizon's reagent is a very mild oxidant (e.g., even milder than Ag_2O),[4] and usually oxidizes the 1,4-diols,[5] 1,5-diols[2b,3c,6] and lactols[2c,3b,3d,6a,7] into lactone. Thus this reaction is also called Fétizon cyclization.[2b] In addition, the Fetizon's reagent also oxidizes geminal diols into α-hydroxyl ketones (or aldehydes),[3m] and sometimes cleaves the diols.[8] In the cases of 1,4-hydroquinones[3j,9] and catechols,[3i,10] they are oxidized into quinone by the Fétizon's reagent. Other applications of the Fétizon's reagent include the deprotection of the benzyl group on carbohydrate along with sodium sulfate,[11] conversion of halide into alcohol,[3g] generation of an aromatic radical,[3i,10b] coupling of indole to chloroquinone,[3a] one-pot synthesis of medium to large ring-fused furans from 1,3-dicarbonyl compounds and vinyl sulfides,[3f] and quinoxaline derivatives from catechol and α-amino anilines or naphthalenes.[4] The advantage of this reaction is that the reagent can be simply removed by filtration.[3a,3f]

B. GENERAL REACTION SCHEME



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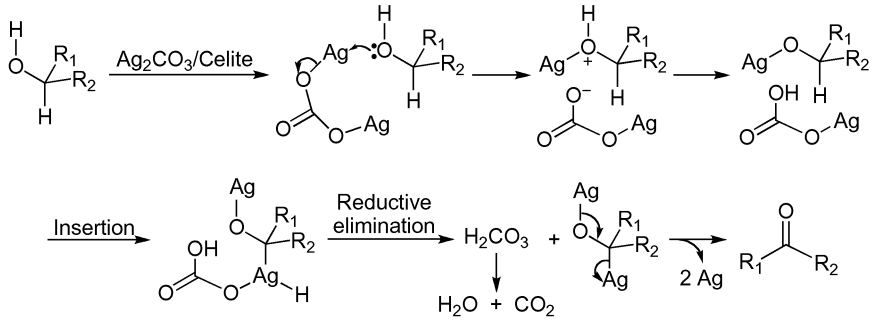
C. PROPOSED MECHANISMS

Displayed here is the reaction mechanism modified from the one reported by Fétizon.[13]



D. MODIFICATION

This reaction has been modified to remove water via azeotropic distillation with toluene.

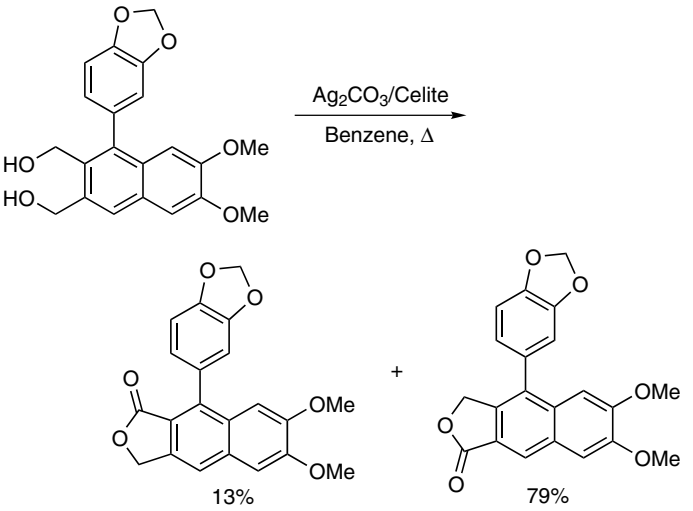
E. APPLICATIONS

This reaction has wide application in the preparation of aldehydes, ketones, lactones, quinones, and quinoxalines.

F. RELATED REACTIONS

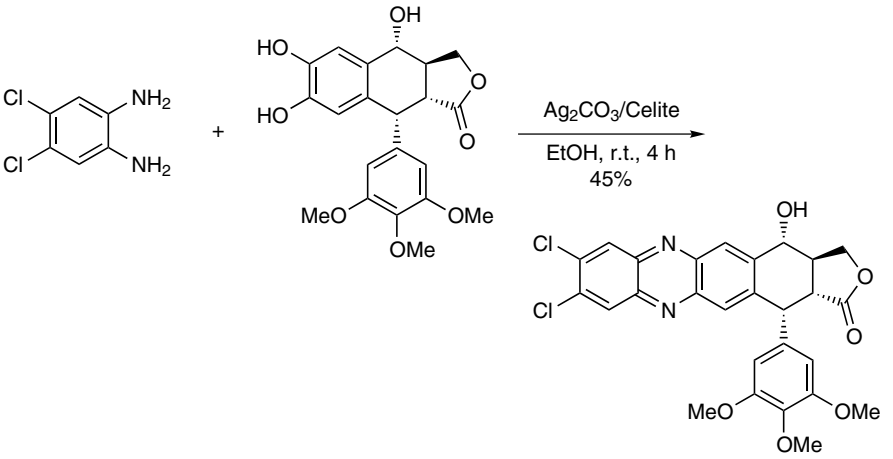
This reaction is related to the *Adkins Catalyst*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 5a.

A stirred suspension of 115 mg 1-(3,4-methylenedioxyphenyl)-6,7-dimethoxynaphthalene-2,3-diyldimethanol (0.312 mmol) and 3.12 g Fétizon's reagent (Ag_2CO_3-Celite) in 50 mL benzene was refluxed for 1.5 h with azeotropic removal of water using a Dean-Stark apparatus. After cooling to room temperature, the mixture was concentrated. The obtained crude product was purified by SiO_2-column chromatography ($CHCl_3$/EtOAc, 30:1) to give 15 mg justicidin B as a colorless crystal (m.p. 240–242°C), in a yield of 13%, and 90 mg retrojusticidin B as a colorless crystal (m.p. 217–219°C), in a yield of 79%.



Reference 4.

Commercially available 4,5-dichloro-1,2-phenylenediamine (44 mg, 0.25 mmol) and 50 mg 7-*O*,*O*-demethylenepodophyllotoxin (0.12 mmol) were dissolved in 5 mL dry ethanol. To this solution was added 357 mg freshly prepared Ag_2CO_3/Celite reagent (0.62 mmol). The reaction mixture was stirred for 4 h at room temperature. The reaction mixture was filtered, and the filtrate was evaporated under reduced pressure. The desired product was purified by silica gel column chromatography ($CHCl_3$:MeOH, 60:1) to give 30 mg 2″,3″-dichloropodophenazine as yellow granules crystallized from methanol, in a yield of 45%, m.p. 270°C (dec.).

Other references related to the Fétizon oxidation are cited in the literature.[14]

H. REFERENCES

1. Fétizon, M. and Golfier, M., *Compt. Rend.,* **1968**, *267*, 900.
2. (a) Von Geldern, T. W.; Tu, N.; Kym, P. R.; Link, J. T.; Jae, H. S.; Lai, C. Q.; Apelqvist, T.; Rhonnstad, P.; Hagberg, L.; Koehler, K.; Grynfarb, M.; Nilsson, A. G.; Sanderg, J.; Österlund, M.; Barkhem, T.; Höglund, M.; Wang, J. H.; Fung, S.; Wilcox, D.; Nguyen, P.; Jakob, C.; Hutchins, C.; Färnegardh, M.; Kauppi, B.; Öhman, L. and Jacobson, P. B., *J. Med. Chem.,* **2004**, *47*, 4213. (b) Nicolaou, K. C.; Theodorakis, E. A.; Rutjes, F. P. J. T.; Sato, M.; Tiebes, J.; Xiao, X.-Y.; Hwang, C.-K.; Duggan, M. E.; Yang, Z.; Couladouros, E. A.; Sato, F.; Shin, J.; He, H.-M. and Bleckman, T., *J. Am. Chem. Soc.,* **1995**, *117*, 10239. (c) Clive, D. L. J.; Murthy, K. S. K.; Wee, A. G. H.; Prasad, J. S.; da Silva, G. V. J.; Majewski, M.; Anderson, P. C.; Evans, C. F.; Haugen, R. D.; Heerze, L. D. and Barrie, J. R., *J. Am. Chem. Soc.,* **1990**, *112*, 3018.

3. (a) Pirrung, M. C.; Liu, Y. F.; Deng, L.; Halstead, D. K.; Li, Z. T.; May, J. F.; Wedel, M.; Austin, D. A. and Webster, N. J. G., *J. Am. Chem. Soc.,* **2005**, *127*, 4609. (b) Barlow, A. J.; Compton, B. J. and Weavers, R. T., *J. Org. Chem.,* **2005**, *70*, 2470. (c) Chandrasekhar, M.; Chandra, K. L. and Singh, V. K., *J. Org. Chem.,* **2003**, *68*, 4039. (d) Yamashita, Y.; Saito, S.; Ishitani, H. and Kobayashi, S., *J. Am. Chem. Soc.,* **2003**, *125*, 3793. (e) Pirrung, M. C.; Deng, L.; Li, Z. T. and Park, K., *J. Org. Chem.,* **2002**, *67*, 8374. (f) Lee, Y. R.; Suk, J. Y. and Kim, B. S., *Org. Lett.,* **2000**, *2*, 1387. (g) Crimmins, M. T.; Pace, J. M.; Nantermet, P. G.; Kim-Meade, A. S.; Thomas, J. B.; Watterson, S. H. and Wagman, A. S., *J. Am. Chem. Soc.,* **2000**, *122,* 8453. (h) Kocovsky, P.; Dunn, V.; Gogoll, A. and Langer, V., *J. Org. Chem.,* **1999**, *64*, 101. (i) Shultz, D. A. and Farmer, G. T., *J. Org. Chem.,* **1998**, *63*, 6254. (j) Hauser, F. M. and Zhou, M. T., *J. Org. Chem.,* **1996**, *61*, 5722. (k) Wee, A. G. H. and Zhang, L., *Org. Prep. Proc. Int.,* **1996**, *28*, 339. (l) Grieco, P. A.; Collins, J. L.; Moher, E. D.; Fleck, T. J. and Gross, R. S., *J. Am. Chem. Soc.,* **1993**, *115*, 6078. (m) Broka, C. A. and Ruhland, B., *J. Org. Chem.,* **1992**, *57*, 4888. (n) Rivett, D. E. A., *South Afri. J. Chem.,* **1986**, *39*, 161. (o) Badiger, R. B.; Mehta, A. M. and Trivedi, G. K., *Indian J. Chem., Sect. B,* **1978**, *16B*, 71. (p) Lenz, G. R., *J. Chem. Soc., Chem. Commun.,* **1972**, 468. (q) Tronchet, J. M. J.; Tronchet, J. and Birkhaeuser, A., *Helv. Chim. Acta,* **1970**, *53*, 1489.
4. Cho, S. J.; Kashiwada, Y.; Bastow, K. F.; Cheng, Y.-C. and Lee, K.-H., *J. Med. Chem.,* **1996**, *39*, 1396.
5. (a) Nishii, Y.; Yoshida, T.; Asano, H.; Wakasugi, K.; Morita, J.-I.; Aso, Y.; Yoshida, E.; Motoyoshiya, J.; Royama, H. and Tanabe, Y., *J. Org. Chem.,* **2005**, *70*, 2667. (b) Mani, N. S. and Townsend, C. A., *J. Org. Chem.,* **1997**, *62*, 636. (c) Coutts, S. J. and Kallmerten, J., *Tetrahedron Lett.*, **1990**, *31*, 4305.
6. (a) Shing, T. K. M.; Jiang, Q. and Mak, T. C. W., *J. Org. Chem.,* **1998**, *63*, 2056. (b) Lee, M.; Ikeda, I.; Kawabe, T.; Mori, S. and Kanematsu, K., *J. Org. Chem.,* **1996**, *61*, 3406.
7. (a) Yamashita, Y.; Saito, S.; Ishitani, H. and Kobayashi, S., *Org. Lett.,* **2002**, *4*, 1221. (b) Walker, D. P. and Grieco, P. A., *J. Am. Chem. Soc.,* **1991**, *121*, 9891.
8. Moher, E. D.; Collins, J. L. and Grieco, P. A., *J. Am. Chem. Soc.,* **1992**, *114*, 2164.
9. (a) Hauser, F. M. and Yin, H., *Org. Lett.,* **2002**, *4*, 1045. (b) Williams, W.; Sun, X. and Jebaratnam, D., *J. Org. Chem.,* **1997**, *62,* 4364.
10. (a) Shultz, D. A.; Fico, R. M.; Bodnar, S. H.; Kumar, R. K.; Vostrikova, K. E.; Kampf, J. W. and Boyle, P. D., *J. Am. Chem. Soc.,* **2003**, *125*, 11761. (b) Shultz, D. A.; Boal, A. K. and Farmer, G. T., *J. Org. Chem.,* **1998**, *63,* 9462.
11. Jobron, L. and Hindsgaul, O., *J. Am. Chem. Soc.,* **1999**, *121*, 5835.
12. Kakis, F. J.; Fetizon, M.; Douchkine, N.; Golfier, M.; Mourgues, P. and Prange, T., *J. Org. Chem.,* **1974**, *39*, 523.
13. Tserng, K.-Y., *J. Lipid Res.,* **1978**, *19*, 501.
14. (a) Santangelo, E. M.; Rotticci, D.; Liblikas, I.; Norin, T. and Unelius, C. R., *J. Org. Chem.,* **2001**, *66,* 5384. (b) Shing, T. K. M. and Jiang, Q., *J. Org. Chem.,* **2000**, *65,* 7059. (c) Krohn, K.; Böker,, N.; Gauhier, A.; Schäfer, G. and Werner, F., *J. Prakt. Chem.,* **1996**, *338*, 349. (d) Wang, T.-Z.; Pinard, E. and Paquette, L. A., *J. Am. Chem. Soc.,* **1996**, *118,* 1309. (e) Langkopf, E. and Schinzer, D., *Chem. Rev.,* **1995**, *95*, 1375. (f) Heathcock, C. H.; Stafford, J. A. and Clark, D. L., *J. Org. Chem.*, **1992**, *57*, 2575. (g) Takeuchi, K.; Kitagawa, T.; Ohga, Y.; Yoshida, M.; Akiyama, F. and Tsugeno, A., *J. Org. Chem.,* **1992**, 57, 280. (h) Lee, T.-J.; Holtz, W. J.; Smith, R. L.; Alberts, A. W. and Gilfillan, J. L., *J. Med. Chem.,* **1991**, *34*, 2474. (i) Templeton, J. F.; Setiloane, P.; Kumar, V. P. S.; Yan, Y. L.; Zeglam, T. H. and LaBella, F. S., *J. Med. Chem.,* **1991**, *34*, 2778. (j) Frye, L. L. and Robinson, C. H., *J. Org. Chem.,* **1990**, *55*, 1579. (k) Danishefsky, S. J. and Simoneau, B., *J. Am. Chem. Soc.,* **1989**, *111*, 2599. (l) Keck, G. E. and Kachensky, D. F., *J. Org. Chem.,* **1986**, *51*, 2487. (m) Le, P. H. and Nes, W. D., *Chem. Phys. Lipids,* **1986**, *40*, 57. (n) Morgans, D. J., *Tetrahedron Lett.,* **1981**, *22*, 3721. (o) McKillop, A. and Young, D. W., *Synthesis,* **1979**, 401. (p) Boschi, G.; Derappe, C. and Rips, R., *Eur. J. Med. Chem.,* **1977**,

12, 227. (q) Fétizon, M.; Golfier, M.; Milcent, R. and Papadakis, I., *Tetrahedron,* **1975**, *31*, 165. (r) Fétizon, M.; Golfier, M. and Louis, J.-M., *Tetrahedron,* **1975**, *31*, 171. (s) Fétizon, M.; Golfier, M.; Montaufier, M. T. and Rens, J., *Tetrahedron,* **1975**, *31*, 987. (t) Pravdic, N.; Danilov, B. and Fletcher, H. G., *Carbohydr. Res.,* **1974**, *36*, 167. (u) Fétizon, M.; Golfier, M. and Morgues, M., *Tetrahedron Lett.,* **1972**, 4445. (v) Balogh, V.; Fetizon, M. and Golfier, M., *J. Org. Chem.,* **1971**, *36*, 1339. (w) Kakis, F. J.; Brase, D. and Oshima, A., *J. Org. Chem.,* **1971**, *36*, 4117. (x) Fétizon, M.; Golfier, M. and Louis, J.-M., *J. Chem. Soc., Chem. Commun.,* **1969**, 1102. (y) Fieser, M. and Fieser, L., *Reagents for Organic Synthesis,* John Wiley & Sons, New York, **1969**, *2*, p. 363. (z) Fétizon, M.; Golfier, M. and Louis, J.-M., *J. Chem. Soc., Chem. Commun.,* **1969**, 1118.

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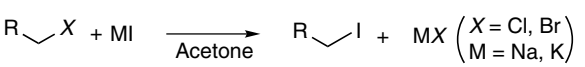
Finkelstein Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Finkelstein in 1910.[1] It is a preparation of alkyl iodide from alkyl bromide or chloride with potassium or sodium iodide in acetone. Therefore, this reaction is generally known as the Finkelstein reaction.[2,3] Occasionally, it is also referred to as the Finkelstein halide exchange,[4] Finkelstein displacement,[5] or Conant-Finkelstein reaction.[6] Mechanistically, this reaction is a simple nucleophilic substitution (often via S_N2), as iodide is a stronger nucleophile than bromide or chloride. The yield of this reaction is very high and can be quantitative if occurs in DMF.[2a] It was found that the trifluoromethyl group retards the displacement of bromide when it presents as an α- or β-substituent but accelerates the reaction as a substituent in an allylic chloride.[2h] Under normal conditions, this type of halide displacement does not occur for aryl halides.[7] For dihalides, unsaturated or cyclic compounds may form via carbocation intermediates, which form transient covalent iodides or are reduced directly by iodide to free radicals.[2g,7] However, the aromatic halide exchange reacts smoothly when 10% CuI is present in the reaction mixture as a catalyst,[2d] and such halide substitution can even occur at $-40^{\circ}C$.[2b]

B. GENERAL REACTION SCHEME



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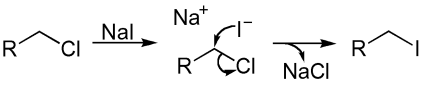
C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified to occur in DMF;[2a] in addition, CuI has been used to catalyze this reaction for aromatic halides.[2d]

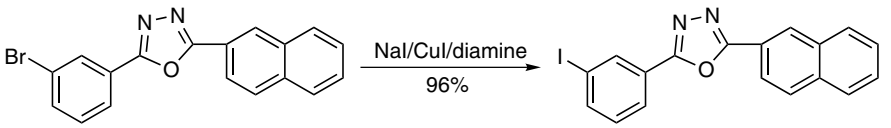
E. APPLICATIONS

This reaction has general applications in the preparation of alkyl and aryl iodides.

F. RELATED REACTIONS

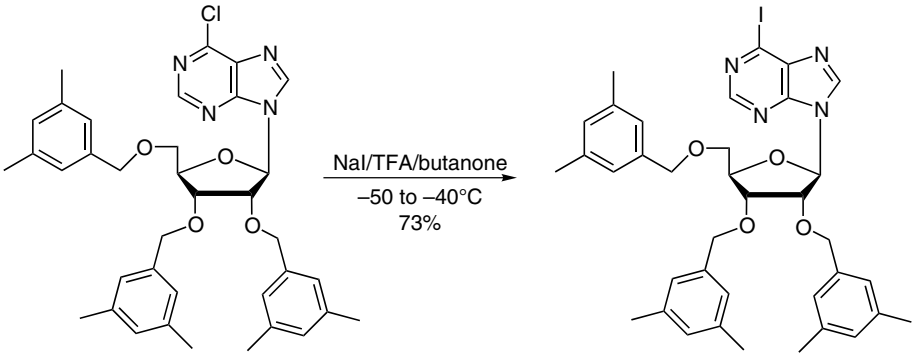
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 2d.

A Schlenk tube charged with 9.6 mg CuI (0.050 mmol, 5.0 mol%), 352 mg 2-(3-bromophenyl)-5-(2-naphthyl)-1,3,4-oxadiazole (1.00 mmol), and 300 mg NaI (2.00 mmol), was briefly evacuated and backfilled with argon. Then 16 μL racemic *trans*-*N*,*N*′-dimethyl-1,2-cyclohexanediamine (0.10 mmol, 10 mol %) and 1.0 mL dioxane were added under argon. The Schlenk tube was sealed with a Teflon valve, and the reaction mixture was stirred at 110°C for 24 h. The resulting light green-gray suspension was allowed to reach room temperature and then was diluted with 5 mL 30% aqueous ammonia, poured into 20 mL water, and extracted with dichloromethane (3 × 15 mL). The combined organic phases were dried over Na_2SO_4 and concentrated to ~ 2 mL volume. The product was allowed to crystallize at room temperature. After 15 min, 20 mL hexane was added; the mixture was kept at room temperature for 15 h and finally filtered to provide 382 mg 2-(3-iodophenyl)-5-(2-naphthyl)-1,3,4-oxadiazole as white, fine needles, in a yield of 96%, m.p., 156–158°C.



Reference 2b.

A mixture of 0.50 g 6-chloro-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine (0.7 mmol), 0.57 g trifluoroacetic acid (5 mmol), and 3.0 g sodium iodide (20 mmol) in 20 mL butanone was stirred at –40 to –50°C for 5 h. The reaction mixture was poured into a saturated $NaHCO_3$ solution and extracted with 50 mL CH_2Cl_2. The organic layer was washed with $NaHSO_3$ solution, H_2O, and brine and dried over Na_2SO_4. Volatiles were evaporated, and the residue was recrystallized from EtOH to afford 0.41 g 6-iodo-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine, in a yield of 73%, m.p. 143–145°C.

Other references related to the Finkelstein reaction are cited in the literature.[8]

H. REFERENCES

1. Finkelstein, H., *Ber.*, **1910**, *43*, 1528.
2. (a) Horn, T.; Lee, B.-C.; Dill, K. A. and Zuckermann, R. N., *Bioconjugate Chem.,* **2004**, *15*, 428. (b) Liu, J. Q.; Janeba, Z. and Robins, M. J., *Org. Lett.,* **2004**, *6*, 2917. (c) Goundry, W. R. F.; Lee, V. and Baldwin, J. E., *Tetrahedron Lett.,* **2002**, *43*, 2745. (d) Klapars, A. and Buchwald, S. L., *J. Am. Chem. Soc.,* **2002**, *124*, 14844. (e) Myers, A. G.; Barbay, J. K. and Zhong, B. Y., *J. Am. Chem. Soc.,* **2001**, *123*, 7207. (f) Epple, M.; Tröger, L. and Hilbrandt, N., *J. Chem. Soc., Faraday Trans.,* **1997**, *93*, 3035. (g) Smith, W. B.; Saint, C. and Branum, G. D., *J. Org. Chem.,* **1983**, *48*, 3828. (h) McBee, E. T.; Battershell, R. D. and Braendlin, H. P., *J. Am. Chem. Soc.,* **1962**, *84*, 3157.
3. (a) Wang, X. H.; Wang, H. Z.; Liu, H. and Kou, Y., *Chinese Chem. Lett.,* **2006**, *17*, 1531. (b) Pace, R. D. and Regmi, Y., *J. Chem. Edu.,* **2006**, *83*, 1344. (c) Zoller, T.; Uguen, D.; De Cian, A. and Fischer, J., *Tetrahedron Lett*., **1998**, *39*, 8089. (d) Landini, D.; Albanese, D.; Mottadelli, S. and Penso, M., *J. Chem. Soc., Perkin Trans. I,* **1992**, 2309. (e) Wang, X. Q.; Xu, R. Q. and Zhang, P., *Huaxue Xuebao*, **1984**, *42*, 1168. (f) Bekkevoll, S.; Svorstoel, I.; Hoeiland, H. and Songstad, J., *Acta Chem. Scand.,* **1983**, *B37*, 935. (g) Ye, X. L.; Xu, R. Q. and Zhang, P., *Huaxue Xuebao*, **1982**, *40*, 1051. (h) Maartmann-Moe, K.; Sanderud, K. A. and Songstad, J., *Acta Chem. Scand.,* **1982**, *B36*, 211. (i) Smith, W. B. and Branum, G. D., *Tetrahedron Lett*., **1981**, *22*, 2055. (j) Kondo, Y.; Nishikata, A.; Yoshioka, A. and Tokura, N., *Bull. Chem. Soc. Jpn.,* **1979**, *52*, 2329. (k) Serita, H.; Ohtani, N.; Matsunaga, T. and Kimura, C., *Kobunshi Ronbunshu*, **1979**, *36*, 527. (l) Hayami, J.; Koyanagi, T. and Kaji, A., *Bull. Chem. Soc. Jpn.,* **1979**, *52*, 1441. (m) Rolla, F.; Roth, W. and Horner, L., *Naturwissenschaften*, **1977**, *64*, 337. (n) Holman, J., *School Sci. Rev.,*

1977, *58*, 476. (o) Kondo, Y.; Tanaka, K. and Tokura, N., *Bull. Chem. Soc. Jpn.,* **1976**, *49*, 3100. (p) Kondo, Y.; Kato, T. and Tokura, N., *Bull. Chem. Soc. Jpn.,* **1975**, *48*, 285. (q) Ledrut, J. H. T. and Point, J. J., *Radiochimica Acta*, **1966**, *5*, 59. (r) Hughes, E. D.; Ingold, C. K. and Parker, A. J., *J. Chem. Soc.,* **1960**, 4400.

4. Boehm, H. M.; Handa, S.; Pattenden, G.; Roberts, L.; Blake, A. J. and Li, W.-S., *J. Chem. Soc*., *Perkin Trans. 1*, **2000**, 3522.
5. O'Brien, D. F., *J. Org. Chem.,* **1968**, *33*, 262.
6. (a) Moulay, S. and Zeffouni, Z., *Chinese J. Poly. Sci.,* **2007**, *25*, 297. (b) Moulay, S. and Zeffouni, Z., *J. Poly. Res.,* **2006**, *13*, 267. (c) Moulay, S. and Mehdi, N., *Chinese J. Poly. Sci.,* **2006**, *24*, 627.
7. Conant, J. B. and Kirner, W. R., *J. Am. Chem. Soc.,* **1924**, *46*, 232.
8. (a) Banwell, M. G.; McLeod, M. D. and Riches, A. G., *Aust. J. Chem.,* **2004**, *57*, 53. (b) Loeser, E.; Prasad, K. and Repic, O., *Synth. Commun.,* **2002**, *32*, 403. (c) Kaldor, I.; Feldman, P. L.; Mook, R. A.; Ray, J. A.; Samano, V.; Sefler, A. M.; Thompson, J. B.; Travis, B. R. and Boros, E. E., *J. Org. Chem.,* **2001**, *66*, 3495. (d) Lucet, D.; Heyse, P.; Gissot, A.; Gall, T. L. and Mioskowski, C., *Eur. J. Org. Chem*., **2000**, 3575. (e) Cibulka, R.; Hampl, F.; Kotoucova, H.; Mazac, J. and Liska, F., *Coll. Czech. Chem. Commun.,* **2000**, *65*, 227. (f) Carman, R. M. and Karoli, T., *Aust. J. Chem.,* **1998**, *51*, 955. (g) Schmidt, A. and Kindermann, M. K., *J. Org. Chem.,* **1997**, *62*, 3910. (h) Myers, A. G. and Gleason, J. L., *J. Org. Chem.,* **1996**, *61*, 813. (i) Pearson, A. J. and Lee, K., *J. Org. Chem.,* **1994**, *59*, 2304. (j) Hatakeyama, S.; Numata, H.; Osanai, K. and Takano, S., *J. Chem. Soc.*, *Chem. Commun.*, **1989**, 1893. (k) Hayami, J.; Tanaka, N.; Hihara, N. and Kaji, A., *Tetrahedron Lett.,* **1973**, 385. (l) Samaan, S. and Rolla, F., *Phosphorus & Sulfur,* **1978**, *4*, 145. (m) Ingold, C. K., *Structure and Mechanism in Organic Chemistry,* 2nd ed., Cornell University Press, London, **1969**, p. 435. (n) Treibs, W.; Hermann, J. and Zimmermann, G., *Ber.,* **1960**, *93*, 2193. (o) Pegolotti, J. A. and Young, W. G., *J. Am. Chem. Soc.,* **1961**, *83*, 3258. (p) Roedig, A., *Method. Org. Chem.,* **1960**, *4*, 595. (q) Tipson, R. S.; Clapp, M. A. and Cretcher, L. H., *J. Org. Chem.,* **1947**, *12*, 133. (r) Conant, J. B.; Kirner, W. R. and Hussey, R. E., *J. Am. Chem. Soc.,* **1925**, *47*, 488.

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Fischer Carbene Complexes

A. GENERAL DESCRIPTION OF THE REACTION

These types of complexes were first reported by Fischer and Maasböl in 1964.[1] The complexes contain a low-valent transition metal (often group VIB), an organic moiety (e.g., alkenyl,[2] alkynyl,[3] and aryl), several strong electron-withdrawing ligands (e.g., CO) and an electron-donating group (OR or NRR′). The combination of these characteristics enhances the stability of the complexes, which are stable even in aqueous solution.[4] In addition, these types of complexes also have metal-carbon multiple bonds, of which the electron configuration of carbon attaching to metal is similar to that of a carbene structure; therefore, these complexes are called Fischer carbene complexes[5] or Fischer-type carbene complexes.[6] Gradually, the Fischer carbene complexes, consisting of a few functionalities, found enormous applications in organic synthesis, as listed below.

- Participation in [2+1] cycloaddition to form cyclopropane derivatives;[5v,7] *Diels-Alder Cycloaddition*;[8] *1,3-Dipolar Cycloaddition*;[9] [3+2+1] cycloaddition (i.e., the *Dötz Benzannulation* to form functionalized phenol derivatives[5u,10]), [3+2+2+1] cycloaddition to give cyclopenta[*b*]-pyrans;[11] and [3+1+1],[12] [3+2+2],[13] [3+2+2+2],[14] and [4+1] cycloaddition.[15]
- Insertion of carbonyl (CO) to form esters or amides upon extrusion of metal.[5v,16]
- Substitution of an alkoxy group by other substituents to generate more derivatives.[4,5r]
- Substitution of metal by nucleophiles (e.g., alkyl anion to form allyl sulfoxide).[17]
- Hegedus photochemical ketene synthesis.[5u,18]

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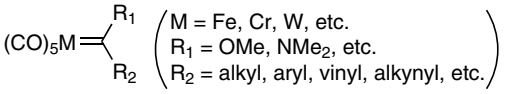
- Transmetallation of a group VI element to other transition metal.[19]
- Reaction of an olefinic or alkynyl group bound to metal.[5v,5x,7b,10b]

More information on the reactivities of such types of complexes are provided in reviews.[5s,18,19a,20]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

No mechanism is necessary for the Fischer carbene complexes.

D. MODIFICATION

N/A

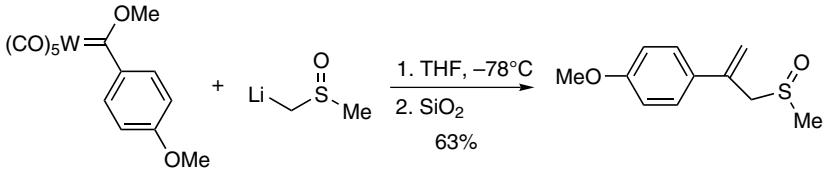
E. APPLICATIONS

These types of complexes have found wide application in organic synthesis as summarized in Section A.

F. RELATED REACTIONS

N/A

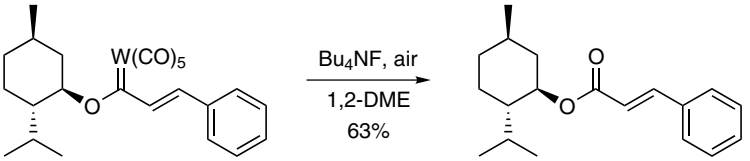
G. CITED EXPERIMENTAL EXAMPLES



Reference 17.

To a solution of 0.195 g DMSO (2.5 mmol) in 15 mL THF cooled at −20°C was added 1.7 mL 1.5 M MeLi in pentane. The resulting mixture was allowed to warm to

room temperature and was added dropwise to a solution of carbene complexe (1 mmol) in 20 mL THF at −78°C. The mixture was stirred at −78°C for 30 min and then warmed to room temperature. Silica gel was added and the solvents were evaporated under reduced pressure. The remaining material was loaded onto a column for chromatography, and 63% 2-(4-methoxyphenyl)allyl methyl sulfoxide was obtained as a yellow oil, $R_f = 0.15$ (EtOAc).



Reference 5w.

Tetrabutylammonium fluoride (1.5 mmol) was added at room temperature to a solution of 1.0 mmol pentacarbonyl[1-(1*R**,3*R**,4*S**)-menthyloxy-*trans*-3-phenyl-2-propenylidene]tungsten(0) in 30 mL 1,2-DME at room temperature. The reaction mixture was stirred at the same temperature and monitored by TLC. When disappearance of the starting material was observed, 1 g silica gel was added. Upon evaporation of solvent under vacuum, the residue adsorbed on silica gel was purified by flash chromatography to afford 63% *trans*-cinnamic acid menthyl ester.

Other references related to the Fischer carbene complexes are cited in the literature.[21]

H. REFERENCES

1. (a) Fischer, E. O. and Maasböl, A., *Angew. Chem. Int. Ed. Engl.,* **1964**, *3*, 580. (b) Fischer, E. O. and Maasböl, A., *Angew. Chem.,* **1964**, *76*, 645.
2. (a) Barluenga, J.; Mendoza, A.; Dieguez, A.; Rodriguez, F. and Fananas, F. J., *Angew. Chem. Int. Ed.,* **2006**, *45*, 4848. (b) Wang, S. L. B.; Liu, X. J.; Ruiz, M. C.; Gopalsamuthiram, V. and Wulff, W. D., *Eur. J. Org. Chem.,* **2006**, 5219.
3. (a) Zheng, Z. Y.; Yu, Z. K.; Luo, N. and Han, X. W., *J. Org. Chem.,* **2006**, *71*, 9695. (b) Zheng, Z. Y.; Yu, Z. K.; Wang, L. D.; He, W.; Liu, Z. S. and Han, X. W., *J. Organomet. Chem.,* **2006**, *691*, 5007. (c) Fernandez, I.; Sierra, M. A. and Cossio, F. P., *J. Org. Chem.,* **2006**, *71*, 6178. (d) Barluenga, J.; Martinez, S.; Suarez-Sobrino, A. L. and Tomas, M., *Organometallics,* **2006**, *25*, 2337. (e) Barluenga, J.; Fernandez-Rodriguez, M. A.; Garcia-Garcia, P.; Aguilar, E. and Merino, I., *Chem. Eur. J.,* **2006**, *12*, 303.
4. Salmain, M.; Licandro, E.; Baldoli, C.; Maiorana, S.; Tran-Huy, H. and Jaouen, G., *J. Organomet. Chem.,* **2001**, *617–618*, 376.
5. (a) Biswas, S. and Ali, M., *J. Organomet. Chem.,* **2007**, *692*, 2897. (b) Kagoshima, H.; Fuchibe, K. and Akiyama, T., *Chem. Record,* **2007**, *7*, 104. (c) Artillo, A.; Della Sala, G.; De Santis, M.; Llordes, A.; Ricart, S. and Spinella, A., *J. Organomet. Chem.,* **2007**, *692*, 1277. (d) Sierra, M. A.; Gomez-Gallego, M. and Martinez-Alvarez, R., *Chem. Eur. J.,* **2007**, *13*, 736. (e) Barluenga, J.; Vicente, R.; Lopez, L. A. and Tomas, M., *ARKIVOC,* **2007**, (*iv*), 356. (f) Barluenga, J.; Perez-Sanchez, I.; Suero, M. G.; Rubio, E. and Florez, J., *Chem. Eur. J.,* **2006**, *12*, 7225. (g) Barluenga, J.; Andina, F. and Aznar, F., *Org. Lett.,* **2006**, *8*, 2703. (h) Barluenga, J.; Garcia-Rodriguez, J.; Martinez, S.; Suarez-Sobrino, A. L. and Tomas, M., *Chem. Eur. J.,* **2006**, *12*, 3201. (i) Zoloff Michoff, M. E.; De Rossi, R. H. and Granados, A. M., *J. Org. Chem.,* **2006**,

71, 2395. (j) Campos, P. J.; Caro, M.; Lopez-Sola, S.; Sampedro, D. and Rodriguez, M. A., *J. Organomet. Chem.,* **2006**, *691*, 1075. (k) Zhang, L. and Herndon, J. W., *Heterocycles*, **2006**, *67*, 233. (l) Kamikawa, K.; Tachibana, A.; Shimizu, Y.; Uchida, K.; Furusyo, M. and Uemura, M., *Tetrahedron*, **2006**, *62*, 922. (m) Wang, S. L. B.; Goldberg, D. R.; Liu, X. J.; Su, J.; Zheng, Q.-H.; Liptak, V. and Wulff, W. D., *J. Organomet. Chem.,* **2005**, *690*, 6101. (n) Bernasconi, C. F. and Ragains, M. L., *J. Organomet. Chem.,* **2005**, *690*, 5616. (o) Samanta, D.; Sawoo, S.; Patra, S.; Ray, M.; Salmain, M. and Sarkar, A., *J. Organomet. Chem.,* **2005**, *690*, 5581. (p) Fernandez, I.; Sierra, M. A.; Gomez-Gallego, M.; Mancheno, M. J. and Cossio, F. P., *Chem. Eur. J.,* **2005**, *11*, 5988. (q) Capriati, V.; Florio, S.; Luisi, R.; Perna, F. M.; Salomone, A. and Gasparrini, F., *Org. Lett.,* **2005**, *7*, 4895. (r) Bernasconi, C. F. and Ali, M., *Organometallics,* **2004**, *23*, 6134. (s) Barluenga, J.; Santamaría, J. and Tomás, M., *Chem. Rev.,* **2004**, *104*, 2259. (t) Gopalsamuthiram, V. and Wulff, W. D., *J. Am. Chem. Soc.,* **2004**, *126*, 13936. (u) Rawat, M. and Wulff, W. D., *Org. Lett.,* **2004**, *6*, 329. (v) Florio, S.; Perna, F. M.; Luisi, R.; Barluenga, J.; Rodríguez, F. and Fañanás, F. J., *J. Org. Chem.,* **2004**, *69*, 5480. (w) Barluenga, J.; Andina, F.; Fernández-Rodríguez, M. A.; García-García, P.; Merino, I. and Aguilar, E., *J. Org. Chem.,* **2004**, *69*, 7352. (x) Barluenga, J., *Pure & Appl. Chem.*, **2002**, *74*, 1317. (y) Barluenga, J.; Muñiz, K.; Ballesteros, A.; Martínez, S. and Tomás, M., *ARKIVOC,* **2002**, 110. (z) Lloyd-Jones, G. C. and Fairlamb, I. J. S., *Annu. Rep. Prog. Chem., Sect. B,* **2001**, *97*, 113.

6. (a) Chen, J. Z.; Yu, Z. K.; Zheng, Z. Y.; Gu, K. C.; Wu, S. Z.; Zeng, F. L.; Tan, W. Q.; Wu, X. W. and Xiao, W. J., *Organometallics,* **2005**, *24*, 302. (b) Raubenheimer, H. G.; Kruger, G. J.; Scott, F. and Otte, R., *Organometallics,* **1987**, *6*, 1789.
7. (a) Barluenga, J.; Fanlo, H.; Lopez, S. and Florez, J., *Angew. Chem. Int. Ed.,* **2007**, *46*, 4136. (b) Florio, S.; Perna, F. M.; Luisi, R.; Barluenga, J.; Fañanás, F. J. and Rodríguez, F., *J. Org. Chem.,* **2004**, *69*, 9204.
8. (a) Barluenga, J.; Aznar, F.; Barluenga, S.; Fernández, M.; Martín, A.; García-Granda, S. and Piñera-Nicolás, A., *Chem. Eur. J.,* **1998**, *4*, 2280. (b) Barluenga, J.; Canteli, R. M.; Flórez, J.; García-Granda, S. and Gutiérrez-Rodríguez, A., *J. Am. Chem. Soc.,* **1994**, *116*, 6949. (c) Merlic, C. A. and Xu, D., *J. Am. Chem. Soc.,* **1991**, *113*, 7418. (d) Wang, S. L. B. and Wulff, W. D., *J. Am. Chem. Soc.,* **1990**, *112*, 4550. (e) Dötz, K. H.; Kuhn, W.; Müller, G.; Huber, B. and Alt, H. G., *Angew. Chem. Int. Ed. Engl.,* **1986**, *25*, 812. (f) Wulff, W. D. and Yang, D. C., *J. Am. Chem. Soc.,* **1984**, *106*, 7565. (g) Wulff, W. D. and Yang, D. C., *J. Am. Chem. Soc.,* **1983**, *105*, 6726.
9. (a) Barluenga, J.; Vicente, R.; Lopez, L. A. and Tomas, M., *J. Am. Chem. Soc.,* **2006**, *128*, 7050. (b) Barluenga, J.; Fernández-Rodríguez, M. A.; Aguilar, E.; Fernández-Marí, F.; Olano, B. and Salinas, A., *Chem. Eur. J.,* **2001**, *7*, 3533. (c) Alcaide, B.; Casarrubias, L.; Domínguez, G. and Sierra, M. A., *Curr. Org. Chem.,* **1998**, *2*, 551.
10. (a) Barluenga, J.; Aznar, F.; Gutiérrez, I.; Martín, A.; Carcía-Granda, S.; Llorca-Baragaño, M. A., *J. Am. Chem. Soc.,* **2000**, *122*, 1314. (b) Wulff, W. D.; Chan, K.-S. and Tang, P.-C., *J. Org. Chem.,* **1984**, *49*, 2293. (c) Dötz, K. H., *Angew. Chem. Int. Ed. Engl.,* **1984**, *23*, 587. (d) Dötz, K. H., *Angew. Chem*., **1984**, *96*, 573. (e) Dötz, K. H., *Angew. Chem. Int. Ed. Engl*., **1975**, *14*, 644. (f) Dötz, K. H., *Angew. Chem*., **1975**, *87*, 672.
11. De Meijere, A.; Schirmer, H.; Stein, F.; Funke, F.; Duetsch, M.; Wu, Y. T.; Noltemeyer, M.; Belgardt, T. and Knieriem, B., *Chem. Eur. J.,* **2005**, *11*, 4132.
12. Kamikawa, K.; Shimizu, Y.; Takemoto, S. and Matsuzaka, H., *Org. Lett.,* **2006**, *8*, 4011.
13. Kamikawa, K.; Shimizu, Y.; Matsuzaka, H. and Uemura, M., *J. Organomet. Chem.,* **2005**, *690*, 5922.
14. (a) Schirmer, H.; Duetsch, M.; Stein, F.; Labahn, T.; Knieriem, B. and de Meijere, A., *Angew. Chem. Int. Ed.,* **1999**, *38*, 1285. (b) Schirmer, H.; Duetsch, M.; Stein, F.; Labahn, T.; Knieriem, B. and de Meijere, A., *Angew. Chem.,* **1999**, *111*, 1369.

15. Moser, W. H.; Feltes, L. A.; Sun, L. D.; Giese, M. W. and Farrell, R. W., *J. Org. Chem.,* **2006**, *71*, 6542.

16. (a) Barluenga, J.; Fernández-Marí, F.; Viado, A. L.; Aguilar, E.; Olano, B.; García-Granda, S. and Moya-Rubiera, C., *Chem. Eur. J.,* **1999**, *5*, 883. (b) Barluenga, J.; Fernández-Marí, F.; Viado, A. L.; Aguilar, E. and Olano. B., *J. Chem. Soc., Perkin Trans. I,* **1997**, 2267.

17. Barluenga, J.; Fañanás-Mastral, M. and Aznar, F., Aznar, *Org. Lett.,* **2005**, *7*, 1235.

18. (a) Hegedus, L. S., *Tetrahedron,* **1997**, *53*, 4105. (b) Hegedus, L. S., "Transition Metal Carbene Complexes: Photochemical Reactions of Carbene Complexes," in *Comprehensive Organometallic Chemistry II*, ed. Abel, E. W.; Stone, F. G. A. and Wilkinson, G., Pergamon, Oxford, **1995**, *12*, pp. 549–576.

19. (a) Gómez-Gallego, M.; Mancheño, M. J. and Sierra, M. A., *Acc. Chem. Res.,* **2005**, *38*, 44. (b) Barluenga, J.; Lopez, L. A.; Lšber, O.; Tomás, O. M.; García-Granda, S.; Alvarez-Rœa, C. and Borge, J., *Angew. Chem. Int. Ed*., **2001**, *40*, 3392.

20. (a) Herndon, J. W., *Coord. Chem. Rev.,* **2003**, *243*, 3. (b) Barluenga, J.; Flórez, J.; Fañanás, F. J., *J. Organomet. Chem*., **2001**, *624*, 5. (c) Dötz, K. H.; Jakel, C. and Haase, W. C., *J. Organomet. Chem.,* **2001**, *617–618*, 119. (d) Sierra, M. A., *Chem. Rev.,* **2000**, *100*, 3591. (e) Aumann, R., *Eur. J. Org. Chem.,* **2000**, 17. (f) Herndon, J. W., *Tetrahedron,* **2000**, *56*, 1257. (g) Barluenga, J. and Fañanás, F. J., *Tetrahedron,* **2000**, *56*, 4597. (h) De Meijere, A.; Schirmer, H. and Duetsch, M., *Angew. Chem. Int. Ed*., **2000**, *39*, 3964. (i) Aumann, R. and Nienaber, H., *Adv. Organomet. Chem.*, **1997**, *41*, 163. (j) Harvey, D. F. and Sigano, D. M., *Chem. Rev*., **1996**, *96*, 271. (k) Grotjahn, D. B. and Dötz, K. H., *Synlett,* **1991**, 381. (l) Dötz, K. H.; Fischer, H.; Hofmann, P.; Kreissl, F. R.; Schubert, U. and Weiss, K., *Transition Metal Carbene Complex*, VCH, Weinheim, **1984**.

21. (a) Bos, M. E.; Loncaric, C.; Wu, C. R. and Wulff, W. D., *Synthesis*, **2006**, 3679. (b) Fernández, I.; Mancheño, M. J.; Gómez-Gallego, M.; Sierra, M. A.; Lejon, T. and Hansen, L. K., *Organometallics,* **2004**, *23*, 1851. (c) Fernández, I.; Cossío, F. P.; Arrieta, A.; Lecea, B.; Mancheño, M. J. and Sierra, M. A., *Organometallics,* **2004**, *23*, 1065. (d) Vázquez, M. A.; Cessa, L.; Vega, J. L.; Miranda, R.; Herrera, R.; Jiménez-Vázquez, H. A.; Tamariz, J. and Delgado, F., *Organometallics,* **2004**, *23*, 1918. (e) Barluenga, J.; Vicente, R.; López, L. A.; Rubio, E.; Tomás, M. and Álvarez-Rúa, C., *J. Am. Chem. Soc.,* **2004**, *126*, 470. (f) Barluenga, J.; Vicente, R.; Barrio, P.; López, L. A.; Tomás, M. and Borge, J., *J. Am. Chem. Soc.,* **2004**, *126*, 14354. (g) Barluenga, J.; Vicente, R.; Barrio, P.; López, L. A. and Tomás, M., *J. Am. Chem. Soc.,* **2004**, *126*, 5974. (h) Jiang, M. X.-W.; Rawat, M. and Wulff, W. D., *J. Am. Chem. Soc.,* **2004**, *126*, 5970. (i) Kamikawa, K.; Tachibana, A.; Shimizu, Y.; Uchida, K.; Furusho, M. and Uemura, M., *Org. Lett.,* **2004**, *6*, 4307. (j) Barluenga, J.; Aznar, F. and Palomero, M. A., *Chem. Eur. J.,* **2001**, *7*, 5318. (k) Wu, H.-P.; Aumann, R.; Venne-Dunker, S. and Saarenketo, P., *Eur. J. Org. Chem.*, **2000**, 3463. (l) Barluenga, J.; Tomás, M.; Ballesteros, A.; Santamaría, J. and Suárez-Sobrino, A., *J. Org. Chem.,* **1997**, *62*, 9229. (m) Wulff, W. D.; Yang, D. C. and Murray, C. K., *J. Am. Chem. Soc.,* **1988**, *110*, 2653. (n) Erker, G.; Lecht, R.; Petersen, J. L. and Bönnemann, H., *Organometallics,* **1987**, *6*, 1962. (o) Wulff, W. D. and Tang, P.-C., *J. Am. Chem. Soc.,* **1984**, *106*, 434. (p) Tang, P.-C. and Wulff, W. D., *J. Am. Chem. Soc.,* **1984**, *106*, 1132. (q) Macomber, D. W., *Organometallics,* **1984**, *3*, 1589. (r) Fischer, E. O. and Dötz, K. H., *Ber.,* **1972**, *105*, 1356. (s) Fischer, E. O. and Dötz, K. H., *Ber.,* **1970**, *103*, 1273.

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Fischer Indole Synthesis
(Fischer Indolization)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Fischer and Jourdan in 1883.[1] It is a synthesis of indole derivatives by the treatment of aryl hydrazones coupled from aromatic hydrazines and ketones or aldehydes with either a mineral or Lewis acid. Therefore, it is generally known as the Fischer indole synthesis.[2] In addition, it is also referred to as Fischer cyclization,[3] Fischer indole cyclization,[4] Fischer indole reaction,[5] Fischer indolization,[6] Fischer reaction,[7] and Fischer indole annulation.[8] Although the mechanism has been extensively studied,[5e,9] the one formulated by Robinson and Robinson is now generally accepted.[10] It involves the following steps: (*a*) initial acid-catalyzed tautomerization of an aromatic hydrazone to an *ene*-hydrazine, (*b*) a [3,3]-sigmatropic rearrangement of *ene*-hydrazine to a *bis*-imine intermediate, (*c*) re-aromatization to aniline, (*d*) intramolecular nucleophilic attack to form aminal, and (*e*) extrusion of an ammonia to afford the indole.

This reaction is often catalyzed by acids, including mineral acids (e.g., PPA[3b]) and Lewis acids. $ZnCl_2$ is found to be a very effective Lewis acid catalyst,[11] and the special case of indole synthesis using 1% $ZnCl_2$ as catalyst is known as the Fischer-Arbuzov reaction.[2z] However, much experimental evidence also indicates that an acidic catalyst is not necessary for this reaction;[2t,2bb,12] in addition, the formation of indole from aromatic hydrazone can occur at high temperatures (e.g., 222°C).[2t] These reaction conditions are called non-catalytic Fischer indole syntheses.[2ac] Even though the Fischer indole synthesis is one of the most common methods for indole, it also has some potential problems. For example, indole isomers[13] and even quinolone[2bb] derivatives will form if unsymmetrical ketones are used to form the aromatic hydrazones. Furthermore, because the Fischer indole synthesis involves a [3,3]-sigmatropic rearrangement and nucleophilic attack, if both the 2 and

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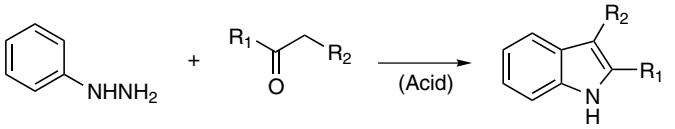
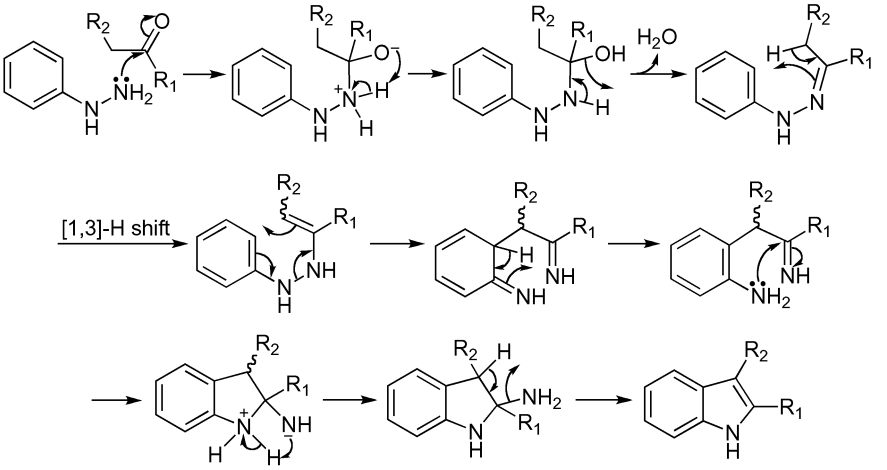
6 positions of the aromatic hydrazines are blocked by substituents, then non-indole product (e.g., carbazole[4b,14]) or abnormal indole product (via 1,4-migration) is obtained,[7,9b,15] usually in poor to fair yield.[16] To overcome this problem, thioether is often used to direct the regiochemistry and is then removed at a later stage;[17] in addition, it was found that Eaton's reagent (P_2O_5/$MeSO_3H$)[13] and diethylaluminum 2,2,6,6-tetramethylpiperidide (DATMP)[18] can facilitate the regioselectivity. As the formed indole is subjected to degradation under acidic conditions, a two-phase reaction was designed for the indole synthesis.[6e] Moreover, a solid-phase supported synthesis of indole has also been developed,[2n,19] and the traceless synthesis of indole is probably the most advanced technique for solid-phase synthesis.[2m,2q,20] Furthermore, as ketones and aldehydes tautomerize under acidic conditions, the dialkyl acetals are used for the indole preparation.[21] It is interesting that a new preparation of aromatic hydrazones with substituted benzaldehydes have been developed from aromatic halides and hydrazines.[6d] Further modifications of this reaction include the reaction in gas phase[2w] and in ionic liquid,[2p] the application of organoaluminium amide as a catalyst,[18] and the generation of hydrazone from aldehydes by hydroformylation of olefins with carbon monoxide.[21a] Because of the importance of indole moiety in alkaloids, this reaction has been extensively investigated and widely applied to pharmaceutical and medicinal chemistry as well as in organic synthesis.

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The detailed mechanism in the absence of an acid is illustrated here.



D. MODIFICATION

This reaction has been extensively modified to various conditions, including a reaction without a catalyst,[2t,2cc,12c] the generation of aldehydes by hydroformylation of olefin,[21aa] two-phase reaction,[6e] and—more important—the solid phase-supported reactions.[2m,2n,2q,19,20]

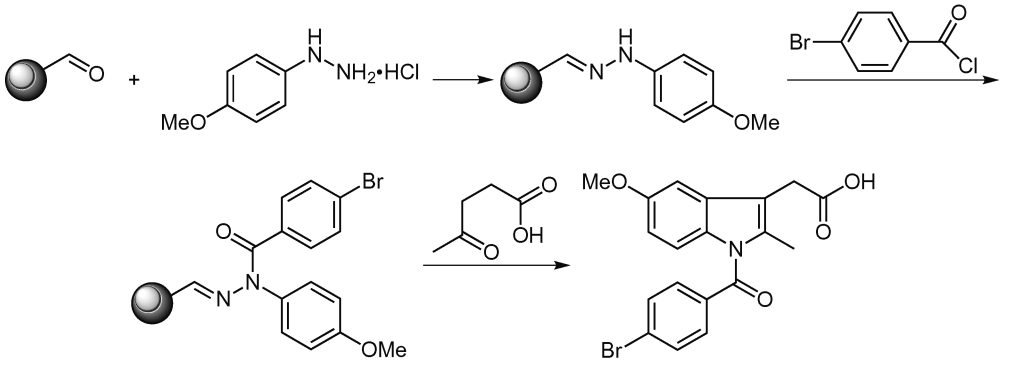
E. APPLICATIONS

This reaction has wide application in the synthesis of indole derivatives.

F. RELATED REACTIONS

This reaction is related to the *Borsche-Drechsel Reaction, Madelung Indole Synthesis*, and *Piloty-Robinson Pyrrole Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2n.

Procedure for Hydrazone Formation

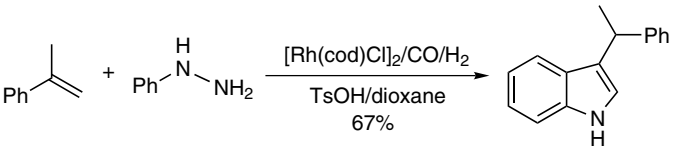
The aldehyde resin (0.5 g, 0.55 mmol) was dried in high vacuum overnight and suspended in 5 mL dichloroethane. To this suspension, 2.75 mmol (5 eq.) *p*-methoxybenzenehydrazine hydrochloride and 194 μL triethylamine (6 eq.) were added under argon atmosphere. The mixture was shaken at 45°C overnight. After cooling, the resin was filtered and washed three times each with 5 mL *N*,*N*-dimethylformamide, DMF/H_2O (v/v = 90/10), DMF, dichloromethane, ethyl acetate, and methanol.

Procedure for Hydrazone Acylation

The hydrazone resin (0.5 g, 0.45 mmol) was dried in high vacuum overnight and suspended in 5 mL pyridine. To this suspension was added 1.35 mmol *p*-bromobenzoyl chloride (3 eq.) under argon. The mixture was shaken at 80°C overnight. After cooling, the resin was filtered and washed three times with DMF, DMF/H_2O (v/v = 90/10), DMF, dichloromethane, ethyl acetate, and methanol.

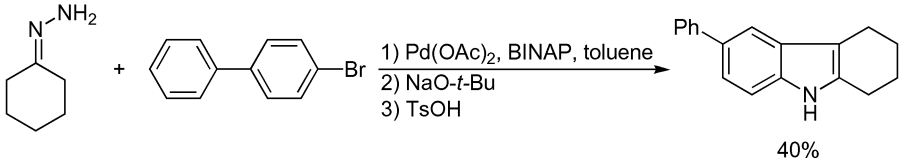
Procedure for Cleavage and Indole Rearrangement

The benzoylated hydrazone resin (150 mg, 0.11 mmol) was suspended in 6 mL dichloroethane/trifluoroacetic acid (1/1). Then 10 eq. laevulinic acid was added, and the mixture was heated for 15 min to 2 h at 70°C. After cooling, the mixture was quenched with methanol, and the resin was filtered and washed with 5 mL dichloromethane, methanol, ethyl acetate, and methanol. The filtrate was evaporated to dryness, and the crude product was purified by preparative HPLC. Finally, [1-(4-bromobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid was obtained as white solid, in a yield of 57% with a purity of > 99% (HPLC), m.p. 151°C.



Reference 21a.

To an autoclave were added 0.60 g α-methylstyrene (5.1 mmol), 0.58 g phenylhydrazine (5.3 mmol), 10 mg $[Rh(cod)Cl]_2$ (0.5 mol %), 0.95 g *p*-toluenesulfonic acid (5.0 mmol), and 30 mL anhydrous dioxane. Then the autoclave was pressurized with 50 bar CO and 20 bar H_2. After being stirred for 2 days at 120°C, the mixture was filtered over alumina. The solvent was evaporated, and the residue was purified by flash chromatography on silica to yield 0.74 g 3-(1-phenylethyl)-indole, in a yield of 67%.



Reference 2r.

To an oven-dried test tube were added 112 mg cyclohexanone hydrazone (1.0 mmol), 0.5 mL toluene, 233 mg 4-bromobiphenyl (1.0 mmol), 11 mg $Pd(OAc)_2$ (0.05 mmol), and 31 mg (±) BINAP (0.05 mmol), followed by an additional 0.5 mL of toluene. The test tube was capped with a septum, purged briefly with argon, and heated to 100°C for 2 min (the reaction mixture turned green and then black during this period). The reaction mixture was cooled to room temperature, the septum was removed, and 134 mg sodium *tert*-butoxide (1.4 mmol) was added, followed by 1 mL toluene. The test tube was recapped with the septum and purged briefly with argon; the resulting purple solution was heated

at 100°C for 8 h (*Caution!* Hydrazine may be evolved during this reaction). The reaction mixture was cooled to room temperature, diluted with 10 mL Et_2O, and filtered through a short pad of Celite. The filter cake was rinsed with 20 mL Et_2O. The filtrate was then concentrated to afford the crude product. The crude product was then refluxed with 380 mg *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) (2.0 mmol) in 5 mL EtOH for 48 h. The reaction mixture was then cooled to room temperature, the septum was removed, and the reaction mixture was diluted with 15 mL Et_2O. The resulting heterogeneous mixture was then filtered through a pad of silica gel (1 inch), and the silica gel was rinsed with an additional portion of Et_2O (20–50 mL). The filtrate was concentrated, and the crude product was purified by flash chromatography (5 → 10% EtOAc/hexanes) to afford 98 mg 6-phenyl-1,2,3,4,-tetrahydrocarbazole, in a yield of 40%, m.p. 142–143°C.

Other references related to the Fischer indole synthesis are cited in the literature.[23]

H. REFERENCES

1. Fischer, E. and Jourdan, F., *Ber.,* **1883**, *16*, 2241.
2. (a) Nielsen, S. D.; Ruhland, T. and Rasmussen, L. K., *Synlet,* **2007**, 443. (b) Xu, D.-Q.; Yang, W.-L.; Luo, S.-P.; Wang, B.-T.; Wu, J. and Xu, Z-Y., *Eur. J. Org. Chem.,* **2007**, 1007. (c) Jiang, J.-Z. and Wang, Y., *Youji Huaxue*, **2006**, *26*, 1025. (d) Linnepe, P.; Schmidt, A. M. and Eilbracht, P., *Org. Biomed. Chem.,* **2006**, *4*, 302. (e) Yasui, E.; Wada, M. and Takamura, N., *Tetrahedron Lett*., **2006**, *47*, 743. (f) Hu, X. C.; Sun, N.; Yu, L. J. and Mo, W. M., *Henan Huagong*, **2005**, *22*, 25. (g) Dhakshinamoorthy, A. and Pitchumani, K., *Appl. Catal., A: Gen.,* **2005**, *292*, 305. (h) Schmidt, A. M. and Eilbracht, P., *Org. Biomed. Chem.,* **2005**, *3*, 2333. (i) Narayana, B.; Ashalatha, B. V.; Vijaya Raj, K. K.; Fernandes, J. and Sarojini, B. K., *Bioorg. Med. Chem.,* **2005**, *13*, 4638. (j) Dhanabal, T.; Sangeetha, R. and Mohan, P. S., *Tetrahedron Lett*., **2005**, *46*, 4509. (k) Schmidt, A. M. and Eilbracht, P., *J. Org. Chem.,* **2005**, *70*, 5528. (l) Hu, Y.-Z. and Chen, Y.-Q., *Synlet.,* **2005**, 42. (m) Mun, H.-S.; Ham, W.-H. and Jeong, J.-H., *J. Comb. Chem.,* **2005**, *7*, 130. (n) Rosenbaum, C.; Röhrs, S.; Müller, O.; Waldmann, H., *J. Med. Chem.*, **2005**, *48* 1179. (o) Ackermann, L. and Born, R., *Tetrahedron Lett*., **2004**, *45*, 9541. (p) Morales, R. C.; Tambyrajah, V.; Jenkins, P. R.; Davies, D. L. and Abbott, A. P., *Chem. Commun.,* **2004**, 158. (q) Rosenbaum, C.; Katzka, C.; Marzinzik, A. and Waldmann, H., *Chem. Commun.,* **2003**, 1822. (r) Wagaw, S.; Yang, B. H. and Buchwald, S. L., *J. Am. Chem. Soc.,* **1999**, *121*, 10251. (s) Schultz, C.; Link, A.; Leost, M.; Zaharevitz, D. W.; Gussio, R.; Sausville, E. A.; Meijer, L. and Kunick, C., *J. Med. Chem.,* **1999**, *42*, 2909. (t) An, J. Y.; Bagnell, L.; Cablewski, T.; Strauss, C. R. and Trainor, R. W., *J. Org. Chem.*, **1997**, *62*, 2505. (u) Li, Q.; Tan, J. and Peng, B.-X., *Molecules,* **1997**, *2*, 91. (v) Bergman, J. and Pelcman, B., *Pure & Appl. Chem.,* **1990**, *62*, 1967. (w) Glish, G. L. and Cooks, R. G., *J. Am. Chem. Soc.,* **1978**, *100*, 6720. (x) Southwick, P. L.; McGrew, B.; Engel, R. R.; Milliman, G. E. and Owellen, R. J., *J. Org. Chem.,* **1963**, *28*, 3058. (y) Robinson, R., *Chem. Rev.,* **1963**, *63*, 373. (z) Carlin, R. B. and Carlson, D. P., *J. Am. Chem. Soc.,* **1959**, *81*, 4673. (aa) Rapoport, H. and Tretter, J. R., *J. Am. Chem. Soc.,* **1958**, *80*, 5574. (bb) Fitzpatrick, J. T. and Hiser, R. D., *J. Org. Chem.,* **1957**, *22*, 1703. (cc) Kissman, H. M.; Farnsworth, D. W. and Witkop, B., *J. Am. Chem. Soc.,* **1952**, *74*, 3948.
3. (a) Bessard, Y., *Org. Proc. Res. Dev.,* **1998**, *2*, 214. (b) Hegde, V.; Madhukar, P.; Madura, J. D. and Thummel, R. P., *J. Am. Chem. Soc.,* **1990**, *112*, 4549.
4. (a) Watson, T. J. N.; Horgan, S. W.; Shah, R. S.; Farr, R. A.; Schnettler, R. A.; Nevill, C. R.; Weiberth, F. J.; Huber, E. W.; Baron, B. M.; Webster, M.. E.; Mishra, R. K.; Harrison, B. L.; Nyce, P. L.; Rand, C. L. and Goralski, C. T., *Org. Proc. Res. Dev.,* **2000**, *4*, 477. (b) Miller, B. and Matjeka, E. R., *J. Am. Chem. Soc.,* **1980**, *102*, 4712. (c) Gannon, W. F.; Benigni, J. D.; Dickson, D. E. and Minnis, R. L., *J. Org. Chem.,* **1969**, *34*, 3002.

5. (a) Simoneau, C. A. and Ganem, B., *Tetrahedron*, **2005**, *61*, 11374. (b) Gorohovsky, S.; Meir, S.; Shkoulev, V.; Byk, G. and Gellerman, G., *Synlett,* **2003**, 1411. (c) Chen, C.-Y.; Senanayake, C. H.; Bill, T. J.; Larsen, R. D.; Verhoeven, T. R. and Reider, P. J., *J. Org. Chem.,* **1994**, *59*, 3738. (d) Douglas, A. W., *J. Am. Chem. Soc.,* **1978**, *100*, 6463. (e) Hughes, D. L. and Zhao, D. L., *J. Org. Chem.,* **1993**, *58*, 228.
6. (a) Alonso, D.; Caballero, E.; Medarde, M. and Tome, F., *Tetrahedron Lett*., **2005**, *46*, 4839. (b) Suzuki, H.; Tsukakoshi, Y.; Tachikawa, T.; Miura, Y.; Adachi, M. and Murakami, Y., *Tetrahedron Lett*., **2005**, *46*, 3831. (c) Finlay, H. J.; Honda, T. and Gribble, G. W., *ARKIVOC*, **2002**, 38. (d) Wagaw, S.; Yang, B. H. and Buchwald, S. L., *J. Am. Chem. Soc.,* **1998**, *120*, 6621. (e) Brodfuehrer, P. R.; Chen, B.-C.; Sattelberg, T. R.; Smith, P. R.; Reddy, J. P.; Stark, D. R.; Quinlan, S. L.; Reid, J. G.; Thottathil, J. K. and Wang, S. P., *J. Org. Chem.,* **1997**, *62*, 9192. (f) Anderson, N. G.; Ary, T. D.; Berg, J. L.; Bernot, P. J.; Chan, Y. Y.; Chen, C.-K.; Davies, M. L.; DiMarco, J. D.; Dennis, R. D.; Deshpande, R. P.; Do, H. D.; Droghini, R.; Early, W. A.; Gougoutas, J. Z.; Grosso, J. A.; Harris, J. C.; Haas, O. W.; Jass, P. A.; Kim, D. H.; Kodersha, G. A.; Kotnis, A. S.; LaJeunesse, J.; Lust, D. A.; Madding, G. D.; Modi, S. P.; Moniot, J. L.; Nguyen, A.; Palaniswamy, V.; Phillipson, D. W.; Simpson, J. H.; Thoraval, D.; Thurston, D. A.; Tse, K.; Polomski, R. E.; Wedding, D. L. and Winter, W. J., *Org. Proc. Res. Dev.,* **1997**, *1*, 300. (g) Bonjoch, J.; Catena, J. and Valls, N., *J. Org. Chem.,* **1996**, *61*, 7106. (h) Bergman, J. and Pelcman, B., *J. Org. Chem.,* **1989**, *54*, 824. (i) Ishii, H., *Acc. Chem. Res.,* **1981**, *14*, 275.
7. (a) Carlin, R. B.; Magistro, A. J. and Mains, G. J., *J. Am. Chem. Soc.,* **1964**, *86*, 5300. (b) Carlin, R. B. and Amoros-Marin, L., *J. Am. Chem. Soc.,* **1959**, *81*, 730. (c) Carlin, R. B.; Wallace, J. G. and Fisher, E. E., *J. Am. Chem. Soc.,* **1952**, *74*, 990.
8. Christoffers, J., *Synlett*, **2006**, 318.
9. (a) Ban, Y. and Iijima, I., *Tetrahedron Lett.,* **1969**, 2523. (b) Carlin, R. B. and Fisher, E. E., *J. Am. Chem. Soc.,* **1948**, *70*, 3421. (c) Allen, C. F. H. and Wilson, C. V., *J. Am. Chem. Soc.,* **1943**, *65*, 611.
10. Robinson, G. M. and Robinson, R., *J. Chem. Soc.,* **1924**, *125*, 827.
11. Janetzky, E. F. J. and Verkade, P. E., *Rec. Trav. Chim.,* **1945**, *64*, 129.
12. (a) Strauss C. R. and Trainor R. W., "Application for New Microwave Reactors for Food and Flavor Research" in *ACS Symposium Series No. 637: Biotechnology for Improved Foods and Flavors*, ed. Takeoka, G. R.; Teranishi, R.; Williams, P. J. and Kobayashi, A., American Chemical Society, Washington, DC, **1996**, p. 272. (b) Strauss, C. R. and Trainor, R. W., *Aust. J. Chem.,* **1995**, *48*, 1665. (c) Wolff, L. *Ann*., **1912**, *394*, 107.
13. Zhao, D. L.; Hughes, D. L.; Bender, D. R.; DeMarco, A. M. and Reider, P. J., *J. Org. Chem.,* **1991**, *56*, 3001.
14. Sumpter, W. C. and Miller, F. M., *Heterocyclic Compounds with Indole and Carbazole Systems,* ed. Weissberger, A., Interscience Publishers, New York, **1954**, p. 3.
15. (a) Bajwa, G. S. and Brown, R. K., *Can. J. Chem.,* **1970**, *48*, 2293. (b) Carlin, R. B. and Larson, G. W., *J. Am. Chem. Soc.,* **1957**, *79*, 934. (c) Carlin, R. B.; Henley, W. O. and Carlson, D. P., *J. Am. Chem. Soc.,* **1957**, *79*, 5712.
16. Conn, R. S. E.; Douglas, A. W.; Karady, S.; Corley, E. G.; Lovell, A. V. and Shinkai, I., *J. Org. Chem.,* **1990**, *55*, 2908.
17. (a) Trofimov, F. A.; Garnova, V. I.; Grinev, A. N. and Tsyshkova, N. G., *Chem. Heterocycl. Compd.*, **1979**, *15*, 63. (b) Trofimov, F. A.; Tsyshkova, N. G.; Garnova, V. I. and Grinve, A. N., *Chem. Heterocycl. Compd.,* **1971**, *11*, 1091.
18. Maruoka, K.; Oishi, M. and Yamamoto, H., *J. Org. Chem.,* **1993**, *58*, 7638.
19. (a) Tanaka, H.; Ohno, H.; Kawamura, K.; Ohtake, A.; Nagase, H. and Takahashi, T., *Org. Lett.,* **2003**, *5*, 1159. (b) Cooper, L. C.; Chicchi, G. G.; Dinnell, K.; Elliott, J. M.; Hollingworth, G. J.; Kurtz, M. M.; Locker, K. L.; Morrison, D.; Shaw, D. E.; Tsao, K.-L.; Watt, A. P.; Williams, A. R.

and Swain, C. J., *Bioorg. Med. Chem. Lett.*, **2001**, *11*, 1233. (c) Yang, L., *Tetrahedron Lett.*, **2000**, *41*, 6981. (d) Tois, J.; Franzèn, R.; Aitio, O.; Kuikko, K. and Taskinen, J., *Tetrahedron Lett.*, **2000**, *41*, 2443. (e) Hutchins, S. M. and Chapman, K. T., *Tetrahedron Lett.*, **1996**, *37*, 4869.

20. Nicolau, K. C.; Roecker, A. J.; Hughes, R.; van Summeren, R.; Pfefferkorn, J. A. and Winssinger, N., *Bioorg. Med. Chem.*, **2003**, *11*, 465.

21. (a) Köhling, P.; Schmidt, A. M. and Eilbracht, P., *Org. Lett.,* **2003**, *5*, 3213. (b) Hughes, D. L., *Org. Prep. Proced. Int.,* **1993**, *25*, 607.

22. (a) Robinson, B., *The Fischer Indole Synthesis,* John Wiley & Sons, New York, **1982**. (b) Remers, W. A., "Properties and Reactions of Indoles, Isoindoles and Their Hydrogenated Derivatives" in *Chemistry of Heterocyclic Compounds*, ed. Houlihan, W. J., John Wiley & Sons, New York, **1972**, 25, *Part 1*, pp. 1–226. (c) Sundberg, R. J. ed., *The Chemistry of Indoles*, Academic Press, New York, **1970**. (d) Robinson, B., *Chem. Rev.,* **1969**, *69*, 227. (e) Roussel, P. A., *J. Chem. Edu.,* **1953**, *30*, 122. (f) Van Order, R. B. and Lindwall, H. G., *Chem. Rev.,* **1942**, *30*, 78.

23. (a) Chen, Y. H.; Shibata, M.; Rajeswaran, M.; Srikrishnan, T.; Dugar, S. and Pandey, R. K., *Tetrahedron Lett*., **2007**, *48*, 2353. (b) Grandini, C.; Camurati, I.; Guidotti, S.; Mascellani, N.; Resconi, L.; Nifant'ev, I. E.; Kashulin, I. A.; Ivchenko, P. V.; Mercandelli, P. and Sironi, A., *Organometallics,* **2004**, *23*, 344. (c) Jiricek, J. and Blechert, S., *J. Am. Chem. Soc.,* **2004**, *126*, 3534. (d) Hajicek, J., *Coll. Czech. Chem. Commun.,* **2004**, *69*, 1681. (e) Fornicola, R. S.; Subburaj, K. and Montgomery, J., *Org. Lett.,* **2002**, *4*, 615. (f) Bhattacharya, G.; Su, T.-L.; Chia, C.-M. and Chen, K.-T., *J. Org. Chem.,* **2001**, *66*, 426. (g) Gribble, G. W., *J. Chem. Soc., Perkin Trans. I,* **2000**, 1045. (h) Abdel-Rahman, A. H.; Khalil, A. M.; El-Desoky, S. I. and Keshk, E. M., *Chem. Papers,* **1999**, *53*, 323. (i) Zhao, W.; Hou, Y. J.; Wang, X. S.; Zhang, B. W.; Cao, Y.; Yang, R.; Wang, W. B. and Xiao, X. R., *Solar Energ. Mater. Solar Cells,* **1999**, *58*, 173. (j) Menciu, C.; Duflos, M.; Fouchard, F.; Le Baut, G.; Emig, P.; Achterrath, U.; Szelenyi, I.; Nickel, B.; Schmidt, J.; Kutscher, B. and Günther, E., *J. Med. Chem.,* **1999**, *42*, 638. (k) Miyata, O.; Kimura, Y.; Muroya, K.; Hiramatsu, H. and Naito, T., *Tetrahedron Lett.,* **1999**, *40*, 3601. (l) Gan, G.; Liu, R. Y.; Yu, P.; Zhao, S. and Cook, J. M., *J. Org. Chem.,* **1997**, *62*, 9298. (m) Miyata, O.; Kimura, Y.; Muroya, K.; Hiramatsu, H. and Naito, T., *Tetrahedron Lett.,* **1997**, *62*, 425. (n) Lajsic, S.; Cetkovic, G.; Popsavin, M.; Popsavin, V. and Miljkovic, D., *Coll. Czech. Chem. Commun.,* **1996**, *61*, 298. (o) Freter, K.; Fuchs, V. and Pitner, T. P., *J. Org. Chem.,* **1983**, *48*, 4593. (p) Miller, F. M. and Schinske, W. Neal, *J. Org. Chem.,* **1978**, *43*, 3384. (q) Miller, F. M. and Lohr, R. A., *J. Org. Chem.,* **1978**, *43*, 3388. (r) Baldwin, J. E. and Tzodikov, N. R., *J. Org. Chem.,* **1977**, *42*, 1878. (s) Nakazaki, M. and Yamamoto, K., *J. Org. Chem.,* **1976**, *41*, 1877. (t) Eberle, M. K. and Brzechffa, L., *J. Org. Chem.,* **1976**, *41*, 3775. (u) Posvic, H.; Dombro, R.; Ito, H. and Telinski, T., *J. Org. Chem.,* **1974**, *39*, 2575. (v) Owellen, R. J.; Fitzgerald, J. A.; Fitzgerald, B. M.; Welsh, D. A.; Walker, D. M. and Southwick, P. L., *Tetrahedron Lett.,* **1967**, 1741. (w) Carlin, R. B. and Harrison, J. W., *J. Org. Chem.,* **1965**, *30*, 563. (x) Elderfield, R. C.; Lagowski, J. M.; McCurdy, O. L. and Wythe, S. L., *J. Org. Chem.,* **1958**, *23*, 435. (y) Carlin, R. B. and Carlson, D. P., *J. Am. Chem. Soc.,* **1957**, *79*, 3605. (z) Plieninger, H. and Nogradi, I., *Ber.,* **1955**, *88*, 1964. (aa) Snyder, H. R. and Smith, C. W., *J. Am. Chem. Soc.,* **1943**, *65*, 2452. (bb) Robinson, G. M. and Robinson, R., *J. Chem. Soc.,* **1918**, *113*, 639. (cc) Fischer, E. and Hess, O., *Ber.,* **1884**, *17*, 559.

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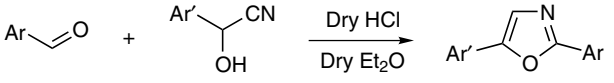
Fischer Oxazole Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Fischer in 1896.[1] It is a synthesis of oxazole derivatives by treatment of equimolar amounts of aldehyde cyanohydrin and aromatic aldehyde in anhydrous ether with dry hydrochloride. Therefore, it is known as the Fischer oxazole synthesis[2] or Fischer synthesis.[3] This method is good for the preparation of 2,5-diaryloxazoles[4] and is usually carried out in dry ether by dissolving aromatic aldehydes and aldehyde cyanohydrins and passing in dry HCl gas.[4] The synthesized oxazole precipitates as its hydrochloride salt, which can be converted into free oxazoles by the addition of water[5] or by boiling with alcohol.[1,6] However, some minor byproducts also form in this reaction, including 4-chlorooxazoles,[7] oxazolidinone,[7] arylenemandeloamide,[8] and diazine.[8] This reaction has been further modified by using aroyl cyanide and aromatic aldehyde in the presence of dry HCl or HBr gas to give 4-chloro- or 4-bromo-oxazoles;[3] another modification is to add $SOCl_2$ to the reaction mixture of nitrile, aromatic aldehyde, and HCl gas to form oxazoles in one step[9] instead of preparing cyanohydrin before reacting with aldehyde.

B. GENERAL REACTION SCHEME



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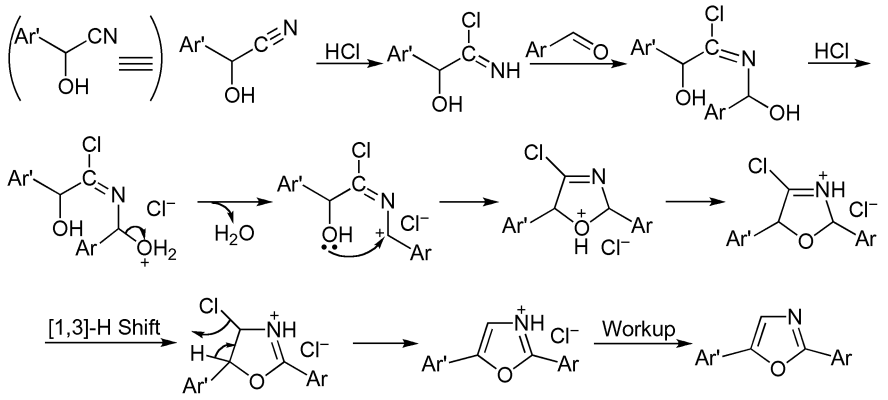
C. PROPOSED MECHANISMS

A mechanism similar to that of Ingham[8a] but with much more detail is given here.



D. MODIFICATION

The modifications of this reaction include the reaction between aroyl cyanide and aromatic aldehyde in the presence of HCl gas[8] and the reaction of nitrile with aromatic aldehyde, HCl and $SOCl_2$.[3]

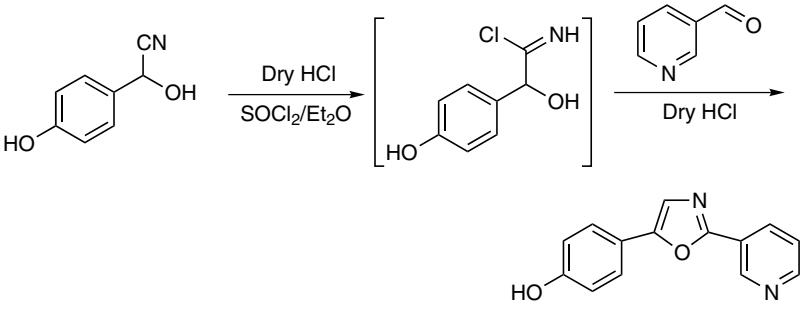
E. APPLICATIONS

This reaction has a general application in the preparation of 2,5-diaryl-oxazoles.

F. RELATED REACTIONS

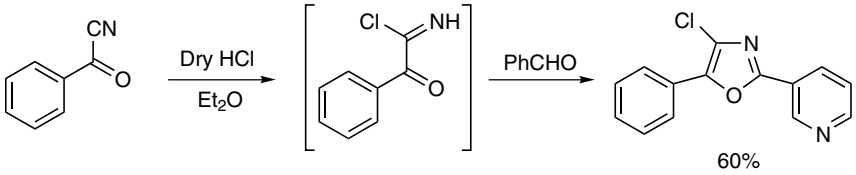
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 9b.

The solution of 0.94 g freshly prepared *p*-hydroxymandelonitrile in 45 mL anhydrous ether was saturated with HCl by bubbling the dry HCl gas into the solution. After an addition of 1.12 g $SOCl_2$, the reaction mixture was stirred for 10 min with external cooling. Then an addition of 0.75 g nicotinaldehyde was followed, and the reaction mixture was saturated with dry HCl once again. After standing at room temperature for 2 days, the reaction solution was poured into water, and the separated organic layer was further washed with aqueous HCl. Neutralization of the combined aqueous layers with Na_2CO_3 resulted in the precipitation of halfordinol, which was collected on a filter and recrystallized from methanol to fine cream needles, in amount of 248 mg (16.5%), m.p. 254–255°C.



Reference 3.

Benzoyl cyanide was prepared by heating a mixture of benzoyl chloride and cuprous cyanide, then 13.1 g purified benzoyl cyanide (0.10 mol), 11.67 g benzaldehyde (0.11 mol), and 100 mL dry ether were cooled in an ice bath and saturated with dry hydrogen chloride. The mixture was kept at 0°C overnight, then transferred onto 300 g crushed ice and extracted with ether (2 × 100 mL). The combined organic layers were washed with water, saturated $NaHSO_3$, and water and dried over Na_2SO_4. Upon removal of the solvent, the residue was recrystallized from acetone or an acetone/methanol mixture to give 15.34 g 2,5-diphenyl-4-chloro-oxazole, in a yield of 60%, m.p. 71–72°C.

Other references related to the Fischer oxazole synthesis are cited in the literature.[10]

H. REFERENCES

1. Fischer, E., *Ber.,* **1896**, *29*, 205.
2. (a) Ionescu, M.; Macarovici, R. and Beu, L., *Studia Univ. Babes-Bolyai, Chem*, **1975**, *20*, 59. (b) Cornforth, J. W. and Cornforth, R. H., *J. Chem. Soc.,* **1949**, 1028.
3. Davis, M.; Lakhan, R. and Ternal, B., *J. Heterocycl. Chem.,* **1977**, *14*, 317.
4. Wiley, R. H., *Chem. Rev.,* **1945**, *37*, 401.
5. Minovici, S.; Nenitzescu, C. D. and Angelescu, B., *Bull. Soc. Chim. Roumania,* **1928**, *10*, 149 [*Chem. Abstr.,* **1929**, *23*, 2716].
6. Minovici, S., *Ber.,* **1896**, *29*, 2097.
7. Turchi, I. J., *Ind. Eng. Chem. Prod. Res. Dev.,* **1981**, *20*, 32.
8. (a) Ingham, B. H., *J. Chem. Soc.,* **1927**, 692. (b) Japp, F. R. and Knox, J., *J. Chem. Soc.,* **1905**, *87*, 701.
9. (a) Truchi, I. J. and Dewar, M. J. S., *Chem. Rev.,* **1975**, *75*, 389. (b) Onaka, T., *Tetrahedron Lett.,* **1971**, 4393.

10. (a) Loughlin, W. A.; Muderawan, I. W.; McCleary, M. A.; Volter, K. E. and King, M. D., *Aust. J. Chem.,* **1998**, *52*, 231. (b) Lakhan, R. and Ternai, B., *Adv. Heterocycl. Chem.,* **1974**, *17*, 99. (c) Onaka, T., *Tetrahedron Lett.,* **1971**, 4391. (d) Viscontini, M. and Raschig, H., *Helv. Chim. Acta,* **1959**, *42*, 570. (e) Lister, J. and Robinson, R., *J. Chem. Soc.,* **1912**, *101*, 1297. (f) McComble, H. and Parry, E., *J. Chem. Soc.,* **1909**, *95*, 584. (g) Robinson, R., *J. Chem. Soc.,* **1909**, *95*, 2167.

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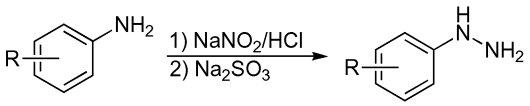
Fischer Phenylhydrazine Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Fischer in 1875.[1] It is a synthesis of phenylhydrazine involving the diazotization of aniline, the reduction of the resulting diazonium salt with an excess amount of sodium sulfite, and the hydrolysis of phenylhydrazine sulfonic acid salt with hydrochloric acid. In addition, the diazonium salt can also be reduced by zinc dust in acetic acid.[2] This process has become a standard industrial method for the production of arylhydrazines.

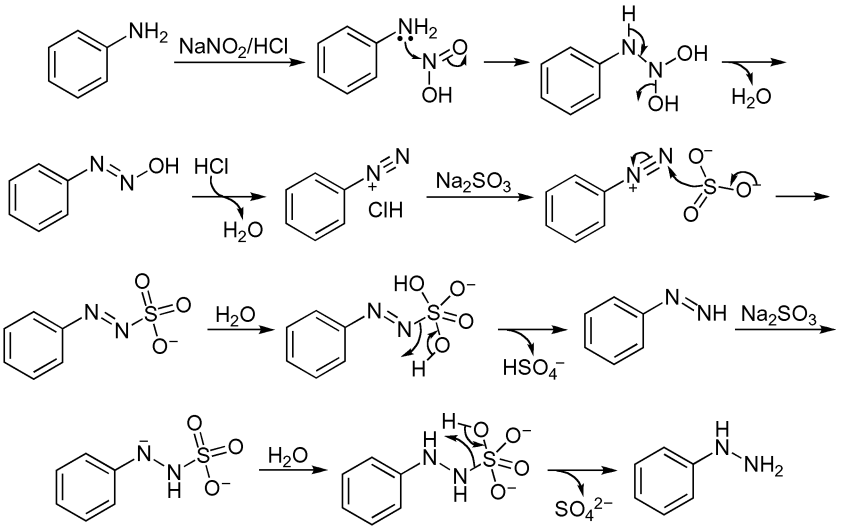
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is assumed that sodium sulfite adds to the diazonium salt to form an azo group, which is further reduced to hydrazine by sulfite as outlined here.

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang



D. MODIFICATION

N/A

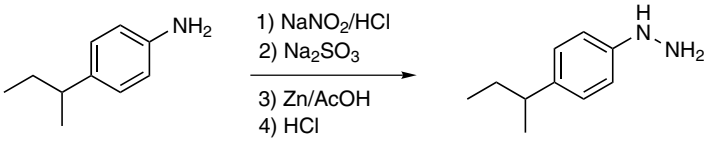
E. APPLICATIONS

This reaction is the general method for preparing arylhydrazines, from a small scale to an industrial scale.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3.

The *p-sec*-butyl aniline was first treated with concentrated hydrochloric acid followed by the slow addition of a $NaNO_2$ solution to maintain the temperature below 0°C. The diazonium salt solution was poured at once into a cold solution of sodium sulfite, giving a

rich red solution, a sample of which was only slightly cloudy after having been boiled for 1 min. This solution was then reduced in the usual way by the Fischer method with zinc dust and acetic acid. The reaction mixture was heated nearly to the boiling point during the reduction to secure completeness of the reduction. From the cooled solution, the solid sulfonate was separated by filtration. The *p-sec*-butyl-phenylhydrazine sodium sulfonate crystallized from a water solution in beautiful white plates with a pearly luster. These are stable in the air for $\sim$ 2 h when they darkened slightly. After one crystallization from 95% alcohol, the crystals were well dried in a vacuum desiccator over sulfuric acid. To obtain the hydrochloride of the hydrazine, the sulfonate was covered with concentrated hydrochloric acid, and the mixture was boiled for 8 h, during which time fresh acid was supplied as needed. The solid hydrochloride was obtained as a mass of white crystals from the cooled solution. These were treated with sodium hydroxide and so on, to give the hydrazine. The pure *p-sec*-butyl-phenylhydrazine can be obtained by vacuum distillation in the atmosphere of hydrogen.

Other references related to the Fischer phenylhydrazine synthesis are cited in the literature.[4]

H. REFERENCES

1. Fischer, E., *Ber.,* **1875**, *8*, 589.
2. Fischer, E., *Ann.,* **1877**, *190*, 67.
3. Glattfeld, J. W. E. and Wertheim, E., *J. Am. Chem. Soc.,* **1922**, *44*, 2682.
4. (a) Huisgen, R. and Lux, R., *Ber.,* **1960**, *93*, 540. (b) Colemann, G. H., *Org. Syn. Coll.* **1932**, *1*, 432. (c) Pechmann, H. V., *Ber.,* **1895**, *28*, 863.

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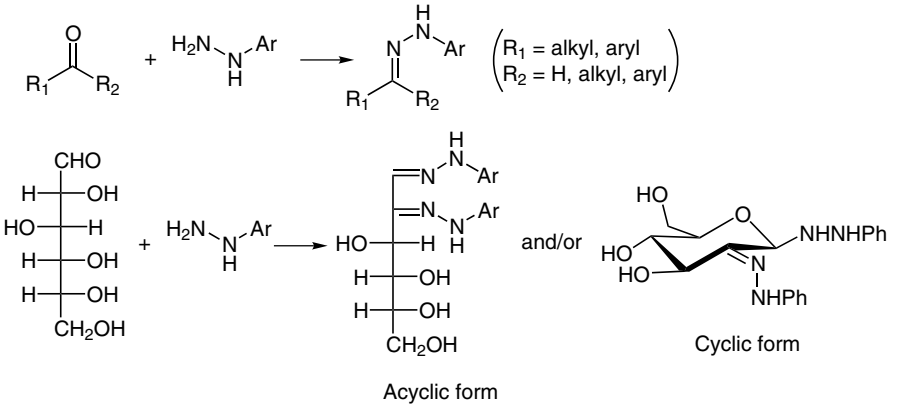
Fischer Phenylhydrazone and Osazone Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

The formation of phenylhydrazone was initially reported by Fischer in 1875.[1] It is a condensation between phenylhydrazine and a carbonyl compound (aldehyde or ketone) to form phenylhydrazone. The compounds condensed from carbohydrates and 2 eq. of phenylhydrazine are generally known as osazones[2] or specifically referred to as glycosazones.[3] Both the phenylhydrazones of carbonyl compounds and glycosazones from carbohydrates often readily crystallize[4] and show sharp melting points; therefore, formation of phenylhydrazone derivatives from carbonyl compounds was a routine method in traditional structure analysis before modern instruments (MS and NMR) came into play. Similarly, the glycosazones were employed by Fischer to elucidate the configuration of sugars.[3a] However, it was found that the phenylhydrazones of aliphatic ketones and aldehydes rapidly tautomerize to the more stable azo isomers in solution;[5] in addition, the glycosazones of carbohydrates also exist as chelated acyclic forms.[6] The phenylhydrazones have been applied as ligand for the coupling reaction,[7] to generate nitrones along with nitrosobenzene,[8] and to prepare *N*-phenylphthalimidine along with carbon monoxide in the presence of a cobalt catalyst.[9] In addition, the acetyl glycosazones can be reduced to amino sugar with zinc dust and acetic acid,[10] or converted into multifunctional hexane via the elimination of acetic acid.[11]

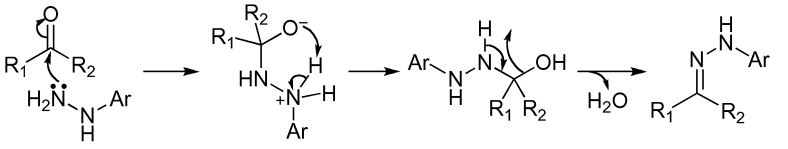
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME

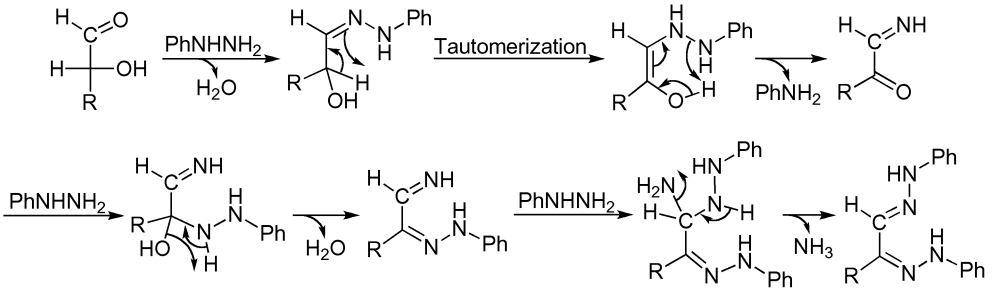


C. PROPOSED MECHANISMS

The mechanism for the formation of arylhydrazone is simply outlined in Scheme 1, and the mechanism for the formation of acyclic osazone[12] is shown in Scheme 2.



SCHEME 1. *Formation of arylhydrazone with ketones or aldehydes.*



SCHEME 2. *Formation of an acyclic osazone.*

D. MODIFICATION

N/A

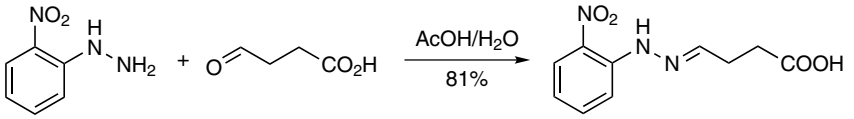
E. APPLICATIONS

This reaction has general application in the preparation of phenylhydrazones of carbonyl compounds and osazone derivatives of carbohydrates.

F. RELATED REACTIONS

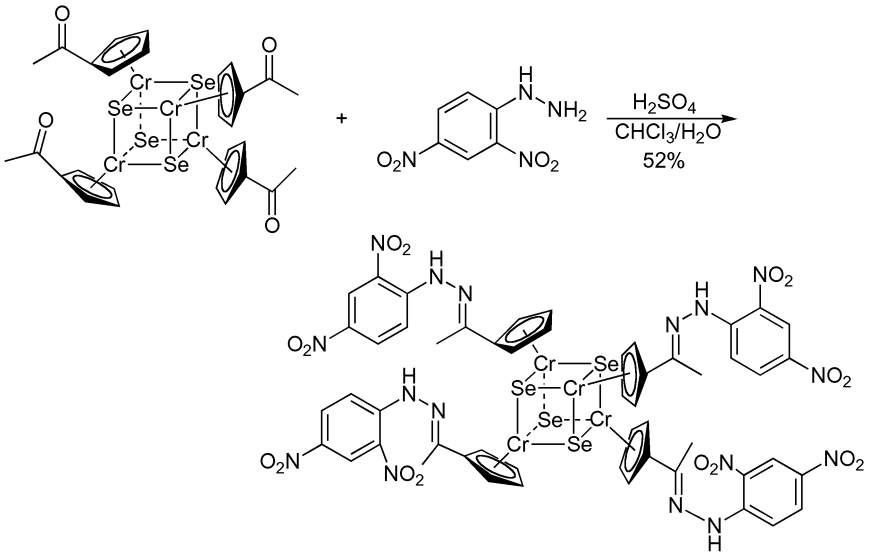
This reaction is related to the *Bamford-Stevens Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



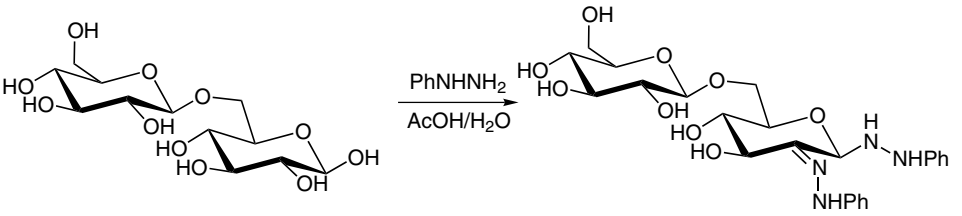
Reference 13.

A hot solution of 7.65 g *o*-nitrophenylhydrazines (0.05 mol) in 150 mL 20% acetic acid was added to 200 mL hot water containing 5.8 g levulinic acid (0.05 mol). The red-orange oil that precipitated crystallized on cooling, affording 10.2 g hydrazone in a yield of 81%. The solid was recrystallized from ethanol with the addition of water, m.p. 150–150.5°C.



Reference 14.

To a deep green solution of 0.190 g $[\eta^5\text{-MeC(O)C}_5\text{H}_4]_4\text{Cr}_4\text{Se}_4$ (0.20 mmol) in 20 mL $CHCl_3$ was added 9.6 mL 2,4-dinitrophenylhydrazine solution ($\sim$ 1.60 mmol, prepared by dissolving 1.0 g 2,4-dinitrophenylhydrazine in 5 mL 98% H_2SO_4, 10 mL H_2O, and 35 mL 95% EtOH). The mixture was stirred at reflux for 2 h, then 30 mL water was added after cooling to room temperature. The organic layer was separated, dried over Na_2SO_4, concentrated, and purified by preparative TLC with acetone/petroleum ether/CH_2Cl_2 (1:2:3) as the eluent to give 0.174 g $[\eta^5\text{-2,4-(NO}_2)_2\text{C}_6\text{H}_3\text{NHNC(Me)-C}_5\text{H}_4]_4\text{Cr}_4\text{Se}_4$ as a brown solid, in a yield of 52%, m.p. $> 280^\circ$C.



Reference 15.

A suspension of 7.2 g β-gentiobiose octa-acetate in 50 mL absolute methyl alcohol was saponified by adding a solution of 0.36 g metallic sodium in 10 mL absolute methyl alcohol; the mixture was allowed to stand for 15 min with occasional shaking. Then 25 mL water, 4.0 g glacial acetic acid, and 6.0 g phenylhydrazine were added, and the mixture was heated on a water bath for 1.5 h. On cooling, the solution deposited crystals of gentiobiose phenylosazone, which were filtered off, washed with cold water, and dried in a vacuum desiccator over sulfuric acid at room temperature to a constant weight (2.1 g). On the addition of water to the filtrate, 0.8 g more of the osazone separated. The total amount of osazone was 2.9 g, in a yield of 52.5%, m.p. 156–158°C. After recrystallization from hydrous ethyl acetate, the osazone, consisting of long needles, melted at 179–181°C.

Other references related to the Fischer phenylhydrazone and osazone synthesis are cited in the literature.[16]

H. REFERENCES

1. Fischer, E., *Ber.,* **1875**, *8*, 579.
2. (a) Roy, A. S.; Tuononen, H. M.; Rath, S. P. and Ghosh, P., *Inorg. Chem.,* **2007**, *46*, 5942. (b) Mirifico, M. V.; Caram, J. A. and Vasini, E. J., *Tetrahedron Lett*., **2006**, *47*, 6919. (c) Vaidya, R. and Gangotri, K. M., *J. Indian Chem. Soc.,* **2004**, *81*, 707. (d) Vaidya, V. K., *J. Photochem. Photobio., A: Chem.,* **1994**, *81*, 135. (e) El Khadem, H. S.; Shalaby, M. A.; Coxon, B. and Fatiadi, A. J., *Carbohydr. Res.,* **1993**, *239*, 85. (f) Catsoulacos, P., *J. Heterocycl. Chem.,* **1985**, *22*, 1671. (g) Garcia, F. J.; Pons, A.; Alemany, M. and Palou, A., *Anal. Biochem.,* **1982**, *120*, 249. (h) Garcia-Castineiras, S.; Bonnet, V. D.; Figueroa, R. and Miranda, M., *J. Liquid Chromatography,* **1981**, *4*, 1619. (i) Jordan, C. and Svehla, G., *Anal. Proc.,* **1981**, *18*, 243. (j) Jordan, C. and Svehla, G., *Anal. Chim. Acta,* **1981**, *129*, 133. (k) El Khadem, H.; El-Shafei, Z. M. and El Sekeili, M., *J. Org. Chem.,* **1972**, *37*, 3523. (l) El Khadem, H., *Carbohydr. Res.,* **1972**, *23*, 311.

3. (a) Avalos, M.; Babiano, R.; Cintas, P.; Clemente, F. R.; Gordillo, R.; Hursthouse, M. B.; Jiménez, J. L.; Light, M. E. and Palacios, J. C., *J. Org. Chem.,* **2002**, *67*, 2378. (b) Bonner, W. A. and Drisko, R. W., *J. Am. Chem. Soc.,* **1951**, *73*, 3701.
4. Wolfrom, M. L.; Shafizadeh, F.; Wehrmüller, J. O. and Armstrong, R. K., *J. Org. Chem.,* **1958**, *23*, 571.
5. O'Connor, R., *J. Org. Chem.,* **1963**, *26*, 4375.
6. Khadem, H. E.; Wolfrom, M. L. and Horton, D., *J. Org. Chem.,* **1965**, *30*, 838.
7. Mino, T.; Shirae, Y.; Sakamoto, M. and Fujita, T., *J. Org. Chem.,* **2005**, *70*, 2191.
8. Angert, J. L.; Hurst, A. F.; Lowry, S. A. and Landolt, R. G., *J. Org. Chem.,* **1981**, *46*, 168.
9. Rosenthal, A. and Weir, M. R. S., *J. Org. Chem.,* **1963**, *28*, 3025.
10. Fischer, E., *Ber.,* **1886**, *19*, 1920.
11. Wolfrom, M. L.; Thompson, A. and Lineback, D. R., *J. Org. Chem.,* **1962**, *27*, 2563.
12. (a) Shemyakin, M. M.; Maimind, V. I.; Ermolaev, K. M. and Bamdas, E. M., *Tetrahedron*, **1965**, *21*, 2771. (b) Glassmann, B. and Rochwarger-Walbe, *Ber.,* **1928**, *61B*, 1444.
13. Stevens, F. J. and Fox, S. W., *J. Am. Chem. Soc.,* **1948**, *70*, 2263.
14. Song, L.-C.; Cheng, H.-W. and Hu, Q.-M., *Organometallics,* **2004**, *23*, 1072.
15. Berlin, H., *J. Am. Chem. Soc.,* **1926**, *48*, 1107.
16. (a) Albert, J.; González, A.; Granell, J.; Moragas, R.; Puerta, C. and Valerga, P., *Organometallics,* **1997**, *16*, 3775. (b) Khan, N. H. and Kidwai, A. R., *J. Org. Chem.,* **1973**, *38*, 822. (c) Berry, D. W.; Bryant, R. W.; Smith, J. K. and Landolt, R. G., *J. Org. Chem.,* **1970**, *35*, 845. (d) Weygand, F. V.; Simon, H. and Klebe, J. F., *Ber.,* **1958**, *91*, 1567. (e) Weygand, F.; Grisebach, H.; Kirchner, K. D. and Haselhorst, M., *Ber.,* **1955**, *88*, 487. (f) Percival, E. G. V., *Adv. Carbohydr. Chem.,* **1948**, *3*, 23. (g) Merrill, A. T.; Hann, R. M. and Hudson, C. S., *J. Am. Chem. Soc.,* **1943**, *65*, 994. (h)Weygand, F., *Ber.,* **1940**, *73*, 1284. (i) Engel, L. L., *J. Am. Chem. Soc.,* **1935**, *57*, 2419. (j) Votocek, E., *Roczniki Chem*., **1932**, *12*, 181. (k) Fischer, E., *Ber.,* **1887**, *20*, 821.

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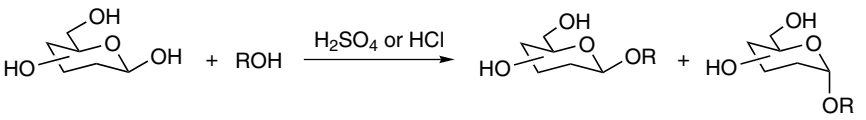
Fischer-Helferich Glycosylation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Fischer in 1893[1] and modified subsequently by his student Helferich.[2] It is a preparation of *O*- or *S*-alkyl glycosides from unprotected carbohydrates and alcohols or thiols using mineral acid (H_2SO_4, HCl, etc.) as a promoter or catalyst. Therefore, this reaction is generally known as the Fischer-Helferich glycosylation.[3] Occasionally, it is referred to as the Fischer-Helferich procedure.[4] This reaction involves the formation of oxocarbenium ion or its reactive equivalent.[5] A variety of simple *O*- or *S*-glycosides have been prepared by this method, including methyl, benzyl, and allyl glycosides.[6] In addition, urea and alkyl-substituted urea also react with carbohydrate in the presence of sulfuric acid.[7] It was found that "solid" alcohol or sugar derivatives are not suitable for this particular glycosylation reaction.[5] This reaction has been modified to use different acids, including Lewis acids, as promoters.[8] Unfortunately, this reaction always gives a mixture of both pyranosides and furanosides, along with their anomeric mixtures.

B. GENERAL REACTION SCHEME



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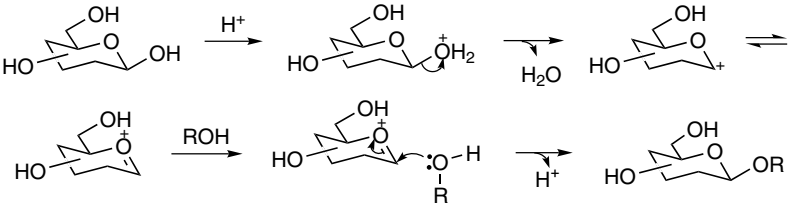
C. PROPOSED MECHANISMS

A mechanism to form alkyl β-D-glycoside using mineral acid as a promoter is illustrated below.



D. MODIFICATION

This reaction has been modified using a Lewis acid as the catalyst or promoter.

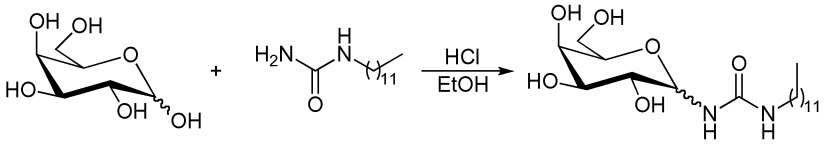
E. APPLICATIONS

This reaction has been used in the preparation of alkyl *O*- or *S*- glycosides.

F. RELATED REACTIONS

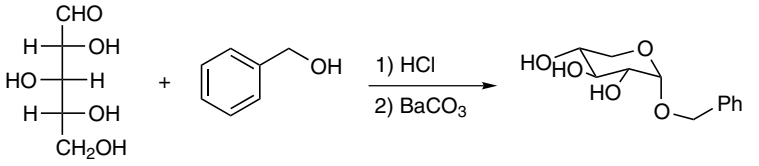
This reaction is related to the *Koenigs-Knorr Glycosylation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

A mixture of 22.8 g dodecylurea (0.1 mol), 19.8 g galactose (0.11 mol), 2.5 g concentrated hydrochloric acid, and 200 mL 95% ethanol was stirred and heated at 50°C for 100 h, it was then cooled and filtered. Washing with water and hot benzene gave 15.6 g dodecylurea *N*-galactoside as a white solid, in a yield of 40%, m.p. 165–188°C.



Reference 9.

A mixture of 50.0 g D-xylose in 250 mL benzyl alcohol was cooled in an ice salt bath and saturated with dry hydrogen chloride gas. The mixture was shaken for 24 h at room temperature, after which a dark solution was obtained. This was poured into 500 mL water,

and solid barium carbonate was added to neutralize the acid. The solid material was removed by filtration, and the excess benzyl alcohol in the filtrate was separated from the water layer by ether extraction. The water layer was concentrated to dryness in vacuo at 50°C, and the mixture of salt and syrup was extracted three times with absolute ethanol. The alcohol layer was then concentrated to a thick syrup, which was dissolved in 40 mL absolute ethanol and left at 5°C in the refrigerator. Crystals formed readily to give 10.0 g benzyl α-D-xylopyranoside after filtration and being washed with ether. The product was recrystallized by dissolving it in a warm absolute ethanol and adding ether to turbidity to form needles with a constant melting point of 127–128.5°C.

Other references related to the Fischer-Helferich glycosylation are cited in the literature.[10]

H. REFERENCES

1. Fischer, E., *Ber.,* **1893**, *26*, 2400.
2. (a) Helferich, B. and Schäfer, W., *Org. Syn. Coll.* **1941**, *1*, 364. (b) Helferich, B. and Hiltmann, R., *Ann.,* **1937**, *531*, 160.
3. (a) Huang, G.-L.; Mei, X.-Y.; Cao, Y.-C. and Liu, M.-X., *Jingxi Huagong*, **2004**, *21*, 544. (b) Kroger, L. and Thiem, J., *J. Carbohydr. Chem.,* **2003**, *22*, 9. (c) Lichtenthaler, F. W., *Carbohydr. Res.,* **1987**, *164*, 1. (d) Wagner, G. and Goebel, D., *Pharmazie*, **1973**, *28*, 184. (e) Pischel, H. and Wagner, G., *Pharmazie*, **1970**, *25*, 45. (f) Pischel, H. and Wagner, G., *Pharmazie*, **1967**, *22*, 686. (g) Pischel, H. and Wagner, G., *Arch. Pharm. Ber. Deut. Pharm. Gesell.,* **1967**, *300*, 602. (h) Gough, G. R. and Maguire, M. H., *J. Med. Chem.,* **1967**, *10*, 475. (i) Wagner, G. and Heller, D., *Arch. Pharm.,* **1966**, *299*, 883. (j) Wagner, G. and Heller, D., *Pharmazie*, **1966**, *21*, 404. (k) Reisser, F. and Pfleiderer, W., *Chem. Ber.,* **1966**, *99*, 547. (l) Todd, A. R., *Bull. Soc. Chim. Fr.,* **1948**, 933. (m) Montgomery, E. M.; Richtmyer, N. K. and Hudson, C. S., *J. Am. Chem. Soc.,* **1942**, *64*, 1483.
4. Piskala, A. and Sorm, F., *Nucleic Acid Chem.*, **1978**, *1*, 455.
5. Hanessian, S. and Lou, B. L., *Chem. Rev.,* **2000**, *100*, 4443.
6. Toshima, K. and Tatsuta, K., *Chem. Rev*., **1993**, *93*, 1503.
7. Erickson, J. G. and Keps, J. S., *J. Am. Chem. Soc.,* **1953**, *75*, 4339.
8. (a) Ferrieres, V.; Bertho, J.-N. and Plusquellec, D., *Tetrahedron Lett.,* **1995**, *36*, 2749. (b) Bertho, J.-N.; Ferrieres, V. and Plusquellec, D., *J. Chem. Soc., Chem. Commun.,* **1995**, 1391. (c) Lubineau, A. and Fischer, J.-C., *Synth. Commun.,* **1991**, *21*, 815. (d) Horito, S.; Tada, M. and Hashimoto, H., *Chem. Lett.,* **1991**, 117. (e) Konradsson, P.; Roberts, C. and Fraser-Reid, B., *Recl. Trav. Chim. Pays-Bas,* **1991**, *110*, 23. (f) Defaye, J.; Gadelle, A. and Pedersen, C., *Carbohydr. Res.,* **1989**, *186*, 177. (g) Wessel, H. P., *J. Carbohydr. Chem.,* **1988**, *7*, 263. (h) Fischer, B.; Nudelman, A.; Ruse, M.; Herzig, J.; Gottlieb, H. E. and Keinan, E., *J. Org. Chem.,* **1984**, *49*, 4988. (i) Pavia, A. A.; Rocheville, J.-M. and Ung, S. N., *Carbohydr. Res.,* **1980**, *79*, 79.
9. Ballou, C. E.; Roseman, S. and Link, K. P., *J. Am. Chem. Soc.,* **1951**, *73*, 1140.
10. (a) Lichtenthaler, F. W., *Eur. J. Org. Chem.,* **2002**, 4095. (b) Schmidt, R. R., "Synthesis of Glycosides" in *Comprehensive Organic Synthesis*, ed. Trost, B. M.; Fleming, I. and Winterfeldt, E., Pergamon Press, Oxford, **1991**, *6*, pp. 33–64. (c) Freudenberg, K., *Adv. Carbohydr. Chem.,* **1966**, *21*, 1. (d) Ulbrich, T. L. V., *Angew. Chem. Int. Ed. Engl.,* **1962**, *1*, 476. (e) Helferich, S. B. and Kosche, W., *Ber.,* **1926**, *59*, 69. (f) Fischer, E., *Untersuchung über Kohlenhydrate und Fermente (1884-1908)*, Springer, Berlin, **1909**. (g) Fischer, E., *Ber.,* **1895**, *28*, 1145. (h) Fischer, E., *Ber.,* **1895**, *28*, 1151.

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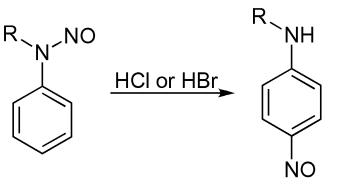
Fischer-Hepp Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Fischer and Hepp in 1886.[1] It is a conversion of *N*-nitroso aromatic amines into *p*-nitroso aromatic amines in the presence of HCl or HBr and is generally known as the Fischer-Hepp rearrangement.[2] Originally, the Fischer-Hepp rearrangement was thought to be intramolecular;[3] however, much experimental evidence indicates that this rearrangement is actually intermolecular. For example, the nitroso group has been found to migrate onto a more reactive aromatic compound,[4] but no rearrangement occurs in the presence of urea.[5] It should be pointed out that the rearrangement is much less effective when sulfuric acid is used rather than HCl or HBr,[2y] because HCl or HBr can easily form a nitroso halide that quickly replaces the proton at the *para*-position of the amino group by electrophilic substitution.[2y]

B. GENERAL REACTION SCHEME



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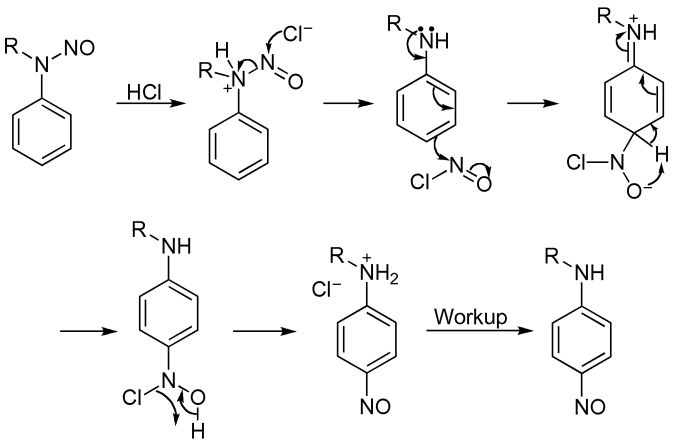
C. PROPOSED MECHANISMS

Illustrated here is the rearrangement of *N*-alkyl-*N*-nitroso aniline with HCl.



D. MODIFICATION

N/A

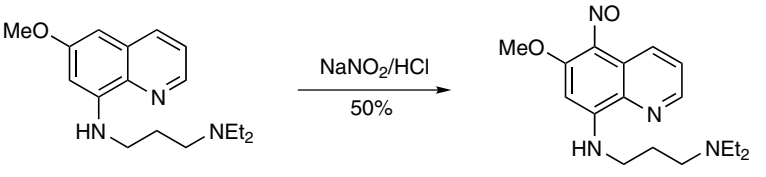
E. APPLICATIONS

This reaction has been used in the preparation of *p*-nitroso arylamines.

F. RELATED REACTIONS

N/A

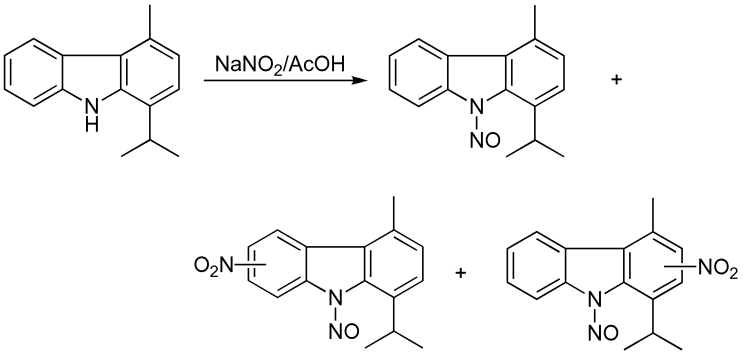
G. CITED EXPERIMENTAL EXAMPLES



Reference 6.

A solution of 17.3 g sodium nitrite (0.25 mol) in 40 mL water was added dropwise with stirring to 72 g 6-methoxy-8-(3-diethylaminopropylamino)-quinoline in 37 mL concentrated HCl and 100 g ice at 3°C. After 1.5 h, the reaction mixture was made slightly basic,

and extracted with warm benzene. Green felt-like lustrous needles (17.5 g) crystallized from the dried, concentrated benzene extract. The dark, oily residue (50 g) that could not be crystallized was recovered as starting material; b.p. 170–180°C (0.2 mmHg); hydrochloride: m.p. 191–192°C. This was reworked to give a total of 41 g nitroso plasmocid, in a yield of 50%.



Reference 2bb.

To a cooled solution of 2.25 g 1-isopropyl-4-methylcarbazole in 45 mL glacial acetic acid (distilled from phosphorus pentoxide) was added 2.5 g sodium nitrite in 4 mL water while the reaction flask was cooled in ice water. A yellow solid separated after 10 min; precipitation was completed by addition of 50 mL water. The solid was separated by filtration, thoroughly washed with water, and pressed dry. Recrystallization from petroleum ether gave 1-isopropyl-4-methyl-9-nitrosocarbazole, m.p. 97–98°C. Attempted recrystallization from petroleum ether containing residual acetic acid yielded a solid with melting point of 158–160°C. Chromatography of this solid on alumina afforded two fractions: 1-isopropyl-4-methyl-6 (or 7)-nitrocarbazole, eluted by benzene, m.p. 204–205°C, and 1-isopropyl-2(or 3)-nitro-4-methylcarbazole, m.p. 210°C (no yield was given in the original paper).

Other references related to the Fischer-Hepp rearrangement are cited in the literature.[7]

H. REFERENCES

1. Fischer, O. and Hepp, E., *Ber.,* **1886**, *19*, 2991.
2. (a) Kannan, P.; Pitchumani, K.; Rajagopal, S. and Srinivasan, C., *J. Mol. Catal. A: Chem.,* **1997**, *118*, 189. (b) Petrisko, M. and Pasek, J., *Chemicky Prumysl*, **1995**, *45*, 17. (c) Titova, S. P.; Arinich, A. K. and Gorelik, M. V., *Zh. Org. Khim.,* **1986**, *22*, 1562. (d) Nikitenkova, L. P.; Karakotov, S. D.; Strepikheev, Y. A. and Naumova, I. I., *Zh. Obsh. Khim.,* **1984**, *54*, 1375. (e) Shevchuk, A. S.; Pavelko, N. V.; Shein, V. D. and Kurapin, A. V., *Osnov. Organ. Sintez Neftekhimiya, Yaroslavl,* **1983**, 53. (f) Williams, D. L. H., *J. Chem. Soc., Perkin Trans. II,* **1982**, 801. (g) Nikitenkova, L. P.; Karakotov, S. D.; Strepikheev, Y. A.; Kashemirov, B. A. and Naumova, I. I., *Zh. Obsh. Khim.,* **1981**, *51*, 1633. (h) Nikitenko, L. P.; Karakotov, S. D.; Naumova, I. I. and Strepikheev, Y. A., *Zh. Obsh. Khim.,* **1981**, *51*, 1382. (i) Nikitenkova, L. P.; Strepikheev, Y. A.; Naumova, I. I.; Karakotov, S. D. and Orlov, S. I., *Zh. Obsh. Khim.,* **1979**, *49*, 2589. (j) Nikitenkova, L. P.; Strepikheev, Y. A.; Naumova, I. I.; Orlov, S. I. and Karakotov, S. D., *Zh. Obsh. Khim.,* **1979**, *49*, 690. (k) Nikitenkova, L. P.; Strepikheev, Y. A.; Naumova, I. I.; Orlov, S. I. and Karakotov,

S. D., *Zh. Obsh. Khim.,* **1979**, *49*, 685. (l) Nikitenkova, L. P.; Strepikheev, Y. A.; Naumova, I. I.; Karakotov, S. D. and Orlov, S. I., *Zh. Obsh. Khim.,* **1979**, *49*, 681. (m) Biggs, I. D. and Williams, D. L. H., *J. Chem. Soc., Perkin Trans. II,* **1977**, 44. (n) Kampel, L. P.; Strepikheev, Y. A.; Naumova, I. I. and Zharynina, L. P., *Zh. Obsh. Khim.,* **1976**, *46*, 2134. (o) Biggs, I. D. and Williams, D. L. H., *J. Chem. Soc., Perkin Trans. II,* **1976**, 691. (p) Biggs, I. D. and Williams, D. L. H., *J. Chem. Soc., Perkin Trans. II,* **1976**, 601. (q) Kampel, L. P.; Naumova, I. I.; Strepikheev, Y. A. and Zhun, V. I., *Zh. Obsh. Khim.,* **1975**, *45*, 2734. (r) Williams, D. L. H., *Tetrahedron*, **1975**, *31*, 1343. (s) Williams, D. L. H., *J. Chem. Soc., Perkin Trans. II,* **1975**, 655. (t) Biggs, I. D. and Williams, D. L. H., *J. Chem. Soc., Perkin Trans. II,* **1975**, 107. (u) Williams, D. L. and Wilson, J. A., *J. Chem. Soc., Perkin Trans. II,* **1974**, 13. (v) Morgan, T. D. B.; Williams, D. L. H. and Wilson, J. A., *J. Chem. Soc., Perkin Trans. II,* **1973**, 473. (w) Morgan, T. D. B. and Williams, D. L. H., *J. Chem. Soc., Perkin Trans. II,* **1972**, 74. (x) Morgan, T. D. B. and Williams, D. L. H., *J. Chem. Soc. D,* **1970**, 1671. (y) Baliga, B. T., *J. Org. Chem.,* **1970**, *35*, 2031. (z) Belyaev, E. Y.; Kumarev, V. P. and Aslapovskaya, T. I., *Fiz., Khim. Khim. Tekhnol.,* **1969**, 321. (aa) Patel, H. P. and Tedder, J. M., *J. Chem. Soc.,* **1963**, 4894. (bb) Drake, N. L.; Winkler, H. J. S.; Kraebel, C. M. and Smith, T. D., *J. Org. Chem.,* **1962**, *27*, 1026.

3. Williams, D. L. H., *Nirosation,* Cambridge University Press, Cambridge, **1988**, pp. 113–128.
4. (a) Glazer, J.; Hughes, E. D.; Ingold, C. K.; James, A. T.; Jones, G. T. and Roberts, E., *J. Chem. Soc.,* **1950**, 2657. (b) Neber, P. W. and Rauscher, H., *Ann.,* **1942**, *550*, 182.
5. Macmillen, W. and Reade, T. H., *J. Chem. Soc.,* **1929**, 585.
6. Elderfield, R. C. and Ressler, C., *J. Am. Chem. Soc.,* **1950**, *72*, 4059.
7. (a) Loeppky, R. N. and Xiong, H. P., *J. Org. Chem.,* **1995**, *60*, 5526. (b) Kyziol, J. B., *J. Heterocycl. Chem.,* **1985**, *22*, 1301. (c) Williams, D. L. H., *Int. J. Chem. Kinetics,* **1975**, *7*, 215. (d) Shine, H. J., *Aromatic Rearrangements,* Elsevier, New York, **1967**, p. 231. (e) Willenz, J., *J. Chem. Soc.,* **1955**, 1677. (f) Schroeder, W. A.; Wilcox, P. E.; Trueblood, K. N. and Dekker, A. O., *Anal. Chem.,* **1951**, *23*, 1740. (g) Fischer, O. and Hepp, E., *Ber.,* **1888**, *21*, 684. (h) Fischer, O. and Hepp, E., *Ber.,* **1887**, *20*, 2471. (i) Fischer, O. and Hepp, E., *Ber.,* **1887**, *20*, 1247.

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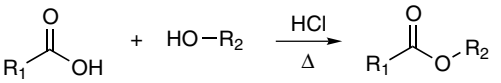
Fischer-Speier Esterification

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Fischer and Speier in 1895.[1] It is the synthesis of ester by refluxing carboxylic acid with an excess amount of alcohol in the presence of an acidic catalyst (e.g., HCl), and is known as the Fischer-Speier esterification.[2] It is known that the formation of ester from alcohol and carboxylic acid is reversible, and an equilibrium always exists between the ester and carboxylic acid. To drive the equilibrium toward ester side, azeotropic refluxing is always applied to remove the newly formed water.[3] At the same time, an acidic catalyst is added to accelerate the esterification, often by passing dry HCl gas into the solution.[1] Compared to the sulfuric acid–promoted esterification, the reaction promoted by HCl does not produce olefin (from alcohol), and does not undergo electrophilic substitution with benzene either. For the special case of preparing methyl esters, it was found that the methyl esters can be synthesized in almost quantitative yield with acetone dimethyl acetal, which functions as a water scavenger, resulting in a self-accelerating reaction. This is because whenever a water molecule is formed after the esterification, two more methanol molecules will be generated by hydrolysis of acetone dimethyl acetal.[3]

B. GENERAL REACTION SCHEME



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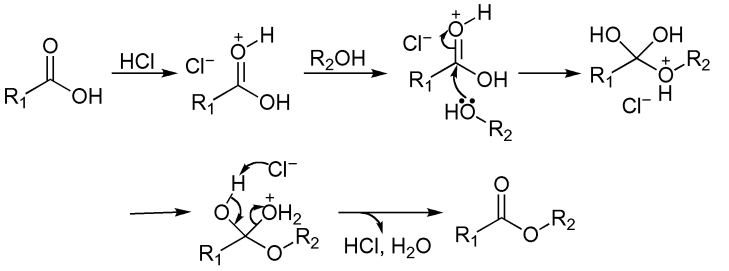
C. PROPOSED MECHANISMS



D. MODIFICATION

More convenient *p*-toluenesulfonic acid (TsOH) is often used when dry HCl is not available.

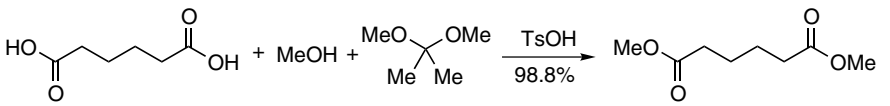
E. APPLICATIONS

N/A

F. RELATED REACTIONS

N/A

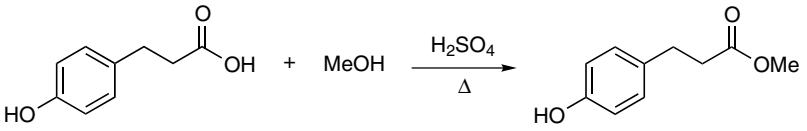
G. CITED EXPERIMENTAL EXAMPLES



Reference 3.

Adipic acid (585 g, 4 mol) was added to 200 mL methanol containing 5 g *p*-toluenesulfonic acid. This mixture was stirred in a 2-L flask and maintained at 40–60°C. As the reaction progressed, acetone dimethyl acetal was added in increments. By the end of 30 min, 200 mL had been added, by the end of 1 h, 600 mL total had been added (at this point, all adipic acid was in solution), and by the end of 1.5 h, a total of 1 L of the acetone dimethyl acetal (8 mol) had been added. At the end of 2 h, only 10% of the acid remained unreacted. After 4 h, the reaction was 99% complete. One half of the crude solution was then distilled at a rate such that by the end of 3 h, all of the acetone and methanol had been removed. This left a 98.8% yield of crude, straw-colored dimethyl adipate. On further distillation, a 94% yield of pure dimethyl adipate with a boiling point of 109°C was recovered.

A similar experiment in which all of the reactants were mixed at one time and left overnight at room temperature (with stirring) resulted in 100% conversion of the adipic acid.



Reference 2a.

The mixture of 1.1 g 3-(*p*-hydroxyphenyl) propionic acid, 5 mL concentrated H_2SO_4, and 100 mL MeOH was refluxed for 4 h. Then the mixture was poured into 200 mL cold $CHCl_3$ and washed with 300 mL 5% $NaHCO_3$ three times and water two times. The organic layer was dried and evaporated, and the residue was distilled under vacuum to give 0.9 g methyl 3-(*p*-hydroxyphenyl) propinate.

Other references related to the Fischer-Speier esterification are cited in the literature.[4]

H. REFERENCES

1. Fischer, E. and Speier, A., *Ber.,* **1895**, *28*, 3252.
2. (a) Pcolinski, M. J.; O'Mathuna, D. P. and Doskotch, R. W., *J. Nat. Prod.,* **1995**, *58*, 209. (b) Fujii, T. and Yoshifuji, S., *Chem. Pharm. Bull.,* **1978**, *26*, 2253. (c) Gladych, J. M. Z. and Taylor, E. P., *J. Chem. Soc.,* **1960**, 2720. (d) Newman, M. S. and Muth, C. W., *J. Am. Chem. Soc.,* **1951**, *73*, 4627. (e) McCombie, H. and Saunders, B. C., *Nature,* **1946**, *158*, 382.
3. Lorette, N. B. and Brown, J. H., *J. Org. Chem.,* **1959**, *24*, 261.
4. (a) Kai, T.; Sun, X.-L.; Tanaka, M.; Takayanagi, H. and Furuhata, K., *Chem. Pharm. Bull.,* **1996**, *44*, 208. (b) Birney, D. M. and Starnes, S. D., *J. Chem. Edu.,* **1996**, *76*, 1560. (c) Fujii, T. and Yoshifuji, S., *Chem. Pharm. Bull*., **1978**, *26*, 2253. (d) Mayer, C.; Green, C. L.; Trueb, W. and Christian, P., *Helv. Chim. Acta,* **1978**, *61*, 905. (e) Hardy, J. P.; Kerrin, S. L. and Manatt, S. L., *J. Org. Chem.,* **1973**, *38*, 4196. (f) Kirby, A. J., "Hydrolysis and Formation of Esters of Organic Acids" in *Comprehensive Chemical Kinetics*, ed. Bamford, C. H. and Tipper, C. F. H., Elsevier, New York, **1972**, *10*, pp. 57–207. (g) Euranto, E. K., "Esterification and Ester Hydrolysis" in *The Chemistry of Carboxylic Acids and Esters*, ed. Patai, S., Interscience, New York, **1969**, pp. 505–588. (h) Ingold, C. K., *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N.Y., **1963**, pp. 752–781. (i) Holmes, H. L. and Trevoy, L. W., *Org. Syn. Coll.,* **1950**, *3*, 300. (j) Hughes, E. D., *Quart. Rev.,* **1948**, *2*, 110. (k) Fischer, E., *Ber.,* **1901**, *34*, 433.

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Fischer-Tropsch Synthesis

(Fischer-Tropsch Technology, Fischer-Tropsch Process)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Fischer and Tropsch at the Kaiser Wilhelm Institute in Germany in 1923.[1] It is the conversion of synthesis gas, a mixture of hydrogen and carbon monoxide, into a mixture of high-value hydrocarbons and their derivatives (e.g., aliphatic alcohols, olefins, aldehydes, and ketones) and some by-products such as water and CO_2. Therefore, this reaction is generally known as the Fischer-Tropsch synthesis,[2,3] Fischer-Tropsch technology,[4] or Fischer-Tropsch process.[5] Occasionally, it is also referred to as the Fischer-Tropsch reaction.[6] In this reaction, the synthesis gas is passed through a reactor containing a solid supported metal catalyst, such as, Ru/SiO_2,[7] Co/Nb_2O_5,[8] Co/TiO_2,[9] Co/Al_2O_3,[10] Co/SiO_2,[11] $Co\text{-}CeO_2/SiO_2$,[12] and Fe/SiO_2,[13] at 200–350°C and a pressure of 15–40 bar. Although the metals with catalytic activity for this reaction are ruthenium, cobalt, and iron,[14] cobalt and iron are the most used ones due to the high cost of ruthenium. However, the cheapest iron-based catalysts also suffer from a low wax selectivity[14] and are deactivated about as high as 4.8% per week[15] and are good for $\sim$ 8 weeks;[16] in contrast, cobalt-based catalysts "are stable and allow high syn-gas conversions,"[14] which can produce heavy wax ($\sim$ C100)[17] and can be used up to 5 years.[18] It was found that the rate of CO conversion increases linearly with cobalt's dispersion rate, regardless of solid support.[2g] This reaction has been practically used for making odorless, colorless, clean diesel fuel containing low levels of sulfur and other impurities.[4i,19] The application of this reaction in the fuel industry is so important that it might solve the energy crisis after we run out of crude oil, because this reaction uses much more enriched coal and sustainable biomass as starting materials.

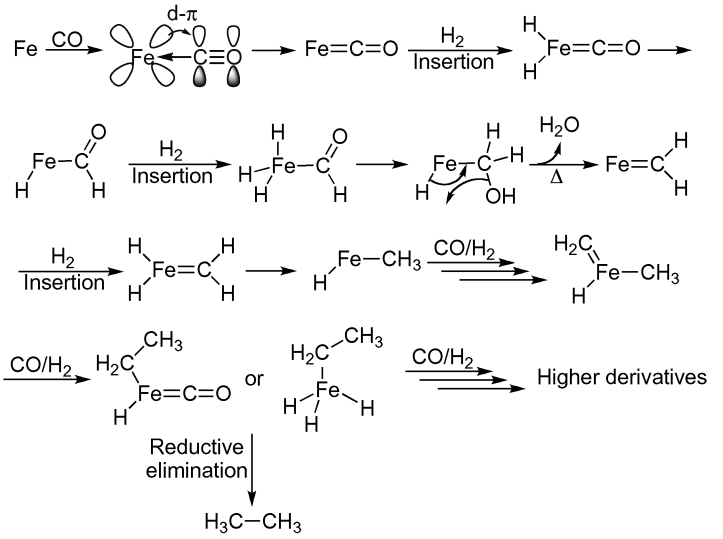
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME

$$CO + H_2 \xrightarrow[200\text{–}350^\circ C]{\text{Co or Fe}} CH_3(CH_2)_n\text{-}H \quad (n = 0, \ldots > 100)$$

C. PROPOSED MECHANISMS

The mechanism is very complicated, as more than 36 reactions have been proposed.[2m] Illustrated here is a simple demonstration of this reaction, where iron is used to indicate the catalytic center only, no other bonds are shown except for the necessary ones. This mechanism is similar to the one in Brady and Pettit.[20]



D. MODIFICATION

This reaction has been modified using a variety of catalysts and different reactors.

E. APPLICATIONS

This reaction has a very important application in industry to produce clean fuels.

F. RELATED REACTIONS

This reaction is related to the *Bergius Process*.

G. CITED EXPERIMENTAL EXAMPLES

No experimental details are given here, because the cited papers provide only the procedures for preparing a particular catalyst and the analysis of product distribution.

Other references related to the Fischer-Tropsch synthesis are cited in the literature.[21]

H. REFERENCES

1. Fischer, F. and Tropsch, H., *Ber.,* **1923**, *56*, 2428.
2. (a) Zhao, T.-S.; Chang, J.; Yoneyama, Y. and Tsubaki, N., *Ind. Eng. Chem. Res.,* **2005**, *44*, 769. (b) Huang, X.; Elbashir, N. O. and Roberts, C. B., *Ind. Eng. Chem. Res.,* **2004**, *43*, 6369. (c) Morales, F.; de Groot, F. M. F.; Glatzel, P.; Kleimenov, E.; Bluhm, H.; Havecker, M.; Knop-Gericke, A. and Weckhuysen, B. M., *J. Phys. Chem. B.,* **2004**, *108*, 16201. (d) Wang, G.; Wang, Y.-N.; Yang, J.; Xu, Y.-Y.; Bai, L.; Xiang, H.-W. and Li, Y.-W., *Ind. Eng. Chem. Res.,* **2004**, *43*, 2330. (e) Okabe, K.; Wei, M. and Arakawa, H., *Energy & Fuels,* **2003**, *17*, 822. (f) Bian, G.; Mochizuki, T.; Fujishita, N.; Nomoto, H. and Yamada, M., *Energy & Fuels,* **2003**, *17*, 799. (g) Ohtsuka, Y.; Arai, T.; Takasaki, S. and Tsubouchi, N., *Energy & Fuels,* **2003**, *17*, 804. (h) Liu, Z.-P. and Hu, P., *J. Am. Chem. Soc.,* **2002**, *124*, 11568. (i) Li, S.; Ding, W.; Meitzner, G. D. and Iglesia, E., *J. Phys. Chem. B.,* **2002**, *106*, 85. (j) Li, S.; Meitzner, G. D. and Iglesia, E., *J. Phys. Chem. B.,* **2001**, *105*, 5743. (k) Wang, Y.-N.; Xu, Y.-Y.; Xiang, H.-W.; Li, Y.-W. and Zhang, B.-J., *Ind. Eng. Chem. Res.*, **2001**, *40*, 4324. (l) Idem, R. O.; Katikaneni, S. P. R.; Sethuraman, R. and Bakhshi, N. N., *Energy & Fuels,* **2000**, *14*, 1072. (m) Rofer-Depoorter, C. K., *Chem. Rev.,* **1981**, *81*, 447.
3. (a) De la Pena O'Shea, V. A.; Alvarez-Galvan, M. C.; Campos-Martin, J. M. and Fierro, J. L. G., *Applied Catalysis, A: General*, **2007**, *326*, 65. (b) Cagnoli, M. V.; Alvarez, A. M.; Gallegos, N. G.; Bengoa, J. F.; Duarte de Souza, C. D.; Schmal, M. and Marchetti, S. G., *Applied Catalysis, A: General*, **2007**, *326*, 113. (c) Perez-Alonso, F. J.; Herranz, T.; Rojas, S.; Ojeda, M.; Lopez Granados, M.; Terreros, P.; Fierro, J. L. G.; Gracia, M. and Gancedo, J. R., *Green Chem*., **2007**, *9*, 663. (d) Guettel, R.; Junz, U. and Turek, T., *Chem. Ing. Tech.*, **2007**, *79*, 531. (e) Liu, Y.; Teng, B.-T.; Guo, X.-H.; Li, Y.; Chang, J.; Tian, L.; Hao, X.; Wang, Y.; Xiang, H.-W.; Xu, Y.-Y. and Li, Y.-W., *J. Mol. Cata. A: Chem.,* **2007**, *272*, 182. (f) Li, T. Z.; Yang, Y.; Zhang, C. H.; An, X.; Wan, H. J.; Tao, Z. C.; Xiang, H. W.; Li, Y. W.; Yi, F. and Xu, B. F., *Fuel*, **2007**, *86*, 921. (g) Ma, X. D.; Sun, Q. W.; Cao, F. H.; Ying, W. Y. and Fang, D. Y., *J. Nat. Gas Chem.,* **2006**, *15*, 335. (h) Tavasoli, A.; Khodadadi, A.; Mortazavi, Y.; Sadaghiani, K. and Ahangari, M. G., *Fuel Proc. Tech*., **2006**, *87*, 641. (i) Vytnova, L. A.; Bogolepova, E. I.; Shuikin, A. N.; Kurkin, V. I.; Marchevskaya, E. V. and Kliger, G. A., *Neftekhimiya*, **2006**, *46*, 120. (j) Wang, T.; Ding, Y. J.; Xiong, J. M.; Yan, L.; Zhu, H. J.; Lu, Y. and Lin, L. W., *Catal. Lett.,* **2006**, *107*, 47. (k) Dupain, X.; Krul, R. A.; Schaverien, C. J.; Makkee, M. and Moulijn, J. A., *Appl. Catal., B: Environ.,* **2006**, *63*, 277. (l) Linghu, W. S.; Li, X. H.; Asami, K. and Fujimoto, K., *Energy & Fuels*, **2006**, *20*, 7. (m) Linghu, W. S.; Li, X. H.; Asami, K. and Fujimoto, K., *Ranliao Huaxue Xuebao*, **2005**, *33*, 520. (n) Pankina, G. V.; Chernavskii, P. A. and Lunin, V. V., *Kinetics & Catal.,* **2005**, *46*, 719. (o) Shen, J. L.; Liu, H. Z.; Li, X. N.; Han, W. F. and Zheng, Y. F., *Chinese Chem. Lett.,* **2005**, *16*, 1393. (p) Krylova, A. Y.; Sineva, L. V. and Tarakanov, D. A., *Kataliz Promyshlennosti*, **2005**, 20. (q) Urquhart, A. J.; Williams, F. J. and Lambert, R. M., *Catal. Lett.,* **2005**, *103*, 137.
4. (a) Steynberg, A. P., *Studies Surface Sci. Catal.,* **2004**, *152*, 1. (b) Steynberg, A. P.; Nel, W. U. and Desmet, M. A., *Studies Surface Sci. Catal.,* **2004**, *147*, 37. (c) Steynberg, A. P. and Nel, H. G., *Fuel*, **2004**, *83*, 765. (d) Shen, S. K.; Yu, C. C.; Dai, X. P.; Pan, Z. Y.; Jiang, Q. Y. and Zhang, Z. B., *Proc. 17th World Petroleum Congress,* **2002**, *4*, 361. (e) Jager, B.;

Van Berge, P. and Steynberg, A. P., *Studies Surface Sci. Catal.,* **2001**, *136*, 63. (f) Geerlings, J. J. C.; Wilson, J. H.; Kramer, G. J.; Kuipers, H. P. C. E.; Hoek, A. and Huisman, H. M., *Appl. Catal, A: Chem.,* **1999**, *186*, 27. (g) Jager, B., *Studies Surface Sci. Catal.,* **1998**, *119*, 25. (h) Jager, B., *Studies Surface Sci. Catal.*, **1997**, *107*, 219. (i) Zhao, Y. L., *Meitan Zhuanhua*, **1994**, *17*, 26. (j) U.S. Environmental Protection Agency, *Clean Alternative Fuels: Fischer-Tropsch*, EPA 420-F-00-036. http://www.eere.energy.gov/afdc/pdfs/epa_fischer.pdf

5. (a) Vandu, C. O.; Heesink, A. B. M.; Versteeg, G. F. and Boerrigter, H., *Chem. Ind. & Chem. Eng. Quarterly,* **2006**, *12*, 195. (b) Savost'yanov, A. P. and Bakun, V. G., *Russ. J. Appl. Chem.,* **2006**, *79*, 1839. (c) Ma, W. P.; Kugler, E. L.; Wright, J. and Dadyburjor, D. B., *Energy & Fuels*, **2006**, *20*, 2299. (d) Dry, M. E., *Appl. Catal., A: Gen.,* **2004**, *276*, 1. (e) Garg, M. O.; Badoni, R. P. and Chand, M., *Chem. Ind. Digest,* **2004**, *17*, 42. (f) Schanke, D.; Rytter, E. and Jaer, F. O., *Studies Surface Sci. Catal.,* **2004**, *147*, 43. (g) Botes, F. G. and Bohringer, W., *Appl. Catal., A: General,* **2004**, *267*, 217. (h) Bytnova, L. A.; Slivinskii, E. V.; Kliger, G. A.; Bololepova, E. I.; Shuikin, A. N.; Kurkin, V. I. and Marchevskaya, E. V., *Neftekhimiya*, **2002**, *42*, 45. (i) Dry, M. E., *J. Chem. Tech. Biotech.,* **2002**, *77*, 43. (j) Meeuse, F. M.; de Deugd, R. M.; Kapteijn, F.; Verheijen, P. J. T. and Ypma, S. M., *Computer-Aided Chem. Eng.,* **2001**, *9*, 699. (k) Pyatnitsky, Y. I. and Lunev, M. K., *Kataliz Neftekhimiya*, **2001**, 1. (l) Kramarz, J. and Wyczesany, A., *Pol. J. Appl. Chem.,* **1992**, *36*, 3. (m) Rao, V. U. S.; Stiegel, G. J.; Cinquegrane, G. J. and Srivastava, R. D., *Fuel Proc. Tech.,* **1992**, *30*, 83. (n) Dry, M. E., *Catal. Today,* **1990**, *6*, 183. (o) Schulz, H.; Beck, K. and Erich, E., *Studies Surface Sci. Catal.,* **1988**, *36*, 457. (p) Kotali, A., *Chemika Chronika, Genike Ekdose*, **1984**, *49*, 279. (q) Falbe, J.; Frohning, C. D.; Cornils, B. and Moraw, K., *ChemSA*, **1984**, *10*, 419. (r) Kurth, G., *Kohleverfluessigung*, **1978**, 23. (s) Nooner, D. W. and Oro, J., *Adv. Chem. Ser.,* **1978**, *178*, 159. (t) Dry, M. E., *Informations Chim*., **1977**, *164*, 133. (u) Basu, S. and Krishnamurthy, V. A., *FRI News*, **1975**, *25*, 12. (v) Krishnamurthy, V. A.; Basu, A. N.; Basak, N. G. and Lahiri, A., *J. Sci. Ind. Res., Sect. B,* **1962**, *21A*, 338. (w) Field, J. H.; Anderson, R. B. and Benson, H. E., *Chem. Eng. Prog.,* **1960**, *56*, 44. (x) Storch, H. H., *Chem. Petroleum Hydrocarbons*, **1954**, *1*, 631. (y) Hall, C. C., *Gas World*, **1954**, *139*, 49. (z) Weller, S. and Friedel, R. A., *J. Chem. Phys.,* **1949**, *17*, 801. (aa) Cotton, E., *Nat. Petroleum News,* **1946**, *38*, R425. (bb) Hall, C. C., *Gas World*, **1947**, *126*, 58. (cc) Schade, H. A.; Foran, E. and Aldrich, R. C., *Chim. Ind. (Paris),* **1946**, *55*, 331. (dd) Kingman, F. E. T. and Cawley, C. M., *Petroleum (London)*, **1946**, *9*, 126. (ee) Lopmann, B., *Oel & Kohle*, **1944**, *40*, 183. (ff) Fischer, F. and Koch, H., *Petroleum Refiner*, **1944**, *23*, 260. (gg) Fischer, F.; Roelen, O. and Feist, W., *Petroleum Refiner*, **1943**, *22*, 429. (hh) Koch, H., *Brennstoff-Chem*., **1938**, *19*, 337. (ii) Muller, B., *Apparatebau*, **1938**, *50*, 97. (jj) Naphtali, M., *Refiner & Nat. Gas. Manuf.*, **1938**, *17*, 47.
6. (a) Quyoum, R.; Berdini, V.; Turner, M. L.; Long, H. C. and Maitlis, P. M., *J. Am. Chem. Soc.,* **1996**, *118*, 10888. (b) Ledakowicz, S. and Zimmerman, W., *Inzynieria Chemiczna Procesowa*, **1992**, *13*, 89. (c) Masters, C., *Adv. Organomet. Chem.,* **1979**, *17*, 61. (d) Basak, G. C. and Niyogi, N. C., *J. Technology,* **1960**, *5*, 117.
7. Okabe, K.; Takahara, I.; Inaba, M.; Murata, K. and Yoshimura, Y., *J. Jpn. Petro. Inst.,* **2007**, *50*, 65.
8. Ahon, V. R.; Lage, P. L. C.; de Souza, C. D. D.; Mendes, F. M. and Schmal, M., *J. Nat. Gas Chem.,* **2006**, *15*, 307.
9. Jalama, K.; Coville, N. J.; Hildebrandt, D.; Glasser, D. and Jewell, L. L., *Fuel,* **2007**, *86*, 73.
10. (a) Lapidus, A. L.; Eliseev, O. L.; Erofeev, A. B.; Kobrakov, I. K.; Tishkova, L. V. and Agafonov, Y. A., *Khimiya Tverdogo Topliva,* **2006**, 81. (b) Dai, X. P.; Yu, C. C. and Shen, S. K., *Petroleum Sci.,* **2004**, *1*, 82.
11. (a) Zhou, W.; Fang, K.-G.; Chen, J.-G. and Sun, Y.-H., *Gaodeng Xuexiao Huaxue Xuebao,* **2006**, *27*, 1080. (b) Zhou, W.; Chen, J.-G.; Fang, K.-G. and Sun, Y.-H., *Fuel Proc. Tech*., **2006**, *87*, 609.
12. Shi, H. B.; Li, Q.; Dai, X. P.; Yu, C. C. and Shen, S. K., *Petroleum Sci.,* **2005**, *2*, 107.

13. Zhang, C.-H.; Wan, H.-J.; Yang, Y.; Xiang, H.-W. and Li, Y.-W., *Catal. Commun.,* **2006**, *7*, 733.
14. Dijk, Henricus A. J. van, *The Fischer-Tropsch Synthesis: A Mechanistic Study Using Transient Isotopic Tracing*, thesis, Technische Universiteit Eindhoven, **2001**.
15. O'Brien, R. J.; Xu, L. G.; Spicer, R. L. and Davis, B. H., *Energy & Fuels,* **1996**, *10*, 921.
16. Karn, F. S.; Shultz, J. F.; Kelly, R. E. and Anderson, R. B., *Ind. Eng. Chem. Prod. Res. Dev.,* **1963**, *2*, 43.
17. Mahajan, D.; Gütlich, P.; Ensling, J.; Pandya, K.; Stumm, U. and Vijayaraghavan, P., *Energy & Fuels,* **2003**, *17*, 1210.
18. Syntroleum Corp., 10-K Annual Report for United States Securities and Exchange Commission, Accession Number : 1029023-1-1, www.secinfo.com/dVCSg.4e.htm.
19. (a) Iglesia, E., *Prepr. Pap. Am. Chem. Soc., Div. Fuel. Chem.,* **2002**, *47*, 128. (b) Dry, M. E., *Catal. Today,* **2002**, *71*, 227. (c) Davis, B. H., *Fuel Proc. Tech*., **2001**, *71*, 157. (d) Schulz, H., *Appl. Catal. A: General,* **1999**, *186*, 3. (e) Xu, L.; Bao, S.; O'Brien, R. J.; Raje, A. and Davis, B. H., *CHEMTECH,* **1998**, 47.
20. Brady, R. C. and Pettit, R., *J. Am. Chem. Soc.,* **1981**, *103*, 1287.
21. (a) Yakubovich, M. N. and Struzhko, V. L., *Neftekhimiya,* **2006**, *46*, 283. (b) Dunn, B. C.; Covington, D. J.; Coel, P.; Pugmire, R. J.; Meuzelaar, H. L. C.; Ernst, R. D.; Heider, E. C.; Eyring, E. M.; Shah, N.; Huffman, G. P.; Seehra, M. S.; Manivannan, A. and Dutta, P., *Energy & Fuels,* **2004**, *18*, 1519. (c) Kahandawala, M. S. P.; Graham, J. L. and Sidhu, S. S., *Energy & Fuels,* **2004**, *18*, 289. (d) Dunn, B. C.; Turpin, G. C.; Cole, P.; Webster, M. C.; Ma, Z. R.; Pugmire, R. J.; Ernst, R. D.; Eyring, E. M.; Shah, N. and Huffman, G. P., *Prepr. Pap. Am. Chem. Soc., Div. Pet. Chem.,* **2004**, *49*, 431. (e) Rowsell, B. D.; Trepanier, S. J.; Lam, R.; McDonald, R. and Cowie, M., *Organometallics,* **2002**, *21*, 3228. (f) Schulz, H., *Appl. Catal.,* **1999**, *186*, 3. (g) Herrmann, W. A., *Angew. Chem. Int. Ed. Engl.,* **1982**, *21*, 117. (h) Benner, L. S.; Lai, Y.-H. and Vollhardt, K. P. C., *J. Am. Chem. Soc.,* **1981**, *103*, 3609. (i) Fraenkel, D. and Gates, B. C., *J. Am. Chem. Soc.,* **1980**, *102*, 2478. (j) Masters, C., *Adv. Organomet. Chem.*, **1979**, *17*, 61. (k) Demitras, G. C. and Muetterties, E. L., *J. Am. Chem. Soc.,* **1977**, *99*, 2796. (l) Kokes, R. J.; Hall, W. K. and Emmett, P. H., *J. Am. Chem. Soc.,* **1957**, *79*, 2989. (m) Shultz, J. F.; Hall, W. K.; Dubs, T. A. and Anderson, R. B., *J. Am. Chem. Soc.,* **1956**, *78*, 282. (n) Sastri, M. V. C. and Srinivasan, S. R., *J. Am. Chem. Soc.,* **1953**, *75*, 2898. (o) Anderson, R. B.; Hofer, L. J. E.; Cohn, E. M. and Seligman, B., *J. Am. Chem. Soc.,* **1951**, *73*, 944. (p) Anderson, R. B.; Shultz, J. F.; Seligman, B.; Hall, W. K. and Storch, H. H., *J. Am. Chem. Soc.,* **1950**, *72*, 3502. (q) Weller, S.; Hofer, L. J. E. and Anderson, R. B., *J. Am. Chem. Soc.,* **1948**, *70*, 799.

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Fleming-Tamao Oxidation
(Tamao Oxidation, Tamao-Fleming Oxidation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Tamao and co-workers in 1983[1] and Fleming and co-workers in 1984.[2] It is the conversion of a silyl group into a hydroxyl group by means of an oxidative desilylation using either hydrogen peroxide or peracetic acid as an oxidant and KF or KHF_2 as an additivie (Tamao's procedure for di-isopropyl-methylalkylsilanes) or using a peroxy acid as an oxidant under acidic conditions (Fleming's procedure for phenyldimethyl-alkylsilanes). Therefore, this reaction is known as the Fleming-Tamao oxidation[3] but more commonly as the Tamao oxidation[4] or Tamao-Fleming oxidation.[4b,5] For the cases of dialkylsilanes, two alcohols can be generated from oxidative desilylation; therefore, this is an important method for the preparation of diols from cyclic silanes.[3b,3d,5c,5g,6] This oxidation has shown its versatility and importance in modern organic synthesis, beacuse organosilicon molecules can be easily prepared from the hydrosilylation of alkenes and alkynes with *cis*[7] or *trans*[8] stereochemistry, and alcohols or other derivatives can be obtained by the oxidative desilylation of the introduced silyl groups. It was found that the phenyldimethylsilyl group can be converted into an hydroxyl group with retention of stereochemistry,[3d,5d] except for cases when allylsilanes are present in the reaction solution.[3d] Unfortunately, this reaction is not feasible for removing the trimethylsilyl group.[3b]

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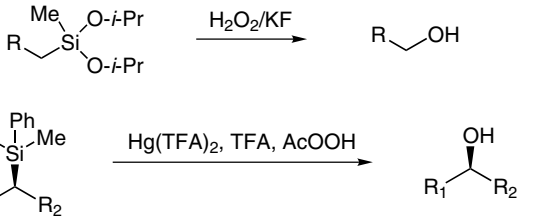
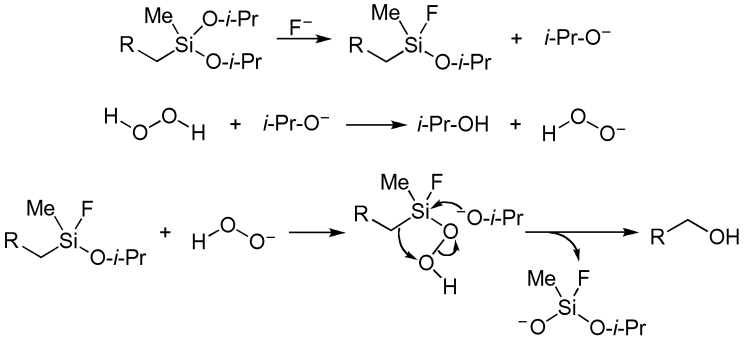
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Listed here is a demonstration of the mechanism using H_2O_2 as an oxidant to yield the alcohol. It is known that fluoride is silicon philic, which can liberate the isopropanol anion and deprotonate the hydrogen peroxide.



D. MODIFICATION

This reaction has been modified by the addition of $KHCO_3$ to further facilitate the reaction.[3d]

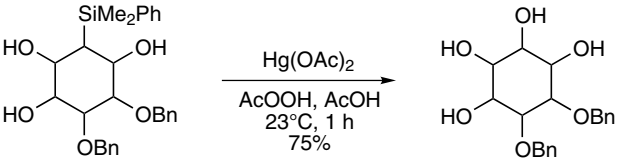
E. APPLICATIONS

This reaction has wide application in the removal of silyl groups and alcohol preparations.

F. RELATED REACTIONS

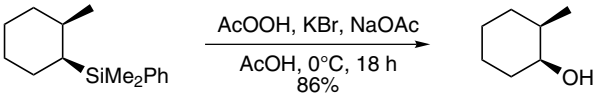
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3a.

To a solution of 16 mg (1*S*,2*S*,3*S*,4*R*,5*S*,6*R*)-5,6-dibenzyloxy-3-(dimethylphenylsilanyl)-cyclohexane-1,2,4-triol (0.03 mmol) in 0.3 mL AcOH were added 12 mg $Hg(OAc)_2$ (0.04 mmol) and 0.2 mL 32% AcOOH (1.0 mmol) at 23°C. After 1 h, the mixture was cooled to 0°C and quenched with 2 mL saturated aqueous $Na_2S_2O_3$ and 3 mL EtOAc. The mixture was stirred for 30 min and the two phases were separated. The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by gradient flash chromatography (10 g SiO_2, 5% MeOH/CH_2Cl_2) to yield 9 mg (1*S*,2*S*,3*S*,4*R*,5*S*,6*R*)-5,6-dibenzyloxy-cyclohexane-1,2,3,4-tetrol, in a yield of 75%.



Reference 5f.

Peracetic acid (Aldrich, 32% solution in acetic acid, 5 mL) was added dropwise at 0°C to a stirred mixture of 3 mmol *cis*-1-(phenyldimethylsilyl)-2-methyl cyclohexane, 500 mg potassium bromide, and 1.2 g anhydrous sodium acetate in 15 mL glacial acetic acid. The mixture was allowed to warm to room temperature and stirred for an additional 18 h. Then the reaction mixture was diluted with ether and carefully neutralized with saturated aqueous $NaHCO_3$ solution. The ethereal layer was washed with saturated aqueous Na_2SO_3 and brine and dried over $MgSO_4$. Ether was removed at ambient pressure, and the residue was purified by preparative column chromatography (eluent hexane, then hexanes/ether, 5:1) to give 294 mg *cis*-2-methylcyclohexanol as a colorless oil, in a yield of 86%.

Other references related to the Fleming-Tamao oxidation are cited in the literature.[9]

H. REFERENCES

1. (a) Tamao, K.; Ishida, N. and Kumada, M., *J. Org. Chem.,* **1983**, *48*, 2120. (b) Tamao, K.; Ishida, N.; Tanaka, T. and Kumada, M., *Organometallics,* **1983**, *2*, 1694.
2. Fleming, I.; Henning, R. and Plaut, H., *J. Chem. Soc., Chem. Commun.,* **1984**, 29.
3. (a) Heo, J.-N.; Holson, E. B. and Roush, W. R., *Org. Lett.,* **2003**, *5*, 1697. (b) Vanecko, J. A. and West, F. G., *Org. Lett.,* **2002**, *4*, 2813. (c) Barrett, A. G. M.; Head, J.; Smith, M. L.; Stock, N. S.; White, A. J. P. and Williams, D. J., *J. Org. Chem.,* **1999**, *64*, 6005. (d) Hunt, J. A. and Roush, W. R., *J. Org. Chem.,* **1997**, *62*, 1112.

4. (a) Li, F. Z. and Miller, M. J., *J. Org. Chem.,* **2006**, *71*, 5221. (b) Jensen, J. F.; Svendsenbn, B. Y.; la Cour, T. V.; Pedersen, H. L. and Johannsen, M., *J. Am. Chem. Soc.,* **2002**, *124*, 4558. (c) Marshall, J. A. and Yanik, M. M., *J. Org. Chem.,* **2001**, *66*, 1373. (d) Yao, Q. W., *Org. Lett.,* **2001**, *3*, 2069. (e) Kanazaki, M.; Ueno, Y.; Ueno, Y.; Shuto, S. and Matsuda, A., *J. Am. Chem. Soc.,* **2000**, *122*, 2422. (f) Degnan, A. P. and Meyers, A. I., *J. Org. Chem.,* **2000**, *65*, 3503. (g) Shuto, S.; Yahiro, Y.; Ichikawa, S. and Matsuda, A., *J. Org. Chem.,* **2000**, *65*, 5547. (h) Shuto, S.; Kanazaki, M.; Ichikawa, S.; Minakawa, N. and Matsuda, A., *J. Org. Chem.,* **1998**, *63*, 746. (i) Ueno, Y.; Nagasawa, Y.; Sugimoto, I.; Kojima, N.; Kanazaki, M.; Shuto, S. and Matsuda, A., *J. Org. Chem.,* **1998**, *63*, 1660.

5. (a) Nahm, M. R.; Linghu, X.; Potnick, J. R.; Yates, C. M.; White, P. S. and Johnson, J. S., *Angew. Chem. Int. Ed.,* **2005**, *44*, 2377. (b) Boglio, C.; Stahlke, S.; Thorimbert, S. and Malacria, M., *Org. Lett.,* **2005**, *7*, 4851. (c) Berkessel, A.; Schröder, M.; Sklorz, C. A.; Tabanella, S.; Vogl, N.; Lex, J. and Neudörfl, J., *J. Org. Chem.,* **2004**, *69*, 3050. (d) Tang, M. Y., *The Asymmetric Synthesis of Polyhydroxylated Pyrrolizidine Alkaloids*, Ph.D. dissertation, The University of Wollongong, **2004**. (e) Jung, M. E. and Piizzi, G., *J. Org. Chem.,* **2003**, *68*, 2572. (f) Rubin, M.; Schwier, T. and Gevorgyan, V., *J. Org. Chem.* **2002,** *67*, 1936. (g) Amrein, S. and Studer, A., *Chem. Commun.,* **2002**, 1592. (h) Denmark, S. E. and Cottell, J. J., *J. Org. Chem.,* **2001**, *66*, 4276. (i) Lee, T. W. and Corey, E. J., *Org. Lett.,* **2001**, *3*, 3337. (j) Itami, K.; Mitsudo, K. and Yoshida, J., *J. Org. Chem.,* **1999**, *64*, 8709.

6. Tanaka, H.; Kamikubo, T.; Yoshida, N.; Sakagami, H.; Taniguchi, T. and Ogasaware, K., *Org. Lett.,* **2001**, *3*, 679.

7. (a) Marciniec, B., *Comprehensive Handbook on Hydrosilylation*, Pergamon Press, Oxford, **1992**. (b) Hiyama, T. and Kusumoto, T., "Hydrosilation of C=C and C-C" in *Compehensive Organic Synthesis*, ed. Trost, B. M. and Fleming, I., Pergamon Press, Oxford, **1991**, *8*, p. 763. (c) Ojima, I., "The Hydrosilation Reaction" in *Chemistry of Organic Silicon Compounds*, ed. Patai, S. and Rappoport, Z., John Wiley & Sons, Chichester, **1989**, p. 1479.

8. (a) Sudo, T.; Asao, N.; Gevorgyan, V. and Yamamoto, Y., *J. Org. Chem*., **1999**, *64*, 2494. (b) Song, Y.-S.; Yoo, B. R.; Lee, G.-H. and Jung, I. N., *Organometallics*, **1999**, *18*, 3109. (c) Asao N.; Sudo, T. and Yamamoto, Y., *J. Org. Chem*., **1996**, *61*, 7654. (d) Yamamoto, K. and Takemae, M., *Synlett,* **1990**, 259. (e) Oertle, K. and Wetter, H., *Tetrahedron Lett.,* **1985**, *26*, 5511.

9. (a) Sanganee, M. J.; Steel, P. G. and Whelligan, D. K., *Org. Biomol. Chem.,* **2004**, *2*, 2393. (b) Studer, A., *Angew. Chem. Int. Ed.,* **1998**, *37*, 462. (c) Mader, M. M. and Edel, J. C., *J. Org. Chem.,* **1998**, *63*, 2761. (d) Dakin, L. A.; Schaus, S. E.; Jacobsen, E. N. and Panek, J. S., *Tetrahedron Lett.,* **1998**, *38*, 8947. (e) Fleming, I., *Chemtracts-Org. Chem.,* **1996**, *9*, 1. (f) Jones, G. R. and Landais, Y., *Tetrahedron*, **1996**, *52*, 7599. (g) Fleming, I.; Newton, T. W.; Sabin, V. and Zammattio, F., *Tetrahedron,* **1992**, *48*, 7793. (h) Kolb, C. H.; Ley, S. V.; Slawin, A. M. Z. and Williams, D. J., *J. Chem. Soc., Perkin Trans. I,* **1992**, 2735. (i) Hayashi, T. and Uozumi, Y., *Pure & Appl. Chem.,* **1992**, *64*, 1911. (j) Uozumi, Y. and Hayashi, T., *J. Am. Chem. Soc.,* **1991**, *113*, 9887. (k) Tamao, K.; Nishida, N.; Ito, Y. and Kumada, M., *Org. Synth*. **1990**, *69*, 96. (l) Koreeda, M.; Teng, K. and Murata, T., *Tetrahedron Lett.,* **1990**, *31*, 5997. (m) Fleming, I. and Sanderson, P. E. J., *Tetrahedron Lett.,* **1987**, *28*, 4229.

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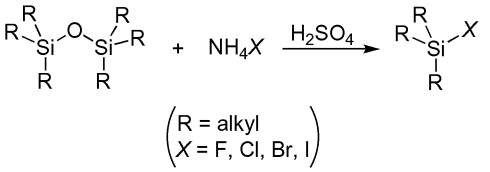
Flood Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Flood in 1933.[1] It is a synthesis of trialkylsilyl halide involving the treatment of the mixture of di-trialkylsilyl oxide and concentrated sulfuric acid with sodium halide or ammonium halide.[2] The resulting trialkylsilyl halide can be extracted by petroleum ether and then purified via distillation.[1] It was found that when di-trimethylsilyl oxide is mixed with concentrated sulfuric acid, trimethylsilyl sulfate can be isolated as a white crystalline (m.p., 56–58°C), which forms trimethylsilyl halide when it reacts with ammonium halide.[3] The reaction has been improved by continuous extraction of the reaction mixture with pentane to yield more and purer trialkylsilyl halide[3] and by the addition of ammonium bisulfate to the reaction mixture.[3]

B. GENERAL REACTION SCHEME



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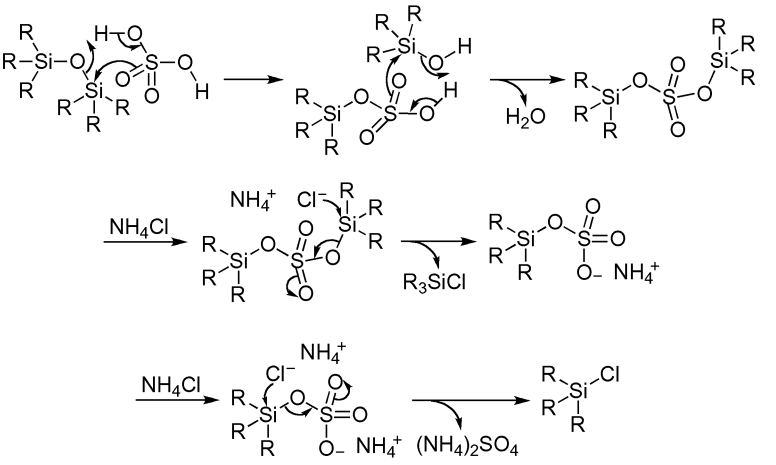
C. PROPOSED MECHANISMS



D. MODIFICATION

N/A

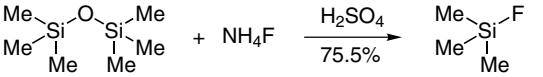
E. APPLICATIONS

This reaction has been used to prepare trialkyl halides.

F. RELATED REACTIONS

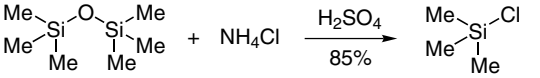
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 4.

To an ice-cold stirred solution of 32.4 g hexamethyldisiloxane (0.2 mol) in 60 mL concentrated sulfuric acid was added 24.2 g ammonium fluoride (0.7 mol) through a dropping bottle within 1 h. Warming gave 31.0 g distillate of clear colorless liquid. Two fractions were collected from fractional distillation: 3.2 g fraction 1, b.p. 15.4°C; and 27.8 g fraction 2, b.p. 15.8°C at 734 mmHg (the pure trimethylfluorosilane), in a yield of 75.5%.



Reference 4.

To a vigorous stirred solution of 324.0 g hexamethyldisiloxane (2 mol) and 1000 g concentrated sulfuric acid cooled in an ice bath was added 321.0 g dry powdered ammonium chloride (6 mol) within 3 h. Upon completion of the addition, the upper layer was separated as quickly as possible. Fraction distillation gave 369.0 g trimethylchlorosilane (3.4 mol), in a yield of 85%, b.p. 58°C.

Other references related to the Flood reaction are cited in the literature.[5]

H. REFERENCES

1. Flood, E. A., *J. Am. Chem. Soc.,* **1933**, *55*, 1735.
2. Sommer, L. H.; Pietrusza, E. W.; Kerr, G. T. and Whitmore, F. C., *J. Am. Chem. Soc.,* **1946**, *68*, 156.
3. Sommer, L. H.; Kerr, G. G. and Whitmore, F. C., *J. Am. Chem. Soc.,* **1948**, *70*, 445.
4. Pray, B. O.; Sommer, L. H.; Goldberg, G. M.; Kerr, G. T.; Giorgio, P. A. D. and Whitmore, F. C., *J. Am. Chem. Soc.,* **1948**, *70*, 433.
5. (a) Birkofer, L and Stuhl, O., *Top. Curr. Chem.,* **1980**, *88*, 33. (b) George, P. D.; Sommer, L. H. and Whitmore, F. C., *J. Am. Chem. Soc.,* **1955**, *77*, 6647. (c) Giorgio, P. A. D.; Strong, W. A.; Sommer, L. H. and Whitmore, F. C., *J. Am. Chem. Soc.,* **1946**, *68*, 1380.

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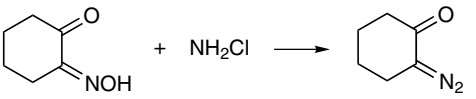
Forster Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Forster in 1915.[1] It is the synthesis of diazoketones, especially for the cyclic diazoketones[2] from α-keto oximes by the reaction with chloramines. Therefore, it is known as the Forster reaction.[3] Although two mechanisms have been proposed for this reaction,[3c] experimental evidence favors the one involving the attack of NH_2Cl by the lone-pair electrons of the oxime nitrogen.[3c,4] This reaction has been modified via the generation of chloramine *in situ*, which is used in the preparation of 2-diazo-1-indanones.[2a]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is believed that this reaction involves the attack of the nitrogen atom of oxime to chloramine.[3c,4]

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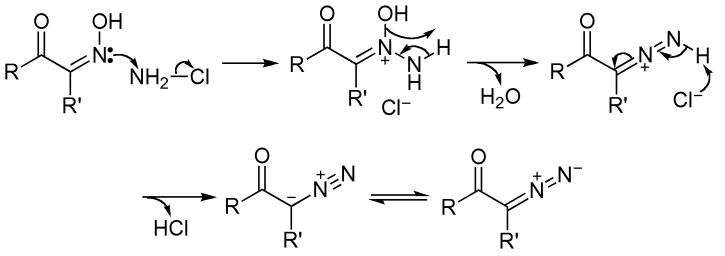


D. MODIFICATION

This reaction has been modified to generate chloramine *in situ* via the reaction of ammonia with sodium hypochlorite.[2a]

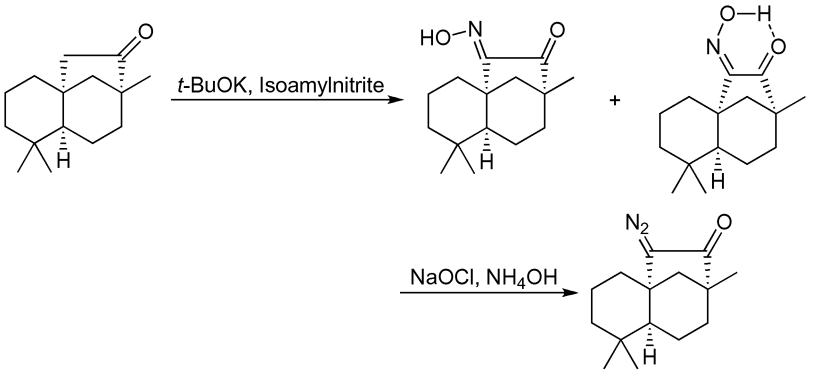
E. APPLICATIONS

This reaction is used to prepare diazoketones, especially for the cyclic diazoketones.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES

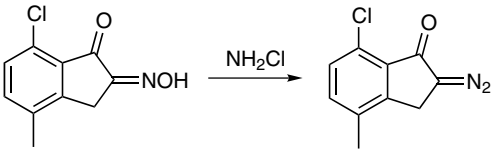


Reference 4.

To a solution of 0.08 M *t*-BuOK in 5.4 mL THF cooled to –78°C in dry ice–acetone bath was added dropwise a solution of 16 mg (1*S*,9*R*)-5,5,9-trimethyltricyclo[7.2.1.$0^{1,6}$]dodecan-10-one (0.073 mmol) and 13 mg isoamyl nitrite (0.11 mmol) in 1 mL THF. Shortly, a reddish color developed. After stirring at –78°C for 1 h, the reaction was allowed to warm up slowly to room temperature over a 30 min period and then was stirred at room temperature for another 30 min. The reaction mixture was then diluted with 20 mL Et_2O and quenched with 5 mL saturated NH_4Cl. The two phases were separated, and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined

organic phases were washed with 10 mL water, saturated aqueous $NaHCO_3$, and brine and dried over $MgSO_4$. After filtration and concentration, the residue was purified through silica gel column chromatography (EtOAc/hexanes, 1:4 to 1:2) to gave (1*R*,6*S*,9*R*,11*Z*)-5,5,9-trimethyltricyclo[7.2.1.$0^{1,6}$]dodecane-10,11-dione 11-oxime in two isomeric forms: *syn*, 5 mg, *anti*, 11 mg (88.4% combined yield).

To a vigorously stirred solution of 6.6 mg *anti*-oxime (0.027 mmol) in 2 mL THF at 0°C was added 0.37 mL 15 M $NH_3 \cdot H_2O$. The mixture was treated with 0.37 mL Clorox (a commercial bleach) dropwise. After the addition, the reaction mixture was stirred for 5 min and then worked up by dilution with Et_2O and water (10 mL each). The resulting two layers were separated, and the aqueous layer was back extracted with ether (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (8:1 hexanes/EtOAc) to afford 3.6 mg diazo ketone, in a yield of 55%.



Reference 2a.

In a 1 L, three-necked flask equipped with a mechanical stirrer, dropping funnel, and thermometer and cooled in an ice bath was placed a solution of 6.3 g oximinoketone (0.03 mol) in a mixture of 200 mL water and 30 mL 1 *N* sodium hydroxide (0.03 mol). The stirred solution was cooled to 2°C, when a portion of the sodium salt of the oxime separated. Then 4 mL 15 *N* ammonium hydroxide (0.60 mol) was added. Next, 100 mL 5.25% sodium hypochlorite solution (0.071 mol) was added dropwise over a period of 20 min. At 1 h after the completion of the addition of the hypochlorite, the ice bath was removed, and stirring was continued for an additional 5 h. The precipitated brown solid was filtered, washed well with water, and dissolved in methylene chloride. The resulting deep red solution was treated with charcoal until orange in color; it was then filtered, concentrated, and chilled to give 3.9 g diazoketone as fine yellow needles, in a yield of 63%, m.p. 173–180°C (dec.).

Other references related to the Forster reaction are cited in the literature.[5]

H. REFERENCES

1. Forster, M. O. J., *J. Chem. Soc.,* **1915**, *107*, 260.
2. (a) Cava, M. P.; Litle, R. L. and Napier, D. R., *J. Am. Chem. Soc.,* **1958**, *80*, 2257. (b) Cava, M. P. and Litle, R. L., *Chem. Ind.*, **1957**, 367.
3. (a) Huneck, S., *Chem. Ber.,* **1965**, *98*, 3204. (b) Rundel, W., *Angew. Chem.,* **1962**, *74*, 469. (c) Meinwald, J.; Gassman, P. G. and Miller, E. G., *J. Am. Chem. Soc.,* **1959**, *81*, 4751.
4. Zhang, L. M. and Koreeda, M., *Org. Lett.,* **2004**, *6*, 537.
5. (a) Ye, T. and McKervey, M. A., *Chem. Rev.* **1994**, *94,* 1091. (b) Cava, M. P. and Vogt, B. R., *J. Org. Chem.,* **1965**, *30*, 3776. (c) Overberger, C. G. and Anselme, J. P., *Tetrahedron Lett*., **1963**, 1405. (d) Rundel, W., *Angew. Chem.,* **1962**, *74*, 469. (e) Meinwald, J.; Curtis, G. G. and Gassman, P. G., *J. Am. Chem. Soc.,* **1962**, *84*, 116. (f) Cava, M. P. and Moroz, E., *J. Am. Chem. Soc.,* **1962**, *84*, 115. (g) Weygand, F. and Bestmann, H. J., *Angew. Chem.,* **1960**, *72*, 535.

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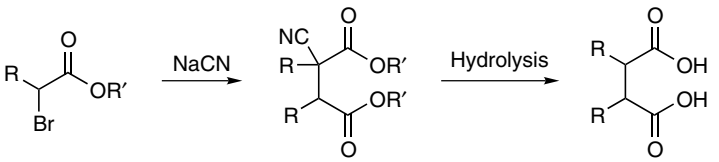
Franchimont Condensation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Franchimont in 1872.[1] It is a condensation of two α-bromocarboxylic acids in absolute alcohol in the presence of sodium cyanide to give 1,2-dicarboxylic acids after hydrolysis and decarboxylation. In the case of α-bromoketones, 1,4-diketones are produced similarly after hydrolysis with phosphoric acid.[2] It was found that the bulky group at the ester end prevents condensation, as in the case of phenyl and naphthyl esters.[3] Although the substituent at β-position does not prevent such condensation, it reduces the overall yield.[3] In addition, a compound with two ester groups at proper position will form cyclic diacid under such reaction conditions; and cyclobutane,[3,4] cyclopentane[5] and cyclohexane[5] dicarboxylic acid have been prepared in such a way. In the case of 1,4-dibromo-1,4-dibenzoylbutane, a derivative of cyclopentanone is produced after acidic hydrolysis.[2] It should be pointed out that other common solvents—including acetone, ether, and acetonitrile– are not good for this reaction.[3]

B. GENERAL REACTION SCHEME



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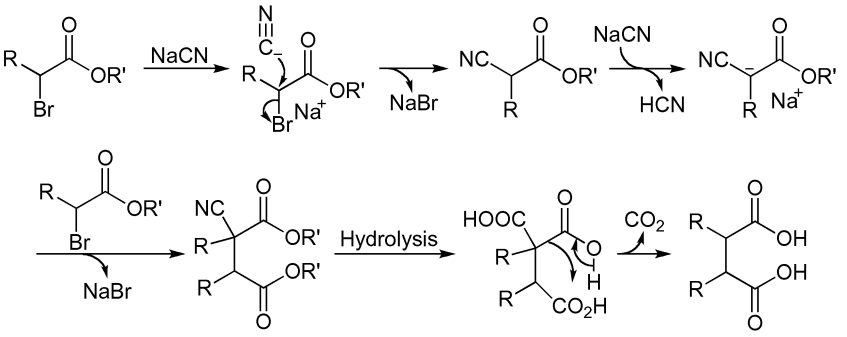
C. PROPOSED MECHANISMS



D. MODIFICATION

The original condensation of two α-bromocarboxylic acids has been extended to the condensation of compounds with two α-bromocarbonyl groups.

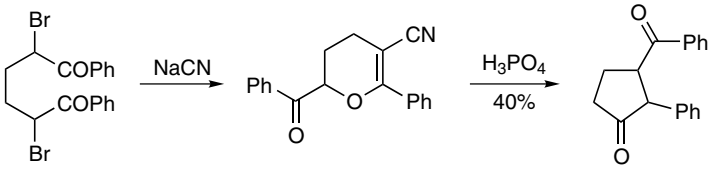
E. APPLICATIONS

This reaction has been used in the synthesis of cyclobutane, cyclopentane, and cyclohexane dicarboxylic acids.

F. RELATED REACTIONS

This reaction is related to the *Acyloin Condensation* and *Benzoin Condensation*.

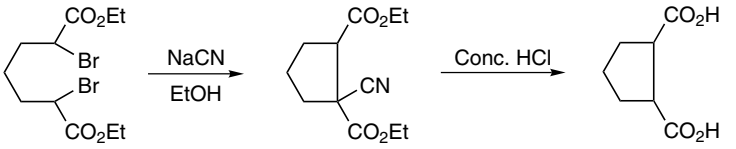
G. CITED EXPERIMENTAL EXAMPLES



Reference 2.

To a mixture of 300 mL 85% phosphoric acid and 25 mL 95% ethanol was added 10.0 g cyano dihydropyran prepared from 1,4-dibromo-1,4-dibenzoylbutane and sodium cyanide. The solution was stirred for 18 h at room temperature and then refluxed for 8 h. When the solution was cooled down, it was diluted to a volume of 1800 mL in a 2-L

beaker by the addition of water. The yellow solid was filtrated after a few hours, and 40% 2-phenyl-3-benzoylcyclopentanone was recrystallized from ethanol, m.p. 159.0–159.5°C.



Reference 5.

A mixture of 50.0 g ethyl α,α'-dibromopimelate, 25.0 g powdered sodium cyanide, and 30 mL absolute ethanol was refluxed for 60 h. Sodium bromide and excess sodium cyanide were removed from the cooled mixture by filtration and washed with 10 mL ethanol. The filtrate, when distilled in vacuo, gave a colorless distillate boiling at 125–130°C at 2 mmHg. Redistillation gave 25–29 g ethyl 1-cyano-1,2-cyclopentanedicarboxylate at 135–136°C at 3.5 mmHg or 126–128°C at 2 mmHg pressure, with a corresponding yield of 80–88%.

Ethyl 1-cyano-1,2-cyclopentanedicarboxylate (15.0 g) was hydrolyzed by refluxing with 75 mL concentrated HCl for 30 h. The ester dissolved completely, giving a light brown solution that deposited, on cooling, 5 g crude *trans*-1,2-cyclopentanedicarboxylic acid with a melting point at 155–158°C. This was converted into the pure *trans* acid by being heated to 160°C with 1 mL concentrated HCl in a sealed tube for 1 h. The pure *trans* acid melted at 161°C.

Other references related to the Franchimont condensation are cited in the literature.[6]

H. REFERENCES

1. Franchimont, A. P. N., *Ber.,* **1872**, *5*, 1048.
2. Fuson, R. C.; Lippert, A.; Young, R. V. and Hully, H. H., *J. Am. Chem. Soc.,* **1936**, *58*, 2633.
3. Fuson, R. C.; Kreimeier, O. R. and Nimmo, G. L., *J. Am. Chem. Soc.,* **1930**, *52*, 4074.
4. Fuson, R. C. and Kao, T. Y., *J. Am. Chem. Soc.,* **1929**, *51*, 1536.
5. Fuson, R. C. and Cole, W., *J. Am. Chem. Soc.,* **1938**, *60*, 1237.
6. (a) Rydon, H. N., *J. Chem. Soc.,* **1936**, 593. (b) Bone, W. A. and Perkin, W. H., *J. Chem. Soc., Trans.,* **1896**, *69*, 253. (c) Poppe, O., *Ber.,* **1890**, *23*, 113. (d) Zelinsky, N., *Ber.,* **1888**, *21*, 3160.

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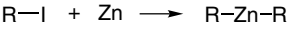
Frankland Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported in 1848 by Frankland,[1] who tried to prepare ethyl radical from zinc and ethyl iodide in a sealed tube.[2] However, he obtained diethyl zinc. This event is probably the origin of organometallic chemistry,[2,3] because diethyl zinc was the first synthetic organometallic compound.[2,4] Therefore, the preparation of dialkyl zinc from zinc and alkyl iodide is called the Frankland reaction.[5] Currently, alkyl zinc has found many applications in organic synthesis,[6] because the addition of alkyl zinc to aldehydes in the presence of a chiral catalyst affords secondary alcohols with a high level of enantioselectivity;[7] in addition, organic zinc reagents can tolerate a broad range of functionalities.[8] It should be pointed out that dialkyl zinc forms a complicated complex rather than a simple zinc alkoxide when it is exposed to oxygen.[9] Moreover, the direct preparation of dialkyl zinc from alkyl iodide and zinc followed by distillation is best for compounds with a short hydrocarbon chain (e.g., from C1 to C4).[10] Besides the Frankland reaction, other methods for preparing dialkyl zinc compounds have been developed, including the reactions between the activated zinc and the alkyl halide,[11] the reaction of zinc with a mixture of alkyl iodide and alkyl bromide,[8a] the transmetalation of lithium[11,12] or magnesium[9] organometallics with zinc salts, and the iodine-zinc exchange.[6]

B. GENERAL REACTION SCHEME



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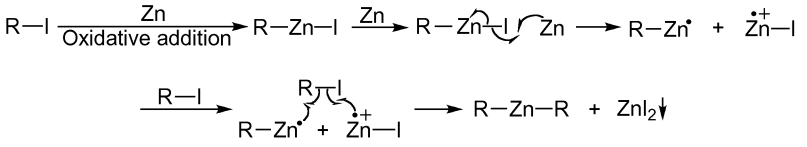
C. PROPOSED MECHANISMS

It is suggested that the reaction between zinc and alkyl bromide involves an electron transfer, but the details of the mechanism are not given.[8a] Therefore, it is reasonable to assume that the reaction between zinc and alkyl iodide also involves electron transfer, as outlined here.



D. MODIFICATION

A few modifications of this reaction are the reaction between alkyl iodide and copper-zinc alloy,[3c,11] the reaction between zinc and a mixture of alkyl iodide and alkyl bromide,[8a] the transmetalation between zinc and lithium,[11,12] magnesium,[9] or tin,[5d] and the iodine-zinc exchange.[6]

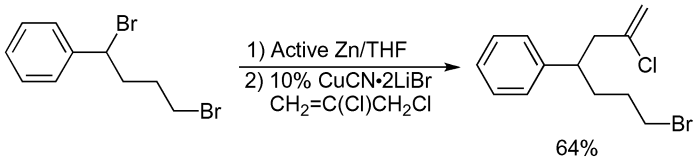
E. APPLICATIONS

The prepared organozinc reagents have wide application in organic synthesis.

F. RELATED REACTIONS

This reaction is related to the *Grignard Reaction*.

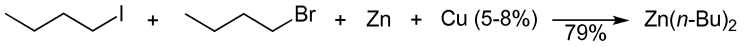
G. CITED EXPERIMENTAL EXAMPLES



Reference 8a.

To a 50-mL centrifuge tube containing 584.1 mg 1,4-dibromo-1-phenylbutane (2.0 mmol) in 10 mL anhydrous THF at 0°C (equipped with a stirring bar and septum) was added 1.5 mL active zinc suspension of THF (2.2 mmol, 10 g/100 mL) via a disposable syringe under argon atmosphere. The mixture was stirred at 0°C for 10 min, then the organozinc reagent was centrifuged for 2 min at 2500 rpm, and the content of the tube was

cannulated to a 100-mL, two-necked flask at –30°C containing 17.9 mg copper (I) cyanide (0.2 mmol) and 17.4 mg LiBr (0.4 mmol) in 10 mL THF. 2,3-Dichloropropene (222 mg, 2.0 mmol) was added immediately to the flask. After 3 h, the temperature was allowed to rise to room temperature, and stirring was maintained for an additional 3 h. After this, 50 mL hexanes was added, the mixture was hydrolyzed with 1 M HBr and extracted with hexanes (2 × 50 mL), the organic phases were dried over magnesium sulfate, and the solvents were removed at 30°C and a pressure of 15 mmHg. Kugelrohr distillation afforded 64% 7-bromo-2-chloro-4-phenyl-1-heptane.



Reference 3c.

To a 1-L round-bottomed flask equipped with a reflux condenser and a heavy stirrer was placed 130.0 g fine turnings of a zinc-copper alloy containing 5–8% copper (~2 mol), 0.5 mol *n*-butyl iodide, and 0.5 mol *n*-butyl bromide. The mixture was gently refluxed with slow stirring. In case the reaction became too vigorous, the flask was cooled with ice water, but only to the point at which the reaction was again under control. At the end of 30 min from the time the heat was removed, the reaction was usually over. The flask was allowed to cool and was connected with a distilling head and condenser; the di-*n*-butyl zinc was distilled directly from the reaction flask at 9 mmHg at 81–82°C. The apparatus need not be swept out with an inert gas before starting the distillation, but at the end, when the vacuum was released, dry carbon dioxide was admitted to the apparatus instead of air. Finally 78–79% of di-*n*-butyl zinc was obtained, and an equal weight of the desired dry solvent was added to the receiving flask. The resulting solution was ready for subsequent reaction of such zinc reagent.

Other references related to the Frankland reaction are cited in the literature.[14]

H. REFERENCES

1. (a) Frankland, E., *Ann.,* **1848**, *71*, 171. (b) Frankland, E., *J. Chem. Soc.,* **1948**, *2*, 263.
2. Seyferth, D., *Organometallics,* **2001**, *20*, 2940.
3. (a) Nicholson, J. W., *J. Chem. Edu.*, **1989**, *66*, 621. (b) Rochow, E. G., *J. Chem. Edu.*, **1966**, *43*, 58. (c) Noller, C. R., *J. Am. Chem. Soc.,* **1929**, *51*, 594.
4. Rieke, R. D.; Hanson, M. V.; Brown, J. D. and Niu, Q. J., *J. Org. Chem.,* **1996**, *61*, 2726.
5. (a) Holland, F. S., *Appl. Organomet. Chem.,* **1987**, *1*, 449. (b) Nosek, J. and Gasparic, J., *Coll. Czech. Chem. Commun.,* **1967**, *32*, 2028. (c) Nosek, J., *Coll. Czech. Chem. Commun.,* **1967**, *32*, 2025. (d) Nosek, J., *Coll. Czech. Chem. Commun.,* **1964**, *29*, 3173. (e) Nosek, J., *Coll. Czech. Chem. Commun.,* **1964**, *29*, 597. (f) Nosek, J., *Chemicke Listy Vedu Prumysl*, **1953**, *47*, 1236.
6. Rozema, M. J.; Sidduri, A. and Knochel, P., *J. Org. Chem.,* **1992**, *57*, 1956.
7. (a) Noyori, R. and Kitamura, M., *Angew. Chem. Int. Ed. Engl.,* **1991**, *30*, 49. (b) Schmidt, B. and Seebach, D., *Angew. Chem. Int. Ed. Engl.,* **1991**, *30*, 99. (c) Oguni, N.; Matsuda, Y. and Kaneko, T., *J. Am. Chem. Soc.,* **1988**, *110*, 7877. (d) Evans, D. A., *Science,* **1988**, *240*, 420. (e) Soai, K.; Ookawa, A.; Kaba, T. and Ogawa, K., *J. Am. Chem. Soc.,* **1987**, *109*, 7111.
8. (a) Guijarro, A.; Rosenberg, D. M. and Rieke, R. D., *J. Am. Chem. Soc.,* **1999**, *121*, 4155. (b) Knochel, P. and Singer, R. D., *Chem. Rev.,* **1993**, *93*, 2117.

9. (a) Thiele, K. H.; Wilcke, S. and Ehrhardt, M., *J. Organomet. Chem.,* **1968**, *14*, 13. (b) Abraham, M. H., *J. Chem. Soc.,* **1960**, 4130.
10. (a) Sorroos, H. and Morgana, M., *J. Am. Chem. Soc.,* **1944**, *66*, 893. (b) Noller, C. R., *Org. Synth. Coll.* **1943**, *2*, 184. (c) Frankland, E., *Ann.,* **1859**, *111*, 44. (d) Frankland, E., *Ann.,* **1855**, *95*, 28.
11. Zhu, L. S.; Wehmeyer, R. M. and Rieke, R. D., *J. Org. Chem.,* **1991**, *56*, 1445.
12. (a) Köbrich, G. and Merkle, H., *Ber.,* **1966**, *99*, 1782. (b) Wittig, G. and Lehmann, G., *Ber.,* **1957**, *90*, 875. (c) Wittig, G.; Meyer, F. J. and Lange, G., *Ann.,* **1951**, *571*, 167.
13. Lewinski, J.; Marciniak, W.; Lipkowski, J. and Justyniak, I., *J. Am. Chem. Soc.,* **2003**, *125*, 12698.
14. (a) Eisch, J. J., *Organometallics,* **2002**, *21*, 5439. (b) Jones, R. G. and Gilman, H., *Chem. Rev.,* **1954**, *54*, 835. (c) Hatch, L. F.; Sutherland, G. and Ross, W. J., *J. Org. Chem.,* **1949**, *14*, 1130. (d) Frankland, E., *Ann.,* **1853**, *85*, 329.

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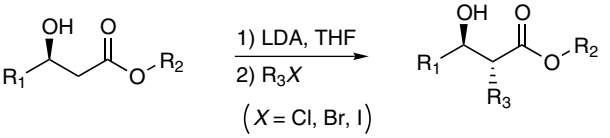
Fráter-Seebach Alkylation

A. GENERAL DESCRIPTION OF THE REACTION

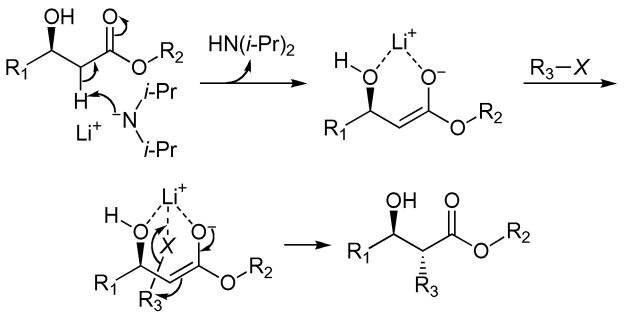
This reaction was initially reported by Fráter in 1979[1] and subsequently by Seebach and Wasmuth in 1980.[2] It is a reaction between a lithium enolate of an enantiomerically pure β-hydroxyl carboxylate and a alkyl halide to give α-alkyl-β-hydroxyl-carboxylate with high diastereoselectivity (> 10:1 of *anti*- preference).[3] Therefore, this special type of alkylation is generally known as the Fráter-Seebach alkylation.[3,4] Occasionally, it is also referred to as the Fráter-Seebach protocol.[5] The high diastereoselectivity is clearly evidenced in one experimental condition, in which only the *anti*-diasteromer forms.[4f,5] The resulting α-alkyl-β-hydroxy-carboxylate is often an important intermediate in natural product synthesis;[3,4d,4h] in addition, it can also be reduced by lithium aluminum hydride (LAH) to form diastereomerically pure 1,3-diol,[4g] which forms 1,3-dioxane with a carbonyl compound (acetal or ketal),[4b,4g] an important intermediate in organic synthesis. It is assumed that the high diastereoselectivity arises from the chelation.[5]

B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS



D. MODIFICATION

This stereoselective alkylation has been extended to γ-hydroxyl-carboxylic acid that exists as a lactone.[4h]

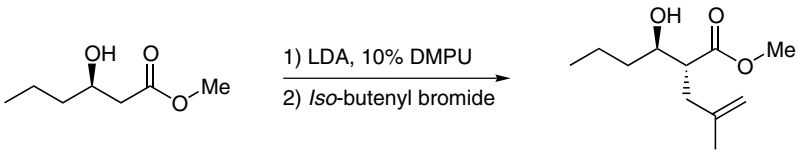
E. APPLICATIONS

This reaction has certain application in the preparation of multifunctional chiral compounds.

F. RELATED REACTIONS

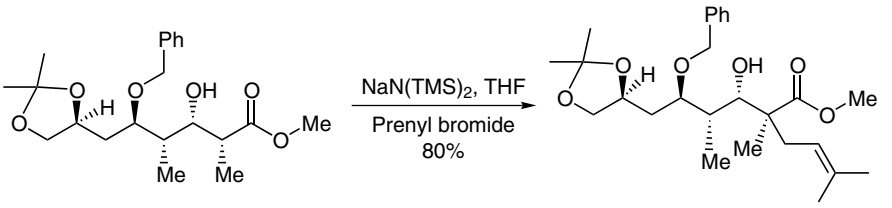
This reaction is related to the *Aldol Reaction* and *Evans Aldol Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 3.

LDA (2.1 eq.) was generated by the addition of 2.55 M *n*-BuLi in THF to a 1.0 M solution of diisopropylamine (2.1 eq.) in THF at 0°C. After 15 min, the LDA solution was cooled to –78°C and 1.0 eq. THF solution of β-hydroxy ester was added dropwise via syringe such that the internal temperature was maintained at or below –65°C. Then 1.1 eq. *iso*-butenyl bromide was added via syringe followed by DMPU (10% v/v). The reaction mixture was stirred at –78°C for 5 min then allowed to come to 0°C over 24–48 h until the reaction was complete by TLC. The reaction mixture was then quenched with saturated NH_4Cl and extracted with ether, the organic layers were combined and washed with 1 N HCl, 5% $NaHCO_3$, and brine and dried over $MgSO_4$. Removal of the solvent and silica gel chromatography afford the product. (No yield was given for this reaction.)



Reference 4f.

To 33.5 mL 1.0 M sodium hexamethyldisilazide in hexane (33.5 mmol) at −78°C was added 2.55 g 2,4,6-trideoxy-2,4-dimethyl-7,8-*O*-(1-methylethylidene)-5-*O*-(phenylmethyl)-D-*glycero*-D-*gluco*-octanoic acid methyl ester (6.70 mmol) in 35 mL THF dropwise via cannula. Once the addition of the ester was complete, the mixture was warmed to –20°C (internal thermometer) for 30 min and was then recooled to –78°C. Prenyl bromide (10 g, 70 mmol, 7.8 mL), freshly distilled from anhydrous K_2CO_3, was added, and stirring was continued at –78°C for 3 h. The reaction mixture was gradually warmed to 0°C over 3 h and was maintained at that temperature for an additional 9 h. The reaction was quenched by the addition of 50 mL saturated aqueous NH_4Cl, followed by the addition of 200 mL Et_2O. The organic layer was washed with 75 mL water and 75 mL brine, and the combined aqueous layers were back extracted with Et_2O (2 × 50 mL). The ethereal extracts were dried over $MgSO_4$, filtered, and concentrated. Silica gel chromatography (23% EtOAc/hexane) gave 2.41 g (2*S*)-2,4,6-trideoxy-2,4-dimethyl-2-(3-methyl-2-butenyl)-7,8-*O*-(1-methylethylidene)-D-*altro*-octonic acid methyl ester as a viscous yellow oil, in a yield of 80%, $R_f = 0.48$ (EtOAc/hexanes, 2:3).

Other references related to the Fráter-Seebach alkylation are cited in the literature.[6]

H. REFERENCES

1. Fráter, G., *Helv. Chim. Acta,* **1979**, *62*, 2825.
2. Seebach, D. and Wasmuth, D., *Helv. Chim. Acta,* **1980**, *63*, 197.
3. Rabinowitz, M. H.; Andrews, R. C.; Becherer, J. D.; Bickett, D. M.; Bubacz, D. G.; Conway, J. G.; Cowan, D. J.; Gaul, M.; Glennon, K.; Lambert, M. H.; Leesnitzer, M. A.; McDougald, D. L.; Moss, M. L.; Musso, D. L. and Rizzolio, M. C., *J. Med. Chem.,* **2001**, *44,* 4252.
4. (a) Kadota, I.; Hu, Y. Q.; Packard, G. K.; Rychnovsky, S. D. and Nicolaou, K. C., *Proc. Nat. Acad. Sci. USA,* **2004**, 101, 11992. (b) Roush, W. R. and Newcom, J. S., *Org. Lett.,* **2002**, *4*, 4739. (c) Roush, W. R.; Bannister, T. D.; Wendt, M. D.; Jablonowski, J. A. and Scheidt, K. A., *J. Org. Chem.,* **2002**, *67,* 4275. (d) Heathcock, C. H.; Kath, J. C. and Ruggeri, R. B., *J. Org. Chem.,* **1995**, *60*, 1120. (e) Rychnovsky, S. D., *Chem. Rev.,* **1995**, *95*, 2021. (f) Williams, D. R.; Rojas, C. M. and Bogen, S. L., *J. Org. Chem.,* **1999**, *64,* 736. (g) Rychnovsky, S. D. and Rodriguez, C., *J. Org. Chem.,* **1992**, *57*, 4793. (h) Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E. and Schreiber, S. L., *J. Am. Chem. Soc.,* **1990**, *112*, 5583.
5. Hunt, K. W. and Grieco, P. A., *Org. Lett.,* **2001**, *3*, 481.
6. (a) Evans, D. A.; Trotter, B. W.; Cté, B. and Coleman, P. J., *Angew. Chem. Int. Ed. Engl.,* **1997**, *36*, 2741. (b) Seebach, D.; Aebi, J. and Wasmuth, D., *Org. Synth. Coll.* **1990**, *7*, p. 153. (c) Fráter, G. and Seebach, D., *Mod. Synth. Methods,* **1986**, *4*, 128. (d) Fráter, G.; Muller, U. and Gunther, W., *Tetrahedron,* **1984**, *40*, 1269. (e) Seebach, D.; Aebi, J. and Wasmuth, D., *Org. Synth.,* **1984**, *63*, 109.

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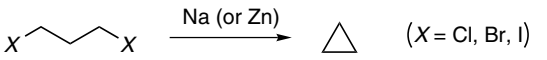
Freund Reaction
(Hass Cyclopropane Process)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Freund in 1881.[1] It is a preparation of cyclopropane derivatives from internal nucleophilic displacement of 1,3-dihalopropanes with the treatment of sodium. The further modification of this reaction by treatment of 1,3-dihalopropane with zinc dust is called the Gustavson reaction,[2] whereas treatment with zinc dust in aqueous alcohol in the presence of a catalytic amount of NaI is called the Hass cyclopropane process.[3] Although the Freund condition is challenged because of its similarity to the *Wurtz Reaction*,[4] the preparation of cyclopropane from 1,3-dihalopropane is more often called the Freund reaction,[4,5] including the condition of Gustavson.[5e,6] Similar to zinc, magnesium also reacts with 1,3-dihalopropane to give cyclopropane.[6] In this reaction, metal zinc or magnesium inserts into a carbon-halogen bond, and the resulting carbanion attacks the nearby alkyl halide to form the cyclopropane ring. It has been reported that 1,3-diiodopropane also cyclizes under radical conditions.[7] Due to the steric effect, the primary, primary 1,3-dibromides give high yields of cyclopropanes; primary, secondary dibromides give fair yields of cyclopropanes; and secondary, secondary dibromides afford poor yields.[5e] In some cases, olefin is produced as the principal or sole product.[5e]

B. GENERAL REACTION SCHEME



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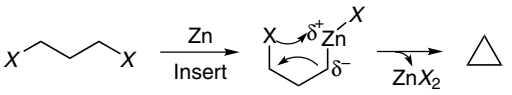
C. PROPOSED MECHANISMS

Illustrated here is the mechanism for the reaction between zinc and 1,3-dibromopropane.



D. MODIFICATION

The Gustavson and Hass conditions are the further modifications of the original Freund procedure.

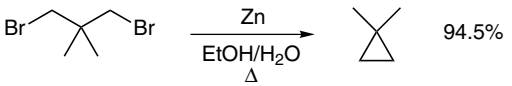
E. APPLICATIONS

This reaction has general application in the preparation of cyclopropanes and probably for cyclobutanes and cyclopentanes as well.

F. RELATED REACTIONS

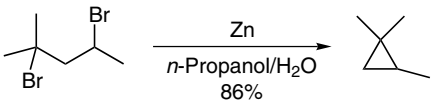
This reaction is related to the *Wurtz Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4.

In a 2-L, three-necked flask equipped with a dropping funnel, mercury-sealed stirrer, and reflux condenser (connected to a trap surrounded by a dry ice–acetone bath) were placed 900 mL 95% ethanol, 90 mL distilled water, and 628 g zinc dust (9.6 mol). It was necessary to maintain vigorous stirring at all times to prevent caking of the zinc. The mixture was brought to gentle reflux, and 562 g 1,3-dibromo-2,2-dimethylpropane (2.4 mol) was added dropwise at this temperature. Heating and stirring were continued for 24 h after the last of the dibromide had been added; the bulk of the hydrocarbon was collected in the trap during this period. The remaining 1,1-dimethylcyclopropane (along with some alcohol) was then distilled from the reaction flask and was collected in the trap. The crude 1,1-dimethylcyclopropane (162 g) was washed with ice water and dried, in a crude yield of 94.5%.



Reference 5e.

To a 1-L, three-necked flask fitted with a reflux condenser, thermometer, dropping funnel, and mercury sealed stirrer was added 100 mL water, 300 mL *n*-propyl alcohol, and 196.0 g oxygen-free zinc dust (3.0 mol, prepared from commercial grade zinc dust). The flask was placed in an ice bath, and 214 g freshly distilled 2-methyl-2,4-dibromopentane (1 mol) was added dropwise with efficient stirring over a period of ~ 90 min. The ice bath was then removed, and the mixture was stirred at room temperature for ~ 32 h. After ~10 h an immiscible layer of hydrocarbon had formed. At the end of the reaction, the hydrocarbon product was separated by distillation. 1,1,2-Trimethylcyclopropane was collected over a temperature range of 49–51°C and weighed 78.1 g, in a yield of 86%. The distillate contained a small amount (2 or 3 mL) propyl alcohol and water; therefore, it was washed twice with 100-mL portions of ice water to remove the alcohol and cooled to freeze the aqueous layer. The hydrocarbon was poured off. The crude 1,1,2-trimethylcyclopropane was purified by distillation in a vertical surface column operating under conditions that gave an efficiency of 100 theoretical plates calculated by the method of Calingaert and Beatty.

Other references related to the Freund reaction are cited in the literature.[8]

H. REFERENCES

1. Freund, A., *Monatsh.,* **1881**, *2*, 642.
2. Gustavson, G., *J. Prakt. Chem.,* **1887**, *[2] 36*, 300.
3. (a) Hass, H. B. and Marshall, J. R., *Ind. Eng. Chem.,* **1931**, *23*, 352. (b) Hass, H. B.; McBee, E. T. and Weber, P., *Ind. Eng. Chem.,* **1935**, *27*, 1190.
4. Shortridge, R. W.; Craig, R. A.; Greenlee, K. W.; Derfer, J. M. and Boord, C. E., *J. Am. Chem. Soc.,* **1948**, *70*, 946.
5. (a) Meislich, E. K.; Meislich, H. and Sharefkin, J., *3000 Solved Problems in Organic Chemistry*, McGraw-Hill, Highstown, **1994**. (b) Berner, I. R., *Brit. J. Anaesth.,* **1965**, *37*, 671. (c) Searles, S.; Lutz, E. F. and Tamres, M., *J. Am. Chem. Soc.,* **1960**, *82*, 2932. (d) Misani, F.; Speers, L. and Lyon, A. M., *J. Am. Chem. Soc.,* **1956**, *78*, 2801. (e) Bartleson, J. D.; Burk, R. E. and Lankelma, H. P., *J. Am. Chem. Soc.,* **1946**, *68*, 2513.
6. (a) Wechter, W. J. and Slomp, G., *J. Org. Chem.,* **1962**, *27*, 2549. (b) Roberts, J. D. and Dev. S., *J. Am. Chem. Soc.,* **1951**, *73*, 1879.
7. Drury, R. F. and Kaplan, L., *J. Am. Chem. Soc.,* **1973**, *95*, 2217.
8. (a) Gragson, J. T.; Greenlee, K. W.; Derfer, J. M. and Boord, C. B., *J. Am. Chem. Soc.,* **1953**, *75*, 3344. (b) Kelso, R. G.; Greenlee, K. W.; Derfer, J. M. and Boord, C. E., *J. Am. Chem. Soc.,* **1952**, *74*, 287. (c) Roberts, J. D. and Chambers, V. C., *J. Am. Chem. Soc.,* **1951**, *73*, 5034. (d) Hass, H. B.; McBee, E. T.; Hinds, G. E. and Gluesenkamp, E. W., *Ind. Eng. Chem.,* **1936**, *28*, 1178. (e) Lespieau, R. and Wakeman, R. L., *Bull. Soc. Chim. Fr.,* **1932**, *51*, 384. (f) Gustavson, G. and Popper, O., *J. Prakt. Chem.,* **1898**, *58*, 458. (g) Gustavson, G., *J. Prakt. Chem.,* **1891**, *[2] 43*, 396. (h) Freund, A., *J. Prakt. Chem.,* **1882**, *26*, 367. (i) Freund, A., *Monatsh.,* **1882**, *3*, 625.

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Friedel-Crafts Acylation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Friedel and Crafts in 1877.[1] It is an electrophilic aromatic substitution by an acyl group derived from carboxylic acid derivatives in the presence of a Lewis acid or Brønsted acid. Therefore, this reaction is generally known as the Friedel-Crafts acylation.[2] Generally speaking, this reaction involves four basic elements: the aromatics, acylating agents, catalysts, and solvents. As of the electrophilic nature, the more enriched the electron is on the aromatic ring, the easier the reaction occurs; therefore, electron-donating groups on aromatic rings usually facilitate the reaction, whereas electron-withdrawing groups normally impede the reaction. Nitrobenzene, with its strong electron-withdrawing nitro group that usually inhibits acylation,[3] is often used as the solvent for Friedel-Crafts acylation.[4] On the other hand, the acylating agents of carboxylic acid derivatives also influence this acylation; the more the electrophilic the acylating agent, the faster the acylation proceeds. Consequently, the commonly used acylating agents are acyl halides (mostly acyl chloride) and acyl anhydrides, though other derivatives—including carboxylic acids,[5] esters,[4,6] and lactams[7]—are also used in the direct acylation. In addition, to increase the electrophilicity of acylating agents, at least 1 eq. of Lewis acid is used in this reaction.[4] The Lewis acids used in the acylation with acyl halides include $AlCl_3$, $AlBr_3$, $BeCl_2$, $CuCl_2$, $FeBr_3$, $HgCl_2$, $MbCl_5$, $SbBr_3$, $SbCl_5$, $TiCl_4$, UCl_4, WCl_6, and $ZrCl_4$.[4] When acyl anhydrides are used as acylating agents, effective catalysts are $AgClO_4$, BF_3, CF_3CO_2H, $(CF_3CO)_2O$, $HClO_4$, HF, H_3PO_4, $SnCl_4$, $SOCl_2$, $ZnCl_2$, etc.[4] Although many compounds that do not undergo the Friedel-Crafts acylation can be used as the solvent, the commonly used solvents are nonpolar carbon disulfide for heterogeneous acylation and polar nitrobenzene for homogenous acylation.[4] It is known that the Lewis acid forms a complex with the

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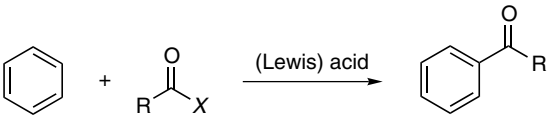
acylating agent that is sufficiently electrophilic to react with an aromatic ring,[8] resulting in a ketone–Lewis acid complex as the actual reaction product, which prevents further reaction (e.g., rearrangement) and gives high yields of pure product. Therefore, water or dilute HCl is often used to decompose the ketone–Lewis acid complex. This is the reason at least 1 eq. of Lewis acid is needed for the acylation with acyl halide. Other acylating agents might need more than 1 eq. of Lewis acid.[4] From this point of view, the Lewis acids are the promoters, not the catalysts, although recent developments have made this acylation catalytic.[6a,9]

The Friedel-Craft acylation is usually considered irreversible; however, if the acyl group is tilted out of the plane of the aromatic ring by a neighboring bulky group, isomers form from the reversible acylation.[10] The intermolecular acylation can provide the aromatics with long hydrocarbon chains without rearrangement after reduction of the carbonyl groups, whereas intramolecular acylation can synthesize benzocyclic ketones including 1-indanones, 1-tetralones, and 1-benzosuberones.[6a] The direction of acylation follows the *Crum-Brown-Gibson Substitution Rule*—that is, the acylation occurs often at the *para*-position of the electron-donating group, and occurs much less at the *ortho*-position because of steric hindrance. It was found that when both amino and thioether groups exist on the same aromatic ring, the amino group is the determining group for acylation direction.[11] Other developments for the Friedel-Crafts acylation include (*a*) application of ionic liquids as recyclable catalyst and media for acylation;[9b,12] (*b*) application of $AgSbF_6$,[13] Bi_2O_3,[9b] $Bi(OTf)_3$,[9b] $[(CuOTf)_2PhH]$,[14] Envirocats,[15] $EtAlCl_2$,[16] Nafion-H,[9a,17] zeolite,[18] and ZnO[19] as new catalysts; (*c*) application of acylals as acylating agents, giving different products depending on the conditions and the amount of catalysts;[20] and (*d*) acylation of alkenes to make β,γ-unsaturated ketones.[16] Further information about the Friedel-Crafts acylation can be found in reviews.[4,21]

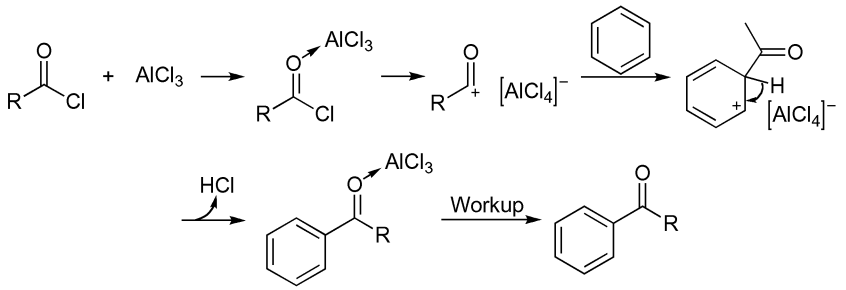
B. GENERAL REACTION SCHEME



(*X* = halogen, OC(O)R′, OR′, NHR′, OH, etc.)

C. PROPOSED MECHANISMS

Demonstrated here is the mechanism of the acylation of benzene using acyl chloride as the acylating agent and $AlCl_3$ as an acylation promoter.



D. MODIFICATION

Because of its importance in aromatic chemistry, the Friedel-Crafts acylation has been extensively modified, including the use of different acylating agents and different acylation promoters.

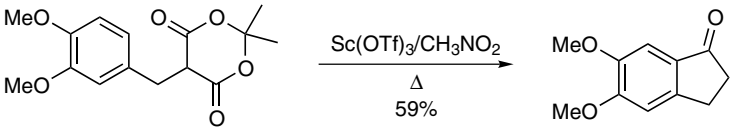
E. APPLICATIONS

This reaction has wide application in the preparation of aromatic derivatives.

F. RELATED REACTIONS

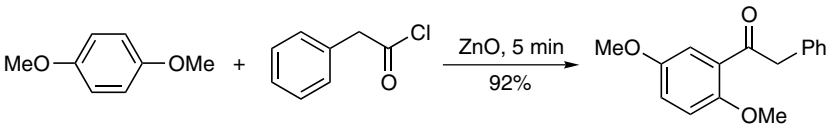
This reaction is related to the *Friedel-Crafts Alkylation, Darzens Olefin Acylation, Fries Rearrangement, Haworth Phenanthrene Synthesis*, and *Nencki Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 6a.

In a flame-dried, round bottomed flask equipped with a magnetic stir bar and a reflux condenser and under inert atmosphere were placed 200 mg 5-(3,4-dimethoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione and 0.1 eq. $Sc(OTf)_3$. Nitromethane was added in one portion by syringe, and the resulting suspension was immediately placed into an oil bath preheated to 100°C. The reaction was maintained at this temperature and monitored by TLC until complete consumption of the starting material was observed (~ 45 min). The reaction mixture was then concentrated under vacuum and directly subjected to flash chromatography, using a small quantity of CH_2Cl_2 to assist column loading, using hexane/EtOAc (6:5) as an eluent to afforded 59% 5,6-dimethoxy-1-indanone as a white solid, m.p. 116–118°C after crystallization from CH_2Cl_2.



Reference 18.

1,4-Dimethoxybenzene (1 mmol) was added to a mixture of 0.04 g ZnO powder (0.5 mmol) and 1 mmol phenyl acetyl chloride at room temperature and stirred with a magnetic stirrer. Color (usually pink) developed immediately and darkened with the progress

of the reaction. The reaction mixture was kept at room temperature with occasional stirring for 5 min as required to complete the reaction (monitored by TLC). The solid mass was then eluted with 20 mL dichloromethane, and the dichloromethane extract was then washed with an aqueous solution of sodium bicarbonate and dried over anhydrous sodium sulfate. Evaporation of solvent furnished practically pure (phenyl)-acetyl-(2,5-dimethoxy)-benzene in 92% of yield.

Other references related to the Friedel-Crafts acylation are cited in the literature.[22]

H. REFERENCES

1. (a) Friedel, C. and Crafts, J. M., *Compt. Rend.,* **1877***, 84*, 1392. (b) Friedel, C. and Crafts, J. M., *Compt. Rend.,* **1877***, 84*, 1450.
2. (a) Khodaei, M. M.; Alizadeh, A. and Nazari, E., *Tetrahedron Lett*., **2007**, *48*, 4199. (b) Zheng, Y.; Li, Y. G.; Pan, L. and Li, Y. S., *Polymer*, **2007**, *48*, 2496. (c) Yadav, G. D. and Pimparkar, K. P., *J. Mol. Catal. A: Chem.,* **2007**, *264*, 179. (d) Begum, S.; Zehra, S. Q. and Siddiqui, B. S., *Synth. Commun.,* **2006**, *36*, 3203. (e) Yadav, G. D. and George, G., *Microporous & Mesoporous Mater.,* **2006**, *96*, 36. (f) Cho, S. Y.; Kang, S. Y.; Ha, J. D.; Ahn, J. H.; Yon, G. H. and Choi, J.-K., *Bull. Korean Chem. Soc.,* **2006**, *27*, 1477. (g) Reim, S.; Lau, M. and Langer, P., *Tetrahedron Lett*., **2006**, *47*, 6903. (h) Ivanov, I.; Nikolova, S. and Statkova-Abeghe, S., *Synth. Commun.,* **2006**, *36*, 1405. (i) Gopalakrishnan, M.; Sureshkumar, P.; Kanagarajan, V. and Thanusu, J., *Catal. Commun.,* **2005**, *6*, 753. (j) Fillion, E. and Fishlock, D., *J. Am. Chem. Soc.,* **2005**, *127*, 13144. (k) Xiao, Y. and Malhotra, S. V., *J. Organomet. Chem.,* **2005**, *690*, 3609. (l) Yi, W.-B. and Cai, C., *J. Fluor. Chem.,* **2005**, *126*, 1191.
3. Schüler, G.; Wasternack, C. and Boland, W., *Tetrahedron,* **1999**, *55*, 3897.
4. Gore, P. H., *Chem. Rev.,* **1955**, *55*, 229.
5. (a) Speer, R. J. and Jeakes, J. K., *J. Am. Chem. Soc.,* **1952**, *74*, 2443. (b) Cullinane, M.; Chards, J. and Leyshond, M., *J. Chem. Soc.,* **1952**, 376. (c) Illari, G., *Gazz. Chim. Ital.,* **1948**, *78*, 687. (d) Newton, A. P. and Groggins, P. H., *Ind. Eng. Chem.,* **1935**, *27*,1397. (e) Nencki, M., *J. Prakt. Chem.,* **1882**, *25*, 273.
6. (a) Fillion, E.; Fishlock, D.; Wilsily, A. and Goll, J. M., *J. Org. Chem.,* **2005**, *70*, 1316. (b) Fillion, E. and Fishlock, D., *Org. Lett.,* **2003**, *5*, 4653.
7. Anderson, K. W. and Tepe, J. J., *Org. Lett.,* **2002**, *4*, 459.
8. Davlieva, M. G.; Linderman, S. V.; Neretin, I. S. and Kochi, J. K., *J. Org. Chem.,* **2005**, *70*, 4013.
9. (a) Prakash, G. K. S.; Mathew, T.; Mandal, M.; Farnia, M. and Olah, G. A., *ARKIVOC*, **2004**, 103. (b) Gmouh, S.; Yang, H. L. and Vaultier, M., *Org. Lett.,* **2003**, *5*, 2219.
10. (a) Agranat, I.; Bentor, Y. and Shih, Y.-S., *J. Am. Chem. Soc.,* **1977**, *99*, 7068. (b) Agranat, I.; Shih, Y.-S. and Bentor, Y., *J. Am. Chem. Soc.,* **1974**, *96*, 1259.
11. (a) Yous, S.; Poupaert, J. H.; Lesieur, I.; Depreux, P. and Lesieur, D., *J. Org. Chem.,* **1994**, *59*, 1574. (b) Litt, M. H.; Summers, J. W. and Shimko, T. M., *J. Org. Chem.,* **1972**, *37*, 1045.
12. (a) Adams, C. J.; Earle, M. J.; Roberts, G. and Seddon, K. R., *J. Chem. Soc., Chem. Commun.,* **1998**, 2097. (b) Boon, J. A.; Levisky, J. A.; Pflug, J. L. and Wilkes, J. S., *J. Org. Chem.,* **1986**, *51*, 480.
13. Fürstner, A.; Voigtländer, D.; Schrader, W.; Giebel, D. and Reetz, M. T., *Org. Lett.,* **2001**, *3*, 417.
14. Kozikowski, A. P. and Ames, A., *J. Am. Chem. Soc.,* **1980**, *102*, 860.
15. Bandgar, B. P. and Kasture, S. P., *J. Chin. Chem. Soc.,* **2000**, *47*, 1243.
16. Snider, B. B. and Jackson, A. C., *J. Org. Chem.,* **1982**, *47*, 5393.

17. Yamato, T.; Hideshima, C.; Prakash, G. K. S. and Olah, G. A., *J. Org. Chem.,* **1991**, *56*, 3955.
18. Chiche, B.; Finiels, A.; Gauthier, C.; Geneste, P.; Graille, J. and Pioch, D., *J. Org. Chem.,* **1986**, *51*, 2128.
19. Sarvari, M. H. and Sharghi, H., *J. Org. Chem.,* **2004**, *69*, 6953.
20. Hurd, C. D. and Iwashige, T., *J. Org. Chem.,* **1959**, *24*, 1321.
21. (a) Yeh, M.-C. P.; Chang, S.-C. and Chang, C.-J., *J. Organometal. Chem.,* **2000**, *599*, 128. (b) Kao, C.-L.; Yen, S. Y. and Chern, J.-W., *Tetrahedron Lett.,* **2000**, *41*, 2207. (c) Bierman, U. and Metzger, J. O., *Angew. Chem. Int. Ed.,* **1999**, *38*, 3675. (d) Knölker, H.-J., *Angew. Chem. Int. Ed.,* **1999**, *38*, 2583. (e) Heaney, H., "Fries Reactions" in *Comprehensive Organic Synthesis,* ed. Trost, B. M. and Fleming, I., Pergamon Press, Oxford, **1991**, *2,* p. 733–752. (f) Olah, G. A., *Friedel-Crafts Chemistry,* John Wiley & Sons, New York, **1973**. (g) Groves, J. K., *Chem. Soc. Rev.,* **1972**, *1*, 73. (h) Olah, G. A., ed., *Friedel-Crafts and Related Reactions,* Interscience, New York, vols. 1–4, **1963–1965**. (i) Price, C. C., *Org. React.,* **1946***, 3*, 1. (j) Johnson, W. S., *Org. React.,* **1944**, *2*, 114.
22. (a) Firouzabadi, H.; Iranpoor, N. and Nowrouzi, F., *Tetrahedron*, **2004**, *60*, 10843. (b) Bernardo, P. H. and Chai, C. L. L., *J. Org. Chem.,* **2003**, *68*, 8906. (c) Ottoni, O.; Neder, A. de V. F.; Dias, A. K. B.; Cruz, R. P. A. and Aquino, L. B., *Org. Lett.,* **2001**, *3*, 1005. (d) Zhang, J. T.; Kirchhoff, E. W.; Zembower, D. E.; Jimenez, N.; Sen, P.; Xu, Z.-Q. and Flavin, M. T., *Org. Proc. Res. Dev.,* **2000**, *4*, 577. (e) Lee, B. S.; Lee, S. Y. and Oh, D. Y., *J. Org. Chem.,* **2000**, *65,* 4175. (f) Smyth, T. P. and Corby, B. W., *J. Org. Chem.,* **1998**, *63,* 8946. (g) Lewis, M. L.; de Meijere, A., *Synlett,* **1997**, 261. (h) Chen, M. F.; Guzei, I.; Rheingold, A. L. and Gibson, H. W., *Macromolecules,* **1997**, *30,* 2516. (i) Song, Z. Z.; Ho, M. S. and Wong, H. N. C., *J. Org. Chem.,* **1994**, *59*, 3917. (j) Cunningham, A. F., *J. Am. Chem. Soc.,* **1991**, *113*, 4864. (k) Schuda, P. F. and Price, W. A., *J. Org. Chem.,* **1987**, *52*, 1972. (l) Uggeri, F.; Giordano, C.; Brambilla, A. and Annunziata, R., *J. Org. Chem.,* **1986**, *51*, 97. (m) Santini, C. C. and Mathey, F., *J. Org. Chem.,* **1985**, *50*, 467. (n) Ketcha, D. M. and Gribble, G. W., *J. Org. Chem.,* **1985**, *50*, 5451. (o) Hyatt, J. A. and Raynolds, P. W., *J. Org. Chem.,* **1984**, *49*, 384. (p) DeHaan, F. P.; Covey, W. D.; Delker, G. L.; Baker, N. J.; Feigon, J. F.; Ono, D.; Miller, K. D. and Stelter, E. D., *J. Org. Chem.,* **1984**, *49*, 3959. (q) Nordlander, J. E.; Payne, M. J.; Njoroge, F. G.; Balk, M. A.; Laikos, G. D. and Vishwanath, V. M., *J. Org. Chem.,* **1984**, *49*, 4107. (r) Zhao, Y.-F.; Xi, S.-K.; Song, A.-T. and Ji, G.-J., *J. Org. Chem.,* **1984**, *49*, 4549. (s) Asscher, Y. and Agranat, I., *J. Org. Chem.,* **1980**, *45*, 3364. (t) Dehaan, F. P.; Covey, W. D.; Delker, G. L.; Baker, N. J.; Feigon, J. F.; Miller, K. D. and Stelter, E. D., *J. Am. Chem. Soc.,* **1979**, *101*, 1136. (u) Seyferth, D.; Williams, G. H.; Wehman, A. T. and Nestle, M. O., *J. Am. Chem. Soc.,* **1975**, *97*, 2107. (v) Seyferth, D.; Nestle, M. O. and Wehman, A. T., *J. Am. Chem. Soc.,* **1975**, *97*, 7417. (w) Elling, G. R.; Hahn, R. C. and Schwab, G., *J. Am. Chem. Soc.,* **1973**, *95*, 5659. (x) Tolentino, L. and Kagan, J., *J. Org. Chem.,* **1972**, *37*, 1444. (y) Winstead, J. A.; McGuire, R. R.; Cochoy, R. E.; Brown, A. D. and Gauthier, G. J., *J. Org. Chem.,* **1972**, *37*, 2055. (z) Olah, G. A. and Kobayashi, S., *J. Am. Chem. Soc.,* **1971**, *93*, 6964. (aa) Collman, J. P.; Marshall, R. L.; Young, W. L. and Sears, C. T., *J. Org. Chem.,* **1963**, *28*, 1449. (bb) Mabille, P. and Buu-Hoï, N. P., *J. Org. Chem.,* **1960**, *25*, 1092. (cc) Buu-Hoï, N. P. and Petit, L., *J. Org. Chem.,* **1959**, *24*, 39. (dd) Rips, R. and Buu-Hoï, N. P., *J. Org. Chem.,* **1959**, *24*, 551. (ee) Olah, G. A. and Kuhn, S. J., *J. Am. Chem. Soc.,* **1958**, *80*, 6541. (ff) Buu-Hoï, N. P. and Riché, J., *J. Org. Chem.,* **1957**, *22*, 668. (gg) Mustafa, A. and Ali, M. I., *J. Am. Chem. Soc.,* **1955**, *77*, 4593. (hh) Benkeser, R. A. and Krysiak, H. R., *J. Am. Chem. Soc.,* **1954**, *76*, 599. (ii) Szmant, H. H. and Skendrovich, S., *J. Am. Chem. Soc.,* **1954**, *76*, 2282. (jj) Man, E. H. and Hauser, C. R., *J. Org. Chem.,* **1952**, *17*, 397. (kk) Leonard, N. J. and Hyson, A. M., *J. Org. Chem.,* **1948**, *13*, 164.

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Friedel-Crafts Alkylation

A. GENERAL DESCRIPTION OF THE REACTION

Although this reaction was first discovered by Wurtz,[1] it is generally known as the Friedel-Craft alkylation[2] after Friedel and Crafts reported their work in 1877.[3] It is a special class of electrophilic aromatic substitution in which the electrophile is a carbocation.[4] Similar to the *Friedel-Crafts Acylation*, the electron-donating groups facilitate the alkylation, whereas the electron-withdrawing groups impede the alkylation. In addition, an acidic catalyst (either a Brønsted acid or a Lewis acid) is needed to enhance the electrophilicity of the alkylating agent. Often this alkylation is carried out between the aromatics and alkyl halides in the presence of a Lewis acid.[5] The Lewis acid generally polarizes the alkyl halide, making the hydrocarbon part to bear a more positive charge and become more electrophilic, which then saturates its electron deficiency from electron-rich aromatics by forming a π-complex that further transforms into a σ-complex while sacrificing the aromaticity. Extrusion of proton in such σ-complex will regain the aromaticity.

Besides the most common alkylating agents of alkyl halides, other types of organic compounds—including alcohols,[6] aldehydes,[6b,7] esters,[8] ethers,[6b] imines,[9] hydrozones,[10] olefins[11]—also react with the aromatics to give the alkylated products. Among these alkylating agents, the esters have shown their advantage over alkyl halides and have been extensively explored. So far, the esters used in alkylation include alkyl sulfates, sulfites, phosphates, orthosilicates, carbonates, borates, chloroformates, hypochlorites, halosulfates, chlorosulfites, arenesulfonates, perchlorate, arenesulfinates, chloro- and fluorosulfates, triflates, pentafluorobenzenesulfonates, trifluoroacetates, acetates, formates, oxalate, silicate, and carboxylate.[8] The solvents can be nitromethane, methylene chloride, carbon disulfide,

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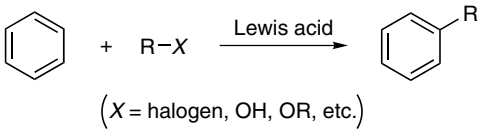
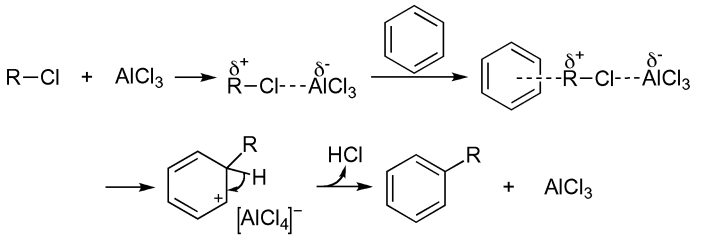
1,1,2-trichlorotrifluormethane, etc.[8a,12] The generally used Lewis acid catalysts in alkylation are arranged in the following order of decreasing Lewis acidity: $Al_2Br_6 > Al_2Cl_6 > Al_2I_6 > Ga_2Br_6 > Ga_2Cl_6 > Fe_2Cl_6 > SbCl_5 > ZrCl_4$, $SnCl_4 > BCl_3$, BF_3, $SbCl_3$.[13] However, the Friedel-Crafts alkylation is also different from the *Friedel-Crafts Acylation*, with its characteristic limitations such as disproportionation,[14] isomerization,[6d,6f,15] over alkylation,[16] sensitivity to trace amounts of water,[17] and side reactions of alkylating agents. All these disadvantages can be linked to the character of carbocation in this reaction. For example, the disproportionation originates from the isomerization of a σ-complex to a more stable σ-complex during the alkylation if more than one alkyl group exist on the aromatic ring; the isomerization of an alkylated group comes from the rearrangement of a carbocation to form a more stable carbocation, as shown in the preparation of *t*-butyl aromatics from *sec*-butyl halide;[15a,15c] in addition, the alkyl group on the alkylated aromatics is normally an electron-donating group that enriches the electron density on the aromatics and facilitates further alkylations; when olefins are used as the alkylating agents, they can polymerize in the presence of a strong Lewis acid. Because of the acidic nature of this alkylation, the acid-labile aromatics are not feasible for this reaction, such as many heterocycles. Although nitrobenzene is known to be inert for the *Friedel-Crafts Acylation*, it can undergo the alkylation with ethanol in sulfuric acid;[18] similarly, many moderately inert aromatics also undergo the alkylation with ethyl, *n*-propyl, isopropyl, and *n*-butyl alcohol (except for methanol and *t*-butyl alcohol) when sulfuric acid, PPA, or 85% phosphoric acid is used as the catalyst.[6c] Even the highly electron deficient pentafluorobenzene can react with methylene chloride or chloroform.[19] Recent advances in the Friedel-Crafts alkylation include (*a*) development of new alkylating catalysts, such as zeolite,[20] cation-exchanged Montmorillonite,[21] hetereobimetallic,[6a] and rare earth metal salts;[6b] (*b*) application of new reaction media, such as supercritical CO_2;[22] (*c*) development of new alkylating agents, such as vinyl chlorosilanes,[16a,23] nitrosoamide,[5] and benzyl *N*-sulfamoylcarbamates,[24] (among which the benzyl *N*-sulfamoylcarbamates can react with aromatics even in the absence of an acidic catalyst); and (*d*) development of an unsymmetrical alkylation system using chiral catalysts to form enantiomerically pure products.[9,10,11a,11c,25] Further information about the Friedel-Crafts alkylation are provided in reviews.[26]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Demonstrated here is the mechanism for the alkylation of benzene with alkyl halide using $AlCl_3$ as the catalyst.



D. MODIFICATION

This reaction has been extensively modified by the application of different catalysts, reaction media, and alkylating agents.

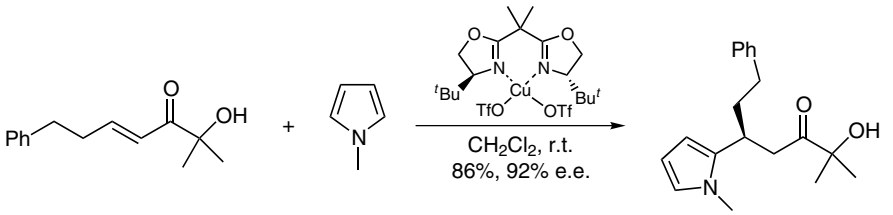
E. APPLICATIONS

This reaction has wide application in the preparation of substituted aromatics.

F. RELATED REACTIONS

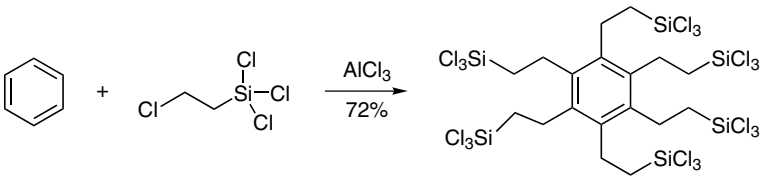
This reaction is related to the *Friedel-Crafts Acylation* and *Baddeley Isomerization*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 11a.

2,2′-Isopropylidene bis[(4*S*)-4-*tert*-butyl-2-oxazoline] (0.06 mmol) was weighed in a flame-dried flask and placed under nitrogen, followed by the addition of 18.0 mg $Cu(OTf)_2$ (0.05 mmol) by rinsing with 1.0 mL dry CH_2Cl_2 from a weighing boat. After stirred at room temperature for 3 h, 0.5 mmol hydroxy enone in 0.5 mL dry CH_2Cl_2 was cannulated into the solution followed by a rinse using 0.5 mL CH_2Cl_2; the resulting mixture was stirred for a further 10 min at room temperature. Then 109 mg *N*-methyl pyrrole (89 μL, 1 mmol) was added dropwise by syringe directly into the reaction, and the mixture was stirred at room temperature under nitrogen for 2 h. The resulting reaction mixture was diluted with 10 mL NH_4Cl and extracted with CH_2Cl_2 (3×10 mL). The CH_2Cl_2 layers were combined, dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by column chromatography on SiO_2 (hexane/EtOAc, 9:1) to afford 129 mg 2-hydroxy-2-methyl-5-(1-methyl-1H-pyrrol-2-yl)-7-phenyl-heptan-3-one as a thick yellow oil, in a yield of 86% with 92% e.e.



Reference 16a.

To a stirring suspension of 1.0 g benzene (12.8 mmol) and 1.0 g $AlCl_3$ (7.5 mmol) was added 16.7 g 2′-chloroethyl-trichlorosilane (84.4 mmol) at a pumping rate of 0.3 mL/min using a syringe pump at 70°C. A moderately exothermic reaction was observed. The reaction mixture was stirred for additional 3 h at 70°C. Dried hexane (100 mL) and 1.9 g NaCl (32.5 mmol) were added to the reaction mixture, and the mixture was then stirred at the reflux temperature of hexane for 2 h. Solid products and NaCl-$AlCl_3$ complex insoluble in hexane were filtered out, washed three times with hexane (20 mL × 3), and dissolved in dried THF. The NaCl-$AlCl_3$ complex insoluble in THF was filtered off. The filtrate was concentrated by evaporation and cooled to −30°C to afford yellowish white crystals. These crystals were powdered and then kept under vacuum conditions (150°C at 0.2 mmHg) for 24 h to give 9.7 g of a mixture of hexa-(trichlorosilylethyl) benzene and THF (∼ 10 mol %), in a yield of 72% , m.p. 260°C (dec. slowly).

Other references related to the Friedel-Crafts alkylation are cited in the literature.[27]

H. REFERENCES

1. Kingston, D. G. I.; Bursey, J. T. and Bursey, M. M., *Chem. Rev.,* **1974**, *74*, 215.
2. (a) Liu, T.-Y.; Cui, H.-L.; Chai, Q.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S. and Chen, Y.-C., *Chem. Commun.,* **2007**, 2228. (b) Prakash, G. K. S.; Linares-Palomino, P. J.; Glinton, K.; Chacko, S.; Rasul, G.; Mathew, T. and Olah, G. A., *Synlett*, **2007**, 1158. (c) Sui, Y.; Liu, L.; Zhao, J.-L.; Wang, D. and Chen, Y.-J., *Tetrahedron*, **2007**, *63*, 5173. (d) Yang, H.; Hong, Y.-T. and Kim, S., *Org. Lett.,* **2007**, *9*, 2281. (e) Singh, P. K.; Bisai, A. and Singh, V. K., *Tetrahedron Lett*., **2007**, *48*, 1127. (f) Yang, S.-M. and Fang, J.-M., *Tetrahedron*, **2007**, *63*, 1421. (g) Khalaf, A. A.; Albar, H. A. and Bahaffi, S. O., *Revue Roumaine Chim*., **2006**, *51*, 895. (h) Bonini, B. F.; Capito, E.; Comes-Franchini, M.; Fochi, M.; Ricci, A. and Zwanenburg, B., *Tetrahedron: Asymmetry,* **2006**, *17*, 3135. (i) Zhao, J.-L.; Liu, L.; Sui, Y.; Liu, Y.-L.; Wang, D. and Chen, Y.-J., *Org. Lett.,* **2006**, *8*, 6127. (j) Zhao, Z. K.; Wang, W. L.; Qiao, W. H.; Wang, G. R.; Li, Z. S. and Cheng, L. B., *Microporous & Mesoporous Mater*., **2006**, *93*, 164. (k) Kirihara, M.; Noguchi, T.; Kakuda, H.; Akimoto, T.; Shimajiri, A.; Morishita, M.; Hatano, A. and Hirai, Y., *Tetrahedron Lett*., **2006**, *47*, 3777. (l) Zhao, J.-L.; Liu, L.; Zhang, H.-B.; Wu, Y.-C.; Wang, D. and Chen, Y. J., *Tetrahedron Lett*., **2006**, *47*, 2511. (m) Li, D.-P.; Guo, Y.-C.; Ding, Y. and Xiao, W.-J., *Chem. Commun.,* **2006**, 799.
3. (a) Friedel, C. and Crafts, J. M., *Compt. Rend.,* **1877**, *84*, 1392. (b) Friedel, C. and Crafts, J. M., *Compt. Rend.,* **1877**, *84*, 1450.
4. Priddy, D., *I & EC Prod. Res. Dev.,* **1969**, *8*, 239.
5. White, E. H.; Darbeau, R. W.; Chen, Y. L.; Chen, S. and Chen, D., *J. Org. Chem.,* **1996**, *61*, 7986.
6. (a) Choudhury, J.; Podder, S. and Roy, S., *J. Am. Chem. Soc.,* **2005**, *127*, 6162. (b) Tsuchimoto, T.; Tobita, K.; Hiyama, T. and Fukuzawa, S.-I., *J. Org. Chem.,* **1997**, *62,* 6997. (c) Shen, Y.-S.; Liu,

H.-X.; Wu, M.; Du, W.-Q.; Chen, Y.-Q. and Li, N.-P., *J. Org. Chem.,* **1991**, *56*, 7160. (d) Olah, G. A.; Olah, J. A. and Ohyama, T., *J. Am. Chem. Soc.,* **1984**, *106*, 5284. (e) Khalaf, A. A. and Roberts, R. M., *J. Org. Chem.,* **1972**, *37*, 4227. (f) Brown, H. C.; Pearsall, H. W.; Eddy, L. P.; Wallace, W. J.; Grayson, M. and Nelson, K. L., *Ind. Eng. Chem.,* **1953**, *45*, 1462.

7. (a) Zhuang, W. and Jørgensen, K. A., *Chem. Commun.,* **2002**, 1336. (b) Stapp, P. R., *J. Org. Chem.,* **1974**, *39*, 2466.
8. (a) Olah, G. A. and Nishimura, J., *J. Am. Chem. Soc.,* **1974**, *96*, 2214. (b) Berman, N. and Lowy, A., *J. Am. Chem. Soc.,* **1938**, *60*, 2596. (c) Kane, H. L. and Lowy, A., *J. Am. Chem. Soc.,* **1936**, *58*, 2605.
9. Uraguchi, D.; Sorimachi, K. and Terada, M., *J. Am. Chem. Soc.,* **2004**, *126*, 11804.
10. Shirakawa, S.; Berger, R. and Leighton, J. L., *J. Am. Chem. Soc.,* **2005**, *127*, 2858.
11. (a) Palomo, C.; Oiarbide, M.; Kardak, B. G.; García, J. M. and Linden, A., *J. Am. Chem. Soc.,* **2005**, *127*, 4154. (b) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W. and Wu, J., *J. Am. Chem. Soc.,* **2003**, *125*, 10780. (c) Paras, N. A. and MacMillan, D. W. C., *J. Am. Chem. Soc.,* **2001**, *123,* 4370.
12. Olah, G. A. and Olah, J. A., *J. Am. Chem. Soc.,* **1976**, *98*, 1839.
13. Russell, G. A., *J. Am. Chem. Soc.,* **1959**, *81*, 4834.
14. (a) Taylor, S. K.; Lilley, G. L.; Lilley, K. J. and McCoy, P. A., *J. Org. Chem.,* **1981**, *46*, 2709. (b) Olah, G. A., *Aldrichimica Acta*, **1979**, *12*, 45. (c) Olah, G.; Kobayashi, S. and Tashiro, M., *J. Am. Chem. Soc.,* **1972**, *94*, 7448.
15. (a) Roberts, R. M. and Shiengthong, D., *J. Am. Chem. Soc.,* **1960**, *82*, 732. (b) Barclay, L. R. C. and Hilchie, J. W., *J. Org. Chem.,* **1957**, *22*, 633. (c) Hurd, C. D. and Oliver, G. L., *J. Am. Chem. Soc.,* **1954**, *76*, 50.
16. (a) Kim, K. M.; Kim, J. H.; Moon, D. H.; Lah, M. S.; Jung, I. N. and Yoo, B. R., *Organometallics,* **2005**, *24,* 226. (b) Olah, G. and Olah, J. A., *J. Org. Chem.,* **1967**, *32*, 1612.
17. DeHaan, F. P.; Chan, W. H.; Chang, J.; Cheng, T. B.; Chiriboga, D. A.; Irving, M. M.; Kaufman, C. R.; Kim, G. Y.; Kumar, A.; Na, J.; Nguyen, T. T.; Nguyen, D. T.; Patel, B. R.; Sarin, N. P. and Tidwell, J. H., *J. Am. Chem. Soc.,* **1990**, *112*, 356.
18. Shen, Y. S.; Liu, H. X. and Chen, Y. Q., *J. Org. Chem.,* **1990**, *55*, 3961.
19. Beckert, W. F. and Lowe, J. U., *J. Org. Chem.*, **1967**, *32*, 582.
20. Espeel, P. H.; Janssens, B. and Jacobs, P. A., *J. Org. Chem.,* **1993**, *58*, 7688.
21. Tateiwa, J.-I.; Horiuchi, H.; Hashimoto, K.; Yamauchi, T. and Uemura, S., *J. Org. Chem.,* **1994**, *59*, 5901.
22. Komoto, I. and Kobayashi, S., *Org. Lett.,* **2002**, *4*, 1115.
23. (a) Han, J. S.; Lim, W. C.; Yoo, B. R.; Jin, J.-I. and Jung, I. N., *Organometallics,* **2002**, *21*, 3803. (b) Ahn, S. Y.; Song, Y.-S.; Yoo, B. R. and Jung, I. N., *Organometallics,* **2000**, *19,* 2777. (c) Lee, B. W.; Yoo, B. R.; Kim, S.-I. and Jung, I. N., *Organometallics,* **1994**, *13*, 1312.
24. Sefkow, M. and Buchs, J., *Org. Lett.,* **2003**, *5*, 193.
25. (a) Lyle, M. P. A.; Draper, N. D. and Wilson, P. D., *Org. Lett.,* **2005**, *7*, 901. (b) Bandini, M.; Umani-Ronchi, A. and Melloni, A. *Angew. Chem. Int. Ed.,* **2004**, *43*, 550. (c) Jørgensen, K. A., *Synthesis,* **2003**, 1117. (d) Austin, J. F. and MacMillan, D. W. C., *J. Am. Chem. Soc.,* **2002**, *124*, 1172. (e) Paras, N. A. and MacMillan, D. W. C., *J. Am. Chem. Soc.,* **2002**, *124*, 7894.
26. (a) Olah, G. A., *Friedel-Crafts and Related Reactions*, Interscience Publishers, **1964**, *2*. (b) Gore, P., *Chem. Rev.,* **1955**, *55*, 229. (c) Price, C. C., *Org. React.,* **1946**, *3*, 1. (d) Calloway, N. O., *Chem. Rev.,* **1935**, *17*, 327.
27. (a) Yadav, G. D. and Sengupta, S., *Org. Proc. Res. Dev.,* **2002**, *6*, 256. (b) Shorthill, B. J. and Glass, T. E., *Org. Lett.,* **2001**, *3*, 577. (c) Gotta, M. F. and Mayr, H., *J. Org. Chem.,* **1998**, *63,* 9769. (d) Tsuchimoto, T.; Tobita, K.; Hiyama, T. and Fukuzawa, S., *Synlett,* **1996**, 557. (e) Olah, G. A.;

Lee, C. S. and Prakash, G. K. S., *J. Org. Chem.,* **1994**, *59*, 2590. (f) Olah, G. A.; Lee, C. S.; Prakash, G. K. S.; Moriarty, R. M. and Rao, M. S. C., *J. Am. Chem. Soc.,* **1993**, *115*, 10728. (g) Piccolo, O.; Azzena, U.; Melloni, G.; Delogu, G. and Valoti, E., *J. Org. Chem.,* **1991**, *56*, 183. (h) Lin, S.-K. and Trapp, C., *J. Org. Chem.,* **1988**, *53*, 698. (i) Bonnet-Delpon, D.; Charpentier-Morize, M. and Jacquot, R., *J. Org. Chem.,* **1988**, *53*, 759. (j) Allen, C. W.; Bedell, S.; Pennington, W. T. and Cordes, A. W., *Inorg. Chem.,* **1985**, *24*, 1653. (k) Mayr, H. and Striepe, W., *J. Org. Chem.,* **1983**, *48*, 1159. (l) Jung, M. E.; Mossman, A. B. and Lyster, M. A., *J. Org. Chem.,* **1978**, *43*, 3698. (m) Roberts, R. M. and Abdel-Baset, M. B., *J. Org. Chem.,* **1976**, *41*, 1698. (n) Olah, G. A.; Nishimura, J. and Yamada, Y., *J. Org. Chem.,* **1974**, *39*, 2430. (o) Olah, G. A.; Kobayashi, S. and Nishimura, J., *J. Am. Chem. Soc.,* **1973**, *95*, 564. (p) Olah, G. A.; DeMember, J. R.; Schlosberg, R. H. and Halpern, Y., *J. Am. Chem. Soc.,* **1972**, *94*, 156. (q) Schwartz, L. H.; Landis, J.; Lazarus, S. B. and Stoldt, S. H., *J. Org. Chem.,* **1972**, *37*, 1979. (r) Olah, G. A. and DeMember, J. R., *J. Am. Chem. Soc.,* **1970**, *92*, 2562. (s) Brauman, J. I. and Pandell, A. J., *J. Am. Chem. Soc.,* **1967**, *89*, 5421. (t) Beckert, W. F. and Lowe, J. U., *J. Org. Chem.,* **1967**, *32*, 1212. (u) Sharman, S. H., *J. Am. Chem. Soc.,* **1962**, *84*, 2945. (v) Barclay, L. R. C. and Betts, E. E., *J. Am. Chem. Soc.,* **1955**, *77*, 5735. (w) Brown, H. C.; Pearsall, H. and Eddy, L. P., *J. Am. Chem. Soc.,* **1950**, *72*, 5347. (x) Gilman, H. and Meals, R. N., *J. Org. Chem.,* **1943**, *8*, 126.

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Friedländer Condensation

(Friedländer Synthesis, Friedländer Reaction, Friedländer Quinoline Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Friedländer in 1882.[1] It is a preparation of nitrogen-containing heterocycle (mostly, 2,3-disubstituted quinolines) from an aromatic *ortho*-aminoaldehyde (or ketone) and an aldehyde (or ketone) bearing an active α-methylene functionality. This reaction is considered to be one of the most successful methods for preparing quinoline derivatives,[2] often in high yield.[2c,3] Therefore, it is generally known as the Friedländer condensation,[4] Friedländer synthesis,[2b,4k,5] or Friedländer reaction.[2a,2c,4i,4o,6] In addition, over the past 120 years, this reaction has been referred to as the Friedländer annulation,[2a,5m,7] Friedländer heteroannulation,[5m,8] Friedländer methodology,[4n,9] and Friedländer quinoline synthesis.[2a,5m,5t,10]

This reaction often occurs in one pot[4c] and involves two distinct steps:[6o] (*a*) condensation between the amino group and the carbonyl group of the aldehyde or ketone to form anil, and (*b*) an irreversible intramolecular condensation between the active methylene or α-methyl group and the carbonyl group attached to the aromatic ring. Therefore, it is assumed that aldol type condensation is involved at a certain stage of the overall condensation.[2a,2d] Consequently, both acid and base can catalyze this reaction; HCl, H_2SO_4, *p*-TsOH, and PPA were widely applied as acid catalysts,[2a,4l,4o,5m] and NaOH and NaOEt were employed as base catalysts.[2a,4m] It has been suggested that an acid catalyst is better than a base catalyst for this condensation.[2d] In addition, this reaction is usually carried out in a polar solvent, such as CH_3CN, THF, DMF, and DMSO;[5m] otherwise, the reaction

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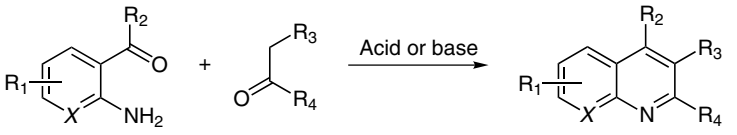
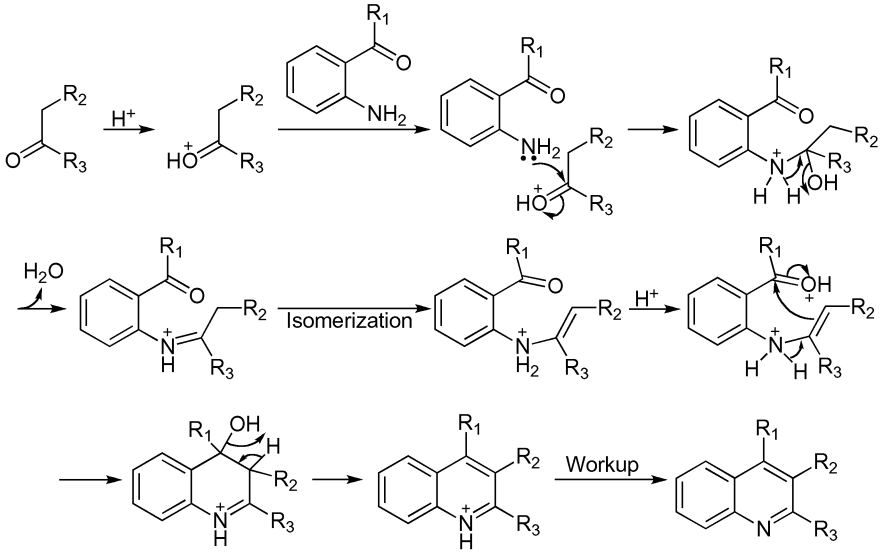
will occur in drastic conditions (e.g., 150–220°C) in the absence of a catalyst and solvent.[2d,5m] Although the Friedländer condensation indeed has some limitations when unsymmetrical ketones participate in the condensation with aromatic *o*-aminoaldehyde or ketones,[2a,2c,2d,5m] it has been extended to occur under various conditions, including the employment of microwaves,[11] gold(III) compounds,[12] NaF (in solid state),[4e] $FeCl_3 \cdot 6H_2O$ in ionic liquids,[6k] $FeCl_3$,[5i] $Mg(ClO_4)_2$,[5i] $SnCl_2 \cdot 2H_2O$,[5k] sulfamic acid,[10b] Lewis acidic ionic liquid,[5l] and pyrrolidine[2a] as promoters or catalysts. Other modifications involve traceless solid phase synthesis[5n] and preparation of polymers containing quinoline moieties.[3,4j,10d] The application of pyrrolidine in particular provides a mild, wide functionality tolerated reaction that occurs even for the unactivated methyl ketone.[2a] So far, this reaction has been used in the synthesis of quinolines, 1,8-naphthyridines,[2a,4c,4i,13] huprines,[6m] and chromeno[2,3-b]pyridines derivatives.[2a]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Demonstrated here is the mechanism for an acid-catalyzed Friedländer condensation between an aromatic *o*-aminoketone and a ketone.



D. MODIFICATION

This reaction has been extensively modified to occur under various conditions as described in Section A.

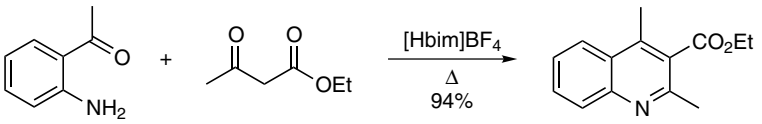
E. APPLICATIONS

This reaction has been used in the preparation of quinolines, naphthyridines, huprines, and other polycyclic heterocycle derivatives.

F. RELATED REACTIONS

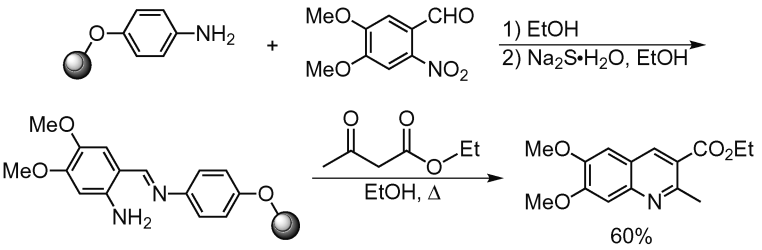
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 5m.

A mixture of 1 mmol *o*-amino-acetophenone, 1 mmol ethyl acetoacetate, and 1 mmol 1-butylimidazolium tetrafluoroborate [Hbim]BF_4 was heated at 100°C with good stirring for 3 h. The completion of reaction was monitored by TLC (EtOAc/petroleum ether, 1:4). After completion of the reaction, the reaction mixture was diluted with 25 mL water. The ethyl 2,4-dimethylquinoline-3-carboxylate was extracted with EtOAc (2 × 10 mL) and dried over Na_2SO_4. After removal of solvent, the crude product was purified by column chromatography (EtOAc/petroleum ether, 1:4), to afford 94% ethyl 2,4-dimethylquinoline-3-carboxylate as oil. The aqueous layer consisting of the ionic liquid was distilled (80°C at 10 mmHg) for 2 h to remove water and recycle 98% of the ionic liquid [Hbim]BF_4.



Reference 5n.

TentaGel resin containing aniline residue (0.25 mmol/g, 1 g, 0.25 mmol) and 211 mg 3,4-dimethoxy-6-nitrobenzaldehyde (1 mmol) were weighed into a 16 × 115 mm test tube. After adding 20 mL ethanol, the test tube was equipped with an agitation magnet, topped with a Teflon cap, and fitted with the parallel reflux bar (First Mate). The resulting mixture was stirred at reflux for 3 h. After being cooled to room temperature, the beads were filtered, successively washed with ethanol (2 × 30 mL) and CH_2Cl_2 (2 × 30 mL), and dried at room temperature under vacuum overnight to afford 1.050 g of resin containing nitrobenzene.

The nitrobenzene-containing resin (0.25 mmol/g, 1 g, 0.25 mmol) and 240 mg $Na_2S{\cdot}H_2O$ (2.5 mmol) were weighed into a 16 × 115 mm test tube. After the addition of 15 mL ethanol, the reaction vessel was equipped with an agitation magnet, topped with a Teflon cap, and fitted with the parallel reflux bar (First Mate). The resulting mixture was stirred at reflux for 20 min. After the reaction vessel was cooled to 0°C for 4 h, the beads were filtered; successively washed with ethanol (2 × 30 mL), water (2 × 40 mL), ethanol (2 × 30 mL), and CH_2Cl_2 (2 × 30 mL); and dried at room temperature under vacuum overnight to afford 1.00 g resin-containing aniline.

The reduced resin (300 mg, 0.25 mmol/g, 0.075 mmol) was placed in a 5-mL Teflon vessel (Quest 210), followed by 1.1 eq. ethyl acetoacetate and 5 mL ethanol. The mixture was heated at 75°C under stirring for 12 h. The resin was filtrated and washed with ethanol (2 × 5 mL), and the combined ethanol phases were concentrated. Column chromatography (EtOAc/cyclohexane, 1:5) and recrystallization from EtOAc afforded 60% ethyl 6,7-dimethoxy-2-methyl-3-quinolinecarboxylate as a beige solid.

Regeneration of Original Resin. The collected resin (3 g) was placed into a 10-mL Teflon reaction vessel on the Quest 210. After adding 3 mL 2 M HCl and 3 mL 1:1 water/THF mixture, the resulting suspension was stirred for 12 h at room temperature. The reaction vessel was drained using nitrogen pressure and subsequently washed in the following order: ethanol, water, 2 M solution of triethylamine in ethanol, water, ethanol, and dichloromethane. The resulting resin was dried under vacuum for 12 h at 40°C before the next use.

Other references related to the Friedländer condensation are cited in the literature.[14]

H. REFERENCES

1. Friedländer, P., *Ber.,* **1882**, *15*, 2572.
2. (a) Dormer, P. G.; Eng, K. K.; Farr, R. N.; Humphrey, G. R.; McWilliams, J. C.; Reider, P. J.; Sager, J. W. and Volante, R. P., *J. Org. Chem.,* **2003**, *68*, 467. (b) Chackal, S.; Houssin, R. and Hénichart, J.-P., *J. Org. Chem.,* **2002**, *67,* 3502. (c) Hsiao, Y.; Rivera, N. R.; Yasuda, N.; Hughes, D. L. and Reider, P. J., *Org. Lett.,* **2001**, *3*, 1101. (d) Fehnel, E., *J. Org. Chem.,* **1966**, *31*, 2899.
3. Norris, S. O. and Stille, J. K., *Macromolecules,* **1976**, *9*, 496.
4. (a) Jachak, M. N.; Avhale, A. B.; Tantak, C. D.; Toche, R. B.; Reidlinger, C. and Stadlbauer, W., *J. Heterocycl. Chem.,* **2005**, *42*, 1311. (b) Yang, D.-Q.; Lu, F. and Guo, W., *Youji Huaxue*, **2004**, *24*, 366. (c) Manley, P. J. and Bilodeau, M. T., *Org. Lett.,* **2004**, *6*, 2433. (d) Yang, D.-Q.; Lu, F.; Li, W.-H.; Jiang, Q.-J. and Guo, W., *Youji Huaxue*, **2004**, *24*, 1465. (e) Mogilaiah, K. and Reddy, C. S., *Synth. Commun.,* **2003**, *33*, 3131. (f) Hu, Y.-Z.; Zhang, G. and Thummel, R. P., *Org. Lett.,* **2003**, *5*, 2251. (g) Mogilaiah, K. and Sudhakar, G. R., *Indian J. Chem., Sect. B,* **2003**, *42B*, 1170. (h) Mogilaiah, K. and Reddy, N. V., *Indian J. Chem., Sect. B,* **2002**, *41B*, 215. (i) Mamo, A.; Nicoletti, S. and Tat, N. C., *Molecules,* **2002**, *7*, 618. (j) Zhan, X. W.; Liu, Y. Q.; Wu, X.; Wang,

S. and Zhu, D. B., *Macromolecules,* **2002**, *35,* 2529. (k) Gladiali, S.; Chelucci, G.; Mudadu, M. S.; Gastaut, M.-A. and Thummel, R. P., *J. Org. Chem.,* **2001**, *66,* 400. (l) Sugimori, M.; Ejima, A.; Ohsuki, S.; Uoto, K.; Mitsui, I.; kawato, Y.; Hirota, Y.; Sato, K. and Terasawa, H., *J. Med. Chem.,* **1998,** *41,* 2308. (m) Boger, D. L. and Hong, J. Y., *J. Am. Chem. Soc.,* **1998**, *120,* 1218. (n) Riesgo, E. C.; Jin, X. Q. and Thummel, R. P., *J. Org. Chem.,* **1996**, *61,* 3017. (o) Lackey, K.; Sternbach, D. D.; Croom, D. K.; Emerson, D. L.; Evans, M. G.; Leitner, P. L.; Luzzio, M. J.; McIntyre, G.; Vuong, A.; Yates, J. and Besterman, J. M., *J. Med. Chem.,* **1996**, *39,* 713. (p) Boger, D. L. and Chen, J.-H., *J. Org. Chem.,* **1995**, *60*, 7369. (q) Bell, T. W.; Cragg, P. J.; Drew, M. G. B.; Firestone, A.; Kwok, A. D.; Liu, J.; Ludwig, R. T. and Rapoulis, A. T., *Pure & Appl. Chem.,* **1993**, *65*, 361. (r) Fehnel, E. A. and Cohn, D. E., *J. Org. Chem.,* **1966**, *31*, 3852.

5. (a) Das, B.; Damodar, K.; Chowdhury, N. and Kumar, R. A., *J. Mol. Catal. A: Chem.,* **2007**, *274*, 148. (b) Das, B.; Damodar, K.; Chowdhury, N. and Suneel, K., *Chem. Lett.,* **2007**, *36*, 796. (c) Zhang, L. and Wu, J., *Adv. Synth. Catal.,* **2007**, *349*, 1047. (d) Ryabukhin, S. V.; Volochnyuk, D. M.; Plaskon, A. S.; Naumchik, V. S. and Tolmachev, A. A., *Synthesis*, **2007**, 1214. (e) Mogilaiah, K. and Sakram, B., *Indian J. Chem., Sect. B,* **2006**, *45B*, 2749. (f) Varala, R.; Enugala, R. and Adapa, S. R., *Synthesis*, **2006**, 3825. (g) Mogilaiah, K. and Rani, J. U., *Indian J. Chem., Sect. B,* **2006**, *45B*, 1051. (h) Mogilaiah, K.; Prashanthi, M. and Kavitha, S., *Indian J. Chem., Sect. B,* **2006**, *45B*, 302. (i) Wu, J.; Zhang, L. and Diao, T.-N., *Synlett,* **2005**, 2653. (j) Na, J. E.; Lee, K. Y.; Park, D. Y. and Kim, J. N., *Bull. Korean Chem. Soc.,* **2005**, *26*, 323. (k) Arumugam, P.; Karthikeyan, G.; Atchudan, R.; Muralidharan, D. and Perumal, P. T., *Chem. Lett.,* **2005**, *34*, 314. (l) Karthikeyan, G. and Perumal, P. T., *J. Heterocycl. Chem.,* **2004**, *41*, 1039. (m) Palimkar, S. S.; Siddiqui, S. A.; Daniel, T.; Lahoti, R. J. and Srinivasan, K. V., *J. Org. Chem.,* **2003**, *68*, 9371. (n) Patteux, C.; Levacher, V. and Dupas, G., *Org. Lett.,* **2003**, *5*, 3061. (o) Strekowski, L.; Czarny, A. and Lee, H., *J. Fluor. Chem.,* **2000**, *104*, 281. (p) Bu, X. Y. and Deady, L. W., *Synth. Commun.,* **1999**, *29*, 4223. (q) Ubeda, J. I.; Villacampa, M. and Avendano, C., *Synthesis*, **1998**, 1176. (r) Ubeda, J. I.; Villacampa, M. and Avendano, C., *Synlett*, **1997**, 285. (s) Lindstrom, S., *Acta Chem. Scand.,* **1995**, *49*, 361. (t) Cheng, C. C. and Yan S. J., "The Friedlander Synthesis of Quinolines" in *Organic Reactions*, ed. Dauben, W. G., John Wiley & Sons, Inc., New York, **1982**, *28*, pp. 37–201. (u) Fehnel, E. A., *J. Heterocycl. Chem.,* **1967**, *4*, 565.
6. (a) Carreiras, M. C.; Eleuterio, A.; Dias, C.; Brito, M. A.; Brites, D.; Marco-Contelles, J. and Gomez-Sanchez, E., *Heterocycles*, **2007**, *71*, 2249. (b) Li, J. R.; Zhang, L. J.; Chen, J. N.; Yang, X. Q.; Wang, L. J.; Zhao, X. F. and Qiu, J. X., *Chinese Chem. Lett.,* **2007**, *18*, 636. (c) Yang, D. Q.; Jiang, K. L.; Li, J. N. and Xu, F., *Tetrahedron*, **2007**, *63*, 7654. (d) Bodrin, G. V.; Lemport, P. S.; Matveev, S. V.; Petrovskii, P. V. and Nifant'ev, E. E., *Mendeleev Commun*., **2007**, *17*, 25. (e) Xu, X.; Yang, D. Q.; Jiang, K. L. and Guo, W., *Chinese Chem. Lett.,* **2006**, *17*, 187. (f) Leon, R.; Garcia, A. G. and Marco-Contelles, J., *J. Chem. Res.,* **2006**, 536. (g) Zhichkin, P.; Cillo Beer, C. M.; Rennells, W. M. and Fairfax, D. J., *Synlett*, **2006**, 379. (h) Rahman, A. F. M. M.; Kwon, Y. J. and Jahng, Y., *Heterocycles*, **2005**, *65*, 2777. (i) Zhong, W.-T.; Yang, D.-Q.; Guo, W. and Zhang, C.-L., *Huaxue Shiji*, **2005**, *27*, 415. (j) Desbois, N.; Chezal, J.-M.; Fauvelle, F.; Debouzy, J.-C.; Lartigue, C.; Gueiffier, A.; Blache, Y.; Moreau, E.; Madelmont, J.-C.; Chavignon, O. and Teulade, J.-C., *Heterocycles*, **2005**, *65*, 1121. (k) Wang, J. J.; Fan, X. S.; Zhang, X. Y. and Han, L. J., *Can. J. Chem.,* **2004**, *82*, 1192. (l) Lu, F.; Yang, D.-Q.; Wang, Z.-Y. and Jiang, Q.-J., *Hecheng Huaxue*, **2003**, *11*, 472. (m) Camps, P.; Gomez, E.; Munoz-Torrero, D. and Arno, M., *Tetrahedron: Asymmetry,* **2001**, *12*, 2909. (n) Martinez, A. G. and Marco, L. J., *Bioorg. Med. Chem. Lett*., **1997**, *7*, 3165. (o) Fehnel, E. A.; Deyrup, J. A. and Davidson, M. B., *J. Org. Chem.,* **1958**, *23*, 1996. (p) Braunholtz, J. T. and Mann, F. G., *J. Chem. Soc.,* **1958**, 3368.
7. (a) Selvam, N. P.; Saravanan, C.; Muralidharan, D. and Perumal, P. T., *J. Heterocycl. Chem.,* **2006**, *43*, 1379. (b) Wu, J.; Xia, H.-G. and Gao, K., *Org. Biomol. Chem.,* **2006**, *4*, 126.
8. Chandratre, S. J. and Filmwala, Z. A., *J. Dispersion Sci. Tech.,* **2007**, *28*, 279.
9. Hu, Y.-Z.; Xiang, Q. and Thummel, R. P., *Inorg. Chem.,* **2002**, *41*, 3423.

10. (a) Zolfigol, M. A.; Salehi, P.; Ghaderi, A. and Shiri, M., *Catal. Commun.,* **2007**, *8*, 1214. (b) Yadav, J. S.; Rao, P. P.; Sreenu, D.; Rao, R. S.; Kumar, V. N.; Nagaiah, K. and Prasad, A. R., *Tetrahedron Lett*., **2005**, *46*, 7249. (c) Muchowski, J. M. and Maddox, M. L., *Can. J. Chem.,* **2004**, *82*, 461. (d) Kim, J. L.; Kim, J. K.; Cho, H. N.; Kim, D. Y.; Kim, C. Y. and Hong, S. I., *Macromolecules,* **2000**, *33,* 5880. (e) Yamada, S. and Chibata, I., *Pharm. Bull.,* **1955**, *3*, 21.
11. Song, S. J.; Cho, S. J.; Park, D. K.; Kwan, T. W. and Jenekhe, S. A., *Tetrahedron Lett.,* **2003**, *44*, 255.
12. Arcadi, A.; Chiarini, M.; Giuseppe, S. D. and Marinelli, F., *Synlett,* **2003**, 203.
13. Litvinov, V. P.; Roman, S. V. and Dyachenko, V. D., *Russ. Chem. Rev.,* **2000**, *69*, 201.
14. (a) Sriram, D.; Yogeeswari, P.; Thirumurugan, R. and Bal, T. R., *Nat. Prod. Res.,* **2005**, *19*, 393. (b) Zhang, X. Y.; Fan, X. S.; Wang, J. J. and Li, Y. Z., *Chin. Chem. Lett.,* **2004**, *15*, 1170. (c) Deady, L. W. and Smith, C. L., *Aust. J. Chem.,* **2003**, *56*, 1219. (d) McNaughton, B. R. and Miller, B. J., *Org. Lett.,* **2003**, *5*, 4257. (e)Bernardino, A. M. R.; Khan, M. A.; Pinheiro, L. C. D. and de Azevedo, A. R., *Heterocycl. Commun.,* **2003**, *9*, 271. (f) Bell, T. W. and Liu, J., *Angew. Chem. Int. Ed. Engl.,* **1990**, *29*, 923. (g) Bell, T. W. and Liu, J., *J. Am. Chem. Soc.,* **1988**, *110*, 3673. (h) Cotts, P. M., *J. Poly. Sci. B: Poly. Phys.,* **1986**, *24*, 1493. (i) Jones, G., "Pyridines and Their Benzo Derivatives: Synthesis" in *Comprehensive Heterocyclic Chemistry II*, ed. Ramsden, C. A., Pergamon Press, Tarrytown, **1996**, *5*, chapter 5.05. (j) Jones, G., "Six-Membered Rings with One Nitrogen" in *Comprehensive Heterocyclic Chemistry*, ed. Boulton, A. J. and McKillop, A., Pergamon Press, New York, **1984**, *2*, chapter 2.08. (k) Lowe, P. A., *Comprehensive Heterocyclic Chemistry*, ed. Boulton, A. J. and McKillop, A., Pergamon Press, New York, **1984**, *2*, chapter 2.11. (l) Friedländer, P. and Gohring, C. F., *Ber.,* **1883**, *16*, 1833.

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Fries Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Fries and co-workers in 1908.[1] It is a Lewis acid–promoted rearrangement of phenolic esters to *ortho*- and/or *para*-acyl phenols and is generally known as the Fries rearrangement.[2] On the basis of extensive investigations, it is known that both Lewis acids[3] (e.g., $AlCl_3$, BCl_3, BF_3,[4] $Bi(OTf)_3$,[5] $FeCl_3$, $HgCl_2$, $SnCl_4$, $ZrCl_4$,[6] and lanthanide triflates.[7]) and Brønsted acids (TsOH, H_3PO_4, HF, etc.) work equally well for this reaction.[3] Among these catalysts, the lanthanide triflates, having high catalytic activity and low toxicity, are both air and moisture tolerant;[5] but $AlCl_3$ is the most commonly used catalyst.[3] During this rearrangement, a mixture of phenolic ester and an equivalent amount of acidic promoter is heated either neat or in a solvent suitable for *Friedel-Crafts Acylation* (e.g., nitrobenzene) to 80–180°C, the subsequent decomposition of the Lewis acid–acyl phenol complex leads to the rearranged product.[3] Depending on the structure of the starting material[8] and the reaction conditions (e.g., reaction temperature[9]), *para*- and/or *ortho*-acyl phenols and simple phenol can be obtained in various ratios. This is because the *para*- and *ortho*-acyl phenols are generated in different reaction pathways. For example, an *ortho* or 1,2-path of intramolecular rearrangement gives an *ortho*-acyl phenol, whereas a *para* or 1,4-path of intermolecular rearrangement produces a *para*-acyl phenol, and the migration of the oxocarbonium ion gives both isomers.[10] Some interesting Fries rearrangements include $Bi(OTf)_3$-promoted direct acylation of phenol,[5] the $BF_3{\cdot}OEt_2$-catalyzed rearrangement of diacyl hydroquinone to 4-ethoxy-2-acyl phenol,[4] and the rearrangement of acyl *p*-phenyl phenol to 4′-acyl 4-hydroxy biphenyl.[11] A similar rearrangement also occurs on acyloxyheteroarenes[9a] (e.g., *N*-acetylcarbazole), and this

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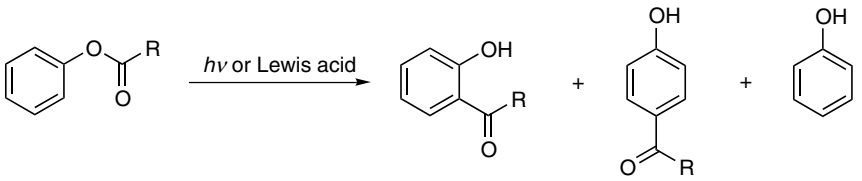
rearrangement is called the Fries-Rosenmund rearrangement.[12] Unfortunately, thioesters do not undergo such rearrangements even if they are treated under harsh conditions.[13] As for the limitation on regioselectivity, a metal-promoted Fries rearrangement[13] or anionic *ortho*-Fries rearrangement[14] was developed by Snieckus in 1983,[15] by which *O*-aryl carbamates are converted only into *ortho*-hydroxy aryl amides,[11,15] and the *N*-aryl carbamates are transformed into *ortho*-amino aryl amides. The latter transformation is called the anionic *N*-Fries rearrangement.[16] A similar migration of a phosphoryl group is referred to as the anionic phospho-Fries rearrangement.[17] Further modifications of this procedure include the lithium-bromo or lithium-iodo exchange to facilitate the *ortho*-lithiation.[13,18]

It should be pointed out that arylsulfonates also undergo a similar rearrangement to afford hydroxyaryl sulfones, and such rearrangement is known as the thia-Fries rearrangement (promoted by $Al_2O_3/MeSO_3H$[19a] or graphite/$MeSO_3H$[19b]). It is surprising that such rearrangement may involve an anionic intermediate, and the corresponding rearrangement is referred to as the anionic thia-Fries rearrangement.[20]

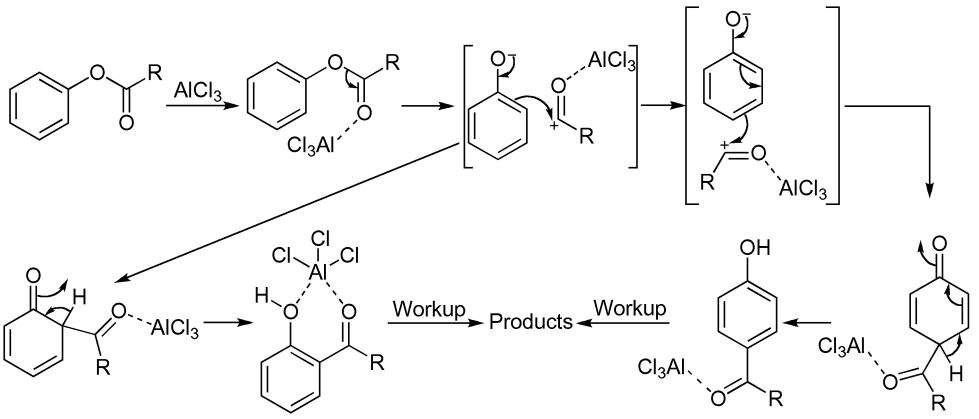
Comparable rearrangement of aryl esters under photo-irradiation were developed in 1960 by Anderson and Reese,[21] which are known as the *Photo-Fries Rearrangement*[22] or *Photo-Fries Reaction*.[23] Similarly, the photo-initiated rearrangement of aryl anilides to amino acyl aromatics is called the photo-anilide rearrangement.[22n] In addition, aryl sulfonanilides,[24] sulfonates,[25] carbamates,[26] sulfamates[27] and cinnamates[28] all undergo a similar rearrangement under photo-irradiation. It is known that the *Photo-Fries Rearrangement* is intramolecular[22k] and occurs through either an excited singlet state[22l,29] (because quantaum yields are not affected by either triplet quenchers[30] or sensitizers[25b]) or an upper triplet state.[27,28] After excitation, the homolytic cleavage of aryl ester leads to the radicals being restrained by a solvent cage that combines to the rearrangement products and starting material.[22k] In addition, the aryloxy radical might escape from the solvent cage and abstract a hydrogen to form a phenol.[22a,22k,23a] It was found that the presence of oxygen[22d,22h,31] or the addition of pentasil zeolite,[22c] Nafion membrane[22c] or β-cyclodextrin[22h,30] all affect the product distribution. Finally, the *Photo-Fries Rearrangement* has been extended to simple vinyl esters[32] as well as 1,3-dienyl esters,[33] by which both 1,3- and 1,5-acyl migration occurs on 1,3-dienyl esters.

B. GENERAL REACTION SCHEME

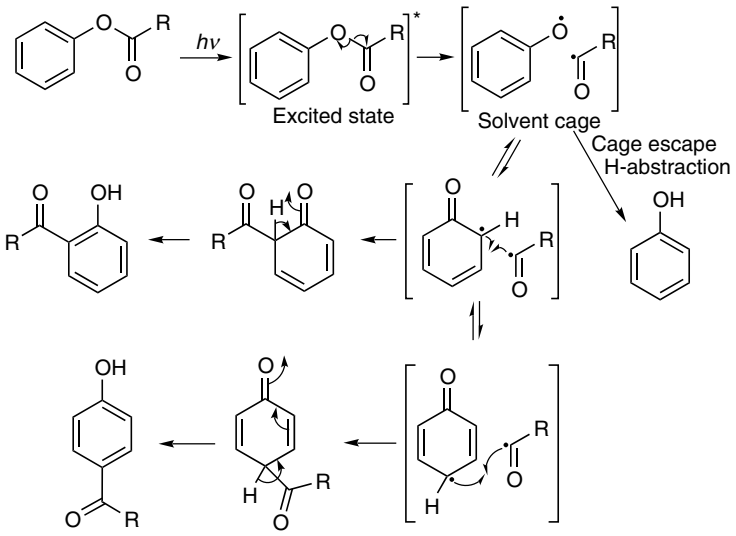


C. PROPOSED MECHANISMS

The mechanism of the Fries rearrangement catalyzed by a Lewis acid (e.g., $AlCl_3$) is demonstrated in Scheme 1, and the mechanism for a *Photo-Fries Rearrangement* is displayed in Scheme 2.



SCHEME 1. *Mechanism for a Lewis acid–promoted Fries rearrangement.*



SCHEME 2. *Mechanism for a photo-Fries rearrangement.*

D. MODIFICATION

The original Fries procedure has been modified extensively to occur under either UV irradiation (*Photo-Fries Rearrangement*) or anionic lithiation or lithium-bromo exchange (anionic ortho-Fries rearrangement). Other modifications include the application of microwaves,[2b,2i,34] electron beam,[2e,2g] BF_3-H_2O,[2a] Y zeolite,[35] zinc powder,[2f] $Bi(OTf)_3$,[2h] and solid acid catalyst[2o] as the promoters.

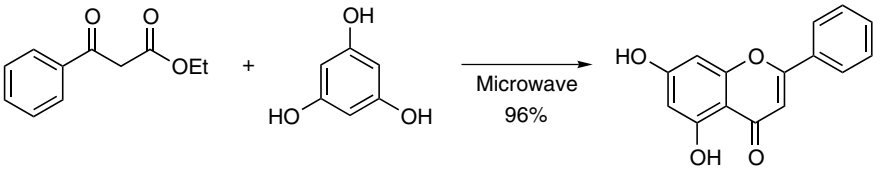
E. APPLICATIONS

This reaction has general application in the preparation of hydroxyl acyl phenols or heteroarenes (coumarin,[8,9a] carbazole,[12] etc.)

F. RELATED REACTIONS

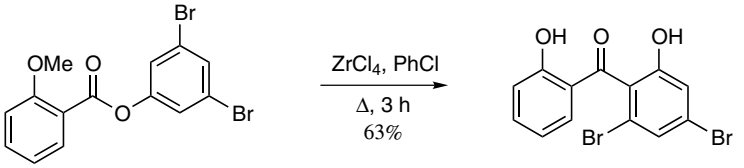
This reaction is related to the *Friedel-Crafts Acylation*.

G. CITED EXPERIMENTAL EXAMPLES



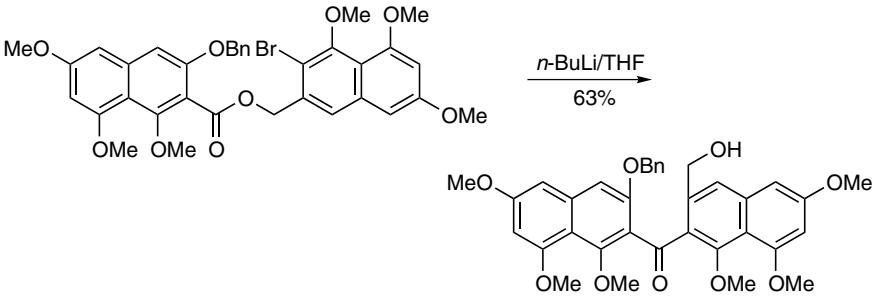
Reference 35.

A mixture of 384 mg ethyl benzoyl acetate (2 mmol) and 126 mg phloroglucinol (1 mmol) was irradiated with microwaves (ETHOS D, Millestone, at 80% of a total output of 1000 W or with the temperature control set to 240°C) for 3 min. The crude product was dissolved in 20 mL 10% aqueous NaOH and washed with diethyl ether (2 × 20 mL); the product was precipitated by adding concentrated HCl. The product was filtered, washed with water, and vacuum dried to give 243 mg chrysin, in a yield of 96%. Pure chrysin can be obtained by crystallization from dichloromethane-methanol, m.p. 288–290°C.



Reference 6.

In a sealed tube, a solution of 200 mg anisic acid 3,5-dibromophenyl ester (0.52 mmol) and 780 mg $ZrCl_4$ (3.1 mmol) in 2 mL chlorobenzene was quickly heated at 160°C and stirred for 3 h. The reaction mixture was cooled to room temperature, hydrolyzed with 5% HCl (which was added dropwise), and finally extracted with ether. The organic layers were combined and washed with 5% HCl, water, and brine and then dried over magnesium sulfate. Chromatography on silica gel (ether/hexane, 1/4) provided 120.9 mg (2,4-dibromo-6-hydroxy-phenyl)-(2-hydroxy-phenyl)-methanone, in a yield of 63%. R_f = 0.25 (ether/hexane,1:9), m.p. 180–183°C.



Reference 19a.

Under argon, 269 mg 3-benzyloxy-1,6,8-trimethoxy-naphthalene-2-carboxylic acid 3-bromo-4,5,7-trimethoxy-naphthalen-2-yl methyl ester was dissolved in 1.59 mL THF (0.25 M), from which residual water had been removed with *n*-butyllithium and *o*-phenanthroline), and cooled to –45 to –55°C. *n*-Butyllithium (203 μL, 0.437 mmol) was then added dropwise. After the solution was stirred for 2 h, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl, allowed to warm to ambient temperature, and diluted with EtOAc. After the usual workup, the crude product was purified by radial thin-layer chromatography (hexane/EtOAc, 9:1, 8:2, 7:3, and then 5:5) to give 130 mg 1-(3-benzyloxy-1,6,8-trimethoxy-naphthalen-2-yl)-1-(3-hydroxymethyl-1,6,8-trimethoxy-naphthalen-2-yl)-methanone as a white solid, in a yield of 55%. Further purification was executed by crystallization from cyclohexane-dichloromethane, m.p., 220–224°C.

Other references related to the Fries rearrangement and the *Photo-Fries Rearrangement* are cited in literature 37 and 38, respectively.

H. REFERENCES

1. Fries, K. and Fink, G., *Ber.,* **1908**, *41*, 4271.
2. (a) Prakash, G. K. S.; Panja, C.; Mathew, T. and Olah, G. A., *Catal. Lett.,* **2007**, *114*, 24. (b) Moghaddam, F. M.; Porkaleh, H. and Zali-Boeini, H., *Lett. Org. Chem.,* **2006**, *3*, 123. (c) Pradhan, T. K.; De, A. and Mortier, J., *Tetrahedron,* **2005**, *61*, 9007. (d) van Grieken, R.; Melero, J. A. and Morales, G., *Appl. Catal., A: General,* **2005**, *289*, 143. (e) Kato, J.; Maekawa, Y. and Yoshida, M., *Chem. Lett.,* **2005**, *34*, 266. (f) Paul, S. and Gupta, M., *Synthesis,* **2004**, 1789. (g) Yuasa, K.; Enomoto, K.; Maekawa, Y.; Kato, J.; Yamashita, T. and Yoshida, M., *J. Photopoly. Sci. Tech.,* **2004**, *17*, 21. (h) Sreedhar, B.; Swapna, V. and Sridhar, C., *Synth. Commun.,* **2004**, *34*, 1433. (i) Yuan, S.-J.; Lu, C.-X. and Cai, C., *Jingxi Huagong*, **2004**, *21*, 230. (j) Bolognini, M.; Cavani, F.; Cimini, M.; Dal Pozzo, L.; Maselli, L.; Venerito, D.; Pizzoli, F. and Veronesi, G., *Compt. Rend. Chim.,* **2004**, *7*, 143. (k) Borzatta, V.; Busca, G.; Poluzzi, E.; Rossetti, V.; Trombetta, M. and Vaccari, A., *Appl. Catal., A: General,* **2004**, *257*, 85. (l) Eshghi, H.; Rafie, M.; Gordi, Z. and Bohloli, M., *J. Chem. Res. (S),* **2003**, 763. (m) Mori, T.; Takamoto, M.; Wada, T. and Inoue, Y., *Photochem. Photobio. Sci.,* **2003**, *2*, 1187. (n) Piettre, A.; Massardier, C.; Chevenier, E.; Gimbert, Y. and Greene, A. E., *Synlett*, **2002**, 2086. (o) Guo, C. X.; Liu, Y.; Li, F.; Sun, P.; Evans, D. G. and Duan, X., *Chinese Chem. Lett.,* **2002**, *13*, 7.
3. Olah, G. A.; Arvanaghi, M. and Krishnamurthy, V. V., *J. Org. Chem.,* **1983**, *48*, 3359.
4. Boyer, J. L.; Krum, J. E.; Myers, M. C.; Fazal, A. N. and Wigal, C. T., *J. Org. Chem.,* **2000**, *65*, 4712.

5. Ollevier, T.; Desyroy, V.; Asim, M.; Brochu, M.-C., *Synlett,* **2004**, 2794.
6. Tisserand, S.; Baati, R.; Nicolas, M. and Mioskowski, C., *J. Org. Chem.,* **2004**, *69*, 8982.
7. (a) Mouhtady, O.; Gaspard-Iloughmane, H.; Roques, N. and Le Roux, C., *Tetrahedron Lett.,* **2003**, *44*, 6379. (b) Kobayashi, S.; Moriwaki, M. and Hachiya, I., *Bull. Chem. Soc. Jpn.,* **1997**, *70*, 267. (c) Kobayashi, S.; Moriwaki, M. and Hachiya, I., *Tetrahedron Lett.,* **1996**, *37*, 2053. (d) Kobayashi, S.; Moriwaki, M. and Hachiya, I., *J. Chem. Soc., Chem. Commun.,* **1995**, 1527.
8. Traven, V. F., *Molecules,* **2004**, *9*, 50.
9. (a) Traven, V. F.; Podhaluzina, N. Y.; Vasilyev, A. V. and Manaev, A. V., *ARKIVOC*, **2000**, *1*, 931. (b) Re, P. D. and Cimatoribus, L., *J. Org. Chem.,* **1961**, *26*, 3650.
10. Warchawsky, A.; Kalir, R. and Patchornik, A., *J. Am. Chem. Soc.,* **1978**, *100*, 4544.
11. Fieser, L. F. and Bradsher, C. K., *J. Am. Chem. Soc.,* **1936**, *58*, 2337.
12. Meitzner, E., *J. Am. Chem. Soc.,* **1935**, *57*, 2327.
13. Miranda, L. P.; Jones, A.; Meutermans, W. D. F. and Alewood, P. F., *J. Am. Chem. Soc.,* **1998**, *120,* 1410.
14. Miller, J. A., *J. Org. Chem.,* **1987**, *52*, 322.
15. (a) Blakemore, P. R.; Kilner, C. and Milicevic, S. D., *J. Org. Chem.,* **2005**, *70*, 373. (b) Clayden, J.; Helliwell, M.; McCarthy, C. and Westlund, N., *J. Chem. Soc*., *Perkin Trans. I*, **2000**, 3232. (c) Middel, O.; Greff, Z.; Taylor, N. J.; Verboom, W.; Reinhoudt, D. N. and Snieckus, V., *J. Org. Chem.,* **2000**, *65*, 667. (d) Beaulieu, F. and Snieckus, V., *J. Org. Chem.,* **1994**, *59*, 6508.
16. Sibi, M. P. and Snieckus, V., *J. Org. Chem.,* **1983**, *48*, 1935.
17. MacNeil, S. L.; Wilson, B. J. and Snieckus, V., *Org. Lett.,* **2006**, *8*, 1133.
18. Taylor, C. M. and Watson, A. J., *Curr. Org. Chem.,* **2004**, *8*, 623.
19. (a) Piettre, A.; Chevneier, E.; Massardier, C.; Gimbert, Y. and Greene, A. E., *Org. Lett.,* **2002**, *4*, 3139. (b) Couture, A.; Deniau, E.; Lebrun, S. and Grandclaudon, P., *J. Chem. Soc., Perkin Trans. I,* **1999**, *7*, 789. (c) Lampe, J. W.; Hughes, P. F.; Biggers, C. K.; Smith, S. H. and Hu, H., *J. Org. Chem.,* **1996**, *61*, 4572. (d) Nicolaou, K. C.; Bunnage, M. E. and Koide, K., *J. Am. Chem. Soc.,* **1994**, *116*, 8402. (e) Horne, S. and Rodrigo, R., *J. Chem. Soc., Chem. Commun.,* **1992**, 164. (f) Horne, S. and Rodrigo, R., *J. Chem. Soc., Chem. Commun.,* **1991**, 1046. (g) Horne, S. and Rodrigo, R., *J. Org. Chem.,* **1990**, *55*, 4520.
20. (a) Sharghi, H. and Shahsavari-Fard, Z., *Phosphorus, Sulfur & Silicon & the Related Elements,* **2005**, *180*, 2491. (b) Sharghi, H. and Shahsavari-Fard, Z., *Helv. Chim. Acta,* **2005**, *88*, 42.
21. (a) Zhao, Z. R.; Messinger, J.; Schoen, U.; Wartchow, R. and Butenschoen, H., *Chem. Commun.,* **2006**, 3007. (b) Charmant, J. P. H.; Dyke, A. M. and Lloyd-Jones, G. C., *Chem. Commun.,* **2003**, 380.
22. Anderson, J. C. and Reese, C. B., *Proc. Chem. Soc.,* **1960**, 217.
23. (a) Siskos, M. G.; Zarkadis, A. K.; Gritzapis, P. S.; Brede, O.; Hermann, R.; Melissas, V. S.; Gurzadyan, G. G.; Triantafyllou, A. S. and Georgakilas, V., *J. Photochem. Photobiol.,* **2006**, *182*, 17. (b) Crevatin, L. K.; Bonesi, S. M. and Erra-Balsells, R., *Helv. Chim. Acta,* **2006**, *89*, 1147. (c) Mori, T.; Weiss, R. G. and Inoue, Y., *J. Am. Chem. Soc.,* **2004**, *126*, 8961. (d) Girard, C.; Tranchant, I.; Nioré, P.-A.; Miramon, M.-L.; Leue, S.; Lederlin, T. and Herscovici, J., *J. Comb. Chem.,* **2002**, *4,* 640. (e) Tung, C.-H.; Wu, L.-Z.; Zhang, L.-P.; Li, H.-R.; Yi, X.-Y.; Song, K.; Xu, M.; Yuan, Z.-Y.; Guan, J.-Q.; Wang, H.-W.; Ying, Y.-M. and Xu, X.-H., *Pure & Appl. Chem.,* **2000**, *72*, 2289. (f) Andraos, J.; Barclay, G. G.; Medeiros, D. R.; Baldovi, M. V.; Scaiano, J. C. and Sinta, R., *Chem. Mater.,* **1998**, *10,* 1694. (g) Pitchumani, K.; Warrier, M. and Ramamurthy, V., *J. Am. Chem. Soc.,* **1996**, *118,* 9428. (h) Gritsan, N. P.; Tsentalovich, Y. P.; Yurkovskaya, A. V. and Sagdeev, R. Z., *J. Phys. Chem.,* **1996**, *100,* 4448. (i) Andrew, D.; Islet, B. T. D.; Margaritis, A. and Weedon, A. C., *J. Am. Chem. Soc.,* **1995**, *117*, 6132. (j) Veglia, A. V. and de Rossi, R. H., *J. Org. Chem.,* **1993**, *58*, 4941. (k) Shine, H. J. and Subotkowski, W., *J. Org. Chem.,*

1987, *52*, 3815. (l) Nakagaki, R.; Hiramatsu, M.; Watanabe, T.; Tanimoto, Y. and Nagakura, S., *J. Phys. Chem.,* **1985**, *89,* 3222. (m) Kalmus, C. E. and Hercules, D. M., *J. Am. Chem. Soc.,* **1974**, *96*, 449. (n) Adam, W.; de Sanabia, J. A. and Fischer, H., *J. Org. Chem.,* **1973**, *38*, 2571. (o) Pappas, S. P.; Alexander, J. E.; Long, G. L. and Zehr, R. D., *J. Org. Chem.,* **1972**, *37*, 1258. (p) Rao, D. V. and Lamberti, V., *J. Org. Chem.,* **1967**, *32*, 2896.

24. (a) Dickerson, T. J.; Tremblay, M. R.; Hoffman, T. Z.; Ruiz, D. I. and Janda, K. D., *J. Am. Chem. Soc.,* **2003**, *125*, 15395. (b) Cui, C. X. and Weisso, R. G., *J. Am. Chem. Soc.,* **1993**, *115*, 9820.
25. Nozaki, H.; Okada, R.; Noyori, R. and Kawanisi, M., *Tetrahedron* **1966**, *22*, 2177.
26. (a) Miranda, P. M. and Factor, A., *J. Polym. Sci. Part A,* **1989**, *27*, 4427. (b) Bellus, D., *Adv. Photochem.,* **1971**, *8*, 109.
27. Herweh, J. E. and Hoyle, C. E., *J. Org. Chem.,* **1980**, *45*, 2195.
28. (a) Lally, J. M. and Spillane, W. J., *J. Chem. Soc., Perkin. Trans. II,* **1991**, 803. (b) Lally, J. M. and Spillane, W. J., *J. Chem. Soc., Chem. Commun.,* **1987**, 8.
29. Subramanian, P.; Greed, D.; Griffin, A. C.; Hoyle, C. E. and Venkataram, K., *J. Photochem. Photobiol. A: Chem.,* **1991**, *61*, 317.
30. Shizuka, H.; Morita, T.; Mori, Y. and Tanaka, I., *Bull. Chem. Soc. Jpn.,* **1969**, *42*, 1831.
31. (a) Shizuka, H., *Bull. Chem. Soc. Jpn.,* **1969**, *42*, 52. (b) Hageman, H. J., *Tetrahedron,* **1969**, *25*, 6015. (c) Plank, D. A., *Tetrahedron Lett.,* **1969**, 4365. (d) Sandner, M. R.; Hedaya, E. and Trecker, D. J., *J. Am. Chem. Soc.,* **1968**, *90*, 7249. (e) Shizuka, H. and Tanaka, T., *Bull. Chem. Soc. Jpn.,* **1968**, *41*, 2343.
32. Veglia, A. V.; Sanchez, A. M. and de Rossi, R. H., *J. Org. Chem.,* **1990**, *55*, 4083.
33. Bellus, D. and Hrdlovic, P., *Chem. Rev.,* **1967**, *67*, 599.
34. Mazur, Y. and Gorodetsky, M., *J. Am. Chem. Soc.,* **1964**, *86*, 5213.
35. Seijas, J. A.; Vázquez-Tato, M. P. and Carballido-Reboredo, R., *J. Org. Chem.,* **2005**, *70*, 2855.
36. Lv, L.; Zhang, D. W.; Kong, A. G.; Cai, Q. H. and Shan, Y. K., *Huaxue Shijie,* **2005**, *46*, 323.
37. (a) Nguyen, T.; Wicki, M. A. and Snieckus, V., *J. Org. Chem.,* **2004**, *69*, 7816. (b) Ribinson, G. E.; Cunningham, O. R.; Dekhane, M.; McManus, J. C.; O'Kearney-McMullan, A.; Mirajkar, A. M.; Mishra, V.; Norton, A. K.; Venugopalan, B. and Williams, E. G., *Org. Proc. Res. Dev.,* **2004**, *8*, 925. (c) Bagno, A.; Kantlehner, W.; Kreß, R. and Saielli, G., *Z. Naturforsch.,* **2004**, *59b*, 386. (d) Mori, T.; Takamoto, M.; Saito, H.; Furo, T.; Wada, T. and Inoue, Y., *Chem. Lett.,* **2004**, *33*, 254. (e) Sakamoto, M.; Yagi, T.; Fujita, S.; Mino, T.; Karatsu, T. and Fujita, T., *J. Org. Chem.,* **2002**, *67*, 1843. (f) Brignmann, G.; Menche, D.; Kraus, J.; Mühlbacher, J.; Peters, K.; Peters, E.-M.; Brun, R.; Bezabih, M. and Abegaz, B. M., *J. Org. Chem.,* **2002**, *67*, 5595. (g) Gu, W. Q. and Weiss, R. G., *J. Org. Chem.,* **2001**, *66*, 1775. (h) Lacova, M.; Loos, D.; Furdik, M.; Matulova, M. and El-Shaaer, H. M., *Molecules,* **1998**, *3*, 149. (i) Kobayashi, S.; Moriwaki, M. and Hachiya, I., *Bull. Chem. Soc. Jpn.,* **1997**, *70*, 267. (j) Cui, C. X.; Wang, X. C. and Weiss, R. G., *J. Org. Chem.,* **1996**, *61,* 1962. (k) Martin, R., *Org. Prep. Proced. Int.,* **1992**, *24,* 369. (l) Vogt, A. H. G. and Kouwenhoven, H. W., *Coll. Czech. Chem. Commun.,* **1992**, *57*, 853. (m) Lown, J. W. and Sondhi, S. M., *J. Org. Chem.,* **1984**, *49*, 2844. (n) Cohen, N.; Lopresti, R. J. and Williams, T. H., *J. Org. Chem.,* **1978**, *43*, 3723. (o) Effenberger, F.; Klenk, H. and Reiter, P. L., *Angew. Chem. Int. Ed. Engl.,* **1973**, *12*, 775. (p) Norell, J. R., *J. Org. Chem.,* **1973**, *38*, 1924. (q) Coppinger, G. M. and Bell, E. R., *J. Phys. Chem.,* **1966**, *70*, 3479. (r) Széll, T. and Egyed, J., *J. Org. Chem.,* **1962**, *27*, 2225. (s) Pakkal, R.; Thomas, F. D. and Fernelius, W. C., *J. Org. Chem.,* **1960**, *25*, 282. (t) Thomas, F. D.; Shamma, M. and Fernelius, W. C., *J. Am. Chem. Soc.,* **1958**, *80*, 5864. (u) Gardner, P. D., *J. Am. Chem. Soc.,* **1955**, *77*, 4674. (v) Smith, L. I. and Holmes, R. R., *J. Am. Chem. Soc.,* **1951**, *73*, 3847. (w) Blatt, A. H., *Org. React.*, **1942**, *1*, 342. (x) Ralston, A. W.; McCorkle, M. R. and Segebrecht, E. W., *J. Org. Chem.,* **1942**, *7*, 750. (y) Fuson, R. C.; Scott, S. L. and Speck, S. B., *J. Am. Chem. Soc.,* **1941**, *63*, 2845. (z) Fries, K. and Pfaffendorf, W., *Ber.,* **1910**, *43*, 212.

38. (a) Griesser, T.; Hoefler, T.; Temmel, S.; Kern, W. and Trimmel, G., *Chem. Mater.,* **2007**, *19*, 3011. (b) Hoefler, T.; Griesser, T.; Gstrein, X.; Trimmel, G.; Jakopic, G. and Kern, W., *Polymer,* **2007**, *48*, 1930. (c) Kaanumalle, L. S.; Gibb, C. L. D.; Gibb, B. C. and Ramamurthy, V., *Org. Biomol. Chem.,* **2007**, *5*, 236. (d) Ferrini, S.; Ponticelli, F. and Taddei, M., *J. Org. Chem.,* **2006**, *71*, 9217. (e) Luo, C. P.; Passin, P. and Weiss, R. G., *Photochem. Photobio.,* **2006**, *82*, 163. (f) Lochbrunner, S.; Zissler, M.; Piel, J.; Riedle, E.; Spiegel, A. and Bach, T., *J. Chem. Phys.,* **2004**, *120*, 11634. (g) Mori, T.; Takamoto, M.; Saito, H.; Furo, T.; Wada, T. and Inoue, Y., *Chem. Lett.,* **2004**, *33*, 256. (h) Park, K. K.; Kim, S.-H. and Park, J. W., *J. Photochem. Photobio., A: Chem.,* **2004**, *163*, 241. (i) Miranda, M. A. and Galindo, F., *CRC Handbook of Organic Photochemistry and Photobiology*, **2004**, 2nd ed., 42/1. (j) Dickerson, T. J.; Tremblay, M. R.; Hoffman, T. Z.; Ruiz, D. I. and Janda, K. D., *J. Am. Chem. Soc.,* **2003**, *125*, 15395. (k) Park, K. K.; Lee, J. J. and Ryu, J., *Tetrahedron*, **2003**, *59*, 7651. (l) Miranda, M. A. and Galindo, F., *Mol. Supramol. Photochem.,* **2003**, *9*, 43. (m) Crouse, D. J.; Hurlbut, S. L. and Wheeler, D. M. S., *J. Org. Chem.,* **1981**, *46*, 374. (n) Humphrey, J. S.; Shultz, A. R. and Jaquiss, D. B. G., *Macromolecules,* **1973**, *6*, 305.

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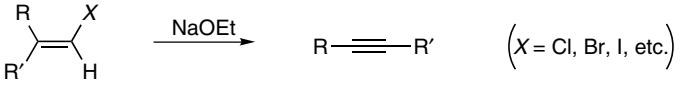
Fritsch-Buttenberg-Wiechell Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Fritsch[1] and Buttenberg,[2] coincidently with Wiechell,[3] in 1894. It is a strong base (e.g., NaOEt) promoted rearrangement of 2,2-diaryl-1-halo-alkenes into diarylacetylenes.[4] Therefore, it is generally known as the Fritsch-Buttenberg-Wiechell rearrangement.[5] This reaction has been found to occur via a carbenoid intermediate[4,5n,5q,5r] rather than the α-elimination of metal halide;[5j] in addition, the electron-donating groups normally facilitate or accelerate the migration of aryl moiety.[5j] It is the aryl moiety *trans* to the halide that undergoes the 1,2-migration,[6] thus this reaction is also called 1,2-Fritsch-Buttenberg-Weichell rearrangement.[5c] Currently, this reaction has been extended to the rearrangement of aryl or alkyl olefinic halides,[5l] and the most recent development for this reaction is the mild transformation of alkyl olefinic dibromides or alkyl alkoxy olefinic halides into alkyne derivatives proceeding via zinc carbenoids with broad tolerance of functionalities.[5e] For the reaction of alkyl alkoxy olefinic halides, the alkoxyalkyl moiety migrates exclusively;[5g,5l] in addition, this rearrangement occurs only when a hydrogen, alkoxy, or aryl moiety is involved in the migration step.[5g] This reaction has been widely used in the synthesis of polyalkynes containing 2–10 acetylene units.[5a]

B. GENERAL REACTION SCHEME



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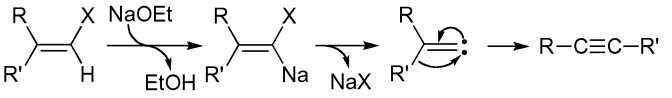
C. PROPOSED MECHANISMS

It is believed that a carbenoid intermediate is involved in this reaction, as displayed below.



D. MODIFICATION

This reaction has been modified via the formation of zinc carbenoids, which undergo a mild rearrangement,[5e] with the retention of the configuration of the migrating group.[5m] In addition, this reaction has been extended to occur under electrochemical[5n] and photochemical conditions. The rearrangement occurs under photo irradiation is known as photo-Fritsch-Buttenberg-Wiechell rearrangement.[7]

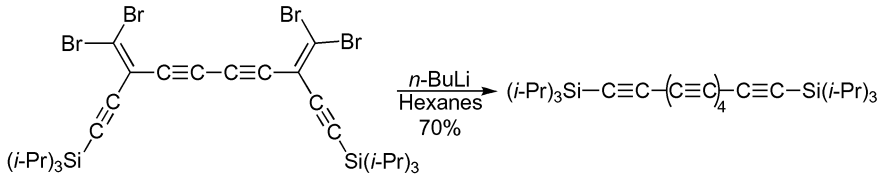
E. APPLICATIONS

This reaction has been used in the synthesis of polyalkynes that contain different acetylene units.

F. RELATED REACTIONS

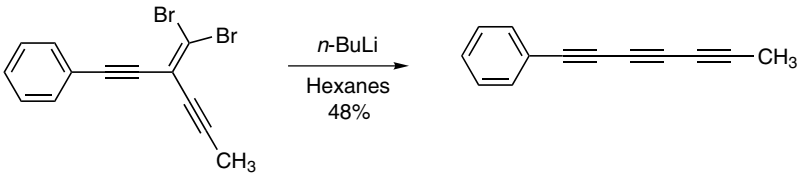
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 5a.

A 0.010–0.016 M solution of the dibromoolefin in hexanes under nitrogen was cooled to −78°C, and 1.1–1.2 eq. *n*-BuLi per dibromoolefin moiety was slowly added over a period of ∼2 min. Reactions were allowed to warm to −10 to −5°C over a period of 30–60 min. The reaction was quenched with 10 mL aqueous NH_4Cl at about −5°C. Diethyl ether was added (20 mL), the organic layer was separated, and washed with aqueous NH_4Cl solution (2 × 20 mL), and dried over $MgSO_4$. The solvent was removed in vacuo to give 70% 1,12-bis(triisopropylsilyl)-1,3,5,7,9,11-dodecahexayne, m.p. 78–80°C, R_f = 0.87 (hexanes).



Reference 5d.

To 10 mL cooled dry hexanes (−78°C) containing 0.131 g dibromoolefin (0.404 mmol) was added dropwise 0.15 mL 2.5 M *n*-BuLi in hexane (0.38 mmol) over 10 min. The mixture was warmed to −40°C for 30 min, recooled to −78°C, and quenched with a saturated aqueous solution of NH_4Cl. Et_2O was added (50 mL), and the organic layer was separated, washed with brine, and dried over magnesium sulfate. Solvent removal in vacuo and by passing the residue through a short plug of silica gel gave 31.9 mg 2-non-1-en-3,5,7-1-phenylhepta-1,3,5-triyne as a white solid, in a yield of 48%, m.p. 58°C, $R_f = 0.40$ (hexanes).

Other references related to the Fritsch-Buttenberg-Wiechell rearrangement are cited in the literature.[8]

H. REFERENCES

1. Fritsch, P., *Ann.,* **1894**, *279*, 319.
2. Buttenberg, W. P., *Ann.,* **1894**, *279*, 324.
3. Wiechell, H., *Ann.,* **1894**, *279*, 337.
4. Knorr, R., *Chem. Rev.,* **2004**, *104*, 3795.
5. (a) Eisler, S.; Slepkov, A. D.; Elliott, E.; Luu, T.; McDonald, R.; Hegmann, F. A. and Tykwinski, R. R., *J. Am. Chem. Soc.,* **2005**, *127*, 2666. (b) Luu, T.; Elliott, E.; Slepkov, A. D.; Eisler, S.; McDonald, R.; Hegmann, F. A. and Tykwinski, R. R., *Org. Lett.,* **2005**, *7*, 51. (c) Liddle, S. T. and Izod, K., *Organometallics,* **2004**, *23*, 5550. (d) Shun, A. L. K. S. and Tykwinski, R. R., *J. Org. Chem.*, **2003**, *68*, 6810. (e) Shun, A. L. K. S.; Chernick, E. T.; Eisler, S. and Tykwinski, R. R., *J. Org. Chem.*, **2003**, *68*, 1339. (f) Simpkins, S. M. E.; Kariuki, B. M.; Aricó, C. S. and Cox, L. R., *Org. Lett.*, **2003**, *5*, 3971. (g) Normant, J. F., *Acc. Chem. Res.*, **2001**, *34*, 640. (h) Deiters, A. and Hoppe, D., *J. Org. Chem.*, **2001**, *66*, 2842. (i) Heuft, M. A.; Collins, S. K.; Yap, G. P. A. and Fallis, A. G., *Org. Lett.*, **2001**, *3*, 2883. (j) Boche, G. and Lohrenz, J. C. W., *Chem. Rev.*, **2001**, *101*, 697. (k) Chernick, E. T.; Eisler, S. and Tykwinski, R. R., *Tetrahedron Lett*., **2001**, *42*, 8575. (l) Rezaei, H.; Yamanoi, S.; Chemla, F. and Normant, J. F., *Org. Lett.*, **2000**, *2*, 419. (m) Creton, I.; Rezaei, H.; Marek, I. and Normant, J. F., *Tetrahedron Lett.*, **1999**, *40*, 1899. (n) Merz, A. and Thumm, G., *Justus Liebigs Ann. Chem.*, **1978**, 1526. (o) Rebois, R.; Chauveau, J.; Deyris, M. and Coudanne, H., *Compt. Rend.*, **1976**, *282*, 947. (p) Fienemann, H. and Koebrich, G., *Chem. Ber.*, **1974**, *107*, 2797. (q) Koebrich, G.; Reitz, G. and Schumacher, U., *Chem. Ber.*, **1972**, *105*, 1674. (r) Kataoka, M.; Ando, T. and Nakagawa, M., *Bull. Chem. Soc. Jpn.*, **1971**, *44*, 177. (s) Ando, T. and Nakagawa, M., *Bull. Chem. Soc. Jpn*., **1971**, *44*, 172. (t) Koebrich, G. and Merkel, D., *Angew. Chem. Int. Ed. Engl.*, **1970**, *9*, 243. (u) Koebrich, G. and Froehlich, H., *Chem. Ber.*, **1965**, *98*, 3637. (v) Franzen, V., *Chemiker-Zeit.*, **1958**, *82*, 220.
6. (a) Curtin, D. Y. and Flynn, E. W., *J. Am. Chem. Soc.*, **1959**, *81*, 4714. (b) Curtin, D. Y.; Flynn, E. W. and Nystrom, R. F., *J. Am. Chem. Soc.*, **1958**, *80*, 4599. (c) Bothner-By, A. A., *J. Am. Chem. Soc.*, **1955**, *77*, 3293.

7. (a) Sket, B. and Zupan, M., *J. Chem. Soc., Perkin Trans. I*, **1979**, 752. (b) Sket, B.; Zupan, M. and Pollak, A., *Tetrahedron Lett*., **1976**, 783.
8. (a) Eisler, S.; Chahal, N.; McDonald, R. and Tykwinski, R. R., *Chem. Eur. J.*, **2003**, *9*, 2542. (b) Yoshifuji, M., *Phosphorus & Sulfur & Silicon Related Element*, **2002**, *177*, 1827. (c) Tobe, Y.; Iwasa, N.; Umeda, R. and Sonoda, M., *Tetrahedron Lett.*, **2001**, *42*, 5485. (d) Eisler, S. and Tykwinski, R. R., *J. Am. Chem. Soc.*, **2000**, *122*, 10736. (e) Mouriès, V.; Waschbüsch, R.; Carran, J. and Savignac, P., *Synthesis*, **1998**, 271. (f) Kirmse, W., *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, 1164. (g) Sato, H.; Isono, N.; Miyoshi, I. and Mori, M., *Tetrahedron*, **1996**, *52*, 8143. (h) Kawase, T.; Darabi, H. R.; Uchimiya, R. and Oda, M., *Chem. Lett.*, **1995**, 499. (i) Satoh, T.; Hayashi, Y. and Yamakawa, K., *Bull. Chem. Soc. Jpn.*, **1993**, *66*, 1866. (j) Stang, P. J. and Fox, D. P., *J. Org. Chem.* **1978**, *43*, 364. (k) Stang, P. J., *Chem. Rev.*, **1978**, *78*, 383. (l) Köbrich, G., *Angew. Chem. Int. Ed. Engl.*, **1972**, *11*, 473. (m) Köbrich, G. and Buck, P., "Synthests of Acetylenes and Poly-acetylenes by Elimination Reactions" in *Chemistry of Acetylenes*, ed. Viehe, H. G., Marcel Dekker, New York, **1969**, p.117. (n) Köbrich, G., *Angew. Chem. Int. Ed. Engl.*, **1965**, *4*, 49. (o) Simonetta, M. and Carra, S., *Tetrahedron*, **1963**, *19*, 467.

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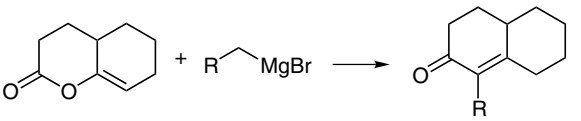
Fujimoto-Belleau Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Fujimoto[1] coincidentally with Belleau in 1951.[2] It is a synthesis of five- or six-membered α-substituted-α,β-enones by the addition of a Grignard reagent prepared from a primary halide to an enol lactone followed by an *Aldol Reaction*.[3] Therefore, it is generally known as the Fujimoto-Belleau reaction.[4] This reaction is especially useful for the transformation of a steroid scaffold[3,5] in which an isotopic carbon can be imbedded using isotopic methyl iodide.[5b,6] In addition, this reaction has been extended to imbed isotopic carbon into the benzo ring, such as in benzazepine.[3] Besides the Grignard reagent, the comparable lithium reagent is also feasible for this reaction and forms cyclic enones.[7]

B. GENERAL REACTION SCHEME



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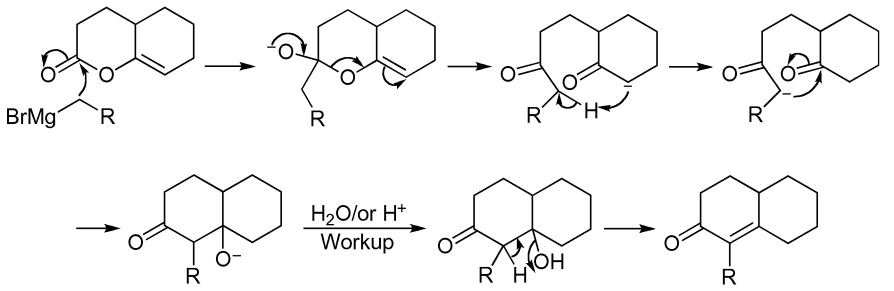
C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been extended to occur with comparable lithium reagents.[7]

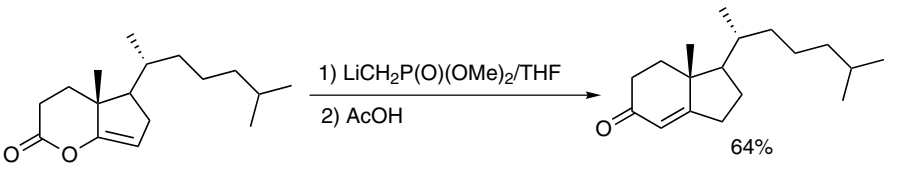
E. APPLICATIONS

This reaction is useful in steroid chemistry that imbeds an isotopic carbon into the cyclic rings.

F. RELATED REACTIONS

This reaction is related to the *Aldol Reaction* and *Grignard Reaction*.

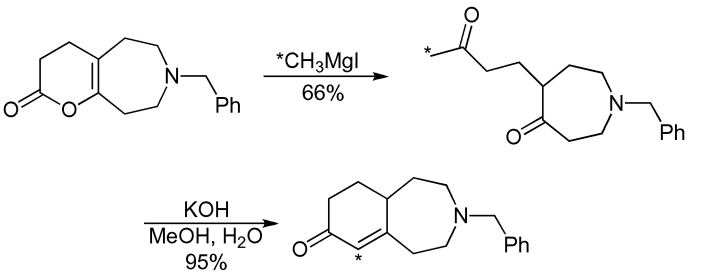
G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

To a 60 mL THF solution containing 0.43 mL $MePO(OMe)_2$ (4 mmol) was added 2.9 mL 1.4 M *n*-BuLi in hexanes (4.1 mmol) at −78°C. After the solution was stirred for 1 h, 0.53 g (1*R**,1′*R**,7a*R**)-1-(1,5-dimethylhexyl)-2,3,4,5,6,7-hexahydro-7aβ-methyl-4-oxaindan-5-one (2 mmol) in 8 mL THF was added, and the solution was stirred for an additional 30 min and warmed to −20°C over 2.5 h. Then 0.11 mL AcOH (1.92 mmol) was added dropwise. The mixture was heated at 55°C for 3 h, then cooled to 0°C; and 1 M HCl was added, followed by water. The aqueous solution was extracted with EtOAc and dried; the solvent was removed. The residue was chromatographed on SiO_2 (3% EtOAc in

hexane) to give 335 mg (1*R**,1′*R**,7a*R*)-1-(1,5-dimethylhexyl)-7aβ-methyl-2,3,5,6,7,7a-hexahydro-1*H*-inden-5-one, in a yield of 64%.



Reference 3.

To 6 mL ether solution containing 153 mg magnesium turnings was added 4.46 mmol [^{14}C] methyl iodide (250 mCi, 56 mCi/mmol) by static vacuum transfer, and the mixture was stirred for 30 min to generate the Grignard reagent. Then the ethereal solution was added dropwise by cannula over 5 min to a vigorously stirred solution of 1.15 g 7-benzyl-4,5,6,7,8,9-hexahydropyranol[2,3-d]azepin-2-(3H)-one (4.47 mmol) in 100 mL ether maintained between -20° and -30°C, resulting in the formation of a voluminous white precipitate. The mixture was allowed to warm to near 0°C over 30 min, then 15 mL water was added. Volatile radioactivity was removed by static vacuum transfer. The organic phase was separated from the aqueous phase, and the latter was extracted twice with ether. The combined organic layers were dried over magnesium sulfate and evaporated in vacuo to provide 1.15 g 1-benzyl-1,2,3,5,6,7-hexahydro-5-(3-oxo[4-^{14}C]butyl)-4H-azepin-4-one as a clear oil, containing 164 mCi radioactivity, in a yield of 66%.

This compound was dissolved in a solution of 517 mg KOH (10.8 mmol) in 4 mL water and 10 mL methanol under an argon atmosphere. The solution was allowed to stand at room temperature for 3 h. Then 25 mL water was added, and the mixture was extracted four times with ether. The combined extracts were washed twice with brine, dried over $MgSO_4$, and evaporated in vacuo to give 760 mg 3-benzyl-1,2,3,4,5,8,9,9a-octahydro-[6-^{14}C]-7H-3-benzazepin-7-one as a pale yellow oil, containing 156 mCi of radioactivity, in a yield of 95%.

Other references related to the Fujimoto-Belleau reaction are cited in the literature.[8]

H. REFERENCES

1. Fujimoto, C. I., *J. Am. Chem. Soc.,* **1951**, *73*, 1856.
2. Belleau, B., *J. Am. Chem. Soc.,* **1951**, *73*, 5441.
3. Heys, J. R. and Senderoff, S. G., *J. Org. Chem.,* **1989**, *54*, 4702.
4. (a) Heys, J. R. and Senderoff, S. G., *Synth. Appl. Isot. Labelled Cpd.*, **1988**, 395. (b) Weill-Raynal, J., *Synthesis,* **1969**, 49.
5. (a) Kutney, J. P.; Grice, P.; Pascoe, K. O.; Piotrowska, K.; Rettig, S. J.; Szykula, J. and Trotter, J., *Helv. Chim. Acta,* **1983**, *66*, 1806. (b) Zwahlen, K. D.; Horton, W. J. and Fujimoto, G. I., *J. Am. Chem. Soc.,* **1957**, *79*, 3131.

6. (a) Hoellinger, H.; Nam, N.-H. and Pichat, L., *J. Labelled Compd. Radiopharm.,* **1974**, *10*, 617. (b) Heard, R. D. H. and Ziegler, P., *J. Am. Chem. Soc.,* **1951**, *73*, 4036.
7. Grzywacz, P.; Marczak, S. and Wicha, J., *J. Org. Chem.,* **1997**, *62*, 5293.
8. (a) Aloui, M.; Lygo, B. and Trabsa, H., *Synlett,* **1994**, 115. (b) Pfau, M.; Revial, G.; Guingant, A. and d'Angelo, J., *J. Am. Chem. Soc.,* **1985**, *107*, 273. (c) Morales-Alanis, H.; Brienne, M.-J.; Jacques, J.; Bouton, M.-M.; Nédélec, L.; Torelli, V. and Tournemine, C., *J. Med. Chem.,* **1985**, *28*, 1796. (d) Weill-Raynal, J., *Synthesis,* **1969**, 49. (e) Fujimoto, G. I. and Jacobson, A. E., *J. Org. Chem.,* **1964**, *29*, 3377. (f) Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K. and McLamore, W. M., *J. Am. Chem. Soc.,* **1952**, *74*, 4223.

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Fukuyama Amine Synthesis

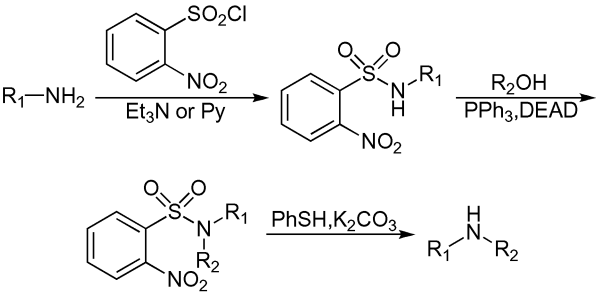
(Fukuyama-Mitsunobu *N*-Alkylation, Fukuyama-Mitsunobu Alkylation)

A. GENERAL DESCRIPTION OF THE REACTION

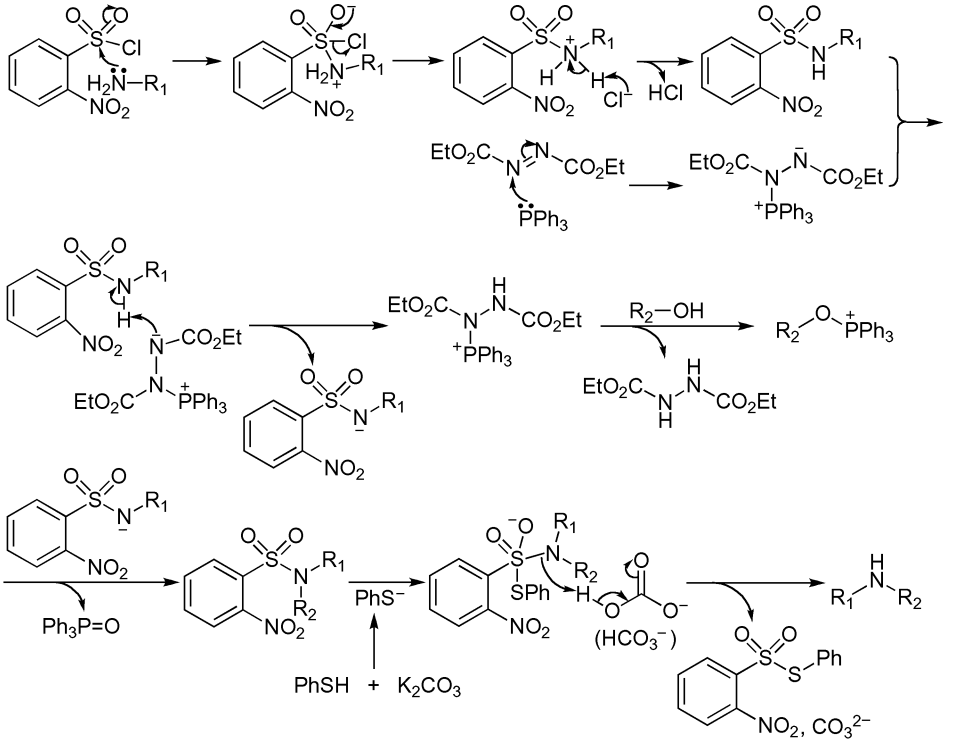
This reaction was initially reported by Fukuyama and co-workers in 1995.[1] It is a two-step conversion of primary amines into secondary amines via *ortho*-nitrobenzenesulfonation in conjunction with the *Mitsunobu Reaction* and subsequent removal of the *o*-nitrobenzenesulfonyl group by thiophenol.[2] Therefore, this reaction is generally known as the Fukuyama amine synthesis.[3] In addition, it is also referred to as the Fukuyama-Mitsunobu *N*-alkylation,[4] Fukuyama-Mitsunobu alkylation,[5] Fukuyama-Mitsunobu condition,[6] Fukuyama-Mitsunobu procedure,[7] or Fukuyama-Mitsunobu Reaction.[2] In this reaction, the *o*-nitrobenzenesulfonyl-protected amine is alkylated with alcohol in the presence of PPh_3 and diethyl azodicarboxylate (DEAD)[8] or diisopropyl azodicarboxylate (DIAD),[2] and the deprotection occurs in a very mild condition[2,8a] (almost neutral[9]). The *o*-nitrobenzenesulfonyl group is simply called the *Fukuyama sulfonamide protecting group*.[10] This reaction has become a versatile method for the synthesis of secondary amines,[11] polyamines,[12] and even tertiary amines[2,4a,13] via a solid-support, in which DIAD is superior to DEAD.[2]

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified by using DIAD to improve the alkylation efficiency.

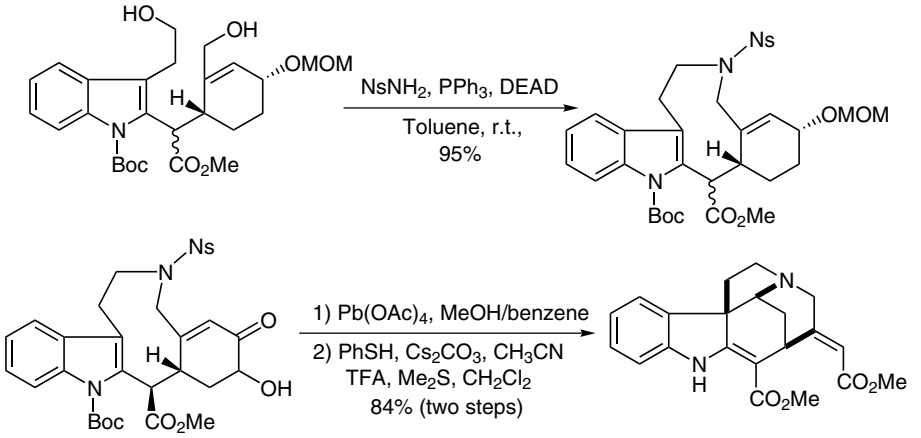
E. APPLICATIONS

This reaction is useful for the synthesis of secondary amines, especially via the solid-supported synthesis.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES

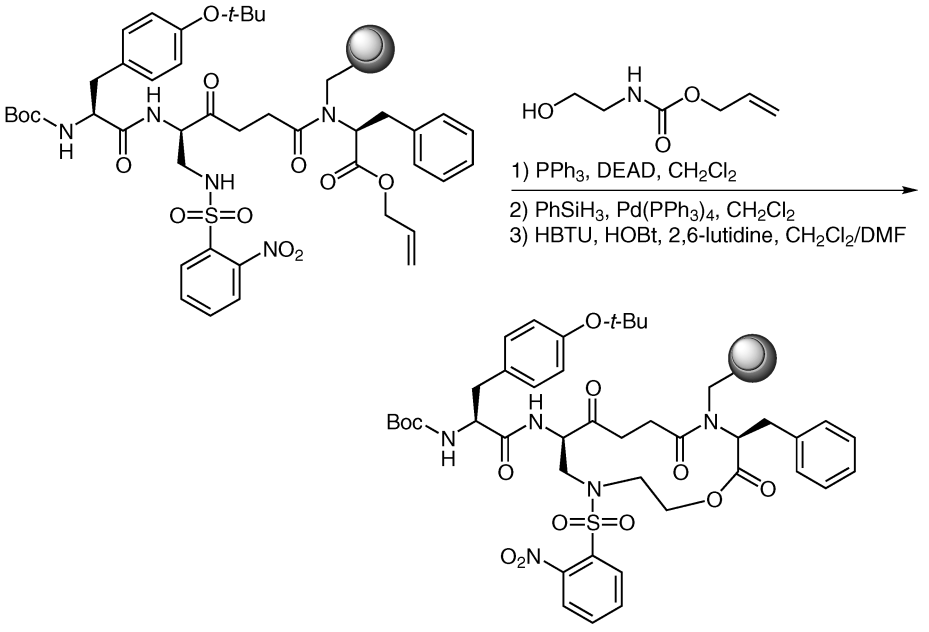


Reference 14.

To a stirred suspension of 663 mg *tert*-butyl 2-((methoxycarbonyl)((1*R*,4*R*)-2-(hydroxymethyl)-4-(methoxymethoxy)-cyclohex-2-enyl)-methyl)-3-(2-hydroxyethyl)-1*H*-indole-1-carboxylate (1.32 mmol), 692 mg PPh_3 (2.64 mmol), and 534 mg $NsNH_2$ (2.64 mmol) in 53 mL toluene at room temperature was added DEAD (40% in toluene, 1.20 mL, 2.65 mmol), and the mixture was stirred for 5 min, at which time the solvent was removed under reduced pressure. Et_2O was added to the residue, and the precipitate was removed by filtration through a pad of Celite. The filter cake was rinsed with Et_2O, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with CH_2Cl_2-Et_2O-hexane (40:30:30) to afford 837 mg (3*R*,14a*R*)-13-*tert*-butyl 14-methyl 1,2,3,5,6,7,8,14,14a-nonahydro-3-(methoxymethoxy)-6-(2-nitrobenzenesulfonyl)benzo-[7,8]azonino[5,4-*b*]indole-13,14(1*H*)-dicarboxylate as a white foam, in a yield of 95%. The diastereomers could be separated by preparative TLC.

To a solution of 249 mg (14*R*,14a*R*)-13-*tert*-butyl 14-methyl 1,2,3,5,6,7,8,14,14a-nonahydro-3-oxo-2-hydroxy-6-(2-nitrobenzenesulfonyl)benzo[7,8]azonino[5,4-*b*]indole-13,14(1*H*)-dicarboxylate (0.389 mmol) in 4 mL MeOH and 4 mL benzene at 0°C was added 345 mg $Pb(OAc)_4$ (0.778 mmol). After being stirred for 10 min, the reaction mixture was quenched with saturated $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was passed through a pad of silica gel eluting with EtOAc/hexane (70:30). Removal of the solvent gave aldehyde, which was dissolved in 3.9 mL acetonitrile. To this solution at room temperature were added 190 mg Cs_2CO_3 (0.583 mmol) and 47.9 μL PhSH (0.484 mmol). The suspension was stirred for 30 min, at which time 2.0 mL Me_2S, 4.0 mL CH_2Cl_2, and 2.0 mL TFA were added. The mixture was heated to 50°C and stirred for 7 h. After being cooled to room temperature, it was

diluted with EtOAc, washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with hexane/CH_2Cl_2/Et_3N (60:40:5 then 0:100:5) to give 120 mg (3a*R*,10*R*,11a*S*)-methyl 1,2,3,10,11,11a-hexahydro-13-(*E*)-[(methoxycarbonyl)methylene]-1,10-ethanopyrrolo[2,3-*d*]carbazole-9-carboxylate as a pale yellow oil, in an overall yield of 84% in two steps.



Reference 2.

To an argon-agitated suspension of the peptide-bound resin (2.06 mmol) and *N*-(allyloxycarbonyl) ethanolamine (5 eq.) in 80 mL THF were added carefully 5.0 eq. DIAD and PPh_3 each at 0°C, and the reaction was agitated at room temperature for 12 h. After successive washings with DMF, MeOH, and CH_2Cl_2 (three times), a solution of $PhSiH_3$ (24 eq.) and a solution of $Pd(PPh_3)_4$ (0.1 eq.) in 20 mL CH_2Cl_2 were added to the resin under argon. The resin was shaken for 10 min, the peptide resin was washed with DMF, MeOH, and CH_2Cl_2 (three times); then the deprotection process was repeated once. The deprotected peptide resin was suspended again in 15 mL DMF/CH_2Cl_2 (v/v = 1:1) and treated with 3.0 eq. of HBTU, 3.0 eq. HOBt, and 4.0 eq. 2,6-lutidine for 12 h. After being washed successively with DMF, MeOH, and CH_2Cl_2 (three times), the resin was dried in vacuo to provide 5.67 g peptide resin (1.95 mmol), in a yield of 95%.

Other references related to the Fukuyama amine synthesis are cited in the literature.[15]

H. REFERENCES

1. Fukuyama, T.; Jow, C.-K. and Cheung, M., *Tetrahedron Lett.,* **1995**, *36*, 6373.
2. Rew, Y. and Goodman, M., *J. Org. Chem.,* **2002**, *67*, 8820.

3. (a) Piscopio, A. D.; Miller, J. F. and Koch, K., *Tetrahedron Lett.,* **1998**, *39*, 2667. (b) Yang, L. and Chiu, K., *Tetrahedron Lett.,* **1997**, *38*, 7307.
4. (a) Olsen, C. A.; Witt, M.; Jaroszewski, J. W. and Franzyk, H., *Org. Lett.,* **2004**, *6*, 1935. (b) Lewis, J. G. and Bartlett, P. A., *J. Comb. Chem.,* **2003**, *5*, 278.
5. (a) Olsen, C. A.; Witt, M.; Hansen, S. H.; Jaroszewski, J. W. and Franzyk, H., *Tetrahedron*, **2005**, *61*, 6046. (b) Olsen, C. A.; Jorgensen, M. R.; Witt, M.; Mellor, I. R.; Usherwood, P. N. R.; Jaroszewski, J. W. and Franzyk, H., *Eur. J. Org. Chem.,* **2003**, 3288.
6. Olsen, C. A.; Witt, M.; Jaroszewski, J. W. and Franzyk, H., *Org. Lett.,* **2003**, *5*, 4183.
7. Guisado, C.; Waterhouse, J. E.; Price, W. S.; Jorgensen, M. R. and Miller, A. D., *Org. Biomol. Chem.,* **2005**, *3*, 1049.
8. (a) Grehn, L. and Ragnarsson, U., *J. Org. Chem.,* **2002**, *67*, 6557. (b) Huang, H.; Martásek, P.; Roman, L. J. and Silverman, R. B., *J. Med. Chem.,* **2000**, *43*, 2938.
9. Johannsen, M. and Jørgensen, K. A., *Chem. Rev.,* **1998**, *98*, 1689.
10. Lin, X. D.; Dorr, H. and Nuss, J. M., *Tetrahedron Lett*., **2000**, *41*, 3309.
11. (a) Renault, J.; Lebranchu, M.; Lecat, A. and Uriac, P., *Tetrahedron Lett.,* **2001**, *42*, 6655. (b) Lee, C. E.; Kick, E. K. and Ellman, J. A., *J. Am. Chem. Soc.,* **1998**, *120*, 9735.
12. (a) Olsen, C. A.; Witt, M.; Jaroszewski, J. W. and Franzyk, H., *Synlett,* **2004**, 473. (b) Strømgaard, K.; Andersen, K.; Ruhland, T.; Krogsgaard-Larsen, P. and Jaroszewski, J. W., *Synthesis,* **2001**, 877. (c) Chhabra, S. R.; Khan, A. N. and Bycroft, B. W., *Tetrahedron Lett.,* **2000**, *41*, 1099. (d) Miller, S. C. and Scanlan, T. S., *J. Am. Chem. Soc.* **1997**, *119*, 2301.
13. Zaragoza, F. and Stephensen, H., *J. Org. Chem.* **2001**, *66*, 2518.
14. Kaburagi, Y.; Tokuyama, H. and Fukuyama, T., *J. Am. Chem. Soc.,* **2004**, *126*, 10246.
15. (a) Bianchi, I.; Porta, E. L.; Barlocco, D. and Raveglia, L. F., *J. Comb. Chem.,* **2004**, *6*, 835. (b) Hudson, R. H. E. and Viirre, R. D., *Nucleoside, Nucleotides & Nucleic Acids,* **2003**, *22*, 1017. (c) Sumi, S.; Matsumoto, K.; Tokuyama, H. and Fukuyama, T., *Org. Lett.,* **2003**, *5*, 1891. (d) Strømgaard, K.; Andersen, K.; Ruhland, T.; Krogsgaard-Larsen, P. and Jaroszewski, J. W., *Synthesis,* **2001**, 877. (e) Kan, T. and Fukuyama, T., *J. Synth. Org. Chem., Jpn*., **2001**, *59*, 779. (f) Combs, A. P. and Rafalski, M.; *J. Comb. Chem.,* **2000,** *2*, 29. (g) Hone, N. D. and Payne, L. J., *Tetrahedron Lett.,* **2000**, *41*, 6149. (h) Gordon, K. and Balasubramanian, S., *J. Chem. Tech. & Biotech.,* **1999**, *74*, 835. (i) Fukuyama, T.; Cheung, M.; Jow, C.-K.; Hidai, Y. and Kan, T., *Tetrahedron Lett.,* **1997**, *38*, 5831. (j) Han, Y.; Albericio, F. and Barany, G., *J. Org. Chem.,* **1997**, *62*, 4307.

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Fukuyama Indole Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Fukuyama in 1994.[1] It is a unique synthesis of 3-substituted or 2,3-disubstituted indole derivatives from a tributyltin-based intramolecular radical cyclization of *o*-alkenylphenylisocyanides[2] (or isonitriles or 2-isocyanostyrene derivatives[1,3]). Therefore, this reaction is generally referred to as the Fukuyama indole synthesis.[4]

It should be pointed out that the Fukuyama indole synthesis has already been upgraded to a second generation.[3] The initial reaction protocol (Scheme 1) involves the treatment of 2-isocyanostyrene derivatives with tributyltin hydride in the presence of a radical initiator (e.g., AIBN), giving a (2-alkenyl)phenylstannoimidoyl radical, which cyclizes intramolecularly and tautomerizes subsequently to afford 3-substituted-2-tributylstannyl indoles.[1] Acidic treatment of the indole tin derivatives will afford simple 3-alkyl-substituted indole derivatives.[1] Moreover, in conjunction with the *Stille Coupling*,[5] 2-alkenyl (or alkynyl, aryl)-3-alkyl-indole derivatives can be obtained, and the *Stille Coupling* can be performed in a one-pot manner.[1] This version of the reaction allows for the preparation of indoles with both acid- and base-sensitive functionalities at positions 2 and 3 from readily accessible phenylisonitriles; however, it would be very difficult to form 2-alkyl-substituted indoles directly.[1] In addition, the reaction from 2-isocyanostyrenes with a *trans*-β-alkyl group might be complicated with the formation of tetrahydroquinolines, while 2-isocyanostyrenes with a *cis*-β-alkyl group will give much less tetrahydroquinolines.[1]

The second generation of the Fukuyama indole synthesis (Scheme 2) generally involves the intramolecular radical cyclization of 2-alkenylthioanilides, which can be readily accessed in a modular fashion from at least three different methods.[3] In the first method, tetrahydropyran-protected *o*-(3-hydroxyallyl)thioanilides are prepared from quinolines by

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means of thiophsogene decomposition, $NaBH_4$ reduction, tetrahydropyran protection, and nucleophilic addition on the isothiocyanate moiety by a carbon nucleophile (e.g., enolate or Grignard reagent).[3] In the second modular reaction, quinolines are treated analogously with thiophosgene followed by $NaBH_4$ reduction; the resulting *o*-(3-hydroxyallyl)phenyl isothiocyantes are converted into *o*-(3-hydroxyallyl)anilines, which are then acylated with acyl chloride and subsequently treated with *Lawesson's Reagent*.[3] The third method involves a *Sonogashira Coupling* of 2-iodoaniline, with terminal alkynes to afford 2-alkynylanilines, which are reduced by activated zinc to give exclusively *o*-aminostyrenes with a β-substituent in *cis*-configuration. Then the anilines are transformed into thioanilides by acylation and subsequent treatment with the *Lawesson's Reagent*.[3] The thioanilides can be easily converted into a variety of 2-substituted and 2,3-disubstituted indoles by tributyltin hydride, followed by desulfurization with Raney nickel.[4b]

It was found that triethylborane (Et_3B) is an effective radical initiator,[5] from which a wide range of both acid- and base-sensitive groups—such as ester, THP ether, and β-lactam—can be implemented at indole's 2- or 3-position.[3] Under such radical reaction conditions, no racemization has been detected for a thioanilide derived from a chiral α-amino acid.[3] In addition, hypophosphorus acid, being a radical reducing reagent, has also been used as a substitute for tin hydride.[3] Overall, the Fukuyama indole synthesis has been successfully applied to the total synthesis of several natural alkaloids containing indole moieties, including aspidophytine,[6] haplophytine,[6] catharanthine,[7] vindoline[8] and the antineoplastic agent of (+)-vinblastine,[8] as shown in Figure 1.

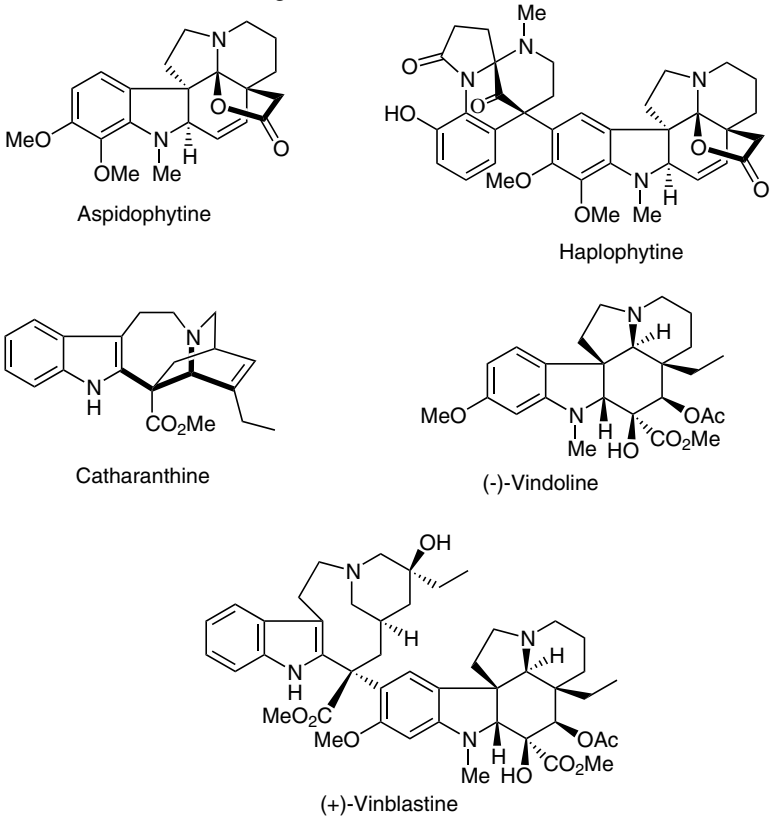
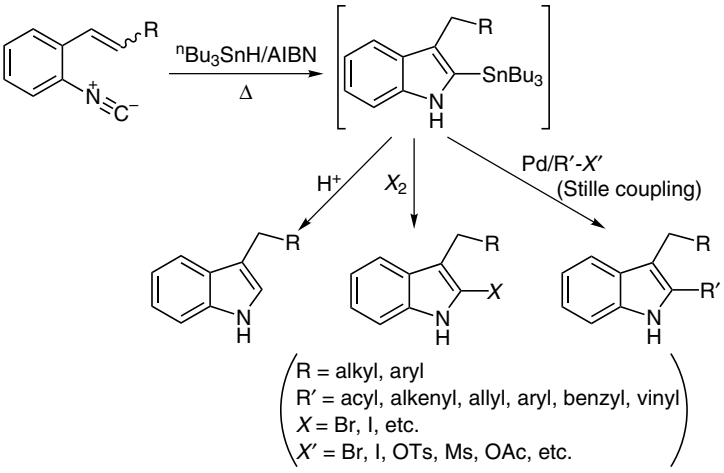
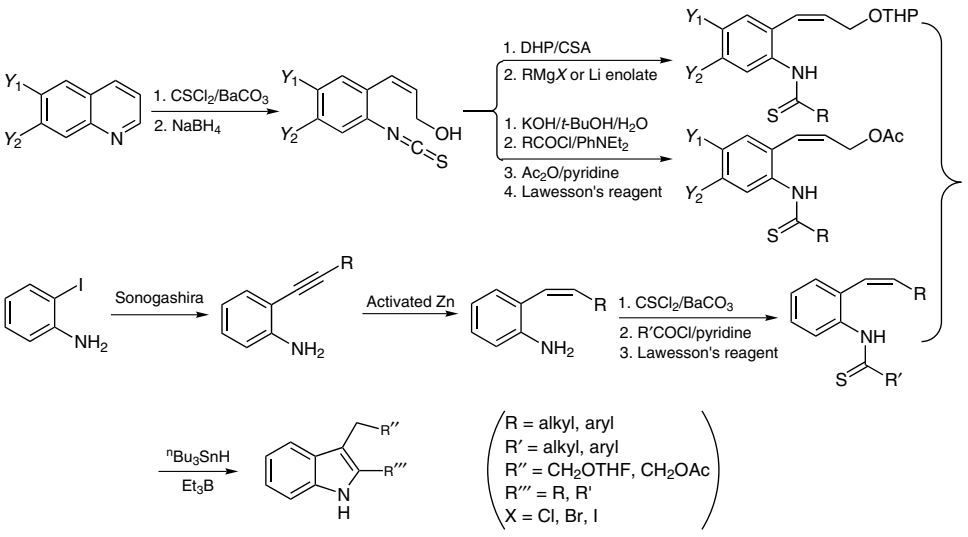


FIGURE 1. *Indole-containing alkaloids that are accessible by the Fukuyama indole synthesis.*

B. GENERAL REACTION SCHEME



SCHEME 1. *First-generation Fukuyama indole synthesis.*

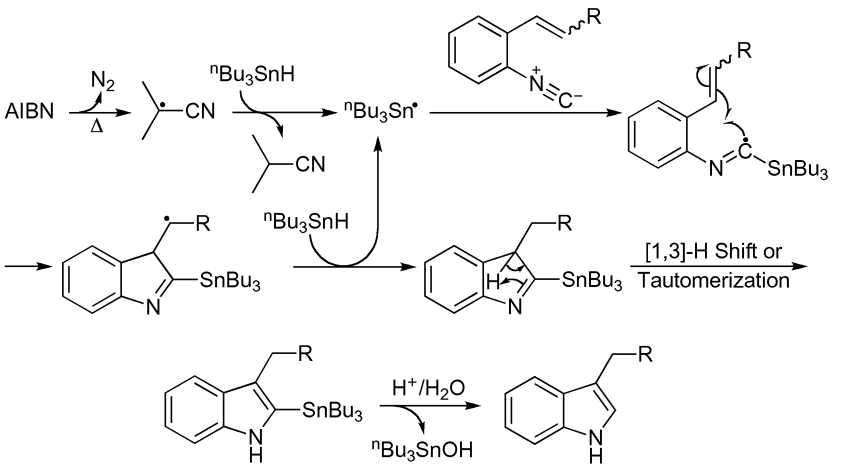


SCHEME 2. *Second-generation Fukuyama indole synthesis.*

C. PROPOSED MECHANISMS

Because both the first and the second generations of Fukuyama indole synthesis involve the intramolecular radical cyclization, only the mechanism for the first generation is pro-

vided here.



D. MODIFICATION

The 2-isocyanostyrene derivatives have also been prepared by the *Pudovik Reaction* with a variety of aldehydes.[4b] In addition, a variant of the 5-*exo-dig* radical cyclization of 2-alkynylphenylisonitriles using thiols as both radical initiators and nucleophiles has been developed. Under these conditions, quinolines can be obtained by a potentially competitive 6-*endo-dig* radical cyclization.[9]

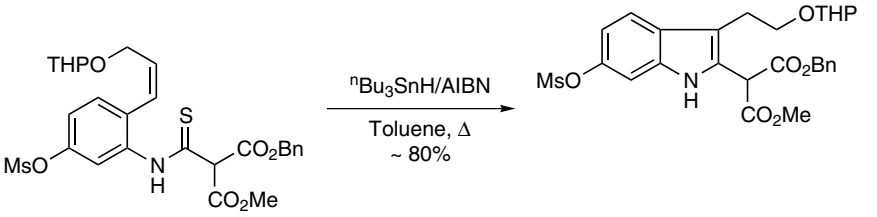
E. APPLICATIONS

This reaction has an important application in the preparation of indole-containing alkaloids.

F. RELATED REACTIONS

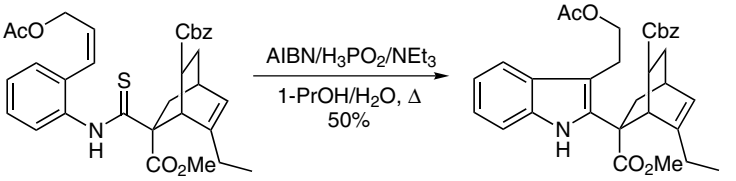
This reaction is related to the *Fürstner Indole Synthesis*, both give the 2,3-disubstituted indole derivatives.

G. CITED EXPERIMENTAL EXAMPLES



Reference 10.

A 3.0-L toluene solution containing 43.3 g 2-{5-methanesulfonyloxy-2-[(*Z*)-3-(tetrahydropyran-2-yloxy)propenyl]-phenylthiocarbamoyl} malonic acid benzyl ester methyl ester (75.0 mmol), 22.2 mL tri-*n*-butyltin hydride (82.5 mmol), and 1.23 g 2,2′-azobisisobutyronitrile (7.50 mmol) was degassed at room temperature with argon for 10 min and then stirred at 110°C for 10 min. After being cooled to room temperature, to the resulting suspension was added 1.0 L half-saturated aqueous potassium fluoride. The resulting two-phase mixture was stirred vigorously for 3 h. After removal of the organic layer, the aqueous layer was extracted with EtOAc twice. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered through a pad of Celite, and concentrated in vacuo to give ~75 g crude syrup, which was purified with flash chromatography using 20–40% EtOAc in hexane to afford 80% 2-{6-methanesulfonyloxy-3-[2-(tetrahydropyran-2-yloxy)ethyl]-1*H*-indol-2-yl}malonic acid benzyl ester methyl ester as a slightly yellow oil.



Reference 9.

To 5 mL 1-propanol were added 414 mg thioanilide (0.74 mmol), 133 mg AIBN (0.81 mmol), 1.4 mL 30% aqueous hypophosphorus acid (7.4 mmol), and 1.55 mL triethylamine (11.1 mmol) under argon. The mixture was first warmed slightly, and then stirred at 90°C under a reflux condenser with an argon balloon. After 45 min, TLC analysis indicated the completion of reaction. The reaction mixture was cooled down to room temperature and diluted with 20 mL ether. The organic solution was then washed with 1 *N* HCl, 1 *N* NaOH, and brine; dried and concentrated to give a yellow oil, which was purified by flash column chromatography using hexanes/EtOAc (10:1 to 5:1) with 0.5% Et_3N as the eluent to afford 198 mg indole product as a clear, faintly yellow oil, in a yield of 50%.

Other references related to the Fukuyama indole synthesis are cited in the literature.[11]

H. REFERENCES

1. Fukuyama, T.; Chen, X. Q. and Peng, G., *J. Am. Chem. Soc.,* **1994**, *116*, 3127.

2. Tokuyama, H. and Fukuyama, T., *Chem. Record,* **2002**, *2*, 37.
3. Tokuyama, H.; Yamashita, T.; Reding, M. T.; Kaburagi, Y. and Fukuyama, T., *J. Am. Chem. Soc.,* **1999**, *121*, 3791.
4. (a) Tsoungas, P. G. and Diplas, A. I., *Curr. Org. Chem.,* **2004**, *8*, 1579. (b) Ketcha, D. M., "Five-membered Rings: Pyrroles and Benzo Derivatives" in *Progress in Heterocyclic Chemistry*, ed. Gribble, G. W. and Gilchrist, T. L., Elsevier Science, Kidlington, UK, **2002**, *14*, p. 126. (c) Nettekoven, M., *Bioorg. Med. Chem. Lett*., **2001**, 2169.
5. Nozaki, K.; Oshima, K. and Utimoto, K., *Tetrahedron,* **1989**, *45*, 923.
6. Sumi, S.; Matsumoto, K.; Tokuyama, H. and Fukuyama, T., *Org. Lett.,* **2003**, *5*, 1891.
7. Reding, M. T. and Fukuyama, T., *Org. Lett.,* **1999**, *1*, 973.
8. Fukuyama, T., "Vinblastine" in *Classics in Total Synthesis II: More Targets, Strategies, Methods*, ed. Nicolaou, K. C. and Snyder, S. A., Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, **2003**, p. 505.
9. Rainier, J. D. and Kennedy, A. R., *J. Org. Chem.,* **2000**, *65*, 6213.
10. Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H. and Fukuyama, T., *J. Am. Chem. Soc.,* **2002**, *124*, 2137.
11. (a) Iwadate, M.; Yamashita, T.; Tokuyama, H. and Fukuyama, T., *Heterocycles,* **2005**, *66*, 241. (b) Kotani, M.; Yamago, S.; Satoh, A.; Tokuyama, H. and Fukuyama, T., *Synlett,* **2005**, 1893. (c) Kuboyama, T.; Yokoshima, S.; Tokuyama, H. and Fukuyama, T., *Proc. Natl. Acad. Sci., USA,* **2004**, *101*, 11966. (d) Benati, L.; Calestani, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Strazzari, S. and Zanardi, G., *J. Org. Chem.,* **2003**, *68*, 3454. (e) Sumi, S.; Matsumoto, K.; Tokuyama, H. and Fukuyama, T., *Tetrahedron,* **2003**, *59*, 8571. (f) Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H. and Fukuyama, T., *Pure & Appl. Chem.,* **2003**, *75*, 29. (g) Reding, M. T.; Kaburagi, Y.; Tokuyama, H. and Fukuyama, T., *Heterocycles,* **2002**, *56*, 313. (h) Tokuyama, H. and Fukuyama, T., *Kagaku Kogyo*, **2001**, *52*, 416. (i) Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H. and Fukuyama, T., *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu*, **2001**, *43*, 163. (j) Tokuyama, H.; Kaburagi, Y.; Chen, X. Q. and Fukuyama, T., *Synthesis,* **2000**, 429. (k) Kobayashi, S.; Ueda, T. and Fukuyama, T., *Synlett,* **2000**, 883. (l) Kobayashi, S.; Peng, G. and Fukuyama, T., *Tetrahedron Lett.,* **1999**, *40*, 1519. (m) Rainier, J. D.; Kennedy, A. R. and Chase, E., *Tetrahedron Lett.,* **1999**, *40*, 6325. (n) Kobayashi, Y. and Fukuyama, T., *J. Heterocycl. Chem.,* **1998**, *35*, 1043.

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Fürstner Indole Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Fürstner in 1991.[1] It is a low-valent titanium-induced or -mediated intramolecular reductive alkylidenation of alkyl (or aryl) 2-*N*-acylamidophenyl ketones to afford 2,3-disubstituted indoles, also known as titanium-induced intramolecular oxoamide coupling[2] or the zipper reaction.[3] Therefore, this reaction is referred to as the Fürstner indole synthesis.[3a,4]

This reaction is best performed with highly reactive titanium on graphite[5] that is prepared from $TiCl_3$ and 2 eq. of KC_8[6,7] (or from $TiCl_3$ and 3 eq. of KC_8[8]), which can produce the corresponding indole derivatives in up to 93% yield in DME.[6] In theory, the Fürstner indole synthesis is an extension of the *McMurry Coupling*,[9] which is usually performed in two steps, involving the reduction of $TiCl_3$ or $TiCl_4$ with a strong reducing agent followed by the addition of a carbonyl compound to the activated titanium slurry.[2,9] In the regular *McMurry Coupling*, the active titanium species vary, depending on the activation conditions, such as $[TiHCl{\cdot}THF_{1/2}]_n$ from an $LiAlH_4$ reduction or [TiCl(MgCl)·*n*THF] or [Ti(MgCl)$_2$) · *n*THF] by magnesium reduction.[10] However, the Fürstner indole synthesis is different from the normal *McMurry Coupling* in both reaction scope and mechanism. For example, the *McMurry Coupling* is assumed to proceed via a radical mechanism in general, whereas a dianion mechanism fits most of the experimental aspects of the Fürstner indole synthesis.[9] For a particular reaction condition, the activated titanium species prepared from $TiCl_3$ with 2 eq. KC_8 gives the most favorable results, whereas other titanium species in the *McMurry Coupling* fail for this reaction.[9] In fact, it was found that in the Fürstner indole synthesis, a series of titanium species at different oxidation states (e.g., 0, +1, +2), such as $Cp_2Ti(PMe_3)_2$, Ti(arene)$_2$ (arene = toluene, biphenyl), and a few non-titanium low-valent metallic species (e.g., $NbCl_5$/Zn), are also suitable coupling reagents.[9] Moreover, the

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Fürstner indole synthesis is not necessarily performed in a two-step fashion, instead it can be efficiently carried out via an "instant" method.[2,3a,9] Under such conditions, $TiCl_3$ is added to form a complex with oxoamide substrates before the addition of an excess amount of zinc; once $TiCl_3$ is reduced to an active oxidation state, it immediately mediates the alkylidenation of two adjacent carbonyl functionalities.[9] Furthermore, unlike the *McMurry Coupling*, the Fürstner indole synthesis is not restricted to THF or DME, it can also be performed in solvents such as EtOAc, DMF, and CH_3CN, although it does not work in toluene and MeOH.[9] What is more, a variety of reducible and acid or base-labile functionalities at other sites of the substrates can sustain the Fürstner indole synthesis.[9] For example, 2-*N*-α-ketoacylamidophenyl ketone with a more electrophilic α-keto group cyclizes only to a indole derivative.[9] In addition, a pair of phenyl/mesityl or benzyl/*tert*-butyl groups at C-2 and C-3 in either possible arrangement does not affect the overall yield of indole derivatives to a noticeable extent.[9]

Overall, the versatility of the Fürstner indole synthesis is probably due to the ready formation of a five-membered ring, the proximity of the two carbonyl groups, the high oxophilicity of low-valent titanium species, and the generation of a new aromatic moiety.[9] So far, the Fürstner indole synthesis has been successfully used in the preparation of 2,3-disubstituted indoles on a multigram scale[5] as well as a series of indole-containing compounds, such as camelexin, indolopyridocolin, flavopereirine, secofascaplysin, aristoleline, and lukianol (Figure 1).[11] However, the Fürstner indole synthesis is also problematic for substrates with two branched alkyl groups at C-2 and C-3, and for the preparation of 3-unsubstituted indoles from *o*-*N*-acylated benzaldehydes.[9]

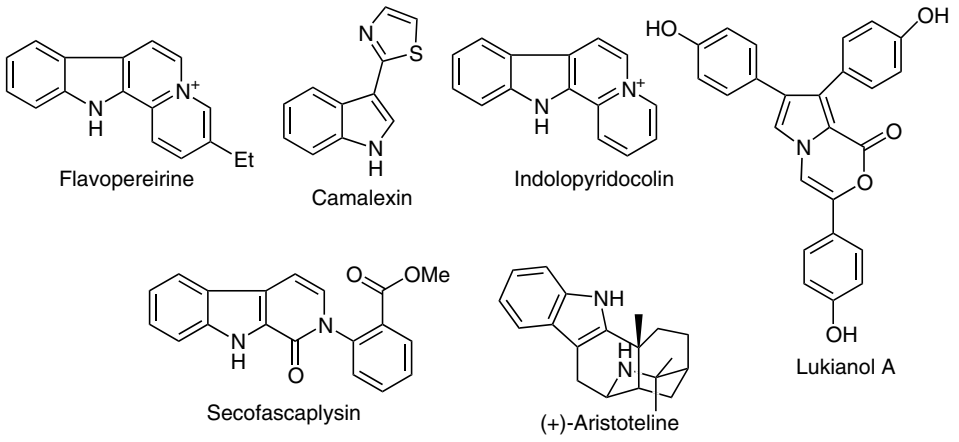
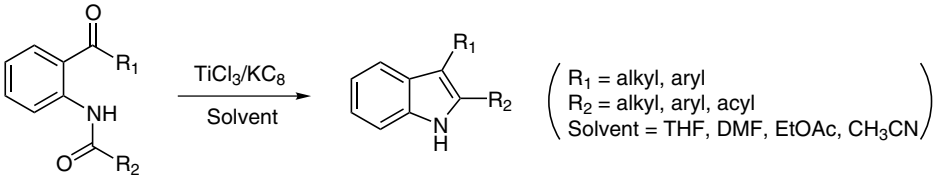


FIGURE 1. *Some indole and pyrrole derivatives accessible from the Fürstner indole synthesis.*

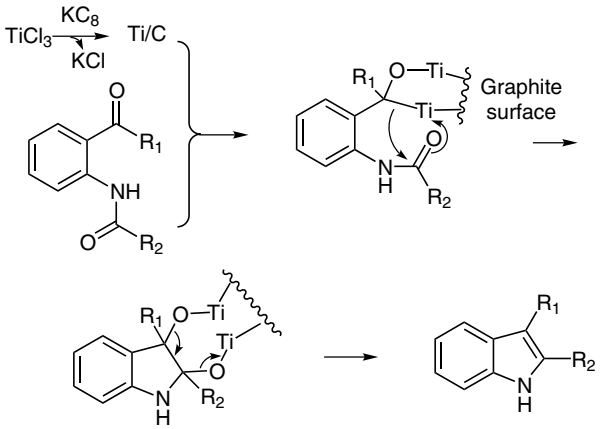
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Although the *McMurry Coupling* proceeds via a single-electron transfer (SET) mechanism involving ketal radical intermediates, the Fürstner indole synthesis does not occur through SET process, due to a series of experimental facts as follows.[9] (*a*) Diaryl ketones react faster than aryl alkyl ketones, and only amido and ester groups in the vicinity of keto group will undergo the reductive cyclization, indicating that the Fürstner indole synthesis occurs initially at the keto group. (*b*) If the reaction occurs via SET, then solvents such as DMF and EtOAc would be unsuitable for this reaction, because the amido or ester group is an electron acceptor. (*c*) In addition, the C-2 and C-3 substituent with different electron properties should greatly affect the reaction; however, all types of amides of a given parent 2-aminophenyl ketone (e.g., formamides, alkanoyl, aroyl, and heteroaroyl and fatty acid amides) react at comparable rates. (*d*) Neither the dimerization product of the ketal anion radical nor the ring-opening product of cyclopropyl group has been observed in the reaction. On the other hand, although Tebbe reagent[12] has been extensively applied to the conversion of esters and amides into vinyl ethers and amines via a titanium carbene intermediate, the Fürstner indole synthesis is not likely to involve a titanium carbene intermediate either, owing to the observation of a substantial amount of *Pinacol Rearrangement* products and the unsuccessful conversion of *gem*-dibromide into the expected indole with a variety of titanium reagents.[9]

However, it is more promising that the Fürstner indole synthesis proceeds through a dianion mechanism, according to the following experimental phenomena.[9] (*a*) The reaction initially takes place at keto group as shown earlier, and once the ketone dianion forms, it attacks on the vicinal ester or amido group equally well by a common titanium template, whereas other distal functionalities are intact. (*b*) *N*-Phenylbenzamide is electrochemically inactive, clearly showing the formation of a ketone dianion before any electron transfer to an amido group. (*c*) The electrochemically generated dianion of diphenyl ketone can be added to admixed acetic anhydride to give 1,1-diphenyl-1-acetoxy-2-propanone, validating the dianion mechanism for the Fürstner indole synthesis. In addition, titanium species have been proved to convert α-hydroxyketones into olefins. Therefore, the Fürstner indole synthesis should involve the transfer of two electrons to keto group to give a titanium alkoxide carbanion in which the carbanion nucleophilically adds to the vicinal carbonyl group to give pinacol intermediate that is then cleaved to give 2,3-disubstituted indole derivatives, as displayed here.



D. MODIFICATION

This reaction has been improved to a catalytic version by heating the mixture of zinc dust, a catalytic amount of $TiCl_3$, the oxoamides, and an excess amount of silane (such as R_3SiCl in MeCN or DME).[2] The scope of such version of Fürstner indole synthesis depends on the competition by uncatalyzed zinc-induced reduction. It is found that bis(chlorosilane)—Such as $(ClSi(Me)_2CH_2CH_2Si(Me)_2Cl$—gives a better turnover number due to the intramolecular siloxane formation.[2] In addition, SmI_2 has been successfully applied to the Fürstner indole synthesis.[13] Moreover, in terms of intramolecular cyclization, the Fürstner indole synthesis has been extended to the preparation of benzofurans.[8c]

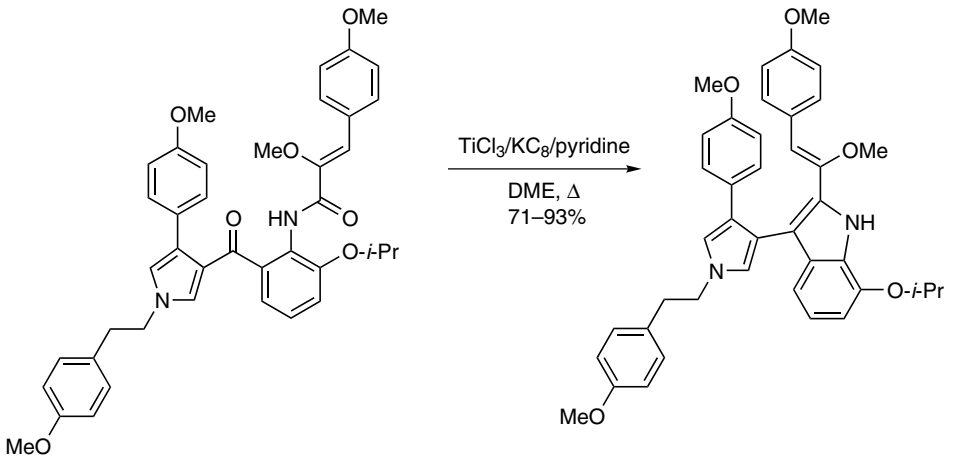
E. APPLICATIONS

This reaction has very broad applications in the preparation of the 2,3-disubstituted indole derivatives as well as pyrrole and benzofuran derivatives.

F. RELATED REACTIONS

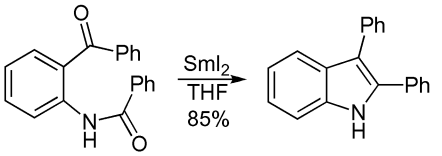
This reaction is related to the *Fukuyama Indole Synthesis*, both give 2,3-disubstituted indole derivatives. In addition, this reaction is very closely related to *McMurry Coupling* in mechanism.

G. CITED EXPERIMENTAL EXAMPLES



Reference 5.

Caution! KC_8 is pyrophoric and must be handled under argon with care! To a mixture of 2.85 g $TiCl_3$ (18.5 mmol) and 4.96 g KC_8 (36.7 mmol) at 0°C under argon was added 40 mL dry DME (exothermic!), and the resulting suspension was refluxed for 1.5 h. After the addition of 1.5 mL dry pyridine (18.5 mmol), the mixture was refluxed for another 15 min. Then 2.49 g 2-*N*-[2-isopropoxy-6-({4-(4-methoxyphenyl)-1-[2-(4-methoxyphenyl)-ethyl]-1*H*-pyrrol-3-yl}carbonyl)phenyl]-2-methoxy-3-(4-methoxyphenyl)-2-propenamide (3.69 mmol) in 10 mL dry DME was introduced, and the mixture was refluxed until the completion of the reaction as monitored by TLC (∼ 1.5 h). After being cooled to ambient temperature, the mixture was filtered through a plug of Celite layered on silica, which was carefully rinsed with 150 mL EtOAc/toluene (1:1); the combined filtrates were concentrated in vacuo. The residue was purified by flash chromatography using EtOAc/hexanes (1:6) with 1% 6 M NH_3/MeOH added, to afford 1.68 g 7-isopropoxy-2-[methoxy-2-(4-methoxyphenyl)ethenyl]-3-{4-(4-methoxyphenyl)-1-[2-(4-methoxyphenyl)-ethyl]-1*H*-pyrrol-3-yl}-1*H*-indole as a yellow oil, in a yield of 71%. The yield was raised to 93% when this reaction was performed on a somewhat smaller scale from 278 mg ketoamide.



Reference 13.

A mixture of 0.6 g pulverized samarium (4.0 mmol) and 1.0 g iodine (4.0 mmol) in 20 mL anhydrous THF was stirred at room temperature until the samarium disappeared. To the resulting dark blue suspension of SmI_2 was added 0.3 g benzoyl 2-*N*-benzoylphenone (1.0 mmol). The mixture was stirred at 65°C for 30 min and then poured into 10 mL H_2O. The aqueous solution was extracted with EtOAc (3 × 15 mL), and the combined extracts were washed subsequently with 15 mL saturated aqueous $Na_2S_2O_3$ solution and 15 mL brine and then dried over anhydrous Na_2SO_4. Upon removal of solvent under reduced pressure, the residue was purified by preparative TLC on silica gel using EtOAc/cyclohexane (1:7) as the eluent, to afford 0.229 g 2,3-diphenylindole as a colorless crystal, in a yield of 85%, m.p. 121–123°C.

Other references related to the Fürstner indole synthesis are cited in the literature.[14]

H. REFERENCES

1. Fürstner, A.; Jumbam, D. N. and Weidmann, H., *Tetrahedron Lett.,* **1991**, *32*, 6695.
2. Fürstner, A. and Hupperts, A., *J. Am. Chem. Soc.,* **1995**, *117*, 4468.
3. (a) Gribble, G. W., *J. Chem. Soc., Perkin Trans. I*, **2000**, 1045. (b) Fürstner, A.; Ptock, A.; Weintritt, H.; Goddard, R. and Krüger, C., *Angew. Chem. Int. Ed. Engl.,* **1995**, *34*, 678.
4. (a) Brückner, R., *Advanced Organic Chemistry: Reaction Mechanism*, Academic Press, San Diego, Calif., **2002**, p. 587. (b) Tokuyama, H.; Yamashita, T.; Reding, M. T.; Kaburagi, Y. and Fukuyama, T., *J. Am. Chem. Soc.,* **1999**, *121*, 3791. (c) Gribble, G. W., *Contemp. Org. Synth.,* **1994**, *1*, 145.

5. Fürstner, A.; Domostoj, M. M. and Scheiper, B., *J. Am. Chem. Soc.,* **2006**, *128*, 8087.
6. Fürstner, A., *Angew. Chem. Int. Ed. Engl.,* **1993**, *32*, 164.
7. (a) Clive, D. J. L.; Zhang, C.; Murthy, K. S. K.; Hayward, W. D. and Daigneault, S., *J. Org. Chem.,* **1991**, *56*, 6447. (b) Clive, D. J. L.; Murthy, K. S. K.; Zhang, C.; Hayward, W. D. and Daigneault, S., *J. Chem. Soc., Chem. Commun.,* **1990**, 509. (c) Clive, D. J. L.; Murthy, K. S. K.; Wee, A. G. H.; Prased, J. S.; da Silva, G. V. J.; Majewski, M.; Anderson, P. C.; Evans, C. F.; Haugen, R. D.; Heerze, L. D. and Barrie, J. R., *J. Am. Chem. Soc.,* **1990**, *112*, 3018.
8. (a) Fürstner, A.; Jumbam, D. N. and Seidel, G., *Ber.,* **1994**, *127*, 1125. (b) Fürstner, A. and Jumbam, D. N., *J. Chem. Soc., Chem. Commun.,* **1993**, 211. (c) Fürstner, A. and Jumbam, D. N., *Tetrahedron,* **1992**, *48*, 5991. (d) Boldrini, G. P.; Savoia, D.; Gagliavini, E.; Trombini, C. and Umani-Ronchi, A., *J. Organomet. Chem.,* **1985**, *280*, 307.
9. Fürstner, A.; Hupperts, A.; Ptock, A. and Janssen, E., *J. Org. Chem.,* **1994**, *59*, 5215.
10. (a) Aleandri, L. E.; Becke, S.; Bogdanovic, B.; Jones, D. J. and Roziere, J., *J. Organomet. Chem.,* **1994**, *472*, 97. (b) Aleandri, L. E.; Bogdanovic, B.; Gaidies, A.; Jones, D. J.; Liao, S.; Michalowicz, A.; Roziere, J. and Schott, A., *J. Organomet. Chem.,* **1993**, *459*, 87.
11. Fürstner, A., *Pure & Appl. Chem.,* **1998**, *70*, 1071.
12. See *Tebbe Olefination* herein (P. 2753).
13. Fan, X. S. and Zhang, Y. M., *Tetrahedron,* **2003**, *59*, 1917.
14. (a) Fürstner, A.; Domostoj, M. M. and Scheiper, B., *J. Am. Chem. Soc.,* **2005**, *127*, 11620. (b) Fürstner, A.; Hupperts, A. and Seidel, G., *Org. Synth.,* **1999**, *76*, 142. (c) Fürstner, A., *Chem. Eur. J.,* **1998**, *4*, 567. (d) Fürstner, A. and Tesche, B., *Chem. Mater.,* **1998**, 10,1968. (e) Fürstner, A. and Bogdanovic, B., *Angew. Chem. Int. Ed. Engl.,* **1996**, *35*, 2442. (f) Fürstner, A.; Ernst, A.; Krause, H. and Ptock, A., *Tetrahedron,* **1996**, *52*, 7329. (g) Fürstner, A.; Weintritt, H. and Hupperts, A., *J. Org. Chem.,* **1995**, *60*, 6637. (h) Fürstner, A. and Ernst, A., *Tetrahedron,* **1995**, *51*, 773. (i) Fürstner, A. and Seidel, G., *Synthesis,* **1995**, 63. (j) Ames, D. E., *Annu. Rep. Prog. Chem., Sect. B: Org. Chem.,* **1991**, *88*, 149.

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Gabriel Primary Amine Synthesis

(Gabriel Synthesis, Gabriel Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Gabriel in 1887.[1] It is a two-step synthesis of primary aliphatic amines involving the *N*-alkylation of phthalimide followed by acidic or basic hydrolysis of *N*-alkyl-phthalimides. In this reaction, phthalimide can be easily deprotonated by KOH or NaOH because of the two electron-withdrawing groups (i.e., carbonyl), resulting in a good nucleophile; after the *N*-alkylation, the *N*-alkyl phthalimide can be decomposed to provide pure primary amines. Therefore, this reaction is known as the Gabriel synthesis,[2] Gabriel synthesis of primary amine,[2a,3] or Gabriel reaction.[4] The major advantage of this reaction is to avoid over alkylation on the nitrogen atom; because the primary or secondary amine is more nucleophilic than ammonia, the direct reaction between ammonia and an alkyl halide would give the mixtures of primary amine, secondary amine, tertiary amine, and even quaternary ammonium salt. It is found that under basic conditions for the hydrolysis of *N*-alkyl phthalimide, the second step is the rate-limiting step, with a $t_{1/2}$ of 264 h in 0.1 M NaOH at 60°C; in contrast, under acidic hydrolysis conditions, the first step is the rate-determining step, with a $t_{1/2}$ of 175 h in 0.1 M HCl at 60°C.[2a] Because the hydrolysis of *N*-alkyl phthalimide in the original protocol takes too much time, the hydrolysis has been modified by using hydrazine to accelerate the hydrolysis,[5] which is known as hydrazinolysis or the Ing-Manske procedure.[2a,3a] In addition, a two-step procedure including a $NaBH_4$/isopropanol reduction and acetic acid hydrolysis has been developed for the generation of primary amines.[6] On the basis of the known mechanism,

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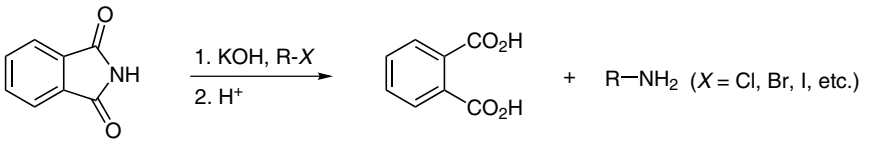
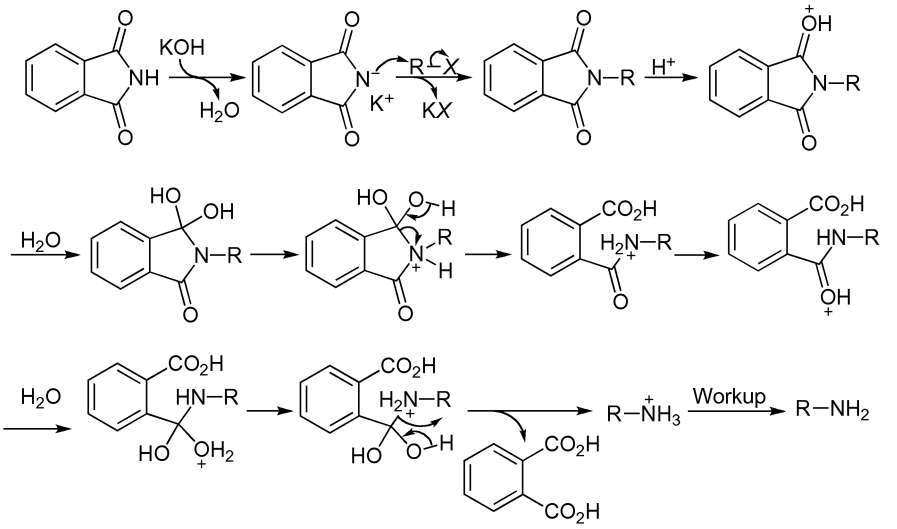
it has been suggested that this reaction be run under a mild acid-base condition within a shorter reaction time.[2a]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The acidic hydrolysis of *N*-alkyl phthalimide is proposed here to illustrate the reaction mechanism.



D. MODIFICATION

This reaction has been modified using hydrazinolysis[5] or hydrolysis after the $NaBH_4$/isopropanol reduction.[6] In addition, other amide,[7] phosphoramidate,[3b] and sulfonamide[8] derivatives have been applied to the preparation of primary amines in a similar manner.

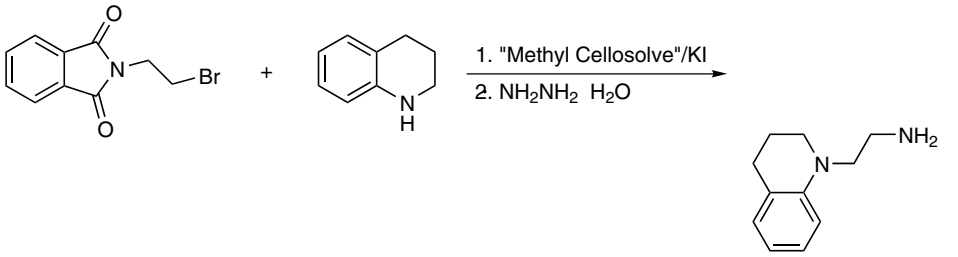
E. APPLICATIONS

This reaction is generally used for the synthesis of aliphatic primary amines.

F. RELATED REACTIONS

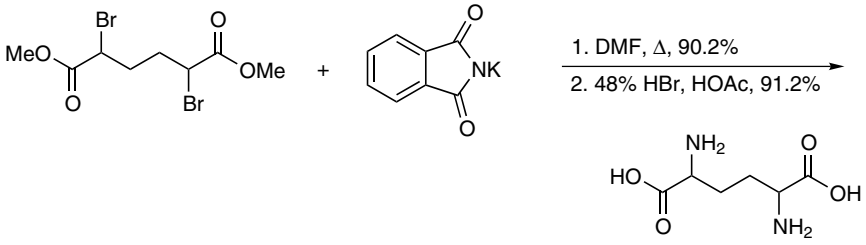
This reaction is related to the *Fukuyama Amine Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 9.

A mixture of 20 g 1,2,3,4-tetrahydroquinoline, 25 mL methyl Cellosolve, 2 g potassium iodide, and 28.1 g 2-bromoethylphthalimide was heated overnight on a steam bath. The solvent was evaporated in vacuo from the dark reaction product, and the residue was dissolved in dilute hydrochloric acid, filtered from insoluble material, and then made alkaline with a sodium carbonate solution. The resulting 2-(1′,2′,3′,4′-tetrahydroquinolino)-ethylphthalimide that recrystallized from aqueous alcohol (m.p. 131–133°C), was suspended in 50 mL absolute alcohol, and 2.4 g 85% hydrazine hydrate was added. After the mixture was warmed gently for 5 h, an excess of dilute hydrochloric acid was added, and the mixture was filtered after standing for 1 h. An excess of 12.5 *N* NaOH was added to the filtrate, and a small amount of oily 2-(1′,2′,3′,4′-tetrahydroquino-1ino)-ethylamine was taken up in methyl acetate.



Reference 10.

A mixture of 69.0 g dimethyl α, δ-dibromoadipate (0.21 mol), 87.0 g potassium phthalimide, and 260 mL DMF was heated to 90°C (a mild exothermic reaction starts at 50°C) and maintained at this temperature for 40 min. The cooled reaction mixture was diluted with 300 mL $CHCl_3$ and poured into 1200 mL water. The chloroform layer was separated, and the aqueous phase was extracted twice with 100 mL chloroform. The combined organic layers were washed with 200 mL cold 0.1 N NaOH and 200 mL water and dried over Na_2SO_4. The chloroform was removed by concentration under reduced pressure to the point of incipient crystallization, the immediate addition of 300 mL ether induced a rapid crystallization. The ether-washed product weighed 87.0 g, in a yield of 90.2%, with a wide melting point (160–185°C). After three recrystallizations from EtOAc and benzene, a pure stereoisomer was obtained with a normal melting point (210.7–211.4°C).

A mixture of 100 mL 48% HBr, 100 mL acetic acid, and 50.0 g dimethyl α,δ-diphthalimidoadipate was refluxed until a clear solution resulted (10 days). On cooling,

the filtrate and water washes were concentrated under reduced pressure practically to dryness. The residue was dissolved in 100 mL water, filtered, and neutralized with concentrated ammonia. After crystallization at 0°C for 12 h, 17.3 g α,δ-diaminoadipic acid was obtained, in a yield of 91.2%.

Other references related to the Gabriel primary amine synthesis are cited in the literature.[11]

H. REFERENCES

1. Gabriel, S., *Ber.,* **1887**, *20*, 2224.
2. (a) Khan, M. N., *J. Org. Chem.,* **1996**, *61*, 8063. (b) Beer, A. A. and Kochetkov, N. K., *Zh. Obsh. Khim.,* **1940**, *10*, 714.
3. (a) Ariffin, A.; Khan, M. N.; Lan, L. C.; May, F. Y. and Yun, C. S., *Synth. Commun.,* **2004**, *34*, 4439. (b) Zwierzak, A. and Pilichowska, S., *Synthesis,* **1982**, 922. (c) Gibson, M. S. and Bradshaw, R. W., *Angew. Chem. Int. Ed. Engl.,* **1968**, *7*, 919.
4. (a) Dzhemilev, U. M.; Fakhretdinov, R. N. and Safuanova, R. M., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1985**, 2098. (b) Dietrich, B.; Hosseini, M. W.; Lehn, J. M. and Sessions, R. B., *J. Am. Chem. Soc.,* **1981**, *103*, 1282.
5. Ing, H. R. and Manske, R. H. F., *J. Chem. Soc.,* **1926**, 2348.
6. Osby, J. O.; Martin, M. G. and Ganem, B., *Tetrahedron Lett*., **1984**, 2093.
7. (a) Grehn, L. and Ragnarsson, U., *Synthesis,* **1987**, 275. (b) Clarke, C. T.; Elliott, D. and Jones, J. H., *J. Chem. Soc., Perkin Trans. I,* **1978**, 1088.
8. (a) Hendrickson, J. B.; Bergeron, R. and Sternbach, D. D., *Tetrahedron,* **1975**, *31*, 2517. (b) Hendrickson, J. B.; Bergeron, R.; Giga, A. and Sternbach, D. D., *J. Am. Chem. Soc.,* **1973**, *95*, 3412.
9. Corse, J.; Bryant, J. T. and Shonle, H. A., *J. Am. Chem. Soc.,* **1946**, *68*, 1911.
10. Sheehan, J. C. and Bolhofer, W. A., *J. Am. Chem. Soc.,* **1950**, *72*, 2786.
11. (a) Kubo, A.; Kubota, H.; Takahashi, M. and Nunami, K.-I., *Tetrahedron Lett.,* **1996**, *37*, 4957. (b) Sen, S. E. and Roach, S. L., *Synthesis,* **1994**, 756. (c) Garro-Helion, F.; Merzouk, A. and Guibé, F., *J. Org. Chem.,* **1993**, *58*, 6109. (d) Ragnarsson, U. and Grehn, L., *Acc. Chem. Res.,* **1991**, *24*, 285. (e) Han, Y. L and Hu, H. W., *Synthesis*, **1990**, 122. (f) Slusarska, E. and Zwierzak, A., *Liebigs Annalen Chemie,* **1986**, 402. (g) Billman, J. H. and Cash, R. V., *Proc. Indiana Acad. Sci.,* **1952**, *62*, 158. (h) Amundsen, L. H.; Mayer, R. H.; Pitts, L. S. and Malentacchi, L. A., *J. Am. Chem. Soc.,* **1951**, *73*, 2118. (i) Chambret, F. and Joly, D., *Bull. Soc. Chim. Fr.,* **1947**, 1023. (j) Chodroff, S.; Kapp, R. and Beckmann, C. O., *J. Am. Chem. Soc.,* **1947**, *69*, 256. (k) Sakellarios, E., *Helv. Chim. Acta,* **1946**, *29*, 1675.

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Gabriel Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Gabriel in 1888[1] and subsequently by Marckwald in 1889.[2] It is the synthesis of ethylenimines (now called aziridines) from aliphatic α-haloamines. Therefore, it is known as the Gabriel reaction.[3] The original Gabriel's procedure is to treat α-bromoethylamine hydrobromide with silver oxide in water;[1] however, the commonly used method is to treat α-haloethylamine hydrohalide with NaOH or KOH in water;[4] and the most successful method is to treat α-aminoethyl hydrogen sulfate with NaOH[5] as α-aminoethyl hydrogen sulfate can be easily prepared from ethanolamine and sulfuric acid.[6] This reaction can be extended for preparing four- (azetidines),[7] five-, and six-membered cyclic amines. The aziridine and substituted aziridines are important intermediates for complicated organic syntheses[8] and monomers for polyamines.[9]

B. GENERAL REACTION SCHEME

C. PROPOSED MECHANISMS

It is known that alkyl amine is a stronger base than water; therefore, NaOH or KOH cannot deprotonate the amino group. On the other hand, the amino group is a good nucleophile that attacks the β-carbon to form an aziridinium cation and then quickly decomposes back to the starting material in the absence of a base. A representative mechanism is illustrated here using 2-bromoethylamine and KOH.

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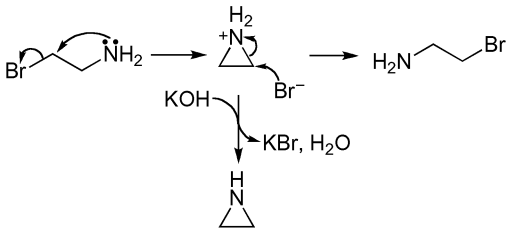


D. MODIFICATION

A convenient method starting from α-aminoethyl sulfate has been adapted for the preparation of aziridines.[5,6]

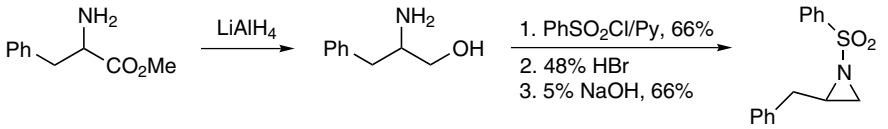
E. APPLICATIONS

This reaction has general application in the preparation of cyclic amines, including aziridines and azetidines.

F. RELATED REACTIONS

N/A

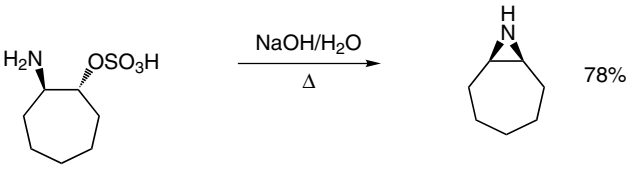
G. CITED EXPERIMENTAL EXAMPLES



Reference 10.

The methyl ester of DL-phenylalanine was recovered from its hydrochloride salt and was reduced with $LiAlH_4$ to 3-phenyl-2-amino-1-hydroxypropane. Then 1.0 g such an alcohol (6.6 mmol) was dissolved in 20 mL cold pyridine containing 2.9 g benzenesulfonyl chloride (16.0 mmol); the solution was held at 5°C overnight. Ice was added (50 g) followed by cold 4 N HCl. The resulting solid was collected and crystallized from 95% ethanol to give 1.9 g 3-phenyl-2-benzenesulfonamido-l-(benzene-sulfonyloxy)propane, in a yield of 66%, m.p., 104.5–106.5°C.

A mixture of 5.0 g dibenzenesulfonyl derivative (10 mmol), 30 mL 48% HBr, and 200 mL ethanol was refluxed for 3 h. The cooled reaction mixture, containing 3-phenyl-2-benzenesulfonamido-1-bromopropane was neutralized with 5% NaOH diluted with 300 mL cold water, and then treated with 185 mL 5% NaOH. After the alkaline mixture was stirred for 15 min, the white precipitate was collected and crystallized from alcohol to furnish 2.2 g 1-benzenesulfonyl-2-benzylethylenimine as needles, in a yield of 66%, m.p., 51–53°C.



Reference 11.

A solution of 12.0 g *trans*-2-aminocycloheptyl hydrogen sulfate and 24.0 g NaOH in 30 mL water was heated in a distilling flask until the residue was nearly dry. The distillate was collected in a cooled receiver containing a little ether and sodium hydroxide pellets. The ethereal solution was separated, and the aqueous solution was extracted with ether (3 × 15 mL). The combined ether solution was dried over solid NaOH and distilled to give 5.0 g cycloheptenimine as a colorless liquid, in a yield of 78%, b.p., 171–172°C.

Other references related to the Gabriel reaction are cited in the literature.[12]

H. REFERENCES

1. Gabriel, S., *Ber.,* **1888**, *21*, 566.
2. (a) Howard, C. C. and Marckwald, W., *Ber.,* **1899**, *32*, 2036. (b) Marckwald, W., *Ber.,* **1900**, *33*, 764. (c) Marckwald, W. and Frobenius, O., *Ber.,* **1901**, *34*, 3544.
3. Ignatova, Yu. L.; Karimova, N. M.; Kil'disheva, O. V. and Knunyants, I. L., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1986**, 732.
4. (a) Gabriel, S. and Stelzner, R., *Ber.,* **1895**, *28*, 2929. (b) Knorr, L. and Meyer, G., *Ber.,* **1905**, *38*, 3130.
5. Jones, G. D.; Langsjoen, A.; Neumann, M. M. C. and Zomlefer, J., *J. Org. Chem.,* **1944**, *9*, 125.
6. Wenker, H., *J. Am. Chem. Soc.,* **1935**, *57*, 2328.
7. (a) Cromwell, N. H. and Phillips, B., *Chem. Rev.,* **1979**, *79*, 331. (b) Schaefer, F. C., *J. Am. Chem. Soc.,* **1955**, *77*, 5928. (c) Howard, C. C. and Warckwald, W., *Ber.,* **1899**, *32*, 2031. (d) Howard, C. C. and Warckwald, W., *Ber.,* **1899**, *32*, 2038. (e) Gabriel, S. and Weiner, J., *Ber.,* **1888**, *21*, 2669.
8. Gronquist, M. R. and Meinwald, J., *J. Org. Chem.,* **2001**, *66*, 1075.
9. (a) Darensbourg, D. J.; Phelps, A. L.; Gall, N. L. and Jia, L., *J. Am. Chem. Soc.,* **2004**, *126*, 13808. (b) Fischer, D.; von Harpe, A.; Kunath, K.; Petersen, H.; Li, Y. X. and Kissel, T., *Bioconjugate Chem.,* **2002**, *13*, 1124.
10. Gensler, W. J. and Dheer, S. K., *J. Org. Chem.,* **1981**, *46*, 4051.
11. Talukdar, P. B. and Fanta, P. E., *J. Org. Chem.,* **1959**, *24*, 555.
12. (a) Sunwoo, K. H.; Kim, D. C.; Shin, K. J.; Yoo, K. H.; Kim, D. J. and Park, S. W., *Dyes & Pigments,* **1999**, *41*, 19. (b) Bartnik, R.; Mloston, G. and Lesniak, S., *Pol. J. Chem.,* **1979**, *53*, 537. (c) Dermer, O. C. and Ham, G. E., *Ethylenimine and Other Aziridines,* Academic Press, New York, **1969**, pp. 1–59. (d) Kolmark, G. and Westergaard, M., *Hereditas*, **1953**, *39*, 209. (e) Reeves, W. A.; Drake, G. L. and Hoffpauir, C. L., *J. Am. Chem. Soc.,* **1951**, *73*, 3522. (f) Jones, G. D., *J. Org. Chem.,* **1945**, *10*, 484.

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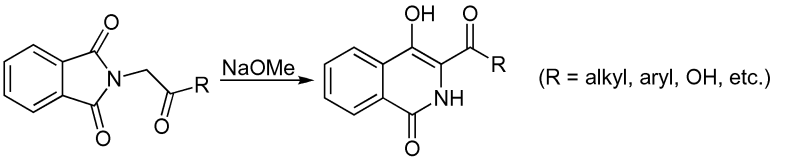
Gabriel-Colman Rearrangement

(Gabriel Isoquinoline Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Gabriel and Colman in 1900.[1] It is the rearrangement of alkyl phthalimidoacetate into isoquinoline derivatives by means of alkoxide treatment. Therefore, it is generally known as the Gabriel-Colman rearrangement.[2] In addition, this reaction is also referred to as Gabriel isoquinoline synthesis.[3] However, this reaction is limited to the phthalimido derivatives containing an enolizable carbon attached to nitrogen.[2e,4] In this reaction, the phthalimido ring is first cleaved and then closed at the methylene carbon to give the ultimate 3-carboethoxy-4-hydroxyisocarbostyril.[4] For the phthalyl derivatives of amino acids other than glycine, the corresponding products are 3-alkyl (or aryl)-4-hydroxyisocarbostyrils.[5] It has been reported that under acidic conditions, the 3-carboethoxyl-4-hydroxyisocarbostyril predominates, whereas in neutral conditions, the tetrahydroisoquinolinedione is the dominating structure of the product.[6]

B. GENERAL REACTION SCHEME



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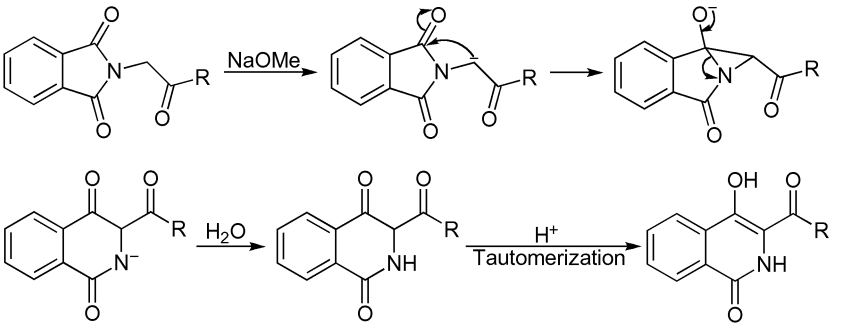
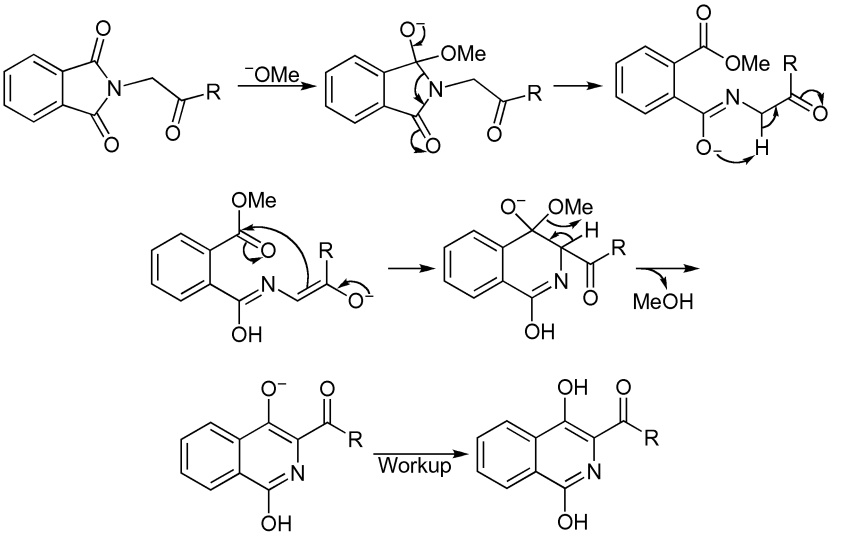
C. PROPOSED MECHANISMS

It is assumed that this reaction involves an α-deprotonation, the formation of aziridine ring, ring opening, and tautomerization to form an isoquinoline skeleton, as shown here in Scheme 1.



SCHEME 1. *Possible mechanism for the Gabriel-Colman rearrangement involving the formation of the aziridine intermediate.*

Alternatively, this reaction may involve the addition of methoxy to the amido group, the opening of the five-membered ring to give an iminol intermediate, followed by the formation of enolate and the final ring closure, as illustrated here in Scheme 2.



SCHEME 2. *Possible mechanism for the Gabriel-Colman rearrangement involving the formation of an iminol intermediate.*

D. MODIFICATION

N/A

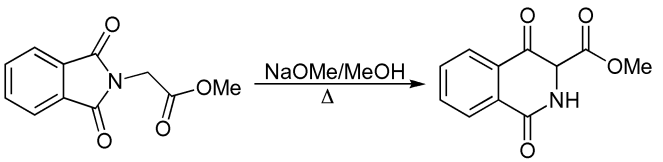
E. APPLICATIONS

This reaction has relatively limited application in isoquinoline syntheses.

F. RELATED REACTIONS

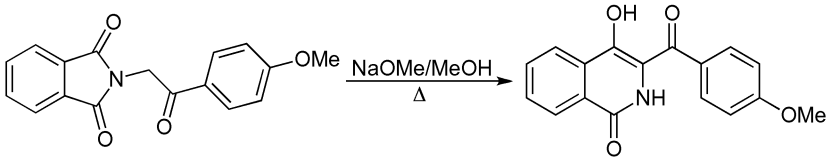
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 6.

To a 1-L, three-neck, round-bottomed flask, fitted with a mercury-seal stirrer and a Friedrichs condenser equipped with a drying tube with CaO were added 21.9 g methyl phthalimidoacetate (0.1 mol), 21.6 g NaOMe, and 200 mL absolute methanol. Stirring and heating were initiated, and the mixture became dark yellow. In ~15 min, a yellow precipitate began to form. At the end of 1 h, the heating was stopped, the mixture was cooled to room temperature, and 100 mL 6 N HCl was added with stirring and cooling. The grayish precipitate was filtered by suction and washed on the filter with 0.1 N HCl until the washings were colorless, then with distilled water until the washings were neutral. The resulting mass was extracted with 500 mL boiling water, and the mixture was filtered through a funnel with a hot water jacket. After the solution cooled down, 13.8 g 3-carbomethoxy-1,2,3,4-tetrahydroisoquinoline-1,4-dione was obtained by filtration, which at dryness melted at 219–220°C (corrected).



Reference 2e.

A solution of *N*-phenacylphthalimide (4 mmol) was added to a flask containing 50 mL 2 M NaOMe in absolute methanol. The mixture was refluxed in the absence of

moisture and carbon dioxide until homogeneous and then for an additional 2 h. After that, the mixture was cooled, and neutralized with dilute HCl. The solid was filtered, washed with water, and crystallized several times from glacial acetic acid to give *p*-methoxybenzoyl-4-hydroisocarbostyril. (No yield was given.)

Other references related to the Gabriel-Colman rearrangement are cited in the literature.[7]

H. REFERENCES

1. (a) Gabriel, S. and Colman, J., *Ber.,* **1900**, *33*, 980. (b) Gabriel, S. and Colman, J., *Ber.,* **1900**, *33*, 996. (c) Gabriel, S. and Colman, J., *Ber.,* **1900**, *33*, 2630.
2. (a) Blanco, M. M.; Shmidt, M. S. and Perillo, I. A., *ARKIVOC,* **2005**, (*xii*), 195. (b) Kwon, S.-K. and Park, M.-S., *J. Korean Chem. Soc.,* **1996**, *40*, 678. (c) Groutas, W. C.; Chong, L. S.; Venkataraman, R.; Epp, J. B.; Kuang, R.; Houser-Archield, N. and Hoidal, J. R., *Bioorg. Med. Chem.,* **1995**, *3*, 187. (d) Groutas, W. C.; Chong, L. S.; Venkataraman, R.; Epp, J. B.; Kuang, R. Z.; Brubaker, M. J.; Houser-Archield, N.; Huang, H. and McClenahan, J. J., *Biochem. Biophys. Res. Commun.,* **1993**, *194*, 1491. (e) Hill, J. H. M., *J. Org. Chem.,* **1965**, *30*, 620.
3. Lions, F. and Ritchie, E., *J. Proc. Royal Soc. New South Wales,* **1941**, *74*, 443.
4. Manske, R. H., *Chem. Rev.,* **1942**, *30*, 145.
5. Ulrich, A., *Ber.,* **1904**, *37*, 1685.
6. Caswell, L. R. and Campbell, R. D., *J. Org. Chem.,* **1961**, *26*, 4175.
7. (a) Parrick, J. and Ragunathan, R., *J. Chem. Soc., Perkin Trans. I,* **1993**, 211. (b) Ivery, M. T. and Gready, J. E., *J. Chem. Res. (S),* **1993**, *9*, 349. (c) Caswell, L. R. and Kao, T. L.-C., *J. Heterocycl. Chem.,* **1966**, *3*, 333. (d) Robison, M. M. and Robison, B. L., *J. Am. Chem. Soc.,* **1958**, *80*, 3443. (e) Hauser, C. R. and Kantor, S. W., *J. Am. Chem. Soc.,* **1951**, *73*, 1437. (f) Allen, C. F. H., *Chem. Rev.,* **1950**, *47*, 284. (g) Findeklee, W., *Ber.,* **1905**, *38*, 3542. (h) Kolshorn, E., *Ber.,* **1904**, *37*, 2474. (i) Kusel, H., *Ber.,* **1904**, *37*, 1971. (j) Gabriel, S. and Colman, J., *Ber.,* **1902**, *35*, 2421.

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Garner Aldehyde

A. GENERAL DESCRIPTION OF THE REACTION

The Garner aldehyde[1]—that is, 1,1-dimethylethyl 4-formyl-2,2-dimethyloxazolidine-3-carboxylate[2] or *N*-Boc D-serinal acetonide[3]—was initially reported by Garner in 1984,[4] and is now commercially available.[2] This compound, a versatile synthon, has wide application in organic synthesis due to its chemical and optical stability, high enantiopurity, and multifunctionality,[5] in which the 4-formyl group can participate in most reactions that occur on regular aldehydes (e.g., *Aldol Reaction, Wittig Reaction*), introducing the contiguous amino-hydroxy functionality that exists in many natural products. In addition, this aldehyde can be readily prepared in the laboratory in multigram quantities[6] without partial racemization.[7] However, it has been reported that the aldehyde itself does epimerize under *Wittig Reaction* conditions when BuLi is used as the base.[3a] To enhance the stability under acidic conditions, the Garner aldehyde is protected by Cbz instead of Boc.[8] It has been reported that olefin predominating in either the *Z*-,[9] or the *E*-configuration[10] can be prepared from this aldehyde, and the allylation with allylindium reagent gives a diastereoselective product in *anti*-form.[11] Some other applications of the Garner aldehyde include the synthesis of glycosyl amino acids,[3a,12] sphingosines,[13] piperidine,[14] and the proteasome inhibitor TMC-95A.[15] The corresponding ester of Garner aldehyde is called the Garner ester.[16]

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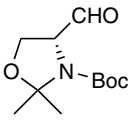
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

N/A

D. MODIFICATION

This aldehyde has been protected by Cbz instead of Boc to improve the stability toward acid.[8]

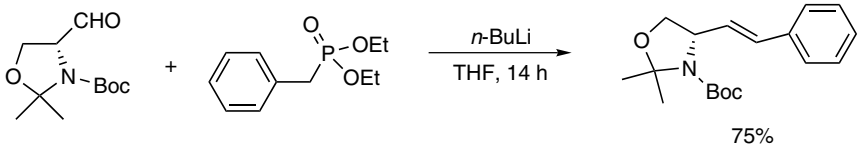
E. APPLICATIONS

This aldehyde has wide application in organic synthesis.

F. RELATED REACTIONS

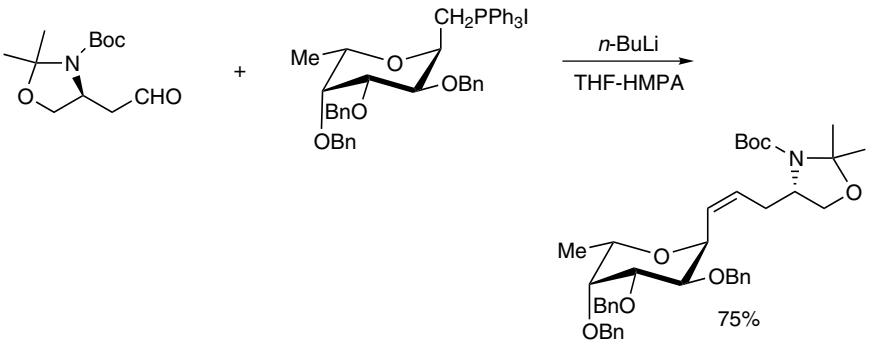
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 10a.

A solution of 6.95 g diethyl benzylphosphonate (30.48 mmol) in 100 mL THF was treated with 15.24 mL 1.6 M BuLi in hexane (24.38 mmol) at −78°C. The resulting mixture was stirred for 30 min at −78°C, and then a 35 mL THF solution containing 3.49 g Garner aldehyde (15.24 mmol) was slowly added over 30 min. After the addition, the mixture was stirred for 2 h at −78°C and 12 h at room temperature. Then the mixture was quenched with water and diluted with Et_2O; the aqueous phase was extracted with Et_2O three times. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (5% EtOAc in petroleum ether) and crystallization in petroleum ether gave 3.46 g (4*S*,1*E*)-2,2-dimethyl-4-styryl-3-*tert*-butyloxycarbonyloxazolidine as colorless crystals, in a yield of 75%, m.p., 85°C.



Reference 3a.

A mixture of 760 mg of phosphonium salt (0.92 mmol), 0.90 g activated 4-Å powdered molecular sieves, 7.1 mL anhydrous THF, and 4.7 mL anhydrous HMPA was stirred at room temperature for 10 min and then cooled to -20°C. The stirred mixture was treated with 580 μL 1.6 M *n*-BuLi in hexanes (0.92 mmol), warmed to 0°C, stirred for an additional 30 min, and then cooled to -20°C. To the stirred mixture was added 336 mg Garner aldehyde in 7.1 mL anhydrous THF over a 15-min period. The mixture was allowed to reach 0°C in 2.5 h, stirred at 0°C for an additional 1 h, and then diluted with 200 mL Et_2O and filtered through a pad of Celite. The ethereal solution was washed with 1 M phosphate buffer at pH 7 (3×30 mL), dried over Na_2SO_4, and concentrated. The residue was eluted from a column of silica gel with 5:1 cyclohexane/EtOAc to give 457 mg 6,10-anhydro-7,8,9-tri-*O*-benzyl-2-*tert*-butoxycarbonylamino-2,3,4,5,11-pentadeoxy-1,2-*N*,*O*-isopropylidene-L-*threo*-D-*ido*-undec-4-(*Z*)-enitol as a syrup, in a yield of 75%.

Other references related to the reactions of the Garner aldehyde are cited in the literature.[17]

H. REFERENCES

1. (a) Inaba, H.; Hiraiwa, Y.; Yoshida, S.; Tamura, M.; Kuroda, A.; Ogawa, A.; Aoyagi, Y.; Ohta, A. and Takeya, K., *Heterocycles*, **2005**, *65*, 2657. (b) Lombardo, M.; Gianotti, K.; Licciulli, S. and Trombini, C., *Tetrahedron*, **2004**, *60*, 11725. (c) Lombardo, M.; Licciulli, S. and Trombini, C., *Tetrahedron Lett*., **2003**, *44*, 9147. (d) Pietruszka, J.; Witt, A. and Frey, W., *Eur. J. Org. Chem.,* **2003**, 3219. (e) Konas, D. W.; Pankuch, J. J. and Coward, J. K., *Synthesis*, **2002**, 2616. (f) Husain, A. and Ganem, B., *Tetrahedron Lett*., **2002**, *43*, 8621. (g) Meffre, P.; Hermann, S.; Durand, P.; Reginato, G. and Riu, A., *Tetrahedron,* **2002**, *58*, 5159. (h) Liang, X. F.; Andersch, J. and Bols, M., *J. Chem. Soc., Perkin Trans. I,* **2001**, 2136. (i) Wroblewski, A. E. and Balcerzak, K. B., *Tetrahedron: Asymmetry*, **2001**, *12*, 427. (j) Ma, D. and Jiang, Y., *Tetrahedron: Asymmetry*, **2000**, *11*, 3727. (k) Marcus, J.; Vandermeulen, G. W. M.; Brussee, J. and van der Gen, A., *Tetrahedron: Asymmetry*, **1999**, *10*, 1617. (l) Aoyagi, Y.; Inaba, H.; Hiraiwa, Y.; Kuroda, A. and Ohta, A., *J. Chem. Soc., Perkin Trans. I,* **1998**, 3975. (m) Qing, F.-L.; Peng, S. and Hu, C.-M., *J. Fluor. Chem.,* **1998**, *88*, 79.
2. Vicario, J. L.; Rodriguez, M.; Badía, D.; Carrillo, L. and Reyes, E., *Org. Lett.,* **2004**, *6*, 3171.
3. (a) Dondoni, A.; Catozzi, N. and Marra, A., *J. Org. Chem.,* **2004**, *69*, 5023. (b) Dondoni, A.; Mariotti, G. and Marra, A., *J. Org. Chem.,* **2002**, *67*, 4475.

4. Garner, P., *Tetrahedron Lett*., **1984**, *25*, 5855.
5. Wills, A. J.; Krishnan-Ghosh, Y. and Balasubramanian, S., *J. Org. Chem.,* **2002**, *67*, 6646.
6. (a) Campbell, A. D.; Raynham, T. M. and Taylor, R. J. K., *Synthesis,* **1998**, 1707. (b) McKillop, A.; Taylor, R. J. K.; Watson, R. J. and Lewis, N., *Synthesis,* **1994**, 31. (c) Meffre, P.; Durand, P.; Branquet, E. and Le Goffic, F., *Synth. Commun.,* **1994**, *24*, 2147. (d) Garner, P. and Park, J. M., *Org. Synth.,* **1992**, *70*, 18.
7. (a) Dondoni, A. and Perrone, D., *Org. Synth.,* **1999**, *77*, 64. (b) Dondoni, A. and Perrone, D., *Synthesis,* **1997**, 527.
8. Chhabra, S. R.; Mahajan, A. and Chan, W. C., *J. Org. Chem.,* **2002**, *67*, 4017.
9. White, J. D.; Kim, T.-S. and Nambu, M., *J. Am. Chem. Soc.,* **1997**, *119*, 103.
10. (a) Felpin, F.-X.; Boubekeur, K. and Lebreton, J., *J. Org. Chem.,* **2004**, *69*, 1497. (b) Nevalainen, M.; Kauppinen, P. M. and Koshinen, A. M. P., *J. Org. Chem.,* **2001**, *66*, 2061.
11. Paquette, L. A.; Mitzel, T. M.; Isaac, M. B.; Crasto, C. F. and Schomer, W. W., *J. Org. Chem.,* **1997**, *62*, 4293.
12. (a) Dondoni, A.; Marra, A. and Massi, A., *J. Org. Chem.,* **1999**, *64*, 933. (b) Dondoni, A.; Marra, A. and Massi, A., *Tetrahedron,* **1998**, *54*, 2827.
13. (a) Chun, J.; Li, G.; Byun, H.-S.; and Bittman, R., *Tetrahedron Lett.,* **2002**, *43*, 375. (b) Jonghe, S. D.; Overmeire, I. V.; Calenbergh, S. V.; Hendrix, C.; Busson, R.; Keukeleire, D. D. and Herewijn, P., *Eur. J. Org. Chem.,* **2000**, 3177. (c) Azuma, H.; Tamagaki, S.; Ogino, K., *J. Org. Chem.,* **2000**, *65*, 3538. d) Hoffman, R. V. and Tao, J., *J. Org. Chem.,* **1998**, *63*, 3979.
14. Takahata, H.; Banba, Y.; Ouchi, H. and Nemoto, H., *Org. Lett.,* **2003**, *5*, 2527.
15. (a) Lin, S. and Danishefsky, S. J., *Angew. Chem. Int. Ed.,* **2002**, *40*, 512. (b) Inoue, M.; Furuyama, H.; Sakazaki, H. and Hirama, M., *Org. Lett.,* **2001**, *3*, 2863. (c) Lin, S. and Danishefsky, S. J., *Angew. Chem. Int. Ed.,* **2001**, *40*, 1967. (d) Ma, D. and Wu, Q., *Tetrahedron Lett.,* **2000**, *41*, 9089.
16. Berkowitz, D. B.; Eggen, M.; Shen, Q. R. and Shoemaker, R. K., *J. Org. Chem.,* **1996**, *61*, 4666.
17. (a) Hallinan, E. A.; Kramer, S. W.; Houdek, S. C.; Moore, W. M.; Jerome, G. M.; Spangler, D. P.; Stevens, A. M.; Shieh, H. S.; Manning, P. T. and Pitzele, B. S., *Org. Biomol. Chem.,* **2003**, *1*, 3527. (b) Triola, G.; Fabriàs, G.; Casas, J. and Llebaria, A., *J. Org. Chem.,* **2003**, *68*, 9924. (c) Takahata, H.; Banba, Y.; Ouchi, H.; Nemoto, H.; Kato, A. and Adachi, I., *J. Org. Chem.,* **2003**, *68*, 3603. (d) Bradley, D. M.; Mapitse, R.; Thomson, N. M. and Hayes, C. J., *J. Org. Chem.,* **2002**, *67*, 7613. (e) Collier, P. N.; Campbell, A. D.; Patel, I.; Raynham, T. M. and Taylor, R. J. K., *J. Org. Chem.,* **2002**, *67*, 1802. (f) Avenoza, A.; Busto, J.; Cativiela, C.; Corzana, F.; Peregrina, J. M. and Zurbano, M., *J. Org. Chem.,* **2002**, *67*, 598. (g) Campbell, J. E.; Englund, E. E. and Burke, S. D., *Org. Lett.,* **2002**, *4*, 2273. (h) Van Brunt, M. P. and Standaert, R. F., *Org. Lett.,* **2000**, *2*, 705. (i) Hertweck, C. and Boland, W., *J. Org. Chem.,* **1999**, *64*, 4426. (j) Merino, P.; Lanaspa, A.; Merchan, F. L. and Tejero, T., *Tetrahedron*: *Asymmetry,* **1998**, *9*, 629. (k) Kauppinen, P. M. and Koskinen, A. M. P., *Tetrahedron Lett*., **1997**, *38*, 3103. (l) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M. and Zurbano, M. M., *Synthesis,* **1997**, 1146. (m) Kumar, J. S. R. and Datta, A., *Tetrahedron Lett*., **1997**, *38*, 6779. (n) Aniello, F. D.; Falorni, M.; Mann, A. and Taddei, M., *Tetrahedron*: *Asymmetry,* **1996**, *7*, 1217. (o) Roush, W. R. and Hunt, J. A., *J. Org. Chem.,* **1995**, *60*, 798. (p) Nicolaou, K. C.; Bunnage, M. E. and Koide, K., *J. Am. Chem. Soc.,* **1994**, *116*, 8402. (q) Sakai, N.;and Ohfune, Y., *Tetrahedron Lett*., **1990**, *31*, 4151. (r) Garner, P. and Park, J. M., *J. Org. Chem.,* **1987**, *52*, 2361.

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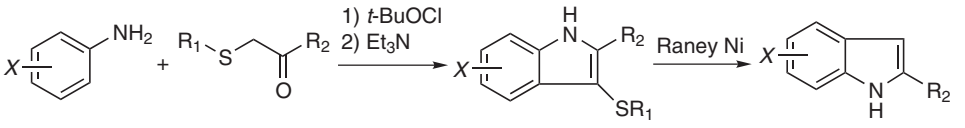
Gassman Indole Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Gassman and co-workers in 1973.[1] It is a versatile method used to prepare many types of substituted indoles via a sequential treatment of anilines by *tert*-butyl chlorite, β-keto sulfide, triethylamine, and Raney nickel if desulfurization is needed.[1a] Although this is a multistep reaction, it essentially is a one-pot reaction[2] and can be applied to synthesize either 1- or 2- substituted and 2,7-disubstituted indoles in good yields.[1a] This method has a few demonstrated advantages over the most common methods for the preparation of indoles, e.g., *Fischer Indole Synthesis*. These advantages include the application of a cheap and readily available starting material; accessibility for 1-, 2-, 4-, 5-, 6-, or 7-substituted indoles; mild reaction conditions without involving a strong acid or base; and higher yield than the average yields from the *Fischer Indole Synthesis*.[1a] In contrast, the common *Fischer Indole Synthesis* needs the appropriately substituted phenylhydrazine or 1,1-disubstituted hydrazine to make the desired indole derivatives.[3] A general mechanism was provided in 1974,[4] and the application of this reaction has been reviewed.[5]

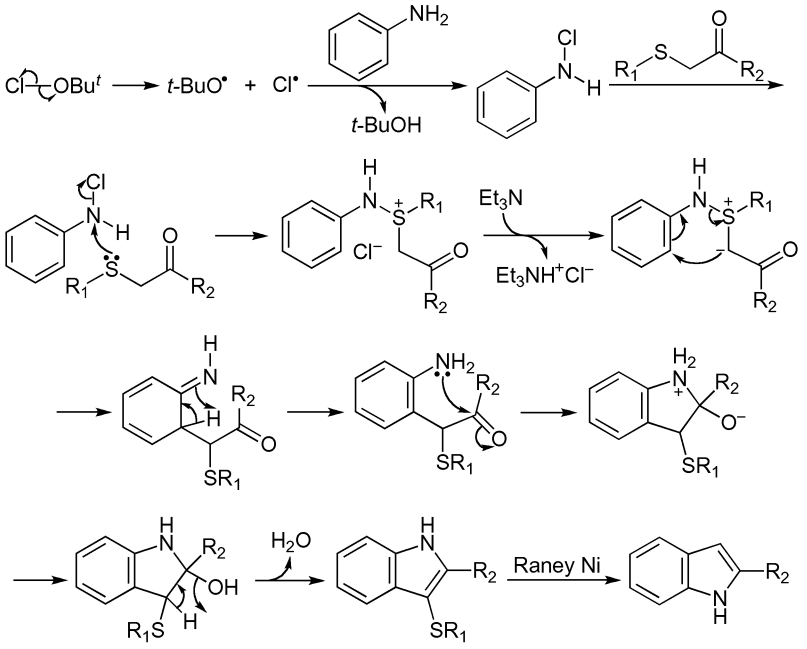
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

This reaction is assumed to begin with the proton abstraction by a *t*-butoxy radical, as shown here.



D. MODIFICATION

N/A

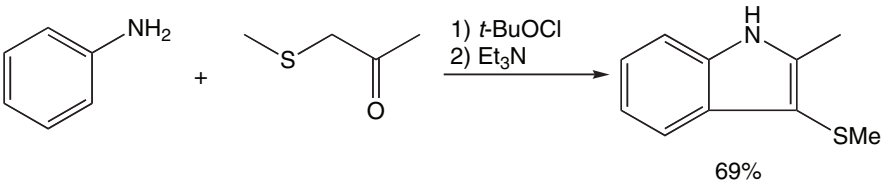
E. APPLICATIONS

This reaction has broad application in the preparation of a variety of substituted indoles.

F. RELATED REACTIONS

This reaction is closely related to the *Gassman Reaction* and *Gassman Oxindole Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4.

To a vigorously stirred solution of 2.05 g aniline (0.022 mol) in 150 mL CH_2Cl_2 at −65°C was added dropwise 2.4 g *tert*-butyl hypochlorite (0.022 mol) in 20 mL CH_2Cl_2. After 5–10 min, 2.3 g methyl acetylmethylene sulfide (0.022 mol) in 20 mL CH_2Cl_2 was added, causing an exotherm; and the mixture was stirred for an additional hour. Subsequently, 2.22 g triethylamine (0.022 mol) in 20 mL CH_2Cl_2 was added. After the addition was completed, the cooling bath was removed and the solution was allowed to warm to room temperature. Water (50 mL) was added, and the organic layer was separated, dried, filtrated, and evaporated. The residue was then purified by column chromatography over silica gel using methylene chloride. Recrystallization then gave 2.68 g 2-methyl-3-methylthioindole, in a yield of 69%, m.p. 58–59°C, b.p. 140–142°C (0.85 mmHg).

Other references related to the Gassman indole synthesis are cited in the literature.[6]

H. REFERENCES

1. (a) Gassman, P. G. and van Bergen, T. J., *J. Am. Chem. Soc.,* **1973**, *95*, 590. (b) Gassman, P. G. and van Bergen, T. J., *J. Am. Chem. Soc.,* **1973**, *95*, 591.
2. Johnson, P. D. and Aristoff, P. A., *J. Org. Chem.,* **1990**, *55*, 1374.
3. See *Fischer Indole Synthesis* herein (P. 1069).
4. Gassman, P. G.; van Bergen, T. J.; Gilbert, D. P. and Cue, B. W., *J. Am. Chem. Soc.,* **1974**, *96*, 5495.
5. Li, J. J., ed., *Name Reactions in Heterocyclic Chemistry*, John Wiley & Sons, New York, **2004**, chap. 3.5.
6. (a) Ishikawa, H.; Uno, T.; Miyamoto, H.; Ueda, H.; Tamaoka, H.; Tominaga, M. and Nakagawa, K., *Chem. Pharm. Bull.,* **1990**, *38*, 2459. (b) Gassman, P. G. and van Bergen, T. J., *Org. Synth. Coll.* **1988**, *6*, 50.

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Gassman Oxindole Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Gassman and co-workers in 1973.[1] It is a multistep process (but a one-pot reaction[2]) for preparing oxindole with an electron-withdrawing group involving sequential treatment of aniline with *tert*-butyl hypochlorite, ethyl (methylthio)acetate, triethylamine, and hydrochloric acid and final treatment with zinc or Raney nickel for the desulfurization.[1,3] Therefore, this reaction is often known as the Gassman oxindole synthesis.[4] For the anilines with an electron-donating group, the nucleophilic attack by a sulfur atom on the nitrogen atom is disfavored, thus an alternative approach is used to prepare the corresponding oxindoles by treatment of the anilines with chlorosulfonium salt.[5] Further oxidation of the resulting oxindole by *N*-chlorosuccinamide/HgO or by direct air oxidation gives relevant isatin.[6] This reaction can tolerate a variety of functional groups, which differ in electron character;[1] in addition, *N*-alkylanilines are also suitable for this reaction.[7] It should be pointed out that when sulfide with a substituent at the active methylene moiety is used, a 3-substituted oxindole will be produced.[1]

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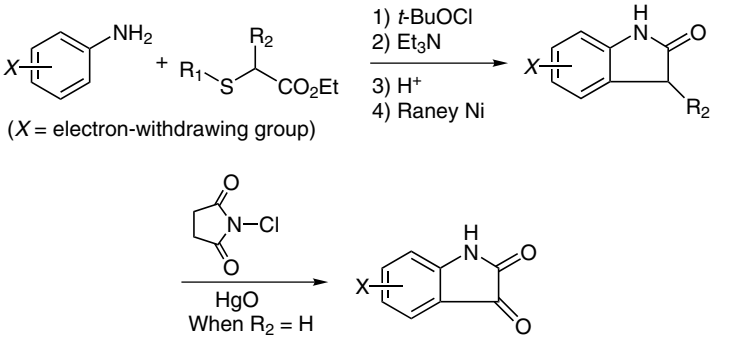
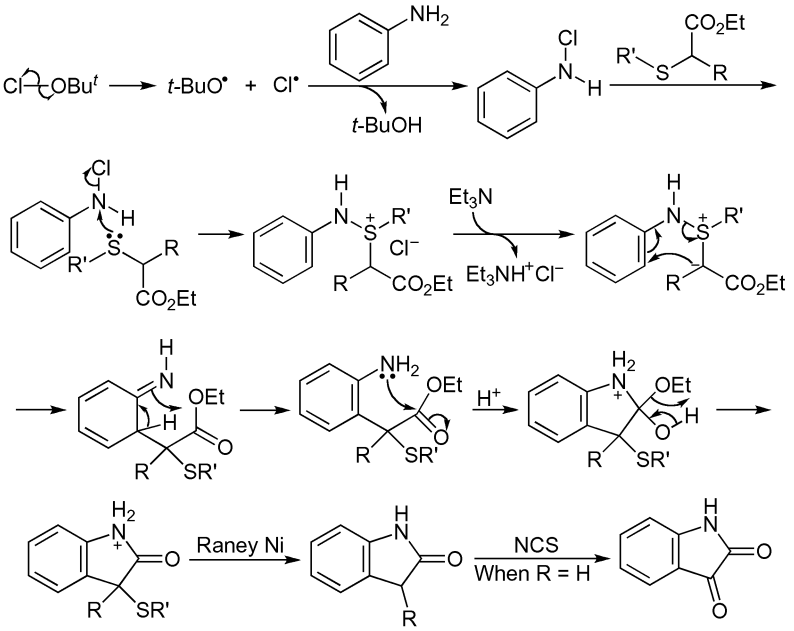
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The mechanism emphasizing the formation of oxindole is illustrated here.



D. MODIFICATION

This reaction has been modified to use a sulfoxide as a synthetic equivalent of a sulfenyl halide.[8] In addition, a procedure that involves the initial mixing of ethyl (methylthio)acetate and sulfuryl chloride, followed by the addition of aniline with one equivalent of proton sponge and final Et_3N treatment can be used to prepare oxindole that is not accessible via the initial Gassman protocol.[2]

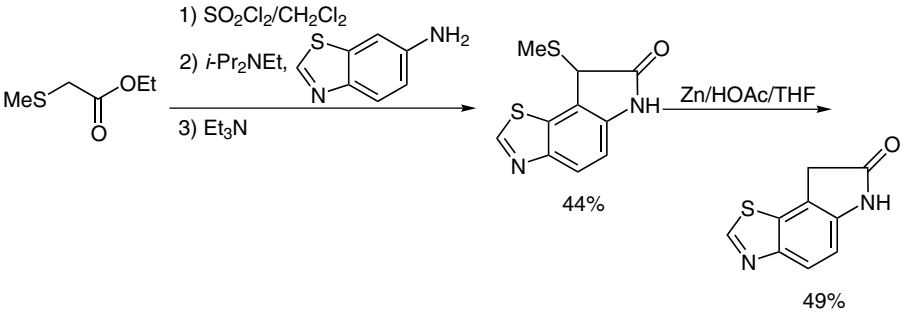
E. APPLICATIONS

This reaction has general application in the preparation of oxindoles and isatins.

F. RELATED REACTIONS

This reaction is closely related to the *Gassman Reaction* and *Gassman Indole Synthesis*.

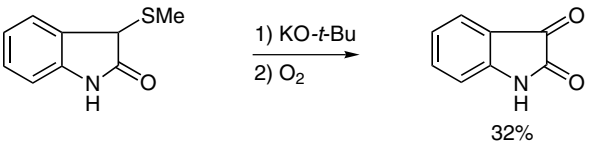
G. CITED EXPERIMENTAL EXAMPLES



Reference 3.

Under a nitrogen atmosphere, a mixture of 121 g ethyl methylthioacetate (116 mL, 0.9 mol) and 1.33 L CH_2Cl_2 was cooled to −74°C with a dry ice acetone bath. Sulfuryl chloride (70.0 mL, 118 g, 0.870 mol) was added over a 5-min period, with the temperature maintained between −70° and −74°C, and the clear colorless solution was stirred at −70° to −74°C for 25 min. Then a mixture of 117 g *N*-ethyl-diisopropylamine (157 mL, 0.9 mol), 131 g 6-aminobenzothiazole (0.87 mol), and 1 L CH_2Cl_2 was added over a period of 100 min with the temperature maintained between −69° and −74°C. An additional 0.9 L CH_2Cl_2 was added to dissolve a cream-colored precipitate, and the solution was stirred for 30 min. Triethylamine was added over a 2-min period, causing a temperature rise to −48°C. After 15 min the cooling bath was removed, and the brown-orange solution was warmed to −30°C over a 45-min period with a heat gun. The solution was concentrated under vacuum at 20°C, and the resulting dark orange oil was treated with 1.4 L 0.5-inch N HCl and 1.3 L *tert*-butylmethyl ether. The mixture was stirred for 2.5 h at room temperature. The golden precipitate was isolated by filtration and dried in a vacuum at room temperature to furnish 92 g 8-(methylsulfanyl)-6,8-dihydro-7*H*-[1,3]thiazolo[5,4-*e*]-indol-7-one, in a yield of 44%.

A mixture of 2.7 g 8-(methylsulfanyl)-6,8-dihydro-7*H*-[1,3]thiazolo[5,4-*e*]indol-7-one (11 mmol), 3.0 g activated zinc, 41 mL acetic acid, and 41 mL THF was heated at 60–65°C for 3.5 h. The gray-green mixture was filtered through a sintered glass funnel containing a 0.5-inch pad of Celite, and the pad was washed with 40 mL hot THF/acetic acid (1:1). Water (200 mL) was added to the filtrate, and the pale yellow mixture was stirred for 10 min. The resulting solid was isolated by filtration, washed with 25 mL water, and dried under vacuum at 70°C to furnish 1.05 g 6,8-dihydro-7*H*-[1,3]thiazolo[5,4-*e*]indol-7-one as a pale yellow solid, in a yield of 49%.



Reference 6.

A mixture of 0.48 g 3-methylthiooxindole and an equimolar amount of sublimed potassium *tert*-butoxide was suspended in 200 mL dry ether at 0°C. The solution immediately became colored. The reaction mixture was then stirred and aerated at 0°C for 4 h and then at 25°C for 20 h. Acidification with diluted HCl prepared from 0.22 mL conc. HCl and 25 mL water followed by extraction with ether, drying of the extracts over $MgSO_4$, filtration, and evaporation of the filtrate gave an orange solid. Recrystallization from chloroform gave 0.13 g pure isatin, in a yield of 32%, m.p., 199–200°C.

Other references related to the Gassman oxindole synthesis are cited in the literature.[9]

H. REFERENCES

1. Gassman, P. G. and van Bergen, T. J., *J. Am. Chem. Soc.,* **1973**, *95*, 2718.
2. Johnson, P. D. and Aristoff, P. A., *J. Org. Chem.,* **1990**, *55*, 1374.
3. Bramson, H. N.; Corona, J.; Davis, S. T.; Dickerson, S. H.; Edelstein, M.; Frye, S. V.; Gampe, R. T.; Harris, P. A.; Hassell, A.; Holmes, W. D.; Hunter, R. N.; Lackey, K. E.; Lovejoy, B.; Luzzio, M. J.; Montana, V.; Rocque, W. J.; Rusnak, D.; Shewchuk, L.; Veal, J. M.; Walker, D. H. and Kuyper, L. F., *J. Med. Chem.,* **2001**, *44*, 4339.
4. (a) Li, C. M.; Chan, C.; Heimann, A. C. and Danishefsky, S. J., *Angew. Chem. Int. Ed.,* **2007**, *46*, 1448. (b) Wright, S. W.; McClure, L. D. and Hageman, D. L., *Tetrahedron Lett*., **1996**, *37*, 4631. (c) Karp, G. M., *J. Org. Chem.,* **1992**, *57*, 4765.
5. (a) da Silva, J. F. M.; Garden, S. J. and Pinto, A. C., *J. Braz. Chem. Soc.,* **2001**, *12*, 273. (b) Gassman, P. G.; Gilbert, D. P. and Luh, T.-Y., *J. Org. Chem.,* **1977**, *42*, 1340.
6. Gassman, P. G. and Halweg, K. M., *J. Org. Chem.,* **1979**, *44*, 628.
7. (a) Gassman, P. G. and Cue, B. W., *Ger. Pat*., **1978**, Oct. 26, 2,815,609. (b) Gassman, P. G. and Cue, B. W., *U.S. Pat*., **1980**, Feb. 12, 4,188,325.
8. Wright, S. W.; McClure, L. D. and Hageman, D. L., *Tetrahedron Lett.,* **1996**, *37*, 4631.
9. (a) Tokunaga, T.; Hume, W. E.; Umezome, T.; Okazaki, K.; Ueki, Y.; Kumagai, K.; Hourai, S.; Nagamine, J.; Seki, H.; Taiji, M.; Noguchi, H. and Nagata, R., *J. Med. Chem.,* **2001**, *44*, 4641. (b) Nakatani, K.; Fukuda, Y. and Terashima, S., *Pure & Appl. Chem.,* **1994**, *66*, 2255. (c) Walsh, D. A.; Shamblee, D. A.; Welstead, W. J. and Sancilio, L. F., *J. Med. Chem.,* **1982**, *25*, 446. (d) Wierenga, W., *J. Am. Chem. Soc.,* **1981**, *103*, 5621. (e) Gassman, P. G.; Cue, B. W. and Luh, T. Y., *J. Org. Chem.,* **1977**, *42*, 1344. (f) Gassman, P. G. and van Bergen, T. J., *J. Am. Chem. Soc.,* **1974**, *96*, 5508. (g) Gassman, P. G.; Gruetzmacher, G. and van Bergen, T. J., *J. Am. Chem. Soc.,* **1974**, *96*, 5512.

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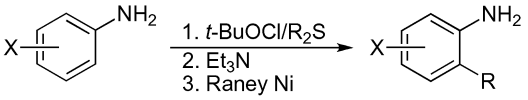
Gassman Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Gassman in 1972.[1] It is a multistep preparation of *ortho*-alkylated anilines by sequential treatment of the anilines with *tert*-butyl hypochlorite, dialkylsulfide, and triethylamine followed by Raney nickel desulfurization. Therefore, it is known as the Gassman reaction.[2] Although it is a multistep process, it is actually a one-pot reaction.[2] In addition, this reaction can be adapted to prepare anilines with vinyl, formyl, and benzyl groups at the *ortho*-position.[3] Furthermore, *para*-substituted anilines can be prepared as well via a modified process by which *N*-*t*-butyl-*N*-chloro anilines, generated from the chlorination of anilines from *tert*-butyl hypochlorite, are treated with silver salt and a nucleophile such as methanol.[4]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

This reaction involves the proton abstraction by a *t*-butoxy radical, followed by the coupling between a S_N2 reaction with thioether, as shown here.

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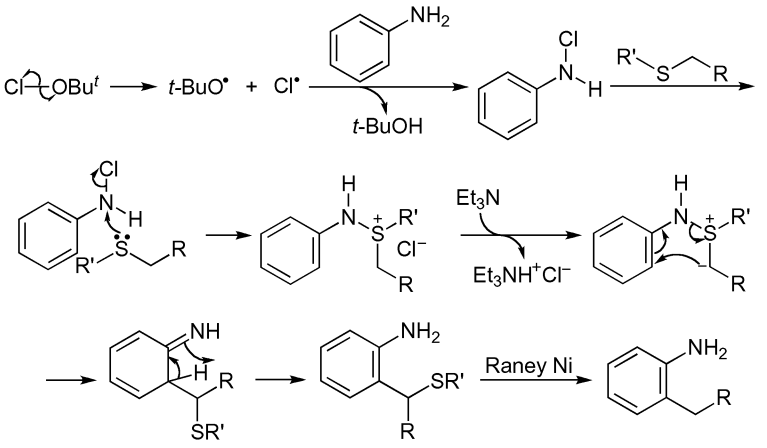


D. MODIFICATION

This reaction has been improved by using sulfuryl chloride as the chlorination reagent.[2]

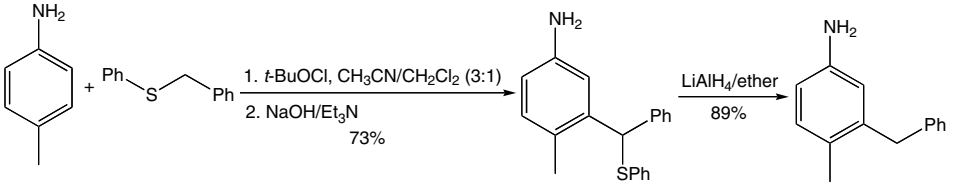
E. APPLICATIONS

This reaction has been used for the preparation of anilines with alkyl, vinyl, formyl, and benzyl groups at the *ortho*-position.

F. RELATED REACTIONS

This reaction is closely related to the *Gassman Indole Synthesis* and *Gassman Oxindole Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES

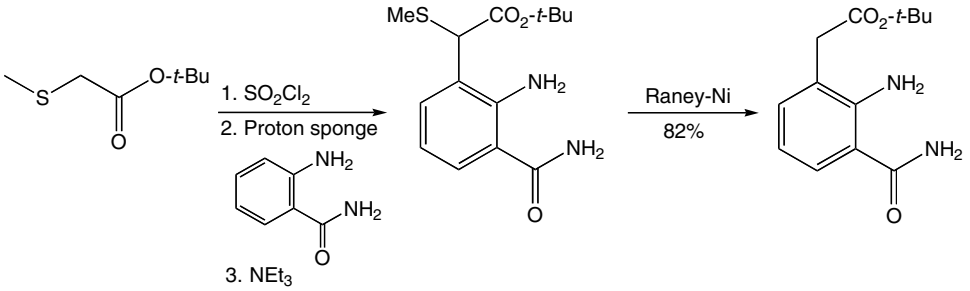


Reference 3.

To a rapidly stirred solution of 2.7 g *p*-tolulidine (0.025 mol) and 0.050–0.080 mol benzyl phenyl sulfide in 300 mL dry acetonitrile and 100 mL methylene chloride under nitrogen at

−40°C was added dropwise 3.5 g *tert*-butyl hypochlorite (0.032 mol) in 25 mL methylene chloride at −78°C in diffuse light. The reaction mixture was stirred for 4 h at −40°C, then allowed to warm slowly to −20°C over a 3-h period. Sodium methoxide (7.0 g, 0.13 mo1) in 50 mL methanol at 25°C was added, and the reaction mixture was stirred for 1 h, during which the reaction mixture warmed to room temperature. The solution was concentrated in vacuo; 250–500 mL dry toluene and 30–50 mL triethylamine were added, and the solution was refluxed for 12 h. The solution was concentrated in vacuo, 100 mL water was added, and the reaction mixture was extracted with CH_2Cl_2 (5 × 100 mL). The combined organic phases were washed with 50 mL 5% aqueous sodium hydroxide and 100 mL brine, dried over $MgSO_4$, and filtered. The solvent was removed in vacuo, leaving an oil that was chromatographed on 300–500 g Fisher basic alumina (activity I) using ether/pentane or ether as the eluant to give 5.7 g 2-amino-5-methyldiphenylthiophenoxymethane as a yellow oil, in a yield of 73%.

To a rapidly stirred suspension of 0.50 g $LiAlH_4$(13.2 mmol) in 100 mL dry ether under nitrogen at room temperature was added 2.0 g 2-amino-5-methyldiphenylthiophenoxymethane (6.6 mmol) in 30 mL ether. The suspension was stirred for 12 h at 25°C. Sulfuric acid (0.5 N, 100 mL) was added, and the product was extracted with ether (5 × 100 mL). The combined organic phases were washed with 50 mL 5% aqueous sodium hydroxide and 100 mL brine, dried over $MgSO_4$, filtered, and concentrated. Distillation of the residue gave 1.16 g 2-amino-5-methyldiphenylmethane, in a yield of 89%, b.p., 124–127°C (0.27 mmHg).



Reference 2.

tert-Butyl (methy1thio)acetate (12.0 g, 74 mmol) in 800 mL methylene chloride at −70°C was treated dropwise with 5.9 mL sulfuryl chloride (73 mmol), and stirred for 30 min, then treated dropwise with a solution of 16 g proton sponge (75 mmol) and 10.0 g anthranilamide (73 mmol) in 1000 mL methylene chloride over 1 h. The resulting pink slurry was then treated with 12 mL triethylamine (86 mmol) and allowed to warm to room temperature. The mixture was washed with water (3 × 250 mL) and brine, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. Flash chromatography on 200 g silica gel, eluting with EtOAc/hexane (1:1) gave 19.5 g *t*-butyl *m*-amido-*o*-amino-α-methylthiophenylacetate as a pale yellow oil.

A solution of 14.5 g of the yellow oil (49 mmol) in 400 mL absolute ethanol was stirred with 50 mL Raney nickel (washed to neutrality with water then with ethanol) at room temperature for 30 minutes and filtered through Celite; the filter cake was washed with THF (2 × 50 mL). The combined filtrates were concentrated in vacuo, and the resulting solid was triturated with EtOAc/hexane (1:1) to give 10.0 g *t*-butyl *m*-amido-*o*-amino-phenylacetate, in a yield of 82%.

Other references related to the Gassman reaction are cited in the literature.[5]

H. REFERENCES

1. Gassman, P. G.; Gruetzmacher, G. and Smith, R. H., *Tetrahedron Lett.,* **1972**, 497.
2. Johnson, P. D. and Aristoff, P. A., *J. Org. Chem.,* **1990**, *55*, 1374.
3. Gassman, P. G. and Drewes, H. R., *J. Am. Chem. Soc.,* **1978**, *100*, 7600.
4. Gassman, P. G.; Campbell, G. A. and Frederick, R. C., *J. Am. Chem. Soc.,* **1972**, *94*, 3884.
5. (a) Davies, I. W.; Marcoux, J.-F.; Kuethe, J. T.; Lankshear, M. D.; Taylor, J. D. O.; Tsou, N.; Dormer, P. G.; Hughes, D. L.; Houk, K. N. and Guner, V., *J. Org. Chem.,* **2004**, *69*, 1298. (b) Gassman, P. G. and van Bergen, T. J., *J. Am. Chem. Soc.,* **1974**, *96*, 5508. (c) Gassman, P. G. and Gruetzmacher, G., *J. Am. Chem. Soc.,* **1973**, *95*, 588. (d) Gassman, P. G. and van Bergen, T. J., *J. Am. Chem. Soc.,* **1973**, *95*, 2718. (e) Gassman, P. G.; van Bergen, T. J. and Gruetzmacher, G., *J. Am. Chem. Soc.,* **1973**, *95*, 6508. (f) Johnson, C. R.; Bacon, C. C. and Kingsbury, W. D., *Tetrahedron Lett.,* **1972**, 501.

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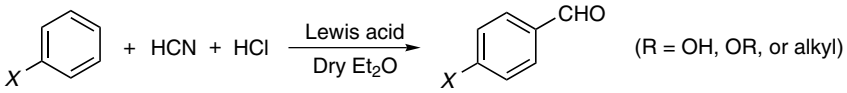
Gattermann Aldehyde Synthesis

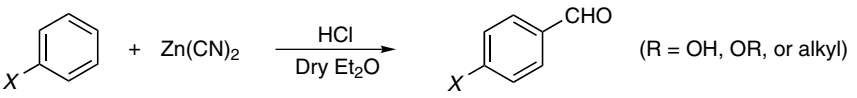
A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Gattermann in 1898.[1] It is the preparation of aromatic aldehydes containing hydroxyl or alkyloxyl groups on the aromatic ring by treatment of the aromatics with hydrogen cyanide and hydrogen chloride in anhydrous solvent (e.g., ether) with or without the presence of a Lewis acid (e.g., $ZnCl_2$, $AlCl_3$) as a catalyst,[2] in which aldimine hydrochloride functions as an intermediate.[2,3] Therefore, it is generally known as the Gattermann aldehyde synthesis[3,4] or simply as the Gatterman synthesis.[5] However, because the application of anhydrous hydrogen cyanide needs extensive precaution and skill during the whole process,[5c] a new condition was adapted by Adams by treating the aromatics in dry ether with zinc cyanide and then passing them in dry hydrogen chloride, in which hydrogen cyanide forms *in situ* and the new formed zinc chloride functions as a catalyst.[5b,5c] It is known that pure zinc cyanide is ineffective for this reaction, but it will work properly in the presence of a trace amount of KCl or NaCl.[2] Currently, this reaction is probably still the only available process for preparing some phenolic aldehydes[5c] and is even suitable for making aromatic aldehydes with multi-alkyl groups, such as mesitaldehyde.[6]

B. GENERAL REACTION SCHEME



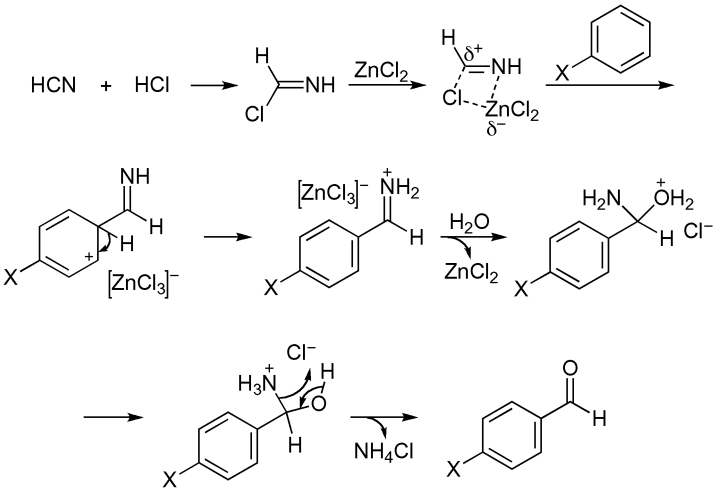
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang



Adam-modified condition

C. PROPOSED MECHANISMS

Because no mechanistic details are available, a mechanism is proposed and illustrated here.



D. MODIFICATION

This reaction has been modified by treating aromatic compounds with zinc cyanide and anhydrous hydrogen chloride.[5b,5c]

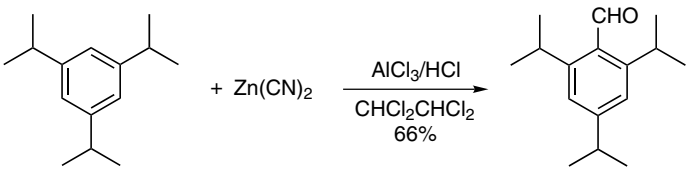
E. APPLICATIONS

This reaction is useful in the preparation of aromatic aldehydes with hydroxyl, alkoxyl, and even mutli-alkyl groups.

F. RELATED REACTIONS

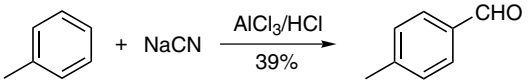
This reaction is related to the *Friedel-Crafts Acylation, Reimer-Tiemann Reaction, Houben-Hoesch Acylation,* and *Vilsmeier-Haack Formylation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 6.

A rapid stream of dry hydrogen chloride was passed into a mixture of 100 g 1,3,5-triisopropylbenzene, 102 g zinc cyanide, and 400 mL tetrachloroethane until the cyanide was decomposed. The mixture was cooled to 0°C, and to it was added 134 g $AlCl_3$ with vigorous stirring. Introduction of hydrogen chloride was resumed and continued for 8 h at 70°C. The mixture was poured into a mixture of ice and hydrochloric acid and allowed to stand for overnight. It was then heated under reflux for 3 h. Final distillation afforded 75.0 g 2,4,6-triisopropylbenzaldehyde, in a yield of 66%.



Reference 3.

Dry hydrogen chloride was passed at a slow rate into a well-stirred mixture of 25 g reagent sodium cyanide (0.4 mol), 100 g anhydrous aluminum chloride (0.77 mol), and 100 mL toluene (in excess amount) at room temperature for 15 min, after which the bath temperature was brought up gradually to 100°C, and the passage of dry hydrogen chloride was maintained for 7 h. The reaction mixture was hydrolyzed by pouring it into 300 mL ice–conc. HCl, and subjected to steam distillation. The distillate was extracted with ether, neutralized, and dried. It was submitted to fractionation, whereby 35 g unreacted toluene was recovered and 26 g *p*-tolualdehyde was obtained, in a yield of 39%, b.p. 204–207°C. It was noticed that the yield of *p*-tolualdehyde was appreciably lower when the reaction was carried out below 100°C.

Other references related to the Gattermann aldehyde synthesis are cited in the literature.[7]

H. REFERENCES

1. Gattermann, L., *Ber.,* **1898**, *31*, 1149.
2. Ferguson, L. N., *Chem. Rev.,* **1946**, *38*, 227.
3. Niedzielski, E. L. and Nord, F. F., *J. Am. Chem. Soc.,* **1941**, *63*, 1462.
4. (a) Kreutzberger, A., *Arch. Pharm. Ber. Deut. Pharm. Gesell.,* **1971**, *304*, 362. (b) Kreutzberger, A., *Zeitsch. Chem.,* **1970**, *10*, 383. (c) Kreutzberger, A., *Arch. Pharm. Ber. Deut. Pharm. Gesell*., **1969**, *302*, 828. (d) Kreutzberger, A., *Angew. Chem. Int. Ed. Engl.,* **1967**, *6*, 940.
5. (a) Malkin, T. and Nierenstein, M., *J. Am. Chem. Soc.,* **1931**, *53*, 239. (b) Adams, R. and Montgomery, E., *J. Am. Chem. Soc.,* **1924**, *46*, 1518. (c) Adams, R. and Levine, I., *J. Am. Chem. Soc.,* **1923**, *45*, 2373.

6. Fuson, R. C.; Horning, E. C.; Ward, M. L.; Rowland, S. P. and Marsh, J. L., *J. Am. Chem. Soc.,* **1942**, *64*, 30.

7. (a) Sato, Y.; Yato, M.; Ohwada, T.; Saito, S. and Shudo, K., *J. Am. Chem. Soc.,* **1995**, *117*, 3037. (b) Jha, H. C.; Zilliken, F. and Breitmaier, E., *Angew. Chem. Int. Ed. Engl.,* **1981**, *20*, 102. (c) Aslam, F. M.; Gore, P. H. and Jehangir, M., *J. Chem. Soc., Perkin Trans. I,* **1972**, 892. (d) Baltazzi, E. and Krimen, L. I., *Chem. Rev.,* **1963**, *63*, 526. (e) Truce, W. E., *Org. React.,* **1957**, *9*, 37. (f) Szmant, H. H.; Segedi, M. J. and Dudek, J., *J. Org. Chem.,* **1953**, *18*, 745. (g) Arnold, R. and Sprung, J., *J. Am. Chem. Soc.,* **1938**, *60*, 1699. (h) Corwin, A. H. and Andrews, J. S., *J. Am. Chem. Soc.,* **1936**, *58*, 1086. (i) Mosettig, E. and Burger, A., *J. Am. Chem. Soc.,* **1933**, *55*, 2981. (j) Karrer, P., *Helv. Chim. Acta,* **1919**, *2*, 89. (k) Gattermann, L., *Ann.,* **1907**, *357*, 313. (l) Gattermann, L., *Ann.,* **1906**, *347*, 347.

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Gattermann Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Gattermann in 1890.[1] It is the preparation of aromatic halides or aromatic cyanides by decomposition of corresponding diazo salts in the presence of copper powder, in which copper powder is freshly obtained from a copper (II) sulfate aqueous solution. Therefore, it is generally known as the Gattermann reaction.[2] Occasionally, it is also referred to as the Gattermann method.[3] It should be pointed out that this reaction is almost equivalent to the *Sandmeyer Reaction*.[2b] It is believed that a radical mechanism might be involved in this reaction,[2c] by which electron transfer occurs at the surface of metallic copper.[2b] However, this reaction is not applicable for the preparation of aromatic fluorides because HF exists as H_2F_2 and ionized as H^+ and HF_2^-.[2e]

B. GENERAL REACTION SCHEME

$$ArN_2X \xrightarrow[\Delta]{\text{Cu/HCl (aq.)}} ArX \quad (X = \text{Cl, Br, I, CN, etc.})$$

C. PROPOSED MECHANISMS

It is known that this reaction involves unstable aryl cupric halide,[2h] therefore, a tentative mechanism involving a radical process is outlined here.

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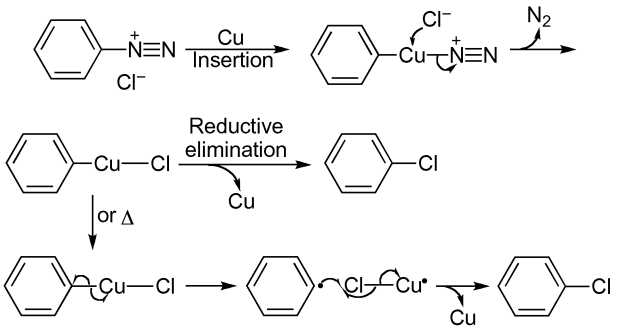


D. MODIFICATION

This reaction has been modified for preparing aromatic mercuric halide.[2h] In addition, a similar procedure for preparing aryl halides from dry arenediazonium *o*-benzenedisulfonimides and quaternary ammonium halides in the presence of copper can be considered a further modification of the Gattermann reaction.[2a]

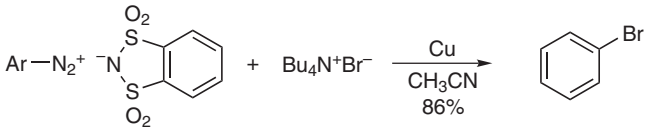
E. APPLICATIONS

This reaction is useful for the preparation of aromatic halides and cyanides.

F. RELATED REACTIONS

This reaction is related to the *Sandmeyer Reaction, Balz-Schiemann Reaction,* and *Bart Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2a.

To a suspension of 3.23 g dry benzenediazonium *o*−benzenedisulfonimide (10 mmol) in 20 mL anhydrous CH_3CN maintained at 20°C was added 0.02 g copper powder and 8.06 g tetrabutylammonium bromide (25 mmol) in one portion under vigorous stirring. A rapid evolution of nitrogen took place at once. The salt dissolved, and the solution became red and then cleared to pale orange. The solution was stirred for an additional 45 min, the reaction mixture was filtered to remove the copper, and the solution was then poured into 200 mL Et_2O/water (1:1). The aqueous layer, containing CH_3CN and a suspension of a fine

white solid substance, was separated and extracted again with 80 mL Et_2O. The combined organic extracts were washed several times with water (4 × 50 mL) to eliminate all the CH_3CN, dried over Na_2SO_4, and evaporated under reduced pressure. The crude residue was column chromatographed, eluting with petroleum ether/CH_2Cl_2 (9:1, v/v), to afford 1.35 g bromobenzene as a colorless oil, in a yield of 86%.

Other references related to the Gattermann reaction are cited in the literature.[4]

H. REFERENCES

1. Gattermann, L., *Ber.,* **1890**, *23*, 1218.
2. (a) Barbero, M.; Degani, I.; Dughera, S. and Fochi, R., *J. Org. Chem.,* **1999**, *64*, 3448. (b) Galli, C., *Chem. Rev.,* **1988**, *88*, 765. (c) Bergmann, E. D.; Berkovic, S. and Ikan, R., *J. Am. Chem. Soc.,* **1956**, *78*, 6037. (d) Bunnett, J. F. and Zahler, R. E., *Chem. Rev.,* **1951**, *49*, 273. (e) Hodgson, H. H., *Chem. Rev.,* **1947**, *40*, 251. (f) Bolth, F. A.; Whaley, W. M. and Starkey, E. B., *J. Am. Chem. Soc.,* **1943**, *65*, 1456. (g) Case, F. H., *J. Am. Chem. Soc.,* **1938**, *60*, 424. (h) McClure, R. E., and Lowy, A., *J. Am. Chem. Soc.,* **1931**, *53*, 319.
3. (a) Doyle, M. P.; Siegfried, B. and Dellaria, J. F., *J. Org. Chem.,* **1977**, *42*, 2426. (b) Hey, D. H. and Waters, W. A., *Chem. Rev.,* **1937**, *21*, 169.
4. (a) Zollinger, H., "Diazotization of Amines and Dediazoniation of Diazonium Ions" in *The Chemistry of Amino, Nitroso, Nitro and Related Groups*, ed. Patai, S., John Wiley & Sons, New York, **1996**, Supplement F2, Part 1, pp. 636–637. (b) Zollinger, H., *Diazo Chemistry I: Aromatic and Heteroaromatic Compounds*, VCH Verlagsgesellschaft mbH, Weinheim, **1994**. (c) Galli, C., *J. Chem. Soc., Perkin Trans. II,* **1984**, 897. (d) Kochi, J. K., *J. Am. Chem. Soc.,* **1957**, *79*, 2942. (e) Cowdrey, W. A. and Davies, D. S., *Quart. Rev.*, **1952**, *6*, 358. (f) Waters, W. A., *J. Chem. Soc.,* **1942**, 266. (g) Gattermann, L., *Practical Methods of Organic Chemistry,* Macmillan, New York, **1927**, p. 237. (h) Gattermann, L., *Ber.,* **1890**, *23*, 1226.

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Gattermann-Koch Formylation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was originally reported by Gattermann and Koch in 1897.[1] It is the preparation of aromatic aldehydes by the treatment of aromatic compounds with CO and HCl in the presence of $AlCl_3$ and cuprous chloride, by which CO and HCl behave like the hypothetical formyl chloride and react in a fashion similar to other acyl chlorides. Therefore, this reaction is generally known as the Gattermann-Koch formylation.[2] Occasionally, it is also referred to as the Gattermann-Koch aldehyde synthesis,[3] Gattermann-Koch reaction,[4] or Gattermann-Koch synthesis.[5] It is known that this reaction can be carried out in two major types of conditions: at atmospheric pressure of CO with Cu_2Cl_2 present and at high-pressure in absence of Cu_2Cl_2,[6] in which the optimal temperature for high-pressure synthesis of benzaldehyde is 35°C.[7] It is found that the $AlCl_3$-benzaldehyde complex can reduce the induction period in the high pressure synthesis of benzaldehyde with $AlCl_3$,[8] although $AlBr_3$ works better than $AlCl_3$ for the synthesis of benzaldehyde.[9] This reaction is highly *para*-regioselective,[10] as reflected both in the observed toluene/benzene rate ratio ($k_T/k_B = 155 \sim 860$) and in the high degree of *para*-substitution (88.7 ~ 96%);[10d] however, if the *para*-position has been blocked by another group, then migration of such substituent might occur.[11] Besides the system of HCl-$AlCl_3$, the Gattermann-Koch formylation also occurs in superacid conditions, such as HF-BF_3,[12] CF_3SO_3H,[13] HSO_3F-SbF_5,[10c,14] HF-SbF_5,[3c,3d,10a,10b,10e] CF_3SO_3H-SbF_5,[3a,3c,3e,13a] and HF-CF_3SO_3H-BF_3,[10d,13a] in which both kinetic features and regioselectivity indicate a typical intra-complex reaction,[3a,3c] and formylation occurs at atmospheric CO pressure and 0°C in HSO_3F-SbF_5.[10c] However, this reaction is not applicable for phenols or their alkyl ethers where *Gattermann Aldehyde Synthesis* takes place.[6]

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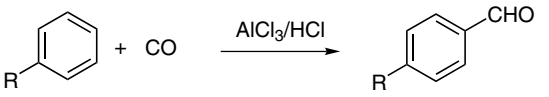
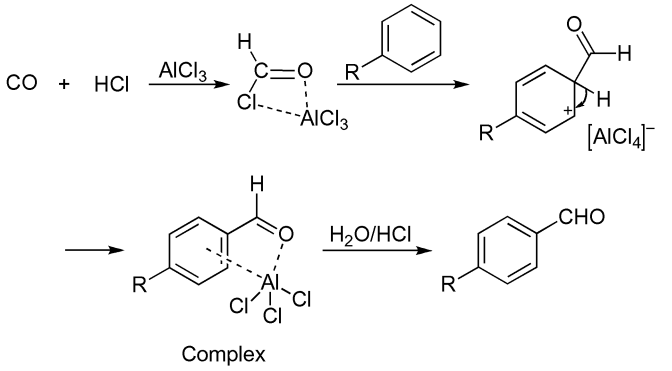
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



Complex

D. MODIFICATION

This reaction has been modified to occur in a variety of superacid systems as mentioned earlier.

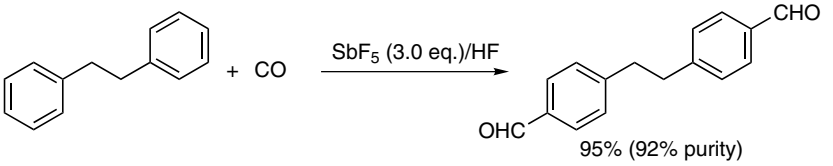
E. APPLICATIONS

This reaction has wide application in the preparation of aromatic aldehydes and is still the major process used to synthesize aromatic aldehydes in industry.

F. RELATED REACTIONS

This reaction is related to the *Friedel-Crafts Acylation, Reimer-Tiemann Reaction*, *Houben-Hoesch Reaction*, *Gatterman Aldehyde Synthesis*, and *Vilsmeier-Haack Formylation*.

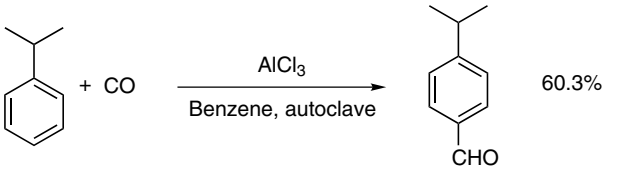
G. CITED EXPERIMENTAL EXAMPLES



95% (92% purity)

Reference 2a.

Dibenzyl (1.82 g, 10 mmol) was added to a solution of Lewis acids with HF or CF_3SO_3H in a Hastelloy autoclave (100 mL) equipped with a Hastelloy magnetic stir bar under temperature control. The autoclave was sealed, and CO was introduced with vigorous stirring until reaching the pressure of 20 atm. After the reaction was over, the autoclave was depressurized and opened. The reaction was quenched with ice water and extracted with benzene. After removal of the solvent, 95% aromatic aldehyde was obtained, where 92% of the aldehyde was p,p'-bisformyl dibenzyl.



Reference 15.

To mixture of 210 g isopropylbenzene (1.75 mol) and 315 g benzene (4.05 mol) saturated with hydrogen chloride in a lead-lined rocking autoclave was added 255 g aluminum chloride (technical, 1.92 mol), which previously had been ground to pass a 20 mesh and exposed in a 1-in. layer to air for 2 h with frequent stirring. The autoclave was then purged with carbon monoxide (commercial) from a cylinder, and carbon monoxide was added to a pressure of 500 psi at 25–30°C. After the pressure dropped to 300 psi, it was again raised to 500 psi. This was repeated until no drop occurred ($\sim$ 2.5 h), whereafter the pressure was maintained for 1 h longer. The reaction mixture was poured onto 2600 g ice acidified with 5 mL conc. HCl and separated. The oil layer was washed with 500-mL portions of water and 55 mL Na_2CO_3 solution and filtered to break the emulsion. After separation, the oil layer was washed twice with 500-mL portions water. The oil was charged to a round-bottomed flask headed by a 36-in. fractionating column packed with glass helices. Distillation was continued under atmospheric pressure until the pot temperature reached 131°C; the distillate was benzene. Then, under a vacuum of 135 mmHg, 40.5 g isopropylbenzene (b.p. 95°C) was recovered. Distillation at 35 mmHg gave 11 g benzaldehyde (b.p., 83–88°C at 35) contaminated with a small amount of isopropylbenzene, 126 g *p*-isopropylbenzaldehyde (b.p., 131–135°C), and 25 g 2,4-diisopropylbenzaldehyde. There was $\sim$ 25 g of residue left after the fractionation. The yield of *p*-isopropylbenzaldehyde was 60.3%, based on the recovered isopropylbenzene.

Other references related to the Gattermann-Koch formylation are cited in the literature.[16]

H. REFERENCES

1. Gattermann, L. and Koch, J. A., *Ber.,* **1897**, *30*, 1622.
2. (a) Tanaka, M.; Fujiwara, M.; Xu, Q.; ando, H. and Raeker, T. J., *J. Org. Chem.*, **1998**, *63*, 4408. (b) Tanaka, M., *Trends in Org. Chem.,* **1998**, *7*, 45. (c) Tanaka, M.; Fujiwara, M.; Xu, Q.; Souma, Y.; Ando, H. and Laali, K. K., *J. Am. Chem. Soc.*, **1997**, *119*, 5100. (d) Tanaka, M.; Fujiwara, M.; Ando, H. and Souma, Y., *J. Chem. Soc., Chem. Commun.*, **1996**, 159. (e) Tanaka, M.; Fujiwara, M. and Ando, H., *J. Org. Chem.*, **1995**, *60*, 2106.

3. Willemse, J. A., "Carbon Monoxide as Reagent in the Formylation of Aromatic Compounds," Master's Thesis, Rand Afrikaans University, **2003**.
4. (a) Fărcasiu, D. and Schlosberg, R. H., *J. Org. Chem.,* **1982**, *47*, 151. (b) Golubev, G. S.; Simonova, T. A.; Aleksandrov, V. N. and Gitis, S. S., *Zh. Prikladnoi Khim.,* **1979**, *52*, 954.
5. Toniolo, L. and Graziani, M., *J. Organomet. Chem.,* **1980**, *194*, 221.
6. Ferguson, L. N., *Chem. Rev.,* **1946**, *38*, 227.
7. Hardy, D. V. N., *J. Soc. Chem. Ind*., **1948**, *67*, 150.
8. (a) Larson, A., *United States Patent,* **1935**, 1,989,700. (b) Holloway, J. H. and Krase, N. W., *Ind. Eng. Chem.,* **1933**, *25*, 497.
9. Reformatsky, S. N., *J. Russ. Phys. Chem. Soc*., **1901**, *33*, 154.
10. (a) Tanaka, M.; Fujiwara, M.; Ando, H. and Souma, Y., *J. Org. Chem.,* **1993**, *58*, 3213. (b) Tanaka, M. and Souma, Y., *J. Chem. Soc., Chem. Commun.,* **1991**, 1551. (c) Tanaka, M.; Iyoda, J. and Souma, Y., *J. Org. Chem.,* **1992**, *57*, 2677. (d) Olah, G. A.; Ohannesian, L. and Arvanaghi, M., *Chem. Rev.,* **1987**, *87*, 671. (e) Olah, G. A.; Pelizza, F.; Kobayashi, S. and Olah, J. A., *J. Am. Chem. Soc.,* **1976**, *98*, 296.
11. (a) Francesconi, L. and Mundici, C., *J. Chem. Soc.,* **1904**, *86*, 897. (b) Francesconi, L. and Mundici, C., *J. Chem. Soc.,* **1903**, *84*, 426.
12. (a) Fujiyama, S. and Kasahara, T., *Hydrocrbon Proc.,* **1978**, *57*, 147. (b) Olah, G. A.; Pelizza, F.; Kobayashi, S. and Olah, J. A., *J. Am. Chem. Soc.,* **1976**, *98*, 296.
13. (a) Olah, G. A.; Laali, K. and Farooq, O., *J. Org. Chem.,* **1985**, *50*, 1483. (b) Booth, B. L.; El-Fekky, T. A. and Noori, G. F. M., *J. Chem. Soc., Perkin Trans. I,* **1980**, 181.
14. (a) Tanaka, M.; Fujiwara, M. and Ando, H., *J. Org. Chem*., **1995**, *60*, 3846. (b) Souma, Y. and Tanaka, M., *Stud. Surf. Sci. Catal*., **1994**, *90*, 93.
15. Crounse, N. N., *J. Am. Chem. Soc.,* **1949**, *71*, 1263.
16. (a) Toniolo, L. and Graziani, M., *J. Organomet. Chem.,* **1980**, *194*, 221. (b) Schlosberg, R. H.; Dougherty, H. W. and Hoff, W., *Fuel*, **1978**, *57*, 571. (c) Bruce, J. M. and Sutcliffe, F. K., *J. Chem. Soc.*, **1956**, 3824. (d) Dilke, M. H. and Eley, D. D., *J. Chem. Soc.,* **1949**, 2601. (e) Dilke, M. H. and Eley, D. D., *J. Chem. Soc.,* **1949**, 2613. (f) Crounse, N. N., *Org. React.,* **1949**, *5*, 290. (g) Harding, E. P. and Cohen, L., *J. Am. Chem. Soc.,* **1902**, *24*, 594.

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Gewald Reaction

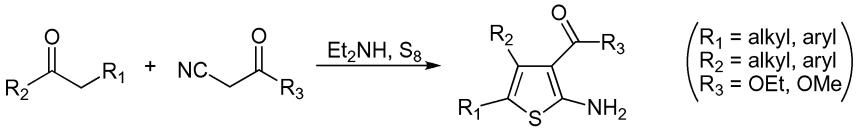
(Gewald Aminothiophene Synthesis, Gewald Synthesis of 2-Aminothiophene)

A. GENERAL DESCRIPTION OF THE REACTION

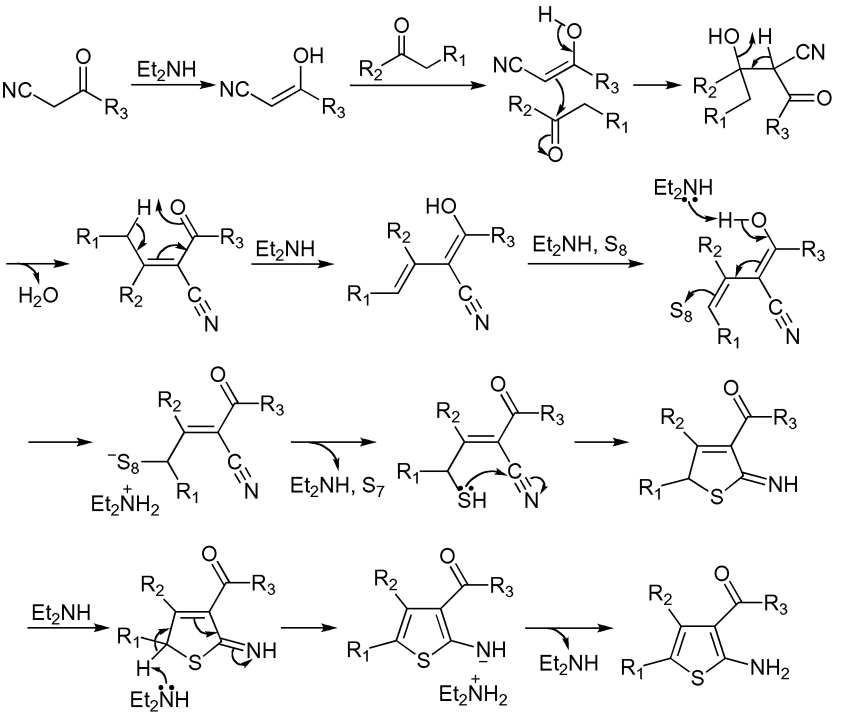
This reaction was initially reported by Gewald in 1965.[1] It is the usual route for synthesizing 2-aminothiophene involving a base-catalyzed condensation of a ketone having an active CH_2 group with α-ketonitrile to form an olefin that cyclizes with sulfur.[2] Therefore, this reaction is known as the Gewald reaction,[3] Gewald synthesis,[2a,3g,3l,4] Gewald thiophene synthesis,[3j] Gewald aminothiophene synthesis,[3g,3j,5] or Gewald synthesis of 2-aminothiophene.[4a,6] This reaction has two major types of variants: a two-step synthesis and a one-pot synthesis. The two-step variant involves the isolation of the olefin intermediate and is primarily used for large-scale synthesis, whereas most current syntheses use the one-pot variant by adding all the reactants and catalyst at once.[2b] In this reaction, diethyl amine is usually the catalyst,[2b] although a solid-phase catalyst has been reported for such reaction.[7] This reaction provides a route for thieno[2,3-d][1,3]-oxazin-4-ones,[3j,3l] a useful moiety for the serine protease inhibitor.[3l] This reaction has been modified to synthesize 2-aminothiophene with a substituent at the 3-, 4-, or 5-position.[2a] Unfortunately, this reaction is limited to the preparation of 2-aminothiophenes with electron-withdrawing groups at the 3-position.[3h] In addition, it produces a significant amount of isomeric by-product if two active CH_2 groups are available.[3g]

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has recently been modified for preparing 2-aminothiophenes with a substituent at the 3-, 4-, or 5-position.[2a]

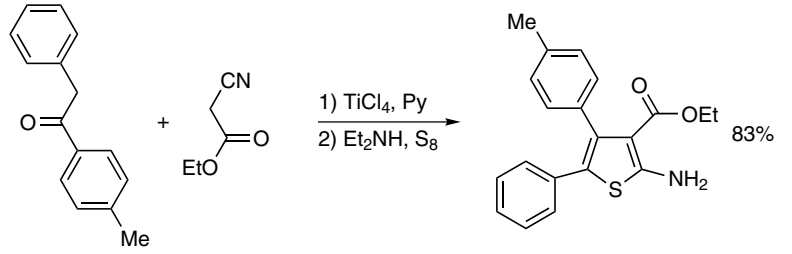
E. APPLICATIONS

This reaction is the usual method used to synthesize 2-aminothiophenes.

F. RELATED REACTIONS

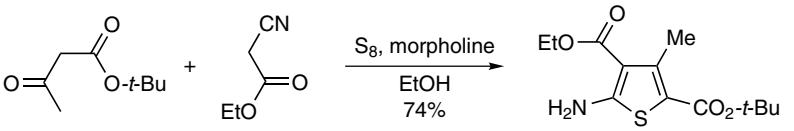
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 2a.

To 60 mL anhydrous THF at 0°C was added 4.9 mL neat $TiCl_4$ (45 mmol) dropwise, followed by a THF solution of 4.33 g deoxybenzoin (22 mmol) and 30 mmol ethyl cyanoacetate. The ice bath was removed, and 1.5 mL dry pyridine was added. The dark blue solution was stirred for 1 h, after the addition of an additional 4.5 mL pyridine, the reaction mixture was stirred overnight at room temperature. The reaction mixture was neutralized with 10% HCl and extracted with EtOAc. The combined organic layers were washed with 2 M NaOH and dried over $MgSO_4$. Evaporation of the solvent afforded a crude Knoevenagel product, which was taken up in 20 mL THF and stirred at room temperature with 710 mg sulfur (22.2 mmol) and 4 mL diethylamine for 1 h. The volatiles were removed in vacuo to afford the crude ethyl 2-amino-4-(4-methylphenyl)-5-phenylthiophene-3-carboxylate, which was recrystallized from hot ethanol in a yield of 83%.



Reference 3j.

A mixture of 15.8 g *tert*-butyl acetoacetate (100 mmol), 11.3 g ethyl cyanoacetate (100 mmol), 3.5 g sulfur (110 mmol), and 25 mL EtOH was stirred at 45°C. Morpholine (10 g, 115 mmol) was added dropwise over 15 min. Then the mixture was stirred at 60°C for 5 h and filtered. The filtrate was diluted with 50 mL water and cooled. The precipitate was collected by filtration, washed with 30% EtOH, and dried to obtain 21.2 g ethyl 2-amino-4-methyl-5-(*tert*-butoxycarbonyl)thiophene-3-carboxlate, in a yield of 74%, m.p., 116–117°C (cyclohexane/hexane).

Other references related to the Gewald reaction are cited in the literature.[8]

H. REFERENCES

1. Gewald, K., *Ber.,* **1965**, *98*, 3571.
2. (a) Lütjens, H.; Zickgraf, A.; Figler, H.; Linden, J.; Olsson, R. A. and Scammells, P. J., *J. Med. Chem.,* **2003**, *46*, 1870. (b) Tranberg, C. E.; Zickgraf, A.; Giunta, B. N.; Lütjens, H.; Figler, H.; Murphree, L. J.; Falke, R.; Fleischer, H.; Linden, J.; Scammells, P. J. and Olsson, R. A., *J. Med. Chem.,* **2002**, *45*, 382.

3. (a) Sridhar, M.; Rao, R. M.; Baba, N. H. K. and Kumbhare, R. M., *Tetrahedron Lett*., **2007**, *48*, 3171. (b) Barnes, D. M.; Haight, A. R.; Hameury, T.; McLaughlin, M. A.; Mei, J. Z.; Tedrow, J. S. and Dalla Riva Toma, J., *Tetrahedron*, **2006**, *62*, 11311. (c) Eller, G. A. and Holzer, W., *Molecules*, **2006**, *11*, 371. (d) Hu, Y.; Wei, P.; Huang, H.; Han, S.-Q. and Ouyang, P.-K., *Synth. Commun.,* **2006**, *36*, 1543. (e) Tuemer, F.; Ekinci, D.; Zilbeyaz, K. and Demir, U., *Turk. J. Chem.,* **2004**, *28*, 395. (f) Reissig, H.-U. and Zimmer, R., *Chem. Rev.,* **2003**, *103*, 1151. (g) Phillips, G.; Fevig, T. L.; Lau, P. H.; Klemm, G. H.; Mao, M. K.; Ma, C.; Gloeckner, J. A. and Clark, A. S., *Org. Proc. Res. Dev.,* **2002**, *6*, 357. (h) Ogawa, K.; Radke, K. R.; Rothstein, S. D. and Rasmussen, S. C., *J. Org. Chem.,* **2001**, *66*, 9067. (i) Buchstaller, H.-P.; Siebert, C. D.; Lyssy, R. H.; Frank, I.; Duran, A.; Gottschlich, R. and Noe, C. R., *Monatsh. Chem.,* **2001**, *132*, 279. (j) Gütschow, M.; Kuerschner, L.; Neumann, U.; Pietsch, M.; Löser, R.; Koglin, N. and Eger, K., *J. Med. Chem.,* **1999,** *42*, 5437. (k) Sabnis, R. W.; Rangnekar, D. W. and Sonawane, N. D., *J. Heterocycl. Chem.,* **1999**, *36*, 333. (l) Gütschow, M. and Neumann, U., *J. Med. Chem.,* **1998**, *41*, 1729. (m) Hallas, G. and Towns, A. D., *Dyes & Pigments,* **1996**, *32*, 135. (n) Guetschow, M.; Schroeter, H.; Kuhnle, G. and Eger, K., *Monatsh. Chem.,* **1996**, *127*, 297.

4. (a) Hu, Y.; Chen, Z.-C.; Le, Z.-G. and Zheng, Q.-G., *Synth. Commun.,* **2004**, *34*, 3801. (b) Sabnis, R. W., *Sulfur Rep.,* **1994**, *16*, 1.

5. (a) Li, J. J., ed., *Name Reactions in Heterocyclic Chemistry*, John Wiley & Sons, New York, **2004**, chap. 5.2. (b) Rajagopal, R.; Jyothi, T. M.; Daniel, T.; Srinivasan, K. V. and Rao, B. S., *Synth. Commun.,* **2001**, *31*, 3113.

6. (a) Tormyshev, V. M.; Trukhin, D. V.; Rogozhnikova, O. Yu.; Mikhalina, T. V.; Troitskaya, T. I. and Flinn, A., *Synlett,* **2006**, 2559. (b) Hu, Y.; Wei, P.; Huang, H.; Han, S.-Q. and Ouyang, P.-K., *Heterocycles*, **2006**, *68*, 375. (c) Zhang, H. Q.; Yang, G. C.; Chen, J. N. and Chen, Z. X., *J. Chem. Res.,* **2004**, 360. (d) Peet, N. P.; Sunder, S.; Barbuch, R. J. and Vinogradoff, A. P., *J. Heterocycl. Chem.,* **1986**, *23*, 129.

7. Simpson, J.; Rathbone, D. L. and Billington, D. C., *Tetrahedron Lett*., **1999**, *40*, 7031.

8. (a) Pinto, I. L.; Jarvest, R. L. and Serafinowska, H. T., *Tetrahedron Lett.,* **2000**, *41*, 1597. (b) Kim, B. S.; Choi, K. S. and Kim, K. T., *J. Org. Chem.,* **1998**, *63*, 6086. (c) Stephensen, H. and Zaragoza, F., *J. Org. Chem.,* **1997**, *60*, 6096. (d) Nakayama, J., *Comp. Heterocycl. Chem. II,* **1996**, *2*, 607. (e) Unverferth, K., *Pharmazie,* **1990**, *45*, 545. (f) Litvinov, V. P.; Sharanin, Yu. A. and Babichev, F. S., *Sulfur Rep.,* **1986**, *6*, 97. (g) Gronowitz, S., ed. *The Chemistry of Heterocyclic Compounds: Thiophene and Its Derivatives*, Vol. 44, Pt. 1, John Wiley & Sons, New York, **1985**, pp. 42–59. (h) Gewald, K., *Z. Chem.,* **1967**, *7*, 186. (i) Gewald, K.; Schinke, E. and Böttcher, H., *Ber.*, **1966**, *99*, 94.

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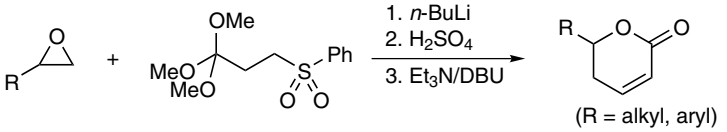
Ghosez Cyclization
(Ghosez Lactonization)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Ghosez and co-workers in 1988.[1] It is the synthesis of α,β-unsaturated δ-lactone and the corresponding dihydropyran reduced from such lactone derivative, involving the reaction of epoxide with the lithio derivative of methyl 3-(phenylsulfonyl)orthopropionate and subsequent acid hydrolysis and base-induced elimination of phenylsulfinic acid. This reaction is thus known as the Ghosez cyclization[2] or the Ghosez lactonization.[3]

In this reaction, methyl 3-(phenylsulfonyl)orthopropionate functioning as a 1,3-dipole equivalent, contains a potential carbanion center at C-3 that is stabilized by a phenylsulfonyl group, and has a masked cationic character at C-1 in the form of an *ortho*-ester.[4] Upon treatment of the base, the carbanion is generated at C-3, which nucleophilically attacks the epoxide ring via a S_N2 reaction; the resulting alkoxide anion undergoes the second S_N2 reaction by replacement of a methoxide to give the cyclic orthoester. Acidic hydrolysis of the cyclic orthoester forms δ-lactone, and the subsequent base-induced elimination of phenylsulfinic acid generates the α,β-unsaturated δ-lactone.

B. GENERAL REACTION SCHEME



(R = alkyl, aryl)

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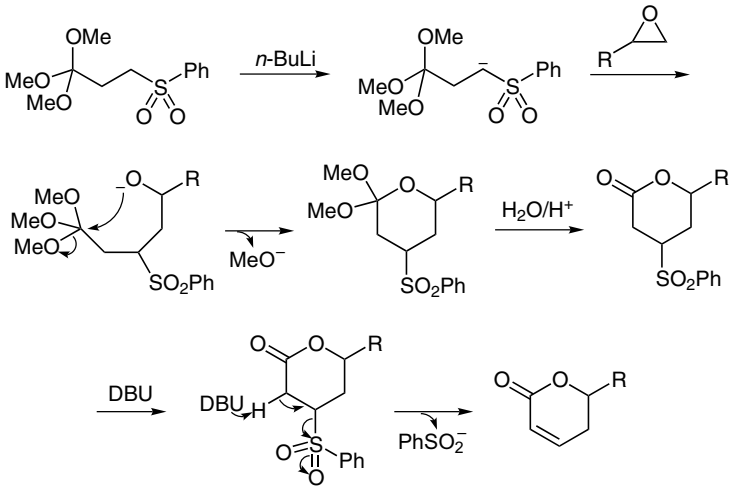
C. PROPOSED MECHANISMS

A simple illustration of the reaction mechanism is provided here.



D. MODIFICATION

A similar reaction involving 2,3-dibromo-1-phenylsulfonyl-1-propene and a carbanion from acetoacetone or 3-methylacetoacetone to form the corresponding 2-methyl-4-[(phenylsulfonyl)methyl]furan or 2-methyl-3-[(phenylsulfonyl)methyl]-2-cyclopenten-1-one could be considered as an extension of this reaction.[5]

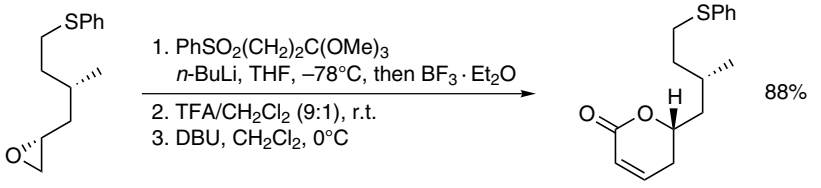
E. APPLICATIONS

This reaction has certain applications in organic synthesis, such as the preparation of hydrindan,[4] glycoside,[3a] and natural product swinholide A.[2b,2c]

F. RELATED REACTIONS

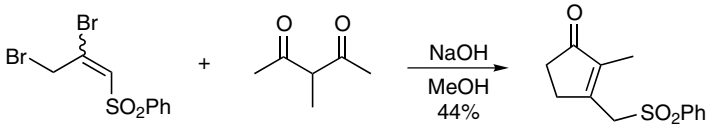
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3b.

To a solution of 3.29 g methyl 3-phenylsulfonyl orthopropionate (12.0 mmol) in 40 mL THF cooled at –78°C was added 7.76 mL 1.6 M *n*-BuLi (12.4 mmol) in hexanes dropwise. After being stirred for 30 min, 1.54 mL $BF_3{\cdot}Et_2O$ (12.1 mmol) was added, followed by 888 mg (2*R*)-2-[(2*R*)-(2-methyl-4-phenylsulfanyl-butyl)]oxirane (4.0 mmol) in 6 mL dry THF. After being stirred for 1.5 h at –78°C, the reaction mixture was poured into a mixture of cold saturated aqueous $NaHCO_3$ (60 mL) and Et_2O (160 mL) with vigorous stirring. The phases were separated, and the aqueous layer was extracted with Et_2O three times. The combined organic phases were dried over $MgSO_4$ and concentrated. The residue was stirred with 40 mL 90% aqueous TFA at room temperature for 3 h and concentrated. The remaining material was dried by repeated co-evaporation with toluene (3 × 50 mL), dissolved in 40 mL dry CH_2Cl_2, and cooled (0°–5°C). To this cold solution was added 2.0 mL DBU (13.4 mmol) dropwise via syringe. The elimination of phenylsulfinic acid completed in 30 min as monitored by TLC (CH_2Cl_2/hexanes/EtOAc, 16:15:1, R_f = 0.39). The solution was concentrated, and the residue was purified by flash chromatography to afford 973 mg (6*R*)-6-[(2*R*)-(2-methyl-4-phenylsulfanyl-butyl)]-5,6-dihydro-2*H*-pyran-2-one as a bright yellow oil, in a yield of 88%.



Reference 5a.

In a 1-L, flame-dried, round-bottomed flask equipped with an addition funnel under a nitrogen atmosphere were placed 20.0 g 2,3-dibromo-1-(phenylsulfonyl)-1-propene (58.8 mmol) and 7.0 mL 3-methyl-2,4-pentanedione (60.0 mmol) in 300 mL methanol. The flask was cooled in an ice water bath. To this mixture was added 140 mL 0.5 *N* NaOH (70.0 mmol) in methanol dropwise over 30 min. The solution was then stirred at 25°C for 5 h and cooled to 0°C. Another 140 mL 0.5 *N* NaOH in methanol was added over 20 min. After being stirred at 25°C for 10 h, the reaction was quenched by 50 mL saturated NH_4Cl solution. The solvent was removed with a rotary evaporator at aspirator vacuum, and the resulting residue was taken up in 100 mL water and 200 mL dichloromethane. The aqueous layer was extracted with dichloromethane (2 × 200 mL). The combined organic layers were washed with 100 mL water, 100 mL brine, and dried over anhydrous $MgSO_4$. After filtration and concentration, the residue was recrystallized from EtOAc to give 6.5 g 2-methyl-3-[(phenylsulfonyl)methyl]-2-cyclopenten-1-one, in a yield of 44%. (*Note*: NaOH was displayed as NaOMe in the original reaction scheme.)

Other references related to the Ghosez cyclization are cited in the literature.[6]

H. REFERENCES

1. Carretero, J. C. and Ghosez, L., *Tetrahedron Lett.,* **1988**, *29*, 2059.
2. (a) Nicolaou, K. C. and Snyder, S. A., *Classics in Total Synthesis II, More Targets, Strategies, Methods,* John Wiley & Sons, Chichester, **2003**. (b) Nicolaou, K. C.; Vourloumis, D.; Winssinger, N. and Baran, P. S., *Angew. Chem. Int. Ed.,* **2000**, *39*, 44. (c) Nicolaou, K. C. and Yue, E. W., *Pure & Appl. Chem.,* **1997**, *69*, 413. (d) Nicolaou, K. C.; Ajito, K.; Patron, A. P.; Khatuya, H.;

Richter, P. K. and Bertinato, P., *J. Am. Chem. Soc.,* **1996**, *118*, 3059. (e) Nicolaou, K. C.; Patron, A. P.; Ajito, K.; Richter, P. K.; Khatuya, H.; Bertinato, P.; Miller, R. A. and Tomaszewski, M. J., *Chem. Eur. J*., **1996**, *2*, 847.

3. (a) Mulzer, J. and Öhler, E., *Chem. Rev.,* **2003**, *103*, 3753. (b) Ahmed, A.; Hoegenauer, E. K.; Enev, V. S.; Hanbauer, M.; Kaehlig, H.; Öhler, E. and Mulzer, J., *J. Org. Chem.,* **2003**, *68*, 3026. (c) Surivet, J.-P. and Vatèle, J.-M., *Tetrahedron,* **1999**, *55*, 13011.
4. Hudlicky, T. and Price, J. D., *Chem. Rev.,* **1989**, *89*, 1467.
5. (a) Watterson, S. H.; Ni, Z. J.; Murphree, S. S. and Padwa, A., *Org. Synth. Coll.* **1998**, *9*, 207. (b) Watterson, S. H.; Ni, Z. J.; Murphree, S. S. and Padwa, A., *Org. Synth.,* **1997**, *74*, 115.
6. (a) Williams, D. R.; Ihle, D. C. and Plummer, S. V., *Org. Lett*., **2001**, *3*, 1383. (b) Murakami, N.; Wang, W.; Aoki, M.; Tsutsui, Y.; Sugimoto, M. and Kobayashi, M., *Tetrahedron Lett*., **1998**, *39*, 2349. (c) Norcross, R. D. and Paterson, I., *Chem. Rev.,* **1995**, *95*, 2041. (d) Patron, A. P.; Richter, P.; Tomaszewski, M. J.; Miller, R. A. and Nicolaou, K. C., *J. Chem. Soc., Chem. Commun.,* **1994**, 1147. (e) Richter, P. K.; Tomaszewski, M. J.; Miller, R.; Patron, A. P. and Nicolaou, K. C., *J. Chem. Soc., Chem. Commun.,* **1994**, 1151. (f) Delombaert, S.; Nemery, I.; Roehens, B.; Carretero, J. C.; Kimmel, T. and Ghosez, L., *Tetrahedron Lett.,* **1986**, *27*, 5099.

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Ghosez Keteniminium-Olefin Cyclization

(Ghosez [2+2] Keteniminium-Olefin Cycloaddition)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Ghosez as early as 1972.[1] It is the synthesis of cyclobutanones from the reaction of alkenes and keteniminium ions. The keteniminium ions are usually generated from tertiary amides by reacting with triflic anhydride and a hindered pyridine base[2] or by the dechlorination of 1-chloro-*N*,*N*,2-trimethyl-1-propylenamine with $AgBF_4$[1,3] followed by the hydrolysis of the resulting iminium salts under biphasic conditions. Therefore, this reaction is known as Ghosez keteniminium-olefin cyclization or Ghosez [2+2] keteniminium-olefin cycloaddition;[4] and 1-chloro-*N*,*N*,2-trimethyl-1-propylenamine, generated by the treatment of *N*,*N*-dimethyl 2-methylpropionamide with phosgene and triethylamine,[3] is known as the Ghosez reagent.[5]

The keteniminium salt, being a ketene equivalent,[6] is superior to ketene in [2+2] cycloaddtion, due to the higher electrophilicity (with a positive charge) and the absence of dimerization owing to charge-charge repulsion;[7] in comparison, ketenes are known to dimerize.[8] As a result, the reaction conditions for keteniminium salt are very mild, and the yields are often satisfactory.[1] In addition, the keteniminium salt with a chiral inducer on the carbon atom usually leads to the formation of cyclobutanone, with the configuration following the known chirality of the inducer.[6] Although the intermolecular reaction of a keteniminium salt with 1,1-disubstituted alkenes gives very low yields of product, the intramolecular cycloaddition occurs with three-, four-, five- and seven-atom tethers; in

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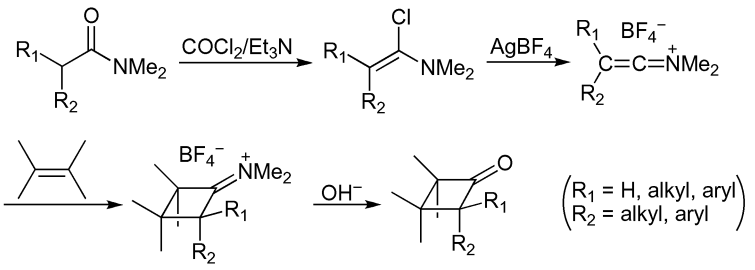
contrast, the corresponding reaction of ketenes normally proceed with three- or four-atom tethers.[7]

It should be pointed out that the *[2+2] Cycloaddition* between keteniminium and imines to form β-lactams was reported by Ghosez even earlier (1970),[9] and azetidiniminium salts are generated from this cycloaddition, which can be converted into many different molecules besides β-lactams, including 2-acetidinethiones, azetidinimines, oxazolidin-2-ones, and 2-amino-1-azetines as well as 1,2-amino alcohols and α-amino acids.[10] In such modifications, the keteniminium salts can be simply prepared from *N*,*N*-dialkyl amides by means of phosgene; the resulting *N*,*N*-dialkyl-2-chloroiminium chloride might take three different routes to give azetidiniminium salts: (*a*) direct reaction with imine in the presence of triethylamine; (*b*) formation of enamine in the presence of Et_3N and coupling with imine; and (*c*) formation of enamine in the presence of Et_3N, conversion of resulting enamine into keteniminium salt by a Lewis acid (e.g., $ZnCl_2$ or $TiCl_4$), and subsequent reaction with imine.[11] In this reaction, path *a* is more practical; however, only path *c* affords 4-alkyl azetidiniminium salts.[11] Although chiral iminium salts usually give chiral azetidiniminium salts of high optical purity, the large α-substituents on the carboxyl moiety play a decisive role on the diastereoselectivity of the reaction, whereas the diastereoselectivity is rather independent of the substituents on corresponding imines.[11]

Upon treatment with base (e.g., hydroxide) followed by acidic hydrolysis, either β-lactams or β-amino amides are obtained from azetidiniminium salts via an exocyclic or endocyclic C-N bond cleavage.[11] It has been reported that the ratio of β-lactams to β-amino amides depends on the relative rate of protonation on the exocyclic and endocyclic nitrogen atom of the tetrahedral intermediate.[11] Likewise, thiolysis or aminolysis by treatment of azetidiniminium salts with sodium hydrosulfide or primary amines (including ammonia and hydroxylamine) affords the corresponding azetidinethiones or azetidinimines (Figure 1).[11] However, during the formation of azetidinimines, the azetidiniminium salts with hydrogen at the α-carbon give a much lower yield of product; in this case, the corresponding azetidinimines can be prepared by the formation of azetidine-2-thione and further reaction with amine in the presence of mercuric acetate.[11] In addition, the *Baeyer-Villiger Oxidation* of azetidiniminium salts give oxazolidinones; similarly, oxidation of azetidiniminium salts with *bis*-trimethylsilyl peroxide in the presence of fluoride affords the five-membered carbamates, which are then hydrolyzed to aminoalcohols (Scheme 1).[11]

B. GENERAL REACTION SCHEME



SCHEME 1. *Extended Ghosez keteniminium-olefin cyclization.*

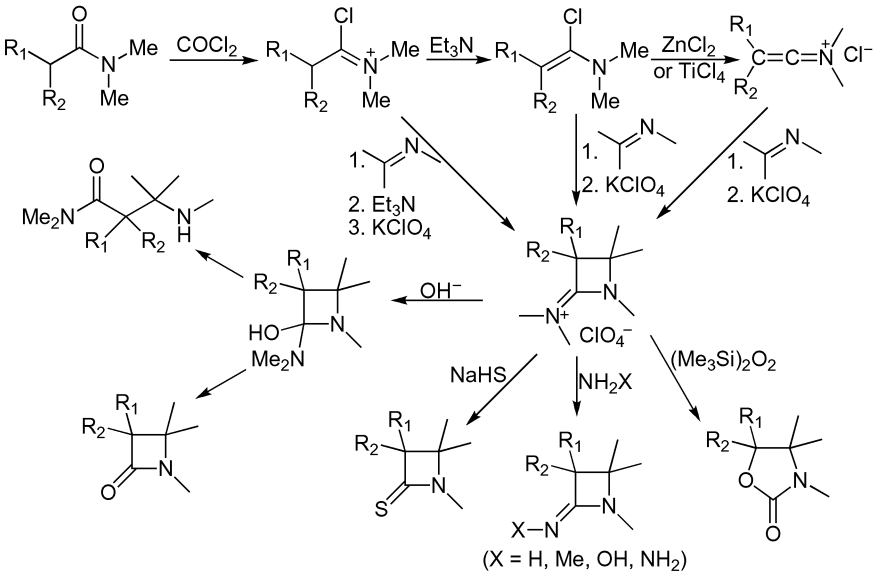
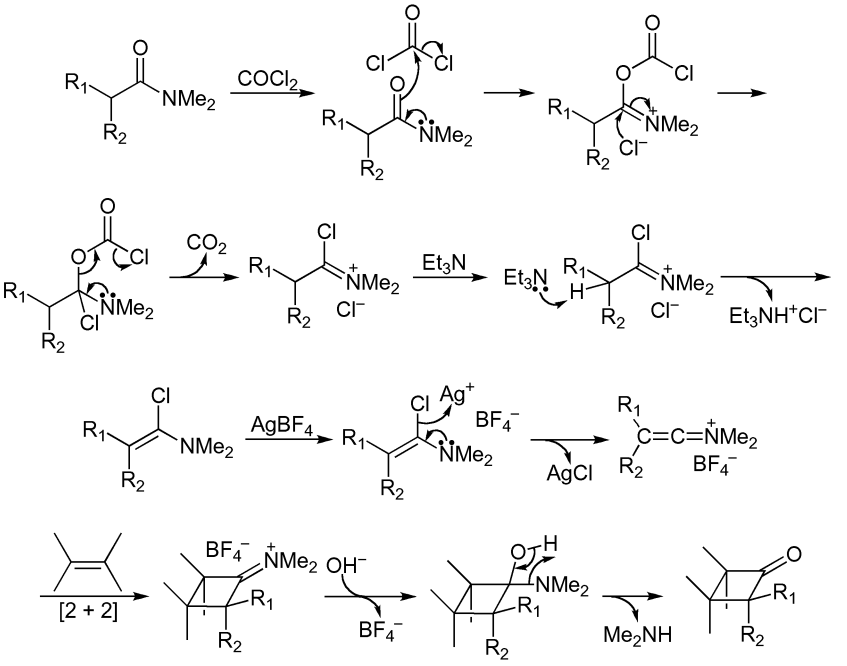


FIGURE 1. *Some possible derivatives from Ghosez keteniminium-olefin cyclization.*

C. PROPOSED MECHANISMS

This reaction proceeds stepwise via a cationic intermediate, as shown below.



D. MODIFICATION

N/A

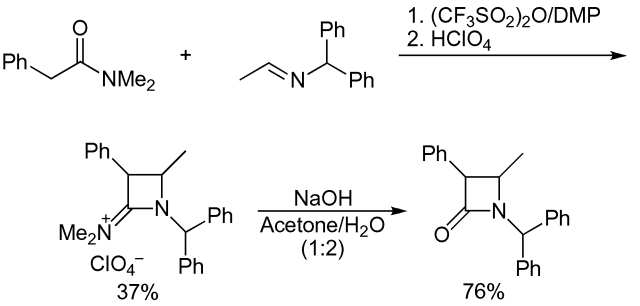
E. APPLICATIONS

This reaction should have wide applications in heterocycle synthesis but has not yet been extensively explored.

F. RELATED REACTIONS

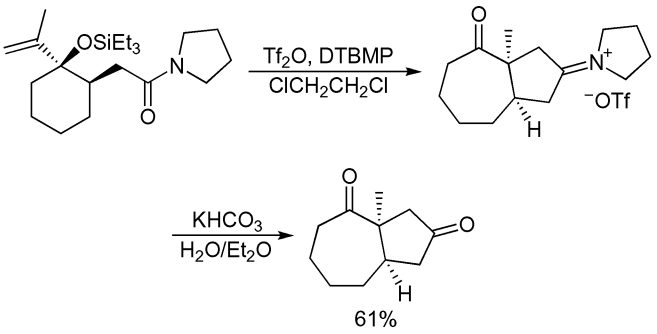
This reaction is related to the *Gilman-Speeter Reaction* and *Staudinger Cycloaddition.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 10.

To a mixture of 0.40 g *N*,*N*-dimethyl phenylacetamide (2.45 mmol) and 0.41 mL triflic anhydride was added a solution of 0.5 g imine prepared from the corresponding acetaldehyde and benzhydrylamine (2.44 mmol) and 0.5 g 2,6-dimethylpyridine (DMP) in 6 mL 1,2-dichloroethane. The solution was stirred at –20°C for 1 h and then at 25°C for 2 h. After conversion of the azetidiniminium triflate to the corresponding perchlorate, the residue was purified by silica gel column chromatography using CH_2Cl_2/CH_3CN (5:1) as the eluent to afford 0.41 g *cis*-3-phenyl-4-methyl-1-benzhydrylazetidine-2-(*N*-dimethyliminium perchlorate), in a yield of 37%. This compound was then dissolved in 10 mL acetone/water (1:2), and 10 mL 1 N NaOH aqueous solution was added. The resulting mixture was stirred at 25°C for 1 h. Acetone was removed under vacuum, and the product was extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography using *n*-pentane/EtOAc (13:2) as the eluent to give 0.22 g *cis*-3-phenyl-4-methyl-1-benzydrylazetidin-2-one as an oil, in a yield of 76%.



Reference 2.

To a 0.1 M solution of 1-pyrrolidin-1-yl-2-[2-triethylsiloxy-2-isopropenylcyclohexyl]-ethanone (95 mg, 0.26 mmol) in 2.6 mL 1,2-dichloroethane containing 66.7 mg 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP, 0.33 mmol, 1.25 eq.) cooled to –20°C was added 92 mg trifluoromethanesulfonic anhydride (0.33 mmol, 1.25 eq.) dropwise. The mixture was allowed to slowly warm to room temperature and then was stirred at 65°C for 18 h. The reaction mixture was cooled to room temperature and concentrated; the resulting residue was dissolved in a mixture of 3 mL aqueous $KHCO_3$ and 3 mL ether, and the mixture was stirred vigorously at room temperature for 5 h. After extraction of the product with ether (3×20 mL), the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel flash chromatography using EtOAc/hexanes (1:9 to 2:8) as the eluent to give 29 mg (3a*R*,5a*R*)-3a-(methyl)octahydroazulene-2,4-dione as a colorless oil, in a yield of 61% and > 20:1 of diasteroselectivity.

Other references related to the Ghosez keteniminium-olefin cyclization are cited in the literature.[12]

H. REFERENCES

1. Marchand-Brynaert, J. and Ghosez, L., *J. Am. Chem. Soc.,* **1972**, *94*, 2870.
2. Overman, L. E. and Wolfe, J. P., *J. Org. Chem.,* **2002**, *67*, 6421.
3. Marchand-Brynaert, J. and Ghosez, L., *J. Am. Chem. Soc.,* **1972**, *94*, 2869.
4. Brown, R. C. D.; Bataille, C. J. R.; Bruton, G.; Hinks, J. D. and Swain, N. A., *J. Org. Chem.,* **2001**, *66*, 6719.
5. Wehlan, H.; Jezek, E.; Lebrasseur, N.; Pavé, G.; Roulland, E.; White, A. J. P.; Burrows, J. N. and Barrett, A. G. M., *J. Org. Chem.,* **2006**, *71*, 8151.
6. Houge, C.; Frisque-Hesbain, A. M.; Mockel, A.; Ghosez, L.; Declercq, J. P.; Germain, G. and Van Meerssche, M., *J. Am. Chem. Soc.,* **1982**, *104*, 2920.
7. Snider, B. B., *Chem. Rev.,* **1988**, *88*, 793.
8. (a) Tidwell, T. T., *Eur. J. Org. Chem.,* **2006**, 563. (b) Parker, G.; Wiseman, D.; Wintner, C. and MacKay, C., *J. Org. Chem.,* **1984**, *49*, 4494. (c) Jug, K.; Dwivedi, C. P. D. and Chickos, J. S., *Theoretica Chim. Acta,* **1978**, *49*, 249. (d) Jug, K. and Chickos, J. S., *Theoretica Chim. Acta,* **1975**, *40*, 207.
9. Fernando, D. and Ghosez, L., *Tetrahedron Lett.,* **1970**, 245.

10. Barbaro, G.; Battaglia, A.; Bruno, C.; Giorgianni, P. and Guerrini, A., *J. Org. Chem.,* **1996**, *61*, 8480.

11. Ghosez, L.; Bogdan, S.; Cérésiat, M.; Frydrych, C.; Marchand-Brynaert, J.; Portuguez, M. M. and Huber, I., *Pure & Appl. Chem.,* **1987**, *59*, 393.

12. (a) Padwa, A.; Rashatasakhon, P. and Rose, M., *J. Org. Chem.,* **2003**, *68*, 5139. (b) Padwa, A.; Crawford, K. R.; Rashatasakhon, P. and Rose, M., *J. Org. Chem.,* **2003**, *68*, 2609. (c) Ghosez, L.; Mahuteau-Betzer, F.; Genicot, C.; Vallribera, A. and Cordier, J. F., *Chem. Eur. J.,* **2002**, *8*, 3411. (d) Schmit, C.; Falmagne, J. B.; Escudero, J.; Vanlierde, H. and Ghosez, L., *Org. Synth. Coll. Col.* **1993**, *8*, 306. (e) Haveaux, B.; Dekoker, A.; Rens, M.; Sidani, A. R.; Toye, J. and Ghosez, L., *Org. Synth. Coll. Col.* **1988**, *6*, 282. (f) Ghosez, L.; Marko, I. and Hesbain-Frisque, A.-M., *Tetrahedron Lett*., **1986**, *27*, 5211. (g) Marchand-Brynaert, J.; Moya-Portuguez, M.; Hubert, J. and Ghosez, L., *J. Chem. Soc., Chem. Commun.,* **1983**, 818. (h) Falmagne, J.-B.; Escudero, J.; Taleb-Sahraoui, S. and Ghosez, L., *Angew. Chem. Int. Ed. Engl.,* **1981**, *20*, 879. (i) Marchand-Brynaert, J.; Moya-Portuguez, M.; Lesuisse, D. and Ghosez, L., *J. Chem. Soc., Chem. Commun.,* **1980**, 173. (j) Devos, A.; Remion, J.; Frisque-Hesbain, A. M.; Colens, A. and Ghosez, L., *J. Chem. Soc. Chem. Commun.,* **1979**, 1180. (k) Ghosez, L. and Marchand-Brynaert, J., *Adv. Org. Chem.,* **1976**, *9*, 421. (l) De Poortere, M.; Marchand-Brynaert, J. and Ghosez, L., *Angew. Chem. Int. Ed. Engl.,* **1974**, *13*, 267. (m) Ghosez, L., *Angew. Chem. Int. Ed. Engl.,* **1972**, *11*, 852.

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Gibbs-Wohl Naphthalene Oxidation

(Gibbs Phthalic Anhydride Process)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Gibbs and Conover in 1918,[1] based on a laboratory process in 1917.[2] It is a simple and direct vapor-phase oxidation of naphthalene to phthalic anhydride in the presence of a catalyst made from Group VB or VIB transition metals. This process was highly supported by the U.S. government[2] in 1910s because phthalic anhydride was an important intermediate for dyes (e.g., indigo) and medicinal molecules.[3] All phthalic anhydride was imported exclusively from Germany and was unfortunately cut off due to World War I.[2] This process is the modification of a German patent by Sapper at Badische Anilin und Soda Fabrik in 1896,[4] in which sulfuric acid was used to oxidize naphthalene with a mercury salt as the catalyst.[3] It was obvious that many disadvantages were associated with the 1896 process, which involves an expensive apparatus to convert SO_2 to SO_3,[5] though it was the primary method to produce phthalic anhydride at that time. The new process uses air and naphthalene and produces phthalic anhydride as the only product,[2] a much more efficient way of carrying out chemical reactions, which has directed inventions of other oxidation of aromatic compounds, such as the production of anthraquinone from anthracene,[6] and phenanthraquinone from phenanthrene.[7] Therefore, this process is known as Gibbs phthalic anhydride process. In the original patent, Gibbs and Conover tested the catalytic efficiency of many metal oxides—including MgO, Al_2O_3, TiO_2, ZrO_2, CeO_2, Cb_2O_5, Cr_2O_3, WO_3, UO_3, Mn_2O_3, Fe_2O_3, NiO, MoO_3, Co_2O_3, Cu_2O, and V_2O_5—by passing a mixture of naphthalene and air through the reaction tube; they found that V_2O_5 was the best catalyst, with 3.7% conversion and 7.5% yield,[5] and MoO_3 was the second best

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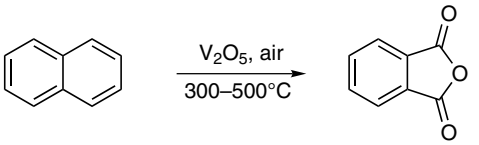
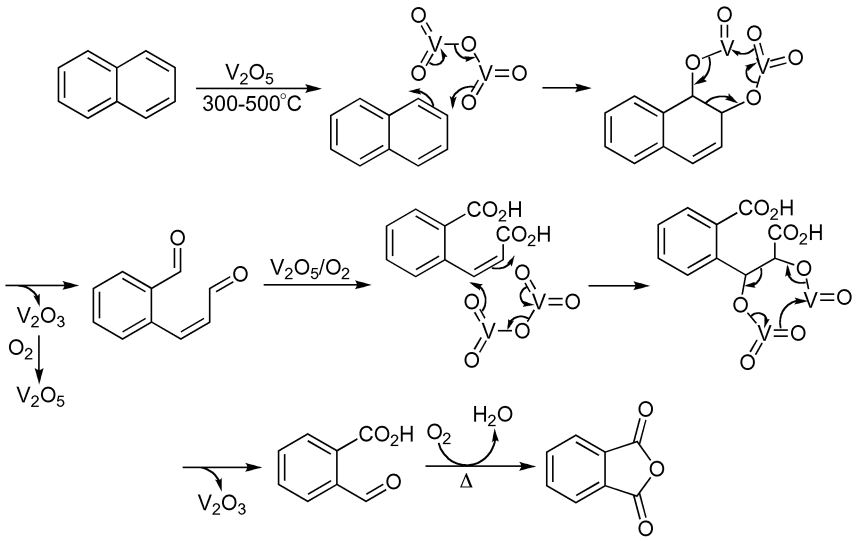
catalyst with a yield of phthalic anhydride at 31.1% and 10.2% conversion.[5] (This should indicate that MoO_3 is the best catalyst!) It was found that the reaction temperature was critical in this reaction, and it reacted at 275°C for V_2O_5 and 325°C for MoO_3 when pure oxygen was used; naphthalene started to combust at 300°C and 350°C, respectively. However, the reaction temperature could be raised to 500°C without the ignition of naphthalene when air was directly used, giving a higher yield of product.[5] It was found that V_2O_5, fused and then finely powdered, was a better catalyst than the light powder obtained from decomposing ammonium metavanadate at low temperature, of which the catalytic efficiency is not effectively lowered by AsO_3 or SO_2 but is lowered by sodium compounds. In this case, phthalic acid was the major product, and CO_2 was the major gaseous product. Benzoic acid and naphthols might exist as minor products, but no CO was detected.[5] It is interesting that Wohl in Germany invented the same synthesis 2–3 months earlier than Gibbs, and he was finally granted the U.S. patent in the 1930s[8] with a validation on August 28, 1951.[2] Therefore, this reaction is also referred to as Gibbs-Wohl oxidation of naphthalene. Unfortunately, Andrews, who claimed an article of manufacturing "phthalic anhydride substantially chemically pure and having a melting point above 130°C., corrected" and "phthalic anhydride in the form of colorless, needle-like crystals substantially chemically pure and having a melting point above 130°C., corrected," was granted a U.S. patent[9] that was later claimed to be not patentable.[10]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

This is a very complicated process, therefore, a tentative mechanism is proposed here.



D. MODIFICATION

N/A

E. APPLICATIONS

This reaction is the primary method for the production of phthalic anhydride in industry.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES

Because this is used in the industrial production of phthalic anhydride, no preparation on a laboratory scale is available; thus no experimental details are collected here.

Other references related to the Gibbs-Wohl naphthalene oxidation are cited in the literature.[11]

H. REFERENCES

1. (a) Gibbs, H. D. and Conover, C., *U.S. Pat*., **1918**, Oct. 29, 1,283,117. (b) Gibbs, H. D. and Conover, C., *U.S. Pat*., **1918**, Nov. 17, 1,284,888.
2. Downs, C. R., *J. Ind. Eng. Chem.,* **1940**, *32*, 1294.
3. Gibbs, H. D., *J. Ind. Eng. Chem.,* **1919**, *11*, 1031.
4. (a) Sapper, E., *Ger. Pat*., **1896**, March 9, 91,202. (b) Sapper, E., *British Patent*, **1896**, 18,221. (c) Sapper, E., *J. Soc. Chem. Ind.,* **1897**, *16*, 676.
5. Conover, C. and Gibbs, H. D., *J. Ind. Eng. Chem.,* **1922**, *14*, 120.
6. Conover, C. and Gibbs, H. D., *U.S. Pat*., **1919**, May 6, 1,303,168.
7. Lewis, and Gibbs, H. D., *U.S. Pat*., **1918**, Dec. 17, 1,288,431.
8. (a) Wohl, A., *U.S. Pat*., **1930**, Dec. 30, 1,787,416. (b) Wohl, A., *U.S. Pat*., **1934**, Aug. 28, 1,971,888.
9. Andrews, C. A., *U.S. Pat*., **1920**, Apr. 6, 1,336,182 (filed Oct. 14, **1919**).
10. Bebie, J., *J. Ind. Eng. Chem.,* **1921**, *13*, 91.
11. (a) Shreve, R. N., *Chem. Met. Eng.,* **1943**, *52*, 103. (b) Shreve, R. N., *Chem. Met. Eng.,* **1943**, *52*, 117. (c) Parks, W. G. and Katz, J., *J. Ind. Eng. Chem.,* **1936**, *28*, 319. (d) Andrews, C. E., *J. Ind. Eng. Chem.,* **1921**, *13*, 167. (e) Gibbs, H. D., *J. Ind. Eng. Chem.,* **1920**, *12*, 1017. (f) Monroe, K. P., *J. Ind. Eng. Chem.,* **1919**, *11*, 1116.

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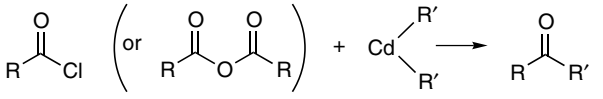
Gilman-Cason Ketone Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Gilman in 1936[1] and was later extensively explored by Cason.[2] It is the preparation of ketones from alkyl (or aryl) cadmium and acyl chloride or anhydride, and is called the Gilman-Cason ketone synthesis. In this reaction, the cadmium reagent is preferentially prepared from a lithium derivative rather than a Grignard reagent,[1] although the aromatic Grignard reagents form cadmium derivatives readily and give good yields of aromatic ketones.[1,2b,3] For the scope of this reaction, it was found that in the case of *n*-butyl halides the chloride is somewhat inferior to the bromide, although it is much better than the corresponding iodide;[2b] in addition, reaction with anhydride seems to be uniformly inferior to that obtained with acid chlorides.[2b–2d,3b] The order of relative reactivity of acyl halides is ArCOI > ArCOBr > ArCOCl > ArCOF.[4] Cadmium chloride is at least as effective as cadmium bromide for preparing the cadmium reagents,[1] and secondary or tertiary alkylcadmium reagents are too unstable to allow their effective use in synthesis, even at a temperature as low as 0°C.[5] It was reported that alkyl cadmium can dissociate and form alkyl radical upon heating.[5] For example, butenylcadmium reagents rapidly dissociate at the boiling temperature of ether and results in the coupling products.[5]

B. GENERAL REACTION SCHEME



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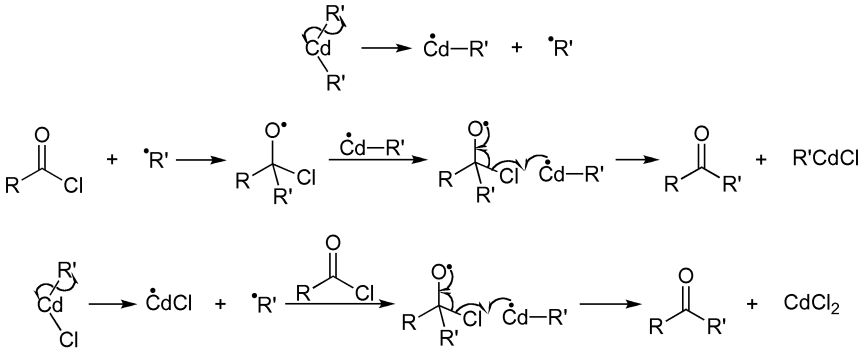
C. PROPOSED MECHANISMS

Cadmium reagent is much milder than corresponding Grignard reagent, and it is believed that cadmium reagent can dissociate into radicals,[5] therefore, the mechanism is tentatively proposed here.



If no radical is involved in this reaction, then the mechanism should be very similar to that of the *Grignard Reaction*. However, as cadmium reagents are much milder than Grignard reagents, they will not further attack the formed ketones.

D. MODIFICATION

N/A

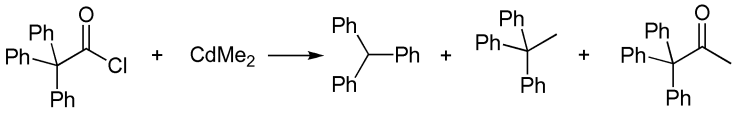
E. APPLICATIONS

This reaction can be used in the synthesis of ketones with multifunctional groups, including carbonyl and esters.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES

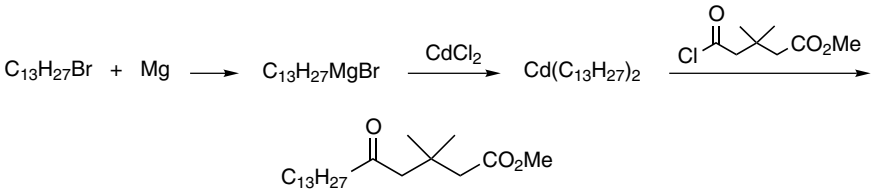


Reference 6.

A Grignard reagent was prepared in 18 mL ether from 0.16 g magnesium turnings and excess methyl bromide, which had been bubbled through sulfuric acid. This reagent

was converted to the cadmium reagent in usual fashion[7] with 0.60 g anhydrous cadmium chloride. After distillation of ether and the addition of 15 mL benzene, a solution of 1.0 g triphenylacetyl chloride in 5 mL benzene was added at 10°C over ~2 min. After the cooling bath had been removed, there was no observable exothermic reaction as the mixture warmed to room temperature.

The reaction was continued with stirring for 1 h at 43°C, then caked solid was scraped from the sides of the flask, and the mixture was heated to reflux for 1 h. As the temperature was raised, sudden boiling occurred, and the mixture turned a bright yellow. The reaction mixture was worked up in the usual fashion for cadmium reactions, and 0.54 g of a yellow oil was obtained, from which no significant crystallization could be obtained in ethanol. Chromatography on alumina of activity III gave 18% triphenylmethane, 33% triphenylethane, and 12% methyl trityl ketone. The melting point of methyl trityl ketone was 137.5–139°C after recrystallization.



Reference 8.

A Grignard reagent was prepared in a nitrogen atmosphere in the usual manner from 4.9 g magnesium turnings (0.2 mol) and 52.7 g *n*-tridecyl bromide (0.2 mol). This was converted to the cadmium reagent with 29.2 g anhydrous cadmium chloride (0.16 mol). Ether was distilled until distillation on a steam bath became slow, then 65 mL benzene was added immediately, and an additional 10 mL distillate was collected. This mixture was cooled to 20°C, and then to the stirred mixture in one portion was added a solution of 19.3 g γ-carbomethoxy-β,β-dimethylbutyryl chloride (0.1 mol) in 70 mL benzene. The temperature of the mixture rose rapidly to 40°C and was maintained at 38–40°C for 80 min, cooling being necessary during the first 20 min. The temperature was then raised to 65°C over 1 h, after which time the mixture was worked up as usual. On distillation, there was obtained 14.5 g of fore run consisting mostly of tridecane, b.p. 115°C (15.5 mmHg), and 30.1 g methyl-3,3-dimethyl-5-ketooctadecanoate (88%), b.p. 191–193°C (2.5 mmHg.)

Other references related to the Gilman-Cason ketone synthesis are cited in the literature.[9]

H. REFERENCES

1. Gilman, H. and Nelson, J. F., *Rev. Trav. Chim.,* **1936**, *55*, 518.
2. (a) Cason, J., *Chem. Rev.,* **1947**, *40*, 15. (b) Cason, J., *J. Am. Chem. Soc.,* **1946**, *68*, 2078. (c) Cason, J. and Prout, F. S., *J. Am. Chem. Soc.,* **1944**, *66*, 46. (d) Cason, J., *J. Am. Chem. Soc.,* **1942**, *64*, 1106.

3. (a) Cole, W. and Julian, P. L., *J. Am. Chem. Soc.,* **1945**, *67*, 1369. (b) de Benneville, P. L., *J. Org. Chem.,* **1941**, *6*, 462.
4. Gilman, H. and Nelson, J. F., *J. Am. Chem. Soc.,* **1939**, *61*, 743.
5. Cason, J. and Fessenden, R., *J. Org. Chem.,* **1960**, *25*, 477.
6. Cason, J. and Schmitz, F. J., *J. Org. Chem.,* **1960**, *25*, 1293.
7. Cason, J. and Prout, F. S., *Org. Syn. Coll.* **1955**, *35*, 601.
8. Cason, J.; Sumrell, G. and Mitchell, R. S., *J. Org. Chem.,* **1950**, *15*, 850.
9. (a) Cason, J. and Schmitz, F. J., *J. Org. Chem.,* **1963**, *28*, 555. (b) Cason, J. and Reist, E. J., *J. Org. Chem.,* **1958**, *23*, 1668. (c) Shirley, D. A. *Org. React.,* **1954**, *8*, 28. (d) Gilman, H. and Nelson, J. F., *J. Am. Chem. Soc.,* **1939**, *61*, 741.

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Gilman-Speeter Reaction
(Gilman-Speeter Condensation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Gilman and Speeter in 1943.[1] It is an efficient preparation of 3-alkyl-substituted or unsubstituted β-lactams by the condensation of a Reformatsky reagent and an imine. Therefore, this reaction is generally known as the Gilman-Speeter reaction[2] or Gilman-Speeter condensation.[2e] In addition, the extended reactions between lithium ester enolate or lithium thioester enolate and imine are also considered as the Gilman-Speeter reaction.

This reaction usually works for nonenolizable imines (e.g., *N*-aryl aldimines)[2g] and has the features of readily accessible starting materials, and simple preparation of 3-substituted or unsubstituted 2-azetidinones (i.e., β-lactams) with direct control of stereoselectivities.[2h] It has been reported that the yield of this reaction depends on the activation and the type of zinc.[3] The stereochemistry of β-lactams depends on the α-substituent of bromoacetates, the solvent, and the alkyl portion of the esters.[2g] For example, when the α-substituent is an alkyl group (e.g., Me, Et, *i*-Pr, cyclohexyl, *t*-Bu), the major product has *cis* geometry, such a trend is especially prevailing for the reaction of acetate with a branched α-substituent (e.g., *i*-Pr, cyclohexyl, *t*-Bu) in THF.[2g] For comparison, the reaction of isopropyl acetate in toluene tends to form β-lactams of *trans* geometry. In addition, phenyl acetates favor the *trans* isomers regardless of the solvents.[2g]

It was found that ultrasound can facilitate the reaction and increase the yields of β-lactams.[2g] However, the Gilman-Speeter reaction has not yet been extensively explored, probably due to the slow reaction rate and relatively low yields[2h] that usually appear at 20–50%.[2h]

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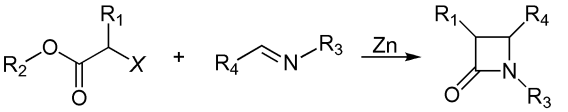
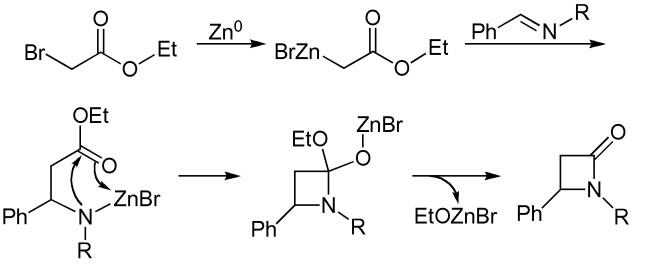
B. GENERAL REACTION SCHEME



R_1 = Me, Et, *i*-Pr, Cy, *t*-Bu, etc.
R_2 = *i*-Pr, *t*-Bu, Cy
R_3 = alkyl, aryl
R_4 = aryl, Me, H, etc.

C. PROPOSED MECHANISMS

The Gilman-Speeter reaction involves the formation of a Reformatsky reagent from α-haloester, nucleophilic addition of the Reformatsky reagent to an imine, and subsequent intramolecular cyclization to form β-lactam, as displayed below.



D. MODIFICATION

The modifications of the Gilman-Speeter reaction include the activation of zinc by trimethylsilyl chloride (TMSCl)[2h] and the application of lithium ester enolate[4] or lithium thioester enolate[5] as the substitute for the traditional Reformatsky reagent. In these modifications, it was found that TMSCl-activated zinc is much more effective in promoting the reaction between ethyl bromoacetate and Schiff bases.[2h] In addition, in the presence of a chiral ether ligand, the reaction between lithium ester enolate and imines affords β-lactams of high enantiomeric excess, probably due to the formation of a ternary complex reagent.[2e,4] The enantioselectivity and reactivity of the ternary complex depend on the size and nature of the lithium amide used. For example, the lithium amide from 2,2,6,6-tetramethylpiperidine (LTMP) is unfavorable for this reaction.[4]

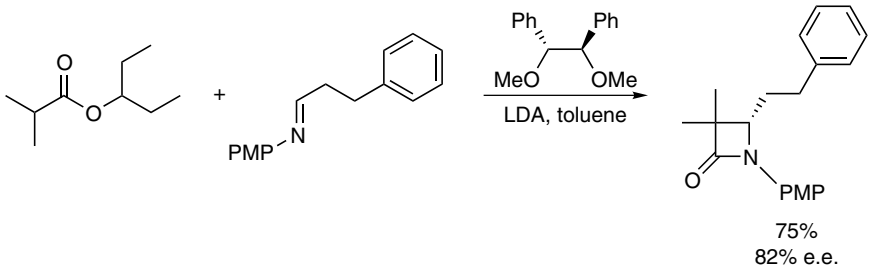
E. APPLICATIONS

This reaction has general application in the synthesis of β-lactams, but has not yet been applied extensively.

F. RELATED REACTIONS

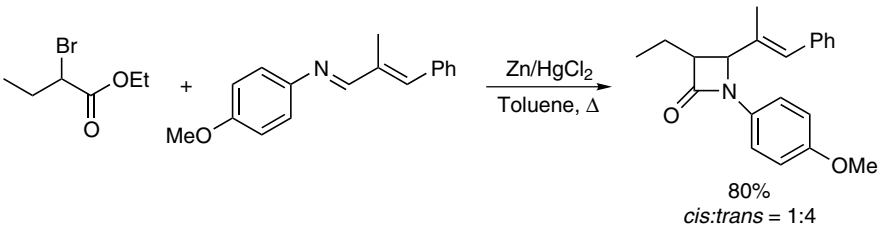
This reaction is related to the *Ghosez Keteniminium-Olefin Cyclization* and *Staudinger Cycloaddition*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4.

To a preformed LDA solution (4.4 mmol) in 9 mL toluene at −78°C was added a solution of 0.31 g 3-pentyl isobutyrate (2.0 mmol) and 48 mg (1*R*,2*R*)-1,2-dimethoxy-1,2-diphenylethane (0.2 mmol) in 3 mL toluene. The mixture was stirred at −25°C for 1.5 h and cooled to −78°C, to this solution was then added a solution of 0.24 g imine (1.0 mmol) prepared from 3-phenylpropinaldehyde and 4-methoxyaniline in 1.5 mL toluene. After being stirred at −78°C for 20 h, the solution was quenched with aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. Upon removal of the solvent, the residue was purified by silica gel column chromatography using EtOAc/hexanes (1:5) as the eluent to afford 75% of (*S*)-α,α-dimethyl-β-(2′-phenyl)ethyl-*N*-(*p*-methoxy)phenyl-β-lactam in 82% e.e. The chiral ligand was recovered for reuse in 99% yield.



Reference 2h.

A mixture of 2.51 g *N*-(α-methylcinnamy1idene)-*p*-anisidine (10 mmol), 0.78 g zinc dust (12.0 mmol), 1.38 mL *dl*-methyl 2-bromobutyrate (12.0 mmol), and a catalytic amount of $HgCl_2$ in 20 mL toluene was refluxed under nitrogen for 8 h. The resulting mixture was cooled to room temperature and poured into an aqueous solution prepared from 20 mL saturated NH_4Cl and 20 mL 25% NH_4OH. The mixture was then extracted with CH_2Cl_2, and the combined organic layers were washed with 20 mL 0.1 *N* HCl and 20 mL water, and dried over $MgSO_4$. Upon removal of the solvent, the residue was purified by column

chromatography using CH_2Cl_2/hexanes (1:2) as the eluent to give 2.57 g 3-ethyl-4-(α-methylstyryl)-l-(4-methoxyphenyl)azetidin-2-one as a 1:4 mixture of *cis* and *trans*-isomers, in a yield of 80%. The *cis*-isomer was separated by trituration in hexane and further crystallization from EtOH, m.p. 99–100°C, and the *trans*-isomer was isolated as an oil.

Other references related to the Gilman-Speeter reaction are cited in the literature.[6]

H. REFERENCES

1. Gilman, H. and Speeter, M., *J. Am. Chem. Soc.,* **1943**, *65*, 2255.
2. (a) Moumné, R.; Denise, B.; Guitot, K.; Rudler, H.; Lavielle, S. and Karoyan, P., *Eur. J. Org. Chem.,* **2007**, 1912. (b) Ye, M.-C.; Zhou, J. and Tang, Y., *J. Org. Chem.,* **2006**, *71*, 3576. (c) Xu, X., *Catalytic, Asymmetric Synthesis of β-Lactams with Cinchona Alkaloid Catalysts*, masters thesis, University of Pittsburgh, **2006**. (d) France, S.; Weatherwax, A.; Taggi, A. E. and Lectka, T., *Acc. Chem. Res.,* **2004**, *37*, 592. (e) Magriotis, P. A., *Angew. Chem. Int. Ed.,* **2001**, *40*, 4377. (f) Magriotis, P. A., *Angew. Chem.,* **2001**, *113*, 4507. (g) Hart, D. J. and Ha, D.-C., *Chem. Rev.,* **1989**, *89*, 1447. (h) Palomo, C.; Cossio, F. P.; Arrieta, A.; Odriozola, J. M.; Oiarbide, M. and Ontoria, J. M., *J. Org. Chem.,* **1989**, *54*, 5736.
3. (a) Bose, A. K.; Gupta, K. and Manhas, M. S., *J. Chem. Soc., Chem. Commun.,* **1984**, 86. (b) Han, B. H. and Boudjouk, P., *J. Org. Chem.,* **1982**, *47*, 5030.
4. Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A. and Tomioka, K., *J. Am. Chem. Soc.,* **1997**, *119* 2060.
5. Benaglia, M.; Cinquini, M. and Cozzi, F., *Eur. J. Org. Chem.,* **2000**, 563.
6. (a) Rappoport, Z. and Marek I., eds., *The Chemistry of Organozinc Compounds: R-Zn*, Patai Series: The Chemistry of Functional Groups, John Wiley & Sons, Chichester, **2007**. (b) Tirayut, V.; Worawan, B.; Yongsak, S.-A., *Curr. Org. Chem.,* **2005**, *9*, 1315. (c) Jian, S.-Z.; Ma, C. and Wang, Y.-G., *Synthesis,* **2005**, 725. (d) Tomioka, K; Fujieda, H.; Hayashi, S.; Hussein, M.A.; Kambara, T.; Nomura, Y.; Kanai, M. and Koga, K., *Chem. Commun.,* **1999**, 715.

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Gomberg Free Radical Reaction

A. GENERAL DESCRIPTION OF THE REACTION

Free radical chemistry can be traced back to the initial preparation of a triphenylmethyl radical from Gomberg in 1900 by halogen abstraction of triphenylmethyl halide with metals,[1] when he stated that he wished to reserve the field for himself.[1a,2] Thus the generation of triphenylmethyl radical is referred to as the Gomberg reaction.[3] This initial work shifted people's attention to trivalent carbon,[4] the so-called free radical. Since then, the generation of radicals and the reactions involving radicals have been extensively explored and has become a part of free radical chemistry. It is known that the triarylmethyl radicals demonstrate different colors while changing temperature,[5] as in quinonoidation.[6] It has been reported that radicals might even be formed during the preparation of Grignard reagents at the initial stage when iodine was used as a catalyst.[7] Up to now, many efficient and convenient methods have been developed to generate free radicals, such as reduction;[8] oxidation;[9] pyrolysis of peroxides, acyl peroxides, and azo compounds;[10] photo irradiation;[11] and trialkylaluminium[12] or trialkylboranes.[12,13] The compounds, which easily decompose and form free radical species, are used as free radical initiators, and the commonly used free radical initiators are summarized in Table 1. On the other hand, compounds that contain one weak bond linking to hydrogen are prepared as proton donors in radical chain reactions, and these compounds are known as hydride transfer reagents; the most common ones are silanes,[14] germanes,[15] and stannanes[16] (Table 2). Because of their reactive nature, radicals are normally transient intermediates in chemical transformations. The lifetime of other radicals can be determined by careful analysis of the product distribution, if these radicals react with the compound that undergoes an intramolecular radical rearrangement with known lifetime. This is a new field in free radical chemistry developed since 1980—the so-called

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

TABLE 1. Common Free Radical Initiators

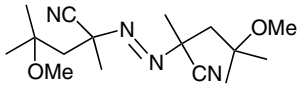
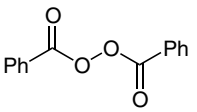
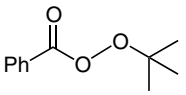
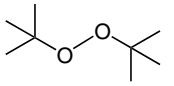
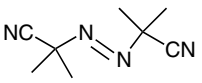
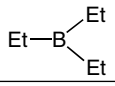
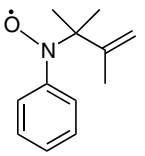
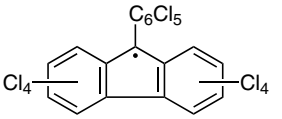
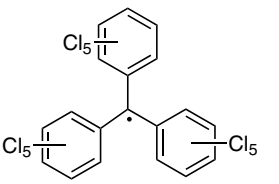
Structure	Name	Structure	Name
	2,2′-Azobis(2,4-dimethyl-4-methoxyvarelonitrile) (V-70)[10b]		Benzoyl peroxide[10d]
	*tert*-Butyl peroxybenzoate[10d]		*tert*-Butyl peroxide[10d]
	Azoisobutyronitrile (AIBN)[10a]		Triethylborane[12,13]

TABLE 2. Common Hydrogen-Transfer Reagents in Free Radical Reactions

n-Bu_3SnH[16]	*n*-Bu_3GeH[15b,15c]	$(Me_3Si)_3GeH$[15a]
$(Me_3Si)_2Si(Me)H$[14a]	$(Me_3Si)_3SiH$[14b]	Et_3SiH[14c]
$PhSiMe_2H$[14c]	$PhSiH_3$[14c]	$Me_3SiSiMe_2H$[14c]

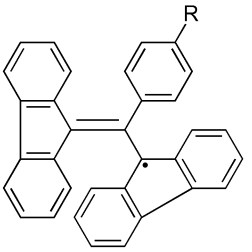
radical-molecule reaction kinetics[17]—and the radicals with a known lifetime are called free radical clocks.[18] Although most of the radicals have short lifetimes, some radicals, like Gomberg's triphenylmethyl radical, with bulky substituents may have longer lifetimes, and these radicals fall into two categories: persistent radicals and stable radicals. A persistent radical has a relatively long lifetime (e.g., minutes) allowing its characterization under the conditions it is generated,[8a] whereas a stable radical is inherently stable and can be isolated without signs of decomposition under inert atmosphere at room temperature.[8a,8b] Some radicals are extremely stable in air, with half-lives of decades, and can withstand typical radical reagents (e.g., nitric oxide) and even highly reactive chemical species (e.g., halogens and sodium hydroxide). In addition, these radicals even possess a very high thermal stability (up to 300°C).[19] Therefore, these types of radicals are called inert free radicals.[4,19,20] Some representative long-living radicals are summarized in Table 3, including the persistent, stable, and inert radicals.[9a,20,21] Overall, the radicals are involved in almost every aspect of organic chemistry, as indicated in reviews about free radical chemistry.[22]

TABLE 3. Representative Persistent, Stable, and Inert Free Radicals

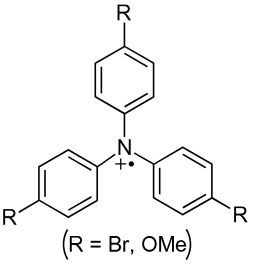
		
Reference 21i	Reference 20	Reference 20

(*continued*)

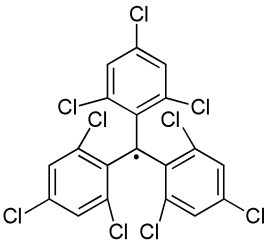
TABLE 3. (*Continued*)



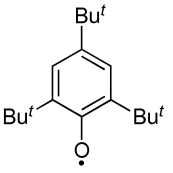
Reference 21j



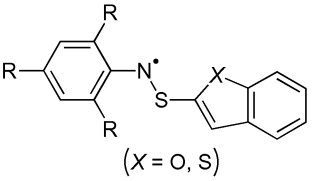
Reference 21f



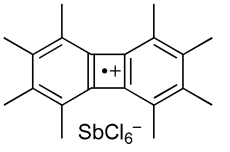
Reference 21d



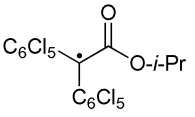
Reference 21l & 21m



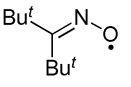
References 9a, 21a & 21b



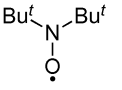
Reference 21c



Reference 20



Reference 21g



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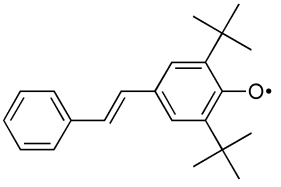
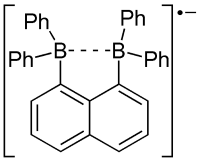
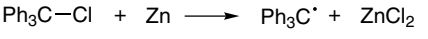


Reference 21h

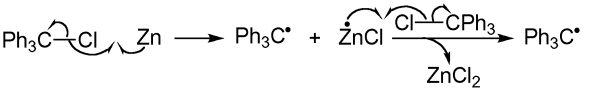


Reference 21e

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

The original initiation of a free radical has been modified extensively, as mentioned earlier.

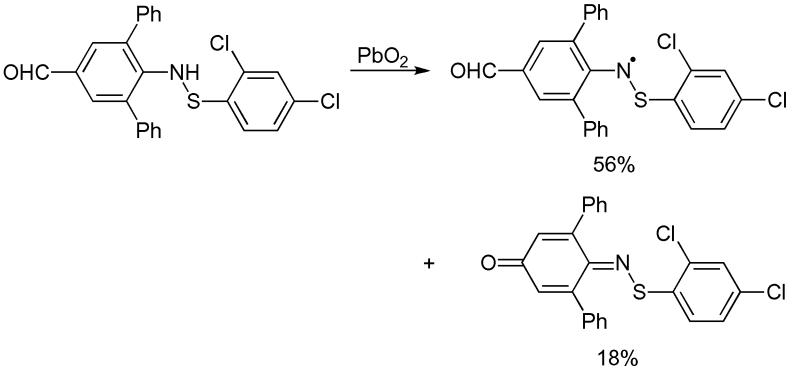
E. APPLICATIONS

The free radical reaction has extremely broad applications in organic synthesis.

F. RELATED REACTIONS

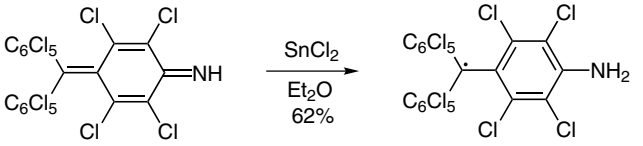
This reaction is related to the *Benkeser Reduction* and *Birch Reduction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 9a.

A mixture of 100 mg *N*-[(2,4-dichlorophenyl)thio]-4-formyl-2,6-diphenylaniline and 300 mg K_2CO_3 in 10 mL benzene was vigorously stirred. Within 30 min, 2.5 g PbO_2 was added in portions; after that, the mixture was further stirred for 1 min and filtered. After the benzene was removed by freeze-drying, the residue was subjected to chromatography on alumina. Elution of the green zone with benzene gave *N*-[(2,4-dichlorophenyl)thio]-4-formyl-2,6-diphenylphenylaminyl in 56% yield in the form of dark green needles from hexane/EtOAc, m.p., 128–130°C. In addition, further elution of the orange zone with EtOAc afforded 18% *N*-[(2,4-dichlorophenyl)thio]-2,6-diphenyl-*p*-benzoquinone monoimine in the form of orange prisms from hexane/EtOAc, m.p., 185–186°C.



Reference 23.

Anhydrous $SnCl_2$ (0.040 g) was added to a solution of 0.080 g crude fuchsonimine in 18 mL anhydrous diethyl ether, and the mixture was stirred in the dark under argon overnight. The green solution was then filtered, washed with aqueous HCl and water, dried, and evaporated. The residue was purified by column flash chromatography (silica gel hexane/CCl_4) to give 0.050 g 4-aminotetradecachlorotriphenylmethyl radical as dark green needles, in a yield of 62%.

Other references related to the Gomberg free radical reaction are cited in the literature.[24]

H. REFERENCES

1. (a) Gomberg, M., *J. Am. Chem. Soc.,* **1900**, *22* , 757. (b) Gomberg, M., *Ber.,* **1900**, *33* , 3150.
2. Foster, S. C. and Miller, T. A., *J. Phys. Chem.,* **1989**, *93*, 5986.
3. (a) Hodgson, H. H., *J. Soc. Dyers & Colourists,* **1949**, *65*, 347. (b) Hodgson, H. H., *J. Soc. Dyers & Colourists,* **1948**, *64* , 99.
4. (a) Ballester, M., *Acc. Chem. Res.,* **1985**, *18* , 380. (b) Ballester, M.; Castañer, J.; Riera, J.; Pujadas, J.; Armet, O.; Onrubia, C. and Rio, J. A., *J. Org. Chem.,* **1984**, *49* , 770.
5. Lewis, G. N.; Lipkin, D. and Magel, T. T., *J. Am. Chem. Soc.,* **1944**, *66* , 1579.
6. Anderson, L. C., *J. Am. Chem. Soc.,* **1935**, *57* , 1673.
7. (a) Gilman, H. and Zoellner, E. A., *J. Am. Chem. Soc.,* **1930**, *52* , 3984. (b) Gilman, H. and Kirby, J. E., *J. Am. Chem. Soc.,* **1929**, *51* , 1571. (c) Gomberg, M. and Bachmannu W. E., *J. Am. Chem. Soc.,* **1927**, *49* , 236.
8. (a) Power, P. P., *Chem. Rev.,* **2003**, *103*, 789. (b) Kosower, E. M. and Poziomek, E. J., *J. Am. Chem. Soc.,* **1964**, *86* , 5515. (c) Conant, J. B. and Sloan, A. W., *J. Am. Chem. Soc.,* **1923**, *45* , 2466.
9. (a) Miura, Y.; Nakamura, S. and Teki, Y., *J. Org. Chem.,* **2003**, *68* , 8244. (b) Miura, Y.; Kurokawa, S.; Nakatsuji, M.; Ando, K. and Teki, Y., *J. Org. Chem.,* **1998**, *63*, 8295. (c) Miura, Y.; Momoki, M.; Nakatsuji, M. and Teki, Y., *J. Org. Chem.,* **1998**, *63*, 1555. (d) Snider, B. B.; Mohan, R. and Kates, S. A., *J. Org. Chem.,* **1985**, *50* , 3559. (e) Heiba, E. I.; Dessau, R. M. and Rodewald, P. G., *J. Am. Chem. Soc.,* **1974**, *96* , 7977.
10. (a) Yamago, S.; Iida, K.; Nakajima, M. and Yoshida, J., *Macromolecules,* **2003**, *36* , 3793. (b) Kita, Y.; Sano, A.; Yamaguchi, T.; Oka, M.; Gotanda, K. and Matsugi, M., *J. Org. Chem.,* **1999**, *64*, 675. (c) Pohlman, A. and Mill, T., *J. Org. Chem.,* **1983**, *48* , 2133. (d) Pryor, W. A.; Morkved, E. H. and Bickley, H. T., *J. Org. Chem.,* **1972**, *37* , 1999.
11. (a) De Lijser, H. J. P. and Arnold, D. R., *J. Org. Chem.,* **1997**, *62*, 8432. (b) Engel, P. S. and Wu, A. Y., *J. Org. Chem.,* **1994**, *59* , 3969. (c) Kharasch, M. S.; Nudenberg, W. and Meltzer, T. H., *J. Org. Chem.,* **1954**, *19* , 1234.
12. Liu, J.-H.; Jang, Y.-J.; Lin, W.-W.; Liu, J.-T. and Yao, C.-F., *J. Org. Chem.,* **2003**, *68* , 4030.
13. (a) Panchaud, P. and Renaud, P., *J. Org. Chem.,* **2004**, *69* , 3205. (b) Liu, J.-T.; Jang, Y.-J.; Shih, Y.-K.; Hu, S.-R.; Chu, C.-M. and Yao, C.-F., *J. Org. Chem.,* **2001**, *66*, 6021. (c) Deprèle, S. and Montchamp, J.-L., *J. Org. Chem.,* **2001**, *66*, 6745 (d) Miyabe, H.; Fujishima, Y. and Naito, T., *J. Org. Chem.,* **1999**, *64*, 2174.
14. (a) Chatgilialoglu, C.; Guerrini, A. and Lucarini, M., *J. Org. Chem.,* **1992**, *57* , 3405. (b) Chatgilialoglu, C.; Dickhaut, J. and Giese, B., *J. Org. Chem.,* **1991**, *56* , 6399. (c) Lusztyk, J.; Maillard, B. and Ingold, K. U., *J. Org. Chem.,* **1986**, *51* , 2457.
15. (a) Bernardoni, S.; Lucarini, M.; Pedulli, G. F.; Valgimigli, L.; Gevorgyan, V. and Chatgilialoglu, C., *J. Org. Chem.,* **1997**, *62*, 8009. (b) Lusztyk, J.; Maillard, B.; Deycard, S.; Lindsay, D. A. and

Ingold, K. U., *J. Org. Chem.,* **1987**, *52* , 3509. (c) Lusztyk, J.; Maillard, B.; Lindsay, D. A. and Ingold, K. U., *J. Am. Chem. Soc.,* **1983**, *105* , 3578.

16. (a) Tamura, O.; Matsukida, H.; Toyao, A.; Takeda, Y. and Ishibashi, H., *J. Org. Chem.,* **2002**, *67*, 5537. (b) Nishiyama, Y.; Kajimoto, H.; Kotani, K.; Nishida, T. and Sonoda, N., *J. Org. Chem.,* **2002**, *67*, 5696. (c) Ziegler, F. E. and Jeroncic, L. O., *J. Org. Chem.,* **1991**, *56*, 3479. (d) Chatgilialoglu, C.; Ingold, K. U. and Scaiano, J. C., *J. Am. Chem. Soc.,* **1981**, *103*, 7739.
17. (a) Kemp, T. J., *Prog. React. Kinet.,* **1999**, *24*, 287. (b) Newcomb, M., *Tetrahedron,* **1993**, *49*, 1151.
18. (a) Kretzschmar, I.; Friend, C. M. and Sigman, M. E., *J. Phys. Chem. B,* **2002**, *106*, 663. (b) Griller, D. and Ingold, K. U., *Acc. Chem. Res.,* **1980**, *13*, 317.
19. Ballester, M.; Riera, J.; Castañer, J.; Badía, C. and Monsó, J. M., *J. Am. Chem. Soc.,* **1971**, *93*, 2215.
20. O'Neill, P. and Hegarty, A. F., *J. Org. Chem.,* **1992**, *57*, 4421.
21. (a) Miura, Y.; Oyama, Y. and Teki, Y., *J. Org. Chem.,* **2003**, *68*, 1225. (b) Miura, Y.; Tomimura, T. and Teki, Y., *J. Org. Chem.,* **2000**, *65*, 7889. (c) Kochi, J. K.; Rathore, R. and Maguères, P. L., *J. Org. Chem.,* **2000**, *65*, 6826. (d) Domingo, V. M.; Burdons, X.; Brillas, E.; Carilla, J.; Rius, J.; Torrelles, X. and Juliá, L., *J. Org. Chem.,* **2000**, *65*, 6847. (e) Hoefelmeyer, J. D. and Gabbai, F. P., *J. Am. Chem. Soc.,* **2000**, *122*, 9054. (f) Breslin, D. T. and Fox, M. A., *J. Org. Chem.,* **1994**, 59, 7557. (g) Brokenshire, J. L.; Mendenhall, G. D. and Ingold, K. U., *J. Am. Chem. Soc.,* **1971**, *93*, 5278. (h) Becker, H.-D., *J. Org. Chem.,* **1969**, *34*, 1211. (i) Sullivan, A. B., *J. Org. Chem.,* **1966**, *31*, 2811. (j) Solar, S. L., *J. Org. Chem.,* **1963**, *28*, 2911. (k) Hoffman, A. K. and Henderson, A. T., *J. Am. Chem. Soc.,* **1961**, *83*, 4671. (l) Cook, C. D.; Kohn, D. A. and Fianu, P., *J. Am. Chem. Soc.,* **1956**, *78*, 2002. (m) Müller, E. and Ley, K., *Ber.,* **1955**, *88*, 601.
22. (a) Fischer, H. and Radom, L., *Angew. Chem. Int. Ed.,* **2001**, *40*, 1340. (b) Kamigaito, M.; Ando, T. and Sawamoto, M., *Chem. Rev.,* **2001**, *101*, 3689. (c) Hawker, C. J.; Bosman, A. W. and Harth, E., *Chem. Rev.,* **2001**, *101*, 3661. (d) McCarroll, A. J. and Walton, J. C., *Angew. Chem. Int. Ed.,* **2001**, *40*, 2224. (e) Robertson, J.; Pillai, J. and Lush, R. K., *Chem. Soc. Rev.*, **2001**, *30*, 94. (f) Kujmamoto, H.; Ogamino, J.; Tanaka, H.; Suzuki, H.; Haraguchi, K.; Miyasaka, T.; Yokomatsu, T. and Shibuya, S., *Tetrahedron*, **2001**, *57*, 3331. (g) Allen, A. D. and Tidwell, T. T., *Chem. Rev*., **2001**, *101*, 1333. (h) Saettel, N. J.; Oxgaard, J. and Wiest, O., *Eur. J. Org. Chem*., **2001**, 1429. (i) Ryu, I., *Chem. Soc. Rev.*, **2001**, *30*, 16. (j) Gosain, R.; Norrish, A. M. and Wood, M. E., *Tetrahedron,* **2001**, *57*, 1399. (k) Li, J. J., *Tetrahedron,* **2001**, *57*, 1. (l) Baciocchi, E.; Bietti, M. and Lanzalunga, O., *Acc. Chem. Res.,* **2000**, *33*, 243. (m) Korolev, G. V. and Marchenko, A. P., *Russ. Chem. Rev*., **2000**, *69*, 409. (n) Chatgilialoglu, C.; Crich, D.; Komatsu, M. and Ryu, I., *Chem. Rev.,* **1999**, *99*, 1991. (o) Patten, T. E. and Matyjaszewski, K., *Acc. Chem. Res*., **1999**, *32*, 895. (p) Sibi, M. P. and Porter, N. A., *Acc. Chem. Res.,* **1999**, *32*, 163. (q) Zipse, H., *Acc. Chem. Res*., **1999**, *32*, 571. (r) Martínez-Grau, A. and Marco-Contelles, J., *Chem. Soc. Rev.,* **1998**, *27*, 155. (s) Frey, P. A., *Curr. Opinion Chem. Biol.,* **1997**, *1*, 347.
23. Canepa, M.; Fox, M. A. and Whitesell, J. K., *J. Org. Chem.,* **2001**, *66*, 3886.
24. (a) Tidwell, T. T., *Chem. Intelligencer,* **2000**, *6*, 33. (b) Sung, K. S. and Tidwell, T. T., *J. Org. Chem.,* **1998**, *63*, 9690. (c) Porter, N. A.; Giese, B. and Curran, D. P., *Acc. Chem. Res.,* **1991**, *24*, 296. (d) Neumann, W. P.; Uzick, W. and Zarkadis, A. K., *J. Am. Chem. Soc.,* **1986**, *108*, 3762. (e) Goerner, R. N.; Cote, P. N. and Vittimberga, B. M., *J. Org. Chem.,* **1977**, *42*, 19. (f) McBride, J. M., *Tetrahedron*, **1974**, *30*, 2009. (g) Fu, J.-J. L. and Bentrude, W. G., *J. Am. Chem. Soc.,* **1972**, *94*, 7710. (h) Kinoshita, M.; Yoshizumi, N. and Imoto, M., *Makromol. Chem.,* **1969**, *127*, 185. (i) Rejdych, J., *Chem. Szkole,* **1970**, *16*, 231. (j) Sevilla, M. D. and Vincow, G., *J. Phys. Chem.*, **1968**, *72*, 3635. (k) Meislich, H.; Costanza, J. and Strelitz, J., *J. Org. Chem.,* **1968**, *33*, 3221. (l) Kochi, J. K.; Bacha, J. D. and Bethea, T. W., *J. Am. Chem. Soc.,* **1967**, *89*, 6538. (m) Binsch, G. and Rüchardt, C., *J. Am. Chem. Soc.,* **1966**,

88, 173. (n) Kampmeier, J. A.; Geer, R. P.; Meskin, A. J. and D'Silva, R. M., *J. Am. Chem. Soc.,* **1966**, *88*, 1257. (o) Curtin, D. Y. and Kauer, J. C., *J. Org. Chem.,* **1960**, *25*, 880. (p) Curtin, D. Y. and Miller, T. C., *J. Org. Chem.,* **1960**, *25*, 885. (q) Russell, G. A., *J. Am. Chem. Soc.,* **1958**, *80*, 4987. (r) Walter, R. I., *J. Am. Chem. Soc.,* **1955**, *77*, 5999. (s) Dannley, R. L.; Gregg, E. C.; Phelps, R. E. and Coleman, C. B., *J. Am. Chem. Soc.,* **1954**, *76*, 445. (t) Dannley, R. L. and Gregg, E. C., *J. Am. Chem. Soc.,* **1954**, *76*, 2997. (u) Dannley, R. L. and Sternfeld, M., *J. Am. Chem. Soc.,* **1954**, *76*, 4543. (v) Curtin, D. Y. and Hurwitz, M. J., *J. Am. Chem. Soc.,* **1952**, *74*, 5381. (w) Bent, H. E. and Gould, R. G., *J. Am. Chem. Soc.,* **1935**, *57*, 1217. (x) Bent, H. E. and Dorfman, M., *J. Am. Chem. Soc.,* **1932**, *54*, 1393. (y) Conant, J. B. and Garvey, B. S., *J. Am. Chem. Soc.,* **1927**, *49*, 2080. (z) Conant, J. B. and Sloan, A. W., *J. Am. Chem. Soc.,* **1925**, *47*, 572. (aa) Gomberg, M., *Chem. Rev.,* **1924**, *1*, 91. (bb) Gomberg, M. and Sullivan, F. W., *J. Am. Chem. Soc.,* **1923**, *45*, 1810. (cc) Gomberg, M., *J. Ind. Eng. Chem.,* **1914**, *6*, 339. (dd) Gomberg, M., *J. Am. Chem. Soc.,* **1914**, *36*, 1144.

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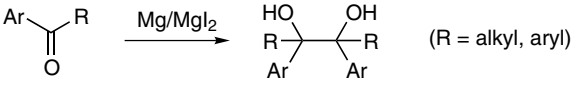
Gomberg-Bachmann Pinacol Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Gomberg and Bachmann in 1927.[1] It is the preparation of pinacols from aromatic aldehyde or ketones in the presence of magnesium and magnesium iodide and is known as the Gomberg-Bachmann pinacol synthesis.[2] It is known that a radical mechanism is involved in this reaction as indicated by the green and brown colors of the reaction solution, which disappear when the solution is exposed to air and reappear when air is removed.[1] During this reaction, the ketone was first reduced to a ketyl radical, then the ketyl radicals combine to give pinacol after workup.[1] This reaction produces pinacols in almost quantitative yields[2] and is especially good for stable ketones, such as xanthone and fluorenone, whose corresponding pinacols have not be prepared by alternative methods yet.[2] It is known in the cases of pyridyl ketones, 2 eq. magnesium iodide is needed for the completion of reduction, where one magnesium iodide complexes with the nitrogen atom of the pyridyl ring, and the second magnesium iodide actually reduces the ketone in combination with magnesium.[2]

B. GENERAL REACTION SCHEME



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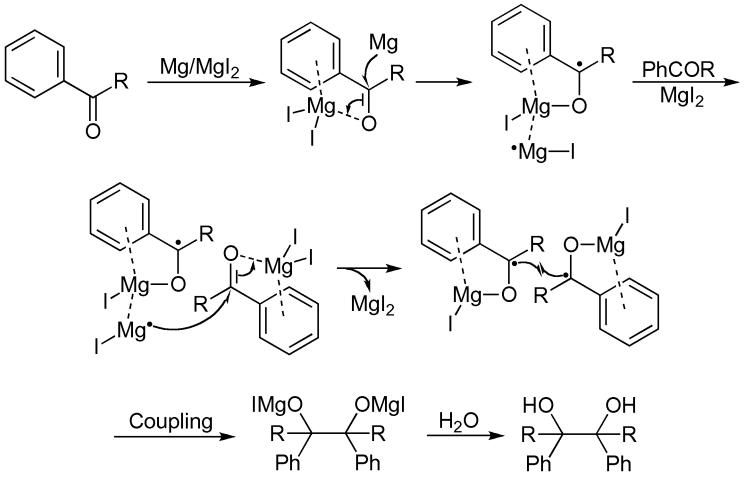
C. PROPOSED MECHANISMS

Illustrated here is the tentative mechanism, using acyl phenone as an example.



D. MODIFICATION

This reaction has been modified using 2 eq. magnesium iodide for heteroaromatic ketones.[2]

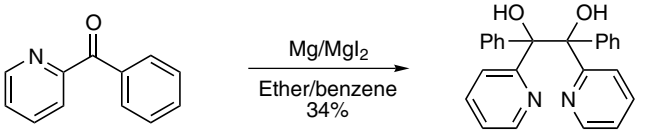
E. APPLICATIONS

This reaction is very useful in the preparation of pinacols from aromatic aldehydes and ketones.

F. RELATED REACTIONS

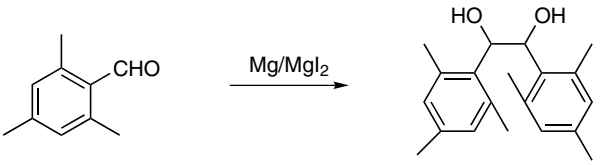
This reaction is related to the *Pinacol Coupling Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2.

To 5 g powdered magnesium (0.21 mol) in 35 mL ether and 50 mL benzene was added with shaking 14 g iodine (0.055 mol) in portions to keep the solution boiling. After the complete addition, the mixture was shaken until the liquid was practically colorless. To this mixture was added 18.3 g phenyl 2-pyridyl ketone (0.1 mol) dissolved in 30 mL benzene. A green precipitate separated, which on shaking slowly turned to a yellow solid. The mixture was shaken and heated on a water bath for 1 h, but no visible change occurred. A small portion of the mixture was withdrawn and hydrolyzed with water. The benzene-ether layer was dried and then evaporated to dryness to give a pale yellow solid, m.p. $< 40^{\circ}$C. To the mixture was added an additional quantity of magnesium and magnesium iodide (prepared from 5 g magnesium and 14 g iodine) and on shaking, the yellow precipitate changed to a green precipitate. The mixture was refluxed on a water bath for 4 h, and then allowed to stand at room temperature for 1 week, after which time no visible change had taken place. The mixture was added to water, and the benzene-ether layer separated. The water layer was washed several times with ether, and the benzene-ether solution was combined with the ether washings and dried over magnesium sulfate. Distillation of the solution yielded an orange oily solid, which on washing with ethanol yielded 7.0 g α,α-di-2-pyridylhydrobenzoin, in a yield of 38%, m.p., 141–142°C, after recrystallization twice from EtOAc. The filtrate on evaporation yielded 4.3 g phenyl 2-pyridyl ketone.



Reference 3.

To the mixture of 15 g magnesium turnings, 100 mL dry ether, 150 mL dry benzene, and 60 g iodine, was added a solution of 67 g mesitaldehyde in 75 mL dry benzene over a period of 1.5 h. The mixture was stirred vigorously and refluxed for 12 h. The product was isolated in a usual manner. The solid was warmed with high-boiling petroleum ether, and the undissolved material was separated and recrystallized from methanol. This yielded the pinacol of mesitaldehyde, m.p. 214–215°C.

Other references related to the Gomberg-Bachmann pinacol synthesis are cited in the literature.[4]

H. REFERENCES

1. Gomberg, M. and Bachmann, W. E., *J. Am. Chem. Soc.,* **1927**, *49*, 236.
2. Ebetino, F. F. and Amstutz, E. D., *J. Org. Chem.,* **1963**, *28*, 3249.
3. Fuson, R. C.; Horning, E. C.; Ward, M. L.; Rowland, S. P. and Marsh, J. L., *J. Am. Chem. Soc.,* **1942**, *64*, 30.
4. (a) Micha-Screttas, M.; Heropoulos, G. A. and Steele, B. R., *J. Chem. Soc., Perkin Trans. II,* **1999**, 2685. (b) Bachmann, W. E. and Shankland, R. V., *J. Am. Chem. Soc.,* **1929**, *51*, 306.

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Gomberg-Bachmann Reaction

(Gomberg-Bachmann-Hey Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

Although this reaction was initially discovered almost concurrently by Kühling[1] and by Bamberger[2] in 1895, it is generally known as the Gomberg-Bachmann reaction[3] after a convenient and much safer experimental procedure was developed by Gomberg and Bachmann in 1924.[4] It is the synthesis of diaryls (mostly unsymmetrical diaryls) by condensation of aryl diazonium salts with aromatic or heterocyclic compounds in the presence of aqueous NaOH. Therefore, this reaction is sometimes referred to as the Gomberg-Bachmann alkaline reaction,[3a] Gomberg arylation,[3a] or Gomberg-Bachmann biaryl synthesis.[5] Hey and co-workers extensively studied the mechanism of this reaction, indicating the involvement of free radicals in this reaction;[6] thus this reaction is also called the Gomberg-Bachmann-Hey reaction,[7] Gomberg-Bachmann-Hey arylation,[8] and Gomberg-Bachmann-Hey aryl coupling.[9] It is known that this reaction is rapid and easy to carry out, especially for the aromatic diazonium salts containing an electron-withdrawing group.[4] However, this reaction does have inherent drawbacks, such as the instability of diazonium salt[3c] and the accompanying side reactions to form tar residue;[3j] therefore, this reaction has been modified to use stable aromatic diazonium tetrafluoroborate under phase transfer conditions.[3c]

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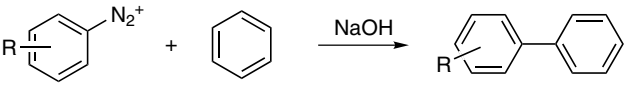
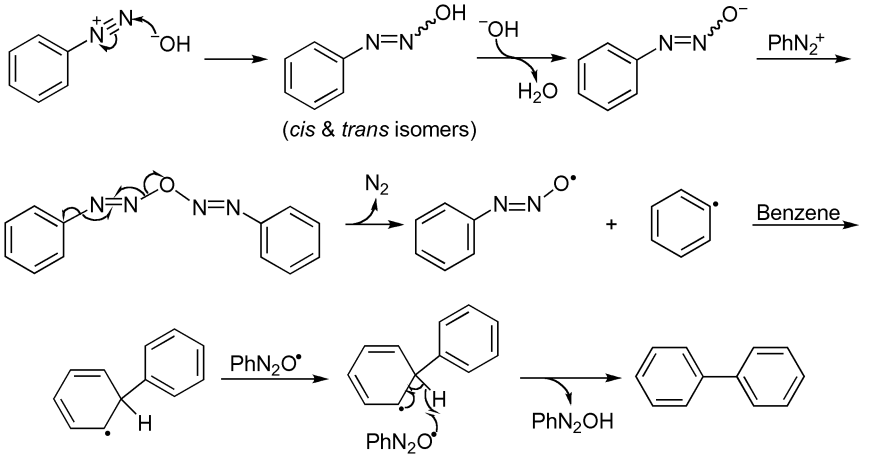
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The mechanism is demonstrated by the coupling between phenyldiazonium salt and benzene as displayed here.



D. MODIFICATION

This reaction has been modified using aryldiazonium tetrafluoroborate under phase transfer conditions to enhance the stability of diazonium salt.[3c]

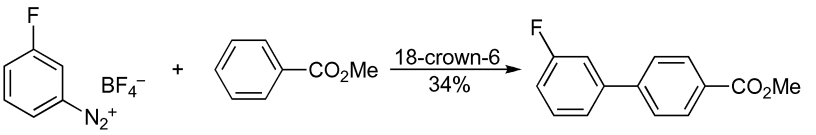
E. APPLICATIONS

This reaction has wide applications in the coupling of aryl compounds or aryl and heteroaromatics.

F. RELATED REACTIONS

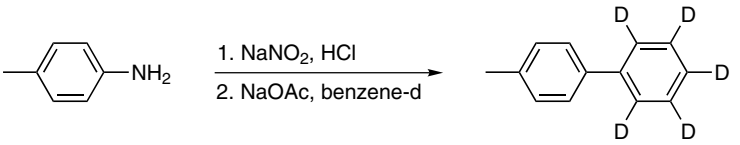
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3c.

Potassium acetate (1.20 g, 12.2 mmol, 2 eq.) was added at ambient temperature to a magnetically stirred mixture of 1.28 g 3-fluorophenyldiazonium tetrafluoroborate (6.0 mmol) and 5 mol % 18-crown-6 in 60 mL methyl benzoate. Stirring was continued for 90 min. The red mixture was filtered, and the filtrate was washed with brine and water. The organic layer was dried over Na_2SO_4 and evaporated, and the residue was chromatographed over alumina (30–50 g) using 10% ether/hexane as the eluent, the collected fraction was further distilled to afford 0.48 g methyl 3′-fluorobiphenyl-2-carboxylate as oil, in a yield of 34%.



Reference 3g.

p-Toluidine (0.58 g, 5.4 mmol) was dissolved in 2 mL concentrated hydrochloric acid and diazotized at 0–5°C with 0.6 g $NaNO_2$ dissolved in 2 mL water. The solution of the resulting diazonium salt was added slowly, with vigorous stirring, to a mixture of 30 g benzene-d (97.02% isotopically pure by mass spectrometry at reduced ionizing voltage, 0.38 mol) and 7.0 mL NaOAc solution containing 3.0 g NaOAc maintained at 6–10°C. After completion of the addition, the mixture was stirred at 6–10°C for 30 min and then at room temperature for 6 h. The dark benzene layer was separated, washed three times with aqueous $NaHCO_3$ followed by water, dried over $CaCl_2$, and concentrated on a steam bath. The residue was dissolved in 5 mL ether, mixed with 2 g activated alumina, and dried in a film evaporator. The residue, impregnated on alumina, was placed on top of an alumina column (25 g) and was extracted repeatedly with petroleum ether (b.p. 60–90°C). The first 100 mL of eluate on concentration gave 350 mg 4-methylbiphenyl, m.p. 42–44.5°C, raised to 46.5–47°C by sublimation under reduced pressure and crystallization from methanol.

Other references related to the Gomberg-Bachmann reaction are cited in the literature.[10]

H. REFERENCES

1. Kühling, O., *Ber.,* **1895**, *28*, 41.
2. Bamberger, E., *Ber.,* **1895**, *28*, 403.
3. (a) Galli, C., *Chem. Rev.,* **1988**, *88*, 765. (b) McKenzie, T. C. and Rolfes, S. M., *J. Heterocycl. Chem.,* **1987**, *24*, 859. (c) Beadle, J. R.; Korzeniowski, S. H.; Rosenberg, D. E.; Garcia-Slanga, B. J. and Gokel, G. W., *J. Org. Chem.,* **1984**, *49*, 1594. (d) Fukata, G.; Kawazoe, Y. and Taguchi,

T., *Yakugaku Zasshi,* **1974**, *94*, 36. (e) Fukata, G.; Kawazoe, Y. and Taguchi, T., *J. Pharm. Soc. Jpn.,* **1974**, *94*, 852. (f) Panaiotov, I. M.; Kasabova, N. and Kirova, P., *Dokl. Bolgarskoi Akad. Nauk*, **1969**, *22*, 675. (g) Eliel, E. L.; Saha, I. G. and Meyerson, S., *J. Org. Chem.*, **1965**, *30*, 2451. (h) Ruechardt, C. and Merz, E., *Tetrahedron Lett*., **1964**, 2431. ((i) Gragerov, I. P. and Turkina, M. Y., *Zh. Obsh. Khim.,* **1963**, *33*, 1907. (j) Detar, D. F. and Chu, C.-C., *J. Am. Chem. Soc.,* **1960**, *82*, 4969. (k) DeTar, D. F. and Kazimi, A. A., *J. Am. Chem. Soc.,* **1955**, *77*, 3842. (l) Detar, D. F. and Relyea, D. I., *J. Am. Chem. Soc.,* **1954**, *76*, 1680.

4. Gomberg, M. and Bachmann, W. E., *J. Am. Chem. Soc.,* **1924**, *46*, 2339.
5. Smith, P. A. S. and Hall, J. H., *J. Am. Chem. Soc.,* **1962**, *84*, 480.
6. (a) Hey, D. H., *Adv. Free Radical Chem.,* **1966**, *2*, 47. (b) Dermer, O. C. and Edmison, M. T., *Chem. Rev.,* **1957**, *57*, 77. (c) Elks, J.; Haworth, J. W. and Hey, D. H., *J. Chem. Soc.,* **1940**, 1284. (d) Grieve, W. S. M. and Hey, D. H., *J. Chem. Soc.*, **1938**, 108. (e) Hey, D. H. and Waters, W. A., *Chem. Rev.,* **1937**, *21*, 169. (f) Grieve, W. S. M. and Hey, D. H., *J. Chem. Soc.*, **1934**, 1797. (g) Grieve, W. S. M. and Hey, D. H., *J. Chem. Soc.*, **1934**, 1966.
7. (a) Nock, H. and Schottenberger, H., *J. Org. Chem.,* **1993**, *58*, 7045. (b) Tarshits, D. L.; Przhiyalgovskaya, N. M. and Suvorov, N. N., *Chem. Heterocycl. Compd.,* **1988**, *24*, 1217. (c) Abramovitch, R. A. and Saha, J. G., *J. Chem. Soc.,* **1964**, 2175.
8. Gurczynski, M. and Tomasik, T., *Org. Prep. Proced. Int.,* **1991**, *23*, 438.
9. Press, J. B.; Eudy, N. H. and Morton, G. O., *J. Org. Chem.,* **1983**, *48*, 4605.
10. (a) Rosenberg, D. E.; Beadle, J. R.; Korzeniowski, S. H. and Gokel, G. W., *Tetrahedron Lett.,* **1980**, *21*, 4141. (b) Mann, N.; Baak, W. and Mutscler, E., *Arch. Pharm.*, **1973**, *306*, 625. (c) Gouki, F.; Yuichi, K. and Tanezo, T., *Tetrahedron Lett.,* **1973**, *15*, 1199. (d) Eliel, E. L.; Meyerson, S.; Welvart, Z. and Wilen, S. H., *J. Am. Chem. Soc.,* **1960**, *82*, 2936. (e) Dermer, O. C. and Edmison, M. T., *Chem. Rev.,* **1957**, *57*, 77. (f) Detar, D. F. and Scheifele, H. J., *J. Am. Chem. Soc.,* **1951**, *73*, 1442. (g) Detar, D. F. and Sagmanli, S. V., *J. Am. Chem. Soc.,* **1950**, *72*, 965. (h) Waters, W.A. *The Chemistry of Free Radicals*, Oxford University Press, London, **1946**, pp. 148, 165. (i) Bachmann, W. E. and Hoffman, R. A., *Org. React.,* **1944**, *2*, 224.

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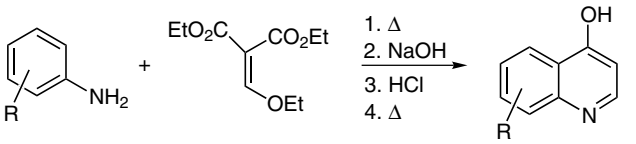
Gould-Jacobs Reaction

(Gould-Jacobs Quinoline Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Gould and Jacobs in 1939.[1] It is the synthesis of 4-hydroxyquinolines from anilines and diethyl ethoxymethylenemalonate involving the condensation to anilinomethylenemalonate, cyclo-acylation to quinolin-4-one nucleus, and subsequent hydrolysis and decarboxylation. Therefore, this reaction is generally known as the Gould-Jacobs reaction.[2] Occasionally, it is also referred to as the Gould-Jacobs cyclization,[3] Gould-Jacobs quinoline synthesis,[4] or Gould-Jacobs synthesis.[5] This reaction works well for anilines with electron-donating groups at the *meta*-position, whereas the electron-withdrawing groups reduce the overall yield.[2k] This reaction can be applied to the synthesis of piperazine and pyrrolidine analogues.[2a]

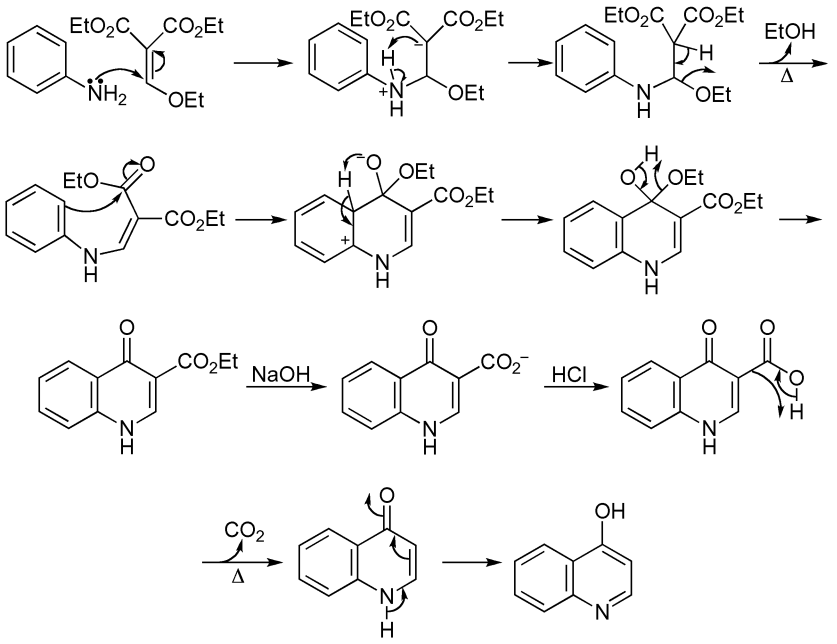
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Displayed here is the demonstration of the reaction mechanism using aniline as example.

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang



D. MODIFICATION

N/A

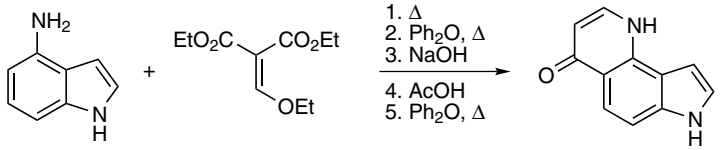
E. APPLICATIONS

This reaction is very useful for preparing 4-hydroxyquinoline derivatives. In addition, *N*-alkyl-quinolin-4-one derivatives can also be prepared if an electrophile is added before the hydrolysis and decarboxylation.[2a]

F. RELATED REACTIONS

This reaction is related to the *Doebner-von Miller Quinoline Synthesis* and *Knorr Quinoline Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES

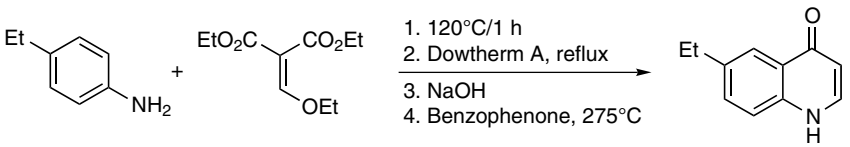


Reference 6.

In a 50-mL round-bottomed flask were placed 0.265 g 4-aminoindole (2.0 mmol) and 0.405 mL diethyl ethoxymethylenemalonate (2.0 mmol, $d = 1.07$); the mixture was heated at 130°C for 3 h. Any unreacted diethyl ethoxymethylenemalonate was removed under vacuum, leaving 0.50 g 2-[(1*H*-indol-4-ylamino)methylene]malonic acid diethyl ester as a brown solid, in a yield of 83%, m.p., 122°C (ethanol). Then 0.50 g of the solid diester (1.7 mmol) was added to 50 mL boiling diphenyl ether in portions; after 20 min of refluxing, the precipitate formed by cooling was collected by filtration, washed many times with diethyl ether, and recrystallized from ethanol, yielding 0.360 g ethyl 4-oxo-4,7-dihydro-1*H*-pyrrolo[2,3-*h*]quinolin-3-carboxylate, in a yield of 83%, m.p. 280°C (dec.), $R_f = 0.45$ (EtOAc/MeOH, 8:2).

In a 100-mL round-bottomed flask were placed 0.260 g of the above ester (1.01 mmol) and 30 mL 2 N NaOH; the suspension was heated to complete solution and was then refluxed for 6 h, the reaction was monitored by TLC analysis (EtOAc/MeOH, 8:2). After cooling, the reaction mixture was acidified to pH 5 by acetic acid/water (1:2). A brown precipitate formed, which was collected, washed with water, and dried at 60°C, affording 0.185 g 4-oxo-4,7-dihydro-1*H*-pyrrolo[2,3-*h*]quinolin-3-carboxylic acid as a crystalline solid, in a yield of 80%, m.p., 320°C (dec.), $R_f = 0.71$ (EtOAc/MeOH, 8:2).

In a two-necked, 100-mL round-bottomed flask, 50 mL diphenyl ether was heated to the boiling temperature. After the portionwise addition of 0.185 g quinolin-3-carboxylic acid (0.81 mmol), the solution was refluxed for 20 min. After cooling, the formed precipitate was collected, washed many times with diethyl ether and dried, providing 0.120 g 1*H*,7*H*-pyrrolo[2,3-*h*]quinolin-4-one, in a yield of 80%, m.p., 351°C (dec.), $R_f = 0.38$ (EtOAc/MeOH, 8:2).



Reference 4h.

Equimolar amounts of 4-ethylaniline and diethyl (ethoxymethylene)-malonate were heated together at 120°C for 1 h and then heated under reflux in Dowtherm A to effect cyclization. The resulting crude ester was saponified to give 6-ethyl-4(1*H*)-quinolone-3-carboxylic acid in an overall yield of 81%, m.p., (DMF) 257°C (dec.). This acid was decarboxylated in benzophenone at 275°C to give 6-ethyl-4(1*H*)-quinolone, in a yield of 77%, m.p., (H_2O) 197.5–198.5°C.

Other references related to the Gould-Jacobs reaction are cited in the literature.[7]

H. REFERENCES

1. Gould, R. G. and Jacobs, W. A., *J. Am. Chem. Soc.,* **1939**, *61*, 2890.
2. (a) Mitscher, L. A., *Chem. Rev.,* **2005**, *105*, 559. (b) O'Dell, D. K. and Nicholas, K. M., *J. Org. Chem.,* **2003**, *68*, 6427. (c) Kim, J. N.; Lee, K. Y.; Kim, H. S. and Kim, T. Y., *Org. Lett.,* **2000**, *2*, 343. (d) Salon, J.; Milata, V.; Pronayova, N. and Lesko, J., *Monatsh. Chem.,* **2000**, *131*, 293. (e) Leyva, E.; Monreal, E. and Hernandez, A., *J. Fluor. Chem.,* **1999**, *94*, 7. (f) Heleyova, K. and

Ilavsky, D., *Coll. Czech. Chem. Commun.,* **1997**, *62*, 99. (g) Ilavsky, D.; Heleyova, K.; Nadaska, J. and Bobosik, V., *Coll. Czech. Chem. Commun.,* **1996**, *61*, 268. (h) Siim, B. G.; Atwell, G. J.; Anderson, R. F.; Wardman, P.; Pullen, S. M.; Wilson, W. R. and Denny, W. A., *J. Med. Chem.,* **1997**, *40*, 1381. (i) Heleyova, K.; Ilavsky, D.; Bobosik, V. and Pronayova, N., *Coll. Czech. Chem. Commun.,* **1996**, *61*, 371. (j) Milata, V.; Ilavsky, D.; Chudik, M.; Zalibera, L.; Lesko, J.; Seman, M. and Belicova, A., *Monatsh. Chem.,* **1995**, *126*, 1349. (k) Mitscher, L. A.; Gracey, H. E.; Clark, G. W. and Suzuki, T., *J. Med. Chem.,* **1978**, *21*, 485. (l) Broom, A. D.; Shim, J. L. and Anderson, G. L., *J. Org. Chem.,* **1976**, *41*, 1095. (m) Baker, B. R. and Bramhall, R. R., *J. Med. Chem.,* **1972**, *15*, 230. (n) Albrecht, R. and Hoyer, G. A., *Ber.,* **1972**, *105*, 3118.

3. (a) Cecchetti, V.; Fravolini, A.; Fringuelli, R.; Mascellani, G.; Pagella, P.; Palmioli, M.; Segre, G. and Terni, P., *J. Med. Chem.,* **1987**, *30*, 465. (b) Coats, E. A.; Shah, K. J.; Milstein, S. R.; Genther, C. S.; Nene, D. M.; Roesener, J.; Schmidt, J.; Pleiss, M. and Wagner, E., *J. Med. Chem.,* **1982**, *25*, 57.
4. (a) Dax, S. L. and Wei, C.-C., *J. Org. Chem.,* **1992**, *57*, 744. (b) Heindel, N. D.; Bechara, I. S.; Lemke, T. F. and Fish, V. B., *J. Org. Chem.,* **1967**, *32*, 4155.
5. Crawford, H. M. and Glesmann, M. C., *J. Am. Chem. Soc.,* **1954**, *76*, 1108.
6. Ferlin, M. G.; Chiarelotto, G.; Gasparotto, V.; Via, L. D.; Pezzi, V.; Barzon, L.; Palù, G. and Castagliuolo, I., *J. Med. Chem.,* **2005**, *48*, 3417.
7. (a) Dave, C. G. and Shah, R. D., *Heterocycles,* **1999**, *51*, 1819. (b) Ukrainets, I. V.; Taran, S. G.; Gorokhova, O. V.; Marusenko, N. A.; Kovalenko, S. N.; Turov, A. V.; Filimonova, N. I. and Ivkov, S. M., *Chem. Heterocycl. Comp.*, **1995**, *31*, 167. (c) Gall-Istok, K. and Deak, G., *Studies Org. Chem.,* **1988**, *35*, 279. (d) Matsumoto, J.-I.; Miyamoto, T.; Minamida, A.; Nishimura, Y.; Egawa, H. and Nishimura, H., *J. Med. Chem.,* **1984**, *27*, 292. (e) Khan, M. A. and Guarcüoni, A. E., *J. Heterocycl. Chem.,* **1977**, *14*, 807. (f) Markees, D. G. and Schwab, L. S., *Helv. Chim. Acta,* **1972**, *55*, 1319. (g) Riskalla, B. H. and Broom, A. D., *J. Org. Chem.,* **1972**, *37*, 3980. (h) Nishigaki, S.; Ogiware, K.; Senga, K.; Fukazawa, S.; Aida, K.; Machica, Y. and Yoneda, F., *Chem. Pharm. Bull.,* **1970**, *18*, 1385. (i) Price, C. C. and Roberts, R. N., *Org. Syn. Coll.* **1955**, 3, 272. (j) Reitsema, R. H., *Chem. Rev.,* **1948**, *43*, 53. (k) Price, C. C. and Roberts, R. N., *J. Am. Chem. Soc.,* **1946**, *68*, 1204. (l) Price, C. C. and Roberts, R. N., *J. Am. Chem. Soc.,* **1946**, *68*, 1255. (m) Tarbell, D. S., *J. Am. Chem. Soc.,* **1946**, *68*, 1227. (n) Lauer, W. M.; Arnold, R. T.; Tiffany, B. and Tinker, J., *J. Am. Chem. Soc.,* **1946**, *68*, 1268.

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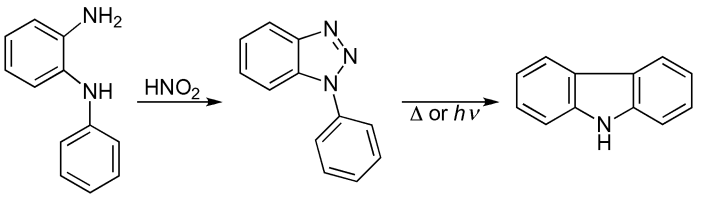
Graebe-Ullmann Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Graebe and Ullmann in 1896.[1] It is the preparation of carbazoles involving the pyrolysis of 1-phenyl-1,2,3-benzotriazole prepared from *ortho*-amino-diphenylamine and nitrous acid.[2] Therefore, it is known as the Graebe-Ullmann reaction,[3] Graebe-Ullmann thermolysis,[4] Graebe-Ullmann synthesis,[5] or Graebe-Ullmann carbazole synthesis.[6] It is known that this reaction involves the cyclization of a diradical or iminocarbene intermediate to 4aH-carbzole, which isomerizes to carbazole via a [1,3] hydrogen shift.[5b] Besides the pyrolysis of benzotriazoles to carbazoles, the photolysis[7] and microwave irradiation[8] of triazoles also produce carbazoles accordingly. In addition, some more complicated heterocycles containing pyrrole moiety can be prepared from this reaction.[9]

B. GENERAL REACTION SCHEME



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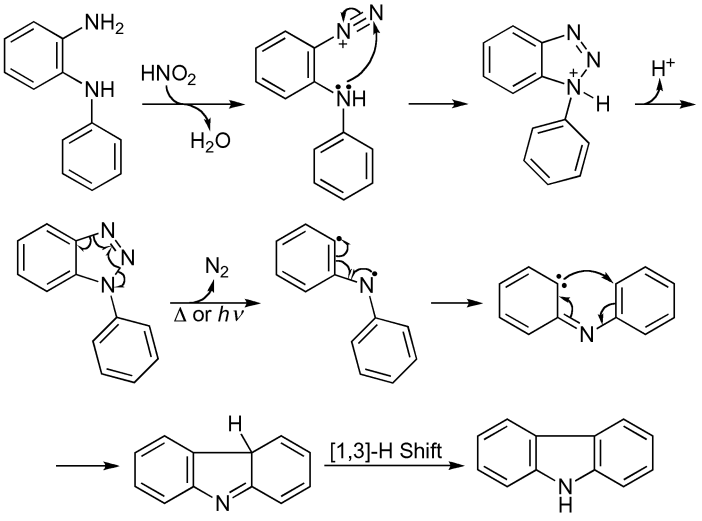
C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified using microwave irradiation.[8]

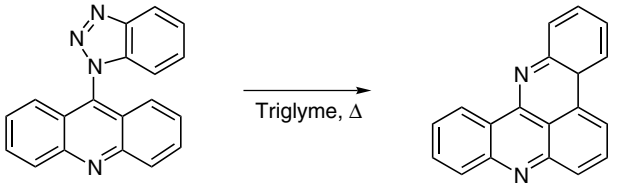
E. APPLICATIONS

This reaction has general application in the preparation of carbazole derivatives.

F. RELATED REACTIONS

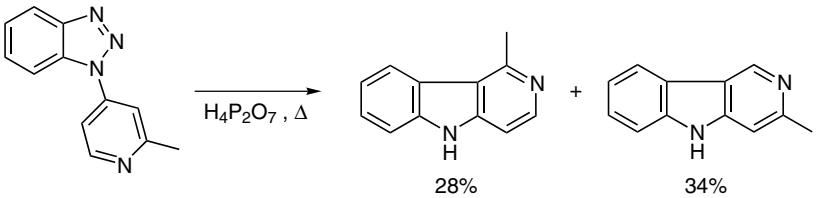
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 10.

A suspension of 1.0 g 9-(1,2,3-benzotriazol-1-yl)acridine in 5 mL triglyme was boiled for 4 h, and the cooled solution was diluted with excess water. The product was collected and washed with water to yield 87% 8H-quino[4,3,2-kl]acridine.



Reference 8.

A mixture of 2 mmol 1-(2-methylpyridin-4-yl)-1*H*-benzotriazole and 6 mmol $H_4P_2O_7$ was heated at 150°C until the evolution of nitrogen ceased (1.5–2 h). The reaction mixture was then triturated with water and basified with a 15% solution of NaOH. The precipitate formed was filtered off and purified by column chromatography to give 102 mg 1-methyl-5*H*-pyrido[4,3-*b*]indole in a yield of 28% (CH_2Cl_2/acetone, 9.5:0.5), m.p., 248–249°C (CH_3CN, cream-colored powder), and 124 mg 3-methyl-5*H*-pyrido[4,3-*b*]-indole, in a yield of 34% (CH_2Cl_2/acetone, 7:3), m.p., 226–227°C (EtOAc, orange prisms).

Other references related to the Graebe-Ullmann synthesis are cited in the literature.[11]

H. REFERENCES

1. Graebe, C. and Ullmann, F., *Ann.,* **1896**, *291*, 16.
2. Campbell, N. and Barclay, B. M., *Chem. Rev.,* **1947**, *40*, 359.
3. (a) Heald, R. A.; Modi, C.; Cookson, J. C.; Hutchinson, I.; Laughton, C. A.; Gowan, S. M.; Kelland, L. R. and Stevens, M. F. G., *J. Med. Chem.,* **2002**, *45*, 590. (b) Cadogan, J. I. G.; Tait, B. S. and Tweddle, N. J., *J. Chem. Soc., Chem. Commun.,* **1975**, 847. (c) Nantka-Namirski, P. and Kalinowski, J., *Acta Poloniae Pharm.,* **1971**, *28*, 219.
4. (a) Hagan, D. J.; Chan, D.; Schwalbe, C. H. and Stevens, M. F. G., *J. Chem. Soc., Perkin Trans. I,* **1998**, 915. (b) Hagan, D. J.; Giménez-Arnau, E.; Schwalbe, C. H. and Stevens, M. F. G., *J. Chem. Soc.*, *Perkin Trans. I,* **1997**, 2739.
5. (a) Knölker, H.-J. and Reddy, K. R., *Chem. Rev.,* **2002**, *102*, 4303. (b) Katritzky, A. R.; Lan, X. F.; Yang, J. Z. and Denisko, O. V., *Chem. Rev.,* **1998**, *98*, 409. (c) Molina, A.; Vaquero, J. J.; Garcia-Navio, J. L. and Alvarez-Builla, J., *Tetrahedron Lett*., **1993**, *34*, 2673. (d) Starkova, B.; Vystrcil, A. and Starka, L., *Coll. Czech. Chem. Commun.,* **1957**, *22*, 1019. (e) Starkova, B.; Vystrcil, A. and Starka, L., *Chem. Listy Vedu Prumysl,* **1957**, *51*, 536. (f) Ashton, B. W. and Suschitzky, H., *J. Chem. Soc.,* **1957**, 4559. (g) Preston, R. W. G.; Tucker, S. H. and Cameron, J. M. L., *J. Chem. Soc.,* **1942**, 500.
6. (a) Coker, G. G.; Plant, S. G. P. and Turner, P. B., *J. Chem. Soc.,* **1951**, 110. (b) Bremer, O., *Ann.,* **1934**, *514*, 279.
7. (a) Mehta, L. K.; Parrick, J. and Payne, F., *J. Chem. Soc., Perkin Trans. I,* **1993**, 1261. (b) Ohashi, M.; Tsujimato, K. and Yonezawa, T., *J. Chem. Soc., Chem. Commun.,* **1970**, 1089. (c) Hubert, A. J., *J. Chem. Soc. C,* **1969**, 1334. (d) Burgess, E. M.; Carithers, R. and McCullagh, L., *J. Am. Chem. Soc.,* **1968**, *90*, 1923.

8. Molina, A.; Vaquero, J. J.; Garcia-Navio, J. L.; Alvarez-Builla, J.; de Pascual-Teresa, B.; Gago, F.; Rodrigo, M. M. and Ballesteros, M., *J. Org. Chem.,* **1996**, *61*, 5587.

9. (a) Katritzky, A. R. and Shcherbakova, I. V., *J. Heterocycl. Chem.,* **1996**, *33*, 2031. (b) Maquestiau, A.; Flammang-Barbieux, M.; Flammang, R. and Chen, L.-Z., *Bull. Soc. Chim. Belg.,* **1988**, *97*, 245. (c) Mitchell, G. and Rees, C. W., *J. Chem. Soc., Perkin Trans. I,* **1987**, 403. (d) Kulagowski, J. J.; Moody, C. J. and Rees, C. W., *J. Chem. Soc., Perkin Trans. I,* **1985**, 2725. (e) Kulagowski, J. J.; Mitchell. G.; Moody, C. J. and Rees, C. W., *J. Chem. Soc., Chem. Commun.,* **1985**, 650. (f) Kulagowski, J. J.; Moody, C. J. and Rees, C. W., *J. Chem. Soc., Perkin Trans. I,* **1985**, 2733.

10. Stanslas, J.; Hagan, D. J.; Ellis, M. J.; Turner, C.; Carmichael, J.; Ward, W.; Hammonds, T. R. and Stevens, M. F. G., *J. Med. Chem.,* **2000**, *43*, 1563.

11. (a) Le, H. P.; Kelbig, A.; Lindauer, A.; Neidlein, R. and Suschitzky, H., *J. Chem. Res.,* **2004**, 453. (b) Ellis, M. J. and Stevens, M. F. G., *J. Chem. Soc., Perkin Trans. I,* **2001**, 3174. (c) Katritzky, A. R.; Yang, B. Z.; Jiang, J. L. and Steel, P. J., *J. Org. Chem.,* **1995**, *60*, 246. (d) Wirth, H. O.; Waese, G. and Kern, W., *Macromol. Chem.*, **1965**, *86*, 139. (e) Grotta, H. M.; Riggle, C. J. and Bearse, A. E., *J. Org. Chem.,* **1964**, *29*, 2474. (f) Abramovitch, R. A. and Spenser, I. D., *Adv. Heterocycl. Chem.*, **1964**, *3*, 128. (g) Colser, C. C.; Plant, S. G. P. and Turner, P. B., *J. Chem. Soc.,* **1951**, 110. (h) Bremer, O., *Ann.,* **1934**, *514*, 279. (i) Hunter, W. H. and Darling, S. F., *J. Am. Chem. Soc.,* **1931**, *53*, 4183. (j) Ullmann, F., *Ann.,* **1904**, *332*, 82.

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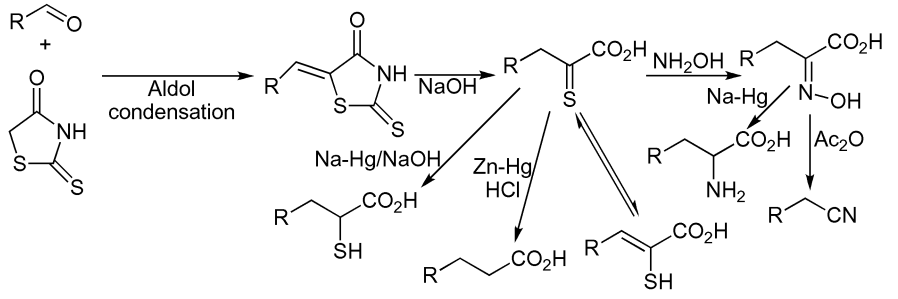
Gränacher Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Gränacher in 1922.[1] It is the preparation of thionic acid by the treatment of *Aldol Condensation* product from an aldehyde and rhodanine with a base (e.g., NaOH).[2] Therefore, this reaction is known as the Gränacher synthesis[3] or Gränacher reaction.[4] The prepared thionic acid in this reaction can be further converted into a variety of derivatives under different conditions.[3,5] For example, it can be transformed into α-thiol acid under a basic sodium amalgam reduction, whereas aliphatic acid is formed under an acidic zinc amalgam reduction. In addition, when the thionic acid is treated with ammonia, α-keto acid is generated, and the thionic acid can be converted into α-carboxyl oxime in reaction with hydroxylamine, from which either α-amino acid or aliphatic nitrile forms via the treatment of sodium amalgam reduction[6] or acetic anhydride, respectively.

B. GENERAL REACTION SCHEME



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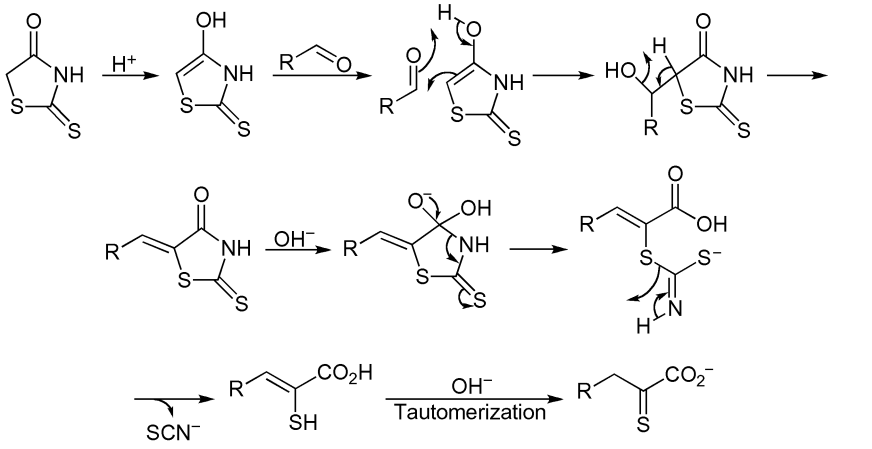
C. PROPOSED MECHANISMS

The possible reaction pathway for the conversion of rhodanine and aldehyde into thionic acid is displayed here. The further transformations of thionic acid into other derivatives, including α-amino acid, aliphatic nitrile, and aliphatic acid, are not provided.



D. MODIFICATION

N/A

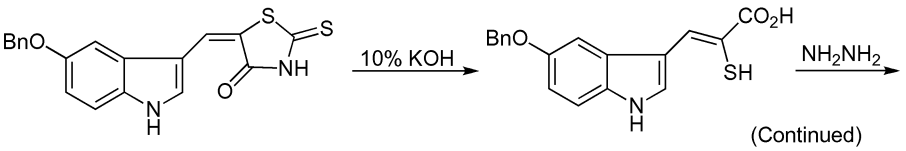
E. APPLICATIONS

This reaction has general application in the preparation of α-keto acids, nitriles, α-amino acids, etc.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



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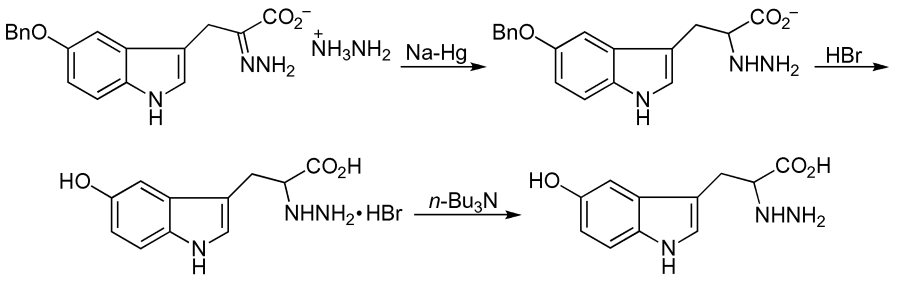

Reference 7.

A stirred mixture of 3.67 g 5-(5-benzyloxyindole-3-methylene)rhodanine (10 mmol) and 112 mL 10% KOH was refluxed under nitrogen for 1 h. The reaction was cooled to room temperature, and 0.82 g 5-benzyloxy-3-indolecarboxaldehyde was removed by filtration. The stirred filtrate was cooled to 0°C and acidified with 2.5 N HCl. The yellow product that separated was filtered, washed with water (2 × 20 mL), and then dried to afford 2.05 g β-(5-benzyloxy-3-indolyl)-α-sulfhydrylacrylic acid.

A stirred slurry of 2.93 g β-(5-benzyloxy-3-indolyl)-α-sulfhydrylacrylic acid (9 mmol) in 10 mL absolute ethanol was treated with 2.4 mL 99–100% hydrazine hydrate (0.048 mol), and the mixture was heated under nitrogen. Reaction occurred at 60°C, accompanied by vigorous evolution of H_2S. After the mixture was refluxed for 2 h, the liberation of H_2S had ceased (no black precipitate when a stream of nitrogen was passed through the reaction solution and exited into aqueous lead acetate), and the flask was allowed to cool to room temperature. The crystalline product, the hydrazine salt of β-(5-benzyloxy-3-indolyl)pyruvic acid hydrazone, was filtered, washed with cold ethanol (3 × 8 mL), and then dried. It weighed 2.35 g and was found to be analytically pure.

To a well-stirred suspension of 1.07 g hydrazine salt (3 mmol) in 15 mL water was added 14 g pulverized 3% NaHg. The system was purged and stirred under nitrogen for 2 days. The aqueous phase was then decanted from the pool of mercury, filtered through Supercel, and treated dropwise with 1.5 mL acetic acid. The zwitterions precipitated voluminously and was filtered, washed with water (2 × 4 mL), and then dried to give 0.75 g β-(5-benzyloxy-3-indolyl)-α-hydrazinopropionic acid, m.p. 217°C (dec.).

A dry flask containing 7.50 g β-(5-benzyloxy-3-indolyl)-α-hydrazinopropionic acid (0.023 mol) was cooled to −75°C in a dry ice–acetone bath, and anhydrous HBr was passed in until 50 mL had condensed. The mixture was stirred at −75°C for 1 h, then all volatile liquid was evaporated via a stream of dry nitrogen (1 h) after the cold bath had been removed. When the flask had warmed to room temperature, the HBr salt was stirred with 50 mL dry ether, filtered, and washed well with ether (5 × 10 mL) to remove traces of HBr and benzyl bromide. The hygroscopic tan powder so obtained was dissolved in 50 mL alcohol and filtered; the pH of the filtrate was adjusted to 3.5 by the addition of 7–8 mL of tri-n-butylamine. The precipitated zwitterion was collected, washed with 5 mL cold ethanol, and then dried to yield 3.60 g DL-β-(5-hydroxy-3-indolyl)-α-hydrazinopropionic acid, m.p., 227–231°C (dec.). This off-white powder was purified by dissolving it in 15 mL 2.5 N HCl and diluting the solution with 25 mL ethanol. After being stirred with 0.36 g charcoal, the mixture was filtered, and the pH of the filtrate was adjusted to 5.5 by the slow addition of tri-*n*-butylamine. The white microcrystalline product was filtered, washed with 7 mL ethanol, and then dried to give 3.00 g pure product.

More experimental details are available in literature,[8] and other references related to the Gränacher synthesis are cited in the literature.[9]

H. REFERENCES

1. Gränacher, C., *Helv. Chim. Acta,* **1922**, *5*, 610.
2. Campaigne, E., *Chem. Rev.,* **1946**, *39*, 1.
3. Brown, F. C., *Chem. Rev.,* **1961**, *61*, 463.
4. Buchbauer, G. and Kern, M., *Arch. Pharm.,* **1980**, *313*, 1043.
5. Fisher, H. E. and Hibbert, H., *J. Am. Chem. Soc.,* **1947**, *69*, 1208.
6. Block, R. J., *Chem. Rev.,* **1946**, *38*, 501.
7. Glamkowski, E. J.; Gal, G.; Sletzinger, M.; Porter, C. C. and Watson, L. S., *J. Med. Chem.*, **1967**, *10*, 852.
8. (a) Burton, W. H.; Budde, W. L. and Cheng, C. C., *J. Med. Chem.,* **1970**, *13*, 1009. (b) Julian, P. L. and Sturgis, B. M., *J. Am. Chem. Soc.,* **1935**, *57*, 1126.
9. (a) Griesbeck, A. G.; Bondock, S. and Lex, J., *J. Org. Chem.,* **2003**, *68*, 9899. (b) Doktorova, N. D.; Ionova, L. V.; Karpeisky, M. Y. A.; Padyukova, N. S.; Turchin, K. F. and Florentiev, V. L., *Tetrahedron,* **1969**, *25*, 3527. (c) Tolstikov, G. A. and Shul'ts, E. E., *J. Org. Chem. USSR,* **1984**, *20*, 2230. (d) Emerson, O. H. and Bickoff, E. M., *J. Am. Chem. Soc.,* **1958**, *80*, 4381. (e) Yoder, L.; Cheng, E. W.-K. and Burroughs, W., *Proc. Iowa Acad. Sci.,* **1954**, *61*, 271. (f) Sheehan, J. C. and Robinson, C. A., *J. Am. Chem. Soc.,* **1951**, *73*, 1207. (g) Crowe, B. F. and Nord, F. F., *J. Org. Chem.,* **1950**, *15*, 81. (h) Bradsher, C. K. and Kittila, R. S., *J. Org. Chem.,* **1950**, *15*, 374. (i) Sheehan, J. C. and Robinson, C. A., *J. Am. Chem. Soc.,* **1949**, *71*, 1436. (j) Hamlin, K. E. and Weston, A. W., *J. Am. Chem. Soc.,* **1949**, *71*, 2210. (k) Kjaer, A., *Acta Chem. Scand.,* **1949**, *3*, 647. (l) Campbell, N. and McKail, J. E., *J. Chem. Soc.,* **1948**, 1251. (m) Sumpter, W. C.; Miller, M. and Hendrick, L. N., *J. Am. Chem. Soc.,* **1945**, *67*, 1037. (n) Plucker, J. and Amstutz, E. D., *J. Am. Chem. Soc.,* **1940**, *62*, 1512. (o) Jones, H. A. and Hann, R. M., *J. Am. Chem. Soc.,* **1928**, *50*, 2491. (p) Gränacher, C. and Kouniniotis, C., *Helv. Chim. Acta,* **1928**, *11*, 1241. (q) Hann, R. M., *J. Am. Chem. Soc.,* **1925**, *47*, 1189. (r) Karrer, P. and Gränacher, C., *Helv. Chim. Acta,* **1924**, *7*, 740. (s) Gränacher, C.; Gero, M.; Ofner, A.; Klopfenstein, A. and Schlatter, E., *Helv. Chim. Acta,* **1923**, *6*, 458. (t) Gränacher, C. and Mahal, A., *Helv. Chim. Acta,* **1923**, *6*, 467.

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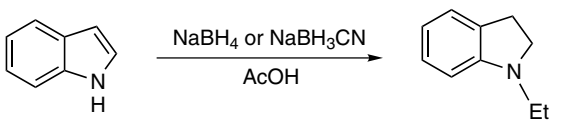
Gribble Reductive Amination

A. GENERAL DESCRIPTION OF THE REACTION

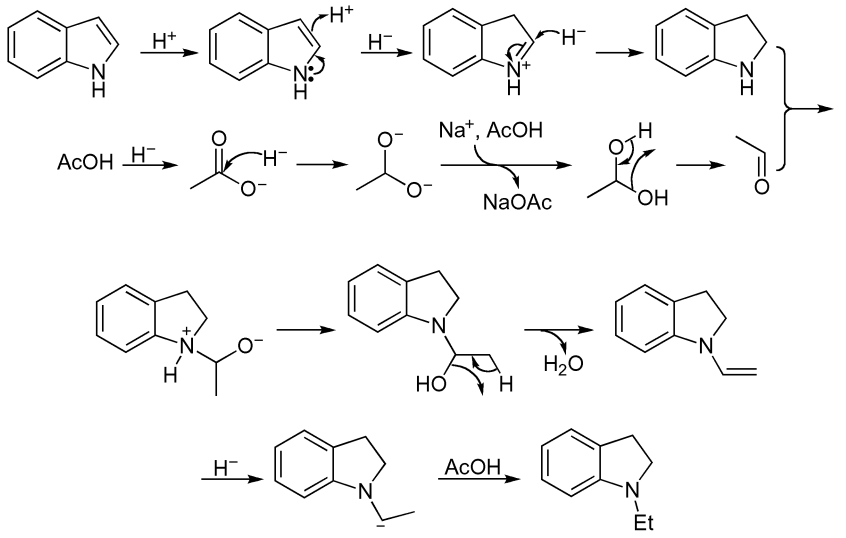
This reaction was initially reported by Gribble and co-workers in 1974.[1] It is the synthesis of indolines or *N*-alkylated indolines from the direct acidic reduction of indoles using $NaBH_4$ or $NaBH_3CN$ in acetic acid or trifluoroacetic acid. Therefore, it is known as the Gribble reductive amination.[2] Under these conditions, an indole derivative can be purely reduced to indoline or further to *N*-ethyl indoline[1] without polymerization that exists in other methods of reduction.[3] It is found that the reduction by $NaBH_4$ in formic acid affords an indole dimmer and other side products besides the normal indoline, whereas the same reduction in trifluoroacetic acid (TFA) gives only the indoline without *N*-alkylation.[1] It has been proven that this reaction involves the protonation at 3-position followed by the reduction of the formed indolenium interemdiate.[1] This reducing method has been extended to reduce primary and secondary aromatic amines and to synthesize unsymmetrical tertiary amines directly from primary amines.[1] In addition, other heterocycles can be reduced by this reduction, such as the conversion of quinoxaline to 1,2,3,4-tetrahydroquinoxaline,[4] quinazoline to 1,2-dihydroquinazoline,[4] and pyrazine to piperazine.[5] Moreover, even some aryl alcohols can be directly converted into their corresponding arylalkanes.[6]

B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS



D. MODIFICATION

N/A

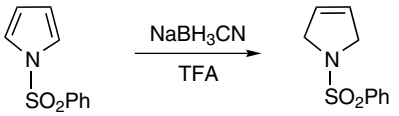
E. APPLICATIONS

This reaction has general application in the reduction of indoles and other nitrogenous heterocycles and the selective preparation of unsymmetrical tertiary amines.

F. RELATED REACTIONS

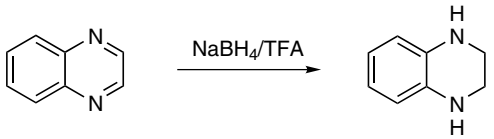
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

To 10 mL magnetically stirred TFA at room temperature was added 0.45 g $NaBH_3CN$ (7.25 mmol) slowly and in portions. (*Caution*! $NaBH_3CN$ reacts with TFA with vigorous evolution of hydrogen, so that minor explosions are possible.) The resulting mixture was stirred for an additional 15 min, and 0.50 g *N*-phenylsulfonylpyrrole (2.41 mmol) was added slowly as a solid. After 1 h, an additional 0.45 g $NaBH_3CN$ (7.25 mmol) was added. The mixture was stirred overnight, quenched with water, and extracted with methylene chloride. The combined organic layers were washed with saturated $NaHCO_3$ and water, dried over Na_2SO_4, filtered, and evaporated in vacuo. Chromatography on silica gel using hexanes/CH_2Cl_2 provided 0.45 g 1-phenylsulfonyl-3-pyrroline, which slowly crystallized in vacuo. Recrystallization from methanol provided 0.38 g pure product, m.p., 120–121°C.



Reference 4.

To 10 mL THF solution containing 1.0 g quinoxaline was added 1.0 g $NaBH_4$, then 10 mL TFA was added over 15 min without cooling, and the mixture was stirred an additional 45 min. Water (5 mL) was added, and the pH was adjusted with a 50% NaOH to pH 7. Dichloroethane (50 mL) was added to the solution, and vigorous stirring was begun. The organic layer was separated, dried over Na_2SO_4, and concentrated at reduced pressure, yielding an oil that solidified when cooled. The formed solid was recrystallized from EtOAc to afford 910 mg 1,2,3,4-tetrahydroquinoxaline as colorless crystals, m.p., 95–96°C.

Other references related to the Gribble reductive amination are cited in the literature.[8]

H. REFERENCES

1. Gribble, G. W.; Lord, P. D.; Skotnicki, J.; Dietz, S. E.; Eaton, J. T. and Johnson, J. L., *J. Am. Chem. Soc.,* **1974**, *96*, 7812.
2. Lipton, M. F.; Mauragis, M. A.; Maloney, M. T.; Veley, M. F.; VanderBor, D. W.; Newby, J. J.; Appell, R. B. and Daugs, E. D., *Org. Proc. Res. Dev.,* **2003**, *7*, 385.
3. Robinson, B., *Chem. Rev*., **1969**, *69*, 785.
4. Bugle, R. C. and Osteryoung, R. A., *J. Org. Chem.,* **1979**, *44*, 1719.
5. Miyake, F. Y.; Yakushijin, K. and Horne, D. A., *Org. Lett.,* **2000**, *2*, 3185.
6. Paderes, G. D.; Metivier, P. and Jorgensen, W. L., *J. Org. Chem.,* **1991**, *56*, 4718.
7. Ketcha, D. M.; Carpenter, K. P. and Zhou, Q., *J. Org. Chem.,* **1991**, *56*, 1318.
8. (a) Morley, J. A.; Elrod, L. and Bauer, J. F., *Anal. Chem.,* **1994**, *66*, 4283. (b) Ketcha, D. M.; Lieurance, B. A.; Homan, D. F. J. and Gribble, G. W., *J. Org. Chem.,* **1989**, *54*, 4350. (c) Gribble, G. W. and Nutaitis, C. F., *Org. Prep. Proced. Int.,* **1985**, *17*, 317. (d) Gribble, G. W.; Jasinski, J. M.; Pellicone, J. T. and Panetta, J. A., *Synthesis,* **1978**, 766. (e) Gribble, G. W.; Kelly, W. J. and Emery, S. E., *Synthesis,* **1978**, 763. (f) Maryanoff, B. E. and McComsey, D. F., *J. Org. Chem.,* **1978**, *43*, 2733. (g) Gribble, G. W.; Jasinski, J. M.; Pelicone, J. T. and Panetta, J. A., *Synthesis,* **1978**, 776. (h) Gribble, G. W. and Hoffman, J. H., *Synthesis,* **1977**, 859. (i) Gribble, G. W. and Leese, R. M., *Synthesis,* **1977**, 172. (j) Gribble, G. W. and Heald, P. W., *Synthesis,* **1975**, 650.

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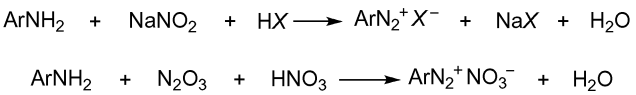
Griess Diazotization

(Knoevenagel Method, Witt Method)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Griess in 1858.[1] It is the preparation of aromatic diazonium salts from primary aromatic amines, N_2O_3, and nitric acid and is generally known as the Griess diazotization[2] or Griess reaction.[3] Subsequently, the preparation of diazonium salt was extended by Knoevenagel in 1890 using organic nitrite as diazotization agent under acidic conditions,[4] by Witt in 1909 using $Na_2S_2O_5$ and nitric acid as the diazotization agents[5] (known as Witt method[6]), and by Houston and Johnson in 1925 using N_2O_4 as the diazotization agent.[7] Recently, other reagents have also been developed for the purpose of diazotization: NOCl,[8] $NaNO_2/HBF_4$,[9] $NaNO_2/CuCl_2$,[10] and $NO^+BF_4^-$[11] (or $NO^+PF_6^-$,[11b] $NO^+SbF_6^-$,[11b] etc.). However, the most popular method of forming diazonium salt is to use nitrous acid generated *in situ* from sodium nitrite and an acid (HCl,[12] H_2SO_4,[13] HCO_2H,[14] AcOH,[15] etc.), although the Knoevenagel's method is also quite popular.[16] The generated diazonium salt is useful for many other reactions, including the *Gatterman Reaction* and *Balz-Schiemann Reaction*.

B. GENERAL REACTION SCHEME



Griess Diazotization

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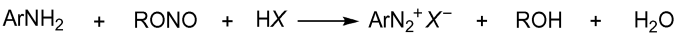
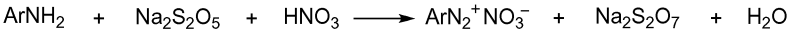
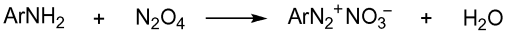


Knoevenagel Modification



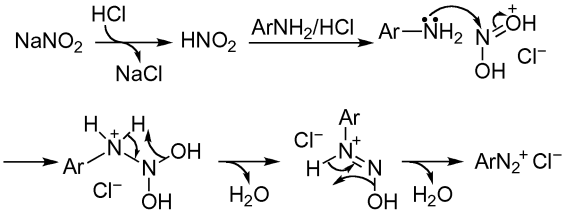
Witt Modification



Houston-Johnson Modification

C. PROPOSED MECHANISMS

The mechanism of diazotization from sodium nitrite and hydrochloric acid is given here.



D. MODIFICATION

The original Griess diazotization has been modified to use different diazotization reagents as noted in Section A.[4,5,7–11]

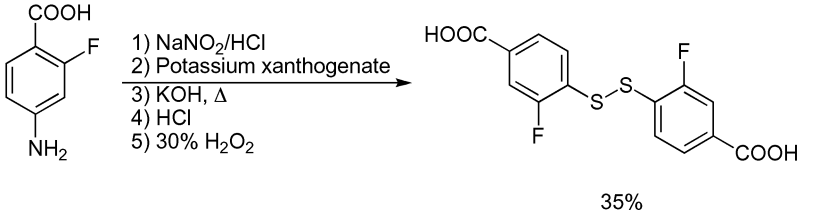
E. APPLICATIONS

This reaction is very useful in the preparation of aromatic diazonium salts.

F. RELATED REACTIONS

This reaction is related to the *Gatterman Reaction* and *Balz-Schiemann Reaction*.

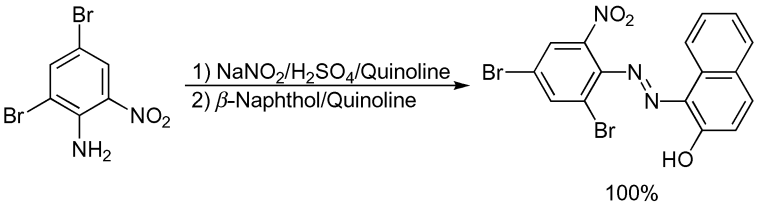
G. CITED EXPERIMENTAL EXAMPLES



35%

Reference 12a.

To a mixture of 12.5 mL concentrated HCl and 12.5 mL water was added 5.0 g substituted 4-amino-2-fluorobenzoic acid (32 mmol) under stirring, and the suspension was warmed to 70°C. After this, the solution was cooled to 0°C and diazotized with 2.2 g $NaNO_2$ (32 mmol) over 20 min. This solution was then added dropwise over 1 h to a solution of 19.0 g potassium xanthogenate (117 mmol) at 80°C, after which the oil that separated was extracted with diethyl ether, dried over $MgSO_4$ for 2 hours, and then evaporated under low pressure to give a brownish oil. This oil was then dissolved in 50 mL ethanol to which 10 g KOH in ethanol was added slowly over 30 min. The solution was heated at 80°C for 8 h. The ethanol was removed under reduced pressure. The residue was dissolved in water and slowly neutralized with concentrated HCl at 0°C to pH 5 and then extracted with EtOAc; dried over $MgSO_4$ and removed under low pressure to give the aryl thiol as a solid with strong thiol odor. The thiol obtained was suspended in ethanol. To this suspension was added 3.8 mL 30% H_2O_2, and the mixture was stirred at room temperature under nitrogen for 24 h. The solvent was then removed, and the residue was chromatographed on silica gel with 1–3% MeOH in $CHCl_3$ to give 1.95 g 2,2′-difluoro-4,4′-dithiobis(benzoic acid) as a light cream solid, in a yield of 35%, m.p., > 245°C (dec.), $R_f = 0.76$ ($CHCl_3$/MeOH, 5:1).



Reference 17.

A solution of 5.91 g 4,6-dibromo-2-nitroaniline in 15 mL quinoline was diazotized with a mixture of 3 g $NaNO_2$ in 40 mL conc. H_2SO_4 and 15 mL water. Coupling took place when to the clear diazonium salt solution was added a solution of 2.88 g β-naphthol in 10 mL quinoline. The coupled product was filtered, washed, and digested with 25% alcohol. The yield was quantitative. Recrystallization of the 4,6-dibromo-2-nitrobenzene-azo-β-naphthol from toluene gave red crystals, m.p., 250°C.

Other references related to the Griess diazotization are cited in the literature.[18]

H. REFERENCES

1. Griess, P., *Ann.,* **1858**, *106*, 123.
2. Hensley, K.; Mou, S. and Pye, Q. N., *Methods Biological Oxidative Stress,* **2003**, 185.
3. (a) Dusse, L. M. S.; Morais e Silva, R. M.; Vieira, L. M. and Carvalho, M. G., *Clin. Chim. Acta,* **2005**, *362*, 195. (b) Barary, M. H.; Blaih, S. M.; Abdine, H. H. and El-Sayed, M. A., *Mansoura J. Pharm. Sci.,* **1994**, *10*, 1.
4. Knoevenagel, E., *Ber.,* **1890**, *23*, 2994.
5. Witt, O. N., *Ber.,* **1909**, *42*, 2953.
6. (a) Elion, L., *Rec. Trav. Chim. Pays-Bas Belg.,* **1923**, *42*, 513. (b) Fuchs, W., *Rec. Trav. Chim. Pays-Bas Belg.,* **1923**, *42*, 511.
7. Houston, B. and Johnson, T. B., *J. Am. Chem. Soc.,* **1925**, *47*, 3011.

8. Scherer, K. V. and Lunt, R. S., *J. Am. Chem. Soc.,* **1966**, *88*, 2860.
9. Thompson, A. M.; Rewcastle, G. W.; Boushelle, S. L.; Hart, B. G.; Kraker, A. J.; Lu, G. H.; Batley, B. L.; Panek, R. L.; Showalter, H. D. H. and Denny, W. A., *J. Med. Chem.,* **2000**, *43*, 3134.
10. Zou, R. M.; Drach, J. C. and Townsend, L. B., *J. Med. Chem.,* **1997**, *40*, 802.
11. (a) Tsuji, M., *J. Org. Chem.,* **2003**, *68*, 9589. (b) Olah, G. A.; Overchuk, N. A. and Lapierre, J. C., *J. Am. Chem. Soc.,* **1965**, *87*, 5785.
12. (a) Gangjee, A.; Jain, H. D.; McGuire, J. J. and Kisliuk, R. L., *J. Med. Chem.,* **2004**, *47*, 6730. (b) Siegrist, U.; Rapold, T. and Blaser, H.-U., *Org. Proc. Res. Dev.,* **2003**, *7*, 429. (c) Jiao, G.-S.; Han, J. W. and Burgess, K., *J. Org. Chem.,* **2003**, *68*, 8264. (d) Li, B.; Kasthurikrishnan, N.; Ragan, J. A. and Young, G. R., *Org. Proc. Res. Dev.,* **2002**, *2*, 64.
13. (a) Zou, R. M.; Drach, J. C. and Townsend, L. B., *J. Med. Chem.,* **1997**, *40*, 811. (b) Antonini, I.; Franchetti, P.; Grifantini, M. and Martelli, S., *J. Org. Chem.,* **1976**, *41*, 158.
14. Pirrung, M. C. and Brown, W. L., *J. Am. Chem. Soc.,* **1990**, *112*, 6388.
15. Cirrincione, G.; Almerico, A. M.; Barraja, P.; Diana, P.; Lauria, A.; Passannanti, A.; Musiu, C.; Pani, A.; Murtas, P.; Minnei, C.; Marongiu, M. E. and Colla, P. L., *J. Med. Chem.,* **1999**, *42*, 2561.
16. (a) Ek, F.; Wistrand, L.-G. and Frejd, T., *J. Org. Chem.,* **2003**, *68*, 1911. (b) Ek, F.; Axelsson, O.; Wistrand, L.-G. and Frejd, T., *J. Org. Chem.,* **2002**, *67*, 6376. (c) Lu, J.; Zhang, J. J.; Shen, X. F.; Ho, D. M. and Pascal, R. A., *J. Am. Chem. Soc.,* **2002**, *124*, 8035. (d) Zou, R. M.; Ayres, K. R.; Drach, J. C. and Townsend, L. B., *J. Med. Chem.,* **1996**, *39*, 3477. (e) Qiao, X. X.; Ho, D. M. and Pascal, R. A., *J. Org. Chem.,* **1996**, *61*, 6748. (f) Doyle, M. P.; Bosch, R. J. and Seites, P. G., *J. Org. Chem.,* **1978**, *43*, 4120. (g) Friedman, L. and Jurewicz, A. T., *J. Am. Chem. Soc.,* **1969**, *91*, 1808. (h) Bayless, J. H. and Friedman, L., *J. Am. Chem. Soc.,* **1967**, *89*, 147. (i) Bayless, J. H.; Mendicino, F. D. and Friedman, L., *J. Am. Chem. Soc.,* **1965**, *87*, 5790.
17. DeMilt, C. and van Zandt, G., *J. Am. Chem. Soc.,* **1936**, *58*, 2044.
18. (a) Chan, D. C. M. and Rosowsky, A., *J. Org. Chem.* **2005**, *70*, 1364. (b) Francom, P. and Robins, M. J., *J. Org. Chem.,* **2003**, *68*, 666. (c) Sonoda, M.; Hashimoto, T.; Satomi, A.; Miyazaki, T.; Ishida, K. and Sakagishi, Y., *Life Sci.,* **1994**, *55*, PL199. (d) Fox, J. B., *Anal. Chem.,* **1979**, *51*, 1493. (e) Butler, R. N., *Chem. Rev*., **1975**, *75*, 241. (f) Friedman, L. and Chlebowski, J. F., *J. Org. Chem.,* **1968**, *33*, 1633. (g) Friedman, L. and Chlebowski, J. F., *J. Org. Chem.,* **1968**, *33*, 1636. (h) Belov, B. I. and Kozlov, V. V., *Russ. Chem. Rev.,* **1963**, *32*, 59. (i) Cowdry, W. A. and Davies, D. S., *Quart. Rev.,* **1952**, *6*, 358. (j) Kornblum, N., *Org. React.,* **1944**, *2*, 264. (k) Schoutissen, H. A. J., *J. Am. Chem. Soc.,* **1933**, *55*, 4531.

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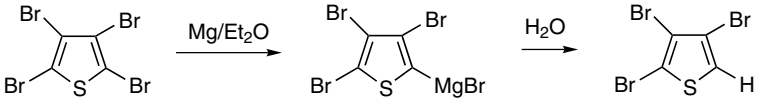
Grignard Degradation

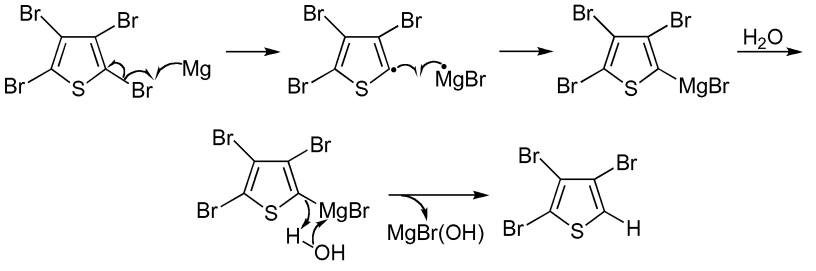
A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Steinkopf in 1934.[1] It is the dehalogenation of polyhalo-compounds via the treatment of the corresponding Grignard reagents with water to produce compounds with one less halogen atom. This reaction primarily works for aromatic compounds.[2] In addition, the dehalogenation of aromatic halides also occurs when the halides are treated with other Grignard reagents in the presence of catalytic amounts of cobaltous chloride[3] or Et_2TiCl_2.[2a]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



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D. MODIFICATION

This reaction has been modified using other Grignard reagents to dehalogenate the aromatic halides in the presence of cobaltous chloride[3] or Et_2TiCl_2.[2a]

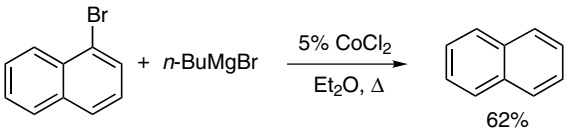
E. APPLICATIONS

This reaction can be applied to the dehalogenation of aryl or alkyl halides.

F. RELATED REACTIONS

This reaction is related to the *Grignard Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 3.

To an ether solution containing 0.05 mol *n*-butylmagnesium bromide (*n*-BuMgBr) was added 5% cobaltous chloride at low temperature; then a solution of 0.05 mol 1-bromonaphthalene in ether was added at a rate sufficient to maintain a gentle refluxing of the ether solution. The mixture was thoroughly agitated throughout the addition. After the addition was complete, the reaction mixture was refluxed for 2 h on a water bath; it was allowed to stand overnight and was poured onto ice. The product was extracted by ether, washed, and dried over $MgSO_4$. Upon removal of solvent via evaporation, the residue was purified to give 62% naphthalene.

Other references related to the Grignard degradation are cited in the literature.[4]

H. REFERENCES

1. Steinkopf, W.; Jacob, H. and Penz, H., *Ann.,* **1934**, *512*, 136.
2. (a) Hara, R.; Sato, K.; Sun, W.-H. and Takahashi, T., *Chem. Commun.,* **1999**, 845. (b) Steinkopf, W. and von Petersdorff, H.-J., *Ann.,* **1940**, *543*, 128.
3. Kharasch, M. S.; Sayles, D. C. and Fields, E. K., *J. Am. Chem. Soc.,* **1944**, *66*, 481.
4. (a) Blicke, F. F., *Heterocyclic Comp.,* **1950**, *1*, 222. (b) Kharasch, M. S.; Lewis, D. W. and Reynolds, W. B., *J. Am. Chem. Soc.,* **1943**, *65*, 498. (c) Kharasch, M. S. and Fields, E. K., *J. Am. Chem. Soc.,* **1941**, *63*, 2316. (d) Gattermann, L., *Ann.,* **1912**, *393*, 230.

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Grignard Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Grignard in 1900.[1] Traditionally, it is the preparation of alkyl or aryl magnesium halides (RMg*X* or ArMg*X*) from corresponding organohalides and magnesium in ethereal solvents (Et_2O or THF) and their nucleophilic addition to carbonyl compounds to form alcohols. Thus the organomagnesium halides are generally known as the Grignard reagents; however, the updated broad meaning of Grignard reaction refers to the reaction of Grignard reagents with many kinds of electrophiles, including CO_2 to form carboxylic acid and nitriles or acyl halides to form ketones, carbonyl compounds to form alcohols (primary alchol from formaldehyde, secondary alcohols from other aldehydes, and tertiary alcohols from ketones). Because the Grignard reagent is equivalent to a carbanion, the preparation of Grignard reagent must be carried out in an anhydrous solvent that can dissolve but not react with the generated carbanion species. Only the ethereal solvents (Et_2O, THF, etc.) that can complex with the Grignard reagent are good for this reaction, and among these ethereal solvents, Et_2O is the best one. On the other hand, as the formation of the Grignard reagents is heterogeneous, a catalytic amount of iodine and 1,2-dibromoethane are often added to the reaction system to initiate the generation of Grignard reagents. It is reported that the reaction rate for the formation of Grignard reagent is proportional to the concentration of organic halide and the surface area of magnesium, and all organic iodides and many secondary alkyl bromides react at a mass transport or diffusion-controlled rate in Et_2O; other less reactive organic bromides (neopentyl, phenyl, etc.) and most organic chlorides react at lower rates.[2] However, since the 1920s,[3] more and more experimental results have indicated that the formation of Grignard reagents involves a free radical[4] or single-electron transfer (SET) process,[5] such as the formation of pinacol via a ketyl radical during the addition of the Grignard reagent to ketone.[5a–5c] The concept that

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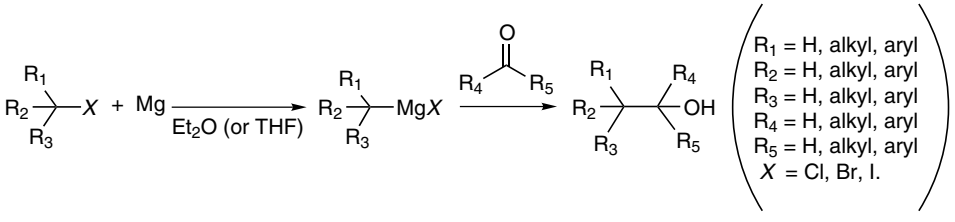
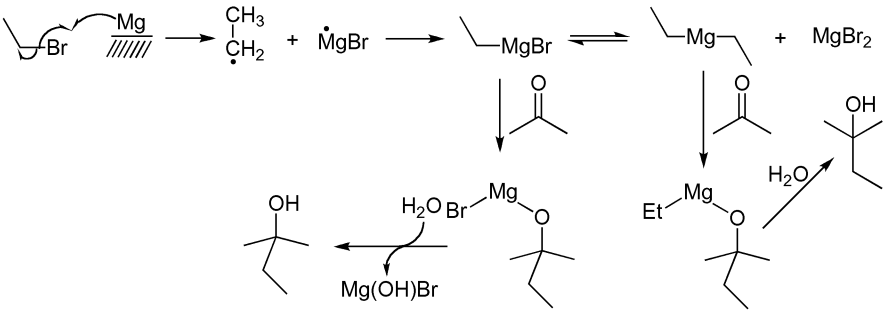
the radicals diffuse freely in solutiuon at all times is called the D-Model,[6] which is consistent with the formation of Grignard reagents from primary alkyl halides.[7] In addition, it is known that the Grignard reagents form an equilibrium with dialkyl (or diaryl) magnesium and magnesium halide,[8] and such an equilibrium is called the Schlenk equilibrium,[9] in which the dialkyl (or diaryl) magnesium is considered to be more reactive.[10] During the addition of a Grignard reagent to ketones, the resulting tertiary alkoxy magnesium halides are often worked up by aqueous ammonium chloride if at least one alkyl groups is present. Other alkoxy magnesium halides from aldehydes can be hydrolyzed using a strong acid, as the tertiary alcohols are easy to dehydrate under acidic conditions. It is interesting that the reaction of benzyl or 1-naphthylmethyl magnesium bromide with ketone form both the normal alcohol and ortho alcohol[11] and PhMgBr with highly hindered cyclobutanones gives both 1,3-butadiene and allene instead of alcohol.[12] For the reaction with acyl halides to form ketones, a reversed order of reactivity of halide displacement applies: acyl fluoride > chloride > bromide.[13] However, in the reaction between CH_3MgI and mesitoyl chloride, mesitil and ethane were found to be the products.[14] Although the reaction between Grignard reagents and esters normally produce tertiary alcohols, different products might form in the special case of allyl esters if the steric effect is strong enough to inhibit the addition of RMg*X* to the carbonyl group,[15] such as the formation of pure *n*-crotylbenzene from the reaction of PhMgBr with *n*-crotyl mesitoate.[16] On the other hand, in the presence of some transition metal salts, the reaction course and mechanism of Grignard reagents with alkyl (or aryl) halides might be altered, as shown by the addition of a silver complex[17] (AgBr works even in a trace amount, e.g., 10^{-5}M[17a]), manganous salts,[18] nickel chloride[19] ($NiCl_2$ + 1,3-butadiene[20]), iron salt,[21] or cobaltous chloride ($CoCl_2$)[22] to the Grignard reaction. Kharasch has elaborated the details of Grignard reaction by addition of cobaltous chloride.[22] It was found that the reaction between Grignard reagent and terminal propargylic chloride leads to the formation of 1,3-butadiene.[23] Finally, the carbenoid homologation of Grignard reagents generated by an iodine/magnesium exchange from the diiodoalkane opens the opportunity to generate secondary Grignard reagents that avoid free radicals as intermediates.[9a]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The mechanism is represented by the reaction between ethyl magnesium bromide and acetone as shown here.



D. MODIFICATION

The original procedure has been extensively modified and improved by the addition of different transition metal salts[17–22] and additives (e.g., 1,3-butadiene).[20]

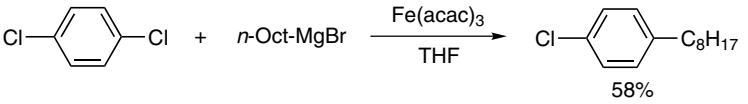
E. APPLICATIONS

This reaction has wide application in organic synthesis and is one of the most popular reactions to form carbon-carbon bonds.

F. RELATED REACTIONS

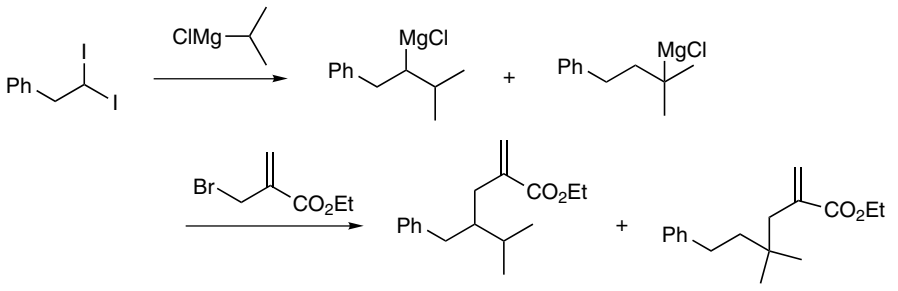
This reaction is related to the *Grignard Degradation* and *Barbier Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 21.

A solution of 120 mL 0.4 M octylmagnesium bromide in THF was added over 15 min to a solution of 4.67 g 1,4-dichlorobenzene (31.8 mmol) and 1.13 g $Fe(acac)_3$ (3.2 mmol) in 200 mL THF and 15 mL NMP, causing an immediate color change from red to dark brown/black and a slight increase in temperature (~40°C). After the mixture was stirred for 30 min, an additional 22 mL 0.4 M octylmagnesium bromide in THF and 565 mg $Fe(acac)_3$ (1.6 mmol) were introduced, and stirring was continued for 30 min. The reaction was quenched with dilute HCl, the aqueous phase was repeatedly extracted with *tert*-butyl methyl ether, the combined organic layers were dried over Na_2SO_4 and evaporated, and the residue was purified by vacuum distillation to give 4.34 g 1-chloro-4-octylbenzene (b.p., 65°C, 10–4 mmHg) as a colorless liquid, in a yield of 58% with 95% GC purity (remainder is hexadecane).



Reference 9a.

A solution of 254 mg ethyl 3-bromo-2-methylenepropanoate (1.32 mmol) in 0.7 mL THF was cooled to −90°C. A Grignard solution of 236 mg 1,1-diiodo-2-phenylethane (0.66 mmol) in ∼2.7 mL THF at −20°C (prepared by the addition of such a compound into a stirred solution of 1.1 mL 1.80 M isopropylmagnesium chloride in Et_2O [2.04 mmol] in 1.5 mL of THF) was added via cannula. The flask of the Grignard reagent was rinsed twice with 0.5 mL THF. The washings were again transferred via cannula into the reagent solution. The latter was allowed to reach −78°C over 30 min. Saturated aqueous NH_4Cl solution (2 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 4 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. Volatile coproducts were removed by bulb to bulb distillation at 4 mmHg from a bath at 100°C. The residue was then subjected to flash chromatography with pentane/*tert*-butyl methyl ether (30:1) to furnish 136 mg ethyl 4-benzyl-5-methyl-2-methylenehexanoate (79%) and 21 mg ethyl 4,4-dimethyl-2-methylene-6-phenylhexanoate (12%).

Other references related to the Grignard reaction are cited in the literature.[24]

H. REFERENCES

1. Grignard, V., *Compt. Rend.,* **1900**, *130*, 1322.
2. Rogers, H. R.; Hill, C. L.; Fujiwara, Y.; Rogers, R. J.; Mitchell, H. L. and Whitesides, G. M., *J. Am. Chem. Soc.,* **1980**, *102*, 217.
3. (a) Gomberg, M. and Bachmann, W. E., *J. Am. Chem. Soc.,* **1927**, *49*, 236. (b) Blicke, F. F. and Powers, L. D., *J. Am. Chem. Soc.,* **1929**, *51*, 3378.
4. (a) Root, K. S.; Hill, C. L.; Lawrence, L. M. and Whitesides, G. M., *J. Am. Chem. Soc.,* **1989**, *111*, 5405. (b) Ashby, E. C. and Bowers, J. R., *J. Am. Chem. Soc.,* **1981**, *103*, 2242. (c) Grovenstein, E.; Cottingham, A. B. and Gelbaum, L. T., *J. Org. Chem.,* **1978**, *43*, 3332. (d) Lopp, I. G.; Buhler, J. D. and Ashby, E. C., *J. Am. Chem. Soc.,* **1975**, *97*, 4966. (e) Gough, R. G. and Dixon, J. A., *J. Org. Chem.,* **1968**, *33*, 2148. (f) Anteunis, M. and van Schook, J., *Bull. Soc. Chim. Belg.,* **1963**, *72*, 787. (g) Ruchhardt, C. and Trautwein, H., *Ber.,* **1962**, *95*, 1197. (h) Walborsky, H. M. and Young, A. E., *J. Am. Chem. Soc.,* **1961**, *83*, 2595. (i) Bryce-Smith, D. and Cox, G. F., *J. Chem. Soc.,* **1958**, 1050.
5. (a) Ashby, E. C. and Wiesemann, T. L., *J. Am. Chem. Soc.,* **1978**, *100*, 189. (b) Ashby, E. C. and Wiesemann, T. L., *J. Am. Chem. Soc.,* **1978**, *100*, 3101. (c) Ashby, E. C.; Buhler, J. D.; Lopp, I. G.; Wiesemann, T. L.; Bowers, J. S. and Laemmle, J. T., *J. Am. Chem. Soc.,* **1976**, *98*, 6561. (d) Ashby, E. C.; Lopp, I. G. and Buhler, J. D., *J. Am. Chem. Soc.,* **1975**, *97*, 1964.
6. Garst, J. F.; Deutsch, J. E. and Whitesides, G. M., *J. Am. Chem. Soc.,* **1986**, *108*, 2490.

7. Walborsky, H. M. and Rachon, J., *J. Am. Chem. Soc.,* **1989**, *111*, 1896.
8. (a) House, H. O. and Oliver, J. E., *J. Org. Chem.,* **1968**, *33*, 939. (b) Holm, T., *Tetrahedron Lett.,* **1966**, 3329. (c) House, H. O. and Traficante, D. D., *J. Org. Chem.,* **1963**, *28*, 355. (d) Cram, D. J.; Elhafez, F. and Nyquist, H., *J. Am. Chem. Soc.,* **1954**, *76*, 22. (e) Swain, C. and Boyles, W. E., *J. Am. Chem. Soc.,* **1951**, *73*, 870.
9. (a) Knopff, O.; Stiasny, H. C. and Hoffmann, R. W., *Organometallics,* **2004**, 23,705. (b) Rudolph, S. E.; Charbonneau, L. F. and Smith, S. G., *J. Am. Chem. Soc.,* **1973**, *95*, 7083.
10. (a) Billet, J. and Smith, S. G., *Tetrahedron Lett.,* **1969**, 4467. (b) Billet, J. and Smith, S. G., *J. Am. Chem. Soc.,* **1968**, *90*, 4108. (c) Singer, M. S.; Salinger, R. M. and Mosher, H. S., *J. Org. Chem.,* **1967**, *32*, 3821. (d) Bikales, N. M. and Becker, E. I., *Can. J. Chem.,* **1963**, *41*, 1329.
11. Bernardon, C. and Deberly, A., *J. Org. Chem.,* **1982**, *47*, 463.
12. Kimbrough, R. D. and Askins, R. W., *J. Org. Chem.,* **1967**, *32*, 3683.
13. Morrison, R. T. and Wishman, M., *J. Am. Chem. Soc.,* **1954**, *76*, 1059.
14. Fuson, R. C. and Corse, J., *J. Am. Chem. Soc.,* **1938**, *60*, 2063.
15. Arnold, R. T. and Liggett, R. W., *J. Am. Chem. Soc.,* **1942**, *64*, 2875.
16. Arnold, R. T. and Liggett, R. W., *J. Am. Chem. Soc.,* **1945**, *67*, 337.
17. (a) Tamura, M. and Kochi, J., *J. Am. Chem. Soc.,* **1971**, *93*, 1483. (b) Bickley, E. A. and Gardner, J. H., *J. Org. Chem.,* **1940**, *5*, 126.
18. Kharasch, M. S.; Hancock, J. W.; Nudenberg, W. and Tawney, P. O., *J. Org. Chem.,* **1956**, *21*, 322.
19. (a) Tamao, K.; Sumitani, K. and Kumada, M., *J. Am. Chem. Soc.* **1972**, *94*, 4374. (b) Corriu, R. J. P. and Masse, J. P., *J. Chem. Soc., Chem. Commun*. **1972**, 144.
20. (a) Terao, J.; Ikumi, A.; Kuniyasu, H. and Kambe, N., *J. Am. Chem. Soc.,* **2003**, *125*, 5646. (b) Terao, J.; Watanabe, H.; Ikumi, A.; Kiniyasu, H. and Kambe, N., *J. Am. Chem. Soc.,* **2002**, *124*, 4222.
21. Scheiper, B.; Bonnekessel, M.; Krause, H. and Fürstner, A., *J. Org. Chem.,* **2004**, *69*, 3943.
22. (a) Kharasch, M. S.; Biritz, L.; Nudenberg, W.; Bhattacharya, A. and Yang, N. C., *J. Am. Chem. Soc.,* **1961**, *83*, 3229. (b) Kharasch, M. S.; Weiner, M.; Nudenberg, W.; Bhattacharya, A.; Wang, T.-I. and Yang, N. C., *J. Am. Chem. Soc.,* **1961**, *83*, 3232. (c) Kharasch, M. S.; Stampa, G. and Nudenberg, W., *J. Org. Chem.,* **1953**, *18*, 575. (d) Kharasch, M. S. and Huang, R. L., *J. Org. Chem.,* **1952**, *17*, 669. (e) Kharasch, M. S. and Urry, W. H., *J. Org. Chem.,* **1948**, *13*, 101. (f) Kharasch, M. S. and Fuchs, C. F., *J. Org. Chem.,* **1946**, *11*, 292. (g) Kharasch, M. S.; Lambert, F. L. and Urry, W. H., *J. Org. Chem.,* **1946**, *11*, 298. (h) Kharasch, M. S.; Engelmann, F. and Urry, W. H., *J. Am. Chem. Soc.,* **1944**, *66*, 365. (i) Urry, W. H. and Kharasch, M. S., *J. Am. Chem. Soc.,* **1944**, *66*, 1438. (j) Kharasch, M. S. and Kleiman, M., *J. Am. Chem. Soc.,* **1943**, *65*, 491. (k) Kharasch, M. S.; Lewis, D. W. and Reynolds, W. B., *J. Am. Chem. Soc.,* **1943**, *65*, 493. (l) Kharasch, M. S.; Nudenberg, W. and Archer, S., *J. Am. Chem. Soc.,* **1943**, *65*, 495. (m) Kharasch, M. S.; Lewis, D. W. and Reynolds, W. B., *J. Am. Chem. Soc.,* **1943**, *65*, 498. (n) Kharasch, M. S. and Reynolds, W. B., *J. Am. Chem. Soc.,* **1943**, *65*, 501. (o) Kharasch , M. S. and Fuchs, C. F., *J. Am. Chem. Soc.,* **1943**, *65*, 504. (p) Kharasch , M. S. and Sayles, D. C., *J. Am. Chem. Soc.,* **1942**, *64*, 2972. (q) Kharasch, M. S.; Kleiger, S. C.; Martin, J. A. and Mayo, F. R., *J. Am. Chem. Soc.,* **1941**, *63*, 2305. (r) Kharasch, M. S. and Tawney, P. O., *J. Am. Chem. Soc.,* **1941**, *63*, 2308. (s) Kharasch, M. S. and Fields, E. K., *J. Am. Chem. Soc.,* **1941**, *63*, 2308.
23. Pasto, D. J.; Shults, R. H.; McGrath, J. A. and Waterhouse, A., *J. Org. Chem.*, **1978**, *43*, 1382.
24. (a) Handy, S. T., *J. Org. Chem.,* **2006**, *71*, 4659. (b) Yamada, T.; Shirasaka, K.; Noto, M.; Kato, H. S. and Kawai, M., *J. Phys. Chem. B.*, **2006**, *110*, 7357. (c) Matsubara, K.; Ueno, K. and Shibata, Y., *Organometallics*, **2006**, *25*, 3422. (d) Wiss, J.; Länzlinger, M. and Wermuth, M., *Org. Proc. Res. Dev.,* **2005**, *9*, 365. (e) Krasovski, A. and Knochel, P., *Angew. Chem.,* **2004**, *116*, 3396. (f) Shintani, R. and Fu, G. C., *Angew. Chem.,* **2002**, *114*, 1099. (g) Liang, X. F. and Bols, M.,

J. Chem. Soc., Perkin Trans. I, **2002**, 503. (h) Kakiya, H.; Yagi, K.; Shinokubo, H. and Oshima, K., *J. Am. Chem. Soc.,* **2002**, *124*, 9032. (i) Bailey, W. F.; Reed, D. P.; Clark, D. R. and Kapur, G. N., *Org. Lett.,* **2001**, *3*, 1865. (j) Alami, M.; Ramiandrasoa, P. and Cahiez, G., *Synlett,* **1998**, 325. (k) Hanna, I. and Wlodyka, P., *J. Org. Chem.,* **1997**, *62*, 6985. (l) McKinley, J.; Aponick, A.; Raber, J. C.; Fritz, C.; Montgomery, D. and Wigal, C. T., *J. Org. Chem.,* **1997**, *62*, 4874. (m) Huryn, D. M., *Comp. Org. Syn.,* **1991**, *1*, 49. (n) Walborsky, H. M., *Acc. Chem. Res.,* **1990**, *23*, 286. (o) Katagiri, T., *J. Phys. Org. Chem.,* **1989**, *2*, 205. (p) Eberson, L. and Greci, L., *J. Org. Chem.,* **1984**, *49*, 2135. (q) Lai, Y. H., *Synthesis,* **1981**, 585. (r) Rogers, H. R.; Deutch, J. and Whitesides, G. M., *J. Am. Chem. Soc.,* **1980**, *102*, 226. (s) Rogers, H. R.; Rogers, R. J.; Mitchell, H. L. and Whitesides, G. M., *J. Am. Chem. Soc.,* **1980**, *102*, 231. (t) Ashby, E. C.; Neumann, H. M.; Walker, F. W.; Laemmle, J. and Chao, L.-C., *J. Am. Chem. Soc.,* **1973**, *95*, 3330. (u) Shirley, D. A., *Org. React.,* **1954**, *8*, 28. (v) Wilds, A. L. and McCormack, W. B., *J. Org. Chem.,* **1949**, *14*, 45. (w) Gilman, H. and Heckert, L. C., *J. Am. Chem. Soc.,* **1920**, *42*, 1010.

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Grob Fragmentation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Grob and Baumann in 1955.[1] It is the cleavage of an amine of a suitable β-leaving group in the presence of a base, where the leaving group is a halogen or tosyl group. Therefore, it is generally known as the Grob fragmentation.[2] Occasionally, it is also referred to as the Grob reaction.[3] In this reaction, the halogen or tosyl group is called a "nucleofuge," and the moiety of the amino group together with the carbon attached to the nitrogen is referred to as an "electrofuge."[4] The difference of the cleavage rate between β-halo (or tosyl) amines and the halides (or tosylate) without a β-amino group results from the frangiomeric acceleration, which can be quantified as the frangiomeric effect, and the largest one recorded so far is as big as 10^5.[5] This reaction occurs via either a concerted[6] or stepwise mechanism,[5] depending on the stereochemical and stereoelectronic factors,[7] but primarily through the concerted one. However, an example of a two-step concerted mechanism with zero activation energy for the second step has also been reported.[4b] Under basic conditions, this reaction has been challenged by nucleophilic substitution, elimination, and cyclization; therefore, some modifications have been developed to carry out such fragmentation under milder conditions, such as to initiate the fragmentation by fluoride,[8] cuprous ion,[9] samarium iodide,[10] and oxidative electron transfer from photo irradiation.[11] In addition, the first example of gas phase fragmentation has recently been reported.[12] The intramolecular version of this reaction has been extensively applied to the synthesis of compounds with medium-size rings.[10a,13] In addition to substituted amines, other types of structures can also undergo fragmentation in a similar manner, such as the oxidative cleavage of β-tributylstannyl alcohol,[6] decomposition of dioxirane and α-peroxy lactone by pyridine *N*-oxide,[14] acid-promoted cleavage of acetonide,[7] and removal of the ether-protecting group (e.g., methoxyethoxymethyl, [trimethylsilyl]ethoxymethyl, benzyloxymethyl).[15] When the

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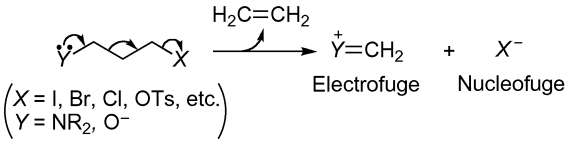
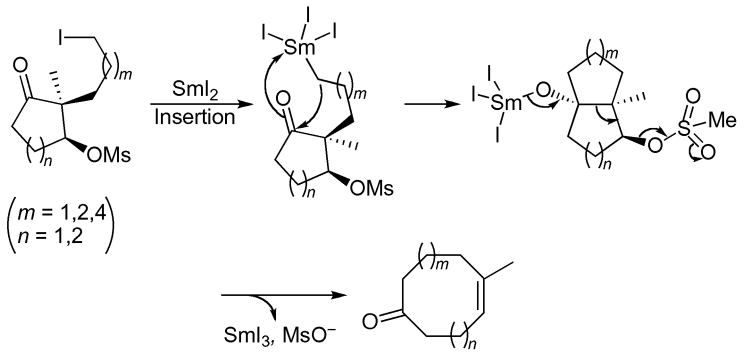
central carbon atom is replaced by a nitrogen atom, the comparable cleavage is called *aza*-Grob fragmentation.[16] It has been found that the fragmentation of *N*-halo-α-amino acid is independent of pH.[4b]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Because this reaction occurs via different mechanisms, depending on the stereochemical and stereoelectronic factors, only the one that results in the enlargement of the ring using SmI_2 is illustrated here.[10]



D. MODIFICATION

This reaction has been modified to different variants, including the initiation from fluoride,[8] cuprous ion,[9] samarium iodide,[10] and oxidative electron transfer[11] and the cleavage of acetonide,[7] β-tributylstannyl alcohol,[6] and different ether protecting groups.[15]

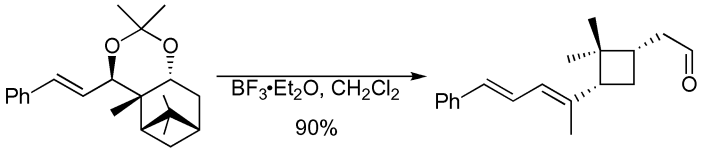
E. APPLICATIONS

This reaction has wide application in natural product synthesis and in the preparation of cyclic compounds with medium-size rings.

F. RELATED REACTIONS

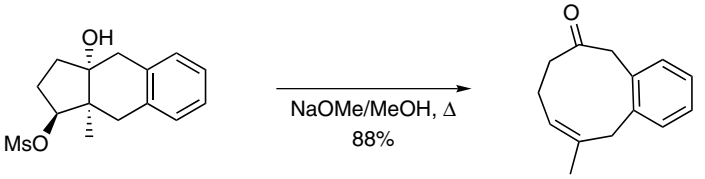
This reaction is related to the *Eschenmoser Fragmentation* and *Wharton Rearrangement*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

To a solution of 163 mg acetonide (0.5 mmol) in 5 mL dried CH_2Cl_2 cooled at $-15^{\circ}C$ was added 12 mL 0.017 M $BF_3{\cdot}OEt_2$ in CH_2Cl_2 (0.2 mmol) under nitrogen. After 10 min, the reaction completed as monitored by TLC. The reaction was quenched at the same temperature with 10 mL saturated $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 (2×10 mL), and the combined organic layers were washed with saturated $NaHCO_3$ solution (2×10 mL) and dried over anhydrous sodium sulfate. Upon removal of the solvent under vacuum, the residue was purified by silica gel flash chromatography (hexane/diethyl ether) to afford 120 mg 2-{(1*S*,3*R*)-2,2-dimethyl-3-[(*E*,*E*)-1-methyl-4-phenyl-1,3-butadienyl]cyclobutyl}ethanal as a colorless liquid, in a yield of 90%, $R_f =$ 0.26 (hexane/diethyl ether, 6:1).



Reference 10a.

To a solution of 11 mg NaOMe (0.2 mmol) in 3 mL MeOH was added 60 mg alcohol (0.2 mmol), and the solution was refluxed for 1 h. After evaporation of MeOH, 3 mL water was added, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the resulting solid was recrystallized from Et_2O/petroleum ether to yield 34 mg (*Z*)-10-methyl-5,7,8,11-tetrahydrobenzocyclononen-6-one as colorless crystals, in a yield of 88%, m.p., 118–120°C.

Other references related to the Grob fragmentation are cited in the literature.[17]

H. REFERENCES

1. Grob, C. A. and Baumann, W., *Helv. Chim. Acta,* **1955**, *38*, 594.
2. (a) Mori, M.; Kimura, M.; Takahashi, Y. and Tamaru, Y., *Chem. Commun.,* **2006**, 4303. (b) Jasti, R. and Rychnovsky, S. D., *Org. Lett.,* **2006**, *8*, 2175. (c) Xiong, Q. B.; Wilson, W. K. and Matsuda, S. P. T., *Angew. Chem. Int. Ed.,* **2006**, *45*, 1285. (d) Vyakaranam, K.; Körbe, S.; Divišová, H. and Michl, J., *J. Am. Chem. Soc.,* **2004**, *126*, 15795. (e) Tada, N.; Miyamoto, K. and Ochiai, M., *Chem. Pharm. Bull.,* **2004**, *52*, 1143. (f) Khripach, V. A.; Zhabinskii, V. N.; Fando, G. P.;

Kuchto, A. I.; Lyakhov, A. S.; Govorova, A. A.; Groen, M. B.; van der Louw, J. and de Groot, A., *Steroids,* **2004**, *69*, 495. (g) Guir, F.; Duc Do, K.; Benchikh-le-Hocine, M. and Fetizon, M., *Synthesis,* **1993**, 775. (h) Risch, N.; Billerbeck, U. and Meyer-Roscher, B., *Chem. Ber.,* **1993**, *126*, 1137. (i) French, L. G. and Charlton, T. P., *Heterocycles*, **1993**, *35*, 305. (j) Harmata, M. and Elahmad, S., *Tetrahedron Lett*., **1993**, *34*, 789. (k) Risch, N.; Langhals, M. and Hohberg, T., *Tetrahedron Lett.,* **1991**, *32*, 4465. (l) Hollenstein, S. and Laube, T., *Angew. Chem.,* **1990**, *102*, 194. (m) Michaelis, R.; Mueller, U. and Schaefer, H. J., *Angew. Chem.,* **1987**, *99*, 1049. (n) Jones, P. G.; Edwards, M. R. and Kirby, A. J., *Acta Crystallographica, Sect. C: Cryst. Struct. Commun.,* **1986**, *C42*, 1372. (o) Seto, H.; Sakaguchi, M.; Fujimoto, Y.; Tatsuno, T. and Yoshioka, H., *Chem. Pharm. Bull.,* **1985**, *33*, 412. (p) Dowd, P.; Schappert, R. and Garner, P., *Tetrahedron Lett*., **1982**, *23*, 7. (q) Jadhav, P. K. and Nayak, U. R., *Indian J. Chem., Sect. B,* **1978**, *16B*, 1051.

3. (a) Kabalka, G. W.; Li, N.-S.; Tejedor, D.; Malladi, R. R. and Trotman, S., *J. Org. Chem.,* **1999**, *64*, 3157. (b) Kabalka, G. W.; Tejedor, D.; Li, N.-S.; Malladi, R. R. and Trotman, S., *Tetrahedron*, **1998**, *54*, 15525. (c) Kabalka, G. W.; Tejedor, D.; Li, N.-S.; Malladi, R. R. and Trotman, S., *J. Org. Chem.,* **1998**, *63*, 6438.
4. (a) Paquette, L. A.; Nakatani, S.; Zydowsky, T. M.; Edmondson, S. D.; Sun, L.-Q. and Sherlj, R., *J. Org. Chem.,* **1999**, *64*, 3244. (b) Armesto, X. L.; Canle, L. M.; Losada, M. and Santaballa, J. A., *J. Org. Chem.,* **1994**, *59*, 4659.
5. Alder, R. W.; Harvey, J. N. and Oakley, M. T., *J. Am. Chem. Soc.,* **2002**, *124*, 4960.
6. Ochiai, M.; Ukita, T.; Iwaki, S.; Nagao, Y. and Fujita, E., *J. Org. Chem.,* **1989**, *54*, 4832.
7. Barluenga, J.; Álvarez-Pérez, M.; Wuerth, K.; Rodríguez, F. and Fañanás, F. J., *Org. Lett.,* **2003**, *5*, 905.
8. Zhang, W., *Curr. Org. Chem.,* **2002**, *6*, 1015.
9. Semmelhack, M. F. and Tomesch, J. C., *J. Org. Chem.,* **1977**, *42*, 2657.
10. (a) Molander, G. A.; Huérou, Y. L. and Brown, G. A., *J. Org. Chem.,* **2001**, *66*, 4511. (b) Li, C.-J.; Chen, D.-L.; Lu, Y.-Q.; Haberman, J. X. and Mague, J. T., *Tetrahedron,* **1998**, *54*, 2347.
11. Li, Z. G. and Kutateladze, A. G., *J. Org. Chem.,* **2003**, *68*, 8236.
12. D'Oca, M. G. M.; Moraes, L. A. B.; Pilli, R. A. and Eberlin, M. N., *J. Org. Chem.,* **2001**, *66*, 3854.
13. (a) Renneberg, D.; Pfander, H. and Leumann, C. J., *J. Org. Chem.,* **2000**, *65*, 9069. (b) Grob, C. A., *Angew. Chem. Int. Ed. Engl.,* **1980**, *19*, 708.
14. Adam, W. and Blancafort, L., *J. Org. Chem.,* **1997**, *62*, 1623.
15. Wang, J.-J. and Hu, W.-P., *J. Org. Chem.,* **1999**, *64*, 5725.
16. (a) Hu, W.-P.; Wang, J.-J. and Tsai, P.-C., *J. Org. Chem.,* **2000**, *65*, 4208. (b) Wang, J.-J.; Hu, W.-P.; Chung, H.-W.; Wang, L.-F. and Hsu, M.-H., *Tetrahedron*, **1998**, *54*, 13149.
17. (a) Mehta, G.; Karmakar, S. and Chattopadhyay, S. K., *Tetrahedron*, **2004**, *60*, 5013. (b) Yang, J.; Long, Y. O. and Paquette, L. A., *J. Am. Chem. Soc.,* **2003**, *125*, 1567. (c) Xu, L.; Chen, Q.-H. and Wang, F. P., *Tetrahedron,* **2002**, *58*, 4267. (d) Paquette, L. A.; Yang, J. and Long, Y. O., *J. Am. Chem. Soc.,* **2002**, *124*, 6542. (e) Jung, M. E. and Davidov, P., *Org. Lett.,* **2001**, *3*, 627. (f) Rosas Alonso, E.; Abbaspour Tehrani, K.; Boelens, M.; Knight, D. W.; Yu, V. and De Kimpe, N., *Tetrahedron Lett*., **2001**, *42*, 3921. (g) Krief, A.; Lorvelec, G. and Jeanmart, S., *Tetrahedron,* **2000**, *41*, 3871. (h) Paquette, L. A.; Edmondson, S. D.; Monck, N. and Rogers, R. D., *J. Org. Chem.,* **1999**, *64*, 3255. (i) Boivin, J.; Pothier, J.; Ramos, L. and Zard, S. Z., *Tetrahedron Lett.,* **1999**, *40*, 9239. (j) Mölm, D. and Risch, N., *Ann.,* **1997**, 1765. (k) De Giacomo, M.; Bettolo, R.M. and Scarpelli, R., *Tetrahedron Lett.,* **1997**, *38*, 3469. (l) Molm, D. and Risch, N., *Liebigs Annalen/Recueil*, **1997**, 1765. (m) De Giacomo, M.; Marini Bettolo, R. and Scarpelli, R., *Tetrahedron Lett*., **1997**, *38*, 3469. (n) Brouwer, A. M. and Krijnen, B., *J. Org. Chem.,* **1995**, *60*, 32. (o) Nagumo, S.; Matsukuma, A.; Suemune, H. and Sakai, K., *Tetrahedron,* **1993**, *49*, 10501. (p) Michaelis, R.; Müller, U. and Schäfer, H. J., *Angew. Chem. Int. Ed. Engl.,* **1987**, *26*, 1026. (q) Schreiber, S., *J. Am. Chem. Soc.,*

1980, *102*, 6163. (r) Becker, K. B. and Grob, C. A., "The Formation of Unsaturated Groups by Heterolytic Fragmentation" in *The Chemistry of Double-Bonded Functional Groups*, ed. Patai, S., John Wiley & Sons, New York, **1977**, Pt. 2, p. 653. (s) Grob, C. A.; Kostka, K. and Kuhnen, F., *Helv. Chim. Acta,* **1970**, *53*, 608. (t) Grob, C. A. and Kostka, K., *Helv. Chim. Acta,* **1970**, *53*, 613. (u) Grob, C. A. and Schiess, P. W., *Angew. Chem. Int. Ed. Engl.*, **1967**, *6*, 1. (v) Grob, C. A., *Angew. Chem. Int. Ed. Engl.,* **1969**, *8*, 535. (w) Grob, C. A.; Kiefer, H. R.; Lutz, H. J. and Wilkens, H. J., *Helv. Chim. Acta,* **1967**, *50*, 416.

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Grosheintz-Fischer-Reissert Aldehyde Synthesis

(Reissert Aldehyde Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Reissert in 1905[1] and extended by Grosheintz and Fischer in 1941.[2] It is the synthesis of aldehyde involving the formation of 1-acyl-2-cyano-1,2-dihydroquinoline derivatives from acyl chlorides, quinoline, and potassium cyanide and the subsequent hydrolysis of said dihydroquinoline derivatives under acidic conditions to produce quinaldic acid and aldehydes.[3] The original procedure occurs smoothly for aroyl or cinnamoyl chloride in liquid SO_2 but not in benzonitrile, ether, dioxane, acetone, or $CHCl_3$.[4] However, the modification from Grosheintz and Fischer using hydrogen cyanide and 2 eq. quinoline in absolute benzene is also adaptable for aliphatic acid chlorides.[2] This is one of the methods that converts acyl chlorides into aldehydes and is found to be superior to the normal *Rosenmund Reduction*. For example, *o*-nitrobenzoyl chloride has been converted into *o*-nitrobenzaldehyde in 60% yield by the current reaction, whereas the *Rosenmund Reduction* is not suitable for such conversion.[5] Therefore, this reaction is referred to as the Grosheintz-Fischer-Reissert aldehyde synthesis or Reissert aldehyde synthesis.[6]

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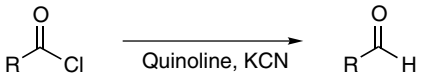
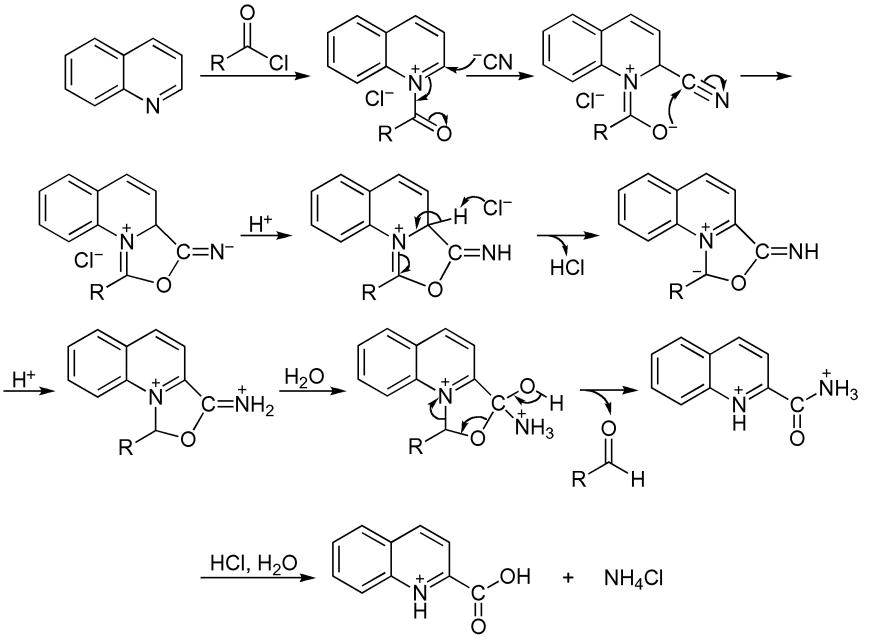
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Many mechanisms have been proposed for this reaction, however, shown here is likely to be correct, according to the literature.[3a]



D. MODIFICATION

This reaction has been modified to improve the yield in a two-phase system.[6]

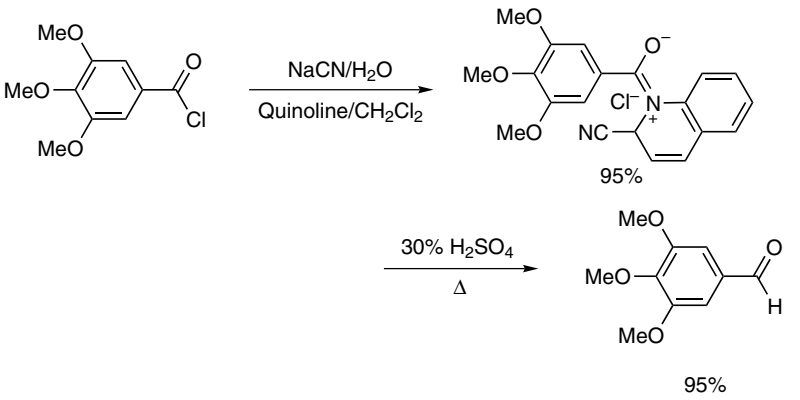
E. APPLICATIONS

This reaction has general application in the synthesis of aldehydes, especially the aromatic aldehydes.

F. RELATED REACTIONS

This reaction is related to the *Reissert Compound*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 6.

To a 250-mL, three-necked round-bottomed flask equipped with mechanical stirrer, baffle, addition funnel, and nitrogen inlet (vented through a safety bubbler) was added 8.3 g NaCN (160 mmol) and 25 mL water. The suspension was stirred to dissolve the salt. Then 22.0 g quinoline (170 mmol) in 50 mL CH_2Cl_2 was added. As the mixture was briskly stirred, 38.6 g 3,4,5-trimethoxybenzoyl chloride (167 mmol) in 75 mL CH_2Cl_2 was added via the addition funnel over 2.5 h. Initially the mixture became orange and then turned yellow. TLC showed that only trace amounts of the acid chloride remained (Et_2O/hexane). After being stirred for an additional 2 h, the mixture was poured into a separatory funnel, and the CH_2Cl_2 layer was withdrawn. The aqueous layer was extracted with CH_2Cl_2 (2×100 mL) and discarded. The combined CH_2Cl_2 layers were extracted first with saturated Na_2CO_3 solution (2×100 mL), then with 10% HCl (2×100 mL), and finally with H_2O (2×100 mL). The CH_2Cl_2 solution was dried over K_2CO_3 and placed in a 500-mL distillation flask with 250 mL EtOH. The solvent was distilled through a Vigreux column to a temperature of 80°C. Crystallization began, and after cooling to 0°C, the crystals were collected, washed with 50 mL EtOH, and vacuum dried at 80°C to give 35.0 g white crystals, m.p. 184–187°C. A second crop of crystals (17.8 g) was obtained from the mother liquors, m.p. 159–161°C. The combined weight (52.8 g) represents a 95% yield of the *Reissert Compound*.

Then 10.5 g *Reissert Compound* was added to a 500-mL three-necked, round-bottomed flask equipped with a thermometer, mechanical stirrer, condenser, baffle, and nitrogen inlet (vented through a safety bubbler); afterwards, 400 mL 30% H_2SO_4 was added. The suspension was heated to 107°C (reflux) with rapid stirring until the mixture became a homogeneous orange solution (∼1 h). Then 1.0 g SG extra charcoal was added, and the mixture was heated at reflux for 15 min, filtered over Celite, and then cooled to room temperature, whereupon the organic product was extracted into CH_2Cl_2 (3×100 mL). This CH_2Cl_2 solution was extracted first with a 10% Na_2CO_3 solution (2×25 mL) and then with H_2O (2×25 mL) and dried over K_2CO_3. The dried solution was placed in a 500-mL distillation flask with 100 mL hexane. Atmospheric distillation of ∼ 350 mL solvent, followed by cooling to 0°C, produced crude solid 3,4,5-trimethoxybenzaldehyde. The crude solid was dissolved in boiling hexane. Insolubles (0.5 g) were filtered and identified as

the *Reissert Compound* (accounting for ∼ %5). The filtered hexane solution was cooled, producing 5.6 g white 3,4,5-trimethoxybenzaldehyde, in a yield of 95%, m.p., 75–77°C.

Other references related to the Grosheintz-Fischer-Reissert aldehyde synthesis are cited in the literature.[7]

H. REFERENCES

1. (a) Reissert, A., *Ber.,* **1905**, *38*, 1603. (b) Reissert, A., *Ber.,* **1905**, *38*, 1610. (c) Reissert, A., *Ber.,* **1905**, *38*, 3415. (d) Reissert, A., *Ber.,* **1905**, *38*, 3427.
2. Grosheintz, J. M. and Fischer, H. O. L., *J. Am. Chem. Soc.,* **1941**, *63*, 2021.
3. (a) Cobb, R. L. and McEwen, W. E., *J. Am. Chem. Soc.,* **1955**, *77*, 5042. (b) McEwen, W. E. and Hazlett, R. N., *J. Am. Chem. Soc.,* **1949**, *71*, 1949.
4. Woodward, R. B., *J. Am. Chem. Soc.,* **1940**, *62*, 1626.
5. McEwen, W. E. and Cobb, R. L. *Chem. Rev*., **1955**, *55*, 511.
6. Schwartz, A., *J. Org. Chem.,* **1982**, *47*, 2213.
7. (a) Popp, F. D., *Bull. Soc. Chim. Belg.,* **1981**, *90*, 609. (b) Popp, F. D., *Adv. Heterocycl. Chem.,* **1979**, *24*, 187. (c) Popp, F. D., *Adv. Heterocycl. Chem.,* **1968**, *9*, 1. (d) Mosettig, E., *Org. React.,* **1954**, *8*, 218. (e) Buchanan, G. L.; Cook, J. W. and Loudon, J. D., *J. Chem. Soc.,* **1944**, 325.

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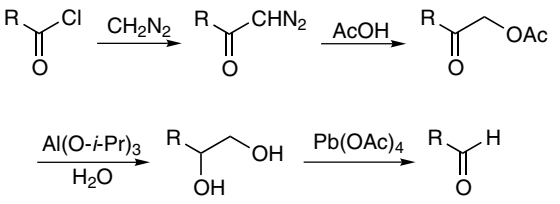
Grundmann Aldehyde Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Grundmann in 1936.[1] It is the conversion of acyl chloride into aldehyde with the exact same carbon skeleton via the following consecutive steps: (*a*) treatment of acyl chloride with diazomethane to form a ketone, (*b*) conversion of such a ketone into ketol acetate with acetic acid, (*c*) reduction of ketol acetate with aluminum isopropylate, and (*d*) hydrolysis and oxidation with lead tetraacetate. This method is especially useful in the preparation of aliphatic aldehydes with methylene-interrupted double bond(s).[2] Although polymers might form in the preparation of highly unsaturated aldehydes during the reduction with aluminum isopropylate, the reduction from lithium aluminum hydride can eliminate such drawbacks.[2]

B. GENERAL REACTION SCHEME



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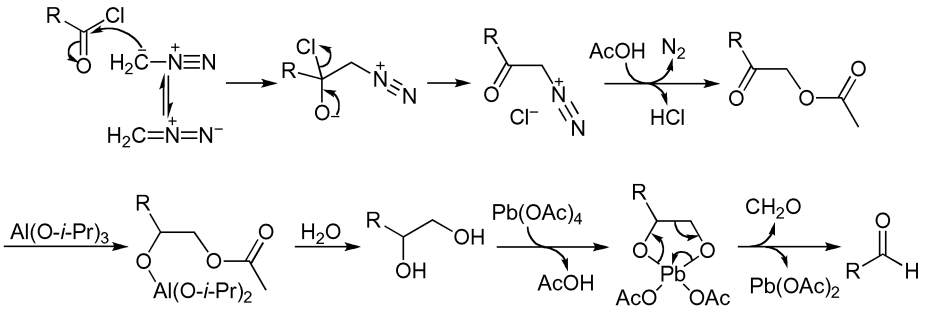
C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified to reduce the ketol acetate from $LiAlH_4$.[2]

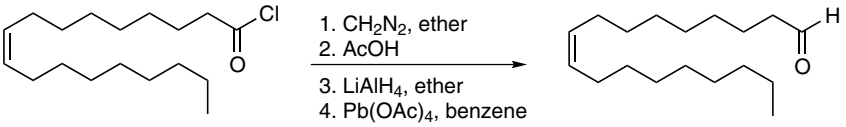
E. APPLICATIONS

This reaction has general application in the conversion of acyl chloride into aldehyde, especially for the unsaturated and isotopic labeled aldehydes.

F. RELATED REACTIONS

This reaction is related to the *Sonn-Müller Reaction* and *Stephen Aldehyde Synthesis.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 2.

Preparation of Glycols

Oleoyl chloride (0.1 mol, 30 g) in 100 mL ether was added during a period of 10 min to a stirred solution of 0.25 mol diazomethane in 590 mL ether kept at 0–5°C. After the mixture warmed to room temperature and stood for 2–4 h, the excess diazomethane and most of the solvent were removed by a stream of nitrogen. The remaining yellow oil was added slowly to 50 mL acetic acid at 50–60°C. After 2 h at this temperature, the decomposition

of the diazo ketone was completed by refluxing for 10 min. The slightly yellow solution was poured into water and the ketol acetate was extracted with ether. The product was washed with water to neutrality and then dried over sodium sulfate. The ether was removed, first by evaporation and finally by heating the residual oil to 50°C under high vacuum. The crude ketol acetate contained ~ 10% chloroketone. The crude ketol acetate in 200 mL ether was treated with an unfiltered solution of 4.0 g $LiAlH_4$ (0.1 mol) in 350 mL ether. The mixture was refluxed for 1 h; after the addition of a little EtOAc, it was poured over 200 g crushed ice. The milky suspension was acidified with dilute H_2SO_4 and extracted several times with ether. The product can be checked for complete reduction by warming a few milligrams with several drops of 50% KOH bath. Residual ketol is indicated by a yellow or brown color. Paper chromatography indicated that these crude preparations contained 10–15% of primary C_{18} alcohol and ~ 5% secondary C_{19} alcohol and/or free acid. The mono alcohols and glycols have boiling points of ~170°C and 190–195°C at 2 mmHg respectively, which can be separated by distillation. A pear-shaped Claisen flask with a modified Pyros-Glover type receiver was used for this purpose. To keep the length of exposure to heat at a minimum, the products were distilled in portions of 0.1 mol or smaller from a bath preheated to 180°C. Additional amounts of pure glycol were obtained by chromatographing the intermediate distilled fractions (6.5 g in 15 mL petroleum ether, 35–60°C) on alumina (40 g, activated, Harshaw) in a tube (2 × 30 cm). The chromatogram was developed successively with 100 mL methylene chloride, 100 mL ether, and 200 mL ethanol. A total of 24 fractions (15 mL each) were collected, and each was spot tested on paper. The first peak of the column chromatogram represented primary and secondary alcohols, which were not separated from each other, and 1.5–2 g pure glycol was recovered from the second peak.

Preparation of Aldehydes

$Pb(OAc)_4$ (0.1 mol, 40–45 g), and 0.5 mL acetic acid were added to a solution of 15 g nonadecene-10-diol-1,2 (0.05 mol) in 100 mL benzene and kept at 60°C for 3 h. Excess of $Pb(OAc)_4$ was destroyed by the addition of ethylene glycol. The solution was cooled to room temperature, poured into 500 mL 20% acetic acid in water, and extracted several times with benzene. The combined extracts were washed first with dilute acetic acid to remove the lead salts and finally with water to neutrality. Such preparations contain small amounts of free acids, which are removed by extracting the benzene solution with 1% Na_2CO_3. The aldehydes obtained in this manner are chromatographically pure and remain as liquid at –20°C, and can be distillated between 150 and 160°C at 2 mmHg.

Other references related to the Grundmann aldehyde synthesis are cited in the literature.[3]

H. REFERENCES

1. Grundmann, C., *Ann.,* **1936**, *524*, 31.
2. Mangold, H. K., *J. Org. Chem.,* **1959**, *24*, 405.
3. (a) Morimoto, K.; Kurata, Y.; Hoshita, N. and Okuda, K., *Hiroshima J. Med. Sci.,* **1968**, *17*, 1. (b) Hoshita, T. and Okuda, K., *J. Biochem.,* **1967**, *62*, 655. (c) Mosetting, E., *Org. React.,* **1954**, *8*, 225.

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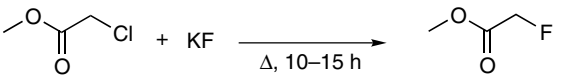
Gryszkiewicz-Trochimowski and McCombie Fluorination

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported almost concurrently by McCombie and co-workers in 1946[1] and Gryszkiewicz-Trochimowski and co-workers in 1947.[2] It is the preparation of methyl fluoroacetate by the treatment of methyl chloroacetate with potassium fluoride at high temperatures (e.g., 190°C) for 10–15 h, with a yield of 60%[3] to 90%.[2] This method has been used to prepare other fluoroacetates[4] and ω-fluoro-alcohols;[5] however, sodium fluoride is not suitable for this reaction because of a very low yield.[4] The best conditions for this reaction require a vigorous agitation of completely dried starting materials at high temperature with potassium fluoride in large excess.[4] This reaction has been scaled up in a pilot plant to prepare methyl fluoroacetate in the United States.[6]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is believed that there is more ionic character in KF than that in KCl, and the dissociation constant of KCl is smaller than that of KF, according to the electronegativities and sizes of ions. This reaction might occur via a S_N2 mechanism.

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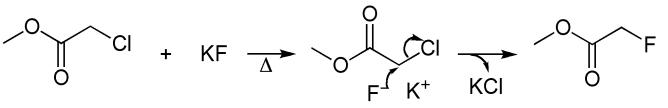


D. MODIFICATION

N/A

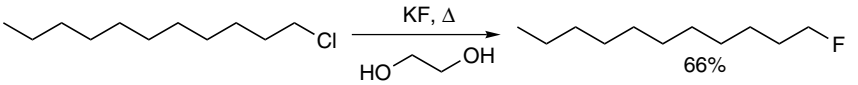
E. APPLICATIONS

This reaction has been used in the preparation of some alkyl fluoroacetates, ω-fluoroalcohols, etc.

F. RELATED REACTIONS

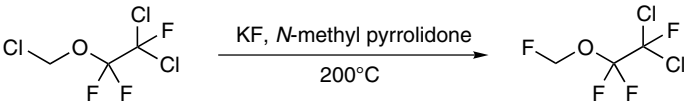
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

A mixture of 15.0 g anhydrous KF (0.26 mol), 80.0 g diethylene glycol and 34.0 g 1-chloroundecane (0.18 mol) was heated at 135°C for 23 h with vigorous stirring. The period of heating may be reduced, with slight diminution of yield. The mixture was cooled and diluted with an equal volume of water. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layer and extracts were treated with bromine in ether until a faint orange color persisted, and then were washed successively with water, aqueous sodium carbonate and water again. The product, after being dried over sodium sulfate and removal of the ether, was fractionally distilled, yielding 15.0 g 1-fluoroundecane, b.p. 102–102.5°C at 23 mmHg and 9.0 g unchanged 1-chloroundecane. The yield was 66%, based on the consumed 1-chloroundecane.



Reference 8.

KF (100 g) was added to 500 mL *N*-methylpyrrolidone, and the mixture was dried by distilling out 50 mL solvent. Then 100 g chloromethyl 1,1,2-trifluoro-2,2-dichloroethyl ether was added slowly with stirring while keeping the reaction temperature at 200°C. A

mixture of product and starting material was distilled out from the reaction mixture, and the distillate was washed with water, dried, and purified by fractional distillation or preparative gas chromatography to give 5–10% fluoromethyl 1,1,2-trifluoro-2,2-dichloroethyl ether.

Other references related to the Gryszkiewicz-Trochimowski and McCombie fluorination are cited in the literature.[9]

H. REFERENCES

1. McCombie, H. and Saunders, B. C., *Nature,* **1946**, *158*, 382.
2. Gryszkiewicz-Trochimowski, E.; Sporzynski, A. and Wnuk, J., *Rec. Trav. Chim.,* **1947**, *66*, 413.
3. Saunders, B. C. and Stacey, G. J., *J. Chem. Soc.,* **1948**, 1773.
4. Sartori, M. F., *Chem. Rev.,* **1951**, *48*, 225.
5. Gryszkiewicz-Trochimowski, E., *Rec. Trav. Chim.,* **1947**, *66*, 427.
6. Atherton, F. R.; Howard, H. T. and Todd, A. R., *J. Chem. Soc.,* **1948**, 1106.
7. Pattison, F. L. M. and Norman, J. J., *J. Am. Chem. Soc.,* **1957**, *79*, 2311.
8. Terrell, R. C.; Speers, L.; Szur, A. J.; Ucciardi, T. and Vitcha, J. F., *J. Med. Chem.,* **1972**, *15*, 604.
9. (a) Ando, T.; Namigata, F.; Kataoka, M.; Yachida, K. and Funasaka, W., *Bull. Chem. Soc. Jpn.,* **1967**, *40*, 1275. (b) Groth, R. H., *J. Org. Chem.,* **1960**, *25*, 102. (c) Bergmann, E. D. and Cohen, S., *J. Chem. Soc.,* **1958**, 2259. (d) Howell, W. C.; Millington, J. E. and Pattison, F. L. M., *J. Am. Chem. Soc.,* **1956**, *78*, 3843. (e) Pattison, F. L. M.; Cott, W. J.; Howell, W. C. and White, R. W., *J. Am. Chem. Soc.,* **1956**, *78*, 3484. (f) Pattison, F. L. M.; Howell, W. C.; McNamara, A. J.; Schneider, J. C. and Walker, J. F., *J. Org. Chem.,* **1956**, *21*, 739. (g) Pattison, F. L. M. and Howell, W. C., *J. Org. Chem.,* **1956**, *21*, 748. (h) Pattison, F. L. M.; Fraser, R. R.; O'Neill, G. J. and Wilshire, J. F. K., *J. Org. Chem.,* **1956**, *21*, 887. (i) Bergmann, F. and Kalmus, A., *J. Am. Chem. Soc.,* **1954**, *76*, 4137. (j) Truce, W. E. and Sack, B. H., *J. Am. Chem. Soc.,* **1948**, *70*, 3959.

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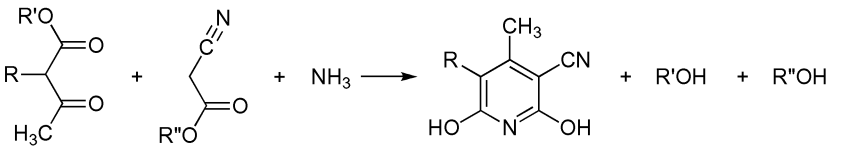
Guareschi Reaction

(Guareschi-Thorpe Pyridine Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Guareschi in 1896[1] and fully extended by Thorpe beginning in 1911.[2] It is the preparation of pyridine derivatives by condensation of acetoacetic esters and cyanoacetic acids (or its esters and amides) in the presence of ammonia. The formed cyclic dicyano-imides are called the Guareschi products[3] or Guareschi imides,[4] and this reaction is known as the Guareschi reaction.[3,4a] It was found that ketones can also condense with cyanoacetic esters or amides in aqueous solution in the presence of piperidine or alkali,[5] but this condensation is limited to methyl alkyl ketones only, including acetone.[6] Ketones with carbonyl group adjacent to a ring junction do not condense with cyanoacetic acid.[2b,2d,5b] Unlike cyanoacetic acid, malonic acid and its esters do not undergo this reaction.[3] This reaction has been adopted to prepare β-alkyl glutaric acid from aldehydes and cyanoacetamide.[7]

B. GENERAL REACTION SCHEME



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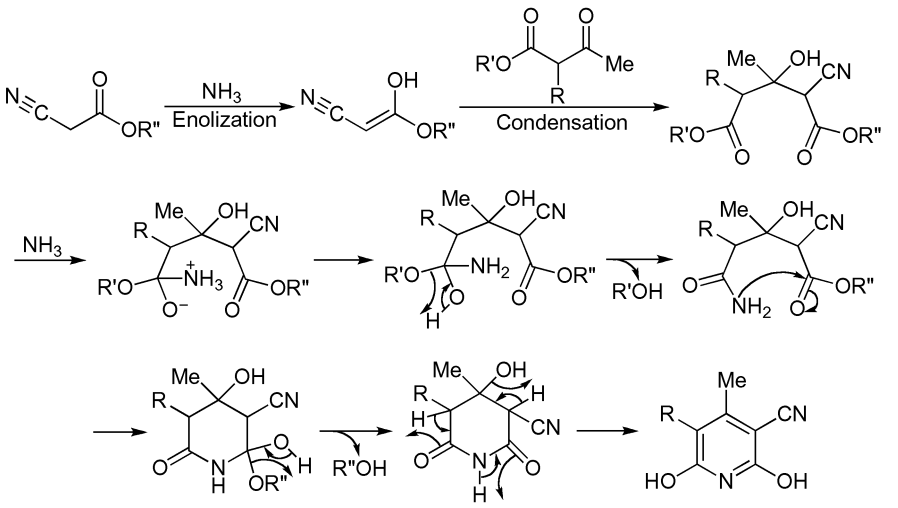
C. PROPOSED MECHANISMS



D. MODIFICATION

A two-step process has been adopted to replace the one-pot synthesis from other ketones that do not regularly undergo this reaction.[4a]

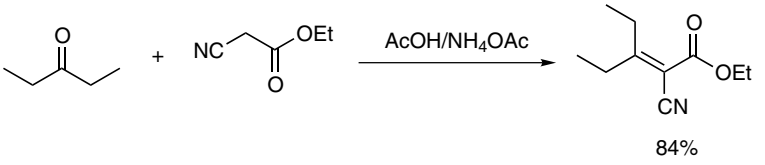
E. APPLICATIONS

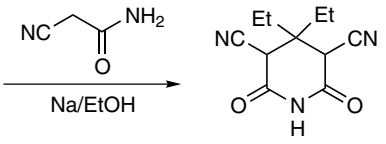
This reaction has been used for the synthesis of pyridine derivatives and β-alkyl glutaric acid.

F. RELATED REACTIONS

This reaction is related to the *Hantzsch Dihydropyridine Synthesis* and *Kröhnke Pyridine Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



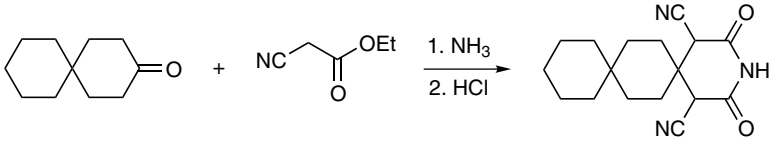


91.7%

Reference 4a.

To a 500-mL round-bottomed flask were added 34.45 g 3-pentanone (0.41 mol), 66.31 g ethyl cyanoacetate (0.59 mol), 8.51 g ammonium acetate (0.11 mol), 28.40 g acetic acid (0.47 mol), and 105 mL benzene. The flask was equipped with a Dean-Stark tube fitted to an efficient condenser attached to a $CaCl_2$ drying tube. The solution was refluxed for 45 h while 17.5 mL water was separated (> 100%). The cooled benzene solution was washed three times with 75 mL water, dried over $CaCl_2$, filtered, and concentrated by rotary evaporation to an orange-red oil. Distillation through a 10-cm Vigreux column afforded 60.51 g ethyl 2-cyano-3-ethyl-2-ene-pentate in a yield of 84%.

To a 500-mL, three-necked, round-bottomed flask equipped with overhead stirrer, water-cooled reflux condenser fitted with a $CaCl_2$ tube, and dropping funnel were added 180 mL absolute ethanol and 10.29 g clean sodium (0.45 mol). After the sodium had disappeared, 84.08 g cyanoacetamide (0.45 mol) was added, and the resulting slurry was refluxed for 15 min while another 20 mL ethanol was added. The mixture was cooled, and a solution of 40.54 g ethyl 2-cyano-3-ethyl-2-ene-pentate (0.224 mol) in 40 mL ethanol was added as a thin stream. The reaction was mildly exothermic, resulting a very thick, yellow-orange mixture. Stirring was continued overnight, and then the slurry was poured into 950 mL water, forming a homogeneous orange solution. With cooling, 47 mL concentrated hydrochloric acid was added, forcing out a heavy precipitate. After cooling thoroughly in an ice water bath, the solid was collected by suction filtration, washed with cold water, air dried for 12 h, and further dried at 100°C for 2 h to afford 44.96 g 2,4-dicyano-3,3-diethylpentanimide as a white fluffy solid, in a yield of 91.7%.



40%

Reference 4b.

Spiro[5.5]undecan-3-one (33.2 g, 0.2 mol) and 47.5 g ethyl cyanoacetate (0.42 mol) were placed in a 500-mL thick-walled flask. The mixture was cooled to 0°C, and 100 mL ethanol saturated with anhydrous ammonia at 0°C was added. A stopper was wedged and the mixture was stored at 0–5°C for 1 week. The precipitated ammonium salt of the Guareschi imide was filtered, dissolved in boiling water, filtered, and acidified with HCl. The Guareschi imide was filtered, washed with water, and dried. It melted at 230–233°C and 232–233°C after recrystallization from alcohol-water. 1,5-Dicyano-3-azadispiro[5.2.5.2] hexadecane-2,4-dione (24 g) was obtained, in a yield of 40%.

Other references related to the Guareschi-Thorpe pyridine synthesis are cited in the literature.[8]

H. REFERENCES

1. (a) Guareschi, I., *Mem. Reale Accad. Sci. Torino II*, **1896**, *46*, 7. (b) Guareschi, I., *Mem. Reale Accad. Sci. Torino II*, **1896**, *46*, 11. (c) Guareschi, I., *Mem. Reale Accad. Sci. Torino II*, **1896**, *46*, 25.
2. (a) Thole, F. B. and Thorpe, J. F., *J. Chem. Soc.*, **1911**, *99*, 422. (b) Thole, F. B. and Thorpe, J. F., *J. Chem. Soc*., **1915**, *99*, 445. (c) Kon, G. A. R. and Thorpe, J. F., *J. Chem. Soc*., **1919**, *115*, 686. (d) Kon, G. A. R. and Thorpe, J. F., *J. Chem. Soc*., **1919**, *115*, 701. (e) Day, J. N. E. and Thorpe, J. F., *J. Chem. Soc.,* **1920**, *117*, 1465. (f) Ingold, C. K.; Perren, E. A. and Thorpe, J. F., *J. Chem. Soc*., **1922**, *121*, 1765. (g) Birch, S. F. and Thorpe, J. F., *J. Chem. Soc*., **1922**, *121*, 1821.
3. Diaper, D. G. M. and Kuksis, A., *Chem. Rev*., **1959**, *59*, 89.
4. (a) Holder, R. W.; Daub, J. P.; Baker, W. E.; Gilbert, R. H. and Graf, N. A., *J. Org. Chem*., **1982**, *47*, 1445. (b) Rice, L. M.; Freed, M. E. and Grogan, C. H., *J. Org. Chem*., **1964**, *29*, 2637.
5. (a) Guareschi, I., *Atti. Accad. Sci. Torino*, **1918**, *53*, 831. (b) Guareschi, I., *Atti. Accad. Sci. Torino*, **1901**, *36*, 443.
6. Birch, A. J. and Robinson, R., *J. Chem. Soc.,* **1942**, 488.
7. Kent, R. E. and McElvains, M., *Org. Synth. Coll.,* **1955**, *3*, 591.
8. (a) Collins, D. J. and James, A. M., *Aust. J. Chem*., **1989**, *42*, 215. (b) Bures, M. G. and Jorgensen, W. L., *J. Org. Chem*., **1988**, *53*, 2504. (c) Kutney, J. P. and Selby, R. C., *J. Org. Chem*., **1961**, *26*, 2733. (d) Lukes, R. and Kutham, J., *Coll. Czech. Chem. Commun*., **1960**, *25*, 2173. (e) Bobbitt, J. M. and Scola, D. A., *J. Org. Chem*., **1960**, *25*, 560. (f) McElvain, S. M. and Lyle, R. E., *J. Am. Chem. Soc*., **1950**, *72*, 384. (g) Vogel, A. I*., J. Chem. Soc*., **1934**, 1758. (h) Hope, E., *J. Chem. Soc*., **1922**, *121*, 2216. (i) Guareschi, I., *Gazz. Chim. Ital*., **1919**, *49*, 126. (j) Ruzicka, L. and Fornasir, V., *Helv. Chim. Acta*, **1919**, *2*, 338. (k) Guareschi, I., *Mem. Reale Accad. Sci. Torino II*, **1905**, *55*, 287. (l) Baron, H.; Remfry, F. G. P. and Thorpe, J. F., *J. Chem. Soc*., **1904**, *85*, 1726. (m) Guareschi, I., *J. Chem. Soc*., **1897**, *72*, 168.

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Guerbet Condensation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Guerbet in 1899.[1] It is the condensation of primary or secondary alcohols at high temperature and pressure in the presence of alkali metal hydroxide or alkoxide. It was reported that this reaction occurs via dehydrogenation to form aldehyde that condenses with a second molecule of aldehyde to give the aldol product, which subsequently is reduced by alcohol to form a higher order of alcohol,[2] known as the Guerbet alcohol.[3] Therefore, this reaction is referred to as the Guerbet condensation,[2a,4] Guerbet dimerization[3] or Guerbet reaction.[2b,4e,5] In this reaction, acid is formed in a yield comparable to alcohol,[2a] so that different reagents have been tried to improve the reaction conditions. Tripotassium phosphate was found to be the best condensation reagent for this reaction.[2a] It was found that 0.225 mol potassium alkoxide is the best ratio for the reaction.[4f] The surfactant made from Guerbet alcohol is known as the Guerbet surfactant.[3,6] Recent developments of this reaction have used solid-state catalysts[7] and copper-supported NaOMe as catalyst.[5a] It is interesting that the primary amines are also found to condense under similar conditions.[4e]

B. GENERAL REACTION SCHEME

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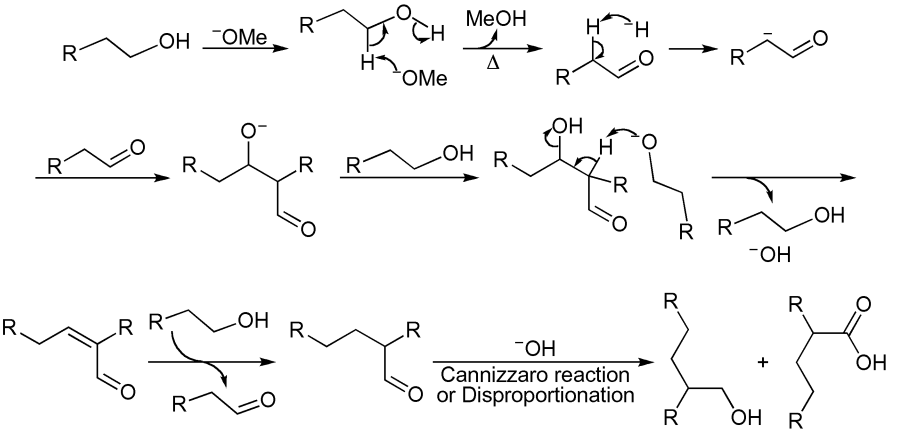
C. PROPOSED MECHANISMS

It is assumed that under these reaction conditions (e.g., high pressure, high temperature), metal alkoxide is strong enough to deprotonate the α-hydrogen. Because no mechanistic details are available, a tentative mechanism, consisting of dehydrogenation to form an aldehyde and subsequent *Aldol Reaction*, is outlined here.



D. MODIFICATION

This reaction has been modified using solid-state catalysts.[5a,7]

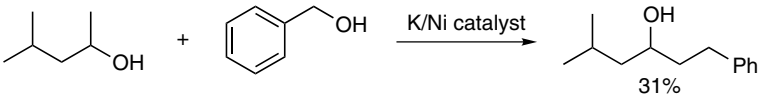
E. APPLICATIONS

This reaction has general application in the preparation of higher-order alcohols from cheap alcohols.

F. RELATED REACTIONS

This reaction is related to the *Lebedev Process* and *Ostromislensky Process*.

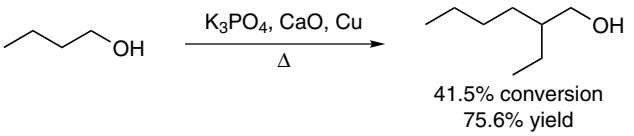
G. CITED EXPERIMENTAL EXAMPLES



Reference 4f.

Total alcohols (benzyl alcohol and 4-methyl-pentanol-2 in ratio of 2:1, 1 mol) was placed in a 500-mL three-necked flask fitted with a stirrer, a thermometer, and a Dean-Stark water trap surmounted by a reflux condenser. The trap was wrapped with asbestos cord for

insulation. After sweeping out the reaction system with a nitrogen flow for several minutes (to reduce the chance of explosion), potassium was added in small portions with slow stirring. Upon the disappearance of potassium, 0.5 g U.O.P nickel catalyst was added, the stirrer was set at a more rapid rate, and the mixture was heated to reflux (143–187°C) with a hemispherical mantle. The temperature and volume of water collected were read at frequent intervals. After 4 h, the reaction mixture was cooled < 100°C and quenched with ∼150 mL water. The catalyst was filtered off, and the layers were separated. The alcohol layer was washed with 10% NaOH, and the combined aqueous layers were extracted with ether. The combined non-aqueous layers were dried over sodium sulfate. After ether was removed at the water aspirator, the product was isolated by vacuum distillation through an 8-in. Vigreux column to give 31% 1-phenyl-5-methyl hexanol-3. The by-product acid was recovered from the combined aqueous layers by acidification with dilute hydrochloric acid, extraction into benzene, and distillation.



Reference 2a.

To a stainless-steel autoclave was added 544.0 g *n*-butanol-1, 53.0 g potassium phosphate, 84.0 g calcium oxide, and 20.0 g activated copper. The autoclave was sealed and tested for leaks with 1000 psi nitrogen. When the autoclave was secure, the nitrogen pressure was slowly bled off through the vent. When the vent valve was closed, the heat was applied with stirring. The reaction attained the desired temperature within 1 h and was maintained at 293–295°C for 4.5 h. The maximum pressure developed during the reaction was 2250 psi. After the reaction was cooled to room temperature, the residual pressure (93 psi) was vented, and the autoclave was emptied. The contents were filtered, and the filtrate was washed with water to remove salts and extracted with benzene. The benzene extracts were combined with the organic materials and dried over $MgSO_4$. Distillation of the mixture yielded 45.5 g *n*-butyl alcohol-water azeotrope, 185.0 g *n*-butyl alcohol, and 162.0 g 2-ethylhexanol distilling at 181–185°C. A residue of 24.5 g remained after distillation. The conversion to 2-ethylhexanol was 41.5%, and the yield was 75.6%.

Other references related to the Guerbet condensation are cited in the literature.[8]

H. REFERENCES

1. Guerbet, M., *Compt. Rend.,* **1899**, *128*, 511.
2. (a) Miller, R. E. and Bennett, G. E., *Ind. Eng. Chem.,* **1961**, *53*, 33. (b) Weizmann, C.; Bergmann, E. and Sulzbacher, M., *J. Org. Chem.,* **1950**, *15*, 54.
3. Varadaraj, R.; Bock, J.; Valint, P.; Zushma, S. and Thomas, R., *J. Phys. Chem.,* **1991**, *95*, 1671.
4. (a) Carlini, C.; Marchionna, M.; Noviello, M.; Raspolli Galletti, A. M.; Sbrana, G.; Basile, F. and Vaccari, A., *J. Mol. Catal. A: Chem.,* **2005**, *232*, 13. (b) Carlini, C.; Flego, C.; Marchionna, M.; Noviello, M.; Raspolli Galletti, A. M.; Sbrana, G.; Basile, F. and Vaccari, A., *J. Mol. Catal. A: Chem.,* **2004**, *220*, 215. (c) Carlini, C.; Di Girolamo, M.; Macinai, A.; Marchionna, M.; Noviello,

M.; Raspolli Galletti, R. and Sbrana, G., *J. Mol. Catal. A: Chem.,* **2003**, *204–205*, 721. (d) Vanin, V. V.; Krutskii, L. N.; Lyubomilov, V. I. and Beer, A. A., *Khim. Promyshlennost, Ser. Azotnaya Promyshlennost,* **1979**, 32. (e) Miller, R. E., *J. Org. Chem.,* **1960**, *25*, 2126. (f) Pratt, E. F. and Kubler, D. G., *J. Am. Chem. Soc.,* **1954**, *76*, 52.

5. (a) Carlini, C.; di Girolamo, M.; Macinai, A.; Marchionna, M.; Noviello, M.; Raspolli Galletti, A. M. and Sbrana, G., *J. Mol. Cat. A: Chem.,* **2003**, *200*, 137. (b) Carlini, C.; Macinai, A.; Marchionna, M.; Noviello, M.; Raspolli Galletti, A. M. and Sbrana, G., *J. Mol. Catal. A: Chem.,* **2003**, *206*, 409. (c) Carlini, C.; Di Girolamo, M.; Marchionna, M.; Noviello, M.; Raspolli Galletti, A. M. and Sbrana, G., *J. Mol. Catal. A: Chem.,* **2002**, *184*, 273. (d) Gotoh, K.; Nakamura, S.; Mori, T. and Morikawa, Y., *Studies Surface Sci. Catal.,* **2000**, *130C*, 2669. (e) Burk, P. L.; Pruett, R. L. and Campo, K. S., *J. Mol. Catal.,* **1985**, *33*, 15. (f) Burk, P. L.; Pruett, R. L. and Campo, K. S., *J. Mol. Catal.,* **1985**, *33*, 1. (g) Slesareva, L. A. and Lyubomilov, V. I., *Zh. Org. Khim.,* **1973**, *9*, 2025. (h) Strassberger, W. and Kaupp, J., *Vom Wachs*, **1970**, *2*, 746.
6. (a) Varadaraj, R.; Bock, J.; Valint, P.; Zushma, S. and Brons, N., *J. Phys. Chem.,* **1991**, *95*, 1677. (b) Varadaraj, R.; Bock, J.; Valint, P.; Zushma, S. and Brons, N., *J. Phys. Chem.,* **1991**, *95*, 1679. (c) Varadaraj, R.; Bock, J.; Valint, P. and Zushma, S., *J. Phys. Chem.,* **1991**, *95*, 1682.
7. Ueda, W.; Ohshida, T.; Kuwabara, T. and Morikawa, Y., *Catal. Lett.,* **1992**, *12*, 97.
8. (a) Varadaraj, R.; Schaffer, H.; Bock, J. and Valint, P., *Langmuir,* **1990**, *6*, 1372. (b) Klein, E.J; Thoemel, F. and Winkler, H., *Ann.,* **1973**, 1004. (c) Gregorio, G.; Pregaglia, G. F. and Ugo, R., *J. Organomet. Chem.,* **1972**, *37*, 385. (d) Veibel, S. and Nielsen, J. T., *Tetrahedron,* **1967**, *23*, 1723. (e) Dvornikoff, M. N. and Farrar, M. W., *J. Org. Chem.,* **1957**, *22*, 540. (f) Sulzbacher, M., *J. Appl. Chem. London,* **1955**, *5*, 637. (g) Machemer, H., *Angew. Chem.,* **1952**, *64*, 213. (h) Bolle, J. and Bourgeois, L., *Compt. Rend.,* **1951**, *233*, 1466. (i) Weizmann, C.; Sulzbacher, M. and Bergmann, E., *J. Chem. Soc.,* **1947**, 851. (j) Weizmann, C.; Bergmann, E. and Haskelberg, L., *Chem. Ind. (London),* **1937**, *15*, 587. (k) Guerbet, M., *Compt. Rend.,* **1912**, *154*, 713. (l) Guerbet, M., *Compt. Rend.,* **1912**, *154*, 1357. (m) Guerbet, M., *Compt. Rend.,* **1912**, *155*, 1156. (n) Guerbet, M., *Compt. Rend.,* **1910**, *150*, 183. (o) Guerbet, M., *Compt. Rend.,* **1909**, *149*, 129. (p) Guerbet, M., *Compt. Rend.,* **1908**, *146*, 300. (q) Guerbet, M., *Compt. Rend.,* **1908**, *146*, 1405.

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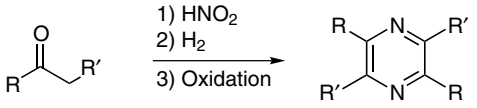
Gutknecht Condensation
(Gutknecht Pyrazine Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Gutknecht in 1879.[1] It is a synthesis of pyrazine involving the treatment of a ketone with nitrous acid to form an oximino ketone[2] followed by reduction to an α-amino ketone that dimerizes to dihydropyrazine via a pinacol-like process.[3] The formed dihydropyrazine is then converted into the pyrazine from the dehydrogenation (or oxidation) with mercury (I) oxide, copper (II) sulfate, or atmospheric oxygen.[4] This reaction is thus known as the Gutknecht condensation[5] or Gutknecht pyrazine synthesis.[6] For example, the α-amino acetone in ammonia solution is converted into dimethylpyrazine by the oxidation of mercuric chloride;[4b] likewise, *p*-methyl-α-aminoacetophenone[7] and α-aminopropiophenone[8] are converted into 2,5-di-*p*-toylypyrazine and 3,6-diphenyl-2,5-dimethylpyrazine, respectively. It should be pointed out that pyrazines were once named ketines, as suggested by Treadwell to indicate their origin, but the structures were falsely presented.[2]

B. GENERAL REACTION SCHEME



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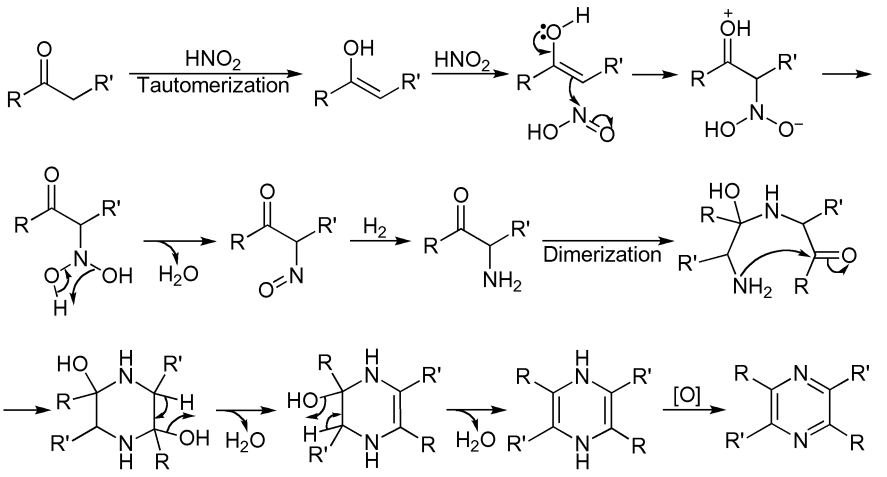
C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified by the treatment of an α-amino ketone with a base (e.g., NH_3,[4a] Grignard reagent[9]) to afford the pyrazine derivative.

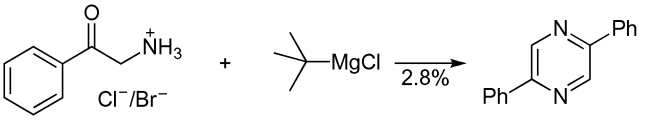
E. APPLICATIONS

This reaction has a general application in the preparation of pyrazine derivatives.

F. RELATED REACTIONS

N/A

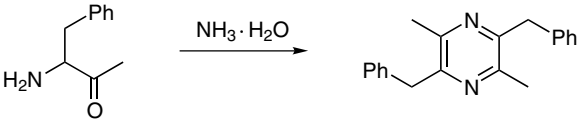
G. CITED EXPERIMENTAL EXAMPLES



Reference 9.

To an ethereal solution of *t*-butylmagnesium chloride prepared from 78.7 g *t*-butyl chloride (0.850 mol) and 20.8 g magnesium (0.855 mol) was added, in portions and with stirring, 30 g of the mixed hydrobromide-hydrochloride salt of α-aminoacetophenone ($\sim$ 0.14 mol). After the mixture was boiled under reflux with stirring for 7 h, it was allowed to stand

overnight under a nitrogen atmosphere and then poured into 50 mL saturated, aqueous solution of ammonium chloride. The mixture was filtered, and the two-phase filtrate was made alkaline with aqueous sodium hydroxide solution, heated to boil, cooled and extracted with ether (5 × 200 mL). The combined extracts were dried over $MgSO_4$ and concentrated. An ethanolic solution of the residue deposited 0.46 g crude 2,5-diphenylpyrazine, in a yield of 2.8%, m.p. 191–194°C. Two additional crystallizations from ether afforded the pure pyrazine as colorless plates, m.p. 197.3–198°C.



Reference 4a.

To a solution of 1.0 g α-benzyl-α-aminoacetone hydrochloride in 5 mL water was added 5 mL concentrated aqueous ammonia. The mixture was allowed to stand in an open dish overnight to afford 2,5-dibenzyl-3,6-dimethylpyrazine. Oily droplets separated out, which later changed to long silky needles. The crystals were dissolved in an excess of hydrochloric acid, filtered from a little oily impurity, and then extracted with ether. The acid extract was disregarded, and the solution again was extracted with ether after being made alkaline with sodium hydroxide. The ether on evaporation left a mass of crystals, which melted in a crude condition at ~ 85°C. After being dried on a porous plate and recrystallized from a few drops of alcohol, a small yield of good crystals, both plates and needles, melting at 92–94°C, was obtained.

Other references related to the Gutknecht condensation are cited in the literature.[10]

H. REFERENCES

1. Gutknecht, H., *Ber.,* **1879**, *12*, 2291.
2. Krems, I. J. and Spoerri, P. E., *Chem. Rev.*, **1947**, *40*, 279.
3. (a) Treadwell, P., *Ber.,* **1881**, *14*, 1461. (b) Treadwell, P., *Ber.,* **1881**, *14*, 2158.
4. (a) Dakin, H. D. and West, R., *J. Biol. Chem.,* **1928**, *78*, 757. (b) Künne, H., *Ber.,* **1895**, *28*, 2040. (c) Gabriel, S. and Pinkus, G., *Ber.,* **1893**, *26*, 2197.
5. O'Brien, C., *Chem. Rev.,* **1964**, *64*, 81.
6. (a) Senning, A., *Elsevier's Dictionary of Chemoetymology*, Elsevier Amsterdam, **2006**. (b) Lewis, R. J. and Hawley, G. G., *Hawley's Condensed Chemical Dictionary*, Van Nostrand Reinhold, New York, **1997**. (c) Honig, J. M.; Jacobs, M. B.; Lewin, S. Z.; Minrath, W. R. and Murphy, G., *The Van Nostrand Chemist's Dictionary*, D. Van Nostrand Co., New York, **1953**.
7. Rüdenburg, K., *Ber.,* **1913**, *46*, 3555.
8. Eberhardt, A., *Arch. Pharm.,* **1920**, *258*, 97.
9. House, H. O. and Grubbs, E. J., *J. Am. Chem. Soc.,* **1959**, *81*, 4733.
10. (a) Brown, D. J., in *The Pyrazines*, ed. Taylor, E. C. and Wipf, P., John Wiley & Sons, New York, **2002**. (b) Newbold, G. T.; Spring, F. S. and Sweeny, W., *J. Chem. Soc.,* **1948**, 1855. (c) Hartung, W. H. and Munch, J. C., *J. Am. Chem. Soc.,* **1929**, *51*, 2262. (d) Dakin, H. D. and West, R., *J. Biol. Chem.,* **1928**, *78*, 91. (e) Gabriel, S., *Ber.,* **1908**, *41*, 1127. (f) Gutknecht, H., *Ber.,* **1880**, *13*, 1116.

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Hajos-Parrish-Eder-Sauer-Wiechert Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was independently reported by two groups in 1971: the group of Hajos and Parrish[1] and the group of Eder, Sauer, and Wiechert.[2] It is an enantioselective *Aldol Reaction* catalyzed by (S)-proline, one of the earliest enantioselectively catalyzed reactions of practical use in synthetic organic chemistry. Owing to its wide application in organic synthesis, it has been extensively explored and extended to asymmetric *Aldol Reaction*,[3] α-alkylation,[4] *Mannich Reaction*,[5] *Michael Addition*,[6] and α-amination[7] of carbonyl compounds. In the literature, this reaction has been referred to by different names: Hajos-Parrish-Eder-Sauer-Wiechert reaction,[8] Hajos-Eder-Sauer-Wiechert reaction,[9] Hajos-Wiechert reaction,[10] and Hajos-Parrish-Wiechert reaction.[11] The asymmetric version of the *Robinson Annulation* catalyzed by (S)-proline is known as the Hajos-Parrish reaction,[12] Hajos-Parrish-Robinson annulation,[13] or Hajos-Wiechert aldol reaction.[14] The resulting cyclic aldol product is called the Hajos-Parrish ketol.[15] In addition, the cyclic (S)-enedione—(7aS)-2,3,7,7a-tetrahydro-7a-methyl-1H-indene-1(5,6H)-dione[16]—is referred to as Hajos-Parrish ketone,[17] Hajos-Parrish diketone,[18] or Hajos-Wiechert ketone.[19] Initially, this reaction was assumed to "involve the formation of a carbinolamine intermediate followed by the displacement of the proline moiety by nucleophilic attack of the enol from ketone,"[8d,20] but more experimental and theoretical evidence indicate that this reaction involves "nucleophilic addition of the neutral enamine to the carbonyl group together with hydrogen transfer from the proline carboxylic acid moiety to the developing alkoxide".[8d]

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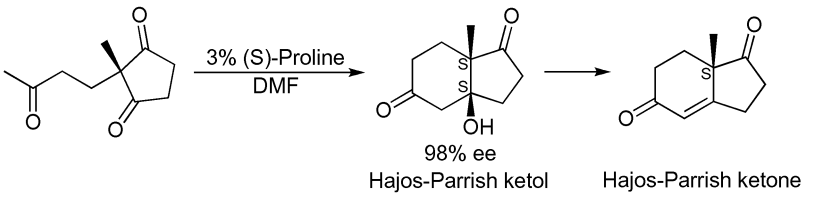
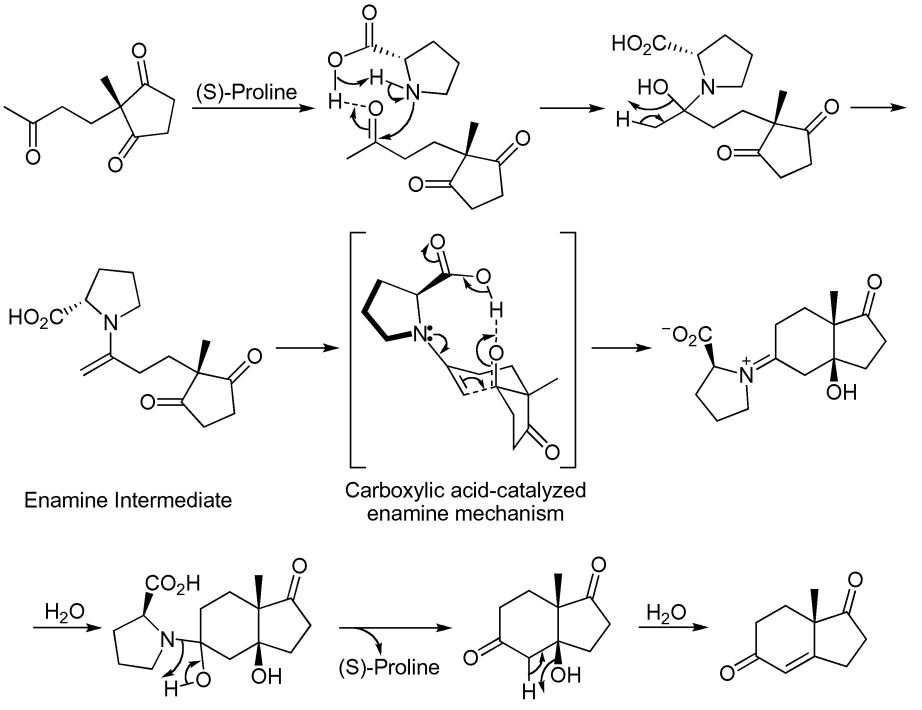
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Illustrated here is the mechanism involved in the nucleophilic addition of the neutral enamine to carbonyl group.[8d]



D. MODIFICATION

This reaction has been extended to other reactions, including α-alkylation,[4] *Mannich Reaction*,[5] *Michael Addition*,[6] and α-amination[7] of ketones.

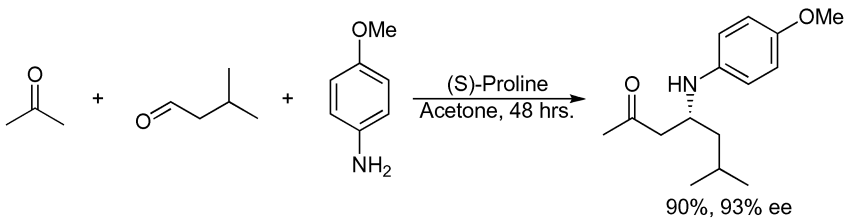
E. APPLICATIONS

This reaction has wide use in the synthesis of enantiomerically pure molecules involving ketones.

F. RELATED REACTIONS

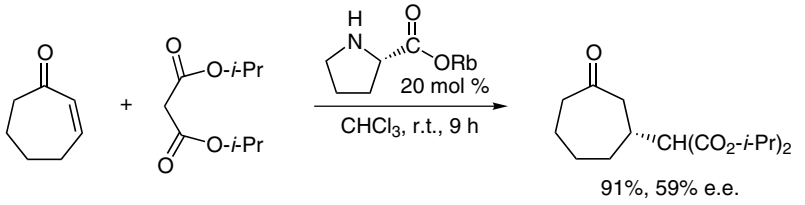
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 5a.

A suspension of 40 mg (*S*)-proline (0.35 mmol), 135 mg *p*-anisidine (1.1 mmol), and 0.86 g isovaleraldehyde (1.0 mmol) in 10 mL acetone was stirred at room temperature for 48 h. The mixture was filtered to recover ∼ 35 mg (S)-proline. Concentration of the filtrate followed by column chromatography (15% EtOAc in hexanes) gave 224 mg (R)-4-(4-methoxy-phenylamino)-6-methyl-heptan-2-one (0.9 mmol), in a yield of 90% and 93% e.e.



Reference 10b.

Under an argon atmosphere, a mixture of 1.30 mL diisopropyl malonate (6.72 mmol), 0.50 mL 2-cycloheptenone (4.48 mmol), and 46 mg L-proline rubidium salt (0.22 mmol) in 5 mL chloroform was stirred for 59 h at 25°C. The reaction was quenched with 2 M HCl, and organic materials were extracted twice with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, concentrated, and flash chromatographed over silica gel to give 1.21 g diisopropyl (*R*)-(+)-(3-oxocycloheptyl)malonate, in a yield of 91%, and 59% e.e.

Other references related to the Hajos-Parrish-Eder-Sauer-Wiechert reaction are cited in the literature.[21]

H. REFERENCES

1. Hajos, Z. G. and Parrish, D. R., *Ger. Pat.*, July 29, **1971**, DE 2102623, (priority date Jan. 21, **1970**).

2. (a) Eder, U.; Sauer, G. and Wiechert, R., *Ger. Pat.*, Oct 7, **1971**, DE 2014757. (b) Eder, U.; Sauer, G.; Wiechert, R., *Angew. Chem. Int. Ed. Engl*., **1971**, *10*, 496. (c) Eder, U.; Sauer, G.; Wiechert, R., *Angew. Chem*., **1971**, *83*, 492.
3. Northrup, A. B. and MacMillan, D. W. C., *J. Am. Chem. Soc*., **2002**, *124*, 6798.
4. Vignola, N. and List, B., *J. Am. Chem. Soc*., **2004**, *126*, 450.
5. (a) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J., *J. Am. Chem. Soc*., **2002**, *124*, 827. (b) List, B., *J. Am. Chem. Soc*., **2000**, *122*, 9336.
6. (a) Alexakis, A. and Andrey, O., *Org. Lett*., **2002**, *4*, 3611. (b) Enders, D. and Seki, A., *Synlett*, **2002**, 26. (c) List, B.; Pojarliev, P. and Martin, H. J., *Org. Lett*., **2001**, *3*, 2423. (d) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R. and Barbas, C. F., *Tetrahedron Lett*., **2001**, *42*, 4441.
7. (a) Bøgevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W. and Jørgensen, K. A., *Angew. Chem. Int. Ed. Engl*., **2002**, *41*, 1790. (b) List, B., *J. Am. Chem. Soc*., **2002**, *124*, 5656.
8. (a) Davies, S. G.; Sheppard, R. L.; Smith, A. D. and Thomson, J. E., *Chem. Commun.,* **2005**, 3802. (b) Ward, D. E.; Jheengut, V. and Akinnusi, O. T., *Org. Lett.,* **2005**, *7*, 1181. (c) Cheong, P. H.-Y.; Houk, K. N.; Warrier, J. S. and Hanessian, S., *Adv. Synth. Catal.,* **2004**, *346*, 1111. (d) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H.-Y. and Houk, K. N., *Acc. Chem. Res.,* **2004**, *37*, 558. (e) List, B., *Acc. Chem. Res.,* **2004**, *37*, 548. (f) Iwamura, H.; Wells, D. H.; Mathew, S. P.; Klussmann, M.; Armstrong, A. and Blackmond, D. G., *J. Am. Chem. Soc.,* **2004**, *126*, 16312. (g) Saito, S. and Yamamoto, H., *Acc. Chem. Res.,* **2004**, *37*, 570. (h) Hoang, L.; Bahmanyar, S.; Houk, K. N. and List, B., *J. Am. Chem. Soc.,* **2003**, *125*, 16.
9. (a) Notz, W.; Tanaka, F. and Barbas, C. F., *Acc. Chem. Res.,* **2004**, *37*, 580. (b) List, B.; Lerner, R. A. and Barbas, C. F., *J. Am. Chem. Soc.,* **2000**, *122*, 2395.
10. (a) Taggi, A. E.; Hafez, A. M. and Lectka, T., *Acc. Chem. Res.,* **2003**, *36*, 10. (b) Yamaguchi, M.; Shiraishi, T. and Hirama, M., *J. Org. Chem.,* **1996**, *61*, 3520.
11. Blaser, H.-U., *Chem. Rev.,* **1992**, *92*, 935.
12. Agami, C.; Levisalles, J. and Puchot, C., *J. Chem. Soc., Chem. Commun*., **1985**, 441.
13. Corey, E. J. and Huang, A. X., *J. Am. Chem. Soc.,* **1999**, *121*, 710.
14. (a) Kitamura, M.; Suga, S.; Oka, H. and Noyori, R., *J. Am. Chem. Soc.,* **1998**, *120*, 9800. (b) Kitamura, M.; Okada, S.; Suga, S. and Noyori, R., *J. Am. Chem. Soc.,* **1989**, *111*, 4028.
15. Cerri, A.; Almirante, N.; Barassi, P.; Benicchio, A.; de Munari, S.; Marazzi, G.; Molinari, I.; Serra, F. and Melloni, P., *J. Med. Chem.,* **2002**, *45*, 189.
16. Scaglione, J. B.; Rath, N. P. and Covey, D. F., *J. Org. Chem.,* **2005**, *70*, 1089.
17. (a) Inomata, K.; Barrague, M. and Paquette, L. A., *J. Org. Chem.,* **2005**, *70*, 533. (b) Deng, W.; Jensen, M. S.; Overman, L. E.; Rucker, P. V. and Vionnet, J.-P., *J. Org. Chem.,* **1996**, *61*, 6760. (c) Isaacs, R. C. A.; di Grandi, M. J. and Danishefsky, S. J., *J. Org. Chem.,* **1993**, *58*, 3938.
18. Renneberg, D.; Pfander, H. and Leumann, C. J., *J. Org. Chem.,* **2000**, *65*, 9069.
19. Winterfeldt, E., *Chem. Rev.,* **1993**, *93*, 827.
20. Jung, M. E., *Tetrahedron,* **1976**, *32*, 3.
21. (a) Hosseini, M.; Stiasni, N.; Barbieri, V. and Kappe, C. O., *J. Org. Chem.,* **2007**, *72*, 1417. (b) Hoang, L.; Bahmanyar, S.; Houk, K. N. and List, B., *J. Am. Chem. Soc.,* **2003**, *125*, 16. (c) List, B., *Tetrahedron,* **2002**, *58*, 5573. (d) Cordova, A.; Notz, W. and Barbas, C. F., *J. Org. Chem.,* **2002**, *67*, 301. (e) Unaleroglu, C.; Aviyente, V. and Arseniyadis, S., *J. Org. Chem.,* **2002**, *67*, 2447. (f) Sakthivel, K.; Notz, W.; Bui, T. and Barbas, C. F., *J. Am. Chem. Soc.,* **2001**, *123*, 5260. (g) List, B.; Pojarliev, P. and Castello, C., *Org. Lett.,* **2001**, *3*, 573. (h) Bahmanyar, S. and Houk, K. N., *J. Am. Chem. Soc.,* **2001**, *123*, 11273. (i) Bahmanyar, S. and Houk, K. N., *J. Am. Chem. Soc.,* **2001**, *123*, 12911. (j) Molander, G. A.; Quirmbach, M. S.; Silva, L. F.; Spencer, K. C. and Balsells, J., *Org. Lett.,* **2001**, *3*, 2257. (k) Gröger, H. and Wilken, J., *Angew. Chem. Int. Ed.,* **2001**, *40*, 529. (l) Notz, W. and List, B., *J. Am. Chem. Soc.,* **2000**, *122*, 7386. (m) Feringa,

B. L., *Acc. Chem. Res.,* **2000**, *33*, 346. (n) Naasz, R.; Arnold, L. A.; Pineschi, M.; Keller, E. and Feringa, B. L., *J. Am. Chem. Soc.,* **1999**, *121*, 1104. (o) Tietze, L. F., *Chem. Rev.,* **1996**, *96*, 115. (p) Agami, C.; Platzer, N. and Sevestre, H., *Bull. Chim. Soc. Fr.,* **1987**, *2*, 358. (q) Hajos, Z. G. and Parrish, D. R., *Org. Synth.,* **1984**, *63*, 26. (r) Buchsacher, P. and Fürst, A., *Org. Synth.,* **1984**, *63*, 37. (s) Hajos, Z. G. and Parrish, D. R., *J. Org. Chem.,* **1974**, *39*, 1615.

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Haller-Bauer Cleavage

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Haller and Bauer in 1909.[1] It is the base-induced cleavage of a carbon-carbon bond of a nonenolizable ketone to give a carboxylic acid derivative (i.e., an amide) and a neutral fragment in which the carbonyl group is replaced by hydrogen. Therefore, it is generally known as the Haller-Bauer cleavage.[2,3] In addition, this reaction is also referred to as the Haller-Bauer reaction,[2g,2j,2n,4] Haller-Bauer fragmentation,[5] Haller-Bauer decarboxylation,[2j] or Haller-Bauer process.[2f,4c,6] The nonenolizable ketones studied include biaryl ketones, and aryl cyclopropyl ketones, and aryl trifluoromethyl ketones. It was found that this reaction overwhelmingly involves a carbanion, with only minor incursions of a competing free-radical pathway,[6a] and the mode of cleavage depends on the relative stability of the carbanions involved.[2n] Therefore, the cleavage is particularly effective when the incipient carbanion is stabilized;[2j] otherwise, the cleavage might fail if at least one of the groups cannot assist in stabilization of the carbanion.[2h] Exceptions are the cleavage of 1-methyl-2,2-diphenylcyclopropyl phenyl ketone[2o,7] and *Z*-2-phenylcyclopropyl phenyl ketone,[2n] which result in reverse cleavage because of the steric interaction between the phenyl group on 2-position and the carbonyl group.[2m] In addition, this reaction occurs with retention of configuration, not only in the cyclopropyl anion[2o,6b,7,8] where the inversion of configuration is impossible[2j] but also in the open chain.[2j,9] Silane has a higher ability to stabilize the anion than normal alkyl groups, thus higher retention of stereochemistry is found during the preparation of chiral tertiary silanes.[2a,2g,2h] On the other hand, the metal cation of used bases also affects this reaction, and it was found that reaction with potassium amide is faster than that with sodium amide.[2g] When other strong bases such as alkoxides are used for this reaction, the LiO-*t*-Bu does not induce this reaction, showing the reactivity trend of KO-*t*-Bu > NaO-*t*-Bu > LiO-*t*-Bu.[4d]

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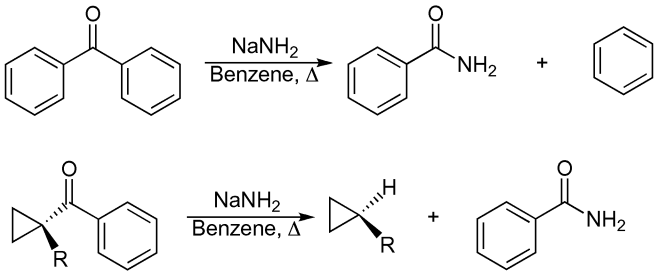
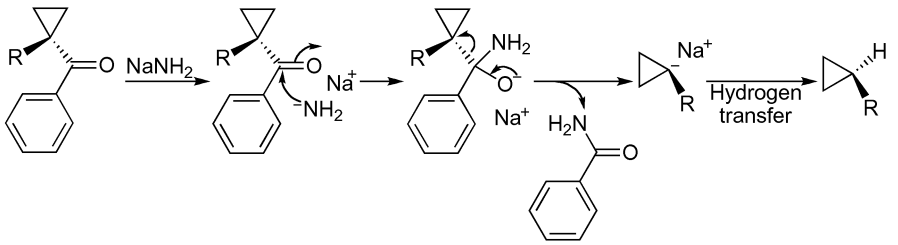
In addition, solvents affect the reaction. Traditionally, this reaction is carried out in boiling benzene with excess amounts of sodium or potassium amide.[9] Substitution of benzene by *t*-BuOH results in the kinetic retardation and modest lowering of stereoselectivity of proton transfer.[4e] It is interesting that a case of cleavage for biaryl ketone is successfully triggered by KO-*t*-Bu but fails when $NaNH_2$ is used.[9] This reaction is useful for preparing chiral compounds[2e,2h,6a] and tertiary carboxamides.[9] Recent modification of this reaction is to induce the cleavage with *N*-alkylamines and *N*,*N*-dialkylamines,[9] and extend the reaction to cyclobutyl ketone.[10]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Shown below is the mechanism according to Paquette and Maynard,[6a] and Ishihara and Yano.[9]



D. MODIFICATION

This reaction has been extended to use potassium *t*-butoxide[11] or *N*-alkylamines and *N*,*N*-dialkylamines[9] to induce the cleavage.

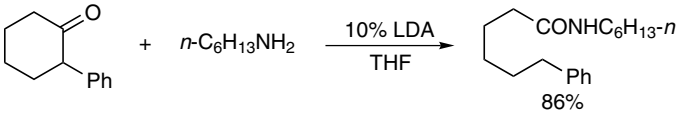
E. APPLICATIONS

This reaction has wide use in the preparation of tertiary carboxamides, tertiary alcohols, and debenzoylation.

F. RELATED REACTIONS

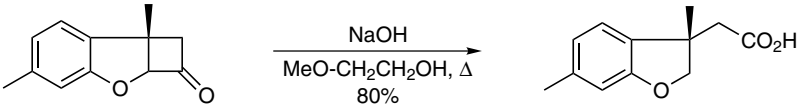
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 9.

To 2 mL THF containing 2.2 mmol hexamine and 28 mL *N*,*N*-diisopropylamine (0.2 mmol) at 0°C under nitrogen atmosphere was added 1.51 mL 1.58 M BuLi in hexane solution (2.4 mmol) dropwise. After being stirred for 15 min, a solution of 2.0 mmol 2-phenyl cyclohexanone in 2.0 mL THF was added, and the mixture was stirred for 30 min at 0°C and at room temperature for 5 h. The reaction was then quenched with 25 mL 1 M HCl, and the mixture was extracted with EtOAc (3 × 20 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel to give 86% *N*-hexyl-6-phenylhexanamide.



Reference 10.

A mixture of 250 mg cyclobutabenzofuranone, 4 mL 15% NaOH, and 10 mL 2-methoxyethanol was refluxed for 10 h. It was then cooled and extracted once with ether. The ethereal layer left no residue. The aqueous portion was acidified with cold 6 N HCl and extracted with ether. The ethereal extracts were washed with water, dried, and concentrated to afford 220 mg of an acid that crystallized from ether-petroleum ether, m.p. 104–105°C, in a yield of 80%.

Other references related to the Haller-Bauer cleavage are cited in the literature .[12]

H. REFERENCES

1. (a) Haller, A. and Bauer, E., *Compt. Rend.,* **1909**, *148*, 70. (b) Haller, A. and Bauer, E., *Compt. Rend.,* **1909**, *148*, 127. (c) Haller, A. and Bauer, E., *Compt. Rend.,* **1909**, *149*, 5.
2. (a) Fleming, I.; Barbero, A. and Walter, D., *Chem. Rev*., **1997**, *97*, 2063. (b) Mehta, G. and Praveen, M., *J. Org. Chem.,* **1995**, *60*, 279. (c) Zhao, B. P. and Snieckus, V., "Combinational Directed ortho and Remote Metalation Route to Condensed Fluorenones. A Study of Haller-Bauer Cleavage of Substituted Fluorenones" in *Polycyclic Aromatic Compounds*, ed. Garrigues, P. and Lamotte, M., Gordon and Breach, Philadelphia, **1993**, pp. 183–190. (d) Griffin, G. W. and Marchand, A. P., *Chem. Rev*., **1989**, *89*, 997. (e) Salaün, J., *Chem. Rev.,* **1989**, *89*, 1247. (f) Paquette, L. A.; Gilday,

J. P. and Maynard, G. D., *J. Org. Chem.,* **1989**, *54*, 5044. (g) Gilday, J. P.; Gallucci, J. C. and Paquette, L. A., *J. Org. Chem.,* **1989**, *54*, 1399. (h) Paquette, L. A.; Gilday, J. P.; Ra, C. S. and Hoppe, M., *J. Org. Chem.,* **1988**, *53*, 704. (i) Ziegler, F. E., *Chem. Rev.,* **1988**, *88*, 1423. (j) Paquette, L. A.; Gilday, J. P. and Ra, C. S., *J. Am. Chem. Soc.,* **1987**, *109*, 6858. (k) Rozov, L. A.; Rafalko, P. W.; Evans, S. M.; Brockunier, L. and Ramig, K., *J. Org. Chem.,* **1985**, *60*, 1319. (l) Eaton, P. E.; Or, Y. S. and Branca, S. J., *J. Am. Chem. Soc.,* **1981**, *103*, 2134. (m) Walborsky, H. M.; Allen, L. E.; Traenckner, H.-J. and Powers, E. J., *J. Org. Chem.,* **1971**, *36*, 2937. (n) Bumgardner, C. L. and McDaniel, K. G., *J. Am. Chem. Soc.,* **1969**, *91*, 6821. (o) Impastato, F. J. and Walborsky, H. M., *J. Am. Chem. Soc.,* **1962**, *84*, 4838.

3. (a) Mehta, G. and Reddy, D. S., *Synlett*, **1996**, 229. (b) Mehta, G.; Reddy, K. S. and Kunwar, A. C., *Tetrahedron Lett*., **1996**, *37*, 2289. (c) Zhao, B.-P. and Snieckus, V., *Polycycl. Aromat. Compd.*, **1993**, *3* (suppl), 183. (d) Dyllick-Brenzinger, R. A.; Patel, V.; Rampersad, M. B.; Stothers, J. B. and Thomas, S. E., *Can. J. Chem.,* **1990**, *68*, 1106. (e) Cheng, A. K. and Stothers, J. B., *Can. J. Chem.,* **1977**, *55*, 4184.
4. (a) Levin, M. D.; Kaszynski, P. and Michl, J., *Chem. Rev.,* **2000**, *100*, 169. (b) Mehta, G. and Venkateswaran, R. V., *Tetrahedron,* **2000**, *56*, 1399. (c) Paquette, L. A. and Ra, C. S., *J. Org. Chem.,* **1988**, *53*, 4978. (d) Paquette, L. A. and Gilday, J. P., *J. Org. Chem.,* **1988**, *53*, 4972. (e) Carr, A. A.; Huber, E. W.; Kane, J. M. and Miller, F. P., *J. Org. Chem.,* **1986**, *51*, 1616.
5. Kende, A. S.; Liu, K. and Brands, K. M. J., *J. Am. Chem. Soc.,* **1995**, *117*, 10597.
6. (a) Paquette, L. A. and Maynard, G. D., *J. Org. Chem.,* **1989**, *54*, 5054. (b) Paquette, L. A.; Uchida, T. and Gallucci, J. D., *J. Am. Chem. Soc.,* **1984**, *106*, 335.
7. Walborsky, H. M. and Impastato, F. J., *Chem. Ind. (London),* **1958**, 1690.
8. (a) Gassman, P. G.; Lumb, J. T. and Zalar, F. V., *J. Am. Chem. Soc.,* **1967**, *89*, 946. (b) Walborsky, H. M., *Rec. Chem. Prog.,* **1962**, *23*, 75. (c) Hamlin, K. E. and Biermacher, U., *J. Am. Chem. Soc.,* **1955**, *77*, 6376. (d) Piehl, F. J. and Brown, W. G., *J. Am. Chem. Soc.,* **1953**, *75*, 5023.
9. Ishihara, K. and Yano, T., *Org. Lett.,* **2004**, *6*, 1983.
10. Mittra, A.; Bhowmik, D. R. and Venkateswaran, R. V., *J. Org. Chem.,* **1998**, *63*, 9555.
11. Streitwieser, A. and Brown, S. M., *J. Org. Chem.,* **1988**, *53*, 904.
12. (a) Namyslo, J. C. and Kaufmann, D. E., *Chem. Rev.,* **2003**, *103*, 1485. (b) Zhang, N. and Vozzolo, J., *J. Org. Chem.,* **2002**, *67*, 1703. (c) Mehta, G. and Reddy, D. S., *Synlett,* **1997**, 612. (d) Boyer, L. E.; Brazzillo, J.; Forman, M. A. and Zanoni, B., *J. Org. Chem.,* **1996**, *61*, 7611. (e) Gilday, J. P. and Paquette, L. A., *Org. Prep. Proced. Int.,* **1990**, *22*, 167. (f) Marchand, A. P., *Chem. Rev*., **1989**, *89*, 1011. (g) Paquette, L. A.; Maynard, G. D.; Ra, C. S. and Hoppe, M., *J. Org. Chem.,* **1989**, *54*, 1408. (h) Paquette, L. A., *Chem. Rev.,* **1986**, *86*, 733. (i) Locher, R. and Seebach, D., *Angew. Chem. Int. Ed. Engl.,* **1981**, *20*, 569. (j) Brand, R. A. and Mulvaney, J. E., *J. Org. Chem.,* **1980**, *45*,633. (k) Kaiser, E. M. and Warner, C. O., *Synthesis,* **1975**, 395. (l) Hamlin, K. E. and Weston, A. W., *Org. React.,* **1957**, *9*, 1. (m) Carter, C. L. and Slater, S. N., *J. Chem. Soc.,* **1946**, 130. (n) Schonberg, A., *Ber.,* **1925**, *58*, 580. (o) Haller, A., *Bull. Soc. Chim. Fr.,* **1922**, *31*, 1117. (p) Haller, A. and Benoist, E., *Ann. Chim.,* **1921**, *17*, 25. (q) Mehta, G. and Reddy, D. S., *J. Chem. Soc., Perkin Trans. I,* **2001**, 1153. (r) Francesconi, I.; Patel, A. and Boykin, D. W., *Synthesis*, **1999**, 61. (s) Mehta, G. and Praveen, M., *Synth. Commun.,* **1997**, *27*, 2593. (t) Guan, X. P.; Sun, J. G. and Yu, Y. Z., *Chinese Chem. Lett.,* **1996**, *7*, 902. (u) Mehta, G. and Reddy, S. H. K., *J. Chem. Soc., Perkin Trans. I,* **1994**, 2949. (v) Patel, H. A.; Stothers, J. B. and Thomas, S. E., *Can. J. Chem.,* **1994**, *72*, 56. (w) Mehta, G. and Praveen, M., *J. Chem. Soc., Chem. Commun.,* **1993**, 1573. (x) Muir, D. J. and Stothers, J. B., *Can. J. Chem.,* **1993**, *71*, 1290. (y) Hasegawa, T.; Nigo, T.; Kuwatani, Y. and Ueda, I., *Bull. Chem. Soc. Jpn.,* **1993**, *66*, 2676. (z) Muir, D. J. and Stothers, J. B., *Can. J. Chem.,* **1993**, *71*, 1099. (aa) Sifton, W.; Stothers, J. B. and Thomas, S. E., *Can. J. Chem.,* **1992**, *70*, 1274. (bb) Zarges, W.; Marsch, M.; Harms, K. and Boche, G., *Ber.,* **1989**, *122*, 2303.

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Hammick Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Hammick and co-workers in 1937.[1] It is the synthesis of α-pyridylcarbinols by the decarboxylation of picolinic acid with excess amount of carbonyl compounds (aldehydes or ketones). Therefore, it is generally known as the Hammick reaction.[2] Occasionally, it is also referred to as the Hammick coupling.[2j] It was found that four types of molecules—picolinic acids,[1] quinaldinic acids,[2k] isoquinaldinic acids,[2k] and isonicotinic acids[2k]—all undergo this reaction. In addition, quaternization (e.g., alkylation[3] or formation of *N*-oxide[4]) of the nitrogen atom in these compounds lead to molecules that decarboxylate especially easily.[5] The solvents feasible for this reaction can be either acidic, basic, or neutral. The acidic solvents include phenol and *p*-nitrophenol, and the basic solvents are aniline, *p*-nitroaniline, *N*,*N*-diethylaniline, quinoline, and tributylamine. The neutral solvents include *o*-, *m*- and *p*-dimethoxybenzene, and *o*-, *m*-, and *p*-nitrotoluene and *p*-cymene.[2h] Therefore, this reaction is not affected strongly by the acidity or basicity of the solvent,[6] and it was found that *p*-cymene is the best solvent for this reaction.[2i] The carbonyl compounds, including benzaldehyde, benzophenone, acetophenone, *m*-nitrobenzaldehyde, and *m*-nitroacetophenone, all couple with the heterocyclic moiety upon decarboxylation; however, *p*-nitrobenzaldehyde, 2,4-dinitrobenzaldehyde, cinnamaldehyde, and *p*-dimethylaminobenzaldehyde do not react in the presence or absence of solvents.[2i] This reaction has been proposed to involve three kinds of intermediates: the cyclic form,[2h,4] zwitterions form,[2h,5] and carbene form.[5,7] Each intermediate is favored by certain experimental results, as shown in the cited literature. In addition, the intermediate can also react with other electrophiles instead of carbonyl compounds.[8] Similar to the structure of picolinic acid, the Schiff bases of α-keto acids also decarboxylate accordingly.[5]

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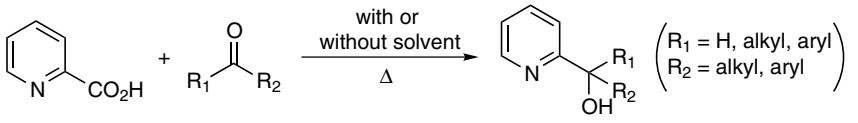
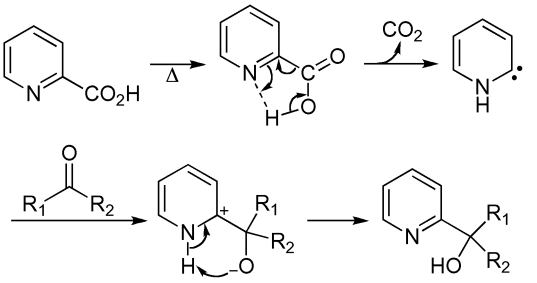
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Shown below is the mechanism involving a carbene intermediate, which then couples with carbonyl compounds.



D. MODIFICATION

N/A

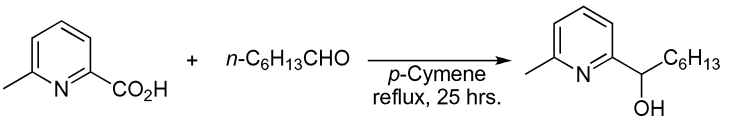
E. APPLICATIONS

This reaction has general application in the preparation of pyridylcarbinols.

F. RELATED REACTIONS

N/A

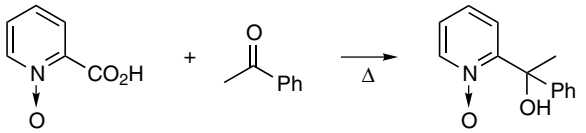
G. CITED EXPERIMENTAL EXAMPLES



24%

Reference 2g.

A solution of 10 g 6-methylpicolinic acid (73 mmol) and 10.0 g *n*-heptaldehyde (87 mmol) in 60 mL *p*-cymene was refluxed for 25 h, after which carbon dioxide evolution ceased (90% of theoretical). The cooled solution was extracted with 2 M HCl (2 × 50 mL), the combined acid extracts were alkalinized and extracted with ether, and the ether extract was dried and distilled to give 24% 1-(6′-methyl-2′-pyridy1)-1-heptanol, b.p. 122–124°C (2 mmHg).



30%

Reference 4.

A solution of 5.0 g 2-carboxypyridine *N*-oxide in 60 mL acetophenone was heated at 150°C until carbon dioxide evolution ceased (1 h). The cold solution was then extracted with 50 mL 2 N HCl; the aqueous layer was made basic and extracted with ether. Concentration of the dried ether extract gave a yellow oil that, on treatment with a mixture of ether-chloroform-petroleum ether, crystallized to give 2.32 g *N*-oxide pyridylcarbinol as white needles, in a yield of 30%, m.p. 112–113°C.

Other references related to the Hammick reaction are cited in the literature.[9]

H. REFERENCES

1. Dyson, P. and Hammick, D. L., *J. Chem. Soc.,* **1937**, 1734.
2. (a) Bohn, B.; Heinrich, N. and Vorbrueggen, H., *Heterocycles,* **1994**, *37*, 1731. (b) Dzvinchuk, I. B. and Lozinskii, M. O., *Khim. Geterotsiklicheskikh Soedinenii*, **1985**, 1570. (c) Brown, E. V. and Shambhu, M. B., *J. Org. Chem.,* **1971**, *36*, 2002. (d) Betts, M. J. and Brown, B. R., *J. Chem. Soc. C,* **1967**, 1730. (e) Beak, P. and Bonham, J., *J. Am. Chem. Soc.,* **1965**, *87*, 3365. (f) Nelson, N. A. and Paquette, L. A., *J. Org. Chem.,* **1962**, *27*, 9654. (g) Rapoport, H. and Volcheck, E. J., *J. Am. Chem. Soc.,* **1956**, *78*, 2451. (h) Cantwell, N. H. and Brown, E. V., *J. Am. Chem. Soc.,* **1955**, *77*, 4466. (i) Cantwell, N. H. and Brown, E. V., *J. Am. Chem. Soc.,* **1953**, *75*, 1489. (j) Cantwell, N. H. and Brown, E. V., *J. Am. Chem. Soc.,* **1952**, *74*, 5967. (k) Mislow, K., *J. Am. Chem. Soc.,* **1947**, *69*, 2559.
3. Haake, P. and Mantecon, J., *J. Am. Chem. Soc.,* **1964**, *86*, 5230.
4. Boekelheide, V. and Lehn, W. I., *J. Org. Chem.,* **1961**, *26*, 428.
5. Breslow, R., *J. Am. Chem. Soc.,* **1958**, *80*, 3719.
6. Clark, L. W., *J. Phys. Chem.,* **1966**, *69*, 2277.
7. Lavorato, D.; Terlouw, J. K.; Dargel, T. K.; Koch, W.; McGibbon, G. A. and Schwarz, H., *J. Am. Chem. Soc.,* **1996,** *118*, 11898.
8. Brown, B. R. and Hammick, D. L., *J. Chem. Soc.,* **1949**, 173.
9. (a) McCarty, F. J.; Tilford, C. H. and van Campen, M. G., *J. Am. Chem. Soc.,* **1957**, *79*, 472. (b) Brown, B. R., *Quart. Rev.* (*London*), **1951**, *5*, 131. (c) Brown, B. R. and Hammick, D. L., *J. Chem. Soc.,* **1949**, 659. (d) Ashworth, M. R. F.; Daffern, R. P. and Hammick, D. L., *J. Chem. Soc.,* **1939**, 809.

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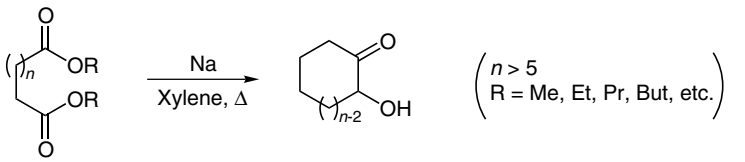
Hansley-Prelog Acyloin Condensation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction, originating from the preparation of open-chain α-ketols,[1] was first reported by Hansley in 1935,[2] and subsequently extended by Prelog in the 1940s–1950s.[3] It is the preparation of cyclic acyloins of 8 or more carbon atoms (e.g., more than 20 carbon atoms) from the reaction of colloidal sodium with esters of saturated or unsaturated dicarboxylic acids in high dilution.[1] The resulting cyclic acyloins can be further converted into cyclic ketones with the same carbon numbers by the reduction of zinc and hydrochloric acid in acetic acid.[4] This reaction is normally carried out above the melting point of sodium[2] while maintaining sodium in colloidal dispersion and then adding the esters of dicarboxylic acid in very diluted concentrations.[5] Toluene and xylene are equally good solvents for this reaction.[2] For the esters of dicarboxylic acids with fewer carbon, the corresponding *t*-butyl or *sec*-butyl esters are preferred, which give higher yields than the methyl esters per unit volume of solvents.[2]

B. GENERAL REACTION SCHEME



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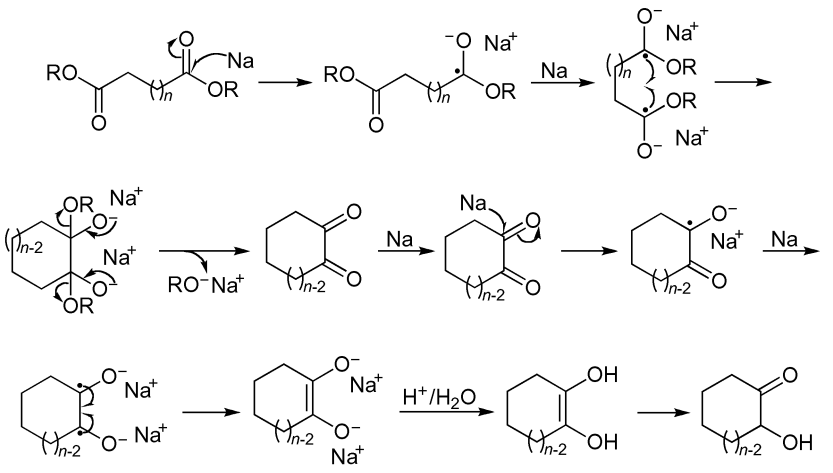
C. PROPOSED MECHANISMS

A radical mechanism is involved in this reaction as shown below.



D. MODIFICATION

N/A

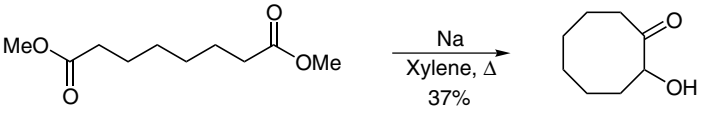
E. APPLICATIONS

This reaction has general application in the preparation of medium to large cyclic ketones.

F. RELATED REACTIONS

This reaction is related to the *Dieckmann Condensation* and *Acyloin Condensation*.

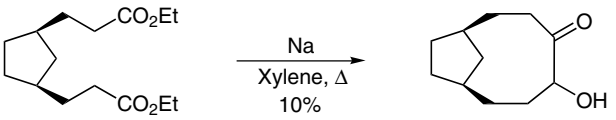
G. CITED EXPERIMENTAL EXAMPLES



Reference 6.

A 250 mL Morton flask was equipped with a high-speed, stainless-steel stirrer and a high-speed (20,000 rpm) stirrer motor. In one of the necks of the flask was placed a Claissen adapter holding a West condenser directly over the flask and a 250-mL Hershberg dropping funnel in the outer arm. In the other neck of the flask was placed a second Claissen adapter,

one arm of which was stoppered and one arm of which held a gas inlet. A gas outlet attached to a U-tube with a small head of mercury was placed in the top of the reflux condenser. The Claissen adapters were wired securely to the necks of the Morton flask. To remove the last traces of moisture, the entire system was heated with a flame while flushing with argon. Then 125 mL xylene, dried over sodium, was placed in the Morton flask, and the last traces of moisture were removed from the solvent by distilling a small amount through the condenser, which was temporarily placed in distilling position; during the distillation, the air in the flask was replaced by argon. The condenser was replaced in reflux position, and 4.9 g freshly cut sodium metal (0.21 mol) was added through the top of the reflux condenser under a stream of argon. After reheating the xylene to reflux, the stirrer was started, and the molten sodium was dispersed by stirring at an estimated rate of 2000 rpm for 15 min. Addition of a solution of 13.9 g *cis*-1,3-bis-(ethoxycarbonyl)ethyl cyclopentane (0.052 mol) in 25 mL dry xylene to the sodium dispersion was completed in 45 h. The reaction mixture was heated with continued stirring for an additional 3 h. After cooling in an ice bath, 14 g glacial acetic acid (0.24 mol) was added dropwise to decompose excess sodium. During the addition of acetic acid, it was necessary to add an additional 50 mL xylene to suspend the sodium acetate formed. Sodium acetate was removed by vacuum filtration and returned to the reaction flask with 50 mL fresh xylene. After being stirred vigorously for several minutes, the solid was again filtered, and the xylene filtrates were combined. The xylene solution was washed with water and dilute sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Xylene was removed by distillation through a 10-cm Vigreux column. Additional product was recovered by dissolving the sodium acetate in 200 mL water and extracting with ether several times. The washed and dried ethereal extract afforded a residue upon evaporation of the solvent. The two samples were combined (4.1 g total) and chromatographed on a 14 × 1.5 cm column of activity grade V Woelm neutral alumina. Evaporation of the benzene eluate gave 0.9 g crude acyloin product, in a yield of 10%.



Reference 7.

A 5-L three-necked flask was equipped with mercury-sealed Hershberg stirrer and a simple high dilution apparatus, to which was attached a reflux condenser and a Hershberg dropping funnel. Sodium (46 g, 2 mol) was powdered by stirring under 1 L refluxing xylene, and a solution of 101 g dimethyl suberate (0.5 mol) in 80 mL xylene was added through the dilution apparatus over a period of 8 h in an atmosphere of dry nitrogen, with stirring and refluxing during that period plus an additional 2 h. The mixture was allowed to stand overnight, and then was cooled with an ice bath. Absolute ethanol (50 mL) was added to destroy any remaining sodium followed by a solution of 120 g glacial acetic acid (2 mol) in 800 mL dry ether, added slowly with stirring to neutralize the mixture. The nitrogen atmosphere was maintained to this point. Sodium acetate was separated by filtration and washed well with ether, and the filtrate was concentrated under reduced pressure in a nitrogen atmosphere. The residue was distilled from a Hickman molecular-type pot still at 60–133°C (0.5 mmHg), and the distillate was fractionated through a 15 × 1-cm Vigreux column under nitrogen, yielding 26 g suberoin, in a yield of 37%, b.p., 66–71°C (1.3 mmHg). The nearly

colorless product crystallized and was purified by redistillation and crystallization from a mixture of ether and pentane, b.p., 64°C (0.3 mmHg), m.p., 37–38.5°C.

Other references related to the Hansley-Prelog acyloin condensation are cited in the literature.[8]

H. REFERENCES

1. Sheehan, J. C.; O'Neill, R. C. and White, M. A., *J. Am. Chem. Soc.,* **1950**, *72*, 3376.
2. Hansley, V. L., *J. Am. Chem. Soc.,* **1935**, *57*, 2303.
3. (a) Prelog, V.; Frenkiel, L.; Kobelt, M. and Barman, P., *Helv. Chim. Acta,* **1947**, *30*, 1741. (b) Prelog, V.; Schenker, K and Günthard, H. H., *Helv. Chim. Acta,* **1952**, *35*, 1598. (c) Prelog, V. and Schenker, K., *Helv. Chim. Acta,* **1952**, *35*, 2044. (d) Prelog, V.; Schenker, K. and Küng, W., *Helv. Chim. Acta,* **1953**, *36*, 471.
4. Leonard, N. J. and Owens, F. H., *J. Am. Chem. Soc.,* **1958**, *80*, 6039.
5. Gardner, P. D.; Haynes, G. R. and Brandon, R. L., *J. Org. Chem.,* **1957**, *22*, 1206.
6. Kober, A. E. and Westman, T. L., *J. Org. Chem.,* **1970**, *35*, 4161.
7. Cope, A. C.; Fenton, S. W. and Spencer, C. F., *J. Am. Chem. Soc.,* **1952**, *74*, 5884.
8. (a) Crowley, J. I. and Rapoport, H., *J. Org. Chem.,* **1980**, *45*, 3215. (b) Gohen, H. and Shubart, R., *J. Org. Chem.,* **1973**, *38*, 1424. (c) Schrauzer, G. N. and Eichler, S., *Angew. Chem. Int. Ed. Engl.,* **1962**, *1*, 454. (d) Djerassi, C. and Krakower, G. W., *J. Am. Chem. Soc.,* **1959**, *81*, 237. (e) Leonard, N. J. and Schimelpfenig, C. W., *J. Org. Chem.,* **1958**, *23*, 1708. (f) Allinger, N. L., *Org. Synth.,* **1956**, *36*, 79. (g) Blomquist, A. T. and Goldstein, A., *J. Am. Chem. Soc.,* **1955**, *77*, 998. (h) Blomquist, A. T.; Burge, R. E. and Sucsy, A. C., *J. Am. Chem. Soc.,* **1952**, *74*, 3636. (i) Cram, D. J. and Steinberg, H., *J. Am. Chem. Soc.,* **1951**, *73*, 5691. (j) Cope, A. C. and Herrick, E. C., *J. Am. Chem. Soc.,* **1950**, *72*, 983. (k) Stoll, M. and Hulstkamp, J., *Helv. Chim. Acta,* **1947**, *30*, 1837. (l) Stoll, M. and Hulstkamp, J., *Helv. Chim. Acta,* **1947**, *30*, 1815. (m) Stoll, M. and Rouve, A., *Helv. Chim. Acta,* **1947**, *30*, 1822. (n) Hansley, V. L., *U.S. Pat.,* **1941**, Jan. 14, 2,228,268, [*Chem. Abstr.,* **1941**, *35*, 2534.]

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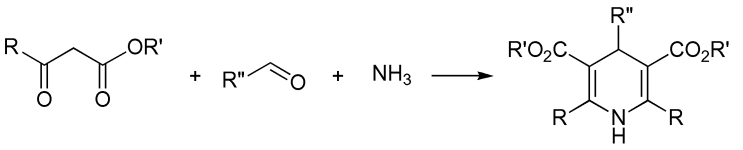
Hantzsch Dihydropyridine Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Hantzsch in 1882.[1] It is the synthesis of dihydropyridine dicarboxylate by condensation of an aldehyde with 2 eq. β-ketoester in the presence of ammonia. Therefore, this reaction is generally known as the Hantzsch dihydropyridine synthesis.[2] In addition, this reaction is also referred to as Hantzsch condensation[2f,3] or Hantzsch reaction;[4] and the formed dihydropyridine dicarboxylate is called the Hantzsch ester.[3a,5] Subsequent oxidation (or dehydrogenation) of the Hantzsch ester gives pyridine-3,5-dicarboxylates, which may also be decarboxylated to yield the corresponding pyridines.[2f,4a,5b,6] The Hantzsch ester, as a calcium antagonist,[3a,7] has important applications in drug design;[8] in addition, it can also be used as a hydrogen source.[9] This reaction has been modified to take place under microwave irradiation with high reaction rate and overall yields.[2b] Other modifications on this reaction include (*a*) the condensation of alkylidene or arylidene 1,3-dicarbonyl compounds with a β-amino-α,β-unsaturated carbonyl compound to form unsymmetrical 1,4-dihydropyridines[10] and (*b*) condensation of aminocrotonic ester with aldehyde under acidic conditions.[11] The latter modification is a useful process for the synthesis of 3,5-dicyanodihydropyidines.[4f] It should be pointed out that the special synthesis of 2,4,6-trimethylpyridine (collidine) is referred to as Hantzsch collidine synthesis.[12]

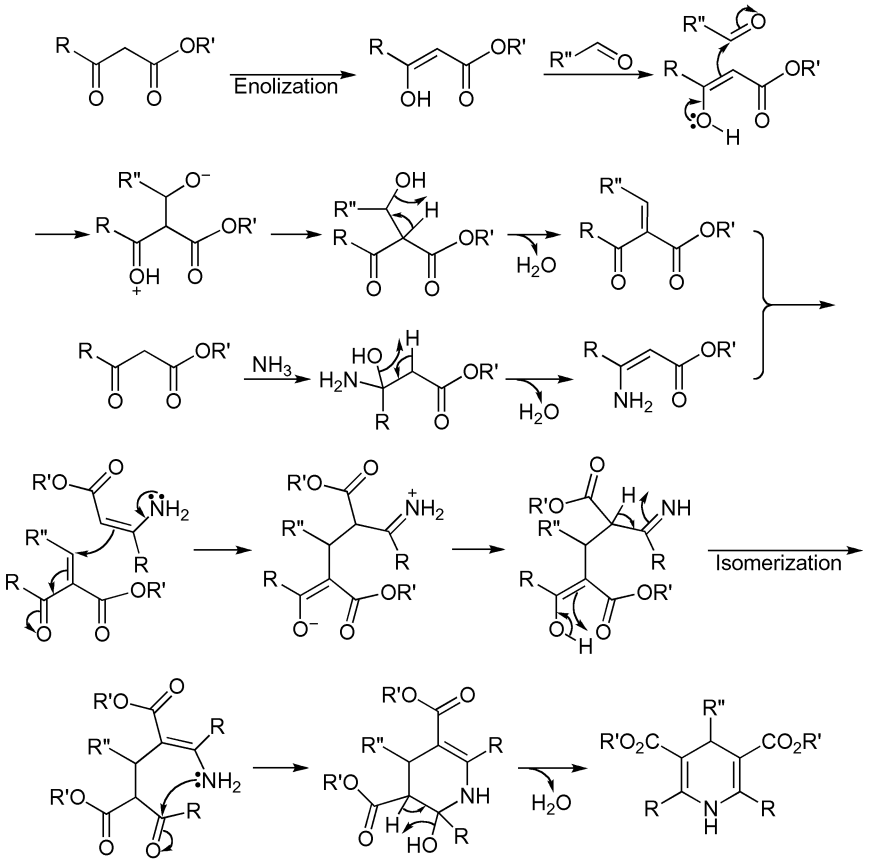
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

This reaction involves the condensation of two important intermediates: the α-alkylidene or α-arylidene β-keto ester condensed from the β-keto ester and aldehyde, and the ester enamine originated from the β-keto ester and amine, as shown below.



D. MODIFICATION

This reaction has been modified to prepare unsymmetrical 1,4-dihydropyridine[10] and 3,5-dicyanodihydropyridine.[4f] In addition, this reaction has been adapted to occur under microwave irradiation.[2b]

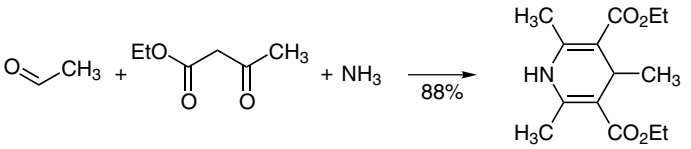
E. APPLICATIONS

This reaction has wide application in the synthesis of substituted 1,4-dihydropyridines and corresponding pyridines.

F. RELATED REACTIONS

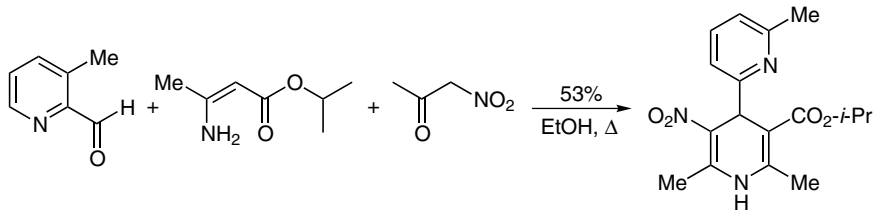
This reaction is related to the *Guareschi-Thorpe Pyridine Synthesis*, *Chichibabin Pyridine Synthesis, Kröhnke Pyridine Synthesis*, and *Petrenko-Kritschenko Piperidone Synthesis.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 9.

The mixture of 26.0 g ethyl acetoacetate (0.2 mol), 4.4 g acetaldehyde (0.1 mol), and 1.7 g ammonia (0.1 mol) in 20 mL ethanol was refluxed for 2 h. The reaction was monitored by TLC. After the completion of the reaction, the mixture was cooled to room temperature; the yellow solid was isolated by filtration and recrystallized from 95% ethanol to give 23.0 g diethyl 2,4,6-trimethyl-1,4-dihydropyridine-3,5-dicarboxylate, in a yield of 88%.



Reference 4c.

A mixture of 1 mmol 3-methyl-2-formyl-pyridine, 1 mmol isopropyl 3-aminocrotonate, and 103 mg nitroacetone (1 mmol) in 5 mL ethanol was stirred at 25°C for 1 h and then refluxed for 16 h. After that, the solvent was removed

in vacuo, and the residue was purified by silica gel column chromatography using EtOAc/hexane (70:30, v/v) to give 53% isopropyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(6-methyl-2-pyridyl)-5-pyridinecarboxylate, m.p. 189–190°C (recrystallized from EtOAc/hexane).

Other references related to the Hantzsch dihydropyridine synthesis are cited in the literature.[13]

H. REFERENCES

1. (a) Hantzsch, A., *Ann.,* **1882**, *215*, 1. (b) Hantzsch, A., *Ann.,* **1882**, *215*, 72.
2. (a) Katritzky, A. R. and Singh, S. K., *ARKIVOC*, **2003**, 68. (b) Öhberg, L. and Westman, J., *Synlett,* **2001**, 1296. (c) Goerlitzer, K.; Heinrici, C. and Ernst, L., *Pharmazie*, **1999**, *54*, 35. (d) Enders, D.; Mueller, S. and Demir, A. S., *Tetrahedron Lett*., **1988**, *29*, 6437. (e) Watanabe, Y.; Shiota, K.; Hoshiko, T. and Ozaki, S., *Synthesis,* **1983**, 761. (f) Kellogg, R. M.; van Bergen, T. J.; van Doren, H.; Hedstrand, D.; Kooi, J.; Kruizinga, W. H. and Troostwijk, C. B., *J. Org. Chem.,* **1980**, *45*, 2854.
3. (a) Poindexter, G. S.; Licause, J. F.; Dolan, P. L.; Foley, M. A. and Combs, C. M., *J. Org. Chem.,* **1993**, *58*, 3811. (b) Baldwin, J. J.; Claremon, D. A.; Lumma, P. K.; McClure, D. E.; Rosenthal, S. A.; Winquist, R. J.; Faison, E. P.; Kaczorowski, G. J.; Trumble, M. J. and Smith, G. M., *J. Med. Chem.,* **1987**, *30*, 690.
4. (a) Nakamichi, N.; Kawashita, Y. and Hayashi, M., *Org. Lett.,* **2002**, *4*, 3955. (b) Ramesh, M.; Matowe, W. C.; Akula, M. R.; Vo, D.; Dagnino, L.; Li-Kwong-Ken, M. C.; Wolowyk, M. W. and Knaus, E. E., *J. Med. Chem.,* **1998**, *41*, 509. (c) Iqbal, N.; Akula, M. R.; Vo, D.; Matowe, W. C.; McEwen, C.-A.; Wolowyk, M. W. and Knaus, E. E., *J. Med. Chem.,* **1998**, *41*, 1827. (d) Espinosa-Mansilla, A.; de la Peña, A. M.; Salinas, F.; Alañón, A. and Murillo, J. A., *J. Agric. Food Chem.,* **1997**, *45*, 172. (e) Yiu, S.-H. and Knaus, E. E., *J. Med. Chem.,* **1996**, *39*, 4576. (f) Love, B.; Goodman, M. M.; Snader, K. M.; Tedeschi, R. and Macko, E., *J. Med. Chem.,* **1974**, *17*, 956. (g) Love, B. and Snader, K. M., *J. Org. Chem.,* **1965**, *30*, 1914.
5. (a) Garden, S. J.; Guimarães, C. R. W.; Corréa, M. B.; de Oliveira, C. A. F.; Pinto, A. C. and de Alencastro, R. B., *J. Org. Chem.,* **2003**, *68*, 8815. (b) Cheng, J.-P.; Lu, Y.; Zhu, X.-Q.; Sun, Y. K.; Bi, F. and He, J. Q., *J. Org. Chem.,* **2000**, *65*, 3853.
6. (a) Mao, Y.-Z.; Jin, M.-Z.; Liu, Z.-L. and Wu, L.-M., *Org. Lett.,* **2000**, *2*, 741. (b) Zhu, X. Q.; Zhao, B.-J. and Cheng, J.-P., *J. Org. Chem.,* **2000**, *65*, 8158. (c) Itoh, T.; Nagata, K.; Matsuya, Y.; Miyazaki, M. and Ohsawa, A., *J. Org. Chem.,* **1997**, *62*, 3582.
7. Bossert, F.; Meyer, H. and Wehinger, E., *Angew. Chem. Int. Ed. Engl.,* **1981**, *20*, 762.
8. (a) Mager, P.; Coburn, R. A.; Solo, A. J.; Triggle, D. J. and Rothe, H., *Drug Design Discovery,* **1992**, *8*, 273. (b) Langs, D. A.; Kwon, Y. W.; Strong, P. D. and Triggle, D. J., *J. Comput.-Aided Mol. Des.,* **1991**, *5*, 95. (c) Langs, D. A. and Triggle, D., *J. Mol. Pharmacol.,* **1985**, *27*, 544.
9. Zhang, D.; Wu, L.-Z.; Zhou, L.; Han, X.; Yang, Q.-Z.; Zhang, L.-P. and Tung, C.-H., *J. Am. Chem. Soc.,* **2004**, *126*, 3440.
10. (a) Visentin, S.; Amiel, P.; Fruttero, R.; Boschi, D.; roussel, C.; Giusta, L.; Barbone, E. and Gasco, A., *J. Med. Chem.,* **1999**, *42*, 1422. (b) Berson, J. A. and Brown, E., *J. Am. Chem. Soc.,* **1955**, *77*, 444. (c) Knoevenagel, E. and Ruschhaupt, W., *Ber.,* **1898**, *31*, 1025. (d) Beyer, C., *Ber.,* **1891**, *24*, 1662.
11. Collie, J. N., *Ann.,* **1884**, *226*, 294.
12. (a) Mann, F. G. and Saunders, B. C., *Practical Organic Chemistry,* Longman, London, **1960**. pp. 295–297. (b) Bergstrom, F. W., *Chem. Rev.,* **1944**, *35*, 77.

13. (a) Litvic, M.; Cepanec, I. and Vinkovic, V., *Heterocycl. Commun.,* **2003**, *9*, 385. (b) Anniyappan, M.; Muralidharan, D. and Perumal, P. T., *Synth. Commun.,* **2002**, *32*, 659. (c) Sambongi, Y.; Nitta, H.; Ichihashi, K.; Futai, M. and Ueda, I., *J. Org. Chem.,* **2002**, *67*, 3499. (d) Zhu, X.-Q.; Wang, H.-Y.; Wang, J.-S. and Liu, Y.-C., *J. Org. Chem.,* **2001**, *66*, 344. (e) Chiu, C. F.; Tang, Z. L. and Ellingboe, J. W., *J. Comb. Chem.,* **1999**, *1*, 73. (f) Iqbal, N.; Vo, D.; McEwen, C.-A.; Wolowyk, M. W. and Knaus, E. E., *Chirality,* **1994**, *6*, 515. (g) Katritzky, A. R.; Ostercamp, D. L. and Yousaf, T. I., *Tetrahedron,* **1987**, *43*, 5171. (h) Katritzky, A. R.; Ostercamp, D. L. and Yousaf, T. I., *Tetrahedron,* **1986**, *42*, 5729. (i) Kuss, L. and Karrer, P., *Helv. Chim. Acta*, **1957**, *40*, 740. (j) Philips, A. P., *J. Am. Chem. Soc.,* **1951**, *73*, 2248. (k) Philips, A. P., *J. Am. Chem. Soc.,* **1949**, *71*, 4003. (l) Knoevenagel, E. and Cremer, W., *Ber.,* **1902**, *35*, 390. (m) Knoevenagel, E. and Fries, A., *Ber.,* **1898**, *31*, 761. (n) Hantzsch, A., *Ber.,* **1886**, *19*, 289. (o) Hantzsch, A., *Ber.,* **1885**, *18*, 1744. (p) Hantzsch, A., *Ber.,* **1884**, *17*, 1515.

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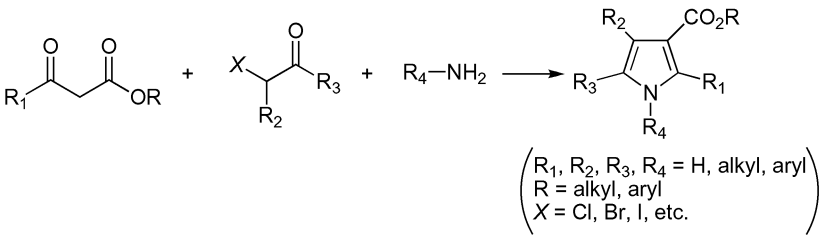
Hantzsch Pyrrole Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Hantzsch in 1890.[1] It is the preparation of 2,5-dialkyl or 2,4,5-trialkylpyrrole derivatives from the condensation of α-halo-ketones, β-ketoesters and ammonia or amines. Therefore, it is often known as the Hantzsch pyrrole synthesis[2] or simply the Hantzsch synthesis.[3] During this synthesis, ammonia or amine reacts quickly with β-keto esters to form enamine esters or 3-amino crotonates that cyclize with α-halo-ketones to form pyrrole derivatives upon heating, and the regioselectivity strongly depends on the substituents on the starting materials.[4] Thus, this reaction can directly start from 3-amino crotonates[1,5] or enamines of β-keto esters.[6] Further extension of this reaction from aromatic amines results in the formation of indole derivatives,[7] or carbazole derivatives if cyclized with α-halo-cyclohexanones.[8] The synthesized pyrroles have wide application in medicinal chemistry,[9] conducting polymers,[10] molecular optics,[11] sensors,[12] etc.

B. GENERAL REACTION SCHEME



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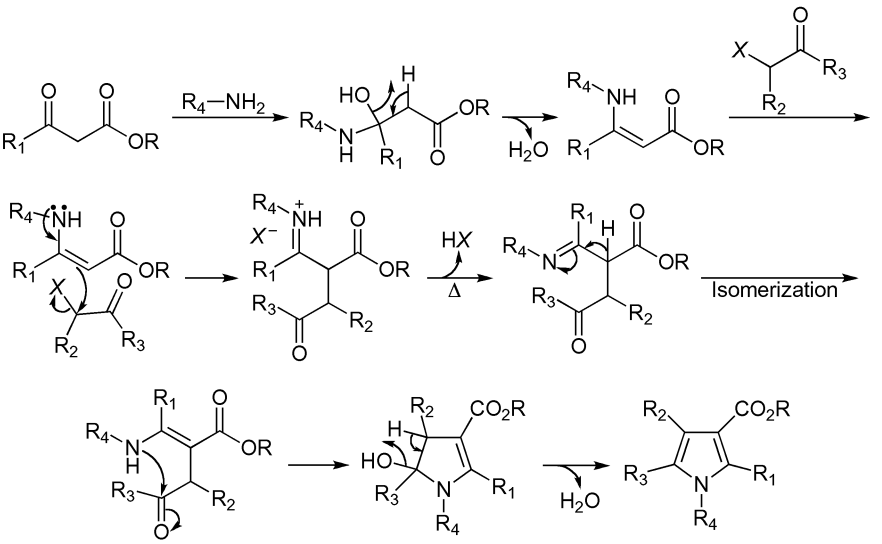
C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified to the direct reaction between enamine of β-keto ester[6] or 3-amino crotonate[1,5] and α-halo-ketones; in addition, this reaction has been extended to prepare indole[7] and carbazole[8] derivatives.

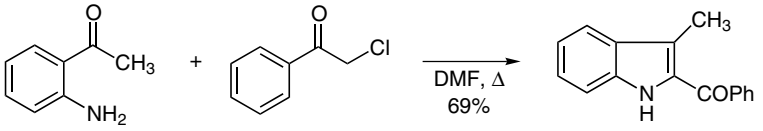
E. APPLICATIONS

This reaction has general applications in the preparation of 2,5-dialkyl- or 2,4,5-trialkyl-substituted pyrrole derivatives.

F. RELATED REACTIONS

This reaction is related to the *Paal-Knorr Pyrrole Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 7g.

The mixture of 2.7 g *o*-amino acetophenone (0.02 mol) and 3.08 g α-chloro-acetophenone (0.02 mol) in 50 mL anhydrous DMF was heated in an oil bath (80–90°C) for 16 h. The reaction mixture was then poured over 1500 mL ice water, and the crystalline 2-benzoyl-3-methyl-indole was isolated by filtration and was further purified by recrystallization from methanol, giving 69% yield, m.p., 138–139°C.

Other references related to the Hantzsch pyrrole synthesis are cited in the literature.[13]

H. REFERENCES

1. Hantzsch, A., *Ber.,* **1890**, *23*, 1474.
2. (a) Tracey, M. R.; Hsung, R. P. and Lambeth, R. H., *Synthesis,* **2004**, 918. (b) Erian, A. W.; Sherif, S. M. and Gaber, H. M., *Molecules,* **2003**, *8*, 793. (c) Trautwein, A. W.; Süßmuth, R. D. and Jung, G., *Bioorg. Med. Chem. Lett.,* **1998**, *8*, 2381. (d) Roomi, M. W. and MacDonald, S. F., *Can. J. Chem.,* **1970**, *48*, 1689.
3. (a) Matiychuk, V. S.; Martyak, R. L.; Obushak, N. D.; Ostapiuk, Yu. V. and Pidlypnyi, N. I., *Chem. Heterocycl. Compd.,* **2004**, *40*, 1218. (b) Periasamy, M.; Srinivas, G. and Bharathi, P., *J. Org. Chem.,* **1999**, *64*, 4204. (c) Kameswaran, V., *Special Pub.–Royal Soc. Chem.,* **1994**, *147*, 141. (d) Baltazzi, E. and Krimen, L. I., *Chem. Rev.,* **1963**, *63*, 511.
4. Henze, H. R. and Shown, J. H., *J. Am. Chem. Soc.,* **1947**, *69*, 1662.
5. Van Beelen, D. C.; Wolters, J. and van der Gen, A., *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 437.
6. Carpio, H.; Galeazzi, E.; Greenhouse, R.; Guzman, A.; Velarde, E.; Antonio, Y.; Franco, F.; Leon, A.; Pérez, V.; Salas, R.; Valdés, D.; Ackrell, J.; Cho, D.; Gallergra, P.; Halpern, O.; Koehler, R.; Maddox, M. L.; Muchowski, J. M.; Prince, A.; Tegg, D.; Thurber, T. C.; van Horn, A. R. and Wren, D., *Can. J. Chem.* **1982**, *60*, 2296.
7. (a) Zav'yalov, S. I.; Zavozin, A. G.; Dorofeeva, O. V. and Rumyantseva, E. E., *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1991**, 509 [*Chem. Abstr.* **1991**, *115*, 8493]. (b) Basanagoudar, L. D.; Mahajanshetti, C. S. and Dambal, S. B., *Ind. J. Chem.* **1991**, *30B*, 1018. (c) Sanchez-Yiesca, F. and Gomez, R., *Rev. Latioam. Quim.,* **1984**, *14*, 106 [*Chem. Abstr.* **1984**, *101*, 38297]. (d) Goerlitzer, K. and Engler, E., *Arch. Pharm.,* **1980**, *313*, 405. (e) Fujiwara, R.; Nitta, K. and Susumu, I., *Japan Kokai,* **1975**, 75 58,059 [*Chem. Abstr.* **1975**, *83*, 193076]. (f) Walter, L. A., *U.S. Pat.*, **1973**, Feb 20, 717,644 [*Chem. Abstr.* **1973**, *78*, 136092]. (g) Jones, C. D. and Suárez, T., *J. Org. Chem.,* **1972**, *37*, 3622.
8. (a) Vice, S. F.; Frisen, R. W. and Dmitrienko, G. I., *Tetrahedron Lett.,* **1985**, *26*, 165. (b) Wender, P. A. and White, A. W., *Tetrahedron,* **1983**, *39*, 3767. (c) Kuroki, M. and Tsunashima, Y., *J. Heterocycl. Chem.,* **1981**, *18*, 709.
9. Sun, L.; Liang, C.; Shirazian, S.; Zhou, Y.; Miller, T.; Cui, J.; Fukuda, J. Y.; Chu, J.-Y.; Nematalla, A.; Wang, X.; Chen, H.; Sistla, A.; Luu, T. C.; Tang, F.; Wei, J. and Tang, C., *J. Med. Chem.,* **2003**, *46*, 1116.
10. (a) Shenoy, S. L.; Cohen, D.; Erkey, C. and Weiss, R. A., *Ind. Eng. Chem. Res.,* **2002**, *41*, 1484. (b) Reynolds, J. R.; Katritzky, A. R.; Soloducho, J.; Belyakov, S.; Sotzing, G. A. and Pyo, M., *Macromolecules,* **1994**, *27*, 7225. (c) Kanatzidis, M. G.; Tonge, L. M.; Marks, T. J.; Marcy, H. O. and Kannewurf, C. R., *J. Am. Chem. Soc.,* **1987**, *109*, 3797.
11. (a) Behnke, M. and Tieke, B. *Langmuir,* **2002**, *18*, 3815. (b) Brockmann, T. W. and Tour, J. M., *J. Am. Chem. Soc.,* **1995**, *117*, 4437.
12. (a) Sessler, J. L.; Anzenbacher, P. Jr.; Miyaji, H.; Jursikova, K.; Bleasdale, E. R. and Gale, P. A., *Ind. Eng. Chem. Res.,* **2000**, *39*, 3471. (b) Panusa, A.; Flamini, A. and Poli, N., *Chem. Mater.,* **1996**, *8*, 1202.

13. (a) Balme, G., *Angew. Chem. Int. Ed.,* **2004**, *43*, 6238. (b) Palacios, F.; Aparicio, D.; de los Santos, J. M. and Vicario, J., *Tetrahedron,* **2001**, *57*, 1961. (c) Zhang, P.-F. and Chen, Z.-C., *Synth. Commun.,* **2001**, *31*, 1619. (d) Ong, C. W.; Chen, C. M.; Wang, L. H.; Jan, J. J. and Shieh, P. C., *J. Org. Chem.,* **1998,** *63*, 9131. (e) Eicher, T. and Hauptmann, S., *Chemie der Heterocyclen.*, Thieme Verlag, Stuttgart, **1994**, p. 94. (f) Bean, G. P. "The Synthesis of ^{1}H-pyrroles", in *The Chemistry of Heterocyclic Compounds*, ed. Jones, A. R., John Wiley & Sons, New York, **1990**, *48*, pt.1, ch. 2, p. 105. (g) Kirschke, K.; Costisella, B.; Ramm, M. and Schulz, B., *J. Prakt. Chem.,* **1990**, *332*, 143. (h) Agosta, W. C., *J. Org. Chem.,* **1961**, *26*, 1724. (i) Huntress, E. H.; Lesslie, T. E. and Hearon, W. M., *J. Am. Chem. Soc.,* **1956**, *78*, 419. (j) Karschum, G., *Ber.,* **1904**, *37*, 2183. (k) Karschum, G., *Ber.,* **1904**, *37*, 2196. (l) Feist, F., *Ber.,* **1902**, *35*, 1538.

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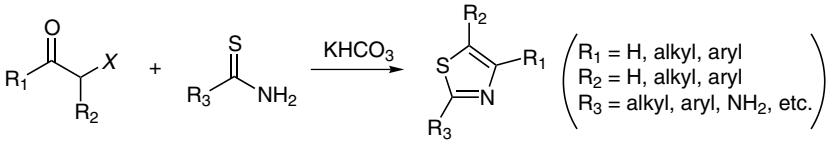
Hantzsch Thiazole Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

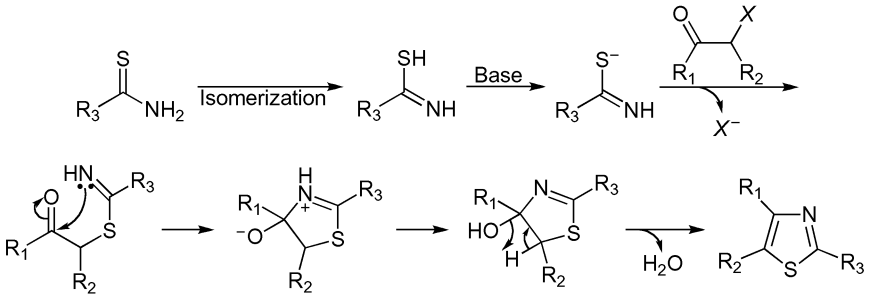
This reaction was first reported by Hantzsch and Weber in 1887.[1] It is the formation of thiazole derivatives by means of condensation of α-haloketones (or aldehydes) and thioamides. Therefore, it is generally known as the Hantzsch thiazole synthesis.[2] In addition, other names, including the Hantzsch synthesis,[2k,3] Hantzsch reaction,[2m,3a,4] and Hantzsch thiazole reaction[5] are also used from time to time. Besides thioamides, other thio-ketone derivatives such as thiourea,[3b,4a,6] dithiocarbamates,[2k] and ketone thiosemicarbazone[2k] can also condense with α-halo ketones (or aldehydes) to form thiazoles. This reaction occurs because of the strong nucleophilicity of the sulfur atom in thioamides or thioureas,[6] and normally gives excellent yields for simple thiazoles but low yields for some substituted thiazoles, as of dehalogenation.[7] This reaction has been proven to be a multistep reaction, and the intermediates have been isolated at low temperatures,[3c] in which the dehydration of cyclic intermediates seems to be the slow step.[2k] It is found that a variety of reaction conditions might result in the racemized thiazoles that contain an enolizable proton at their chiral center, and it is the intermediate not the final product that is involved in the racemization.[2k] Therefore, some modifications have been made to reduce or even eliminate the epimerization upon thiazole formation.[8] In addition, this reaction has been modified using α-tosyloxy ketones to replace α-haloketones.[9]

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified to reduce the epimerization upon the formation of thiazole.[8] In addition, α-tosyloxy ketones have been used to replace α-haloketones for such reactions.[9]

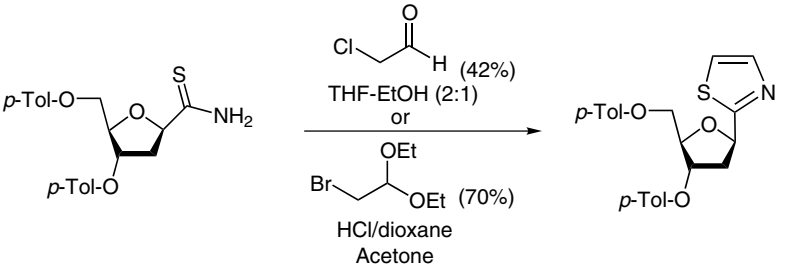
E. APPLICATIONS

This reaction, the classic method for thiazoles, has wide application in the preparation of thiazole derivatives.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



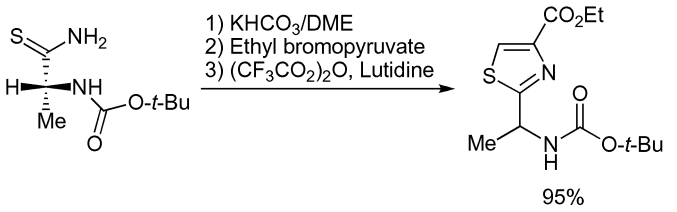
Reference 10.

Method A

2,5-Anhydro-3-deoxy-4,6-di-*O*-*p*-toluoyl-D-*ribo*-hexonthioamide (1.16 g, 3.0 mmol) was dissolved in a mixture of 33 mL THF and 16 mL EtOH. Then 50% chloroacetaldehyde solution (3.18 mL, 25 mmol) was added, and the reaction mixture was refluxed for 24 h. Another equivalent of chloroacetaldehyde solution (3.18 mL, 25 mmol) was added, and the reaction mixture was refluxed for another 24 h. The solvents were evaporated, and the residue was dissolved in EtOAc, washed with saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. Silica gel column chromotography (EtOAc/hexanes) yielded 42% 2-(2′-deoxy-3′,5′-di-*O*-*p*-toluoyl-β-D-ribofuranosyl)thiazole as a light yellow solid.

Method B

2,5-Anhydro-3-deoxy-4,6-di-*O*-*p*-toluoyl-D-*ribo*-hexonthioamide (0.50 g, 1.21 mmol) was dissolved in 7.1 mL dry acetone and 0.9 mL bromoacetaldehyde diethyl acetal (0.69 g, 3.5 mmol); then 13 mL of a 4 M HCl/dioxane solution was added. The resulting clear solution was refluxed under argon for 24 h. The brown-colored solution was evaporated to a dark oil, then dissolved in 100 mL EtOAc and washed with 100 mL saturated aqueous $NaHCO_3$ and 100 mL brine. The organic layer was dried over Na_2SO_4, filtered, and evaporated to a dark brown liquid. Purification by silica gel chromatography (EtOAc/hexanes) provided 0.370 g 2-(2′-deoxy-3′,5′-di-*O*-*p*-toluoyl-β-D-ribofuranosyl)thiazole as a light brown gum, in a yield of 70%. Crystallization from ethanol converted the compound as a solid.



Reference 4b.

A solution of Boc-D-alanine thioamide (1.17 g, 5.74 mmol) in 35 mL DME was cooled to −13°C, followed by the addition of 4.97 g $KHCO_3$ (49.7 mmol) under a nitrogen atmosphere. The suspension was vigorously stirred for 15 min, followed by the addition of 2.4 mL ethyl bromopyruvate (19.1 mmol) under the inert atmosphere at −13°C. The reaction mixture was further incubated at −13°C for 0.5 h, and then at room temperature for 0.5 h. After the reactants were cooled to −13°C again, a solution of 3.6 mL trifluoroacetic anhydride (25.5 mmol) and 6.2 mL lutidine (53.2 mmol) in 10 mL DME was added dropwise. The reaction mixture was allowed to warm from 0°C to room temperature and incubated for 12 h. After removal of the volatile components in vacuo and the addition of 100 mL water, the solution was extracted with $CHCl_3$ (3 × 50 mL). The $CHCl_3$ phase was dried over Na_2SO_4, and after the removal of the solvent, the residue was chromatographed on a silica gel column ($CHCl_3$/EtOAc, 2:1) to afford 1.64 g ethyl (*R*)-2-(1-*N*-Boc-amino)ethylthiazole-4-carboxylate as a yellow semisolid, in a yield of 95%, $R_f = 0.53$ ($CHCl_3$/EtOAc, 2:1).

Other references related to the Hantzsch thiazole synthesis are cited in the literature.[11]

H. REFERENCES

1. Hantzsch, A. and Weber, J. H., *Ber.,* **1887**, *20*, 3118.
2. (a) Bagley, M. C.; Dale, J. W.; Jenkins, R. L. and Bower, J., *Chem. Commun.,* **2004**, 102. (b) Lagoja, I. M.; Nauwelaerts, K.; Balmahieu, C.; Pasqualini, M.; Bailly, C. and Herdewijn, P., *Coll. Czech. Chem. Commun.,* **2004**, *69*, 1491. (c) Kumar, P. V.; Reddy, R. V. and Rao, V. R., *Indian J. Chem., Sect. B,* **2003**, *42B*, 1738. (d) Qiao, Q.; So, S. S. and Goodnow, R. A., *Org. Lett.,* **2001**, *3*, 3655. (e) Wipf, P. and Venkatraman, S., *J. Org. Chem.,* **1996**, *61*, 8004. (f) Katritzky, A. R.; Chen, J. and Yang, Z. J., *J. Org. Chem.,* **1995**, *60*, 5638. (g) Aguilar, E. and Meyers, A. I., *Tetrahedron Lett.*, **1994**, *35*, 2473. (h) Singh, S. P.; Sehgal, S. and Sharma, P. K., *Indian J. Chem., Sect. B,* **1990**, *29B*, 533. (i) Singh, S. P.; Sehgal, S.; Singh, L. and Dhawan, S. N., *Indian J. Chem., Sect. B,* **1987**, *26B*, 154. (j) Bramley, S. E.; Dupplin, V.; Goberdhan, D. G. C. and Meakins, G. D., *J. Chem. Soc., Perkin Trans. I,* **1987**, 639. (k) Holzapfel, C. W. and Pettit, G. R., *J. Org. Chem.,* **1985**, *50*, 2323. (l) Arakawa, K.; Miyasaka, T. and Ohtsuka, H., *Chem. Pharm. Bull.,* **1972**, *20*, 1041. (m) Egan, R. S.; Tadanier, J.; Garmaise, D. L. and Gaunce, A. P., *J. Org. Chem.,* **1968**, *33*, 4422. (n) Beyer, H. and Lassig, W., *Ber.,* **1951**, *84*, 463.
3. (a) Bagley, M. C.; Bashford, K. E.; Hesketh, C. L. and Moody, C. J., *J. Am. Chem. Soc.,* **2000**, *122*, 3301. (b) Eriks, J. C.; van der Goot, H.; Stark, G. J. and Timmerman, H., *J. Med. Chem.,* **1992**, *35*, 3239.
4. (a) Ochiai, M.; Nishi, Y.; Hashimoto, S.; Tsuchimoto, Y. and Chen, D.-W., *J. Org. Chem.,* **2003**, *68*, 7887. (b) Xia, Z. P. and Smith, C. D., *J. Org. Chem.,* **2001**, *66*, 3459. (c) Sowinski, J. A. and Toogood, P. L., *J. Org. Chem.,* **1996**, *61*, 7671.
5. (a) Babadjamian, A.; Gallo, R.; Metzger, J. and Chanon, M., *J. Heterocycl. Chem.,* **1976**, *13*, 1205. (b) Babadjamian, A.; Metzger, J. and Chanon, M., *J. Heterocycl. Chem.,* **1975**, *12*, 643.
6. Galvani, M.; Rovatti, L.; Hamdan, M.; Herbert, B. and Righetti, P. G., *Electrophoresis,* **2001**, *22*, 2066.
7. Hodgetts, K. J. and Kershaw, M. T., *Org. Lett.,* **2002**, *4*, 1363.
8. Bredenkamp, M. W.; Holzapfel, C. W. and van Zyl, W. J., *Synth. Comm.,* **1990**, *20*, 2235.
9. (a) Prakash, O.; Saini, N. and Sharma, P. K., *Synlett,* **1994**, 221. (b) Moriarty, R. M.; Vaid, B. K.; Duncan, M. P.; Levy, S. G.; Prakash, O. and Goyal, S., *Synthesis,* **1992**, 845. (c) Prakash, O.; Rani, N. and Goyal, S., *J. Chem. Soc., Perkin Trans. I,* **1992**, 707.
10. Miller, T. J.; Farquar, H. D.; Sheybani, A.; Tallini, C. E.; Saurage, A. S.; Fronczek, F. R. and Hammer, R. P., *Org. Lett.,* **2002**, *4*, 877.
11. (a) Kumar, A.; Prakash, R. and Singh, S. P., *Synth. Commun.,* **2005**, *35*, 461. (b) Mustafa, S. M.; Nair, V. A.; Chittoor, J. P. and Krishnapillai, S., *Mini-Rev. Org. Chem.,* **2004**, *1*, 375. (c) Arcadi, A.; Attanasi, O. A.; Filippone, P.; Perrulli, F. R.; Rossi, E. and Santeusanio, S., *Synlett,* **2004**, 2681. (d) Ikemoto, N.; Liu, J.; Brands, K. M. J.; McNamara, J. M. and Reider, P. J., *Tetrahedron,* **2003**, *59*, 1317. (e) You, S.-L. and Kelly, J. W., *J. Org. Chem.,* **2003**, *68*, 9506. (f) Pattenden, G. and Thompson, T., *Chem. Commun.*, **2001**, 717. (g) Maehr, H. and Yang, R., *Bioorg. Med. Chem.* **1997**, *5*, 493. (h) Badorc, A.; Bordes, M.-F.; de Cointet, P.; Savi, P.; Bernat, A.; Lalé, A.; Petitou, M.; Maffrand, J.-P. and Herbert, J.-M., *J. Med. Chem.,* **1997**, *40*, 3393. (i) Williams, D. R.; Brooks, D. A.; Moore, J. L. and Stewart, A. O., *Tetrahedron Lett*., **1996**, *37*, 983. (j) Prakash, O.; Saini, S.; Saini, N.; Prakash, I. and Singh, S. P., *Indian J. Chem., Sect. B,* **1995**, *34B*, 660. (k) Shin, C.; Okumura, K.; Ito, A. and Nakamura, Y., *Chem. Lett.* **1994**, 1301. (l) Pattenden, G. and Thom, S. M., *J. Chem. Soc., Perkin Trans. I,* **1993**, 1629. (m) Martin, B. J.; Clough, J. M.; Pattenden, G. and Waldron, I. R., *Tetrahedron Lett.,* **1993**, *34*, 5151. (n) Hamada, Y.; Hayashi, K. and Shioiri, T., *Tetrahedron Lett.,* **1991**, *32*, 931. (o) Singh, S. P. and Sehgal, S., *Indian J. Chem., Sect. B,* **1988**, *27B*, 941. (p) Schmidt, U.; Utz, R.; Lieberknecht, A.; Griesser, H.; Potzolli, B.; Bahr, J.; Wagner, K. and Fischer, P., *Synthesis,* **1987**, 233. (q) Kelly, R. C.; Gebhard, I. and Wicnienski, N., *J. Org. Chem.,* **1986**, *51*, 4590. (r) Metzger, J. V., Thiazoles and Their Benzo Derivatives, in

Comprehensive Heterocyclic Chemistry, ed., Potts, K. T., Pergamon Press, New York, **1984**, *6*, pp. 235–331. (s) Vernin, G., "General Synthetic Methods for Thiazole and Thiazolium Salts", in *Heterocyclic Compounds: Thiazole and Its Derivatives,* ed. Metzger, J. V., John Wiley & Sons, New York, 1979, pp. 165–335. (t) Choudhari, S. R.; Goswami, D. D. and Thakar, K. A., *J. Indian Chem. Soc.,* **1978**, *55*, 48. (u) Joshua, C. P. and Nambisan, P. N. K., *Ind. J. Chem.,* **1973**, *11*, 118. (v) Sherman, W. R. and Dickson, D. E., *J. Org. Chem.,* **1962**, *27*, 1351. (w) Wetherill, J. P. and Hann, R. M., *J. Am. Chem. Soc.,* **1934**, *56*, 970. (x) Johnson, T. B. and Gatewood, E., *J. Am. Chem. Soc.,* **1929**, *51*, 1815. (y) Hantzsch, A., *Ann.,* **1889**, *250*, 269. (z) Hantzsch, A., *Ann.,* **1889**, *250*, 257. (aa) Hantzsch, A., *Ann.,* **1888**, *249*, 1.

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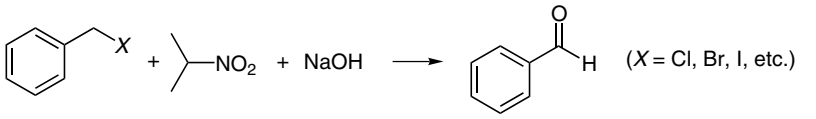
Hass-Bender Oxidation

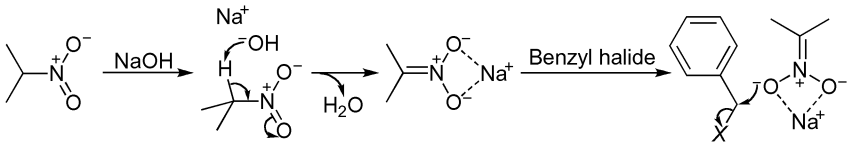
A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Hass and Bender in 1949.[1] It is the synthesis of aromatic aldehydes by treatment of substituted benzyl halides with sodium nitropropane salt (also called sodium propane-nitronate[2]). Therefore, this reaction is called the Hass-Bender reaction[3] or Hass-Bender oxidation.[4] This reaction also takes place on aromatic polycyclic compounds.[5]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



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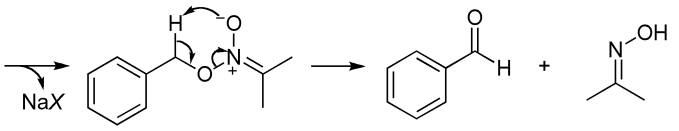


D. MODIFICATION

N/A

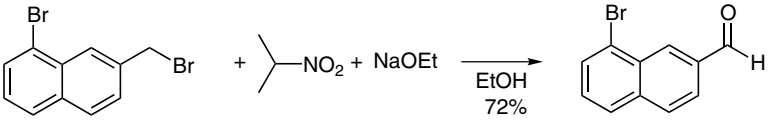
E. APPLICATIONS

This reaction is useful for the conversion of the α-halomethylene group on an aromatic nucleus into a formyl group (i.e., in the synthesis of aromatic aldehydes.)

F. RELATED REACTIONS

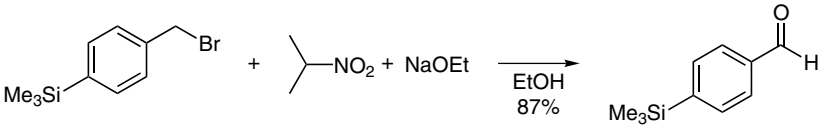
This reaction is related to *Sommelet Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4.

2-Nitropropane (350 μL, 3.9 mmol) was added to a solution of NaOEt (3.8 mmol) in 8 mL EtOH. A colorless precipitate was formed immediately. Then 1.13 g 1-bromo-7-bromomethylnaphthalene (3.8 mmol) was added to the mixture and stirred for 65 h at room temperature. The reaction mixture was filtered, and the liquid was concentrated on an evaporator. To the residue were added 100 mL Et_2O and 15 mL water. The organic phase was washed with 10% aqueous NaOH solution (2 $\times$ 10 mL) and 10 mL water, dried and evaporated. Column chromatography of the residue gave 640 mg 8-bromonaphthalene-2-carbaldehyde as colorless crystal, in a yield of 72%, m.p. 83–84°C.



Reference 3b.

Under a nitrogen atmosphere, 2.3 g sodium (0.1 mol) was dissolved in 100 mL absolute ethanol. After the sodium had dissolved, 11.6 g 2-nitropropane (0.13 mol) was added followed by 24.3 g *p*-trimethylsilylbenzyl bromide (0.1 mol). After thorough mixing, the reaction mixture was allowed to stand at room temperature under a nitrogen atmosphere for 15 h. The precipitated sodium bromide was removed by filtration, and the filtrate was concentrated by evaporation (*Note*: The original procedure was to remove the ethanol at atmospheric pressure). During this process, additional sodium bromide precipitated. The residue was mixed with ether and the water. The ethereal solution was washed with 10% sodium hydroxide, followed by water, and was then dried over Drierite. The ether was removed by distillation, and the residue was fractionally distilled through a small Vigreux column, giving 13.87 g *p*-trimethylsilylbenzaldehyde, in a yield of 87%, b.p. 118–119°C (16 mmHg).

Other references related to the Hass-Bender oxidation are cited in the literature.[6]

H. REFERENCES

1. Hass, H. B. and Bender, M. L., *J. Am. Chem. Soc.,* **1949**, *71*, 1767.
2. Blomquist, A. T.; Stahl, R. E.; Meinwald, Y. C. and Smith, B. H., *J. Org. Chem.,* **1961**, *26*, 1687.
3. (a) Klein, T. A. and Schkeryantz, J. M., *Tetrahedron Lett*., **2005**, *46*, 4535. (b) Severson, R. G.; Rosscup, R. J.; Lindberg, D. R. and Engberg, R. D., *J. Am. Chem. Soc.,* **1957**, *79*, 6540.
4. Frølund, B.; Jensen, L. S.; Guandalini, L.; Canillo, C.; Vestergaard, H. T.; Kristiansen, U.; Nielsen, B.; Stensbøl, T. B.; Madsen, C.; Krogsgaard-Larsen, P. and Liljefors, T., *J. Med. Chem.,* **2005**, *48*, 427.
5. (a) Klanderman, B. H., *J. Org. Chem.*, **1966**, *31*, 2618. (b) Blomquist, A. T.; Stahl, R. E.; Meinwald, Y. C. and Smith, B. H., *J. Org. Chem.*, **1961**, *26*, 1687.
6. (a) Williams, R. H. and Snyder, H. R., *J. Org. Chem.,* **1973**, *38*, 809. (b) Kornblum, N. and Brown, R. A., *J. Am. Chem. Soc.,* **1964**, *86*, 2681. (c) Hass, H. B. and Bender, M. L., *J. Am. Chem. Soc.,* **1949**, *71*, 3482.

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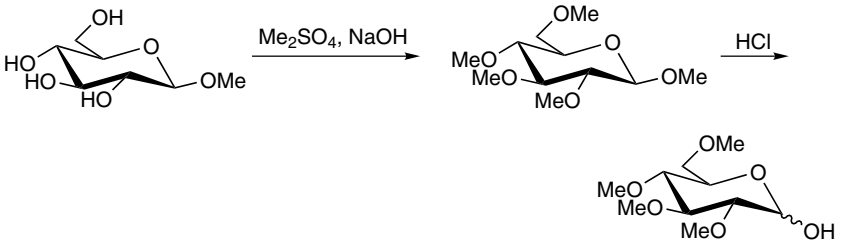
Haworth Methylation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Denham and Woodhouse in 1913,[1a] and extended by Haworth in 1915.[1b–1d] It is the preparation of the methylated methyl glycoside from methyl glycosides with dimethyl sulfate and 30% sodium hydroxide. The glycosidic methyl group of the methylated glycosides can be removed via hydrolysis in hydrochloric acid. This reaction is very useful at earlier stages of carbohydrate chemistry to elucidate the sugar structures, including the linkages between monosaccharide units in disaccharides or oligosaccharides and the ring structures. This reaction was optimized by West and Holden by means of the treatment of concentrated sugar or a methyl glycosides solution and carbon tetrachloride solution of methyl sulfate with 60% sodium hydroxide for 8–10 h. Then the crude or isolated methylated glycosides were hydrolyzed with 2 N HCl through steam distillation to give pure crystalline tetramethyl-monosaccharides.[2]

B. GENERAL REACTION SCHEME



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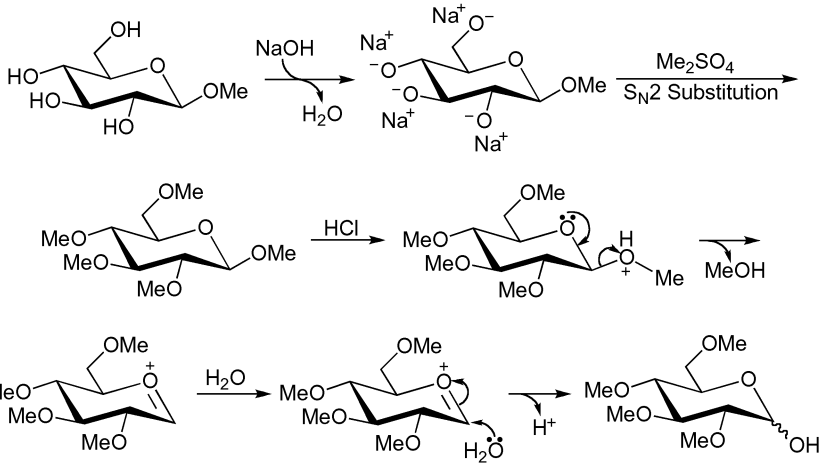
C. PROPOSED MECHANISMS

Under these conditions, the sodium hydroxide is strong enough to deprotonate the hydroxyl groups on glycosides. It should be pointed out that such deprotonation should be stepwise; however, only one step of deprotonation is provided here to illustrate the methylation process.



D. MODIFICATION

This reaction has been modified by West and Holden by means of the treatment of glycosides with carbon tetrachloride solution of methyl sulfate and 60% sodium hydroxide.[2]

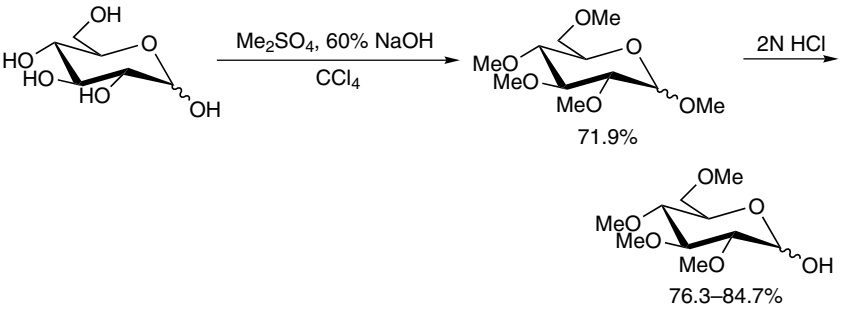
E. APPLICATIONS

This reaction has wide application at earlier stages of carbohydrate chemistry, for the sake of structural analysis of carbohydrates.

F. RELATED REACTIONS

This reaction is related to *Irvine-Purdie Methylation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2.

Glucose (25 g) and 15 mL water were placed in a methylating flask in a water bath at 55°C under rapid stirring, which was maintained throughout the reaction. Then 90 mL methyl sulfate in 125 mL carbon tetrachloride was added quickly through the dropping tube, followed by the addition of 400 mL 60% NaOH at the rate of 1 drop in 2 seconds for 5 min, then 1 drop for 5 min, and then 3 drops until the distillation of carbon tetrachloride slackened or ceased, which was usually accomplished in 20 min, and after the addition of 70–90 mL NaOH solution. The heat of reaction generally maintained the proper temperature of 50–55°C throughout this stage, and it was not necessary to heat the bath externally. The remainder of the alkali was added to the flask as quickly as possible, and the bath temperature was raised rapidly to and maintained at 70–75°C. Then 160 mL methyl sulfate was placed in the reservoir and added at 3–4 drops/second (slower if the mixture foamed seriously). After the addition of all the methyl sulfate, the bath was heated to boil for 30 min (stirring continued), after which the contents of the flask were cooled, diluted with sufficient water to dissolve most of the separated sodium sulfate, and extracted with chloroform (4 × 150 mL). The combined chloroform extracts were dried with sodium sulfate and filtered; the chloroform was distilled off. The syrup distilled at 88–90°C at 0.15 mmHg to give 25 g α,β-tetramethylmethylglucose, in a yield of 71.9%

The undried, filtered chloroform solution of α,β-tetramethylmethylglucoside (or the isolated syrup) obtained in the direct methylation of glucose was placed in a 2–3 L distilling flask with 400 mL 2 N hydrochloric acid, and the chloroform was distilled off. A vigorous current of steam was then passed through the solution for 1 h, care being taken to maintain the volume of solution approximately constant by heating the flask. Norit (5 g) was added to the hot solution, which was then cooled and filtered. The filtrate was saturated with sodium sulfate and extracted with $CHCl_3$ (4 × 150 mL). The combined chloroform extracts were dried with sodium sulfate; 1 g Norit was added and filtered. Chloroform was distilled off as much as possible without vacuum and then in a boiling water bath at the water pump. The syrup was treated with 40–50 mL petroleum ether (30–60°C) and shaken for a short time, whereupon it set to a mass of crystals. After cooling in an ice bath for 30 min, the crystals were filtered off, washed with a little cold petroleum ether, and dried over calcium chloride in a vacuum, yielding 18–20 g tetramethylglucose, in a yield of 76.3% to 84.7%.

Other references related to the Haworth methylation are cited in the literature.[3]

H. REFERENCES

1. (a) Denham, W. S. and Woodhouse, H., *J. Chem. Soc.,* **1913**, *103*, 1735. (b) Haworth, W. N., *J. Chem. Soc.,* **1915**, *107*, 8. (c) Haworth, W. N., *J. Chem. Soc.,* **1915**, *107*, 11. (d) Haworth, W. N., *J. Chem. Soc.,* **1915**, *107*, 13.
2. West, E. S. and Holden, R. F., *J. Am. Chem. Soc.,* **1934**, *56*, 930.
3. (a) Klok, J.; Cox, H. C.; De Leeuw, J. W. and Schenck, P. A., *J. Chromatography,* **1982**, *253*, 55. (b) Hall, D. M. and Stamm, O. A., *Carbohydr. Res.,* **1970**, *12*, 421. (c) Bourne, E. J. and Peat, S., *Adv. Carbohydr. Chem.,* **1950**, *5*, 146. (d) Barker, C. C.; Hirst, E. L. and Jones, J. K. N., *J. Chem. Soc.,* **1946**, 783. (e) Evans, T. H.; Levi, I.; Hawkins, W. L. and Hibbert, H., *Can. J. Res.,* **1942**, *20B*, 175. (f) Pacsu, E. and Trister, S. M., *J. Am. Chem. Soc.,* **1939**, *61*, 2442. (g) Hendricks, B. C. and Rundle, R. E., *J. Am. Chem. Soc.,* **1938**, *60*, 2563. (h) Muskat, I. E., *J. Am. Chem. Soc.,* **1934**, *56*, 693. (i) Haworth, W. N. and Machemer, H., *J. Chem. Soc.,* **1932**, 2270. (j) Whitnah, C. H., *J. Am. Chem. Soc.,* **1929**, *51*, 3490. (k) Haworth, W. N., *J. Chem. Soc.,* **1918**, *113*, 188.

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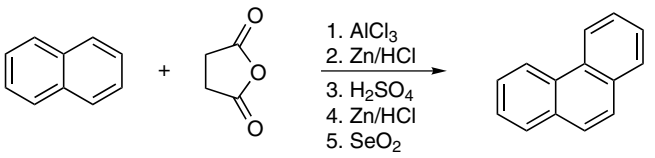
Haworth Synthesis
(Haworth Phenanthrene Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

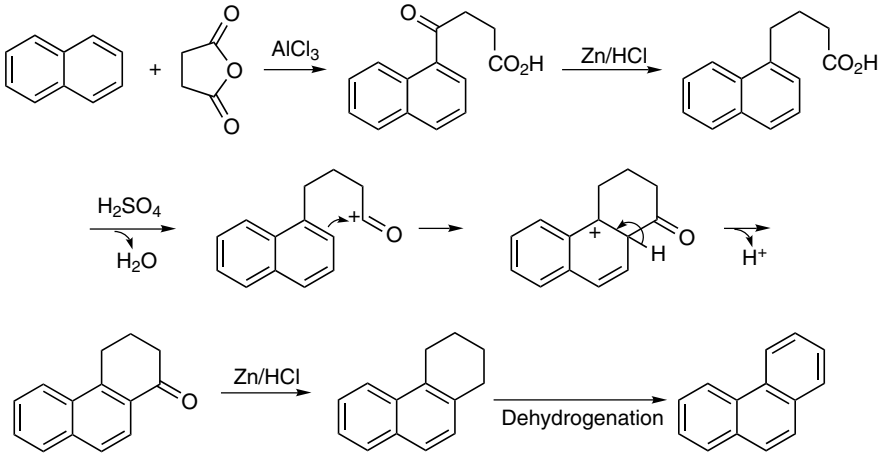
This reaction was first reported by Haworth in 1932.[1] It is a multistep preparation of phenanthrenes from naphthalenes by means of the *Friedel-Crafts Acylation* with succinic anhydride, followed by a *Clemmensen Reduction* or *Wolff-Kishner Reduction*, cyclization, reduction, and dehydrogenation. Therefore, it is generally known as the Haworth synthesis.[2] Occasionally, it is also referred to as the Haworth phenanthrene synthesis.[3] In addition, the same procedure used for the preparation of naphthalenes[2b,4] from benzenes is called the Haworth reaction.[4a] It is known that naphthalene also reacts with mono or symmetrical dialkyl derivatives of succinic anhydride.[3] Substituted naphthalenes often give only one naphthoylpropionic acid derivative, as of the directive effect of the substituent.[3] The cyclization is often executed by the direct reaction of naphthalene-butyric acid with sulfuric acid,[4b,5] HF,[6] or polyphosphoric acid (PPA)[2b] or by intramolecular *Friedel-Crafts Acylation* from the corresponding acyl chloride. The dehydrogenation reagents used include 2,3-dichloro-5,6-dicyano-benzoquinone (DDQ),[4a] 3,4,5,6-tetrachloro-1,2-benzoquinone (TCQ),[2b] triphenylmethanol (TPM),[2b] sulfur,[2b] and SeO_2.[7] This reaction has been modified by alkylation with 4-pentenoic acid ester in the presence of HCl, from which the phenanthrenes with alkyl substituents can be synthesized directly.[8] In addition, the first step of the *Friedel-Crafts Acylation* with succinic anhydride has been substituted by the *Grignard Reaction* between succinic anhydride and the naphthalene Grignard reagent.[6] This reaction has been used for the synthesis of optically active polysubstituted naphthalene derivatives[2b] and the isotopic-labeled naphthalene and phenanthrene derivatives.[4a]

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified to react with 4-pentenoic acid ester to form alkyl-substituted phenanthrenes directly.[8] In addition, the first step of acylation has alternatively been carried out by the reaction of succinic anhydride with an aryl Grignard reagent.[6]

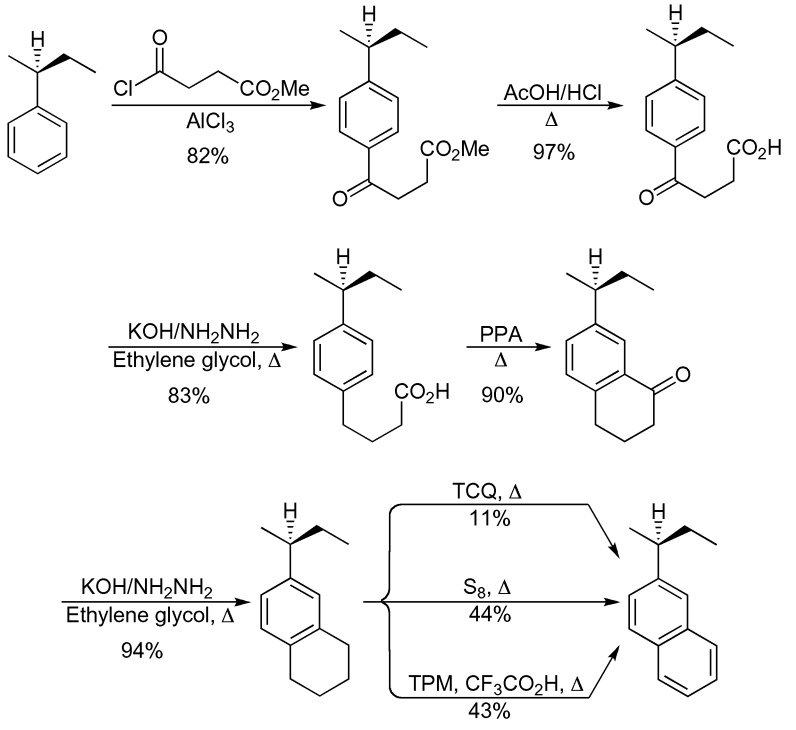
E. APPLICATIONS

This reaction has general application in the preparation of fused aromatics, including naphthalenes and phenanthrenes.

F. RELATED REACTIONS

This reaction is related to *Friedel-Crafts Acylation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2b.

To a filtered solution prepared from 35.6 g $AlCl_3$ (0.266 mol) and 27.2 g 3-(carbomethoxy)propionyl chloride (0.180 mol) in 150 mL dry CH_2Cl_2 was added 27.5 g (S)-isobutyl-benzene (0.205 mol) in 70 mL dry CH_2Cl_2 at 0°C. The mixture was stirred at 0°C for 1 h and hydrolyzed with ice and 10% HCl. Then the organic layer was dried and evaporated, and the residue was distilled to give 36.6 g 99% pure methyl (S)-3-[4-(1-methylpropyl)benzoyl]propionate in 82% yield with respect to the acyl chloride, besides 4.1 g 99% pure (S)-isobutyl-benzene.

A mixture of 36.5 g methyl (S)-3-[4-(1-methylpropyl)benzoyl]propionate (0.147 mol) dissolved in 600 mL glacial acetic acid and 725 mL 36% HCl was heated at 70°C for 8 h. After the mixture was cooled, 10 L of water was added; the organic product was extracted with ether, washed by water and dried; evaporation gave 33.6 g (S)-3-[4-(1-methylpropyl)benzoyl]propionic acid, in a yield of 97%, m.p. 94–95°C.

A mixture of 34.5 g (S)-3-[4-(1-methylpropyl)benzoyl]propionic acid (0.147 mol) and 30.0 g KOH (0.535 mol) in 200 mL diethylene glycol was heated at 50°C for 30 min; after cooling, 21.7 g 85% hydrazine hydrate (0.434 mol) was added. After the mixture was refluxed for 15 h, the water and the excess of hydrazine were removed under reduced pressure (18 mmHg), and the residue was heated at 180°C for 6 h. The reaction mixture was diluted with 2 L water, neutralized with HC1, and extracted with ether. The solvent was removed, and the residue was distilled to give 27.0 g 99% pure (S)-4-[4-(1-methylpropyl)phenyl]butanoic acid, in a yield of 83%, b.p. 138°C (0.3 mmHg).

To a hot solution (90–100°C) of PPA, obtained from 672.5 g P_2O_5 (4.75 mol) and 727.0 g 85% H_3PO_4 (7.42 mol) was added 26.0 g (S)-4-[4-(1-methylpropyl)phenyl]butanoic acid (0.118 mol). After 2 h, the mixture was cooled, diluted with ice water, and extracted with ether. The ethereal extracts were washed with 10% NaOH and water and dried over Na_2SO_4. The solvent was removed, and 21.5 g 99% pure 7-(1-methylpropyl)-1-tetralone was obtained, in a yield of 90%, b.p. 111°C (0.3 mmHg).

To a solution of 16.0 g 7-(1-methylpropyl)-1-tetralone (79.1 mmol) in 40 mL diethylene glycol was added 11.6 g 85% hydrazine hydrate (0.231 mol) at 0°C. After the mixture had been refluxed for 1 h, 7.1 g KOH (0.126 mol) dissolved in 25 mL diethylene glycol was added; then the mixture was refluxed for an additional hour. The water and excess of hydrazine were removed under reduced pressure (18 mmHg), and the residue was heated at 180°C for 4 h. The mixture was worked up as usual to give 14.0 g 99% pure (S)-1,2,3,4-tetrahydro-6-(1-methylpropyl)naphthalene, in a yield of 94%, b.p. 83°C (0.5 mmHg).

A mixture of 0.62 g sulfur (19.3 mmol) and 1.4 g (S)-1,2,3,4-tetrahydro-6-(1-methylpropyl)naphthalene was heated at 250°C for 2 h. By distillation under reduced pressure, 0.6 g 98% of (S)-2-(1-methylpropyl)naphthalene was obtained.

The aromatization of tetralin can also be completed by the following two methods. (a) aromatization with TCQ. To a solution of 12.0 g TCQ (51.4 mmol) in 25 mL dry benzene, was added at 80°C 4.0 g (S)-1,2,3,4-tetrahydro-6-(1-methylpropyl)naphthalene (21.2 mmol) dissolved in 15 mL dry benzene. After being refluxed for 4 h, the mixture was diluted with water and extracted with pentane. The organic phase was washed with 30% NaOH and water and dried over Na_2SO_4. The solvent was removed, and the crude product was distilled to give 2.7 g of a 2.2:1 mixture of (S)-1,2,3,4-tetrahydro-6-(1-methylpropyl)naphthalene and (S)-2-(1-methylpropyl)naphthalene. By GLC purification (2-m column, BDS; 140°C), 0.43 g 98% pure (S)-2-(1-methylpropyl)naphthalene was obtained, b.p. 90°C (0.8 mmHg).

(b) Aromatization with triphenylmethanol. A solution of 1.5 g (S)-1,2,3,4-tetrahydro-6-(1-methylpropyl)naphthalene (8.0 mmol) and 4.6 g triphenylmethanol (17.7 mmol) in 20 mL trifluoroacetic acid was refluxed under nitrogen for 18 h. The reaction mixture was cooled, diluted with ice water, and extracted with ether. The ethereal solution was washed with 10% NaOH and water, and dried over Na_2SO_4. In the crude product, no trace of the starting material was detected. After accurate distillation to remove the triphenylmethane, 0.6 g 99% pure (S)-2-(1-methylpropyl)naphthalene was obtained, in a yield of 40%.

Other references related to the Haworth synthesis are cited in the literature.[9]

H. REFERENCES

1. Haworth, R. D., *J. Chem. Soc.,* **1932**, 1125.
2. (a) Agranat, A. I. and Shih, Y. S., *Synthesis,* **1974**, 865. (b) Menicagli, R. and Piccolo, O., *J. Org. Chem.,* **1980**, *45*, 2581. (c) Agranat, A. I. and Shih, Y., *J. Chem. Edu.,* **1976**, *53*, 488.
3. Floyd, A. J.; Dyke, S. F. and Ward, S. E., *Chem. Rev.,* **1976**, *76*, 509.
4. (a) Singleton, D. R.; Powell, S. N.; Sangaiah, R.; Gold, A.; Ball, L. M. and Aitken, M. D., *App. & Environ. Microbio.,* **2005**, *71*, 1202. (b) Fieser, L. F. and Holmes, H. L., *J. Am. Chem. Soc.,* **1936**, *58*, 2319.
5. Fieser, L. F. and Holmes, H. L., *J. Am. Chem. Soc.,* **1938**, *60*, 2548.

6. Fieser, L. F. and Daudt, W. H., *J. Am. Chem. Soc.,* **1941**, *63*, 782.
7. Mousseron, M.; Jacquier, R. and Christol, H., *Compt. Rend.,* **1956**, *243*, 1532.
8. Mukherji, S. M. and Bhattacharyya, N. K., *J. Org. Chem.,* **1952**, *17*, 1202.
9. (a) Berliner, E., *Org. React.,* **1949**, *5*, 229. (b) Huang, M. L., *J. Am. Chem. Soc.,* **1946**, *68*, 2487. (c) Bachmann, W. E. and Cortes, G. D., *J. Am. Chem. Soc.,* **1943**, *65*, 1329. (d) Haworth, R. D. and Barker, R. L., *J. Chem. Soc.,* **1939**, 1299. (e) Fieser, L. F. and Hershberg, E. B., *J. Am. Chem. Soc.,* **1939**, *61*, 1272. (f) Burger, A. and Mosettig, E., *J. Am. Chem. Soc.,* **1937**, *59*, 1302. (g) Fieser, L. F. and Price, C. C., *J. Am. Chem. Soc.,* **1936**, *58*, 1838. (h) Fieser, L. F. and Hershberg, E. B., *J. Am. Chem. Soc.,* **1936**, *58*, 1324. (i) Haworth, R. D.; Mavin, C. R. and Sheldrick, G., *J. Chem. Soc.,* **1934**, 454. (j) Haworth, R. D. and Mavin, C. R., *J. Chem. Soc.,* **1933**, 1012. (k) Haworth, R. D., *J. Chem. Soc.,* **1932**, 2717. (l) Haworth, R. D. and Mavin, C. R., *J. Chem. Soc.,* **1932**, 2720. (m) Haworth, R. D. and Boiam, F. M., *J. Chem. Soc.,* **1932**, 2248. (n) Haworth, R. D.; Letsky, B. M. and Mavin, C. R., *J. Chem. Soc.,* **1932**, 1784.

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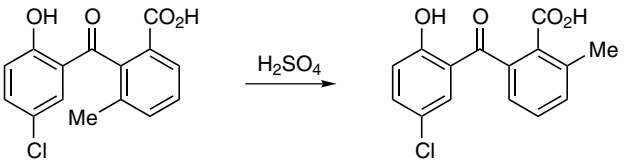
Hayashi Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Hayashi in 1927.[1] It is the rearrangement of substituted *o*-benzoylbenzoic acids in the presence of sulfuric acid or phosphorous pentoxide. Therefore, it is referred to as the Hayashi rearrangement.[2] Under normal conditions, the *o*-benzoylbenzoic acid cyclizes to form anthraquinones in the presence of acylating reagents, including sulfuric acid;[2b] however, when the aryl group is activated[2b] through conjugation or hyperconjugation,[2c] 1,4-aryl migration involving an acyl carbonium ion occurs.[2b] It has been found that the direction of carbonium center transfer is determined by sulfuric acid concentration and reaction temperature.[2a] Catalysts such as trifluoroacetic acid, methanesulfonic acid, and PPA have no effect on this rearrangement.[2a] Similar reactions also occur in other aromatic compounds, such as naphthalenes[3] and benzhydryls.[2b]

B. GENERAL REACTION SCHEME



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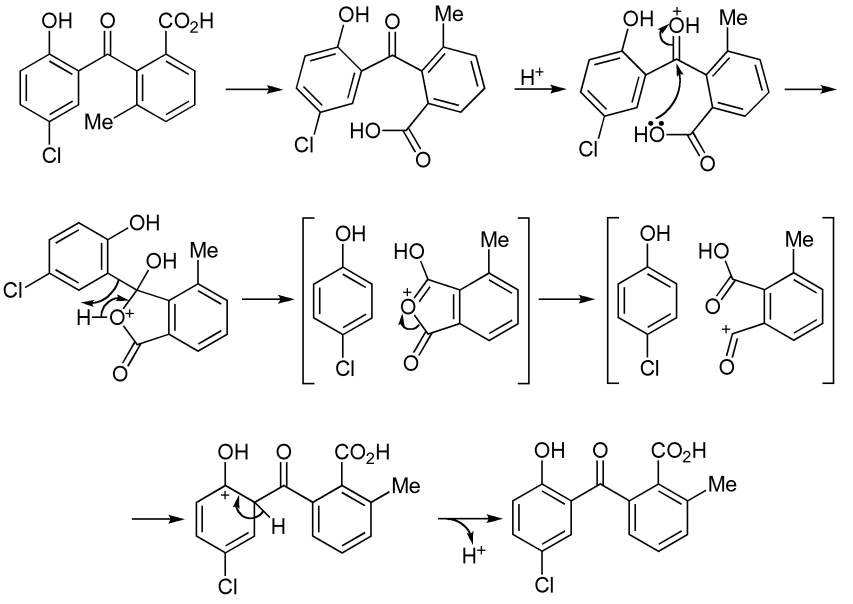
C. PROPOSED MECHANISMS



D. MODIFICATION

N/A

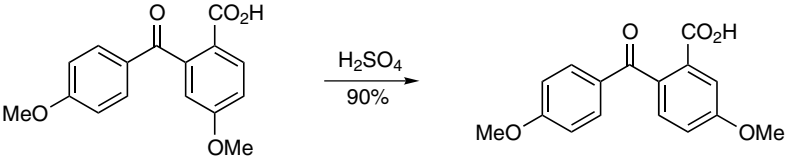
E. APPLICATIONS

This reaction occurs in a limited number of cases as reported, and is good only for the preparation of the reported derivatives.

F. RELATED REACTIONS

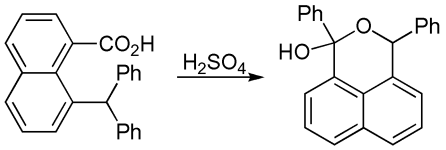
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 2c.

2-(4′-Methoxybenzoyl)-4-methoxybenzoic acid (0.5 g) in 3 mL conc. H_2SO_4 was heated at 65°C for 6 h; then the mixture was cooled and diluted with ice and water. The reaction mixture was made basic with NaOH, and any cyclized material was separated. The filtrate was acidified to yield unchanged or rearranged keto acid. It was found that 0.5 g keto acid was obtained, m.p. 170–172°C; after crystallization from dilute alcohol, 0.45 g pure keto acid was obtained, m.p. 173–175°C.



Reference 2b.

8-Benzhydryl-1-naphthoic acid (0.50 g) was heated on a steam bath for 2 h with 16 mL H_2SO_4 and 4 mL H_2O (not all of the solid went into solution). The orange mixture was then cooled and poured onto crushed ice; the precipitate was taken up in ether. After extraction with 10% Na_2CO_3 solution, it was acidified with HCl to give 0.3 g starting material (60% recovery). After the ether layer was washed and treated with petroleum ether (b.p. 60–70°C), the residue solid was recrystallized from $CHCl_3$-petroleum ether to give 0.10 g colorless, crystalline 1-phenylhydroxymethyl-8-benzoylnaphthanlene, m.p. 136.5–137°C.

Other references related to the Hayashi rearrangement are cited in the literature.[4]

H. REFERENCES

1. Hayashi, M., *J. Chem. Soc.,* **1927**, 2516.
2. (a) Zolotukhin, M. G.; Calleja, F. J. B.; Rueda, D. R.; Bruix, M.; Sorokina, Y. L. and Sedova, E. A., *Macromolecules,* **1995**, *28*, 7325. (b) Lansbury, P. T. and Letsinger, R. L., *J. Am. Chem. Soc.,* **1959**, *81*, 940. (c) Sandin, R. B.; Melby, R.; Crawford, R. and McGreer, D., *J. Am. Chem. Soc.,* **1956**, *78*, 3817.
3. Cook, J. W., *J. Chem. Soc.,* **1932**, 1472.
4. (a) Sekiya, R.; Kiyo-oka, K.; Imakubo, T. and Kobayashi, K., *J. Am. Chem. Soc.,* **2000**, *122*, 10282. (b) Opitz, A.; Roemer, E.; Haas, W.; Gorls, H.; Werner, W. and Grafe, U., *Tetrahedron*, **2000**, *56*, 5147. (c) Amitina, S. A. and Shubin, V. G., *Studies Surface Sci. Catal.,* **1993**, *75*, 2565. (d) Cushman, M.; Choong, T.-C.; Valko, J. T. and Koleck, M. P., *J. Org. Chem.,* **1980**, *45*, 5067. (e) Cristol, S. and Caspar, M. L., *J. Org. Chem.,* **1968**, *33*, 2020. (f) Cadogan, J. I. G.; Kulik, S. and Tood, M. J., *Chem. Commun. (London),* **1968**, 736. (g) Birkinshaw, J. H. and Gourlay, R., *J. Chem. Soc.,* **1963**, 716. (h) Newman, M. S. and Ihrman, K. G., *J. Am. Chem. Soc.,* **1958**, *80*, 3652. (i) Goncalves, R.; Kegelman, M. R. and Brown, E. V., *J. Org. Chem.,* **1952**, *17*, 705. (j) Sandin, R. B. and Fieser, L. F., *J. Am. Chem. Soc.,* **1940**, *62*, 3098. (k) Hayashi, M.; Tsuruoka, S.; Morikawa, T. and Namikawa, H., *Bull. Chem. Soc. Jpn.,* **1936**, *11*, 184. (l) Fieser, L. F., *The Chemistry of Natural Product Related to Phenanthrene*, Reinhold, New York, **1936**, p. 95. (m) Hayashi, M., *J. Chem. Soc.,* **1930**, 1513. (n) Hayashi, M., *J. Chem. Soc.,* **1930**, 1520. (o) Hayashi, M., *J. Chem. Soc.,* **1930**, 1524.

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Heck Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Heck in 1968.[1] It is the palladium-catalyzed coupling between an aryl (or vinyl) halide and an alkene without an allylic hydrogen. Accordingly, this reaction is generally known as the Heck reaction.[2] Occasionally, this reaction is also referred to as the Heck arylation,[3] Heck coupling,[4] Heck ethylenation,[5] Heck insertion,[6] Heck olefination,[7] and Heck vinylation.[8] In addition, the intramolecular version of this reaction to form cyclic olefin is called the Heck cyclization.[9] Unfortunately, the terms Heck-Mizoroki reaction,[7] Mizoroki-Heck reaction,[10] and Mizoroki-Heck arylation[11] are also used for this reaction, because people have mistakenly cited Mizoroki's 1971 work[12] and Heck's 1972 paper.[13] The Heck reaction is a powerful tool for constructing a C-C bond in a single transformation employing a variety of aryl or vinyl halides and alkenes, which tolerate almost any sensitive functionalities, including amino, hydroxy, aldehyde, ketone, carboxy, ester, cyano, and nitro groups.[14] The traditional Heck reaction uses 1–5 mol % of a palladium catalyst along with a phosphine ligand (PPh_3) in the presence of a suitable base (soluble as Et_3N or insoluble as K_2CO_3, Ag_2CO_3), which scavenges the generated hydrogen halide in the β-elimination step of the catalytic cycle. Although it is known that this reaction involves a Pd(0)/Pd(II) catalytic cycle, in which Pd(II) is reduced by a phophsine to Pd(0), a few cases that involve the catalytic cycle of Pd(II)/Pd(IV) also exist with some ligands.[15] The palladium complex in the former case is known as a neutral palladium complex, in which regiochemistry is controlled by steric effect; whereas in the latter Pd(II)/Pd(IV) catalytic cycle, it is known as the *cationic palladium complex*, in which regiochemistry is influenced by an electric effect and the cationic Pd complex increases the polarization of the alkene in favor of the transfer of the vinyl or aryl group to the site of least electron density. In addition, the Heck reaction catalyzed by a neutral palladium complex

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

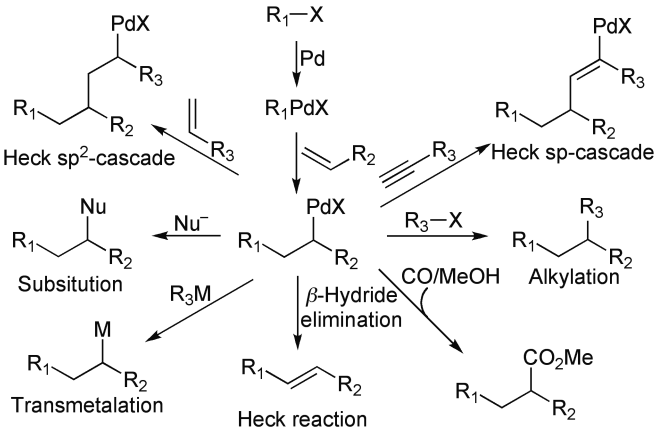


FIGURE 1. *Possible Heck-tandem product under various conditions.*

or cationic palladium complex can give different stereochemical outcomes.[16] The reaction mechanism is illustrated by a catalytic cycle, in which the palladium complex is reduced to a Pd(0) complex with a 14-electron—that is the active species, which inserts into aryl halide via oxidative addition—and the resulting palladium complex then adds to the C=C bond of an alkene on the same face; the addition product then rotates to have the β-hydride and the palladium in *syn*-coplanar geometry to undergo elimination and complete the catalytic cycle. Reversible β-hydride elimination can lead to alkene isomerization, which is minimized in the presence of silver salt.[17] If the addition product does not (or cannot) decompose via elimination, the tandem reaction occurs (Figure 1). Likewise, alkyl halides having hydrogen at the β-position to halide atom are not suitable for the Heck reaction due to the β-hydride elimination.[2u,18] The palladium complex is so efficient in this reaction and with high turnover number that only a small amount of palladium is required to complete the coupling. For active aryl halide (aryl iodide), the concentration of the palladium complex can be down to the ppm level;[19] and in aqueous solution under microwave radiation, the concentration of Pd can be even lowered to 500 ppb.[4b] The ligands suitable for this reaction include triaryl phosphine,[5] *N*,*N*-bis(2,6-diisopropyl-phenyl)dihydroimidazolium,[10e] *N*-acyl-substituted dipyridyl,[20] *N*-acyl-substituted dipyrimidylamines,[21] Pfaltz ligand,[2w,22] and ketopinic acid–based ligands.[2w] In addition, the palladium has been enclosed in silica[10b] or NaY-zeolite[23] as a heterogeneous catalyst or bound to a fluoros tail.[11] Some representative palladium complexes used for the Heck reaction are listed in Figure 2.

On the other hand, it is known that the combination of a phase transfer reagent (e.g., tetraalkylammonium salt) and an insoluble base can accelerate the reaction rate, which lowers the reaction temperature.[24]

Besides the traditional coupling between alkenes and aryl (vinyl) halides, other functionalized aryl derivatives can also couple with alkenes in the Heck reaction, including aryl silanes,[10c,10g,25] stannanes,[26] bismuth,[27] antimony,[28] triflates,[4a,9b,29] boric acid,[30] phosphonic acid,[31] carboxylic acid,[32] and diazonium salt.[33]

Furthermore, the Heck reaction also takes place under some unconventional conditions, such as superheated water (e.g., 260°C),[4e] aqueous solution,[6] ionic liquid,[34] and even without the presence of ligand .[10b,23] On the other hand, some other transition metals also catalyze the Heck reaction, such as cobalt,[18] copper,[34a] and rhodium.[10g]

This reaction has been extensively reviewed.[35]

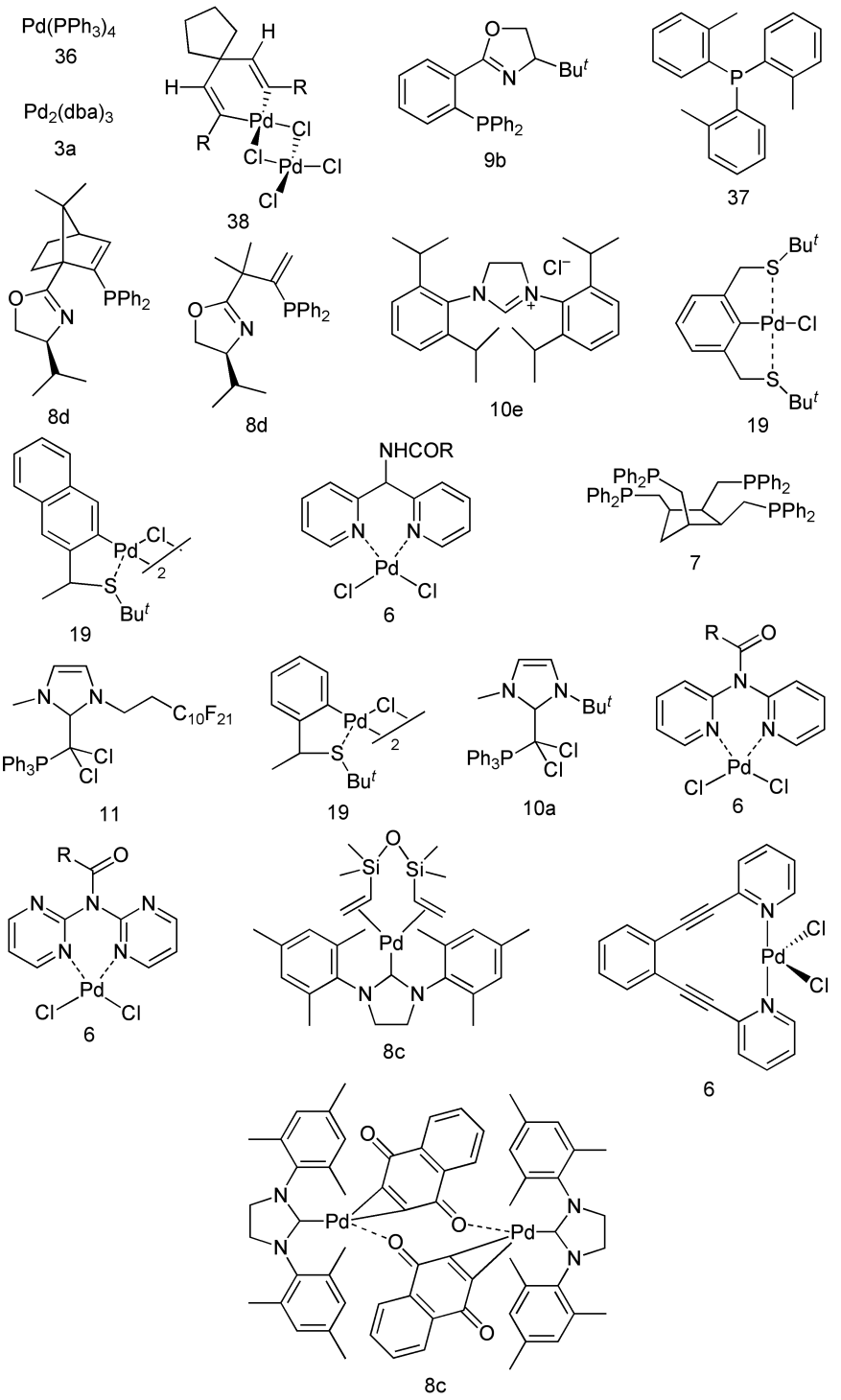
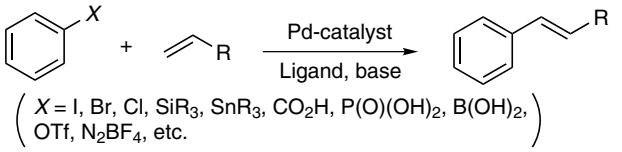


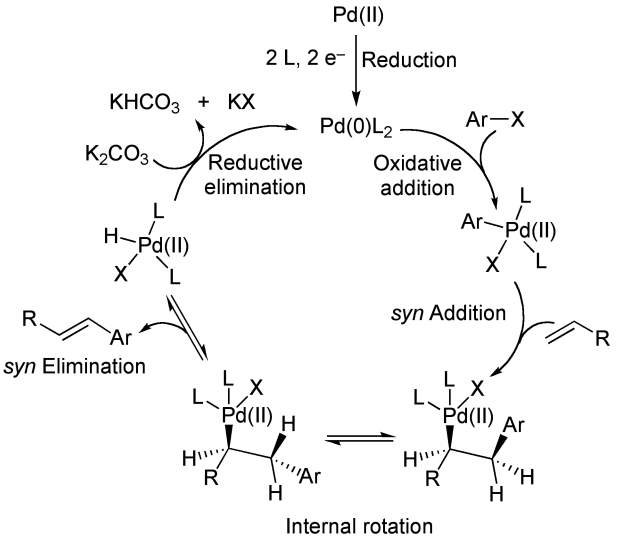
FIGURE 2. *Representative palladium catalysts and ligands in the Heck reaction. Numbers below the respective structures refer to the corresponding citations.*

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The mechanism of the Heck reaction catalyzed by a neutral palladium complex is illustrated below.



D. MODIFICATION

This reaction has extensively been modified, including the modification of ligands and the substitution of transition metals (Cu, Rh, Co).

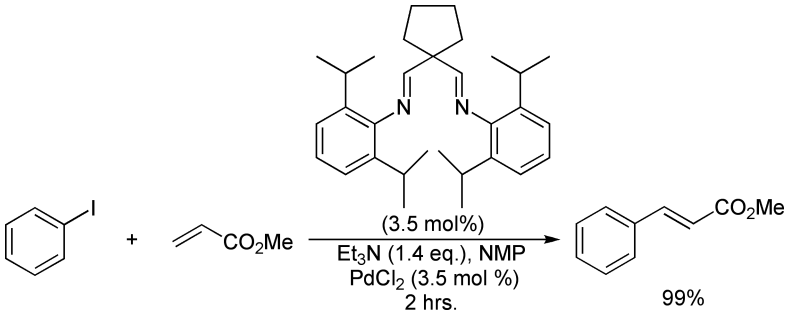
E. APPLICATIONS

This reaction has wide applications in organic synthesis.

F. RELATED REACTIONS

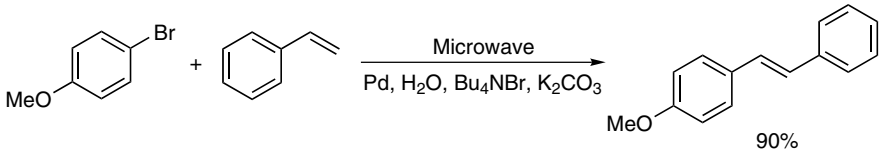
This reaction is related to the *Stille Coupling, Suzuki Coupling, Hiyama Coupling*, and *Sonogashira Coupling*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 38.

Under an atmosphere of argon, a solution of 0.035 mmol $PdCl_2$, 0.035 mmol *N*,*N*′-(1,1-cyclopentylidene-dimethylidyne)bis(2,6-bis-(1-methylethyl)benzenamine) in 3 mL 1-methyl-2-pyrrolidinone was stirred at 140°C for 30 min. Then 1.0 mmol iodobenzene, 1.2 mmol methyl acrylate, and 1.4 mmol Et_3N were added, and the mixture was stirred at 140°C. After completion of coupling (2 h), 10 mL saturated NH_4Cl solution was added, and the mixture was extracted with CH_2Cl_2 (3 ×10 mL). The combined organic layers were washed with 2 M HCl (5 × 10 mL), water (1 × 10 mL), and saturated NaCl solution (2 × 10 mL), dried over Na_2SO_4, and filtered. The solvent was evaporated, and the crude product was purified by flash chromatography to give 99% of methyl 2-*trans*-phenyl acrylate.



Reference 4b.

In a 10-mL glass tube were placed 187 mg 4-bromoanisole (0.125 mL, 1.0 mmol), 208 mg styrene (0.230 mL, 2.0 mmol), 511 mg K_2CO_3 (3.7 mmol), 322 mg tetrabutylammonium bromide (1.0 mmol), 0.4 mL palladium stock solution (a 1000 ppm solution in water), and 1.6 mL water to give a total volume of water to 2 mL and a total palladium concentration of 200 ppm. The vessel was sealed with a septum, shaken and placed into the microwave cavity. Initial microwave irradiation of 70 W was used, the temperature being ramped from room temperature to the desired temperature of 170°C. Once this was reached, the reaction mixture was held at this temperature for 10 min. After allowing the mixture to cool to room temperature, the reaction vessel was opened, and the contents were poured into a separating funnel. Water (30 mL) and 30 mL EtOAc were added, and the organic material was extracted and removed. After further extraction of the aqueous layer with EtOAc, combining the organic washings and drying them over $MgSO_4$, the ethyl acetate was removed in vacuo to give a crude product that was purified via chromatography, in a yield of 90%.

Other references related to the Heck reaction are cited in the literature.[39]

H. REFERENCES

1. Heck, R. F., *J. Am. Chem. Soc.,* **1968**, *90*, 5518.
2. (a) Vogel, M. A. K.; Stark, C. B. W. and Lyapkalo, I. M., *Adv. Synth. Catal.,* **2007**, *349*, 1019. (b) Pei, W.; Shen, C.; Mo, J. and Xu, X.-L., *Youji Huaxue*, **2007**, *27*, 653. (c) Oikawa, M.; Takeda, Y.; Naito, S.; Hashizume, D.; Koshino, H. and Sasaki, M., *Tetrahedron Lett*., **2007**, *48*, 4255. (d) Zhu, M.; Song, Y. L. and Cao, Y., *Synthesis,* **2007**, 853. (e) Pathak, D. D.; Maheswaran, H.; Prasanth, K. L. and Kantam, M. L., *Synlett*, **2007**, 757. (f) Ozdemir, I.; Demir, S. and Cetinkaya, B., *Synlett*, **2007**, 889. (g) Bauman, V. T.; Shul'ts, E. E.; Shakirov, M. M. and Tolstikov, G. A., *Russ. J. Org. Chem.,* **2007**, *43*, 526. (h) Cheung, L. L. W.; Aktoudianakis, E.; Chan, E.; Edward, A. R.; Jarosz, I.; Lee, V.; Mui, L.; Thatipamala, S. S. and Dicks, A. P., *Chem. Edu.,* **2007**, *12*, 77. (i) Fall, Y.; Doucet, H. and Santelli, M., *Tetrahedron Lett*., **2007**, *48*, 3579. (j) Lee, M.-T.; Lee, H. M. and Hu, C.-H., *Organometallics*, **2007**, *26*, 1317. (k) Wang, R. H.; Xiao, J.-C.; Twamley, B. and Shreeve, J. M., *Org. Biomol. Chem.,* **2007**, *5*, 671. (l) Wang, R. H.; Zeng, Z.; Twamley, B.; Piekarski, M. M. and Shreeve, J. M., *Eur. J. Org. Chem.,* **2007**, 655. (m) Lu, N.; Lin, Y.-C.; Chen, J.-Y.; Fan, C.-W. and Liu, L.-K., *Tetrahedron*, **2007**, *63*, 2019. (n) Lapierre, A. J. B.; Geib, S. J. and Curran, D. P., *J. Am. Chem. Soc.,* **2007**, *129*, 494. (o) Putey, A.; Joucla, L.; Picot, L.; Besson, T. and Joseph, B., *Tetrahedron*, **2007**, *63*, 867. (p) Huang, L.; Wang, Z.; Ang, T. P.; Tan, J. and Wong, P. K., *Catal. Lett.,* **2006**, *112*, 219. (q) Pryjomska-Ray, I.; Gniewek, A.; Trzeciak, A. M.; Ziolkowski, J. J. and Tylus, W., *Topics Catal.,* **2006**, *40*, 173. (r) Konno, T.; Yamada, S.; Tani, A.; Miyabe, T. and Ishihara, T., *Synlett*, **2006**, 3025. (s) Aulenta, F. and Reissig, H.-U., *Synlett*, **2006**, 2993. (t) Arnold, L. A.; Luo, W. C. and Guy, R. K., *Org. Lett.,* **2004**, *6*, 3005. (u) Fujioka, T.; Nakamura, T.; Yorimitsu, H. and Oshima, K., *Org. Lett.,* **2002**, *4*, 2257. (v) Selvakumar, K.; Zapf, A. and Beller, M., *Org. Lett.,* **2002**, *4*, 3031. (w) Gilbertson, S. R. and Fu, Z. C., *Org. Lett.,* **2001**, *3*, 161.
3. (a) Nilsson, P.; Larhed, M. and Hallberg, A., *J. Am. Chem. Soc.,* **2003**, *125*, 3430. (b) Severino, E. A. and Correia, C. R. D., *Org. Lett.,* **2000**, *2*, 3039.
4. (a) Hansen, A. L. and Skrydstrup, T., *J. Org. Chem.* **2005**, *70*, 5997. (b) Arvela, R. K. and Leadbeater, N. E., *J. Org. Chem.,* **2005**, *70*, 1786. (c) Chandrasekhar, S.; Narsihmulu, C.; Sultana, S. S. and Reddy, N. R., *Org. Lett.,* **2002**, *4*, 4399. (d) Bars, J. L.; Specht, U.; Bradley, J. S. Blackmond, D. G., *Langmuir,* **1999**, *15*, 7621. (e) Diminnie, J.; Metts, S. and Parsons, E. J., *Organometallics,* **1995**, *14*, 4023.
5. Raggon, J. W. and Snyder, W. M., *Org. Proc. Res. Dev.,* **2002**, *6*, 67.
6. Oppolzer, W. and DeVita, R. J., *J. Org. Chem.,* **1991**, *56*, 6256.
7. Nájera, C.; Gil-Moltó, J.; Karlström, S. and Falvello, L. R., *Org. Lett.,* **2003**, *5*, 1451.
8. Feuerstein, M.; Doucet, H. and Santelli, M., *J. Org. Chem.,* **2001**, *66*, 5923.
9. (a) Dounay, A. B.; Overman, L. E. and Wrobleski, A. D., *J. Am. Chem. Soc.,* **2005**, *127*, 10186. (b) Coe, J. W., *Org. Lett.,* **2000**, *2*, 4205. (c) Frey, D. A.; Duan, C. M. and Hudlicky, T., *Org. Lett.,* **1999**, *1*, 2085.
10. (a) Aggarwal, V. K.; Staubitz, A. C. and Owen, M., *Org. Proc. Res. Dev.,* **2006**, *10*, 64. (b) Kitamura, M.; Kudo, D. and Narasaka, K., *ARKIVOC,* **2006**, 148. (c) Hagio, H.; Sugiura, M. and Kobayashi, S., *Org. Lett.,* **2006**, *8*, 375. (d) Ogo, S.; Takebe, Y.; Uehara, K.; Yamazaki, T.; Nakai, H.; Watanabe, Y. and Fukuzumi, S., *Organometallics,* **2006**, *25*, 331. (e) Oi, S.; Sakai, K. and Inoue, Y., *Org. Lett.,* **2005**, *7*, 4009. (f) Frey, G. D.; Schütz, J.; Herdtweck, E. and Herrmann, W. A., *Organometallics,* **2005**, *24*, 4416. (g) Muraoka, N.; Mineno, M.; Itami, K. and Yoshida, J.-I., *J. Org. Chem.,* **2005**, *70*, 6933. (h) Andrade, C. K. Z. and Alves, L. M., *Curr. Org. Chem.,* **2005**, *9*, 195. (i) Crudden, C. M.; Sateesh, M. and Lewis, R., *J. Am. Chem. Soc.,* **2005**, *127*, 10045. (j) Dubbaka, S. R. and Vogel, P., *Chem. Eur. J.*, **2005**, *11*, *2633*. (k) Liu, S. F.; Fukuyama, T.; Sato, M. and Ryu, I., *Org. Proc. Res. Dev.,* **2004**, *8*, 477. (l) Ikeda, Y.; Yorimitsu, H.; Shinokubo, H. and Oshima, K., *Adv. Synth. Catal.,* **2004**, *346*, 1631. (m) Hagiwara, H.; Sugawara, Y.; Isobe, K.;

Hoshi, T. and Suzuki, T., *Org. Lett.,* **2004**, *6*, 2325. (n) Itami, K.; Ushiogi, Y.; Nokami, T.; Ohashi, Y. and Yoshida, J.-I., *Org. Lett.,* **2004**, *6*, 3695. (o) Mori, K.; Rikimaru, K.; Kan, T. and Fukuyama, T., *Org. Lett.,* **2004**, *6*, 3095. (p) Roland, S.; Audouin, M. and Mangeney, P., *Organometallics,* **2004**, *23*, 3075. (q) Hernández, S.; San Martin, R.; Tellitu, I. and Domínguez, E., *Org. Lett.,* **2003**, *5*, 1095. (r) Doi, T.; Fujimoto, N.; Watanabe, J. and Takahashi, T., *Tetrahedron Lett.*, **2003**, *44*, 2161. (s) Andrus, M. B.; Song, C. and Zhang, J. Q., *Org. Lett.,* **2002**, *4*, 2079. (t) Hirai, G.; Koizumi, Y.; Moharram, S. M.; Oguri, H. and Hirama, M., *Org. Lett.,* **2002**, *4*, 1627. (u) Mori, A.; Danda, Y.; Fujii, T.; Hirabayashi, K. and Osakada, K., *J. Am. Chem. Soc.,* **2001**, *123*, 10774. (v) Hirai, G.; Oguri, H.; Moharram, S. M.; Koyama, K. and Hirama, M., *Tetrahedron Lett*., **2001**, *42*, 5783. (w) Uto, Y.; Hirata, A.; Fujita, T.; Takubo, S.; Nagasawa, H. and Hori, H., *J. Org. Chem.,* **2002**, *67*, 2355. (x) Inoue, M.; Furuyama, H.; Sakazaki, H. and Hirama, M., *Org. Lett.,* **2001**, *3*, 2863.

11. Fukuyama, T.; Arai, M.; Matsubara, H. and Ryu, I.,*J. Org. Chem.,* **2004**, *69*, 8105.
12. Mizoroki, T.; Mori, K. and Ozaki, A., *Bull. Chem. Soc. Jpn.,* **1971**, *44*, 581.
13. Heck, R. F. and Nolley, J. P., *J. Org. Chem.,* **1972**, *37*, 2320.
14. Yao, Q. W.; Kinney, E. P. and Yang, Z., *J. Org. Chem.,* **2003**, *68*, 7528.
15. (a) Reetz, M. T. and Westermann, E., *Angew. Chem. Int. Ed*., **2000**, *39*, 165. (b) Amatore, C. and Jutand, A., *J. Organomet. Chem.,* **1999**, *576*, 254. (c) Shaw, B. L.; Perera, S. D. and Staley, E. A., *J. Chem. Soc., Chem. Commun.,* **1998**, 1361. (d) Shaw, B. L., *New J. Chem.,* **1998**, *22*, 77. (e) Ohff, M.; Ohff, A.; van der Boom, M. E. and Milstein, D., *J. Am. Chem. Soc.,* **1997**, *119*, 11687.
16. Ashimori, A.; Bachand, B.; Overman, L. E. and Poon, D. J., *J. Am. Chem. Soc.,* **1998**, *120*, 6477.
17. (a) Sakamoto, T.; Kondo, Y.; Uchiyama, M. and Yamanaka, H., *J. Chem. Soc*., *Perkin Trans. I,* **1993**, 1941. (b) Abelman, M. M.; Oh, T. and Overman, L. E., *J. Org. Chem.,* **1987**, *52*, 4133.
18. Ikeda, Y.; Nakamura, T.; Yorimitsu, H. and Oshima, K., *J. Am. Chem. Soc.,* **2002**, *124*, 6514.
19. Gruber, A. S.; Zim, D.; Ebeling, G.; Monteiro, A. L. and Dupont, J., *Org. Lett.,* **2000**, *2*, 1287.
20. Buchmeiser, M. R. and Wurst, K., *J. Am. Chem. Soc.,* **1999**, *121*, 11101.
21. (a) Silberg, J.; Schareina, T.; Kempe, R.; Wurst, K. and Buchmeiser, M. R., *J. Organomet. Chem.,* **2001**, *622*, 6. (b) Buchmeiser, M. R.; Schareina, T.; Kempe, R. and Wurst, K., *J. Organomet. Chem.,* **2001**, *634*, 39.
22. (a) Ripa, L. and Hallberg, A., *J. Org. Chem.* **1997**, *62*, 595. (b) Loiseleur, O.; Meier, P. and Pfaltz, A., *Angew. Chem. Int. Ed. Engl.,* **1996**, *35*, 200. (c) Koch, G.; Lloyd-Jones, G. C.; Loiseleur, O.; Pfaltz, A.; Pretot, R.; Schaffner, S.; Schnider, P. and von Matt, P., *Recl. Trav. Chim. Pays-Bas,* **1995**, *114*, 206.
23. Djakovitch, L. and Koehler, K., *J. Am. Chem. Soc.,* **2001**, *123*, 5990.
24. Jeffery, T., *Tetrahedron,* **1996**, *52*, 10113.
25. Hirabayashi, K.; Nishihara, Y.; Mori, A. and Hiyama, T., *Tetrahedron Lett.,* **1998**, *39*, 7893.
26. (a) Hirabayashi, K.; Ando, J.; Kawashima, J.; Nishihara, Y.; Mori, A. and Hiyama, T., *Bull. Chem. Soc. Jpn.,* **2000**, *73*, 1409. (b) Hirabayashi, K.; Ando, J.; Nishihara, Y.; Mori, A. and Hiyama, T., *Synlett*, **1999**, 99.
27. (a) Kawamura, T.; Kikukawa, K.; Takagi, M. and Matsuda, T., *Bull. Chem. Soc. Jpn.,* **1977**, *50*, 2021. (b) Asano, R.; Moritani, I.; Fujiwara, Y. and Teranishi, S., *Bull. Chem. Soc. Jpn.,* **1973**, *46*, 2910.
28. Motoba, K.; Motofusa, S.; Cho, C. S.; Ohe, K. and Uemura, S., *J. Organomet. Chem.,* **1999**, *574*, 3.
29. Karabelas, K. and Hallberg, A., *J. Org. Chem.,* **1988**, *53*, 4909.
30. (a) Du, X. L.; Suguro, M.; Hirabayashi, K.; Mori, A.; Nishikata, T.; Hagiwara, N.; Kawata, K.; Okeda, T.; Wang, H. F.; Fugami, K. and Kosugi, M., *Org. Lett.,* **2001**, *3*, 3313. (b) Cho, C. S. and Uemura, S., *J. Organomet. Chem.,* **1994**, *465*, 85.
31. Inoue, A.; Shinokubo, H. and Oshima, K., *J. Am. Chem. Soc.,* **2003**, *125*, 1484.

32. Myers, A. G.; Tanaka, D. and Mannion, M. R., *J. Am. Chem. Soc.,* **2002**, *124*, 11250.

33. Masllorens, J.; Moreno-Manas, M.; Pla-Quintana, A. and Roglans, A., *Org. Lett.,* **2003**, *5*, 1559.

34. (a) Calò, V.; Nacci, A.; Monopoli, A.; Leva, E. and Cioffi, N., *Org. Lett.,* **2005**, *7*, 617. (b) Böhm, V. P. W. and Herrmann, W. A., *Chem. Eur. J.,* **2000**, *6*, 1017. (c) Xu, L.; Chen, W. and Xiao, J., *Organometallics,* **2000**, *19*, 1123. (d) Calò, V.; Nacci, A.; Lopez, L. and Mannarini, N., *Tetrahedron Lett.,* **2000**, *41*, 8973. (e) Carmichael, A. J.; Earle, M. J.; Holbrey, J. D.; McCormac, P. B. and Seddon, K. R., *Org. Lett.,* **1999**, *1*, 997. (f) Kaufmann, D. E.; Nouroozian, M. and Henze, H., *Synlett,* **1996**, 1091.

35. (a) Link, J., *Org. React.,* **2002**, *60*, 157. (b) Littke, A. F. and Fu, G. C., *Angew. Chem. Int. Ed.,* **2001**, *41*, 4176. (c) Beletskaya, I. P. and Cheprakov, A. V., *Chem. Rev*., **2000**, *100*, 3009. (d) Franzén, R., *Can. J. Chem.,* **2000**, *78*, 957. (e) Shibasaki, M. and Vogl, E. M., *J. Organomet. Chem.,* **1999**, 576, 1. (f) Iserloh, U. and Curran, D. P., *Chemtracts,* **1999**, *12*, 289. (g) Reetz, M. T., "Selective allylation reactions" in *Transition Metal Catalyzed Reactions*, ed. Davies, S. G. and Murahashi, S.-I., Blackwell, Oxford, **1999**. (h) Crisp, G. T., *Chem. Soc. Rev.,* **1998**, *27*, 427. (i) Malleron, J.-L.; Fiaud, J.-C. and Legros, J.-Y., *Handbook of Palladium-Catalyzed Organic Reactions*, Academic Press, London, **1997**. (j) Herrmann, W. A., "*Acrolein and Acrylonitrile from Propene*" in *Applied Homogeneous Catalysis with Organometallic Compounds*, ed. Cornils, B. and Herrmann, W. A., VCH Publishers, Weinheim, N.Y., **1996**. pp. 1156–1163. (k) Cabri, W. and Candiani, I., *Acc. Chem. Res.,* **1995**, *28*, 2. (l) Overman, L. E., *Pure & Appl. Chem.,* **1994**, *66*, 1423. (m) De Meijere, A. and Meyer, F. E., *Angew. Chem. Int. Ed. Engl.,* **1994**, *33*, 2379. (n) Heck, R. F. in *Palladium Reagents in Organic Syntheses*, ed. Katritzky, A. R.; Meth-Cohn O. and Rees, C. W., Academic Press, London, **1985**, p. 2. (o) Heck, R. F., *Org. React.,* **1982**, *27*, 345.

36. (a) Cheung, W. S.; Patch, R. J. and Player, M. R., *J. Org. Chem.,* **2005**, *70*, 3741. (b) Negishi, E., Ma, S.; Sugihara, T. and Noda, Y., *J. Org. Chem.,* **1997**, *62*, 1922.

37. Cantello, B. C. C.; Connor, S. C.; Dean, D. K. and Hindley, R. M., *Synlett,* **1997**, 263.

38. Domin, D.; Benito-Garagorri, D.; Mereiter, K.; Fröhlich, J. and Kirchner, K., *Organometallics,* **2005**, *24*, 3957.

39. (a) Couty, S.; Liégault, B.; Meyer, C. and Cossy, J., *Org. Lett.,* **2004**, *6*, 2511. (b) Battistuzzi, G.; Cacchi, S. and Fabrizi, G., *Org. Lett.*, **2003**, *5*, 777. (c) Pinho, P.; Minnaard, A. J. and Feringa, B. L., *Org. Lett.,* **2003**, *5*, 259. (d) Liu, C.-Y. and Luh, T.-Y., *Org. Lett.,* **2002**, *4*, 4305. (e) Lawson, E. C.; Kinney, W. A.; Luci, D. K.; Yabut, S. C.; Wisnoski, D. and Maryanoff, B. E., *Tetrahedron Lett.,* **2002**, *43*, 1951. (f) Bengtson, A.; Larhed, M. and Hallberg, A., *J. Org. Chem.,* **2002**, *67*, 5854. (g) Chou, M.-Y.; Mandal, A. B. and Leung, M.-K., *J. Org. Chem.,* **2002**, *67*, 1501. (h) Choudary, B. M.; Madhi, S.; Chowdari, N. S.; Kantam, M. L. and Sreedhar, B., *J. Am. Chem. Soc.,* **2002**, *124*, 14127. (i) Biffis, A.; Zecca, M. and Basato, M., *Eur. J. Inorg. Chem.,* **2001**, 1131. (j) Howarth, J. and Dallas, A., *Molecules,* **2000**, *5*, 851. (k) Loiseleur, O.; Hayashi, M.; Schmees, N. and Pfaltz, A., *Synthesis,* **1997**, 1338. (l) Tietze, L. F. and Raschke, T., *Synlett,* **1995**, 597. (m) Ohari, K.; Kondo, K.; Sodeoka, M. and Shibasaki, M., *J. Am. Chem. Soc.,* **1994**, *116*, 11737. (n) Hong, C. Y. and Overman, L. E., *Tetrahedron Lett.,* **1994**, *35*, 3453. (o) Hong, C. Y.; Kado, N. and Overman, L. E., *J. Am. Chem. Soc.,* **1993**, *115*, 11028. (p) Trost, B. M.; Dumas, J. and Villa, M., *J. Am. Chem. Soc.,* **1992**, *114*, 9836. (q) Ozawa, F.; Kubo, A. and Hayashi, T., *Chem. Lett.,* **1992**, 2177. (r) Cabri, W.; Candiani, I.; Bedeschi, A.; Penco, S. and Santi, R., *J. Org. Chem.* **1992**, *57*, 1481. (s) Amatore, C.; Azzabi, M. and Jutand, A., *J. Am. Chem. Soc.,* **1991**, *113*, 8375. (t) Ziegler, F. E.; Chakraborty, U. R. and Weisenfeld, R. B., *Tetrahedron,* **1981**, *37*, 4035. (u) Cortese, N. A.; Ziegler, C. B.; Hrnjez, B. J. and Heck, R. F., *J. Org. Chem.,* **1978**, *43*, 2952. (v) Patel, P.A.; Ziegler, C.B.; Cortese, N. A.; Plevyak, J. E.; Zebovitz, T. C.; Terpko, M. and Heck, R. F., *J. Org. Chem.,* **1977**, *42*, 3903.

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Hegedus Indole Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

The Hegedus indole synthesis,[1] also known as the Hegedus reaction,[1b,1d] Hegedus-Mori-Heck indole synthesis,[1b,2] and Hegedus-Mori-Heck reaction,[1b,3] in general contains at least two types of reactions for indole derivatives. They are the palladium (II) complex–catalyzed oxidative *N*-heterocyclization of *o*-allylaniline (developed in 1976)[4] or *o*-aminostyrenes (reported in 1978)[5] and the palladium-catalyzed intramolecular cyclization of *o*-halo *N*-allylaniline (reported in 1980);[6] the latter preparation is also referred to as the Hegedus cyclization.[7]

A simple procedure for the Hegedus indole synthesis would be as follows: the addition of *o*-allylaniline to the THF solution of $PdCl_2(CH_3CN)_2$ affords a yellow-brown precipitate, which dissolves again on addition of triethylamine; the resulting cherry red solution starts to deposit metallic palladium. After the completion of palladium deposition, the solution is filtered, and the filtrate is concentrated to give 2-methylindole, which may be contaminated with a small amount of $Et_3N{\cdot}HCl$.[4] It is apparent that stoichiometric amounts of palladium dichloride are needed for this reaction,[8] which is reduced to metallic palladium. However, the Hegedus indole synthesis can be performed catalytically in the presence of an oxidant, which can convert Pd(0) to Pd(II). It has been found that benzoquinone is the oxidant of choice to reoxidize Pd(0) to Pd(II),[5] and in some cases, higher yields of indoles are obtained under catalytic conditions than those using a stoichiometric amount of catalyst.[8] In this reaction $Pd(OAc)_2$ and lithium chloropalladate are not effective catalysts.[8]

The Hegedus indole synthesis is not only compatible with a wide range of functional groups on the aromatic ring but is also tolerable for the alkyl groups at the 2 or 3 position of the allyl side chain.[4] Other features of this reaction include (*a*) general accessibility for the intramolecular amination of mono-olefin from primary amines and weakly basic

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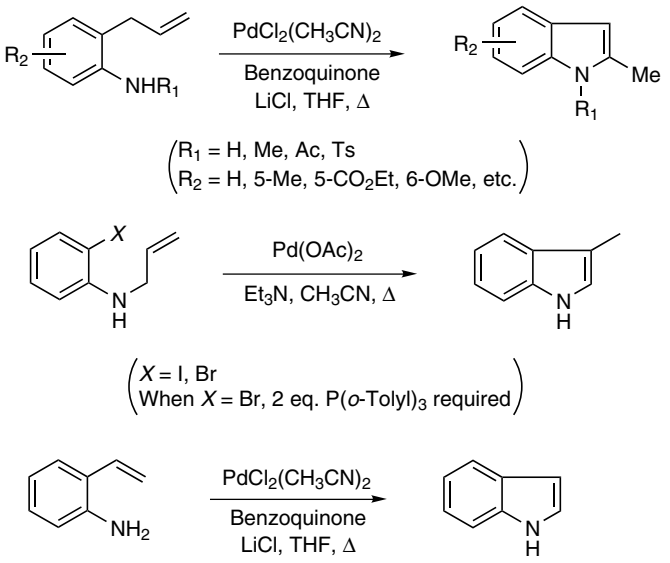
amines, such as aniline; (*b*) unnecessary removal of amine to form the olefin-palladium complex; and (*c*) intramolecular amination of cyclohexene and 2-methylbutene moiety.[4] All these reactions are generally unfeasible under other reaction conditions, and the failure for the amination of mono-olefin from primary amines is probably due to the strong linkage between nitrogen and palladium that eliminates the amine as an effective nucleophile.[1c] In addition, the reaction is not restricted to nitrogen nucleophiles; it works for oxygen nucleophiles as well. As an example, treatment of *o*-allylbenzoic acid with $PdCl_2$ and Na_2CO_3 in THF affords 3-methylisocoumarin in good yield.[4] Although *p*-toluenesulfonamides are not considered good nucleophiles, they are effective for the attack on Pd(II)-coordinated olefins. Indeed, the *N*-tosyl *o*-allylanilines cyclize much faster and more efficiently to give *N*-tosylindole derivatives.[9]

On the other hand, for the preparation of an indole from *o*-halo *N*-allylaniline, the iodo aromatics usually give good yields of indole in the presence of $Pd(OAc)_2$ and Et_3N in CH_3CN at 110°C for 72 h. However, due to the deactivation of the palladium catalyst, it is necessary to add fresh catalyst periodically.[6] For instance, during 72 h of reaction, better results are obtained by adding one third of the catalyst each day than the reactions using same amount of catalyst in one portion. However, for the less reactive bromo aromatics, 2 equivalents of tris(*o*-tolyl)phosphine per Pd is necessary for an acceptable yield.[6]

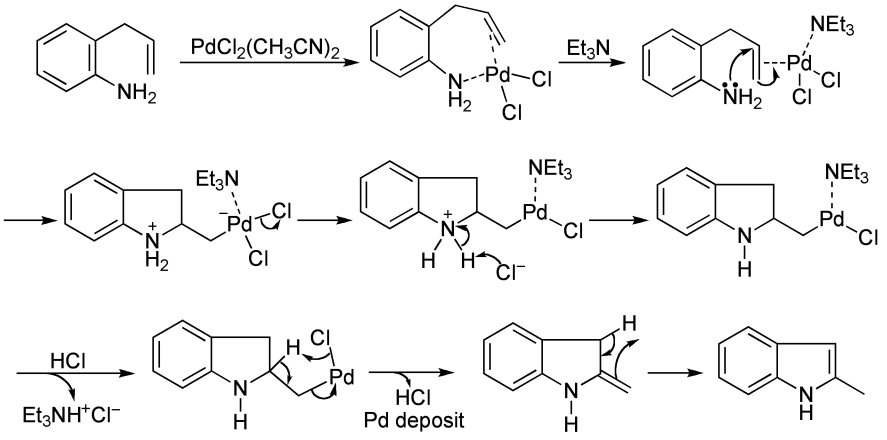
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The formation of indole from *o*-allylaniline with $PdCl_2$ is believed to involve the formation of palladium complex in which both the amino group and the olefinic moiety are

coordinated in a chelating fashion. Subsequently added triethylamine displaces the basic aromatic amine to form another complex in which the aromatic amine obtains a *trans*-geometry required for the amination of coordinated olefin. Attacking the coordinated olefin by the aromatic amines gives a σ-alkylpalladium complex, which upon elimination of HCl and β-elimination of "Pd-H", undergoes the spontaneous rearrangement to 2-methylindole via a [1,3]-H shift.[4,8] An illustrative scheme of the reaction course is provided below.



D. MODIFICATION

This reaction has been extended to form 3-methylindole in higher yields and under milder conditions without using a phosphine ligand.[10] In addition, the cyclization of *o*-halo-*N*-allylanilines has been performed in a homogeneous water/CH_3CN medium in the presence of a water soluble tris(3-sulfonatophenyl)phosphine sodium salt (TPPTS) ligand,[11] and in supercritical CO_2 in the presence of $Pd(OAc)_2$ and a fluorinated phosphine ligand, e.g., phenyl bis(2-perfluorohexyl)-ethylphosphine.[12]

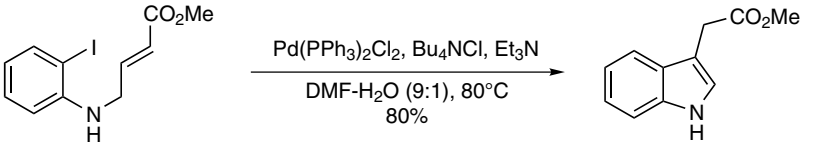
E. APPLICATIONS

The cyclization of *o*-halo *N*-allylaniline has been applied to the preparation of cycloprop[c]indol-5-ones,[7] indole-3-acetic acids and hetero analogs,[13] indole-3-pyruvic acid oxime ether,[14] 5-(sulfamoylmethyl)indoles,[15] the *anti*-migraine agent CP-122,288,[16] and the protected A-unit of CC-1065.[17] In addition, the cyclization of *o*-vinylaniline has been applied to *o*-vinyl-*N*-tosylanilines,[9,18] *o*-vinylacetanilides,[19] and *o*-vinyl-*N*-alkylanilines.[20]

F. RELATED REACTIONS

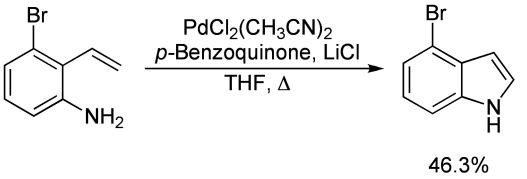
This reaction is related to the *Larock Indole Synthesis*, and mechanistically is relevant to the *Wacker Oxidation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 21.

To a 2 mL DMF-H_2O solution (9:1) containing 22 mg 4-[(2-iodophenyl)amino]but-2-enoic acid methyl ester (0.069 mmol), 29 mg tetrabutylammonium chloride (0.10 mmol), and 40 mg triethylamine (0.40 mmol) was added 5.0 mg bis(triphenylphosphine)palladium(II) chloride (0.007 mmol). The resulting mixture was stirred under nitrogen at 80°C for 2 days; the volatiles were then removed under vacuum. The residue was separated by preparative TLC using hexane/EtOAc (2:1) as the eluent to afford 10.5 mg indole-3-acetic acid methyl ester as a colorless viscous solid, in a yield of 80%. (*Note*: The yield has been given as 20% in reaction scheme but 80% in the experimental section.)



Reference 9.

A mixture of 0.606 g crude 3-bromo-2-ethenylaniline (3.06 mmol), 0.496 g *p*-benzoquinone (4.59 mmol), 0.616 g LiCl (15.0 mmol), 39 mg $PdCl_2(CH_3CN)_2$ (0.15 mmol), and 15 mL THF was purged with argon and then heated in a sealed tube at 100°C for 22 h. After cooling to room temperature, the solvent was removed in vacuo. The residue was chromatographed on silica gel by using hexanes as eluent to afford 0.277 g 4-bromoindole as a yellow oil, in a yield of 46.3%.

Other references related to the Hegedus indole synthesis are cited in the literature.[22]

H. REFERENCES

1. (a) Li, J. J., ed., *Name Reactions in Heterocyclic Chemistry*, John Wiley & Sons, Inc., New York, **2005**. (b) Lachance, N.; April, M. and Joly, M.-A., *Synthesis,* **2005**, 2571. (c) Gribble, G. W., "Indoles", in *Palladium in Heterocyclic Chemistry: A Guide for the Synthetic Chemist*, ed. Li, J. J. and Gribble, G. W., Elsevier, Oxford, **2000**, pp. 81–188. (d) Heathcock, C. H.; Stafford, J. A. and Clark, D. L., *J. Org. Chem.,* **1992**, *57*, 2575.
2. Gribble, G. W., *J. Chem. Soc*., *Perkin Trans. I*, **2000**, 1045.
3. Schirok, H., *J. Org. Chem*., **2006**, *71*, 5538.
4. Hegedus, L. S.; Allen, G. F. and Waterman, E. L., *J. Am. Chem. Soc.,* **1976**, *98*, 2674.
5. Hegedus, L. S.; Allen, G. F.; Bozell, J. J. and Waterman, E. L., *J. Am. Chem. Soc.,* **1978**, *100*, 5800.

6. Odle, R.; Blevins, B.; Ratcliff, M. and Hegedus, L. S., *J. Org. Chem.,* **1980**, *45*, 2709.
7. Sundberg, R. J. and Pitts, W. J., *J. Org. Chem.,* **1991**, *56*, 3048.
8. Cacchi, S. and Fabrizi, G., *Chem. Rev.,* **2005**, *105*, 2873.
9. Harrington, P. J. and Hegedus, L. S., *J. Org. Chem.,* **1984**, *49*, 2657.
10. Larock, R. C. and Babu, S., *Tetrahedron Lett.,* **1987**, *28*, 5291.
11. Genet, J. P.; Blart, E. and Savignac, M., *Synlett,* **1992**, 715.
12. Carrol, M. A. and Holmes, A. B., *Chem. Commun.,* **1998**, 1395.
13. Wensbo, D.; Annby, U. and Gronowitz, S., *Tetrahedron,* **1995**, *51*, 10323.
14. Wensbo, D.; Annby, U. and Gronowitz, S., *Tetrahedron,* **1996**, *52*, 14975.
15. Bosch, J.; Roca, T.; Armengol, M. and Fernández-Forner, D., *Tetrahedron,* **2001**, *57*, 1041.
16. Macor, J. E.; Ogilvie, R. J. and Wythes, M. J., *Tetrahedron Lett.,* **1996**, *37*, 4289.
17. (a) Tietze, L. F. and Buhr, W., *Angew. Chem. Int. Ed. Engl.,* **1995**, *34*, 1366. (b) Tietze, L. F. and Grote, T., *J. Org. Chem.,* **1994**, *59*, 192.
18. (a) Adams, D. R.; Duncton, M. A. J.; Roffey, J. R. A. and Spencer, J., *Tetrahedron Lett.,* **2002**, *43*, 7581. (b) Krolski, M. E.; Renaldo, A. F.; Rudisill, D. E. and Stille, J. K., *J. Org. Chem.,* **1988**, *53*, 1170. (c) Harrington, P. J.; Hegedus, L. S. and McDaniel, K. F., *J. Am. Chem. Soc.,* **1987**, *109*, 4335.
19. Kasahara, A.; Izumi, T.; Murakami, S.; Miyamoto, K. and Hino, T., *J. Heterocycl. Chem.,* **1989**, *26*, 1405.
20. Yamaguchi, M.; Arisawa, M. and Hirama, M., *Chem. Commun.,* **1998**, 1399.
21. Zhang, H.-C. and Maryanoff, B. E., *J. Org. Chem.,* **1997**, *62*, 1804.
22. (a) Abbiati, G.; Arcadi, A.; Bellinazzi, A.; Beccalli, E.; Rossi, E. and Zanzola, S., *J. Org. Chem.,* **2005**, *70*, 4088. (b) Pirrung, M. C.; Fujita, K. and Park, K., *J. Org. Chem.,* **2005**, *70*, 2537. (c) Nazaré, M.; Schneider, C.; Lindenschmidt, A. and Will, D. W., *Angew. Chem. Int. Ed.,* **2004**, *43*, 4526. (d) Takeda, A.; Kamijo, S. and Yamamoto, Y., *J. Am. Chem. Soc.,* **2000**, *122*, 5662. (e) Hegedus, L. S., *Transition Metals in the Synthesis of Complex Organic Molecules*, University Science Books, Sausalito, Calif., **1999**. (f) Söderberg, B. C. and Shriver, J. A., *J. Org. Chem.,* **1997**, *62*, 5838. (g) Steglich, W., *Chem. Eur. J.,* **1997**, *3*, 70. (h) Akazome, M.; Kondo, T. and Watanabe, Y., *J. Org. Chem.,* **1994**, *59*, 3375. (i) Larock, R. C. and Yum, E. K., *J. Am. Chem. Soc.,* **1991**, *113*, 6689. (j) Hegedus, L. S.; Sestrick, M. R.; Michaelson, E. T. and Harrington, P. J., *J. Org. Chem.,* **1989**, *54*, 4141. (k) Hegedus, L. S., *Angew. Chem. Int. Ed. Engl*., **1988**, *27*, 1113. (l) Sakamoto, T.; Kondo, Y. and Hiroshi, Y., *Heterocycles,* **1988**, *27*, 2225. (m) Abelman, M. M.; Oh, T. and Overman, L. E., *J. Org. Chem.,* **1987**, *52*, 4130. (n) Hegedus, L. S.; Toro, J. L.; Miles, W. H. and Harrington, P. J., *J. Org. Chem.,* **1987**, *52*, 3319. (o) Hegedus, L. S.; Weider, P. R.; Mulhern, T. A.; Asada, H. and D'Andrea, S., *Gazz. Chim. Ital.,* **1986**, *116*, 213. (p) Hegedus, L. S.; Winton, P. M. and Varaprath, S., *J. Org. Chem.,* **1981**, *46*, 2215. (q) Mori, M. and Ban, Y., *Tetrahedron Lett.*, **1979**, 1133. (r) Terpko, M. O. and Heck, R. F., *J. Am. Chem. Soc.*, **1979**, *101*, 5281. (s) Mori, M.; Kudo, S. and Ban, Y., *J. Chem. Soc., Perkin Trans. I,* **1978**, 771. (t) Mori, M.; Chiba, K. and Ban, Y., *Tetrahedron Lett.*, **1977**, 1037. (u) Isomura, K.; Uto, K. and Taniguchi, H., *J. Chem. Soc., Chem. Commun.,* **1977**, 664.

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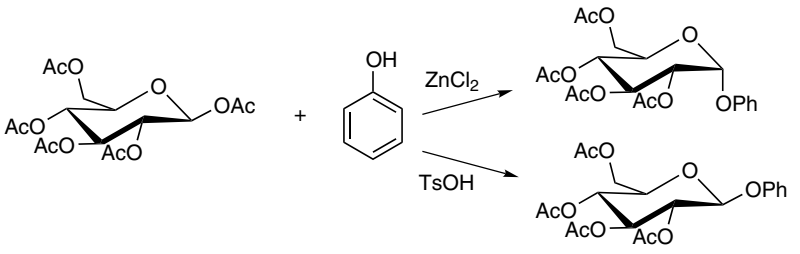
Helferich Condensation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Helferich and Schmitz-Hillebrecht in 1933.[1] It is the direct synthesis of acetylated phenyl glycosides from the fusion of monosaccharide pentaacetate and phenol in the presence of an acidic catalyst. Therefore, this reaction is known as the Helferich condensation,[2] Helferich and Schmitz-Hillebrecht fusion,[3] or Helferich and Schmitz-Hillebrecht synthesis.[4] In the presence of fused $ZnCl_2$, the α-anomer is produced from the condensation, whereas in the presence of *p*-toluenesulfuric acid, the β-anomer is formed.[1] This reaction has been improved by carrying out the condensation under vacuum where released acetic acid is removed immediately from the reaction system;[5] however, in the presence of acetic acid and acetic anhydride, even higher yields are obtainable compared to the original procedure.[6] It should be pointed out that this reaction is not suitable for the less common or harder to obtain phenols, such as tetrahydrocannabinol; in such cases, a high yield of glycosylation occurs in benzene solution in the presence of moist phosphorus oxychloride.[7]

B. GENERAL REACTION SCHEME



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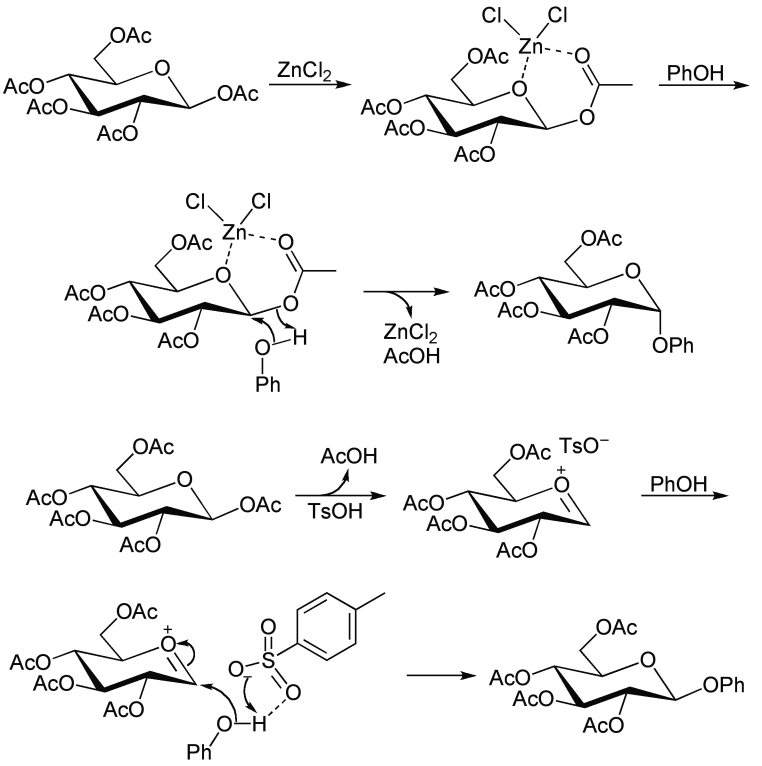
C. PROPOSED MECHANISMS

Although no mechanistic study is reported about this reaction, it is possible that $ZnCl_2$ chelates with the oxygen from the carbohydrate ring and 1-acetyl group, favoring the attack of phenol from the bottom of the carbohydrate ring and resulting in a phenyl α-glycoside. In the presence of TsOH, the 1-acetyl group directly evolves from the ring, giving a cation associated with tosylate. When coupling with phenol, the hydrogen bond between the phenol and the sulfonic group favors the geometry to give phenol β-glycoside. The said mechanism is illustrated here.



D. MODIFICATION

This reaction has been modified to take place under vacuum to remove acetic acid,[5] or in the presence of acetic acid and acetic anhydride.[6] Furthermore, phosphorus oxychloride is used to condense the carbohydrate with difficultly attainable phenols.[7]

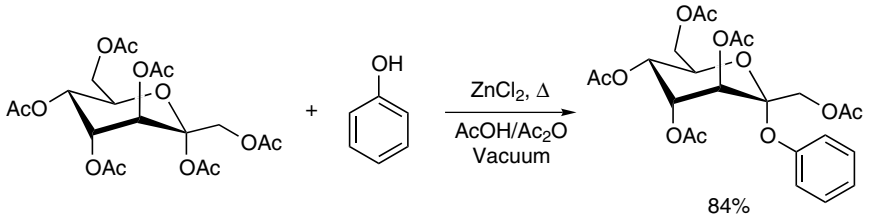
E. APPLICATIONS

This reaction has been used to prepare aryl glycosides.

F. RELATED REACTIONS

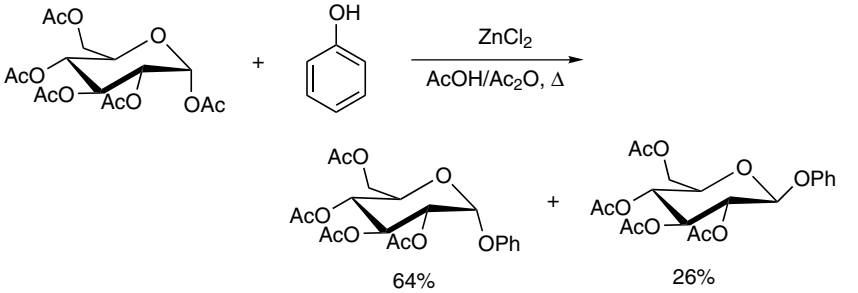
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 8.

A mixture of 4.0 g sedoheptulose hexaacetate, 8.0 g phenol, 2.0 g fused zinc chloride, 7.2 mL acetic acid, and 0.8 mL acetic anhydride was warmed until homogeneous and then heated in vacuo (water pump) for 2 h at 75–80°C. The residue was dissolved in 125 mL $CHCl_3$, and the extract was washed with water, twice with 3% aqueous NaOH and water. The washed extract was dried over Na_2SO_4, filtered through decolorizing carbon, and concentrated in a current of air. The crystalline residue was filtered and washed with pentane to yield 3.6 g phenyl α-D-altro-heptulopyranoside pentaacetate, in a yield of 84%. After two recrystallizations from aqueous acetone, the clusters of prismatic needles melted at 148–150°C.



Reference 6.

To a melt mass in a Claisen distilling flask from 25 g α-pentaacetylglucose (0.064 mol) and 24 g phenol (0.255 mol) was added 6.3 g fused $ZnCl_2$ dissolved in 20 mL of a 95:5 $AcOH/Ac_2O$ mixture. This homogeneous reaction mixture was heated in a bath at 120–125°C for 2 h. The acetic acid formed in the reaction, as well as that added with the zinc chloride, was removed by evacuating the flask with a water pump during the heating. The resulting red syrup was dissolved in 300 mL ethylene dichloride, and the zinc chloride and phenol were removed by washing with water and aqueous sodium hydroxide, respectively. The solution was dried with granular calcium chloride, concentrated in vacuo, and the product crystallized at 0°C from 150 mL ethanol. A dense mass of isomeric acetates was obtained, with a total yield of 92%. Separation of the α-form was effected

by allowing this mixture to crystallize slowly from 350 mL ethanol. After four recrystallizations, pure crystalline tetraacetyl-α-phenyl-D-glucoside, was isolated as shining needles with a total yield of 64%, m.p. 115°C. From the mother liquor was obtained the anomeric tetraacetyl-β-phenyl-D-glucoside in a yield of 26%.

Other references related the Helferich condensation are cited in the literature.[9]

H. REFERENCES

1. Helferich, B. and Schmitz-Hillebrecht, E., *Ber.,* **1933**, *66*, 378.
2. Fisher, J. H.; Hawkins, W. L. and Hibbert, H., *J. Am. Chem. Soc.,* **1941**, *63*, 3031.
3. Hurd, C. D. and Bonner, W. A., *J. Am. Chem. Soc.,* **1945**, *67*, 1764.
4. Hurd, C. D. and Bonner, W. A., *J. Org. Chem.,* **1946**, *11*, 50.
5. Shishido, K., *J. Soc. Chem. Ind. Jpn.,* **1936**, 39, Suppl. Binding 217 (in German) [*Chem. Abstr.,* **1936**, *30*, 7118].
6. Montgomery, E. M.; Richtmyer, N. K. and Hudson, C. S., *J. Am. Chem. Soc.,* **1942**, *64*, 690.
7. Bembry, T. H. and Powell, G., *J. Am. Chem. Soc.,* **1942**, *64*, 2419.
8. Zissis, E. and Richtmyer, N. K., *J. Org. Chem.,* **1965**, *30*, 462.
9. (a) Witkowski, S. and Walejko, P., *Z. Naturforsch.,* **2001**, *56b*, 411. (b) Samoshina, N. S.; Denisenko, V. A. and Uvarova, N. I., *Chem. Nat. Compd.,* **1986**, *21*, 613. (c) Durette, P. L. and Shen, T. Y., *Carbohydr. Res.,* **1980**, *81*, 261. (d) Seymour, F. R.; Knapp, R. D.; Nelson, T. E. and Pfannemueller, B., *Carbohydr. Res.,* **1979**, *70*, 125. (e) Miyai, K. and Jeanloz, R. W., *Carbohydr. Res.,* **1972**, *21*, 45. (f) Gasman, R. C. and Johnson, D. C., *J. Org. Chem.,* **1966**, *31*, 1830. (g) Conchie, J. and Levvy, G. A., *Methods Carbohydr. Chem.,* **1963**, *2*, 345. (h) Bollenback, G. N.; Long, J. W.; Benjamin, D. G. and Lindquist, J. A., *J. Am. Chem. Soc.,* **1955**, *77*, 3310. (i) Jermyn, M. A., *Aust. J. Chem.,* **1955**, *8*, 403. (j) Jermyn, M. A., *Aust. J. Chem.,* **1954**, *7*, 202. (k) Dyfverman, A. and Lindberg, B., *Acta Chem. Scand.,* **1950**, *4*, 878. (l) Hurd, C. D. and Zelinski, R. P., *J. Am. Chem. Soc.,* **1947**, *69*, 243. (m) Hurd, C. D. and Bonner, W. A., *J. Org. Chem.,* **1945**, *10*, 603. (n) Montgomery, E. M.; Richtmyer, N. K. and Hudson, C. S., *J. Am. Chem. Soc.,* **1943**, *65*, 1848. (o) Bambry, T. H. and Powell, G., *J. Am. Chem. Soc.,* **1942**, *64*, 2419. (p) Williams, R. T., *J. Chem. Soc.,* **1940**, 1402. (q) Pigman, W. W., *J. Am. Chem. Soc.,* **1940**, *62*, 1371. (r) Spath, E. and Tyray, E., *Ber.,* **1939**, *72B*, 2089. (s) Richtmyer, N. K., *J. Am. Chem. Soc.,* **1934**, *56*, 1633.

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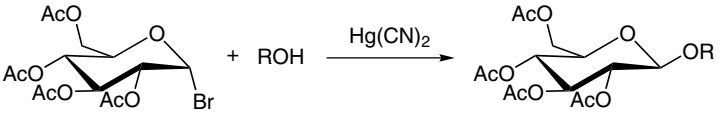
Helferich Glycosylation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Helferich and Weiss in 1956.[1] It is the synthesis of *O*-glycosides from protected glycosyl bromide and alcohol (or another carbohydrate) in the presence of mercuric cyanide. Therefore, it is generally known as the Helferich glycosylation.[2] Occasionally, it is also referred to as the Helferich condition.[3] This reaction is especially suitable for the glycosylation of hindered secondary alcohols of allocyathin.[4] According to the anomeric effect, glycosyl bromide is primarily an α-anomer, so that the resulting glycoside is a β-glycoside[2a,2b,4b] via a S_N2 mechanism.

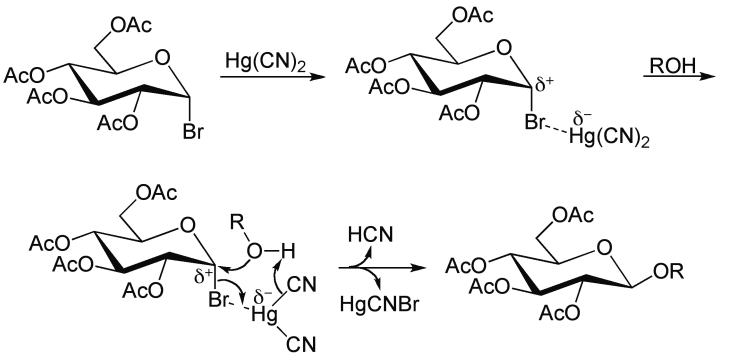
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Part of the mechanism is illustrated here, in which mercuric cyanide coordinates with a bromine atom from glycosyl bromide and polarizes the carbon-bromide bond, then S_N2 substitution occurs leading to the formation of β-glycoside and releasing HgCNBr, which might enter the glycosylation again.

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang



D. MODIFICATION

N/A

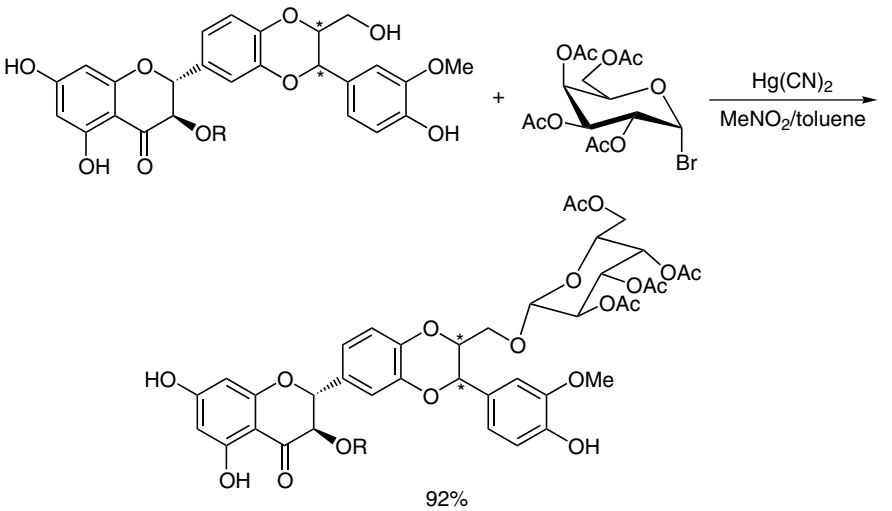
E. APPLICATIONS

This reaction has general application in the formation of glycosides.

F. RELATED REACTIONS

This reaction is related to the *Koenigs-Knorr Glycosylation*.

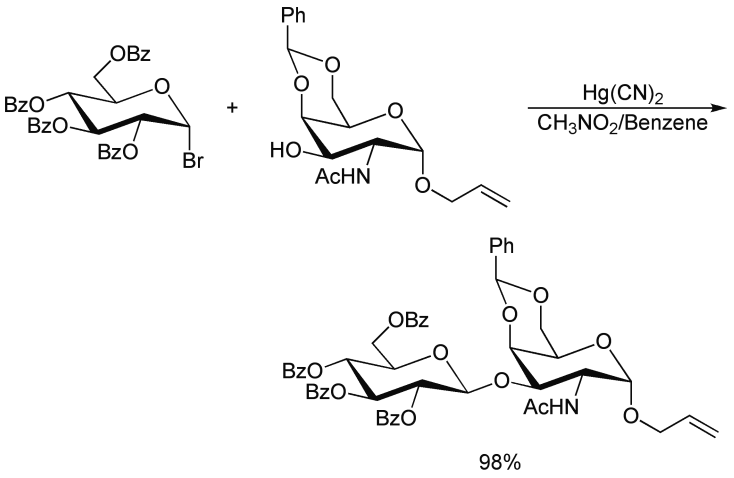
G. CITED EXPERIMENTAL EXAMPLES



92%

Reference 2d.

Silybin, dried by azeotropic distillation with toluene to remove crystal-bound water, (5.3 g, 11.0 mmol) was dissolved in a total of 450 mL mixed solvent of nitromethane and toluene (v/v = 14 : 11), from which 10–20 mL was distilled off using the Distler apparatus to remove traces of water. The mixture was stirred at 60°C under nitrogen and 2.8 g $Hg(CN)_2$ (11.0 mmol) was added. When all catalyst was dissolved, a solution of 5.2 g 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (12.5 mmol) in a minimal amount of the solvent mixture was added, and stirring the mixture at 60°C was continued for 20 h. Then 2.1 g tetraacetyl-α-bromo-galactose (5 mmol) and 0.76 g $Hg(CN)_2$ (3 mmol) were added. The addition of 1.0 g carbohydrate and 0.25 g $Hg(CN)_2$ was repeated after another 20 h and the reaction was terminated after a total of 50 h. The mixture was evaporated to one fifth its original volume and cooled, and the bulk of precipitated $Hg(CN)_2$ was filtered off. The rest of the mercury was removed by extraction with 3% aqueous KI (3 × 100 mL). The organic phase was dried over Na_2SO_4. The crude mixture of per-acetylated silybin glycosides was separated from any unchanged silybin and glycosyl donor by flash chromatography on silica gel (toluene/dichloromethane/MeOH, 1:10:0.8). Final purification and separation of the per-acetylglycosides of two silybin diastereoisomers was achieved by medium-pressure liquid chromatography on a prepacked Lobar column (silica gel, size C) by the solvent mixture of toluene/HCO_2H/AcOH (40:0.7:0.7; 9.9 mL/min) with a linear acetone gradient of 12–20% (v/v). Before evaporation, pooled fractions were neutralized by successive washings with water, saturated aqueous $NaHCO_3$, and brine. The yield of crude silybin 23-*O*-β-D-2,3,4,6-tetraacetylgalactopyranoside was 8.3 g (92%).



Reference 2b.

A solution of 1.67 g allyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-galactopyranoside (4.78 mmol) in 60 mL nitromethane/benzene mixture (v/v = 1:1) was stirred for a couple of hours at room temperature. To ensure dryness, the solution was concentrated under reduced pressure. This process was repeated three times by adding the same volume of solvent and then concentrated until one half the volume remained. The temperature was adjusted to 25°C and 4.70 g 2,3,4,6-tetra-*O*-benzoyl-α-D-galactopyranosyl bromide (7.13 mmol) and 1.80 g $Hg(CN)_2$ (7.13 mmol) were added successively at N_2

atmosphere. The resulting solution was stirred at room temperature for 18 h. The solvent was removed under vacuum. The residue was dissolved in 40 mL $CHCl_3$ and then filtered through a Celite pad. The filtrate was successively washed with 10% aqueous KI, saturated $NaHCO_3$, and distilled water, and then was dried over Na_2SO_4. After concentration, the residue was purified by silica gel column chromatography (benzene/EtOAc = 15:1) to give 4.31 g allyl (2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-(1$\rightarrow$3)-2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-galactopyranoside as a white foamy solid, in a yield of 98%, m.p. 109.7–111.0°C, $R_f = 0.59$ (benzene/EtOAc,1:2).

Other references related to the Helferich glycosylation are cited in the literature.[5]

H. REFERENCES

1. Helferich, B. and Weiss, K., *Ber.,* **1956**, *89*, 314.
2. (a) Backinowsky, L. B.; Abronina, P. I.; Shashkov, A. S.; Grachev, A. A.; Kochetkov, N. K.; Nepogodiev, S. A. and Stoddart, J. F., *Chem. Eur. J.,* **2002**, *8*, 4412. (b) Roy, R.; Baek, M.-G. and Rittenhouse-Olson, K., *J. Am. Chem. Soc.,* **2001**, *123*, 1809. (c) Kren, V.; Ulrichova, J.; Kosina, P.; Stevenson, D.; Sedmera, P.; Prikrylova, V.; Halada, P. and Simanek, V., *Drug Metabol. Dispos.,* **2000**, *28*, 1513. (d) Kren, V.; Kubisch, J.; Sedmera, P.; Halada, P.; Prikrylova, V.; Jegorov, A.; Cvak, L.; Gebhardt, R.; Ulrichova, J. and Simanek, V., *J. Chem. Soc., Perkin Trans. I,* **1997**, 2467. (e) Leigh, D. A.; Smart, J. P. and Truscello, A. M., *Carbohydr. Res.,* **1995**, *276*, 417. (f) Polt, R.; Szabo, L.; Treiberg, J.; Li, Y. S. and Hruby, V. J., *J. Am. Chem. Soc.,* **1992**, *114*, 10249. (g) Kochetkov, N. K.; Zhulin, V. M.; Klimov, E. M.; Malysheva, N. N. and Makarova, Z. G., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1987**, 1686. (h) Winnik, F. M.; Carver, J. P. and Krepinsky, J. J., *J. Org. Chem.,* **1982**, *47*, 2701.
3. (a) Palian, M. M. and Polt, R., *J. Org. Chem.,* **2001**, *66*, 7178. (b) Pozsgay, V.; Brisson, J.-R.; Jennings, H. J.; Allen, S. and Paulson, J. C., *J. Org. Chem.,* **1991**, *56*, 3377.
4. (a) Snider, B. B.; Vo, N. H. and O'Neil, S. V., *J. Org. Chem.,* **1998**, *63*, 4732. (b) Snider, B. B.; Vo, N. H.; O'Neil, S. V. and Foxman, B. M., *J. Am. Chem. Soc.,* **1996**, *118*, 7644.
5. (a) Aich, U. and Loganathan, D., *Carbohydr. Res.,* **2007**, *342*, 704. (b) Chauvin, A.-L.; Nepogodiev, S. A. and Field, R. A., *Carbohydr. Res.,* **2004**, *339*, 21. (c) Ress, D. K. and Linhardt, R. J., *Curr. Org. Synth.,* **2004**, *1*, 31. (d) Sokolov, V. M.; Zakharov, V. I. and Studentsov, E. P., *Russ. J. Gen. Chem.,* **2002**, *72*, 806. (e) Witkowski, S. and Walejko, P., *Zeitsch. Naturforsch., B: Chem. Sci.,* **2001**, *56*, 411. (f) Backinowsky, L. V.; Abronina, P. L.; Nepogodiev, S. A.; Grachev, A. A. and Kochetkov, N. K., *Russ. Chem. Bull.,* **1998**, *47*, 1589. (g) Roy, R.; Page, D.; Perez, S. F. and Bencomo, V. V., *Glycoconjugate J.,* **1998**, *15*, 251. (h) Khatuntseva, E. A.; Sherman, A. A.; Shashkov, A. S.; Dabrowski, J. and Nifant'ev, N. E., *Bioorg. Khim.,* **1997**, *23*, 228. (i) Vogel, C.; Steffan, W.; Boye, H.; Kristen, H.; Betaneli, V. I.; Ott, A. Y. and Kochetkov, N. K., *Carbohydr. Res.,* **1992**, *237*, 131. (j) Klaffke, W.; Pudlo, P.; Springer, D. and Thiem, J., *Liebigs Annalen der Chemie*, **1991**, 509. (k) Smith, A. B.; Rivero, R. A.; Hale, K. J. and Vaccaro, H. A., *J. Am. Chem. Soc.,* **1991**, *113*, 2092. (l) Ojika, M.; Wakamatsu, K.; Niwa, H. and Yamada, K., *Tetrahedron,* **1987**, *43*, 5275. (m) Betaneli, V. I.; Backinowsky, L. V.; Byramova, N. E.; Ovchinnikov, M. V.; Litvak, M. M. and Kochetkov, N. K., *Carbohydr. Res.,* **1983**, *113*, C1. (n) Winnik, F. M.; Brisson, J.-R.; Carver, J. P. and Krepinsky, J. J., *Carbohydr. Res.,* **1982**, *103*, 15. (o) Ekborg, G.; Sone, Y. and Glaudemans, C. P. J., *Carbohydr. Res.,* **1982**, *110*, 55. (p) Eklind, K.; Garegg, P. J. and Gotthammar, B., *Acta Chem. Scand., Ser. B.,* **1976**, *B30*, 300. (q) Ekborg, G.; Garegg, P. J. and Gotthammar, B., *Acta Chem. Scand., Ser. B,* **1975**, *B29*, 765. (r) Helferich, B. and Zinner, J., *Ber.,* **1962**, *95*, 2604. (s) Helferich, B. and Bettin, K. L., *Ber.,* **1961**, *94*, 1159.

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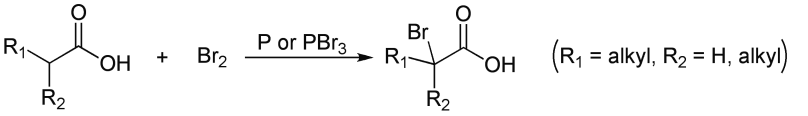
Hell-Volhard-Zelinsky Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Hell in 1881[1] and subsequently extended by Volhard[2] and Zelinsky[3] in 1887. It is the synthesis of α-bromocarboxylic acid by treatment of aliphatic acid containing at least one α-hydrogen with bromine in the presence of a catalytic amount of phosphorus or phosphorus tribromide. Therefore, this reaction is generally known as the Hell-Volhard-Zelinsky reaction[4] or simply referred to as the Zelinsky reaction.[5] Even though the same procedure can be applied to the chlorination of carboxylic acid[6]—the reaction known as the Hell-Volhard-Zelinsky chlorination[7]—appreciable amounts of carboxylic acids with chlorine atom at various positions rather than the α-position are also produced.[8] Therefore, the Hell-Volhard-Zelinsky reaction is primarily good for the bromination, that occurs smoothly even for the carboxylic acid with an alkyl substituent at the α-position;[9] in addition, phosphorous trichloride and thionyl chloride have also been used to catalyze the bromination of aliphatic acid.[10] However, it should be pointed out that thionyl chloride is usually used to convert carboxylic acid into acyl chloride, so the formation of acyl chloride can be combined with the bromination by performing the bromination in thionyl chloride.[11] Although a few mechanisms have been proposed for this bromination, the majority of experimental evidence supports the formation of an enol[8,12] instead of a ketene[6,7] intermediate, which is analogous to the acid-catalyzed halogenation of ketones.[12a] It is interesting that the bromination of levulinic acid with one equivalent of bromine in the presence of 1.6 mol% phosphorus gives rise to 3,5-dibromolevulinic acid as the major product.[13] This reaction is synthetically useful because the α-halogen can easily be replaced by other functional groups, such as CN, and the resulting α-cyano carboxylic acid yields malonic ester in the presence of aqueous acid and ethanol.

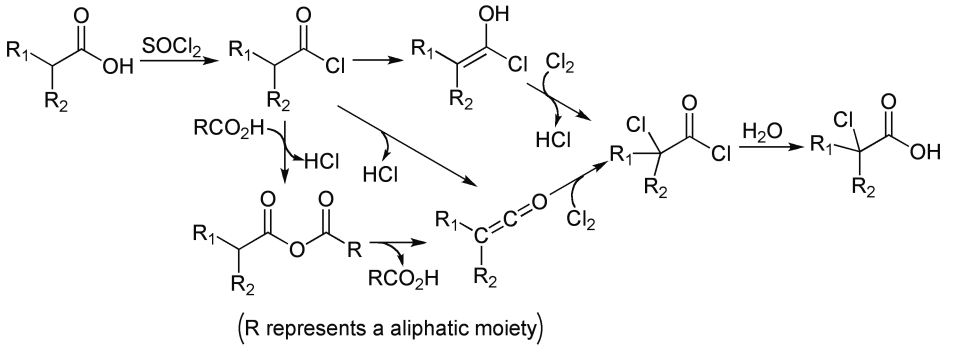
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME

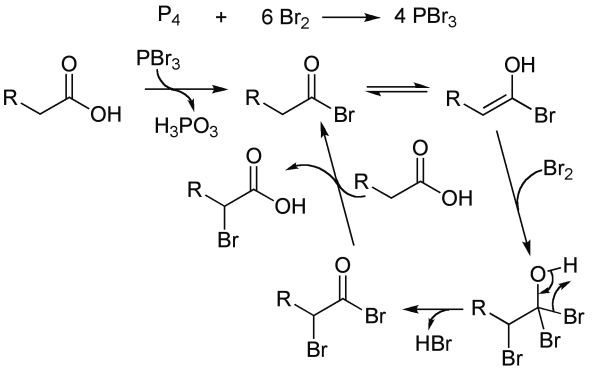


C. PROPOSED MECHANISMS

The general reaction mechanism of chlorination outlined by Little et al.[6] is given in Scheme 1, followed by an alternative mechanism proposed in this book (Scheme 2).



SCHEME 1. *Reaction mechanism involving a ketene intermediate.*



SCHEME 2. *Bromination mechanism involving an enol intermediate.*

D. MODIFICATION

N/A

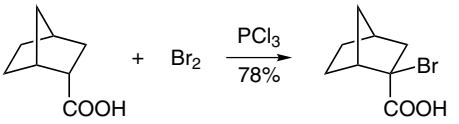
E. APPLICATIONS

This reaction has been used to prepare α-halo aliphatic acids.

F. RELATED REACTIONS

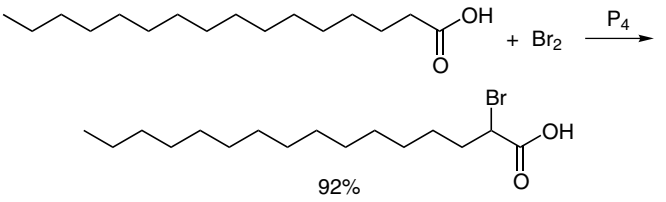
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 14.

A mixture of 49.2 g norbornane-2-endocarboxylic acid (0.35 mol), 63.8 g bromine (0.4 mol), and 1.5 mL phosphorus trichloride was heated on a steam bath at 80–90°C for 7.5 h. After being cooled, the mixture was taken up in Et_2O. The ether solution was washed with $NaHSO_3$ and then several times with water, and finally dried over $MgSO_4$. Upon removal of solvent, 60.4 g α-bromo-norbornane-2-endocarboxylic acid was obtained as a yellow crystalline solid, in a yield of 78%. The solid, after being washed with petroleum ether and decolorized with Norite, recrystallized from benzene or nitroethane with a melting point of 151°C.



Reference 15.

To a 1-L three-necked flask equipped with a stirrer, dropping funnel, and condenser protected with a calcium chloride tube were added 100 g palmitic acid (0.39 mol) and 5.0 g red phosphorus. The acid was melted on a water bath at 70°C, and 50 mL dry bromine (0.975 mol) was dropped in over 8 h with continuous stirring, then heated and stirred for an additional 4 h, at which time the evolution of HBr ceased. The clear, dark red reaction mixture was heated on a boiling water bath for 30 min until all the excess bromine had been removed, giving a clear straw-colored oil. Then the hot product was poured into 2 L water and allowed to stand overnight. The hydrolyzed acid was washed several times with water, and finally was heated in water with stirring. The cooled gel was taken up in 500 mL ether. The ether solution was washed until the washings were neutral to litmus and was dried over Na_2SO_4. Upon removal of ether, 121.0 g α-bromo palmitic acid was obtained, in a yield of 92%. After recrystallization from petroleum ether with Norite and finally from ethanol, the product had a melting point of 52.3–52.5°C.

Other references related to the Hell-Volhard-Zelinsky reaction are cited in the literature.[16]

H. REFERENCES

1. Hell, C., *Ber.,* **1881**, *14*, 891.
2. Volhard, J., *Ann.,* **1887**, *242*, 141.
3. Zelinsky, N., *Ber.,* **1887**, *20*, 2026.
4. (a) Chatterjee, N. R., *Indian J. Chem., Sect. B,* **1978**, *16B*, 730. (b) Turner, J. A. and Kubler, D. G., *Furman Univ. Bull., Furman Studies*, **1965**, *12*, 45.
5. Mrachkovskaya, L. B.; Anisimova, O. S.; Turchin, K. F. and Yakhontov, L. N., *Zh. Org. Khim.,* **1976**, *12*, 914.
6. Little, J. C.; Tong, Y.-L. C. and Heeschen, J. P., *J. Am. Chem. Soc.,* **1969**, *91*, 7090.
7. Little, J. C.; Sexton, A. R.; Tong, Y.-L. C. and Zurawic, T. E., *J. Am. Chem. Soc.,* **1969**, *91*, 7098.
8. (a) Harpp, D. N.; Bao, L. Q.; Black, C. J.; Gleason, J. G. and Smith, R. A., *J. Org. Chem.,* **1975**, *40*, 3420. (b) Rodin, R. L. and Gershon, H., *J. Org. Chem.,* **1973**, *38*, 3919.
9. Gensler, W. J., *Chem. Rev.,* **1957**, *57*, 191.
10. Cheronis, N. D. and Spitzmueller, K. H., *J. Org. Chem.,* **1941**, *6*, 349.
11. Schwenk, E. and Papa, D., *J. Am. Chem. Soc.,* **1948**, *70*, 3626.
12. (a) Kwart, H. and Scalzi, F. V., *J. Am. Chem. Soc.,* **1964**, *86*, 5496. (b) Sontag, N. O., *Chem. Rev.,* **1953**, *52*, 358. (c) Watson, H. B., *Chem. Rev.,* **1930**, *7*, 173.
13. Hurd, C. D. and Ferraro, J. R., *J. Org. Chem.,* **1951**, *16*, 1639.
14. Kwart, H. and Null, G., *J. Am. Chem. Soc.,* **1959**, *81*, 2765.
15. Sweet, R. S. and Estes, F. L., *J. Org. Chem.,* **1956**, *21*, 1426.
16. (a) Liu, H.-J. and Luo, W., *Synth. Commun.,* **1991**, *21*, 2097. (b) Itoh, K.; Kori, M.; Inada, Y.; Nishikawa, K.; Kawamatsu, Y. and Sugihara, H.,*Chem. Pharm. Bull.,* **1986**, *34*, 2078. (c) Febres, A.; Layrisse, I.; Marquez M., H.; Bentolila, J.; De Marcano, D. and Marquez, C., *Revista Tecnica INTEVEP*, **1985**, *5*, 53. (d) Crawford, R. J., *J. Org. Chem.,* **1983**, *48*, 1364. (e) Lange, G. L. and Otulakowski, J. A., *J. Org. Chem.,* **1982**, *47*, 5093. (f) Ogata, Y. and Sugimoto, T., *J. Org. Chem.,* **1978**, *43*, 3684. (g) Prasad, K. and Thakur, M. M., *J. Indian Chem. Soc.,* **1978**, *55*, 722. (h) Ogata, Y.; Harada, T.; Matsuyama, K. and Ikejiri, T., *J. Org. Chem.,* **1975**, *40*, 2960. (i) Chow, A. W.; Jakas, D. R. and Hoover, J. R. E., *Tetrahedron Lett.*, **1966**, 5427. (j) Kempter, G. and Moser, G., *J. Prakt. Chem.,* **1966**, *34*, 104. (k) Vaughan, W. R.; Caple, R.; Csapilla, J. and Scheiner, P., *J. Am. Chem. Soc.,* **1965**, *87*, 2204. (l) Harwood, H. J., *Chem. Rev.,* **1962**, *62*, 102. (m) Sonntag, N. O. V., *Chem. Rev.,* **1953**, *52*, 237. (n) Nelson, N. K. and Morris, H. H., *J. Am. Chem. Soc.,* **1953**, *75*, 3337. (o) Cason, J.; Allinger, N. L. and Williams, D. E., *J. Org. Chem.,* **1953**, *18*, 842. (p) Dziewiatkowski, D. D. and Lewis, H. B., *J. Biol. Chem.,* **1945**, *158*, 77. (q) Marvel, C. S., *Org. Synth.,* **1941**, *21*, 74.

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Hemetsberger Indole Synthesis

(Hemetsberger Reaction, Hemetsberger-Knittel Indole Synthesis)

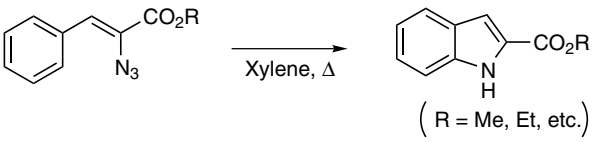
A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Hemetsberger and Knittel et al in 1969.[1] It is the synthesis of indole-2-carboxylic esters via the thermal decomposition of 3-aryl-2-azidopropenoic esters. Although this reaction has not been explored extensively due to the instability and difficult accessibility of the starting material, it has been given a variety of names, including the Hemetsberger azide pyrolysis,[2] Hemetsberger cyclization,[3] Hemetsberger reaction,[2–4] Hemetsberger rearrangement,[5] Hemetsberger-Rees styryl azide thermolysis,[6] Hemetsberger indole synthesis,[7] Hemetsberger-Knittel indole synthesis,[8] Hemetsberger-Knittel reaction,[9] and Hemetsberger synthesis.[7c,10]

In this reaction, the starting materials are usually prepared by the *Claisen-Schmidt Condensation*[11] between aromatic aldehydes and methyl azidoacetate; for example, upon treatment with 4 eq. ethyl azidoacetate and sodium methoxide in methanol, the corresponding azidocinnamic ester was prepared from 2-*O*-(1′-methyl)hexyl-5-bromo 2-hydroxylbenzaldehyde.[3] On the other hand, the thermal decomposition is usually carried out in refluxing xylene,[3,4a,4c,4d,7a] yielding indole derivatives of highly regiospecificity.[4d]

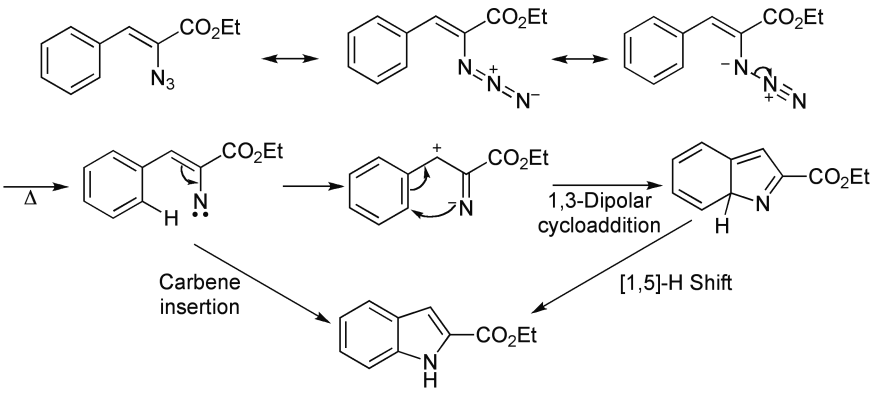
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Although the mechanism of Hemetsberger indole synthesis is not quite clear, the reaction is postulated to proceed via a highly electrophilic singlet nitrene species,[11] which then inserts into an aromatic ring to form the indole derivatives. In addition, 2H-azirines are also proposed as the intermediates for this reaction,[7b] arising from the insertion of nitrene to the adjacent double bond. A tentative mechanism is given below.



D. MODIFICATION

This reaction has been extended to the synthesis of thiophene[4b] and pyridine[7a] fused pyrrole derivatives.

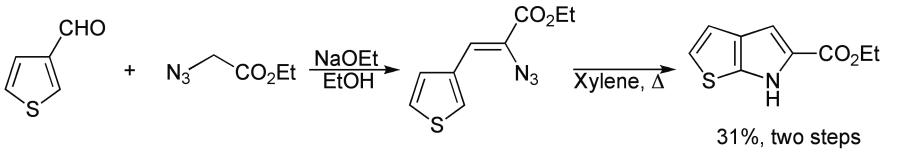
E. APPLICATIONS

This reaction has been successfully used for the synthesis of a number of indole alkaloids.[3,9b,12]

F. RELATED REACTIONS

N/A

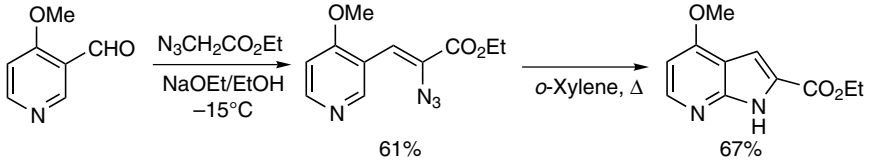
G. CITED EXPERIMENTAL EXAMPLES



Reference 4b.

To a 0.15 M NaOEt (4 eq.) solution in ethanol at 0°C was added dropwise a solution of 1 eq. 3-formylthiophene and 4 eq. ethyl azidoacetate. The resulting mixture was stirred at 0°C for 1 h and at room temperature for an additional 1 h; then it was poured into a saturated NH_4Cl solution. The product was extracted with ether, and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography to provide ethyl α-azido-β-(3-thiophenyl) acrylate.

A 100-mL toluene solution of acrylate (0.2 M, 20 mmol) was heated at 145°C for 60 min and then cooled to room temperature. After evaporation of the solvent, the residue was purified by column chromatography to afford 1.2 g 6*H*-thieno[2,3-b]pyrrole-5-carboxylic acid ethyl ester as a white solid, in a yield of 31% for two steps, $R_f = 0.5$ (EtOAc/hexanes, 1:4).



Reference 7a.

A mixture of 4.15 g ethyl azidoacetate (32 mmol) and 1.1 g 3-formyl-4-methoxypyridine (8.02 mmol) in 50 mL anhydrous EtOH was added dropwise under nitrogen at –15°C to a 30 mL well-stirred solution containing 0.74 g Na (32.1 mmol). The mixture was stirred at –15°C for 72 h and poured into 50 mL 30% NH_4Cl aqueous solution. The separated solid was washed with H_2O, air-dried, and recrystallized from EtOAc/*n*-hexane (1:1) to give 1.21 g ethyl α-azido-β-(4-methoxypyrid-3-yl)-acrylate as colorless needles, in a yield of 61%, m.p. 106–108°C.

A stirred solution of 1.0 g ethyl α-azido-β-(4-methoxypyrid-3-yl)-acrylate (4.03 mmol) in 140 mL dry *o*-xylene was heated in a molten salts bath at 170°C for 25 min. After being cooled at −10°C, the precipitated white solid was collected by filtration, washed with Et_2O, and recrystallized from CH_2Cl_2 to give 0.59 g 2-ethoxycarbonyl-4-methoxypyrrolo-[2,3-b]pyridine as white needles, in a yield of 67%, m.p. 216–217°C.

Other references related to the Hemetsberger indole synthesis are cited in the literature.[13]

H. REFERENCES

1. Hemetsberger, H.; Knittel, D. and Weidmann, H., *Monatsh. Chem.,* **1969**, *100*, 1599.
2. Blair, J. B.; Kurrasch-Orbaugh, D.; Marona-Lewicka, D.; Cumbay, M. G.; Watts, V. J.; Barker, E. L. and Nichols, D. E., *J. Med. Chem.,* **2000**, *43*, 4701.

3. Tercel, M.; Gieseg, M. A.; Denny, W. A. and Wilson, W. R., *J. Org. Chem.,* **1999**, *64*, 5946.
4. (a) Sechi, M.; Casu, F.; Campesi, I.; Fiori, S. and Mariani, A., *Molecules,* **2006**, *11*, 968. (b) Venable, J. D.; Cai, H.; Chai, W. Y.; Dvorak, C. A.; Grice, C. A.; Jablonowski, J. A.; Shah, C. R.; Kwok, A. K.; Ly, K. S.; Pio, B.; Wei, J. M.; Desai, P. J.; Jiang, W.; Nguyen, S.; Ling, P.; Wilson, S. J.; Dunford, P. J.; Thurmond, R. L.; Lovenberg, T. W.; Karlsson, L.; Carruthers, N. I. and Edwards, J. P., *J. Med. Chem.,* **2005**, *48*, 8289. (c) Sechi, M.; Derudas, M.; Dallocchio, R.; Dessì, A.; Bacchi, A.; Sannia, L.; Carta, F.; Palomba, M.; Ragab, O.; Chan, C.; Shoemaker, R.; Sei, S.; Dayam, R. and Neamati, N., *J. Med. Chem.,* **2004**, *47*, 5298. (d) da Rosa, F. A. F.; Rebelo, R. A. and Nascimento, M. G., *J. Braz. Chem. Soc.,* **2003**, *14*, 11. (e) Soll, R. M.; Humber, L. G.; Deininger, D.; Asselin, A. A.; Chau, T. T. and Weichman, B. M., *J. Med. Chem.,* **1986**, *29*, 1457.
5. Bräse, S.; Gil, C.; Knepper, K. and Zimmermann, V., *Angew. Chem. Int. Ed.,* **2005**, *44*, 5188.
6. Boger, D. L. and Coleman, R. S., *J. Am. Chem. Soc.,* **1987**, *109*, 2717.
7. (a) Molina, P.; Fresneda, P. M. and Delgado, S., *J. Org. Chem.,* **2003**, *68*, 489. (b) Gilchrist, T. L., *Aldrichimica Acta,* **2001**, *34*, 51. (c) Gribble, G. W., *J. Chem. Soc*., *Perkin Trans. I*, **2000**, 1045.
8. Borza, I.; Bozó, É.; Barta-Szalai, G.; Kiss, C.; Tárkányi, G.; Demeter, Á.; Gáti, T.; Háda, V.; Kolok, S.; Gere, A.; Fodor, L.; Nagy, J.; Galgóczy, K.; Magdó, I.; Ágai, B.; Fetter, J.; Bertha, F.; Keserü, G. M.; Horváth, C.; Farkas, S.; Greiner, I. and Domány, G., *J. Med. Chem.,* **2007**, *50*, 901.
9. (a) Schirok, H., *J. Org. Chem.,* **2006**, *71*, 5538. (b) Murakami, Y.; Watanabe, T.; Suzuki, H.; Kotake, N.; Takahashi, T.; Toyonari, K.; Ohno, M.; Takase, K.; Suzuki, T. and Kondo, K., *Chem. Pharm. Bull.,* **1997**, *45*, 1739.
10. Milbank, J. B. J.; Tercel, M.; Atwell, G. J.; Wilson, W. R.; Hogg, A. and Denny, W. A., *J. Med. Chem.,* **1999**, *42*, 649.
11. Lindley, J. M.; McRobbie, I. M.; Meth-Cohn, O. and Suschitzky, H., *Tetrahedron Lett.,* **1976**, 4513.
12. (a) Magnus, P. and Mansley, T. E., *Tetrahedron Lett.,* **1999**, *40*, 6909. (b) Samanta, S. S.; Ghosh, S. C. and De, A., *J. Chem. Soc.*, *Perkin Trans. I*, **1997**, 3673. (c) Molina, P.; Alcántara, J. and López-Leonardo, C., *Tetrahedron*, **1997**, *53*, 3281. (d) Kiselyov, A. S.; van Aken, K.; Gulevich, Y. and Strekowski, L., *J. Heterocycl. Chem.*, **1994**, *31*, 1299.
13. (a) Tietze, L. F. and Major, F., *Eur. J. Org. Chem.,* **2006**, 2314. (b) Roy, P. J.; Dufresne, C.; Lachance, N.; Leclerc, J.-P., Boisvert, M.; Wang, Z. and Leblanc, Y., *Synthesis,* **2005**, 2751. (c) Sechi, M.; Angotzi, G.; Dallocchio, R.; Dessì, A.; Carta, F. L.; Sannia, Mariani, A.; Fiori, S.; Sanchez, T.; Movssessian, L.; Plasencia, C. and Neamati, N., *Antivir. Chem. & Chemother.,* **2004**, *15*, 67. (d) Ludwig, J. and Lehr, M., *Synth. Commun.,* **2004**, *34*, 3691. (e) Fresneda, P. M.; Molina, P.; Delgado, S. and Bleda, J. A., *Tetrahedron Lett.,* **2000**, *41*, 4777. (f) Kondo, K.; Morohoshi, S.; Mitsuhashi, M. and Murakami, Y., *Chem. Pharm. Bull.,* **1999**, *47*, 1227. (g) Boger, D. L. and McKie, J. A., *J. Org. Chem*., **1995**, *60*, 1271. (h) Boger, D. L.; Cerbone, L. R. and Yohannes, D., *J. Org. Chem.,* **1988**, *53*, 5163. (i) Knittel, D., *Synthesis*, **1985**, 186. (j) Eras, J.; Galvez, C. and Garcia, F., *J. Heterocycl. Chem.,* **1984**, *21*, 215. (k) MacKenzie, A. R.; Moody, C. J. and Rees, C. W., *J. Chem. Soc., Chem. Commun.,* **1983**, 1372. (l) Hickey, D. M. B. and Moody, C. J., *J. Chem. Soc., Chem. Commun.,* **1982**, 3. (m) Hickey, D. M. B.; Moody, C. J. and Rees, C. W., *J. Chem. Soc., Chem. Commun.,* **1982**, 1419. (n) Kim, P. T.; Guilard, R.; Dodey, P. and Sornay, R., *J. Heterocycl. Chem.,* **1981**, 1365. (o) Kim, P. T.; Guilard, R.; Samreth, S. and Sornay, R., *J. Heterocycl. Chem.,* **1981**, 1373. (p) Hemetsberger, H. and Knittle, D., *Monatsh. Chem.,* **1972**, *103*, 194. (q) Hemetsberger, H. and Knittel, D., *Monatsh. Chem*., **1972**, *103*, 205. (r) Hemetsberger, H. and Knittel, D., *Monatsh. Chem*., **1972**, *103*, 194. (s) Hemetsberger, H.; Knittel, D. and Weidmann, H., *Monatsh. Chem.,* **1970**, *101*, 161.

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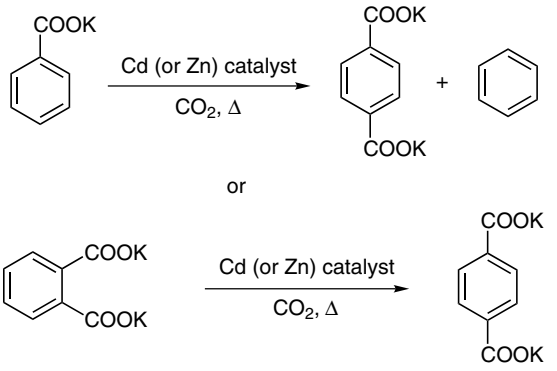
Henkel Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Raecke from Henkel et Cie in 1952.[1] It is a thermal rearrangement or disproportionation of alkaline salts of aromatic acids to symmetrical diacids in the presence of a metallic salt and carbon dioxide. Therefore, it is generally known as the Henkel reaction.[2] Occasionally, it is also referred to as the Raecke process[2j] or Henkel process.[2b,2i,3] For this reaction, the alkaline salts of benzoic acids, including potassium, rubidium, and cesium benzoates, give satisfactory yields,[2i,2j] whereas sodium benzoate and lithium benzoate react at even higher temperatures and give much lower yields.[2b,2j] It should be pointed out that the disproportionated symmetrical diacids are the major products but not the sole products in this reaction; other possible products from the Henkel reaction of potassium benzoate include diphenylmethane, benzophenone, triphenylmethane, and 9-phenylfluorene.[2a] Although the alkaline earth metal salts of benzoic acid also pyrolyze at high temperatures, they might give different products. For example, the pyrolysis of calcium benzoate proceeds via an anionic mechanism to form benzene and benzophenone as the major products without formation of any calcium phthalate; in addition, even the formation of diphenylmethane, benzophenone, etc. was slowed down considerably.[2a] It has been reported that this reaction can be catalyzed by a cadmium[2a,2j] or zinc salt.[4] Under the high pressure of carbon dioxide, the yield is improved; in contrast, lowering the pressure of CO_2 or under high pressures of nitrogen, the yield is lowered as well.[2b] In addition, other gas components such as hydrogen, water, and oxygen are toxic to this reaction.[2j] The alkaline salt of other aromatic acids, besides benzoic acid, disproportionate similarly, as shown by the ZnI_2-catalyzed transformation of disodium naphthalenedicarboxylate to 2,3,6,7-naphthalenetetracarboxylic acid (NTC) dianhydride.[4]

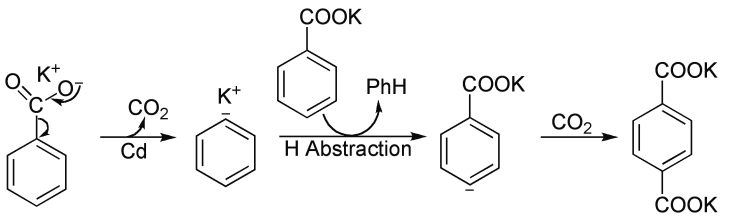
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A simple mechanism is proposed here for the disproportionation of potassium benzoate in the presence of cadmium catalyst.



D. MODIFICATION

N/A

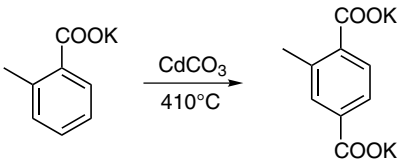
E. APPLICATIONS

This reaction has been used in the production of terephthalic acid at an industrial scale.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3d.

A mixture of 3.0 g finely powdered potassium *o*-toluate and 0.24 g cadmium carbonate in a test tube with a rubber stopper fitted with a constricted glass tube was heated for 1.5 h at 410°C in a metal bath. While heating, continuous evolution of toluene was observed. The toluene was collected by cooling and confirmed as 2,4-dinitrotoluene, m.p. 69.7°C. The solid product was dissolved in boiling water. Colloidal black material was removed by filtration with the aid of zinc sulfate, the filtrate being acidified with hydrochloric acid and then extracted with ether. After evaporation of ether, white solid was obtained. The petroleum ether–soluble portion of this material consisted of pure starting material, whereas the 0.13 g insoluble portion was shown to be 2-methylterephthalic acid by converting it into the dimethyl ester, m.p. 75.5°C. Better yields were obtained by using cadmium iodide rather than cadmium carbonate. (*Note*: I do not understand how 2,4-dinitrotoluene is formed in this reaction).

Other references related to the Henkel reaction are cited in the literature.[5]

H. REFERENCES

1. (a) Raecke, B., *Ger. Pat.*, **1952**, Dec. 1, 936,036. (b) Raecke, B., *Ger. Pat.*, **1957**, Feb. 28, 958,920, to Henkel et Cie.
2. (a) Dabestani, R.; Britt, P. F. and Buchanan, A. C., *Energy & Fuels,* **2005**, *19*, 365. (b) Clayton, T. W.; Britt, P. F. and Buchanan, A. C., *Reprints of Symposia-Am. Chem. Soc., Division of Fuel Chem.,* **2001**, *46*, 228. (c) Fujishiro, K. and Mitamura, S., *Bull. Chem. Soc. Jpn.,* **1989**, *62*, 786. (d) Suzuki, S.; Tanaka, M.; Sekiguchi, T. and Ogata, I., *Kagaku Gijutsu Kenkyusho Hokoku*, **1983**, *78*, 403. (e) Szammer, J. and Otvos, L., *Radiochem. Radioanal. Lett.,* **1980**, *45*, 359. (f) Szammer, J. and Otvos, L., *Chem. Ind. (London),* **1978**, 38. (g) Furuyama, S., *Shokubai*, **1967**, *9*, 238. (h) Furuyama, S., *Bull. Chem. Soc. Jpn.,* **1967**, *40*, 1212. (i) Patton, J. W. and Son, M. O., *J. Org. Chem.,* **1965**, *30*, 2869. (j) McNelis, E., *J. Org. Chem.,* **1965**, *30*, 1209.
3. (a) Jiao, N.-N. and Wang, J.-M., *Shihua Jishu Yu Yingyong*, **2002**, *20*, 410. (b) Ogata, Y. and Nakagawa, K., *Chem. Ind. (London),* **1966**, 1964. (c) Ogata, Y.; Furuya, Y.; Hojo, M.; Noshiro, T. and Maekawa, J., *Kogyo Kagaku Zasshi*, **1964**, *67*, 578. (d) Ogata, Y.; Hojo, M.; Morikawa, M. and Maekawa, J., *J. Org. Chem.,* **1962**, *27*, 3373.
4. Mori, H. and Nakao, H., *JFE Technical Report*, **2005**, *8*, 49.
5. (a) Dabestani, R.; Britt, P. F. and Buchanan, A. C., *Energy & Fuels,* **2005**, *19*, 365. (b) Shen, J. P.; Ma, J.; Jiang, D. Z. and Min, E. Z., *Xiandai Huagong*, **1993**, *13*, 10. (c) Kosugi, Y. and Takeuchi, T., *Bull. Chem. Soc. Jpn.,* **1978**, *51*, 2008. (d) Szammer, J.; Szabolcs, A. and Noszko, L., *Radiochem.*

Radioanal. Lett., **1975**, *21*, 241. (e) Szammer, J., *Acta Chim. Acad. Sci. Hungaricae,* **1975**, *85*, 97. (f) Parausanu, V.; Constantin, A. and Dima, L., *Revistade Chim.,* **1968**, *19*, 481. (g) Amemiya, T.; Nakamura, E. and Tanji, S., *Bull. Jpn. Petro. Inst.,* **1967**, *9*, 112. (h) Ogeta, Y.; Hojo, M. and Morikawa, M., *J. Org. Chem*., **1960**, *25*, 2082. (i) Ratusky, J. and Sorm, F., *Coll. Czech. Chem. Commun.,* **1959**, *24*, 2553. (j) Raecke, B., *Angew. Chem.,* **1958**, *70*, 1. (k) Ogata, Y., *Chem. Chem. Ind. (Japan),* **1958**, *11*, 148. (l) Ogata, Y.; Tsuchida, M. and Muramoto, A., *J. Am. Chem. Soc.,* **1957**, *79*, 6005.

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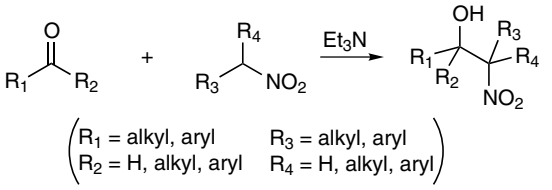
Henry Reaction

A. GENERAL DESCRIPTION OF THE REACTION

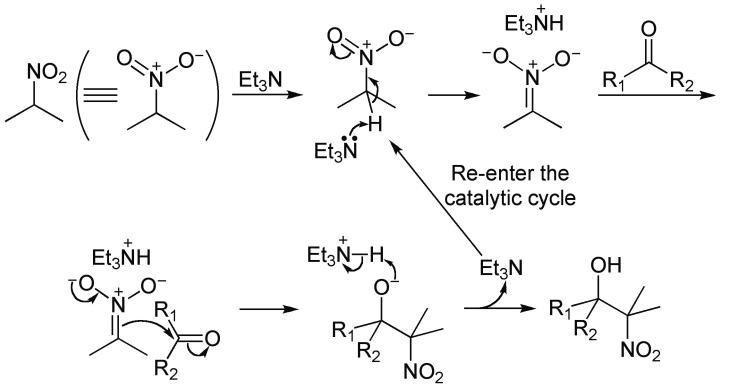
This reaction was initially reported by Henry in 1895.[1] It is the base-catalyzed condensation between a carbonyl compound (aldehyde or ketone) and a nitroalkane having at least one α-hydrogen atom to yield 1,2-nitroalcohol. This reaction, though commonly known as the Henry reaction,[2] is also referred to as the nitroaldol reaction.[2bb,2ff,3] Analogously, the condensation between nitroalkane and imine is known as the *aza*-Henry reaction[2cc,4] or nitro-Mannich reaction.[2cc] The resulting 1,2-nitroalcohol may further undergo reactions such as oxidation, reduction, and elimination.[2bb] During the condensation with aldehyde, the Henry reaction is also complicated with the *Cannizarro Reaction*,[2ff] though it can be suppressed under special conditions;[5] in addition, the condensation with aromatic aldehyde is often accompanied by dehydration to form nitroalkene.[2ff] Similar to the regular *Aldol Reaction*, the Henry reaction is also reversible[2x] and is an equilibrium-controlled reaction.[6] The most attractive feature of the Henry reaction is its potential for the control of stereochemistry, depending on the catalyst and solvent systems.[2x] Due to the strong electron-withdrawing ability of the nitro group, the α-hydrogen can easily be deprotonated, even in the presence of a weak base, so that Et_3N is often used for this purpose.[2bb] In addition, polymer-supported amines, such as KG-60-NEt_2 are also applied as catalysts.[2z] Other catalysts for this reaction include copper(II)-(*S*)-*tert*-butyl bisoxazoline,[2bb] chiral heterobimetallic catalyst,[3m] and ketoiminatocobalt complexes,[2y] which lead to asymmetric Henry reaction products. It is interesting that the electron-deficient aromatic aldehydes, but not the aliphatic aldehydes, undergo the Henry reaction in the presence of an acidic catalyst—such as $TiCl_3$(O-i-Pr)—at room temperature, leading to 2-nitro alcohols enriched in the *erythro* diastereoisomer.[7]

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been improved to produce asymmetric 1,2-nitro alcohols.[2y,2z,3m]

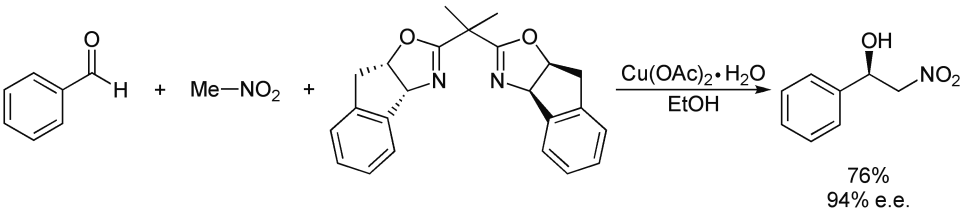
E. APPLICATIONS

This reaction has wide application in organic synthesis, such as in the preparation of 1,2-nitro alcohol and 1,2-amino alcohol.

F. RELATED REACTIONS

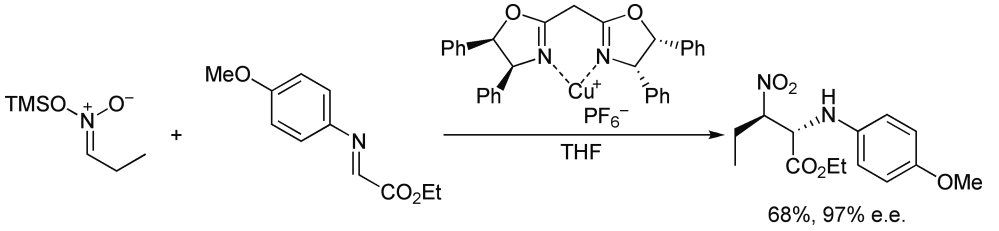
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3x.

To a screw-capped vial containing a stir bar were added 19.7 mg indabox ligand (0.055 mmol), 10.0 mg $Cu(OAc)_2 \cdot H_2O$ (0.05 mmol), and 1.5 mL ethanol; the mixture was stirred for 1 h. To the resulting clear blue solution were added 0.54 mL nitromethane (10 mmol) and 0.106 g benzaldehyde (1 mmol). After being stirred for 22 h, the volatile components were removed under reduced pressure, and the crude product was purified by column chromatography (10% Et_2O/CH_2Cl_2) to give 76% of product as a colorless oil, with 94% e.e.



Reference 2cc.

To a THF solution containing the shown catalyst was added 39.0 mg ethyl α-(4-methoxyphenyl)iminoacetate (0.2 mmol); the solution was cooled to -100°C using an ether/liquid N_2 cooling bath. A solution of 42.0 mg trimethylsilyl propanenitronate (0.3 mmol) in 1.0 mL THF was added over 1 h using a syringe pump. The reaction was left to warm to -20°C overnight and quenched with 0.5 mL ethanol. The crude material was purified by flash chromatography using CH_2Cl_2/pentane (1:1) as the eluent, giving 68% ethyl (2R,3R)-2-(4-methoxyphenyl)amino-3-nitropentanoate, with a diastereomeric ratio of 10:1, and 97% *e.e.* of *erythro* isomer and 88% *e.e.* of *threo* isomer.

Other references related to the Henry reaction are cited in the literature.[8]

H. REFERENCES

1. (a) Henry, L., *Compt. Rend.,* **1895**, *120*, 1265. (b) Henry, L., *Bull. Soc. Chim. Fr.,* **1895**, *13*, 999.
2. (a) Xiong, Y.; Wang, F.; Huang, X.; Wen, Y. H. and Feng, X. M., *Chem. Eur. J.,* **2007**, *13*, 829. (b) Oriyama, T.; Aoyagi, M. and Iwanami, K., *Chem. Lett.,* **2007**, *36*, 612. (c) Alcaide, B.; Almendros, P.; Luna, A.; Paz de Arriba, M. and Torres, M. R., *ARKIVOC,* **2007**, (*iv*), 285. (d) Arai, T.; Watanabe, M.; Fujiwara, A.; Yokoyama, N. and Yanagisawa, A., *Angew. Chem. Int. Ed.,* **2006**, *45*, 5978. (e) Wang, Y.-J.; Shen, Z.-X. and Zhang, Y.-W., *Youji Huaxue*, **2006**, *26*, 1291. (f) Blay, G.; Climent, E.; Fernandez, I.; Hernandez-Olmos, V. and Pedro, J. R., *Tetrahedron: Asymmetry*, **2006**, *17*, 2046.

(g) Nguyen, Q. T. and Jeong, J. H., *Polyhedron*, **2006**, *25*, 1787. (h) Chakraborty, C. and Dhavale, D. D., *Carbohydr. Res.,* **2006**, *341*, 912. (i) Lei, L.-J. and He, X.-C., *Hecheng Huaxue*, **2006**, *14*, 7. (j) Gan, C. S.; Chen, X.; Lai, G. Y. and Wang, Z. Y., *Synlett*, **2006**, 387. (k) Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J. H. and Hiemstra, H., *Angew. Chem. Int. Ed.,* **2006**, *45*, 929. (l) Sohtome, Y.; Takemura, N.; Iguchi, T.; Hashimoto, Y. and Nagasawa, K., *Synlett,* **2006**, 144. (m) Gogoi, N.; Boruwa, J. and Barua, N. C., *Tetrahedron Lett*., **2005**, *46*, 7581. (n) Fan, N. J.; Guo, W. and Xia, C. Z., *Shanxi Daxue Xuebao, Ziran Kexueban*, **2005**, *28*, 283. (o) Du, D.-M.; Lu, S.-F.; Fang, T. and Xu, J. X., *J. Org. Chem.,* **2005**, *70*, 3712. (p) Khan, F. A.; Sudheer, C. and Sahu, N., *Synth. Commun.,* **2005**, *35*, 201. (q) Chung, W. K. and Chiu, P., *Synlett*, **2005**, 55. (r) Lu, S.-F.; Du, D.-M.; Zhang, S.-W. and Xu, J. X., *Tetrahedron: Asymmetry*, **2004**, *15*, 3433. (s) El Blidi, L.; Crestia, D.; Gallienne, E.; Demuynck, C.; Bolte, J. and Lemaire, M., *Tetrahedron: Asymmetry*, **2004**, *15*, 2951. (t) Kogami, Y.; Nakajima, T.; Ikeno, T. and Yamada, T., *Synthesis*, **2004**, 1947. (u) Chetia, A.; Longchar, M.; Lekhok, K. C. and Boruah, R. C., *Synlett*, **2004**, 1309. (v) Kudyba, I.; Raczko, J.; Urbanczyk-Lipkowska, Z. and Jurczak, J., *Tetrahedron*, **2004**, *60*, 4807. (w) Zhong, Y.-W.; Tian, P. and Lin, G.-Q., *Tetrahedron: Asymmetry*, **2004**, *15*, 771. (x) Parratt, A. J.; Adams, D. J.; Clifford, A. A. and Rayner, C. M., *Chem. Commun.,* **2004**, 2720. (y) Kogami, Y.; Nakajima, T.; Ashizawa, T.; Kezuka, S.; Ikeno, T. and Yamada, T., *Chem. Lett.,* **2004**, *33*, 614. (z) Ballini, R.; Bosica, G.; Livi, D.; Palmieri, A.; Maggi, R. and Sartori, G., *Tetrahedron Lett.,* **2003**, *44*, 2271. (aa) Hughes, C. C. and Trauner, D., *Angew. Chem. Int. Ed.,* **2002**, *41*, 4556. (bb) Christensen, C.; Juhl, K.; Hazell, R. G. and Jørgensen, K. A., *J. Org. Chem.,* **2002**, *67*, 4875. (cc) Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V. and Jørgensen, K. A., *J. Am. Chem. Soc.,* **2001**, *123*, 5843. (dd) Lin, W.-W.; Jang, Y.-J.; Wang, Y.; Liu, J.-T.; Hu, S.-R.; Wang, L.-Y. and Yao, C.-F., *J. Org. Chem.,* **2001**, *66*, 1984. (ee) Kisanga, P. B. and Verkade, J. G., *J. Org. Chem.,* **1999**, *64*, 4298. (ff) Ballini, R. and Bosica, G., *J. Org. Chem.,* **1997**, *62*, 425.

3. (a) Colak, M.; Aral, T.; Hosgoeren, H. and Demirel, N., *Tetrahedron: Asymmetry*, **2007**, *18*, 1129. (b) Ma, K. Y. and You, J. S., *Chem. Eur. J.,* **2007**, *13*, 1863. (c) Bandini, M.; Piccinelli, F.; Tommasi, S.; Umani-Ronchi, A. and Ventrici, C., *Chem. Commun.,* **2007**, 616. (d) Maheswaran, H.; Prasanth, K. L.; Krishna, G. G.; Ravikumar, K.; Sridhar, B. and Kantam, M. L., *Chem. Commun.,* **2006**, 4066. (e) Saa, J. M.; Tur, F.; Gonzalez, J. and Vega, M., *Tetrahedron: Asymmetry*, **2006**, *17*, 99. (f) Sohtome, Y.; Hashimoto, Y. and Nagasawa, K., *Eur. J. Org. Chem.,* **2006**, 2894. (g) Purkarthofer, T.; Gruber, K.; Gruber-Khadjawi, M.; Waich, K.; Skranc, W.; Mink, D. and Griengl, H., *Angew. Chem. Int. Ed.,* **2006**, *45*, 3454. (h) Bhatt, A. P.; Pathak, K.; Jasra, R. V.; Kureshy, R. I.; Khan, N. H. and Abdi, S. H. R., *J. Mol. Catal. A: Chem.,* **2006**, *244*, 110. (i) Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J. H. and Hiemstra, H., *Synlett,* **2005**, 2817. (j) Sohtome, Y.; Hashimoto, Y. and Nagasawa, K., *Adv. Synth. Catal.,* **2005**, *347*, 1643. (k) Zubia, Z.; Cossio, F. P.; Morao, I.; Rieumont, M. and Lopez, X., *J. Am. Chem. Soc.,* **2004**, *126*, 5243. (l) Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T. and Downey, C. W., *J. Am. Chem. Soc.,* **2003**, *125*, 12692. (m) Trost, B. M.; Yeh, V. S. C.; Ito, H. and Bremeyer, N., *Org. Lett.,* **2002**, *4*, 2621.
4. (a) Trost, B. M. and Lupton, D. W., *Org. Lett.,* **2007**, *9*, 2023. (b) Garcia Ruano, J. L.; Lopez-Cantarero, J.; De Haro, T.; Aleman, J. and Cid, M. B., *Tetrahedron*, **2006**, *62*, 12197. (c) Gao, F. F.; Zhu, J.; Tang, Y.; Deng, M. Z. and Qian, C. T., *Chirality*, **2006**, *18*, 741. (d) Petrini, M. and Torregiani, E., *Tetrahedron Lett*., **2006**, *47*, 3501. (e) Palomo, C.; Oiarbide, M.; Halder, R.; Laso, A. and Lopez, R., *Angew. Chem. Int. Ed.,* **2006**, *45*, 117. (f) Bernardi, L.; Fini, F.; Herrera, R. P.; Ricci, A. and Sgarzani, V., *Tetrahedron*, **2006**, *62*, 375. (g) Xu, X. N.; Furukawa, T.; Okino, T.; Miyabe, H. and Takemoto, Y., *Chem. Eur. J.,* **2005**, *12*, 466. (h) Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R. P.; Bernardi, L. and Ricci, A., *Angew. Chem. Int. Ed.,* **2005**, *44*, 7975. (i) Palomo, C.; Oiarbide, M.; Laso, A. and Lopez, R., *J. Am. Chem. Soc.,* **2005**, *127*, 17622. (j) Knudsen, K. R. and Jorgensen, K. A., *Org. Biomol. Chem.,* **2005**, *3*, 1362. (k) Nugent, B. M.; Yoder, R. A. and Johnston, J. N., *J. Am. Chem. Soc*., **2004**, *126*, 3418.
5. (a) Costantino, V.; Curini, M.; Marmottini, F.; Rosati, O. and Pisani, E., *Chem. Lett.,* **1994**, 2215. (b) Baer, H. H. and Urbas, L., "Activating and Directing Effects of the Nitro Group in Aliphatic

Systems" in *The Chemistry of the Nitro and Nitroso Groups,* ed., Feuer, H., Interscience, New York, **1970**. (c) Vaderbilt, B. M. and Hass, H. B., *Ind. Eng. Chem.,* **1940**, *32*, 34.

6. Green, D. and Johnson, T., *Innovations in Pharm. Technol.,* **2000**, 79.
7. Barrett, A. G. M.; Robyr, C. and Spilling, C. D., *J. Org. Chem.,* **1989**, *54*, 1233.
8. (a) Luzzio, F. A.; Ott, J. P. and Duveau, D. Y., *J. Org. Chem.,* **2006**, *71*, 5027. (b) Boruwa, J.; Gogoi, N.; Saikia, P. P. and Barua, N. C., *Tetrahedron: Asymmetry*, **2006**, *17*, 3315. (c) Palacios, F.; de los Santos, J. and Aparicio, D., *ARKIVOC,* **2005**, 405. (d) Lubisch, W.; Beckenbach, E.; Bopp, S.; Hofmann, H.-P.; Kartal, A.; Kaestel, C.; Lindner, T.; Metz-Garrecht, M.; Reeb, J.; Regner, F.; Vierling, M. and Moeller, A., *J. Med. Chem*., **2003**, *46*, 2404. (e) Luzzio, F. A., *Tetrahedron,* **2001**, *57*, 915. (f) Ono, N., *The Nitro Group in Organic Synthesis*, Wiley-VCH: New York, **2001**. (g) Yamada, K.; Harwood, S. J.; Gröger, H. and Shibasaki, M., *Angew. Chem. Int. Ed.,* **1999**, *38*, 3504. (h) Maiorana, S.; Licandro, E.; Capella, L.; Perdicchia, D. and Papagni, A., *Pure & Appl. Chem.,* **1999**, *71*, 1453. (i) Ayerbe, M.; Arrieta, A. and Cossio, F. P., *J. Org. Chem.,* **1998**, *63*, 1795. (j) Varma, R. S.; Dahiya, R. and Kumar, S., *Tetrahedron Lett.,* **1997**, *38*, 5131. (k) Arai, T.; Yamada, Y. M. A.; Yamamoto, N.; Sasai, H. and Shibasaki, M., *Chem. Eur. J.,* **1996**, *2*, 1368. (l) Torssell, K. B. G.; Gothelf, K. V., "Nitroethane", in *Encyclopaediea of Reagents for Organic Synthesis*, ed. Paquette, L., Wiley, New York, **1995**, *6*, p. 3735. (m) Garg, N.; Hossain, N. and Chattopadhyaya, J., *Tetrahedron,* **1994**, *50*, 5273. (n) Hossain, N.; Garg, N. and Chattopadhyaya, J., *Tetrahedron,* **1993**, *49*, 10061. (o) Garg, N.; Palvec, J. and Chattopadhyaya, J., *Tetrahedron,* **1993**, *49*, 5189. (p) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T. and Shibasaki, M., *J. Am. Chem. Soc.,* **1992**, *114*, 4418. (q) Solladie-Cavallo, A. and Khiar, N., *J. Org. Chem*., **1990**, *55*, 4750. (r) Ono, N.; Kamimura, A. and Kaji, A., *Tetrahedron Lett.,* **1984**, *25*, 5319. (s) Rosini, G. and Ballini, R., *Synthesis,* **1988**, 833. (t) Baumberger, F. and Vasella, A., *Helv. Chim. Acta,* **1983**, *66*, 2210. (u) Seebach, D.; Beck, A. K.; Mukhopadhyay, T. and Thomas, E., *Helv. Chim. Acta,* **1982**, *65*, 1101. (v) Aebischer, B.; Bieri, J. H.; Prewo, R. and Vasella, A., *Helv. Chim. Acta,* **1982**, *65*, 2251. (w) Lichtenthaler, F. W., *Angew. Chem. Int. Ed. Engl.,* **1964**, *3*, 211. (x) Hass, H. B. and Riley, E. F., *Chem. Rev.,* **1943**, *32*, 373. (y) Hodgson, H. H. and Beard, H. G., *J. Chem. Soc.,* **1925**, 875.

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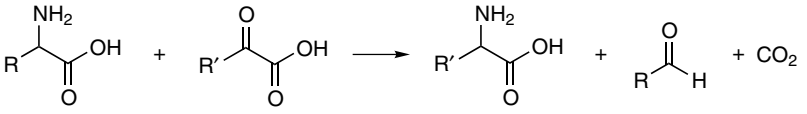
Herbst-Engel Transamination

A. GENERAL DESCRIPTION OF THE REACTION

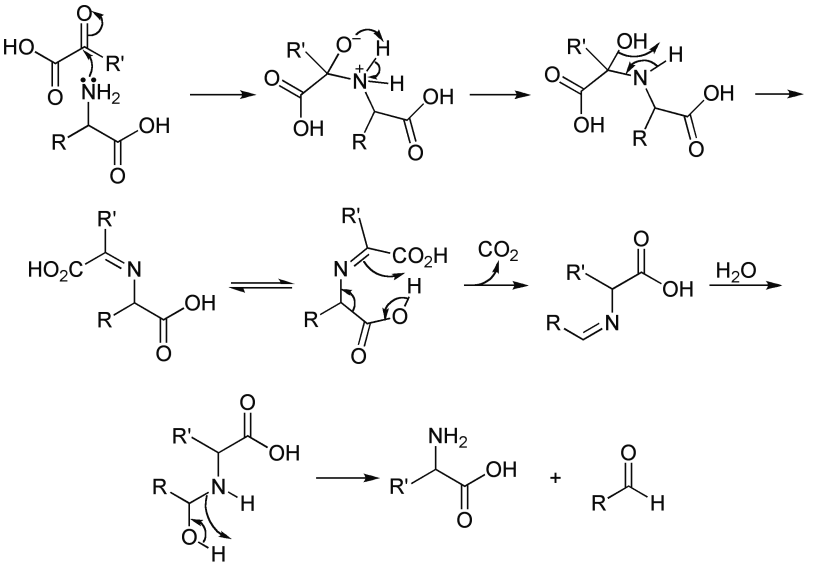
This reaction was first reported by Herbst and Engel in 1934.[1] It is the transfer of an amino group from an α-amino acid to an α-keto acid to form a new α-amino acid. The amino acids without α-hydrogen, such as α-aminoisobutyric acid, are inactive for this reaction.[2] It is believed that this reaction involves a few steps, including the formation of imino group between an amino and a carbonyl group, hydrogen transfer to the α-carbon of the ketonic acid moiety accompanied with the elimination of carbon dioxide, and the addition of water (hydrolysis) resulting in fission along with the formation of an aldehyde and the new α-amino acid.[3] It was found that the substituent on both α-amino acids and α-keto acids affect the extent of decarboxylation[3b] and that carbon dioxide evolution is much faster for transamination with arylaminoacetic acid than that with aliphatic amino acids.[3a] In addition, the evolution of carbon dioxide is even more rapid with arylaminoacetic acid with an *ortho*-substituent than that with a *para*-substituent, and the one with the electron-withdrawing group is faster than the one with the electron-donating group.[3a] A reaction similar to this transamination but catalyzed by enzymes under physiological conditions is also known,[4] which is an important process in amino acid metabolism.[2] However, no decarboxylation occurs for the enzyme-catalyzed reaction.[2,5] It has been reported that the transamination between α-amino acid and glyoxylate to form glycine and the corresponding keto acid without decarboxylation completes in about 10 min when the reaction is catalyzed by copper or iron salts.[6]

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

N/A

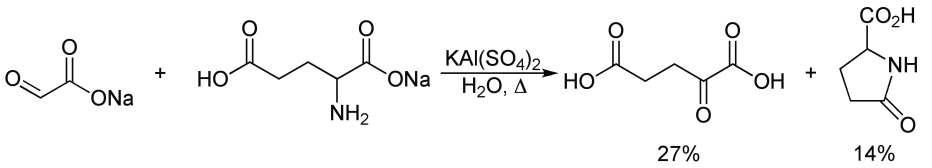
E. APPLICATIONS

This reaction has been used to synthesize aldehydes and α-amino acids.

F. RELATED REACTIONS

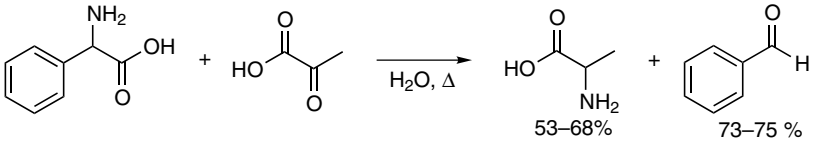
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 6.

A mixture of 0.025 mol sodium glyoxylate, 0.025 mol glutamic acid, and 0.0025 mol potassium aluminum sulfate was dissolved in 500 mL water, and the pH was adjusted to 5.0 with NaOH. The solution was heated in a boiling water bath to 100°C, held 10 min, and cooled. The pH was adjusted to 1.0 with H_2SO_4, and the solution was subjected to continuous ether extraction. The ether extract was evaporated in vacuo, the residue was taken up in boiling nitromethane, cooled, and held overnight in the refrigerator. A first crop of 0.52 g α-pyrrolidonecarboxylic acid was separated. Concentration of the mother liquors in vacuum and cooling yielded 1.01 g α-ketoglutaric acid, in a yield of 27%, m.p. 110–111°C (corr.)



Reference 7.

A mixture of 4.53 g α-aminophenylacetic acid (0.03 mol), 7.9 g pyruvic acid (0.09 mol), and 200 mL water (3.5% deuterium) was boiled under reflux for 3 h. A homogeneous solution was formed within a few minutes after the mixture began to boil. On completion of the reaction, benzaldehyde was removed by distillation through a declining condenser and extracted from the distillate with several small portions of chloroform. The aqueous portion of the distillate and the aqueous reaction mixture were reserved. After drying the chloroform solution over sodium sulfate, the solvent was evaporated and the residual benzaldehyde was converted into the phenylhydrazone by treatment with phenylhydrazine in 50% alcoholic solution. After recrystallization from 60% alcohol, the yield of benzaldehyde phenylhydrazone was 4.3–4.4 g, m.p. 155.5–157°C for various preparations.

After being thoroughly chilled, the aqueous reaction mixture was filtered to remove a trace amount of α-aminophenylacetic acid, which had separated. The filter was washed with the aqueous distillate from the benzaldehyde fraction. The entire filtrate was evaporated to a thick, syrupy consistency on the water bath under reduced pressure, care being taken to recover the aqueous distillate as completely as possible. The residual syrup was taken up in 100 mL ordinary water, and the evaporation was repeated. A second similar treatment with 100 mL water sufficed to easily remove the exchangeable deuterium completely. The residual syrup was then taken up in 10 mL hot 95% alcohol and transferred to a small Erlenmeyer flask; the distilling flask was rinsed with four 5-mL portions of hot 95% alcohol. Alanine crystallized spontaneously from the alcoholic solution on cooling; complete separation was ensured by the addition of 5 mL pyridine to the cold solution. After thorough chilling in the

refrigerator, the alanine was filtered by suction, washed thoroughly with cold 95% alcohol, and dried in a vacuum desiccator. The yield of crude alanine varied from 1.4 g to 1.8 g in different experiments.

Other references related to the Herbst-Engel transamination are cited in the literature.[8]

H. REFERENCES

1. Herbst, R. M. and Engel, L. L., *J. Biol. Chem.,* **1934**, *107*, 505.
2. Cooper, A. J. L.; Ginos, J. Z. and Meister, A., *Chem. Rev.,* **1983**, *83*, 321.
3. (a) Harvill, E. K. and Herbst, R. M., *J. Org. Chem.,* **1944**, *9*, 21. (b) Herbst, R. M., *J. Am. Chem. Soc.,* **1936**, *58*, 2239.
4. (a) Cohen, P. P., *J. Biol. Chem.,* **1940**, *136*, 565. (b) Cohen, P. P., *Biochem, J.,* **1939**, *33*, 1478. (c) Braunshtein, A. E., *Biokhimiya,* **1939**, *4*, 667. (d) Virtanen, A. I. and Laine, T., *Nature,* **1938**, *141*, 748. (e) Braunshtein, A. E. and Kritsman, M. G., *Nature,* **1937**, *140*, 503. (f) Braunshtein, A. E. and Kritsman, M. G., *Enzymologia,* **1937**, *2*, 129.
5. Cooper, A. J. L. and Meister, A. "Metabolic Significance of Transamination", in *Transaminases (Biochemistry: A Series of Monographs)*, ed. Christen, P. and Metzler, D. E., John Wiley & Sons, New York, **1985**.
6. Metzler, D. E.; Olivard, J. and Snell, E. E., *J. Am. Chem. Soc.,* **1954**, *76*, 644.
7. Herbst, R. M. and Rittenberg, D., *J. Org. Chem.,* **1943**, *8*, 380.
8. (a) Wnorowski, A. and Yaylayan, V. A., *J. Agric. Food Chem.,* **2003**, *51*, 6537. (b) Lamartiniere, C. A.; Itoh, H. and Dempsey, W. B., *Biochemistry,* **1971**, *10*, 4783. (c) Dempsey, W. B., *J. Bacteriol.,* **1969**, *97*, 182. (d) Cram, D. J. and Guthrie, R. D., *J. Am. Chem. Soc*., **1966**, *88*, 5760. (e) Aaslestad, H. G. and Larson, A. D., *J. Bacteriol.,* **1964**, *88*, 1296. (f) Kalyankar, G. D. and Snell, E. E., *Biochemistry,* **1962**, *1*, 594. (g) Brewer, S. D. and Herbst, R. M., *J. Org. Chem.,* **1941**, *6*, 867. (h) Shemin, D. and Herbst, R. M., *J. Am. Chem. Soc.,* **1938**, *60*, 1951.

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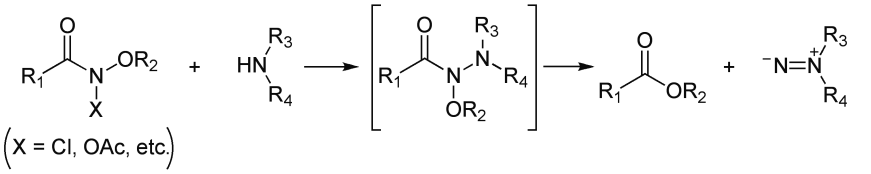
Heron Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

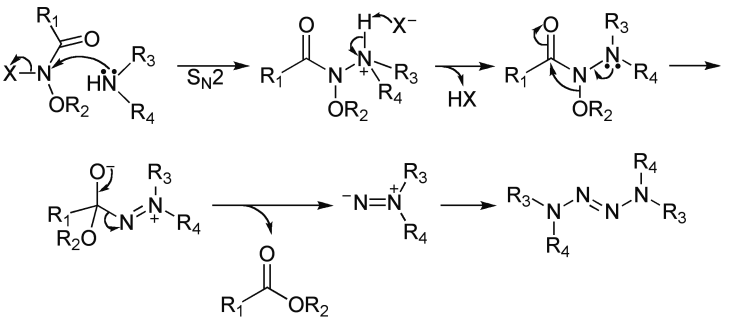
This reaction was first reported by Glover at the Second Heron Island Conference on Reactive Intermediates and Unusual Molecules, Heron Island, Australia in 1994,[1] thus it was called the HERON rearrangement,[2] or HERON reaction.[1,3] HERON is an acronym for heteroatom rearrangements on nitrogen.[4] It is the rearrangement of amides, with two heteroatoms (e.g., oxygen) substituted at nitrogen (RC(O)NXY), to esters and 1,1-diazenes via the migration of oxygen from the nitrogen to the carbonyl carbon.[4] Amides of the type that can undergo such rearrangement are collectively called HERON amides.[4] In this rearrangement, a heteroatom (X) bearing a high-energy pair of electrons (i.e., oxygen) initiates rearrangement from nitrogen to carbon through a strong anomeric overlap with the σ^* orbial of the adjacent N-heteroatom bond (N-Y), and the so-called anomeric interactions at nitrogen are enhanced when the second heteroatom (Y) is strongly electronegative.[5] Analogues of N,N'-diacyl-N,N'-dialkoxyhydrazines thermally decompose to esters and nitrogen through two consecutive rearrangements.[6]

B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS



D. MODIFICATION

N/A

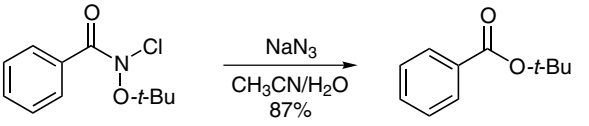
E. APPLICATIONS

This reaction is useful for the preparation of ester with a bulky alcohol moiety.[2a]

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 2a.

To a solution of 58 mg *N*-*tert*-butoxy-*N*-chlorobenzamide (0.0255 mmol) in 5 mL CH_3CN was added a solution of 0.20 g sodium azide (3.08 mmol) in 20 mL CH_3CN/H_2O (1:1). A pale pink color was formed immediately. The reaction mixture was stirred at room temperature for 2 h, during which time 9.7 mL nitrogen was collected (85%). The reaction solution was extracted with 50 mL CH_2Cl_2, and the solution was dried and concentrated to give 40 mg *tert*-butyl benzoate as a yellow oil, in a yield of 87%.

Other references related to the HERON rearrangement are cited in the literature.[7]

H. REFERENCES

1. Glover, S. A.; Hammond, G. P. and Bonin, A. M., *J. Org. Chem.,* **1998**, *63*, 9684.
2. (a) Glover, S. A.; Mo, G. N., *J. Chem. Soc., Perkin Trans. II,* **2002**, 1728. (b) Glover, S. A.; Mo, G. N. and Rauk, A., *Tetrahedron*, **1999**, *55*, 3413. (c) Buccigross, J. M. and Glover, S. A., *J. Chem. Soc., Perkin Trans. II,* **1995**, 595.
3. Glover, S. A.; Rauk, A.; Buccigross, J. M.; Campbell, J. J.; Hammond, G. P.; Mo, G. N.; Andrews, L. E. and Gillson, A.-M. E., *Can. J. Chem.,* **2005**, *83*, 1492.
4. Glover, S. A. and Rauk, A., *J. Org. Chem.,* **1999**, *64*, 2340.
5. (a) Glover, S. A., *Tetrahedron,* **1998**, *54*, 7229. (b) Glover, S. A. and Rauk, A., *J. Org. Chem.,* **1996**, *61*, 2337.
6. Glover, S. A.; Mo, g. N.; Rauk, A.; Tucker, D. J. and Turner, P., *J. Chem. Soc., Perkin Trans. II,* **1999**, 2053.
7. (a) Glover, S. A. and Rauk, A., *J. Chem. Soc., Perkin Trans. II,* **2002**, 1740. (b) Campbell, J. J. and Glover, S. A., *J. Chem. Res. (S),* **1999**, 474. (c) Buccigross, J. M.; Glover, S. A.; Hammond, G. P. and Rowbottom, C. A., *Aust. J. Chem.,* **1995**, *48*, 353.

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Herz Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Herz in 1914.[1] It is the reaction between primary aromatic amines, their salts, or *N*-acetyl derivatives with sulfur monochloride either in the presence or absence of an inert solvent (such as benzene, nitrobenzene, or acetic acid) to form 1,3,2-benzothiazathiolium chlorides,[2] known as the Herz compounds[3] or Herz salts.[3,4] Therefore, this reaction is generally referred to as the Herz reaction.[5] In addition, the terms Herz process[2] and Herz condensation[2] are also used for this reaction. The Herz compounds decompose on heating and are difficult to purify,[3] so that they are normally converted into other derivatives. For example, hydrolysis of these compounds results in 1,2,3-benzodithiazole 2-oxide,[3] whereas basic hydrolysis of these compounds by NaOH results in *o*-amino thiophenol,[2] and treatment of these compounds with acetic-formic anhydride leads to the synthesis of substituted benzothiozoles.[2] Furthermore, treatment of Herz compounds with chloroacetic acid leads to *o*-aminophenylthioglycolic acid derivatives, the intermediates used to produce thioindigo dyestuffs in industry.[6] It has been observed that this reaction is always accompanied with the chlorination on aromatic nucleus, primarily at the *para*-position of the amino group,[2,3,7] even the *para*-position is replaced by an NO_2, CO_2H, or SO_2 group.[2] For example, both *o*-nitroaniline and *o*-chloroaniline afforded only 4,6-dichlorobenzothiazole when their corresponding crude Herz compounds were treated with acetic-formic anhydride.[2]

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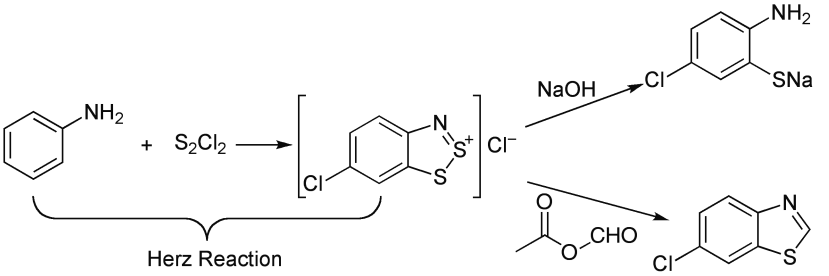
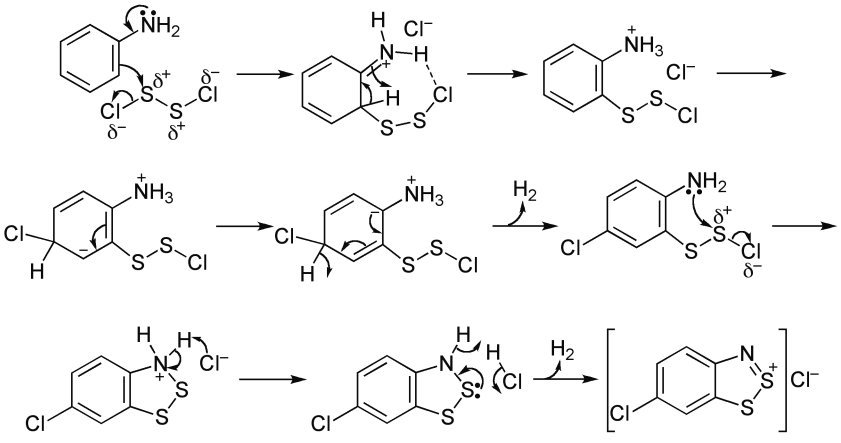
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It has been observed that no further chlorination occurs on Herz compounds in the presence of a chlorination reagent (e.g., $SOCl_2$), thus the chlorination on aromatic nucleus probably occurs before the formation of the Herz compounds. A tentative mechanism is outlined here.



D. MODIFICATION

N/A

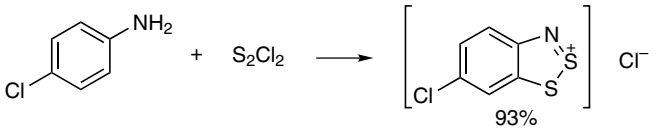
E. APPLICATIONS

This reaction is used to prepare *o*-amino thiophenols and benzothiozoles.

F. RELATED REACTIONS

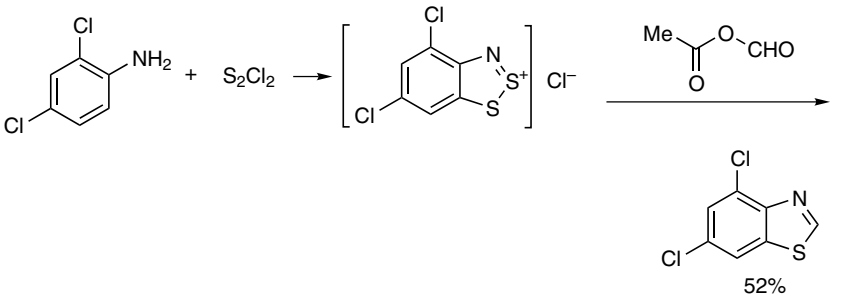
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3.

A solution of 5.7 g *p*-chloroaniline (0.045 mol) in 7.0 mL anhydrous acetic acid was added to 25 mL cold redistilled sulfur monochloride (42.0 g, 0.31 mol). This mixture was stirred for 3 h at room temperature, and then at 70–80°C for 3 h. After being cooled to room temperature, the dark mixture was stirred with 50 mL dry benzene ($CaC1_2$) and then filtered. The solid was washed with dry benzene and then dried in vacuo to give 9.3 g 6-chloro-1,3,2-benzothiazathiolium chloride as a yellow-brown solid, which decomposed at 210–225°C. The yield was 93%.



Reference 2.

A solution of 32.0 g 2,4-dichloroaniline was mixed with sulfur monochloride to give an orange-red Herz condensation product, which was then treated with alkaline solution and filtered. The filtered alkaline solution was further treated with acetic-formic anhydride to gave a crude 4,6-dichlorobenzothiazole, m.p. 136–138°C. Recrystallization from ethanol gave 21.0 g pure 4,6-dichlorobenzothiazole as white needle-like crystals, in a yield of 52%, m.p., 142–142.5°C.

Other references related to the Herz reaction are cited in the literature.[8]

H. REFERENCES

1. (a) Herz, R., *Ger. Pat*., **1914**, Apr. 12, 360,690. (b) Herz, R., *Ger. Pat*., **1914**, June 21, 364,822. (c) Herz, R., *Ger. Pat*., **1914**, June 21, 367,346. (d) Herz, R., *Ger. Pat*., **1914**, June 25, 367,493.
2. Blomquist, A. T. and Diuguid, L. I., *J. Org. Chem.,* **1947**, *12*, 718.
3. Huestis, L. D.; Walsh, M. L. and Hahn, N., *J. Org. Chem.,* **1965**, *30*, 2763.
4. Strelets, B. K. and Efros, L. S., *Tezisy Dokl.-Simp. Khim. Tekhnol. Geterotsikl. Soedin. Goryuch. Iskop., 2nd*, **1973**, 195.

5. (a) Chenard, B. L., *J. Org. Chem.,* **1984**, *49*, 1224. (b) Hope, P. and Wiles, L. A., *J. Chem. Soc. C,* **1967**, 1642. (c) Maior, O. and Arsenescu, N., *Analele Univ. Bucuresti, Ser. Stiint. Nat.*, **1965**, *14*, 25. (d) Vasiliu, G.; Maior, O. and Arsenescu, N.,*Analele Univ. Bucuresti, Ser. Stiint. Nat.*, **1963**, *12*, 47.
6. Hixson, A. W. and Cauwenberg, W. J., *J. Am. Chem. Soc.,* **1930**, *52*, 2118.
7. (a) Ast, M. G. and Bogert, M. T., *Rec. Trav. Chim.,* **1935**, *54*, 917. (b) König, W., *Ber.,* **1928**, *61*, 2065.
8. (a) Beer, L.; Brusso, J. L.; Cordes, A. W.; Haddon, R. C.; Itkis, M. E.; Kirschbaum, K.; MacGregor, D. S.; Oakley, R. T.; Pinkerton, A. A. and Reed, R. W., *J. Am. Chem. Soc.,* **2002**, *124*, 9498. (b) Mayer, R., *Phosphorus & Sulfur & Related Elements,* **1985**, *23*, 277. (c) Warburton, W. K., *Chem. Rev.,* **1957**, *57*, 1011. (d) Farrington, K. J. and Warburton, W. K., *Aust. J. Chem.,* **1956**, *9*, 480. (e) Farrington, K. J. and Warburton, W. K., *Aust. J. Chem.,* **1955**, *8*, 545. (f) For, H. H. and Bogert, M. T., *J. Am. Chem. Soc.,* **1939**, *61*, 2013. (g) Herz, R., *Chem. Zentr.,* **1922**, *4*, 948.

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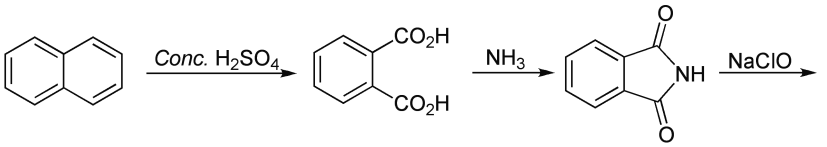
Heumann Indigo Process

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Heumann in 1890.[1] It is the industrial production of indigo from basic fusion of *N*-phenylglycine-*o*-carboxylic acid into indoxylic acid, which decarboxylated to indoxyl; the latter is then oxidized into indigo by air. This process, which was modified by the Badische company[2] and commercialized in 1897 after Heumann died,[3] produced indigo from naphthalene via a sequential processes that included (a) the oxidation of naphthalene to phthalic acid by concentrated sulfuric acid, (b) the conversion of phthalic acid into phthalimide by ammonia, (c) the production of anthranilic acid by means of sodium hypochlorite oxidation of phthalimide, (d) the conversion of anthranilic acid into phenylglycocollorthocarboxylic acid by chloroacetic acid, (e) the fusion of phenylglycocollorthocarboxylic acid with caustic soda to produce indoxyl or indoxylic acid depending on conditions, and (f) oxidation of indoxyl into indigo by air in presence of alkaline.[4] This process resulted in an annual production of indigo of 3,000,000 lb from Badische, one quarter of world's supply in the 1900s,[4] leading to the monopoly of dyestuff of Germany in the early 20th century. The thioindigo analogues can be produced similarly from thiosalicylic acid,[5] which can be produced from the *Herz Reaction*.[6]

B. GENERAL REACTION SCHEME



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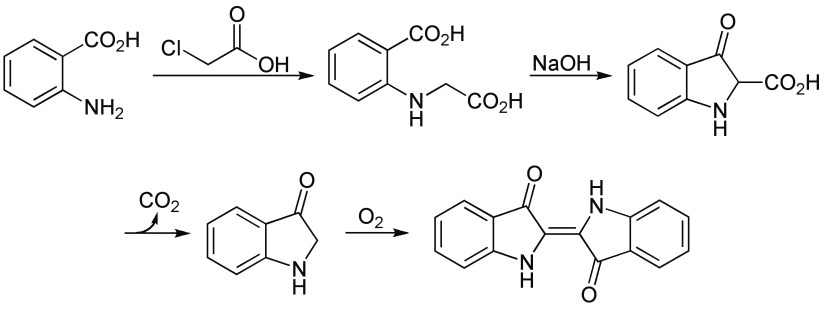
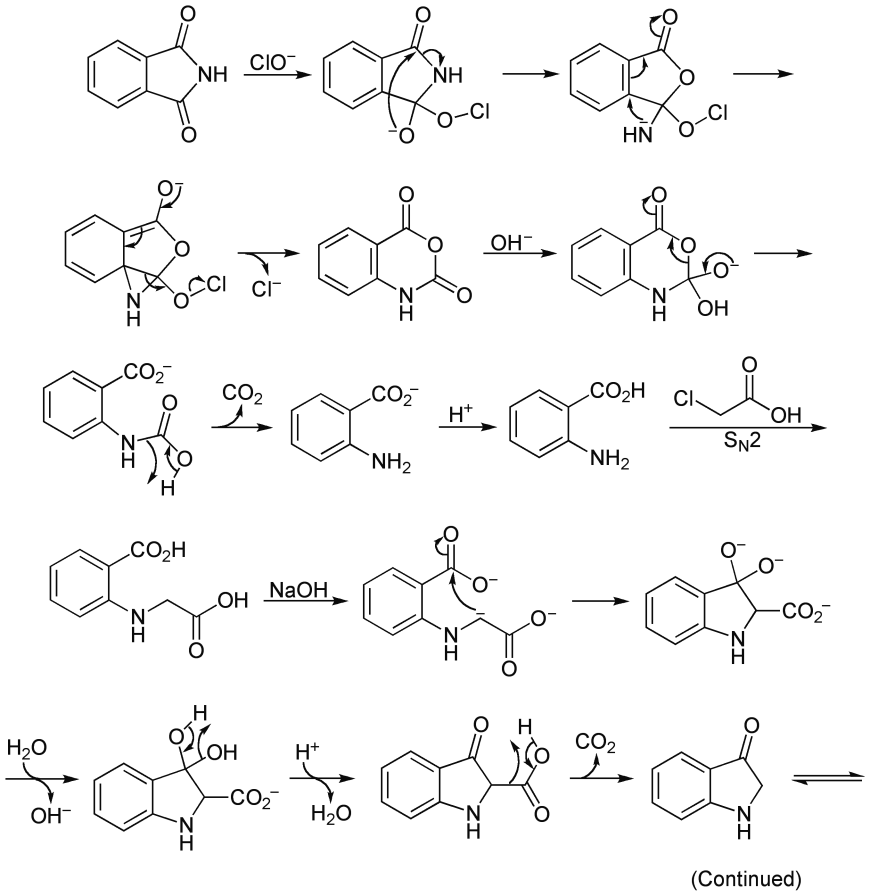


C. PROPOSED MECHANISMS

Because this is an industrial process, many of the reaction details have not been released to public,[4] the mechanism outlined here is a tentative one. This mechanism provides a possible reaction path from phthalimide because the oxidation of naphthalene to phthalic acid is well known and the formation of phthalimide is obvious.



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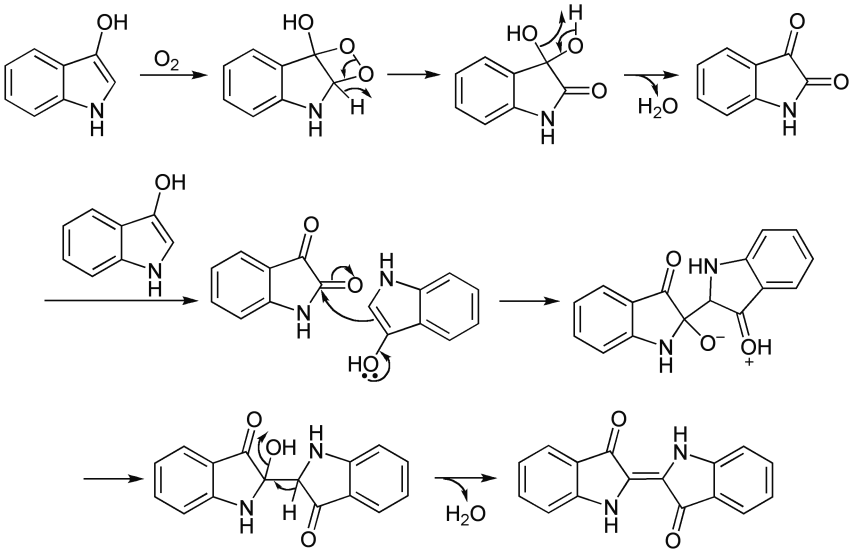


D. MODIFICATION

The Badische process described here is a modification of the original Heumann process.

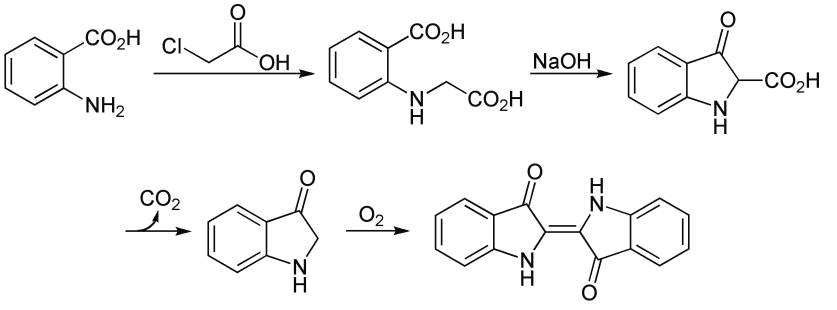
E. APPLICATIONS

This process has been extensively used in the production of indigo on an industrial scale.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

To a 2-L flask equipped with a condenser were added 137 g anthranilic acid (1 mol), 94.5 g chloroacetic acid (1 mol), and 1 L water; the mixture was heated for 3 h. On cooling, crystals of phenylglycine-*o*-carboxylic acid were separated out. These were filtered off and recrystallized from hot water to give ~1000 g of such acid.

The mixture of 1 eq. phenylglycine-*o*-carboxylic acid, 3 eq. NaOH, and 1 eq. water was heated at 235–265°C in the absence of air until the alkaline mass assumed an intense orange color, whereupon it was allowed to cool and subsequently dissolved in water. Passing a stream of air through the aqueous solution resulted in the precipitation of indigo. No yield was given. (*Note*: This is a summary from Phillips.[7])

Other references related to the Heumann indigo process are cited in the literature.[8]

H. REFERENCES

1. (a) Heumann, K., *Ber.,* **1890**, *23*, 3043. (b) Heumann, K., *Ber.,* **1890**, *23*, 3431.
2. (a) von Richter, V., *The Chemistry of the Carbon Compounds,* Elsevier Publishing Company, New York, **1922**, p. 354. (b) Hale, A. J., *The Synthetic Use of Metals in Organic Chemistry,* J. & A. Churchill, London, **1914**, p. 152.
3. Cubme, G. O., *Ind. Eng. Chem.,* **1933**, *25*, 582.
4. Lachman, A., *J. Am. Chem. Soc.,* **1901**, *23*, 902.
5. Hixson, A. W. and Cauwenberg, W. J., *J. Am. Chem. Soc.,* **1930**, *52*, 2118.
6. Herz, R., *Chem. Zentr.,* **1922**, *4*, 948.
7. Phillips, M., *J. Ind. Eng. Chem.,* **1921**, *13*, 759.
8. (a) Gillam, E. M. J.; Motley, L. M.; Cai, H. L.; de Voss, J. J. and Guengerich, F. P., *Biochemistry,* **2000**, *39*, 13817. (b) Schmidt, H., *Chem. Unserer Zeit,* **1997**, *31*, 121. (c) Hixson, A. W. and Cauwenberg, W. J., *J. Am. Chem. Soc.,* **1930**, *52*, 2125. (d) Haller, H. L., *J. Ind. Eng. Chem.,* **1922**, *14*, 1040. (e) Heumann, K., *U.S. Pat*., **1899**, Jan. 10, 617,652. (f) Heumann, K., *U.S. Pat*., **1899**, Feb. 28, 620,442. (g) Hentschel, W., *J. Prakt. Chem.,* **1898**, *57*, 198. (h) Frankel, J. and Spiro, K., *Ber.,* **1895**, *28*, 1685.

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Heyns Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Heyns, probably as early as 1952.[1] It is a rapid[2] rearrangement of α-hydroxy imines (including α-hydroxy Schiff bases) into stable α-amino carbonyl compounds (i.e., α-ketoamines[3]) under nonreducing conditions and is generally known as the Heyns rearrangement.[4,5] The corresponding α-ketoamines are referred to as the Heyns rearrangement products[4b,4e,4m,4p,4r,4s,4v,6] or Heyns products.[2,4b,4m,4p,4s,6b]

It should be pointed out that the formation of imines or Schiff base derivatives is thermodynamically reversible,[2,4f,4o] whereas the α-hydroxyl group facilitates the Heyns rearrangement, leading to the formation of stable α-ketoamines.[2,3,4c,4f,4x] In this reaction, the formation of Schiff base is the rate-limiting step, while the Heyns rearrangement is fast.[2] For example, the imine formed from an amine of lens protein and the C-20 carbonyl of corticoids undergoes Heyns rearrangement, and the resulting Heyns product is reported to be involved in the cataract formation.[4l,7] However, under reducing conditions, such as in the presence of sodium cyanoborohydride, the imine or Schiff base is reduced to secondary α-hydroxyamine and no Heyns rearrangement occurs.[2] In addition, the α-ketoamines can be destroyed by acidic hydrolysis, whereas α-hydroxyamines formed under reducing conditions are stable in acidic hydrolysis.[2]

With α-hydroxy carbonyl scaffold, carbohydrates undergo two different reactions with proteins requiring no group protection manipulations—that is, the *Amadori Rearrangement* and Heyns rearrangement. Aldoses give the Amadori products,[4g] existing only in the keto form with an α-hydroxy carbonyl function in the open chain form;[4m] in contrast, ketoses form several Heyns products,[4s] but mainly in the aldehyde form without the α-hydroxy carbonyl functionality[4m] (e.g., the conversion of lactoulose into different lactosamine derivatives[4n]). Both Amadori and Heyns products can undergo further reactions,

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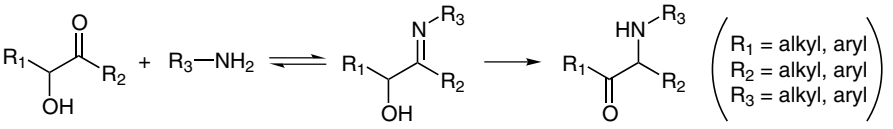
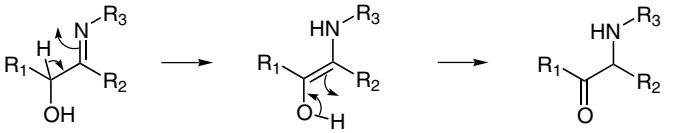
depending on the reactivity of the carbonyl group.[4m] The Amadori products, bearing an α-hydroxy carbonyl group, more readily undergo the enolization, dehydration, elimination, cyclization, migration of carbonyl group, and retro-aldol reaction.[4m] For instance, the Heyns products brown slower than those of Amadori products at 110°C under free access of oxygen.[4v] All these transformations make up the *Maillard Reaction*, leading to the formation of highly reactive compounds that may decompose into small volatile flavor compounds; polymerization into high molecular weight brown pigments known as mellanoidins,[4m] or the formation of fluorescent compounds widely applied in food, cosmetic, and pharmaceutical industries.[8]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The Heyns rearrangement is believed to take place via a hydroxy enamine intermediate, which is analogous to the enediol intermediate proposed in the internal rearrangement between aldoses and ketoses as displayed here.



Hydroxy enamine

D. MODIFICATION

N/A

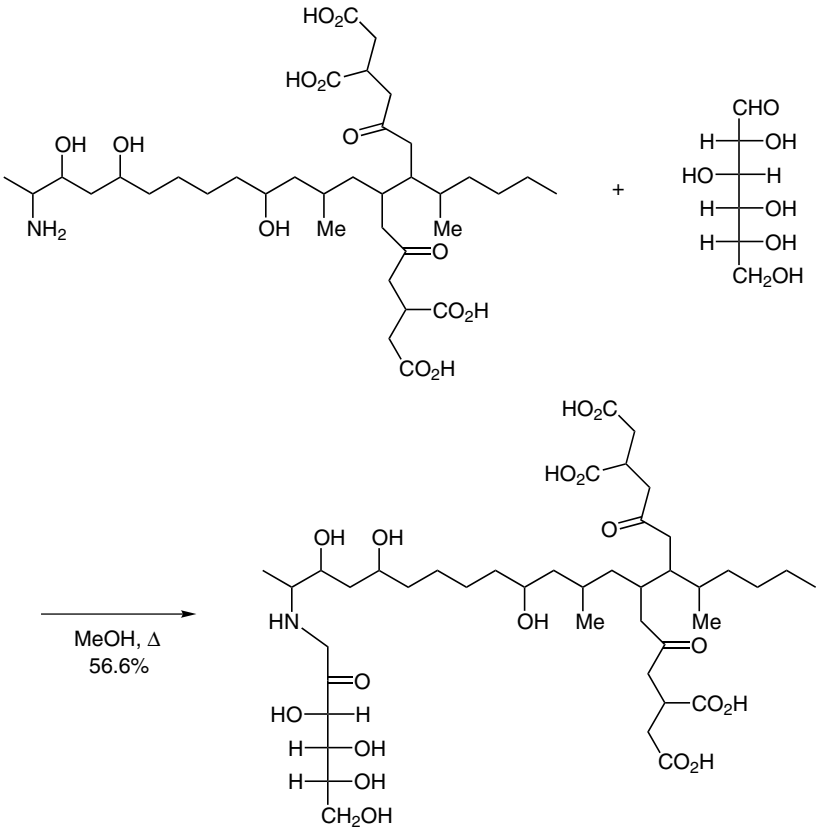
E. APPLICATIONS

This rearrangement is very popular in food chemistry.

F. RELATED REACTIONS

This reaction is related to the *Amadori Rearrangement* and *Maillard Reaction*.

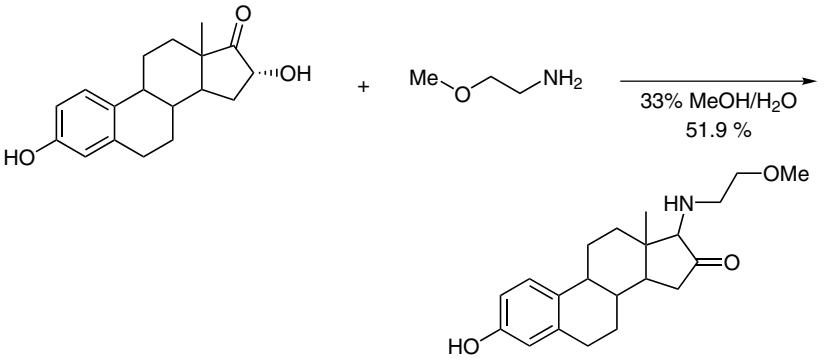
G. CITED EXPERIMENTAL EXAMPLES



Reference 4g.

Four 4.5-mL amber septum vials, each containing 12 mg fumonisin B_1 (16.6 μmol), D-glucose (108 mg, 600 μmol) and 4 mL methanol, were sealed and heated at 64°C for 6 h. The vials were removed briefly and shaken every 1–1.5 h. The glucose did not completely dissolve until the vials had been heated ~ 5 h. The contents of the vials were combined and diluted with 64 mL water (four times the volumes). The products were recovered from the diluted reaction mixture by passing it through a 2-g tC_{18} cartridge (Sep-Pak Vac 12 cm^3 [2 g] tC_{18} cartridge, Waters Corp., Milford, Mass.) that had been preconditioned with 20 mL MeOH, followed by 20 mL MeOH/H_2O (20:80). After the products were loaded, the cartridge was washed with 20 mL MeOH/H_2O (20:80) and then 20 mL CH_3CN/H_2O (10:90). The products were eluted with 20 mL 50:50 CH_3CN/H_2O. The procedure was then repeated using 8 vials, and the products were recovered using a 2-g tC_{18} cartridge. The 50:50 eluates from the 4- and 8-vial preparations were combined. A total of 153 mg fumonisin B_1 (212 mmol) were used for the 12 vials. Fumonisin B_1 and *N*-(1-deoxy-D-fructos-1-yl) fumonisin B_1 were separated using a 10-g strong cation exchange (SCX) Mega Bond Elut, 40 μm, SCX cartridge (Varian Sample Preparation Products, Harbor City, Califo). The cartridge was conditioned with 100 mL MeOH followed by 100 mL 50:50 CH_3CN/H_2O.

The combined 50:50 eluates were loaded onto the SCX cartridge. The cartridge was eluted with the following solvents, and the fractions were collected and analyzed: 100 mL 20:80 CH_3CN/H_2O, 100 mL 1% HCOOH in 20:80 CH_3CN/H_2O, and 2 × 100 mL and then 6 × 50 mL 5% HCOOH in 20:80 CH_3CN/H_2O. *N*-(1-Deoxy-D-fructos-1-yl)fumonisin B_1 started eluting in the first 100-mL portion of the latter solvent, whereas fumonisin B_1 did not start eluting until the second 50-mL portion. The first three portions were combined, diluted with an equal volume of water (250 mL), and loaded onto a 2-g tC_{18} cartridge that had been preconditioned with 20 mL MeOH, followed by 20 mL 10:90 CH_3CN/H_2O. The cartridge was washed with 20 mL of the latter solvent and eluted with 20 mL 50:50 CH_3CN/H_2O. The 50:50 CH_3CN/H_2O eluate was freeze-dried to give 106 mg *N*-(1-deoxy-D-fructos-1-yl) fumonisin B_1 (120 μmol), in a yield of 56.6%.



Reference 4t.

The mixture of 360 mg 3,16α-dihydroxy-estra-1,3,5(10)-trien-17-one and 4 mL 2-methoxy ethylamine was stirred at room temperature for 3 h. The formation of imine intermediate was monitored by the reduction of an aliquot of the reaction mixture with $NaBH_4$ and subsequent TLC analysis using $CHCl_3$/MeOH (10:1) as a developing solvent. After removing the excess reagent under reduced pressure, the residue was dissolved in 33% aqueous MeOH and stirred at room temperature for 2 h. The precipitate formed was collected by filtration. The filtrate was adjusted to pH 1 with 5% HCl, washed with EtOAc, readjusted to pH 11 with 10% NaOH, and extracted with $CHCl_3$. The combined organic layers were washed with half-saturated NaCl, dried over anhydrous Na_2SO_4, and evaporated. The residue was combined with the precipitate and recrystallized from methanol to give 224 mg 3-hydroxy-17β-(2-methoxyethylamino)estra-1,3,5(10)trine-16-one as colorless needles, in a yield of 65.5%, m.p. 190–191°C.

Other references related to the Heyns rearrangement are cited in the literature.[9]

H. REFERENCES

1. Heyns, K. and Koch, W., *Z. Naturforsch.,* **1952**, *7B*, 486.
2. Bucala, R.; Fishman, J. and Cerami, A., *Proc. Natl. Acad. Sci. USA,* **1982**, *79*, 3320.
3. Howard, P. C.; Churchwell, M. I.; Couch, L. H.; Marques, M. M. and Doerge, D. R., *J. Agric. Food Chem.,* **1998**, *46*, 3546.

4. (a) Wrodnigg, T. M.; Lundt, I. and Stütz, A. E., *J. Carbohydr. Chem.*, **2006**, *25*, 33. (b) Monnier, V. M., *Biochem. J.,* **2005**, *392*, e1. (c) Bodor, N. and Buchwald, P., *AAPS J.,* **2005**, *7*, E820. (d) Stütz, A. E.; Dekany, G.; Eder, B.; Illaszewicz, C. and Wrodnigg, T. M., *J. Carbohydr. Chem.,* **2003**, *22*, 253. (e) Dickerson, T. J. and Janda, K. D., *Proc. Natl. Acad. Sci. USA,* **2002**, *93*, 15084. (f) Jobling, A. I. and Augusteyn, R. C., *Clin. Exp. Optom.,* **2002**, *85*, 61. (g) Poling, S. M.; Plattner, R. D. and Weisleder, D., *J. Agric. Food Chem.,* **2002**, *50*, 1318. (h) Wrodnigg, T. M. and Eder, B., *Top. Curr. Chem.,* **2001**, *215*, 115. (i) Farouk, M. A.; Pudil, F.; Janda, V. and Pokorny, J., *Czech J. Food Sci.,* **2001**, *19*, 24. (j) He, X. M.; Agnihotri, G. and Liu, H.-W., *Chem. Rev.,* **2000**, *100*, 4615. (k) Bearne, S. L. and Blouin, C., *J. Biol. Chem.,* **2000**, *275*, 135. (l) Watanabe, H.; Kosano, H. and Nishigori, H., *Invest Ophthalmol Vis. Sci.,* **2000**, *41*, 1846. (m) Yeboah, F. K.; Alli, I. and Yaylayan, V. A., *J. Agric. Food Chem.,* **1999**, *47*, 3164. (n) Wrodnigg, T. M. and Stütz, A. E., *Angew. Chem. Int. Ed*., **1999**, *38*, 827. (o) Zhu, B. T. and Conney, A. H., *Carcinogenesis,* **1998**, *19*, 1. (p) Miyazawa, N.; Kawasaki, Y.; Fujii, J.; Theingi, M.; Hoshi, A.; Hamaoka, R.; Matsumoto, A.; Uozumi, N.; Teshima, T. and Taniguchi, N., *Biochem. J.,* **1998**, *336*, 101. (q) Bearne, S. L. and Wolfenden, R., *Biochemistry,* **1995**, *34*, 11515. (r) Tressl, R.; Kersten, E. and Rewicki, D., *J. Agric. Food Chem.,* **1993**, *41*, 2278. (s) Dills, W. L., *Am. J. Clin. Nutr.,* **1993**, *58*, 779S. (t) Miyairi, S.; Ichikawa, T. and Nambara, T., *Steroids,* 1991, 56, *361*. (u) Longcope, C., *J. Natl. Cancer Inst.,* **1990**, *82*, 896. (v) Pilková, L.; Pokorný, J. and Davídek, J., *Food/Nahrung,* **1990**, *34*, 759. (w) Suárez, G.; Rajaram, R.; Oronsky, A. L. and Gawinowicz, M. A., *J. Biol. Chem.,* **1989**, *264*, 3674. (x) Eriksson, C.-G. and Eneroth, P., *J. Biol. Chem.,* **1988**, *263*, 2824. (y) Kowollik, W.; Janairo, G. and Voelter, W., *J. Org. Chem.,* **1988**, *53*, 3943.
5. (a) Shipar, M. A. H., *Food Chem.,* **2006**, *97*, 231. (b) Miyairi, S.; Maeda, K.; Oe, T.; Kato, T. and Naganuma, A., *Steroids*, **1999**, *64*, 252. (c) Altena, J. H.; Van den Ouweland, G. A. M.; Teunis, C. J. and Tjan, S. B., *Carbohydr. Res.,* **1981**, *92*, 43. (d) Van den Ouweland, G. A. M.; Peer, H. G. and Tjan, S. B., *Flavor Foods Beverages: Chem. Technol.,* **1978**, 131.
6. (a) Hinton, D. J. S. and Ames, J. M., *Amino Acids,* **2006**, *30*, 425. (b) Yaylayan, V. A.; Harty-Majors, S. and Ismail, A. A., *J. Agric. Food Chem.,* **1999**, *47*, 2335.
7. Manabe, S.; Bucala, R. and Cerami, A., *J. Clin. Invest.,* **1984**, *74*, 1803.
8. Tateyama, M., "Development of Polymer-Supported Synthetic Procedure for Heyns Rearrangement Products," Master's Thesis, Department of Food Science and Agricultural Chemistry, Macdonald Campus, McGill University, **1999**.
9. (a) Hinton, D. J. S. and Ames, J. M., *Amino Acids*, **2006**, *30*, 425. (b) Yeboah, F. K.; Alli, I. and Yaylayan, V. A., *J. Agri. Food Chem.,* **1999**, *47*, 3164. (c) Morita, J. and Kashimura, N., *Agri. Biol. Chem.,* **1991**, *55*, 1359. (d) Handwerk, R. L. and Coleman, R. L., *J. Agri. Food Chem.,* **1988**, *36*, 231. (e) Bucala, R.; Ulrich, P. C.; Chait, B. T.; Bencsath, F. A. and Cerami, A., *J. Steroid Biochem.,* **1986**, *25*, 127. (f) Bucala, R.; Gallati, M.; Manabe, S.; Cotlier, E. and Cerami, A., *Exp. Eye Res.,* **1985**, *40*, 853. (g) Skala, L., *Radioisotopy*, **1984**, *25*, 331. (h) Bucala, R. and Cerami, A., *Mol. Immunology,* **1983**, *20*, 1289. (i) Bucala, R.; Fishman, J. and Cerami, A., *Proc. Nat. Acad. Sci. USA,* **1982**, *79*, 3320. (j) Day, J. F.; Thorpe, S. R. and Baynes, J. W., *J. Biol. Chem.,* **1979**, *254*, 595. (k) Heyns, K. and Beilfuss, W., *Ber.,* **1973**, *106*, 2680. (l) Heyns, K. and Beilfuss, W., *Ber.,* **1973**, *106*, 2693. (m) Heyns, K.; Heukeshoven, J. and Brose, K.-H., *Angew. Chem.,* **1968**, *80*, 627. (n) Heyns, K. and Noack, H., *Ber.,* **1964**, *97*, 415. (o) Heyns, K.; Paulsen, H. and Schroeder, H., *Tetrahedron,* **1961**, *13*, 247. (p) Heyns, K. and Rolle, M., *Ber.,* **1959**, *92*, 2439. (q) Heyns, K. and Rolle, M., *Ber.,* **1959**, *92*, 2451. (r) Heyns, K. and Paulsen, H., *Ann.,* **1959**, *622*, 160. (s) Heyns, K. and Breuer, H., *Ber.,* **1958**, *91*, 2750. (t) Heyns, K.; Breuer, H. and Paulsen, H., *Ber.,* **1957**, *90*, 1374. (u) Heyns, K.; Paulsen, H.; Eichstedt, R. and Rolle, M., *Ber.,* **1957**, *90*, 2039.

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Hilbert-Johnson Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Johnson and Hilbert in 1929.[1] It is the synthesis of pyrimidine nucleosides from the glycosylation of protected glycosyl halides with 2,4-dialkoxypyrimidines. Thus it is generally known as the Hilbert-Johnson reaction.[2] Occasionally, it is also referred to as the Hilbert-Johnson synthesis,[3] Hilbert-Johnson glycosylation,[2e,4] Hilbert-Johnson pyrimidine nucleoside synthesis[5] or Hilbert-Johnson method.[6] It should be pointed out that the Lewis acid ($SnCl_4$, TMSOTf, etc.) promoted glycosylation from labile trimethylsilyl-protected pyrimidine and glycosyl acetate, developed initially by Birkofer,[7] and greatly extended by Vorbrüggen,[8] is more versatile and successful for the preparation of pyrimidine nucleosides, which is generally referred to as silyl-Hilbert-Johnson reaction[8i,9] and, in a rare case, as the silyl-Hilbert-Johnson synthesis.[9f] On the other hand, 2-methylthio protected pyrimidine stops at the quaternization step, yielding an intermediate of glycosylpyrimidinium salt that can be converted into 2-oxo, 2-thio, and 2-aminopyrimidine nucleosides.[2t] This reaction is highly efficient and proceeds with high regioselectivity and stereoselectivity,[4c] by which β-anomer predominates in the products,[2r,4a] either condensed from α-glycosyl halide or β-glycosyl halide,[10] except for the case of condensation with 3,5-di-*O*-p-toluyl-2-*deoxy*-D-ribofuranosyl chloride into 2′-deoxyribofuranosylpyrimidines, which resulted in 66% of α-anomeric product.[3a] This reaction has been used for the synthesis of a variety of 2-oxo-pyridimine nucleosides, including uracil,[4c,9b,11] cytosine,[2t,11a,11d] and thymine[11a,11d] nucleosides. In addition, The Hilbert-Johnson reaction also works for nonaromatic aglycons, such as 6-oxadihydrouracil.[12] It was observed that suitably blocked pyranose derivatives also undergo such glycosylation, but under more stringent conditions at slower rates than their corresponding furanose isomers.[13] The protection

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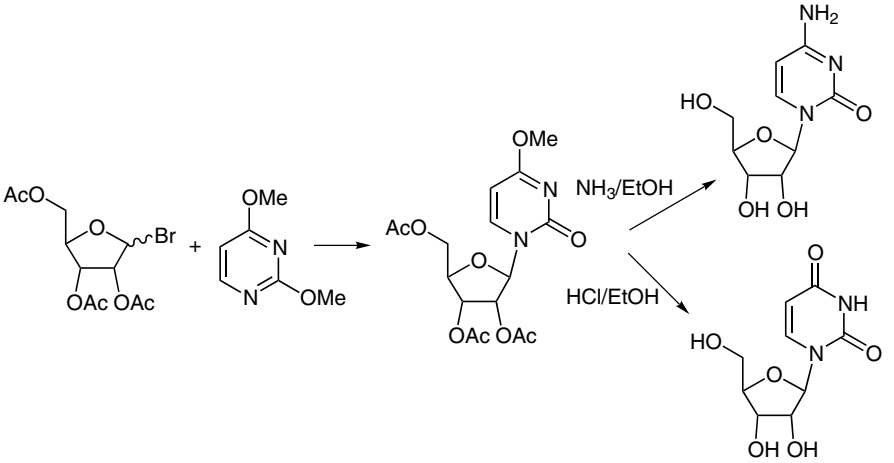
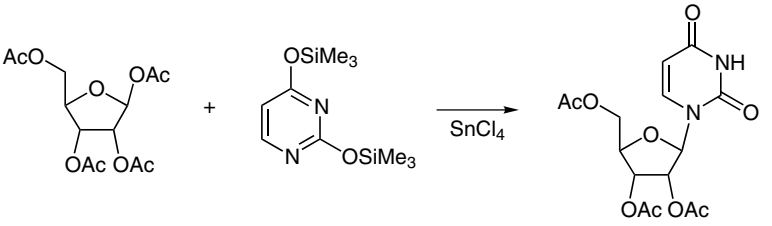
by acetyl rather than benzoyl group leads to an improved yield.[7e] Moreover, reaction in nitrobenzene is significantly faster than that in acetonitrile, the typical solvent used for this reaction.[9e] This reaction has been extended to the preparation of purine nucleosides.[14]

B. GENERAL REACTION SCHEME

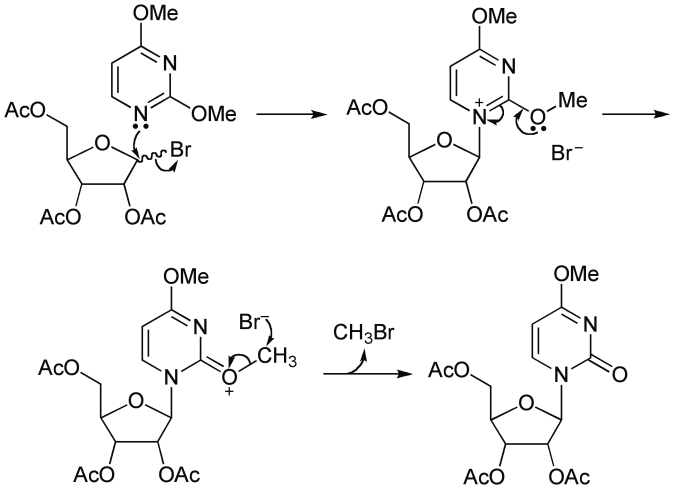
Hilbert-Johnson reaction.



Silyl Hilbert-Johnson reaction.



C. PROPOSED MECHANISMS



D. MODIFICATION

The original Hilbert-Johnson reaction has been modified using trimethylsilyl protected pyrimidine as aglycons to condense with glycosyl acetate and has been applied extensively to the synthesis of a variety of nucleoside derivatives. In addition, the substitution of 2-alkyl pyrimidine for 2-methylthio-protected pyrimidine allows the preparation of 2-oxo, 2-thio, and 2-aminopyrimidine nucleosides.

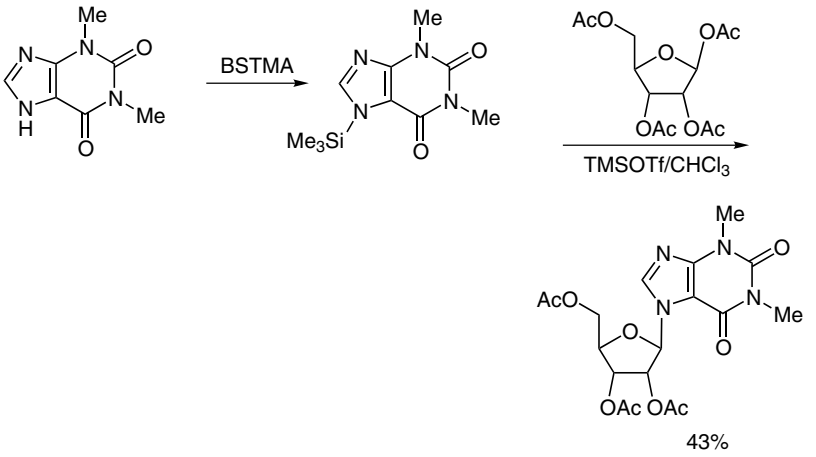
E. APPLICATIONS

This reaction has wide application in the synthesis of pyrimidine nucleosides and their analogues.

F. RELATED REACTIONS

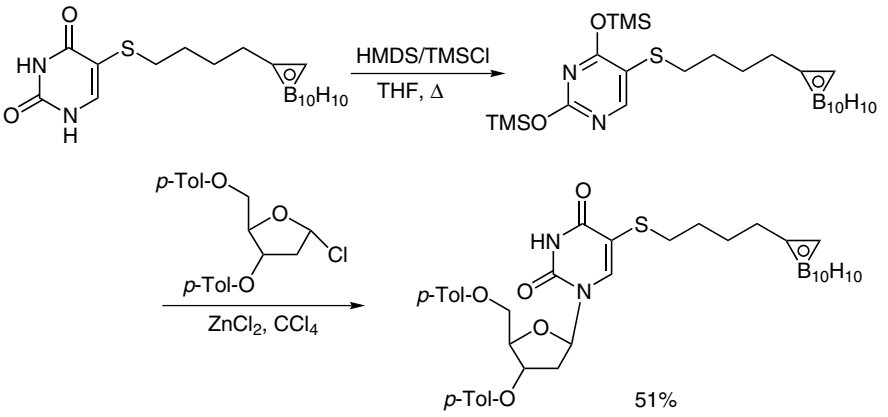
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 14.

A mixture of 4.80 mmol theophylline and 1.4 mL *N*,*O*-bis(trimethylsilyl)acetamide (BSTMA, 5.80 mmol) in 15 mL dry $CHCl_3$ was stirred under nitrogen for 40 min at 20°C. A solution of 4.0 mmol tetraacetyl ribose and 0.1 mL trimethylsilyl trifluoromethanesulfonate (5.80 mmol) in 5 mL $CHCl_3$ was then added, and the reaction mixture was heated at reflux under nitrogen for 4 h. Saturated aqueous $NaHCO_3$ (120 mL) and dichloromethane were then added. After the system had been stirred for 15 min, the two layers were separated, and the aqueous one was extracted with dichloromethane (3 × 120 mL). The combined organic layers and extracts were combined and washed with brine, dried over anhydrous $MgSO_4$, and filtered. The solvents were evaporated to dryness. The residue was crystallized from MeOH to provide 43% 7-(2′,3′,4′-tri-*O*-acetyl-β-D-ribofuranosyl)theophylline as a white solid, m.p. 106°C.



Reference 9b.

5-[4-(*o*-Carboran-1-yl)butylmercapto]uracil (0.86 g, 2.5 mmol) was dissolved in 30 mL anhydrous THF, followed by the addition of 5.0 mmol hexamethyldisilazane (HMDS) and catalytic amounts of TMSCl (0.01 eq.). The mixture was refluxed under argon atmosphere. The byproduct, NH_4Cl, sublimed and was periodically removed from the condenser tips. The cessation of NH_4Cl sublimation indicated that the reactions were complete about 4–6 hours. Removal of THF and excess HMDS by evaporation left clear oil residues, which were immediately used for the condensation step. The oils were dissolved in 25 mL anhydrous CCl_4, and freshly prepared α-D-2-*deoxy*-3,5-di-*O*-*p*-toluoylribofuranosyl chloride (1.25 eq.) and $ZnCl_2$ (0.01 eq.) were added all at once. The reactions were stirred at room temperature for 2–4 days, and then CCl_4 was removed, leaving crude oils, which were purified by silica gel column chromatography, to give 0.90 g 5-[4-(*o*-carboran-1-yl)butylmercapto]-3′,5′-di-*O*-*p*-toluoyl-β-D-2′-deoxyuridine as a white foam, in a yield of 51%, m.p. 92–97°C, R_f = 0.35 (hexane/EtOAc, 3:2).

Other references related to the Hilbert-Johnson reaction are cited in the literature.[15]

H. REFERENCES

1. Johnson, T. B. and Hilbert, G. E., *Science,* **1929**, *69*, 579.
2. (a) Matsumoto, K.; Ikemi, Y.; Suda, M.; Iida, H. and Hamana, H., *Heterocycles*, **2007**, *72*, 187. (b) Wang, Y.; Shang, Z.-C.; Fan, J.-C. and Chen, X., *THEOCHEM*, **2006**, *761*, 39. (c) Oresic, M.; Danilovski, A.; Dumic, M. and Kosutic-Hulita, N., *J. Heterocycl. Chem.,* **2001**, *38*, 785. (d) Liu, G.; Miller, S. C. and Bruenger, F. W., *Synth. Commun.,* **1996**, *26*, 2681. (e) Sheppard, T. L.; Rosenblatt, A. T. and Breslow, R., *J. Org. Chem.,* **1994**, *59*, 7243. (f) Huang, Z.; Schneider, K. C. and Benner, S. A., *J. Org. Chem.,* **1991**, *56*, 3869. (g) Bères, J.; Bentrude, W. G.; Balzarini, J.; de Clercq, E. and Ötvös, L., *J. Med. Chem.,* **1986**, *29*, 494. (h) Kim, C.-H.; Marquez, V. E.; Mao, D. T.; Haines, D. R. and McCormack, J. J., *J. Med. Chem.,* **1986**, *29*, 1374. (i) Kelley, J. L.; Kelsey, J. E.; Hall, W. R.; Krochmal, M. P. and Schaeffer, H. J., *J. Med. Chem.,* **1981**, *24*, 753. (j) Brown, D. J. and Strekowski, L., *Aust. J. Chem.,* **1981**, *34*, 1157. (k) Kulikowski, T.; Zawadzki, Z. and Shugar, D., *J. Med. Chem.,* **1979**, *22*, 647. (l) Prystasz, M., *Nucleic Acid Chem.*, **1978**, *1*, 77. (m) Holy, A., *Coll. Czech. Chem. Common.,* **1977**, *42*, 902. (n) Stevens, C. L.; Radhakrishnan, R. and Pillai, P. M., *J. Carbohydr. Nucleosides, Nucleotides,* **1976**, *3*, 71. (o) Koomen, G. J. and

Pandit, U. K., *Heterocycles*, **1975**, *3*, 539. (p) Lee, W. W.; Martinez, A. P.; Goodman, L. and Henry, D. W., *J. Org. Chem.,* **1972**, *37*, 2923. (q) Mertes, M. P., *J. Med. Chem.,* **1970**, *13*, 149. (r) Walton, E.; Jenkins, S. R.; Nutt, R. F.; Holly, F. W. and Nemes, M., *J. Med. Chem.,* **1969**, *12*, 306. (s) Kotick, M. P.; Szantay, C. and Bardos, T. J., *J. Org. Chem.,* **1969**, *34*, 3806. (t) Ueda, T. and Nishino, H., *J. Am. Chem. Soc.,* **1968**, *90*, 1678. (u) Pliml, J. and Prystas, M., *Adv. Heterocycl. Chem.,* **1967**, *8*, 115. (v) Prystas, M. and Sorm, F., *Coll. Czech. Chem. Commun.,* **1966**, *31*, 1035. (w) Keller, F.; Bunker, J. E. and Brown, L. H., *J. Org. Chem.,* **1966**, *31*, 3840. (x) Walton, E.; Holly, F. W.; Boxer, G. E. and Nutt, R. F., *J. Org. Chem.,* **1966**, *31*, 1163. (y) Prystas, M. and Sorm, F., *Coll. Czech. Chem. Commun.,* **1965**, *30*, 2960. (z) Prystas, M. and Sorm, F., *Coll. Czech. Chem. Commun.,* **1964**, *29*, 2956. (aa) Farkas, J.; Kaplan, L. and Fox, J. J., *J. Org. Chem.,* **1964**, *29*, 1469. (bb) Stevens, C. L. and Nagarajan, K., *J. Med. Chem.,* **1962**, *5*, 1124.

3. (a) Winkley, M. W. and Robins, R. K., *J. Org. Chem.,* **1968**, *33*, 2822. (b) Ryan, K. J.; Acton, E. M. and Goodman, L., *J. Org. Chem.,* **1966**, *31*, 1181. (c) Goodman, L.; Benitez, A. and Baker, B. R., *J. Am. Chem. Soc.,* **1958**, *80*, 1680.
4. (a) Li, N.-S.; Tang, X.-Q. and Piccirilli, J. A., *Org. Lett.,* **2001**, *3*, 1025. (b) Zhu, Z. J.; Lippa, B. and Townsend, L. B., *J. Org. Chem.,* **1999**, *64*, 4159. (c) Sun, S. G.; Tang, X.-Q.; Merchant, A.; Anjaneyulu, P. S. R. and Piccirilli, J. A., *J. Org. Chem.,* **1996**, *61*, 5708.
5. Ueda, T. and Ohtsuka, H., *Chem. Pharm. Bull.,* **1973**, *21*, 1451.
6. (a) Prystas, M. and Sorm, F., *Coll. Czech. Chem. Commun.,* **1964**, *29*, 131. (b) Prystas, M.; Farkas, J. and Sorm, F., *Coll. Czech. Chem. Commun.,* **1963**, *28*, 3140.
7. (a) Birkofer, L.; Ritter, A. and Kühlthau, A., *Angew. Chem.,* **1963**, *75*, 209. (b) Nishimura, T.; Shimizu, B. and Iwai, I., *Chem. Pharm. Bull.,* **1963**, *11*, 1470.
8. (a) Vorbrüggen, H. and Ruh-Pohlenz, C., *Org. React.,* John Wiley & Sons, New York, **1999**, *55*. (b) Vorbrüggen, H., *Acta, Biochim. Pol.,* **1996**, *43*, 25. (c) Vorbrüggen, H., *Acc. Chem. Res.,* **1995**, *28*, 509. (d) Vorbrüggen, H.; Krolikiewicz, K. and Bennua, B., *Ber.,* **1981**, *114*, 1234. (e) Vorbrüggen, H. and Hofle, G., *Ber.,* **1981**, *114*, 1256. (f) Vorbrüggen, H., "Methods of Nucleoside Synthesis" in *Nucleoside Analogues. Chemistry, Biology and Medical Applications*, ed. Walker, R. T.; de Clercq, E. and Eckstein, F., Plenum Press, New York, **1979**, pp. 35–69. (g) Vorbrüggen, H. F.; Niedballa, U.; Krolikiewicz, K.; Bennua, B. and Hofle, G., "On the Mechanism of Nucleoside Synthesis" in *Chemistry and Biology of Nucleosides and Nucleotides*, ed. Harmon, R. E.; Robins, R. K.; Townsend, L. B., Academic Press, New York, **1978**, pp. 251–265. (h) Vorbrüggen, H. and Bennua, B., *Tetrahedron Lett.,* **1978**, *39*, 1339. (i) Niedballa, U. and Vorbrüggen, H., *J. Org. Chem.,* **1976**, *41*, 2084. (j) Vorbrüggen, H. and Krolikiewica, K., *Angew. Chem. Int. Ed. Engl.,* **1975**, *14*, 421. (k) Niedballa, U. and Vorbrüggen, H., *J. Org. Chem.,* **1974**, *39*, 3660. (l) Niedballa, U. and Vorbrüggen, H., *J. Org. Chem.,* **1974**, *39*, 3668. (m) Niedballa, U. and Vorbrüggen, H., *J. Org. Chem.,* **1974**, *39*, 3672. (n) Niedballa, U. and Vorbrüggen, H., *Angew. Chem. Int. Ed. Engl.,* **1970**, *9*, 461.
9. (a) Caddell, J. M.; Chapman, A. M.; Cooley, B. E.; Downey, B. P.; LeBlanc, M. P.; Jackson, M. M.; O;Connell, T. M.; Phung, H.-M.; Roper, T. D. and Xie, S. P., *J. Org. Chem.,* **2004**, *69*, 3212. (b) Lunato, A. J.; Wang, J. H.; Woollard, J. E.; Anisuzzaman, A. K. M.; Ji, W. H.; Rong, F.-G.; Ikeda, S.; Soloway, A. H.; Eriksson, S.; Ives, D. H.; Blue, T. E. and Tjarks, W., *J. Med. Chem.,* **1999**, *42*, 3378. (c) Beijer, F. H.; Sijbesma, R. P.; Vekemans, J. A. J. M.; Meijer, E. W.; Koojiman, H. and Spek, A. L., *J. Org. Chem.,* **1996**, *61*, 6371. (d) El-Barbary, A. A.; Khodair, A. I. and Pedersen, E. B., *J. Org. Chem.,* **1993**, *58*, 5994. (e) Ikemoto, N. and Schreiber, S. L., *J. Am. Chem. Soc.,* **1990**, *112*, 9657. (f) Bambury, R. E.; Feeley, D. T.; Lawton, G. C.; Weaver, J. M. and Wemple, J., *J. Med. Chem.,* **1984**, *27*, 1613. (g) Nishitani, T.; Horikawa, H.; Iwasaki, T.; Matsumoto, K.; Inoue, I. and Miyoshi, M., *J. Org. Chem.,* **1982**, *47*, 1706. (h) Nishitani, T.; Iwasaki, T.; Mushika, Y. and Miyoshi, M., *J. Org. Chem.,* **1979**, *44*, 2019. (i) Niedballa, U. and Vorbruggen, H., *Nucleic Acid Chem.*, **1978**, *1*, 431. (j) Niedballa, U. and Vorbruggen, H., *Nucleic Acid Chem.*, **1978**, *1*, 481. (k) Niedballa, U. and Vorbrüggen, H., *J. Org. Chem.,* **1974**, *39*, 3654. (l) Niedballa, U. and Vorbrüggen, H., *J. Org. Chem.,* **1974**, *39*, 3664.

10. Fox, J. J.; Codington, J. F.; Yung, N. S. C.; Kaplan, L. and Lampen, J. O., *J. Am. Chem. Soc.,* **1958**, *80*, 5155.

11. (a) Lopin, C.; Gautier, A.; Gouhier, G. and Piettre, S. R., *J. Am. Chem. Soc.,* **2002**, *124*, 14668. (b) Beauchamp, L. M.; Serling, B. L.; Kelsey, J. E.; Biron, K. K.; Collins, P.; Selway, J.; Lin, J.-C. and Schaeffer, H. J., *J. Med. Chem.,* **1988**, *31*, 144. (c) Kaye, H., *Macromolecules,* **1971**, *4*, 147. (d) Newmark, P. and Goodman, I., *J. Am. Chem. Soc.,* **1957**, *79*, 6446.

12. Marquez, V. E.; Liu, P. S. and Kinevsky, J. K., *J. Org. Chem.,* **1982**, *47*, 1712.

13. Efange, S. M. N.; Alessi, E. M.; Shih, H. C.; Cheng, Y.-C. and Bardos, T. J., *J. Med. Chem.,* **1985**, *28*, 904.

14. Rico-Gómez, R.; Rodríguez-González, A.; Ríos-Ruízz, J.; Nájera, F. and López-Romero, J. M., *Eur. J. Org. Chem.,* **2003**, 4023.

15. (a) Seela, F. and Peng, X. H., *Coll. Czech. Chem. Commun.,* **2006**, *71*, 956. (b) Pati, A.; Patra, M. and Behera, R. K., *Synth. Commun.,* **2006**, *36*, 1801. (c) Seela, F. and Peng, X. H., *Curr. Topics Med. Chem.,* **2006**, *6*, 867. (d) Seela, F. and Peng, X. H., *J. Org. Chem.,* **2006**, *71*, 81. (e) Novikov, M. S. and Ozerov, A. A., *Chem. Heterocycl. Compd.,* **2005**, *41*, 766. (f) Novikov, M. S.; Ozerov, A. A.; Orlova, Yu. A. and Buckheit, R. W., *Chem. Heterocycl. Compd.,* **2005**, *41*, 625. (g) Ichikawa, Y.; Hirata, K.; Ohbayashi, M. and Isobe, M., *Chem. Eur. J.,* **2004**, *10*, 3241. (h) Sharma, P. K. and Nielsen, P., *J. Org. Chem.,* **2004**, *69*, 5742. (i) Lee, S.-G.; Kim, J.-J.; Kim, H.-K.; Kweon, D.-H.; Kang, Y.-J.; Cho, S.-D.; Kim, S.-K. and Yoon, Y.-J., *Curr. Org. Chem.,* **2004**, *8*, 1463. (j) Seela, F. and Peng, X. H., *Nucleosides, Nucleotides & Nucleic Acids,* **2004**, *23*, 227. (k) Henry, A. A.; Yu, C. Z. and Romesberg, F. E., *J. Am. Chem. Soc.,* **2003**, *125*, 9638. (l) Wu, X. L.; Guntha, S.; Ferencic, M.; Krishnamurthy, R. and Eschenmoser, A., *Org. Lett.,* **2002**, *4*, 1279. (m) Stokes, D. M.; Paul, B.; Alderfer, J. L.; Wollman, R. M. and Srikrishnan, T., *Nucleosides, Nucleotides & Nucleic Acids*, **2002**, *21*, 863. (n) Zhuo, J.-C.; Soloway, A. H.; Beeson, J. C.; Ji, W. H.; Barnum, B. A.; Rong, F.-G.; Tjarks, W.; Jordan, G. T.; Liu, J. P. and Shore, S. G., *J. Org. Chem.,* **1999**, *64*, 9566. (o) Christensen, N. K.; Petersen, M.; Nielsen, P.; Jacobsen, J. P.; Olsen, C. E. and Wengel, J., *J. Am. Chem. Soc.,* **1998**, *120*, 5458. (p) Rosler, A. and Pfleiderer, W., *Helv. Chim. Acta,* **1997**, *80*, 1869. (q) Mourabit, A. A., *Tetrahedron: Asymmetry,* **1996**, *7*, 3455. (r) Knapp, S., *Chem. Rev.,* **1995**, *95*, 1859. (s) Kristinsson, H.; Nebel, K.; O'Sullivan, A. C.; Struber, F.; Winkler, T. and Yamaguchi, Y., *Tetrahedron*, **1994**, *50*, 6825. (t) Dueholm, K. L.; Aly, Y. L.; Joergensen, P. T.; El-Barbary, A. A.; Pedersen, E. B. and Nielsen, C., *Monatsh. Chem.,* **1993**, *124*, 37. (u) Goulaouic, C.; Adams, D. R.; Chiaroni, A.; Riche, C. and Grierson, D. S., *J. Org. Chem.,* **1993**, *58*, 3030. (v) Haas, A.; Lieb, M. and Steffens, B., *J. Fluor. Chem.,* **1992**, *56*, 55. (w) Showalter, H. D.; Putt, S. R. and Baker, D. C., *Nucleic Acid Chem.*, **1991**, 308. (x) Wengel, J.; Lau, J.; Pedersen, E. B. and Nielsen, C. M., *J. Org. Chem.,* **1991**, *56*, 3591. (y) Chow, K. and Danishefsky, S., *J. Org. Chem.,* **1990**, *55*, 4211. (z) Cristescu, C. and Tomas, S., *Rev. Roumaine Chim.,* **1989**, *34*, 1321. (aa) Schlimme, E.; Frister, H. and Raezke, K. P., *Nucleosides & Nucleotides*, **1988**, *7*, 577. (bb) Holshouser, M. H.; Shipp, A. M. and Ferguson, P. W., *J. Med. Chem.,* **1985**, *28*, 242. (cc) Ogilvie, K. K.; Hamilton, R. G.; Gillen, M. F.; Radatus, B. K.; Smith, K. O. and Galloway, K. S., *Can. J. Chem.,* **1984**, *62*, 16. (dd) Bambury, R. E.; Feeley, D. T.; Lawton, G. C.; Weaver, J. M. and Wemple, J., *J. Chem. Soc., Chem. Commun.,* **1984**, 422. (ee) Cristescu, C., *Rev. Roumaine Chim.,* **1983**, *28*, 989. (ff) Szemzo, A.; Szabolcs, A.; Sagi, J. and Otvos, L., *J. Carbohydr., Nucleosides, Nucleotides,* **1980**, *7*, 365. (gg) Watanabe, K. and Ito, Y., *Lifechem (Tokyo)*, **1979**, *2*, 36. (hh) Miyai, K.; Tolman, R. L.; Robins, R. K. and Cheng, C. C., *J. Med. Chem.,* **1978**, *21*, 427. (ii) Brown, S. G. and Dewar, M. J. S., *J. Org. Chem.,* **1978**, *43*, 1331. (jj) Skulnick, H., *J. Org. Chem.,* **1978**, *43*, 3188. (kk) Newkome, G. R.; Nayak, A.; Otemaa, J.; Van, D. A. and Benton, W. H., *J. Org. Chem.,* **1978**, *43*, 3362. (ll) Fourrey, J. L. and Jouin, P., *Tetrahedron Lett.*, **1977**, 951. (mm) Szabolcs, A.; Sàgi, J.; Ötvös, L., *J. Carbohydr., Nucleosides, Nucleotides,* **1975**, *2*, 197. (nn) Kulikowski, T. and Shugar, D., *J. Med. Chem.,* **1974**, *17*, 269. (oo) Holy, A. and Ivanova, G. S., *Nucleic Acids Res.,* **1974**, *1*, 19. (pp) Wightman, R. and Holy, A., *Coll. Czech. Chem. Commun.,* **1973**, *38*, 1381. (qq) Ueda, T. and Ohtsuka, U., *Chem. Pharm. Bull.,* **1973**, *21*, 1450.

(rr) Ueda, T. and Ohtsuka, U., *Chem. Pharm. Bull.,* **1973**, *21*, 1530. (ss) Doerr, I. L. and Willette, R. E., *J. Org. Chem.,* **1973**, *38*, 3878. (tt) Zorbach, W., *Methods Carbohydr. Chem.,* **1972**, *6*, 445. (uu) Szekeres, G. L. and Bardos, T. J., *J. Med. Chem.,* **1970**, *13*, 708. (vv) Wong, J. L. and Fuchs, D. S., *J. Org. Chem.,* **1970**, *35*, 3786. (ww) Winkley, M. W. and Robins, R. K., *J. Org. Chem.,* **1969**, *34*, 431. (xx) Vorbrueggen, H. and Niedballa, U., *Tetrahedron Lett*., **1970**, 3571. (yy) Lichtenthaler, F. W.; Bambach, G. and Scheidegger, U., *Ber.,* **1969**, *102*, 986. (zz) Prystas, M. and Sorm, F., *Coll. Czech. Chem. Commun.,* **1969**, *34*, 331. (aaa) Wittenburg, E., *Ber.,* **1968**, *101*, 1095. (bbb) Iwai, I.; Nishimura, T. and Shimizu, B., *Synth. Proced. Nucleic Acid Chem.,* **1968**, *1*, 388. (ccc) Schmidt, G. and Farkas, J., *Tetrahedron Lett*., **1967**, 4251. (ddd) Prystas, M., *Coll. Czech. Chem. Commun.,* **1967**, *32*, 4260. (eee) Prystas, M. and Sorm, F., *Coll. Czech. Chem. Commun.,* **1967**, *32*, 1298. (fff) Prystas, M. and Sorm, F., *Coll. Czech. Chem. Commun.,* **1966**, *31*, 1053. (ggg) Reisser, F. and Pfleiderer, W., *Ber.,* **1966**, *99*, 547. (hhh) Mertes, M. P.; Saheb, S. E. and Miller, D., *J. Med. Chem.,* **1966**, *9*, 876. (iii) Keller, F.; Sugisaka, N.; Tyrrill, A. R.; Brown, L. H.; Bunker, J. E. and Botvinick, I. J., *J. Org. Chem.,* **1966**, *31*, 3842. (jjj) Keller, F. and Tyrrill, A. R., *J. Org. Chem.,* **1966**, *31*, 1289. (kkk) Angyal, S. J. and Rutherford, D., *Ann. Rev. Biochem.,* **1965**, *34*, 77. (lll) Shen, T. Y.; Lewis, H. M. and Ruyle, W. V., *J. Org. Chem.,* **1965**, *30*, 835. (mmm) Pliml, J. and Sorm, F., *Coll. Czech. Chem. Commun.,* **1965**, *30*, 3744. (nnn) Prystas, M. and Sorm, F., *Coll. Czech. Chem. Commun.*, **1965**, *30*, 1900. (ooo) Prystas, M. and Sorm, F., *Coll. Czech. Chem. Commun.,* **1964**, *29*, 121. (ppp) Nishimura, T. and Iwai, I., *Chem. Pharm. Bull.,* **1964**, *12*, 352. (qqq) Wittenburg, E., *Z. Chem.,* **1964**, *8*, 303. (rrr) Fox, J. J. and Wempen, I., *Adv. Carbohydr. Chem.,* **1959**, *14*, 283. (sss) Fox, J. J.; Yung, N. S.; Davoll, J. and Brown, G. B., *J. Am. Chem. Soc.,* **1956**, *78*, 2117. (ttt) Howard, G. A.; Lythgoe, B. and Todd, A. R., *J. Chem. Soc.,* **1947**, 1052. (uuu) Hilbert, G. E., *J. Am. Chem. Soc.,* **1937**, *59*, 330. (vvv) Hilbert, G. E. and Rist, C. E., *J. Biol. Chem.,* **1937**, *117*, 371. (www) Hilbert, G. E. and Jansen, E. F., *J. Am. Chem. Soc.,* **1936**, *58*, 60. (xxx) Hilbert, G. E. and Johnson, T. B., *J. Am. Chem. Soc.,* **1930**, *52*, 2001. (yyy) Hilbert, G. E. and Johnson, T. B., *J. Am. Chem. Soc.,* **1930**, *52*, 4489.

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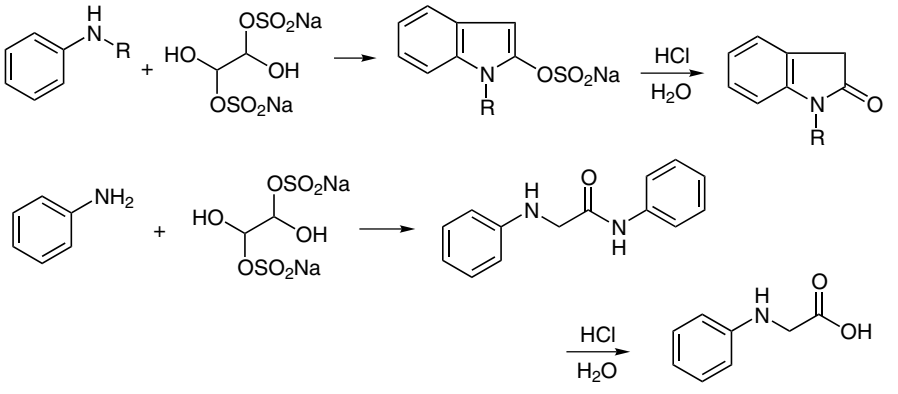
Hinsberg Oxindole Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Hinsberg in 1888.[1] It is the synthesis of *N*-alkyl-oxindole from *N*-alkyl aniline and the glyoxal-bisulfite adduct after hydrolysis by hydrochloric acid.[2] Similarly, the reaction of *N*-alkyl naphthylamine with glyoxal-bisulfite adduct leads to benzo-oxindole.[3] In contrast, the reaction between primary aryl amines and glyoxal-bisulfite adduct produces the substituted glycines.

B. GENERAL REACTION SCHEME



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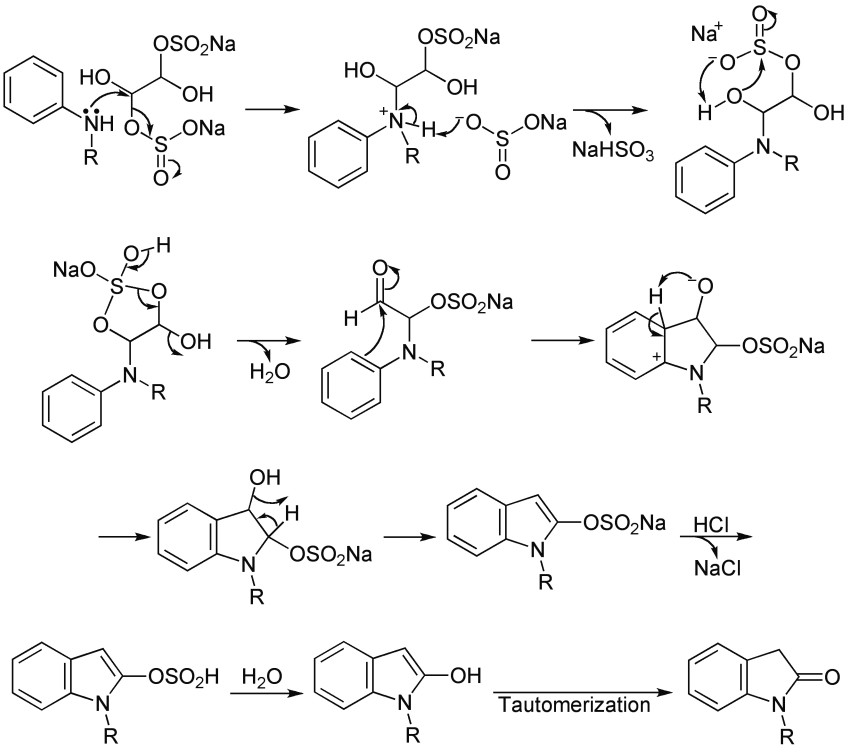
C. PROPOSED MECHANISMS

As this reaction has not been extensively studied and not much mechanistic information is available, a tentative mechanism is outlined here. It is possible that the primary aryl amine has less steric hindrance than the secondary aryl amine during the substitution, hence substituted glycine is produced as the product.



D. MODIFICATION

N/A

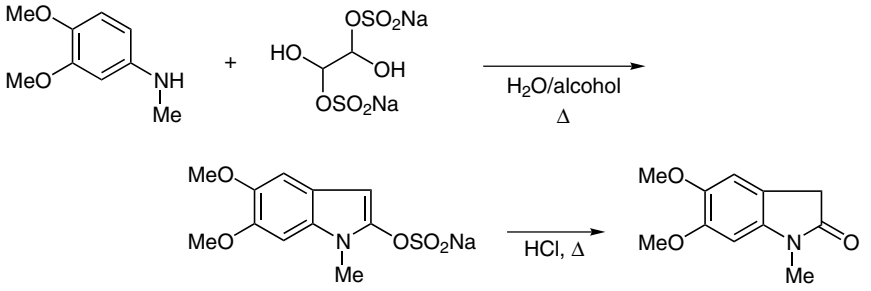
E. APPLICATIONS

This reaction has certain applications in the preparation of oxindoles.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 4.

A solution of 32.0 g glyoxal sodium bisulfate in 250 mL water was mixed with a solution of 20.0 g 4-methyl aminoveratrole in 150 mL alcohol, and the resulting mixture was boiled under reflux for 48 h. The greenish yellow solution was filtered while hot and then cooled at $\sim 0^{\circ}$C. The solid was separated and crystallized from water to afford 19.0 g sodium 5,6-dimethoxy-1-methylindolyl 2-sulfite as small prisms, m.p. 187°C (dec.)

The mixture of 5.0 g sodium 5,6-dimethoxy-1-methylindolyl 2-sulfite, 25 mL water, and 50 mL HCl was boiled for 30 min, and the resulting solution was neutralized. A small amount of insoluble material separated. Extraction of the basified solution with ether afforded 5,6-dimethoxy-1-methyloxindole, which dissolved readily in water and crystallized from light petroleum ether (b.p. 100–120°C) in clusters of needles, m.p. 120–121°C.

Other references related to the Hinsberg oxindole synthesis are cited in the literature.[5]

H. REFERENCES

1. Hinsberg, O., *Ber.,* **1888**, *21*, 110.
2. Sumpter, W. C., *Chem. Rev.,* **1945**, *37*, 443.
3. Goldsmith, E. A. and Lindwall, H. G., *J. Org. Chem.,* **1953**, *18*, 507.
4. Burton, H., *J. Chem. Soc.,* **1932**, 546.
5. (a) Rodrigo, G. A.; Renou, S.; Bekerman, D. G.; Abasolo, M. I. and Fernandez, B. M., *J. Heterocycl. Chem.,* **1997**, *34*, 505. (b) Abasolo, M. I.; Fernandez, B. M. and Magrini, E., *J. Heterocycl. Chem.,* **1992**, *29*, 1279. (c) Abasolo, M. I.; Bianchi, D.; Atlasovich, F.; Gaozza, C. and Fernandez, B. M., *J. Heterocycl. Chem.,* **1990**, *27*, 157. (d) Hinsberg, O., *Ber.,* **1908**, *41*, 1367. (e) Hinsberg, O. and Simcoff, *Ber.,* **1898**, *31*, 250. (f) Hinsberg, O. and Rosenzweig, J., *Ber.,* **1894**, *27*, 3253. (g) Hinsberg, O. and Rosenzweig, J., *Ber.,* **1894**, *27*, 3257. (h) Hinsberg, O., *Ber.,* **1892**, *25*, 2545.

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Hinsberg Reaction

A. GENERAL DESCRIPTION OF THE REACTION

Although the preparation of arenesulfonamides had been known since 1853,[1] it was Hinsberg who applied the method to prepare secondary amines in 1890[2] and explored the application of this reaction,[3] thus comes the name of the Hinsberg reaction[4] or Hinsberg method.[4b,5] It is the preparation of sulfonamides involving the treatment of primary or secondary amines with arenesulfonyl chloride, the further alkylation of resulting sulfonamides from primary amines, and the hydrolysis of sulfonamides into primary or secondary amines. With a quite acidic hydrogen attached to the nitrogen in the arenesulfonamides of primary amines,[6] the primary amines can be distinguished by observing the mode of reaction with a sulfonyl chloride and aqueous alkali, in which the primary amine forms an alkali-soluble sulfonamide, but the secondary amine results in an alkali insoluble sulfonamide, and the tertiary amine does not react with sulfonyl chloride.[4b] Therefore, arenesulfonyl chloride has been widely used to protect the amino group,[7] differentiate the type of amines,[4b] etc. It should be pointed out that in some cases, the primary amines (e.g., aniline and *m*-xylidine) might be oversulfonated to form disulfonylamides that are not soluble in alkali solution, and some monosulfonamides of primary amines are still not soluble in alkali solution.[5c] Therefore, the reaction using arenesulfonyl chloride to differentiate the types of amines (i.e., primary, secondary, and tertiary amines) is also known as the Hinsberg test.[8] Because the formed sulfonamides are very stable,[4b] different methods have been tried to hydrolyze the sulfonamides, including the treatment of sulfonamides with chlorosulfonic acid,[9] 80% sulfuric acid,[10] sulfuric acid, acetic acid,[11] hydrochloric acid,[12] and 48% hydrobromic acid in acetic acid in the presence of phenol.[5a,7] However, the sulfonation on the aromatic nucleus may occur along with the hydrolysis of sulfonamide of the aromatic amines;[13] and the hydrolysis of sulfonamides under basic conditions is not successful.[14]

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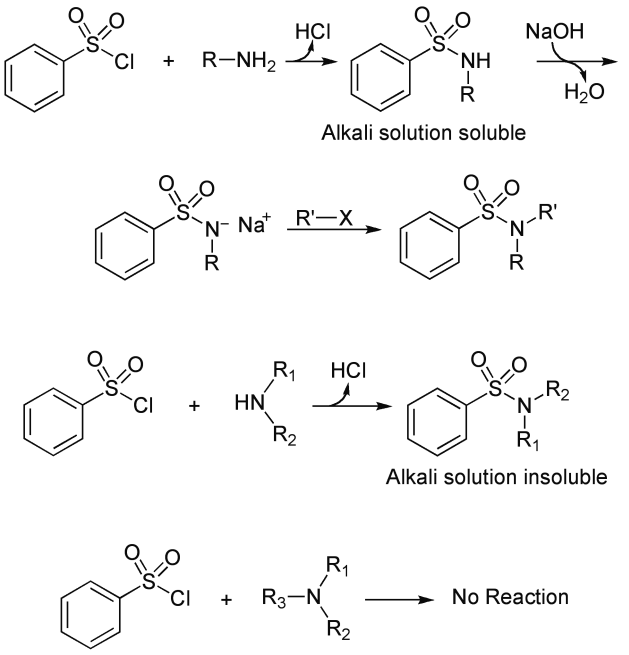
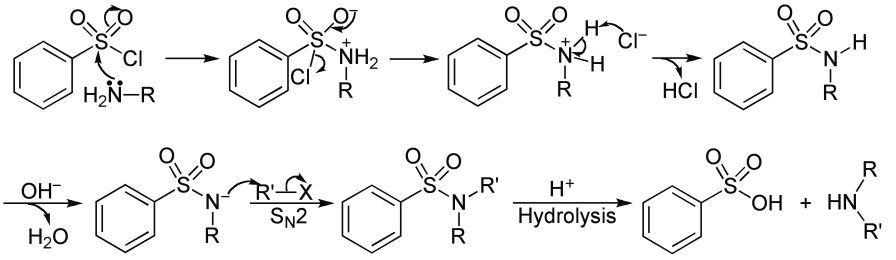
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The mechanism for the preparation of secondary amines from primary amines is given below.



D. MODIFICATION

This reaction has been modified to use *p*-phenylazobenzenesulfonyl chloride to react with amines to monitor the reaction.[15]

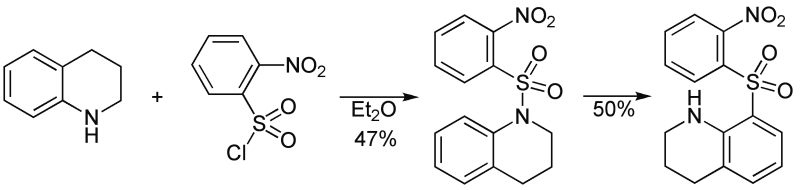
E. APPLICATIONS

This reaction has applications in the protection of primary and secondary amino groups and selective conversion of primary amines into secondary amines.

F. RELATED REACTIONS

N/A

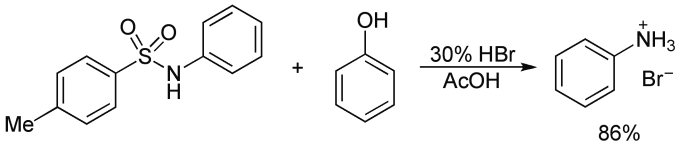
G. CITED EXPERIMENTAL EXAMPLES



Reference 15.

A solution of 67.0 g *o*-nitrobenzenesulfonyl chloride (0.3 mol) in 400 mL anhydrous ether was added gradually with stirring to a cooled solution of 80.0 g 1,2,3,4-tetrahydroquinoline (0.6 mol) in 120 mL anhydrous ether. After the addition was complete, the cooling bath was removed, and the mixture was refluxed for 1 h. The cooled reaction mixture was filtered, and the precipitate was washed with hot water to remove the amine hydrochloride. The residue was combined with the ether filtrate, and the solvent was stripped to give ~50 g crude product. The product was dissolved in ethanol, decolorized, and recrystallized to give 43 g 1-(phenylsulfonyl)-1,2,3,4-tetrahydroquinoline as a pale yellow solid, in a yield of 47%, m.p. 131–132°C.

A mixture of 2.0 g 1-(phenylsulfonyl)-1,2,3,4-tetrahydroquinoline with 6 mL concentrated sulfuric acid gradually colored; and when complete solution occurred, it was heated in a steam bath for 45 min, cooled, and poured over ice. A pale gummy solid precipitated, which was isolated, washed thoroughly with water, and recrystallized from ethanol to give 1.0 g 8-(phenylsulfonyl)-1,2,3,4-tetrahydroquinoline as pale yellow needles, in a yield of 50%.



Reference 7.

A solution of 2.5 g *p*-toluenesulfonanilide (0.01 mol) and 2.0 g phenol (0.02 mol) in 23 g 30% hydrogen bromide in acetic acid was permitted to stand at 26°C for 16 h. The reaction mixture was poured into 150 mL anhydrous ether. The precipitate was filtered, washed with 100 mL ether, and dried to give 1.48 g aniline bromide, in a yield of 86%, m.p. 283°C (dec.).

Other references related to the Hinsberg reaction are cited in the literature.[16]

H. REFERENCES

1. Gerhardt, C. and Chiozza. L., *Ann*., **1853**, *87*, 296.
2. Hinsberg, O., *Ber.,* **1890**, *23*, 2962.
3. (a) Hinsberg, O. and Kessler, J., *Ber.,* **1905**, *38*, 906. (b) Hinsberg, O. and Strupler, A., *Ann.,* **1895**, *287*, 220. (c) Hinsberg, O., *Ann.,* **1891**, *265*, 178.
4. (a) Graafland, T.; Wagenaar, A.; Kirby, A. J. and Engberts, J. B. F. N., *J. Am. Chem. Soc.,* **1979**, *101*, 6981. (b) Searles, S. and Nukina, S., *Chem. Rev.,* **1959**, *59*, 1077. (c) Ham, G. E. and Gann, P. W., *Ind. Eng. Chem.,* **1953**, *45*, 2320.
5. (a) Snyder, H. R. and Heckert, R. E., *J. Am. Chem. Soc.,* **1952**, *74*, 2006. (b) Barkenbus, C. and Landis, P. S., *J. Am. Chem. Soc.,* **1948**, *70*, 684. (c) Seaman, W.; Norton, A. R.; Woods, J. T. and Bank, H. N., *J. Am. Chem. Soc.,* **1945**, *67*, 1571.
6. Closson, W. D.; Ji, S. C. and Schulenberg, S., *J. Am. Chem. Soc.,* **1970**, *92*, 650.
7. Weisblat, D. I.; Magerlein, B. J. and Myers, D. R., *J. Am. Chem. Soc.,* **1953**, *75*, 3630.
8. Blades, C. E. and Wilds, A. L., *J. Org. Chem.,* **1956**, *21*, 1013.
9. Marckwald, W. and von Droste-Huelshoff, A. F., *Ber.,* **1898**, *31*, 3261.
10. Witt, O. N. and Uermenyl, D., *Ber.,* **1913**, *46*, 296.
11. Ullman, F., *Ann.,* **1903**, *327*, 104.
12. (a) von Braun, J. and Weismantel, J., *Ber.,* **1955**, *88*, 3165. (b) Carothers, W. H.; Brickford, C. F. and Hurwitz, G. J., *J. Am. Chem. Soc.,* **1927**, *49*, 2908.
13. Gennaro, A. R. and Zanger, M., *J. Org. Chem.,* **1971**, *36*, 1321.
14. Johnson, T. B. and Ambler, J. A., *J. Am. Chem. Soc.,* **1914**, *36*, 372.
15. Woolfolk, E. O.; Reynolds, W. E. and Mason, J. L., *J. Org. Chem.,* **1959**, *24*, 1445.
16. (a) Kavallieratos, K., Rosenberg, J. M. and Bryan, J. C., *Inorg. Chem*., **2005**, *44*, 2573. (b) Gribble, G. W. and Saulnier, M. G., *J. Org. Chem.,* **1983**, *48*, 607. (c) Deacon, T.; Farrar, C. R.; Sikkel, B. J. and Williams, A. J., *J. Am. Chem. Soc.,* **1978**, *100*, 2525. (d) Carpenter, P. D. and Lennon, M., *J. Chem. Soc., Chem. Commun.,* **1973**, 664. (e) Ryabova, R. S.; Vinnik, M. I.; Lazareva, V. T. and Erlikh, R. D., *Zh. Org. Khim.,* **1970**, *6*, 797. (f) Vinnik, M. I.; Raybova, R. S. and Lazareva, V. T., *Zh. Org. Khim.,* **1970**, *6*, 1434. (g) Vinnik, M. I.; Raybova, R. S. and Lazareva, V. T., *Zh. Org. Khim.,* **1970**, *6*, 1438. (h) Ichii, T., *J. Pharm. Soc. Jpn.,* **1962**, *82*, 992. (i) Davoll, J., *J. Chem. Soc.,* **1960**, 308. (j) Stetter, H., *Ber.,* **1953**, *86*, 197. (k) Klamann, D. and Hofbauer, G., *Ann.,* **1953**, *581*, 182. (l) Fanta, P. E. and Wang, C. S., *J. Chem. Edu.,* **1964**, *41*, 280. (m) Amundsen, L. H., *J. Am. Chem. Soc.,* **1937**, *59*, 1466. (n) Hill, A. J. and Donleavy, J. J., *J. Ind. Eng. Chem.,* **1921**, *13*, 504. (o) Pschorr, R. and Karo, W., *Ber.,* **1906**, *39*, 3140. (p) Hinsberg, O. and Strupler, A., *Ann.,* **1895**, *287*, 220.

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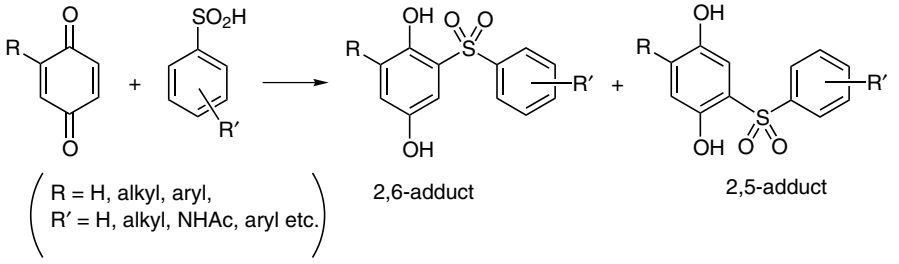
Hinsberg Sulfone Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

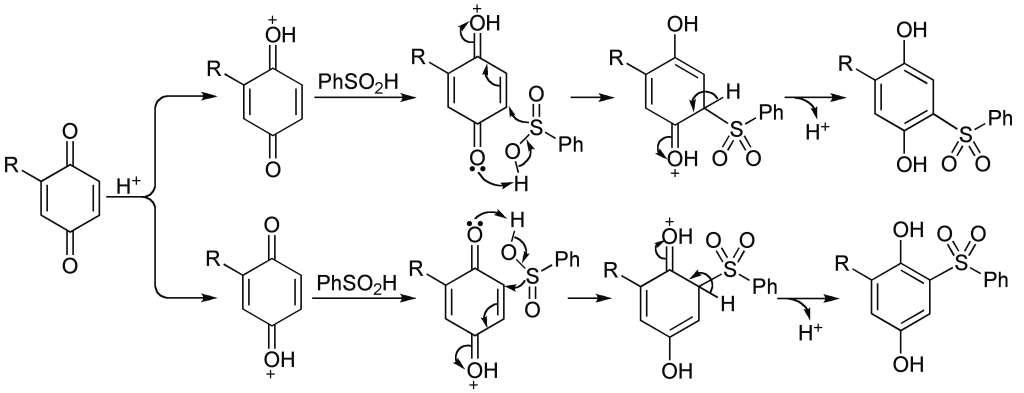
This reaction was first reported by Hinsberg in 1894.[1] It is the formation of sulfonylquinol derivatives from the addition of sulfinic acids to quinones. This reaction can be carried out in both aqueous solutions[2] and nonaqueous aprotic solvents (e.g., THF).[3] However, the reaction of unsymmetric quinone will form two isomeric products in various ratios, depending on the solvent and acidity of the reaction system.[4] For example, the addition of phenylsulfinic acid to 2-methyl quinone results in 2-methyl-5-phenylsulfonylhydroquinone (i.e., the 2,5-adduct) and 2-methyl-6-phenylsulfonylhydroquinone (2,6-adduct), in which the 2,5-adduct predominates in acetic buffer at pH 4.5, and the 2,6-adduct dominates in either more acidic (e.g., pH 1) or more basic (e.g., pH 5.5) conditions.[4] In addition, the 2,6-adduct is also the major product in strong acidic two-phase systems[5] and aprotic solvent systems (e.g., THF, acetone, acetonitrile, or acetoacetone).[4] In the alcoholic aqueous solution, the percentage of 2,6-adduct increases along with the decreasing of alcohol percentage in the solution.[4] These results indicated that the protonated quinone is the actual species that sulfinic acid adds, and the product ratio reflects the selectivity of protonation on the carbonyl group.[4] Although both the resonance theory and frontier molecular orbital theory predict the preference of 2,5-adduct,[5] the substituents on quinones may inhibit the protonation in acidic condition, leading to the preferred 2,6-adduct.[4,5]

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

N/A

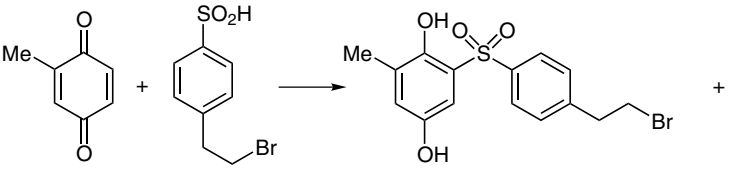
E. APPLICATIONS

This reaction is useful for the preparation of arylsulfonyl hydroquinones.

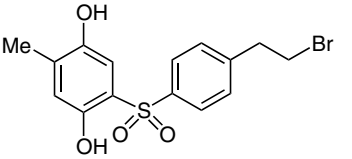
F. RELATED REACTIONS

This reaction is related to *Thiele-Winter Acetoxylation*.

G. CITED EXPERIMENTAL EXAMPLES



Major product isolated when carried out in $AcOH/H_2O$ (1:1), 91%



Major product isolated when carried out in $EtOH/H_2O$ (5:7), 87%

Reference 4.

A solution of 1.2 g 2-methyl-1,4-benzoquinone (10 mmol) in 20 mL 95% ethanol was added dropwise to a stirred suspension of 3.0 g 4-(2-bromoethyl)benzenesulfinic acid (12 mmol) in 100 mL 30% aqueous ethanol. As the quinone color faded, a solid precipitate appeared and was filtered under vacuum. The filtrate was diluted with 300 mL ice water, and a second crop was obtained. After the mixture was allowed to stand overnight, a third crop was present. Each of the three fractions was a mixture of two sulfones as shown by TLC and NMR. A representative total crude yield was 11.0 g, in 87% yield. Recrystallization from aqueous ethanol yielded 2-[[4′-(2-bromoethyl)phenyl]sulfonyl]-5-methylhydroquinone, m.p. 119–121°C.

A solution of 410 mg 2-methyl-1,4-benzoquinone (3.4 mmol) in 10 mL AcOH was added, in one portion, to a stirred suspension of 1.2 g 4-(2-bromoethyl)benzenesulfinic acid (4.8 mmol) in 10 mL water. The quinone color disappeared along with the sulfinic acid. After stirring for 0.5 h, the light tan solid was suction filtered. After an additional 1 h of stirring, more tan solid was filtered. The reaction mixture was diluted with 200 mL ice water, and a third crop was obtained. Each of the three fractions was a mixture of two sulfones as shown by TLC and NMR. A representative total crude yield was 1.2 g, in a yield of 91%. Recrystallization from aqueous ethanol yielded 2-[[4′-(2-bromoethyl)phenyl]sulfonyl]-6-methylhydroquinone, m.p. 145–146°C.

Other references related to the Hinsberg sulfone synthesis are cited in the literature.[7]

H. REFERENCES

1. Hinsberg, O., *Ber.,* **1894**, *27*, 3259.
2. Brown, E. R.; Finley, K. T. and Reeves, R. L., *J. Org. Chem*., **1971**, *36*, 2849.
3. Davies, R. and Pierpoint, W. S., *Biochem. Soc. Trans.,* **1975**, *3*, 671.

4. Allgeier, D. E.; Herbert, S. A.; Nee, R.; Schlecht, K. D. and Finley, K. T., *J. Org. Chem.,* **2003**, *68*, 4988.

5. Bruce, J. M. and Lloyd-Williams, P., *J. Chem. Soc., Perkin Trans. I*, **1992**, 2877.

6. (a) Rozeboom, M. D.; Tegmo-Larsson, I.-M. and Houk, K. N., *J. Org. Chem.*, **1981**, *46*, 2338. (b) Thomson, R. H., *J. Org. Chem.*, **1951**, *16*, 1082.

7. (a) Lau, P. T. S. and Gompf, T. E., *J. Org. Chem.*, **1970**, *35*, 4103. (b) Wanzlick, H. W., "Syntheses With Nascent Quinones" in *Newer Methods of Preparative Organic Chemistry*, ed. Foerst, W., Academic Press, New York, **1968**, *4*, pp. 139–154. (c) Scribner, R. M., *J. Org. Chem.,* **1966**, *31*, 3671. (d) Wilgus, H. S.; Frauenglass, E.; Jones, E. T.; Porter, R. F. and Gates, J. W., *J. Org. Chem.*, **1964**, *29*, 594. (e) Spinner, I. H.; Raper, W. D. and Metanomski, W., *Can. J. Chem.*, **1963**, *41*, 483. (f) Bradley, W. and Hannon, J. D., *J. Chem. Soc.,* **1962**, 4438. (g) Janczewski, M. and Prager, L., *Roozniki Chem.,* **1955**, *29*, 343. (h) Janczewski, M. and Prager, L., *Roozniki Chem.,* **1954**, *28*, 152. (i) Ioffe, I. S., *Zh. Obsh. Khim.,* **1953**, *23*, 125. (j) Janczewski, M., *Roozniki Chem.,* **1953**, *27*, 74. (k) Ettel, V. and Semonsky, M., *Coll. Czech. Chem. Commun.,* **1948**, *13*, 601. (l) Pickholz, S., *J. Chem. Soc.,* **1946**, 685. (m) Walker, J., *J. Chem. Soc.,* **1945**, 630. (n) Price, W. B. and Smiles, S., *J. Chem. Soc.,* **1928**, 3154. (o) Troger, J. and Nolte, E., *J. Prakt. Chem.,* **1920**, *101*, 136. (p) Hinsberg, O., *Ber.,* **1917**, *50*, 953. (q) Hinsberg, O, *Ber.,* **1910**, *43*, 1877. (r) Hinsberg, O., *Ber.,* **1897**, *30*, 2803. (s) Hinsberg, O., *Ber.,* **1896**, *29*, 2023. (t) Hinsberg, O., *Ber.,* **1895**, *28*, 1315.

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Hinsberg Thiophene Synthesis

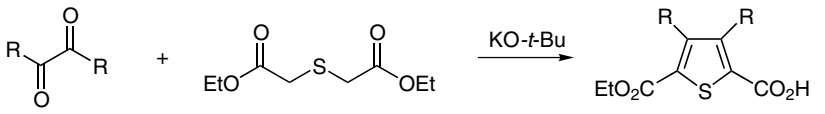
(Hinsberg Condensation)

A. GENERAL DESCRIPTION OF THE REACTION

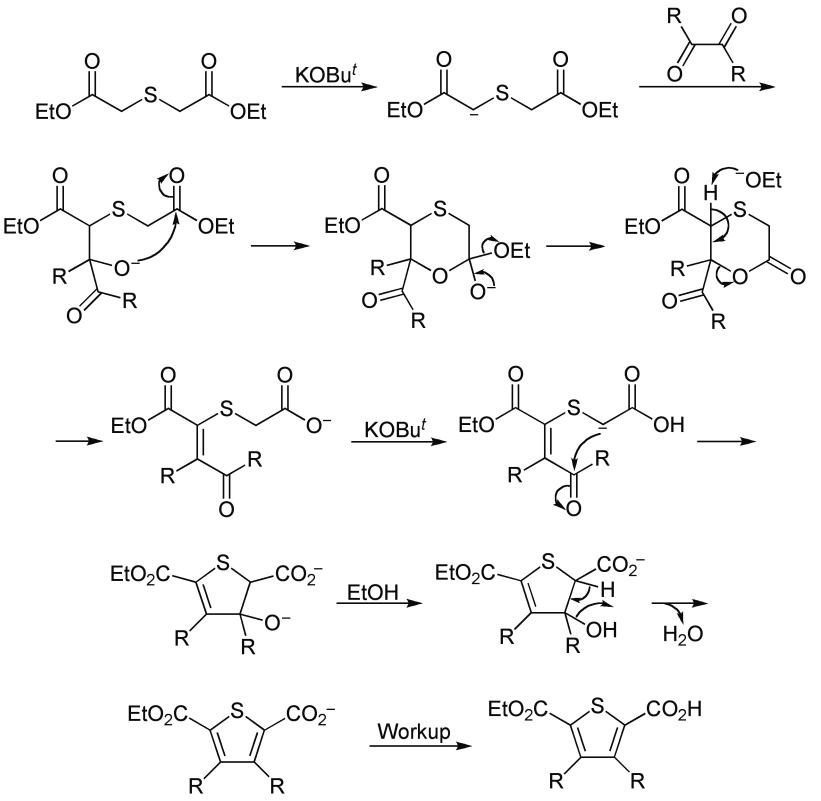
This reaction was first reported by Hinsberg in 1910.[1] It is the synthesis of thiophene carboxylic acids from 1,2-diketones and dialkyl thiodiacetate (i.e., thiodiglycolate) via an intermediate of δ-lactone in the presence of sodium or potassium alkoxide. Therefore, it is known as the Hinsberg reaction,[2] Hinsberg method,[3] Hinsberg condensation,[4] Hinsberg thiophene synthesis,[5] or Hinsberg thiophene ring synthesis.[6] The reaction mixture is often worked up by diluting the alcoholic alkaline solution with water and boiling and isolating the free carboxylic acid thus formed;[4f] however, experimental evidence indicates that both diester[7] and half acid, half ester thiophene derivatives[4f] also form in this reaction. In addition, this reaction has been extended to 1,4-diketones, such as the reaction between *o*-phthalaldehyde and diethyl thiodiacetate to form 3-benzothiepin-2,4-dicarboxylic acid, which desulfurizes upon refluxing in ethanol, leading to the formation of naphthalene-2,3-dicarboxylic acid.[8] It is reported that the reaction of thiodiacetate with 1,2,3-triketone, such as indan-1,2,3-trione, is unsuccessful.[4e] Similarly, di-(trimethylsilyl)methyl sulfoxide when treated with bis-(trimethylsilyl)acetylene, also gives thiophene derivative after DDQ treatment.[9] The formed thiophene derivatives can be easily oxidized to sulfone derivatives by perbenzoic acid.[10]

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

N/A

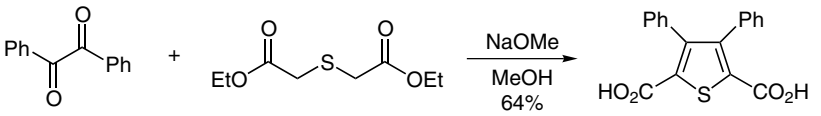
E. APPLICATIONS

This reaction has been used to synthesize thiophene derivatives as well as furan, selenophene, and pyrrole derivatives by varying the ester component from sulfur to oxygen, selenium, and nitrogen analogs.[11]

F. RELATED REACTIONS

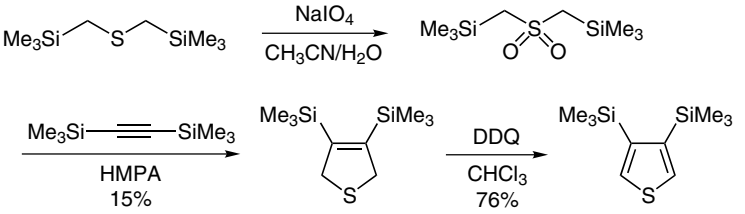
This reaction is related to the *Stobbe Condensation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2a.

To a mixture of 2.0 g diethyl thiodiacetate (9.71 mmol) and 2.04 g benzil (9.71 mmol) in 15 mL methanol was added 1.57 g NaOMe (29.1 mmol). The mixture was stirred at ambient temperature for 3 days. After addition of water, the alcohol was evaporated. The formed solid (benzil) was filtered off, and the filtrate was acidified with HCl, upon which 3,4-diphenylthiophene-2,5-dicarboxylic acid precipitated. After filtration, 2.02 g of a white solid was obtained, in a yield of 64%.



Reference 9.

To a 50-mL flask were added 3 mL acetonitrile, 206 mg bis[(trimethylsilyl)methyl] sulfide (1 mmol), and 3 mL aqueous solution containing 257 mg sodium metaperiodate (1.2 mmol) at $-10°$C by ice salt bath cooling. The solution was stirred at $-10°$ to 0°C for 12 h and then the cold solution was filtered and extracted with cold dichloromethane (3×5 mL). The dichloromethane extracts were dried over Na_2SO_4 and concentrated under vacuum to yield bis(trimethylsilylmethyl)sulfoxide as a colorless oil that is pure enough for subsequent reaction.

To a 100-mL, flame-dried, three-necked flask equipped with a condenser and a dropping funnel was added a solution of 666 mg bis(trimethylsilylmethyl)sulfoxide (3.0 mmol) in 2 mL HMPA (distilled from CaH_2), then 340 mg bis(trimethylsilyl)-acetylene (2 mmol) in 2 mL HMPA was added rapidly from a dropping funnel. The resulting solution was warmed at 100°C and stirred at this temperature for 30 min under nitrogen atmosphere. The cooled reaction mixture was diluted with 40 mL benzene, washed with brine (4×15 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was subjected to column chromatography on silica gel (50 g, hexanes) to give 69 mg 3,4-bis(trimethylsilyl)-2,5-dihydrothiophene as a colorless oil, in a yield of 15%.

To 8 mL chloroform solution containing 230 mg 3,4-bis(trimethylsilyl)-2,5-dihydrothiophene (1.0 mmol) was added a hot solution of 363 mg DDQ (1.6 mmol)

in 45 mL chloroform. The mixture was stirred at 60–65°C for 10 h. The cooled reaction mixture was washed with 10% aqueous sodium carbonate (3 × 10 mL) and 10 mL water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (30 g, hexanes) to afford 173 mg 3,4-bis(trimethylsilyl)thiophene as a colorless oil, in a yield of 76%.

Other references related to the Hinsberg thiophene synthesis are cited in the literature.[12]

H. REFERENCES

1. Hinsberg, O., *Ber.,* **1910**, *43*, 901.
2. (a) Henckens, A.; Colladet, K.; Fourier, S.; Cleij, T. J.; Lutsen, L.; Gelan, J. and Vanderzande, D., *Macromolecules,* **2005**, *38*, 19. (b) Chadwick, D. J.; Chambers, J.; Meakins, G. D. and Snowden, R. L., *J. Chem. Soc., Perkin Trans. I,* **1972**, 2079.
3. (a) Wakamiya, A.; Yamazaki, D.; Nishinaga, T.; Kitagawa, T. and Komatsu, K., *J. Org. Chem.,* **2003**, *68*, 8305. (b) Akoudad, S.; Frère, P.; Mercier, N. and Roncali, J., *J. Org. Chem.,* **1999**, *64*, 4267.
4. (a) Hui, X.; Schmidt, F.; Fakhfakh, M. A.; Franck, X. and Figadere, B., *Heterocycles*, **2007**, *72*, 353. (b) Shields, J. E.; Remy, D. E. and Bornstein, J., *J. Org. Chem.,* **1975**, *40*, 477. (c) Paranjpe, P. P. and Bagavant, G.,*Curr. Sci.,* **1972**, *41*, 879. (d) Birch, A. and Crombie, D. A., *Chem. Ind. (London),* **1971**, 177. (e) MacDowell, D. W. H. and Jeffries, A. T., *J. Org. Chem.,* **1970**, *35*, 871. (f) Wynberg, H. and Kooreman, H. J., *J. Am. Chem. Soc.,* **1965**, *87*, 1739. (g) Dann, O. and Hauck, G., *Arch. Pharm.*, **1960**, *293*, 187.
5. Traversone, A. and Brill, W. K.-D., *Tetrahedron Lett*., **2007**, *48*, 3535.
6. Wynberg, H. and Kooreman, H. J., *J. Am. Chem. Soc.,* **1965**, *87*, 1739.
7. Fager, E. W., *J. Am. Chem. Soc.,* **1945**, *67*, 2217.
8. Scott, G. P., *J. Am. Chem. Soc.,* **1953**, *75*, 6333.
9. Ye, X.-S. and Wong, H. N. C., *J. Org. Chem.,* **1997**, *62*, 1940.
10. Overberger, C. G.; Mallon, H. J. and Fine, R., *J. Am. Chem. Soc.,* **1950**, *72*, 4958.
11. (a) Dimroth, K. and Pintschovius, U., *Ann.,* **1961**, *639*, 102. (b) Dimroth, K. and Freyschlag, H., *Ber.,* **1956**, *89*, 2602. (c) Wolf, D. E. and Folkers, K., *Org. React.,* **1951**, *6*, 410. (d) Backer, H. J. and Stevens, W., *Rec. Trav. Chim. Pays-Bas Belg.,* **1940**, *59*, 423. (e) Backer, H. J. and Stevens, W., *Rec. Trav. Chim.,* **1940**, *59*, 899. (f) Hinsberg, O., *Ber.,* **1912**, *45*, 2413.
12. (a) Koparr, M.; Cansz, A.; Ahmedzade, M. and Çetin, A., *Heteroatom Chem.,* **2004**, *15*, 26. (b) MacDowell, D. W. H. and Patrick, T. B., *J. Org. Chem.,* **1967**, *32*, 2441. (c) Wynberg, H. and Zwanenburg, D. J., *J. Org. Chem.,* **1964**, *29*, 1919.

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Hiyama Coupling

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Hatanaka and Hiyama in 1988.[1] It is a palladium-catalyzed cross-coupling reaction between organosilanes and aryl (or vinyl) halides or triflates. This reaction is known as the Hiyama coupling,[2] Hiyama cross-coupling,[3] or Hiyama reaction,[2f,3d,4] which tolerates a wide spectrum of functional groups including ethers, acetals, nitriles, esters, and amides,[2f] except for amino groups that might poison the palladium catalyst. Typically, the Hiyama coupling is promoted by the activation of the organosilanes with a stoichiometric amount of fluoride source,[3d] such as tetrabutylammonium fluoride (TBAF) or tris(dimethylamino)sulfur(trimethylsilyl)difluoride (TASF)[3d] and by using chlorosilancs or fluorosilanes instead of trimethylsilanes.[5] The presence of a fluoride source is essential to facilitate the transmetalation of the organic group through the formation of a five-coordinate silicate species.[6] This reaction is known to be accelerated by microwave.[7] On the other hand, this reaction is analogous to the *Stille Coupling* but with advantages of lower toxicity and easier handling.[3d] In the presence of Ag_2O and catalytic amount of $Pd(PPh_3)_4$, even organic silanols can couple with aryl iodide; however, TBAF fails to promote the reaction under this condition.[8] Recently, this reaction has been extended to the coupling of alkyl halides with silanes, using the combination of $PdBr_2$/$P(t\text{-}Bu)_2Me$/TBAF; this modification is especially good for electron-rich silanes. In addition, replacement of $P(t\text{-}Bu)_2Me$ with $[HP(t\text{-}Bu)_2Me]BF_4$ allows the coupling to occur in the presence of air or moisture.[2f]

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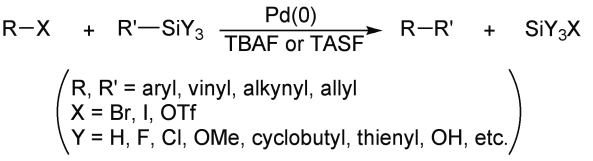
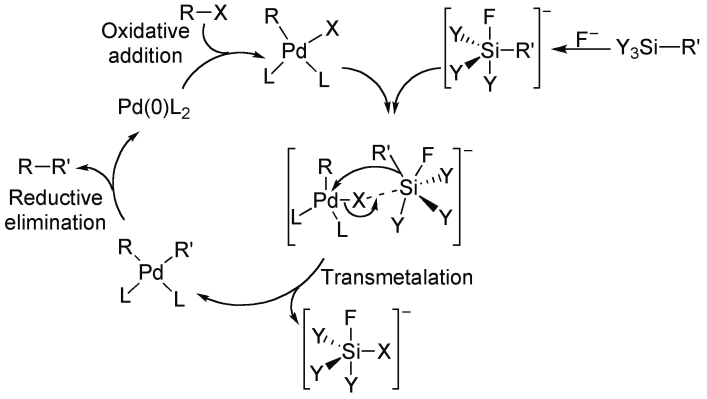
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified to undergo the coupling with alkyl halides using the combination of $PdBr_2$/P(*t*-Bu)$_2$Me/TBAF as a catalytic system.[2f]

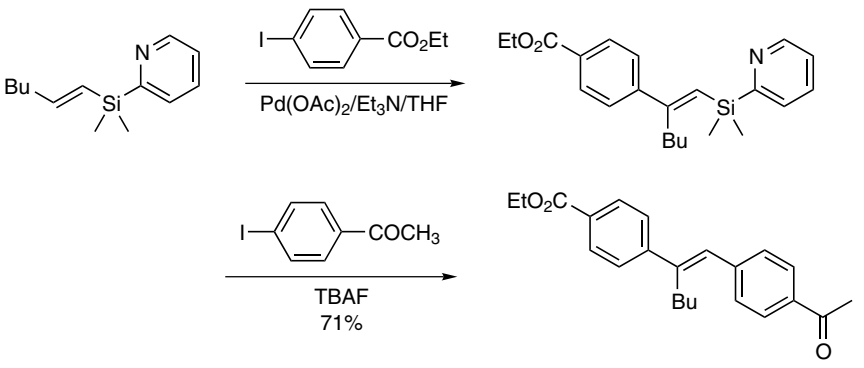
E. APPLICATIONS

This reaction has wide application in organic synthesis during the coupling of aryl and vinyl moieties.

F. RELATED REACTIONS

This reaction is closely related to the *Stille Coupling* and *Suzuki Coupling*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2g.

To a 0.9 mL THF solution containing 4.3 mg $Pd(OAc)_2$ (0.02 mmol, 10 mol %), tri-2-furylphosphine (5.1 mg, 0.02 mmol, 10 mol %), 32.7 mg triethylamine (0.32 mmol), and 75.2 mg 4-iodobenzoic acid ethyl ester (0.27 mmol), was added 65.7 mg (2-pyridyl)-1-hexenyl-dimethylsilane (0.30 mmol) under argon; the reaction mixture was stirred at 60°C for 3 h. After the mixture was cooled to room temperature, 48.2 mg 4-iodoacetophenone (0.20 mmol) and 0.46 mL 1 M TBAF solution in THF were added to the reaction mixture, and this reaction mixture was stirred at 60°C for 14 h. The catalyst was removed by filtration through a short silica gel pad (EtOAc). The filtrate was evaporated, and the residue was chromatographed on silica gel (hexane/EtOAc, 10/1) to afford 48.6 mg (*E*)-1-(4-acetyl)phenyl-2-(4-ethoxycarbonyl)phenyl-1-hexene as a colorless oil, in a yield of 71%.

Other references related to the Hiyama coupling are cited in the literature.[9]

H. REFERENCES

1. Hatanaka, Y. and Hiyama, T., *J. Org. Chem.,* **1988**, *53*, 918.
2. (a) Prukala, W.; Marciniec, B.; Majchrzak, M. and Kubicki, M., *Tetrahedron*, **2007**, *63*, 1107. (b) Prukala, W.; Majchrzak, M.; Pietraszuk, C. and Marciniec, B., *J. Mol. Catal. A: Chem.,* **2006**, *254*, 58. (c) Clarke, M. L., *Adv. Synth. Catal.,* **2005**, *347*, 303. (d) Clarke, M. L., *Org. Lett.,* **2005**, *7*, 697. (e) Domin, D.; Benito-Garagorri, D.; Mereiter, K.; Fröhlich, J. and Kirchner, K., *Organometallics,* **2005**, *24*, 3957. (f) Lee, J.-Y. and Fu, G. C., *J. Am. Chem. Soc.,* **2003**, *125*, 5616. (g) Itami, K.; Nokami, T.; Ishimura, Y.; Mitsudo, K.; Kamei, T. and Yoshida, J.-I., *J. Am. Chem. Soc.,* **2001**, *123*, 11577. (h) Suzuki, A., "Hiyama Coupling," in *Metal-Catalyzed Cross-Coupling Reactions*, ed. Diederich, F. and Stang, P. Wiley-VCH, Weinheim, **1988**, chap. 2.
3. (a) Vitale, M.; Prestat, G.; Lopes, D.; Madec, D. and Poli, G., *Synlett*, **2006**, 2231. (b) Duran Pachon, L.; Thathagar, M. B.; Hartl, F. and Rothenberg, G., *Phys. Chem. Chem. Phys.,* **2006**, *8*, 151. (c) Pierrat, P.; Gros, P. and Fort, Y., *ChemInform,* **2005** (issue 28), 36. (d) Mateo, C.; Fernández-Rivas, C.; Echavarren, A. M. and Cárdenas, D. J., *Organometallics,* **1997**, *16*, 1997.

4. (a) Alacid, E. and Najera, C., *Adv. Synth. Catal.,* **2006**, *348*, 2085. (b) Casado, A. L.; Espinet, P. and Gallego, A. M., *J. Am. Chem. Soc.,* **2000**, *122*, 11771. (c) Mateo, C.; Fernández-Rivas, C.; Cárdenas, D. J. and Echavarren, A. M., *Organometallics,* **1998**, *17*, 3661.

5. (a) Saeki, T.; Matsunaga, T.; Son, E.-C. and Tamao, K., *Adv. Synth. Catal.,* **2004**, *346*, 1689. (b) Gouda, K.; Hagiwara, E.; Hatakana, Y. and Hiyama, T., *J. Org. Chem.,* **1996**, *61*, 7232.

6. (a) Hiyama, T.; Matsuhashi, H.; Fujita, A.; Tanaka, M.; Hirabayashi, K.; Shimizu, M. and Mori, A., *Organometallics,* **1996**, *15*, 5762. (b) Takahashi, K.; Minami, T.; Ohara, Y. and Hiyama, T., *Bull. Chem. Soc. Jpn.,* **1995**, *68*, 2649. (c) Chuit, C.; Corriu, R. J. P.; Reye, C. and Young, J. C., *Chem. Rev.,* **1993**, *93*, 1371. (d) Hatanaka, Y. and Hiyama, T., *J. Am. Chem. Soc.,* **1990**, *112*, 7793.

7. Sørensen, U. S.; Wede, J. and Pombo-Villar, E., *ECSOC-5,* September **2001**. http://www.mdpi.net/ecsoc/ecsoc5/Papers/e0019/e0019.htm

8. (a) Hirabayashi, K.; Mori, A.; kawashima, J.; Suguro, M.; Nishihara, Y. and Hiyama, T., *J. Org. Chem.,* **2000**, *65*, 5342. (b) Hirabayashi, K.; Kawashima, J.; Nishihara, Y.; Mori, A. and Hiyama, T., *Org. Lett.,* **1999**, *1*, 299.

9. (a) Pidaparthi, R. R.; Welker, M. E.; Day, C. S. and Wright, M. W., *Org. Lett.,* **2007**, *9*, 1623. (b) Ju, J. H.; Nam, H.; Jung, H. M. and Lee, S. W., *Tetrahedron Lett*., **2006**, *47*, 8673. (c) Alacid, E.; Alonso, D. A.; Botella, L.; Najera, C. and Pacheco, M. C., *Chem. Record,* **2006**, *6*, 117. (d) Gordillo, A.; de Jesus, E. and Lopez-Mardomingo, C., *Org. Lett.,* **2006**, *8*, 3517. (e) Katayama, H.; Nagao, M.; Ozawa, F.; Ikegami, M. and Arai, T., *J. Org. Chem.,* **2006**, *71*, 2699. (f) Marciniec, B.; Majchrzak, M.; Prukala, W.; Kubicki, M. and Chadyniak, D., *J. Org. Chem.,* **2005**, *70*, 8550. (g) Itami, K.; Ohashi, Y. and Yoshida, J.-I., *J. Org. Chem.,* **2005**, *70*, 2778. (h) Stock, C.; Hoefer, F. and Bach, T., *Synlett*, **2005**, 511. (i) Shaughnessy, K. H. and DeVasher, R. B., *Curr. Org. Chem.,* **2005**, *9*, 585. (j) Kappe, C. O., *Angew. Chem. Int. Ed.,* **2004**, *43*, 6650. (k) Nokami, T.; Itami, K. and Yoshida, J.-I., *Chem. Lett.,* **2004**, *33*, 596. (l) Itami, Y.; Marciniec, B. and Kubicki, M., *Organometallics*, **2003**, *22*, 3717. (m) Littke, A. F. and Fu, G. C., *Angew. Chem. Int. Ed.,* **2002**, *41*, 4176. (n) Littke, A. F. and Fu, G. C., *Angew. Chem.,* **2002**, *114*, 4350. (o) Itami, K.; Mitsudo, K.; Nokami, T.; Kamei, T.; Koike, T and Yoshida, J.-I., *J. Organomet. Chem.,* **2002**, *653*, 105. (p) Hiyama, T., *J. Organomet. Chem.,* **2002**, *653*, 58. (q) Chang, S.; Yang, S. H. and Lee, P. H., *Tetrahedron Lett.,* **2001**, *42*, 4833. (r) Nishihara, Y.; Takemura, M.; Mori, A. and Osakada, K., *J. Organomet. Chem.,* **2001**, *620*, 282. (s) Nishihara, Y.; Ikegashira, K.; Hirabayashi, K.; Ando, J.; Mori, A. and Hiyama, T., *J. Org. Chem.,* **2000**, *65*, 1780. (t) Nishihara, Y.; Ando, J.; Kato, T.; Mori, A. and Hiyama, T., *Macromolecules,* **2000**, *33*, 2779. (u) Nishihara, Y.; Ikegashira, K.; Mori, A. and Hiyama, T., *Chem. Lett.,* **1997**, 1233. (v) Hiyama, T. and Hatanaka, Y., *Pure & Appl. Chem.,* **1994**, *66*, 1471. (w) Hatanaka, Y. and Hiyama, T., *Synlett,* **1991**, 845. (x) Hatanaka, Y. and Hiyama, T., *J. Am. Chem. Soc.,* **1990**, *112*, 7794.

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Hoch-Campbell Reaction

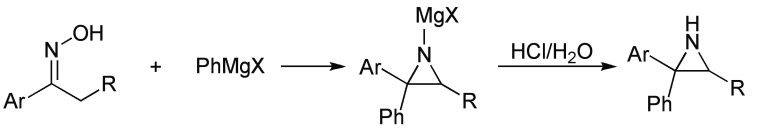
(Hoch-Campbell Aziridine Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

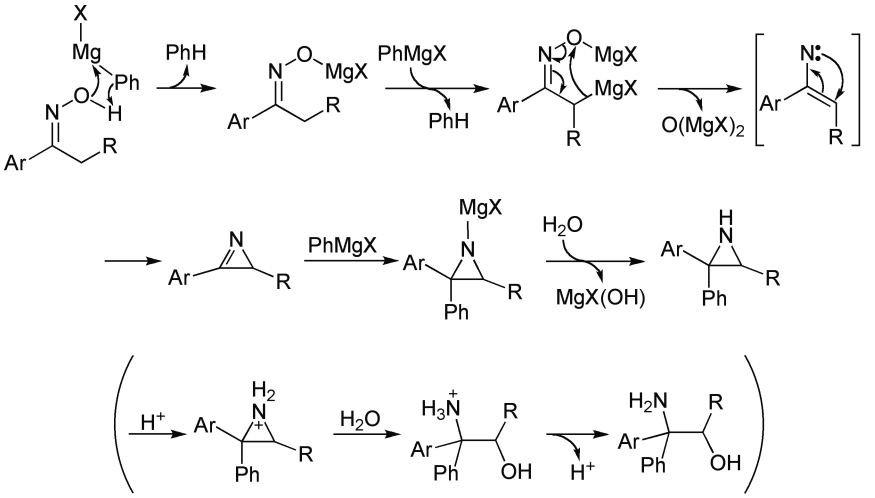
This reaction was first reported by Hoch in 1934[1] and subsequently extended by Campbell in the early 1940s.[2] It is the synthesis of aziridines (also known as ethylenimines[3]) by treatment of ketoximes with excess amounts of Grignard reagent followed by the hydrolysis of the resulting organometallic complex. Therefore, it is generally known as the Hoch-Campbell reaction.[4] Occasionally, this reaction is also referred to as the Hoch-Campbell aziridine synthesis or Hoch-Campbell ethylenimine synthesis,[5] and the formed aziridines are called the Hoch-Campbell products.[3,6] On the other hand, α-amino alcohols can also be the products instead of aziridines, depending on the conditions used in the hydrolysis of the organometallic complex.[2d,3,7] It is known that this reaction proceeds regiospecifically through a vinyl nitrene intermediate leading to an azirine,[8] and the subsequent addition of Grignard reagent occurs on the less hindered side of the azirine to give diastereomeric aziridines.[8b,8e,9] In this reaction, solvents also play an important role;[10] for example, reactions in toluene give one major product, whereas two isomers form in THF.[10a] Similarly, the aziridines can be prepared from oxime tosylate and organolithium reagents.[7,11] It is interesting that the ketoximes can be directly reduced to aziridines when cyclohexylmagnesium or isobutylmagnesium chloride is used as a Grignard reagent.[6] However, oximes from simple ketones such as acetone and 2-butanone do not undergo such reaction.[12]

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

N/A

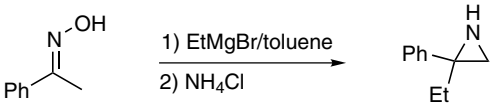
E. APPLICATIONS

This reaction has general application in the synthesis of aziridines, especially the fully substituted aziridines.

F. RELATED REACTIONS

This reaction is related to the *Neber Rearrangement*.

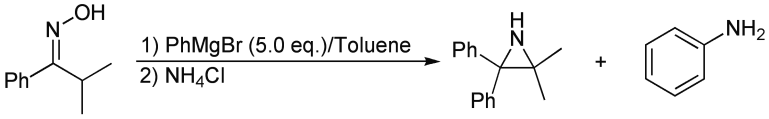
G. CITED EXPERIMENTAL EXAMPLES



37%

Reference 2a.

A solution of ethylmagnesium bromide prepared from 24 g magnesium turnings, 115 g ethyl bromide, and 350 mL dry ether was distilled until 200 mL ether was removed; dry toluene (200 mL) was added, and then a solution of 34 g acetophenone oxime (0.25 mol) in 200 mL dry toluene was added dropwise over a period of 2 h. The oil bath surrounding the flask was kept at 90–95°C during the addition, and continued for 30 min afterward. The mixture was hydrolyzed at once by pouring onto ice and a NH_4Cl solution; the water layer was extracted several times with ether, and the combined ether solutions were dried over magnesium sulfate. The residue remaining after removal of the ether and toluene was distilled under reduced pressure to yield 14.4 g 2-phenyl-2-ethyl aziridine, b.p. 85–86°C (7.0 mmHg), in a yield of 37%.



Reference 13.

The procedure is same as the one just described. Isobutyrophenone oxime (33 g; 0.2 mol) and 1 mol phenylmagnesium bromide were used. The reaction mixture was hydrolyzed with a solution of ammonium chloride and extracted with ether. The ethereal extracts were dried over calcium sulfate and saturated with hydrogen chloride. The precipitate that formed was filtered off, washed with ether, and recrystallized from dry acetone. It weighed 8 g and melted at 192–193°C. It was dissolved in 45 mL concentrated ammonium hydroxide, and the solution was extracted with ether. The ether solution after drying over calcium sulfate was concentrated by evaporation. The residual oil was fractionated to yield two substances. One boiled at 49–51°C (1 mmHg) (i.e., aniline) and gave a hydrochloride salt that, after one recrystallization from acetone, melted at 193–194°C, two more recrystallizations from the same solvent did not depress the melting point of aniline hydrochloride (196–198°C). The second fraction, 2,2-diphenyl-3,3-dimethylaziridine, distilled at 128–129°C (1 mmHg). On standing, this material crystallized partially to form large plates that melted at 181–185°C with softening at 60°C. A hydrochloride of this material was prepared in an ether solution saturated with hydrogen chloride. After recrystallization from acetone, this salt melted at 227–228°C. (No yields are given for either product.)

Other references related to the Hoch-Campbell reaction are cited in the literature.[14]

H. REFERENCES

1. Hoch, J., *Compt. Rend.,* **1934**, *198*, 1865.
2. (a) Campbell, K. N.; Campbell, B. K.; Hess, L. G. and Schaffner, I. J., *J. Org. Chem.,* **1944**, *9*, 184. (b) Campbell, K. N.; Campbell, B. K.; McKenna, J. F. and Chaput, E. P., *J. Org. Chem.,* **1943**, *8*, 103. (c) Campbell, K. N.; Campbell, B. K. and Chaput, E. P., *J. Org. Chem.,* **1943**, *8*, 99. (d) Campbell, K. N. and McKenna, J. F., *J. Org. Chem.,* **1939**, *4*, 198.
3. Erdik, E. and Ay, M., *Chem. Rev.,* **1989**, *89*, 1947.
4. (a) De Kimpe, N.; Verhé, R.; de Buyck, L. and Schamp, N., *J. Org. Chem.,* **1980**, *45*, 5319. (b) Sasaki, T.; Eguchi, S. and Hattori, S., *Heterocycles,* **1978**, *11*, 235. (c) Alvernhe, G. and Laurent, A., *J. Chem. Res. (S),* **1978,** 28. (d) Takehisa, Y.; Kawazoe, Y. and Taguchi, T., *Chem. Pharm. Bull.,* **1976**, *24*, 1691. (e) Imai, K.; Kawazoe, Y. and Taguchi, T., *Yakugaku Zasshi*, **1974**, *94*, 452.
5. Ishii, Y.; Eguchi, S. and Hironaka, T., *Kogyo Kagaku Zasshi*, **1965**, *68*, 293.
6. Imai, K.; Kawazoe, Y. and Taguchi, T., *Chem. Pharm. Bull.,* **1976**, *24*,1083.
7. Freeman, J. P., *Chem. Rev.,* **1973**, *73*, 283.
8. (a) Diab, Y.; Laurent, A. and Mison, P., *Tetrahedron Lett.,* **1974**, 1605. (b) Chaabouni, R.; Laurent, A. and Mison, P., *Tetrahedron Lett.,* **1973**, 1343. (c) Chaabouni, R. and Laurent, A., *Bull. Soc. Chim. Fr.,* **1973**, 2680. (d) Alvernhe, G. and Laurent, A., *Bull. Soc. Chim. Fr.,* **1970**, 3003. (e) Laurent, A. and Müller, A., *Tetrahedron Lett.,* **1969**, 759.
9. (a) Bartnik, R. and Laurent, A., *Bull. Soc. Chim. Fr.,* **1975**, 173. (b) Bartnik, R.; Laurent, A. and Normant, M. H., *Compt. Rend.,* **1974**, *279*, 289.
10. (a) Alvernhe, G. and Laurent, A., *Bull. Soc. Chim. Fr.,* **1970**, 3304. (b) Kotera, K. and Kitahonoki, K., *Org. Prep. Proced. Int.,* **1969**, *1*, 305. (c) Eguchi, S. and Ishii, Y., *Bull. Chem. Soc. Jpn.,* **1963**, *36*, 1434.
11. Gabel, N. W., *J. Org. Chem.,* **1964**, *29*, 3129.
12. Closs, G. L. and Brois, S. J., *J. Am. Chem. Soc.,* **1960**, *82*, 6068.
13. Kissman, H. M.; Tarbell, D. S. and Williams, J., *J. Am. Chem. Soc.,* **1953**, *75*, 2959.
14. (a) Arseniyadis, S.; Laurent, A. and Mison, P., *Bull. Soc. Chim. Fr.,* **1980**, 246. (b) Ricart, G.; Clouturier, D. and Normant, M. H., *Compt. Rend.,* **1977**, *284*, 191. (c) Dermer, O. C. and Ham, G. E., *Ethylenimine and Other Aziridines,* Academic Press, New York, **1969**, pp. 65–68. (d) Brois, S. J., *J. Org. Chem.,* **1962**, *27*, 3532. (e) Henze, H. R. and Compton, W. D., *J. Org. Chem.,* **1957**, *22*, 1036. (f) Hoch, J., *Compt. Rend.,* **1937**, *204*, 358. (g) Hoch, J., *Compt. Rend.,* **1936**, *203*, 799.

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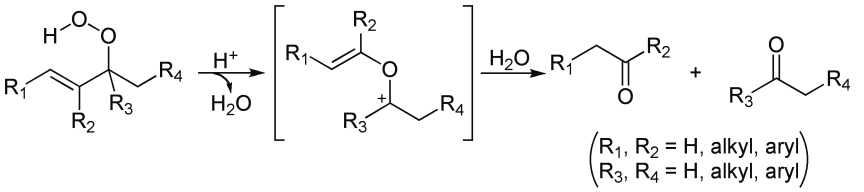
Hock Rearrangement
(Hock Cleavage)

A. GENERAL DESCRIPTION OF THE REACTION

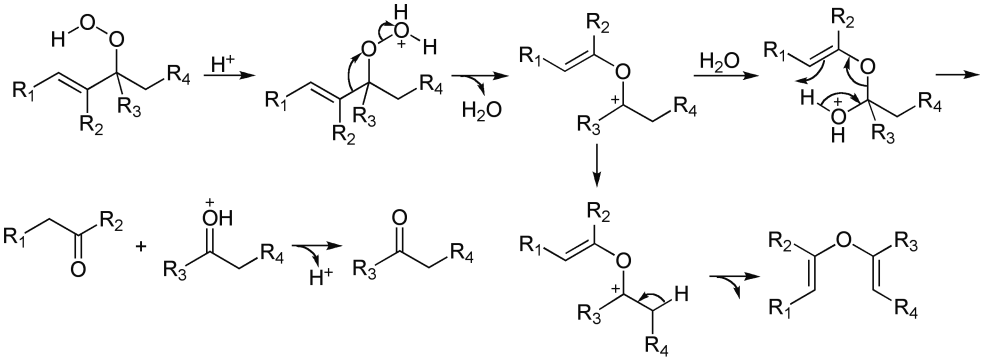
This reaction was first reported by Hock and Schrader in 1936.[1] It is the protic or Lewis acid–promoted rearrangement of hydroperoxides that have unsaturated unit(s) attached to the carbon bearing the hydroperoxide group to oxycarbonium ion, which undergoes nucleophilic attack by water, leading to the cleavage of C-C bond and the formation of two carbonyl compounds. Therefore, this reaction is known as the Hock rearrangement,[2,3] or Hock cleavage.[2d,2e,4,5] This reaction occurs quite frequently on lipids and fatty acids[2d,4a,6] where allylic and dienylic hydroperoxides often form upon radical hydrogen abstraction in the presence of air or oxidation by singlet oxygen ($^1O_2$).[2c,4e] Although this reaction is generally promoted by acid, it also occurs in the absence of an added acid,[7] such as in the case where the *ene* reaction solution is injected onto a gas chromatography column for product isolation.[8] In addition, some Hock rearrangements even occur at temperatures substantially below room temperature.[9] Depending on the substrate structure and the choice of Lewis acid, dialkyl peroxide and ozonides might decompose via Hock rearrangement path, such as the decomposition of the substrate with groups of high migratory aptitude in the presence of $SnCl_4$ or $BF_3{\cdot}OEt_2$.[2e] The qualitative migratory aptitude of groups is generally in the order of cyclobutyl > aryl > vinyl > hydrogen > cyclopentyl $\approx$ cyclohexyl >> alkyl.[10] Moreover, the silver ion adducts of hydroperoxides and cyclic peroxides also undergo such rearrangement to give aldehydes and epoxides.[11] On the other hand, the intermediate oxycarbonium ion in this reaction might undergo another reaction path of β-proton elimination instead of attacking by a water molecule, affording a product of divinyl ether.[12]

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

N/A

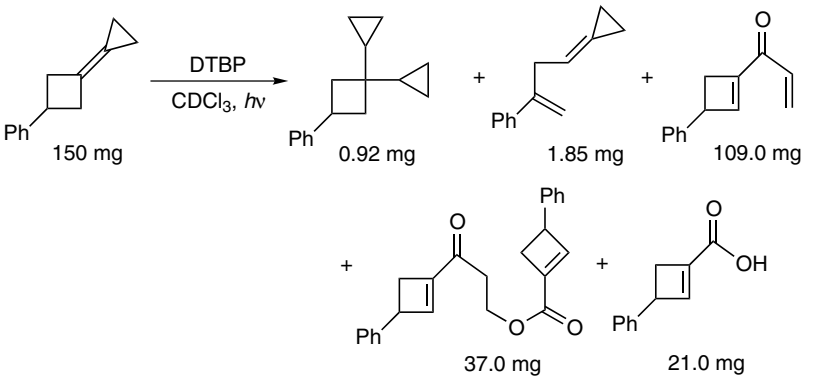
E. APPLICATIONS

This reaction has applications in the degradation of long hydrocarbon chains with unsaturated unit(s) into carbonyl compounds.

F. RELATED REACTIONS

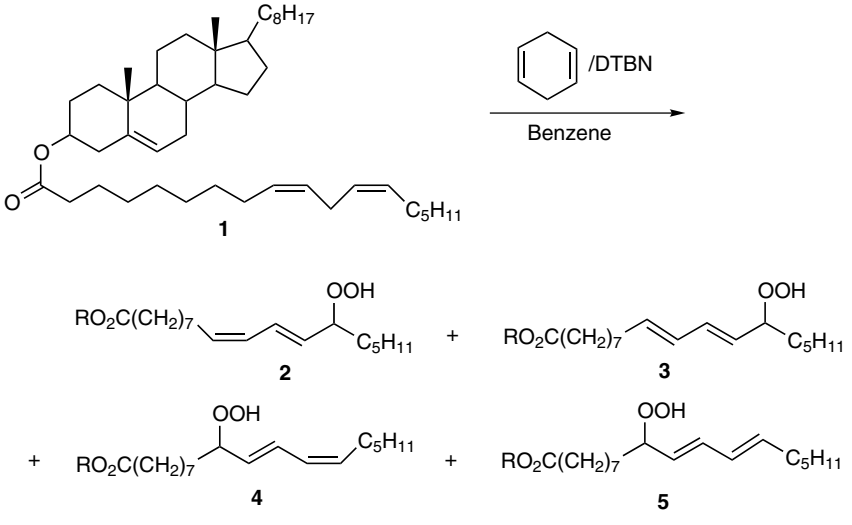
This reaction is related to the *Criegee Rearrangement*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 13.

The water-cooled photooxidation on 150 mg 1-cyclopropylidene-3-phenylcyclobutane (0.88 mmol) in 3 mL $CDCl_3$ in the presence of a small amount of the radical inhibitor 2,6-di-*tert*-butylphenol (DTBP) proceeded essentially to completion within 2 h. Silica column chromatography, using a 0–20% gradient of EtOAc in hexane, yielded three fractions. The first one was 4 mg of a mixture (∼2% total) of 1-cyclopropylidene-3-phenylcyclobutane, 1,1-dicyclopropyl-3-phenylcyclobutane, 1-cyclopropylidene-3-phenyl-3-butene and 2,6-di-*tert*-butylphenol in a 1:1.5:3:1 ratio, respectively. Compounds 1,1-dicyclopropyl-3-phenylcyclobutane and 1-cyclopropylidene-3-phenyl-3-butene were impurities in the starting material (vide supra). This was followed by 109.0 mg 1-(3-phenylcyclobut-1-enyl)-propenone at higher eluent polarity (0.59 mmol, 67% yield) as a yellow liquid, 37.0 mg 3-oxo-3-(3-phenylcyclobut-1-enyl)propyl 3-phenylcyclobut-1-enecarboxylate (0.103 mmol, 12%) as a viscous yellow oil, and 21.0 mg 3-phenylcyclobut-1-enecarboxylic acid (0.12 mmol, 14% yield) as a white solid, m.p. 87°C.



Reference 11.

A round-bottomed flask was charged with 300 mg cholesteryl linoleate (0.462 mmol) and was diluted to 0.20 M with 0.876 mL 1,4-cyclohexadiene (9.26 mmol) and 1.43 mL dry benzene. DTBN (2 mg) was added to the solution, and the sealed flask was heated to 37°C under an oxygen atmosphere. After 24 h, TLC indicated the formation of peroxidic products. Butylated hydroxytoluene (BHT, 2 mg) was added to the reaction. Analytical HPLC (tandem silicon columns, 0.5% 2-propanol in hexanes, $\lambda = 234$ nm) indicated the formation of four major components in the mixture: **2**, $t_R = 15.0$ min; **3**, $t_R = 17.5$ min; **4**, $t_R = 20.1$ min; and **5**, $t_R = 20.5$ min. Semipreparative HPLC (0.66% 2-propanol in hexane) was used to separate the components. Compounds **4** and **5** were isolated as a mixture.

Other references related to the Hock rearrangement are cited in the literature.[14]

H. REFERENCES

1. Hock, H. and Schrader, O., *Angew. Chem.,* **1936**, *49*, 595.
2. (a) Jian, W. Y.; Lee, S. H.; Arora, J. S.; Elipe, M. V. S. and Blair, I. A., *Chem. Res. Toxicol.,* **2005**, *18*, 599. (b) Lee, S. H.; Elipe, M. V. S.; Arora, J. S. and Blair, I. A., *Chem. Res. Toxicol.,* **2005**, *18*, 566. (c) Thompson, D. H.; Inerowicz, H. D.; Grove, J. and Sarna, T., *Photochem. Photobiol.,* **2003**, *78*, 323. (d) Schneider, C.; Tallman, K. A.; Porter, N. A. and Brash, A. R., *J. Biol. Chem.,* **2001**, *276*, 20831. (e) Dussault, P. H.; Lee, H.-J. and Liu, X. J., *J. Chem. Soc*., *Perkin Trans. I*, **2000**, 3006.
3. (a) Jian, W. Y.; Lee, S. H.; Arora, J. S.; Silva Elipe, M. V. and Blair, I. A., *Chem. Res. Toxicol.,* **2005**, *18*, 599. (b) Gardner, H. W.; Weisleder, D. and Nelson, E. C., *J. Org. Chem.,* **1984**, *49*, 508. (c) Ruecker, G. and Molls, U., *Liebigs Annalen der Chemie,* **1979**, 608. (d) Kropf, H. and Bernert, C. R., *Ann.,* **1971**, *751*, 109. (e) Kropf, H. and Bernert, C. R., *Ann.,* **1971**, *751*, 121.
4. (a) Yin, H. Y.; Morrow, J. D. and Porter, N. A., *J. Biol. Chem.,* **2004**, *279*, 3766. (b) Yu, M. K.; Moos, P. J.; Cassidy, P.; Wade, M. and Fitzpatrick, F. A., *J. Biol. Chem.,* **2004**, *279*, 28028. (c) Zorn, H.; Langhoff, S.; Scheibner, M.; Nimtz, M. and Berger, R. G., *Biol. Chem.,* **2003**, *384*, 1049. (d) Sy, L.-K. and Brown, G. D., *J. Chem. Soc*., *Perkin Trans. I*, **2001**, 2421. (e) Frimer, A. A., *J. Photochem.,* **1984**, *25*, 211. (f) Takeshita, H.; Shimooda, I. and Hatsui, T., *Bull. Chem. Soc. Jpn.,* **1980**, *53*, 3721.
5. (a) Schneider, C.; Boeglin, W. E.; Yin, H. Y.; Stec, D. F.; Hachey, D. L.; Porter, N. A. and Brash, A. R., *Lipids,* **2005**, *40*, 1155. (b) Soker, U.; Sasse, F.; Kunze, B. and Hofle, G., *Eur. J. Org. Chem.,* **2000**, 1497. (c) Frimer, A. A.; Weiss, J.; Gottlieb, H. E. and Wolk, J. L., *J. Org. Chem.,* **1994**, *59*, 780. (d) Chan, Y.; Li, X. Y.; Zhu, C.; Liu, X. H.; Zhang, Y. D. and Leung, H., *J. Org. Chem.,* **1990**, *55*, 5497. (e) Boon, A. J., *J. Nat. Rubber Res.,* **1988**, *3*, 90. (f) Chan, Y.; Zhu, C. and Leung, H., *J. Am. Chem. Soc.,* **1985**, *107*, 5274. (g) Koerner von Gustorf, E.; Grevels, F. W. and Schenck, G. O., *Ann.,* **1969**, *719*, 1.
6. (a) Yin, H. Y.; Havrilla, C. M.; Gao, L.; Morrow, J. D. and Porter, N. A., *J. Biol. Chem.,* **2003**, *278*, 16720. (b) Khaselev, N. and Murphy, R. C., *J. Lipid Res.,* **2000**, *41*, 564. (c) Frankel, E. N. and Gardner, H. W., *Lipids,* **1989**, *24*, 603.
7. Frimer, A. A., *Chem. Rev.,* **1979**, *79*, 359.
8. (a) Frimer, A. A. and Roth, D., *J. Org. Chem.,* **1979**, *44*, 3882. (b) Frimer, A. A.; Roth, D. and Sprecher, M., *Tetrahedron Lett.,* **1977**, 1927.
9. Turner, J. A. and Herz, W., *J. Org. Chem.,* **1977**, *42*, 1657.
10. Hiatt, R., "Hydroperoxides" in *Organic Peroxides,* ed. Swern, D., Wiley-Interscience, New York, **1971**, *2*, p. 67.

11. Havrilla, C. M.; Hachey, D. L. and Porter, N. A., *J. Am. Chem. Soc.,* **2000**, *122*, 8042.
12. (a) Jeffrey, A. M. and Jerina, D. M., *J. Am. Chem. Soc.,* **1972**, *94*, 4048. (b) Fox, J. E.; Scott, A. I. and Young, P. W., *J. Chem. Soc., Chem. Commun.,* **1967**, 1105.
13. Sharon, O. and Frimer, A. A., *Tetrahedron,* **2003**, *59*, 8153.
14. (a) Yin, H. Y. and Porter, N. A., *Antioxid. & Redox Signal.,* **2005**, *7*, 170. (b) Berry, K. A. Z. and Murphy, R. C., *Antioxid. & Redox Signal.,* **2005**, *7*, 157. (c) Carini, M.; Aldini, G. and Facino, R. M., *Mass Spectr. Rev.,* **2004**, *23*, 281. (d) Yin, H. Y.; Havrilla, C. M.; Morrow, J. D. and Porter, N. A., *J. Am. Chem. Soc.,* **2002**, *124*, 7745. (e) Söker, U.; Sasse, F.; Kunze, B. and Höfle, G., *Eur. J. Org. Chem.,* **2000**, 1497. (f) Adam, W.; Putterlik, J.; Schuhmann, R. M. and Sundermeyer, J., *Organometallics,* **1996**, *15*, 4586. (g) Lauterbach, G.; Pritzkow, W.; Tien, T. D. and Voerckel, V., *J. Prakt. Chem.,* **1988**, *330*, 933. (h) Jefford, C. W.; Rossier, J.-C.; Kohmoto, S. and Boukouvalas, J., *Helv. Chim. Acta,* **1985**, *68*, 1804. (i) Tanigawa, S.; Kajiware,T. and Hatanaka, A., *Phytochemistry,* **1984**, *23*, 2439. (j) Gardner, H. W. and Planter, R. D., *Lipids,* **1984**, *19*, 294.

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Hofer-Moest Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Hofer and Moest in 1902.[1] It is the conversion of aliphatic acids into corresponding alcohols with one less carbon by electrolytic decarboxylation in neutral or alkaline solutions in the presence of an inert anion, such as sulfate, phosphate, perchlorate, carbonate, or bicarbonate.[2] This reaction is generally carried out with a platinum anode.[2] The added salt of the inert anion favors carbonium ion product relative to the normal radical product;[2] the latter leads to the formation of hydrocarbon (or paraffin),[3] a process known as the *Kolbe Electrolysis*.[4] Therefore, this reaction is generally known as the Hofer-Moest reaction.[5] Occasionally, this reaction is also referred to as the Hofer-Moest oxidation,[5i,6] abnormal Kolbe reaction,[7] etc. The alcohols produced in this reaction are called Hofer-Moest products.[5i] Besides the major product of alcohols, some minor products also form in this reaction, such as olefins,[5b] carbonyl compounds (e.g., ketone),[8] esters[2] and ethers,[2,4c] which originate from the proton elimination, further oxidation of alcohols, coupling of resulting alcohols with parent acids, and so on. In addition, the Hofer-Moest products are also favored by increasing the frequency in pulsed electrolysis.[5i] On the other hand, it was found that a carbon anode has some advantages over platinum anode, by which the Kolbe product is practically eliminated even without the help of added salts or increased pH.[2] This reaction has been extended to decarboxylation of amino acid derivatives, such as the stepwise degradation of polypeptides from the carboxyl terminal[9] and the anodic methoxylation of amides or carbamates to *N*-acyliminium ions[10] for amidoalkylation.

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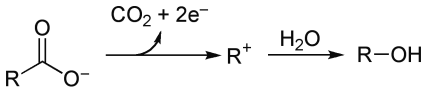
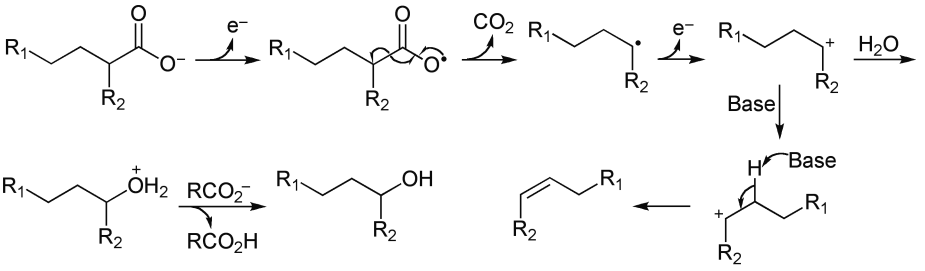
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Displayed below is the mechanism to form an alcohol or an olefin.



D. MODIFICATION

N/A

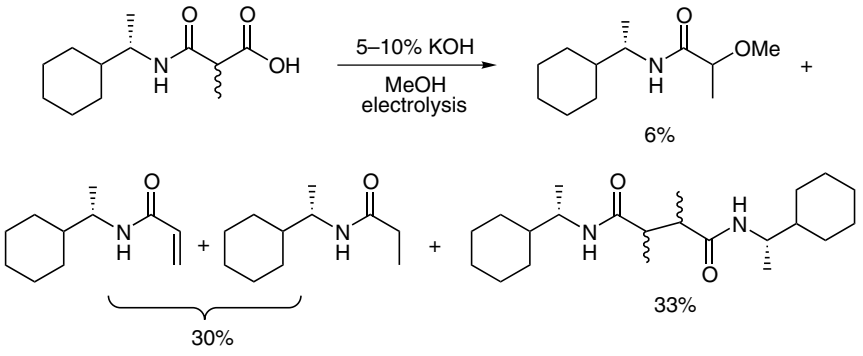
E. APPLICATIONS

This reaction is useful for the conversion of carboxylic acids into alcohols with one less carbon, and the decarboxylation of amino acids and polypeptides.

F. RELATED REACTIONS

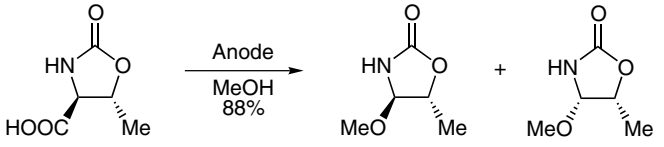
This reaction is closely related to *Kolbe Electrolysis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4a.

To an undivided jacketed cell with platinum as both anode and cathode were added 5–10% methanolic KOH with 0.5 mM *N*-[(1S)-cyclohexylethyl)-2-methylmalonamic acid. The cell was put into a cryostat precooled to –40°C and was charged with an electric current of 250 mA/cm^2, 1.7F/mol; the temperature was maintained between 10° and 60°C. The reaction was monitored by pH measurement (until acid to neutral). When passivation or coverage of electrodes was noticed, polarity inversion was used. After the reaction, the normal workup process and column chromatography yielded 6% *N*-[(1S)-1-cyclohexylethyl]-2-methoxypropanamide, 33% *N*-[(1S)-1-cyclohexylethyl]-acrylamide (white solid, m.p. 70–72°C), *N*-[(1S)-1-cyclohexylethyl]-propanamide (white solid, m.p. 107–110°C), and 30% *N*,*N*′-bis-(1-cyclohexylethyl)-2,3-dimethylsuccino-diamide (white solid, m.p. > 300°C), but only 0.7 % mixed Kolbe dimmer (the regular Kolbe product).



Reference 10.

A stirred solution of 2.9 g (4S,5R)-5-methyl-2-oxazolidinone-4-carboxylic acid (20 mmol) in 500 mL 0.02 N NaOAc/MeOH was electrolyzed at room temperature under galvanostatic conditions using graphite electrodes (3 × 30 × 100 mm) in an undivided cell. After consumption of 3F/mol at a current density of 5 mA/cm^2, the solvent was evaporated, the white residue was purified, and the diasteromers were separated by flash chromatography on silica gel with Et_2O as the eluent to afford 2.1 g (4R/S,5R)-4-methoxy-5-methyl-2-oxazolidinone as white crystals, in a yield of 88%, m.p. 87–90°C. The (4R,5R)-4-methoxy-5-methyl-2-oxazolidinone was formed with 77% ds.

Other references related to the Hofer-Moest reaction are cited in the literature.[11,12]

H. REFERENCES

1. Hofer, H. and Moest, M., *Ann.,* **1902**, *323*, 284.
2. Koehl, W. J., *J. Am. Chem. Soc.,* **1964**, *86*, 4686.
3. Kunugi, T., *J. Am. Chem. Soc.,* **1953**, *75*, 1597.

4. (a) Goulart, M. O. F. and Schäfer, H.-Y., *J. Braz. Chem. Soc.,* **1999**, *10*, 153. (b) Skell, P. S. and Reichenbacher, P. H., *J. Am. Chem. Soc.,* **1968**, *90*, 2309. (c) Farber, L. and Cohen, L. A., *Biochemistry,* **1966**, *5*, 1027.
5. (a) Brettle, R. and Khan, M. A., *J. Chem. Res. (S),* **1989**, 15. (b) Sakata, T.; Kawai, T. and Hashimoto, K., *J. Phys. Chem.,* **1984**, *88*, 2344. (c) Brettle, R.; Khan, M. A. and Rowbottom, J. D., *J. Chem. Soc., Perkin Trans. I,* **1981**, 2927. (d) Iwasaki, T.; Horikawa, H.; Matsumoto, K. and Miyoshi, M., *J. Org. Chem.,* **1977**, *42*, 2419. (e) Simonson, L. A. and Murray, R. W., *Anal. Chem.,* **1975**, *47*, 290. (f) Kornienko, A. G.; Mirkind, L. A. and Fioshin, M. Y., *Katalitich. Reaktsii Zhidk. Faze.,* **1974**, ch. 2, p. 482. (g) Tyurin, Y. M. and Afon'shin, G. N., *Elektrokhimiya*, **1969**, *5*, 1198. (h) Atherton, G.; Fleischmann, M. and Goodridge, F., *Trans. Faraday Soc.,* **1967**, *63*, 1468. (i) Vijh, A. K. and Conway, B. E., *Chem. Rev.,* **1967**, *67*, 623. (j) Kunugi, T., *Denki Kagaku*, **1952**, *20*, 69. (k) Kunugi, T., *Denki Kagaku*, **1952**, *20*, 206. (l) Kunugi, T., *Denki Kagaku*, **1952**, *20*, 154. (m) Kunugi, T., *Denki Kagaku*, **1952**, *20*, 111. (n) Glasstone, S. and Hickling, A., *Chem. Rev.,* **1939**, *25*, 407. (o) Glasstone, S. and Hickling, A., *J. Chem. Soc.,* **1934**, 1878.
6. Bonner, W. A. and Mango, F. D., *J. Org. Chem.,* **1964**, *29*, 430.
7. Keating, J. T. and Skell, P. S., *J. Org. Chem.,* **1969**, *34*, 1479.
8. (a) Peterson, J., *Z. Phys. Chem.,* **1900**, *33*, 116. (b) Kolbe, H., *Ann.,* **1849**, *69*, 257.
9. Boissonas, R. A., *Nature,* **1953**, *171*, 304.
10. Zietlow, A. and Steckhan, E., *J. Org. Chem.,* **1994**, *59*, 5658.
11. (a) Moinet, C.; Hurvois, J.-P. and Jutand, A., *Adv. Org. Synth.,* **2005**, *1*, 403. (b) Klotz-Berendes, B.; Schäfer, H.-J.; Grehl, M.; Fröhlich, R., *Angew. Chem. Int. Ed. Engl.,* **1995**, *34*, 189. (c) Schäfer, H.-J., *Top. Curr. Chem.,* **1990**, *152*, 91. (d) Papadoulos, A.; Lewall, B.; Steckhan, E.; Ginzel, K.-D.; Knoch, F. and Nioer, M., *Tetrahedron,* **1991**, *47*, 563. (e) Thomas, H. G. and Kessel, St., *Ber.,* **1988**, *121*, 1575. (f) Bobbitt, J. M. and Cheng, T. Y., *J. Org. Chem.,* **1976**, *41*, 443. (g) Hobbs, C. C., *Ind. Eng. Chem. Prod. Res. Dev.,* **1970**, *9*, 497. (h) Reichenbacher, P. H.; Morris, M. D. and Skell, P. S., *J. Am. Chem. Soc.,* **1968**, *90*, 3432. (i) Weedon, B. C. L., *Adv. Org. Chem.,* **1960**, *1*, 1. (j) Walling, C., *Free Radicals in Solution,* John Wiley & Sons., New York, **1957**, p. 581. (k) Overberger, C. G. and Kabasakalian, P., *J. Org. Chem.,* **1956**, *11*, 1124. (l) Weedon, B. C. L., *Quart. Rev., (London),* **1952**, *6*, 380. (m) Fichter, F., *Trans. Electrochem. Soc.,* **1939**, *75*, 309.
12. (a) Brungs, P.; Danielmeier, K.; Jakobi, J.; Nothhelfer, C.; Stahl, A.; Zietlow, A. and Steckhan, E., *J. Chim. Phys. Phys.-Chim. Biol.,* **1996**, *93*, 575. (b) Weiper, A.; Dralle, G.; Aus dem Kahmen, M.; Luebbers, T.; Klocke, E. and Schaefer, H. J., *DECHEMA Monographien*, **1992**, *125*, 595. (c) Elofson, R. M.; Gadallah, F. F. and Laidler, J. K., *Can. J. Chem.,* **1985**, *63*, 1170. (d) Utley, J. H. P., *Tech. Chem. (New York),* **1974**, *5*, *Pt. 1*, 793. (e) Kornienko, A. G.; Mirkind, L. A.; Fioshin, M. Y. and Korobanov, A. A., *Elektrokhimiya*, **1974**, *10*, 350. (f) Nadebaum, P. R. and Fahidy, T. Z., *Electrochimica Acta*, **1972**, *17*, 1659. (g) Fleischmann, M. and Goodridge, F., *Discuss. Faraday Soc.,* **1968**, 254. (h) Fichter, F. and Maritz, A., *Helv. Chim. Acta,* **1939**, *22*, 265. (i) Fichter, F. and Lapin, H., *Helv. Chim. Acta,* **1929**, *12*, 993. (j) Fichter, F. and Zumbrunn, R., *Helv. Chim. Acta,* **1927**, *10*, 869. (k) Fichter, F. and Lichtenhahn, T., *Ber.,* **1915**, *48*, 1949.

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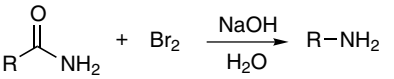
Hofmann Degradation
(Hofmann rearrangement)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Hofmann in 1881.[1] It is the conversion of carboxylic amides into primary amines with one less carbon atom via the isocyanate intermediate by means of basic hypohalite treatment. Hence it is known as the Hofmann rearrangement,[2] Hofmann degradation,[2,3] or Hofmann reaction.[2,3y,3z] In this reaction, heat is needed; and in some cases, cyanate is also formed.[4] On the other hand, the Hofmann rearrangement of carboxylic amides with α-halogen yields a certain amount of ketones as well.[5] This reaction is often used as a method for cuting a single carbon atom out of a chain. In addition, the configuration of the hydrocarbon chain is retained during the migration.[6] However, the corresponding amide of pyrazine-2,5-dicarboxylic acid was found to be stable toward both hypochlorous and hypobromous acids.[3z]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is known that this reaction proceeds in the following steps: base abstraction of an acidic N-H proton to yield an anion, which reacts with bromine to form *N*-bromoamide; further base abstraction of the remaining N-H proton to give a bromoamide anion, which rearranges to isocyanate through the migration of an R group attaching to the carbonyl carbon and

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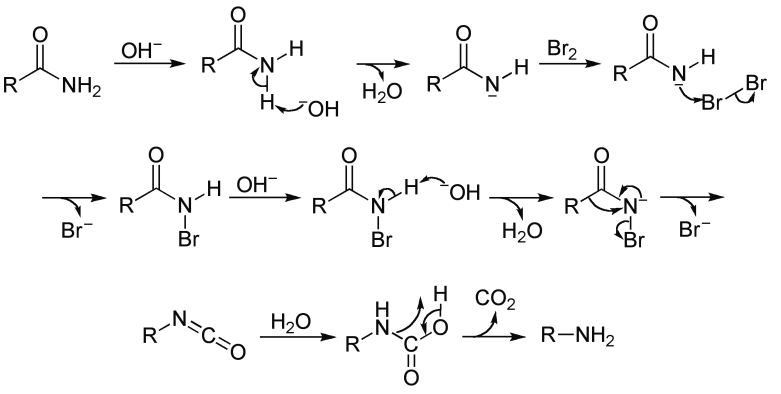
cleavage of a bromide ion; nucleophilic addition of water to isocyanate affording a carbamic acid, which loses carbon dioxide spontaneously to yield the primary amine.



D. MODIFICATION

This reaction has been modified by the substitution of a hypohalite with (diacetoxyiodo)benzene.[7]

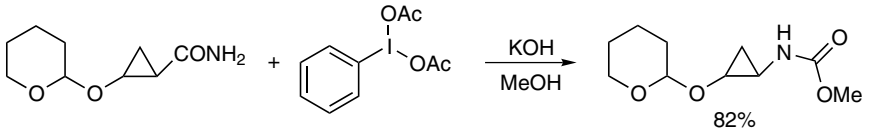
E. APPLICATIONS

This reaction has general application for the conversion of carboxylic amides into amines.

F. RELATED REACTIONS

This reaction is related to *Curtius Rearrangement*, *Lossen Rearrangement*, *Schmidt Reaction*, *Weerman Degradation*, and *Wolff Rearrangement*.

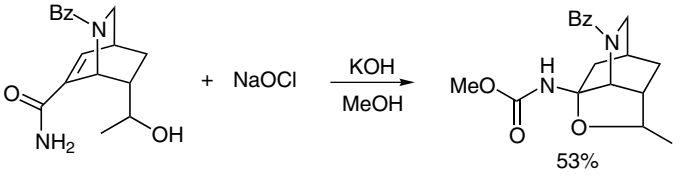
G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

To 100 mL methanol solution containing 7.75 g (±)-*trans*-2-tetrahydro-2H-2-pyranyloxy-1-cyclopropane carboxamide (41.84 mmol) and 6.03 g KOH (107.47 mmol) was added 13.42 g (diacetoxyiodo)benzene (41.66 mmol) at 5°C under stirring, and the stirring was continued at room temperature for an additional 2 h. The solvents were removed under reduced pressure, the residue was mixed with 70 mL water and 30 mL

dichloromethane, and the aqueous layer was extracted with dichloromethane (4 × 30 mL). The combined organic layers were washed with water and brine (50 mL each), dried, and evaporated. After column chromatography (hexane → EtOAc/hexane, 1:2), 7.37 g (±)-methyl *N*-[*trans*-2-tetrahydro-2H-2-pyranyloxycyclopropyl]carbamate was obtained as a colorless oil, in a yield of 82%, $R_f = 0.5$ (EtOAc/hexane, 1:1).



Reference 2.

The crystalline mixture of 2.30 g hydroxyamide and its epimer (8.05 mmol) in 65 mL methanol was treated with 0.85 g potassium hydroxide (15.2 mmol) in 15.7 mL 5.25% aqueous NaOCl solution (11.0 mmol). The resulting solution turned yellow and warmed spontaneously to ∼ 50°C. After 1 h it was poured into 300 mL brine, and the resulting mixture was extracted five times with chloroform. The dried extracts were evaporated to an oil, which crystallized from ether in colorless needles, 1.51 g tricyclic urethane was obtained, in a yield of 53%, m.p., 147.5–149°C.

Other references related to the Hofmann degradation are cited in the literature.[8]

H. REFERENCES

1. Hofmann, A. W., *Ber.,* **1881**, *14*, 2725.
2. (a) Moriarty, R. M., *J. Org. Chem.,* **2005**, *70*, 2893. (b) Büchi, G.; Coffen, D. L.; Kocsis, K.; Sonnet, P. E. and Ziegler, F. E., *J. Am. Chem. Soc.,* **1966**, *88*, 3099.
3. (a) Shan, Y. H.; Wei, K. N.; Li, W. M.; Wu, G. Y. and Mao, Y. X., *Huaxue Gongye Yu Gongcheng Jishu*, **2005**, *26*, 25. (b) Begam, T.; Tomar, R. S.; Nagpal, A. K. and Singhal, R., *J. Appl. Poly. Sci.,* **2004**, *94*, 40. (c) Hu, Z.-Y.; Zhang, S.-F.; Yang, J.-Z.; Tang, B.-T. and Tang, Y.-F., *Dalian Ligong Daxue Xuebao*, **2002**, *42*, 659. (d) Moulay, S., *Chem. Edu.: Res. Pract. Eur.,* **2002**, *3*, 33. (e) Lou, H. X.; Hou, B. L.; Li, X.; Zhu, T. R.; Wang, L. and Hong, B. K., *Zhongguo Yaoxue Zazhi (Beijing)*, **1995**, *30*, 291. (f) Bicak, N.; Sarac, A. S.; Koza, G.; Atay, T. and Senkal, F., *Reactive Polymers,* **1993**, *21*, 135. (g) Wrobel, J. T.; Scholl-Aleksandrowicz, A.; Cybulski, J. and Wojtasiewicz, K., *Coll. Czech. Chem. Commun.,* **1989**, *54*, 2229. (h) Sonnenschein, H. and Schmitz, E., *Synthesis*, **1989**, 443. (i) Leis, H. J., *Rapid Commun. Mass Spectr.,* **1989**, *3*, 342. (j) Leis, H. J. and Gleispach, H., *J. Chromatography,* **1989**, *494*, 324. (k) Turchin, K. F.; Levkovskaya, L. G.; Solov'eva, N. P.; Safonova, T. S. and Sheinker, Yu. N., *Dokl. Akad. Nauk SSSR,* **1987**, *293*, 379. (l) Guo, J.; Lu, D. and Ye, X. L., *Gaodeng Xuexiao Huaxue Xuebao*, **1985**, *6*, 1000. (m) Cybulski, J.; Wojtasiewicz, K. and Wrobel, J. T., *Heterocycles*, **1984**, *22*, 2541. (n) Kajigaeshi, S.; Nakagawa, T.; Fujisaki, S.; Nishida, A. and Noguchi, M., *Chem. Lett.,* **1984**, 713. (o) Cybulski, J. and Wojtasiewicz, K., *J. Mol. Struct.,* **1984**, *116*, 1. (p) Cybulski, J.; Wojtasiewicz, K. and Wrobel, J. T., *Heterocycles*, **1983**, *20*, 1773. (q) Wert, K. L.; Chackalamannil, S.; Miller, E.; Dalton, D. R.; Zacharias, D. E. and Glusker, J. P., *J. Org. Chem.,* **1982**, *47*, 5141. (r) Kanmera, T.; Waki, M.; Kato, T. and Izumiya, N., *Peptide Chem.,* **1980**, *18*, 199. (s) Kanmera, T.; Aoyagi, H.; Waki, M.; Kato, T.; Izumiya, N.; Noda, K. and Ueno, T., *Tetrahedron Lett*., **1981**, *22*, 3625. (t) Nomoto, S.; Sano, A. and Shiba, T.,

Tetrahedron Lett., **1979**, 521. (u) Nomoto, S.; Sano, A. and Shiba, T., *Peptide Chem.,* **1978**, *16*, 35. (v) Tanaka, H., *J. Poly. Sci., Poly. Lett. Ed.,* **1978**, *16*, 87. (w) Takano, S.; Kuzukawa, M. and Yamanaka, M., *J. Am. Oil Chem. Soc.,* **1977**, *54*, 484. (x) Baliah, V. and Jeyaraman, R., *Indian J. Chem., Sect. B,* **1977**, *15B*, 796. (y) Stevens, C. L.; Mukherjee, T. K. and Traynelis, V. J., *J. Am. Chem. Soc.,* **1956**, *78*, 2264. (z) Spoerri, P. E. and Erickson, A., *J. Am. Chem. Soc.,* **1938**, *60*, 400.

4. (a) Arcus, C. L. and Prydal, B. S., *J. Chem. Soc.,* **1954**, 4018. (b) Arcus, C. L. and Greenwood, D. B., *J. Chem. Soc.,* **1953**, 1937.
5. Stevens, C. L. and Coffield, T. H., *J. Am. Chem. Soc.,* **1951**, *73*, 103.
6. Wallis, E. S. and Moyer, W. W., *J. Am. Chem. Soc.,* **1933**, *55*, 2598.
7. Csuk, R. and Kern, A., *Z. Naturforsch.,* **2002**, *57B*, 1169.
8. (a) Matsumura, Y.; Satoh, Y.; Shirai, K.; Onomura, O. and Maki, T., *J. Chem. Soc., Perkin Trans. I,* **1999**, 2057. (b) Rane, D. S. and Sharma, M. M., *J. Chem. Tech. Biotechnol.,* **1994**, *59*, 271. (c) Jew, S. S.; Park, H. G.; Kang, M. H.; Lee, T. H. and Cho, Y. S., *Arch. Pharm. Res.,* **1992**, *15*, 333. (d) Kajigaeshi, S.; Asano, K.; Fujisaki, S.; Kakinami, T. and Okamoto, T., *Chem. Lett.,* **1989**, 463. (e) Hori, I.; Igarashi, M. and Midorikawa, H., *J. Org. Chem.,* **1961**, *26*, 4511. (f) Applequist, D. E. and Roberts, J. D., *Chem. Rev.,* **1954**, *54*, 1083. (g) Wallis, E. S. and Lane, J. F., *Org. React.,* **1949**, *3*, 267. (h) Franklin, E. C., *Chem. Rev.,* **1934**, *14*, 219. (i) Hofmann, A. W., *Ber.,* **1885**, *18*, 2734. (j) Hofmann, A. W., *Ber.,* **1884**, *17*, 1406. (k) Hofmann, A. W., *Ber.,* **1882**, *15*, 407. (l) Hofmann, A. W., *Ber.,* **1882**, *15*, 752. (m) Hofmann, A. W., *Ber.,* **1882**, *15*, 762.

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Hofmann Elimination

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Hofmann in 1851.[1] It is the thermal decomposition of tetraalkylammonium hydroxide to form an olefin and a tertiary amine. Therefore, this reaction is generally known as the Hofmann elimination[2,3] or Hofmann degradation.[2i,2l,2m,2aa,2gg,4] Sometimes, it is also referred to as the Hofmann decomposition,[5] Hofmann cleavage,[6] or Hofmann pyrolysis.[7] In addition, Hofmann elimination also includes the pyrolysis of tetraalkylammonium salts (often in the form of trimethylalkylammonium salt) to olefins and tertiary amines (e.g., trimethylamine) in the presence of a strong base. Thus the conversion of amines into quaternary ammonium salts maximized with methyl groups along with the formation of olefins and a tertiary amine (mostly trimethylamine) is known as the Hofmann exhaustive methylation.[2dd,2gg,8] As the nature of pyrolysis, the Hofmann elimination is often carried out in a solvent with a high boiling point,[2ee] involving a single-step (or one-step)[2hh,9] bimolecular E2 mechanism.[10] For most of aliphatic quaternary ammonium salts with a β-hydrogen atom *trans* to the amino group, stereochemical studies have shown that the Hofmann elimination proceeds almost exclusively by *anti*-elimination,[11] giving the olefins with less substituents unless a substituent on the β-carbon enhances the acidity of that particular proton (the *Hofmann Rule*).[2m] The *anti*-elimination also predominates on six-membered rings.[2o] However, a few exceptions that proceed E2 elimination via the *cis* transition state are also known, due to the enhanced acidity of proton, or conformational or steric hindrance. Examples for the violation of the *Hofmann Rule* via such elimination are the conversion of *trans*-2-phenylcyclohexyltrimethylammonium hydroxide into 1-phenylcyclohexene,[11b] the elimination of *N*,*N*,*N*-trimethyl-3,3-dimethylcyclopentylammonium hydroxide to

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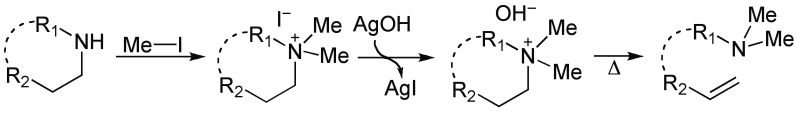
3,3-dimethylcyclopentene and 4,4-dimethylcyclopentene,[2o] the elimination of *N*,*N*,*N*-trimethyl-2-*exo*-norbornylammonium-3-*exo*-D iodide,[2y] and the *cis*-ylide elimination of *N*,*N*,*N*-trimethyl-2-*t*-butyl-3,3-dimethylbutylammonium hydroxide.[2y] It has been found that the mechanism is quite susceptible to alternation by steric factors for cyclic systems.[2o] For example, the *syn* elimination is dominated on four-membered rings, whereas *trans* elimination is favored on six-membered rings; however, steric and electronic factors can alter the elimination to a *syn* manner on six-membered rings.[2o] Furthermore, the eclipsing effects of substituents and the van der Waals interaction with bulky trimethylammonium groups can alter the mechanism as well.[12] The elimination of substituted 2-phenylethyltrimethylammonium ions gives a linear Hammett plot with ρ values usually greater than +3.0, indicating a substantial negative charge development at the β-carbon in the transition state.[11a] In addition, it has been reported that the proton transfer in the transition state is greater in the *syn* elimination than that in the *anti*-elimination.[2x] For the quaternary ammonium salts with a hydroxyl group on the β-carbon that is allowed to rotate into *anti*-coplanar to the leaving nitrogen, an epoxide forms upon the pyrolysis. If a proton occupies the position *anti*-coplanar to leaving nitrogen, however, an enol forms, which quickly tautomerizes to a ketone.[2m] In cases in which the hydroxyl group sits in the neighborhood of the ammonium group, the ether might form.[2q] For the quaternary ammonium salt with an allyl group, migration of the double bond takes place to give 1,3-diene during the elimination.[4k]

Although most of Hofmann eliminations are promoted by strong bases, some weak bases have also been reported to trigger the Hofmann elimination, such as diisopropylethylamine,[13] a mixture of diisopropylethylamine and potassium carbonate,[13] and gaseous ammonia (NH_3);[14] and ammonia has been found to be the ideal reagent for vapor-phase Hofmann elimination.[2g] On the other hand, some Hofmann eliminations are found to proceed under very mild conditions, such as the reaction in a concentrated aqueous solution of alkyltrimethylammonium hydroxide surfactants at room temperature.[2e] Furthermore, dried tetrabutylammonium fluoride (TBAF) has been reported to decompose at room temperature via the Hofmann elimination.[2a] Overall, the Hofmann elimination has been applied extensively for the structural elucidation of alkaloids[15] and analysis of alkylbenzyldimethylammonium chloride (ABDAC) in river water and sewage effluent.[4b] It is interesting that, for the alkaloid of apomorphinium system containing two β-carbons, there are two possible cleavage pathways that can be controlled under different conditions.[16]

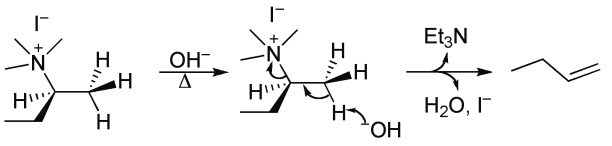
B. GENERAL REACTION SCHEME



(R_1 = H, alkyl; R_2 = H, alkyl, aryl)

C. PROPOSED MECHANISMS

Illustrated here is the elimination of isobutyl trimethylammonium iodide with hydroxide to give 1-butene.



D. MODIFICATION

This reaction has been extended to resin for the preparation of tertiary amine library.[6,13,17]

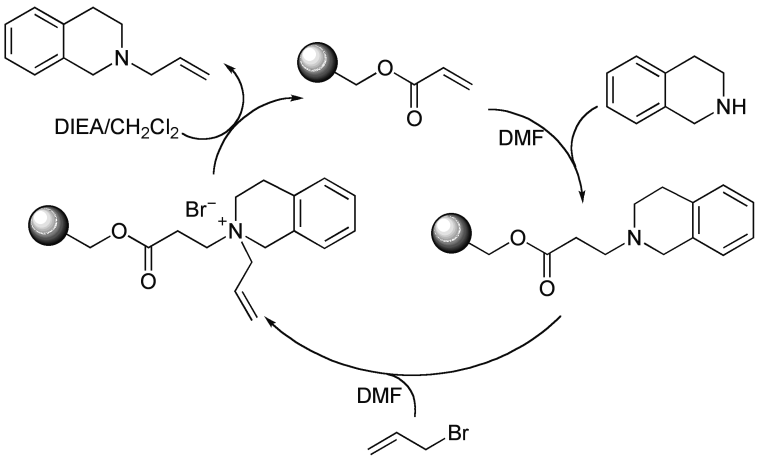
E. APPLICATIONS

This reaction has wide application in the structural elucidation of alkaloids and in the synthesis of olefins with less substituents.

F. RELATED REACTIONS

This reaction is related to the *Emde Degradation* and *Cope Elimination*.

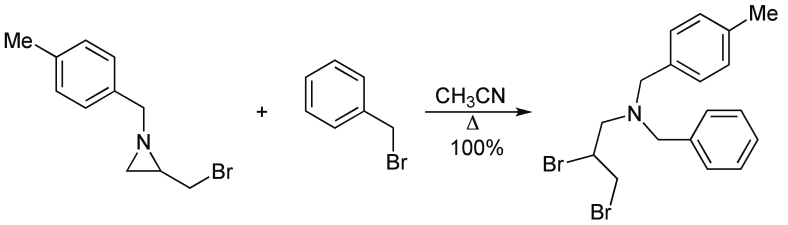
G. CITED EXPERIMENTAL EXAMPLES



Reference 13.

REM resin (a polystyrene resin) (1.0 g, 0.74 mmol) was suspended in a mixture of 927 μL 1,2,3,4-tetrahydroisoquinoline (7.4 mmol) and 7 mL DMF in a 15-mL polypropylene tube and agitated on a rotator for 2.5 h. The resin was drained and washed using a VacMaster station with DMF (4 × 2.5 mL) and then briefly dried under reduced pressure. The resin was resuspended in a solution of 326 μL allyl bromide (3.7 mmol) in 7 mL DMF and agitated on the rotator for 2.5 h. The resin was drained and washed using a VacMaster station with DMF (4 × 2.5 mL) and CH_2Cl_2 (4 × 2.5 mL), then briefly dried under reduced pressure.

The resin was resuspended in a solution of 266 μL diisopropylethylamine (1.48 mmol) in 7 mL CH_2Cl_2 and agitated on the rotator for 2.5 h. The resin was drained and washed using a VacMaster station with CH_2Cl_2 (3 $\times$ 3 mL). The filtrate was collected and evaporated. The residue was partitioned between diethyl ether (3 mL) and aqueous sodium carbonate (2 mL, 5% w/v). The organic layer was separated, and the aqueous layer was reextracted with ether (2 $\times$ 2 mL). The combined organic extracts were dried over K_2CO_3 and evaporated to dryness. 2-Allyl-1,2,3,4-tetrahydroisoquinoline was obtained as a colorless oil in a 88% yield and 99% purity. (*Note:* An aqueous extraction was used in this case for purification, because too much material was obtained for purification using a 500-mg silica SPE cartridge.)



Reference 2b.

To a solution of 3.60 g 2-(bromomethyl)-1-((4-methylphenyl)methyl)aziridine (15 mmol) in 50 mL acetonitrile was added 2.56 g benzyl bromide (15 mmol). After the solution was refluxed for 5 h, the solvent was removed in vacuo, resulting in 6.15 g *N*-benzyl-*N*-(2,3-dibromopropyl)-*N*-((4-methylphenyl)methyl)amine, in a crude yield of 100%. Pure compound can be obtained by column chromatography on silica gel using a mixture of hexane and EtOAc as an eluent.

Other references related to the Hofmann elimination are cited in the literature.[18]

H. REFERENCES

1. Hofmann, A. W., *Annalen,* **1851**, *78*, 253.
2. (a) Sun, H. R. and DiMagno, S. G., *J. Am. Chem. Soc.,* **2005**, *127*, 2050. (b) D'hooghe, M.; van Brabandt, W. and de Kimpe, N., *J. Org. Chem.,* **2004**, *69*, 2703. (c) Wrzyszczynski, A.; Pietrzak, M.; Bartoszewicz, J.; Kozubek, H.; Hug, G. L.; Marciniak, B. and Paczkowski, J., *J. Am. Chem. Soc.,* **2003**, *125*, 11182. (d) Heinz, H.; Castelijns, H. J. and Suter, U. W., *J. Am. Chem. Soc.,* **2003**, *125*, 9500. (e) Jiménez, R. M.; Soltero, J. F. A.; Manríquez, R.; López-Dellamary, F. A.; Palacios, G.; Puig, J. E.; Morini, M. and Schulz, P. C., *Langmuir,* **2002**, *18*, 3767. (f) Zhu, J.; Morgan, A. B.; Lamelas, F. J. and Wilkie, C. A., *Chem. Mater.,* **2001**, *13*, 3774. (g) Brown, A. R., *J. Comb. Chem.,* **1999**, *1*, 283. (h) Della, E. W. and Smith, P. A., *J. Org. Chem.,* **1999**, *64*, 1798. (i) Goralski, C. T.; Hasha, D. L.; Henton, D. R. and Peet, N. P., *Org. Proc. Res. Dev.,* **1997**, *1*, 280. (j) Bach, R. D. and Braden, M. L., *J. Org. Chem.,* **1991**, *56*, 7194. (k) Eubanks, J. R. I.; Sims, L. B. and Fry, A., *J. Am. Chem. Soc.,* **1991**, *113*, 8821. (l) Doshi, H.; Cardis, A. B.; Crelling, J. K.; Miller, S. I.; Dalton, D. R.; Zacharias, D. E. and Glusker, J. P., *J. Org. Chem.,* **1987**, *52*, 2604. (m) Wert, K. L.; Chackalamannil, S.; Miller, E.; Dalton, D. R.; Zacharias, D. E. and Glusker, J. P., *J. Org. Chem.,* **1982**, *47*, 5141. (n) Minch, M. J.; Chen, S.-S. and Peters, R., *J. Org. Chem.,* **1978**, *43*, 31. (o) Coke, J. L.; Smith, G. D. and Britton, G. H., *J. Am. Chem. Soc.,* **1975**, *97*, 4323. (p) Cannon, J. G.; Khonje, P. R. and Long, J. P., *J. Med. Chem.,* **1975**, *18*, 110.

(q) Liu, J. H. and Kovacic, P., *J. Org. Chem.,* **1975**, *40*, 1183. (r) Naghaway, J.; Shaath, N. A. and Soine, T. O., *J. Org. Chem.,* **1975**, *40*, 539. (s) Hirsch, J. A.; Cross, F. J. and Meresak, W. A., *J. Org. Chem.,* **1974**, *39*, 1966. (t) Adams, B. L. and Kovacic, P., *J. Org. Chem.,* **1974**, *39*, 3090. (u) Bach, R. D.; Bair, K. W. and Andrzejewski, D., *J. Am. Chem. Soc.,* **1972**, *94*, 8608. (v) Eisenbraun, E. J.; Auda, H.; Schorno, K. S.; Waller, G. R. and Appel, H. H., *J. Org. Chem.,* **1970**, *35*, 1364. (w) Aeberli, P. and Houlihan, W. J., *J. Org. Chem.,* **1969**, *34*, 2715. (x) Coke, J. L. and Mourning, M. C., *J. Am. Chem. Soc.,* **1968**, *90*, 5561. (y) Coke, J. L. and Cooke, M. P., *J. Am. Chem. Soc.,* **1967**, *89*, 2779. (z) Coke, J. L. and Cooke, M. P., *J. Am. Chem. Soc.,* **1967**, *89*, 6701. (aa) Bonner, W. A. and Kakis, F. J., *J. Org. Chem.,* **1965**, *30*, 4248. (bb) Stoffel, P. J., *J. Org. Chem.,* **1964**, *29*, 2794. (cc) White, E. H. and Dunathan, H. C., *J. Am. Chem. Soc.,* **1964**, *86*, 453. (dd) Cope, A. C.; Howell, C. F. and Knowles, A., *J. Am. Chem. Soc.,* **1962**, *84*, 3190. (ee) Cristol, S. J. and Stermitz, F. R., *J. Am. Chem. Soc.,* **1960**, *82*, 4692. (ff) Rogers, M. A. T., *J. Org. Chem.,* **1957**, *22*, 350. (gg) Weinstock, J., *J. Org. Chem.,* **1956**, *21*, 540. (hh) Doering, W. von E. and Meislich, H., *J. Am. Chem. Soc.,* **1952**, *74*, 2099.

3. (a) Valpuesta, M.; Diaz, A.; Suau, R. and Torres, G., *Eur. J. Org. Chem.,* **2006**, 964. (b) Gronert, S. and Fong, L.-M., *Aust. J. Chem.,* **2003**, *56*, 379. (c) Morphy, J. R.; Rankovic, Z. and York, M., *Tetrahedron Lett*., **2002**, *43*, 6413. (d) Berkes, D.; Netchitailo, P.; Morel, J. and Decroix, B., *Synth. Commun.,* **1998**, *28*, 949. (e) Bhonsle, J. B., *Synth. Commun.,* **1995**, *25*, 289. (f) Jiang, S.; Li, B. T. and Wu, Z. H., *Huaxue Tongbao*, **1993**, 33. (g) Ye, X. L., *Daxue Huaxue*, **1993**, *8*, 12. (h) Sepulveda-Arques, J.; Rosende, E. G.; Marmol, D. P.; Garcia, E. Z.; Yruretagoyena, B. and Ezquerra, J., *Monatsh. Chem.,* **1993**, *124*, 323. (i) Lai, Y. H. and Eu, H. L., *J. Chem. Soc., Perkin Trans. I,* **1993**, 233. (j) Sarkar, A. K. and Sarkar, N., *J. Chem. Res. (S),* **1992**, 309. (k) Troev, K. and Roundhill, D. M., *Phosphorus & Sulfur & Related Elements,* **1988**, *37*, 243. (l) Lu, S. T. and Tsai, I. L., *Heterocycles*, **1988**, *27*, 751. (m) Glatzhofer, D. T. and Longone, D. T., *Tetrahedron Lett*., **1986**, *27*, 5923. (n) Davies, J. A. and Eagle, C. T., *Organometallics*, **1986**, *5*, 2149. (o) Glatzhofer, D. T. and Longone, D. T., *Tetrahedron Lett*., **1983**, *24*, 4413. (p) Chalk, A. J.; Wertheimer, V. and Magennis, S. A., *J. Mol. Catal.,* **1983**, *19*, 189.
4. (a) Lee, D.-U., *Bull. Korean Chem. Soc*., **2002**, *23*, 1548. (b) Ding, W.-H. and Liao, Y.-H., *Anal. Chem.,* **2001**, *73*, 36. (c) Lee, S.-S. and Doskotch, R. W., *J. Nat. Prod.,* **1996**, *59*, 738. (d) Don, A. W. and Jones, T. H., *New Zealand Entomologist,* **1993**, *16*, 45. (e) Burch, R. R. and Manring, L. E., *Marcomolecules,* **1991**, *24*, 1731. (f) Cope, A. C.; Funke, W. R. and Jones, F. N., *J. Am. Chem. Soc.,* **1966**, *88*, 4694. (g) Paquette, L. A. and Wise, L. D., *J. Org. Chem.,* **1965**, *30*, 228. (h) Culberson, C. F. and Wilder, P., *J. Org. Chem.,* **1962**, *27*, 4205. (i) Winberg, H. E.; Fawcett, F. S.; Mochel, W. E. and Theobald, C. W., *J. Am. Chem. Soc.,* **1960**, *82*, 1428. (j) Highet, P. F. and Wildman, W. C., *J. Org. Chem.,* **1960**, *25*, 287. (k) Boekelheide, V.; Ceder, O.; Natsume, M. and Zürcher, A., *J. Am. Chem. Soc.,* **1959**, *81*, 2256.
5. Grundon, M. F. and Boekelheide, V., *J. Am. Chem. Soc.,* **1953**, *75*, 2537.
6. Barn, D.; Caulfield, W.; Cowley, P.; Dickins, R.; Bakker, W. I.; McGuire, R.; Morphy, J. R.; Rankovic, Z. and Thorn, M., *J. Comb. Chem.,* **2001**, *3*, 534.
7. Seuron, P. and Solladie, G., *J. Org. Chem.,* **1980**, *45*, 715.
8. Beltrame, P.; Beltrame, P. L.; Carniti, P.; Delogu, P.; Pina, C. and Zuretti, G., *Ind. Eng. Chem. Res.,* **1989**, *28*, 1125.
9. Shiner, V. J. and Smith, M. L., *J. Am. Chem. Soc.,* **1958**, *90*, 4095.
10. Arnold, R. T. and Richardson, P. N., *J. Am. Chem. Soc.,* **1954**, *76*, 3649.
11. (a) Lewis, D. E.; Sims, L. B.; Yamataka, H. and McKenna, J., *J. Am. Chem. Soc.,* **1980**, *102*, 7411. (b) Cope, A. C. and Mehta, A. S., *J. Am. Chem. Soc.,* **1963**, *85*, 1949.
12. Cooke, M. P. and Coke, J. L., *J. Am. Chem. Soc.,* **1968**, *90*, 5556.
13. Brown, A. R.; Rees, D. C.; Rankovic, Z. and Morphy, J. R., *J. Am. Chem. Soc.,* **1997,** *119*, 3288.
14. Fu, H. and Lam, Y. L., *J. Comb. Chem.,* **2005**, *7*, 734.

15. (a) Cope, A. C. and Trumbull, E. R., *Org. React.,* **1960**, *11*, 317. (b) Weinstock, J. and Boekelheide, V., *J. Am. Chem. Soc.,* **1953**, *75*, 2546.
16. Cannon, J. G.; Borgman, R. J.; Aleem, M. A. and Long, J. P., *J. Med. Chem.,* **1973**, *16*, 219.
17. Ouyang, X. H.; Armstrong, R. W. and Murphy, M. M., *J. Org. Chem.,* **1998**, *63*, 1027.
18. (a) Fujiwara, K.; Maeda, Y.; Shirai, N. and Sato, Y., *J. Org. Chem.,* **2000**, *65*, 7055. (b) Woolhouse, A. D.; Gainsford, G. J. and Crump, D. R., *J. Heterocycl. Chem.,* **1993**, *30*, 873. (c) Katritzky, A. R. and El-Mowafy, A. M., *J. Org. Chem.,* **1982**, *47*, 3506. (d) Short, M. R., *J. Org. Chem.,* **1972**, *37*, 2201. (e) Biale, G.; Parker, A. J.; Smith, S. G.; Stevens, I. D. R. and Winstein, S., *J. Am. Chem. Soc.,* **1970**, *92*, 115. (f) Cope, A. C.; Banholzer, K.; Jones, F. N. and Keller, H., *J. Am. Chem. Soc.,* **1966**, *88*, 4700. (g) Cope, A. C.; Lebel, N. A.; Moore, P. T. and Moore, W. R., *J. Am. Chem. Soc.,* **1961**, *83*, 3861. (h) MacPhillamy, H. B. and Scholz, C. R., *J. Org. Chem.,* **1949**, *14*, 643. (i) Pailer, M. and Bilek, L., *Monatsh.,* **1948**, *79*, 135. (j) Hanhart, W. and Ingold, C. K., *J. Chem. Soc.,* **1927**, 997. (k) Freund, M. and Frnakforter, G. B., *Ann.,* **1893**, *277*, 20. (l) Hofmann, A. W., *Ber.,* **1881**, *14*, 659.

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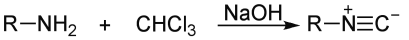
Hofmann Isonitrile Synthesis
(Hofmann carbylamine reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Hofmann in 1868.[1] It is the synthesis of isonitriles (also known as isocyanides) from primary amines and chloroform in the presence of alkali and is known as the Hofmann isonitrile synthesis,[2] Hofmann carbylamine reaction,[3] or Hofmann carbylamine synthesis.[2] This reaction has been used to test the presence of primary amines from the order of isocyanides. Alternatively, the isonitriles can be prepared by means of the treatment of formamide of primary amines with toluenesulfonyl chloride[4] or phosphorus oxychloride ($POCl_3$).[4,5] Currently, the isonitriles have gained much attention in organic synthesis because of their application as versatile building blocks for heterocycles[6] and in multicomponent reactions to generate combinatorial libraries, such as that in the *Passerini reaction* and *Ugi reaction*.[7]

B. GENERAL REACTION SCHEME



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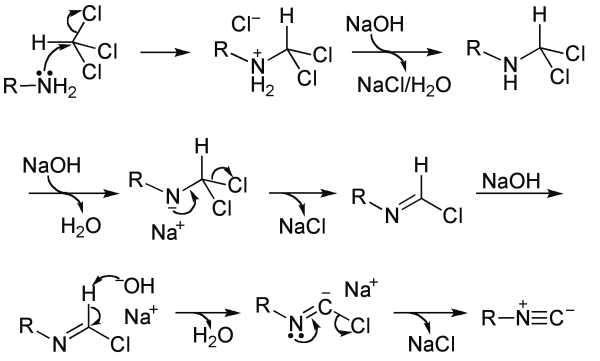
C. PROPOSED MECHANISMS

Shown below is a putative mechanism for this reaction.



D. MODIFICATION

This reaction has been modified using the conditions of phase transfer catalysis.[8]

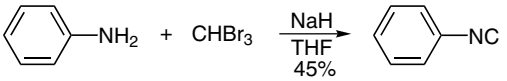
E. APPLICATIONS

This reaction is generally used to convert primary amines into isonitriles.

F. RELATED REACTIONS

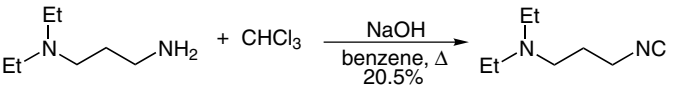
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 9.

The mixture of 0.1 mol aniline and 0.105 mol bromoform was added to a suspension of 0.33 mol sodium hydride (dispersed in mineral oil) in THF. After the reaction was complete, water was added dropwise to destroy any excess sodium hydride. Ether was added, and the ether solution was washed with H_2O (4 × 50 mL), dilute HCl solution (3 × 20 mL), and water. After drying over Na_2SO_4, the ether was evaporated and the residue was distilled to yield 4.65 g phenylisonitrile, in a yield of 45%, b.p., 50–55°C (13 mmHg). Redistillation gave 3.5 g of product, b.p. 52–53°C (13 mmHg). The material was light green but became colorless upon bulb-to-bulb distillation at 10^{-5} mmHg.



Reference 10.

A mixture of 40 g powdered potassium hydroxide and 100 mL benzene was placed in a 1-L round-bottomed flask equipped with a reflux condenser, drying tube, stirrer, and dropping funnel. The mixture was stirred and heated under reflux, and gradually a solution of 15.8 g 3-diethylaminopropylamine in 29 mL chloroform was added. At a point during the addition, the reaction became violently exothermic, heating was immediately discontinued, and the reaction was moderated (but not quenched) by cooling the mixture externally with ice water. The remainder of the chloroform solution was added at a rate to maintain vigorous refluxing, and the mixture was then allowed to stand until cool. It was then filtered, the brown, tarry precipitate was washed with benzene, and the washings were added to the filtrate. Solvent was removed, and further distillation gave a fraction of b.p. 87–107°C (45 mmHg), and a tarry residue. Attempted further distillation of this residue at 1.0 mmHg resulted only in decomposition. The distillate was redistilled to give 2.49 g 3-diethylaminopropylamine; 2.37 g of a mixture with a boiling point of 86–105°C (45 mmHg); and 2.99 g 3-diethylaminopropyl isocyanide (20.5%) as a clear, colorless liquid, b.p. 105–107°C at 45 mmHg.

Other references related to the Hofmann isonitrile synthesis are cited in the literature.[11]

H. REFERENCES

1. Hofmann, A. W., *Ann.,* **1868**, *146*, 107.
2. Weber, W. P. and Gokel, G. W., *Tetrahedron Lett.,* **1972,** 1637.
3. (a) Zakrzewski, J.; Jezierska, J. and Hupko, J., *Org. Lett.,* **2004**, *6*, 695. (b) Jia, G. C.; Puddephatt, R. J.; Vittal, J. J. and Payne, N. C., *Organometallics*, **1993**, *12*, 263. (c) Kobayashi, S.; Miyamoto, M. and Saegusa, T., *Macromolecules*, **1981**, *14*, 1584. (d) Gokel, G. W.; Widera, R. P. and Weber, W. P., *Org. Synth.,* **1976**, *55*, 96.
4. Casanova, J.; Werner, N. D. and Schuster, R. E., *J. Org. Chem.,* **1966**, *31*, 3473.
5. Berg, F. J. and Petersen, J. L., *Organometallics,* **1991**, *10*, 1599.
6. (a) Kobayashi, K.; Nakahashi, R.; Takanohashi, A.; Kitamura, T.; Morikawa, O. and Konishi, H., *Chem. Lett.,* **2002**, 624. (b) Tsunenishi, Y.; Ishida, H.; Itoh, K. and Ohno, M., *Synlett,* **2000**, 1318. (c) Moderhack, D.; Daoud, A.; Ernst, L. and Jones, P. G., *J. Prakt. Chem.,* **2000**, *342*, 707.
7. (a) Beck, B.; Larbig, G.; Mejat, B.; Magnin-Lachaux, M.; Picard, A.; Herdtweck, E. and Doemling, A., *Org. Lett.,* **2003**, *5*, 1047. (b) Wright, D. L.; Robotham, C. V. and Aboud, K., *Tetrahedron Lett.,* **2002**, *43*, 943. (c) Xia, Q. and Ganem, B., *Org. Lett.,* **2002**, *4*, 1631. (d) Kim, Y. B.; Choi, E. H.; Keum, G.; Kang, S. B.; Lee, D. H.; Koh, H. Y. and Kim, Y., *Org. Lett.,* **2001**, *3*, 4149.
8. Zakrzewski, J. and Hupko, J., *Org. Prep. Proced. Int.,* **2003**, *35*, 387.
9. Johnson, H. W. and Krutzsch, H., *J. Am. Chem. Soc.,* **1967**, *89*, 1939.
10. Smith, P. A. S. and Kalenda, N. W., *J. Org. Chem.,* **1958**, *23*, 1599.
11. (a) Jackson, H. L. and McKusick, B. C., *Org. Syn. Coll. Vol. IV,* **1963**, 438. (b) Frankel, M. B.; Feuer, H. and Bank, J., *Tetrahedron Lett.,* **1959**, 5. (c) Hofmann, A. W., *Ber.,* **1870**, *3*, 767.

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Hofmann Rule

A. GENERAL DESCRIPTION OF THE REACTION

The Hofmann rule is formulated on the basis of product distribution in the decomposition of a quaternary ammonium hydroxide initially reported by Hofmann in 1851 (i.e., *Hofmann Elimination*).[1] The Hofmann rule[2] states that the major product will be an olefin having the smallest number of attached alkyl groups[3]—that is, the product of less thermodynamical stability.[4] This rule was extensively studied first by Hughes and Ingold, who proposed that the Hofmann rule was applicable to a bimolecular elimination (E2), which was controlled by the polar factor from the positive charge in the "onium ion," whereas the elimination (e.g., of the alkyl halides) that gives the most substituted olefin follows the *Saytzeff Rule*, which is controlled by the electronic factor.[5] However, Hughes and Ingold's proposition was challenged by a group of researchers including Brown,[2d,2e,4,6] Saunders,[7] Cope,[8] Baumgarten,[9] Bailey,[3,10] DePuy,[11] Bartsch,[12] and Brawerman.[13] In particular, the extensive experimental evidence from Brown, Saunders, Bailey, and Cope indicated that the elimination of quaternary ammoniums,[3,7b,7c,8,11] tertiary sulfonium salts,[2d,3,7c,11] pyrolysis of secondary and tertiary esters of acetic acid,[3,10b] and so on all follow the Hofmann rule and are primarily controlled by the steric effect, not the polar factor (e.g., the acidity of hydrogen to be eliminated[11]). These experiments also showed that except for the highly strained molecules, first-order elimination reactions tend to follow the *Saytzeff Rule*, but bimolecular elimination reactions may follow either the *Saytzeff Rule* or the Hofmann rule,[3] depending on the steric nature of the alkyl groups on the incipient double bond,[2d] the attacking base,[2d,13] and the leaving group.[2d] In addition, the hyperconjugative effect[11] and the strength of the base[7a,7b] used also affect the elimination direction. Only when the steric factors are canceled out, or the electronic effects become overwhelming, do Saytzeff products dominate.[11] Thus the formation of desired olefins can be controlled by choosing different attacking bases, as

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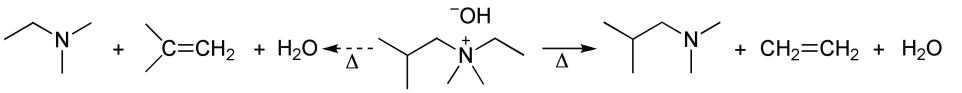
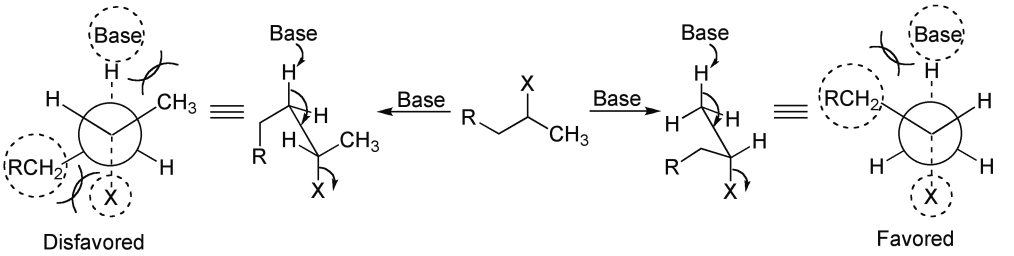
in the case for the elimination of 2-haloalkane:1-alkene is obtained predominantly when potassium *t*-butoxide is used, whereas 2-alkene is the major product when an ethoxide base is applied.[13] However, the elimination of alkyl fluorides[7d] and the pyrolysis of cyclohexyl carbinol acetate always give Hofmann products; in the latter case, the formation of an *exo* double bond to the six-membered ring is avoided.[14] In addition, the functional groups that can conjugate with the forthcoming double bond might alter the direction of elimination too (e.g., as a carbonyl group or a nitro group[10b]); however, one phenyl group is not strong enough to turn over the preference in the elimination direction.[10b] On the other hand, the effect of the base on the *trans*:*cis* ratio depends on the stereochemistry of the reaction.[7b] For example, the stronger base in a pure *anti* elimination gives more *cis*-olefin, but, if a *syn* elimination competes with *anti*-elimination, the application of a stronger base results in a higher proportion of *trans*-olefin. In the former case, known as the "normal" pattern, the increase in the Hofmann rule product is accompanied by a decrease in the *trans*:*cis* ratio of the olefins. In the latter case, known as "abnormal" pattern, the Hofmann rule product and the *trans*:*cis* ratio of the olefins increase in the same direction.[7b]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

N/A

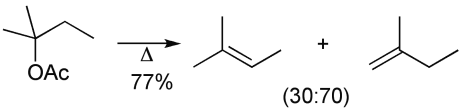
E. APPLICATIONS

This rule is useful in predicting and rationalizing the structures of elimination products.

F. RELATED REACTIONS

This rule is related to *Saytzeff Rule*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 10a.

To a pyrolysis apparatus consisting of a Vycor tube packed with Pyrex helices and externally heated with a 12-in. Hoskins furnace at 400°C was added dropwise 16.0 g *t*-amyl acetate (0.12 mol) at the rate of 1 g/min to the top of the tube. In the end of the pyrolysis, a small sample of the pyrolysate was immediately analyzed by GC, indicating a mixture of 70% 2-methyl-1-butene and 30% 2-methyl-2-butene. After the pyrolysate had been washed with water until neutral, the aqueous extracts were titrated with standard base to indicate that 77% of acetic acid has been librated.

Other references related to the Hofmann rule are cited in the literature.[15]

H. REFERENCES

1. (a) Hofmann, A. W., *Ann.,* **1851**, *78*, 253. (b) Hofmann, A. W., *Ann.,* **1851**, *79*, 11.
2. (a) Freedman, L. D., *J. Chem. Edu.,* **1966**, *43*, 662. (b) Rigaudy, J. and Thang, K.-V., *Bull. Soc. Chim. Fr.,* **1959**, 1618. (c) Rigaudy, J. and Thang, K.-V., *Compt. Rend.,* **1959**, *249*, 1008. (d) Brown, H. C. and Moritani, I., *J. Am. Chem. Soc.,* **1956**, *78*, 2203. (e) Brown, H. C. and Moritani, I., *J. Am. Chem. Soc.,* **1955**, *77*, 3607.
3. Bailey, W. J. and King, C., *J. Am. Chem. Soc.,* **1955**, *77*, 75.
4. Brown, H. C. and Klimisch, R. L., *J. Am. Chem. Soc.,* **1966**, *88*, 1425.
5. (a) Ingold, C. K., *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N.Y., **1953**, pp. 420-472. (b) Hughes, E. D.; Ingold, C. K. and Shiner, V. J., *J. Chem. Soc.,* **1953**, 3827. (c) Dhar, M. L.; Hughes, E. D.; Ingold, C. K.; Mandour, A. M. M.; Maw, G. A. and Woolf, L. I., *J. Chem. Soc.,* **1948**, 2093. (d) Hughes, E. D.; Ingold, C. K. and Woolf, L. I., *J. Chem. Soc.,* **1948**, 2084.
6. (a) Brown, H. C. and Nakagawa, M., *J. Am. Chem. Soc.,* **1956**, *78*, 2197. (b) Brown, H. C.; Moritani, I. and Nakagawa, M., *J. Am. Chem. Soc.,* **1956**, *78*, 2190.
7. (a) Feit, I. N.; Schadt, F.; Lubinkowski, J. and Saunders, W. H., *J. Am. Chem. Soc.,* **1971**, *93*, 6606. (b) Feit, I. N. and Saunders, W. H., *J. Am. Chem. Soc.,* **1970**, *92*, 5615. (c) Saunders, W. H.; Bushman, D. G. and Cockerill, A. F., *J. Am. Chem. Soc.,* **1968**, *90*, 1775. (d) Saunders, W. H.; Fahrenholtz, S. R.; Caressm E. A.; Lowe, J. P. and Schreiber, M., *J. Am. Chem. Soc.,* **1965**, *87*, 3401.
8. (a) Cope, A. C.; Ciganek, E.; Howell, C. F. and Schweizer, E. E., *J. Am. Chem. Soc.,* **1960**, *82*, 4663. (b) Cope, A. C.; Bumgardner, C. L. and Schweizer, E. E., *J. Am. Chem. Soc.,* **1957**, *79*, 4729. (c) Cope, A. C.; Lebel, N. A.; Lee, H.-H. and Moore, W. R., *J. Am. Chem. Soc.,* **1957**, *79*, 4720.

9. (a) Baumgarten, H. E.; Bower, F. A.; Setterquist, R. A. and Allen, R. E., *J. Am. Chem. Soc.,* **1958**, *80*, 4588. (b) Baumgarten, H. E.; Bower, F. A. and Okamoto, T. T., *J. Am. Chem. Soc.,* **1957**, *79*, 3145.
10. (a) Bailey, W. J. and Hale, W. F., *J. Am. Chem. Soc.,* **1959**, *81*, 647. (b) Bailey, W. J. and King, C., *J. Org. Chem.,* **1956**, *21*, 858. (c) Bailey, W. J.; Hewitt, J. J. and King, C., *J. Am. Chem. Soc.,* **1955**, *77*, 357.
11. Depuy, C. H. and Leary, R. E., *J. Am. Chem. Soc.,* **1957**, *79*, 3705.
12. Bartsch, R. A.; Allaway, J. R.; Ingram, D. D. and Lee, J.-G., *J. Am. Chem. Soc.,* **1975**, *97*, 6873.
13. Brawerman, G. and Chargaff, E., *J. Am. Chem. Soc.,* **1953**, *75*, 4112.
14. Benkeser, R. A. and Hazdra, J. J., *J. Am. Chem. Soc.,* **1959**, *81*, 228.
15. (a) Cockerill, A. F. and Saunders, W. H., *J. Am. Chem. Soc.,* **1967**, *89*, 4985. (b) Cope, A. C. and Mehta, A. S., *J. Am. Chem. Soc.,* **1963**, *85*, 1949. (c) Botteron, D. G. and Shulman, G. P., *J. Org. Chem.,* **1962**, *27*, 785. (d) Ainsworth, C. and Easton, N. R., *J. Org. Chem.,* **1962**, *27*, 4118. (e) Cope, A. C.; Lebel, N. A.; Moore, P. T. and Moore, W. R., *J. Am. Chem. Soc.,* **1961**, *83*, 3861. (f) Becker, F., *Z. Naturforsch.,* **1960**, 15*B*, 252. (g) Cope, A. C. and Trumbull, E. R., *Org. React.,* **1960**, *11*, 348. (h) Shiner, V. J. and Smith, M. L., *J. Am. Chem. Soc.,* **1958**, *80*, 4095. (i) Brown, H. C.; Moritani, I. and Okamoto, Y., *J. Am. Chem. Soc.,* **1956**, *78*, 2193.

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Hofmann-Löffler-Freytag Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Hofmann in 1883,[1] and then extended by Löffler et al. after 1909.[2] It is the synthesis of pyrrolidine or piperidine derivatives by thermal or photochemical decomposition of the protonated aliphatic *N*-haloamines. Historically, this reaction has been known as the Löffler method,[3] Löffler-Freytag reaction,[4] Hofmann-Löffler reaction,[5] and Hofmann-Löffler-Freytag cyclization,[6] but the Hofmann-Löffler-Freytag reaction[7] is the most commonly used name today. Corey[5d,7p] and Wawzonek[8] provided many experimental evidences to support the radical mechanism of this reaction, such as the initiation of the reaction by either photo-irradiation or traditional radical initiators and the inhibition of reaction by oxygen. Without radical initiation (e.g., UV light), the *N*-haloamines are stable even in 85% sulfuric acid in the dark at room temperature;[5b] in contrast, the same protonated *N*-haloamines disappear within 3 h if irradiated by even a weak UV light source, such as a chromatography column scanner.[5d] In this reaction, hydrogen abstraction is the chain-propagating step.[7h] It is known that the bond energy of secondary C-H (e.g., Me_2CH-H) is 358 KJ/mol, and the bond energy of Me_2N-H is 383 KJ/mol.[7h] Obviously, it is mildly exothermic for hydrogen abstraction by aminyl radicals on hydrocarbons. Moreover, the protonation of aminyl radicals to give aminium radicals considerably enhances the electron deficiency of nitrogen, which would dramatically facilitate the hydrogen abstraction.[9] On the other hand, even though both pyrrolidines and piperidines are potential products of this reaction, pyrrolidines are the most favored products,[5c,5d,7p] possibly because of the kinetic factor. Currently, many other methods have been established to generated aminium radicals, including electrochemistry,[10] pulse radiolysis,[11] and the reduction of photosensitizers (e.g., ketone triplet, dicyanobenzene).[12] It should be pointed out that this reaction has been extended to amidyl radicals.[7c,13]

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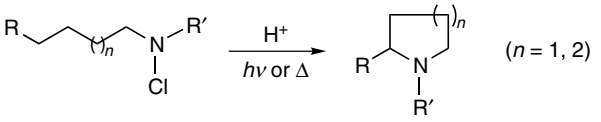
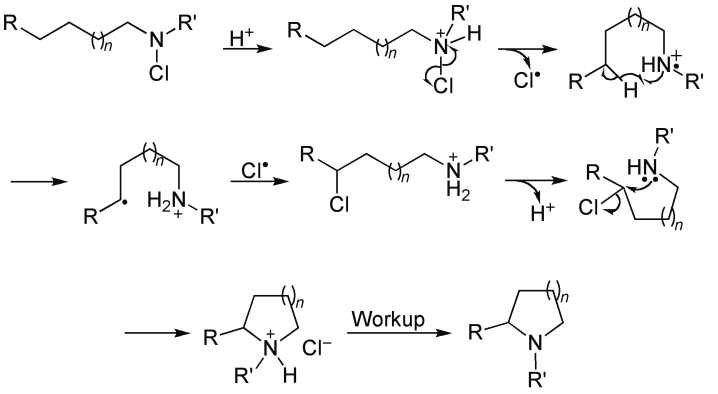
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Proposed here is a tentative mechanism for the Hofmann-Löffler-Freytag reaction.



D. MODIFICATION

This reaction has been extended to amidyl radical,[7c,13] sulfonamidyl radical,[7b] and other nitrogenous radicals.[14]

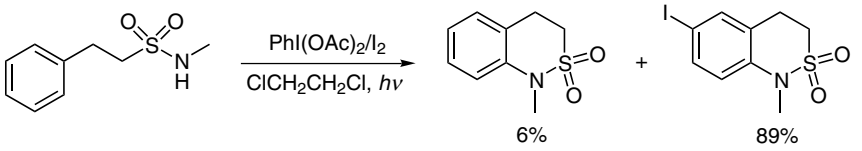
E. APPLICATIONS

This reaction has been widely used in the synthesis of substituted pyrrolidines and piperidines.

F. RELATED REACTIONS

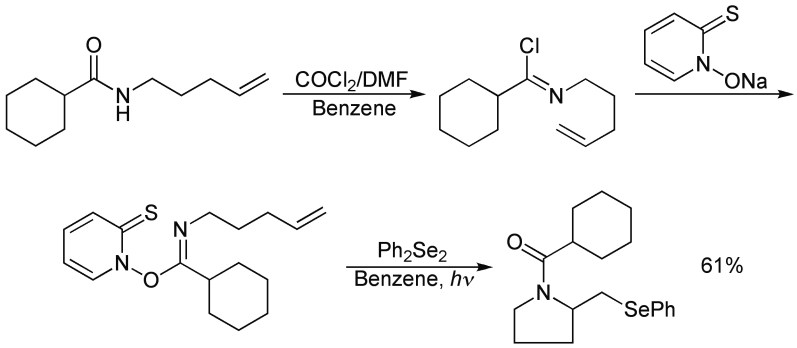
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 7b.

(Diacetoxyiodo)benzene (0.8 mmol) and 0.5 mmol iodine were added to a solution of 0.5 mmol *N*-methyl phenylethylsulfonamide in 5 mL dichloroethane. The mixture was irradiated with a 500-W tungsten lamp at 20–30°C for 2 h under an argon atmosphere. After the reaction, the mixture was poured into a saturated aqueous sodium sulfite (Na_2SO_3) solution and extracted with $CHCl_3$ three times. The organic layers were combined and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was chromatographed by preparative TLC on silica gel using a mixture of hexane, EtOAc, and $CHCl_3$ (6:3:1) as the eluent, to give 6% *N*-methyl-3,4-dihydro-2,1-benzothiazine-2,2-dioxide, m.p. 77.0–79.0°C and 89% *N*-methyl-6-iodo-3,4-dihydro-2,1-benzothiazine-2,2-dioxide, m.p. 139.0–141.0°C.



Reference 13a.

To a solution of 402 mg *N*-(4-pentenyl)cycloyexanecarboxamide (2.15 mmol) in 21.5 mL benzene containing a catalytic amount of DMF at ~ 5°C was transferred 1.5 eq. phosgene (1.9 M of phosgene in toluene). The solution was allowed to warm slowly to ambient temperature with stirring. The slow evolution of CO_2 was monitored via a mineral oil bubbler. After ~ 12 h, the evolution of CO_2 was complete. Excess amounts of phosgene and solvent were removed by distillation at room temperature under reduced pressure to give the imidoyl chloride as a clear liquid. Dry ether was added to give a 0.1 M solution of imidoyl chloride. The flask was wrapped in aluminum foil, and 1.2 eq. anhydrous 2-mercaptopyridine *N*-oxide sodium salt was added via a solid addition tube under nitrogen. The mixture was stirred for 4–8 h. The residual salts were removed by filtration under nitrogen and were washed with dry ether. Concentration of the filtrate in vacuo gave 1-[(*N*-(4′-pentenyl)cyclohexanecarboximidyl)oxy-2(1H)-pyridinethione as a yellow oil.

The product was dissolved in benzene at 0.05 M concentration; then under a nitrogen atmosphere was added 1.2 g diphenyl diselenide (3.8 mmol). The solution was irradiated

for 10 h. Removal of the solvent and then radial chromatography (hexane/EtOAc, 4:1) gave 456 mg *N*-(cyclohexylcarbonyl)-2-[(phenylseleno)methyl]pyrrolidine, in a yield of 61%. Recrystallization from hexanes gave a material with a melting point of 81–83°C.

Other references related to the Hofmann-Löffler-Freytag reaction are cited in the literature.[15]

H. REFERENCES

1. Hofmann, A. W., *Ber.,* **1883**, *16*, 558.
2. (a) Löffler, K. and Kober, S., *Ber.,* **1909**, *42*, 3421. (b) Löffler, K. and Freytag, C., *Ber.,* **1909**, *42*, 3427. (c) Löffler, K., *Ber.,* **1910**, *43*, 2025.
3. Coleman, G. H. and Goheen, G. E., *J. Am. Chem. Soc.,* **1938**, *60*, 730.
4. (a) Madsen, J.; Viuf, C. and Bols, M., *Chem. Eur. J.* **2000**, *6*, 1140. (b) Pliml, J., *Chemie (Prague)*, **1958**, *10*, 879. (c) Lukes, R. and Ferles, M., *Coll. Czech. Chem. Commun.,* **1955**, *20*, 1227. (d) Lukes, R. and Ferles, M., *Chem. Listy Vedu Prumysl*, **1955**, *49*, 510.
5. (a) Tyukhteneva, Z. I. and Badovskaya, L. A., *Russ. J. Org. Chem.,* **2005**, *41*, 937. (b) Minisci, F., *Chem. Ind. (Milan),* **1964**, *46*, 57. (c) Wolff, M. E., *Chem. Rev.,* **1963**, *63*, 55. (d) Corey, E. J. and Hertler, W. R., *J. Am. Chem. Soc.,* **1960**, *82*, 1657.
6. Schreiber, K. and Adam, G., *Tetrahedron*, **1964**, *20*, 1719.
7. (a) Cordero, F. M.; Pisaneschi, F.; Goti, A.; Ollivier, J.; Salaün, J. and Brandi, A., *J. Am. Chem. Soc.,* **2000**, *122*, 8075. (b) Togo, H.; Harada, Y. and Yokoyama, M., *J. Org. Chem.,* **2000**, *65*, 926. (c) Horner, J. H.; Musa, O. M.; Bouvier, A. and Newcomb, M., *J. Am. Chem. Soc.,* **1998**, *120*, 7738. (d) Togo, H.; Hoshina, Y.; Muraki, T.; Nakayama, H. and Yokoyama, M., *J. Org. Chem.,* **1998**, *63*, 5193. (e) Togo, H.; Hoshina, Y.; Nogami, G. and Yokoyama, M., *Yuki Gosei Kagaku Kyokaishi*, **1997**, *55*, 90. (f) Jasperse, C. P.; Curran, D. P. and Fevig, T. L., *Chem. Rev.,* **1991**, *91*, 1237. (g) Laird, E. R. and Jorgensen, W. L., *J. Org. Chem.,* **1990**, *55*, 9. (h) Boyd, R. J.; Glover, J. N. M. and Pincock, J. A., *J. Am. Chem. Soc.,* **1989**, *111*, 5152. (i) Betancor, C.; Concepción, J. I.; Hernández, R.; Salazar, J. A. and Suárez, E., *J. Org. Chem.,* **1983**, *48*, 4430. (j) Paquette, L. A. and Haluska, R. J., *J. Org. Chem.,* **1970**, *35*, 132. (k) Gassman, P. G. and Cryberg, R. L., *J. Am. Chem. Soc.,* **1969**, *91*, 2047. (l) Gassman, P. G. and Fox, B. L., *J. Org. Chem.,* **1967**, *32*, 3679. (m) Kabasakalian, P. and Townley, E. R., *J. Am. Chem. Soc.,* **1962**, *84*, 2711. (n) Walling, C. and Padwa, A., *J. Am. Chem. Soc.,* **1961**, *83*, 2207. (o) Schaffner, K.; Arigoni, D. and Jeger, O., *Experientia,* **1960**, *16*, 169. (p) Corey, E. J. and Hertler, W. R., *J. Am. Chem. Soc.,* **1959**, *81*, 5209.
8. (a) Wawzonek, S. and Culbertson, T. P., *J. Am. Chem. Soc.,* **1959**, *81*, 3367. (b) Wawzonek, S.; Nelson, M. F. and Thelen, P. J., *J. Am. Chem. Soc.,* **1951**, *73*, 2806. (c) Wawzonek, S. and Thelen, P. J., *J. Am. Chem. Soc.,* **1950**, *72*, 2118.
9. Wagner, B. D.; Ruel, G. and Lusztyk, J., *J. Am. Chem. Soc.,* **1996**, *118*, 13.
10. (a) Nelsen, S. F.; Chen, L.-J.; Petillo, P. A.; Evans, D. H. and Neugebauer, F. A., *J. Am. Chem. Soc.,* **1993**, *115*, 10611. (b) Handoo, K. L.; Cheng, J.-P. and Parker, V. D., *Acta Chem. Scand.,* **1993**, *47*, 626.
11. (a) Jonsson, M.; Lind, J.; Merenyi, G. and Eriksen, T. E., *J. Chem. Soc., Perkin Trans. II,* **1995**, 61. (b) Jonsson, M.; Lind, J.; Eriksen, T. E. and Merenyi, G., *J. Am. Chem. Soc.,* **1994**, *116*, 1423. (c) Werst, D. W. and Trifunae, A., *J. Phys. Chem.,* **1991**, *95*, 1268. (d) Gebicki, J.; Marcinek, A. and Stradowski, C., *J. Phys. Org. Chem.,* **1990**, *3*, 606.
12. (a) Zhang, X.; Yeh, S.-R.; Hong, S.; Freccero, M.; Albini, A.; Falvey, D. E. and Mariano, P. S., *J. Am. Chem. Soc.,* **1994**, *116*, 4211. (b) Devadoss, C. and Fessenden, R. W., *J. Phys. Chem.,*

1990, *94*, 4540. (c) Scaiano, J. C.; Stewart, L. C.; Livant, P. and Majors, A. W., *Can. J. Chem.,* **1984**, *62*, 1339.

13. (a) Esker, J. L. and Newcomb, M., *J. Org. Chem.,* **1993**, *58*, 4933. (b) Newcomb, M. and Ha, C., *Tetrahedron Lett.,* **1991**, *32*, 6493. (c) Newcomb, M. and Weber, K. A., *J. Org. Chem.,* **1991**, *56*, 1309. (d) Newcomb, M. and Kumar, M. U., *Tetrahedron Lett.,* **1990**, *31*, 1675.
14. (a) Magdzinski, L. J. and Chow, Y. L., *J. Am. Chem. Soc.,* **1978**, *100*, 2444. (b) Yip, R. W.; Vidoczy, T.; Snyder, R. W. and Chow, Y. L., *J. Phys. Chem.,* **1978**, *82*, 1194. (c) Cessna, A. J.; Sugamori, S. E.; Yip, R. W.; Lau, M. P.; Snyder, R. S. and Chow, Y. L., *J. Am. Chem. Soc.,* **1977**, *99*, 4044. (d) Mojelsky, T. and Chow, Y. L., *J. Am. Chem. Soc.,* **1974**, *96*, 4549. (e) Lau, M. P.; Cessna, A. J.; Chow, Y. L. and Yip, R. W., *J. Am. Chem. Soc.,* **1971**, *93*, 3808.
15. (a) Francisco, C. G.; Herrera, A. J. and Suárez, E., *J. Org. Chem.,* **2003**, *68*, 1012. (b) Togo, H. and Katohgi, M., *Synlett*, **2001**, 565. (c) Zheng, Z.-R.; Evans, D. H. and Nelsen, S. F., *J. Org. Chem.,* **2000**, 65,1793. (d) Schmittel, M. and Burghart, A., *Angew. Chem. Int. Ed. Engl.,* **1997**, *36*, 2550. (e) Stella, L., *Angew. Chem. Int. Ed. Engl.,* **1983**, *22*, 337. (f) Titouani, S. L.; Lavergne, J. P.; Viallefont, P. and Jacquier, R., *Tetrahedron*, **1980**, *36*, 2961. (g) Chow, Y. L.; Danen, W. C.; Nelsen, S. F. and Rosenblatt, D. H., *Chem. Rev.,* **1978**, *78*, 243. (h) Minisci, F., *Acc. Chem. Res.,* **1975**, *8*, 165. (i) Chow, Y. L., *Acc. Chem. Res.,* **1973**, *6*, 354. (j) Minisci, F., *Synthesis,* **1973**, 1. (k) Neale, R. S., *Synthesis,* **1971**, 1. (l) Furstoss, R.; Teissier, P. and Waegell, B., *Tetrahedron Lett.,* **1970**, 1263. (m) Neale, R. S. and Walsh, M. R., *J. Am. Chem. Soc.,* **1965**, *87*, 1255. (n) Hornke, G.; Krauch, W. and Kunz, W., *Chem. Ztg.,* **1965**, *89*, 440. (o) Tanner, D., *J. Am. Chem. Soc.,* **1964**, *86*, 4674. (p) Hofmann, A. W., *Ber.,* **1885**, *18*, 5. (q) Hofmann, A. W., *Ber.,* **1885**, *18*, 109.

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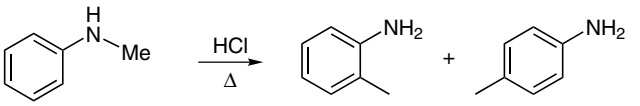
Hofmann-Martius Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Hofmann and Martius in 1871.[1] It is the thermal conversion of hydrohalides of *N*-alkylated aromatic amines to *o*-alkylated and *p*-alkylated aromatic amine derivatives and is generally known as the Hofmann-Martius rearrangement.[2] It is known that the *N*-alkylated aromatic amine hydrochlorides dissociate upon heating[3] and then the new components undergo the intermolecular alkylation,[2h,4] involving the migration of an alkyl group in the form of free radical,[4b] olefin[3,4b] or carbocation.[3,4a] However, evidence also indicates the combination of both radical and olefin pathways.[4b] The Hofmann-Martius rearrangement in the solid state mostly gives *ortho*-alkylated products, possibly because of limited diffusion.[5] In addition, the Hofmann-Martius rearrangement can be triggered by photo-irradiation.[6]

B. GENERAL REACTION SCHEME



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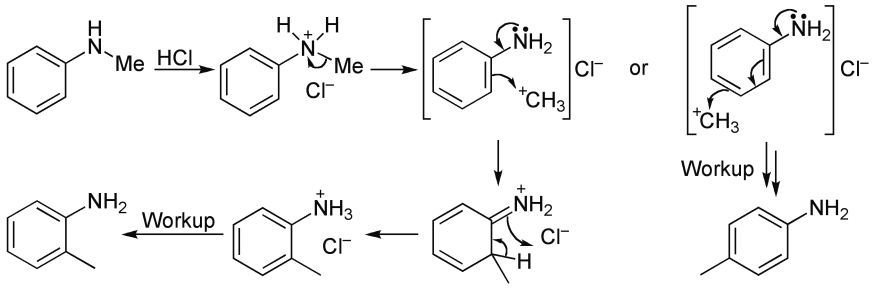
C. PROPOSED MECHANISMS

A cationic mechanism is displayed here for the thermal rearrangement of *N*-methyl aniline hydrochloride, without the formation of methyl chloride as a reaction intermediate.



D. MODIFICATION

This reaction has been modified to the conditions promoted by photo-irradiation.[6]

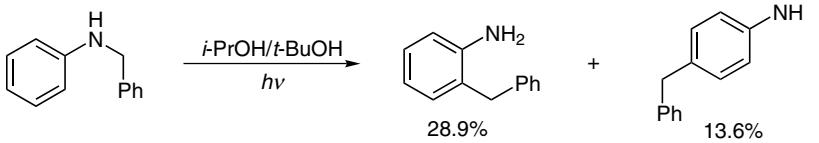
E. APPLICATIONS

This reaction is useful for the preparation of substituted aromatic amines.

F. RELATED REACTIONS

This reaction is related to *Fischer-Hepp Rearrangement*, *Orton Rearrangement*, and *Reilly-Rickinbottom Rearrangement.*

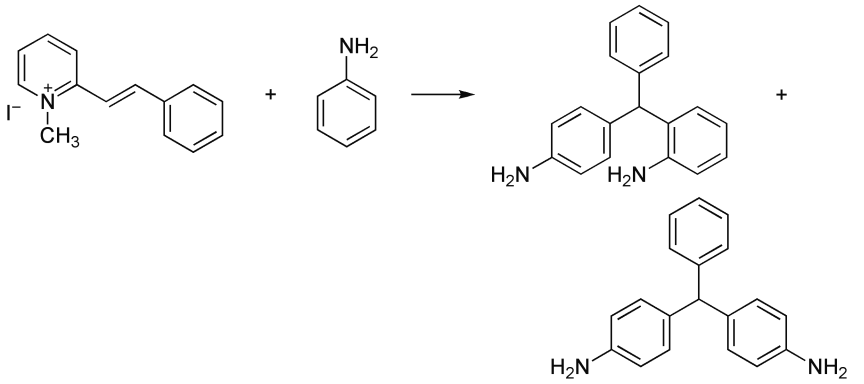
G. CITED EXPERIMENTAL EXAMPLES



Reference 6.

A solution of 300 mL isopropyl alcohol/*t*-butyl alcohol containing 3.83 g *N*-phenylbenzylamine was irradiated under nitrogen gas for 30 h. The concentrated reaction mixture was chromatographed on a 15 × 300-mm column, slurry packed in benzene/3% acetone with 100-mesh silica gel, using benzene/3% acetone as the eluent. Three components

were obtained in the order of *N*-phenylbenzylamine, *o*-benzyl-aniline (28.9% yield), and *p*-benzyl-aniline (13.6% yield), in a total conversion of 55.4%.



Reference 7.

A mixture of 25.0 g *trans*-2-styrylpyridine methiodine and 50.0 g aniline was heated under reflux for 1 h. The cooled reaction mixture was washed with dilute ammonium hydroxide solution, and organic material was extracted with ether. The ether extract was washed with water and dried over $MgSO_4$. The excess aniline and ether was removed under reduced pressure to give a brown oil that crystallized from benzene to yield 15.0 g of colorless prisms. A portion of this material (4.25 g) was chromatographed on silica gel with an increasing percentage of EtOAc in benzene as the eluent. The desired portions were evaporated to yield 0.6 g 2,4′-diaminotriphenylmethane and 1.95 g 4,4′-diaminotriphenylmethane. An intermediate cut yielded 1.15 g of a mixture of these two compounds. Pure 4,4′-diaminotriphenylmethane (1.2 g) was obtained as colorless prisms from crystallization in benzene, m.p. 137–138°C, and a sublimed sample of this molecule had a melting point of 142–144°C. Similarly, 0.4 g pure 2,4′-diaminotriphenylmethane was obtained from the crystallization in benzene, m.p. 99–104°C (with benzene in presence), and the sublimed sample had a melting point of 131–132°C.

Other references related to the Hofmann-Martius rearrangement are cited in the literature.[8]

H. REFERENCES

1. Hofmann, A. W. and Martius, C. A., *Ber.,* **1871**, *4*, 742.
2. (a) Magnus, P. and Turnbull, R., *Org. Lett.,* **2006**, *8*, 3497. (b) Anderson, L. L.; Arnold, J. and Bergman, R. G., *J. Am. Chem. Soc.,* **2005**, *127*, 14542. (c) Moehrle, H. and Schake, D., *Zeitsch. Naturforsch. B: Chem. Sci.,* **1995**, *50*, 1859. (d) Moehrle, H. and Schake, D., *Arch. Pharm.,* **1992**, *325*, 695. (e) Moehrle, H.; Schake, D. and Bluhme-Hensen, K., *Arch. Pharm.,* **1992**, *325*, 665. (f) Hori, M.; Kataoka, T.; Shimizu, H.; Hsu, C. F.; Hasegawa, Y. and Eyama, N., *J. Chem. Soc., Perkin Trans. I,* **1988**, 2271. (g) Rhee, E. S. and Shine, H. J., *J. Am. Chem. Soc.,* **1986**, *108*, 1000. (h) Wright, G. E., *J. Org. Chem.,* **1980**, *45*, 3128. (i) Johnston, T. P.; Shortnacy, A. T. and James, R. H., *J. Labelled Compd. Radiopharm.,* **1978**, *15* (Suppl. Vol.), 599. (j) Giumanini,

A. G.; Roveri, S. and Del Mazza, D., *J. Org. Chem.,* **1975**, *40*, 1677. (k) Grillot, G. F., *Mechanism Mol. Migration,* **1971**, *3*, 237. (l) Russell, G. J.; Topsom, R. D. and Vaughan, J., *Chem. Commun. (London),* **1965**, 529. (m) Bartok, M., *Acta Phys. Chem.,* **1963**, *9*, 131. (n) Archer, D. A. and Booth, H., *Chem. Ind. (London),* **1962**, 1570. (o) Dittmer, D. C. and Marcantonio, A. F., *Chem. Ind. (London),* **1960**, 1237. (p) Tsuboyama, K. and Yanagita, M., *Sci. Papers Inst. Phys. Chem. Res. (Jpn.),* **1959**, *53*, 329. (q) Thesing, J. and Mayer, H., *Ber.,* **1954**, *87*, 1084. (r) Okazaki, N., *Nippon Kagaku Kaishi*, **1941**, *62*, 52.

3. Hart, H. and Kosak, J. R., *J. Org. Chem.,* **1962**, *27*, 116.
4. (a) Banthorpe, D. V., *Chem. Rev.,* **1970**, *70*, 295. (b) Drumm, P. J.; O'Connor, W. F. and Reilly, J., *J. Am. Chem. Soc.,* **1940**, *62*, 1241.
5. Site, A. D., *J. Org. Chem.,* **1966**, *31*, 3413.
6. Ogata, Y. and Takagi, K., *J. Org. Chem.,* **1970**, *35*, 1642.
7. Grisdale, P. J.; Doty, J. C.; Regan, T. H. and Williams, J. L. R., *J. Org. Chem.,* **1967**, *32*, 2401.
8. (a) Siskos, M. G.; Tzerpos, N. and Zarkadis, A., *Bull. Soc. Chim. Belg.,* **1996**, *105*, 759. (b) Engman, L. and Persson, J., *Organometallics,* **1993**, *12*, 1068. (c) Burgoyne, W. F. and Dixon, D. D., *J. Mol. Catal.,* **1990**, *62*, 61. (d) Ogata, Y.; Tabuchi, H. and Yoshida, K., *Tetrahedron,* **1964**, *20*, 2717. (e) Dittmer, D. C. and Marcantonio, A. F., *J. Am. Chem. Soc.,* **1964**, *86*, 5621. (f) Fischer, A.; Topsom, R. D. and Vaughan, J., *J. Org. Chem.,* **1960**, *25*, 463. (g) Hurd, C. D. and Jenkins, W. W., *J. Org. Chem.,* **1957**, *22*, 1418. (h) Hart, H. and Kosak, J. R., *J. Org. Chem.,* **1957**, *22*, 1752. (i) Hughes, E. D. and Ingold, C. K., *Quart. Rev., Chem. Soc.,* **1952**, *6*, 34. (j) Howard, D., *J. Am. Chem. Soc.,* **1924**, *46*, 166. (k) Hofmann, A. W., *Ber.,* **1874**, *7*, 526. (l) Hofmann, A. W., *Ber.,* **1872**, *5*, 720. (m) Hofmann, A. W., *Ber.,* **1872**, *5*, 704.

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Hofmann-Sand Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Hofmann and Sand in 1900.[1] It is the reaction between mercuric salt (acetates, halides, nitrates, or sulfates) and compounds containing a carbon-carbon double bond in aqueous or alcoholic solutions to form either addition products or coordination complexes or both. In addition, the solvents also participate in this reaction causing hydrolysis or alcoholysis to give products containing hydroxyl or alkoxyl groups. The formed compounds characteristically decompose to regenerate the olefins in the presence of hydrochloric acid, often in only 5% concentration, except for the product of dibenzoyl derivative and mercurated 1,2-dihydrobenzofurans.[2] For example, 1-chloromercurimethyl-1,2-dihydrobenzofuran is perfectly stable in boiling acetic acid and does not decompose after standing in 15% hydrochloric acid or 50% sulfuric acid for several days at ordinary temperatures;[2b] in addition, the corresponding sulfate is even more stable to acids than chloride.[2b] The overall reaction outcome depends on the following factors:[3] the structure of olefin, the acidity of the solution, the anion in mercuric salt, and the temperature and the concentration of solution. For example, allyl alcohol usually gives an internal ether product.[2,4] In this reaction, the *trans*-olefin normally reacts more sluggishly than the *cis*-isomers,[5] by which unsymmetrical olefins give products with the mercury atom attaching to the carbon of fewer substituents[3] and the existing negative group hinders and may even prevent the reaction.[3] On the other hand, mercuric nitrate and acetate are the best salts for general use, and the reaction usually completes when the solution of the reactants no longer gives a precipitate of mercuric oxide with caustic alkali.[3] It should be pointed out that the Hofmann-Sand reaction occurs most readily in methanol solution in which even *trans*-olefins with negative groups attached would react.[6] In this reaction, the mercuric salt-olefin adducts are crystalline substances with relatively high thermal stability[3]—for

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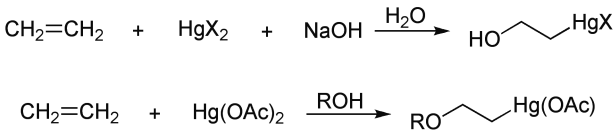
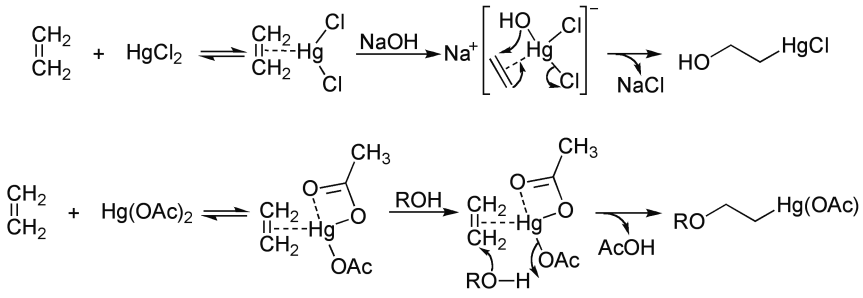
example, both *cis*- and *trans*-1-methoxy-2-(chlormercuri)-cyclohexanes can be distilled under vacuum without decomposition.[7] Except for their greater density, the mercurate salt-olefin adducts are typical organic compounds, which can further react with a variety of compounds.[3] Some of the reactions that the mercurate salt-olefin adducts undergo are (*a*) conversion into iodohydrin by treatment with iodine in KI solution,[2b] (*b*) reduction to alcohol by sodium amalgam,[3] (*c*) conversion into ether compound in 5% H_2SO_4,[8] (*d*) regeneration of olefin in aqueous solution of cyanides and thiocyanates,[1a] (*e*) conversion to sulfide from hydrogen sulfide,[1a,1b] (*f*) reaction with alkyl halide to form alkyl alcohol along with the evolution of the original olefin,[9] (*g*) liberation of olefin when reacting with Grignard reagent[5c] along with the isomerization of *cis*-olefin to *trans*-olefin,[10] and (*h*) formation of aldehyde when reacting with diazonium salt.[11]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Based on many experimental details, it is strongly believed that olefins form a coordination complex with mercuric salts in solution, which can decompose to release olefins again. As only 10 outer electrons are available for Hg^{2+}, the complexes from olefin and mercuric halides that do not have a stable 18-electron configuration require additional ligands of hydroxide in aqueous solution; for comparison, the complexes from olefin and mercuric acetate are stable because acetate is bidental. Olefin is activated as of coordination, so that the formation of an addition product is quite possible. A tentative mechanism is outlined here to show the dynamic equilibrium between the coordination complex and the addition product.



D. MODIFICATION

N/A

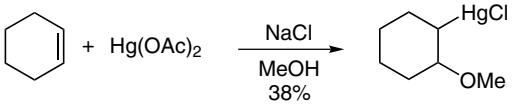
E. APPLICATIONS

This reaction is very useful for the determination of olefinic configuration and the conversion of *cis*-olefins into *trans*-olefins.

F. RELATED REACTIONS

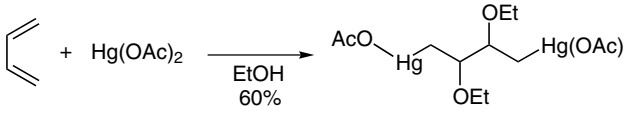
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

When 1.96 g cyclohexene (0.024 mol) and 3.19 g mercuric acetate (0.01 mol) were left to stand 11 days, a residue remained after 1 h of evaporation under 12 mmHg. This gummy residue was dissolved in 25 mL methanol. After 3 days, the solution was poured into dilute sodium chloride to yield 1.32 g α-1-chloromercuri-2-methoxycyclohexane, in a yield of 38%.



Reference 12.

Mercuric acetate (40 g; 0.125 mol) and 225 mL absolute ethanol were placed in a 500-mL filtering flask fitted with a large expansion bulb reaching nearly to the bottom of the flask. Gaseous 1,3-butadiene (0.067 mol) from the sulfone, or from a measured quantity of liquid butadiene in a test tube was introduced through the side tube of the filtering flask. The reaction mixture was shaken to facilitate absorption of the gas. After the absorption started, the flask was placed on a hot plate and maintained just below the boiling point of the ethanol. The mercuration can be carried out with good results at room temperature, but a longer time is required because the mercuric acetate dissolves quite slowly. When all of the butadiene had been absorbed, a test portion of the solution was withdrawn and made alkaline with aqueous sodium hydroxide. If a yellow precipitate of mercuric oxide formed, a small additional quantity of butadiene was introduced, and the absorption process continued until the sodium hydroxide test was negative. The mercuration mixture was allowed to cool

to 20°C, and the crystals of the less soluble product (α-isomer) were filtered with suction and washed twice with ether. The first crop of crystals weighed 20–23 g. The filtrate and washings were subjected to distillation on a steam bath until most of the alcohol had been removed. The residue was filtered when cold, and the filtrate was reserved for isolation of the more soluble product (β-isomer). The second crop of crystals of the α-isomer was washed with ether and combined with the first crop, giving a total amount of 25 g α-isomer (60% yield, based on mercuric acetate). The product formed colorless crystals from ethanol, m.p. 162–163°C.

Other references related to the Hofmann-Sand reaction are cited in the literature.[13]

H. REFERENCES

1. (a) Hofmann, K. A. and Sand, J., *Ber.,* **1900**, *33*, 1340. (b) Hofmann, K. A. and Sand, J., *Ber.,* **1900**, *33*, 1353. (c) Hofmann, K. A. and Sand, J., *Ber.,* **1900**, *33*, 2692.
2. (a) Mills, L. E. and Adams, R., *J. Am. Chem. Soc.,* **1923**, *45*, 1842. (b) Adams, R.; Roman, F. L. and Sperry, W. N., *J. Am. Chem. Soc.,* **1922**, *44*, 1781.
3. Chatt, J., *Chem. Rev.,* **1951**, *48*, 7.
4. Sand, J. and Singer, F., *Ann.,* **1903**, *329*, 166.
5. (a) Birks, A. M. and Wright, G. F., *J. Am. Chem. Soc.,* **1940**, *62*, 2412. (b) Brown, W. H. and Wright, G. F., *J. Am. Chem. Soc.,* **1940**, *62*, 1991. (c) Wright, G. F., *J. Am. Chem. Soc.,* **1935**, *57*, 1993.
6. (a) Sandborn, L. T. and Marvel, C. S., *J. Am. Chem. Soc.,* **1926**, *48*, 1409. (b) Schrauth, W.; Schoeller, W. and Struensee, R., *Ber.,* **1910**, *43*, 695.
7. Romeyn, J. and Wright, G. F., *J. Am. Chem. Soc.,* **1947**, *69*, 697.
8. Sand, J., *Ann.,* **1903**, *329*, 135.
9. (a) Manchot, W. and Klüg, A., *Ann.,* **1920**, *420*, 170. (b) Sand, J., *Ber.,* **1901**, *34*, 2906.
10. Downing, D. C. and Wright, G. F., *J. Am. Chem. Soc.,* **1946**, *68*, 141.
11. Freidlina, R. Kh.; Nesmeyanov, A. N. and Takareva, F. A., *Ber.,* **1936**, *69*, 2019.
12. Johnson, J. R.; Jobling, W. H. and Bodamer, G. W., *J. Am. Chem. Soc.,* **1941**, *63*, 131.
13. (a) Kitching, W., *Organomet. Chem. Rev.,* **1968**, *3*, 35. (b) Lucas, H. J.; Hepner, F. R. and Winstein, S., *J. Am. Chem. Soc.,* **1939**, *61*, 3102. (c) van Loon, E. J. and Carter, H. E., *J. Am. Chem. Soc.,* **1937**, *59*, 2555. (d) Nesmeyanov, A. N. and Freidlina, R. C., *Ber.,* **1936**, *69B*, 1631. (e) Griffith, E. and Marvel, C. S., *J. Am. Chem. Soc.,* **1931**, *53*, 789. (f) Middleton, E. B., *J. Am. Chem. Soc.,* **1923**, *45*, 2763. (g) Sand, J. and Brenst, F., *Z. Physik. Chem*., **1907**, *59*, 424. (h) Sand, J., *Ber.,* **1901**, *34*, 1385. (i) Sand, J., *Ber.,* **1901**, *34*, 2910.

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Hooker Oxidation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Hooker in 1936.[1] It is the oxidation of 2-hydroxy-3-alkyl (or alkenyl)-1,4-benzoquinones into its homologs with alternated hydroxy and alkyl groups of one less carbon by alkaline permanganate or the combination of hydrogen peroxide and sodium carbonate. Therefore, it is generally known as the Hooker oxidation.[2] This reaction is known to occur through at least three stages:[2d] initial cleavage of the C=C bond to form aromatics with keto acid and ketyl side chains, subsequent *Aldol Condensation* of an activated methylene group to a neighboring keto acid to form a six-membered ring, further decarboxylation and aromatization resulting in 1,4-hydroquinone with alternated hydroxy and alkyl groups of one less carbon, and the final oxidation of 1,4-benzohydroquinones into 1,4-benzoquinones. This mechanism has been proved either by comparison of oxidized derivatives with different substituents (e.g., Br)[2e] or isotopic labeling.[2a] It has been suggested that for the oxidation of quinones with saturated side chains a rather strong alkaline solution is required, and the reaction is normally conducted at 0–5°C by quickly mixing the solution of hydroxyquinone in 1% alkali and potassium permanganate in 10% alkali.[3] This reaction usually gives very pure products with yields generally in the range of 70–80%. In addition, in some cases, the yield is even better if the reaction is conducted in more concentrated alkali solution.[3] However, the oxidation of those benzoquinone with unsaturated side chains requires a much less strong alkaline medium—for example, using aqueous potassium permanganate without alkali—and gives much lower yields, in the range of 35–40% or even lower.[3] This reaction can be repeated until the side alkyl chain is completely cut off.[3] This reaction is a valuable tool for the preparation of substances that might otherwise be difficult to make and is also useful for the determination of the side chains of benzoquinones.[3]

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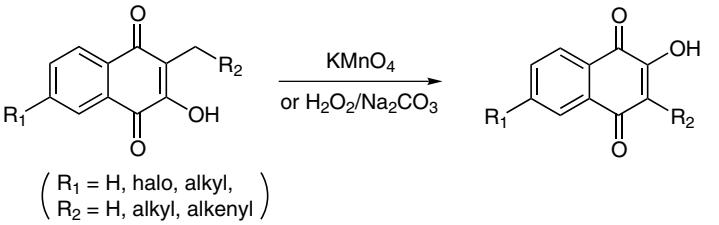
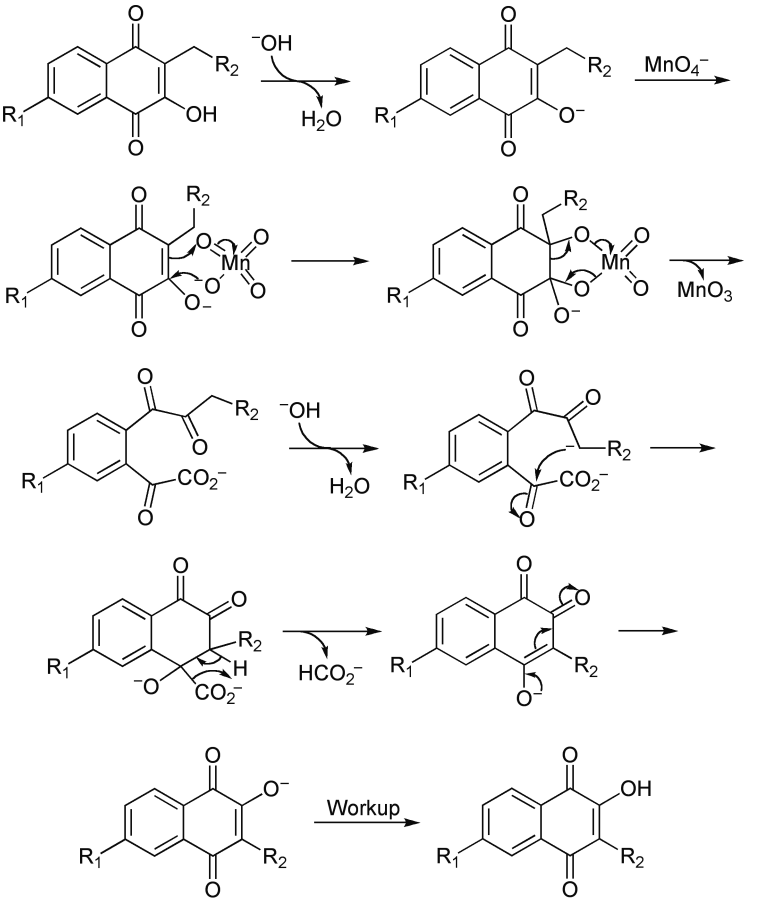
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified using alkaline hydrogen peroxide as an oxidant.

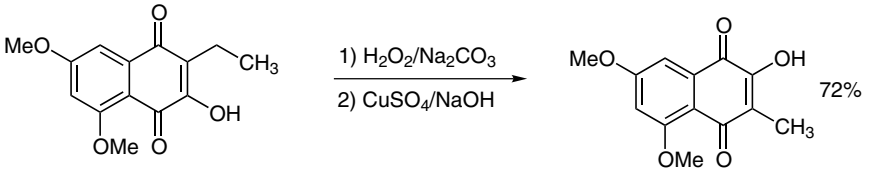
E. APPLICATIONS

This reaction is useful for the structural determination of hydroxy quinone, and in the preparation of some quinone derivatives that might be difficult to make.

F. RELATED REACTIONS

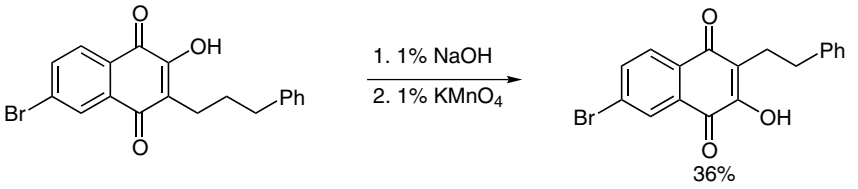
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 2a.

To a 50-mL round-bottomed flask charged with 1.5 mL dioxane, 1.5 mL H_2O, and 64 mg Na_2CO_3 (0.6 mmol) was added 131 mg 2-ethyl-3-hydroxy-5,7-dimethoxy-1,4-naphthoquinone (0.5 mmol). The resulting burgundy colored mixture was heated with H_2O_2 (30%, 0.2 mL) at 60°C until the solution became colorless to pale yellow. Upon cooling in ice bath, the reaction mixture was treated with 5 drops 36% HCl and H_2O saturated with SO_2. A stream of nitrogen was then bubbled through the solution for 30 min. Next, the mixture was treated with 1 mL 25% NaOH solution and a solution containing 0.5 g $CuSO_4$ (3 mmol) in 4 mL H_2O; the mixture was heated at 70°C until the starting blue solution became red in color (∼ 1 h). The solid components were removed by vacuum filtration through a pad of Celite. The filtrate was then treated with conc. HC1, resulting in a yellow solution (pH 1–2). Extraction with $CHC1_3$ (3 × 50 mL) was followed by a back washing of the aqueous layer with $CHCl_3$ (2 × 25 mL). The combined organic portions were washed with 10 mL brine, dried over $MgSO_4$, and concentrated in vacuo. Flash column chromatography (3:l, hexanes/EtOAc) gave 89 mg 2-hydroxy-5,7-dimethoxy-3-methyl-1,4-naphthoquinone as a yellow solid, m.p. 223–225°C.



Reference 2e.

A solution of 3.0 g 2-hydroxy-3-(γ-phenyl)propyl-6-bromo-1,4-naphthoquinone in the required amount of benzene was stirred in 600 mL hot 1% NaOH solution, and the red solution was cooled to 0°C and treated with 189 mL 1% $KMnO_4$ also at 0°C. The solution becoming practically colorless (spot test) and then reaching a maximum intensity of red in 1 to 2 h. The yield of precipitated, nearly pure material was 36%. Crystallization from alcohol containing acetic acid afforded 3-hydroxy-2-(β-phenyl)ethyl-6-bromo-1,4-naphthoquinone as golden yellow needles, m.p. 173–175°C.

Other references related to the Hooker oxidation are cited in the literature.[4]

H. REFERENCES

1. Hooker, S. C., *J. Am. Chem. Soc.,* **1936**, *58*, 1163.
2. (a) Lee, K.; Turnbull, P. and Moore, H. W., *J. Org. Chem.,* **1995**, *60*, 461. (b) Pratt, Y. T. and Drake, N. L., *J. Am. Chem. Soc.,* **1957**, *79*, 5024. (c) Pratt, Y. T. and Drake, N. L., *J. Am. Chem. Soc.,* **1955**, *77*, 4664. (d) Fieser, L. F. and Fieser, M., *J. Am. Chem. Soc.,* **1948**, *70*, 3215. (e) Fieser, L. F.; Hartwell, J. L. and Seligman, A. M., *J. Am.* Chem. Soc.,**1936**, *58*, 1223.
3. Hooker, S. C., *J. Am. Chem. Soc.,* **1936**, 58, 1174.
4. (a) Spyroudis, S., *Molecules,* **2000**, *5*, 1291. (b) Lee, K. H. and Moore, H. W., *Tetrahedron Lett.,* **1993**, *34*, 235. (c) Otten, S. and Rosazza, J. P., *Appl. Environ. Microbio.,* **1978**, *35*, 554. (d) Elwood, T. A.; Dudley, K. H.; Tesarek, J. M.; Rogerson, P. F. and Bursey, M. M., *Org. Mass Spectr.,* **1970**, *3*, 841. (e) Fieser, L. F. and Bader, A. R., *J. Am. Chem. Soc.,* **1951**, *73*, 681. (f) Hooker, S. C. and Steyermark, Al., *J. Am. Chem. Soc.,* **1936**, *58*, 1179.

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Horenstein-Pählicke Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Horenstein and Pählicke in 1938.[1] It is the reaction between substituted aryl carboxylic acid and *N*,*N*-dialkylamino alkyl halide to give a corresponding *N*,*N*-dialkylaminoalkyl arylcarboxylate hydrochloride,[2] specifically for the preparation of a group of molecules with anesthetic activity.[3] Therefore, this reaction is often known as the Horenstein-Pählicke reaction.[2b,4] In addition, it is also referred to as the Horenstein-Pählicke process[5] or Horenstein-Pählicke condensation.[2a] Under these reaction conditions, the common self-condensation of *N*,*N*-dialkylamino alkyl halides[4c] is minimized. Often, the aryl carboxylic acid, such as 2-hydroxy-4-nitrobenzoic acid, is refluxed with *N*,*N*-diakylamino alkyl chloride in isopropanol in the presence of a base (e.g., K_2CO_3). However, the protection of hydroxyl group by a benzyl other than acetyl will increase the yield.[2b] In addition, it has been found that the reaction in butanol will give a higher yield than that in isopropanol and the direct reaction between aryl carboxylic acid and alkyl halide will give even higher yields.[6] This reaction works mainly for primary alkyl halides and is not good for secondary alkyl halides, such as 1-methyl-3-chloro-pyrrolidine.[6] Besides the alcoholic solvent, this reaction is often carried out in dry toluene under basic conditions.[4c,7]

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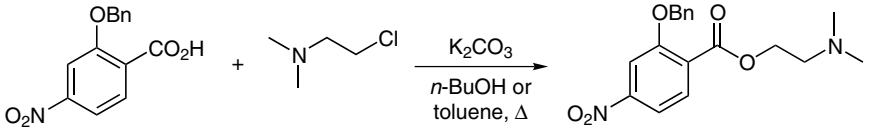
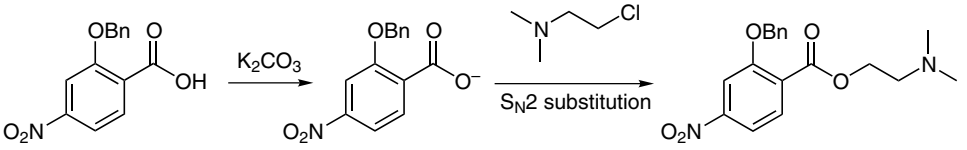
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified to occur in sodium-dried toluene.[7]

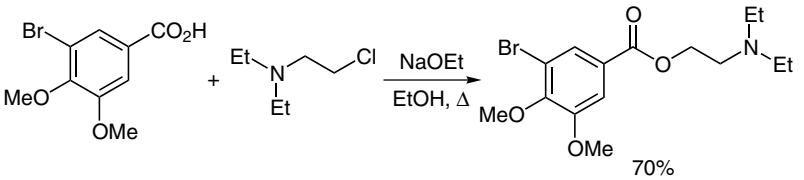
E. APPLICATIONS

This reaction is specifically used for the preparation of *N*,*N*-dialkyl alkyl arylcarboxylates.

F. RELATED REACTIONS

N/A

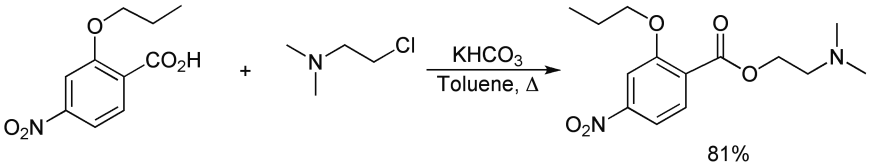
G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

To 150 mL absolute ethanol containing 3.3 g clean, freshly cut sodium (0.15 mol) was added, with stirring, 13 g 5-bromomethylvanillic acid (0.05 mol). The mixture was

then stirred and refluxed for 30 min. After the mixture was cooled to room temperature, the salt was filtered off, washed with absolute ethanol, and allowed to dry. The dried salt was then suspended in 200 mL sodium-dried toluene and treated with 8.5 g β-diethylaminochloroethane hydrochloride (0.05 mol). The mixture was then stirred and refluxed for 18–20 h. The hot mixture was then filtered. On cooling, the filtrate was washed with 10% NaOH (2 × 75 mL) followed by water. The toluene layer of the basic ester was then dried for several hours over $MgSO_4$. Anhydrous HCl was then bubbled through the toluene solution until salt formation was complete. The product was filtered, allowed to dry in a desiccator, and then recrystallized from a mixture of absolute ethanol and anhydrous ether, to give 70% of a water-soluble product, which melted at 164–165°C.



Reference 4c.

A mixture of 22.5 g 4-nitro-2-*n*-propoxy benzoic acid (0.10 mol), 11.0 g $KHCO_3$, and 400 mL dry toluene was stirred and refluxed under a water trap until dehydration was complete (~ 2 h). The water trap was removed, and 12.9 g 2-dimethylaminoethyl chloride (0.12 mol) was added. Stirring and refluxing were continued for 20 h. The mixture was filtered while hot, and the filter cake was washed well with hot toluene. The toluene was removed from the combined filtrates in vacuo and the residual oil was dissolved in dilute hydrochloric acid. After decolorization, the solution was treated with solid K_2CO_3, and the liberated base was taken up in EtOAc. After drying over Drierite, EtOAc was evaporated in vacuo and 24.0 g 2-dimethylaminoethyl 4-nitro-2-*n*-propoxy benzoate was obtained as oil, in a yield of 81%.

Other references related to the Horensetin-Pählicke reaction are cited in the literature.[8]

H. REFERENCES

1. Horenstein, H. and Pählicke, H., *Ber.,* **1938**, *71*, 1644.
2. (a) Steinberg, E.; Conrad, G. A. and Ruddy, A. W., *J. Am. Chem. Soc.,* **1954**, *76*, 5445. (b) Clinton, R. O.; Laskowski, S. C.; Salvador, U. J. and Wilson, M., *J. Am. Chem. Soc.,* **1951**, *73*, 3674.
3. Rabjohn, N. and Mendel, A., *J. Org. Chem.,* **1956**, *21*, 218.
4. (a) Clinton, R. O.; Laskowski, S. C.; Salvador, U. J. and Carroll, P. M., *J. Am. Chem. Soc.,* **1957**, *79*, 2290. (b) Clinton, R. O. and Laskowski, S. C., *J. Am. Chem. Soc.,* **1952**, *74*, 2226. (c) Clinton, R. O.; Salvador, U. J.; Laskowski, S. C. and Wilson, M., *J. Am. Chem. Soc.,* **1952**, *74*, 592.
5. Blicke, F. F. and Lu, C.-J., *J. Am. Chem. Soc.,* **1955**, *77*, 29.
6. Wu, Y.-H.; Feldkamp, R. F.; Corrigan, J. R. and Rhodes, H. J., *J. Org. Chem.,* **1961**, *26*, 1524.
7. Perry, R. P.; Jones, D. C. and Pratt, C., *J. Am. Chem. Soc.,* **1956**, *78*, 3403.
8. (a) Craig, P. N.; Witt, I. H.; Macko, E.; Dacanay, J. G.; Fellows, E. J. and Ullyot, G. E., *J. Am. Chem. Soc.,* **1951**, *73*, 1339. (b) Cusic, J. W. and Robinson, R. A., *J. Org. Chem.,* **1951**, *16*, 1921. (c) Murphy, H. W. and Jenkins, G. L., *J. Am. Pharm. Assoc.,* **1943**, *32*, 83.

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Horner-Wadsworth-Emmons Olefination

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Horner et al. in 1958[1] and subsequently modified by Wadsworth and Emmons in 1961.[2] In fact, it is the further modification of the *Wittig Reaction*.[3] The Horner-Wadsworth-Emmons (HWE) olefination is the synthesis of olefins from the condensation between carbonyl compounds (both aldehydes and ketones) and carboanions derived from alkyl phosphine oxides (Horner's condition),[1] phosphonates (Wadsworth and Emmons's condition),[2] phosphonamides (Corey),[4] and their thiono counterparts (Corey).[5] All these reaction conditions have obvious advantages over the original *Wittig Reaction*, such as the higher nucleophilicity and the basicity of phosphonate-stablized carbanion compared to the corresponding phosphonium ylides and the easy removal of dialkylphosphate salt (by-product of this reaction) by simple aqueous extraction. Historically, this reaction has been known as the Horner-Wadsworth-Emmons reaction (HWE reaction),[6,7] Horner-Wadsworth-Emmons olefination (HWE olefination),[8,9] Horner-Wadsworth-Emmons condensation,[6k,10] Horner-Wadsworth-Emmons coupling,[11] Horner-Wadsworth-Emmons homologation,[12] etc. The starting materials of dialkyl phosphonates can be prepared by the *Michaelis-Arbuzov Rearrangement*,[13] *Michaelis-Becker Reaction*,[14] acylation of alkyl phosphonate anion,[15] and phosphonate ester interchange.[16] In this reaction, the rate-determining step is the addition of phosphonate anion into the carbonyl group,[17] where the carbanion-stabilizing group is necessary for the elimination to occur;[5] otherwise, the β-hydroxyphosphonates form from the nonstabilized phosphonates.[18] During the elimination, both *Z*-olefins and *E*-olefins are possible, and the ratio depends on the stereochemical outcome of the initial addition and the ability of the intermediate to equilibrate. Generally speaking, for disubstituted olefins (from aldehydes), the $E : Z$ ratio increases when the reversibility of the nucleophilic addition increases (i.e., increasing of the retroaddition rate relative to the rate of elimination).[19] Other conditions that favor the

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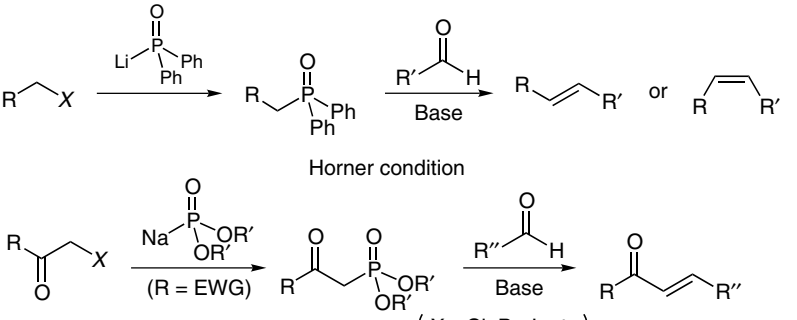
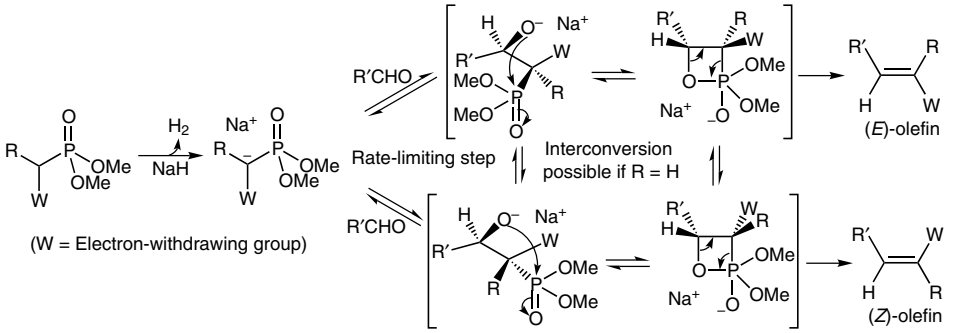
E-selectivity are: bulky phosphonate and ester substituents,[20] substitution solvent of THF with DME, higher reaction temperature, increased α-substitution of the aldehyde, and a cation order of $Li^+ > Na^+ > K^+$. For comparison, the trisubstituted olefins can be synthesized either from the α-branched phosphonates with aldehyde or phosphonates with ketones. Some hindered ketones do not undergo the original *Wittig Reaction* but do take place for the HWE olefination.[21] On the other hand, the HWE olefination is normally performed in the presence of a relatively strong base such as *n*-BuLi, KOBu^t, or NaH;[22] therefore, this reaction is complicated by the *Aldol Condensation*[6k,22] or other reactions that aldehydes and ketones normally undergo under such conditions. Therefore, Masamune and Roush introduced mild conditions (LiCl, amine base, ambient temperature) for the olefination of base-sensitive substrates or phosphonates.[23] In addition, Ando improved the condition to enhance the *Z*-selectivity by using a combination of NaI/DBU/THF.[6e,6h,22,24] Similarly, Still and Gennari reported the synthesis of trisubstituted olefins with high *Z*-selectivity from methyl [bis(trifluoroethyl)phosphono]propionate in THF in the presence of KHMDS/18-crown-6.[16a] Further modifications on this reaction include the application of chiral phosphonates (phosphonamides),[25] parallel kinetic resolution according to the difference in rates of enantiomeric aldehydes,[6c] control of the 1,4-asymmetric addition and 1,2-addition to α,β-unsaturated carbonyl compounds,[26] and synthesis of tetrahydrofuran and pyran derivatives.[27] This reaction has successfully been applied to the preparation of some macrolides, including (-)-Vermiculine,[28] (-)-Asperdiol,[29] Amphotericin B[30] FR182877,[31] and dactylolide.[32] This reaction has been extensively reviewed.[13,18,33]

B. GENERAL REACTION SCHEME

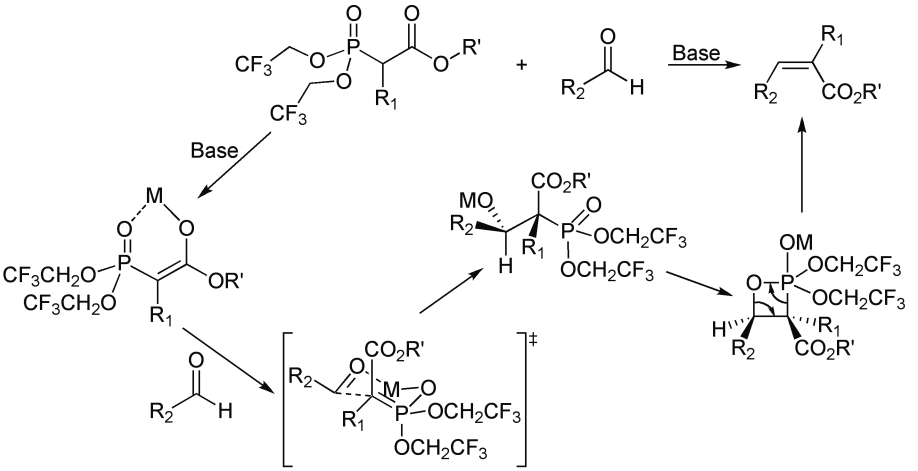


C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified to occur under mild conditions such as those of Masamune and Roush, Still, and Ando. In addition, chiral phosphonates (or phosphonamides) have been used for this reaction. In particular, the method developed by Still and Gennari using [bis(trifluoroethyl)phosphono] esters, generally known as Gennari-Still phosphonates,[34] is very useful in the preparation of *Z*-olefins.[16a] Illustrated is the HWE reaction using Gennari-Still phosphonates to give *cis*-olefins, and its mechanism.



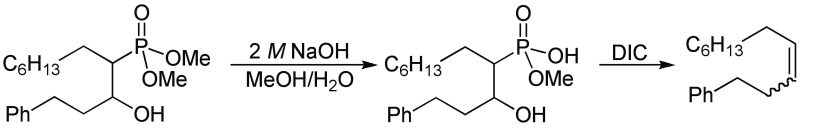
E. APPLICATIONS

This reaction has very wide application in the synthesis of compounds containing carbon-carbon double bond(s).

F. RELATED REACTIONS

This reaction is closely related to *Wittig Reaction*. This reaction is also related to *Peterson Reaction* and *Tebbe Reaction.*

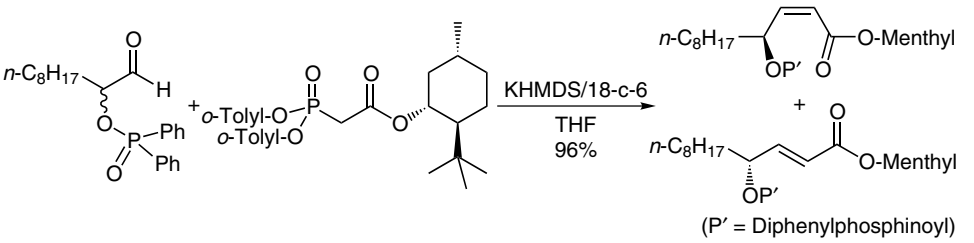
G. CITED EXPERIMENTAL EXAMPLES



Reference 35.

To a solution of 1.1 mmol [1-(1-hydroxy-3-phenyl-propyl)-octyl]-phosphonic acid dimethyl ester in 5.0 mL methanol was added 5.0 mL 4 M NaOH. After being stirred at room temperature for 16 h, the reaction mixture was acidified to pH < 2 with 1 M HCl, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated in vacuo. The reaction residue

was dissolved in 5.0 mL $CHCl_3$ and treated with 2.2 mmol diisopropylcarbodiimide. After being stirred at room temperature for 4 h, the reaction mixture was concentrated in vacuo. Purification of the residue by flash chromatography (SiO_2, hexane) afforded 99.0 mg 1-phenyl-3-undecene (0.382 mmol) as a colorless oil, $R_f = 0.65$ (hexane).



Reference 36.

To a solution of phosphonate (1.0 eq. 0.02 M in THF) and 18-crown-6 (5 eq.), precooled to -78°C, was added KHMDS (1.0 eq.) under argon. The mixture was stirred for 30 min and then transferred via cannula to a precooled solution of 1.1–2.2 eq. of 2-diphenylphosphinoyloxy-n-deca-aldehyde. The mixture was stirred at -78°C under argon for 3 h, whereafter a 1 M solution of acetic acid in methanol was added. After the mixture was stirred for 5 min more, phosphate buffer at pH 7 was added, and the mixture was allowed to warm to room temperature. Extraction with EtOAc afforded a crude mixture that was purified by flash chromatography (twice; 20–25% EtOAc in hexanes) to give (1′*R*,2′*S*,5′*R*)-8–phenylmenthyl (2*Z*,4*S*)-4-diphenyl-phosphinoyloxy-2-dodecenoate and (1′*R*,2′*S*,5′*R*)-8′-phenylmenthyl (2*E*,4*R*)-4-diphenylphosphinoyloxy-2-dodecenoate, both as a colorless oil, in a combined yield of 96%.

Other references related to the Horner-Wadsworth-Emmons olefination[37] and to the Still-Gennari modification[38] are cited in the corresponding literature.

H. REFERENCES

1. Horner, L.; Hoffmann, H. M. R. and Wippel, H. G., *Ber.,* **1958**, *91*, 61.
2. Wadsworth, W. S. and Emmons, W. D., *J. Am. Chem. Soc.,* **1961**, *83*, 1733.
3. Wittig, G. and Geissler, G., *Ann.,* **1953**, *580*, 44.
4. (a) Corey, E. J. and Cane, D. E., *J. Org. Chem.,* **1969**, *34*, 3053. (b) Corey, E. J. and Kwiatkowski, G. T., *J. Am. Chem. Soc.* **1968**, *90*, 6816. (c) Corey, E. J. and Kwiatkowski, G. T., *J. Am. Chem. Soc.,* **1966**, *88*, 5652. (d) Corey, E. J. and Kwiatkowski, G. T., *J. Am. Chem. Soc.* **1966**, *88*, 5653.
5. Corey, E. J. and Kwiatkowski, G. T., *J. Am. Chem. Soc.,* **1966**, *88*, 5654.
6. (a) Díez-Barra, E.; Carcía-Martínez, J. C. and Rodríguez-López, J., *J. Org. Chem.,* **2003**, *68*, 832. (b) Simoni, D.; Rossi, M.; Rondanin, R.; Mazzali, A.; Baruchello, R.; Malagutti, C.; Roberti, M. and Invidiata, F. P., *Org. Lett.,* **2000**, *2*, 3765. (c) Pedersen, T. M.; Jensen, J. F.; Humble, R. E.; Rein, T.; Tanner, D.; Bodmann, K. and Reiser, O., *Org. Lett.,* **2000**, *2*, 535. (d) Norrby, P.-O.; Brandt, P. and Rein, T., *J. Org. Chem.,* **1999**, *64*, 5845. (e) Ando, K., *J. Org. Chem.,* **1998**, *63*, 8411. (f) Tullis, J. S.; Vares, L.; Kann, N.; Norrby, P.-O. and Rein, T., *J. Org. Chem.,* **1998**, *63*, 8284. (g) Brandt, P.; Norrby, P.-O.; Martin, I. and Rein, T., *J. Org. Chem.,* **1998**, *63*, 1280. (h) Sano, S.; Ando, T.; Yokoyama, K. and Nagao, Y., *Synlett*, **1998**, *7*, 777. (i) Tsai, H.-J.; Thenap-

pan, A. and Burton, D. J., *J. Org. Chem.,* **1994**, *59*, 7085. (j) Meanwell, N. A.; Roth, H. R.; Smith, E. C. R.; Wedding, D. L. and Wright, J. J. K., *J. Org. Chem.,* **1991**, *56*, 6897. (k) Hammond, G. B.; Cox, M. B. and Wiemer, D. F., *J. Org. Chem.,* **1990**, *55*, 128.

7. (a) Gester, S.; Pietzsch, J. and Wuest, F. R., *J. Labelled Compd. Radiopharm.,* **2007**, *50*, 105. (b) Yao, H. Q.; Gao, Y.; Liu, P.; Sun, B. F. and Xu, X. X., *Synlett*, **2007**, 571. (c) Sano, S.; Abe, S.; Azetsu, T.; Nakao, M.; Shiro, M. and Nagao, Y., *Lett. Org. Chem.,* **2006**, *3*, 798. (d) Schauer, D. J. and Helquist, P., *Synthesis*, **2006**, 3654. (e) Gottschling, S. E.; Krasik, P. and Levin, D., *Org. Proc. Res. Dev.,* **2006**, *10*, 1296. (f) Etayo, P.; Badorrey, R.; Diaz-de-Villegas, M. D. and Galvez, J. A., *Chem. Commun.,* **2006**, 3420. (g) Hernandez-Fernandez, E.; Fernandez-Zertuche, M.; Garcia-Barradas, O.; Munoz-Muniz, O. and Ordonez, M., *Synlett*, **2006**, 440. (h) Katayama, M.; Nagase, R.; Mitarai, K.; Misaki, T. and Tanabe, Y., *Synlett*, **2006**, 129. (i) Mulzer, J.; Sieg, A.; Bruecher, C.; Mueller, D. and Martin, H. J., *Synlett*, **2005**, 685. (j) Cativiela, C.; Diaz-De-Villegas, M. D.; Gilvez, J. A. and Su, G. F., *ARKIVOC,* **2004**, (*iv*), 59. (k) Inagaki, H.; Takeda, T.; Miyauchi, R. N.; Kawakami, K.; Takahashi, H. and Takemura, M., *Heterocycles*, **2004**, *63*, 699. (l) Weber, C.; Bielik, A.; Szendrei, G. I.; Keseru, G. M. and Greiner, I., *Bioorg. Med. Chem. Lett.,* **2004**, *14*, 1279. (m) Sano, S.; Takemoto, Y. and Nagao, Y., *Tetrahedron Lett*., **2003**, *44*, 8853. (n) Sano, S.; Takemoto, Y. and Nagao, Y., *ARKIVOC,* **2003**, (*viii*), 93. (o) Huang, X. and Xiong, Z.-C., *Chem. Commun.,* **2003**, 1714. (p) Harrison, J. R. and Moody, C. J., *Tetrahedron Lett*., **2003**, *44*, 5189. (q) Sano, S.; Teranishi, R.; Nakano, F.; In, K.; Takeshige, H.; Ishii, T.; Shiro, M. and Nagao, Y., *Heterocycles*, **2003**, *59*, 793. (r) Comins, D. L. and Ollinger, C. G., *Tetrahedron Lett*., **2001**, *42*, 4115. (s) Tanaka, K.; Ohta, Y.; Fuji, K. and Taga, T., *Tetrahedron Lett*., **1993**, *34*, 4071.
8. (a) Taillier, C.; Gille, B.; Bellosta, V. and Cossy, J., *J. Org. Chem.,* **2005**, *70*, 2097. (b) Taillier, C.; Bellosta, V. and Cossy, J., *Org. Lett.,* **2004**, *6*, 2149. (c) Teichert, A.; Jantos, K.; Harms, K. and Studer, A., *Org. Lett.,* **2004**, *6*, 3477. (d) Inoue, H.; Nagaoka, Y. and Tomioka, K., *J. Org. Chem.,* **2002**, *67*, 5864. (e) Aggarwal, V. K.; Roseblade, S. J.; Barrell, J. K. and Alexander, R., *Org. Lett.,* **2002**, *4*, 1227. (f) Poigny, S.; Nouri, S.; Chiaroni, A.; Guyot, M. and Samadi, M., *J. Org. Chem.,* **2001**, 66,7263. (g) Groth, T. and Meldal, M., *J. Comb. Chem.,* **2001**, 3,34. (h) Kawasaki, T.; Nonaka, Y.; Watanabe, K.; Ogawa, A.; Higuchi, K.; Terashima, R.; Masuda, K. and Sakamoto, M., *J. Org. Chem.,* **2001**, 66,1200. (i) Groth, T. and Meldal, M., *J. Comb. Chem.,* **2001**, 3,45.
9. (a) Kotkar, S. P.; Chavan, V. B. and Sudalai, A., *Org. Lett.,* **2007**, *9*, 1001. (b) Seo, S.-Y.; Jung, J.-K.; Paek, S.-M.; Lee, Y.-S.; Kim, S.-H. and Suh, Y.-G., *Tetrahedron Lett*., **2006**, *47*, 6527. (c) Molander, G. A. and Figueroa, R., *J. Org. Chem.,* **2006**, *71*, 6135. (d) Quesada, E. and Taylor, R. J. K., *Synthesis*, **2005**, 3193. (e) Blasdel, L. K. and Myers, A. G., *Org. Lett.,* **2005**, *7*, 4281. (f) Touchard, F. P., *Eur. J. Org. Chem.,* **2005**, 1790. (g) Touchard, F. P.; Capelle, N. and Mercier, M., *Adv. Synth. Catal.,* **2005**, *347*, 707. (h) Davis, R.; Abraham, S.; Rath, N. P. and Das, S., *New J. Chem.,* **2004**, *28*, 1368. (i) Xu, C. F. and Yuan, C. Y., *Synthesis,* **2004**, 2449. (j) Touchard, F. P., *Tetrahedron Lett*., **2004**, *45*, 5519. (k) Pihko, P. M. and Salo, T. M., *Tetrahedron Lett*., **2003**, *44*, 4361. (l) Nagaoka, Y.; Inoue, H. and Tomioka, K., *Phosphorus, Sulfur & Silicon & Related Elements,* **2002**, *177*, 1843. (m) Reddy, A. M.; Gopal, V. R. and Rao, V. J., *Indian J. Chem., Sect. B,* **1996**, 35*B*, 312. (n) Pipelier, M.; Ermolenko, M. S.; Zampella, A.; Olesker, A. and Lukacs, G., *Synlett*, **1996**, 24. (o) Bonadies, F.; Cardilli, A.; Lattanzi, A.; Pesci, S. and Scettri, A., *Tetrahedron Lett*., **1995**, *36*, 2839. (p) Janecki, T.; Bodalski, R.; Wieczorek, M. and Bujacz, G., *Tetrahedron*, **1995**, *51*, 1721. (q) Bonadies, F.; Cardilli, A.; Lattanzi, A.; Orelli, L. R. and Scettri, A., *Tetrahedron Lett*., **1994**, *35*, 3383. (r) Koskinen, A. M. P. and Koskinen, P. M., *Synlett*, **1993**, 501.
10. (a) Chu, Q. H.; Pang, Y.; Ding, L. M. and Karasz, F. E., *Macromolecules,* **2003**, *36*, 3848. (b) Chen, X. M. and Wiemer, D. F., *J. Org. Chem.,* **2003**, *68*, 6597. (c) Sanders, T. C.; Golen, J. A.; Williard, P. G. and Hammond, G. B., *J. Fluor. Chem.,* **1997**, *85*, 173. (d) Lee, K.; Jackson, J. A. and Wiemer, D. F., *J. Org. Chem.,* **1993**, *58*, 5967. (e) Hammond, G. B.; Cox, M. B. and Wiemer, D. F., *J. Org. Chem.,* **1990**, *55*, 128.

11. (a) Reichwein, J. F. and Pagenkopf, B. L., *J. Org. Chem.,* **2003**, *68*, 1459. (b) Nicolaou, K. C.; Li, Y. W.; Sugita, K.; Monenschein, H.; Guntupalli, P.; Mitchell, H. J.; Fylaktakidou, K. C.; Vourloumis, D.; Giannakakou, P. and O'Brate, A., *J. Am. Chem. Soc.,* **2003**, *125*, 15443. (c) Nesnas, N.; Rando, R. R. and Nakanishi, K., *Tetrahedron,* **2002**, *58*, 6577.
12. Singh, R. P. and Singh, V. K., *J. Org. Chem.,* **2004**, *69*, 3425.
13. (a) Bhattacharya, A. K. and Thyagarajan, G., *Chem. Rev.,* **1981**, *81*, 415. (b) Arbusov, A. E. and Durin, A. A., *J. Russ. Phys. Chem. Soc.,* **1914**, *46*, 295.
14. Kosolapoff, G. M., *J. Am. Chem. Soc.,* **1946**, *68*, 1103.
15. Mathey, F. and Savignac, P., *Tetrahedron,* **1978**, *34*, 649.
16. (a) Still, W. C. and Gennari, C., *Tetrahedron, Lett.,* **1983**, *24*, 4405. (b) Bodnarchuk, N. D.; Malovik, V. V. and Derkach, G. I., *Zh. Obsh Khim.,* **1970**, *40*, 1210.
17. Larsen, R. O. and Aksnes, G., *Phosphorus Sulfur,* **1983**, *15*, 219.
18. (a) Nicalaou, K. C.; Harter, M. W.; Gunzner, J. L. and Nadin, A., *Liebigs Ann. Recl.,* **1997**, 1283. (b) Wadsworth, W. A., *Org. React.,* **1977**, *25*, 73. (c) Boutagy, J. and Thomas, R., *Chem. Rev.,* **1974**, *74*, 87.
19. Thompson, S. K. and Heathcock, C. H., *J. Org. Chem.,* **1990**, *55*, 3386.
20. Nagaoka, H. and Kishi, Y., *Tetrahedron,* **1981**, *37*, 3873.
21. (a) Mulzer, J.; Steffin, U.; Zorn, L.; Schneider, C.; Weinhold, E.; Münch, W.; Rudert, R.; Luger, P. and Hartl, H., *J. Am. Chem. Soc.,* **1988**, *110*, 4640. (b) Tadano, K.; Idogaki, Y.; Yamada, H. and Suami, T., *J. Org. Chem.,* **1987**, *52*, 1201.
22. Ando, K.; Oishi, T.; Hirama, M.; Ohno, H. and Ibuka, T., *J. Org. Chem.,* **2000**, *65*, 4745.
23. Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R. and Sakai, T., *Tetrahedron Lett.,* **1984**, *25*, 2183.
24. (a) Ando, K., *J. Org. Chem*., **1997**, *62*, 1934. (b) Ando, K., *J. Org. Chem*., **1999**, *64*, 8406.
25. (a) Denmark, S. E. and Chen, C.-T., *J. Org. Chem.,* **1994**, *59*, 2922. (b) Denmark, S. E. and Chen, C.-T., *J. Am. Chem. Soc.,* **1992**, *114*, 10674.
26. Arai, T.; Sasai, H.; Yamaguchi, K. and Shibasaki, M., *J. Am. Chem. Soc.,* **1998**, *120*, 441.
27. (a) Vares, L. and Rein, T., *J. Org. Chem.,* **2002**, *67*, 7226. (b) Vares, L. and Rein, T., *Org. Lett.,* **2000**, *2*, 2611.
28. Burri, K. F.; Cardone, R. A.; Chen, W. Y. and Rosen, P., *J. Am. Chem. Soc.,* **1978**, *100*, 7069.
29. (a) Tius, M.A. and Fauq, A., *J. Am. Chem. Soc.,* **1986**, *108*, 6389. (b) Tius, M. A. and Fauq, A. H., *J. Am. Chem. Soc.,* **1986**, *108*, 1035.
30. (a) Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K. and Ogawa, Y., *J. Am. Chem. Soc.,* **1988**, *110*, 4685. (b) Nicolaou, K.C.; Daines, R. A.; Ogawa, Y. and Chakraborty, T. K., *J. Am. Chem. Soc.,* **1988**, *110*, 4696.
31. Vanderwal, C. D.; Vosburg, D. A. and Sorensen, E. J., *Org. Lett.,* **2001**, *3*, 4307.
32. Sanchez, C. C. and Keck, G. E., *Org. Lett.,* **2005**, *7*, 3053.
33. (a) Rein, T. and Reiser, O., *Acta Chem. Scand.,* **1996**, *50*, 369. (b) Vedejs, E. and Peterson, M. J., *Top. Stereochem.,* **1994**, *21*, 1. (c) Maryanoff, B. E. and Reitz, A. B., *Chem. Rev.,* **1989**, *89*, 863. (d) Gosney, I and Rowley, A. G., "*Transformations via Phosphorus-Stabilized Anions. 1: Stereoselective Syntheses of Alkenes via the Wittig Reaction"* in *Organophosphorus Reagents in Organic Synthesis*, ed. Cadogan, J. I. G., Academic Press, London, **1979**, pp. 17–153. (e) Walker, B. J., in *Organophosphorus Reagents in Organic Synthesis*, ed. Cadogan, J. I. G., Academic Press; New York, **1979**, pp. 155–205. (f) Vollhardt, K. P. C., *Synthesis,* **1975**, 765. (g) Maercker, A., *Org. React.,* **1965**, *14*, 270.
34. White, J. D.; Blakemore, P. I.; Green, N. J.; Hauser, E. B.; Holoboski, M. A.; Koewn, L. E.; Kolz, C. S. N. and Phillips, B. W., *J. Org. Chem.,* **2002**, *67*, 7750.

35. Reichwein, J. F. and Pagenkopf, B. L., *J. Am. Chem. Soc.,* **2003**, *125*, 1821.

36. Pedersen, T. M.; Hansen, E. L.; Kane, J.; Rein, T.; Helquist, P.; Norrby, P.-O. and Tanner, D., *J. Am. Chem. Soc.,* **2001**, *123*, 9738.

37. (a) Jessop, C. M.; Parsons, A. F.; Routledge, A. and Irvine, D. J., *Eur. J. Org. Chem.,* **2006**, 1547. (b) Healy, M. P.; Parsons, A. F. and Rawlinson, J. G., *Org. Lett.,* **2005**, *7*, 1597. (c) Clayden, J.; Knowles, F. E. and Baldwin, I. R., *J. Am. Chem. Soc.,* **2005**, *127*, 2412. (d) Strand, D. and Rein, T., *Org. Lett.,* **2005**, *7*, 199. (e) Strand, D. and Rein, T., *Org. Lett.,* **2005**, *7*, 2779. (f) Fangour, S. E.; Guy, A.; Despres, V.; Vidal, J.-P.; Rossi, J.-C. and Durand, T., *J. Org. Chem.,* **2004**, *69*, 2498. (g) Jiang, Y. H.; Hong, J. and Burke, S. D., *Org. Lett.,* **2004**, *6*, 1445. (h) Suzuki, t.; Usui, K.; Miyake, Y.; Namikoshi, M. and Nakada, M., *Org. Lett.,* **2004**, *6*, 553. (i) Gurjar, M. K.; Cherian, J. and Ramana, C. V., *Org. Lett.,* **2004**, *6*, 317. (j) Allmendinger, T.; Fujimoto, R.; Gasparini, F.; Schilling, W. and Satoh, Y., *Chimia,* **2004**, *58*, 133. (k) Cativiela, C.; Díaz-de-Villegas, M.; Gálvez, J. A. and Su, G. F., *ARKIVOC*, **2004**, 59. (l) Díez-Barra, E.; García-Martínez, J. C.; del Rey, R.; Rodríguez-López, J.; Giacalone, F.; Segura, J. L. and Martín, N., *J. Org. Chem.,* **2003**, *68*, 3178. (m) Wang, G. and Yao, S. Q., *Org. Lett.,* **2003**, *5*, 4437. (n) Gaul, C.; Njardarson, J. T. and Danishefsky, S. J., *J. Am. Chem. Soc.,* **2003**, *125*, 6042. (o) Abreu, P. M. and Branco, P. S., *J. Braz. Chem. Soc.,* **2003**, *14*, 675. (p) Aggarwal, V. K.; Fulton, J. R.; Sheldon, C. G. and de Vicente, J., *J. Am. Chem. Soc.,* **2003**, *125*, 6034. (q) Kimber, M. C. and Taylor, D. K., *J. Org. Chem.,* **2002**, 67, 3142. (r) Vicario, J. L.; Job, A.; Wolberg, M.; Müller, M. and Enders, D., *Org. Lett.,* **2002**, *4*, 1023. (s) Beck, B.; Magnin-Lachaux, M.; Herdtweck, E. and Doemling, A., *Org. Lett.*, **2001**, *3*, 2875. (t) Hijikuro, I.; Doi, T. and Takahashi, T., *J. Am. Chem. Soc.,* **2001**, 123,3716. (u) Diez-Barra, E.; Carcía-Martínez, J. C.; Merino, S.; del Rey, R.; Rodríguez-López, J.; Sánchez-Verdú, P. and Tejeda, J., *J. Org. Chem.,* **2001**, *66*, 5664. (v) Pazos, Y.; Iglesias, B. and de Lera, A. R., *J. Org. Chem.,* **2001**, *66*, 8483. (w) Petroski, R. J. and Weisleder, D., *Synth. Commun.,* **2001**, *31*, 89. (x) Denmark, S. E. and Middleton, D. S., *J. Org. Chem.,* **1998**, *63*, 1604. (y) Murata, T.; Ishikawa, M.; Nishimaki, R. and Tadano, K., *Synlett,* **1997**, 1291. (z) Nicolaou, K. C. and Yue, E. W., *Pure & Appl. Chem.,* **1997**, *89*, 413. (aa) Johnson, C. R. and Zhang, B., *Tetrahedron Lett.,* **1995**, *36*, 9253. (bb) Denmark, S. E. and Rivera, I., *J. Org. Chem.,* **1994**, *59*, 6887. (cc) Kann, N. and Rein, T., *J. Org. Chem.,* **1993**, *58*, 3802. (dd) Kann, N.; Rein, T.; Akermark, B. and Helquist, P., *J. Org. Chem.,* **1990**, *55*, 5312. (ee) Rathke, M. W. and Nowak, M., *J. Org. Chem.,* **1985**, *50*, 2624. (ff) Wadsworth, W. S. and Emmons, W. D., *J. Org. Chem.,* **1961**, *83*, 1733. (gg) Horner, L.; Hoffmann, H. M. R.; Wippel, H. G. and Klahre, G., *Ber.,* **1959**, *92*, 2499.

38. (a) Bräse, S.; Gil, C.; Knepper, K. and Zimmermann, V., *Angew. Chem.,* **2005**, *117*, 5320. (b) Paterson, I. and Lyothier, I., *J. Org. Chem.,* **2005**, *70*, 5494. (c) Franci, X.; Martina, S. L. X.; McGrady, J. E.; Webb, M. R.; Donald, C. and Taylor, R. J. K., *Tetrahedron Lett.,* **2003**, *44*, 7735. (d) Paterson, I. and Florence, G. J., *Eur. J. Org. Chem.,* **2003**, 2193. (e) Fortin, S.; Dupont, F. and Deslongchamps, P., *J. Org. Chem.,* **2002**, *67*, 5437. (f) Zapata, A. J.; Gu, Y. H. and Hammond, G. B., *J. Org. Chem.,* **2000**, *65*, 227. (g) Sampson, P.; Hammond, G. B. and Wiemer, D. F., *J. Org. Chem.,* **1986**, *51*, 4342.

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Hosomi-Sakurai Allylation

(Hosomi-Sakurai Reaction, Sakurai Allylation)

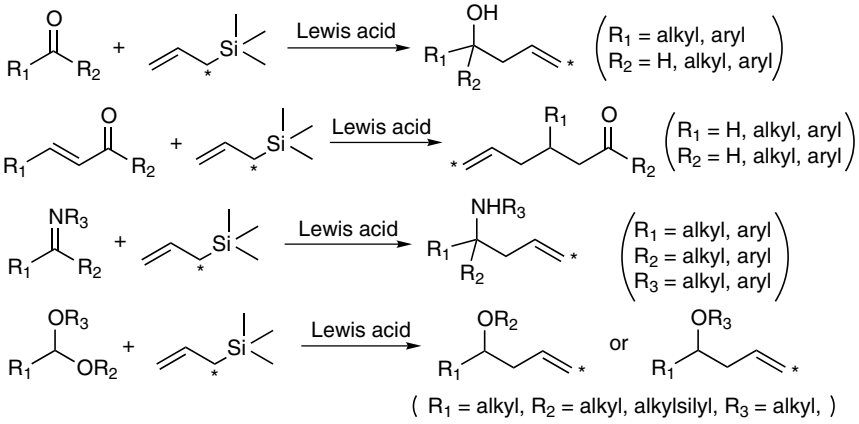
A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Hosomi and Sakurai in 1976.[1] It is the Lewis acid- or fluoride-promoted[2] allylation of various carbon electrophiles (e.g., aldehydes,[3] ketones,[2a] aldimines,[2a] alkenes,[4] imines,[5] α,β-unsaturated carbonyl compounds,[2b,5,6] acetals[3b,7]) with allyltrimethylsilane accompanied by the regiospecific transposition of allylic moiety and possible generation of new chiral center(s).[7c] This reaction is therefore known as the Homosi-Sakurai reaction,[3b,4,5,6,7d,8] Hosomi-Sakurai allylation,[2b,3a,8c,8e,9] Sakurai-Hosomi allylation,[10] Sakurai allylation,[11] and Sakurai addition.[12] When the electrophiles are acetals, the allylation might occur in the presence of a catalytic amount of Lewis acid, such as 2% $FeCl_3$.[7a] In addition, many other Lewis acids have been applied as promoters or catalysts for the allylation of acetals, including $TiCl_4$,[13] $BF_3{\cdot}Et_2O$,[3a] $SnCl_4$,[2b] $AlCl_3$,[7a] TMSI,[14] TMSOTf,[15] $TMSNTf_2$,[16] $Sc(OTf)_3$,[17] $Bi(OTf)_3$,[18] and trityl perchlorate.[19] On the other hand, the allylation of alkylsilyl mixed acetals leads to the replacement of either an alkoxyl or an alkylsiloxyl group, depending on the Lewis acid applied.[3b] For electrophiles of aldehydes, such as benzaldehyde, it has been found that even the use of an excess amount of Lewis acid ($BF_3{\cdot}Et_2O$) does not drastically increase the yield of homoallylic alcohol;[3a] in contrast, a catalytic amount of $FeCl_3$ can promote the allylation of aliphatic aldehydes.[7a] For the electrophiles of α,β-unsaturated ketones or aldehydes, it has been found that allylsilanes undergo regiospecific conjugate addition to double bond in the presence of strong Lewis acid catalyst,[2b] except for the application of auxiliaries;[20] however, all monoactivated α,β-unsaturated esters, nitriles, and amides do not undergo such allylation, regardless of the choice of catalyst.[2b] For the allylation of aldehydes with substituted allylsilane, such as

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

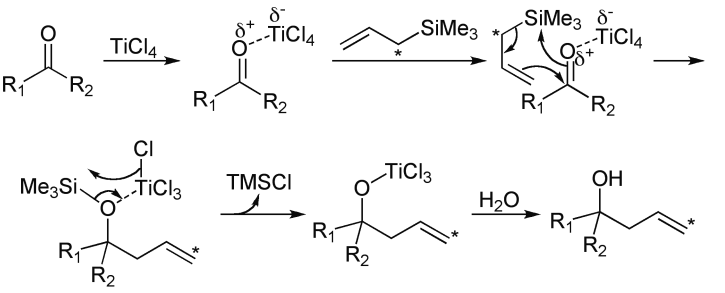
crotylsilane, the *syn*-homoallylic alcohols form predominantly from either *cis*-crotylsilane or *trans*-crotylsilane.[3b] In addition, the allylation of aldehydes also results in the formation of ether.[6b] This reaction has been improved to occur in the presence of a catalytic amount of Lewis acid using allylsilyl chlorides instead of allyltrimethylsilane.[21]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Displayed below is a representative mechanism for the reaction between allyltrimethylsilane and ketone in the presence of Lewis acid $TiCl_4$.



D. MODIFICATION

This reaction has been extensively modified using different Lewis acids as catalysts.

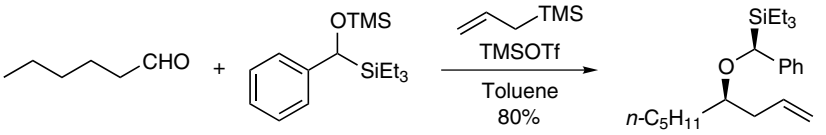
E. APPLICATIONS

This reaction has wide applications in organic synthesis.

F. RELATED REACTIONS

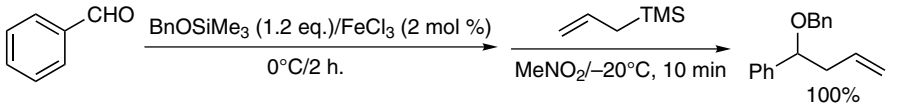
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 20.

To a 0.1 M toluene solution containing 0.11 g (±)-1-phenyl-1-(triethylsilyl)methanol TMS ether (0.38 mmol, 1.0 eq.) precooled to −78°C was added 52 μL hexanal (0.42 mmol, 1.1 eq.), allyltrimethylsilane (1.1 eq.), and TMSOTf (0.2 eq.). The mixture was maintained at −78°C for 1 h, and then the reaction was quenched by saturated aqueous $NaHCO_3$. The mixture was allowed to warm to ambient temperature, diluted with CH_2Cl_2, and washed once with saturated $NaHCO_3$ and then three times with brine. The combined aqueous phases were extracted twice with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$ and then concentrated in vacuo. Purification by flash chromatography (5% CH_2Cl_2/hexanes) afforded 0.10 g triethyl [(1-pentylbut-3-enyloxy)phenylmethyl]silane as a colorless oil, in a yield of 80%.



Reference 7a.

To a mixture of 2.0 mg $FeCl_3$ (0.012 mmol) and 63 μL benzaldehyde (0.62 mmol) was added 146 μL benzyloxytrimethylsilane (0.74 mmol) at 0°C under argon atmosphere. After the reaction mixture was stirred for 2 h, allyltrimethylsilane (112 μL, 0.71 mmol) in nitromethane was added at –20°C. The resultant mixture was stirred for 10 min and quenched with saturated aqueous $NaHCO_3$. The organic materials were extracted with Et_2O and dried over anhydrous $MgSO_4$. The solvent was evaporated, and 165.6 mg (1-benzyloxy-but-3-enyl)benzene was isolated by thin-layer chromatography on silica gel (ether/hexane, 1:30), in a yield of 100%.

Other references related to the Hosomi-Sakurai allylation are cited in the literature.[22]

H. REFERENCES

1. (a) Hosomi, A. and Sakurai, H., *Tetrahedron Lett.,* **1976**, 1295. (b) Hosomi, A.; Endo, M. and Sakurai, H., *Chem. Lett.,* **1976**, 941.
2. (a) Wang, D.-K.; Zhou, Y.-G.; Tang, Y.; Hou, X.-L. and Dai, L.-X., *J. Org. Chem.,* **1999**, *64*, 4233. (b) Majetich, G.; Casares, A.; Chapman, D. and Behnke, M., *J. Org. Chem.,* **1986**, *51*, 1745.
3. (a) Ooi, T.; Takahashi, M.; Yamada, M.; Tayama, E.; Omoto, K. and Maruoka, K., *J. Am. Chem. Soc.,* **2004**, *126*, 1150. (b) Fujita, K.; Inoue, A.; Shinokubo, H. and Oshima, K., *Org. Lett.,* **1999**, *1*, 917.
4. Miura, K.; Saito, H.; Nakagawa, T.; Hondo, T.; Tateiwa, J.-I.; Sonoda, M. and Hosomi, A., *J. Org. Chem.,* **1998**, *63*, 5740.
5. Angle, S. R.; Belanger, D. S. and El-Said, N. A., *J. Org. Chem.,* **2002**, *67*, 7699.
6. (a) Angle, S. R. and El-Said, N. A., *J. Am. Chem. Soc.,* **2002**, *124*, 3608. (b) Angle, S. R. and El-Said, N. A., *J. Am. Chem. Soc.,* **1999**, *121*, 10211.
7. (a) Watahiki, T.; Akabane, Y.; Mori, S. and Oriyama, T., *Org. Lett.,* **2003**, *5*, 3045. (b) Roberson, C. W. and Woerpel, K. A., *J. Am. Chem. Soc.,* **2002**, *124*, 11342. (c) Sames, D.; Liu, Y. Q.; DeYoung, L. and Polt, R., *J. Org. Chem.,* **1996**, *60*, 2153.
8. (a) Kampen, D. and List, B., *Synlett,* **2006**, 2589. (b) Sur, S.; Mandal, S. K.; Ganesh, S.; Puranik, V. G. and Sarkar, A., *Indian J. Chem., Sect. B,* **2001**, *40B*, 1063. (c) Macsári, I.; Hupe, E. and Szabó, K. J., *J. Org. Chem.,* **1999**, *64*, 9547. (d) Tokoroyama, T. and Aoto, T., *J. Org. Chem.,* **1998**, *63*, 4151. (e) Sur, S.; Ganesh, S.; Pal, D.; Puranik, V. G.; Chakrabarti, P. and Sarkar, A., *J. Org. Chem.,* **1996**, *61*, 8362.
9. (a) Mayr, H.; Kempf, B. and Ofial, A. R., *Acc. Chem. Res.,* **2003**, *36*, 67. (b) Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A. and González, J. M., *J. Am. Chem. Soc.,* **2003**, *125*, 9028. (c) Smitrovich, J. H. and Woerpel, K. A., *J. Org. Chem.,* **2000**, *65*, 1601. (d) Majetich, G.; Desmond, R. W. and Soria, J. J., *J. Org. Chem.,* **1986**, *51*, 1753.
10. (a) Wadamoto, M. and Yamamoto, H., *J. Am. Chem. Soc.*, **2005**, *127*, 14556. (b) Wadamoto, M.; Ozasa, N.; Yanagisawa, A. and Yamamoto, H., *J. Org. Chem.,* **2003**, *68*, 5593. (c) Itsuno, S. and Kumagai, T., *Helv. Chim. Acta,* **2002**, *85*, 3185. (d) Itsuno, S. and Kumagai, T., *Helv. Chim. Acta,* **2002**, *85*, 3185. (e) Kumagai, T. and Itsuno, S., *Jasco Report,* **2001**, *43*, 28. (f) Ishihara, K.; Hiraiwa, Y. and Yamamoto, H., *Synlett,* **2001**, 1851.
11. (a) Williams, D. R.; Morales-Ramos, A. I. and Williams, C. M., *Org. Lett.,* **2006**, *8*, 4393. (b) Trost, B. M.; Thiel, O. R. and Tsui, H.-C., *J. Am. Chem. Soc.,* **2003**, *125*, 13155. (c) Nosse, B.; Chhor, R. B.; Jeong, W. B.; Böhm, C. and Reiser, O., *Org. Lett.,* **2003**, *5*, 941. (d) Cesarotti, E.; Araneo, S.; Rimoldi, I. and Tassi, S., *J. Mol. Catal. A: Chem.,* **2003**, *204–205*, 221. (e) Williams, D. R.; Myers, B. J. and Mi, L., *Org. Lett.,* **2000**, *2*, 945. (f) Bonjoch, J.; Cuesta, J.; Daz, S. and Gonzalez, A., *Tetrahedron Lett.,* **2000**, *41*, 5669. (g) Brocherieux-Lanoy, S.; Dhimane, H.; Vanucci-Bacqué, C. and Lhommet, G., *Synlett,* **1999**, 405. (h) Bianchini, C. and Glendenning, L., *Chemtracts: Org. Chem.,* **1996**, *9*, 331. (i) Bianchini, C. and Glendenning, L., *Chemtracts: Inorg. Chem.,* **1995**, *7*, 107. (j) Hollis, T. K. and Bosnich, B., *J. Am. Chem. Soc.,* **1995**, *117*, 4570.
12. (a) Organ, M. G.; Dragan, V.; Miller, M.; Froese, R. D. J. and Goddard, J. D., *J. Org. Chem.,* **2000**, *65*, 3666. (b) Pellissier, H.; Toupet, L. and Santelli, M., *J. Org. Chem.,* **1998**, *63*, 2148.
13. Shing, T. K. M. and Li, L.-H., *J. Org. Chem.,* **1997**, *62*, 1230.
14. Sakurai, H.; Sasaki, H. and Hosomi, A., *Tetrahedron Lett*., **1981**, *22*, 745.
15. Tsunoda, T.; Suzuki, M. and Noyori, R., *Tetrahedron Lett*., **1980**, *21*, 71.
16. Ishii, A.; Kotera, O.; Saeki, T. and Mikami, K., *Synlett*, **1997**, 1145.
17. Yadav, J. S.; Subba, B. V. and Srihari, P., *Synlett*, **2001**, 673.
18. Wieland, L. C.; Zerth, H. M. and Mohan, R. S., *Tetrahedron Lett*., **2002**, *43*, 4597.

19. Mukaiyama, T.; Nagaoka, H.; Murakami, M. and Ohsima, M., *Chem. Lett*., **1985**, 977.

20. Huckins, J. R. and Rychnovsky, S. D., *J. Org. Chem.,* **2003**, *68*, 10135.

21. Fürstner, A. and Voigtländer, D., *Synthesis*, **2000**, 959.

22. (a) Furman, B.; Frelek, J.; Dziedzic, M. and Kaminska, A., *Pol. J. Chem.,* **2005**, *79*, 1919. (b) Rikimaru, K.; Mori, K.; Kan, T. and Fukuyama, T., *Chem. Commun.,* **2005**, 394. (c) Zerth, H. M.; Leonard, N. M. and Mohan, R. S., *Org. Lett.*, **2003**, *5*, 55. (d) Malkov, A. V.; Orsini, M.; Pernazza, D.; Muir, K. W.; Langer, V.; Meghani, P. and Kocovsky, P., *Org. Lett.*, **2002**, *4*, 1047. (e) Shibata, I.; Kano, T.; Kanazawa, N.; Fukuoka, S. and Baba, A., *Angew. Chem. Int. Ed*., **2002**, *41*, 1389. (f) Mayer, P. S. and Morton, T. H., *J. Am. Chem. Soc.,* **2002**, *124*, 12928. (g) Yamasaki, S.; Fujii, K.; Wada, R.; Kanai, M. and Shibasaki, M., *J. Am. Chem. Soc.,* **2002**, *124*, 6536. (h) Onishi, Y.; Ito, T.; Yasuda, M. and Baba, A., *Tetrahedron*, **2002**, *58*, 8227. (i) Ishihara, K.; Hasegawa, A. and Yamamoto, H., *Angew. Chem. Int. Ed.,* **2001**, *40*, 4077. (j) Wang, M. W.; Chen, Y. J. and Wang, D., *Heteroatom Chem.,* **2001**, *12*, 534. (k) Speckamp, W. N. and Moolenaar, M. J., *Tetrahedron,* **2000**, *56*, 3817. (l) Mandal, S. K. and Sarkar, A., *J. Org. Chem.,* **1999**, *64*, 2454. (m) Bonini, B. F.; Comes-Franchini, M.; Fochi, M.; Laboroi, F.; Mazzanti, G.; Ricci, A. and Varchi, G., *J. Org. Chem.,* **1999**, *64*, 8008. (n) Masse, C. E.; Yang, M.; Solomon, J. and Panek, J. S., *J. Am. Chem. Soc.,* **1998**, *120*, 4123. (o) Marko, I. and Bayston, D. J., *Tetrahedron Lett.,* **1993**, *34*, 6595. (p) Fleming, I.; Dunogues, J. and Smithers, R., *Org. React.,* **1989**, *37*, 57. (q) Sakurai, H., *Synlett,* **1989**, 1. (r) Hosomi, A., *Acc. Chem. Res*., **1988**, *21*, 200. (s) Sakurai, H., *Pure & Appl. Chem.,* **1982**, *54*, 1. (t) Wilson, S. R. and Price, M. F., *J. Am. Chem. Soc.,* **1982**, *104*, 1124. (u) Sakurai, H.; Sasaki, K. and Hosomi, A., *Tetrahedron Lett.,* **1981**, *22*, 745. (v) Hosomi, A.; Shirhata, A. and Sakurai, H., *Tetrahedron Lett.,* **1978**, *19*, 3043. (w) Hosomi, A. and Sakurai, H., *J. Am. Chem. Soc.,* **1977**, *99*, 1673.

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Houben-Hoesch Reaction
(Houben-Hoesch Acylation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Hoesch in 1915[1] and was extended subsequently by Houben in 1926.[2] It is the acylation of electron-rich aromatics—such as multi-hydroxy phenols, their ethereal derivatives, and some heterocyclic compounds—from organic nitriles via the intermediate of ketimines in the presence of hydrochloric acid or Lewis acid or both. Therefore, this reaction is generally known as the Houben-Hoesch reaction.[3] In addition, this reaction is also referred to as the Hoesch synthesis,[4] Houben-Hoesch condensation,[5] Houben-Hoesch acylation,[6] Houben-Hoesch synthesis,[7] or Hoesch reaction.[8] Moreover, the intramolecular version of such reaction is also known as the Houben-Hoesch cyclization.[9] The acidic catalysts used for this reaction include $ZnCl_2$,[1a,3r] $AlCl_3$,[3r,3x,10] the combination of BCl_3 and $AlCl_3$,[3r] many superacids,[9,11] and even the cation-exchange resin (Amberlite IR-120).[12] It has been reported that simple phenol does not undergo acylation and forms only a salt of iminomethyl phenyl ether; however, phenol can be *ortho*-acylated from nitriles by using the combination of BCl_3 and $AlCl_3$ as the catalyst.[3r] It has been found that the dications—that is, the carbocation destabilized by an iminium cation group—are the real acylation species.[3i,3l] This reaction has been modified using a palladium-catalyzed approach, which is good for both intermolecular and intramolecular acylation of less electron-rich arenes.[3b] In addition, because protonated nitriles exist in very low concentration ($pKa \sim -10$),[6a] many current acylating reagents are Meerwein's alkylated nitrilium ions developed in 1956,[13] which show enhanced electrophilicity of the intermediate; under these conditions, the incoming aryl group is located in the position *cis* to the *N*-substituent.[14]

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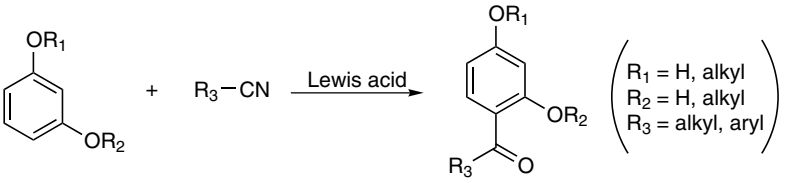
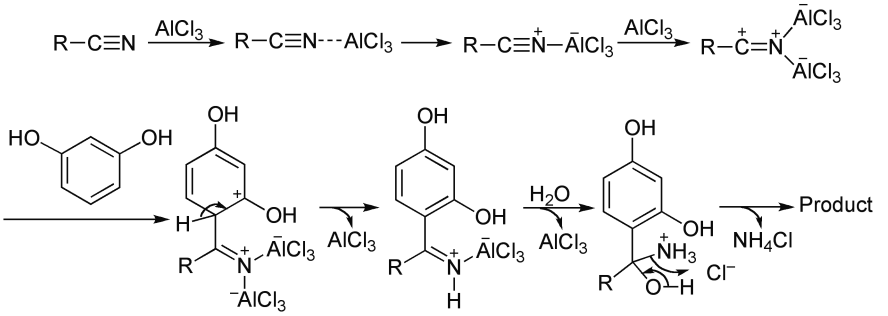
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Shown below is the reaction mechanism for the $AlCl_3$ catalyzed reaction between 1,3-dihydroxybenzene and a general nitrile.



D. MODIFICATION

This reaction has been modified using either a palladium-catalyzed approach,[3b] the combination of BCl_3 and $AlCl_3$ as the catalyst,[3r] and the *N*-alkylated nitrilium salt as the acylating reagent.[6a,14]

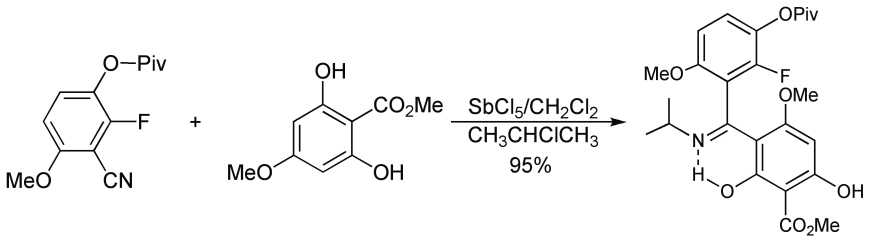
E. APPLICATIONS

This reaction has been applied to the acylation of phenols, their ethereal derivatives, and some heterocyclic compounds.

F. RELATED REACTIONS

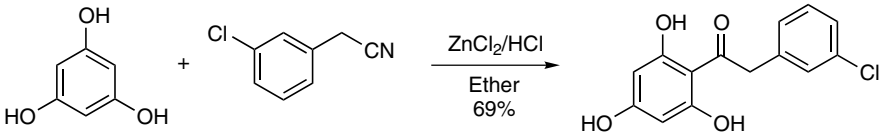
This reaction is related to the *Friedel-Crafts Acylation* and *Gatterman Aldehyde Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 3e.

To 460 mL CH_2Cl_2 solution containing 7.0 g 2-fluoro-3-pivaloyl-6-methoxyl benzonitrile (27.89 mmol) and 25.5 mL 2-chloropropane (278.89 mmol) was added 27.9 mL $SbCl_5$ prepared as a 1 M CH_2Cl_2 solution (36.26 mmol) over 8 min. After 40 min, 13.81 g methyl 2,6-dihydroxy-4-methoxybenzoate (69.72 mmol) was added by cannula in 80 mL CH_2Cl_2 solution, and the reaction mixture was stirred for 2 h at room temperature. The volume was reduced to 200 mL, and the reaction mixture was filtered through a short silica pad and washed with 5% CH_3OH/CH_2Cl_2 to remove the antimony salts. Column chromatography (40→60% EtOAc/hexanes→20% CH_3CN/EtOAc) provided 12.98 g 2,4-dihydroxy-6,6′-dimethoxy-2′-fluoro-3-methoxycarbonyl-3′-pivaloylbenzophenone-*N*-(2-methylethyl)ketimine as a yellow oil, in a yield of 95%, R_f =0.6 (2% $MeOH/CH_2Cl_2$).



Reference 15.

Phloroglucinol (i.e., 1,3,5-trihydroxybenzene) (9.2 g; 72.9 mmol) and 11.05 g 3-chlorobenzyl cyanide (72.9 mmol) were dissolved in 70 mL anhydrous ether. Zinc chloride was added, and a stream of dry hydrogen chloride was bubbled through the reaction mixture for 4 h. A viscous yellowish mass separated from the slightly brown solution. The flask was left closed overnight, and then the ethereal layer was removed by decantation; HCl (2 M, 150 mL) was added, and the partly dissolved mass was heated to 100°C for 2.5 h. The hot solution was filtered, and the yellow solid was collected. A lower second phase formed in the filtrate as a brown oil, which crystallized upon cooling to give 14.05 g 2-(3-chlorophenyl)-1-(2,4,6-trihydroxyphenyl)ethanone, in a yield of 69%. Crystallization from EtOAc/pentane gave pure product as light yellow crystals, m.p. 182.6–184.7°C.

Other references related to the Houben-Hoesch reaction are cited in the literature.[16]

H. REFERENCES

1. (a) Hoesch, K., *Ber.,* **1915**, *48*, 1122. (b) Hoesch, K., *Ber.,* **1915**, *48*, 1125.
2. (a) Houben, J., *Ber.,* **1926**, *59*, 2878. (b) Houben, J., *Ber.,* **1926**, *59*, 2887.
3. (a) Fillion, E.; Fishlock, D.; Wilsily, A. and Goll, J. M., *J. Org. Chem.,* **2005**, *70*, 1316. (b) Zhou, C. X. and Larock, R. C., *J. Am. Chem. Soc.,* **2004**, *126*, 2302. (c) Friscic, T.; Drab, D. M. and MacGillivray, L. R., *Org. Lett.,* **2004**, *6*, 4647. (d) Sanchez-Viesca, F.; Gomez, M. R. and Berros, M., *Org. Prep. Proc. Int.,* **2004**, *36*, 135. (e) Udwary, D. W.; Casillas, L. K. and Townsend, C. A., *J. Am. Chem. Soc.,* **2002**, *124*, 5294. (f) Zhang, C. M.; Liu, F. C. and Zhu, H. Y., *Yingyong Huaxue*, **1998**, *15*, 68. (g) Arkhipov, V. V.; Smirnov, M. N. and Khilya, V. P., *Chem. Heterocycl. Compd.,* **1997**, *33*, 515. (h) Moustafa, A. H.; Hitzler, M. G.; Lutz, M. and Jochims, J. C., *Tetrahedron*, **1997**, *53*, 625. (i) Sato, Y.; Yato, M.; Ohwada, T.; Saito, S. and Shudo, K., *J. Am. Chem. Soc.,* **1995**, *117*, 3037. (j) Rama Rao, A. V.; Gaitonde, A. S.; Prakash, K. R. C. and Rao, S. P., *Tetrahedron Lett.,* **1994**, *35*, 6347. (k) Bigi, F.; Maggi, R.; Sartori, G.; Casnati, G. and Bocelli, G., *Gazz. Chim. Ital.,* **1992**, *122*, 283. (l) Yato, M.; Ohwada, T. and Shudo, K., *J. Am. Chem. Soc.,* **1991**, *112*, 691. (m) Nimtz, M. and Haefelinger, G., *Liebigs Annalen der Chemie*, **1987**, 765. (n) Alagona, G. and Tomasi, J., *THEOCHEM*, **1983**, *8*, 263. (o) Amer, M. I.; Booth, B. L.; Noori, G. F.; Proenca, M. and Fernanda, J. R. P., *J. Chem. Soc. Perkin Trans. I,* **1983**, 1075. (p) Scannell, R. T. and Stevenson, R., *J. Org. Chem.,* **1983**, *48*, 127. (q) Cameron, D. W.; Deutscher, K. R.; Feutrill, G. I. and Hunt, D. E., *Aust. J. Chem.,* **1982**, *35*, 1451. (r) Toyoda, T.; Sasakura, K. and Sugasawa, T., *J. Org. Chem.,* **1981**, *46*, 189. (s) Gless, R. D. and Rapoport, H., *J. Org. Chem.,* **1979**, *44*, 1324. (t) Sanchez-Viesca, F. and Reina Gomez, M., *Revista Latinoamer. Quim.,* **1979**, *10*, 162. (u) Jeffery, E. A. and Satchell, D. P. N., *J. Chem. Soc. B,* **1966**, 579. (v) Patterson, J. M.; Brasch, J. and Drenchko, P., *J. Org. Chem.,* **1962**, *27*, 1652. (w) Spruit, C. J. P., *Rec. Trav. Chim. Pays-Bas Belg.,* **1948**, *67*, 285. (x) Calloway, N. O., *Chem. Rev.,* **1935**, *17*, 327.
4. Buu-Hoï, Ng. Ph. And Seailles, J., *J. Org. Chem.,* **1955**, *20*, 606.
5. (a) Bosch, J.; Mauleón, D.; Feliz, M. and Granados, R., *J. Org. Chem.,* **1983**, *48*, 4836. (b) Ranieri, R. L. and McLaughlin, J. L., *J. Org. Chem.,* **1976**, *41*, 319.
6. (a) Casillas, L. K. and Townsend, C. A.,*J. Org. Chem.,* **1999**, *64*, 4050. (b) Beutler, J. A.; Hamel, E.; Vlietinck, A. J.; Haemers, A.; Rajan, P.; Roitman, J. N.; Cardellina, J. H. and Boyd, M. R., *J. Med. Chem.,* **1998**, *41*, 2333.
7. Hornbaker, E. D. and Burger, A., *J. Am. Chem. Soc.,* **1955**, *77*, 5314.
8. (a) Kawecki, R.; Mazurek, A.; Kozerski, L. and Maurin, J. K., *Synthesis,* **1999**, 751. (b) Sanchez-Viesca, F. and Gomez, M. R., *Revista Latinoamer. Quim.,* **1982**, *13*, 24.
9. Colquhoun, H. M.; Lewis, D. F. and Williams, D. J., *Org. Lett.,* **2001**, *3*, 2337.
10. Bruson, H. A.; Riener, E. and Riener, T., *J. Am. Chem. Soc.,* **1948**, *70*, 483.
11. Olah, G. A. and Kiovsky, T. E., *J. Am. Chem. Soc.,* **1968**, *90*, 4666.
12. Price, P. and Israelstam, S. S., *J. Org. Chem.,* **1964**, *29*, 2800.
13. Meerwein, H.; Laasch, P.; Mersch, R. and Spille, J., *Ber.,* **1956**, *89*, 209.
14. Henninger, J.; Polborn, K. and Mayr, H., *J. Org. Chem.,* **2000**, *65*, 3569.
15. Traxler, P.; Green, J.; Mett, H.; Séquin, U. and Furet, P., *J. Med. Chem.,* **1999**, *42*, 1018.
16. (a) Camacho, E.; León, J.; Carrión, A.; Entrena, A.; Escames, G.; Khaldy, H.; Acuña-Castroviejo, D.; Gallo, M. A. and Espinosa, A., *J. Med. Chem.,* **2002**, *45*, 263. (b) Hammond, M. L.; Zambias, R. A.; Chang, M. N.; Jensen, N. P.; McDonald, J.; Thompson, K.; Boulton, D. A.; Kopka, I. E.; Hand, K. M.; Opas, E. E.; Luell, S.; Bach, T.; Davies, P.; MacIntyre, D. E.; Bonney, R. J. and Humes, J. L., *J. Med. Chem.,* **1990**, *33*, 908. (c) Hegarty, A. F., *Acc. Chem. Res.,* **1980**, *13*, 448. (d) Sugasawa, T.; Adachi, M.; Sasakura, K. and Kitagawa, A., *J. Org. Chem*., **1979**, *44*, 573. (e) Laidlaw, G. M.; Collins, J. C.; Archer, S.; Rosi, D. and Schulenberg, J. W., *J. Org. Chem.,*

1973, *38*, 1743. (f) Sasaki, T.; Eguchi, S. and Toru, T., *J. Org. Chem.,* **1970**, *35*, 4109. (g) Gabel, N. W., *J. Heterocycl. Chem.,* **1967**, *4*, 627. (h) Layer, R. W., *Chem. Rev.,* **1962**, *62*, 489. (i) Cheney, L. C.; Smith, R. R. and Binkley, S. B., *J. Am. Chem. Soc.,* **1949**, *71*, 53. (j) Spoerri, P. E. and DuBois, A. S., *Org. React.,* **1949**, *5*, 387. (k) Hunsberger, I. M. and Amstutz, E. D., *J. Am. Chem. Soc.,* **1948**, *70*, 671. (l) Houben, J. and Fischer, W., *J. Prakt. Chem.,* **1929**, *123*, 89. (m) Hoesch, K., *Ber.,* **1917**, *50*, 462.

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Houdry Cracking Process

A. GENERAL DESCRIPTION OF THE REACTION

It was first reported by Eugene Houdry in 1934.[1] It is an industrial process to degrade petroleum or heavy petroleum fractions into more useful lower-boiling materials by heating the oil at 500°C and 30 psi, over a clay catalyst containing silica, alumina, and magnanese oxide. Therefore, it is known as the Houdry cracking process.[2] Soon after the invention of this process, the first commercial fixed-bed, three-case cracker was constructed (in 1936), which could crack 2000 barrels of oil daily.[3] By this time, the Houdry process corporation was founded, and its research branch—known as Houdry Laboratories—was also established in Marcus Hook, pennsylvania to concentrate on the studies of catalysts for such petroleum-cracking processes.[4] During the thermolytical degradation of oil, continuous coking occurs which deactivates the catalyst. Therefore, in the first three-case cracker, vaporized gas oil and air were passed alternately over the catalyst bed in each case, so that whenever the oil deposits coked on the catalyst, the coke after purging, would be burned off by the passage of air.[3] Thus in a single cycle of a three-case cracker, one case is cracking, another is burning carbon, and the third is being purged.[5] The typical cycle duration is ~10 min.[5] It has been found that a few factors affect the effectiveness of a catalyst, such as the chemical nature of the oil gas, the time and temperature for the exposure of the catalyst to oil gas, contamination of the catalyst by metals entrained in the stock, and the type of catalyst.[6] Heavy metals—such as iron, nickel, vanadium, and copper—are all harmful for the catalyst.[6] It is believed that at such high cracking temperatures, the decomposition of oil undergoes a radical mechanism.[7] More information about this process is available.[8]

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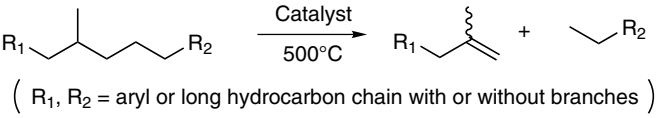
B. GENERAL REACTION SCHEME

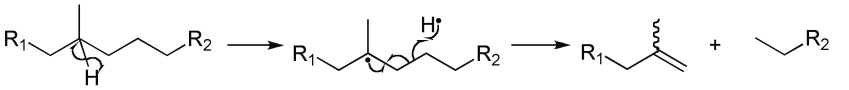
An example with branched hydrocarbon is used to illustrate this cracking process.



(R_1, R_2 = aryl or long hydrocarbon chain with or without branches)

C. PROPOSED MECHANISMS

A radical mechanism is proposed for this process, because the C-H bond at the allylic carbon, benzylic carbon, or tertiary carbon is relatively weaker than other C-H bonds, which can homolytically cleave and form radicals, as shown below.



D. MODIFICATION

This process has been modified for the thermofor process in which the catalyst bed is in continuous motion propelled by oil gas steam.[5]

E. APPLICATIONS

This process has been extensively used in oil refinery manufacturing plants to produce gas and other petrochemicals.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES

Because this is an industrial process for cracking petroleum oil, no practical experiments on the laboratory scale are provided here.

H. REFERENCES

1. (a) Houdry, E., *U.S. Pat*., **1934**, May 8, 1,957,648. (b) Houdry, E., *U.S. Pat*., **1934**, May 8, 1,957,649.
2. (a) Smith, E. A. and Bland, R. E., *Oil & Gas J*., **1944**, *42*, 209. (b) Smith, E. A. and Bland, R. E., *Oil & Gas J*., **1944**, *42*, 213. (c) Smith, E. A. and Bland, R. E., *Oil & Gas J*., **1944**, *42*, 214. (d) Smith, E. A. and Bland, R. E., *Oil & Gas J*., **1944**, *42*, 217. (e) Vellinger, E., *Bull. Assoc. Fr. Tech. Petrole,* **1939**, (47), 61.
3. Shearon, W. H., *Ind. Eng. Chem.,* **1959**, *51*, 720.
4. Kirsch, F. W.; Heinemann, H. and Stevenson, D. H., *Ind. Eng. Chem.,* **1957**, *49*, 646.
5. Van Antwerpen, F. J., *Ind. Eng. Chem.,* **1944**, *36*, 694.
6. Mills, G. A., *Ind. Eng. Chem.,* **1950**, *42*, 182.
7. Weiss, A. H. and Friedman, L., *I & EC Proc. Des. Dev.,* **1963**, *2*, 163.
8. (a) Nishimura, Y., *Petrotech.,* **1998**, *21*, 605. (b) Mosley, C. G., *J. Chem. Ed.,* **1984**, *61*, 655. (c) Mills, G. A., *Chemtech.,* **1986**, 72. (d) Weiss, A. H., *Hydrocarbon Proc. Petrol. Refiner,* **1962**, *41*, 185. (e) Weiss, A. H.; Macrker, J. B. and Newirth, R., *Oil & Gas J.,* **1962**, *60*, 64. (f) Rothrock, J. J.; Birkhimer, E. R. and Leum, L. N., *Ind. Eng. Chem.,* **1957**, *49*, 272. (g) Silsby, R. I. and Sawyer, E. W., *J. Appl. Chem. (London),* **1956**, *6*, 347. (h) Whitaker, A. C. and Kinzer, A. D., *Ind. Eng. Chem.,* **1955**, *47*, 2153. (i) Hindin, S. G.; Oblad, A. G. and Mills, G. A., *J. Am. Chem. Soc.,* **1955**, *77*, 535. (j) Hindin, S. G.; Mills, G. A. and Oblad, A. G., *J. Am. Chem. Soc.,* **1955**, *77*, 538. (k) Oblad, A. G.; Hindin, S. G. and Mills, G. A., *J. Am. Chem. Soc.,* **1953**, *75*, 4096. (l) Melpolder, F. W.; Brown, R. A.; Young, W. S. and Headington, C. E., *Ind. Eng. Chem.,* **1952**, *44*, 1142. (m) Hindin, S. G.; Mills, G. A. and Oblad, A. G., *J. Am. Chem. Soc.,* **1951**, *73*, 278. (n) Zabor, R. C. and Emmett, P. H., *J. Am. Chem. Soc.,* **1951**, *73*, 5639. (o) Mills, G. A.; Boedeker, E. R. and Oblad, A. G., *J. Am. Chem. Soc.,* **1950**, *72*, 1554. (p) Mills, G. A. and Hindin, S. G., *J. Am. Chem. Soc.,* **1950**, *72*, 5549. (q) Haensel, V. and Sterba, M. J., *Ind. Eng. Chem.,* **1948**, *40*, 1662. (r) Thomas, C. L., *Ind. Eng. Chem.,* **1945**, *37*, 543. (s) Murphree, E. V.; Brown, C. L.; Fischer, H. G. M.; Gohr, E. J. and Sweeney, W. J., *Ind. Eng. Chem.,* **1943**, *35*, 768. (t) Houdry, E., *U.S. Pat*., **1936**, Mar. 31, 2,035,478.

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Huisgen Pyrrole Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Huisgen in 1960.[1] It is a general synthesis of pyrrole derivatives, especially *penta*-substituted pyrroles,[2] involving the *1,3-Dipolar Cycloaddition* of the mesoionic Δ^2-oxazilium-5-olates to the corresponding acetylenic or olefinic dipolarophiles, followed by carbon dioxide evolution and subsequent aromatization or tautomerization.[3] Therefore, this reaction is generally known as the Huisgen pyrrole synthesis.[2,4] It should be pointed out that the mesoionic Δ^2-oxazilium-5-olates, which behave like cyclic azomethine ylides,[3] are simply referred to as munchnones,[2,3,5] owing to their initial development in Munch, Germany. Depending on the nature of dipolarophiles, either pyrrolidines, dihydropyrroles, or pyrroles can be prepared from this reaction,[6] and the resulting dihydropyrroles can be converted into pyrroles directly by the oxidation from manganese dioxide[6a] or sulfur.[7]

In this reaction, the munchnones can be easily prepared by the acetic anhydride–induced dehydrative cyclization of *N*-alkyl-*N*-acyl-α-amino acids at high temperatures,[5] and such reactions can also be performed in a one-pot fashion in which the α-amino acids, the acylating agents, and acetylenic dipolarophiles are combined at once to give pyrroles by the way of the intermediate munchnones.[2] It has been found that the reaction between asymmetric electron-deficient dipolarophiles and monocyclic munchnones gives a mixture of regioisomers,[5] whereas the reaction between such dipolarophiles and polycyclic munchnones is regiospecific,[8] and the regioselectivity is controlled by the nature of substituents on the 1,3-dipoles.[9] On the other hand, the azomethine ylides can also be generated by the ring opening of aziridines,[6b,10] by which the *trans*-azomethine ylides combine stereospecifically with dipolarophiles, even with the weak dipolarophiles; in contrast, the *1,3-Dipolar Cycloaddition* of

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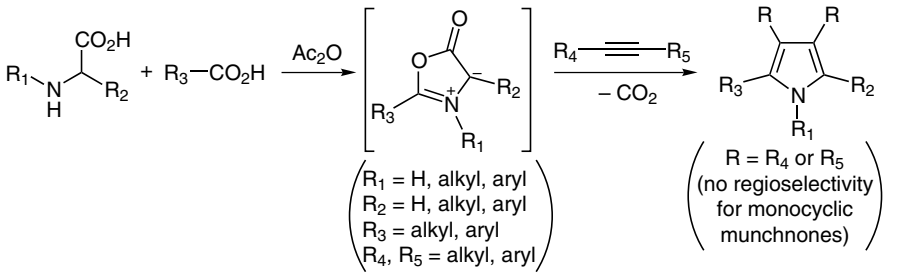
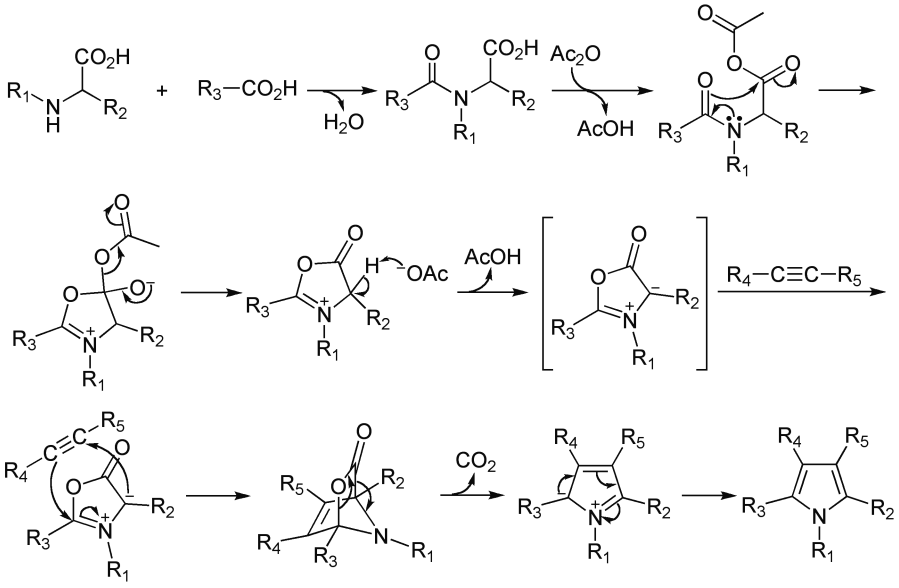
cis-azomethine ylides with dipolarophiles is competed by the isomerization to *trans*-azomethine ylides.[10]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

This reaction involves the formation of cyclic 1,3-dipoles, followed by *1,3-Dipolar Cycloaddition* with dipolarophiles, the evolution of carbon dioxide, and the subsequent tautomerization to give pyrroles, as shown below.



D. MODIFICATION

This reaction was extended by Huisgen to the reaction of proline, acetic anhydride, and dimethyl acetylenedicarboxylate to give pyrrole derivatives.[11] In addition, a method for generating the munchnone from 1,3-oxazolium perchlorate with triethylamine at low temperatures has been developed.[12] Moreover, an analogous pyrrole synthesis via a tran-

sient azomethine ylide involving a di-rhodium (II) salt–catalyzed three-component coupling between an imine, diazoacetonitrile, and activated alkynyl coupling partner to give 1,2-diarylpyrrole has been recently established.[13]

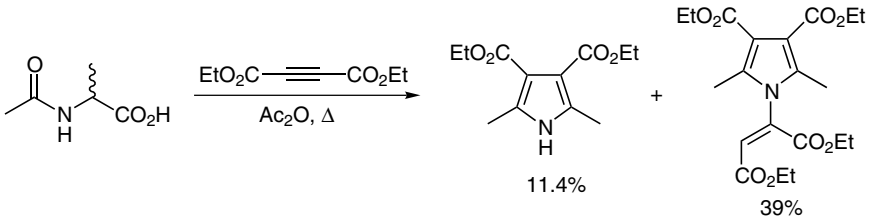
E. APPLICATIONS

This reaction has wide applications in the preparation of pyrrole derivatives.

F. RELATED REACTIONS

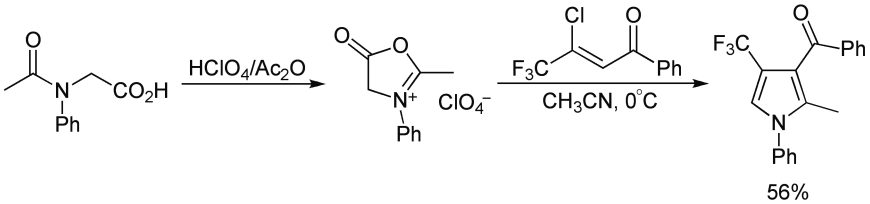
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 14.

To a suspension of 1.31 g *N*-acetyl-D,L-alanine (10 mmol) in 10 mL acetic anhydride was added 3.2 mL diethyl acetylenedicarboxylate (20 mmol). The reaction mixture was maintained at 110°C for 2 h, cooled, and then evaporated under reduced pressure. The oily residue was dissolved in hot cyclohexane and left in the refrigerator overnight with crystal seeds. Diethyl 2,5-dimethyl pyrrole-3,4-dicarboxylate was isolated as white needles by filtration, in amount of 274 mg, in a yield of 11.4%. The filtrate was evaporated and chromatographed (dry column vacuum chromatography) using CH_2Cl_2 and then CH_2Cl_2/EtOH (99:1 to 98:2) to afford 1.58 g 2-(2,5-dimethyl-3,4-diethoxycarbonyl)-pyrrolyl maleic acid diethyl ester as a yellowish oil, in a yield of 39%.



Reference 5.

To a solution of 5 mL CH_3CN containing 505 mg Et_3N (5.0 mmol) at 0°C was added 117 mg 2-chloro-2-trifluoro-vinyl benzophenone (0.5 mmol) dropwise under a nitrogen atmosphere. Then a solution of 413 mg *N*-phenyl-2-methyl-1,3-oxazolium perchlorate (1.5 mmol) in 1 mL CH_3CN was slowly added while the temperature was maintained below 0°C. The resulting mixture was stirred at 0°C for 3 h and then at room temperature overnight. After evaporation of the solvent in vacuo, the residue was purified by silica gel column chromatography using *n*-hexane/EtOAc (5:1 then 5:2) as the eluent to afford 93 mg 3-benzoyl-2-methyl-1-phenyl-4-(trifluoromethyl)pyrrole as a pale yellow solid, in a yield of 56%, m.p. 73–7°C.

Other references related to the Huisgen pyrrole synthesis are cited in the literature.[15]

H. REFERENCES

1. Huisgen, R. and Laschtuvka, E., *Ber.,* **1960**, *93*, 65.
2. Rebek, J.; Shaber, S. H.; Shue, Y.-K.; Gehret, J.-C. and Zimmerman, S., *J. Org. Chem.,* **1984**, *49*, 5164.
3. Hershenson, F. M., *J. Org. Chem.,* **1972**, *37*, 3111.
4. Lalezari, I. and Schwartz, E. L., *J. Med. Chem.,* **1988**, *31*, 1427.
5. Okano, T.; Uekawa, T.; Morishima, N. and Eguchi, S., *J. Org. Chem.,* **1991**, *56*, 5259.
6. (a) Coldham, L. and Hufton, R., *Chem. Rev.,* **2005**, *105*, 2765. (b) Overman, L. E. and Tellew, J. E., *J. Org. Chem.,* **1996**, *61*, 8338.
7. Bashiardes, G.; Safir, I.; Mohamed, A. S.; Barbot, F. and Laduranty, J., *Org. Lett.,* **2003**, *5*, 4915.
8. (a) Bayer, H. O.; Gotthardt, H. and Huisgen, R., *Ber.,* **1970**, *103*, 2356. (b) Gotthardt, H. and Huisgen, R., *Ber.,* **1970**, *103*, 2625. (c) Huisgen, R.; Gotthardt, H. and Bayer, H. O., *Angew. Chem. Int. Ed. Engl.,* **1964**, *3*, 135. (d) Huisgen, R.; Gotthardt, H.; Bayer, H. O. and Schaefer, F. C., *Angew. Chem. Int. Ed. Engl.,* **1964**, *3*, 136.
9. Padwa, A.; Burgess, E. M.; Gingrich, H. L. and Rousch, D., *J. Org. Chem.,* **1982**, *47*, 786.
10. Huisgen, R. and Mäder, H., *J. Am. Chem. Soc.,* **1971**, *92*, 1777.
11. Huisgen, R.; Gotthard, H.; Bayer, H. O. and Schaefer, F. C., *Ber.,* **1970**, *103*, 2611.
12. (a) Boyd, G. V. and Wright, P. H., *J. Chem. Soc., Perkin Trans. I,* **1972**, 909. (b) Boyd, G. V. and Wright, P. H., *J. Chem. Soc., Perkin Trans. I,* **1972**, 914.
13. Galliford, C. V. and Scheidt, K. A., *J. Org. Chem.,* **2007**, *72*, 1811.
14. Galezowski, M. and Gryko, D. T., *J. Org. Chem.,* **2006**, *71*, 5942.
15. (a) Meade, E. A.; Wotring, L. L.; Drach, J. C. and Townsend, L. B., *J. Med. Chem.,* **1997**, *40*, 794. (b) Avalos, M.; Babiano, R.; Cabanillas, A.; Cintas, P.; Jiménez, J. L.; Palacios, J. C.; Aguilar, M. A.; Corchado, J. C. and Espinosaq-García, J., *J. Org. Chem.,* **1996**, *61*, 7291. (c) Gupton, J. T.; Krolikowski, D. A.; Yu, R. H.; Reisinger, S. W. and Sikorski, J. A., *J. Org. Chem.,* **1990**, *55*, 4735. (d) Padwa, A.; Fryxell, G. E.; Gasdaska, J. R.; Venkatramanan, M. K. and Wong, G. S. K., *J. Org. Chem.,* **1989**, *54*, 644. (e) Vedejs, E.; Larsen, S. and West, F. G., *J. Org. Chem.,* **1985**, *50*, 2170. (f) Barluenga, J.; Rubio, V. and Gotor, V., *J. Org. Chem.,* **1982**, *47*, 1696. (g) Myers, J. A.; Moore, L. D.; Whitter, W. L.; Council, S. L.; Waldo, R. M.; Lanier, J. L. and Omoji, B. U., *J. Org. Chem.,* **1980**, *45*, 1202. (h) Taylor, E. C. and Turchi, I. J., *Chem. Rev.,* **1979**, *79*, 181. (i) Caramella, P.; Huisgen, R. and Schmolke, B., *J. Am. Chem. Soc.,* **1974**, *96*, 2997. (j) Huisgen, R., *Angew. Chem. Int. Ed. Engl.,* **1967**, *2*, 565. (k) Huisgen, R.; Gotthardt, H.; Bayer, H. O.; Schaefer, F. C., *Angew. Chem.*, **1964**, *76*, 185.

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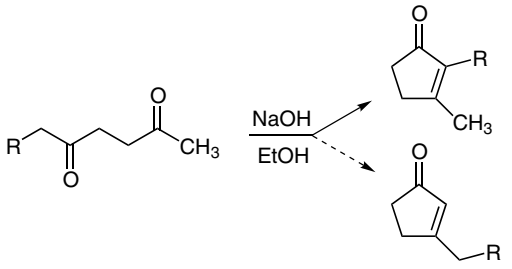
Hunsdiecker Condensation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Hunsdiecker in 1942.[1] It is the synthesis of 2,3-disubstituted cyclopentenones via an intramolecular condensation of 1,4-diketone (or γ-dicarbonyl compounds) by means of base treatment. When 2-acetyl ketone is treated with a base, two possible cyclopentenones—2-alkyl-3-methyl cyclopentenone and 3-alkyl cyclopentenone might form. However, only former has been reported as the isolated product[2] because the intramolecular condensation occurs via a reversible *Aldol Reaction*, and the transition state leading to the formation of 2-alkyl-3-methyl cyclopentenone is 2 Kcal/mol more stable than that needed to give 3-alkyl cyclopentenone.[3] This reaction has been modified to occur under the milder conditions of K_2CO_3/methanol.[4]

B. GENERAL REACTION SCHEME



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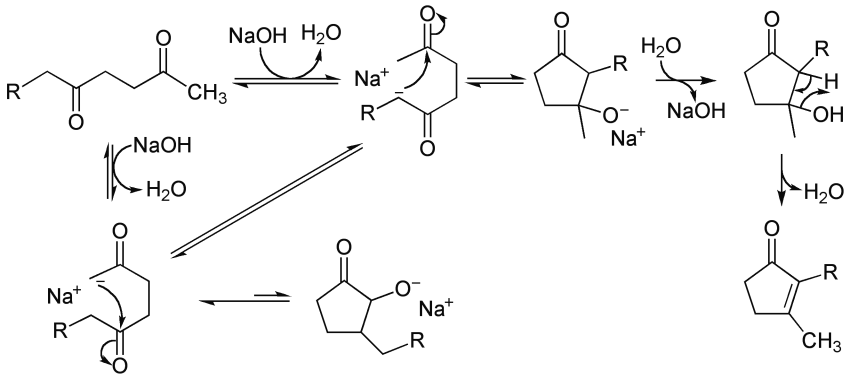
C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified using a mild basic system, such as K_2CO_3/MeOH.[4]

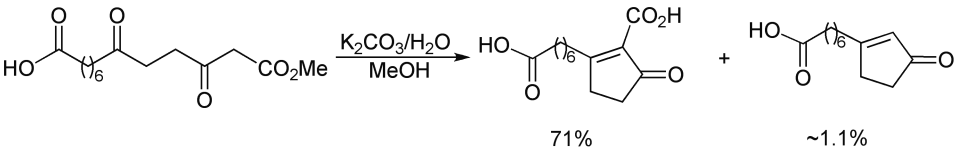
E. APPLICATIONS

This reaction is one of the general reactions used to prepare substituted cyclopentenones.[4]

F. RELATED REACTIONS

This reaction is related to *Aldol Condensation.*

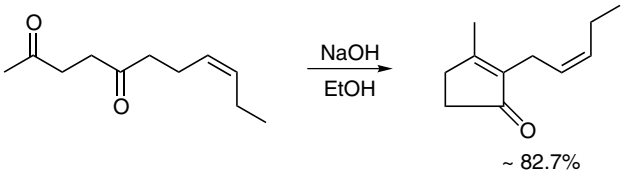
G. CITED EXPERIMENTAL EXAMPLES



Reference 4.

12-Methoxycarbonyl-8,11-dioxolauric acid (24.84 g, 82.8 mmol) was dissolved in 125 mL methanol, and 250 mL 20% aqueous K_2CO_3 solution was added. The mixture was refluxed for 1 h. After the solution was concentrated to one-third volume, cooled, and acidified with 2 *N*HCl, a crystalline precipitate (15.5 g) was separated. The filtrate was extracted with EtOAc, and the resulting 2.1 g extract was mixed with the crystalline precipitate. The mixture was recrystallized from ether to give 15.0 g 7-(2′-carboxy-3′-oxo-1′-cyclopentene)heptanoic acid, in a yield of 71%, m.p., 60–62°C.

Evaporation of the ethereal mother liquor gave 2.4 g of an oil that on trituration with ether gave 240 mg 7-(3′-oxo-1′-cyclopenten) heptanoic acid, m.p., 100–101°C.



Reference 5.

A mixture of 2.799 g *cis*-undec-8-ene-2,5-dione, 7 mL ethanol, and 25 mL 0.5 N NaOH was refluxed under nitrogen for 5 h. The mixture was cooled, extracted with pentane, washed with water, dried over Na_2SO_4, and evaporated. The remaining oil (2.522 g) was distilled through a microspinning-band column at 80–100°C (bath temperature) and 0.05 mmHg pressure, giving 2.087 g of *cis*-jasmone.

Other references related to the Hunsdiecker condensation are cited in literature.[6]

H. REFERENCES

1. (a) Hunsdiecker, H., *Ber.,* **1942**, *75*, 447. (b) Hunsdiecker, H., *Ber.,* **1942**, *75*, 455.
2. (a) Ito, Y.; Konoike, T.; Harada, T. and Saegusa, T., *J. Am. Chem. Soc.,* **1977**, *99*, 1487. (b) Mukaiyama, T.; Narasaka, K. and Furusato, M., *J. Am. Chem. Soc.,* **1972**, *94*, 8641. (c) Stork, G. and Borch, R., *J. Am. Chem. Soc.,* **1964**, *86*, 936. (d) Sommer, L. H. and Pioch, R. P., *J. Am. Chem. Soc.,* **1954**, *76*, 1606. (e) LaForge, F. B.; Green, N. and Gersdorff, W. A., *J. Am. Chem. Soc.,* **1948**, *70*, 3707.
3. McCurry, P. M. and Singh, R. K., *J. Org. Chem.,* **1974**, *39*, 2316.
4. Finch, N.; Fitt, J. J. and Hsu, I. H. C., *J. Org. Chem.,* **1971**, *36*, 3191.
5. Büchi, G. and Wüest, H., *J. Org. Chem.,* **1966**, *31*, 977.
6. (a) Dessau, R. M. and Heiba, E. I., *J. Org. Chem.,* **1974**, *39*, 3457. (b) Schechter, M. S.; Green, N. and LaForge, F. B., *J. Am. Chem. Soc.,* **1949**, *71*, 1517.

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Hunsdiecker Reaction

A. GENERAL DESCRIPTION OF THE REACTION

Although this reaction was first reported by Borodine in 1861[1] for the preparation of bromomethane from silver acetate and bromine, it was Hunsdiecker who extensively investigated this reaction and turned it into practice.[2] Therefore, the decomposition of carboxylic acid salts of Ag(I) in combination with halogen source (e.g., bromine) into organic halides with one less carbon atom than the original acids is generally known as the Hunsdiecker reaction.[3] In addition, this reaction is also referred to as the Borodine reaction,[4] Hunsdiecker-Borodine reaction,[5] Hunsdiecker decarboxylation,[6] Hunsdiecker bromodecarboxylation,[7] and Hunsdiecker degradation.[8] It should be pointed out that this reaction is also falsely called the *Simonini Reaction*.[9]

In this reaction, besides the often used silver salts, the corresponding Hg(II), Ti(I), or Pb(IV) salt of the carboxylic acids also undergoes a similar reaction.[5,10] This reaction works for aliphatic acids with either long or short hydrocarbon chains, by which the yields of halides decrease in the order of primary acid > secondary acid > tertiary acid.[3hh] However, this reaction is also accompanied with isomerization and racemization when the carboxylic acid salt group is attached to an asymmetric carbon of aliphatic acid.[3gg] Many experimental results support a free radical mechanism for this reaction,[3d,3y,3bb,3dd,3gg,6,11] involving the decomposition of intermediate hypohalite,[3m,3cc] although the ionic pathways are also favored by some experimental evidence.[3m,12] It should be pointed out that in a few cases, the Hunsdiecker reaction of corresponding carboxylic acid does not lead to the normal product of halides. For example, the reaction with iodine results in the formation of ester,[3hh] the decomposition of silver salts of α-hydroxy or α-amino acids produce aldehydes of one less carbon,[3hh] the decomposition of 1-hydroxycyclopentylacetic acid or 1-hydroxycyclohexylacetic acid leads to a product with a cleaved cyclic ring,[3y] and

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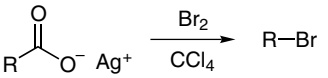
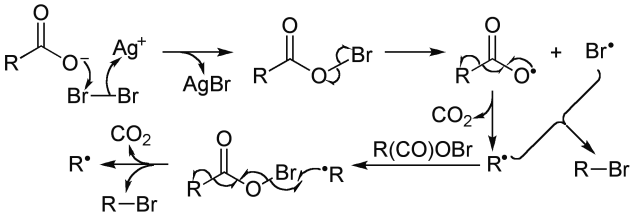
the Hunsdiecker reaction of β,β,β-triarylpropionic acid forms aryl β,β-diarylacrylate.[13] To address the moisture sensitivity and heat instability of silver salts,[3w] the original protocol was modified by Cristol and Firth by the addition of bromine into the slurry mixture of carboxylic acid and red mercuric oxide in carbon tetrachloride,[14] and this modification has been widely applied in organic synthesis because of its tolerance for moisture.[3z,3bb,13a,15] Other modifications of this reaction include the direct bromination of carboxylic acid with bromine at very high temperatures (e.g., 350°C),[3aa] photochemical initiation of ester bound to the *N*-hydroxy thiazole 2(3)-thione on a Wang resin,[3d] bromination or iodination from *N*-bromo-succinimide (NBS) or *N*-iodo-succinimide (NIS) in the presence of lithium acetate,[10] direct bromination of carboxylic acid from selectfluor,[5] triethylamine catalyzed bromination,[3c] and bromination of Barton's 2(1H)-thioxo-1-pyridyl ester in the presence of bromotrichloromethane or iodoform.[7,16] The last modification is also known as Barton-Hunsdiecker decarboxylation or Hunsdiecker-Barton decarboxylation.[16]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been extensively modified for various conditions as mentioned in section A. In addition, the α,β-unsaturated carboxylic acids, including cinnamic acids, can be converted into α,β-unsaturated nitro compounds when treated with nitric acid and a catalytic amount of AIBN in acetonitrile via nitrodecarboxylation.[17]

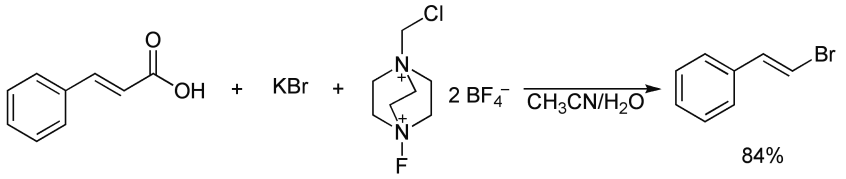
E. APPLICATIONS

This reaction has general application in the synthesis of aliphatic halides.

F. RELATED REACTIONS

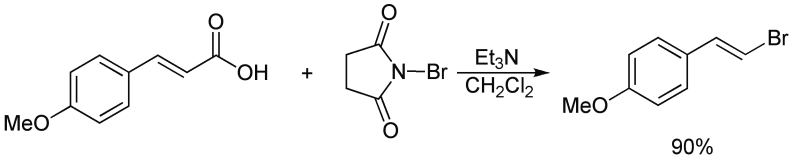
This reaction is related to *Kochi Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 5.

To a stirred mixture of 1.48 g *trans*-cinnamic acid (10.0 mmol), 4.20 g KBr (35.0 mmol), and 25.0 mL CH_3CN, were added 1 mL water and 4.24 g Selectfluor (13.0 mmol). The reaction was monitored by TLC. After completion of the reaction, it was diluted with water and extracted with CH_2Cl_2 (25 mL × 3). The organic layers were combined and washed with dilute solutions of $NaHCO_3$, Na_2SO_3, and brine. It was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude products, which were purified by silica gel column chromatography to afford 1.54 g 1-(2-bromovinyl)benzene with an E/Z ratio of 95:5, in a yield of 84%.



Reference 3c.

Triethylamine (7 mL) was added to 3.0 mL dichloromethane containing 0.178 g 4-methoxy-*trans*-cinnamic acid (1.0 mmol). After the mixture was stirred for 5 min at room temperature, 1.2 mmol *N*-bromo-succinimide (1.2 mmol) was added. The solution was stirred for 5 min, and the solvent was removed under reduced pressure. The residue was subjected to silica gel column chromatography (1% EtOAc in hexanes) to afford 90% 4-methoxy-β-bromostyrene.

Other references related to the Hunsdiecker reaction are cited in the literature.[18]

H. REFERENCES

1. Borodine, B., *Ann.,* **1861**, *119*, 121.
2. (a) Hunsdiecker, C.; Hunsdiecker, H. and Vogt, E., *Brit. Pat.,* Nov. 11, **1936**, 456,565. [*Chem. Abstr.,* **1937**, *31*, 2233]. (b) Hunsdiecker, C.; Hunsdiecker, H. and Vogt, E., *French Pat.,* Dec. 10, **1936**, 803,941. [*Chem. Abstr.,* **1937**, *31*, 2616]. (c) Hunsdiecker, C.; Hunsdiecker, H. and Vogt, E., *U.S. Pat.,* Oct. 17, **1939**, 2,176,181. [*Chem. Abstr.,* **1940**, *34*, 1685]. (d) Hunsdiecker, C.;

Hunsdiecker, H. and Vogt, E., *Ger. Pat.,* Apr. 9, **1935**, 695,062. [*Chem. Abstr.,* **1941**, *35*, 5132]. (e) Hunsdiecker, C. and Hunsdiecker, H., *Ber.,* **1942**, 75, 291. (f) Hunsdiecker, C. and Hunsdiecker, H., *Ber.,* **1942**, *75*, 295. (g) Hunsdiecker, C.; Hunsdiecker, H. and Vogt, E., *Ger. Pat.,* Apr. 9, **1935**, 722,464. [*Chem. Abstr.,* **1943**, *37*, 5078]. (h) Hunsdiecker, C.; Hunsdiecker, H. and Vogt, E., *Ger. Pat.,* Apr. 9, **1935**, 730,410 [*Chem. Abstr.,* **1944**, *38*, 374].

3. (a) Howton, D. R.; Davis, a) Ramgopal, S.; Ramesh, K.; Chakradhar, A.; Reddy, N. M. and Rajanna, K. C., *Tetrahedron Lett*., **2007**, *48*, 4043. (b) Kuang, C. X.; Yang, Q.; Senboku, H. and Tokuda, M., *Synthesis*, **2005**, 1319. (c) Das, J. P. and Roy, S., *J. Org. Chem.,* **2002**, *67*, 7861. (d) Luca, L. D.; Giacomelli, G.; Porcu, G. and Taddei, M., *Org. Lett.,* **2001**, *3*, 855. (e) Sinha, J.; Layek, S.; Mandal, G. C. and Bhattacharjee, M., *Chem. Commun.,* **2001**, 1916. (f) Kuang, C. X.; Senboku, H. and Tokuda, M., *Synlett*, **2000**, 1439. (g) Naskar, D. and Roy, S., *Tetrahedron*, **2000**, *56*, 1369. (h) Naskar, D.; Das, S. K.; Giribabu, L.; Maiya, B. G. and Roy, S., *Organometallics,* **2000,** 19,1464. (i) Chowdhury, S. and Roy, S., *Tetrahedron Lett*., **1996**, *37*, 2623. (j) El Amouri, H.; Gruselle, M.; Vaissermann, J.; McGlinchey, M. J. and Jaouen, G., *J. Organomet. Chem.,* **1995**, *485*, 79. (k) Gilday, J. P. and Paquette, L. A., *Tetrahedron Lett*., **1988**, *29*, 4505. (l) Barton, D. H. R.; Crich, D. and Motherwell, W. B., *Tetrahedron Lett*., **1983**, *24*, 4979. (m) Uemura, S.; Tanaka, S.; Okano, M. and Hamana, M., *J. Org. Chem.,* **1983**, *48*, 3297. (n) Ando, T.; Ishihara, T.; Yamashita, A. and Matsumoto, M., *Bull. Chem. Soc. Jpn.,* **1981**, *54*, 3873. (o) Brace, N. O., *J. Fluor. Chem.,* **1981**, *18*, 515. (p) Cambie, R. C.; Hayward, R. C.; Jurlina, J. L.; Rutledge, P. S. and Woodgate, P. D., *J. Chem. Soc., Perkin Trans. I,* **1981**, 2608. (q) Zanati, G. and Rahim, N. Y. A., *Libyan J. Sci*., **1979**, *9A*, 43. (r) Kobayashi, K. and Lambert, J. B., *J. Org. Chem.,* **1977**, *42*, 1254. (s) Ando, T.; Yamashita, A.; Matsumoto, M.; Ishihara, T. and Yamanaka, H., *Chem. Lett.,* **1973**, 1133. (t) Shatkina, T. N.; Lovtsova, A. N.; Leont'eva, E. V. and Reutov, O. A., *Dokl. Akad. Nauk SSSR,* **1972**, *207*, 1373. (u) Cason, J. and Walba, D. M., *J. Org. Chem.,* **1972**, *37*, 669. (v) Bunce, N. J., *J. Org. Chem.,* **1972**, *37*, 664. (w) Susan, A. B. and Nystrom, R. F., *J. Labelled Compd.,* **1971**, *7*, 269. (x) Avram, M.; Mateescu, G. D. and Nenitzescu, C. D., *Rev. Roumaine Chim.,* **1969**, *14*, 101. (y) Kundu, N. G. and Sisti, A. J., *J. Org. Chem.,* **1969**, *34*, 229. (z) Davis, J. A.; Herynk, J.; Carroll, S.; Bunds, J. and Johnson, D., *J. Org. Chem.,* **1965**, *30*, 415. (aa) Scribner, R. M., *J. Org. Chem.,* **1964**, *29*, 284. (bb) Baker, F. W.; Holtz, H. D. and Stock, L. M., *J. Org. Chem.,* **1963**, *28*, 514. (cc) Kochi, J. K.; Graybill, B. M. and Kurz, M., *J. Am. Chem. Soc.,* **1964**, *86*, 5257. (dd) Applequist, D. E. and Peterson, A. H., *J. Am. Chem. Soc.,* **1960**, *82*, 2372. (ee) Cristol, S. J.; Douglass, J. R.; Firth, W. C. and Krall, R. E., *J. Am. Chem. Soc.,* **1960**, *82*, 1829. (ff) Eliel, E. L. and Acharya, R. V., *J. Org. Chem.,* **1959**, *24*, 151. (gg) Abell, P. I., *J. Org. Chem.,* **1957**, *22*, 769. (hh) Johnson, R. G. and Ingham, R. K., *Chem. Rev.,* **1956**, *56*, 219. (ii) Wilt, J. W. and Oathoudt, D. D., *J. Org. Chem.,* **1956**, *21*, 1550. (jj) Merten, H. and Gilman, H., *J. Am. Chem. Soc.,* **1954**, *76*, 5798. (kk) Stanek, J., *Chem. Listy Vedu Prumysl,* **1953**, *47*, 1244.
4. R. H. and Nevenzel, J. C., *J. Am. Chem. Soc.,* **1954**, *76*, 4970.
5. Ye, C. F. and Shreeve, J. M., *J. Org. Chem.,* **2004**, *69*, 8561.
6. Stein, R. A. and Kayama, M., *J. Org. Chem.,* **1961**, *26*, 5231.
7. Toyota, S.; Akinaga, T.; Kojima, H.; Aki, M. and Oki, M., *J. Am. Chem. Soc.,* **1996**, *118*, 11460.
8. Knapp, F. F., *Steroids*, **1979**, *33*, 245.
9. (a) Wagner, R. B. and Zook, H. D., *Synthetic Organic Chemistry,* John Wiley & Sons, New York, **1953**, p. 96. (b) Henne, A. L. and Zimmer, W. F., *J. Am. Chem. Soc.,* **1951**, *73*, 1362.
10. Chowdhury, S. and Roy, S., *J. Org. Chem.,* **1997**, *62*, 199.
11. (a) Wilt, J. W. and Oathoudt, D. D., *J. Org. Chem.,* **1958**, *23*, 218. (b) Wilson, C. V., *Org. React.,* **1957**, *9*, 332.
12. Pandit, U. K. and Dirk, I. P., *Tetrahedron Lett.,* **1963**, 891.
13. (a) Wilt, J. W. and Lundquist, J. A., *J. Org. Chem.,* **1964**, *29*, 921. (b) Wilt, J. W. and Finnerty, J. L, *J. Org. Chem.,* **1961**, *26*, 2173.
14. Cristol, S. J. and Firth, W. C., *J. Org. Chem.,* **1961**, *26*, 280.

15. Cristol, S. J.; Gaston, L. K. and Tiedeman, T., *J. Org. Chem.,* **1964**, *29*, 1279.
16. Porter, N. A.; Breyer, R.; Swann, E.; Nally, J.; Pradhan, J.; Allen, T. and McPhail, A. T., *J. Am. Chem. Soc.,* **1991**, *113*, 7002.
17. Das, J. P.; Sinha, P. and Roy, S., *Org. Lett.,* **2002**, *4*, 3055.
18. (a) Moriarty, R. M., *J. Org. Chem.,* **2005**, *70*, 2893. (b) Tabushi, I.; Aoyama, Y.; Koji, S.; Hamuro, J. and Yoshida, Z.-I., *J. Am. Chem. Soc.,* **1972**, *94*, 1177. (c) Belohlav, L. R. and McBee, E. T., *Ind. Eng. Chem.,* **1961**, *53*, 1015. (d) Arnold, R. T. and Morgan, P., *J. Am. Chem. Soc.,* **1948**, *70*, 4248.

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Hydroformylation
(Oxo Reaction, Oxo Process, Oxo Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Smith et al. in 1930[1] and subsequently by Roelen in 1938.[2] It is an industrial process for synthesizing aldehydes and alcohols from olefins and synthesis gas (i.e., carbon monoxide and hydrogen) in the presence of a cobalt or rhodium catalyst at high pressures (100–200 atm) and high temperatures (115–190°C) with the attachment of a new carbon to the less-substituted end of the double bonds.[3] In the literature, this reaction is often known as hydroformylation,[2b,2c,4] as well as oxo process,[2b,4i,4j,5] oxo reaction[2c,3,4l–4o,6] oxo synthesis,[4k,7] and Roelen reaction.[8] This reaction is one of the most extensively used reactions in the field of organometallic chemistry,[9] resulting in the production of 2.6 million metric tons of aldehydes and alcohols in 1969. Generally, aldehydes dominate in the product mixtures at relatively low temperatures (e.g., 115–125°C), whereas alcohols are almost the sole products at temperature >180°C.[3] This process is sometimes carried out in two stages: the production of aldehydes and the further reduction of aldehydes into alcohols. In addition, the straight-chain terminal olefins often lead to two isomeric aldehydes or alcohols,[4m] while ketones are the major product when ethylene is subjected to the hydroformylation.[4k] However, α,β-unsaturated aldehydes and ketones undergo direct reduction to saturated aldehydes and ketones without any hydroformylation at 120–125°C and 200–300 atm, yet these unsaturated carbonyl compounds are completely reduced under similar pressure, but at temperatures of 180–185°C. For comparison, conjugated dienes and furans undergo both types of reactions, by which one double bond is reduced and the other is extended by a formyl group; in contrast, thiophene and phenanthrene undergo only slow reductions, and benzene is inert under such hydroformylation

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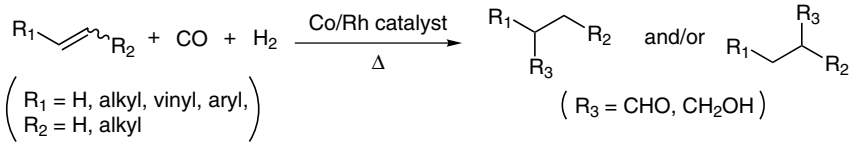
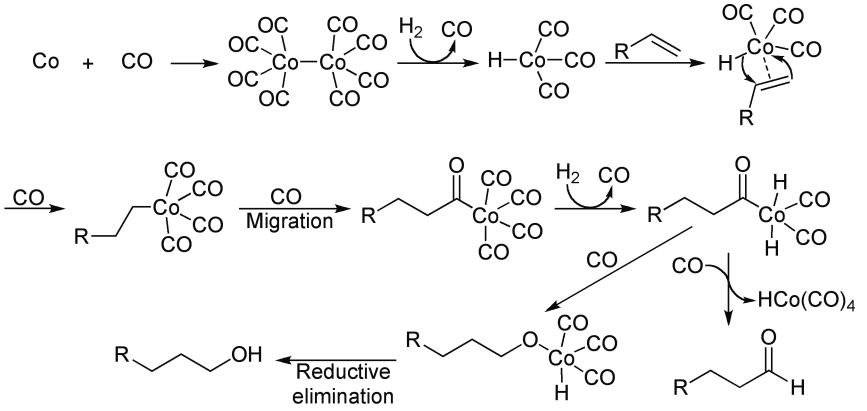
conditions. For vinyl aromatics or vinyl heteroaromatics, the corresponding aldehydes are the major products, except for 4-vinyl pyridine and 2-vinyl pyridine, which form either hydrogenation or hydroformylation products, depending on the catalyst employed.[10] For rhodium-catalyzed hydroformylation, it has been found that hydrogen and formyl groups add to both *cis* and *trans* internal olefins from the same side with high stereospecificity.[11] Because of the high cost of rhodium catalyst, this process has been modified using a VIB group metal (Cr, Mo, W) complex as the major component of the binary catalyst system in combination with trace amounts of cobalt or rhodium carbonyl, which can be adjusted in terms of catalytic activity and selectivity.[4i]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is believed that this process involves the following steps: (a) formation of dicobaltoctacarbonyl from cobalt and CO, which equilibrates with cobalt hydrocarbonyl by reaction with hydrogen; (b) substitution of one carbon monoxide by olefin to form a π-complex; (c) conversion of a π-complex to cobalt alkyltetracarbonyl via a cobalt tricarbonyl intermediate after the addition of carbon monoxide; and (d) fast rearrangement of the cobalt alkyltetracarbonyl compound into the acyl cobalt tricarbonyl compound, which reacts with hydrogen to give aldehyde and cobalt hydrocarbonyls.[4k] A detailed mechanism is shown below.



D. MODIFICATION

This reaction has been modified using a group VIB metal complex as catalyst in combination with trace amounts of cobalt or rhodium carbonyl complex.[4i]

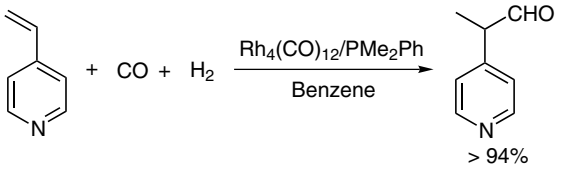
E. APPLICATIONS

This reaction has extensive application in the industrial production of aldehydes and alcohols with carbon chains from C_4 to C_{13}.[12]

F. RELATED REACTIONS

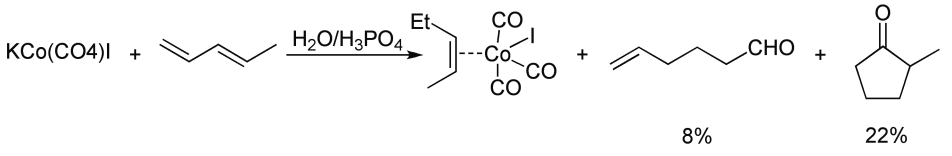
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 9.

A solution of 0.8 mL 4-vinyl pyridine (7.42 mmol), 3.0 mg $Rh_4(CO)_{12}$ (0.004 mmol), and 9.0 mg PMe_2Ph (0.064 mmol) in 4.0 mL benzene was introduced by suction into an evacuated 25-mL stainless-steel autoclave equipped with a magnetic stirrer. The reactor was transferred to an oil bath, and carbon monoxide was introduced; the autoclave was then heated to 100°C (45 atm), and hydrogen was rapidly introduced up to 100 atm total pressure (CO/H_2,1:1). During the reaction, the drop in pressure was restored by injection of a carbon monoxide–hydrogen mixture (1:1 from a high-pressure container). After 75 min, GC analysis of a siphonated sample indicated that 4-vinyl pyridine had been completely transformed into branched and linear aldehydes (96:4 isomeric ratio), and the hydrogenation product was $< 2\%$. The reactor was cooled, and the CO/H_2 gas mixture was vented. After evaporation of the solvent, a pure sample was obtained as a yellow-green oil by distillation of the crude product at reduced pressure (0.1 mmHg, 120–125°C).



Reference 4k.

A solution of 0.2 mol potassium tetracarbonylcobaltate(-I) in 300 mL water was placed in a 1-L steel autoclave; then 120 mL concentrated phosphoric acid and 0.2 mol 1,4-pentadiene were added without mixing, and the autoclave was closed, inverted to mix the reactants, and rocked for 24 h. The vessel was opened under a stream of nitrogen, and 100 mL hexane was added to extract the products. The hexane layer was separated, washed with distilled water, dried over sodium sulfate, and transferred to a distillation apparatus. The hexane was removed by aspirator vacuum; the product was distilled under high vacuum. The material distilling at 45°C (1 mmHg) was collected as one fraction; the material distilling at 45°C was predominantly π-(l-ethylallyl) tricarbonylcobaltate(-I). The first fraction was further separated into two pure compounds in a Beckman Megchrom gas chromatograph equipped with a silicone rubber column. The first component (8% yield) was identified as 5-hexenal. The second component (22% yield) was identified as 2-methylcyclopentanone.

Other references related to the hydroformylation are cited in the literature.[13]

H. REFERENCES

1. Smith, D. F.; Hawk, C. D. and Golden, P. L., *J. Am. Chem. Soc.,* **1930**, *52*, 3221.
2. (a) Roelen, O., *U.S. Pat.,* Aug. 17, **1943**, 2,327,066. (b) Roelen, O., *Ger. Pat.,* Sept. 15, **1952**, 849,548. (c) Weber, H. and Falbe, J., *Ind. Eng. Chem.,* **1970**, *62*, 33. (d) Hughes, V. L. and Kirshenbaum, I., *Ind. Eng. Chem.,* **1957**, *49*, 1999.
3. Beal, P. F.; Rebenstorf, M. A. and Pike, J. E., *J. Am. Chem. Soc.,* **1959**, *81*, 1231.
4. (a) Guazzelli, G.; Settambolo, R. and Lazzaroni, R., *Synth. Commun.,* **2007**, *37*, 1211. (b) Li, C.; Yuan, M. L.; Fu, H. Y.; Chen, H. and Li, X. J., *Huaxue Yanjiu Yu Yingyong*, **2006**, *18*, 9. (c) Thomas, P. J.; Axtell, A. T.; Klosin, J.; Peng, W.; Rand, C. L.; Clark, T. P.; Landis, C. R. and Abboud, K. A., *Org. Lett.,* **2007**, P. 2665. (d) Zou, Y. P.; Yan, Y. J. and Zhang, X. M., *Tetrahedron Lett*., **2007**, *48*, 4781. (e) Breit, B.; Gruenanger, C. U. and Abillard, O., *Eur. J. Org. Chem.,* **2007**, 2497. (f) Odinets, I.; Kortvelyesi, T.; Kegl, T.; Kollar, L. and Keglevich, G., *Trans. Metal Chem.,* **2007**, *32*, 299. (g) Ricken, S.; Osinski, P. W.; Eilbracht, P. and Haag, R., *J. Mol. Catal. A: Chem.,* **2006**, *257*, 78. (h) Axtell, A. T.; Klosin, J. and Abboud, K. A., *Organometallics*, **2006**, *25*, 5003. (i) Tucci, E. R., *Ind. Eng. Chem. Prod. Res. Dev.,* **1985**, *24*, 38. (j) Jones, W. D. and Bergman, R. G., *J. Am. Chem. Soc.,* **1979**, *101*, 5447. (k) Bertrand, J. A.; Aldridge, C. L.; Husebye, S. and Jonassen, H. B., *J. Org. Chem.,* **1964**, *29*, 790. (l) Kirch, L. and Orchin, M., *J. Am. Chem. Soc.,* **1958**, *80*, 4428. (m) LoCicero, J. C. and Johnson, R. T., *J. Am. Chem. Soc.,* **1952**, *74*, 2094. (n) Wender, I.; Metlin, S. and Orchin, M., *J. Am. Chem. Soc.,* **1951**, *73*, 5704. (o) Wender, I.; Levine, R. and Orchin, M., *J. Am. Chem. Soc.,* **1950**, *72*, 4375.
5. (a) Shi, L.; Ma, Z.-F.; Sheng, C.-B. and Yao, H.-Q., *Tianranqi Huagong*, **2002**, *27*, 48. (b) Chen, Z., *Huagong Keji*, **1998**, *6*, 5. (c) Cronils, B. and Wiebus, E., *Rec. Trav. Chim. Pays-Bas,* **1996**, *115*, 211. (d) Claveau, A. and Epiney, M., *Pulp & Paper Canada*, **1990**, *91*, 31. (e) Macho, V.; Mistrik, E. J. and Polievka, M., *Petrochemia*, **1975**, *15*, 16. (f) Lemke, H., *Ind. Chim. (Paris),* **1965**, *52*, 169.
6. (a) Hynninen, P. H., *Liebigs Annalen der Chemie*, **1990**, 835. (b) Borovikov, M. S. and Rybakov, V. A., *Kinetika Kataliz,* **1986**, *27*, 1478. (c) Macek, V. and Kubicka, R., *Ropa Uhlie,* **1986**, *28*, 164. (d) Mizoroki, T.; Kioka, M.; Suzuki, M.; Sakatani, S.; Okumura, A. and Maruya, K., *Bull. Chem. Soc. Jpn.,* **1984**, *57*, 577. (e) Stevenz, D. and Doering, C. E., *Zeitsch. Chem.,* **1979**, *19*, 140. (f) Pino, P.; Piacenti, F. and Bianchi, M., *Org. Synth. Met. Carbonyls*, **1977**, *2*, 43.
7. (a) Wang, S. G.; Xiong, X. D.; Wu, C.; Li, M. L. and Li, Z. Y., *Xiyou Jinshu*, **2005**, *29*, 482. (b) Cornils, B., *Multiphase Homogeneous Catalysis*, **2005**, *1*, 291. (c) Cornils, B. and Kuntz, E.

G., *Aqueous-Phase Organometallic Catalysis*, 2nd ed., **2004**, p. 351. (d) Natta, G.; Ercoli, R. and Castellano, S., *Chim. Ind. (Milan),* **2003**, *85*, 9. (e) Poli, R., *Chemtracts*, **2001**, *14*, 690. (f) Drent, E. and Budzelaar, P. H. M., *J. Organomet. Chem.,* **2000**, *593–594*, 211. (g) Cornils, B. and Kuntz, E. G., *Aqueous-Phase Organometallic Catalysis*, **1998**, 271.

8. Cornils, B., "Hydroformylation, Oxo Synthesis, Roelen Reaction," in *New Syntheses with Carbon Monoxide,* ed., Falbe, J., Springer-Verlag, Berlin, **1980**, pp. 1–225.
9. Klingler, R. J. and Rathke, J. W., *J. Am. Chem. Soc.,* **1994**, *116*, 4772.
10. Lazzaroni, R.; Settambolo, R.; Caiazzo, A. and Bennett, M. A., *Organometallics,* **2002**, *21*, 2454.
11. Stefani, A.; Consiglio, G.; Botteghi, C. and Pino, P., *J. Am. Chem. Soc.,* **1973**, *95*, 6504.
12. Bartlett, J. H.; Kirshenbaum, I. and Muessig, C. W., *Ind. Eng. Chem.,* **1959**, *51*, 257.
13. (a) Lowary, T.; Meldal, M.; Helmboldt, A.; Vasella, A. and Bock, K., *J. Org. Chem.,* **1998**, *63*, 9657. (b) Keim, W.; Herwig, J. and Pelzer, G., *J. Org. Chem.,* **1997**, *62*, 422. (c) Johnson, J. R.; Cuny, G. D. and Buchwald, S. L., *Angew. Chem. Intl. Ed. Engl.,* **1995**, *34*, 1760. (d) Massoudi, R.; Kim, J. H.; King, R. B. and King, A. D., *J. Am. Chem. Soc.,* **1987**, *109*, 7428. (e) Pruett, R. L., *J. Chem. Edu.,* **1986**, *63*, 196. (f) Tucci, E. R., *Ind. Eng. Chem. Prod. Res. Dev.,* **1986**, *25*, 27. (g) Planalp, R. P. and Andersen, R. A., *J. Am. Chem. Soc.,* **1983**, *105*, 1114. (h) Pruett, R. L., *Acc. Chem. Res.,* **1979**, *17*, 1. (i) Casey, C. P. and Cyr, C. R., *J. Am. Chem. Soc.,* **1971**, *93*, 1280. (j) Piacenti, F.; Pucci, S.; Bianchi, M.; Lazzaroni, R. and Pino, P., *J. Am. Chem. Soc.,* **1968**, *90*, 6847. (k) Wender, I.; Orchin, M. and Storch, H. H., *J. Am. Chem. Soc.,* **1950**, *72*, 4842. (l) Kleman, A. M. and Abraham, M. A., *Ind. Eng. Chem. Res.,* **2006**, *45*, 1324. (m) Riisager, A.; Fehrmann, R.; Haumann, M.; Gorle, B. S. K. and Wasserscheid, P., *Ind. Eng. Chem. Res.,* **2005**, *44*, 9853. (n) Tannenbaum, R. and Bor, G., *J. Phys. Chem. A,* **2004**, *108*, 7105. (o) Huo, C.-F.; Li, Y.-W.; Beller, M. and Jiao, H. J., *Organometallics,* **2004**, *23*, 765. (p) Huo, C.-F.; Li, Y.-W.; Beller, M. and Jiao, H. J., *Organometallics,* **2003**, *22*, 4665. (q) Breit, B., *Acc. Chem. Res.,* **2003**, *36*, 264. (r) Decker, S. A. and Cundari, T. R., *Organometallics,* **2001**, *20*, 2827. (s) Alagona, G.; Ghio, C.; Lazzaroni, R. and Settambolo, R., *Organometallics,* **2001**, *20*, 5394. (t) Moiseev, I. I., *Kinetics and Catalysis,* **2001**, *42*, 1. (u) Snyder, G.; Tadd, A. and Abraham, M. A., *Ind. Eng. Chem. Res.,* **2001**, *40*, 5317. (v) Massick, S. M.; Rabor, J. G.; Elbers, S.; Marhenke, J.; Bernhard, S.; Schoonover, J. R. and Ford, P. C., *Inorg. Chem.,* **2000**, *39*, 3098. (w) Davis, T. and Erkey, C., *Ind. Eng. Chem. Res.,* **2000**, *39*, 3671. (x) Eilbracht, P.; Bärfacker, L.; Buss, C.; Hollmann, C.; Kitsos-Rzychon, B. E.; Kranemann, C. L.; Rische, T.; Roggenbuck, R. and Schmidt, A., *Chem. Rev.,* **1999**, *99*, 3329. (y) Gleich, D.; Schmid, R. and Herrmann, W. A., *Organometallics,* **1998**, *17*, 2141. (z) Guo, Y. and Akgerman, A., *Ind. Eng. Chem. Res.,* **1997**, *36*, 4581. (aa) Ritter, U.; Winkhofer, N.; Murugavel, R.; Voigt, A.; Stalke, D. and Roesky, H. W., *J. Am. Chem. Soc.,* **1996**, *118*, 8580. (bb) Agbossou, F.; Carpentier, J.-F. and Mortreux, A., *Chem. Rev.,* **1995**, *95*, 2485. (cc) Gholap, R. V.; Kut, O. M. and Bourne, J. R., *Ind. Eng. Chem. Res.,* **1992**, *31*, 2446. (dd) Mills, P. L.; Tremont, S. J. and Remsen, E. E., *Ind. Eng. Chem. Res.,* **1990**, *29*, 1443. (ee) Mirbach, M. J.; Mirbach, M. F.; Saus, A.; Topalsavoglou, N. and Phu, T. N., *J. Am. Chem. Soc.,* **1981**, *103*, 7594. (ff) Schulz, H. F. and Bellstedt, F., *Ind. Eng. Chem. Prod. Res. Dev.,* **1973**, *12*, 176. (gg) Tucci, E. R., *I&EC Prod. Res. Dev.,* **1968**, *7*, 32. (hh) Greenfield, H.; Wotiz, J. H., and Wender, I., *J. Org. Chem.,* **1957**, *22*, 542. (ii) Wender, I.; Metlin, S.; Ergun, S.; Sternberg, H. W. and Greenfield, H., *J. Am. Chem. Soc.,* **1956**, *78*, 5401. (jj) Wender, I.; Sternberg, H. W. and Orchin, M., *J. Am. Chem. Soc.,* **1953**, *75*, 3041. (kk) Adkins, H. and Krsek, G., *J. Am. Chem. Soc.,* **1949**, *71*, 3051.

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Iodolactonization

A. GENERAL DESCRIPTION OF THE REACTION

The halo cyclization was initially reported by Stobbe in 1902[1] and Fittig in 1904,[2] and the iodolactonization is believed to be established first by Bougault from 1904 to 1908.[3,4] It is the transformation of β,γ- or γ,δ-unsaturated carboxylic acid derivatives into either a five- or six-membered lactone in the presence of a positive iodine source with concomitant group and face selectivity. Therefore, this reaction is commonly known as the iodolactonization.[4–6] Occasionally, it is also referred to as the iodo cyclization.[7] Likewise, similar reactions with bromine sources are called bromolactonization.[5m] The iodine sources used for this reaction include $I_2 + NaHCO_3 + H_2O$,[5f,5o] $KI + I_2 + NaHCO_3$,[5k,8] $I_2 + AgOTF$,[5h] cyanogen iodide (CNI),[4c] ICl,[4a] IBr,[9] N-iodosuccinimide (NIS),[5a] iodonium dicollidine perchlorate,[4a,10] chalcogen iodine complex,[11] etc. On the other hand, the β,γ- or γ,δ-unsaturated carboxylic acid derivatives can be acids themselves,[5a,5c,5l,5m,5o,5p,8] their esters,[5h,9] amides,[4a,5e,7,12] or the phosphate.[4b] Although the β,γ- or γ,δ-unsaturated bonds are mostly double bonds, they could be triple bonds as well.[9] It has been reported that this reaction can occur in a two-phase system.[5d,5l] It is believed that this reaction involves the initial addition of positive iodine on the unsaturated bond followed by the carboxylate anion displacement on the resulting iodonium ion.[4c] The success of this reaction, therefore, depends on the ability to form either a five- or six-membered ring and on the electron density on the unsaturated bond.[4c] If the unsaturated bond is in conjugation with the carbonyl group, as in the case of α-keto-β,γ-unsaturated acid and α,β-γ,δ-unsaturated acid, there is an ineffectual addition of positive iodine to the unsaturated bond because of the reduction of electron density on the unsaturated bond.[4c] On the other hand, the increase of electron density on the carbonyl group[13] or the presence of substituents at the α position of carboxylic group facilitates this reaction and accelerates the reaction rate.[14] In particular, the substitution at the α position

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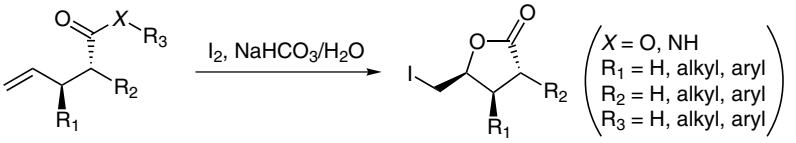
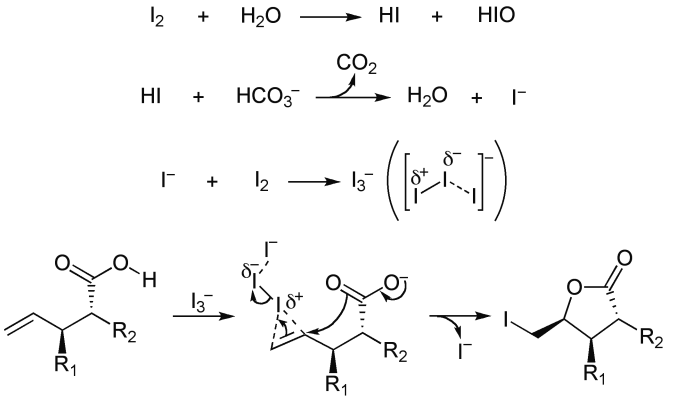
results in the high 1,3-asymmetric induction, where the *trans* selectivity is associated with amides and *cis* selectivity is associated with acids.[5b] The stereochemistry of the products, in most cases, depends on the substrates; however, in some cases, the reagents also control the outcome of the stereochemistry, such as when dihydroquinidine-iodine complex[15] or ICl[4a] is used as the source of I^+. Furthermore, the overall asymmetric induction can also be achieved in a thermodynamically[5m,16] or kinetically[17] controlled manner. This reaction has very broad applications in organic syntheses; some recent applications are the synthesis of nucleosides[18] and the change of stereochemistry of unsaturated carboxylic acid.[5i] In a special case, the iodolactonization is also competed by iodosultinization.[5h]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The mechanism is demonstrated by the reaction between γ,δ-unsaturated acid and $I_2/NaHCO_3$.



D. MODIFICATION

The original reaction protocol has been extensively modified using different positive iodine sources and different unsaturated acid derivatives, such as esters and amides, as mentioned.

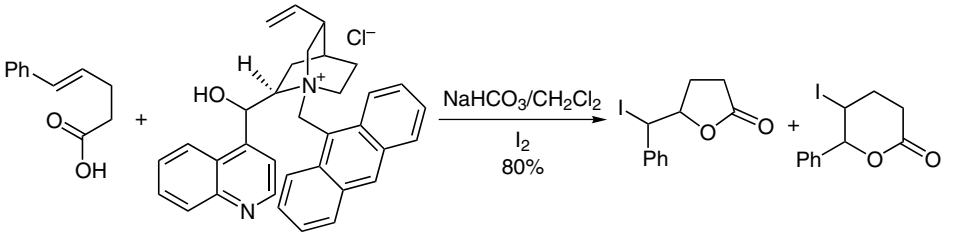
E. APPLICATIONS

This reaction has wide application in organic synthesis, especially in the preparation of nucleosides and lactones with desired stereochemistry.

F. RELATED REACTIONS

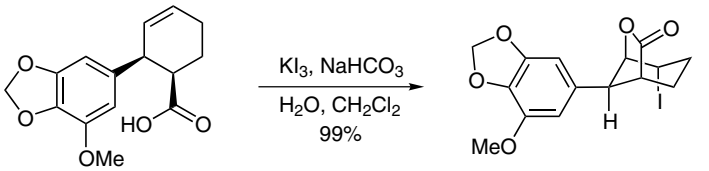
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 19.

To a solution of 176 mg *trans*-5-phenyl-4-pentenoic acid (1 mmol) and 150 mg *N*-anthrancenyl cinchonidinium chloride (0.3 mmol, as chiral phase transfer catalyst) in 10 mL CH_2Cl_2, was added 5 mL saturated aqueous $NaHCO_3$. After the mixture was stirred for 10 min, 380 mg iodine (1.5 mmol) was added to this rapidly stirred two-phase reaction mixture at 0°C. The flask was protected from light and stirred at 0°C for 10 h. The reaction mixture was diluted with 100 mL CH_2Cl_2 and then quenched with saturated aqueous $Na_2S_2O_3$. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (2×60 mL) and brine (60 mL) and dried over $MgSO_4$. After removal of solvent in vacuo, the resulting crude iodolactones were purified by column chromatography (silica, ether-petroleum ether) to give 242 mg two regioisomeric products, in a total yield of 80%. The two isomers are identified as 5-(iodo-phenyl-methyl)-dihydrofuran-2-one, in 16.0% e.e. and 5-iodo-6-phenyl-tetrahydro-pyran-2-one, in 30.5% e.e.



Reference 5d.

At room temperature, to a solution of 863 mg 2-(7-methoxybenzo[1,3]dioxol-5-yl)cyclohex-3-enecarboxylic acid (3.12 mmol) in 10 mL CH_2Cl_2, were added 15 mL 1 *N* $NaHCO_3$ solution and 40 mL aqueous KI_3 solution containing 24.3 g KI, 12.1 g iodine. The mixture was stirred for 20 h and poured into a saturated aqueous $Na_2S_2O_3$ solution. The mixture was extracted with EtOAc (2×50 mL); the combined organic layers were washed with brine, drived over Na_2SO_4, and evaporated. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 1:1) to give 1.24 g 4-iodo-8-(7-methoxbenzo [1,3]dioxol-5-yl)-6-oxabicyclo-[3.2.1]octan-7-one as a colorless oil, in a yield of 99%.

Other references related to the iodolactonization are cited in literature.[20]

H. REFERENCES

1. Stobbe, H., *Ann.,* **1902**, *321*, 119.
2. Fittig, R., *Ann.,* **1904**, *331*, 142.
3. (a) Bougault, M. J., *Compt. Rend.,* **1904**, *139*, 864. (b) Bougault, M. J., *Ann. Chim. Phys.,* **1908**, *14*, 145. (c) Bougault, M. J., *Ann. Chim. Phys.,* **1908**, *15*, 296.
4. (a) Haas, J.; Piguel, S. and Wirth, T., *Org. Lett.,* **2002**, *4*, 297. (b) Chai, W.-G.; Ye, M.-C.; Yan, L. and Zhao, Y.-F., *J. Org. Chem.,* **1987**, *52*, 1617. (c) Van Tamelen, E. E. and Shamma, M., *J. Am. Chem. Soc.,* **1954**, *76*, 2315.
5. (a) Ma, S. M. and Lu, L. H., *J. Org. Chem.,* **2005**, *70*, 7629. (b) Blot, V.; Reboul, V. and Metzner, P., *J. Org. Chem.,* **2004**, *69*, 1196. (c) Dams, I.; Bialonska, A.; Ciunik, Z. and Wawrzenczyk, C., *J. Agric. Food Chem.,* **2004**, *52*, 1630. (d) Ko, H. J.; Kim, E. Y.; Park, J. E.; Kim, D. J. and Kim, S. H., *J. Org. Chem.,* **2004**, *69*, 112. (e) Price, M. D.; Kurth, M. J. and Schore, N. E., *J. Org. Chem.,* **2002**, *67*, 7769. (f) Jung, M.; Ham, J. and Song, J., *Org. Lett.,* **2002**, *4*, 2763. (g) Paruch, E.; Ciunik, Z.; Nawrot, J. and Wawrzenczyk, C., *J. Agric. Food Chem.* **2000**, 48, 4973. (h) Lear, Y. and Schwan, A. L., *J. Org. Chem.,* **1999**, *64*, 8138. (i) Metz, P. and Hungerhoff, B., *J. Org. Chem.,* **1997**, *62*, 4442. (j) McKew, J. C.; Olmstead, M. M. and Kurth, M. J., *J. Org. Chem.,* **1994**, *59*, 3389. (k) Richardson, D. P.; Smith, T. E.; Lin, W. W.; Kiser, C. N. and Mahon, B. R., *Tetrahedron Lett.,* **1990**, *31*, 5973. (l) Kurth, M. J. and Brown, E. G., *J. Am. Chem. Soc.,* **1987**, *109*, 6844. (m) Bartlett, P. A. and Myerson, J., *J. Am. Chem. Soc.,* **1978**, *100*, 3950. (n) Do Amaral, L. and Melo, S. C., *J. Org. Chem.,* **1973**, *38*, 800. (o) House, H. O.; Carlson, R. G. and Babad, H., *J. Org. Chem.,* **1963**, *28*, 3359. (p) Klein, J., *J. Am. Chem. Soc.,* **1959**, *81*, 3611.
6. (a) Crouch, R. D.; Tucker-Schwartz, A. and Barker, K., *J. Chem. Edu.,* **2006**, *83*, 921. (b) Ullah, E.; Rotzoll, S.; Schmidt, A.; Michalik, D. and Langer, P., *Tetrahedron Lett*., **2005**, *46*, 8997. (c) Fu, C. L. and Ma, S. M., *Eur. J. Org. Chem.,* **2005**, 3942. (d) Metzner, P.; Blot, V. and Reboul, V., *Phosphorus, Sulfur & Silicon & Related Elements*, **2005**, *180*, 1517. (e) GowriSankar, S.; Lee, M. J.; Lee, S. and Kim, J. N., *Bull. Korean Chem. Soc.,* **2004**, *25*, 1963. (f) Rousseau, G.; Strzalko, T. and Roux, M.-C., *Tetrahedron Lett*., **2004**, *45*, 4503. (g) Wang, M.; Gao, L. X.; Yue, W. and Mai, W. P., *Synth. Commun.,* **2004**, *34*, 1023. (h) Lu, T.-M. and Wu, F.-H., *Youji Huaxue*, **2003**, *23*, 763. (i) Rossi, R.; Carpita, A.; Bellina, F.; Stabile, P. and Mannina, L., *Tetrahedron*, **2003**, *59*, 2067. (j) Chavan, S. P. and Sharma, A. K., *Tetrahedron Lett*., **2001**, *42*, 4923. (k) Bellina, F.; Biagetti, M.; Carpita, A. and Rossi, R., *Tetrahedron*, **2001**, *57*, 2857.
7. Moon, H.-S.; Schore, N. E. and Kurth, M. J., *J. Org. Chem.,* **1992**, *57*, 6088.
8. Corey, E. J.; Guzman-Perez, A. and Lazerwith, S. E., *J. Am. Chem. Soc.,* **1997**, 119, 11769.
9. Marshall, J. A. and Yanik, M. M., *J. Org. Chem.,* **1999**, *64*, 3798.
10. Burgey, C. S.; Vollerthun, R. and Fraser-Reid, B., *J. Org. Chem.,* **1996**, *61*, 1609.
11. Leonard, K. A.; Zhou, F. and Detty, M. R., *Organometallics,* **1996**, *15*, 4285.
12. Moon, H.-S.; Eisenberg, S. W. E.; Wilson, M. E.; Schore, N. E. and Kurth, M. J., *J. Org. Chem.,* **1994**, *59*, 6504.
13. Campos, M. M., *An. Acad. Brasil Ciênc.,* **1955**, *27*, 405.
14. (a) Campos, M. M. and do Amaral, L., *Arch. Pharm.,* **1965**, *298*, 92. (b) Campos, M. M, *Ber.,* **1960**, *93*, 1075.
15. Grossman, R. B. and Trupp, R. J., *Can. J. Chem.,* **1998**, *76*, 1233.
16. Bartlett, P. A.; Richardson, D. P. and Myerson, J., *Tetrahedron,* **1984**, *40*, 2317.
17. (a) Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.-I.; Yoshida, Z. I.; Yanagi, K. and Minobe, M., *J. Am. Chem. Soc.,* **1984**, *106*, 1079. (b) Günther, H. J.; Guntrum, E. and Jãger, V., *Liebigs Ann. Chem.,* **1984**, 15. (c) Chamberlin, A. R.; Dezube, M.; Dussault, P. and McMills, M. C., *J. Am. Chem. Soc.,* **1983**, *105*, 5819.

18. (a) Xu, Q. and Rozners, E., *Org. Lett.,* **2005**, *7*, 2821. (b) Rozners, E. and Liu, Y., *Org. Lett.,* **2003**, *5*, 181. (c) Rozners, E. and Xu, Q., *Org. Lett.,* **2003**, *5*, 3999.

19. Wang, M.; Gao, L. X.; Mai, W. P.; Xia, A. X.; Wang, F. and Zhang, S. B., *J. Org. Chem.,* **2004**, *69*, 2874.

20. (a) Yadav, J. S.; Sundar, P. and Reddy, R., *Synthesis*, **2007**, 1070. (b) Fuchs, S.; Berl, V. and Lepoittevin, J.-P., *Eur. J. Org. Chem.,* **2007**, 1145. (c) Putey, A.; Popowycz, F. and Joseph, B., *Synlett*, **2007**, 419. (d) Yokoe, H.; Sasaki, H.; Yoshimura, T.; Shindo, M.; Yoshida, M. and Shishido, K., *Org. Lett.,* **2007**, *9*, 969. (e) Eidman, K. F. and MacDougall, B. S., *J. Org. Chem.,* **2006**, *71*, 9513. (f) Padwa, A. and Ginn, J. D., *J. Org. Chem.,* **2005**, *70*, 5197. (g) Carrillo, A.; Gujraty, K. V.; Rai, P. R. and Kane, R. S., *Nanotechnology,* **2005**, *16*, S416. (h) Anderson, J. C. and Whiting, M., *J. Org. Chem.,* **2003**, *68*, 6160. (i) Ginn, J. D. and Padwa, A., *Org. Lett.,* **2002**, *4*, 1515. (j) Kim, S. H.; Ko, H. J.; Kim, E. Y. and Kim, D. J., *Org. Lett.,* **2002**, *4*, 1343. (k) Cuzzupe, A. N.; di Florio, R. and Rizzacasa, M. A., *J. Org. Chem.,* **2002**, *67*, 4392. (l) Rousseau, G. and Robin, S., *Tetrahedron,* **1998**, *54*, 13681. (m) Schultz, A. G. and Kirincich, S. J., *J. Org. Chem.,* **1996**, *61*, 5626. (n) Reetz, M. T. and Lauterbach, E. H., *Heterocycles,* **1993**, *35*, 627. (o) Ireland, R. E.; Wipf, P. and Xiang, J.-N., *J. Org. Chem*., **1991**, *56*, 3572. (p) Mulzer, J., in *Organic Synthesis Highlights*, ed. Mulzer, J.; "Halolactonization: the carrer of a reaction", Altenbach, H. J.; Braun, M.; Krohn, K. and Reissig, H. U., VCH: Weinheim, **1991**, pp. 158–164. (q) Cardillo, G. and Orena, M., *Tetrahedron,* **1990**, *46*, 3321. (r) Najdi, S.; Reichlin, D. and Kurth, M. J., *J. Org. Chem.,* **1990**, *55*, 6241. (s) Mori, K. and Nakazano, Y., *Tetrahedron,* **1986**, *42*, 283. (t) Gonzãlez, F. B. and Bartlett, P. A., *Org. Synth.,* **1985**, *64*, 175. (u) Bartlett, P. A.; Richardson, D. P. and Myerson, J., *Tetrahedron,* **1984**, *40*, 2317. (v) Bartlett, P. A. and Myerson, J., *J. Org. Chem.,* **1979**, *44*, 1625. (w) Dowle, M. D. and Davies, D. I., *Chem. Soc. Rev*., **1979**, 171. (x) Schrecker, A. W.; Greenberg, G. Y. and Hartwell, J. L., *J. Am. Chem. Soc.,* **1952**, *74*, 5669. (y) Linstead, R. P. and May, C. J., *J. Chem. Soc.,* **1927**, 2565.

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Irvine-Purdie Methylation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Irvine and Purdie in 1903.[1] It is the exhaustive methylation of alkyl glycoside by repeated treatment of said glycoside with methyl iodide and silver oxide and the deprotection of anomeric alkyl group by hydrolysis of the resulting methyl saccharide ether with dilute acid. In addition, this reaction also stands for the mere methylation of sugars from methyl iodide and silver oxide. This reaction is often carried out in neutral solvent under mild conditions,[2] in which the profound side reactions, such as racemization, the *Walden Inversion*, or interconversion of glycosides (α- and β-forms), do not occur.[2] For example, the methylation of fructose tetraacetate by this reaction gives an almost quantitative yield of pure crystalline tetraacetyl monomethoxy fructose, without any affect on the acetyl groups in fructose tetraacetate.[3] However, bacause of the high cost of methyl iodide and silver oxide, and the limited solvents suitable for dissolving the initial glycosides,[2] this reaction has widely been replaced by the *Haworth Methylation* by treatment of sugar derivatives with methyl sulfate and sodium hydroxide,[4] and the *Haworth Methylation* has been further modified to occur in carbon tetrachloride using a high concentrated alkali base.[4] Nonetheless, both reactions do not yield the completely methylated glycosides, thus these two methods are often used together to yield the fully methylated glycosides for structural analysis, and the Irvine-Purdie methylation is often the last step. For example, the repeated four Irvine-Purdie methylations of sucrose yields a product with a methoxy content of 50.93%, smaller than the theoretical content of 54.63%. For comparison, one *Haworth Methylation* of sucrose gives a product with a methoxyl content of 50.5%, and further treatment of the product by *Haworth Methylation* does not increase the methoxyl content; however, two subsequent Irvine-Purdie methylations of such methyl sucrose can bring the methoxyl content up to 54.12%.[5] Overall, to fulfill the

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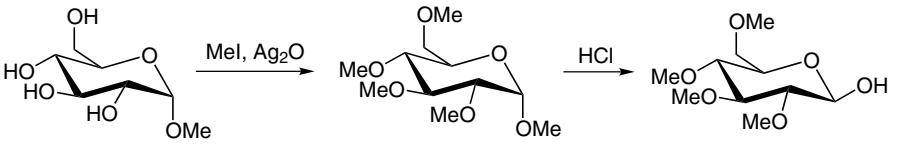
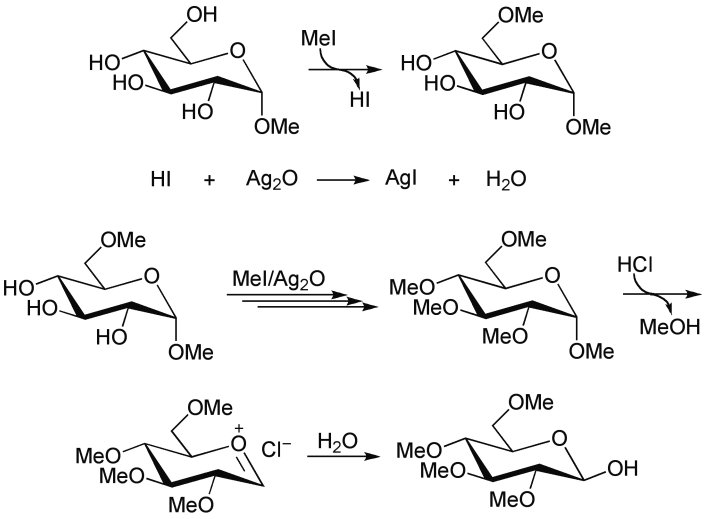
per-*O*-methylation for both methods, the repeated methylation on the materials recovered by extraction is necessary.[6] However, bacause per-*O*-methylation of sugars, especially the polysaccharides, is the prerequisite for the elucidation of polysaccharide structures,[6] this reaction has been further modified for a one-step per-*O*-methylation of polysaccharide by adding a solution of sodium methylsulfinyl carbanion (Na dimsyl) and methyl iodide to a DMSO solution of carbohydrate,[7] which has also been improved by adding potassium dimsyl and lithium dimsyl.[8]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified to become the *Haworth Methylation*,[4] which was extended to treat sugars with sodium methylsulfinyl carbanion and methyl iodide for the purpose of per-*O*-methylation in one step.[7,8]

E. APPLICATIONS

This reaction has been used for the structural analysis of polysaccharide and the methylation of sugars.

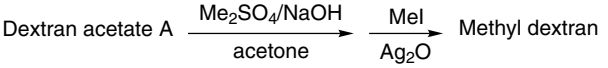
F. RELATED REACTIONS

This reaction is related to the *Haworth Methylation*.

G. CITED EXPERIMENTAL EXAMPLES

Reference 6.

Sodium dimsyl was prepared in a dry 500-mL, three-necked, round-bottom flask by adding 8 g dry sodium hydride to 100 mL anhydrous dimethyl sulfoxide under a dry nitrogen atmosphere. The magnetically stirred reaction mixture was heated slowly to 50°C and maintained at this temperature until hydrogen evolution had ceased. The mixture was centrifuged to produce a clear, gray-green solution. The solution was then aliquoted in 1-mL portions under nitrogen into Teflon-lined screw-capped vials and frozen at −20°C. For permethylation, the carbohydrates (5–7 mg) were introduced into a conical vial, which was dried overnight under vacuum, and then sealed with dry nitrogen. Dimethyl sulfoxide (1 mL) was added by dry syringe, followed by 0.3 mL nitrogen dimsyl solution (3 eq. per mol of replaceable hydrogen), and the reaction mixture was stirred at room temperature for 1 h. Methyl iodide (90 μL, 3 eq. per mol of replaceable hydrogen) was added after cooling the reaction mixture in an ice bath. After the mixture was fushed with dry nitrogen, stirring was continued at room temperature for 2 h.



Reference 9.

To 200 mL acetone was added 4.35 g dextran acetate A, which was methylated with NaOH (30%, 300 mL) and 110 mL dimethyl sulfate over a period of 3 h. The bath temperature was kept at 25°C for the first 2 h, and at 55°C for 1 h; it was then raised to 100°C for 0.5 h. The excess alkali was neutralized, and the reaction mixture was dialyzed. The dialyzed material was concentrated to a small volume, and the methylation was repeated four times in the same way with the bath temperature maintained at 55°C; acetone was added in to keep the product in solution. After the fifth methylation the product was extracted with chloroform, and the extract was washed with dilute acetic acid and water and concentrated to give 3.39 g syrup. The syrupy product was methylated with 50 mL methyl iodide (50 mL) and 6 g silver oxide, added in 12 portions under continual stirring and refluxing for 22 h. The product was extracted with chloroform, and after the removal of solvent it was remethylated four times in the same manner to give 1.96 g product with a methoxyl content of 44.93%. On fractionation of the methylated dextran from chloroform with petroleum ether, 90% of the product precipitated at 90–92% petroleum ether, a second

fraction recovered by concentration of the mother liquor was not investigated further. (*Note*: this procedure used a ridiculous amount of sodium hydroxide and methyl sulfate, and, later on, also used a great excess of methyl iodide and silver oxide to obtain the methylated dextran. It is an unacceptable practice in terms of cost-effectiveness. This procedure is cited for comparison).

Other references related to the Irvine-Purdie methylation are cited in the literature.[10,11]

H. REFERENCES

1. Purdie, T. and Irvine, J. C., *J. Chem. Soc.,* **1903**, *83*, 1021.
2. Hibbert, H.; Platt, M. E. and Carter, N. M., *J. Am. Chem. Soc.,* **1929**, *51*, 3644.
3. Hudson, C. S. and Brauns, D. H., *J. Am. Chem. Soc.,* **1916**, *38*, 1216.
4. (a) Hendricks, B. C. and Rundle, R. E., *J. Am. Chem. Soc.,* **1938**, *60*, 2563. (b) West, E. S. and Holden, R. F., *J. Am. Chem. Soc.,* **1934**, *56*, 930.
5. Pacsu, E. and Trister, S. M., *J. Am. Chem. Soc.,* **1939**, *61*, 2442.
6. Ciucanu, I. and Costello, C. E., *J. Am. Chem. Soc.,* **2003**, *125*, 16213.
7. Hakomori, S.-I., *J. Biochem. (Tokyo),* **1964**, *55*, 205.
8. (a) Blakeney, A. B. and Stone, B. A., *Carbohydr. Res.,* **1985**, *140*, 319. (b) Phillips, L. R. and Fraser, B. A., *Carbohydr. Res.,* **1981**, *90*, 149. (c) Sandford, P. A. and Conrad, H. E., *Biochemistry,* **1966**, *5*, 1508.
9. Lewis, B. A.; Cyr, M. J. St. and Smith, F., *J. Org. Chem.,* **1968**, *33*, 3136.
10. (a) Kovac, P. V.; Hirsch, J. and Kovacik, V., *Carbohydr. Res.,* **1977**, *58*, 327. (b) Springer, G. F.; Desai, P. R. and Kolecki, B., *Biochemistry*, **1964**, *3*, 1076. (c) Dutton, G. G. S. and Hunt, K., *J. Am. Chem. Soc.,* **1958**, *80*, 5697. (d) Dutton, G. G. S. and Smith, F., *J. Am. Chem. Soc.,* **1956**, *78*, 3744. (e) Montgomery, R.; Smith, F. and Srivastava, H. C., *J. Am. Chem. Soc.,* **1956**, *78*, 6169. (f) Bourne, E. J. and Peat, S., *Adv. Carbohydr. Chem.,* **1950**, *5*, 146. (g) Barker, C. C.; Hirst, E. L. and Jones, J. K. N., *J. Chem. Soc.,* **1946**, 753. (h) Richtmyer, N. K. and Hudson, C. S., *J. Am. Chem. Soc.,* **1941**, *63*, 1727. (i) Pacsu, E. and Trister, S. M., *J. Am. Chem. Soc.,* **1940**, *62*, 2301. (j) Whistler, R. L. and Hixon, R. M., *J. Am. Chem. Soc.,* **1937**, *59*, 2047. (k) Padgett, A. R. and Degering, E. F., *J. Org. Chem.,* **1936**, *1*, 336. (l) Wolfrom, M. L. and Lewis, W. L., *J. Am. Chem. Soc.,* **1928**, *50*, 837. (m) Gustus, E. L. and Lewis, W. L., *J. Am. Chem. Soc.,* **1927**, *49*, 1512. (n) Hudson, C. S., *J. Am. Chem. Soc.,* **1925**, *47*, 268. (o) Irvine, J. C. and Moodie, A. M., *J. Chem. Soc.,* **1906**, *89*, 1578. (p) Purdie, T. and Irvine, J. C., *J. Chem. Soc.,* **1904**, *85*, 1049. (q) Irvine, J. C. and Purdie, T., *J. Chem. Soc.,* **1904**, *85*, 1052. (r) Purdie, T. and Irvine, J. C., *J. Chem. Soc.,* **1904**, *85*, 1054. (s) Purdie, T. and Irvine, J. C., *J. Chem. Soc.,* **1904**, *85*, 1060. (t) Irvine, J. C. and Cameron, A., *J. Chem. Soc.,* **1904**, *85*, 1071.
11. (a) Saxena, S. and Shrivastava, R. M., *Orient. J. Chem.,* **1998**, *14*, 339. (b) Banerji, N.; Murty, V. L. N. and Mukherjee, A. K., *Indian J. Chem.,* **1965**, *3*, 457. (c) Kochetkov, N. K.; Khorlin, A. Ya. and Ovodov, Y. S., *Tetrahedron Lett.*, **1963**, 477. (d) Mukherjee, S. and Shrivastava, A. N., *J. Am. Chem. Soc.,* **1958**, *80*, 2536. (e) Chatterjee, A. K. and Mukherjee, S., *J. Am. Chem. Soc.,* **1958**, *80*, 2538. (f) Sugihara, J. M. and Wolfrom, M. L., *J. Am. Chem. Soc.,* **1949**, *71*, 3357. (g) Hudson, C. S., *J. Am. Chem. Soc.,* **1926**, *48*, 1434. (h) Pryde, J., *J. Chem. Soc., Trans.,* **1924**, *125*, 520.

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Jacobsen Rearrangement
(Jacobsen Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was studied extensively by Jacobsen starting in 1886,[1] although the first reaction of this series was reported by Herzig in 1881.[2] It is the conversion of polysubstituted aromatics into corresponding sulfonated aromatics with the migration of substituents in contact with concentrated sulfuric acid. Under such conditions, the halogenated polyalkylaromatics undergo disproportionation of halogen atoms. Therefore, this reaction is generally known as the Jacobsen rearrangement[3] or Jacobsen reaction.[4,5] Generally speaking, among the polyalkyl benzenes, only the tetraalkyl or pentaalkyl benzenes undergo this reaction, in which the pentaalkyl benzenes give 1,2,3,4-tetraalkyl benzenesulfonic acid and hexaalkyl benzenes,[1b,4i] and the tetraalkyl benzenes intramolecularly rearrange to 1,2,3,4-tetralkyl benzene as the major product.[4d] In addition, it has been found that tetraethylbenzenes rearrange much more smoothly and quickly than tetramethylbenzenes; whereas pentamethylbenzene undergoes this reaction more readily than pentaethylbenzene.[4c] In contrast, hexaalkyl benzenes, as the end point of the reaction, are stable toward concentrated sulfuric acid, even if they are in contact with concentrated sulfuric acid for several months.[4i] However, for less alkyl-substituted benzenes, such as trialkyl benzenes and dialkyl benzenes, no rearrangement but the mere sulfonation of aromatics are found.[4i] Moreover, this reaction is always accompanied by the evolution of sulfur dioxide,[3f,4d,4e] together with the production of amorphous tarry byproducts in 30% of the weight of the starting material, which are soluble in excess amounts of acetone and show green fluorescence.[4d] Furthermore, only those primary alkyl groups on the aromatic rings migrate properly; both secondary and tertiary alkyl groups, such as isopropyl and *tert*-butyl groups are eliminated in this reaction.[3e] On the other hand, for the aromatics with cyclic alkyl substituents, such as the tetralins, the cyclic alkyl group almost always remains unchanged while other groups migrate;[3g,4b] however,

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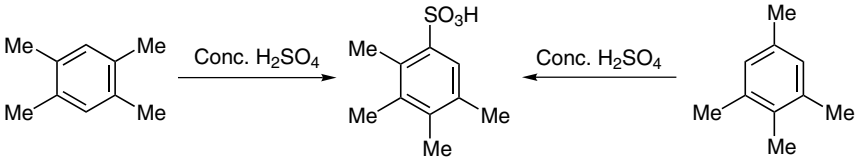
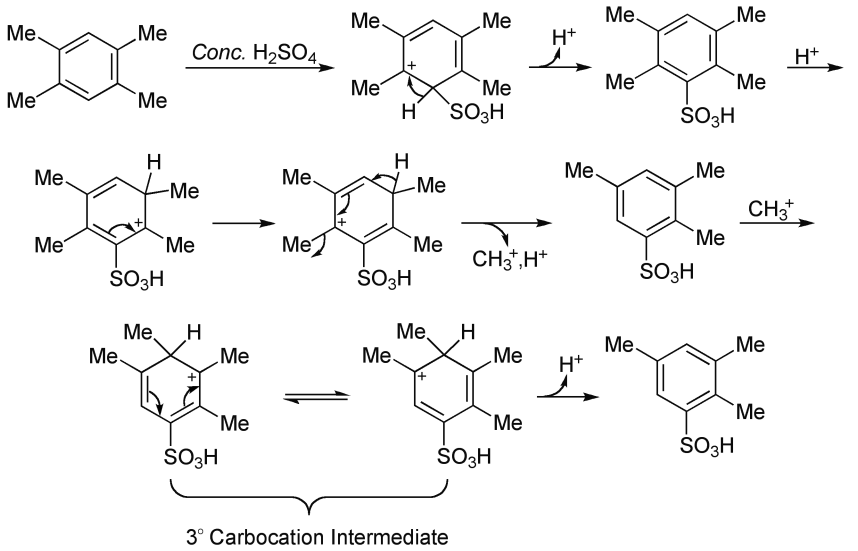
in pure cyclic alkyl–substituted aromatics, the group does migrate. For example, the octahydroanthrance rearranges into octahydrophenanthrene.[3i] In addition, the Jacobsen rearrangement not only works for polyalkyl aromatics but also works for halogenated aromatics as well,[3e,4d–4f,4j] even for mono-halogenated aromatics. The fluorinated aromatics are exceptions.[6] For the case of halogenated aromatic compounds, halogen atoms often migrate to give disproportionated products. For example, bromobenzene rearranges to dibromobenzene and presumably benzene when treated with concentrated sulfuric acid,[4i] dibromobenzene produces tetrabromobenzene and hexabromobenzene, and tribromobenzene yields hexabromobenzene.[4i] For chlorinated alkyl aromatics, the rearrangement does not always occur; chlorine migration might be either intramolecular or intermolecular. For example, 5- and 6-chloropseudocumenes rearrange to 3-chloropseudocumene; chloromesitylene and 4-chlorohemimellithene do not undergo this rearrangement but only the sulfonation.[4d] It has been found that concentrated sulfuric acid is used to reverse the desulfonation of aromatic sulfonic acids that occur in diluted sulfuric acid.[3f]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is proposed that this reaction involves the sulfonation and protonation of an aromatic ring as shown below.[3e]



D. MODIFICATION

N/A

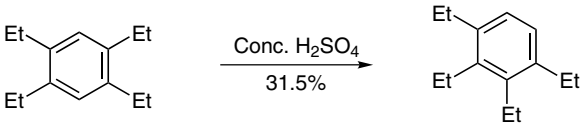
E. APPLICATIONS

This reaction has been used to prepare multisubstituted alkyl aromatics with substituents in the vicinal position, which might be more difficult to prepare from traditional *Friedel-Crafts Alkylation* with large amounts of *meta* alkyl substituent.[4e]

F. RELATED REACTIONS

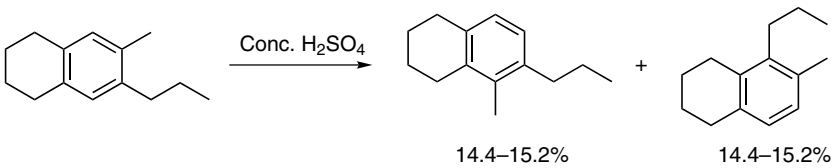
This reaction is related to the *Friedel-Crafts Alkylation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 3h.

Labeled tetraethylbenzene (8 g, 42 mmol) was mixed with 28.90 g reagent-grade sulfuric acid, and the mixture was heated rapidly to 100°C. Rapid mixing produced complete solution in ~ 30 min. This solution was maintained at 100°C for 10 min and was then poured onto 29 g crushed ice. Steam distillation of the diluted mixture at 140°C was carried out until only a few traces of insoluble residue remained in the still pot. The distillate was saturated with sodium chloride and extracted with ether. The ether solution was dried over calcium chloride, and the hydrocarbon was isolated by distillation through a 12-in. Vigreux column, b.p. 55–56°C (0.25 mmHg), in the amount of 2.52 g (13.3 mmol).



Reference 3g.

Pure 6-methyl-7-*n*-propyltetralin (20 g, 0.11 mol) was mixed with 125 mL concentrated sulfuric acid, and the rearrangement was performed according to Smith and Lo.[4b] Hydrolysis of the product with superheated steam at 155°C gave 6.7 g of a light oil, b.p. 60–66°C (0.2 mmHg), in a yield of 32%. Analysis by GPC showed 11 peaks with 2 major peaks retained at 52.5 and 61.0 min, respectively, made up 90–95% of the total; they are identified

as 6-methyl-5-*n*-propyltetralin and 5-methyl-6-*n*-propyltetralin, respectively, presenting as equivalent amounts.

Other references related to the Jacobsen rearrangement are cited in the literature.[7]

H. REFERENCES

1. (a) Jacobsen, O., *Ber.,* **1886**, *19*, 1209. (b) Jacobsen, O., *Ber.,* **1887**, *20*, 896. (c) Jacobsen, O., *Ber.,* **1887**, *20*, 901. (d) Jacobsen, O., *Ber.,* **1887**, *20*, 2837. (e) Jacobsen, O., *Ber.,* 1888, *21*, 2814.
2. Herzig, J., *Ber.,* **1881**, *14*, 1205.
3. (a) Solari, E.; Musso, F.; Ferguson, R.; Floriani, C.; Chiesi-Villa, A. and Rizzoli, C., *Angew. Chem. Int. Ed.,* **1995**, *34*, 1510. (b) Nakada, M.; Ishibashi, K.; Fukushi, S. and Hirota, M., *Bull. Chem. Soc. Jpn.,* **1979**, *52*, 3671. (c) Koeberg-Telder, A. and Cerfontain, H., *J. Chem. Soc., Perkin Trans. II,* **1977**, 717. (d) Norula, J. L. and Gupta, R. P., *Chemical Era*, **1974**, *10*, 7. (e) Hart, H. and Janssen, J. F., *J. Org. Chem.,* **1970**, *35*, 3637. (f) Marvell, E. N. and Graybill, B. M., *J. Org. Chem.,* **1965**, *30*, 4014. (g) Marvell, E. N.; Olafson, P. G.; Lini, D.; Barbour, R. and Dueltgen, R., *J. Org. Chem.,* **1963**, *28*, 3248. (h) Marvell, E. N. and Webb, D., *J. Org. Chem.,* **1962**, *27*, 4408. (i) Arnold, R. T. and Barnes, R. A., *J. Am. Chem. Soc.,* **1944**, *66*, 960.
4. (a) Musso, F.; Solari, E.; Floriani, C. and Schenk, K., *Organometallics,* **1997**, *16*, 4889. (b) Smith, L. I. and Lo, C.-P., *J. Am. Chem. Soc.,* **1948**, *70*, 2209. (c) Smith, L. I. and Guss, C. O., *J. Am. Chem. Soc.,* **1940**, *62*, 2631. (d) Smith, L. I. and Kiess, M. A., *J. Am. Chem. Soc.,* **1939**, *61*, 989. (e) Moyle, C. L. and Smith, L. I., *J. Org. Chem.,* **1938**, *3*, 112. (f) Smith, L. I. and Moyle, C. L., *J. Am. Chem. Soc.,* **1936**, *58*, 1. (g) Smith, L. I. and Moyle, C. L., *J. Am. Chem. Soc.,* **1933**, *55*, 1676. (h) Smith, L. I. and Cass, O. W., *J. Am. Chem. Soc.,* **1932**, *54*, 1614. (i) Smith, L. I. and Lux, A. R., *J. Am. Chem. Soc.,* **1929**, *51*, 2994.
5. (a) Suzuki, H. and Sugiyama, T., *Bull. Chem. Soc. Jpn.,* **1973**, *46*, 586. (b) Suzuki, H. and Kawamura, K., *Bull. Chem. Soc. Jpn.,* **1972**, *45*, 1945. (c) Suzuki, H. and Yoshida, M., *Bull. Chem. Soc. Jpn.,* **1972**, *45*, 287. (d) Suzuki, H. and Yamamoto, N., *Bull. Chem. Soc. Jpn.,* **1972**, *45*, 289. (e) Gordon, D.; Frye, L. and Sheffer, H., *Acta Chem. Scand.,* **1969**, *23*, 3577. (f) Suzuki, H., *Bull. Chem. Soc. Jpn.,* **1969**, *42*, 2618. (g) Suzuki, H. and Tamura, Y., *Chem. Commun. (London),* **1969**, 244. (h) Suzuki, H.; Maruyama, K. and Goto, R., *Bull. Chem. Soc. Jpn.,* **1965**, *38*, 1474. (i) Suzuki, H.; Sugiyama, T. and Goto, R., *Bull. Chem. Soc. Jpn.,* **1964**, *37*, *1858*. (j) Bohlmann, F. and Riemann, J., *Chem. Ber.,* **1964**, *97*, 1515. (k) Suzuki, H., *Bull. Chem. Soc. Jpn.,* **1963**, *36*, 1642. (l) Gore, R. and Suzuki, H., *Nippon Kagaku Zasshi*, **1963**, *84*, 167. (m) Moyle, C. L. and Smith, L. I., *J. Org. Chem.,* **1937**, *2*, 112.
6. Smith, L. I., *Org. React.,* **1942**, *1*, 370.
7. (a) Shklyaev, Y. V.; Ismagilov, R. R.; Rozhkova, Y. S.; Fatykhov, A. A.; Abdrakhmanov, I. B. and Tolstikov, A. G., *Russ. Chem. Bull.,* **2004**, *53*, 906. (b) Dotrong, M.; Lovejoy, S. M.; Wolfe, J. F. and Evers, R. C., *J. Heterocycl. Chem.,* **1997**, *34*, 817. (c) Belen'kii, L. I.; Brokhovetskii, D. B. and Krayushkin, M. M., *Chem. Scripta,* **1989**, *29*, 81. (d) Cerfontain, H. and Koeberg-Telder, A., *Can. J. Chem.,* **1988**, *66*, 162. (e) Koeberg-Telder, A. and Cerfontain, H., *Recl. Trav. Chim. Pays-Bas,* **1987**, *106*, 85. (f) Schneller, S. W., *Int. J. Sulfur Chem.,* **1976**, *8*, 579. (g) Schneller, S. W., *Int. J. Sulfur Chem.,* **1973**, *8*, 485. (h) Suzuki, H.; Wada, H.; Maruyama, K. and Goto, R., *Bull. Chem. Soc. Jpn.,* **1966**, *39*, 1201. (i) Stille, J. K. and Rix, C. E., *J. Org. Chem.,* **1966**, *31*, 1591. (j) Brown, H. C. and Wirkkala, R. A., *J. Am. Chem. Soc.,* **1966**, *88*, 1453. (k) Suzuki, H.; Maruyama, K. and Goto, R., *Bull. Chem. Soc. Jpn.,* **1965**, *38*, 1590. (l) Suzuki, H.,*Bull. Chem. Soc. Jpn.,* **1963**, *36*, 1642. (m) Price, C. C., *Org. React.,* **1947**, *3*, 1.

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Jacobsen-Katsuki Epoxidation

A. GENERAL DESCRIPTION OF THE REACTION

Although the epoxidation of olefins catalyzed by oxomanganese salen *N*,*N*′-ethylene-bis(salicylideneaminato) complex was first reported by Kochi in 1980s,[1] it is Jacobsen[2] and Katsuki[3] who concurrently reported the improvement of such olefin epoxidation in 1990, using a sophisticated chiral salen ligand for manganese complexes, which resulted in high enantioselectivity. They extensively studied different aspects of this reaction[4,5] to convert it into one of the most useful and widely applicable methods for the epoxidation of unfunctionalized olefins.[6] Therefore, this reaction is often referred to as the Jacobsen-Katsuki epoxidation.[7] Occasionally, it is also known as the Jacobsen epoxidation,[8] Jacobsen oxidation,[9] Jacobsen asymmetric epoxidation,[10] or Kochi-Jacobsen-Katsuki oxygenation.[11] This reaction is usually carried out in dichloromethane or acetonitrile. Generally, Jacobsen's catalysts have two stereogenic centers, while Katsuki's catalysts have four.[3,5g–5j] Some of the Jacobsen-type catalysts (Figure 1) and Katsuki-type catalysts (Figure 2) are listed, respectively. It is known that the conformation of the chiral substituents attached to the C_8- and C_8'-positions have considerable influence on asymmetric induction.[3,5g–5j] In addition, the presence of a bulky group (e.g., *t*-butyl) at C_3- and C_3'-position of salen ligand achieves high enantioselectivity;[41] however, the groups larger than *t*-butyl have not shown apparent advantages for enhancing the enantioselectivity.[41] What is worse, the bulky trialkylsilyl group at C_3- and C_3'-position significantly lower the enantioselectivity, presumably because of the long carbon-silicon bond.[13] Furthermore, it is known

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that this reaction is a strongly electrophilic one,[4c,7b] and the presence and properties of substituents at the C_5- and C_5'-position of salen ligand also affect the enantioselectivity, as well as the epoxidation rate.[14] It has been reported that electron-withdrawing groups accelerate the epoxidation reaction but lower the enantioselectivity via an early transition state, whereas the electron-donating substituents attenuate the reaction rate but enhance the enantioselectivity.[6a] On the other hand, the enantioselectivity of this epoxidation also depends on the structure of substrates. Generally, Jacobsen's catalysts work better for *cis*-olefins and Katsuki's catalysts are better for *trans*-olefins.[7d] The substrates with a *cis*-olefinic bond in conjugation with an aryl, alkenyl or alkynyl, or in connection with a bulky group or an allylic oxygen often result in high enantioselectivity when Jacobsen's catalysts are applied,[4j,15] especially for the epoxidation of 2,2-dialkylchromene derivatives with all terminal oxidants.[16] It has been found that simple nonconjugated olefins react slower than the conjugated ones and give both low yields and poor enantioselectivities.[4j,4k] Aryl-substituted alkenes often afford *cis*-epoxides, while conjugated dienes and enynes generally give *trans*-epoxides.[17] In addition, the counterion of Mn(salen)X complexes (Cl^-, PF_6^-, etc.),[7b] the additive as an axial ligand,[18] and the oxygen donors (i.e., oxidant)[7c] all have effects on the outcome of the asymmetric epoxidation. The oxidants used for this epoxidation include iodosylbenzene (PhIO) with chromium-salen complex,[19] sodium hypochlorite (NaOCl),[41,20] oxygen/reductant,[21] hydrogen peroxide (H_2O_2),[22] alkylhydroperoxide (e.g., *t*-butylperoxide),[23] peroxyacids (e.g., *m*CPBA),[18d,21b,23,24] potassium monoperoxysulfate ($KHSO_5$, oxone),[23,25] dimethyldioxirane,[26] and triphenyl phosphorus oxide (Ph_3PO).[27] Even though the mechanism of this reaction is controversial, it is generally agreed that this reaction consists of a two-step catalytic cycle—the formation of Mn(salen)^{v} complex and the transfer of activated oxygen to an olefinic double bond.[6a] To complete the catalytic cycle, at least three mechanisms have been proposed, including the concerted,[7b,7f] stepwise radical[7b,7f] and manganaoxetane pathways.[7i,28] In addition, a multichannel process including singlet, triplet and quintet spin states[7f] and proximal and distal approach (vectors) have been proposed to explain the stereochemical outcome of the epoxidation.[7b] Nevertheless, the transition state is held to be asynchronous;[4c] therefore, the order of mixing the reacting components is important for this reaction.[7h] This reaction has been extended to occur in the presence of the ionic liquid[7e,12,29] ($BMIMPF_6$), to resolve the racemic epoxides in a highly selective manner using a cobalt salen complex,[30] and then oxidize the stilbene into diarylacetaldehyde under basic conditions.[9]

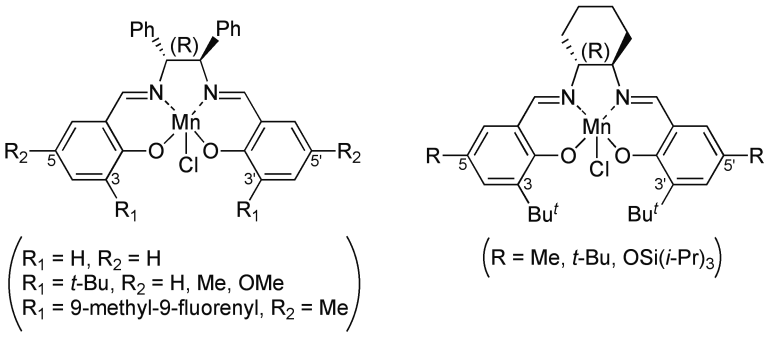


FIGURE 1. *Jacobsen-type catalysts.*

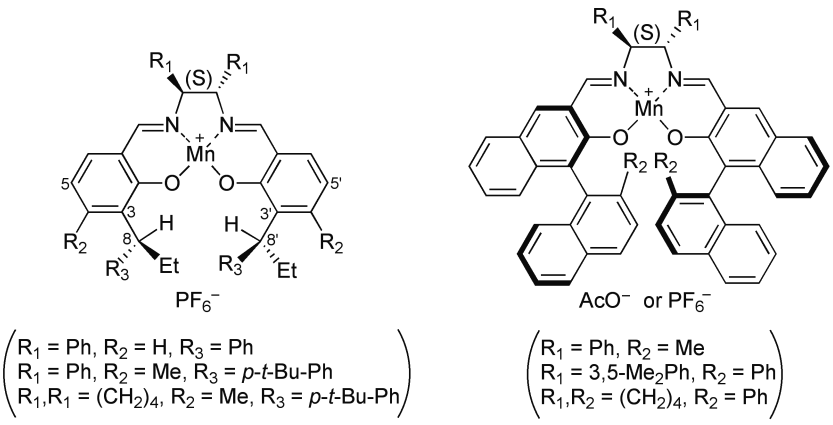
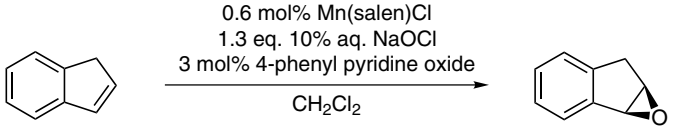


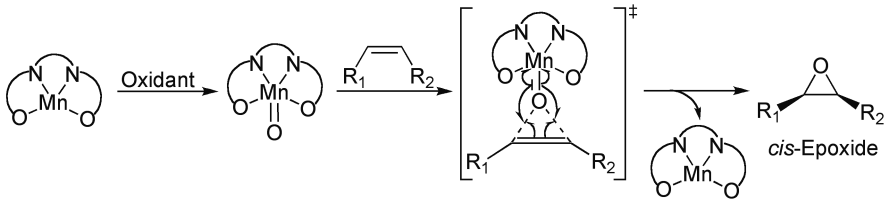
FIGURE 2. *Katsuki-type catalysts.*

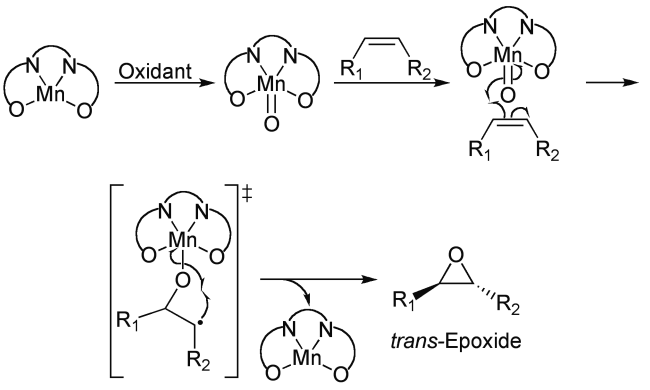
B. GENERAL REACTION SCHEME



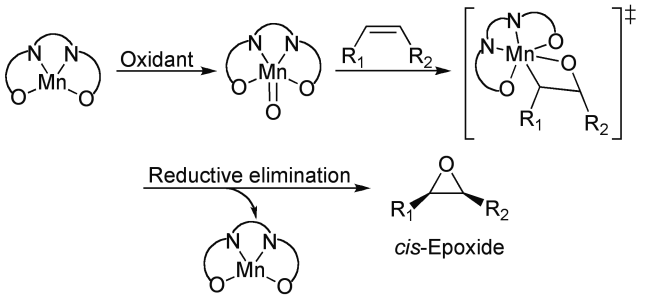
C. PROPOSED MECHANISMS

Outlined below is the proposed mechanism for the epoxidation in which the salen scaffold is simplified.





Radical mechanism



Mechanism involving manganaoxetane transition state

D. MODIFICATION

This reaction has been extended to occur in ionic liquid,[7e,12,29] and used for the highly selective hydrolytic kinetic resolution of epoxides.[30]

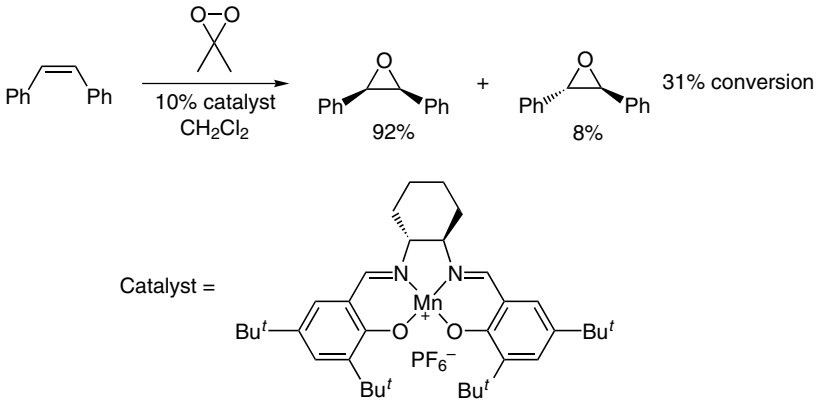
E. APPLICATIONS

This reaction has been widely used for the asymmetric epoxidation of olefins, especially for unfunctionalized olefins.

F. RELATED REACTIONS

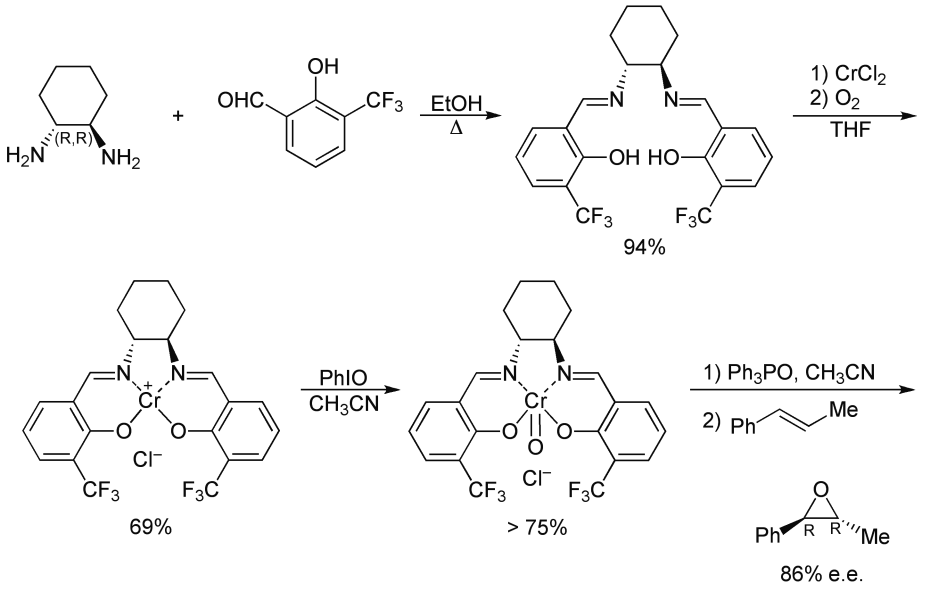
This reaction is related to the *Sharpless Epoxidation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 7c.

A solution of 37.5 μmol (10 mol%) of the particular Mn(salen)PF_6 in 3.75 mL CH_2Cl_2 was stirred for 3 min at ~20°C. After addition of 375 μmol of *cis*-stilbene, the mixture was stirred for another 2 min and 375 μmol of acetone-free dimethyldioxirane in CH_2Cl_2 (0.185 M) was administered in small portions over 2 min. After the mixture was stirred for up to 16 h, the solvent was removed at 20°C at a pressure of 400 mbar, and the residue was transferred onto a short column of silica gel (~10 g) and eluted with 200 mL of a mixture of petroleum ether/Et_2O (1:1). The solvent was evaporated at 30°C and 10 mbar, to give 31% conversion in a 92:8 of *cis/trans*-epoxide.



Reference 27

To 70 mL of ethanol was added 2.30 g (*R*,*R*)-(-)-*trans*-cyclohexane-1,2-diamine (20.1 μmol) and 7.66 g 2-hydroxy-3-(trifluoromethyl)benzaldehyde (40.3 μmol). The resulting bright yellow mixture was refluxed for 2 h, and cooled; the solvent was removed

in vacuo to yield a solid that was recrystallized from hexane to give 8.65 g of (*R*,*R*)-(-)-*N*,*N*′-bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine as bright yellow needles, in a yield of 94%, m.p. 126–128°C.

To a 100 mL, two-necked, round-bottomed flask equipped with a nitrogen inlet and outlet was added 26 mL of dry and degassed THF containing 600 mg (*R*,*R*)-(-)-*N*,*N*′-bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine (1.31 mmol). To this yellow solution was then added 177 mg anhydrous chromium(II) chloride (1.44 mmol). The resulting brown solution was stirred for 3 h under a blanket of nitrogen and then exposed to air for a further 3 h. The brown solution was diluted with 120 mL *tert*-butyl methyl ether, washed with 80 mL saturated ammonium chloride, and 80 mL of brine. The organic phase was dried over sodium sulfate, and the solvent was removed *in vacuo* to yield 489 mg (*R*,*R*)-(-)-*N*,*N*′-bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine chromium(III) chloride as a brown solid, in a yield of 69%, m.p. > 230°C.

(*R*,*R*)-(-)-*N*,*N*′-Bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine chromium(III) chloride (435 μmol) was dissolved in CH_3CN, and 115 mg of iodosylbenzene (522 μmol) was added. After being stirred for 30 min, the reaction was filtered and the solvent was removed *in vacuo*. Addition of Et_2O precipitated a black solid that was collected by filtration, washed thoroughly with Et_2O, dried, and stored under a nitrogen atmosphere to give > 75% of (*R*,*R*)-(-)-*N*,*N*′-bis(3-trifluoromethyl-salicylidene)-*trans*-cyclohexane-1,2-diamine oxochromium(V) chloride.

To 5 mL of acetonitrile, was added 30 mg (*R*,*R*)-(-)-*N*,*N*′-bis(3-trifluoromethyl-salicylidene)-*trans*-cyclohexane-1,2-diamine oxochromium(V) chloride, under stirring, 1-2 eq. of iodosylbenzene was added, and a deep blue/black color appeared almost immediately. After stirring for 30 min, the solution was filtered, and the filtrate was cooled to 0°C using an ice/water bath. Then 1 eq. of triphenylphosporus oxide was added, and five min later, 1 eq. of *trans*-β-methyl styrene was added. The reaction mixture was stirred at 0°C until the brown color of the Cr(III)(salen) complex returned completely (∼1.5 h). The solvent was removed *in vacuo*, and the residue was treated with Et_2O. The Et_2O washings were flushed through a short alumina column using Et_2O as the eluant. The eluant was concentrated *in vacuo* to give (*R*,*R*)-1-phenyl-2-methyl-*trans*-ethylene oxide, in 86 ee%.

Other references related to the Jacobsen-Katsuki epoxidation are cited in literature.[31]

H. REFERENCES

1. (a) Sidall, T. L.; Miyaura, N.; Huffmann, J. C. and Kochi, J. K., *J. Chem. Soc., Chem. Commun.,* **1983**, 1185. (b) Srinivasan, K. and Kochi, J. K., *Inorg. Chem.,* **1985**, *24*, 4671. (c) Srinivasan, K.; Michaud, P. and Kochi, J. K., *J. Am. Chem. Soc.,* **1986**, *108*, 2309.
2. Zhang, W.; Loebach, J. L.; Wilson, S. R. and Jacobsen, E. N., *J. Am. Chem. Soc.,* **1990**, *112*, 2801.
3. Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N. and Katsuki, T., *Tetrahedron Lett.,* **1990**, *31*, 7345.
4. (a) Ready, J. M. and Jacobsen, E. N., *J. Am. Chem. Soc.,* **2001**, *123*, 2687. (b) Jacobsen, E. N., *Acc. Chem. Res.,* **2000**, *33*, 421. (c) Palucki, M.; Finney, N. S.; Pospisil, P. J.; Güler, M. L.; Isida, T. and Jacobsen, E. N., *J. Am. Chem. Soc.,* **1998**, *120*, 948. (d) Palucki, M.; Finney, N. S.; Pospisil, P. J.; Guler, M. L.; Ishida, T. and Jacobsen, E. N., *J. Am. Chem. Soc.,* **1998**, *120*, 948. (e) Konsler, R. G.; Karl, J. and Jacobsen, E. N., *J. Am. Chem. Soc.,* **1998**, *120*, 10780. (f) Pospisil, P. J.; Carsten, D. H. and Jacobsen, E. N., *Chem. Eur. J.,* **1996**, *2*, 974. (g) Hansen, K. B.; Leighton, J. L. and Jacobsen, E. N., *J. Am. Chem. Soc.,* **1996**, *118*, 10924. (h) Martinez, L. E.; Leighton, J. L.; Carsten, D. H. and Jacobsen, E. N., *J. Am. Chem. Soc.,* **1995**, *117*, 5897. (i) Jacobsen, E. N., in

Comprehensive Organometallic Chemistry II, Vol. 12, Wilkinson, G. W.; Stone, F. G. A.; Abel, E. W. and Hegedus, L. S. ed., Pergamon, New York, **1995**, chapter 11.1. (j) Chang, S.; Galvin, J. M. and Jacobsen, E. N., *J. Am. Chem. Soc.,* **1994**, *116*, 6937. (k) Jacobsen, E. N., "*Asymmetric Catalytic Epoxidation of Unfunctionalized Olefins*" in *Catalytic Asymmetric Synthesis*, Ojima, I., Ed., VCH: New York, **1993**, Chapter 4.2. (l) Zhang, W. and Jacobsen, E. N., *J. Org. Chem.,* **1991**, *56*, 2296. (m) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R. and Deng, L., *J. Am. Chem. Soc.,* **1991**, *113*, 7063.

5. (a) Shimizu, H.; Onitsuka, S.; Egami, H. and Katsuki, T., *J. Am. Chem. Soc.,* **2005**, *127*, 5396. (b) Katsuki, T., "*Asymmetric Epoxidation of Unfunctionalized Olefins and Related Reactions*" in *Catalytic Asymmetric Synthesis*, Ojima, I., Ed., Wiley-VCH, **2000**, pp. 287–326. (c) Ito, Y. N. and Katsuki, T., *Bull. Chem. Soc. Jpn.,* **1999**, *72*, 603. (d) Katsuki, T., *J. Mol. Catal. A: Chem.,* **1996**, *113*, 87. (e) Katsuki, T., *Coord. Chem. Rev.,* **1995**, *140*, 189. (f) Irie, R.; Hosoya, N. and Katsuki, T., *Synlett,* **1994**, 255. (g) Hosoya, N.; Hatayama, A.; Yanai, K.; Fujii, H.; Irie, R. and Katsuki, T., *Synlett*, **1993**, 641. (h) Hosoya, N. and Katsuki, T., *Synlett*, **1993**, 261. (i) Irie, R.; Noda, K.; Ito, Y. and Katsuki, T., *Tetrahedron Lett.,* **1991**, *32*, 1055. (j) Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N. and Katsuki, T., *Tetrahedron: Asymmetry,* **1991**, *2*, 481.
6. (a) Cavallo, L. and Jacobsen, H., *J. Org. Chem.,* **2003**, *68*, 6202. (b) El-Bahraoui, J.; Wiest, O.; Feichtinger, D. and Plattner, D. A., *Angew. Chem. Int. Ed.,* **2001**, *40*, 2073.
7. (a) Jonsson, S.; Odille, F. G. J.; Norrby, P.-O. and Waernmark, K., *Org. Biomol. Chem.,* **2006**, *4*, 1927. (b) Fristrup, P.; Dideriksen, B. B.; Tanner, D. and Norrby, P.-O., *J. Am. Chem. Soc.,* **2005**, *127*, 13672. (c) Adam, W.; Roschmann, K. J.; Saha-Möller, C. R. and Seebach, D., *J. Am. Chem. Soc.,* **2002**, *124*, 5068. (d) Adam, W.; Humpf, H.-U.; Roschmann, K. J. and Saha-Möller, C. R., *J. Org. Chem.,* **2001**, *66*, 5796. (e) Sheldon, R., *Chem. Commun.,* **2001**, 2399. (f) Abashkin, Y. G.; Collins, J. R. and Burt, S. K., *Inorg. Chem.,* **2001**, *40*, 4040. (g) El-Bahraoui, J.; Wiest, O.; Feichtinger, D. and Plattner, D. A., *Angew. Chem. Int. Ed.,* **2001**, *40*, 2073. (h) Adam, W.; Mock-Knoblauch, C.; Saha-Moeller, C. R. and Herderich, M., *J. Am. Chem. Soc.,* **2000**, *122*, 9685. (i) Cavallo, L. and Jacobsen, H., *Angew. Chem. Int. Ed.,* **2000**, *39*, 589. (j) Adam, W.; Mock-Knoblauch, C.; Saha-Möller, C. R. and Herderich, M., *J. Am. Chem. Soc.,* **2000**, *122*, 9685. (k) Cavallo, L. and Jacobsen, H., *Angew. Chem. Int. Ed. Engl.,* **2000**, *39*, 589. (l) Adam, W. and Wirth, T., *Acc. Chem. Res.,* **1999**, *32*, 703. (m) Linker, T., *Angew. Chem. Int. Ed. Engl.,* **1997**, *36*, 2060.
8. (a) Brandt, P.; Södergren, M. J.; Andersson, P. G. and Norrby, P.-O., *J. Am. Chem. Soc.,* **2000**, *122*, 8013. (b) Draper, R. W.; Hou, D.; Iyer, R.; Lee, G. M.; Liang, J. T.; Mas, J. L.; Tormos, W. and Vater, E. *J., Org. Proc. Res. Dev.,* **1998**, *2*, 175. (c) Lynch, J. E.; Choi, W.-B.; Churchill, H. R. O.; Volante, R. P.; Reamer, R. A. and Ball, R. G., *J. Org. Chem.,* **1997**, *62*, 9223.
9. Pettit, G. R.; Toki, B.; Herald, D. L.; Verdier-Pinard, P.; Boyd, M. R.; Hamel, E. and Pettit, R. K., *J. Med. Chem.,* **1998**, *41*, 1688.
10. Hughes, D. L.; Smith, G. B.; Liu, J.; Dezeny, G. C.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R. and Reider, P. J., *J. Org. Chem.,* **1997**, *62*, 2222.
11. Khavrutskii, I. V.; Musaev, D. G. and Morokuma, K., *J. Am. Chem. Soc.,* **2003**, *125*, 13879.
12. Zhao, H. and Malhotra, S. V., *Aldrichimica Acta,* **2002**, *35*, 75.
13. O'Connor, K. J.; Wey, S. J. and Burrows, C. J., *Tetrahedron Lett.,* **1992**, *33*, 1001.
14. Jacobsen, E. N.; Zhang, W. and Güler, M. L., *J. Am. Chem. Soc.,* **1991**, *113*, 6703.
15. Jacobsen, E. N.; Deng, L.; Furukawa, Y. and Martinez, L. E., *Tetrahedron,* **1994**, *50*, 4323.
16. Lee, N. H.; Muci, A. R. and Jacobsen, E. N., *Tetrahedron Lett.,* **1991**, *32*, 5055.
17. Lee, N. H. and Jacobsen, E. N., *Tetrahedron Lett.,* **1991**, *32*, 6533.
18. (a) Finney, N. S.; Pospisil, P. J.; Chang, S.; Palucki, M.; Konsler, R. G.; Hansen, K. B. and Jacobsen, E. N., *Angew. Chem. Int. Ed. Engl.,* **1997**, *36*, 1720. (b) Janssen, K. B. M.; Parton, R. F. and Jacobs, P. A., *Tetrahedron: Asymmetry,* **1997**, *8*, 3039. (c) Senanayake, C. H.; Smith, G. B.;

Ryan, K. M.; Fredenburgh, L. E.; Liu, J.; Roberts, F. E.; Hughes, D. L.; Larsen, R. D.; Verhoeven, T. R. and Reider, P. J., *Tetrahedron Lett.,* **1996**, *37*, 3271. (d) Palucki, M.; Pospisil, P. J.; Zhang, W. and Jacobsen, E. N., *J. Am. Chem. Soc.,* **1994**, *116*, 9333. (e) Irie, R.; Ito, Y. and Katsuki, T., *Synlett,* **1991**, 265.

19. (a) Samsel, E. G.; Srinivasan, K. and Kochi, J. K., *J. Am. Chem. Soc.,* **1985**, *107*, 7606. (b) Srinivasan, K. and Kochi, J. K., *Inorg. Chem.,* **1985**, *24*, 4671. (c) Sidall, T. L.; Miyaura, N.; Huffman, J. C. and Kochi, J. K., *J. Chem. Soc., Chem. Commun.,* **1983**, 1185.
20. (a) Mikame, D.; Hamada, T.; Irie, R. and Katsuki, T., *Synlett*, **1995**, 827. (b) Deng, L. and Jacobsen, E. N., *J. Org. Chem.,* **1992**, *57*, 4320.
21. (a) Imagawa, K.; Nagata, T.; Yamada, T. and Mukaiyama, T., *Chem. Lett.,* **1994**, 527. (b) Yamada, T.; Imagawa, K.; Nagata, T. and Mukaiyama, T., *Bull. Chem. Soc. Jpn.,* **1994**, *67*, 2248. (c) Lu, W. Y.; Bartoli, J. F.; Battioni, P. and Mansuy, D., *New J. Chem.,* **1992**, *16*, 621. (d) Yamada, T.; Imagawa, K.; Nagata, T. and Mukaiyama, T., *Chem. Lett.,* **1992**, 2231. (e) Horwitz, C. P.; Creager, S. E. and Murray, R. W., *Inorg. Chem.,* **1990**, *29*, 1006.
22. (a) Pietikäinen, P., *Tetrahedron*, **1998**, *54*, 4319. (b) Berkessel, A.; Frauenkron, M.; Schwenkreis, T.; Steinmetz, A.; Baum, G. and Fenske, D., *J. Mol. Catal. A: Chem.,* **1996**, *113*, 321. (c) Garcia, M.-A.; Meou, A. and Brun, P., *Synlett,* **1996**, 1049. (d) Pietikäinen, P., *Tetrahedron Lett.,* **1994**, *35*, 941. (e) Schwenkreis, T. and Berkessel, A., *Tetrahedron Lett.,* **1993**, *34*, 4785. (f) Palucki, M.; Hanson, P. and Jacobsen, E. N., *Tetrahedron Lett.,* **1992**, *33*, 7111.
23. Palucki, M.; McCormick, G. J. and Jacobsen, E. N., *Tetrahedron Lett.,* **1995**, *36*, 5457.
24. Nagata,, T.; Imagawa, K.; Yamada, T. and Mukaiyama, T., *Bull. Chem. Soc. Jpn.,* **1995**, *68*, 1455.
25. Gurjar, M. K.; Sarma, B. V. N. B. S. and Rama Rao, A. V., *Indian J. Chem., Sect. B,* **1997**, *36B*, 213.
26. (a) Levai, A.; Adam, W.; Fell, R. T.; Gessner, R.; Patonay, T.; Simon, A. and Toth, G., *Tetrahedron*, **1998**, *54*, 13105. (b) Adam, W.; Jeko, J.; Nemes, C.; Patonay, T. and Sebok, P., *Tetrahedron Lett.,* **1995**, *36*, 3669.
27. Daly, A. M.; Renehan, M. F. and Gilheany, D. G., *Org. Lett.,* **2001**, *3*, 663.
28. Norrby, P.-O.; Linde, C. and Åkermark, B., *J. Am. Chem. Soc.,* **1995**, *117*, 11035.
29. (a) Gaillon, L. and Bedioui, F., *Chem. Commun.,* **2001**, 1458. (b) Song, C. E. and Roh, E., *J. Chem. Commun.,* **2000**, 837.
30. (a) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E. and Jacobsen, E. N., *J. Am. Chem. Soc.,* **2002**, *124*, 1307. (b) Annis, D. A. and Jacobsen, E. N., *J. Am. Chem. Soc.,* **1999**, *121*, 4147. (c) Johnson, D. W. and Singleton, D. A., *J. Am. Chem. Soc.,* **1999**, *121*, 9307.
31. (a) Scheurer, A.; Maid, H.; Hampel, F.; Saalfrank, R. W.; Toupet, L.; Mosset, P.; Puchta, R. and van Eikema Hommes, N. J. R., *Eur. J. Org. Chem.,* **2005**, 2566. (b) Armstrong, A. and Knight, J. D., *Ann. Rep. Sec. B, (Org. Chem.),* **2004**, *100*, 51. (c) Ramon, D. J. and Yus, M., *Curr. Org. Chem.,* **2004**, *8*, 149. (d) Abashkin, Y. G. and Bur, S. K., *Org. Lett.,* **2004**, *6*, 59. (e) Cavallo, L. and Jacobsen, H., *Inorg. Chem.,* **2004**, *43*, 2175. (f) Larrow, J. F.; Roberts, E.; Verhoeven, T. R.; Ryan, K. M.; Senanayake, C. H.; Reider, P. and Jacobsen, E. N., *Org. Synth. Coll. Vol. X*, **2004**, 29. (g) Abashkin, Y. G. and Burt, S. K., *Org. Lett.,* **2004**, *6*, 59. (h) Cavallo, L. and Jacobsen, H., *J. Phys. Chem. A,* **2003**, *107*, 5466. (i) Cavallo, L. and Jacobsen, H., *Eur. J. Inorg. Chem.,* **2003**, 892. (j) Cavallo, L. and Jacobsen, H., *J. Phys. Chem. A,* **2003**, *107*, 5466. (k) Hsieh, W.-Y. and Pecoraro, V. L., *Inorg. Chim. Acta,* **2002**, *341*, 113. (l) Lipkowitz, K. B. and Schefzick, S., *Chirality*, **2002**, *14*, 677. (m) Pietikäinen, P., *Academic Dissertation*, University of Helsinki, Finland, **2001**. (n) Adam, W.; Stegmann, V. R. and Saha-Möller, C. R., *J. Am. Chem. Soc.,* **1999**, *121*, 1879. (o) Strassner, T. and Houk, K. N., *Org. Lett.,* **1999**, *1*, 419. (p) Aggarwal, V. K.; Ford, J. G.; Fonquerna, S.; Adams, H.; Jones, R. V. H. and Fieldhouse, R., *J. Am. Chem. Soc.,* **1998**, *120*, 8328. (q) Linker, T., *Angew. Chem. Int. Ed. Engl.,* **1997**, *36*, 2060.

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Janovsky Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Janovsky and Erb in 1886.[1] It is the reaction between aromatics containing multinitro groups and aldehydes or ketones with an activated α-proton in the presence of a strong base to form coloring molecules, for detection of both carbonyl compounds and nitroaromatics. Therefore, this reaction is generally known as the Janovsky reaction.[2,3] Occasionally, it is also referred to as the Janovsky test.[4] It is known that this reaction involves the addition of an enolate from the ketone or aldehyde to multinitro aromatics (the rate-determining step[2b]), resulting in the formation of a cyclohexadienate ion,[2b] an anionic σ complex[5] that is also known as Janovsky complex.[6] In addition, the product of this reaction is called Janovsky adduct[7] or Janovsky product.[8] It has been reported that substituents other than the nitro groups on the aromatic rings may influence the reactivity of substrates or alter the resonance of the nitro groups in the quinoid ion.[9] On the other hand, the relative location of the nitro groups also affect the outcome of this reaction. For example, *meta*-dinitrobenzene readily responds to this reaction, *para*-dinitrobenzene yields a reddish yellow color and quickly changes into a greenish yellow color, and *ortho*-dinitrobenzene does not yield any color.[10] When potassium hydroxide is applied as the base, the formation of the addition product is reversible, the color develops relatively slowly; however, when sodium methylate is used as the base, the successive color change is indistinct and too quick to follow, occurring via an irreversible pathway.[2g] A study on this reaction found that at very low temperatures (e.g., -40°C), the addition of enolate to the nitroaromatics is primarily through an *O*-attack, whereas at relatively high temperatures (e.g., -20°C), the *O*-attack intermediate gradually changes to the anion originated from *C*-attack, which is stable for days at room temperature.[2a] Although this reaction has not found much synthetic application, it has been widely used for the detection of nitroaromatics, in the fields of

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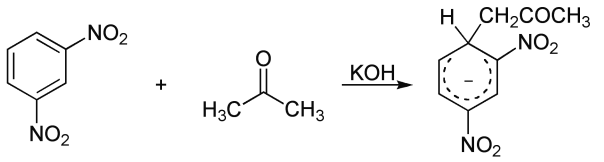
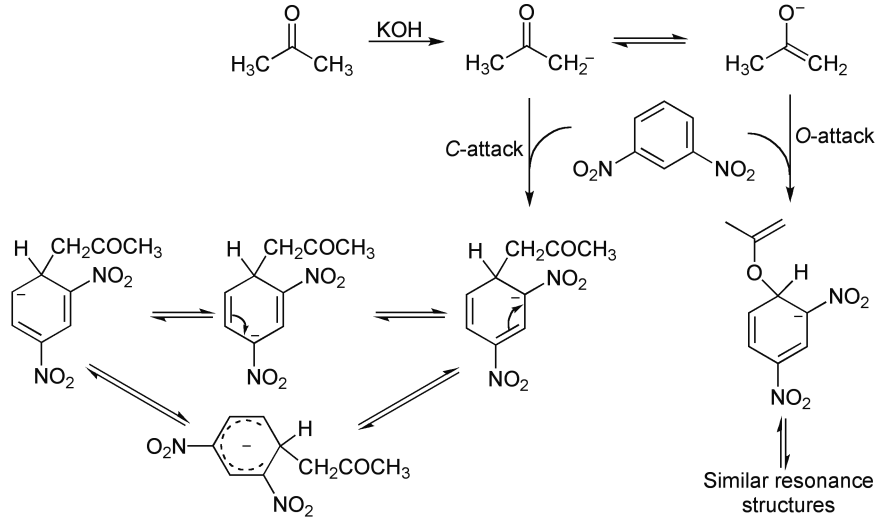
forensic toxicology,[2g] agriculture,[3z] etc. For example, 2,4-dinitrobenzene can be detected at concentration level of < 1 ppm,[10] while DDT can be detected as small as 1 μg.[2g] However, it is difficult to detect dinitro compounds in the presence of trinitro compounds.[10] It has been found that this reaction will behave differently in the presence of an excess amount of nitroaromatics, which will oxidize the Janovsky complex and reduce the excess nitro compounds.[2c] This reaction has been extended to measure 3,5-dinitrobenzamide using ammonium hydroxide as base.[3z]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A mechanism including both a *C*-attack and an *O*-attack of enolate is outlined here.



D. MODIFICATION

This reaction has been extended to 3,5-dinitrobenzamide using ammonium hydroxide as base.[3z]

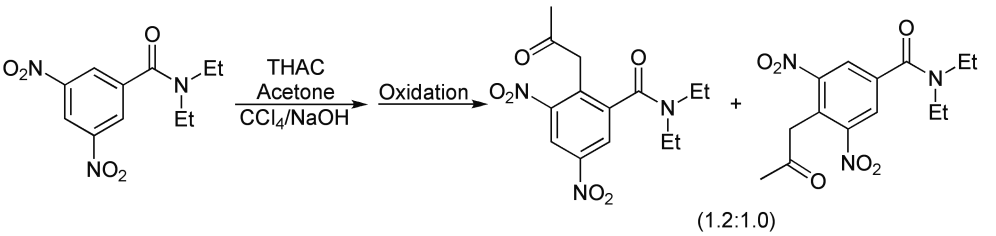
E. APPLICATIONS

This reaction has been widely used for forensic toxicology, and agriculture and pharmaceutical testing.

F. RELATED REACTIONS

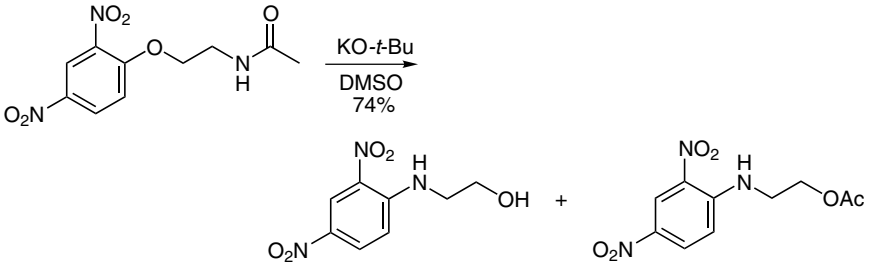
This reaction is related to the *Meisenheimer Complexes* and *Zimmermann Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 8.

To a scintillation vial equipped with a stir bar were added 134 mg *N*,*N*-diethyl-3,5-dinitrobenzamide (0.5 mmol) and 196 mg tetrahexylammonium chloride (THAC, 0.5 mmol). The aluminum foil lining of the cap was replaced with a Teflon lining. To this vial was added 10 mL carbon tetrachloride, followed by 50 μL acetone via a syringe, and then 5 mL 2 M NaOH. The organic layer turned dark blue immediately upon addition of NaOH. The mixture was stirred vigorously for 4 h in the capped vial. Stirring was stopped to allow for phase separation. The organic layer was diluted with 10 mL CH_2Cl_2 and separated from the aqueous layer. The organic phase was combined with 10 mL 6 M HCl and stirred for an additional 10 min. The color of the organic phase changed from dark blue to yellow-orange. The organic phase was extracted sequentially with saturated solutions of $NaHCO_3$ and NaCl, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified through flash column chromatography using 10% Et_2O in CH_2Cl_2 to recover 53 mg *N*,*N*-diethyl-3,5-dinitrobenzamide (40%), 14 mg of an oily mixture of the *o*- and *p*-acetonate adducts in an *ortho*/*para* ratio of 1.2:1.0.



Reference 5.

To a stirred solution of 0.778 g *N*-acetyl-β-aminoethyl-2,4-dinitrophenyl ether (2.89 mmol) in 10 mL Me_2SO was added at room temperature 2.37 mL 1.22 N potassium *t*-butoxide (2.89 mmol). After the mixture had been stirred for 1 h and then 2.89 mL HCl (2.0 N) solution was added, the mixture was poured into 100 mL water, extracted with chloroform, and dried over anhydrous Na_2SO_4. The solvent was evaporated to produce the crude products, which were separated by column chromatography on silica gel with benzene as a developing solvent to give 74% *N*-β-hydroxylethyl 2,4-dinitroaniline and *N*-β-acetoxyethyl 2,4-dinitroaniline as a mixture.

Other references related to the Janovsky reaction are cited in the literature.[11]

H. REFERENCES

1. Janovsky, J. V. and Erb, L., *Ber.,* **1886**, *19*, 2155.
2. (a) Buncel, E.; Dust, J. M. and Manderville, R. A., *J. Am. Chem. Soc.,* **1996**, *118*, 6072. (b) Artamkina, G. G.; Egorov, M. P. and Beletskaya, I. P., *Chem. Rev.,* **1982**, *82*, 427. (c) Strauss, M. J., *Chem. Rev.,* **1970**, *70*, 667. (d) Nakadate, M.; Takano, Y.; Hirayama, T.; Sakaizawa, S.; Hirano, T.; Okamoto, K.; Hirao, K.; Kawanura, T. and Kimura, M., *Chem. Pharm. Bull.,* **1965**, *13*, 113. (e) Russell, G. A.; Janzen, E. G. and Strom, E. T., *J. Am. Chem. Soc.,* **1964**, *86*, 1807. (f) Kilgore, W. W.; Cheng, K. W. and Ogawa, J. M., *J. Agri. Food Chem.,* **1962**, *10*, 399. (g) Irudayasamy, A. and Natarajan, A. R., *Anal. Chem.,* **1961**, *33*, 630.
3. (a) Sutherland, R. G.; Chowdhury, T. L.; Piorko, A. and Lee, C. C., *Can. J. Chem.,* **1986**, *64*, 2031. (b) Prousek, J., *Chemicke Listy*, **1986**, *80*, 714. (c) Ciurlizza G., A. and Ramirez A., J., *Acta Mexicana Ciencia Tecnologia*, **1985**, *3*, 35. (d) Sutherland, R. G.; Chowdhury, R. L.; Piorko, A. and Lee, C. C., *J. Chem. Soc., Chem. Commun.,* **1985**, 1296. (e) Nabi, S. A.; Haque, S. and Qureshi, P. M., *Talanta,* **1983**, *30*, 989. (f) Ciurlizza, G. A. and Ordunez, M. R., *Acta Politecnica Mexicana*, **1978**, *19*, 37. (g) Sosonkin, I. M.; Kaminskii, A. Y. and Strogov, G. N., *Zh. Obsh. Khim.,* **1975**, *45*, 482. (h) Tanaka, A. and Fujimoto, Y., *Agri. Biol. Chem.,* **1974**, *38*, 1575. (i) Lehmann Feither, P. A. and Ciurlizza G., A., *Revista Latinoamer. Quim.*, **1974**, *5*, 72. (j) Kovar, K. A., *Arch. Pharm.,* **1974**, *307*, 76. (k) Kohashi, K.; Kabeya, T.; Ohkura, Y. and Momose, T., *Chem. Pharm. Bull.,* **1973**, *21*, 2187. (l) Lehmann F., P. A. and Ciurlizza G., A., *Revista Soc. Quim. Mexico*, **1972**, *16*, 78. (m) Bartos, J., *Chim. Anal. (Paris),* **1971**, *53*, 384. (n) Bartos, J., *Chim. Anal. (Paris),* **1971**, *53*, 18. (o) Gitis, S. S.; Sosonkin, I. M. and Kaminskii, A. Y., *Dokl. Akad. Nauk SSSR,* **1970**, *193*, 1301. (p) Kimura, M.; Obi, N. and Kawazoi, M., *Chem. Pharm. Bull.,* **1969**, *17*, 531. (q) Bartos, J., *Talanta,* **1969**, *16*, 551. (r) Kaminskii, A. Ya. and Gitis, S. S., *Zh. Org. Khim.,* **1968**, *4*, 1826. (s) Kimura, M.; Kawata, M.; Nakadate, M.; Obi, N. and Kawazoe, M., *Chem. Pharm. Bull.,* **1968**, *16*, 634. (t) Ashworth, M. R. F. and Schupp, R., *Mikrochimica Acta*, **1968**, 366. (u) Fyfe, C. A. and Foster, R., *Chem. Commun. (London),* **1967**, 1219. (v) Ashworth, M. R. F. and Gramsch, E., *Mikrochimica Acta*, **1967**, 358. (w) Pollitt, R. J. and Saunders, B. C., *J. Chem. Soc.,* **1965**, 4615. (x) Nakadate, M.; Matsuyama, C. and Kimura, M., *Chem. Pharm. Bull.,* **1964**, *12*, 1138. (y) Foster, R. and Mackie, R. K., *Tetrahedron*, **1963**, *19*, 691. (z) Beckman, H. F. and De Mottier, J., *J. Agri. Food Chem.,* **1959**, *7*, 280. (aa) Kimura, M. and Thoma, M., *Yakugaku Zasshi*, **1958**, *78*, 1401.
4. (a) Parkes, G. D. and Farthing, A. C., *J. Chem. Soc.,* **1948**, 1275. (b) Huntress, E. H. and Hearon, W. M., *J. Am. Chem. Soc.,* **1942**, *64*, 86.
5. Sekiguchi, S. and Okada, K., *J. Org. Chem.,* **1975**, *40*, 2782.
6. (a) Wubbels, G. G.; Winitz, S. and Whitaker, C., *J. Org. Chem.,* **1990**, *55*, 631. (b) RajanBabu, T. V.; Reddy, G. S. and Fukunaga, T., *J. Am. Chem. Soc.,* **1985**, *107*, 5473. (c) Burlinson, N. E.; Sitzman, M. E.; Kaplan, L. A. and Kayser, E., *J. Org. Chem.,* **1979**, *44*, 3695. (d) Okada, K.

and Sekiguchi, S., *J. Org. Chem.,* **1978**, *43*, 441. (e) Bernasconi, C. F., *J. Org. Chem.,* **1971**, *36*, 1671. (f) Byrne, W. E.; Fendler, E. J.; Fendler, J. H. and Griffin, C. E., *J. Org. Chem.,* **1967**, *32*, 2506.

7. Russell, G. A.; Moye, A. J.; Janzen, E. G.; Mak, S. and Talaty, E. R., *J. Org. Chem.,* **1967**, *32*, 137.
8. Snyder, S. E.; Carey, J. R.; Shvets, A. B. and Pirkle, W. H., *J. Org. Chem.,* **2005**, *70*, 4073.
9. Porter, C. C., *Anal. Chem.,* **1955**, *27*, 805.
10. Bost, R. W. and Nicholson, F., *Ind. Eng. Chem., Anal. Ed.*, **1935**, *7*, 190.
11. (a) Artiss, J. D.; Karcher, R. E.; Collins, S. L. and Zak, B., *Microchem. J.,* **2000**, *65*, 277. (b) Mahacek, V.; Sterba, A.; Lycka, A. and Snoble, D., *J. Chem. Soc., Perkin Trans. II,* **1982**, 355. (c) Kohashi, K.; Kabeya, T. and Ohkura, Y., *Chem. Pharm. Bull.,* **1977**, *25*, 50. (d) Neufer, J. E.; Zirin, M. H. and Trivich, D., *J. Phys. Chem.,* **1964**, *68*, 2023. (e) Foster, R. and Mackie, R. K., *Tetrahedron,* **1962**, *18*, 1131. (f) Akatsuka, M., *Yakugaku Zasshi,* **1960**, *80*, 389. (g) von Bittó, B., *Ann.,* **1892**, *269*, 377. (h) Janovsky, J. V., *Ber.,* **1891**, *24*, 971.

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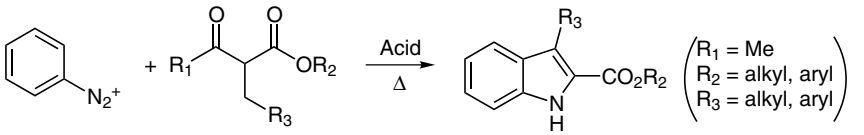
Japp-Klingemann Fischer Indole Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction combines the *Japp-Klingemann Reaction* and *Fischer Indole Synthesis*, involving the condensation between aryldiazonium salt and an active methylene or methinyl compound under acidic or basic conditions to form a hydrazone derivative followed by cyclization to give a substituted indole. This reaction is therefore known as the Japp-Klingemann Fischer indole protocol,[1] Japp-Klingemann/Fischer indole process,[2] Japp-Klingemann Fischer indole synthesis,[3] or the Japp-Klingemann indole synthesis[4] or Japp-Klingemann indole formation.[5] This reaction was probably first reported by Findlay and Dougherty in 1948,[6] to avoid the use of arylhydrazines, which are difficult to prepare and handle in some cases.[7]

B. GENERAL REACTION SCHEME



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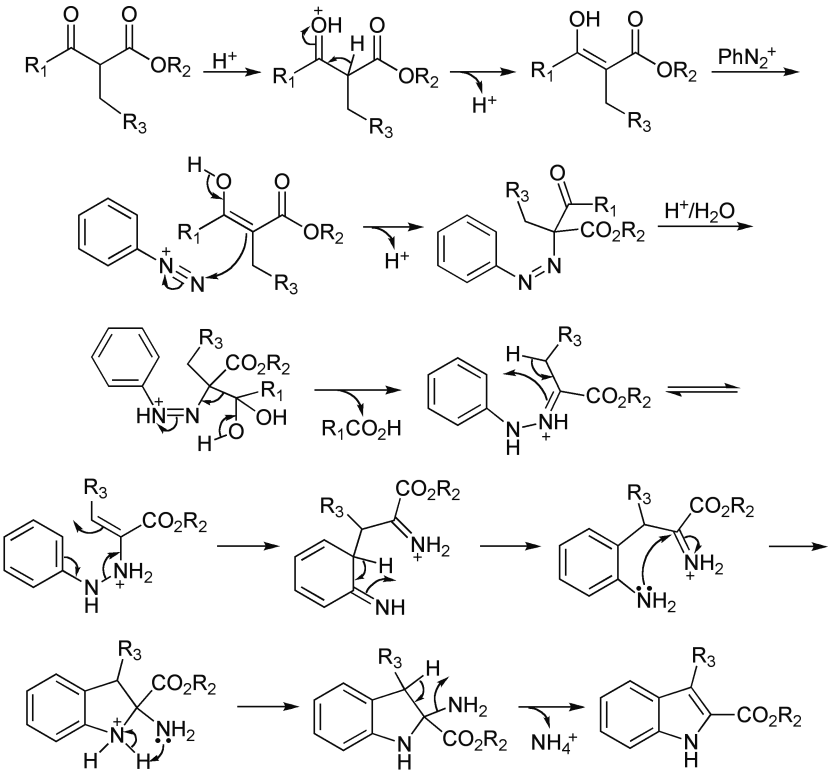
C. PROPOSED MECHANISMS

This reaction involves the elelctrophilic attack of an aryldiazonium cation on the enol carbon atom of an active methinyl compound to give an azo intermediate, which then hydrolyzes to form an arylhydrazone.[8] Tautomerization of aryl hydrazone yields the vinyl hydrazine, which undergoes [3,3] sigmatropic rearrangement and subsequently cyclizes to give an indoline derivative which, upon evolution of ammonium ion, yields the indole derivative, as shown below.



D. MODIFICATION

N/A

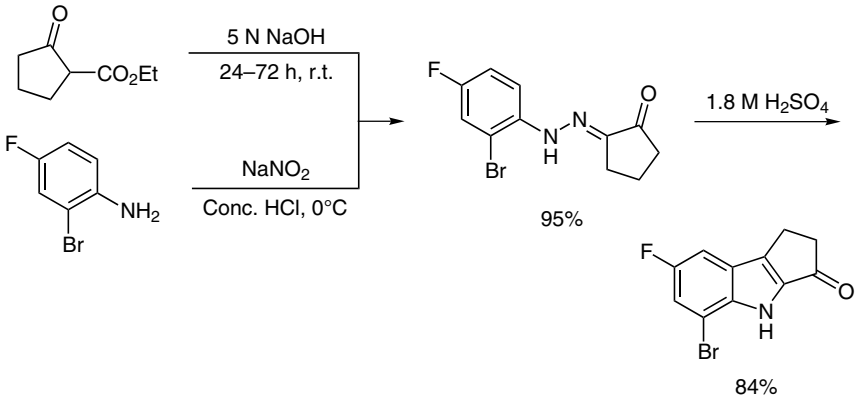
E. APPLICATIONS

This reaction is very useful for the preparation of indole derivatives.

F. RELATED REACTIONS

This reaction is related to the *Japp-Klingemann Reaction* and *Fischer Indole Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES

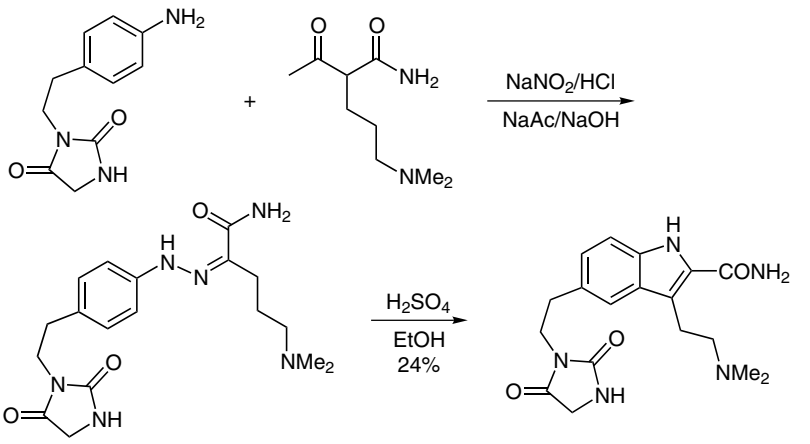


Reference 9.

To a three-necked flask were added 156.2 g ethyl 2-oxocyclopentanecarboxylate (1.0 mol), 2 L water, and 220 mL 5 N NaOH solution (1.1 mol); the resulting solution was stirred for 48 h at room temperature. This mixture was extracted with methyl *tert*-butyl ether (2 × 400 mL) to remove any residual unreacted starting material, and the aqueous phase containing the sodium carboxylate was returned to the original three-necked flask. This solution was cooled to 0°C, treated dropwise with concentrated HCl (1.1 mol) over 15 min, and aged at this temperature for 45 min.

Mean while, to a mixture of 190.0 g 2-bromo-4-fluoro-aniline (1 mol) and 0.6 L water at room temperature was added 3 mol concentrated HCl; the resulting thick white slurry was cooled to 0°C. A solution of 1 mol $NaNO_2$ in 0.7 L water was added slowly over 25 min, at such a rate as not to exceed an internal temperature of 10°C, and the reaction was aged for 30 min before filtration to remove any insoluble precipitate. This filtered diazonium solution was added to the prepared sodium carboxylate solution at 0°C dropwise over a period of 40 min (*Note*: If added to the solution of sodium carboxylate, then it was not necessary to acidify the sodium carboxylate with concentrated HCl.) The resulting thick yellow slurry was stirred to room temperature, filtered, and dried under a stream of nitrogen to give 270.9 g (4:1 ratio) 1-(*E*/*Z*)-cyclopentane-1,2-dione (2-bromo-4-fluorophenyl)hydrazone as a yellow solid, in a yield of 95%, m.p. 182–187°C.

To a three-necked, round-bottomed flask equipped with a mechanical stirrer, a condenser, and a nitrogen inlet were added 2.85 g of the hydrazone (10 mmol) and 25 mL CH_3CN. To this solution was then added 17 mL 1.8 M H_2SO_4 (30 mmol) in one portion. The resulting mixture was refluxed under stirring for 5–6 h. After the reaction was judged complete by HPLC analysis, 50 mL water was added, and the resultant slurry was stirred at room temperature for 1–2 h before filtration. The collected precipitate was washed with 50 mL CH_3CN/water (1:3), water (3 × 50 mL) and dried to give 3.24 g 5-bromo-7-fluoro-1,4-dihydrocyclopenta[*b*]indol-3(*2H*)-one, in a yield of 84%, m.p. 204–206°C.



Reference 4c.

To a mixture of 2.0 mL ethanol and 6.5 mL water, was added 1.0 g 3-(4-aminophenethyl) imidazolidine-2,4-dione (3.91 mmol), followed by 0.78 mL concentrated HCl (7.42 mol). The solution was cooled to 0˚C, and a solution of 0.54 g $NaNO_2$ (7.82 mmol) in 2.5 mL water was added. The solution was stirred for 30 min, after which the excess $NaNO_2$ was destroyed with 0.29 g urea (4.8 mmol). Meanwhile, 0.72 g 2-(3′-*N*,*N*-dimethylamino)propyl acetoacetamide (3.91 mmol) in 3.5 mL EtOH was stirred with 2.77 g sodium acetate trihydrate (20 mmol) in 3.5 mL water at 0°C for 20 min, after which the solution was added quickly to the cold diazonium solution. The resulting mixture was allowed to stir at 0°C for an additional 30 min and then allowed to stir up to room temperature for 1 h. The pH was adjusted to 9 with 10% NaOH solution, and the solution was left in the refrigerator overnight. The residue was extracted with ethyl acetate (3 × 30 mL); the combined organic layers were dried and filtered; and the solvent was evaporated to give a red gum, which was purified by column chromatography to afford 300 mg of the desired hydrazone intermediate, in 90% purity. A portion of the hydrazone (30 mg, 0.08 mmol) was dissolved in 3.0 mL ethanol, and 0.13 mL concentrated H_2SO_4 was added. After gentle refluxing overnight, the solution was cooled, and the solvent was evaporated under reduced pressure. The residue was mixed with water, and the pH was adjusted to 9 with K_2CO_3. The basic solution was extracted with EtOAc, and the combined organic layers were dried, filtered and evaporated. The yellow residue was purified by column chromatography using CH_2Cl_2/EtOH/NH_3 (50:8:1) as the eluent to afford 3-[2-(dimethylamino)ethyl]-5-[2-(2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide as an off white solid. Further purification using preparative HPLC gave 13.0 mg of the acetate salt of the indole as a white lyophylate, in a yield of 24%.

Other references related to the Japp-Klingemann Fischer indole synthesis are cited in the literature.[10]

H. REFERENCES

1. Jiricek, J. and Blechert, S., *J. Am. Chem. Soc.,* **2004**, *126*, 3534.
2. Zhao, S.; Liao, X. B.; Wang, T.; Flippen-Anderson, J. and Cook, J. M., *J. Org. Chem.,* **2003**, *68*, 6279.

3. Böttcher, H.; Barnickel, G.; Hausberg, H.-H.; Haase, A. F.; Seyfried, C. A. and Eiermann, V., *J. Med. Chem.,* **1992**, *35*, 4020.
4. (a) Moloney, G. P.; Martin, G. R.; Mathews, N.; Hobbs, H.; Dodsworth, S.; Sang, P. Y.; Knight, C.; Maxwell, M. and Glen, R. C., *J. Chem. Soc*., *Perkin Trans. I*, **1999**, 2699. (b) Moloney, G. P.; Martin, G. R.; Mathews, N.; Hobbs, H.; Dodsworth, S.; Sang, P. Y.; Knight, C.; Maxwell, M. and Glen, R. C., *J. Chem. Soc*., *Perkin Trans. I*, **1999**, 2713. (c) Moloney, G. P.; Martin, G. R.; Mathews, N.; Milne, A.; Hobbs, H.; Dodsworth, S.; Sang, P. Y.; Knight, C.; Williams, M.; Maxwell, M. and Glen, R. C., *J. Med. Chem.,* **1999**, *42*, 2504.
5. Moloney, G. P.; Robertson, A. D.; Martin, G. R.; MacLennan, S.; Mathews, N.; Dodsworth, S.; Sang, P. Y.; Knight, C. and Glen, R., *J. Med. Chem.,* **1997**, *40*, 2347.
6. Findlay, S. P. and Dougherty, G., *J. Org. Chem.,* **1948**, *13*, 560.
7. Humphrey, G. R. and Kuethe, J. T., *Chem. Rev.,* **2006**, *106*, 2875.
8. Robinson, B., *Chem. Rev.,* **1963**, *63*, 373.
9. Hilier, M. C.; Marcoux, J.-F.; Zhao, D. L.; Grabowski, E. J. J.; McKeown, A. K. and Tillyer, R. D., *J. Org. Chem.,* **2005**, *70*, 8385.
10. (a) Silvestri, R.; Artico, M.; La Regina, G. and De Martino, G., *ARKIVOC,* **2004** (v) 26. (b) Heinrich, T. and Bottcher, H., *Bioorg. Med. Chem. Lett.,* **2004**, *14*, 2681. (c) Horton, D. A.; Bourne, G. T. and Smythe, M. L., *Chem. Rev.,* **2003**, *103*, 893. (d) Knölker, H.-J. and Reddy, K. R., *Chem. Rev.,* **2002**, *102*, 4303. (e) Ma, C. R.; Liu, X. X.; Li, X. Y.; Flippen-Anderson, J.; Yu, S. and Cook, J. M., *J. Org. Chem.,* **2001**, *66*, 4525. (f) Skibo, E. B.; Xing, C. G. and Dorr, R. T., *J. Med. Chem.,* **2001**, *44*, 3545. (g) Tois, J.; Franzén, R.; Aitio, O.; Huikko, K. and Taskinen, J., *Tetrahedron Lett.,* **2000**, *41*, 2443. (h) Menciu, C.; Duflos, M.; Fouchard, F.; Le Baut, G.; Emig, P.; Achterrath, U.; Szelenyi, I.; Nickel, B.; Schmidt, J.; Kutscher, B. and Günther, E., *J. Med. Chem.,* **1999**, *42*, 638. (i) Font, M.; Monge, A.; Cuartero, A.; Elorriaga, A.; Martínez-Irujo, J. J.; Alberdi, E.; Santiago, E.; Prieto, I.; Lasarte, J. J.; Sarobe, P. and Borrás, F., *Eur. J. Med. Chem.,* **1995**, *30*, 963. (j) Salituro, F. G.; Harrison, B. L.; Baron, B. M.; Nyce, P. L.; Stewart, K. T.; Kehne, J. H.; White, H. S. and McDonald, I. A., *J. Med. Chem.,* **1992**, *35*, 1791. (k) Itoh, S.; Fukui, Y.; Ogino, M.; Haranou, S.; Komatsu, M. and Ohshiro, Y., *J. Org. Chem.,* **1992**, *57*, 2788. (l) Salituro, F. G.; Harrison, B. L.; Baron, B. M.; Nyce, P. L.; Stewart, K. T. and McDonald, I. A., *J. Med. Chem.,* **1990**, *33*, 2944. (m) Meyer, R. B. and Skibo, E. B., *J. Med. Chem.,* **1979**, *22*, 944. (n) Fahrenholtz, K. E.; Silverzweig, M. Z.; Germane, N.; Crowley, H. J.; Simko, B. A. and Dalton, C., *J. Med. Chem.,* **1979**, *22*, 948. (o) Japp, F. R. and Klingemann, P., *Methoden der Organischen Chemie,* Thieme-Verlag, Stuttgart, **1965**. (p) Heath-Brown, B. and Philpott, P. G., *J. Chem. Soc*., **1965**, 7185. (q) Phillips, R. R., *Org. React.,* **1959**, *10*, 143. (r) Abramovitch, R. A. and Shapiro., D. S., *J. Chem. Soc.,* **1956**, 4589. (s) Morton, A. A. and Slaunwhite, W. R., *J. Biol. Chem.,* **1949**, *179*, 259.

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Japp-Klingemann Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Japp and Klingemann in 1887.[1] It is the reaction between aryldiazonium salt and compounds with methylene protons activitated by electron-withdrawing groups in which at least one of such activating groups is an acyl, carboxyl, or ester group to form an unstable azo intermediate that rearranges into a stable hydrazone derivative by expelling of the above acyl, carboxyl or ester group. Therefore, this reaction is often known as the Japp-Klingemann reaction.[2,3] Occasionally, it is also referred to as the Japp-Klingemann degradation,[4] Japp-Klingemann rearrangement,[5] Japp-Klingemann synthesis,[6] Japp-Klingemann condensation,[2a,7] Japp-Klingemann coupling,[8] or Japp-Klingemann cleavage.[9] This reaction is found to be very mild and occurs under almost neutral conditions,[2k] with an optimal pH of 6.2.[10] In most cases, the hydrazone can be isolated when a limited amount of diazonium salt is used or by working at a lower pH.[2k] In addition, the hydrazone formed might exist in a tautomeric form of ene-hydrazine.[11] Especially, under more alkaline conditions or when an excess of diazonium salt is used, the second diazonium ion can couple to the generated hydrazone.[11] In this reaction, the functional group of acyl (e.g., acetyl,[2k,12] benzoyl), carboxyl, ester[2k] and even hydrogen[2k] and bromonium ion[13] can be expelled during the formation of hydrazone. It has been found that the yield of such reaction can be improved dramatically by prior treatment of the extreme acidic diazonium salt with sodium acetate;[14] on the other hand, ammonium salts (e.g., NH_4Cl or NH_4Ac) are found to promote the coupling rate.[2j] This reaction has been extended to the coupling of diazonium salt with 2-pyridylacetic acids,[2m] and has been used in the syntheses of various amino acids,[2j] naphthazoleacetic acid,[2n] tetrahydrocarbazoles[15] and indole derivatives.[2c–2e,2l,2n,5,16]

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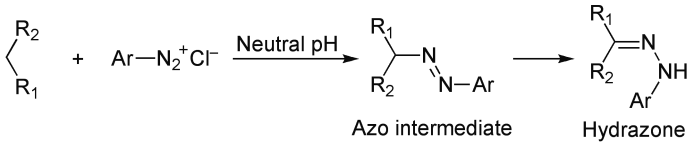
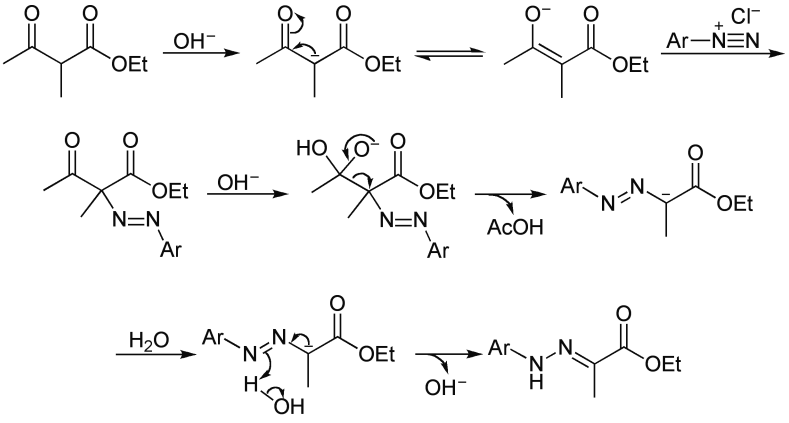
B. GENERAL REACTION SCHEME



$(R_1, R_2 = NO_2, CHO, C(O)R, C(O)NR_2, COOH, SOR, SO_2R, etc.)$

C. PROPOSED MECHANISMS

Displayed below is the reaction mechanism between ethyl α-methyl-acetoacetate and aryl diazonium chloride.



D. MODIFICATION

This reaction has been modified to treat the acidic diazonium salt with sodium acetate before the addition of compounds with active methylene groups.[14] In addition, this reaction has been carried out in the presence of an ammonium salt.[2j]

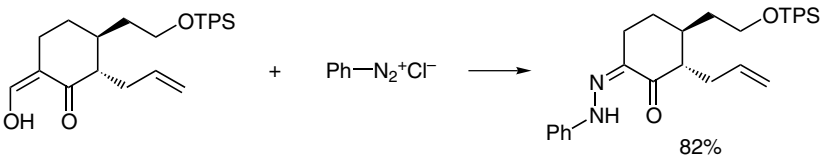
E. APPLICATIONS

This reaction has been used to synthesize a variety of amino acids and nitrogenous heterocycles, such as indole and tetrahydrocarbazole derivatives.

F. RELATED REACTIONS

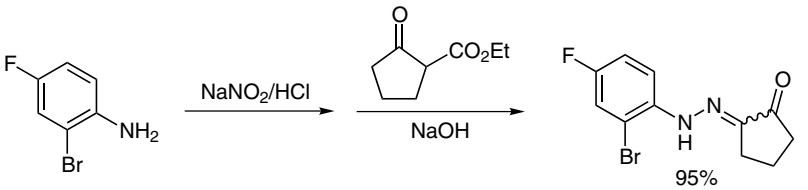
This reaction is related to the *Japp-Klingemann Fischer Indole Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 14.

Aniline (0.90 mL, 9.98 mmol) was added to a 3 mL 6 M HCl solution at 0°C. After the mixture was stirred for 10 min, 10 mL cold 0.998 M $NaNO_2$ solution (688 mg $NaNO_2$ in 10 mL H_2O) was added slowly at 0°C under temperature control. The solution was neutralized with NaOAc, followed by addition of an ice-chilled THF solution containing 2.985 g (2S,3S)-2-allyl-3-[2-(*tert*-butyldiphenylsilanyloxy)-ethyl]-6-hydroxymethylene-cyclohexanone (6.65 mmol). The reaction mixture was stirred for 1 h at 0°C, then diluted with methyl *tert*-butyl ether (MTBE). The aqueous layer was extracted twice with MTBE. The combined organic layers were washed with brine and dried over magnesium sulfate. The solvent was removed in vacuo and the crude oil was purified by column chromatography on silica, eluting with hexanes/MTBE (16:1) to give 2.86 g (2S,3S)-2-allyl-3-[2-(*tert*-butyl-diphenylsilanyloxy)-ethyl]-6-(phenyl-hydrazono)-cyclohexanone, as an orange oil, in a yield of 82%.



Reference 2a.

Sodium Carboxylate Preparation

A three-necked flask was charged with 156.2 g ethyl 2-oxocyclopentanecarboxylate (1 mol), 2 L water, and 220 mL 5 N NaOH (1.1 mol), and the resulting solution was stirred for 48 h at room temperature. This mixture was extracted with MTBE (2 × 400 mL) to remove any residual unreacted ester, and the aqueous phase containing the sodium carboxylate was returned to the original three-necked flask. This solution was cooled to 0°C.

Diazonium Salt Preparation

To a mixture of 190 g 2-bromo-4-fluoroaniline (1.0 mol) in 0.6 L water was added 250 mL concentrated HCl, and the resulting thick white slurry was cooled to 0°C. Aqueous solution (0.7 L) containing 69 g $NaNO_2$ (1 mol) was added slowly over 25 min, at such a rate as not to exceed an internal temperature of 10°C, and the reaction was aged for 30 min before filtration to remove any insoluble precipitate.

Japp-Klingemann Reaction

To the prepared sodium carboxylate solution at 0°C was added the filtered diazonium solution dropwise over 40 min at a temperature range of 0–4°C. The resulting thick yellow slurry was stirred to room temperature, filtered, and dried under a stream of nitrogen to give 95% (1*E*/*Z*)-cyclopentane-1,2-dione (2-bromo-4-fluorophenyl) hydrazone, as a yellow solid of steric mixture in 4:1 ratio, m.p. 182–187°C.

Other references related to the Japp-Klingemann reaction are cited in the literature.[17]

H. REFERENCES

1. (a) Japp, F. R. and Klingemann, F., *Ber.,* **1887**, *20*, 2942. (b) Japp, F. R. and Klingemann, F., *Ber.,* **1887**, *20*, 3284. (c) Japp, F. R. and Klingemann, F., *Ber.,* **1887**, *20*, 3398.
2. (a) Hillier, M. C.; Marcoux, J.-F.; Zhao, D. L.; Grabowski, E. J. J.; McKeown, A. E. and Tillyer, R. D., *J. Org. Chem.,* **2005**, *70*, 8385. (b) Kavitha, C. and Prasad, K. J. R., *Heterocycl. Commun.,* **1999**, *5*, 481. (c) Itoh, S.; Fukui, Y.; Ogino, M.; Haranou, S.; Komatsu, M. and Ohshiro, Y., *J. Org. Chem.,* **1992**, *57*, 2788. (d) Narayanan, K.; Schindler, L. and Cook, J. M., *J. Org. Chem.,* **1991**, *56*, 359. (e) Salituro, F. G.; Harrison, B. L.; Baron, B. M.; Nyce, P. L.; Stewart, K. T. and McDonald, I. A., *J. Med. Chem.,* **1990**, *33*, 2944. (f) Gainor, J. A. and Weinreb, S. M., *J. Org. Chem.,* **1982**, *47*, 2833. (g) Gainor, J. A. and Weinreb, S. M., *J. Org. Chem.,* **1981**, *46*, 4317. (h) Witte, J. and Boekelheide, V., *J. Org. Chem.,* **1972**, *37*, 2849. (i) Phillips, R. R., *Org. React.,* **1959**, *10*, 143. (j) Shapiro, D.; Segal, H. and Flowers, H. M., *J. Am. Chem. Soc.,* **1958**, *80*, 1194. (k) Nineham, A. W., *Chem. Rev.,* **1955**, *55*, 355. (l) Goldsmith, E. A. and Lindwall, H. G., *J. Org. Chem.,* **1953**, *18*, 507. (m) Frank, R. L. and Phillips, R. R., *J. Am. Chem. Soc.,* **1949**, *71*, 2804. (n) Findlay, S. P. and Dougherty, G., *J. Org. Chem.,* **1948**, *13*, 560.
3. (a) Chen, Y. H.; Shibata, M.; Rajeswaran, M.; Srikrishnan, T.; Dugar, S. and Pandey, R. K., *Tetrahedron Lett*., **2007**, *48*, 2353. (b) Sofan, M. A.; Fouda, A. M. and Asfah, E. M., *Pol. J. Chem*., **2004**, *78*, 837. (c) Atlan, V.; Kaim, L. E. and Supiot, C., *Chem. Commun.,* **2000**, 1385. (d) Delfourne, E.; Roubin, C. and Bastide, J., *J. Org. Chem.,* **2000**, *65*, 5476. (e) Prabhakar, C.; Kumar, N. V.; Reddy, M. R.; Sarma, M. R. and Reddy, G. O., *Org. Proc. Res. Dev.,* **1999**, *3*, 155. (f) Bazavova, I. M.; Esipenko, A. N.; Neplyuev, V. M. and Lozinskii, M. O., *Zh. Org. Khim.,* **1996**, *32*, 1278. (g) Black, D. St C.; Deacon, G. B. and Edwards, G. L., *Aust. J. Chem.,* **1991**, *44*, 1771. (h) Buzykin, B. I.; Sokolov, M. P.; Pavlov, V. A.; Ivanova, V. N.; Chertanova, L. F. and Zyablikova, T. A., *Zh. Obsh. Khim.,* **1990**, *60*, 546. (i) Neplyuev, V. M.; Bazavova, I. M. and Lozinskii, M. O., *Zh. Org. Khim.,* **1989**, *25*, 2225. (j) Chetcuti, P. A.; Knobler, C. B. and Hawthorne, M. F., *Organometallics,* **1988**, *7*, 650. (k) Noar, J. B. and Bruice, T. C., *J. Org. Chem.,* **1987**, *52*, 1942. (l) Heckendorn, R., *Bull. Soc. Chim. Belg.,* **1986**, *95*, 921. (m) Rusinov, V. L.; Pilicheva, T. L.; Chupakhin, O. N.; Klyuev, N. A. and Allakhverdieva, D. T., *Khim. Geterotsiklicheskikh Soedinenii,* **1986**, 662. (n) Abdelhamid, A. O.; Hassaneen, H. M. and Shawali, A. S., *J. Heterocycl. Chem.,* **1983**, *20*, 719. (o) Abdelhamid, A. O.; Hassaneen, H. M.; Abbas, I. M. and Shawali, A. S., *Tetrahedron*, **1982**, *38*, 1527. (p) Dubenko, R. G.; Gorbenko, E. F. and Pel'kis, P. S., *Zh. Org. Khim.,* **1980**, *16*, 1816. (q) Dubenko, R. G.; Gorbenko, E. F. and Pel'kis, P. S., *Zh. Org. Khim.,* **1979**, *15*, 1483. (r) Genkina, N. K.; Gordeev, E. N. and Suvorov, N. N., *Zh. Org. Khim.,* **1978**, *14*, 1501. (s) Reichardt, C. and Wuerthwein, E. U., *Chem. Ber.,* **1976**, *109*, 3735. (t) Genkina, N. K.; Gordeev, E. N. and Suvorov, N. N., *Zh. Org. Khim.,* **1976**, *12*, 1462. (u) Dubenko, R. G.; Konysheva, V. D.; Gorbenko, E. F. and Pel'kis, P. S., *Zh. Org. Khim.,* **1976**, *12*, 553. (v) Genkina, N. K.; Gordeev, E. N. and Suvorov, N. N., *Khim. Farmakol. Indol'n. Soedinenii,* **1975**, 15. (w) Shawali, A. S. and Fahmi, A. A., *Indian J. Chem.,* **1975**, *13*, 105. (x) Neplyuev, V. M.; Lekar, M. G.; Dubenko, R. G. and Pel'kis, P. S., *Zh. Org. Khim.,* **1974**, *10*, 2172. (y) Dubenko, R. G. and

Konysheva, V. D., *Zh. Org. Khim.,* **1974**, *10*, 183. (z) Gassman, P. G. and Gruetzmacher, G. D., *J. Am. Chem. Soc.,* **1974**, *96*, 5487. (aa) Gassman, P. G.; van Bergen, T. J.; Gilbert, D. P. and Cue, B. W., *J. Am. Chem. Soc.,* **1974**, *96*, 5495. (bb) Reichardt, C. and Halbritter, K., *Chem. Ber.,* **1973**, *106*, 1661. (cc) Neplyuev, V. M.; Lekar, M. G.; Dubenko, R. G. and Pel'kis, P. S., *Zh. Org. Khim.,* **1972**, *8*, 815. (dd) Lozinskii, M. O. and Gershkovich, A. A., *Zh. Org. Khim.,* **1972**, *8*, 785. (ee) Dubenko, R. G.; Konysheva, V. D.; Neplyuev, V. M. and Pel'kis, P. S., *Zh. Org. Khim.,* **1971**, *7*, 1932. (ff) Barrett, G. C.; El-Abadelah, M. M. and Hargreaves, M. K., *J. Chem. Soc. C,* **1970**, 1986. (gg) Neplyuev, V. M.; Usenko, Yu. N.; Dubenko, R. G. and Pel'kis, P. S., *Zh. Org. Khim.,* **1970**, *6*, 801. (hh) Ried, W. and Baumbach, E. A., *Ann.,* **1969**, *726*, 81. (ii) Ried, W. and Kleemann, A., *Ann.,* **1968**, *713*, 127. (jj) Robinson, B., *Chem. Rev.,* **1968**, *68*, 227. (kk) Chakraborty, D. P. and Chowdhury, B. K., *J. Org. Chem.,* **1968**, *33*, 1265. (ll) Yasuda, H. and Midorikawa, H., *Bull. Chem. Soc. Jpn.,* **1966**, *39*, 1596. (mm) Heath-Brown, B. and Philpott, P. G., *J. Chem. Soc.,* **1965**, 7185. (nn) Stetter, H.; Engl, R. and Rauhut, H., *Chem. Ber.,* **1959**, *92*, 1184. (oo) Elderfield, R. C. and Fischer, B. A., *J. Org. Chem.,* **1958**, *23*, 949. (pp) Carlin, R. B.; Henley, W. O. and Carlson, D. P., *J. Am. Chem. Soc.,* **1957**, *79*, 5712. (qq) Henecka, H.; Timmler, H.; Lorenz, R. and Geiger, W., *Chem. Ber.,* **1957**, *90*, 1060. (rr) Bachmann, W. E. and Controulis, J., *J. Am. Chem. Soc.,* **1951**, *73*, 2636. (ss) Witkop, B.; Patrick, J. B. and Rosenblum, M., *J. Am. Chem. Soc.,* **1951**, *73*, 2641. (tt) Bell, J. B. and Lindwall, H. G., *J. Org. Chem.,* **1948**, *13*, 547. (uu) Sempronj, A., *Gazz. Chim. Ital.,* **1938**, *68*, 263. (vv) Lions, F., *J. Proc. Royal Soc. New South Wales*, **1933**, *66*, 516.

4. Loubinoux, B.; Sinnes, J.-L.; O'Sullivan, A. C. and Winkler, T., *J. Org. Chem.,* **1995**, *60*, 953.
5. Bessard, Y., *Org. Proc. Res. Dev.,* **1998**, *2*, 214.
6. Traven, V. F.; Suslov, V. V. and Gordeev, E. N., *ARKIVOC,* **2000**, (*iv*), 603.
7. (a) McLaughlin, M.; García Rubio, S.; Tilstam, U.; Muthyala, R.; Antunes, O. A. C.; Yadav, G. D.; Zlota, A. and Laird, T., *Org. Proc. Res. Dev.,* **2006**, *10*, 2. (b) Morton, A. A. and Slaunwhite, W. R., *J. Biol. Chem.,* **1949**, *179*, 259.
8. (a) Moloney, G. P.; Robertson, A. D.; Martin, G. R.; MacLennan, S.; Mathews, N.; Dodsworth, S.; Sang, P. Y.; Knight, C. and Glen, R., *J. Med. Chem.,* **1997**, *40*, 2347. (b) Sundberg, R. J.; Baxter, E. W.; Pitts, W. J.; Ahmed-Schofield, R. and Nishiguchi, T., *J. Org. Chem.,* **1988**, *53*, 5097. (c) Taborsky, R. G. and McIsaac, W. M., *J. Med. Chem.,* **1964**, *7*, 135.
9. (a) Regitz, M. and Eistert, B., *Chem. Ber.,* **1963**, *96*, 3120. (b) Eistert, B. and Schank, K., *Chem. Ber.,* **1963**, *96*, 2304. (c) Eistert, B. and Regitz, M., *Chem. Ber.,* **1963**, *96*, 2290.
10. Shapiro, D.; Abramovitch, R. A. and Pinchas, S., *J. Am. Chem. Soc.,* **1956**, *78*, 2144.
11. Yao, H. C. and Resnick, P., *J. Am. Chem. Soc.,* **1962**, *84*, 3514.
12. Yao, H. C., *J. Org. Chem.,* **1964**, *29*, 2959.
13. Cirrincione, G.; Almerico, A. M.; Aiello, E. and Dattolo, G., *J. Heterocycl. Chem.,* **1990**, *27*, 983.
14. Jiricek, J. and Blechert, S., *J. Am. Chem. Soc.,* **2004**, *126*, 3534.
15. Shoeb, A.; Anwer, F.; Kapil, R. S.; Popli, S. P.; Dua, P. R. and Dhawan, B. N., *J. Med. Chem.,* **1973**, *16*, 425.
16. (a) Zhao, S.; Liao, X. B.; Wang, T.; Flippen-Anderson, J. and Cook, J. M., *J. Org. Chem.,* **2003**, *68*, 6279. (b) Cirrincione, G.; Almerico, A. M.; Barraja, P.; Diana, P.; Lauria, A.; Passannanti, A.; Musiu, C.; Pani, A.; Murtas, P.; Minnei, C.; Marongiu, M. E. and la Colla, P., *J. Med. Chem.,* **1999**, *42*, 2561.
17. (a) Nada, A. A.; Mahran, A. M. and Shawali, A. S., *Phosphorus & Sulfur & Silicon Related Elements*, **2005**, *180*, 2111. (b) Rühl, T.; Daghish, M.; Buchynskyy, A.; Barche, K.; Volke, D.; Stembera, K.; Kempin, U.; Knoll, D.; Hennig, L.; Findeisen, M.; Oehme, R.; Giesa, S.; Ayala, J. and Welzel, P., *Bioorg. Med. Chem.,* **2003**, *11*, 2965. (c) Mosselhi, M. A. N.; Abdallah, M. A.; Mohamed, Y. F. and Shawali, A. S., *Phosphorus & Sulfur & Silicon Related Elements,* **2002**, *177*, 487. (d) Pete, B.; Bitter, I.; Harsanyi, K. and Toke, L., *Heterocycles,* **2000**, *53*, 665. (e) Menciu, C.; Duflos, M.; Fouchard, F.; le Baut, G.; Emig, P.; Achterrath, U.; Szelenyi, I.; Nickel, B.; Schmidt,

J.; Kutscher, B. and Günther, E., *J. Med. Chem.,* **1999**, *42*, 638. (f) Kempin, U.; Hennig, L.; Knoll, D.; Welzel, P.; Müller, D.; Markus, A. and van Heijenoort, J., *Tetrahedron,* **1997**, *53*, 17669. (g) Chetoni, F.; Da Settimo, F.; Marini, A. M. and Primofiore, G., *J. Heterocycl. Chem.,* **1993**, *30*, 1481. (h) Heckendorn, R., *Helv. Chim. Acta,* **1987**, *70*, 2118. (i) Fahrenholtz, K. E.; Silverzweig, M. Z.; Germane, N.; Crowley, H. J.; Simko, B. A. and Dalton, C., *J. Med. Chem.,* **1979**, *22*, 948. (j) Kozikowski, A. and Floyd, W. C., *Tetrahedron Lett.,* **1978**, 19. (k) Khan, N. H. and Kidwai, A. R., *J. Org. Chem.,* **1973**, *38*, 822. (l) von Strandtmann, M.; Puchalski, C. and Shavel, J., *J. Med. Chem.,* **1964**, *7*, 141. (m) Eistert, B. and Schank, K., *Ber.,* **1963**, *96*, 2304. (n) Shapiro, D. and Abramovitch, R. A., *J. Am. Chem. Soc.,* **1955**, *77*, 6690. (o) Ek, A. and Witkop, B., *J. Am. Chem. Soc.,* **1954**, *76*, 5579. (p) Snyder, H. R. and Robison, M. M., *J. Am. Chem. Soc.,* **1952**, *74*, 5945. (q) Fox, S. W. and Bullock, M. W., *J. Am. Chem. Soc.,* **1951**, *73*, 2756. (r) Linstead, R. P. and Wang, A., *J. Chem. Soc.,* **1937**, 807. (s) Japp, F. R. and Klingemann, F., *Ann.,* **1888**, *247*, 190.

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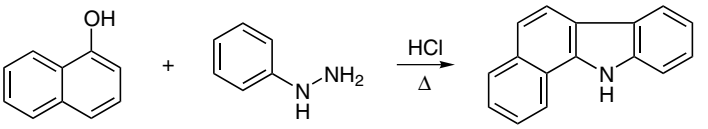
Japp-Maitland Condensation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Japp and Maitland in 1903.[1] It is the acid promoted thermal condensation between arylhydrazine and aromatic compounds activated by a hydroxyl group to give carbazole derivatives. Therefore, this reaction is known as the Japp-Maitland condensation,[2] or Maitland-Japp reaction.[3] For example, the condensation between 6-alkyl-2-naphthols and phenylhydrazine affords 3-alkyl-7*H*-benzo-[c]carbazoles in good yield.[2] However, due to the heat sensitivity of naphthylhydrazines and their salts, the condensation with naphthylhydrazines gives corresponding carbazoles in very low yields.[4] In addition, the condensation with simple 2-naphthol also affords poor yields.[2]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is believed that α-naphthol, functioning as an enol, undergoes a semi-*Michael Addition* with protonated arylhydrazine while accompanying the evolution of ammonia during

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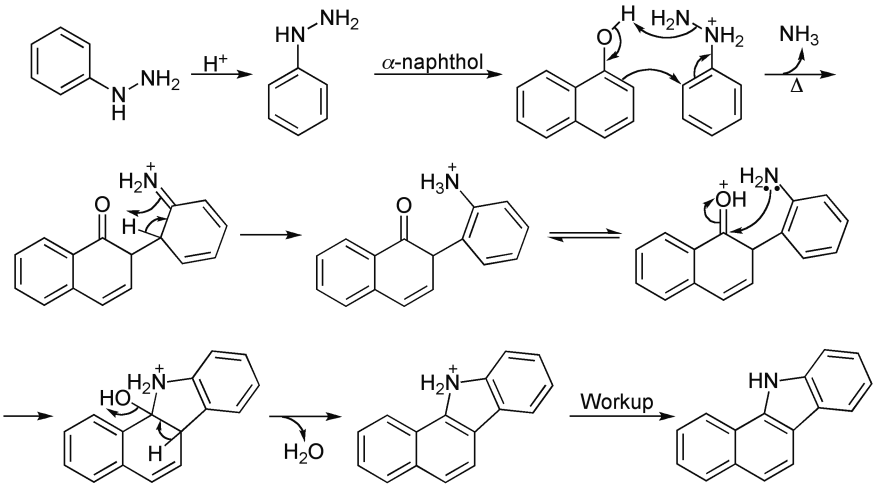
heating. The amino group then attacks the carbonyl group and closes the ring. Upon extrusion of water, the benzocarbozole is produced as illustrated below.



D. MODIFICATION

N/A

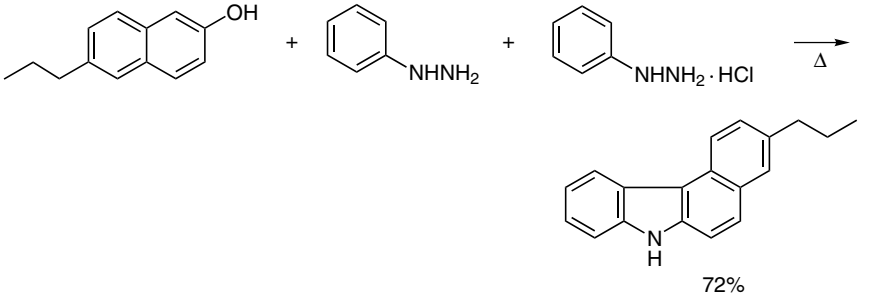
E. APPLICATIONS

This reaction is generally used for the preparation of carbazole derivatives.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 2.

A mixture of 4.0 g 6-propyl-2-naphthol, 4.0 g phenylhydrazine, and 4.0 g phenylhydrazine hydrochloride was cautiously refluxed for 1 h. After cooling, dilute aqueous NaOH was added, and the reaction product was taken up in toluene. The combined organic layers were washed with water and dried over Na_2SO_4. Upon removal of solvent, the residue was vacuum fractioned. The portion boiling at 280–305°C at 17 mmHg in a total of 4.0 g (72%) was recrystallized from cyclohexane to afford pure 3-propyl-7*H*-benzo[c]carbazole in lustrous colorless leaflets, m.p. 127°C.

Other references related to the Japp-Maitland condensation are cited in the literature.[5]

H. REFERENCES

1. (a) Japp, F. R. and Maitland, W., *J. Chem. Soc.,* **1903**, *83*, 267. (b) Japp, F. R. and Maitland, W., *J. Chem. Soc.,* **1903**, *83*, 273.
2. Buu-Hoï, N. P.; Lavit, D. and Collard, J., *J. Org. Chem.,* **1958**, *23*, 542.
3. Clarke, P. A.; Martin, W. H. C.; Hargreaves, J. M.; Wilson, C. and Blake, A. J., *Org. Biomol. Chem.,* **2005**, *3*, 3551.
4. Buu-Hoï, N. P.; Hoán, N. and Khôi, N. H., *J. Org. Chem.,* **1949**, *14*, 492.
5. (a) Clarke, P. A. and Martin, W. H. C., *Tetrahedron Lett*., **2004**, *45*, 9061. (b) Bender, D. F.; Sawicki, E. and Wilson, R. M., *Anal. Chem.,* **1964**, *36*, 1011. (c) Yates, P.; Yoda, N.; Brown, W. and Mann, B., *J. Am. Chem. Soc.,* **1958**, *80*, 202.

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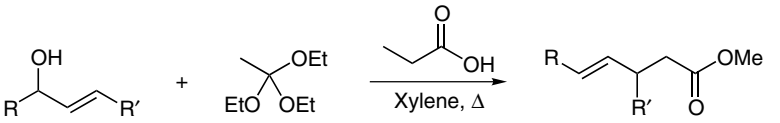
Johnson Orthoester Claisen Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Johnson et al. in 1970.[1] It is a highly stereoselective[2] synthesis of γ,δ-unsaturated esters from the reaction between allylic alcohols and an orthoester in the presence of a trace amount of weak acid, such as propionic acid.[1,2] Because this reaction is the modification or variant of the *Claisen Rearrangement*, it is often referred to as the Johnson orthoester Claisen rearrangement.[3] Occasionally, this reaction is also known as the Claisen-Johnson orthoester rearrangement,[2,4] or Johnson orthoester protocol.[5] This reaction involves the formation of mixed orthoester from allyl alcohol and the added orthoester, which loses an alcoholic component to form a ketene acetal[1] then migrates to unsaturated carbonyl compounds via the *Claisen Rearrnagement* with high *syn* selectivity.[3f] Posner further extended this reaction to use sulfonyl orthoester.[6] Overall, this reaction has been applied to the synthesis of a variety of complicated natural products, such as squalenes.[1,7]

B. GENERAL REACTION SCHEME



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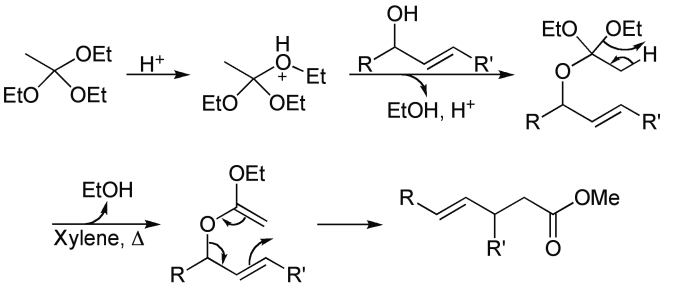
C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been extended to start with sulfonyl orthoesters.[6]

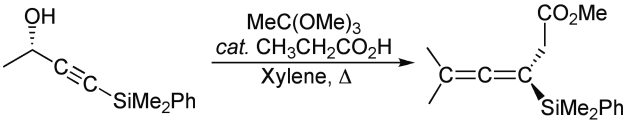
E. APPLICATIONS

This reaction has been used for the synthesis of a variety of natural products, including squalenes.[1,7]

F. RELATED REACTIONS

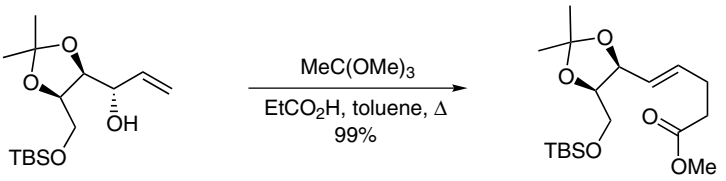
This reaction is related to the *Claisen Rearrangement*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 3h.

A mixture of 5.0 g (*S*)-4-(dimethyl(phenyl)silyl)-but-3-yn-2-ol (24.46 mmol), 12.45 mL trimethylorthoacetate (97.84 mmol), 0.1 mL propionic acid (1.22 mmol), and 100 mL xylenes was refluxed for 24 h. An additional 6.23 mL trimethylorthoacetate (48.92 mmol) was added, and the solution was refluxed for 16 h longer. Then the solution was concentrated, and the residue was purified over silica gel using hexanes/EtOAc (95:5) as the eluent to give 5.0 g (*R*)-methyl 3-(dimethyl(phenyl)silyl)hexa-3,4-dienoate as a clear slightly yellow oil, in a yield of 78.5%.



Reference 3a.

To a 1-L round-bottomed flask equipped with distillation apparatus were added 500 mL toluene and 27.9 g (3*S*,4*S*,5*R*)-6-[(*tert*-butyldimethylsilyl)oxy]-4,5-(isopropylidenedioxy)-1-hexen-3-ol (92.3 mmol), followed by 77 mL trimethyl orthoacetate (640 mmol) and 1.9 mL propionic acid (26 mmol). The mixture was heated at reflux, distilling off methanol as it formed. Gas chromatography was used to monitor the disappearance of starting material (t_R = 4.0 min) and the appearance of product (t_R = 5.2 min). After 24 h, the mixture was cooled to room temperature and concentrated by rotary evaporation to give 32.7 g methyl (*E*)-(6*S*,7*R*)-8-[(*tert*-butyldimethylsilyl)oxy]-6,7-(isopropylidenedioxy)-4-octenoate as a pale yellow oil, in a yield of 99%, $R_f = 0.40$ (hexane/EtOAc, 6:1).

Other references related to the Johnson orthoester Claisen rearrangement are cited in the literature.[8]

H. REFERENCES

1. Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-T.; Faulkner, D. J. and Petersen, M. R., *J. Am. Chem. Soc.,* **1970**, *92*, 741.
2. Giardina, A.; Marcantoni, E.; Mecozzi, T. and Petrini M., *Eur. J. Org. Chem*., **2001**, 713.
3. (a) Brawn, R. A. and Panek, J. S., *Org. Lett.,* **2007**, *9*, 2689. (b) Ko, O. H. and Hong, J. H., *Tetrahedron Lett*., **2002**, *43*, 6399. (c) Parvez, M.; Yadav, V. K. and Senthil, G., *Acta Crystallograph., Sect. C: Cryst. Struct. Commun.,* **2001**, *C57*, 79. (d) Giner, J.-L. and Li, X., *Tetrahedron*, **2000**, *56*, 9575. (e) Frank, S. A.; Works, A. B. and Roush, W. R., *Can. J. Chem.,* **2000**, *78*, 757. (f) Yadav, V. K.; Jeyaraj, D. A. and Parvez, M., *J. Chem. Soc*., *Perkin Trans. 1*, **2000**, 1423. (g) Yadav, V. K.; Jeyaraj, D. A.; Parvez, M. and Yamdagni, R., *J. Org. Chem.,* **1999**, *64*, 2928. (h) Pearson, W. H. and Hembre, E. J., *J. Org. Chem.,* **1996**, *61*, 7217. (i) Feldman, K. S.; Weinreb, C. K.; Youngs, W. J. and Bradshaw, J. D., *J. Am. Chem. Soc.,* **1994**, *116*, 9019. (j) Feldman, K. S.; Kraebel, C. M. and Parvez, M., *J. Am. Chem. Soc.,* **1993**, *115*, 3846.
4. Csende, F., *Acta Chim. Slov.,* **2002**, *49*, 663.
5. Jones, G. B.; Huber, R. S. and Chau, S., *Tetrahedron,* **1993**, *49*, 369.
6. (a) Posner, G. H. and Johnson, N., *J. Org. Chem.,* **1994**, *59*, 7855. (b) Posner, G. H.; Crouch, R. D.; Kinter, C. M. and Carry, J.-C., *J. Org. Chem.,* **1991**, *56*, 6981.
7. Johnson, W. S.; Brocksom, T. J.; Loew, P.; Rich, D. H.; Werthemann, L.; Arnold, R. A.; Li, T.-T. and Faulkner, D. J., *J. Am. Chem. Soc.,* **1970**, *92*, 4463.
8. (a) Hiersemann, M. and Nubbemeyer, U., *The Claisen Rearrangement: Methods and Applications*, Wiely-VCH, Weinheim **2007**. (b) Michael, J. P., *Nat. Prod. Rept.,* **2004**, *21*, 625. (c) Heuger, G.; Kalsow, S. and Göttlich, R., *Eur. J. Org. Chem.,* **2002**, 1848. (d) Frank, S. A. and Roush, W. R., *J. Org. Chem.,* **2002**, *67*, 4316. (e) Snider, B. B. and Smith, R. B., *Synth. Commun.,* **2001**, *31*, 2667. (f) Nicolaou, K. C.; Vourloumis, D.; Winssinger, N. and Baran, P. S., *Angew. Chem. Int. Ed.,* **2000**, *39*, 44. (g) Santini, C.; Ball, R. G. and Berger, G. D., *J. Org. Chem.,* **1994**, *59*, 2261. (h) Huber, R. S. and Jones, G. B., *J. Org. Chem.,* **1992**, *57*, 5778. (i) Johnson, W. S.; Gravestock, M. B.; Parry, R. J.; Myers, R. F.; Bryson, T. A. and Miles, D. H., *J. Am. Chem. Soc.,* **1971**, *93*, 4330.

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Jones Oxidation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Jones et al. in 1946.[1] It is the oxidation of primary alcohols into carboxylic acids or the conversion of secondary alcohols into ketones using acidic chromic acid. Therefore, this reaction is generally known as the Jones oxidation,[2,3] and the reagent of CrO_3-H_2SO_4-H_2O is called the Jones reagent.[2f,2k,4]Occasionally, the Jones oxidation is also referred to as Jones chromic acid oxidation.[5] This reaction is generally carried out in aqueous acetone[4a,4d] and is fast with low selectivity. Although it has been suggested that this reaction might involve a radical intermediate[6] or the conversion of Cr(IV) into Cr(II) species,[7] the predominant mechanism is the transformation of Cr(VI) into Cr(IV) species. If the hydroxylic group is protected by a silyl ether,[8] the deprotection and oxidation can be combined as a one-step reaction if the Jones reagent is applied. For example, the enediol bis-trimethylsilyl ether has been oxidized to α-diketone directly in high yield.[2f] Even though the 1,2-diols and α-hydroxy ketones are susceptible to cleavage,[9] the peroxide group is tolerable for this oxidation.[10] However, the benzylic group will be oxidized into carbonyl group when the Jones oxidation is carried out in acetic acid;[5] thus indans and tetralins can be oxidized to 1-indanones and 1-tetralones, respectively.[5] Furthermore, olefins in acetone can also be oxidized by the Jones reagent, especially in the presence of 20 mol % mercuric acetate or mercuric propionate, so that terminal olefins are oxidized to methyl ketones, and 1,2-disubstituted olefins are converted into ketones (but in low yields), respectively.[4d]

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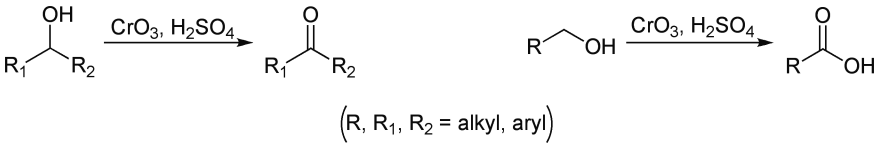
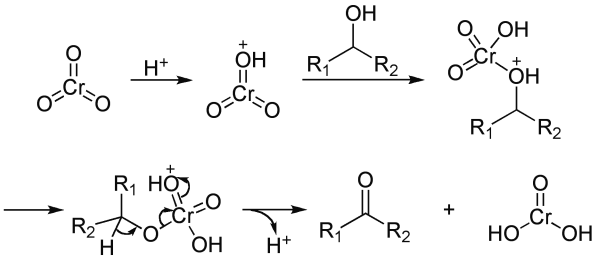
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The mechanism for the oxidation of a secondary alcohol is illustrated below.



D. MODIFICATION

Because this reaction is so fast and does not show much selectivity, more mild oxidation methods using chromium (VI) have been developed, such as the *Corey-Schmidt Oxidation* (PDC oxidation) and *Corey-Suggs Oxidation* (PCC oxidation)

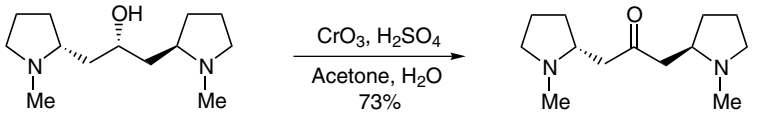
E. APPLICATIONS

This reaction has wide application in organic synthesis for preparing different ketones.

F. RELATED REACTIONS

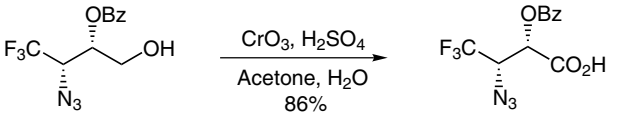
This reaction is related to the *Corey-Schmidt Oxidation* and *Corey-Suggs Oxidation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4a.

To a stirred solution of 30 mg (*R*,*R*)-dihydrocuscohygrine (0.13 mmol) in 1 mL acetone was added 0.2 mL 1.8 M Jones reagent at 0°C. After 2 h, the solution was cooled to 0°C and 1 mL ice-cold saturated $NaHSO_3$ solution was added. The solution was brought to pH 13 with ice-cold 5 N KOH. Then the solution was immediately extracted with precooled $CHCl_3$ (3 × 5 mL), and the combined organic layers were washed with cold brine and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure at room temperature gave 22 mg racemic cuscohygrine as a colorless oil, in a yield of 73%, R_f = 0.27 (cyclohexane/$CHCl_3$/Et_2NH, 5:4:1).



Reference 1b.

To a mixture of 549 mg (2*S*,3*S*)-benzoic acid 2-azido-3,3,3-trifluoro-1-hydroxymethylpropyl ester (1.9 mmol) and 60 mL acetone was added 15 mL 1 M Jones reagent (15 mmol) at 0°C. The mixture was stirred for 20 min at 0°C under nitrogen. The reaction was quenched with 7 mL isopropyl alcohol and then diluted with 60 mL water and 60 mL ethyl acetate. The aqueous layer was then extracted with ethyl acetate. The combined organic layers were dried, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 1:1) to give 495 mg (2*S*,3*S*)-benzoic acid 2-azido-1-carboxy-3,3,3-trifluoropropyl ester, in a yield of 86%.

Other references related to the Jones oxidation are cited in the literature.[12]

H. REFERENCES

1. Bowden, K.; Heilbron, I. M.; Jones, E. R. H. and Weedon, B. C. L., *J. Chem. Soc.,* **1946**, 39.
2. (a) Krstic, N. M.; Bjelakovic, M. S.; Lorenc, L. B. and Pavlovic, V. D., *J. Serb. Chem. Soc.,* **2003**, *68*, 785. (b) Pettus, T. R. R. and Schlessinger, R. H., *Synth. Commun.,* **2002**, *32*, 3019. (c) Yadav, J. S.; Reddy, E. J. and Ramalingam, T., *New J. Chem.,* **2001**, *25*, 223. (d) Szurmai, Z.; Rako, J.; Agoston, K.; Danan, A. and Charon, D., *Org. Lett.,* **2000**, *2*, 1839. (e) Tong, Y. S.; Olczak, J.; Zabrocki, J.; Gershengorn, M. C.; Marshall, G. R. and Moeller, K. D., *Tetrahedron,* **2000**, *56*, 9791. (f) Fakhri, S. A. and Yousefi, B. H., *Acta Chim. Slov.,* **2000**, *47*, 317. (g) Schrake, O.; Rahn, V. S.; Frackenpohl, J.; Braje, W. M. and Hoffmann, H. M. R., *Org. Lett.,* **1999**, *1*, 1607. (h) Rogers, L. L.; Zeng, L.; Kozlowski, J. F.; Shimada, H.; Alali, F. Q.; Johnson, H. A. and McLaughlin, J. L., *J. Nat. Prod.,* **1998**, *61*, 64. (i) Sivik, M. R.; Bauer, W.; Schleyer, P. von R. and Paquette, L. A., *Organometallics,* **1996**, *15*, 5202. (j) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Nugiel, D. A.; Abe, Y.; Reddy, K. B.; DeFrees, S. A.; Reddy, D. R.; Awartani, R. A.; Conley, S. R.; Rutjes, F. P. J. T. and Theodorakis, E. A., *J. Am. Chem. Soc.,* **1995**, *117*, 10227. (k) Liang, G.-B.; Desper, J. M. and Gellman, S. H., *J. Am. Chem. Soc.,* **1993**, *115*, 925. (l) Evans, D. A.; Thomas, E. W. and Cherpeck, R. E., *J. Am. Chem. Soc.,* **1982**, *104*, 3695. (m) McDaniel, D. M. and Turro, N. J., *Tetrahedron Lett.,* **1972**, 3035. (n) Dalton, J. C.; Dawes, K.; Turro, N. J.; Weiss, D. S.; Barltrop, J. A. and Coyle, J. D., *J. Am. Chem. Soc.,* **1971**, *93*, 7213.

3. (a) Hunter, A. C. and Priest, S.-M., *Steroids*, **2006**, *71*, 30. (b) Allanson, N. M.; Llu, D. S.; Chi, F.; Jain, R. K.; Chen, A.; Ghosh, M.; Hong, L. W. and Sofia, M. J., *Tetrahedron Lett*., **1998**, *39*, 1889. (c) Petersen, Q. R.; Cambie, R. C. and Russell, G. B., *Aust. J. Chem.,* **1993**, *46*, 1961. (d) Vaidya, S. P. and Nayak, U. R., *Indian J. Chem., Sect. B,* **1988**, *27B*, 969. (e) Ahmed, S. M.; Ahmad, F.; Siddiqui, S. F. and Osman, S. M., *J. Am. Oil Chem. Soc.,* **1988**, *65*, 774. (f) Badaisha, K. K. and Kohli, J. C., *J. Chromatography*, **1983**, *268*, 549. (g) Ballio, A.; Casinovi, C. G.; Capasso, R.; Ferrara, A. and Randazzo, G., *Gazz. Chim. Ital.,* **1981**, *111*, 129. (h) Uusvuori, R.; Hase, T. and Suokas, E., *Acta Chem. Scand., Ser. B,* **1978**, *B32*, 531.
4. (a) Stapper, C. and Blechert, S., *J. Org. Chem.,* **2002**, *67*, 6456. (b) Malabarba, A.; Ciabatti, R.; Maggini, M.; Ferrai, P.; Colombo, L. and Denaro, M., *J. Org. Chem.,* **1996**, *61*, 2151. (c) Latli, B.; Wood, E. and Casida, J. E., *Chem. Res. Toxicol.,* **1996**, *9*, 445. (d) Rogers, H. R.; McDermott, J. X. and Whitesides, G. M., *J. Org. Chem.,* **1975**, *40*, 3577.
5. Rangarajan, R. and Eisenbraun, E. J., *J. Org. Chem.,* **1985**, *50*, 2435.
6. Wiberg, K. B. and Szeimies, G., *J. Am. Chem. Soc.,* **1974**, *96*, 1884.
7. Scott, S. L.; Bakac, A. and Espenson, J. H., *J. Am. Chem. Soc.,* **1992**, *114*, 4205.
8. (a) Evans, P. A.; Murthy, V. S.; Roseman, J. D. and Rheingold, A. L., *Angew. Chem. Int. Ed. Engl.,* **1999**, *38*, 3175. (b) Lu, S.-F.; Oyang, Q. Q.; Guo, Z.-W.; Yu, B. and Hui, Y.-Z., *J. Org. Chem.,* **1997**, *62*, 8400.
9. Corey, E. J.; Trybulski, E. J.; Melvin, L. S.; Nicolaou, K. C.; Secrist, J. A.; Lett, R.; Sheldrake, P. W.; Flack, J. R.; Brunelle, D. J.; Haslanger, M. F.; Kim, S. and Yoo, S., *J. Am. Chem. Soc.,* **1978**, *100*, 4618.
10. Ferraz, H. M. C. and Silva, L. F., *J. Braz. Chem. Soc.,* **2001**, *12*, 548.
11. Jiang, Z.-X. and Qing, F.-L., *J. Org. Chem.,* **2004**, *69*, 5486.
12. (a) Mathad, V. T.; Kumar, S. and Raj, K., *Nat. Prod. Res.,* **2006**, *20*, 1053. (b) Jiang, Z.-X. and Qing, F.-L., *J. Org. Chem.,* **2004**, *69*, 5486. (c) Takahashi, S.; Souma, K.; Hashimoto, R.; Koshino, H. and Nakata, T., *J. Org. Chem.,* **2004**, *69*, 4509. (d) Felpin, F.-X. and Lebreton, J., *Curr. Org. Synth.,* **2004**, *1*, 83. (e) Shkumatov, V. M.; Usova, E. V.; Radyuk, V. G.; Kashkan, Z. N.; Kovganko, N. V.; Juretzek, T. and Mauersberger, S., *Russ. J. Bioorg. Chem.,* **2003**, *29*, 581. (f) Sharma, A. K. and Hergenrother, P. J., *Org. Lett.,* **2003**, *5*, 2107. (g) Khripach, V. A.; Zhabinskii, V. N.; Konstantinova, O. V.; Antonchick, A. P. and Schneider, B., *Steroids,* **2002**, *67*, 587. (h) Kaiser, F.; Schwink, L.; Velder, J. and Schmalz, H.-G., *J. Org. Chem.,* **2002**, *67*, 9248. (i) Kraus, G. A. and Kim, J. W., *J. Org. Chem.,* **2002**, *67*, 2358. (j) Lescop, C.; Mévellec, L. and Huet, F., *J. Org. Chem.,* **2001**, *66*, 4187. (k) Barboni, L.; Datta, A.; Dutta, D.; Georg, G. I.; Velde, D. G. V.; Himes, R. H.; Wang, M. M. and Snyder, J. P., *J. Org. Chem.,* **2001**, *66*, 3321. (l) Zarbin, P. H. G.; Reckziegel, A.; Plass, E.; de Oliveira, A. R. M.; Simonelli, F. and Marques, F. de A., *J. Braz. Chem. Soc.,* **2000**, *11*, 572. (m) Abad, J.-L.; Fabriás, G. and Camps, F., *J. Org. Chem.,* **2000**, *65*, 8582. (n) Vermeer, H. J.; Halkes, K. M.; van Kuik, J. A.; Kamerling, J. P. and Vliegenthart, J. F. G., *J. Chem. Soc., Perkin Trans. I.,* **2000**, 2249. (o) Clayden, J.; Westlund, N.; Beddoes, R. L. and Helliwell, M., *J. Chem. Soc., Perkin Trans. I,* **2000**, 1351. (p) Hiroshi, H., *Trends Glycosci. Glycotech.,* **2000**, *12*, 185. (q) Crimmins, M. T.; Carroll, C. A. and King, B. W., *Org. Lett.,* **2000**, *2*, 597. (r) Dondoni, A.; Marra, A. and Massi, A., *J. Org. Chem.,* **1999**, *64*, 933. (s) Cheng, M. Y.; De, B.; Almstead, N. G.; Pikul, S.; Dowty, M. E.; Dietsch, C. R.; Dunaway, C. M.; Gu, F.; Hsieh, L. C.; Janusz, M. J.; Taiwo, Y. O.; Natchus, M. G.; Hudlicky, T. and Mandel, M., *J. Med. Chem.*. **1999**, *42*, 5426. (t) Allanson, N. M.; Liu, D. S.; Chi, F.; Jain, R. K.; Chen, A.; Ghosh, M.; Hong, L. W. and Sofia, M. J., *Tetrahedron Lett.,* **1998**, *39*, 1889. (u) Jiang, S. D. and Singh, G., *Tetrahedron,* **1998**, *54*, 4697. (v) Cox, C. and Lectka, T., *J. Am. Chem. Soc.,* **1998**, *120*, 10660. (w) Gurjar, M. K. and Lalitha, S. V. S., *Pure & Appl. Chem.,* **1998**, *70*, 303. (x) Cerny, I.; Slavikova, T. and Pouzar, V., *Coll. Czech. Chem. Commun.,* **1997**, *62*, 1642. (y) Sha, C.-K.; Chiu, R.-T.; Yang, C.-F.; Yao, N.-T.; Tseng, W.-H.; Liao, F.-L. and Wang, S.-L.,

J. Am. Chem. Soc., **1997**, *119*, 4130. (z) Huben, K.; Zhu, Z. D.; Bally, T. and Gebicki, J., *J. Am. Chem. Soc.,* **1997**, *119*, 2825. (aa) Katoh, T. and Terashima, S., *Pure & Appl. Chem.,* **1996**, *68*, 703. (bb) Berks, A. H., *Tetrahedron,* **1996**, *52*, 331. (cc) Stork, G. and Kahne, D. E., *J. Am. Chem. Soc.,* **1983**, *105*, 1072. (dd) Nishizawa, M.; Nishide, H.; Kosela, S. and Hayashi, Y., *J. Org. Chem.,* **1983**, *48*, 4462. (ee) Djerassi, C.; Engle, R. R. and Bowers, A., *J. Org. Chem.,* **1956**, *21*, 1547. (ff) Heilbron, I. M.; Jones, E. R. H. and Sondheimer, F., *J. Chem. Soc.,* **1949**, 604. (gg) Haynes, L. J.; Heilbron, I. M.; Jones, E. R. H. and Sondheimer, F., *J. Chem. Soc.,* **1947**, 1583. (hh) Heilbron, I. M.; Jones, E. R. H. and Sondheimer, F., *J. Chem. Soc.,* **1947**, 1586.

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Jourdan-Ullmann Reaction
(Ullmann Condensation)

A. GENERAL DESCRIPTION OF THE REACTION

In 1885, Jourdan reported the reaction between aniline and activated aryl halides (e.g., 2,4-dinitro-chlorobenzene) to form diarylamine;[1] since 1902, Ullmann extended this reaction to unactivated or slightly activated aryl halides using copper or copper reagents as a catalyst and K_2CO_3 as the base.[2] At almost the same time, Ullmann's assistant and wife, Goldberg, reported the extension of this reaction from acetanilide to form diarylamines regardless of the degree of activation of the aryl halides.[3] Thus the copper-promoted amination of aryl halides with aniline to form diarylamines in the presence of a base is now known as the Jourdan-Ullmann condensation,[4] Jourdan-Ullmann diphenylamine synthesis,[5] Jourdan-Ullmann reaction,[4d,6] and Jourdan-Ullmann synthesis[6f,6h] as well as the Ullmann condensation,[7] Ullmann reaction,[7d,8] Ullmann-Goldberg condensation,[9] Ullmann-Goldberg coupling,[10] Ullmann-Goldberg reaction,[10b,11] and Ullmann-Jourdan reaction.[12] In general, the aryl halides of the electron-withdrawing groups work better than the ones of electron-donating substituents in the Jourdan-Ullmann condensation,[8c] and the reactivity of halides are in the order of I > Br > Cl > F;[7i] in comparison, anilines with electron-withdrawing groups proceed poorly in this reaction,[4b,4d] except for the reaction between *o*-chlorobenzoic acid and anthranilic acid, which occurs at 100–120°C to give 2,2′-dicarboxyl-diphenylamine in almost a quantitative yield within 30 min.[4d] Some of the reaction pairs between aryl halide and anilines are *o*-chlorobenzoic acid with *p*-iodoaniline,[7a] *o*-aminobenzoic acid,[7f] *p*-aminobenzoic acid,[10a] and *o*-anisidine;[8a] *o*-bromobenzoic acid with *o*-phenylenediamine;[13] *o*-bromotoluene with *m*-methylanthranilic acid;[14] and 3-bromo-2-naphthoic acid with 5-amino-2,2-dimethyl-2H-chromene.[7g]

It is known that both copper acetate and cuprous iodide are effective catalysts for this reaction, as well as pure copper metal in the presence of oxygen.[7m] In addition, the salts

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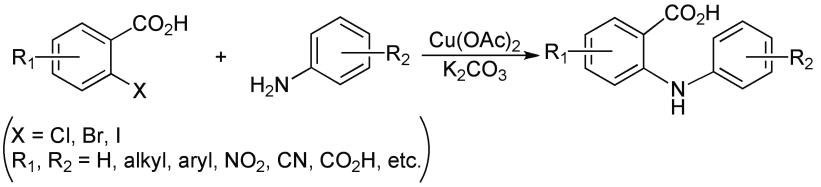
of some other metals—such as iron, nickel, platinum, and zinc—are active catalysts in this reaction; the salts of tin and manganese are inactive reagents.[7m] The addition of a base such as K_2CO_3 is critical for this reaction, because the base will neutralize the generated hydrogen halide; especially for the reaction of *o*-halobenzoic, the base will convert the carboxyl group into carboxylate so that the chance for decarboxylation is reduced and the resinous by-products are dramatically diminished.[7m] Consequently, the overall yield and purity of diarylamines are enhanced. Because copper and copper salts are not soluble in organic solvents, the heterogeneous Jourdan-Ullmann reaction proceeds slowly in general;[7i] however, the application of high-boiling aprotic solvents containing oxygen, nitrogen, and sulfur atoms (e.g, nitrobenzene,[7m] amyl alcohol,[7a,7m,10b] pyridine,[7m,10b] quinoline,[7i] or DMSO[8e,15]) will facilitate the reaction by partially converting the reaction into homogenous reaction due to coordination. In particular, the mono-ether of ethylene glycol and its oligomers have shown considerable advantages for being solvents for this condensation, due to their different boiling points, their ability to accelerate the reaction rate because of high solubility for the reaction components, and their miscibility with water to simplify the workup process.[6i] One example is that the yield of the reaction between *o*-chlorobenzoic and *p*-aniline was increased from 20% to 48% when it was carried out in 2-methoxyethanol.[7a] However, all the solvents used for this reaction must be dry because the existing water may coordinate with copper and deplete the active catalyst,[7i] as evidenced by the lower yield by extraction of the reaction intermediate with 95% ethanol than that with absolute ethanol.[8i] Furthermore, under the conditions of the Jourdan-Ullmann condensation, many other nucleophiles can also couple with aryl halides, such as ammonia, potassium phenoxide, alkoxide, hydroxide, and even the sodium derivative of ethyl malonate and similar compounds of active methylene groups.[7m] However, this reaction suffers from high reaction and the need for a large excess of copper or copper salts.[12b] In addition, this reaction is often accompanied with reductive dehalogenation of aryl halides.[7m,8c]

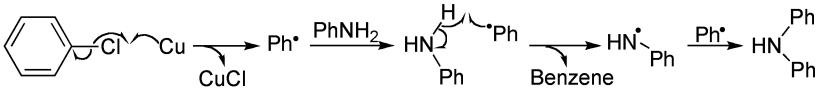
B. GENERAL REACTION SCHEME



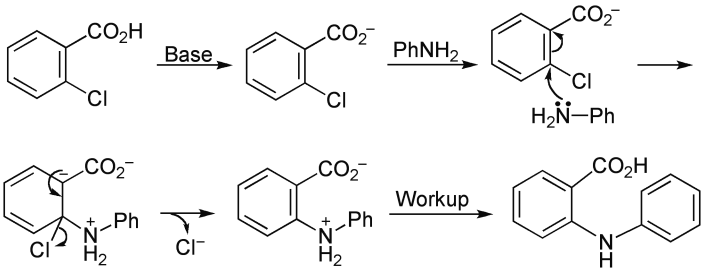
C. PROPOSED MECHANISMS

Even though the Jourdan-Ullmann condensation has been known for more than a century, the mechanism is still not quite clear. On the one hand, the reaction may proceed via a free-radical mechanism, pertaining to the reductive dehalogenation of aryl halides and the acceleration of the reaction rate by ultraviolet irradiation,[7m] as outlined in Scheme 1. On the other hand, the reaction may involve halonium and proceed as a simple aromatic nucleophilic substitution,[7k,7m] as displayed in Scheme 2. However, for the reaction of *o*-halobenzoic acid, it is believed that the copper ion coordinates with both carboxyl and

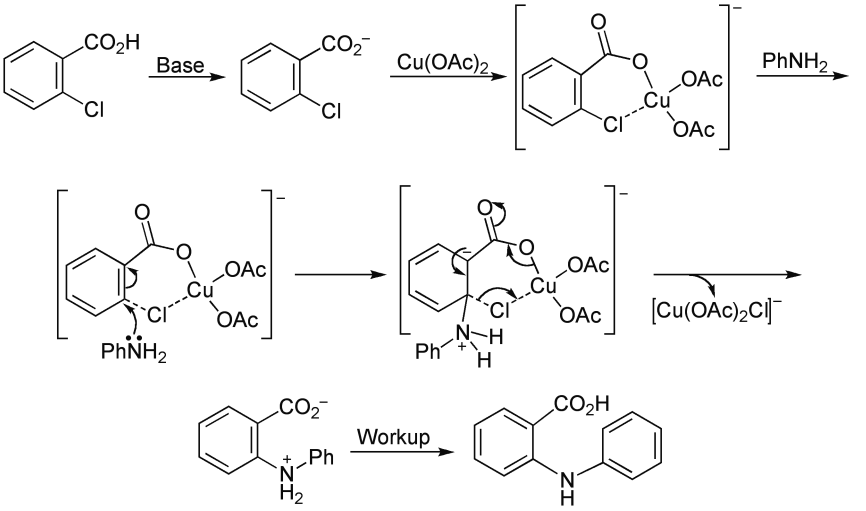
o-halogen so that the carbon-halogen bond is weakened, and an aromatic nucleophilic substitution occurs subsequently, as illustrated in Scheme 3. This mechanism is supported by the evidence that neither ethyl *o*-bromobenzoate nor *p*-bromobenzoic acid can participate in the Jourdan-Ullmann condensation.[7m]



SCHEME 1. *Radical mechanism for the Jourdan-Ullmann reaction.*



SCHEME 2. *Ionic aromatic nucleophilic substitution mechanism for the Jourdan-Ullmann reaction.*



SCHEME 3. *Alternative mechanism for the Jourdan-Ullmann reaction.*

D. MODIFICATION

Both ultrasound[12a] and microwave[7b,7c] have been applied to accelerate the reaction; the Jourdan-Ullmann condensation under microwave irradiation can be carried out in

either dry media[7b] or in aqueous solution.[7c] In addition, this reaction has been extended to *O*- and *S*-arylation in the presence of polycoordinate ligand,[8b] such as the application of 2-methylaminomethyl-3-hydroxypyridine for the preparation of diaryl ether.[8c] It should be mentioned that the reaction under Jourdan-Ullmann condensation to form diaryl ether is known as the *Ullmann Diaryl Ether Synthesis*.[16] Moreover, this reaction has been extended to the preparation of triarylamines using 10-phenanthroline as a ligand.[7h] Other modifications include the couplings of anilines with aryl amides (e.g., isatin),[15] diphenyliodonium-2-carboxylate,[4a,17] and arylboronic acids.[18] The condensation with arylboronic acids in particular is considerably versatile and is known as the Chan-Lam-Evans modified *Ullmann Condensation*.[19]

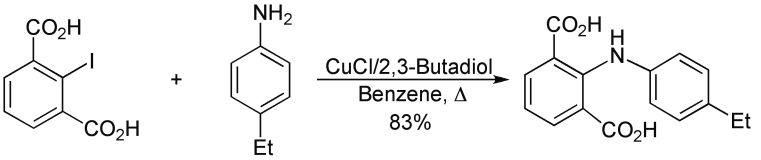
E. APPLICATIONS

This reaction has wide application in the preparation of diarylamines, many of the diarylamines have been converted into acridone and acridine derivatives.

F. RELATED REACTIONS

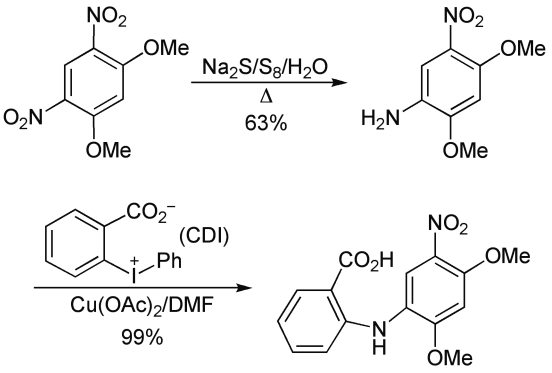
This reaction is related to the *Rosemound-von Braun Nitrile Synthesis, Ullman Diaryl Ether Synthesis*, and *Ullmann Acridine Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 15.

A mixture of 2.92 g 2-iodoisophthalic acid (10 mmol), 1.82 g 4-ethylaniline (15 mmol), 1 g CuCl, 12 mL 2,3-butanediol, and 10 mL benzene was heated and stirred, with the benzene being allowed to distill off. When the internal temperature of the reaction mixture reached 100°C, 6 mL *N*-ethylmorpholine was added, and the reaction mixture was stirred for an additional 4 h at 120°C. The reaction mixture was then diluted with 50 mL 0.5 M NH_4OH, treated with charcoal, and filtered through Celite. Acidification with 2 M HCl afforded a precipitate that was extracted into EtOAc (2 × 100 mL), filtered through Celite, and further extracted with 100 mL 0.5 M aqueous NH_3. Acidification with concentrated HCl and recrystallization of the isolated product gave 2.36 g 2-[(4-ethylphenyl)amino]isophthalic acid, in a yield of 83%, m.p. (EtOAc/petroleum ether) 194–195.5°C.



Reference 4a.

A suspension of 20.1 g 1,5-dimethoxy-2,4-dinitrobenzene (90.0 mmol) in 117 mL water was stirred under reflux and treated dropwise over 30 min with a solution of sodium polysulfide, prepared by heating 28.6 g $Na_2S{\cdot}9H_2O$ (119 mmol) and 6.8 g sulfur (213 mmol) in 120 mL water. The reaction mixture was stirred under reflux for a further 3 h and then cooled and evaporated under reduced pressure at 45°C to give a dark residue. This was extracted several times with warm EtOAc, and the combined extracts were filtered through a short column of silica gel. The eluates were washed with water and evaporated to dryness. The residue was dissolved in 1 N HCl, filtered, and basified with aqueous NaOH to give 11.0 g 1-amino-2,4-dimethoxy-5-nitrobenzene, in a yield of 63%, m.p. 126–128°C.

A mixture of 6.0 g 1-amino-2,4-dimethoxy-5-nitrobenzene (30.9 mmol), 20.0 g diphenyliodonium-2-carboxylate (61.4 mmol), and 0.4 g copper(II) acetate (2.2 mmol) in 180 mL dry DMF was stirred at 90°C (bath temperature) for 7 h and then at 20°C for overnight. Most of the DMF was evaporated under reduced pressure, and the residue was taken up into CH_2Cl_2, washed twice with water, and extracted into 0.5 N KOH. The alkaline layer was back extracted with CH_2Cl_2 and filtered, and the filtrate was acidified at 0°C to give 9.7 g 2-[(2,4-dimethoxy-5-nitrophenyl)amino]-benzoic acid, in a yield of 99%, m.p. ($CHCl_3$/MeOH) 283–285°C.

Other references related to the Jourdan-Ullmann reaction are cited in the literature.[20]

H. REFERENCES

1. Jourdan, F., *Ber.,* **1885**, *18*, 1444.
2. (a) Ullmann, F., *Ber.,* **1902**, *35*, 316. (b) Ullmann, F., *Ber.,* **1902**, *35*, 2670. (c) Ullmann, F., *Ger. Pat.,* Jan. 25, **1901** 117,472. (d) Ullmann, F., *Ger. Pat.,* Feb. 26, **1901**, 118,439. (e) Ullmann, F., *Ger. Pat.,* Jan. 17, **1902**, 127,586. (f) Ullmann, F., *Ger. Pat.,* Feb. 15, **1902**, 128,754. (g) Ullmann F., *Ber.,* **1903**, *36*, 2382. (h) Ullmann, F. and Sponagel, P., *Ber.,* **1905**, *38*, 2211. (i) Ullmann, F., *Ann.*, **1907**, *355*, 312.
3. (a) Goldberg, I., *Ber.,* **1906**, *39*, 1691. (b) Goldberg, I., *Ber.,* **1907**, *40*, 4541.
4. (a) Lee, H. H.; Wilson, W. R.; Ferry, D. M.; van Zijl, P.; Pullen, S. M. and Denny, W. A., *J. Med. Chem.,* **1996**, *39*, 2508. (b) Wilson, W. R.; Anderson, R. F. and Denny, W. A., *J. Med. Chem.,* **1989**, *32*, 23. (c) Stewart, G. M.; Rewcastle, G. W. and Denny, W. A., *Aust. J. Chem.,* 1984, 37, 1939. (d) Denny, W. A.; Atwell, G. J. and Baguley, B. C., *J. Med. Chem.,* **1983**, *26*, 1619.

5. Cain, B. F. and Atwell, G. J., *J. Med. Chem.,* **1976**, *19*, 1124.
6. (a) Wakelin, L. P. G.; Bu, X. Y.; Eleftheriou, A.; Parmar, A.; Hayek, C. and Stewart, B. W., *J. Med. Chem.,* **2003**, *46*, 5790. (b) Rewcastle, G. W. and Denny, W. A., *Synth. Commun.,* **1987**, *17*, 309. (c) Rewcastle, G. W. and Denny, W. A., *Synthesis,* **1986**, *2*, 217. (d) Rewcastle, G. W.; Atwell, G. J.; Chambers, D.; Baguley, B. C. and Denny, W. A., *J. Med. Chem.,* **1986**, *29*, 472. (e) Rewcastle, G. W. and Denny, W. A., *Synthesis*, **1985**, 217. (f) Cain, B. F.; Atwell, G. J. and Denny, W. A., *J. Med. Chem.,* **1977**, *20*, 987. (g) Denny, W. A.; Atwell, G. J. and Cain, B. F., *J. Med. Chem.,* **1977**, *20*, 1242. (h) Cain, B. F.; Atwell, G. J. and Denny, W. A., *J. Med. Chem.,* **1975**, *18*, 1110. (i) Cain, B. F.; Seelye, R. N. and Atwell, G. J., *J. Med. Chem.,* **1974**, *17*, 922.
7. (a) Géci, I.; Filichev, V. V. and Pedersen, E. B., *Bioconjugate Chem.,* **2006**, *17*, 950. (b) Martin, A.; Mesa, M.; Docampo, M. L.; Gomez, V. and Pellon, R. F., *Synth. Commun.,* **2006**, *36*, 271. (c) Martin, A.; Pellon, R. F.; Mesa, M.; Docampo, M. L. and Gomez, V., *J. Chem. Res. (S),* **2005**, 561. (d) Manifar, T.; Rohani, S.; Bender, T. P.; Goodbrand, H. B.; Gaynor, R. and Saban, M., *Ind. Eng. Chem. Res.,* **2005**, *44*, 789. (e) Mosher, M. D.; Holmes, K. L. and Frost, K. S., *Molecules,* **2004**, *9*, 102. (f) Dzierzbicka, K. and Kolodziejczyk, A., *J. Med. Chem.,* **2003**, *46*, 183. (g) Mai, H. D. T.; Gaslonde, T.; Michel, S.; Tillequin, F.; Koch, M.; Bongui, J.-B.; Elomri, A.; Seguin, E.; Pfeiffer, B.; Renard, P.; David-Cordonnier, M.-H.; Laine, W.; Bailly, C.; Kraus-Berthier, L.; Léonce, S.; Hickman, J. A. and Pierre, A., *J. Med. Chem.,* **2003**, *46*, 3072. (h) Goodbrand, H. B. and Hu, N.-X., *J. Org. Chem.,* **1999**, *64*, 670. (i) Chandnani, K. H. and Chandalia, S. B., *Org. Proc. Res. Dev.,* **1999**, *3*, 416. (j) Palmer, B. D.; Rewcastle, G. W.; Atwell, G. J.; Baguley, B. C. and Denny, W. A., *J. Med. Chem.,* **1988**, *31*, 707. (k) Weingarten, H., *J. Org. Chem.,* **1964**, *29*, 3624. (l) Rausch, M. D., *J. Org. Chem.,* **1961**, *26*, 1802. (m) Bunnett, J. F. and Zahler, R. E., *Chem. Rev.,* **1951**, *49*, 274. (n) Tittle, N., *J. Am. Chem. Soc.,* **1923**, *45*, 1906.
8. (a) Tanaka, T.; Tasaki, T. and Aoyama, Y., *J. Am. Chem. Soc.,* **2002**, *124*, 12453. (b) Pinet, J. P.; Fedorov, A. Y.; Combes, S. and Boyer, G., *Curr. Org. Chem.,* **2002**, *6*, 597. (c) Fagan, P. J.; Hauptman, E.; Shapiro, R. and Casalnuovo, A., *J. Am. Chem. Soc.,* **2000**, *122*, 5043. (d) Gamage, S. A.; Spicer, J. A.; Atwell, G. J.; Finlay, G. J.; Baguley, B. C. and Denny, W. A., *J. Med. Chem.,* **1999**, *42*, 2383. (e) Rosario, C. A.; Holder, G. M. and Duke, C. C., *J. Org. Chem.,* **1987**, *52*, 1064. (f) Ozaki, K.-I.; Yamada, Y.; Oine, T.; Ishizuka, T. and Iwasawa, Y., *J. Med. Chem.,* **1985**, *28*, 568. (g) Moore, G. G. I.; Harrington, J. K. and Swingle, K. F., *J. Med. Chem.,* **1975**, *18*, 386. (h) Craig, D., *J. Am. Chem. Soc.,* **1935**, *57*, 195. (i) Weston, P. E. and Adkins, H., *J. Am. Chem. Soc.,* **1928**, *50*, 859. (j) Gomberg, M. and Tabern, D. L., *J. Am. Chem. Soc.,* **1926**, *48*, 1345.
9. (a) Comdon, R. F. P. and Palacios, M. L. D., *Synth. Commun.,* **2003**, *33*, 921. (b) Pellon, R. F.; Carrasco, R.; Marquez, T. and Mamposo, T., *Tetrahedron Lett.,* **1997**, *38*, 5107. (c) Pellon, R. F.; Carrasco, R.; Millian, V. and Rodés, L., *Synth. Commun.,* **1995**, *25*, 1077. (d) Kovala-Demertzi, D.; Dokorou, V.; Kruszynski, R.; Wiecek, J.; Bartczak, T. J. and Demertzis, M. A., *Zeit. Anorg. Allgem. Chem.,* **2005**, *631*, 2481.
10. (a) Goodell, J. R.; Svensson, B. and Ferguson, D. M., *J. Chem. Inf. Model.,* **2006**, *46*, 876. (b) Bauman, D. R.; Rudnick, S. I.; Szewczuk, L. M.; Jin, Y.; Gopishetty, S. and Penning, T. M., *Mol. Pharmacol.,* **2005**, *67*, 60. (c) Goodell, J. R.; Puig-Basagoiti, F.; Forshey, B. M.; Shi, P.-Y. and Ferguson, D. M., *J. Med. Chem.,* **2006**, *49*, 2127.
11. (a) Artamkina, G. A.; Ermolina, M. V. and Beletskaya, I. P., *Mendeleev Commun.,* **2003**, 158. (b) Chalmers, D. K.; Scholz, G. H.; Topless, D. J.; Kolliniatis, E.; Munro, S. L. A.; Craik, D. J.; Iskander, M. N. and Stockigt, J. R., *J. Med. Chem.,* **1993**, *36*, 1272.
12. (a) Mei, X. F.; August, A. T. and Wolf, C., *J. Org. Chem.,* **2006**, *71*, 142. (b) Csuk, R.; Barthel, A. and Raschke, C., *Tetrahedron,* **2004**, *60*, 5737. (c) Szymanska, A.; Wiczk, W. and Lankiewicz, L., *Chem. Heterocycl. Compd.,* **2000**, *36*, 801. (d) Taraporewala, I. B. and Kauffman, J. M., *J. Pharm. Sci.,* **1990**, *79*, 173.
13. Shimia, K.; Boyer, G.; Finet, J.-P. and Galy, J.-P., *Lett. Org. Chem.,* **2004**, *1*, 34.
14. Moloney, G. P.; Kelly, D. P. and Mack, P., *Molecules,* **2001**, *6*, 230.

15. Spicer, J. A.; Gamage, S. A.; Atwell, G. J.; Finlay, G. J.; Baguley, B. C. and Denny, W. A., *J. Med. Chem.,* **1997**, *40*, 1919.

16. (a) Luo, Y. T.; Wu, J. X. and Ren, R. X., *Synlett,* **2003**, 1734. (b) Buck, E.; Song, Z. J.; Tschaen, D.; Dormer, P. G.; Volante, R. P. and Reider, P. J., *Org. Lett.,* **2002**, *4*, 1623.

17. Askonas, L. J. and Penning, T. M., *Biochemistry,* **1991**, *30*, 11553.

18. (a) Chiang, G. C. H. and Olsson, T., *Org. Lett.,* **2004**, *6*, 3079. (b) Ley, S. V. and Thomas, A. W., *Angew. Chem. Int. Ed.,* **2003**, *42*, 5400. (c) Sasaki, M.; Dalili, S. and Yudin, A. K., *J. Org. Chem.,* **2003**, *68*, 2045. (d) Yu, S.; Saenz, J. and Srirangam, J. K., *J. Org. Chem.,* **2002**, *67*, 1699.

19. Jacobsen, M. F.; Knudsen, M. M. and Gothelf, K. V., *J. Org. Chem.,* **2006**, *71*, 9183.

20. (a) Wolf, C.; Liu, S. L.; Mei, X. F.; August, A. T. and Casimir, M. D., *J. Org. Chem.,* **2006**, *71*, 3270. (b) Elslager, E. F.; Moore, A. M.; Short, F. W.; Sullivan, M. J. and Tendick, F. H., *J. Am. Chem. Soc.,* **1957**, *79*, 4699. (c) Shepard, E. R. and Shonle, H. A., *J. Am. Chem. Soc.,* **1948**, *70*, 1979. (d) Dauben, W. G., *J. Am. Chem. Soc.,* **1948**, *70*, 2420.

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Julia Olefination

(Julia-Kocienski Olefination or Julia-Lythgoe Olefination)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Julia in 1973.[1] It is primarily a multistep preparation of *trans*-olefins involving the addition of phenylsulfonyl carbanion to aldehydes or ketones to form β-hydroxysulfones, followed by the esterification of hydroxyl group (benzoyl or acetyl) and reductive elimination of β-sulfonyl esters with sodium amalgam. Therefore, this reaction is generally known as the Julia olefination.[2,3] Occasionally, this reaction is also referred to as the Julia reaction[4] or Julia coupling.[2c,2h,2s,4b,5] Because of its intrinsic weaknesses—including multiple steps, low tolerance for reducible functional groups, and the presence of mercury reagent—the original protocol has been extensively modified and extended by researchers such as Kocienski (Kociensky) and Lythgoe,[6] Julia,[7] and Keck.[8] These modifications employ the one-step reaction between heterocyclic sulfonyl carbanion and aldehyde (or ketone) to give either *cis*- or *trans*-olefins or replace the reduction from the sodium amalgam by samarium iodide (SmI_2).[8] Therefore, the modified olefination methods are referred to as the Kocienski olefination,[2p] Julia-Kocienski olefination,[2a,9] Kocienski-Julia olefination,[10] Julia-Kociensky olefination,[9d] Kocienski-Julia coupling,[2d] Julia-Lythgoe olefination,[2r,4a,8b,11] Julia-Lythgoe reaction,[11f]

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

or Julia-Lythgoe coupling.[2g,8b,11j] The applied heterocyclic sulfones in this olefination include benzothiazol-2-yl sulfones (BT), 1-phenyl-1*H*-tetrazol-5-yl sulfones (PT), 2-pyridinyl sulfones (Pyr), and *tert*-butyl-1*H*-tetrazol-5-yl sulfones (TBT), as shown in Figure 1. Besides improving the weakness associated with the original Julia protocol, the application of heterocyclic sulfones in this olefination provides extra advantages, such as enabling more or less pronounced complexation between the heterocycle and metal cation to influence the selectivity, and undergoing nucleophilic substitution at the carbon attached to the sulfonyl group, which then becomes a leaving group. It has been found that when benzothiazol-2-yl sulfones are applied as the carbanion source, the stereoselectivity is controlled by solvent.[12] In general, more *cis*-olefins are formed when this reaction is carried out in solvents such as toluene, methylene chloride and diethyl ether; more *trans*-olefins are produced in solvents such as DME and DMF.[12] In addition, the electronic and steric nature of such sulfones do not affect the yield and the selectivity of olefination.[2i] Unfortunately, the application of benzothiazol-2-yl sulfones is often accompanied with a side product from the nucleophilic addition of sulfonyl carbanion to a second benzothiazol-2-yl sulfone,[7c] thus the Julia olefination involving benzothiazol-2-yl sulfone is best carried out by adding base into the mixture of aldehyde and sulfone. Further modification for the application of benzothiazol-2-yl sulfone as the starting material is to trap the reaction with trimethylsilyl chloride to form a cyclic sulfone intermediate, which is then converted exclusively to *trans*-olefin under acidic conditions, or alternatively transformed into the mixture of *cis*- and *trans*-olefin with the treatment of a base, e.g., TBAF.[2f] On the other hand, both 2-pyridinyl sulfones[7b] and *tert*-butyl-1*H*-tetrazol-5-yl sulfones exhibit high *cis*-selectivity for olefins, in addition, *tert*-butyl-1*H*-tetrazol-5-yl sulfone is especially good for the synthesis of aliphatic olefins, resulting in a higher yield and selectivity than the application of PT or BT. In contrast, 1-phenyl-1*H*-tetrazol-5-yl sulfone gives somewhat better *trans*-selectivity than the BT sulfones because of the steric demands of the phenyl group.[2d,10b] In addition, PTs do not show the tendency of self-condensation like BT does, so that they can be deprotonated and then react with aldehydes. Thus PTs are suitable for coupling with base sensitive aldehydes. In addition, PT also shows the metal cation effect by which higher *cis*-selectivity is achieved when potassium is applied as the metal rather than lithium.[10b]

It has been found that the original Julia olefination protocol occurs via two mechanisms, depending heavily on the reducing agent.[4a] However, more recent experimental evidence prefers initial elimination of the ester to form vinyl sulfone, which would then undergo homolytic cleavage to give vinyl radical and finally transform into *trans*-olefin through vinyl anion, as illustrated in Scheme 2.[8b] However, modified Julia olefination using heterocyclic sulfones proceeds via a different mechanism, involving the reversible addition of carbanion to carbonyl group. A closed transition state forms from the chelation when lithium is used as the counterion and in nonpolar solvent, whereas an open transition state is possible in polar solvent and when a larger potassium cation is applied as the counterion, leading to either *cis*- or *trans*-olefins.[13] This reaction has been widely used to prepare predominantly *trans*-olefins, especially in convergent synthesis of complex structures of natural products.[8b] However, one should be aware that a potential problem exists during the preparation of allyl sulfones through the oxidation of allyl sulfide, by which allyl alcohol might be generated as a side product.[14]

B. GENERAL REACTION SCHEME

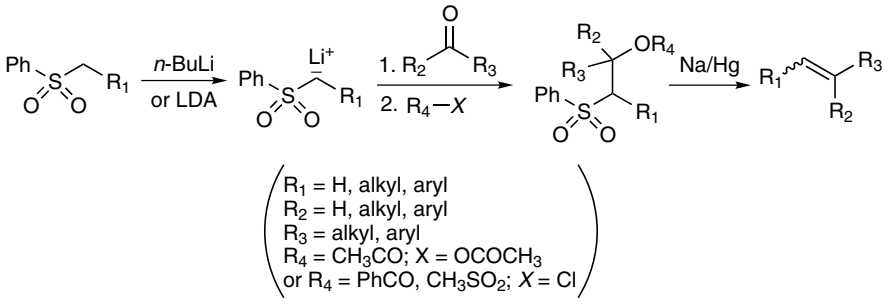
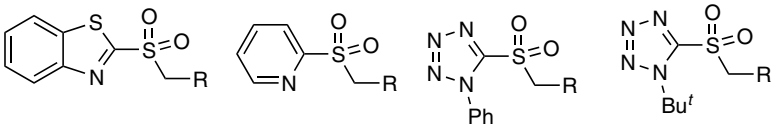
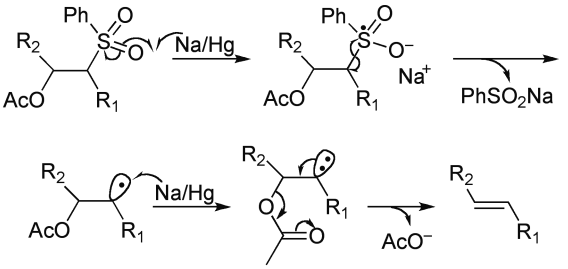


FIGURE 1. *Heterocyclic sulfones used in the modified Julia olefination.*

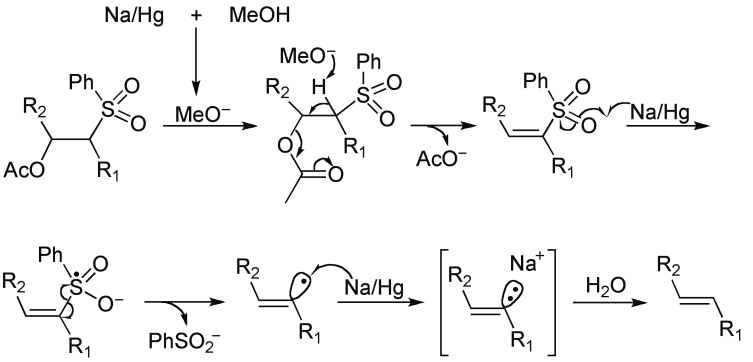


C. PROPOSED MECHANISMS

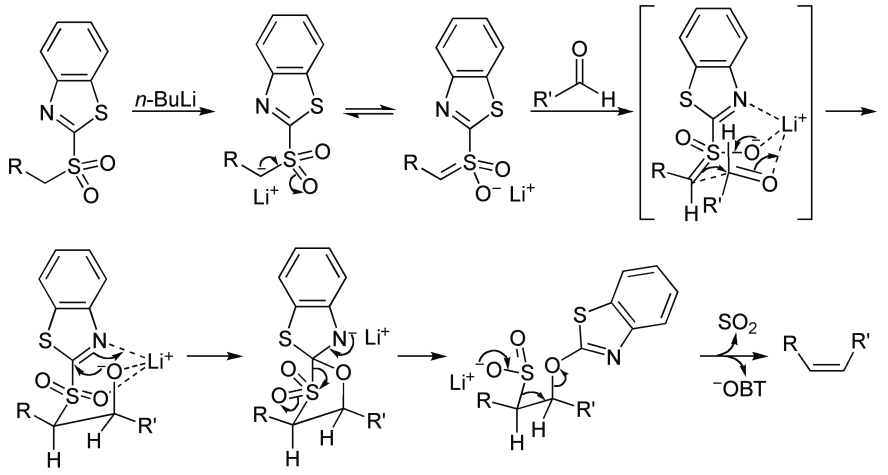
The original mechanism for the Julia olefination is shown in Scheme 1 (the reduction step only). The revised mechanism is shown in Scheme 2, and the mechanism for the modified Julia olefination (i.e., the Julia-Kocienski olefination) is shown in Scheme 3.



SCHEME 1. *Original mechanism for the Julia olefination (partial).*



SCHEME 2. *Revised mechanism for the Julia olefination.*



SCHEME 3. *Mechanism of the modified Julia olefination in a nonpolar solvent.*

D. MODIFICATION

The original Julia olefination protocol has been extensively modified using heterocyclic sulfones as the starting materials to control the stereochemistry.

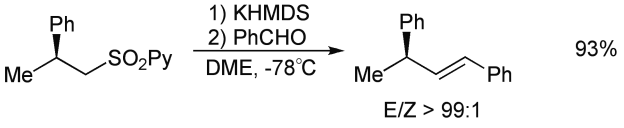
E. APPLICATIONS

This reaction has been widely used in the preparation of olefins, especially in the convergent synthesis of complex natural products.

F. RELATED REACTIONS

This reaction is related to the *Wittig Reaction* and *Petersen Olefination*.

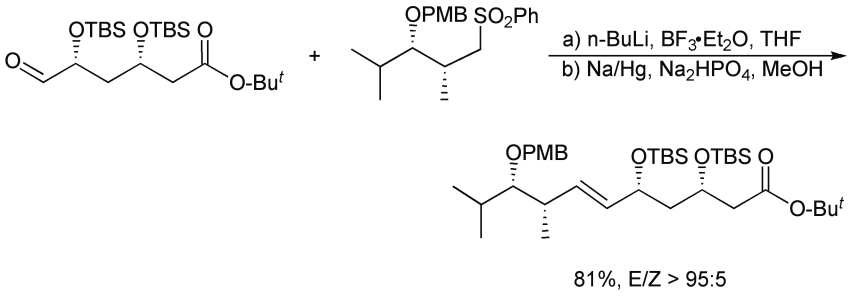
G. CITED EXPERIMENTAL EXAMPLES



Reference 9d.

To a stirred solution of 46 mg chiral (*S*)-2-phenyl-1-((2-pyridyl)sulfonyl)propane (0.176 mmol) dissolved in 4.6 mL anhydrous DME (0.033 M) under argon and cooled at –78°C were added 530 μL 0.5 M potassium hexamethyldisilazide in toluene via syringe.

The yellow-orange solution was stirred for 3 min, then 27 μL benzaldehyde (0.264 mmol) was added, and the mixture was stirred at –78°C for 2 h. The pale yellow solution was quenched with saturated NH_4Cl at the same temperature and diluted with 5 mL CH_2Cl_2, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, the solvent was removed in vacuo and the resulting pale yellow oil was purified by column chromatography (hexanes) to give 34 mg (1*E*,3*R*)-1,3-diphenyl-1-butene, in a yield of 93% with an E/Z ratio ~ 99:1.



Reference 2g.

To a solution of 673 mg ({(3*S*,2*R*)-3-[(4-methoxyphenyl)methoxy]-2,4-dimethyl-pentyl}sulfonyl)-benzene(1.80 mmol) in 17 mL THF at −78°C was added 1.2 mL 1.55 M *n*-BuLi in hexanes (1.90 mmol), and the canary yellow solution was stirred for 1 h before the addition of 0.22 mL $BF_3{\cdot}OEt_2$(1.80 mmol). After being stirred for 15 min, a −78°C solution of *tert*-butyl (3*S*,5*R*)-3,5-bis(*tert*-butyldimethylsilyloxy)-6-oxohexanoate in 5 mL THF was added dropwise via cannula. After an additional 1 h of stirring, the reaction mixture was quenched with 5 mL saturated aqueous NH_4Cl, diluted with 30 mL Et_2O, and allowed to warm to room temperature. The aqueous phase was extracted with Et_2O (2 × 30 mL), and the combined organic layers were washed with 60 mL each saturated aqueous $NaHCO_3$ and brine before being dried over $MgSO_4$ and concentrated in vacuo. To a solution of the residue in 17 mL CH_3OH at −40°C was added 1.20 g Na_2HPO_4 (8.60 mmol) followed by 4 g 5% Na/Hg amalgam (8.30 mmol) in two portions. The cold bath was removed, and the mixture was stirred vigourously for 1.5 h and then quenched by the addition of 5 mL saturated aqueous NH_4Cl and diluted with 50 mL Et_2O. The aqueous phase was extracted with Et_2O (2 × 50 mL), and the combined organic layers were washed with 75 mL each saturated aqueous $NaHCO_3$ and brine before being dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (5% EtOAc/hexanes) to afford 470 mg *tert*-butyl (6*E*)(3*S*,8*S*,9*S*,5*R*)-3,5-bis(*tert*-butyldimethyl-silyloxy)-9-[(4-methoxyphenyl)methoxy]-8,10-dimethyl-undec-6-enoate as a clear colorless oil, in an overall yield of 81% for the two steps.

Other references related to the Julia olefination are cited in the literature.[15]

H. REFERENCES

1. Julia, M. and Paris, M.-M., *Tetrahedron Lett.,* **1973**, 4833.
2. (a) Robinson, J. E. and Brimble, M. A., *Chem. Commun.*, **2005**, 1560. (b) Wang, Q. and Sasaki, N. A., *J. Org. Chem.,* **2004**, *69*, 4767. (c) Jiang, Y. H.; Hong, J. and Burke, S. D., *Org. Lett.,* **2004**, *6*,

1445. (d) Haidle, A. M. and Myers, A. G., *Proc. Natl. Acad. Sci.,* **2004**, *101*, 12048. (e) Li, D. R.; Sun, C. Y.; Su, C.; Lin, G.-Q. and Zhou, W.-S., *Org. Lett.,* **2004**, *6*, 4261. (f) Xu, D. D.; Waykole, L.; Calienni, J. V.; Ciszewski, L.; Lee, G. T.; Liu, W. M.; Szewczyk, J.; Vargas, K.; Prasad, K.; Repic, O. and Blacklock, T. J., *Org. Proc. Res. Dev.,* **2003**, *7*, 856. (g) Evans, D. A. and Connell, B. T., *J. Am. Chem. Soc.,* **2003**, *125*, 10899. (h) Ono, K.; Yoshida, A.; Saito, N.; Fujishima, T.; Honzawa, S.; Suhara, Y.; Kishimoto, S.; Sugiura, T.; Waku, K.; Takayama, H. and Kittaka, A., *J. Org. Chem.,* **2003**, *68*, 7407. (i) Surprenant, S.; Chan, W. Y. and Berthelette, C., *Org. Lett.,* **2003**, *5*, 4851. (j) Hale, K. J.; Frigerio, M.; Manaviazar, S.; Hummersone, M. G.; Fillingham, I. J.; Barsukov, I. G.; Damblon, C. F.; Gescher, A. and Roberts, G. C. K., *Org. Lett.,* **2003**, *5*, 499. (k) Blakemore, P. R., *J. Chem. Soc., Perkin Trans. I,* **2002**, 2563. (l) Khripach, V. A.; Zhabinskii, V. N.; Antonchick, A. P.; Konstantinova, O. V. and Schneider, B., *Steroids,* **2002**, *67*, 1101. (m) Evans, D. A.; Rajapakse, H. A.; Chiu, A. and Stenkamp, D., *Angew. Chem. Int. Ed.,* **2002**, *41*, 4573. (n) Takano, D.; Nagamitsu, T.; Ui, H.; Shiomi, K.; Yamaguchi, Y.; Masuma, R.; Kuwajima, I. and Omura, S., *Org. Lett.,* **2001**, *3*, 2289. (o) Smith, A. B.; Minbiole, K. P.; Verhoest, P. R. and Schelhaas, M., *J. Am. Chem. Soc.,* **2001**, *123*, 10942. (p) Hale, K. J.; Hummersone, M. G.; Cai, J.; Manaviazar, S.; Bhatia, G. S.; Lennon, J. A.; Frigerio, M.; Delisser, V. M.; Chumnongsaksarp, A.; Jogiya, N. and Lemaitre, A., *Pure Appl. & Chem.,* **2000**, *72*, 1659. (q) Ma, D. W. and Sun, H. Y., *J. Org. Chem.,* **2000**, *65*, 6009. (r) Evans, D. A.; Carter, P. H.; Carreira, E. M.; Charette, A. B.; Prunet, J. A. and Lautens, M., *J. Am. Chem. Soc.,* **1999**, *121*, 7540. (s) Padwa, A.; Ishida, M.; Muller, C. L. and Murphree, S. S., *J. Org. Chem.,* **1992**, *57*, 1170.

3. (a) Bonini, C.; Chiummiento, L. and Videtta, V., *Synlett,* **2006**, 2079. (b) Pospisil, J. and Marko, I. E., *Tetrahedron Lett*., **2006**, *47*, 5933. (c) Manjunath, B. N.; Sane, N. P. and Aidhen, I. S., *Eur. J. Org. Chem.,* **2006**, 2851. (d) Mirk, D.; Grassot, J.-M. and Zhu, J. P., *Synlett*, **2006**, 1255. (e) Ghosh, A. K. and Zajc, B., *Org. Lett.,* **2006**, *8*, 1553. (f) Lebrun, M.-E.; Le Marquand, P. and Berthelette, C., *J. Org. Chem.,* **2006**, *71*, 2009. (g) Li, W.-D. Z. and Peng, Y., *Org. Lett.,* **2005**, *7*, 3069. (h) Gueyrard, D.; Haddoub, R.; Salem, A.; Bacar, N. S. and Goekjian, P. G., *Synlett*, **2005**, 520. (i) Vaz, B.; Alvarez, R.; Souto, J. A. and De Lera, A. R., *Synlett*, **2005**, 294. (j) Compostella, F.; Franchini, L.; Panza, L.; Prosperi, D. and Ronchetti, F., *Tetrahedron,* **2002**, *58*, 4425. (k) Charette, A. B.; Berthelette, C. and St-Martin, D., *Tetrahedron Lett*., **2001**, *42*, 6619. (l) Charette, A. B.; Berthelette, C. and St-Martin, D., *Tetrahedron Lett*., **2001**, *42*, 5149. (m) Valla, A.; Laurent, A.; Prat, V.; Andriamialisoa, Z.; Cartier, D.; Giraud, M.; Labia, R. and Potier, P., *Tetrahedron Lett*., **2001**, *42*, 4795. (n) Bellingham, R.; Jarowicki, K.; Kocienski, P. and Martin, V., *Synthesis*, **1996**, 285. (o) Lee, G. H.; Lee, H. K.; Choi, E. B.; Kin, B. T. and Pak, C. S., *Tetrahedron Lett*., **1995**, *36*, 5607.

4. (a) Marino, J. P.; McClure, M. S.; Holub, D. P.; Comasseto, J. V. and Tucci, F. C., *J. Am. Chem. Soc.,* **2002**, *124*, 1664. (b) White, J. D.; Hanselmann, R.; Jackson, R. W.; Porter, W. J.; Ohba, Y.; Tiller, T. and Wang, S., *J. Org. Chem.,* **2001**, *66*, 5217. (c) Katritzky, A. R.; Cheng, D.; Henderson, S. A. and Li, J. Q., *J. Org. Chem.,* **1998** *63*, 6704.

5. (a) Zhou, X.-T. and Carter, R. G., *Chem. Commun.,* **2004**, 2138. (b) Albrecht, B. K. and Williams, R. M., *Org. Lett.,* **2003**, *5*, 197. (c) Grimm, E. L.; Methot, J.-L. and Shamji, M., *Pure Appl. & Chem.,* **2003**, *75*, 231. (d) Kalaï, C.; Tate, E. and Zard, S. Z., *Chem. Commun.,* **2002**, 1430. (e) Kirkland, T. A.; Colucci, J.; Geraci, L. S.; Marx, M. A.; Schneider, M.; Kaelin, D. E. and Martin, S. F., *J. Am. Chem. Soc.,* **2001**, *123*, 12432. (f) Smith, A. B. and Brandt, B. M., *Org. Lett.,* **2001**, *3*, 1685. (g) Eguchi, T.; Ibaragi, K. and Kakinuma, K., *J. Org. Chem.,* **1998**, *63*, 2689. (h) Kigoshi, H.; Suenaga, K.; Mutou, T.; Ishigaki, T.; Atsumi, T.; Ishiwata, H.; Sakakura, A.; Ogawa, T.; Ojika, M. and Yamada, K., *J. Org. Chem.,* **1996**, *61*, 5326.

6. Kocienski, P. J.; Lythgoe, B. and Ruston, S., *J. Chem. Soc., Perkin Trans. I,* **1978**, 829.

7. (a) Baudin, J. B.; Hareau, G.; Julia, S. A. and Ruel, O., *Tetrahedron Lett.,* **1991**, *32*, 1175. (b) Baudin, J. B.; Hareau, G.; Julia, S. A. and Ruel, O., *Bull. Soc. Chim. Fr.,* **1993**, *130*, 336. (c) Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R. and Ruel, O., *Bull. Soc. Chim. Fr.,* **1993**, *130*, 856.

8. (a) Pospisil, J.; Pospisil, T. and Marko, I. E., *Org. Lett.*, **2005**, *7*, 2373. (b) Keck, G. E.; Savin, K. A. and Weglarz, M., *J. Org. Chem.,* **1995**, *60*, 3194.
9. (a) Huang, H.-J. and Yang, W.-B., *Tetrahedron Lett*., **2007**, *48*, 1429. (b) Alonso, D. A.; Fuensanta, M. and Nijera, C., *Eur. J. Org. Chem.,* **2006**, 4747. (c) Alonso, D. A.; Fuensanta, M.; Najera, C. and Varea, M., *J. Org. Chem.,* **2005**, *70*, 6406. (d) Mauleón, P. and Carretero, J. C., *Org. Lett.,* **2004**, *6*, 3195. (e) Fürstner, A.; Albert, M.; Mlynarski, J.; Matheu, M. and DeClercq, E., *J. Am. Chem. Soc.,* **2003**, *125*, 13132. (f) Ahmed, A.; Hoegenauer, E. K.; Enev, V. S.; Hanbauer, M.; Kaehlig, H.; Öhler, E. and Mulzer, J., *J. Org. Chem.,* **2003**, *68*, 3026. (g) Metternich, R.; Denni, D.; Thai, B. and Sedrani, R., *J. Org. Chem.,* **1999**, *64*, 9632.
10. (a) Smith, A. B.; Safonov, I. G. and Corbett, R. M., *J. Am. Chem. Soc.,* **2001**, *123*, 12426. (b) Liu, P. and Jacobsen, E. N., *J. Am. Chem. Soc.,* **2001**, *123*, 10772.
11. (a) D'Herde, J. N. and De Clercq, P. J., *Molecules*, **2006**, *11*, 655. (b) Pospisil, J.; Pospisil, T. and Marko, I. E., *Coll. Czech. Chem. Commun.,* **2005**, *70*, 1953. (c) Bernard, A. M.; Frongia, A.; Piras, P. P. and Secci, F., *Synlett*, **2004**, 1064. (d) D'herde, J. N. P. and De Clercq, P. J., *Tetrahedron Lett*., **2003**, *44*, 6657. (e) Zanoni, G.; Porta, A.; Castronovo, F. and Vidari, G., *J. Org. Chem.,* **2003**, *68*, 6005. (f) Zanoni, G.; Porta, A. and Vidari, G., *J. Org. Chem.,* **2002**, *67*, 4346. (g) Marko, I. E.; Murphy, F.; Kumps, L.; Ates, A.; Touillaux, R.; Craig, D.; Carballares, S. and Dolan, S., *Tetrahedron*, **2001**, *57*, 2609. (h) Satoh, T.; Hanaki, N.; Yamada, N. and Asano, T., *Tetrahedron*, **2000**, *56*, 6223. (i) Satoh, T.; Yamada, N. and Asano, T., *Tetrahedron Lett*., **1998**, *39*, 6935. (j) Hart, D. J.; Li, J.; Wu, W.-L. and Kozikowski, A. P., *J. Org. Chem.,* **1997**, *62*, 5023. (k) Marko, I. E.; Murphy, F. and Dolan, S., *Tetrahedron Lett*., **1996**, *37*, 2089.
12. Charette, A. B. and Lebel, H., *J. Am. Chem. Soc.*, **1996**, *118*, 10327.
13. see www.organic-chemistry.org/
14. (a) Hilpert, H. and Wirz, B., *Tetrahedron*, **2001**, *57*, 681. (b) Evans, D. A. and Andrews, G. C., *Acc. Chem. Res.*, **1974**, *7*, 147.
15. (a) Metz, P., *Top. Curr. Chem.* **2005**, *244*, 215. (b) Blakemore, P. R.; Ho, D. K. H. and Nap, W. M., *Org. Biomol. Chem.,* **2005**, *3*, 1365. (c) Alonso, D. A.; Fuensanta, M.; Nájera, C. and Varea, M., *Phosphorus & Sulfur & Silicon Related Elements*, **2005**, *180*, 1119. (d) Takeda, T., *Modern Carbonyl Olefination*,Wiley-VCH Verlag, Weinheim **2004**. (e) Alonso, D. A.; Najera, C. and Varea, M., *Tetrahedron Lett.,* **2004**, *45*, 573. (f) Wipf, P.; Reeves, J. T. and Day, B. W., *Curr. Pharm. Design,* **2004**, *10*, 1417. (g) Furuichi, N.; Hara, H.; Osaki, T.; Nakano, M.; Mori, H. and Katsumura, S., *J. Org. Chem.,* **2004**, *69*, 7949. (h) Li, W.-D. Z. and Yang, J.-H., *Org. Lett.,* **2004**, *6*, 1849. (i) Kitano, Y.; Yokoyama, A.; Nogata, Y.; Shinshima, K.; Yoshimura, E.; Chiba, K.; Tada, M. and Sakaguchi, I., *Biofouling,* **2003**, *19*, 187. (j) Fürstner, A.; Mlynarski, J. and Albert, M., *J. Am. Chem. Soc.,* **2002**, *124*, 10274. (k) Dogan, Ö. And Oppolzer, W., *Turk. J. Chem.,* **2001**, *25*, 273. (l) Chakraborty, T. K. and Das, S., *Curr. Med. Chem. Anti-Cancer Agents,* **2001**, *1*, 131. (m) Ghosh, A. K.; Wang, Y. and Kim, J. T., *J. Org. Chem.,* **2001**, *66*, 8973. (n) Kocienski, P. J.; Bell, A. and Blakemore, P. R., *Synlett,* **2000**, 365. (o) Shimizu, T.; Masuda, K.; Hiramoto, K. and Nakata, T., *Org. Lett.,* **2000**, *2*, 2153. (p) Wender, P. A.; Hinkle, K. W.; Koehler, M. F. T. and Lippa, B., *Med. Res. Rev.,* **1999**, *19*, 388. (q) Charrier, C.; Ettouati, L. and Paris, J., *Tetrahedron Lett.,* **1999**, *40*, 5705. (r) Blakemore, P. R.; Kocienski, P. J.; Marzcak, S. and Wicha, J., *Synthesis,* **1999**, *7*, 1209. (s) Ley, S. V.; Humphries, A. C.; Eick, H.; Downham, R.; Ross, A. R.; Boyce, R. J.; Pavey, J. B. J. and Pietruszka, J., *J. Chem. Soc., Perkin Trans. I,* **1998**, 3907. (t) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J. and Morley, A., *Synlett*, **1998**, 26. (u) Carretero, J. C. and Arrayás, R. G., *J. Org. Chem.,* **1998**, *63*, 2993. (v) Takeda, K.; Nakajiama, A. and Yoshii, E., *Synlett,* **1995**, 249. (w) Williams, D. R.; Coleman, P. J.; Nevill, C. R. and Robinson, L. A., *Tetrahedron Lett.,* **1993**, *34*, 7895. (x) Kelly, S. E., "Alkene Synthesis," in *Comprehensive Organic Synthesis*, ed. Trost, B. M. and Fleming, I., Pergamon Press, Oxford, **1991**, *1*, p. 729. (y) Acmatovich, B.; Baranowska, E.; Daniewski, A. R.; Pankowski, J. and Wicha, J., *Tetrahedron,* **1988**, *44*, 4989. (z) Kocienski, P., *Phosphorus & Sulfur,* **1985**, *24*, 97. (aa) Kocienski, P. J. and Lythgoe, B., *J. Chem. Soc., Perkin Trans, I,* **1980**, 1045.

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Juliá-Colonna Asymmetric Epoxidation

(Juliá Asymmetric Epoxidation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Juliá in 1980[1] and was extended by Juliá and Colonna in 1982.[2] It is the oxidation of electron-deficient *trans*-α,β-enones into *trans*-α,β-epoxyketones by a hydroperoxide anion in the presence of polyamino acid. Therefore, this reaction is known as the Juliá epoxidation,[3] Juliá asymmetric epoxidation,[4] Juliá-Colonna epoxidation,[5] Juliá-Colonna reaction,[6] Juliá-Colonna oxidation,[7] or Juliá-Colonna stereoselective epoxidation;[8] however, it is more generally referred to as the Juliá-Colonna asymmetric epoxidation.[5f,6,9] The initial epoxidation protocol is limited to electron-deficient enones, such as chalcone in a three-phase reaction, by which the enones, dissolved in an organic solvent (such as hexane, CCl_4, or toluene), are oxidized by hydroperoxide anion (H_2O_2 + NaOH) in aqueous solution, under the catalysis of insoluble polyalanine or polyleucine.[2,10] This protocol has been extended to a two-phase reaction by dissolving enones in THF and using anhydrous urea-H_2O_2 as an oxidant in the presence of insoluble polyamino acid as the catalyst.[11] In addition, this reaction has also been carried out homogenously in a mixed solvent of water and DME, using sodium percarbonate as both base and oxidant.[12] Following this direction, further modification of this reaction has immobilized the catalyst of polyamino acid onto silica gel[8b,13] or polyethylene glycol (PEG).[5f] The modification by immobilizing the catalyst on silica gel bears the obvious advantages of improved filtration properties, high catalyst activity, ease of recycling, and higher stability.[6,8b,13] In this case, the best solvent is pyridine.[8b] It has been found that enones bind to the *N*-terminus

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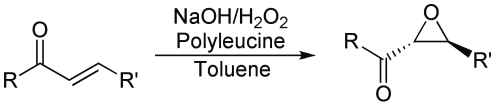
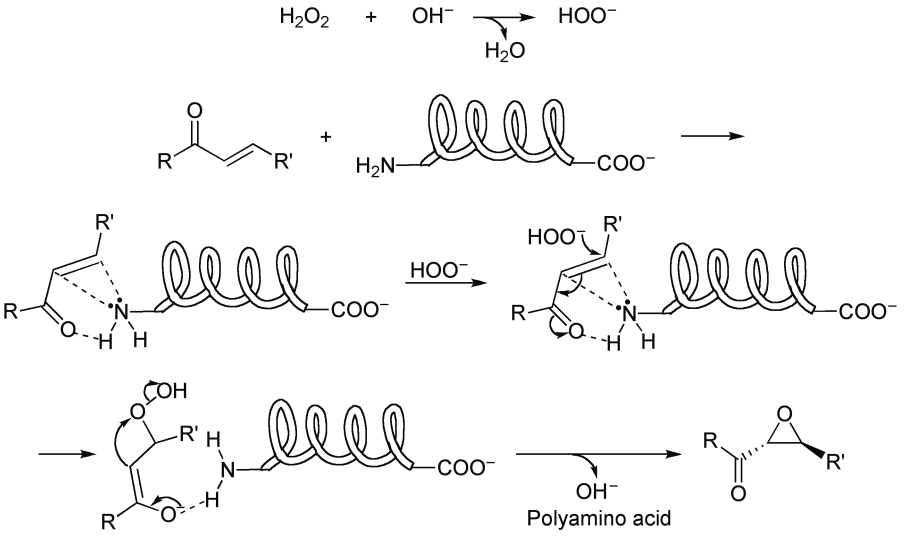
of the polypeptide, and it is the α-helicity of the polypeptide that determines the configuration of the epoxide through the face-selective delivery of a hydroperoxide anion.[5f,5g,9h] Furthermore, it has been reported that the peptide would be active as short as five amino acid residues, just enough to form one complete α-helix.[5g] Common polypeptides used for this reaction are $\sim$ 30 amino acid residues;[6] among these polypeptides, poly-neopentylglycine has higher catalytic activity than polyleucine.[6,14] It should be pointed out that this reaction is not suitable for the epoxidation of endocyclic enones, such as cyclohexenones or quinones and *cis*-enones.[5g]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A tentative mechanism is proposed here for the epoxidation of enone.



D. MODIFICATION

This reaction has been modified to occur in two phases using urea-H_2O_2 as the oxidant[11] or to take place homogenously using sodium percarbonate as the oxidant.[12] Further modifications of this reaction include the immobilization of catalyst onto PEG[5f] or silica gel[8b,13] to simplify the purification process.

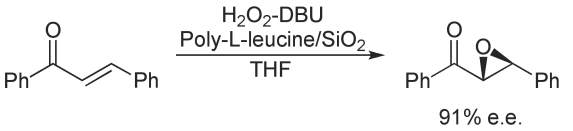
E. APPLICATIONS

This reaction has been widely used for the epoxidation of *trans*-enones.

F. RELATED REACTIONS

This reaction is related to the *Sharpless Epoxidation*.

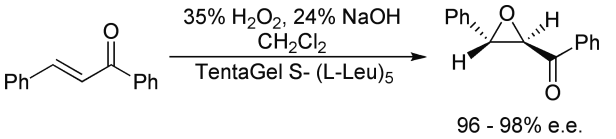
G. CITED EXPERIMENTAL EXAMPLES



Reference 6.

To a stirred 0.16 M solution of L-leucine NCA in anhydrous THF under a nitrogen atmosphere was added an initiator (0.0313 amino equivalents, either amino methyl polystyrene or 1,3-diaminopropane). The course of the reaction was followed by IR spectroscopy and TLC. After polymerization was judged complete, the reaction was filtered, and the solid poly-L-leucine was washed with further solvent and then dried in vacuo at 50°C. Then the poly-L-leucine was mounted on silica gel in THF according to Geller and Roberts.[8b]

To solution of chalcone (1 eq.) in anhydrous tetrahydrofuran was added urea-hydrogen peroxide (1.2 eq.), diazabicycloundecene (1.2 eq.), and poly-L-leucine (12 mol % optionally immobilized on silica, i.e., one part catalyst, three parts silica). The mixture was stirred at room temperature until the reaction was complete (TLC) ($\sim$ 7 days). The catalyst was removed by rapid filtration and washed with EtOAc. The combined organic fractions were evaporated in vacuo to yield crude epoxide. It was found that $\sim$ 45% of chalcone had been oxidized within the first 30 min, and the overall epoxyketone has 91% e.e.



Reference 5g.

To a stoppered test tube, equipped with a magnetic stir bar (10 × 3 mm) and thermostated to 20°C by a water jacket, was added 0.0219 mmol of penta-L-leucine on Tenta Gel S, and 1.6 mL dichloromethane containing 40.0 mg *trans*-chalcone (0.192 mmol). The reaction was started by the addition of 2.0 mL of a prethermostated mixture of three parts 24% NaOH and four parts 35% H_2O_2. The magnetic stirrer was set to 1200 rpm, and the test tubes were protected from light. After 24 h, 20 μL of the organic phase (lower layer) was withdrawn by means of a syringe, diluted with 1.0 mL dichloromethane, and analysized by HPLC, indicating that the product had a 96–98 % e.e.

Other references related to the Juliá-Colonna asymmetric epoxidation are cited in the literature.[15]

H. REFERENCES

1. Juliá, S.; Masana, J. and Vega, J. C., *Angew. Chem.,* **1980**, *92*, 968.
2. Juliá, S.; Guixer, J.; Masana, J.; Rocas, J.; Colonna, S.; Annuziata, R. and Molinari, H., *J. Chem. Soc., Perkin Trans. I,* **1982**, 1317.
3. Pettus, L. H.; van de Water, R. W. and Pettus, T. R. R., *Org. Lett.,* **2001**, *3*, 905.
4. (a) Bentley, P. A.; Kroutil, W.; Littlechild, J. A. and Roberts, S. M., *Chirality*, **1997**, *9*, 198. (b) Kroutil, W.; Lasterra-Sanchez, E.; Maddrell, S. J.; Mayon, P.; Morgan, P.; Roberts, S. M.; Thornton, S. R.; Todd, C. J. and Tuter, M., *J. Chem. Soc., Perkin Trans. I,* **1996**, 2837. (c) Lasterra-Sanchez, M. E.; Felfer, U.; Mayon, P.; Roberts, S. M.; Thornton, S. R. and Todd, C. J., *J. Chem. Soc., Perkin Trans. I,* **1996**, 343.
5. (a) Geller, T.; Gerlach, A.; Krueger, C. M. and Militzer, H.-C., *J. Mol. Catal. A: Chem.,* **2006**, *251*, 71. (b) Gerlach, A. and Geller, T., *Adv. Synth. Catal.,* **2004**, *346*, 1247. (c) Kelly, D. R.; Caroff, E.; Flood, R. W.; Heal, W. and Roberts, S. M., *Chem. Commun.,* **2004**, 2016. (d) Geller, T.; Krueger, C. M. and Militzer, H.-C., *Tetrahedron Lett*., **2004**, *45*, 5069. (e) Geller, T.; Gerlach, A.; Krueger, C. M. and Militzer, H.-C., *Tetrahedron Lett*., **2004**, *45*, 5065. (f) Flood, R. W.; Geller, T. P.; Petty, S. A.; Roberts, S. M.; Skidmore, J. and Volk, M., *Org. Lett.,* **2001**, *3*, 683. (g) Berkessel, A.; Gasch, N.; Glaubitz, K. and Koch, C., *Org. Lett.,* **2001**, *3*, 3839.
6. Baars, S.; Drauz, K.-H.; Krimmer, H.-P.; Roberts, S. M.; Sander, J.; Skidmore, J. and Zanardi, G., *Org. Proc. Res. Dev.,* **2003**, *7*, 509.
7. Geller, T.; Gerlach, A.; Krueger, C. M. and Militzer, H. C., *Chimica Oggi*, **2003**, *21*, 6.
8. (a) Ray, P. C. and Roberts, S. M., *J. Chem. Soc., Perkin Trans. I,* **2001**, 149. (b) Geller, T. and Roberts, S. M., *J. Chem. Soc., Perkin Trans. I,* **1999**, 1397.
9. (a) Takagi, R.; Begum, S.; Siraki, A.; Yoneshige, A.; Koyama, K.-i. and Ohkata, K., *Heterocycles*, **2004**, *64*, 129. (b) Hauer, B.; Bickley, J. F.; Massue, J.; Pena, P. C. A.; Roberts, S. M. and Skidmore, J., *Can. J. Chem.,* **2002**, *80*, 546. (c) Tsogoeva, S. B.; Woltinger, J.; Jost, C.; Reichert, D.; Kuhnle, A.; Krimmer, H.-P. and Drauz, K., *Synlett*, **2002**, 707. (d) Coffey, P. E.; Drauz, K.-H.; Roberts, S. M.; Skidmore, J. and Smith, J. A., *Chem. Commun.,* **2001**, 2330. (e) Bentley, P. A.; Flood, R. W.; Roberts, S. M.; Skidmore, J.; Smith, C. B. and Smith, J. A., *Chem. Commun.,* **2001**, 1616. (f) Takagi, R.; Manabe, T.; Shiraki, A.; Yoneshige, A.; Hiraga, Y.; Kojima, S. and Ohkata, K., *Bull. Chem. Soc. Jpn.,* **2000**, *73*, 2115. (g) Chen, W.-P. and Roberts, S. M., *J. Chem. Soc., Perkin Trans. I,* **1999**, 103. (h) Bentley, P. A.; Cappi, M. W.; Flood, R. W.; Roberts, S. M. and Smith, J. A., *Tetrahedron Lett*., **1998**, *39*, 9297. (i) Allen, J. V.; Bergeron, S.; Griffiths, M. J.; Mukherjee, S.; Roberts, S. M.; Williamson, N. M. and Wu, L. E., *J. Chem. Soc., Perkin Trans. I,* **1998**, 3171. (j) Cappi, M. W.; Chen, W.-P.; Flood, R. W.; Liao, Y.-W.; Roberts, S. M.; Skidmore, J.; Smith, J. A. and Williamson, N. M., *Chem. Commun.,* **1998**, 1159. (k) Adger, B. M.; Barkley, J. V.; Bergeron, S.; Cappi, M. W.; Flowerdew, B. E.; Jackson, M. P.; McCague, R.; Nugent, T. C. and Roberts, S. M., *J. Chem. Soc., Perkin Trans. I,* **1997**, 3501.
10. Flisak, J. R.; Gombatz, K. J.; Holmes, M. M.; Jarmes, A. A.; Lantos, I.; Mendelson, W. L.; Novack, V. J.; Remich, J. J. and Snyder, L., *J. Org. Chem.,* **1993**, *58*, 6247.
11. Lauret, C. and Roberts, S. M., *Aldrichimica Acta,* **2002**, *35*, 47.
12. Allen, J. V.; Drauz, K. H.; Flood, R. W.; Roberts, S. M. and Skidmore, J., *Tetrahedron Lett.,* **1999**, *40*, 5417.
13. Carde, L.; Davies, H.; Geller, T. P. and Roberts, S. M., *Tetrahedron Lett.,* **1999**, *40*, 5421.
14. Dhanda, A.; Drauz, K.-H.; Geller, T. P. and Roberts, S. M., *Chirality,* **2000**, *12*, 313.
15. (a) Yi, H.; Zou, G.; Li, Q.; Chen, Q.; Tang, J. and He, M.-Y., *Tetrahedron Lett*., **2005**, *46*, 5665. (b) Carrea, G.; Colonna, S.; Meek, A. D.; Ottolina, G. and Roberts, S. M., *Tetrahedron: Asymmetry*, **2004**, *15*, 2945. (c) Kelly, D. R. and Roberts, S. M., *Chem. Commun.,* **2004**, 2018. (d) Kelly, D. R.; Meek, A. and Roberts, S. M., *Chem. Commun.,* **2004**, 2021. (e) Lopez-Pedrosa, J.-M.; Pitts, M.

R.; Roberts, S. M.; Saminathan, S. and Whittall, J., *Tetrahedron Lett*., **2004**, *45*, 5073. (f) Carrea, G.; Colonna, S.; Meek, A. D.; Ottolina, G. and Roberts, S. M., *Chem. Commun.,* **2004**, 1412. (g) Chang, D. L.; Zhang, J.; Witholt, B. and Li, Z., *Biocatalysis & Biotransformation,* **2004**, *22*, 113. (h) Takagi, R.; Shiraki, A.; Manabe, T.; Kojima, S. and Ohkata, K., *Chem. Lett.,* **2000**, 366. (i) Lasterra-Sánchez, M. E.; Felfer, U.; Mayon, P.; Roberts, S.M.; Thornton, S. R. and Todd, C. J., *J. Chem. Soc., Perkin Trans. I,* **1996**, 343. (j) Banfi, S.; Colonna, S.; Molinari, H.; Julia, S. and Guixer, J., *Tetrahedron,* **1984**, *40*, 5207.

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Kabachnik-Fields Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported concurrently in 1952 by Kabachnik and Medved[1] and Fields.[2] It is a one-pot synthesis of α-amino phosphonate via the three-component coupling of aldehyde (or ketone), an amine, and a dialkylphosphite. Therefore, it is generally known as the Kabachnik-Fields reaction.[3,4] Occasionally, it is also referred to as the Kabachnik-Fields synthesis.[5] It has been found that ketones undergo the coupling more readily than aldehydes, especially for aliphatic ketones that react vigorously with amine and phosphite.[6] However, alicyclic and aromatic-aliphatic ketones react with amine at a relatively slow rate, and aromatic ketones react with even more difficulty.[3m] On the other hand, both primary and secondary amines can undergo this reaction.[2] Even though some reactions are carried out without any catalysts,[7] in most cases, this reaction is catalyzed by an acid or promoted by a base, such as CF_3CO_2H,[8] $InCl_3$,[9] $La(OTf)_3$,[10] $LiClO_4$,[11] $Sc(O_3SOC_{12}H_{25})_3$,[12] SiO_2,[13] or $TaCl_5$-SiO_2.[14] In addition, this reaction can also be promoted by microwave.[3j] The resulting α-amino phosphonates are useful for chelating agents.[15] It has been found that the direct reaction between phosphonate and imine results in the same product as the three-component coupling from phosphite, amine, and carbonyl compound; high yields are achieved if the anhydrous ammonia and carbonyl compounds are mixed before the dialkyl phosphite is added.[16]

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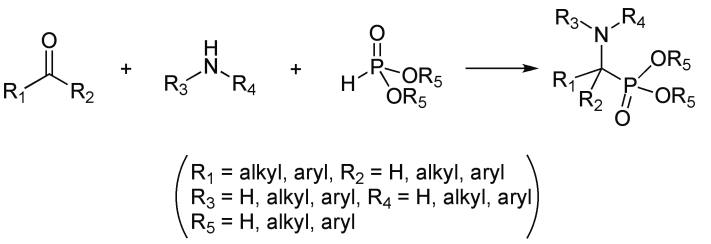
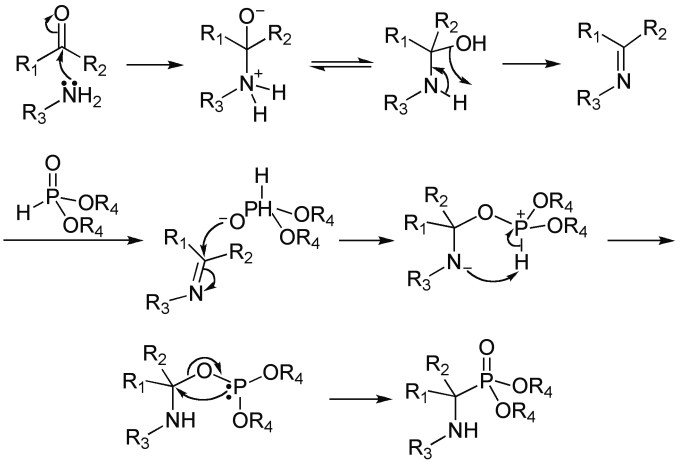
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is believed that this reaction occurs through the addition of dialkyl phosphite to the imine intermediate formed from the carbonyl compound and amine. It is known that both acid and base can accelerate the formation of the imine. Outlined here is a tentative mechanism for this reaction.



D. MODIFICATION

This reaction has been modified by using different catalysts as described in section A.

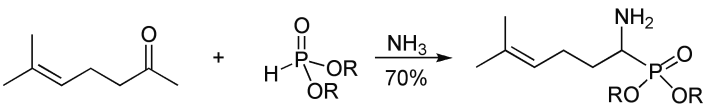
E. APPLICATIONS

This reaction has been used for the preparation of α-amino phosphonates.

F. RELATED REACTIONS

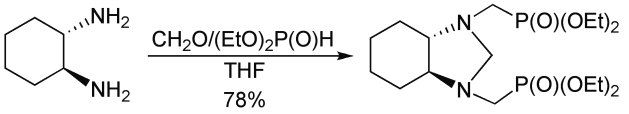
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 17.

Gaseous ammonia was bubbled through a stirred mixture of hept-5-en-2-one (0.10 mol) and dialkyl phosphite (0.11 mol) at 60°C. The reaction was monitored by TLC and generally finished within 4 h. The reaction mixture was then treated with 1 M aqueous HCl and extracted with ether. Aqueous NaOH was then added to adjust the pH to 10, and the mixture was then extracted with ether. The organic phase was washed with brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded 70% dialkyl (1-amino-1,5-dimethyl-4-enyl)phosphonate as a yellow oil.



Reference 3h.

To a magnetically stirred solution of 3.42 g *trans*-1,2-diaminocyclohexane (30 mmol) in 40 mL anhydrous THF was added slowly 8.3 g diethyl phosphite (60 mmol). The reaction mixture was refluxed before the addition of 2.8 g paraformaldehyde (93 mmol). After heating under reflux for 4 h, the solvent was evaporated under reduced pressure. The residue was dissolved in 50 mL $CHCl_3$, and the organic layer was washed twice with H_2O (2×10 mL) and dried over Na_2SO_4. The chloroform was evaporated under vacuum to obtain 10 g of a crude yellow oil that was purified by Kugelrohr distillation to yield 78% [3-(diethoxyphosphorylmethyl)-octohydro-benzoimidazol-1-ylmethyl]-phosphonic acid diethyl ester ($T = 280$°C, 0.1 mmHg).

Other references related to the Kabachnik-Fields reaction are cited in the literature.[18]

H. REFERENCES

1. Kabachnik, M. I. and Medved, T. Y., *Dokl. Akad. Nauk. SSSR Khim.,* **1952**, *83*, 689.
2. Fields, E. K., *J. Am. Chem. Soc.,* **1952**, *74*, 1528.
3. (a) van Meenen, E.; Moonen, K.; Acke, D. and Stevens, C. V., *ARKIVOC,* **2006**, 31. (b) Cholakova, T.; Zagraniarsky, Y.; Hägele, G.; Gosheva, T.; Ivanova, B.; Scopelliti, R. and Varbanov, S., *Z. Naturforsch.,* **2005**, *60b*, 215. (c) Nifantyev, E. E.; Kukhareva, T. S.; Khodarev, D. V.; Vasyanina, L. K. and Vasilev, A. V., *Phosphorus, Sulfur & Silicon & Related Elements,* **2005**, *180*, 331. (d) Kabachnic, M. M.; Zobnina, E. V.; Pavlov, V. Y.; Konstantinov, I. O.; Ponomarev, G. V. and Beletskaya, I. P., *Russ. Chem. Bull.,* **2005**, 262. (e) Wang, Q. Z.; Deng, Y. J. and Ju, Y., *Tsinghua Sci. & Tech*., **1997**, *2*, 809. (f) Habermann, J.; Ponzi, S. and Ley, S. V., *Mini-Rev. Org. Chem.,* **2005**, *2*, 125. (g) Moonen, K.; Laureyn, I. and Stevens, C. V., *Chem. Rev.,* **2004**, *104*, 6177.

(h) Bailly, T.; Burgada, R.; Lecouvey, M.; Neuman, A. and Prangé, T., *ARKIVOC,* **2003**, 140. (i) Dimukhametov, M. N.; Bayandina, E. V.; Davydova, E. Y.; Gubaidullin, A. T. and Alfonsov, V. A., *Mendeleev Commun.,* **2003**, *13*, 150. (j) Lee, S.-G.; Lee, J. K.; Song, C. E. and Kim, D.-C., *Bull. Korean Chem. Soc.,* **2002**, *23*, 667. (k) Kaboudin, B., *Phosphorus, Sulfur & Silicon & Related Elements,* **2002**, *177*, 1749. (l) Cherkasov, R. A. and Galkin, V. I., *Russ. Chem. Rev.,* **1998**, *67*, 857. (m) Freedman, L. D. and Doak, G. O., *Chem. Rev.,* **1957**, *57*, 479.

4. (a) Bhagat, S. and Chakraborti, A. K., *J. Org. Chem.,* **2007**, *72*, 1263. (b) Mu, X.-J.; Lei, M.-Y.; Zou, J.-P. and Zhang, W., *Tetrahedron Lett*., **2006**, *47*, 1125. (c) Garifzyanov, A. R.; Vasil'ev, R. I. and Cherkasov, R. A., *Russ. J. Gen. Chem.,* **2005**, *75*, 217. (d) Garifzyanov, A.; Vasilév, R. and Cherkasov, R., *Russ. J. Gen. Chem.,* **2005**, *75*, 217. (e) Matveeva, E. D.; Podrugina, T. A.; Tishkovskaya, E. V.; Tomilova, L. G. and Zefirov, N. S., *Synlett*, **2003**, 2321. (f) Dimukhametov, M. N.; Bayandina, E. V.; Davydova, E. Yu.; Gubaidullin, A. T.; Litvinov, I. A. and Alfonsov, V. A., *Mendeleev Commun*., **2003**, 150. (g) Dimukhametov, M. N.; Galieva, L. F.; Shlyamina, O. V.; Levinson, F. S. and Al'fonsov, V. A., *Russ. J. Gen. Chem.,* **1998**, *68*, 1485. (h) Matevosyan, G. L. and Zavlin, P. M., *Russ. J. Gen. Chem.,* **1998**, *68*, 1467. (i) Galkina, I. V.; Galkin, V. I. and Cherkasov, R. A., *Russ. J. Gen. Chem.,* **1998**, *68*, 1402. (j) Galkina, I. V.; Sobanov, A. A.; Galkin, V. I. and Cherkasov, R. A., *Russ. J. Gen. Chem.,* **1998**, *68*, 1398. (k) Galkina, I. V.; Zvereva, E. R.; Galkin, V. I. and Cherkasov, R. A., *Russ. J. Gen. Chem.,* **1998**, *68*, 1391. (l) Galkina, I. V.; Zvereva, E. R.; Galkin, V. I.; Sobanov, A. A. and Cherkasov, R. A., *Russ. J. Gen. Chem.,* **1998**, *68*, 1387. (m) Trishin, Y. G. and Maslov, V. I., *Russ. Chem. Bull.,* **1998**, *47*, 2047. (n) Cherkasov, R. A. and Galkin, V. I., *Uspekhi Khim*., **1998**, *67*, 940. (o) Fazylov, S. D.; Gazaliev, A. M.; Vlasova, L. M.; Kasenov, R. Z. and Byistro, V. K., *Zh. Obsh. Khim.,* **1996**, *66*, 238. (p) Gancarz, R.; Gancarz, I. and Walkowiak, U., *Phosphorus, Sulfur & Silicon & Related Elements*, **1995**, *104*, 45. (q) Galkin, V. I.; Zveneva, E. R.; Sobanov, A. A.; Galkina, I. V. and Cherkasov, R. A., *Zh. Obsh. Khim.,* **1993**, *63*, 2224. (r) Krutikov, V. I.; Sukhanovskaya, E. V. and Tsarkova, I. A., *Zh. Obsh. Khim.,* **1992**, *62*, 2708. (s) Krutikov, V. I.; Lavrent'ev, A. N. and Sukhanovskaya, E. V., *Zh. Obsh. Khim.,* **1991**, *61*, 1321. (t) Krutikov, V. I.; Kovalenko, A. L. and Sukhanovskaya, E. V., *Zh. Obsh. Khim.,* **1991**, *61*, 257. (u) Nifant'ev, E. E.; Kukhareva, T. S.; Popkova, T. N. and Davydochkina, O. V., *Zh. Obsh. Khim.,* **1986**, *56*, 304. (v) Matevosyan, G. L.; Zhuravlev, A. V. and Zavlin, P. M., *Zh. Obsh. Khim.,* **1983**, *53*, 2401.
5. (a) Matveeva, E. D.; Podrugina, T. A.; Prisyajnoy, M. V. and Zefirov, N. S., *Russ. Chem. Bull.,* **2006**, *55*, 1209. (b) Gancarz, R., *Phosphorus, Sulfur & Silicon & Related Elements,* **1993**, *83*, 59.
6. (a) Medved, T. Y. and Kabachnik, M. I., *Izv. Akad. Nauk. SSSR, Otd. Khim. Nauk,* **1954**, 314. *Chem. Abstr.,* **1954**, *48*, 10541. (b) Medved, T. Y. and Kabachnik, M. I., *Dokl. Akad. Nauk. SSSR Khim.,* **1952**, *84*, 717 [*Chem. Abstr.,* **1953**, *47*, 3226].
7. (a) Chandrasekhar, S.; Narsihmulu, C.; Shameem Sultana, S.; Saritha, B. and Jaya Prakash, S., *Synlett,* **2003**, 505. (b) Takahashi, H.; Yoshioka, M.; Imai, N.; Onimura, K. and Kobayashi, S., *Synthesis,* **1994**, 763.
8. Akiyama, T.; Sanada, M. and Fuchibe, K., *Synlett,* **2003**, 1463.
9. Ranu, B. C.; Hajra, A. and Jana, U., *Org. Lett.,* **1999**, *1*, 1141.
10. Lee, S.; Park, J. H.; Kang, J. and Lee, J. K., *Chem. Commun.,* **2001**, 1698.
11. (a) Azizi, N. and Saidi, M. R., *Eur. J. Org. Chem.,* **2003**, 4630. (b) Heydari, A.; Karimian, A. and Ipaktschi, J., *Tetrahedron Lett.,* **1998**, *39*, 6729.
12. Manabe, K. and Kobayashi, S., *Chem. Commun.,* **2000**, 669.
13. Kaboudin, B. and Rahmani, A., *Synthesis,* **2003**, 2705.
14. Chandrasekhar, S.; Prakash, S. J.; Jagadeshwar, V. and Narsihmulu, C., *Tetrahedron Lett.,* **2001**, *42*, 5561.
15. Holz, R. C.; Meister, G. E. and Horrocks, W. D., *Inorg. Chem.,* **1990**, *29*, 5183.
16. Chalmers, M. E. and Kosolapoff, G. M., *J. Am. Chem. Soc.,* **1953**, *75*, 5278.

17. Moigne, F. L. and Tordo, P., *J. Org. Chem.,* **1994**, *59*, 3365.

18. (a) Li, C. H.; Song, B. A.; Yan, K.; Xu, G. F.; Hu, D. Y.; Yang, S.; Jin, L. H.; Xue, W. and Lu, P., *Molecules*, **2007**, *12*, 163. (b) Khodarev, D. V.; Kukhareva, T. S.; Lipovtsin, E. V. and Nifant'ev, E. E., *Russ. J. Gen. Chem.,* **2006**, *76*, 198. (c) Zamorano-Octaviano, J.; Hernandez-Martinez, A.; Ortega-Guevara, A.; Linzaga-Elizalde, I. and Hopfl, H., *Heteroatom Chem*., **2006**, *17*, 75. (d) Cholakova, T.; Zagraniarsky, Y.; Haegele, G.; Tosheva, T.; Ivanova, B.; Scopelliti, R. and Varbanov, S., *Z. Naturforsch., B: Chem. Sci.,* **2005**, *60*, 215. (e) Stoikov, I. I.; Fitseva, N. A.; Akhmetzyanova, L. R.; Gafioullina, L. I.; Antipin, I. S.; Zheltukhin, V. F.; Devyaterikova, A. I.; Al'fonsov, V. A. and Konovalov, A. I., *Russ. Chem. Bull.,* **2004**, *53*, 1577. (f) Zakharov, S. V.; Nuriazdanova, G. Kh.; Garifzyanov, A. R.; Galkin, V. I. and Cherkasov, R. A., *Russ. J. Gen. Chem.,* **2004**, *76*, 873. (g) Matevosyan, G. L.; Yukha, Y. S. and Zavlin, P. M., *Russ. J. Gen. Chem.,* **2003**, *73*, 1725. (h) Cristau, H.-J.; Herve, A. and Virieux, D., *Tetrahedron,* **2004**, *60*, 877. (i) Vasil'ev, R. I.; Durmanova, N. V.; Garifzyanov, A. R. and Cherkasov, R. A., *Russ. J. Gen. Chem.,* **2003**, *73*, 994. (j) Najdenova, E.; Vassilev, A.; Popova, Y. and Troev, K., *Heteroatom Chem*., **2003**, *14*, 229. (k) Cristau, H.-J.; Coulombeau, A.; Genevois-Borella, A.; Sanchez, F. and Pirat, J.-L., *J. Organomet. Chem.,* **2002**, *643-644*, 381. (l) Mao, J.-G.; Wang, Z. K. and Clearfield, A., *Inorg. Chem.,* **2002**, *41*, 3713. (m) Grozav, M.; Neamtiu, I. and Doresencu, M., *Revista Chim. (Bucharest),* **2001**, *52*, 693. (n) Stoikov, I. I.; Repejkov, S. A.; Antipin, I. S. and Konovalov, A. I., *Heteroatom Chem*., **2000**, *11*, 518. (o) Clearfield, A.; Poojary, D. M.; Zhang, B.; Zhao, B. and Derecskei-Kovacs, A., *Chem. Mater.,* **2000**, *12*, 2745. (p) Grabowski, G.; Lewkowski, J. A.; Nazarski, R. B.; Skowronski, R. and Karolak-Wojciechowska, J., *Pol. J. Chem.,* **1999**, *73*, 307. (q)Zaitsev, V. N.; Vasilik, L. S.; Evans, J. and Brough, A., *Russ. Chem. Bull.,* **1999**, *48*, 2315. (r) Antipin, I. S.; Stoikov, I. I. and Konovalov, A. I., *Phosphorus, Sulfur & Silicon & Related Elements,* **1999**, 144 – 146, 347. (s) Antipin, S.; Stoikov, I. I.; Repeikov, S. A. and Konovalov, A. I., *Russ. Chem. Bull.,* **1998**, *47*, 1697. (t) Cristau, H.-J.; Lambert, J.-M. and Pirat, J.-L., *Synthesis*, **1998**, 1167. (u) Cherkasov, R. A. and Galkin, V. I., *Russ. Chem. Rev.,* **1998**, *67*, 897. (v) Bligh, S. W. A.; Choi, N.; Geraldes, C. F. G. C.; Knoke, S.; McPartlin, M.; Sanganee, M. J. and Woodroffe, T. M., *J. Chem. Soc., Dalton Trans.,* **1997**, 4119. (w) Antipin, I. S.; Stoikov, I. I.; Pinkhassik, E. M.; Fitseva, N. A.; Stibor, I. and Konovalov, A. I., *Tetrahedron Lett*., **1997**, *38*, 5865. (x) Galkina, I. V.; Saakyan, G. M.; Cherkasov, M. R.; Galkin, V. I.; Cherkasov, R. A. and Pudovik, A. N., *Zh. Obsh. Khim.,* **1996**, *66*, 355. (y) Fazylov, S. D.; Gazaliev, A. M.; Vlasova, L. M. and Zhurinov, M. Zh., *Zh. Obsh. Khim.,* **1996**, *66*, 696. (z) Petrov, P.; Valceanu, R.; Vlad, F.-I. and Muresan, S., *Revista Chim. (Bucharest),* **1996**, *47*, 427. (aa) Gancarz, R., *Tetrahedron,* **1995**, *51*, 10627. (bb) Frejaville, C.; Karoui, H.; Tuccio, B.; Le Moigne, F.; Culcasi, M.; Pietri, S.; Lauricella, R. and Tordo, P., *J. Med. Chem.,* **1995**, *38*, 258. (cc) Yurchenko, R. I.; Voitsekhovskaya, O. M.; Klepa, T. I. and Yurchenko, A. G., *Zh. Obsh. Khim.,* **1995**, *65*, 1449. (dd) Bailly, T. and Burgada, R., *Phosphorus, Sulfur & Silicon & Related Elements*, **1995**, *101*, 131. (ee) Frejaville, C.; Karoui, H.; Tuccio, B.; Le Moigne, F.; Culcasi, M.; Pietri, S.; Lauricella, R. and Tordo, P., *J. Chem. Soc., Chem. Commun.*. **1994**, 1793. (ff) Kabachnik, M. I.; Antipin, M. Y.; Shcherbakov, B. K.; Baranov, A. P.; Struchkov, Y. T.; Medved, T. Y. and Polikarpov, Y. M., *Koord. Khim.,* **1988**, *14*, 536. (gg) Antipin, M. Y.; Baranov, A. P.; Kabachnik, M. I.; Medved, T. Y.; Polikarpov, Y. M.; Struchkov, Y. T. and Shcherbakov, B. K., *Dokl. Akad. Nauk SSSR,* **1986**, *287*, 130.

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Kahne Glycosylation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Kahne in 1989.[1] It is a convenient synthesis of glycosides and disaccharides or oligosaccharides between glycosyl phenyl sulfoxide (i.e., the glycosyl donor) and an acceptor in the presence of a glycosylation promoter. Because of its obvious advantages, including the mild reaction condition,[2] good to excellent anomeric stereocontrol, compatibility with both solution and solid-phase glycosylation[3] and high reactivity of glycosyl donor, this reaction has been widely used for the synthesis of oligosaccharides. Therefore, this reaction is generally known as the Kahne glycosylation[4] and is especially useful for unreactive acceptors, or the most hindered alcohols.[5] So far, the glycosides of acetamide,[6] hindered bile acids,[1] hydroxylamines,[7] hydroxylated amino acids,[8] phenols,[1] tertiary alcohols,[9] and a variety of carbohydrates[1,10] have been prepared by this method. Alcohols have sometimes been converted into their tributylstannyl ether derivatives before being mixed with glycosyl sulfoxides (known as sulfinil glycosides[11]), presumably because of the enhanced nucleophilicity of the acceptors.[2] The promoters for this reaction are triflic anhydride (Tf_2O)[12] and trimethylsilyl triflate (TMSOTf)[13] in a stoichiometric amount or triflic acid in a catalytic amount.[11] In addition, this reaction is often carried out in a nonpolar solvent[11] at low temperature[14] in the presence of an acid scavenger (e.g. di-*t*-butyl methyl pyridine);[11] however, when a catalytic amount of triflic acid is used as the glycosylation promoter, methyl propionate is applied as the sulfenlic acid scavenger.[10a] It should be pointed out that the glycosylation is not restricted to glycosyl phenyl sulfoxides, glycosyl alkyl sulfoxides[2] and sulfimides[15] are suitable for glycosyl donors as well. It is found that the protecting groups on sulfinil glycosides have an apparent effect on the stereochemistry of glycosides. For example, the glycosylations of pivalate-protected glucosyl phenyl sulfoxide always give β-glycosides,[2] whereas reaction of the corresponding

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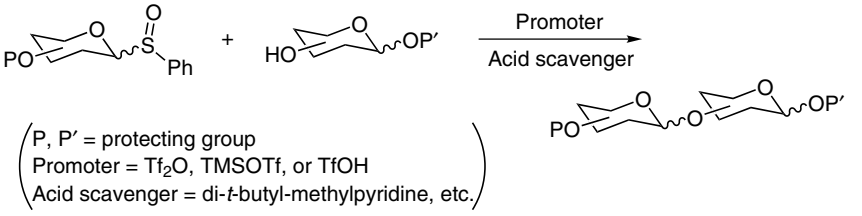
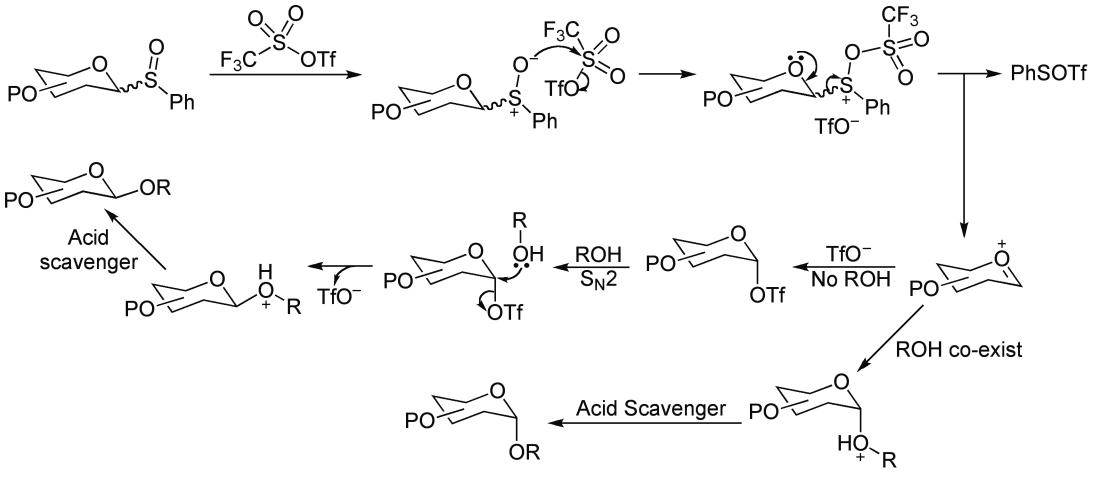
perbenzyl derivatives results in a mixture of α- and β-anomers by which the β:α ratio increases with solvent polarity and approaches the optimal selectivity in propionitrile.[2] It has also been found that even the mixing sequence of a promoter and acceptor can influence the stereochemical outcome, such as the formation of mainly α-anomer if the donor, acceptor, and base are mixed before the addition of triflic anhydride; prior activation of the donor with Tf_2O reverses the stereoselectivity.[16] Thus it is generally recommended to activate the sulfoxide donor with Tf_2O before the adding the glycosyl acceptor.[2]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It has been suggested[2] that glycosyl sulfoxide is converted into sulfonium salt, which collapses immediately to the oxacarbenium ion and the sulfenyl triflate. In the presence of a glycosyl acceptor, the oxacarbenium ion is trapped directly by the acceptor along the axial attack, leading to α-glycoside; in the absence of an acceptor, the oxacarbenium ion is trapped by triflate to form glycosyl triflate as an intermediate, which then couples with the following added acceptor to form β-glycoside, as shown below.



D. MODIFICATION

This reaction has been extended to glycosyl alkyl sulfoxide[2] and glycosyl disulfide.[17] In addition, reverse Kahne glycosylation has also been made possible by coupling between carbohydrate and alkyl sulfoxides.[4a]

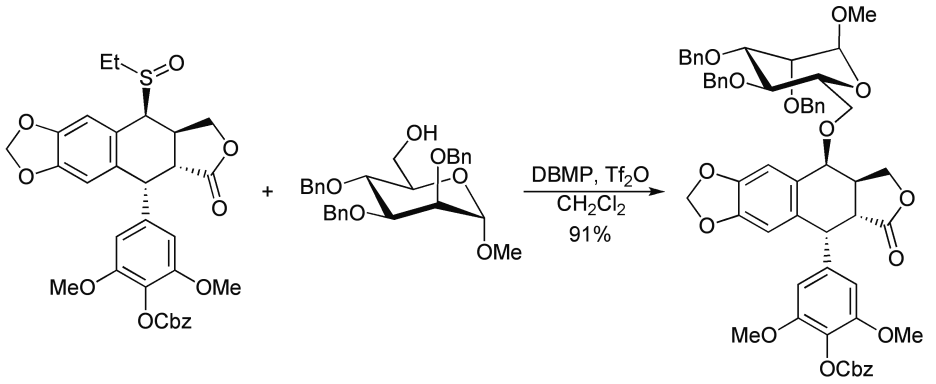
E. APPLICATIONS

This reaction has wide application in the preparation of glycosides, disaccharides, and oligosaccharides.

F. RELATED REACTIONS

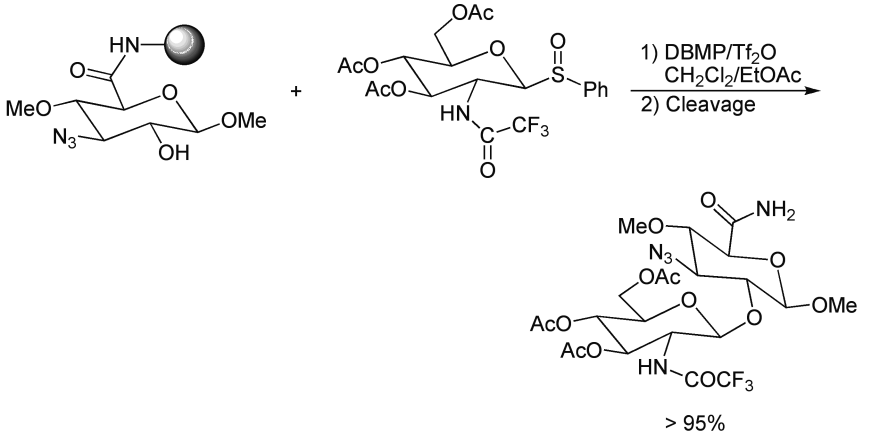
This reaction is related to the *Helferich Glycosylation*, *Hilbert-Johnson Reaction*, and *Koenigs-Knorr Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4a.

To a solution of 10.0 mg sulfoxide (0.017 mmol) and 7.0 mg 2,6-di-*tert*-butyl-4-methylpyridine (DBMP, 0.034 mmol) in 1 mL CH_2Cl_2 at −78°C was added 5.0 μL trifluoromethanesulfonic anhydride (25 μmol). After 10 min, a solution of 24 mg methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (50 μmol) in 0.5 mL CH_2Cl_2 was added via cannula, and the reaction mixture was left stirring at −78°C for 3 h. The reaction mixture was diluted with CH_2Cl_2 and washed with water, followed by drying over Na_2SO_4, filtration, and evaporation. Flash chromatography (0 ∼ 50% EtOAc/hexanes) afforded 15 mg of the desired compound as a single (C_4-*S*) diastereomer, in a yield of 91%, R_f = 0.4 (EtOAc/hexanes, 1:1).



Reference 3.

Rink amide resin (20 mg, 9 μmol) containing the glycosyl acceptor was dried under high vacuum and kept under argon. To the resin was added a solution of 2-deoxy-2-*N*-trifluoroacetyl-3,4,6-*O*-triacetyl-β-D-glucosyl phenyl sulfoxide (4 eq., in concentration of 0.14 M) and 4.5 mg 2,6-di-*tert*-butyl-4-methylpyridine (2 eq.) in 300 μL of mixed solvent of CH_2Cl_2/EtOAc (5:1). The mixture was stirred at room temperature for 5 min and cooled to -78°C. Trifluoromethanesulfonic anhydride (7 μL, 4 eq.) was slowly added, and the system was kept at -70°C for 1 h. The temperature was slowly raised to -45°C and kept constant for 5.5 h. The reaction was quenched with 100 μL of a 2:1 mixture of methanol and DIPEA at -45°C. The reaction mixture was allowed to warm to room temperature, and the resin was washed with DMF (three times), THF (twice), CH_3OH (twice), and CH_2Cl_2 (twice) and dried to give > 95% of product. The final glycoside was then cleaved with 20% TFA-CH_2Cl_2.

Other references related to the Kahne glycosylation are cited in the literature.[18]

H. REFERENCES

1. Kahne, D.; Walker, S.; Cheng, Y. and Engen, D. V., *J. Am. Chem. Soc*., **1989**, *111*, 6881.
2. Crich, D. and Sun, S. X., *J. Am. Chem. Soc.,* **1997**, *119*, 11217.
3. Silva, D. J.; Wang, H. M.; Allanson, N. M.; Jain, R. and Sofia, M. J., *J. Org. Chem.,* **1999**, *64*, 5926.
4. (a) Berkowitz, D. B.; Choi, S. J.; Bhuniya, D. and Shoemaker, R. K., *Org. Lett.,* **2000**, *2*, 1149. (b) Franck, R. W. and Marzabadi, C. H., *J. Org. Chem.,* **1998**, *63*, 2197.
5. (a) Crich, D. and Sun, S. X., *J. Am. Chem. Soc.,* **1998**, *120*, 435. (b) Crich, D. and Sun, S. X., *Tetrahedron,* **1998**, *54*, 8321.
6. Garcia, B. A. and Gin, D. Y., *J. Am. Chem. Soc.,* **2000**, *122*, 4269.
7. Walker, S.; Gange, D.; Gupta, V. and Kahne, D., *J. Am. Chem. Soc.,* **1994**, *116*, 3197.
8. Hamilton Andreotti, A. and Kahne, D., *J. Am. Chem. Soc.,* **1993**, *115*, 3352.
9. Yan, L. and Kahne, D., *Synlett,* **1995**, 523.
10. (a) Raghavan, S. and Kahne, D., *J. Am. Chem. Soc.,* **1993**, *115*, 1580. (b) Yang, D.; Kim, S.-H. and Kahne, D., *J. Am. Chem. Soc.,* **1991**, *113*, 4715.
11. Robina, I., Glycosylation Methods in Oligosaccharide Synthesis [lecture notes], Department of Organic Chemistry, University of Seville, Spain, **2005**, p. 31.
12. Yan, L.; Taylor, C. M.; Goodnow, R. and Kahne, D., *J. Am. Chem. Soc.* **1994**, *116*, 6953.
13. Sliedregt, L. A. J. M.; van der Marel, G. A. and van Boom, J. H., *Tetrahedron Lett.,* **1994**, *35*, 4015.
14. Crich, D. and Smith, M., *J. Am. Chem. Soc.,* **2001**, *123*, 9015.
15. Cassel, S.; Plessis, I.; Wessel, H. P. and Rollin, P., *Tetrahedron Lett.,* **1998**, *39*, 8097.
16. Crich, D. and Sun, S. X., *J. Org. Chem.*, **1996**, *61*, 4506.
17. Grayson, E. J.; Ward, S. J.; Hall, A. L.; Rendle, P. M.; Gamblin, D. P.; Batsanov, A. S. and Davis, B. G., *J. Org. Chem.,* **2005**, *70*, 9740.
18. (a) Crich, D. and Vinod, A. U., *J. Org. Chem.,* **2005**, *70*, 1291. (b) Kim, K. S.; Kim, J. H.; Lee, Y. J.; Lee, Y. J. and Park, J., *J. Am. Chem. Soc.,* **2001**, *123*, 8477. (c) Gadikota, R. R.; Callam, C. S. and Lowary, T. L., *Org. Lett.,* **2001**, *3*, 607. (d) Baraznenok, I. L.; Nenajdenko, V. G. and Balenkova, E. S., *Tetrahedron,* **2000**, *56*, 3077. (e) Chang, G. X. and Lowary, T., *Org. Lett.,* **2000**, *2*, 1505. (f) Crich, D.; Dai, Z. M. and Gastaldi, S., *J. Org. Chem.,* **1999**, *64*, 5224. (g) Alonso, I.; Khiar, N. and Martin-Lomas, M., *Tetrahedron Lett.*, **1996**, *37*, 1477. (h) Yan, L. and Kahne, D., *J. Am. Chem. Soc.,* **1996**, *118*, 9239. (i) Silva, D. J.; Kraml, C. M. and Kahne, D., *Bioorg. Med. Chem.,* **1994**, *2*, 1251.

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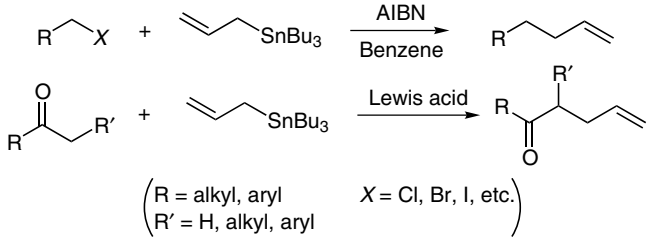
Keck Allylation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Keck in 1982.[1] It is a three-carbon chain extension of alkyl halides with allyl tri-*n*-butylstannane in the presence of a radical initiator[2] or an extension of carbonyl compound with allyl tri-*n*-butylstannane in the presence of a Lewis acid.[3] Therefore, it is generally known as the Keck allylation.[2b,2c,3a,3b,4] Occasionally, it is also referred to as the Pereyre-Keck allylation,[5] Keck reaction,[6] or Keck radical coupling.[7] When allyl tri-*n*-butylstannane reacts with α-hydroxyaldehyde, either *erythro* or *threo* products can be controlled with excellent stereoselectivity,[3d] depending on the order of the addition of the reagent, solvent, and Lewis acid involved.[8] It has been found that the *threo* product is formed under chelation control, and the *erythro* product predominates in the absence of Lewis acid; however, a strong electron-donating solvent can overturn the stereochemistry.[8] The Lewis acids suitable for this reaction include $BF_3{\cdot}OEt_2$, $MgBr_2$, $MgCl_2$, $Mg(ClO_4)_2$, $ZnBr_2$, ZnI_2, $TiCl_4$, and $AlMe_3$.

B. GENERAL REACTION SCHEME



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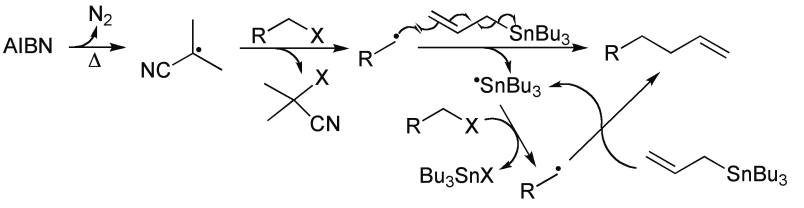
C. PROPOSED MECHANISMS

Demonstrated here is the mechanism of the Keck allylation proceeding via a radical pathway.



D. MODIFICATION

N/A

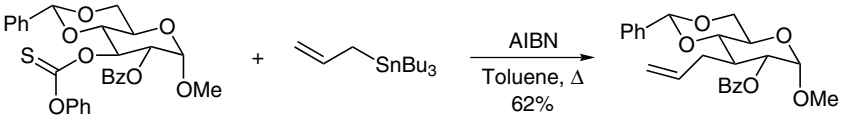
E. APPLICATIONS

This reaction has wide application in the extension of carbon chains in organic synthesis.

F. RELATED REACTIONS

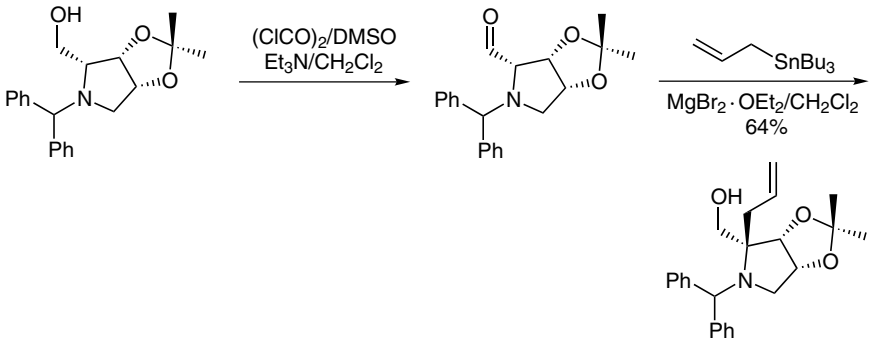
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 4b.

A mixture of 4.98 g methyl 2-benzoyl-3-phenoxythiocarbonyl-4,6-benzylidene-α-D-glucoside (9.5 mmol), 7.40 mL allyltributyltin (23.9 mmol), 313 mg AIBN, and 15 mL toluene was refluxed for 4 h at which point TLC showed complete consumption of the starting material. The solution was concentrated, and the residue was flash chromatographed on silica gel using 5% EtOAc in toluene as the eluent to give 3.48 g methyl (3S)-2-*O*-benzoyl-4,6-di-*O*-benzylidene-3-allyl-3-deoxy-α-D-glucopyranoside as a solid, in a yield of 62%, m.p. 138–139°C, R_f = 0.38 (EtOAc/hexanes, 1:9).



Reference 9.

2,3-*O*-Isopropylidene-*N*-diphenylmethyl-1,4-dideoxy-1,4-imino-D-lyxitol (139 mg, 0.411 mmol) was oxidized to aldehyde by Swern oxidation. Then the crude aldehyde was treated with 150 mg activated 4-Å molecular sieves and 6 mL CH_2Cl_2 containing 212 mg $MgBr_2{\cdot}OEt_2$ (0.822 mmol) at -20°C. The resulting mixture was stirred at -20°C for 30 min, and 140 μL allyltributylstannane (0.452 mmol) was added. The reaction mixture was stored at -23°C. After 20 h, ether (10 mL) and 1 mL aqueous KF prepared from 1 mL saturated KF and 4 mL H_2O were added, and the mixture was vigorously stirred at room temperature for 30 min. The phases were separated, and the aqueous layer was extracted with ether. The organic layers were pooled, washed with 5 mL $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. The residue was purified on silica gel (10% EtOAc/hexanes) to afford 99.6 mg 4-*C*-allyl-2,3-*O*-isopropylidene-*N*-diphenylmethyl-1,4-dideoxy-1,4-imino-D-lyxitol as an oil, in a yield of 64% with > 20:1 dr.

Other references related to the Keck allylation are cited in the literature.[10]

H. REFERENCES

1. Keck, G. E. and Yates, J. B., *J. Am. Chem. Soc.,* **1982**, *104*, 5829.
2. (a) Birman, V. B. and Danishefsky, S. J., *J. Am. Chem. Soc.,* **2002**, *124*, 2080. (b) Evans, P. A. and Manangan, T., *J. Org. Chem.,* **2000**, *65*, 4523. (c) Roe, B. A.; Boojamra, C. G.; Griggs, J. L. and Betrozzi, C. R., *J. Org. Chem.,* **1996**, *61*, 6442.
3. (a) Padwa, A. and Ginn, J. D., *J. Org. Chem.,* **2005**, *70*, 5197. (b) Ginn, J. D. and Padwa, A., *Org. Lett.,* **2002**, *4*, 1515. (c) Knapp, S. and Dong, Y., *Tetrahedron Lett.,* **1997**, *38*, 3813. (d) Keck, G. E. and Boden, E. P., *Tetrahedron Lett.,* **1984**, *25*, 265.
4. (a) Padwa, A., *Pure Appl. & Chem.,* **2003**, *75*, 47. (b) Postema, M. H. D.; Piper, J. L.; Liu, L.; Shen, J.; Faust, M. and Andreana, P., *J. Org. Chem.,* **2003**, *68*, 4748. (c) Beigelman, L.; Karpeisky, A.; Matulic-Adamic, J.; Haeberli, P.; Sweedler, D. and Usman, N., *Nucleic Acids Res.,* **1995**, *23*, 4434.
5. Stojanovic, A. and Renaud, P., *Helv. Chim. Acta,* **1998**, *81*, 353.
6. Francisco, C. G.; González, C. C.; Paz, N. R. and Suárez, E., *Org. Lett.,* **2003**, *5*, 4171.
7. Mootoo, D.; Wilson, P. and Jammalamadaka, V., *J. Carbohydr. Chem.,* **1994**, *13*, 841.
8. Yamamoto, Y. and Asao, N., *Chem. Rev.,* **1993**, *93*, 2207.
9. Razavi, H. and Polt, R., *J. Org. Chem.,* **2000**, *65*, 5693.

10. (a) Boruwa, J.; Gogoi, N. and Barua, N. C., *Org. Biomol. Chem.,* **2006**, *4*, 3521. (b) Yadav, J. S.; Reddy, M. S. and Prasad, A. R., *Tetrahedron Lett*., **2006**, *47*, 4995. (c) Chandrasekhar, S.; Prakash, S. J. and Shyamsunder, T., *Tetrahedron Lett*., **2005**, *46*, 6651. (d) Kurosu, M. and Lorca, M., *Synlett*, **2005**, 1109. (e) Postema, M. H. D.; Piper, J. L.; Komanduri, V. and Liu, L., *Angew. Chem. Int. Ed.,* **2004**, *43*, 2915. (f) Wender, P. A.; Baryza, J. L.; Brenner, S. E.; Clarke, M. O.; Gamber, G. G.; Horan, J. C.; Jessop, T. C.; Kan, C.; Pattabiraman, K. and Williams, T. J., *Pure Appl. & Chem.,* **2003**, *75*, 143. (g) Evans, D. A. and Connell, B. T., *J. Am. Chem. Soc.,* **2003**, *125*, 10899. (h) De Fatima, A. and Pilli, R. A., *ARKIVOC*, **2003**, 118. (i) Crimmins, M. T., Stanton, M. G. and Allwein S. P., *J. Am. Chem. Soc.,* **2002**, *124*, 5958. (j) Liu, L. and Postema, M. H. D., *J. Am. Chem. Soc.,* **2001**, *123*, 8602. (k) Marshall, J. A. and Palovich, M. R., *J. Org. Chem.,* **1998**, *63*, 4381. (l) Keck, G. E. and Krishnamurthy, D., *Org. Synth.,* **1998**, *75*, 12. (m) Evans, P. A. and Murthy, V. S., *Tetrahedron Lett*., **1998**, *39*, 9627. (n) Lipshutz, B. H.; James, B.; Vance, S. and Carrico, I., *Tetrahedron Lett*., **1997**, *38*, 753. (o) Yu, C. M.; Choi, H. S.; Yoon, S. K. and Jung, W. H., *Synlett,* **1997**, 889. (p) Fürstner, A. and Langemann, K., *J. Am. Chem. Soc.,* **1997**, *119*, 9130. (q) Morimoto, Y.; Iwahashi, M.; Nishida, K.; Hayashi, Y. and Shirahama, H., *Angew. Chem. Int. Ed. Engl.,* **1996**, *35*, 904. (r) Wipf, P.; Kim, Y. and Goldstein, D. M., *J. Am. Chem. Soc.,* **1995**, *117*, 11106. (s) Chen, C. Y. and Hart, D. J., *J. Org. Chem.,* **1993**, *58*, 3840. (t) Campbell, J. A. and Hart, D. J., *Tetrahedron Lett*., **1992**, *33*, 6247. (u) Chen, C. Y. and Hart, D. J., *J. Org. Chem.,* **1990**, *55*, 6236. (v) Keck, G. E. and Castellino, S. J., *J. Am. Chem. Soc*., **1986**, *108*, 3847. (w) Keck, G. E.; Enholm, E. J.; Yates, J. B. and Wiley, M. R., *Tetrahedron,* **1985**, *41*, 4079. (x) Keck, G. E. and Boden, E. P., *Tetrahedron Lett.,* **1984**, *25*, 265.

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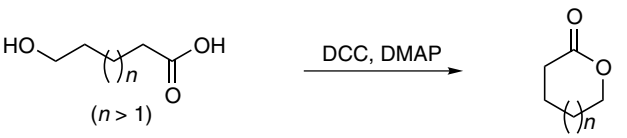
Keck Macrolactonization

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Keck in 1985.[1] It is a carbodiimide[2] (e.g., DCC[3]) promoted esterification to form a macrolactone in the presence of a nitrogenous base (e.g., DMAP,[4] *N*,*N*-dimethylalanine[5]). This reaction has been used in the preparation of a variety of macrolactones, thus is known as the Keck macrolactonization.[3,4b,6]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The reaction promoted by DCC in a catalytic amount of DMAP is outlined here.

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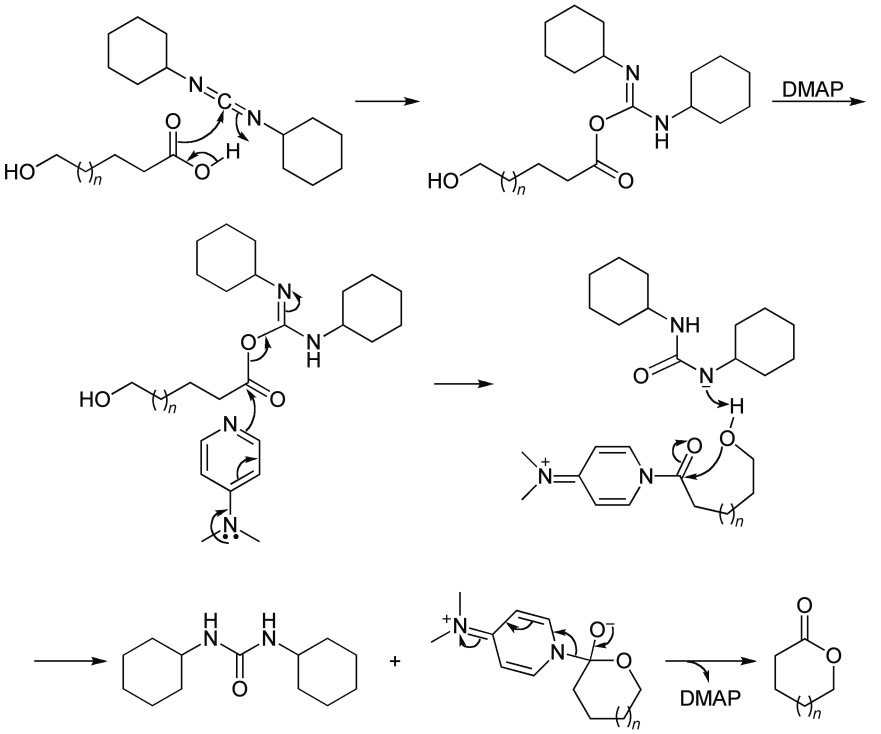


D. MODIFICATION

N/A

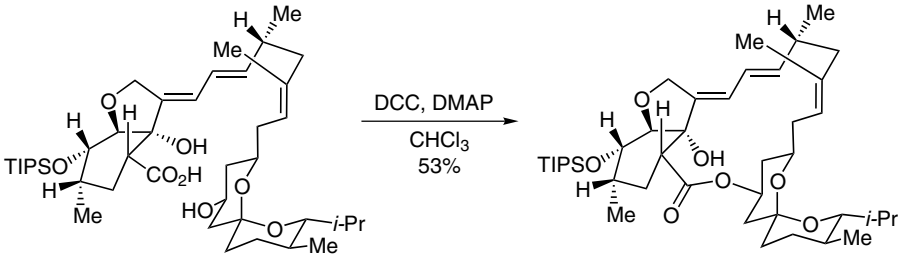
E. APPLICATIONS

This reaction has general application in the preparation of macrolactones.

F. RELATED REACTIONS

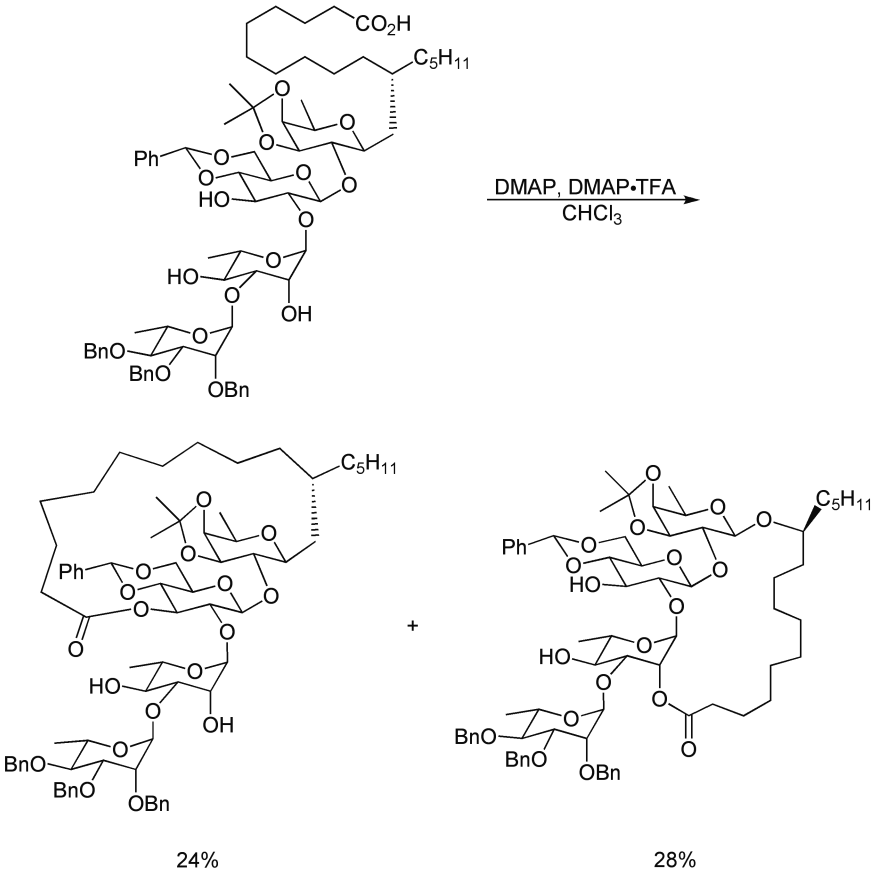
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 6.

A solution of 0.138 g *N*,*N*-dicyclohexylcarbodiimide (DCC, 0.67 mmol), 0.122 g 4-(dimethylamino)pyridine (1.0 mmol), and 0.106 g DMAP·HCl (0.67 mmol) in 350 mL dry $CHCl_3$ (ethanol free) was heated to reflux. Hydroxy acid (0.240 g, 0.33 mmol) in 20 mL dry $CHCl_3$ (ethanol free) was added to the refluxing solution via a syringe pump over a period of 16 h. The long needle was inserted through the condenser and placed directly over the refluxing solution so that the refluxing chloroform washed the substrate droplets forming at its tip. Upon completion of the addition, the flask and syringe containing the substrate were washed by more chloroform (2 × 2 mL), and these solutions were delivered by syringe pump over a period of 1 h. The reaction mixture was cooled to room temperature, and excess DCC was consumed by adding 0.45 mL MeOH and 0.11 mL acetic acid. The resulting solution was stirred at room temperature for 2 h, concentrated in vacuo, and purified by column chromatography on silica gel (0–10% EtOAc/hexanes) to afford macrolactone (0.125 g) as a white foam, in a yield of 53%.



Reference 7.

DMAP (14 mg, 0.11 mmol) and 23 mg DMAP·TFA (0.097 mmol) were combined and azeotroped from benzene. To the dried reagents were added 20 mg DCC (0.097 mmol) and 25 mL EtOH-free $CHCl_3$. The reaction solution was then heated to reflux. In another flask, 25 mg (11*S*)-11-[[(2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-(α-L-rhamnopyranosyl)-(1→2)-(4,6-*O*-benzylidene-β-D-glucopyranosyl)-(1→2)-3,4-*O*-isopro-

pylidene-β-D-fucopyranosyl]oxy]hexadecanoic acid (25 mg, 0.020 mmol) was azeotroped from benzene, dissolved in 7 mL EtOH-free $CHCl_3$, and added to the DMAP solution over 20 h. After the addition was complete, the reaction solution was heated at reflux for 1 h, cooled, and concentrated to 2 mL. The solution was diluted with 25 mL Et_2O, filtered, and concentrated. The residue was purified by chromatography on silica gel with 5 ~ 20% EtOAc in toluene as the eluent to give 6 mg (11*S*)-11-[[(2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-(α-L-rhamnopyranosyl)-(1→2)-(4,6-*O*-benzylidene-β-D-glucopyranosyl)-(1→2)-3,4-*O*-isopropylidene-β-D-fucopyranosyl]oxy]hexadecanoic acid 2_{rha}-lactone as white solid (24%) and 7 mg (11*S*)-11-[[(2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-(α-L-rhamnopyranosyl)-(1 → 2)-(4,6-*O*-benzylidene-β-D-glucopyranosyl)-(1 → 2)-3,4-*O*-isopropylidene-β-D-fucopyranosyl]oxy]hexadecanoic acid 3_{glu}-lactone (28%).

Other reference related to the Keck macrolactonization are cited in the literature.[8]

H. REFERENCES

1. Boden, E. P. and Keck, G. E., *J. Org. Chem.,* **1985**, *50*, 2394.
2. Christie, H. S. and Heathcock, C. H., *Proc. Natl. Acad. Sci.,* **2004**, *101*, 12079.
3. Dai, W.-M.; Guan, Y. C. and Jin, J., *Curr. Med. Chem.,* **2005**, *12*, 1947.
4. (a) Kobayashi, Y.; Kumar, G. B.; Kurachi, T.; Acharya, H. P.; Yamazaki, T. and Kitazume, T., *J. Org. Chem.,* **2001**, *66*, 2011. (b) Evans, D. A.; Ng, H. P. and Rieger, D. L., *J. Am. Chem. Soc.,* **1993**, *115*, 11446.
5. Kigoshi, H.; Suenaga, K.; Mutou, T.; Ishigaki, T.; Atsumi, T.; Ishiwata, H.; Sakakmura, A.; Ogawa, T.; Ojika, M. and Yamada, K., *J. Org. Chem.,* **1996**, *61*, 5326.
6. Crimmins, M. T.; Al-awar, R. S.; Vallin, I. M.; Hollis, W. G.; O'Mahony, R.; Lever, J. G. and Bankaitis-Davis, D. M., *J. Am. Chem. Soc.,* **1996**, *118*, 7513.
7. Larson, D. P. and Heathcock, C. H., *J. Org. Chem.,* **1997**, *62*, 8406.
8. (a) Sabitha, G.; Swapna, R.; Babu, R. S. and Yadav, J. S., *Tetrahedron Lett*., **2005**, *46*, 6145. (b) Ahmed, A.; Hoegenauer, E. K.; Enev, V. S.; Hanbauer, M.; Kaehlig, H.; Öhler, E. and Mulzer, J., *J. Org. Chem.,* **2003**, *68*, 3026. (c) Marino, J. P.; McClure, M. S.; Holub, D. P.; Comasseto, J. V. and Tucci, F. C., *J. Am. Chem. Soc.,* **2002**, *124*, 1664. (d) Hanessian, S.; Ma, J. G. and Wang, W. G., *J. Am. Chem. Soc.,* **2001**, *123*, 10200. (e) Keck, G. E.; Wager, T. T. and McHardy, S. F., *Tetrahedron,* **1999**, *55*, 11755. (f) Sunazuka, T.; Hirose, T.; Harigaya, Y.; Takamatsu, S.; Hayashi, M.; Komiyama, K.; Omura, S.; Sprengeler, P. A. and Smith, A. B., *J. Am. Chem. Soc*., **1997**, *119*, 10247. (g) Keck, G. E.; Savin, K. A. and Weglarz, M. A., *J. Org. Chem*., **1995**, *60*, 3194. (h) Evans, D. A.; Kaldor, S. W. and Jones, T. K., *J. Am. Chem. Soc.,* **1990**, *112*, 7001. (i) Crimmins, M. T.; Hollis, W. G. and Bankaitis-Davis, D, M., *Tetrahedron Lett.,* **1987**, *28*, 3651.

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Kemp Elimination
(Kemp Decarboxylation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Kemp in 1973.[1] It is a general base-catalyzed ring-opening of a benzisoxazole by cleaving a *N*−*O* bond along with the deprotonation of carbon (C-3) to give *o*-cyano phenol derivatives. This reaction is an exothermic concerted reaction[2] involving an E2 mechanism;[2a] therefore, it is commonly known as the Kemp elimination.[2a,3] When a carboxyl group exists on carbon-3, the corresponding reaction also occurs by *N*−*O* cleavage accompanied by the decarboxylation,[3h,4] thus the Kemp elimination for this special case is referred to as Kemp decarboxylation.[3h,4] It has been found that this reaction is highly sensitive to medium effects. For example, the decarboxylation of 3-carboxy benzisoxazole is over 10^8 times faster in an aprotic dipolar solvent (e.g., CH_3CN) than that in an aqueous solution.[5] This dramatic rate enhancement is due to the destabilization of the carboxylate ion in microenvironments that are deficient in hydrogen bond donors (e.g., in CH_3CN).[3f] As a result, some other materials that can mimic the microenvironment to facilitate the deprotonation can be used as catalysts for the Kemp elimination, such as serum albumins,[2b,3a,3b,3g,3h,6] amino-cyclodextrins,[3i,7] antibody 38C2,[3g] commercially available coals (especially those of lower commercial value),[2a] and vesicles formed from dimethyldioctadecylammonium chloride.[3e] On the other hand, because the Kemp elimination is a simple, one-step transformation without any intermediate[2a] and is sensitive to the medium,[2] it has been selected as a model for studying many enzyme-catalyzed proton transfer reactions,[2a] in which the carboxylate, amino, and imidazole group of amino acid residues (histidine) on enzymes can function as general bases. Carboxyl, sulfurhydryl and hydroxyl groups, on the other hand, can function as general acids. Because of the effect of microenvironment, enzymes can catalyze many reactions that would not be possible under pure chemical conditions, such as the enolization of ketones,[8] of which the α-proton has

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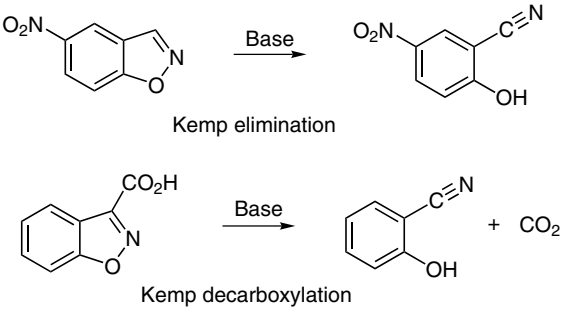
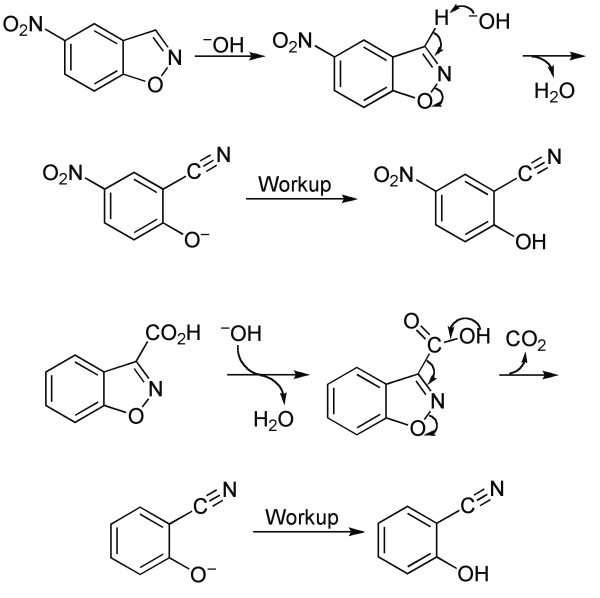
a pKa of 16–24,[1a,9] indicating the α-proton would not be deprotonated under neutral conditions. However, many reactions in which ketones or aldehydes participate in biological systems occur easily in the presence of an enzyme, such as *Aldol Reactions*. This phenomenon has become an interesting and extensively debated topic, known as the hard-soft acid-base (HSAB) theory.[10]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The mechanism of both the Kemp elimination and Kemp decarboxylation are outlined here.



D. MODIFICATION

This reaction has been modified for the use of different catalysts, such as albumin, cyclodextrin, and even commercial coals.

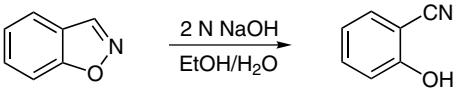
E. APPLICATIONS

This reaction does not show much application in actual organic synthesis but functions as an important model in enzyme studies.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 1b.

A solution of 0.5 g benzisoxazole in 5–8 mL ethanol and 5 mL water was mixed with 2 *N* NaOH (15 mL) solution and allowed to stand for 10 min, at which time HC1 was added to bring the pH to 1. The solution was extracted with dichloromethane (3 × 10 mL), and the organic layers were combined, dried, and evaporated. The residue was recrystallized from water, water-ethanol, or acetonitrile; dried under vacuum for 6 h, and stored in foil-wrapped vials in a desiccator. No yield was given in the original reference.

Other references related to the Kemp elimination are cited in the literature.[11]

H. REFERENCES

1. (a) Kemp, D. S. and Casey, M. L., *J. Am. Chem. Soc.,* **1973**, *95*, 6670. (b) Casey, M. L.; Kemp, D. S.; Paul, K. G. and Cox, D. D., *J. Org. Chem.,* **1973**, *38*, 2294.
2. (a) Shulman, H. and Keinan, E., *Org. Lett.,* **2000**, *2*, 3747. (b) Hollfelder, F.; Kirby, A. J.; Tawfik, D. S.; Kikuchi, K. and Hilvert, D., *J. Am. Chem. Soc.* **2000**, *122*, 1022.
3. (a) Boucher, G.; Robin, S.; Fargeas, V.; Dintinger, T.; Mathé-Allainmat, M.; Lebreton, J. and Tellier, C., *ChemBioChem,* **2005**, *6*, 807. (b) Bornscheuer, U. T.; and Kazlauskas, R. J., *Angew. Chem. Int. Ed.,* **2004**, *43*, 6032. (c) Klijn, J. E. and Engberts, J. B. F. N., *Org. Biomol. Chem.,* **2004**, *2*, 1789. (d) Robins, S.; Petrov, K.; Dintinger, T.; Kujumdzieva, A.; Tellier, C. and Dion, M., *Molecular Immunology,* **2003**, *39*, 729. (e) Klijn, J. E. and Engberts, J. B. F. N., *J. Am. Chem. Soc.,* **2003**, *125*, 1825. (f) Hollfelder, F.; Kirby, A. J. and Tawfik, D. S., *J. Org. Chem.,* **2001,** 66, 5866. (g) James, L. C. and Tawfik, D. S., *Protein Science,* **2001**, *10*, 2600. (h) Stevenson, J. D. and Thomas, N. R., *Nat. Prod. Rep.*, **2000**, *17*, 535. (i) McCracken, P. G.; Ferguson, C. G.; Vizitiu, D.; Walkinshaw, C. S.; Wang, Y. and Thatcher, G. R. J., *J. Chem. Soc., Perkin Trans. II,* **1999**, 911. (j) Genre-Grandpierre, A.; Tellier, C.; Loirat, M.-J.; Blanchard, D.; Hodgson, D. R. W.; Hollfelder, F. and Kirby, A. J., *Bioorg. Med. Chem. Lett.,* **1997**, *7*, 2497. (k) Hollfelder, F.; Kirby, A. J. and Tawfik, D. S., *Nature,* **1996**, *383*, 60.
4. Acevedo, O. and Jorgensen, W. J., *J. Am. Chem. Soc.,* **2005**, *127*, 8829.

5. Kemp, D. S.; Cox, D. D. and Paul, K. G., *J. Am. Chem. Soc.,* **1975**, *97*, 7312.
6. Benedetti, F.; Berti, F.; Donati, I. and Fregonese, M., *Chem. Commun.,* **2002**, 828.
7. Rao, K. R.; Nageswar, Y. V. D.; Krishnaveni, V. S. and Surendra, K., *Adv. Org. Synth.,* **2005**, *1*, 301.
8. (a) Davioud-Charvet, E.; McLeish, M. J.; Veine, D. M.; Giegel, D.; Arscott, L. D.; Andricopulo, A. D.; Becker, K.; Müller, S.; Schirmer, R. H.; Williams, C. H. and Kenyon, G. L., *Biochemistry,* **2003**, *42*, 13319. (b) Oliva, M.; Safont, V. S. and Andrés, J., *J. Phys. Chem. A,* **2001**, *105*, 9243. (c) Goncalves, O.; Dintinger, T.; Lebreton, J.; Blanchard, D. and Tellier, C., *Biochem. J.,* **2000**, *346*, 691. (d) Jez, J. M. and Penning, T. M., *Biochemistry,* **1998**, *37*, 9695.
9. (a) Zhao, Y. Y. and Bordwell, F. G., *J. Org. Chem.,* **1995**, *60*, 3932. (b) Keeffe, J. R.; Kresge, A. J. and Yia, Y., *J. Am. Chem. Soc.,* **1988**, *110*, 1982. (c) Ross, A. M.; Whalen, D. L.; Eldin, S. and Pollack, R. M., *J. Am. Chem. Soc.,* **1988**, *110*, 1981. (d) Bordwell, F. G.; Bartmess, J. E.; Drucker, G. E.; margolin, Z. and Matthews, W. S., *J. Am. Chem. Soc.,* **1975**, *97*, 3226.
10. (a) Olah, J.; Proft, F. D.; Veszpremi, T. and Geerlings, P., *J. Phys. Chem. A.,* **2005**, *109*, 1608. (b) Deka, R. C.; Ajitha, D. and Hirao, K., *J. Phys. Chem. B.,* **2003**, *107*, 8574. (c) Loos, R.; Kobayashi, S. and Mayr, H., *J. Am. Chem. Soc.,* **2003**, *125*, 14126. (d) Chandrakumar, K. R. S. and Pal, S., *J. Phys. Chem. A.,* **2003**, *107*, 5755. (e) Chandrakumar, K. R. S. and Pal, S., *J. Phys. Chem. A.,* **2002**, *106*, 5737. (f) Chandrakumar, K. R. S. and Pal, S., *J. Phys. Chem. A.,* **2002**, *106*, 11775. (g) Roy, R. K.; Tajima, N. and Hirao, K., *J. Phys. Chem. A.,* **2001**, *105*, 2117. (h) Vetrivel, R.; Deka, R. Ch. and Pal, S., *J. Phys. Chem. A.,* **1999**, *103*, 5978. (i) Mendez, F. and Garcia-Garibay, M. A., *J. Org. Chem.,* **1999**, *64*, 7061. (j) Krishnamurty, S.; Roy, R. K.; Vetrivel, R.; Iwata, S. and Pal, S., *J. Phys. Chem. A.,* **1997**, *101*, 7253. (k) Li, Y. and Evans, J. N. S., *J. Am. Chem. Soc.,* **1995**, *117*, 7756. (l) Douglas, J. and Kollman, P., *J. Phys. Chem.,* **1981**, *85*, 2717. (m) Ho, T.-L., *Chem. Rev.,* **1975**, *75*, 1. (n) Drago, R. S., *Inorg. Chem.,* **1973**, *12*, 2211. (o) Drago, R. S. and Kabler, R. A., *Inorg. Chem.,* **1972**, *11*, 3144.
11. (a) Asaad, N.; den Otter, M. J. and Engberts, J. B. F. N., *Org. Biomol. Chem.,* **2004**, *2*, 1404. (b) Klijn, J. E. and Engberts, J. B. F. N., *Org. Biomol. Chem.,* **2004**, *2*, 1789. (c) Hu, Y. F.; Houk, K. N.; Kikuchi, K.; Hotta, K. and Hilvert, D., *J. Am. Chem. Soc.,* **2004**, *126*, 8197. (d) Kirby, A. J.; Hollfelder, F. and Tawfik, D. S., *Appl. Biochem. Biotech.,* **2000**, *83*, 173. (e) Golinelli-Pimpaneau, B.; Goncalves, O.; Dintinger, T.; Blanchard, D.; Knossow, M. and Tellier, C., *Proc. Natl. Acad. Sci.,* **2000**, *97*, 9892. (f) Liu, X.-C. and Mosbach, K., *Macromol. Rapid Commun.*, **1998**, *19*, 671. (g) Hollfelder, F.; Kirby, A. J. and Tawfik, D. S., *J. Am. Chem. Soc.,* **1997**, *119*, 9578. (h) Thorn, S. N.; Daniels, R. G.; Auditor, M.-T. M. and Hilvert, D., *Nature,* **1995**, *373*, 228. (i) Reichardt, C., *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed., VCH Publishers, Weinheim, **1988**.

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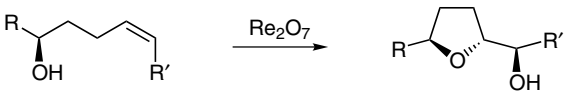
Kennedy Oxidative Cyclization

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Kennedy in 1992.[1] It is a highly stereoselective conversion of 5-hydroxyl alkene into a *trans*-tetrahydrofuran derivative with *erythro* stereochemistry at the two vicinal carbinol centers via rhenium (VII) oxide (Re_2O_7) promoted *syn*-oxidative cyclization.[2] Therefore, it is referred to as the Kennedy oxidative cyclization.[3] During this reaction, the hydroxy group of substrate binds to Re_2O_7, and the substrate itself turns into an alkoxyperrhenate intermediate along with the formation of 1 eq. perrhenic acid ($HOReO_3$); then the Re=O double bond couples with carbon-carbon double bond via [2+2] addition and releases the tetrahydrofuran derivative via reductive elimination.[4] It is interesting that the comparable oxidative cyclization promoted with $VO(acac)_2$ yields a *cis*-tetrahydrofuran ring with *threo* stereochemistry at the two vicinal carbinol centers.[4] This reaction is very powerful in converting polyenes into polyoxygenated chiral derivatives, especially in combination with the Sharpless asymmetric oxidation,[3] and has been successfully applied to the synthesis of many acetogenins of the first and second subgroups, such as solamin, reticulatacin, asimicin, bullatacin, trilobacin, and trilobin.[3b]

B. GENERAL REACTION SCHEME



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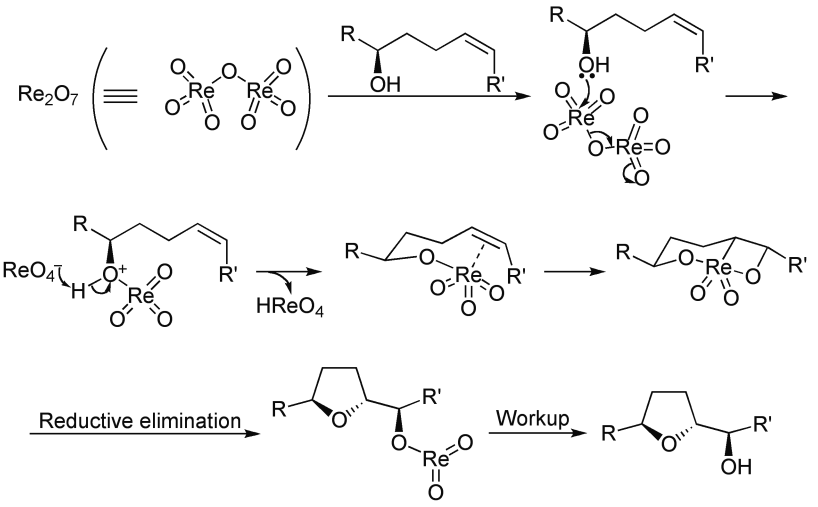
C. PROPOSED MECHANISMS



D. MODIFICATION

N/A

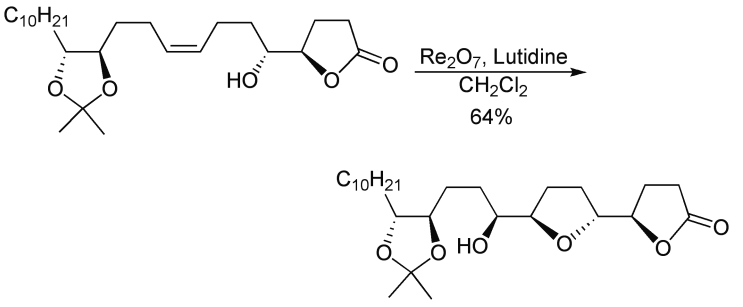
E. APPLICATIONS

This reaction has been used to prepare tetrahydrofuran derivatives.

F. RELATED REACTIONS

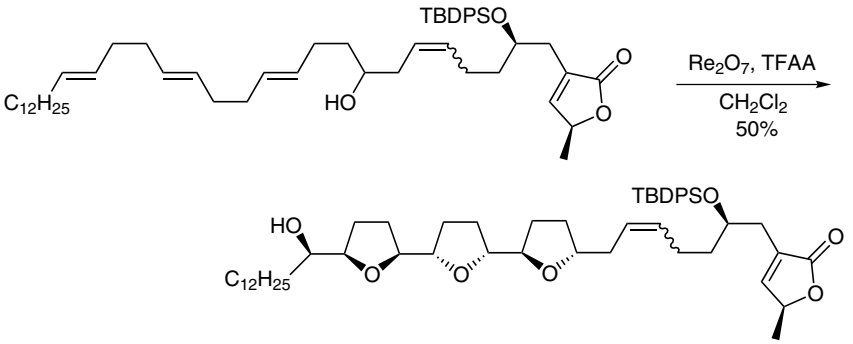
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3a.

To a mixture of 20 mL dry CH_2Cl_2, 2.4 mL lutidine (20.4 mmol), and 1.0 g (*cis*-4*R*,5*R*,12*R*,13*R*)-5-hydroxy-12,13-isopropylidenedioxytricosa-8-en-1,4-olide (2.7 mmol) was added 3.3 g Re_2O_7 (6.81 mmol) in portions. The mixture was stirred overnight at room temperature and then quenched by dropwise addition of 8 mL saturated $NaHCO_3$ solution and 8 mL 35% H_2O_2. After being stirred for 20 min, the mixture was extracted with CH_2Cl_2, the organic layer was washed with water and dried over $MgSO_4$; the solvents were removed under reduced pressure, and the residue was purified by silica gel column chromatography using an eluent of hexanes/EtOAc (3:1) to give 0.654 g (4*R*,5*R*,8*R*,9*S*,12*R*,13*R*)-9-hydroxy-12,13-isopropylidenedioxy-5,8-oxidotricosa-1,4-olide as a colorless oil, in a yield of 64%.



Reference 3b.

Re_2O_7 (230 mg, 0.47 mmol) was placed in a dry flask under argon, then 10 mL dry THF was added followed by 0.12 mL TFAA (0.85 mmol), and the mixture was stirred at room temperature for 1 h. Solvents were removed under reduced pressure at 0°C, and the residue was washed twice with cold dry pentane. Then 5 mL CH_2Cl_2 and 0.09 mL TFAA (0.64 mmol) were added at 0°C, followed by 95 mg alcohol (0.12 mmol). The resulting mixture was stirred at 0°C to room temperature for 3 h and then quenched by the slow addition of 2 mL saturated $NaHCO_3$ solution, followed by 0.3 mL 35% H_2O_2. The aqueous solution was extracted with ether. Upon removal of the solvent under reduced pressure, the residue was purified on silica gel column chromatography using hexanes/EtOAc (4:1) as the eluent to afford 50 mg product, in a yield of 50%.

Other references related to the Kennedy oxidative cyclization are cited in the literature.[5]

H. REFERENCES

1. (a) Tang, S. and Kennedy, R. M., *Tetrahedron Lett.,* **1992**, *33*, 3729. (b) Tang, S. and Kennedy, R. M., *Tetrahedron Lett.,* **1992**, *33*, 5299. (c) Tang, S. and Kennedy, R. M., *Tetrahedron Lett.,* **1992**, *33*, 5303.
2. Towne, T. B. and McDonald, F. E., *J. Am. Chem. Soc.,* **1997**, *119*, 6022.
3. (a) Avedissian, H.; Sinha, S. C.; Yazbak, A.; Sinha, A.; Neogi, P.; Sinha, S. C. and Keinan, E., *J. Org. Chem.,* **2000**, *65*, 6035. (b) Sinha, S. C.; Sinha, A.; Sinha, S. C. and Keinan, E., *J. Am. Chem. Soc.,* **1997**, *119*, 12014. (c) Sinha, S. C.; Sinha, A.; Yazbak, A. and Keinan, E., *J. Am.*

Chem. Soc., **1996**, *118*, 7640. (d) Sinha, S. C.; Sinha-Bagchi, A. and Keinan, E., *J. Am. Chem. Soc.,* **1995**, *117*, 1447.

4. Keinan, E.; Sinha, A.; Yazbak, A.; Sinha, S. C. and Sinha, S. C., *Pure & Appl. Chem.,* **1997**, *69*, 423.
5. (a) Cecil, A. R. L. and Brown, R. C. D., *Org. Lett.,* **2002**, *4*, 3715. (b) Sinha, S. C.; Sinha, S. C. and Keinan, E., *J. Am. Chem. Soc.,* **1998**, *120*, 4017. (c) Morimoto, Y. and Iwai, T., *J. Am. Chem. Soc.,* **1998**, *120*, 1633. (d) Sinha, S. C.; Sinha-Bagchi, A.; Yazbak, A. and Keinan, E., *Tetrahedron Lett.,* **1995**, *36*, 9257. (e) McDonald, F. E. and Towne, T. B., *J. Org. Chem.,* **1995**, *60*, 5750. (f) Boyce, R. S. and Kennedy, R. M., *Tetrahedron Lett.,* **1994**, *35*, 5133.

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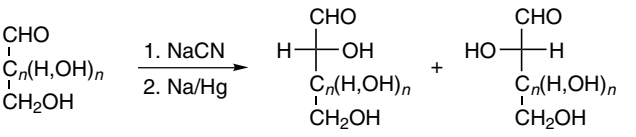
Kiliani-Fischer Cyanohydrin Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Kiliani in 1885,[1] and then extended by Fischer in 1889.[2] It is the conversion of an aldose into two one-carbon-higher epimeric homologs, which involves a nucleophilic addition of a cyanide to the terminal carbonyl group of an aldose, hydrolysis of cyanohydrin, and reduction of the resulting lactone. Therefore, it is known as the Kiliani synthesis,[3] Kiliani-Fischer reaction,[4] Kiliani cyanohydrin synthesis,[5] Kiliani-Fischer synthesis,[3a,6] Kiliani-Fischer cyanohydrin synthesis,[3a,7] Fischer-Kiliani cyanohydrin synthesis,[8] or cyanohydrin reaction.[9] This reaction is carried out under alkaline conditions[9] (e.g., at pH > 9.1) to maintain a high effective concentration of cyanide ion;[6a] in addition, the resulting cyanohydrins are not isolated[6a] but hydrolyzed to aldonic acid lactones,[9] which are then reduced either by sodium amalgam[3b,4,5,6a,9] or catalytic hydrogenation[6a] or with $NaBH_4$ at pH 3–4 in an aqueous solution[6a] to yield higher homologs. This reaction is the traditional[9] and earliest[6a] carbohydrate synthesis without protection and is used commonly for the preparation of rare or unnatural carbohydrates as well as sugars labeled with ^{13}C or ^{14}C at the end.[3a,8]

B. GENERAL REACTION SCHEME



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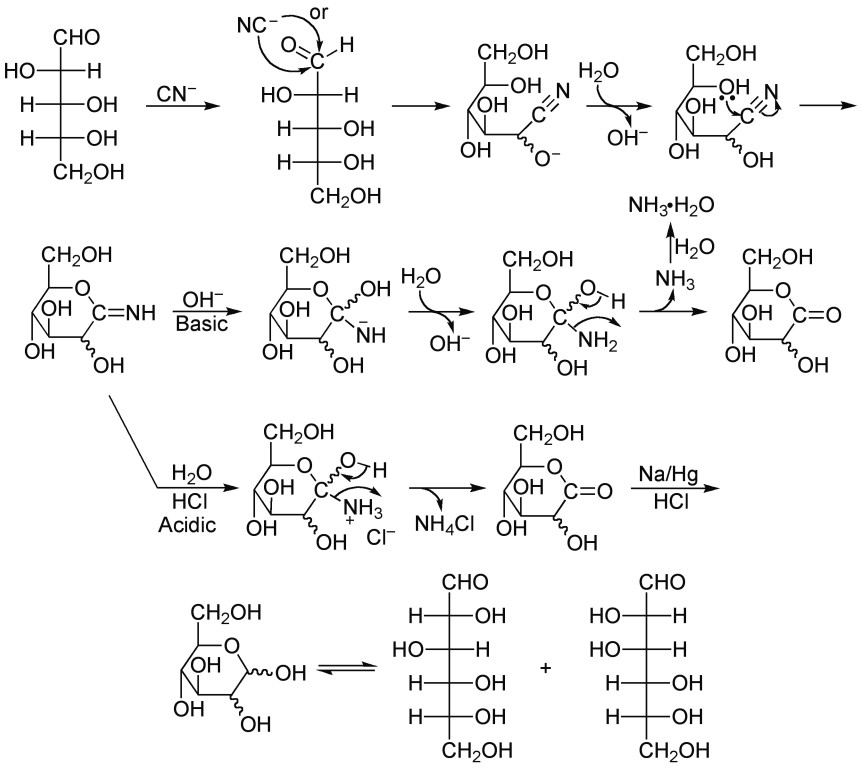
C. PROPOSED MECHANISMS

A reaction to prepare D-mannose and D-glucose from D-arabinose is used to demonstrate the mechanism.



D. MODIFICATION

This reaction is modified by replacing sodium cyanide with thiazole.[7a]

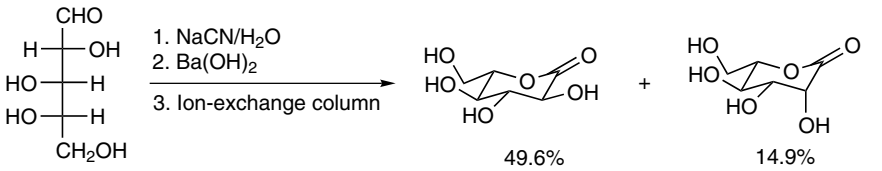
E. APPLICATIONS

This reaction has been used to prepare higher-order aldoses and isotope-labeled carbohydrates.

F. RELATED REACTIONS

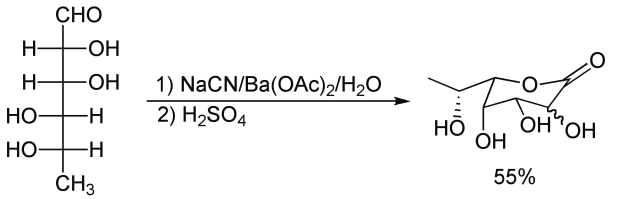
This reaction is related to the *Urech Cyanohydrin Method.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 3c.

An ice-cooled solution containing 30 g pure L-arabinose and 13 g NaCN in 300 mL water was kept near 5°C in a refrigerator until the Fehling test became faint (4 days). $Ba(OH)_2 \cdot 10H_2O$ (10 g) was added, and the solution was boiled with renewal of water to expel all ammonia for 3–4 h. The barium was then removed as carbonate after the addition of activated carbon, and the sodium ions were adsorbed by passing the solution through an ion-exchange column. Concentration to a syrup, lactonization, and solution of the residue in methyl cellosolve led to only 2.5 g crystalline L-mannoic γ-lactone. Removal of solvent from the mother liquor, conversion of the acidic residue to its neutral barium salt, and crystallization from aqueous ethanol produced 26.1 g barium L-gluconate. Removal of barium ion from the mother liquor permitted the recovery of 5 g L-mannonic lactone. By this treatment, 49.6% L-gluconic and 14.9% L-mannonic acid were prepared.



Reference 3e.

To 400 g ice were added successively 100 g rhamnose hydrate (200 mL), 105 g $Ba(OAc)_2$ (in 150 mL solution), and 32 g NaCN (100 mL). After the mixture was kept 1 h and then in the refrigerator for 70 h, 122 g $Ba(OH)_2 \cdot 8H_2O$ was added, and the mixture was boiled for 6 h. Water was then added to maintain about half the original volume. The barium was balanced with H_2SO_4, 15 g carbon was added, the mixture was boiled for 30 min. $BaSO_4$ was filtered off and washed with water. Then 141.6 mL 4.61 N H_2SO_4 was added to balance the sodium ions, and the combined solutions from three runs were distilled to dryness under reduced pressure. The residue was mixed with 500 mL 95% ethanol; the distillation was repeated, and the organic products were extracted from sodium sulfate by hot 95% ethanol followed by methanol. Concentration of the alcohol solution under reduced pressure gave several crops of colorless crystals and a syrup, which yielded more crystals with acetone as the solvent. A total of 200 g α-rhamnohexonic acid, its lactone, and ester were yielded after air-drying. To convert the acid and ester into lactone, a solution of the crystals in 2 L water was evaporated to dryness on the steam bath. The operation was repeated with less water, and the residue was heated at 100°C for several hours, washed with cold acetone, and dried at 95–100°C for 3 h, to give 175 g rhamnohexonic lactone, in a yield of 55%.

Other references related to the Kiliani-Fischer cyanohydrin synthesis are cited in the literature.[10]

H. REFERENCES

1. Kiliani, H., *Ber.,* **1885**, *18*, 3066.
2. Fischer, E., *Ber.,* **1889**, *22*, 2204.
3. (a) Blazer, R. M. and Whaley, T. W., *J. Am. Chem. Soc.,* **1980**, *102*, 5082. (b) Serianni, A. S.; Pierce, J. and Barker, R., *Biochemistry,* **1979**, *18*, 1192. (c) Hudson, C. S., *J. Am. Chem. Soc.,* **1951**, *73*, 4498. (d) Hudson, C. S.; Hartley, O. and Purves, C. B., *J. Am. Chem. Soc.,* **1934**, *56*, 1248. (e) Jackson, E. L. and Hudson, C. S., *J. Am. Chem. Soc.,* **1934**, *56*, 2455.
4. Serianni, A. S.; Nunez, H. A. and Barker, R., *J. Org. Chem.,* **1980**, *45*, 3329.
5. Merrill, A. T.; Hann, R. M. and Hudson, C. S., *J. Am. Chem. Soc.,* **1943**, *65*, 994.
6. (a) Li, C.-J., *Chem. Rev*., **2005**, *105*, 3095. (b) Adje, N.; Vogeleisen F. and Uguen D., *Tetrahedron Lett.,* **1996**, *37*, 5893.
7. (a) Dondoni, A. and Marra, A., *Chem. Rev.,* **2004**, *104*, 2557. (b) Kjoelberg, O. and Vellan, E., *Acta Chem. Scand.,* **1966**, *20*, 2081. (c) Sowden, J. C. and Strobach, D. R., *J. Am. Chem. Soc.,* **1960**, *82*, 956.
8. Kohn, P.; Samaritano, R. H. and Lerner, L. M., *J. Am. Chem. Soc.,* **1965**, *87*, 5475.
9. Barker, R. and Serianni, A. S., *Acc. Chem. Res.,* **1986**, *19*, 307.
10. (a) Hernández, R.; León, E. I.; Moreno, P.; Riesco-Fagundo, C. and Suárez, E., *J. Org. Chem.,* **2004**, *69*, 8437. (b) Roos, J. and Effenberger, F., *Tetrahedron: Asymmetry,* **1999**, *10*, 2817. (c) Adjé, N.; Vogeleisen, F. and Uguen, D., *Tetrahedron Lett.,* **1996**, *37*, 5893. (d) Varma, R. and French, D., *Carbohydr. Res.,* **1972**, *25*, 71. (e) Kohn, P.; Samaritano, R. H. and Lerner, L. M., *J. Am. Chem. Soc.,* **1964**, *86*, 1457. (f) Sugihara, J. M.; Teerlink, W. J.; MacLeod, R.; Dorrence, S. M. and Springer, C. H., *J. Org. Chem.,* **1963**, *28*, 2079. (g) Kuhn, R. and Klesse, P., *Ber.,* **1958**, *91*, 1989. (h) Mowry, T., *Chem. Rev.,* **1948**, *42*, 239. (i) Wolfrom, M. L.; Thompson, A. and Hooper, I. R., *J. Am. Chem. Soc.,* **1946**, *68*, 2343. (j) Hudson, C. S., *Adv. Carbohydr. Chem.,* **1945**, *1*, 2. (k) Rosanoff, M. A., *J. Am. Chem. Soc.,* **1906**, *28*, 114. (l) Kiliani, H., *Ber.,* **1887**, *20*, 282. (m) Kiliani, H., *Ber.,* **1886**, *19*, 221. (n) Kiliani, H., *Ber.,* **1886**, *19*, 767. (o) Kiliani, H., *Ber.,* **1886**, *19*, 772. (p) Kiliani, H., *Ber.,* **1886**, *19*, 1128. (q) Kiliani, H., *Ber.,* **1886**, *19*, 3029.

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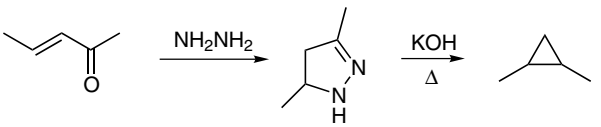
Kishner Decomposition

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Kishner in 1911.[1] It is the preparation of cyclopropane derivatives by decomposition of pyrazolines formed from hydrazine and α,β-unsaturated ketones or aldehydes. Therefore, it is known as the Kishner reaction,[2] Kishner decomposition,[3] or Kishner method.[4] In addition, this reaction has been modified to prepare pyrazoline intermediates from diazomethane and unsaturated carbonyl compounds, such as maleic and fumaric esters, resulting in an ester group in the *trans* position. However, when maleic anhydride or maleimide is used, the corresponding pyrazoline is formed with carbonyl groups in the *cis* configuration.[5] It has been found that the stability of pyrazolines varies considerably, decomposing to cyclopropanes at different rates.[5] Moreover, the transformation of pyrazolines into cyclopropanes can be catalyzed by a trace amount of mercuric ion.[5]

B. GENERAL REACTION SCHEME



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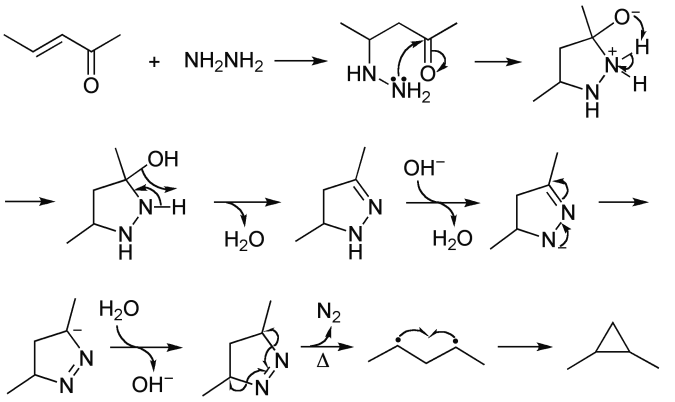
C. PROPOSED MECHANISMS



D. MODIFICATION

The preparation of pyrazoline has been modified by using unsaturated carbonyl compounds and diazomethane.[5]

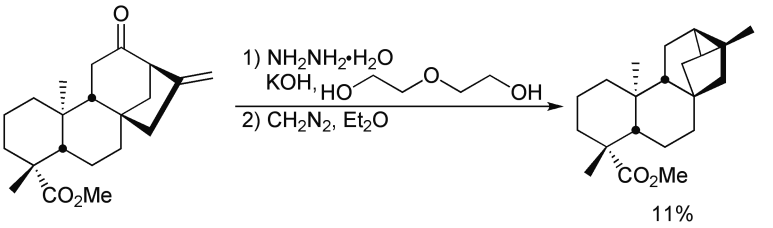
E. APPLICATIONS

This reaction has been used in the preparation of cyclopropane derivatives.

F. RELATED REACTIONS

N/A

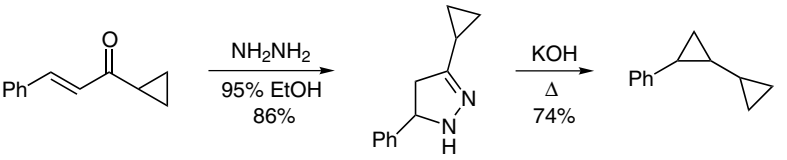
G. CITED EXPERIMENTAL EXAMPLES



Reference 6.

(±) Methyl 12-oxokaur-16-en-19-oate (43.7 mg, 0.132 mmol) was dissolved in 4 mL bis-(ethylene glycol), and then 1 mL $NH_2NH_2 \cdot H_2O$ (20.62 mmol) was added. The resulting mixture was refluxed at 135°C for 2 h. After the mixture was cooled to room temperature, 83.1 mg KOH (1.26 mmol) was added at room temperature, and the mixture was heated to 200°C over a period of 2 h. After being heated for 6.5 h, 4 mL 5% HCl was added at room

temperature, and then the resulting mixture was extracted with EtOAc. The organic layer was washed with 2 mL H_2O and brine, dried, and evaporated to leave 32.1 mg of a white solid, which was taken up into 2 mL Et_2O. The resulting solution was treated with an ethereal solution of diazomethane at room temperature. After 1 h of stirring at room temperature, AcOH was added until the evolution of nitrogen gas ceased. Saturated K_2CO_3 (1 mL) was added, and the mixture was extracted with Et_2O. The ethereal layer was washed with brine, dried, and evaporated to afford a white solid. Chromatography of the residue on a column of silica gel impregnated with 30% silver nitrate with a 1:3 mixture of benzene/petroleum ether as a solvent furnished 4.6 mg (±)-methyl trachyloban-19-oate, in a yield of 11%.



Reference 7.

Styryl cyclopropyl ketone (42 g, 0.245 mol) was added to a solution of 26 mL aqueous hydrazine (0.42 mol) in 70 mL 95% ethanol. The mixture became warm and acquired a green color. It was allowed to stand for 45 min, and then was warmed on the steam bath for 1 h, after which excess hydrazine and solvent were removed under reduced pressure. Distillation of the residue at 164°C (1 mmHg) gave 37.8 g 3-cyclopropyl-5-phenyl-2-pyrazoline as a light green liquid, in a yield of 86%. To a 100-mL round-bottomed flask equipped for distillation and immersed in a metal bath, was added 7.2 g KOH and 3.2 g platinized asbestos. When the bath was heated to 220°C, 37.8 g 3-cyclopropyl-5-phenyl-2-pyrazoline was added slowly. After the rapid evolution of nitrogen ceased, the product was distilled from the reaction mixture at 92–96°C (0.8 mmHg), and 22.5 g 2-phenylbicyclopropyl was obtained, in a yield of 74%.

Other references related to the Kishner decomposition are cited in the literature.[8]

H. REFERENCES

1. Kishner, N. M. and Zavadovskii, A., *J. Russ. Phys. Chem. Soc.,* **1911**, *43*, 1132.
2. Katsiobachvili, Ya. R.; Tsodikov, M. V.; Krapivin, A. M. and Shishkina, M. V., *Russ. Chem. Bull. (Hist. Arch.),* **1982**, *31*, 2457.
3. (a) Katsobashvili, Ya. R.; Kachalova, V. B.; Tsodikov, M. V.; Koshevnik, A. Yu. And shishkin, M. V., *Russ. Chem. Bull. (Hist. Arch.),* **1981**, *30*, 2299. (b) Grandberg, I. I.; Kost, A. N.; Krasnoshchek, A. P. and Moskalenko, V. A., *Chem. Heterocycl. Comp. (Hist. Arch.),* **1971**, *4*, 644.
4. Meshcheryakov, A. P.; Petrova, L. V. and Glukhovtsev, V. G., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1961**, 114.
5. Baltzly, R.; Mehta, N. B.; Russell, P. B.; Brooks, R. E.; Grivsky, E. M. and Steinberg, A. M., *J. Org. Chem.,* **1961**, *26*, 3669.
6. Toyota, M.; Wada, T.; Fukumoto, K. and Ihara, M., *J. Am. Chem. Soc.,* **1998**, *120*, 4916.
7. Smith, L. I. and Rogier, E. R., *J. Am. Chem. Soc.,* **1951**, *73*, 3840.

8. (a) Hoffmann, J. M.; Graham, K. J. and Rowell, C. F., *J. Org. Chem.,* **1975**, *40*, 3005. (b) Crawford, R. J. and Ohno, M., *Can. J. Chem.,* **1974**, *52*, 3134. (c) Crawford, R. J. and Tokinaga, H., *Can. J. Chem.,* **1974**, *52*, 4033. (d) House, H. O. and Blankley, C. J., *J. Org. Chem.,* **1968**, *33*, 47. (e) Kostyanovskii, R. G.; Solodovnikov, S. P. and Yuzhakova, O. A., *Russ. Chem. Bull. (Hist. Arch.),* **1966**, *15*, 696. (f) Hammond, G. S. and Todd, R. W., *J. Am. Chem. Soc.,* **1954**, *76*, 4081. (g) Rogers, M. T., *J. Am. Chem. Soc.,* **1947**, *69*, 2544. (h) Davidson and Feldman, *J. Am. Chem. Soc.,* **1944**, *66*, 488. (i) Kishner, N. M., *J. Russ. Phys. Chem. Soc.,* **1912**, *44*, 165. (j) Kishner, N. M., *J. Russ. Phys. Chem. Soc.,* **1912**, *44*, 849. (k) Kishner, N. M., *J. Russ. Phys. Chem. Soc.,* **1913**, *45*, 949. (l) Kishner, N. M., *J. Russ. Phys. Chem. Soc.,* **1913**, *45*, 957. (m) Kishner, N. M., *J. Russ. Phys. Chem. Soc.,* **1913**, *45*, 987.

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Knoevenagel Condensation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Emil Knoevenagel in 1894.[1] It is a nucleophilic addition of a compound with an active methylene component to a ketone or aldehyde, followed by the elimination of water to form an olefin. Therefore, it is generally known as the Knoevenagel condensation.[2,3] Occasionally, it is also referred to as the Knoevenagel reaction.[2d,2x,2jj,2ll,4] For the condensation between compounds with two active methylene groups and two carbonyl groups to form polymers, the corresponding condensation is called the Knoevenagel condensation polymerization[2p,5] or Knoevenagel polycondensation.[6] This is an atom-economic and cleaner tool for the synthesis of α,β-unsaturated compounds.[2d] Theoretically, this reaction is an extension of aldol addition and is reversible.[2ll] The yield of this reaction depends not only on the relative reactivity of the reactants, the strength of the bases employed, and the nature of solvents,[2y] but also on the removal of the formed water during the reaction.[2ll] Essentially, the methylene group can be activated by at least one electron-withdrawing group, such as nitro, cyano, carbonyl, or sulfonyl group. As a result, the compounds with any combination of these electron-withdrawing groups adjacent to a methylene group can function as nucleophiles, including malonic acid,[2a,2w,2hh,7] malonic esters (diethyl malonate,[2b,4h] dimethyl malonate[8]), malonic amides,[2v] cyclohexa-1,3-dione,[9] Meldrum's acid,[2b,2i,2t] β-ketoacid,[2r] β-ketoester[2v] (ethyl acetoacetate[2ll]), β-ketoamide,[2x] ethyl cyanoacetate,[2jj,2ll] malononitrile,[2u,2bb,2jj] phenylcinnamonitriles,[2q] *o*-nitroarylacetonitriles,[2ee] cyanoacetamides,[2v] oxindole,[2ff] benzene-1,4-diacetonitrile, benzene-2,5-bis(methoxy)benzene-1,4-diacetonitrile,[2n,2p,2y] isatin,[10] homophthalic acid system,[11] α-perfluoroalkanesulfonyl acetate esters or α-keto aryl sulfones,[2m] α-keto sulfones,[2s] and keto-thioester.[12] On the other hand, the carbonyl compounds, mostly aldhydes, applied for this reaction are acrolein,[2a] citronellal,[2j]

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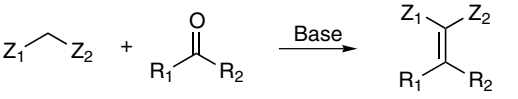
2-hydroxybenzaldehydes,[2b] (*R*)-2-(*tert*-butyldimethylsiloxymethoxy) propanal,[2f,2x] α-alkoxyaldehydes,[2x] benzaldehyde,[2bb,2x,4h] isobutyraldehyde,[2x] terephthaldialdehyde,[2hh] salicylaldehyde,[2y] crotonaldehyde[4f] and enaminones.[2i]

This reaction is generally catalyzed by weak bases, such as tetrabutylammonium hydroxide,[13] potassium phosphate,[2g,2z] morpholinium acetate,[14] K_2CO_3,[2ee] NH_4Ac,[8] ethylenediammonium diacetate,[2o] piperidine,[2g,2h,2j,2l,2m,2s,4h,4j] diethylamine,[4j] zinc chloride-aniline,[4j] pyridine,[2h,2t,2hh] amino acids,[15] aminophenols,[15] and strong bases (including NaOH,[2h] KOH,[2h] and sodium ethoxide[4j]). In addition, this reaction has been catalyzed by solid-state supported bases, such as KF/Al_2O_3,[2d] $AlPO_4$-Al_2O_3,[2aj] alumino-vanadate oxynitride,[2bb] amino group immobilized silica gel,[2ii] basic ion-exchange resins and their organic salts (such as Amberlite IR-4B, Deacidite, and Amberlite IRA-400[2ll]), and basic zeolites (such as Cs-exchanged NaX [CsNaX] and GeX[2h]). In addition, this reaction has been modified to undergo in ionic liquid[2o] or under microwave assistance.[2v,16] It is interesting that malononitrile can react directly with aromatic aldehydes under grinding in the absence of solvents and catalysts;[2u] furthermore, β-ketonitrile and β-ketothioester selectively afford the completely opposite stereoisomers when reacted with aldehydes, by which β-ketonitrile always give *E*-olefins.[2x] This reaction has been used to synthesize some interesting molecules, such as coumarin,[2b] indole,[2ae] quinoline,[2s,2ee] stilbenes,[2g] niphendipine,[2h] nitrendipine,[2h] and azepinones.[2i]

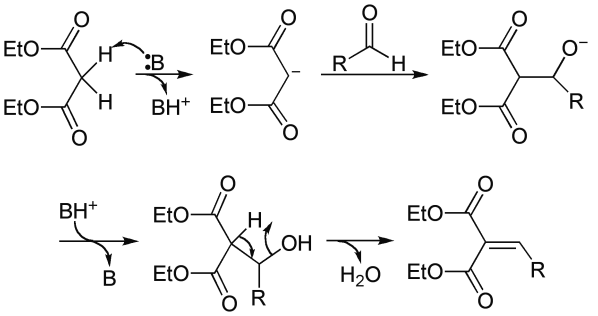
B. GENERAL REACTION SCHEME



(Z_1, Z_2 = NO_2, CN, CO_2R, COOH, SO_2R, COR, Ar
R_1 = alkyl, aryl
R_2 = H, alkyl, aryl)

C. PROPOSED MECHANISMS

Illustrated here is the mechanism for the condensation between diethyl malonate and a general aldehyde catalyzed by a weak base generally represented by B.



D. MODIFICATION

This reaction has been extensively modified for various conditions (as mentioned in Section A) by using different nucleophiles, different carbonyl compounds, and different bases as catalysts.

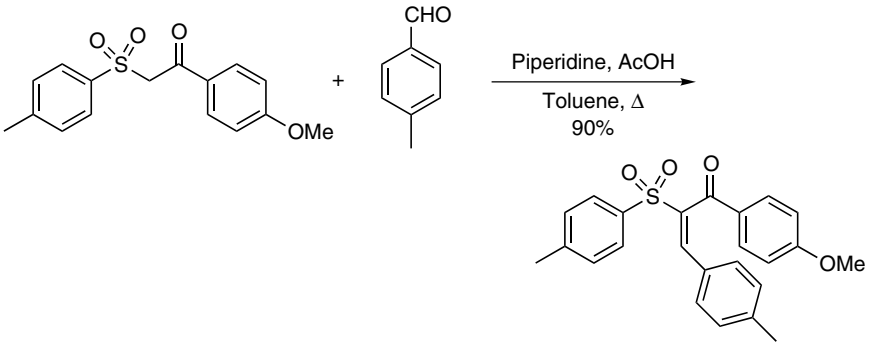
E. APPLICATIONS

This reaction has very broad application in organic synthesis.

F. RELATED REACTIONS

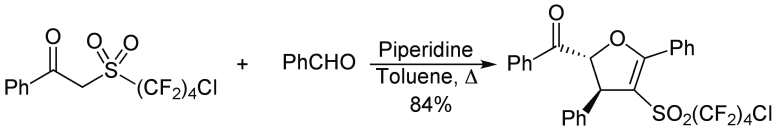
This reaction is related to the *Aldol Condensation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2s.

A mixture of 4.6 g 2-(*p*-toluenesulfonyl)-4′-methoxyacetophenone (15 mmol), 2.0 g *p*-tolualdehyde (16.5 mmol), 0.18 g piperidine (2 mmol), and 0.42 g acetic acid (7 mmol) in 40 mL toluene was refluxed for 2 h with azeotropic removal of water using a Dean-Stark trap. The mixture was cooled to room temperature and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc/toluene, 3:1:1) to give 5.5 g pure 1-(4′-methoxyphenyl)-3-(4′-methylphenyl)-2-(*p*-toluenesulfonyl)-2-(*E*)-propen-1-one as a solid, in a yield of 90%, m.p. 141.0–142.0°C.



Reference 2m.

A mixture of 356 mg $ClC_4F_8SO_2CH_2COPh$ (0.84 mmol), 43 mg benzaldehyde (0.4 mmol), and 78 μL piperidine in 16 mL toluene was refluxed for 1 h with azeotropic removal of water using a Dean-Stark trap. TLC analysis indicated the reaction was completed. The mixture was cooled to room temperature, the solvent was removed under reduced pressure, and the residue was column chromatographed (hexane/ethyl ether, 10:1) to give 213 mg (2*R*,3*S*)-2-benzoyl-3-phenyl-4-(4′-chloro-perfluorobutylsulfonyl)-4-phenyl-2,3-dihydrofuran, in a yield of 84%.

Other references related to the Knoevenagel condesation are cited in the literature.[17]

H. REFERENCES

1. Knoevenagel, E., *Ber.,* **1894**, *27*, 2346.
2. (a) Furness, M. S.; Robinson, T. P.; Ehlers, T.; Hubbard, R. B.; Arbiser, J. L.; Goldsmith, D. J. and Bowen, J. P., *Curr. Pharm. Design,* **2005**, *11*, 357. (b) Alvim, J.; Dias, R. L. A.; Castilho, M. S.; Oliva, G. and Corrêa, A. G., *J. Braz. Chem. Soc.,* **2005**, *16*, 763. (c) Kuster, G. J. T.; van Berkom, L. W. A.; Kalmoua, M.; van Loevezijn, A.; Sliedregt, L. A. J. M.; van Steen, B. J.; Kruse, C. G.; Rutjes, F. P. J. T. and Scheeren, H. W., *J. Comb. Chem.,* **2006**, *8*, 85. (d) Perin, G.; Jacob, R. G.; Botteselle, G. V.; Kublik, E. L.; Lenardão, E. J.; Cella, R. and dos Santos, P. C. S., *J. Braz. Chem. Soc.,* **2005**, *16*, 857. (e) Mandal, M.; Yun, H. D.; Dudley, G. B.; Lin, S. N.; Tan, D. S. and Danishefsky, S. J., *J. Org. Chem.,* **2005**, *70*, 10619. (f) Nagumo, Y.; Kakeya, H.; Yamaguchi, J.; Uno, T.; Shoji, M.; Hayashi, Y. and Osada, H., *Bioorg. Med. Chem. Lett.,* **2004**, *14*, 4425. (g) Al-Shihry, S. S., *Molecules,* **2004**, *9*, 658. (h) Zhang, X. F.; Lai, E. S. M.; Martin-Aranda, R. and Yeung, K. L., *App. Catalysis A: General,* **2004**, *261*, 109. (i) McNab, H., *Aldrichimica Acta,* **2004**, *37*, 19. (j) Andrade, C. K. Z.; Vercillo, O. E.; Rodrigues, J. P. and Silveira, D. P., *J. Braz. Chem. Soc.,* **2004**, *15*, 813. (k) Ragoussis, V.; Panopoulou, M. and Ragoussis, N., *J. Agri. Food. Chem.,* **2004**, *52*, 5047. (l) Saüczewski, F.; Reszka, P.; Gdaniec, M.; Grünert, R. and Bednarski, P. J., *J. Med. Chem.,* **2004**, *47*, 3438. (m) Xing, C. H. and Zhu, S. Z., *J. Org. Chem.,* **2004**, *69*, 6486. (n) Pepitone, M. F.; Hardaker, S. S. and Gregory, R. V., *Chem. Mater.,* **2003**, *15*, 557. (o) Su, C.; Chen, Z.-C. and Zheng, Q.-G., *Synthesis,* **2003**, 555. (p) Zhan, X. W.; Wang, S.; Liu, Y. Q.; Wu, X. and Zhu, D. B., *Chem. Mater.,* **2003**, *15*, 1963. (q) Katritzky, A. R.; Nair, S. K.; Witek, R. M. and Hutchins, S. M., *ARKIVOC*, **2003**, 9. (r) Kourouli, T.; Kefalas, P.; Ragoussis, N. and Ragoussis, V., *J. Org. Chem.,* **2002**, *67*, 4615. (s) Swenson, R. E.; Sowin, T. J. and Zhang, H. Q., *J. Org. Chem.,* **2002**, *67*, 9182. (t) Pearson, A. J. and Mesaros, E. F., *Org. Lett.,* **2002**, *4*, 2001. (u) Ren, Z. J.; Cao, W. G. and Ton, W. Q., *Synth. Commun.,* **2002**, *32*, 3475. (v) Strohmeier, G. A. and Kappe, C. O., *J. Comb. Chem.,* **2002**, *4*, 154. (w) Brunet, E.; García-Losada, P.; Rodríguez-Ubis, J.-C. and Juanes, O., *Can. J. Chem.,* **2002**, *80*, 169. (x) Hayashi, Y.; Kanayama, J.; Yamaguchi, J. and Shoji, M., *J. Org. Chem.,* **2002**, *67*, 9443. (y) Boucard, V., *Macromolecules,* **2001**, *34*, 4308. (z) Li, Y.-Q., *J. Chem. Res.,* **2000**, 524. (aa) Groenendaal, L. B.; Jonas, F.; Freitag, D.; Pielartzik, H. and Reynolds, J. R., *Adv. Mater.,* **2000**, *12*, 481. (bb) Wiame, H. M.; Cellier, C. M. and Grange, P., *J. Phys. Chem. B,* **2000**, *104*, 591. (cc) Xia, Y.; Yang, Z.-Y.; Brossi, A. and Lee, K.-H., *Org. Lett.,* **1999**, *1*, 2113. (dd) Reddy, T. I. and Varma, R. S., *Tetrahedron Lett.,* **1997**, *38*, 1721. (ee) Makosza, M., *Pure & Appl. Chem.,* **1997**, *69*, 559. (ff) Fukuyama, T. and Liu, G., *Pure & Appl. Chem.,* **1997**, *69*, 501. (gg) Wang, Z.-M.; Zhang, X.-L.; Sharpless, K. B.; Sinha, S. C.; Sinha-Bagchi, A. and Keinan, E., *Tetrahedron Lett.,* **1992**, *33*, 6407. (hh) Mao, G. Z.; Tsao, Y.-H.; Tirrell, M.; Davis, H. T.; Hessel, V.; van Esch, J. and Ringsdorf, H., *Langmuir,* **1994**, *10*, 4174. (ii) Angeletti, E.; Canepa, C.; Martinetti, G. and Venturello, P., *J. Chem. Soc., Perkin Trans. I,* **1989**, 105. (jj) Cagello, J. A.; Campelo, J. M.; Garcia, A.; Luna, D. and Marinas, J. M., *J. Org. Chem.,* **1984**, *49*, 5195. (kk) Hein, R. W.; Astle, M. J. and Shelton, J. R., *J. Org. Chem.,* **1961**, *26*, 4874. (ll) Astle, M. J. and Zaslowsky, J. A., *Ind. Eng. Chem.,* **1952**, *44*, 2867.

3. (a) Gao, G.-H.; Lu, L.; Zou, T.; Gao, J.-B.; Liu, Y. and He, M.-Y., *Chem. Res. Chinese Univ.,* **2007**, *23*, 169. (b) Li, J.-Y.; Peng, J.-J.; Qiu, H.-Y.; Jiang, J.-X.; Wu, J.-R.; Ni, Y. and Lia, G.-Q., *Youji Huaxue*, **2007**, *27*, 483. (c) Kantevari, S.; Bantu, R. and Nagarapu, L., *J. Mol. Catal. A: Chem.,* **2007**, *269*, 53. (d) Feroci, M.; Orsini, M.; Palombi, L. and Inesi, A., *Green Chem*., **2007**, *9*, 323. (e) Liu, X.-W.; Jiang, H. and Gong, H., *Youji Huaxue*, **2007**, *27*,131. (f) Heravi, M. M.; Tehrani, M. H.; Bakhtiari, K. and Oskooie, H. A., *J. Chem. Res.,* **2006**, 561. (g) Chakrabarty, M.; Mukherjee, R.; Chakrabarty, M.; Arima, S. and Harigaya, Y., *Lett. Org. Chem.,* **2006**, *3*, 868. (h) Zhang, J. C.; Jiang, T.; Han, B. X.; Zhu, A. L. and Ma, X. M., *Synth. Commun.,* **2006**, *36*, 3305. (i) Balalaie, S.; Bararjanian, M.; Hekmat, S. and Salehi, P., *Synth. Commun.,* **2006**, *36*, 3703. (j) Shindalkar, S. S.; Madje, B. R. and Shingare, M. S., *Indian J. Chem., Sect. B,* **2006**, *45B*, 2571. (k) Gao, G. H.; Gao, J. B.; Zhou, W. J.; Lu, L. and He, M. Y., *Chinese Chem. Lett.,* **2006**, *17*, 1293. (l) Abaee, M. S.; Mojtahedi, M. M.; Zahedi, M. M. and Khanalizadeh, G., *ARKIVOC*, **2006**, (*xv*), 48. (m) Oskooie, H. A.; Heravi, M. M.; Derikvand, F.; Khorasani, M. and Bamoharram, F. F., *Synth. Commun.,* **2006**, *36*, 2819. (n) Darvatkar, N. B.; Deorukhkar, A. R.; Bhilare, S. V. and Salunkhe, M. M., *Synth. Commun.,* **2006**, *36*, 3043. (o) Bian, Y.-J.; Qin, Y.; Xiao, L.-W. and Li, J.-T., *Youji Huaxue*, **2006**, *26*, 1165. (p) Alves de Souza, A. M.; Guarda, V. L. de M.; Leite, L. F. C. da C.; Barbosa Filho, J. M.; Alves de Lima, M. do C.; Galdino, S. L. and Pitta, I. da R., *Quim. Nova*, **2006**, *29*, 1106. (q) Reddy, B. M.; Patil, M. K.; Rao, K. N. and Reddy, G. K., *J. Mol. Catal. A: Chem.,* **2006**, *258*, 302. (r) Ranu, B. C. and Jana, R., *Eur. J. Org. Chem.,* **2006**, 3767. (s) Martins, L.; Bonagamba, T. J.; de Azevedo, E. R.; Bargiela, P. and Cardoso, D., *Appl. Catalysis A: General,* **2006**, *312*, 77. (t) Bartoli, G.; Beleggia, R.; Giuli, S.; Giuliani, A.; Marcantoni, E.; Massaccesi, M. and Paoletti, M., *Tetrahedron Lett*., **2006**, *47*, 6501. (u) Wang, Y.; Shang, Z.-C.; Wu, T.-X.; Fan, J.-C. and Chen, X., *J. Mol. Catal. A: Chem.,* **2006**, *253*, 212. (v) Zhang, X.-R.; Chao, W.; Chuai, Y.-T.; Ma, Y.; Hao, R.; Zou, D.-C.; Wei, Y.-G. and Wang, Y., *Org. Lett.,* **2006**, *8*, 2563. (w) Heravi, M. M.; Derikvand, F.; Haghighi, M. and Bakhtiari, K., *Lett. Org. Chem.,* **2006**, *3*, 297. (x) Wen, X. M., *Indian J. Chem., Sect. B,* **2006**, *45B*, 762. (y) Wang, C.-Q.; Ren, Z.-J.; Cao, W.-G.; Tong, W.-Q. and Wang, G.-P., *Youji Huaxue*, **2006**, *26*, 107. (z) Balalaie, S. and Bararjanian, M., *Synth. Commun.,* **2006**, *36*, 533. (aa) Inokuchi, T. and Kawafuchi, H., *J. Org. Chem.,* **2006**, *71*, 947. (bb) Saravanamurugan, S.; Palanichamy, M.; Hartmann, M. and Murugesan, V., *Appl. Catalysis A: General,* **2006**, *298*, 8. (cc) Hu, Y.; Wei, P.; Huang, H.; Le, Z.-G. and Chen, Z.-C.,*Synth. Commun.,* **2005**, *35*, 2955. (dd) Shindalkar, S. S.; Madje, B. R.; Hangarge, R. V.; Patil, P. T.; Dongare, M. K. and Shingare, M. S., *J. Korean Chem. Soc.,* **2005**, *49*, 377. (ee) Chen, W.-H. and Ding, J.-M., *Guangzhou Huaxue*, **2005**, *30*, 30. (ff) Shindalkar, S. S.; Madje, B. R. and Shingare, M. S., *Indian J. Chem., Sect. B,* **2005**, *44B*, 1519. (gg) Wang, J.-L.; Liu, J.-G.; Miao, C.-Q. and Li, G.-A., *Hecheng Huaxue,* **2005**, *13*, 278. (hh) Zhang, J.; Blazecka, P. G.; Angell, P.; Lovdahl, M. and Curran, T. T., *Tetrahedron*, **2005**, *61*, 7807. (ii) Yakaiah, T.; Reddy, G. V.; Lingaiah, B. P. V.; Rao, P. S. and Narsaiah, B., *Indian J. Chem., Sect. B,* **2005**, *44B*, 1301. (jj) Zhang, M.; Zhang, A.-Q. and Tang, X.-H., *Huaxue Shiji*, **2005**, *27*, 185. (kk) Serban, G.; Coman, M. and Curea, E., *Farmacia (Bucharest),* **2005**, *53*, 78. (ll) Mitra, A. K.; Karchaudhuri, N. and De, A., *J. Indian Chem. Soc.,* **2005**, *82*, 177. (mm) Hu, Y.; Chen, Z.-C.; Le, Z.-G. and Zheng, Q.-G., *Synth. Commun.,* **2004**, *34*, 4521.

4. (a) Paun, C.; Barklie, J.; Goodrich, P.; Gunaratne, H. Q. N.; McKeown, A.; Parvulescu, V. I. and Hardacre, C., *J. Mol. Catal. A: Chem.,* **2007**, *269*, 64. (b) Cai, Y. Q.; Peng, Y. Q. and Song, G. H., *Catal. Lett.,* **2006**, *109*, 61. (c) Forbes, D. C.; Law, A. M. and Morrison, D. W., *Tetrahedron Lett*., **2006**, *47*, 1699. (d) Isobe, K.; Hoshi, T.; Suzuki, T. and Hagiwara, H., *Molecular Diversity,* **2005**, *9*, 317. (e) Gronnow, M. J.; White, R. J.; Clark, J. H. and Macquarrie, D. J., *Org. Proc. Res. Dev.,* **2005**, *9*, 516. (f) Bensa, D.; constantieux, T. and Rodriguez, J., *Synthesis,* **2004**, 923. (g) Jin, Y. G.; Ju, J. M.; Kim, J. W.; Lee, S. G.; Kim, J. Y.; Park, S. H.; Son, S.-M.; Jin, S.-H.; Lee, K. H. and Suh, H. S., *Macromolecules,* **2003**, *36*, 6970. (h) Ogata, Y. and Tsuchida, M., *J. Am. Chem. Soc.,* **1959**, *81*, 2092. (i) Astle, M. J. and Gergel, W. C., *J. Org. Chem.,* **1956**, *21*, 493. (j) Cope, A. C., *J. Am. Chem. Soc.,* **1937**, *59*, 2327.

5. Zhan, X. W.; Liu, Y. Q.; Wu, X.; Wang, S. and Zhu, D. B., *Macromolecules,* **2002**, *35*, 2529.
6. Liao, J. and Wang, Q., *Macromolecules,* **2004**, *37*, 7061.
7. Ragoussis, N., *Tetrahedron Lett.,* **1987**, *28*, 93.
8. Takayama, H., *Chem. Pharm. Bull.,* **2004**, *52*, 916.
9. D'yachenko, E. V.; Glukhareva, T. V.; Dyudya, L. V.; Eltsov, O. V. and Morzherin, Y. Yu., *Molecules,* **2005**, *10*, 1101.
10. Braude, F. and Lindwall, H. G., *J. Am. Chem. Soc.,* **1933**, *55*, 325.
11. Girotra, N. N. and Wendler, N. L., *J. Org. Chem.,* **1969**, *34*, 3192.
12. Bozdag, O.; Ayhan-Kilcigil, G.; Tuncbilek, M. and Ertan, R., *Turk. J. Chem.,* **1999**, *23*, 163.
13. Tabata, M.; Boucard, V.; Adès, D.; Siove, A.; Sone, T.; Seino, T. and Mawatari, Y., *Macromolecules,* **2001**, *34*, 8101.
14. Kappe, C. O., *Acc. Chem. Res.,* **2000**, *33*, 879.
15. Prout, F. S.; Abdel-Latif, A. A. and Kamal, M. R., *J. Chem. Eng. Data,* **1963**, *8*, 597.
16. Yadav, J. S.; Reddy, B. V. S.; Basak, A. K.; Visali, B.; Narsaiah, A. V. and Nagaiah, K., *Eur. J. Org. Chem.,* **2004**, 546.
17. (a) Li, Z. B.; Liao, C. Z.; Ko, B. C. B.; Shan, S.; Tong, E. H. Y.; Yin, Z. H.; Pan, D. S.; Wong, V. K. W.; Shi, L. M.; Ning, Z.-Q.; Hu, W. M.; Zhou, J. J.; Chung, S. S. M. and Lu, X.-P., *Bioorg. Med. Chem. Lett.,* **2004**, *14*, 3507. (b) Ramachary, D. B.; Anebouselvy, K.; Chowdari, N. S. and Barbas, C. F., *J. Org. Chem.,* **2004**, *69*, 5838. (c) Seshadri, V. and Sotzing, G. A., *Chem. Mater.,* **2004**, *16*, 5644. (d) Kwak, G. and Fujiki, M., *Macromolecules,* **2004**, *37*, 2021. (e) Gallos, J. K. and Koumbis, A. E., *ARKIVOC,* **2003**, 135. (f) Clarke, P. A. and Martin, W. H. C., *Org. Lett.,* **2002**, *4*, 4527. (g) Ravi, S.; Padmanabhan, D. and Mamdapur, V. R., *J. Indian Inst. Sci.,* **2001**, *81*, 299. (h) Heravi, M. M.; Tajbakhsh, M.; Mohajerani, B. and Ghassemzadeh, M., *Z. Naturforsch.,* **1999**, *54B*, 541. (i) Rousselot, I.; Taviot-Gueho, C. and Besse, J. P., *Int. J. Inorg. Mater.,* **1999**, *1*, 165. (j) Watson, B. T. and Christiansen, G. E., *Tetrahedron Lett.,* **1998**, *39*, 6087. (k) Nicolaou, K. C.; Xu, J. Y.; Kim, S.; Pfefferkorn, J.; Ohshima, T.; Vourloumis, D. and Hosokawa, S., *J. Am. Chem. Soc.,* **1998**, *120*, 8661. (l) Kwon, P.-S.; Kim, Y.-M.; Kang, C.-J. and Kwon, T.-W., *Synth. Commun.,* **1997**, *27*, 4091. (m) Chafin, A.; Lindsay, G.; Merwin, L.; Ostrom, G. and Stenger-Smith, J., *Macromolecules,* **1997**, *30*, 1515. (n) Roncali, J., *Chem. Rev.*, **1997**, *97*, 173. (o) De la Cruz, P.; Diez-Barra, E.; Loupy, A. and Langa, F., *Tetrahedron Lett.,* **1996**, *37*, 1113. (p) Wright, M. E. and Sigman, M. S., *Macromolecules,* **1992**, *25*, 6055. (q) Tietze, L. F.; Beifuss, U. and Ruther, M.; *J. Org. Chem*., **1989**, *54*, 3120. (r) Kulp, S. S., *J. Chem. Ed.,* **1988**, *65*, 742. (s) Jones, G., *Org. React.,* **1967**, *15*, 204. (t) Rorig, K., *J. Am. Chem. Soc.,* **1951**, *73*, 1290. (u) Rorig, K., *J. Org. Chem.,* **1950**, *15*, 391. (v) Johnson, J. R., *Org. React.,* **1942**, *1*, 210. (w) Knoevenagel, E., *Ber.,* **1898**, *31*, 730. (x) Knoevenagel, E., *Ber.,* **1896**, *29*, 172.

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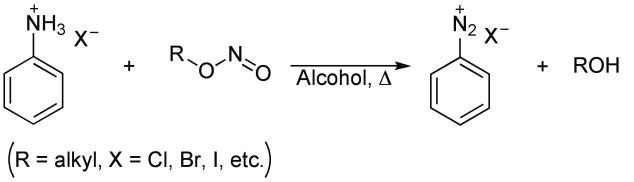
Knoevenagel Diazotization Method

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Knoevenagel in 1890.[1] It is the preparation of an anhydrous diazonium salt by the treatment of primary amine with amyl nitrite in an acidified absolute alcohol, by which a crystalline precipitate of the diazonium salt is formed on standing or on the addition of a small quantity of ether. Therefore, this reaction is known as the Knoevenagel diazotization method.[2] Under these conditions, nitrous acid is generated *in situ*, which then diazotizes the amines.[3] For example, the bisulfates of *p*-nitrobenzenediazonium, *p*-methoxybenzenediazonium, *p*-methylbenzenediazonium, and benzenediazonium ions can be made in an ethanol-sulfuric acid solution with amyl nitrite, which then crystallizes as colorless platelets from either absolute methanol or the mixture of methanol and ethanol.[4] However, the bisulfate of *m*-nitrobenzenediazonium will not crystallize under these conditions, so it is prepared in an acetic-sulfuric acid mixture with butyl nitrite.[4,5] It should be pointed out that the reaction of aromatic amine with amyl nitrite in aromatic solvents affords a moderate yield of biaryls, in which the variation of the reaction temperature, nitrite concentration, and the order of addition of the reagents do not affect the yield of biaryls, indicating the presence of aryl radicals.[6]

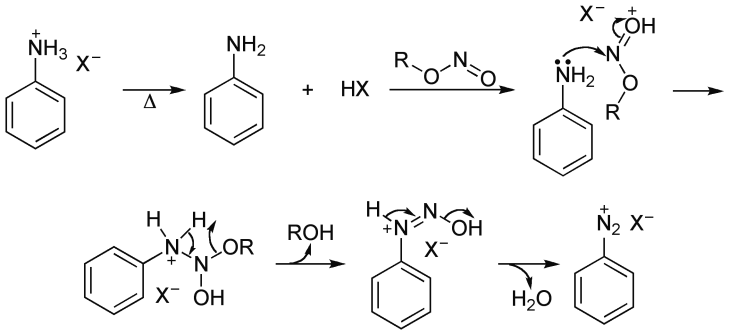
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is assumed that nitrous acid forms *in situ* under the Knoevenagel diazotizaiton condition,[3] which then combines with aniline to give a diazohydroxide, which can decomposes to yield the phenyl radical. However, in the presence of a strong acid, the diazohydroxide is further protonated and converted into the corresponding diazonium salt which may undergo a heterolytical or homolytical decomposition to give radicals or a cation intermediate,[6] as shown below.



D. MODIFICATION

The modifications of the Knoevenagel diazotization method include the addition of isoamyl nitrite to an appropriate amine salt suspended in cold acetic acid[7] and the diazotization of amine by the addition of a solution of N_2O_4 in ether.[8] In addition, a specific method for the preparation of anhydrous diazonium tetrafluoroborate has been developed in which the amine is mixed with an alkyl nitrite and an excess amount of $BF_3{\cdot}Et_2O$. For this preparation, the excess BF_3 can trap the alcohol and water produced during the diazotization, and the diazonium tetrafluoroborate precipitates from the reaction solution as it is formed.[9]

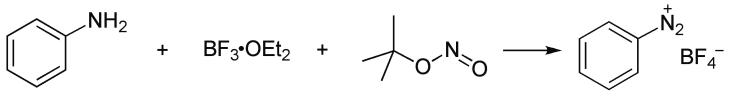
E. APPLICATIONS

This reaction is very useful for the preparation of anhydrous diazonium salts.

F. RELATED REACTIONS

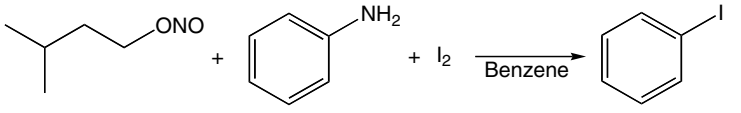
This reaction is related to the *Griess Diazotization*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 9.

To a three-necked, round-bottomed flask fitted with two addition funnels and a reflux condenser connected to a gas buret was added 1.06 g boron trifluoride etherate (7.5 mmol), which was then cooled to −15°C in an ice acetone bath. Then 5.0 mmol of the aromatic amine in a minimal volume of the anhydrous solvent (usually 10 mL) was added. If a solid of amine/BF_3 complex had formed, additional solvent or ethyl ether was added to produce homogeneous solution. *tert*-Butyl nitrite (0.618 g. 6.0 mmol) in 5 mL of the same solvent was added dropwise to the rapidly stirred solution over a period of 10 min. After the complete addition, the temperature of the reaction was maintained at –15°C for 10 min and then allowed to warm to 5°C in an ice water bath over a 20-min period. A crystalline precipitate usually formed during the addition of *tert*-butyl nitrite, and after 20 min at 5°C, precipitation was complete. Pentane (40 mL) was then added to the reaction solution, and the solid was suction filtered, washed with cold ether, air dried, and weighed.



Reference 6b.

Amyl nitrite (1.4 g, 0.012 mol) was added to a stirred mixture of 0.93 g aniline (0.01 mol), 1.26 g iodine (0.005 mol), and 30 mL benzene (or other aromatic solvent) in a 50-mL, round-bottomed flask equipped with a reflux condenser and gas bubbler. The flask was then placed in an oil bath and gradually heated to solvent reflux. The temperature of the oil bath was maintained at 100°C. The reaction was allowed to continue until gas evolution ceased. The mixture was then allowed to cool to room temperature and an internal standard was added. GC analysis indicated a composition of 78% iodobenzene, 21% 1,4-diiodobenzene, and 1% higher benzene oligomer, in a total yield of 60%.

Other references related to the Knoevenagel diazotization method are cited in the literature.[10]

H. REFERENCES

1. Knoevenagel, E., *Ber.,* **1890**, *23*, 2094.
2. (a) Anton, A. and Marechal, E., *Bull. Soc. Chim. Fr.,* **1971**, 2256. (b) Sachs, F. and Hilpert, S., *Ber.,* **1906**, *39*, 899.
3. Clark, L. V., *Ind. Eng. Chem.,* **1933**, *25*, 663.
4. Kochi, J. K., *J. Am. Chem. Soc.,* **1955**, *77*, 3208.
5. Hodgson, H. H. and Mahadevan, A. P., *J. Chem. Soc.,* **1947**, 325.
6. (a) Friedman, L. and Chlebowski, J. F., *J. Org. Chem.,* **1968**, *33*, 1633. (b) Friedman, L. and Chlebowski, J. F., *J. Org. Chem.,* **1968**, *33*, 1636.
7. (a) Hantzsch, A. and Jochem, E., *Ber.,* **1901**, *34*, 3337. (b) Hantzsch, A. and Daridson, W. B., *Ber.,* **1896**, *29*, 1832.
8. Scribner, R. M., *J. Org. Chem.,* **1964**, *29*, 3429.
9. Doyle, M. P. and Bryker, W. J., *J. Org. Chem.,* **1979**, *44*, 1572.
10. (a) Latacz, G.; Pekala, E.; Ciopinska, A. and Kiec-Kononowicz, K., *Acta Poloniae Pharm*., **2006**, *63*, 430. (b) Fortt, R.; Wootton, R. C. R. and de Mello, A. J., *Org. Proc. Res. Dev.,* **2003**, *7*, 762. (c) Sabitha, G.; Reddy, M. M.; Archana, B. and Yadav, J. S., *Synth. Commun.,* **1998**, *28*, 573. (d) Zollinger, H., "Diazotization of Amines and Dediazoniation of Diazonium Ions" in *Amino, Nitroso, Nitro and Related Groups, Supplement F2, The Chemistry of Functional Groups*, ed. Patai, S., John Wiley & Sons, chichester, **1996**. (e) Boivin, J.; Huppe, S. and Zard, S. Z., *Tetrahedron Lett*., **1996**, *37*, 8735. (f) Kornblum, N.; Cooper, G. D. and Gaylor, J. E., *J. Am. Chem. Soc.,* **1950**, *72*, 3013. (g) Saunders, K. H., *The Aromatic Diazo Compounds and Their Technical Applications,* 2nd ed., Arnold, London, **1949**. (h) Raiford, L. C. and Bren, B. C., *J. Am. Chem. Soc.,* **1929**, *51*, 2539. (i) Morgan, G. T. and Porter, J. W, *J. Chem. Soc.,* **1915**, *107*, 645.

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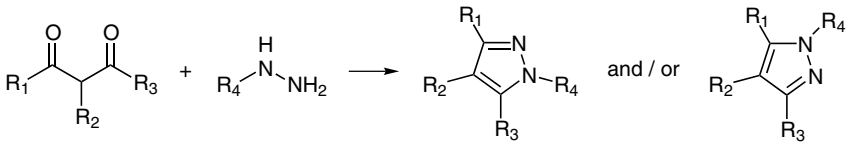
Knorr Pyrazole Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Knorr in 1883.[1] It is the preparation of pyrazole derivatives from 1,3-dicarbonyl compounds and hydrazines. Similarly, pyrazole derivatives can also be prepared from hydrazines and equivalent molecules of 1,3-dicarbonyl compounds, such as α-ethoxymethylene α-phenylacetone.[2] In a special case, β-carbonyl aldehyde reacts with a simple hydrazine to afford tautomers of 3- and 5-substituted pyrazoles, of which the proton oscillates rapidly back and forth between two nitrogen atoms.[3] These two tautomers are distinguishable only at sufficiently low temperatures.[4] It should be pointed out that the reaction of hydrazine with β-carbonyl ester leads to the formation of pyrazolone.[2,5]

B. GENERAL REACTION SCHEME



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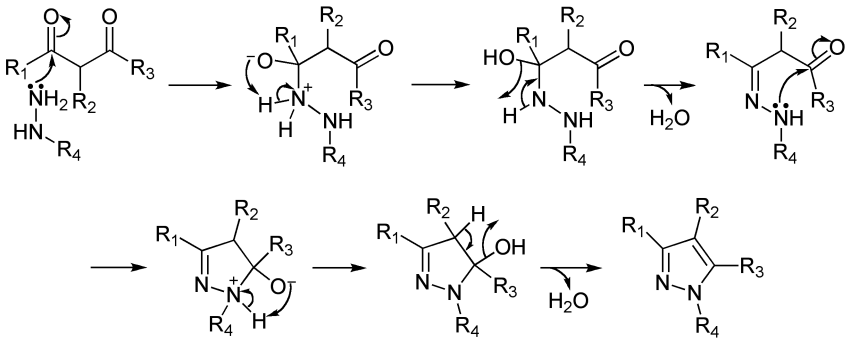
C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified to occur between β-alkoxyl α,β-unsaturated carbonyl compounds and hydrazines.[2]

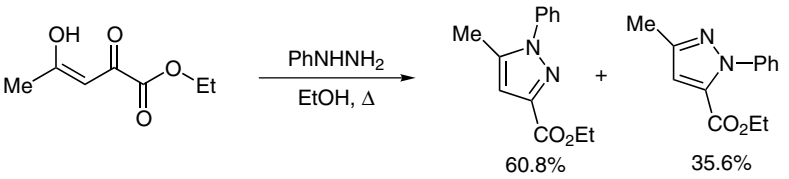
E. APPLICATIONS

This reaction has general application in the preparation of pyrazole derivatives.

F. RELATED REACTIONS

N/A

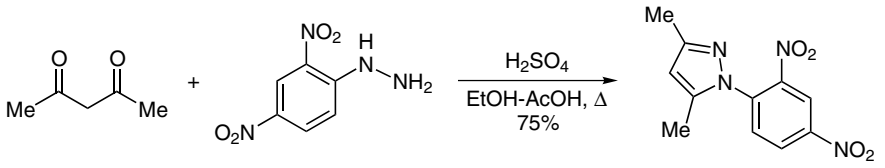
G. CITED EXPERIMENTAL EXAMPLES



Reference 6.

2,4-Dioxo-4-phenylbutyric acid ethyl ester (0.14 mL, 1.0 mmol) in 10 mL ethanol was treated dropwise with 0.12 mL phenyl hydrazine (1.2 mmol), and the resulting solution was refluxed over a period of 3 h. After the mixture was cooled to room temperature, the solvent was distilled off in vacuo. The residue was purified by means of silica gel column chromatography (petroleum ether/EtOAc, 4:1) to give 140 mg 5-methyl-1-phenyl-pyrazole-3-carboxylic acid ethyl ester as a pale brownish solid (0.61 mmol), in a yield of 60.8%, m.p.

37°C. In the meantime, 82 mg 5-methyl-2-phenyl-pyrazole-3-carboxylic acid ethyl ester was also obtained as a pale yellow solid (0.36 mmol), in a yield of 35.6%, m.p. 39–40°C.



Reference 7.

A solution of 1.98 g 2,4-dinitrophenylhydrazine (10 mmol) in 3 mL conc. H_2SO_4 was added to the solution of 10 mmol acetoacetone in EtOH-AcOH, and the mixture was heated on a water bath for several hours. On cooling and diluting, shining crystals of 1-(2,4-dinitrophenyl)-3,5-dimethyl-pyrazole was separated, which was recrystallized from EtOH or AcOH as a lemon yellow solid, in a yield of 75%, m.p. 114°C.

Other references related to the Knorr pyrazole synthesis are cited in the literature.[8]

H. REFERENCES

1. Knorr, L., *Ber.,* **1883**, *16*, 2587.
2. Habraken, C. L. and Moore, J. A., *J. Org. Chem.,* **1965**, *30*, 1892.
3. Kirchhoff, W. H., *J. Am. Chem. Soc.,* **1967**, *89*, 1312.
4. Knorr, L., *Ann.,* **1894**, *279*, 188.
5. Svenstrup, N.; Simonsen, K. B.; Thorup, N.; Brodersen, J.; Dehaen, W. and Becher, J., *J. Org. Chem.,* **1999**, *64*, 2814.
6. Schmidt, A.; Habeck, T.; Kindermann, M. K. and Nieger, M., *J. Org. Chem.,* **2003**, *68*, 5977.
7. Garg, H. G. and Joshi, S. S., *J. Org. Chem.,* **1961**, *26*, 946.
8. (a) Bhat, B. A.; Puri, S. C.; Qurishi, M. A.; Dhar, K. L. and Qazi, G. N., *Synth. Commun.,* **2005**, *35*, 1135. (b) Stadlbauer, W. and Hojas, G., *J. Heterocycl. Chem.,* **2004**, *41*, 681. (c) Garcia-Egido, E.; Spikmans, V.; Wond, S. Y. F. and Warrington, B. H., *Lab Chip,* **2003**, *3*, 67. (d) Zhao, Y.; Wu, X.-R.; Yin, J.-G. and Wang, J.-J., *Yantai Daxue Xuebao, Ziran Kexue Yu Gongchengban*, **2002**, *15*, 113. (e) Parham, W. E. and Dooley, J. F., *J. Am. Chem. Soc.,* **1967**, *89*, 985. (f) Burness, D. M., *J. Org. Chem.,* **1956**, *21*, 97. (g) Koenigs, E. and Freund, J., *Chem. Ber.,* **1947**, *80*, 143. (h) Buchner, E. and von der Heide, C., *Ber.,* **1902**, *35*, 31. (i) Knorr, L., *Ann.,* **1894**, *279*, 232. (j) Knorr, L. and Oettinger, B., *Ann.,* **1894**, *279*, 247. (k) Buchner, E., *Ber.,* **1894**, *27*, 3247. (l) Knorr, L. and Duden, P., *Ber.,* **1893**, *26*, 111. (m) Knorr, L. and Blank, A., *Ber.,* **1885**, *18*, 311.

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Knorr Pyrrole Synthesis
(Knorr Pyrrole Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Knorr in 1884.[1] It is the synthesis of pyrrole derivatives by the condensation of α-amino ketones with carbonyl compounds containing active α-methylene groups. Therefore, it is generally known as the Knorr pyrrole synthesis.[2] Occasionally, it is also referred to as the Knorr reaction,[3] Knorr pyrrole reaction,[2a] Knorr synthesis,[4] or Knorr condensation.[5] This reaction, as one of the principal routes for pyrroles, is highly regioselective[2a,6] and always gives high yields of pyrrole derivatives.[2a] Because α-amino ketones easily undergo a self-condensation, the α-amino ketones are often generated *in situ* from either isonitrosoketones, oximes,[3] or hydrazones[2a] in the presence of zinc dust, NaOAc and HOAc. However, such reduction results in an environmental problem when it is carried out on large scale, so the reduction has been improved by replacing the zinc reduction with hydrogenation.[2g] In addition, carbonyl groups can also be produced *in situ* by deprotection of the masked carbonyl group, such as ketal. It is interesting that it has been found that the oxygen atmosphere plays an important role in this reaction during the reduction of isonitrosoketones because no or a very low yield of expected pyrroles is obtained when oxygen is excluded under a helium or argon atmosphere.[2g] On the other hand, it has been reported that even more pyrrole derivatives could be yielded if α-amino ketone hydrochlorides are used directly rather than generated *in situ*.[2g] In the cases of a reaction

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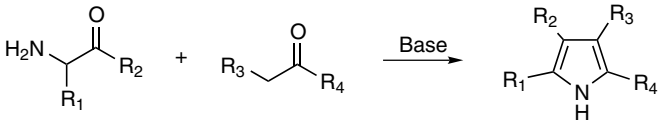
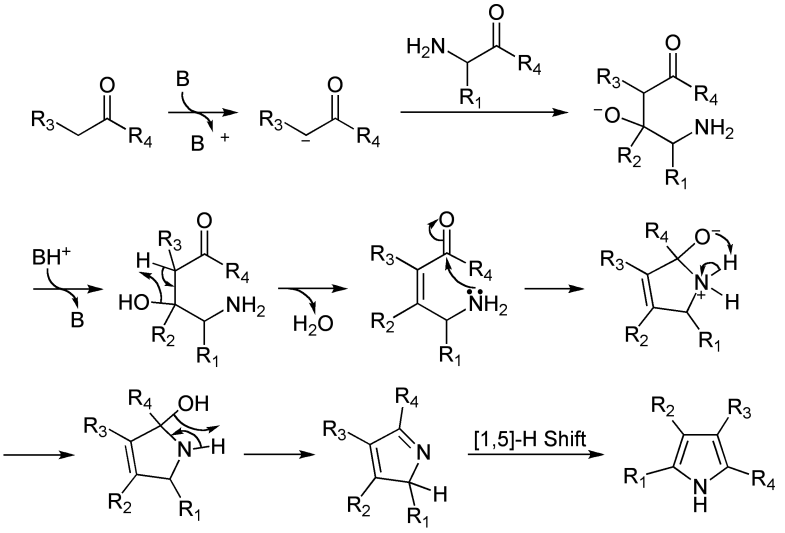
between α-amino ketones and β-ketoesters, the formed pyrroles are typically isolated by a water knockout.[3]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified by directly using α-amino ketone hydrochloride[2g] or reducing α-nitrosoketone or hydrazone via hydrogenation[3] to form pyrrole derivatives.

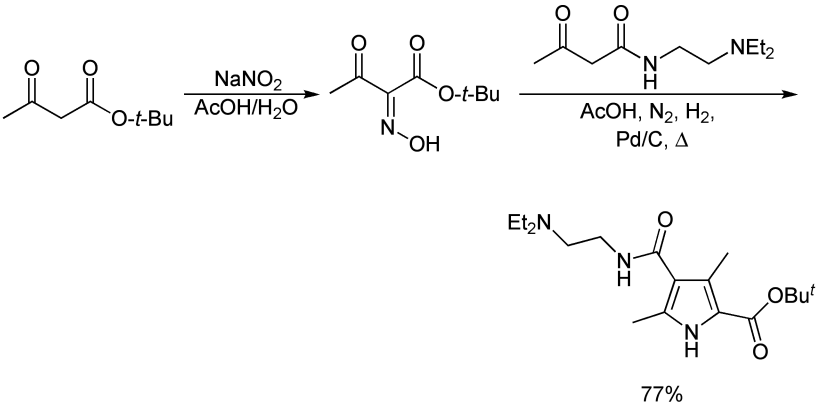
E. APPLICATIONS

This reaction has general application in the preparation of pyrrole derivatives, especially for the porphyrins with exocyclic rings.[7]

F. RELATED REACTIONS

This reaction is related to the *Hantzsch Pyrrole Synthesis* and *Paal-Knorr Pyrrole Synthesis*.

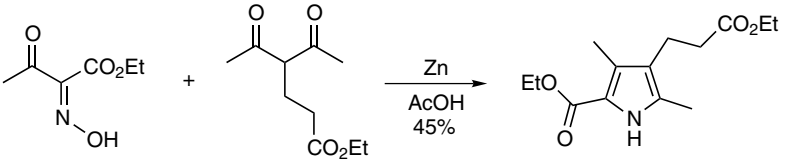
G. CITED EXPERIMENTAL EXAMPLES



Reference 3.

To a three-necked, round-bottomed flask was added 30 g *tert*-butyl acetoacetate (190 mmol) along with 30 mL acetic acid. After the mixture was cooled to 0–3°C under nitrogen a solution of 18.3 g $NaNO_2$ (265 mmol) in 35 mL H_2O was added dropwise by maintaining the temperature < 10°C. Once the addition was complete, the reaction solution was slowly warmed to room temperature. When the reaction was deemed complete by TLC (2 h), the mixture was partitioned between 40 mL aqueous KCl solution and 50 mL diethyl ether. The aqueous layer was extracted further with diethyl ether (3 × 25 mL). The combined organics were washed with H_2O (3 × 35 mL), dried over Na_2SO_4, and concentrated in vacuo to afford oxime as a pale yellow oil, which was used in the next step without further purification.

To a 500-mL Parr hydrogenation vessel was added 20.0 g oxime (107 mmol), along with 2.0 g 5% dry Pd/C, followed by 21.4 g *N*-(2′-diethylamino-ethyl) acetoacetamide (107 mmol) dissolved in 220 mL acetic acid. The vessel was purged with nitrogen and hydrogen, and the mixture was hydrogenated at 45 psi by heating at 65°C for 7 h. After this time, the reaction mixture was cooled to room temperature and filtered to remove palladium, and the cake was washed with acetic acid. The filtrate was neutralized with 50% aqueous NaOH, and 500 mL CH_2Cl_2 was added, followed by more 50% aqueous NaOH until the pH of the aqueous phase was 13. The mixture was transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 350 mL), and the combined organics were washed with H_2O (2 × 250 mL). The washes were back extracted with 250 mL CH_2Cl_2, and the combined organics were concentrated in vacuo. The residue was dissolved in hot CH_3CN, and the resulting solution was filtered and cooled. The solids that formed were isolated by filtration to afford 27.7 g *tert*-butyl 4-[[[2-(diethylamino)ethyl]amino]carbonyl]-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (83 mmol), in a yield of 77%.



Reference 8.

To a 250-mL three-necked flask was added 14.0 g methyl 4-acetyl-5-oxohexanoate (75 mmol) in 35 mL acetic acid. The internal temperature was maintained at 65–80°C while the oxime solution (preparation same as the one described for Reference 3) was added over 80 min, along with 12 g each of zinc dust and anhydrous sodium acetate in small portions. The mixture was stirred an additional 10 min and poured onto 400 g ice. The precipitate was collected and dissolved in benzene, unreacted zinc was removed, and the benzene solution was evaporated to dryness. The formed pyrroles were recrystallized from methanol, benzene-hexane, and carbon tetrachloride.

Other references related to the Knorr pyrrole synthesis are cited in the literature.[9]

H. REFERENCES

1. Knorr, L., *Ber.,* **1884**, *17*, 1635.
2. (a) Bellingham, R. K.; Carey, J. S.; Hussain, N.; Morgan, D. O.; Oxley, P. and Powling, L. C., *Org. Proc. Res. Dev.,* **2004**, *8*, 279. (b) Alberola, A.; Ortega, A. G.; Sadaba, M. L. and Sanudo, C., *Tetrahedron*, **1999**, *55*, 6555. (c) Zhang, Y.; Jiang, Y.-Z. and Liang, X.-T., *Chinese J. Chem.,* **1997**, *15*, 371. (d) Hamby, J. M. and Hodges, J. C., *Heterocycles*, **1993**, *35*, 843. (e) Fabiano, E. and Golding, B. T., *J. Chem. Soc., Perkin Trans. I,* **1991**, 3371. (f) Tamura, Y.; Kato, S. and Ikeda, M., *Chem. Ind. (London),* **1971**, 767. (g) Castro, A. J.; Giannini, D. D. and Greenlee, W. F., *J. Org. Chem.,* **1970**, *35*, 2815. (h) Hauptmann, S. and Martin, M., *Zeitsch. Chem.,* **1968**, *8*, 333. (i) Treibs, A.; Schmidt, R. and Zinsmeister, R., *Chem. Ber.,* **1957**, *90*, 79. (j) MacDonald, S. F. and Stedman, R. J., *Can. J. Chem.,* **1954**, *32*, 812.
3. Manley, J. M.; Kalman, M. J.; Conway, B. G.; Ball, C. C.; Havens, J. L. and Vaidyanathan, R., *J. Org. Chem.,* **2003**, *68*, 6447.
4. Paine, J. B. and Dolphin, D., *J. Heterocycl. Chem.,* **1975**, *12*, 1317.
5. Umio, S.; Kariyone, K.; Tanaka, K. and Nakamura, H., *Chem. Pharm. Bull.,* **1969**, *17*, 559.
6. Elghamry, I., *Synth. Commun.,* **2002**, *32*, 897.
7. Lash, T. D., *Tetrahedron,* **1998**, *54*, 359.
8. Harbuck, J. W. and Rapoport, H., *J. Org. Chem.,* **1971**, *36*, 853.
9. (a) Cheng, L. and Lightner, D. A., *Synthesis,* **1999**, 46. (b) Harrington, P. E. and Tius, M. A., *Org. Lett.,* **1999**, *1*, 649. (c) Alberola, A.; Ortega, A. G.; Sadaba, M. L. and Sanudo, C. , *Tetrahedron,* **1999**, *55*, 6555. (d) Bastian, J. A. and Lash, T. D., *Tetrahedron,* **1998**, *54*, 6299. (e) Fabiano, E. and Golding, B. T., *J. Chem. Soc., Perkin Trans. I,* **1991,** 3371. (f) Tamura, Y.; Kato, S. and Ikeda, M., *Chem. & Ind. (London),* **1971**, 767. (g) Hauptmann, S. and Martin, M., *Z. Chem.,* **1968**, *8*, 333. (h) Fischer, H., *Org. Syn. Coll.* **1955**, *3*, 573. (i) Treibs, A. and Hintermeier, K., *Ber.,* **1954**, *86*, 1167. (j) Davidson, D., *J. Org. Chem.,* **1939**, *4*, 361. (k) Knorr, L. and Lange, H., *Ber.,* **1902**, *35*, 2998. (l) Knorr, L., *Ann.,* **1886**, *236*, 290.

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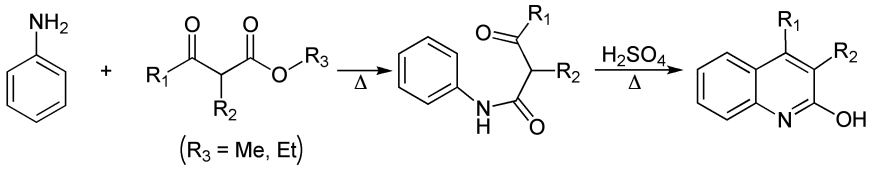
Knorr Quinoline Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Knorr in 1886.[1] It is the synthesis of 2-hydroxyquinolines via the cyclization and dehydration of an anilide intermediate condensed from β-ketoesters and anilines at a relatively high temperature. Right after this report, Conrad and Limpach also reported a similar reaction between anilines and β-ketoesters but at low temperatures, which resulted in the formation of 4-hydroxyquinolines from the intermediate of alkyl crotonate.[2] Thus this reaction is known as the Knorr synthesis,[3] Knorr-Limpach method,[4] Knorr cyclization,[5] Conrad-Limpach-Knorr reaction,[6] or Knorr quinoline synthesis.[7] It has been reported that the formation of an alkyl crotonate intermediate is favored at moderate or low temperature in the presence of iodine or an acid catalyst, whereas intermediate anilide is formed at high temperatures.[6b]

B. GENERAL REACTION SCHEME



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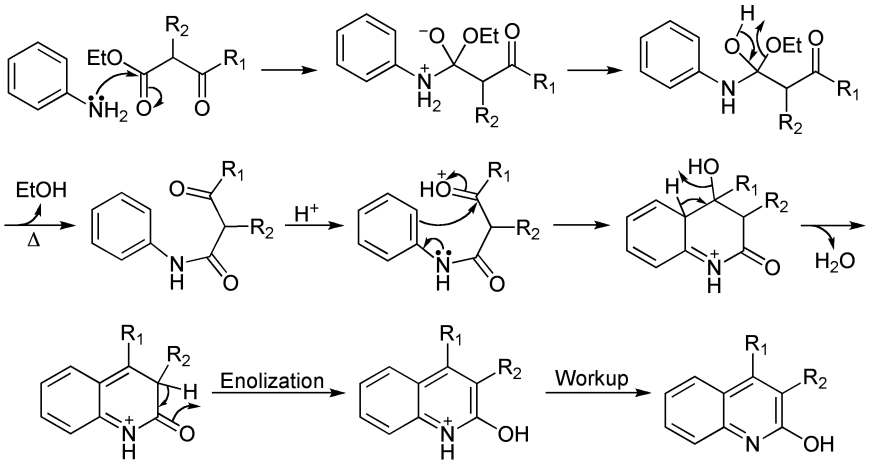
C. PROPOSED MECHANISMS

The mechanism is illustrated by the reaction between aniline and ethyl β-ketoester.



D. MODIFICATION

N/A

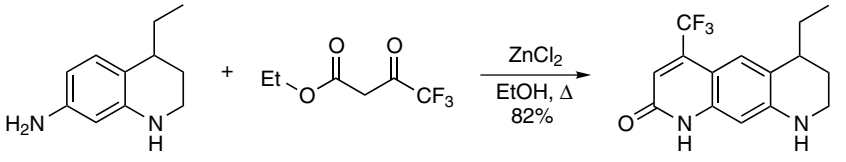
E. APPLICATIONS

This reaction has general application in the preparation of 2-hydroxyquinoline derivatives.

F. RELATED REACTIONS

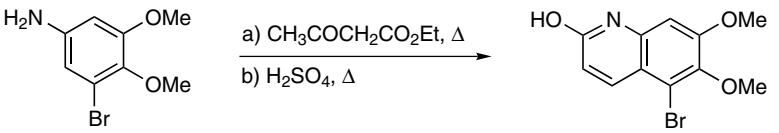
This reaction is related to the *Conrad-Limpach Quinoline Synthesis*, *Doebner-von Miller Quinoline Synthesis*, and *Gould-Jacobs Quinoline Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 8.

To a flame-dried, 100-mL, round-bottomed flask containing 210 mg aminotetrahydroquinoline (1.19 mmol) and 20 mL ethanol at room temperature was added 190 μL ethyl-4,4,4-trifluoroacetoacetate (1.31 mmol, 1.10 eq.) and 244 mg $ZnCl_2$ (1.79 mmol, 1.50 eq.). The reaction mixture was heated to reflux for 6 h, at which time TLC analysis indicated complete consumption of the starting material. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. Dichloromethane (20 mL) was added, and the organic phase was washed with saturated $NaHCO_3$ (2×10 mL) and brine (10 mL), then dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 15:1) to give 24.4 mg 4-ethyl-1,2,3,4-tetrahydro-6-(trifluoromethyl)-8-pyridono[5,6-g]quinoline as a yellow solid, in a yield of 82%, $R_f = 0.37$ (CH_2Cl_2/MeOH, 9:1). Recrystallization from EtOAc provided an analytically pure sample as yellow needles, m.p. 264–265°C.



Reference 6b.

To 20 mL ethyl acetoacetate heated to 160–165°C was added 5.5 g 4-amino-6-bromoveratrole over 3 min. After continuing the heating for an additional 30 min, the excess ethyl acetoacetate was distilled off under reduced pressure, and the residue was washed with light petroleum ether, leaving a thick oil in an apparently quantitative yield. This thick oil was mixed with 8 mL concentrated H_2SO_4, and the mixture was heated for 2 min at 60–70°C. The mixture immediately solidified, which was thrown into water. The solid was filtered out and crystallized from a mixture of chloroform and alcohol to give 60% 2-hydroxy-5-bromo-6,7-dimethoxylepidine as long white needles, m.p. 274–276°C (dec.).

Other references related to the Knorr quinoline synthesis are cited in the literature.[9]

H. REFERENCES

1. Knorr, L., *Ann.,* **1886**, *236*, 69.
2. (a) Conrad, M. and Limpach, L., *Ber.,* **1887**, *20*, 944. (b) Conrad, M. and Limpach, L., *Ber.,* **1887**, *20*, 948.
3. (a) Outt, P. E.; Ares, J. J.; Roberts, G. E.; Wang, X. D.; Cupps, T. L. and Wireko, F. C., *J. Org. Chem.,* **1998**, *63*, 5762. (b) Curran, D. P. and Kuo, S.-C., *J. Org. Chem.,* **1984**, *49*, 2063.
4. (a) Nasr, M.; Zayed, A. and Nabih, I., *Pharmazie,* **1978**, *33*, 424. (b) Dudley, K. H. and McKee, R. L., *J. Org. Chem.,* **1967**, *32*, 3210. (c) Benson, R. E. and Hamilton, C. S., *J. Am. Chem. Soc.,* **1946**, *68*, 2644.
5. (a) Hamann, L. G.; Higuchi, R. I.; Zhi, L.; Edwards, J. P.; Wang, X.-N.; Marschke, K. B.; Kong, J. W.; Farmer, L. J. and Jones, T. K., *J. Med. Chem.,* **1998**, *41*, 623. (b) Lopez-Alvarado, P.; Avendano, C. and Menendez, J. C., *Synthesis*, **1998**, 186.
6. (a) Yoshikawa, T., *Yakugaku Zasshi*, **1961**, *81*, 1323. (b) Misani, F. and Bogert, M. T., *J. Org. Chem.,* **1945**, *10*, 347. (c) Misani, F. and Bogert, M. T., *J. Org. Chem.,* **1945**, *10*, 458.
7. (a) Tikotikar, N. L.; Navalgund, I. M.; Munavalli, S. N.; Kulkarni, S. N. and Nargund, K. S., *J. Karnatak Univ.,* **1956**, *1*, 43. (b) Seide, O, *Ber.,* **1925**, *58B*, 352.

8. Hamann, L. G.; Mani, N. S.; Davis, R. L.; Wang, X.-N.; Marschke, K. B. and Jones, T. K., *J. Med. Chem.,* **1999**, *42*, 210.

9. (a) Hodgkinson, A. J. and Staskum, B., *J. Org. Chem.,* **1969**, *34*, 1709. (b) Hauser, C. R. and Reynolds, G. A., *Org. Syn. Coll.,* **1955**, *3*, 593. (c) Hauser, C. R. and Reynolds, G. A., *J. Am. Chem. Soc.,* **1948**, *70*, 2402. (d) Kaslow, C. E. and Stayner, R. D., *J. Am. Chem. Soc.,* **1948**, *70*, 3350. (e) Bergstrom, F. W., *Chem. Rev.,* **1944**, *35*, 77. (f) Bergstrom, F. W., *Chem. Rev.,* **1944**, *35*, 157. (g) Manske, R. H. F, *Chem. Rev.,* **1942**, *30*, 113. (h) Ainley, A. D. and King, H., *Proc. Roy. Soc. (London),* **1938**, *B125*, 84. (i) Coffey, S.; Thompson, J. K. and Wilson, F. J., *J. Chem. Soc.,* **1936**, 856. (j) Monti, L. and Cirelli, V., *Gazz. Chim. Ital.,* **1936**, *66*, 723. (k) Knorr, L., *Ann.,* **1888**, *245*, 357. (l) Knorr, L., *Ann.,* **1888**, *245*, 378.

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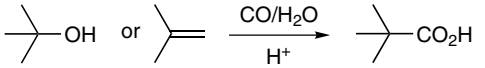
Koch-Haaf Carboxylation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Koch in 1955[1] and subsequently modified by Koch and Haaf.[2] It is the formation of tertiary carboxylic acids or esters by treatment of alcohols or alkenes with anhydrous formic acid that functions as both an acidic catalyst and a source of carbon monoxide.[3] This reaction was quickly modified to an industrial production of carboxylic acid from the reaction between alcohols or alkenes and carbon monoxide in the presence of a strong acid.[4] Therefore, this reaction is generally known as the Koch-Haaf reaction[4,5] or Koch-Haaf carboxylation.[5c,6] In one case, it is also referred to as Koch reaction.[7] The carboxylation of alcohols occurs in two steps: the formation of an acyl cation from carbon monoxide or carbocation generated from acidic dehydration followed by the coupling between the acyl cation and water or alcohol to form the acid or ester derivative.[4] For example, pivalic acid can be generated from isobutylene or *tert*-butyl alcohol and carbon monoxide.[4] In addition, the corresponding aryl esters are formed in the presence of phenol.[5a] It has been found that a variety of Brønsted and Lewis acids can catalyze this reaction,[5a] among these acids, BF_3 is the most effective catalyst.[8] However, in the presence of a super acid, it is possible to formylate isoalkanes to aldehydes that subsequently rearrange to the corresponding branched ketones.[4]

B. GENERAL REACTION SCHEME



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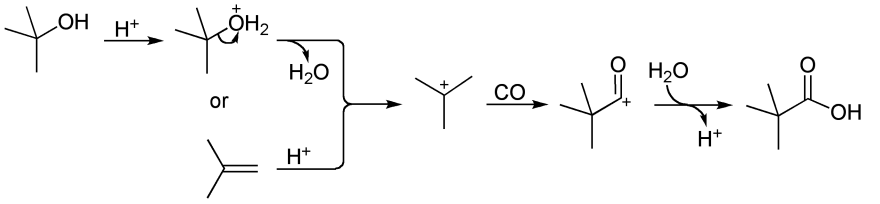
C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified to use different Lewis acids as catalysts.

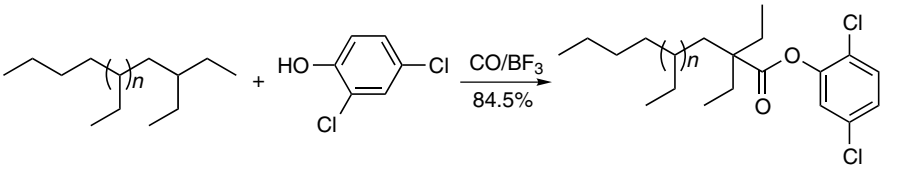
E. APPLICATIONS

This reaction has important application in industry for producing carboxylic acids.

F. RELATED REACTIONS

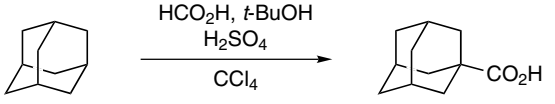
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 5a.

An autoclave was pressured to 199 psi with BF_3 at 50°C, followed by 301 psi of CO to bring the total pressure to 500 psi. Ethylene-1-butene copolymer (EB, Mn = 4600, 20 wt % ethylene, 406 g) and 100.6 g 2,4-dichlorophenol (pKa = 7.85) at 50°C were charged to the autoclave and pressured to 1430 psi with CO. The autoclave contents were stirred under these conditions for 2 h and depressurized. The reaction product was stripped to remove the BF_3 gas and excess substituted phenol to give 84.5% EB copolymer aryl ester.



Reference 2.

To a 1-L three-necked flask equipped with a stirrer a thermometer, a dropping funnel, and a gas-outlet tube were added 255 mL 96% H_2SO_4 (4.8 mol), 100 mL CCl_4, and 13.6 g

adamantine (0.1 mol). The well-stirred mixture was cooled to 17–19°C in an ice bath, and 1 mL 98% formic acid was added. Then a mixture of 38 mL *t*-butyl alcohol (0.4 mol) and 55 g of 98–100% formic acid (1.2 mol) was added dropwise, during which the rate of addition and the cooling were regulated so that the temperature of the reaction mixture was kept at 17–25°C. After the completion of addition, the reaction mixture was stirred for an additional 30 min and poured onto 700 g crushed ice. The layers were separated, and the upper, acid layer was extracted with CCl_4 (3 × 100 mL). The combined carbon tetrachloride layers were shaken with 110 mL 15 *N* ammonium hydroxide, and the crystalline ammonium 1-adamantanecarboxlate that separated was collected on a Büchner funnel with a coarse fritted disk. The salt was washed with 20 mL cold acetone and suspended in 250 mL water. The suspension was made strongly acidic with 25 mL 12 *N* HCl and extracted with 100 mL chloroform. The chloroform layer was dried over anhydrous Na_2SO_4, and evaporated to dryness on a steam bath. The residue, in amount of 12–13 g, was crude 1-adamantanecarboxylic acid, in a yield of 67–72%, m.p. 173–174°C. Recrystallization of this product from a mixture of 30 mL methanol and 10 ∼mL water afforded 10–11 g pure 1-adamantanecarboxylic acid, in a yield of 56–61%, m.p. 175–176.5°C.

Other references related to the Koch-Haaf carboxylation are cited in the literature.[9]

H. REFERENCES

1. Koch, H., *Brennstoff Chem.,* **1955**, *36*, 321.
2. Koch, H. and Haaf, W., *Org. Syn. Coll.,* **1973**, *5*, 20.
3. (a) Bahrmann, N., "Koch Reactions" in *New Syntheses with Carbon Monoxide*, ed. Falbe, J., Springer-Verlag, Berlin, **1980**, pp. 372–413. (b) Pino, P.; Piacenti, F. and Bianchi, M., "Hydrocarboxylation of Olefins and Related Reactions" in *Organic Synthesis via Metal Carbonyls,* ed. Wender, I. and Pino, P., Wiley, New York, **1977**, 2, pp. 233–296.
4. Olah, G. A., *J. Org. Chem.,* **2001**, *66*, 5943.
5. (a) Emert, J. I.; Dankworth, D. C.; Gutierrez, A.; Martella, D. J.; Rucker, S. P.; Stokes, J. P.; Thaler, W.; Worku, A.; Padias, A. B. and Hall, H. K., *Macromolecules,* **2001**, *34*, 2766. (b) Leonte, C. and Carp, E., *Rev. Roumaine Chim.,* **1989**, *34*, 1241. (c) Farooq, O.; Marcelli, M.; Prakash, G. K. S. and Olah, G. A., *J. Am. Chem. Soc.,* **1988**, *110*, 864. (d) Moiseev, I. K. and Doroshenko, R. I., *Zh. Org. Khim.,* **1983**, *19*, 1117. (e) Langhals, H.; Mergelsberg, I. and Ruechardt, C., *Tetrahedron Lett*., **1981**, *22*, 2365.
6. (a) Rao, R. R. and Bhattacharya, S., *Indian J. Chem., Sect. B,* **1982**, *21B*, 405. (b) Rao, R. R. and Bhattacharya, S., *Indian J. Chem., Sect. B,* **1981**, *20B*, 207. (c) Peters, J. A.; Rog, J. and van Bekkum, H., *Rec. Trav. Chim. Pays-Bas,* **1974**, *93*, 248. (d) Nambudiry, M. E. N. and Rao, G. S. K., *Tetrahedron Lett*., **1972**, 4707. (e) Peters, J. A. and van Bekkum, H., *Rec. Trav. Chim. Pays-Bas,* **1973**, *92*, 379. (f) Peters, J. A. and van Bekkum, H., *Rec. Trav. Chim. Pays-Bas,* **1971**, *90*, 65.
7. Gros, I.; Florita, C.; Maties, R. and Vilics, T., *Revistade Chim. (Bucharest),* **1986**, *37*, 274.
8. (a) Eidus, Y. T.; Puzitskii, K. V. and Yang, Y.-P., *Neftekhimiya*, **1972**, *12*, 754. (b) Yang, Y.-P.; Puzitskii, K. V. and Eidus, Ya. T., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1970**, 424.
9. (a) Lopez-Alvarado, P.; Avendano, C. and Menendez, J. C., *Synthesis*, **1998**, 186. (b) Chern, Y.-T. and Wang, W.-L., *J. Poly. Sci. A: Poly. Chem.,* **1996**, *34*, 1501. (c) Kurzer, F. an; Patel, J. N., *J. Org. Chem.,* **1988**, *53*, 258. (d) Vodicka, L.; Burkhard, J. and Janku, J., *Coll. Czech. Chem. Commun.,* **1986**, *51*, 867. (e) Adcock, W. and Kok, G. B., *J. Org. Chem.,* **1985**, *50*, 1079. (f) Vodicka, L.;

Isaev, S. D.; Burkhard, J. and Janku, J., *Coll. Czech. Chem. Commun.,* **1984**, *49*, 1900. (g) Kurzer, F. and Patel, J. N., *Monatsh. Chem.,* **1984**, *115*, 809. (h) Kurzer, F. and Patel, J. N., *Monatsch. Chem.,* **1984**, *115*, 793. (i) Woo, E. P. and Cheng, F. C. W., *J. Org. Chem.,* **1981**, *51*, 3704. (j) Arai, H.; Nagai, S. and Hatada, M., *Radiation Phys. Chem.,* **1981**, *17*, 211. (k) Janku, J.; Burkhard, J. and Vodicka, L., *Zeitsch. Chem.,* **1981**, *21*, 67. (l) Gray, G. W. and Kelly, S. M., *J. Chem. Soc., Chem. Commun.,* **1979**, 974. (m) Burns, W.; Mitchell, T. R. B.; McKervey, M. A.; Rooney, J. J.; Ferguson, G. and Roberts, P., *J. Chem. Soc., Chem. Commun.,* **1976**, 893. (n) Takaishi, N.; Fujikura, Y.; Inamoto, Y.; Ikeda, H.; Aigami, K. and Osawa, E., *J. Chem. Soc., Chem. Commun.,* **1975**, 371. (o) Stepanov, F. N.; Smirnova, N. A.; Baklan, V. F. and Yurchenko, A. B., *Zh. Org. Khim.,* **1974**, *10*, 234. (p) McKervey, M. A.; Quinn, H. A. and Rooney, J. J., *J. Chem. Soc. C,* **1971**, 2430. (q) Raber, D. J.; Fort, R. C.; Wiskott, E.; Woodworth, C. W.; Schleyer, P. v. R.; Weber, J. and Stetter, H., *Tetrahedron*, **1971**, *27*, 3. (r) Van Bekkum, H.; Van de Graaf, B.; Van Minnen-Pathuis, G.; Peters, J. A. and Wepster, B. M., *Rec. Trav. Chim. Pays-Bas,* **1970**, *89*, 521. (s) Mannschreck, A. and Kölle, U., *Angew. Chem. Int. Ed. Engl.,* **1969**, *8*, 528. (t) Hauser, C. R. and Reynolds, G. A., *Org. Syn. Coll.,* **1955**, *3*, 593. (u) Hauser, C. R. and Reynolds, G. A., *J. Am. Chem. Soc.,* **1948**, *70*, 2402.

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Kochi Reaction

(Kochi Oxidative Decarboxylation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Kochi in 1965.[1] It is the conversion of carboxylic acids into corresponding halides via the oxidative degradation of carboxylic acid by lead tetraacetate (LTA) accompanied by a simultaneous replacement with a halogen under free-radical conditions in the presence of a stoichiometric amount of metal halide. Thus it is known as the Kochi reaction[2] or Kochi oxidative decarboxylation.[3] In the absence of metal halide, the carboxylic acids will be oxidized into various compounds, depending on the experimental conditions, either thermally or photochemically.[4] It has been found that for the photochemical reaction, the initial process involves the formation of an acyloxy radical, whereas under the thermal reaction conditions, the alkyl radical occurs directly;[4a] however, the photochemical reaction at 30°C and thermal reaction at 80°C give almost the same products.[4c] In addition, the structure of the substrates also affects the oxidation outcome, and the relative rates of oxidation by Pb(IV) determine the distribution of products.[4c] For example, tertiary and α-arylalkyl carboxylic acids are readily converted into alkenes and esters.[1d,5] In this reaction, the tertiary and secondary radicals undertake a long free-radical chain mechanism, whereas the primary radicals undergo a short-chain mechanism, due to the facile chain transfer of the primary radicals.[1c] Besides LTA, a variety of oxidants, such as manganese (III) salt,[5] and silver (II) salt,[6] are effective for oxidative decarboxylation. Moreover, it has been found that such oxidative decarboxylation can be enhanced by pyridine,[1c,1d] trialkylamines,[1d] or peroxides[1c] or catalyzed by a copper salt,[1c] but it will be inhibited by oxygen.[1c,1d] For the copper salt catalyzed reaction the thermal and pyridine-induced short free-radical chain reaction is replaced by a long-chain reaction because the alkyl radicals are oxidized by Cu(II).[1c] Consequently, the oxidation of valeric acid in benzene via the thermal and the pyridine-induced reactions yields butanes, butenes, butyl esters, and butylbenzenes, whereas only butenes are formed in the presence of a catalytic amount of copper salts.[1c] On the other hand, in the presence of metal halide, the alkyl halides form as major

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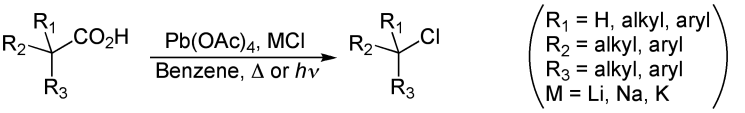
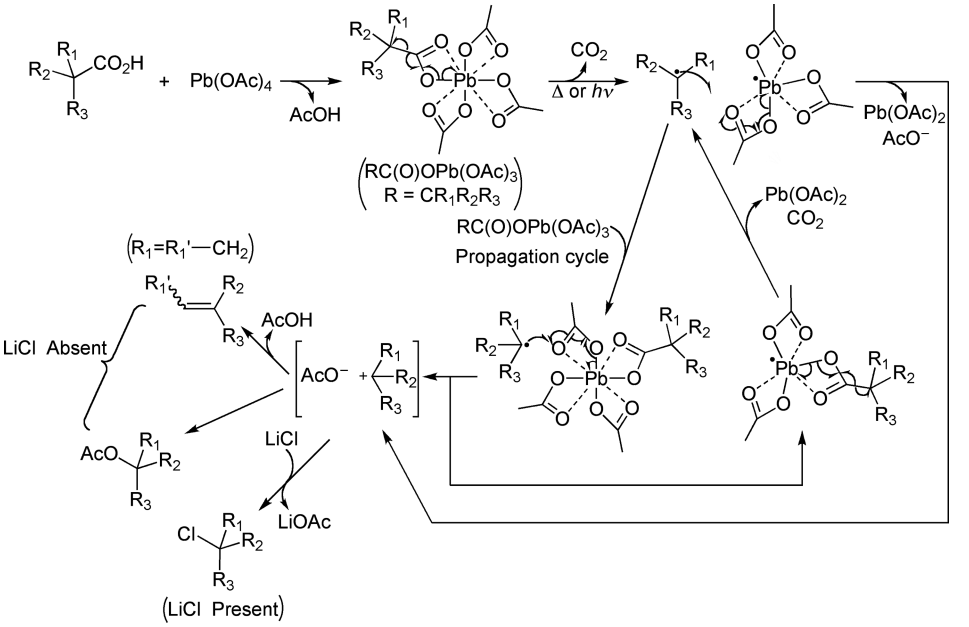
products, depending on the reaction conditions. In general, the yields of alkyl chlorides from secondary and tertiary acids are excellent, if a stoichiometric amount of metal chloride is present; whereas alkyl chlorides vanish if an excess amount of metal chlorides are present.[1d] Moreover, the chloride salts also affect the reaction results, and tetraalkyl ammonium chloride, being soluble, gives no expected product. Potassium or sodium chloride gives the best yield but a slower reaction rate than lithium chloride.[1d] It is interesting that no evidence for the rearrangement of the alkyl moiety has been observed for this reaction, as indicated from the formation of neopentyl chloride from β,β-dimethylbutyric acid. Similarly, alkyl bromides and iodides can also be formed from the oxidative decarboxylation in the presence of corresponding bromide and iodide salts, though relative low yields are obtained.[1d] Although this reaction does not work well for benzoic acid,[1d] the α,β-unsaturated carboxylic acids can undergo the oxidative decarboxylation to afford halogenated olefins using iodosylbenzene or iodosylbenzene diacetate and *N*-bromo, *N*-chloro, or *N*-iodosuccinimide as oxidants.[6] Such modification is especially feasible for the preparation of olefinic bromide with a phenyl group at the β-position.[6] In contrast, no detectable radical intermediate was found for the oxidative decarboxylations of 2-hydroxycarboxylic acids by lead tetraacetate in anhydrous acetic acid.[7]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A general mechanism for this reaction, including the metathesis, initiation by either heat or light, the propagation cycle, and the termination steps in the presence or absence of LiCl, is outlined below.



D. MODIFICATION

This reaction has been modified to occur using different oxidants, such as Mn (III)[5] and silver (II)[6] salts. In particular, the oxidation from iodosylbenzene or iodosylbenzene diacetate with NBS allows the easy preparation of olefinic bromides.[6]

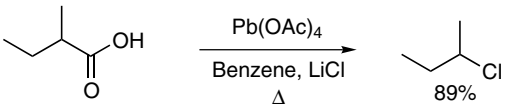
E. APPLICATIONS

This reaction is generally useful for the preparation of secondary and tertiary halides.

F. RELATED REACTIONS

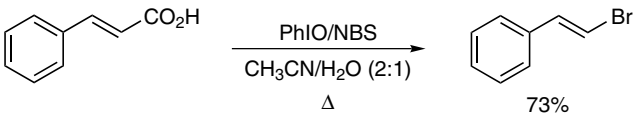
This reaction is related to the *Hunsdiecker Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 1d.

To 10 mL benzene solution containing 0.48 g α-methylbutyric acid (4.7 mmol) was added 2.0 g lead tetraacetate (4.5 mmol). The mixture was stirred at room temperature until homogeneous. Then 0.196 g LiCl (4.5 mmol) was added, and the mixture was immediately flushed with nitrogen to remove oxygen. The surface of the salt at room temperature rapidly achieved a yellow coloration with LiCl. The mixture was placed in a constant-temperature oil bath (81 $\pm$ 0.3°C), and the rate of gas evolution was followed volumetrically. The induction period was very short and gas evolution followed apace. The completion of the reaction resulted in a clear colorless solution and a colorless amorphous solid, and the solution was decanted and extracted with dilute aqueous perchloric acid, followed by a Na_2CO_3 wash. The organic layer was dried over Na_2SO_4. About 89% *sec*-butyl chloride was yielded from this reaction.



Reference 6.

Trans-cinnamic acid (1.0 mmol) and 0.5 mmol iodosylbenzene were dissolved in 10 mL CH_3CN and H_2O (2:1) at 60°C. This mixture was stirred for 10 min, and 1.0 mmol NBS was added. The mixture was stirred for additional 30 min at 60°C. After the reaction was complete, the solvent was evaporated. The aqueous phase was extracted three times with 10 mL ether. The ether phases were dried over $MgSO_4$ and evaporated. The crude reaction

mixture was separated by flash chromatography using petroleum ether as the eluent to afford 73% 2-*trans*-bromo styrene.

Other references related to the Kochi reaction are cited in the literature.[8]

H. REFERENCES

1. (a) Kochi, J. K., *J. Am. Chem. Soc.,* **1965**, *87*, 1811. (b) Kochi, J. K., *J. Am. Chem. Soc.,* **1965**, *87*, 2500. (c) Kochi, J. K., *J. Am. Chem. Soc.,* **1965**, *87*, 3609. (d) Kochi, J. K., *J. Org. Chem.,* **1965**, *30*, 3265.
2. (a) Monnier, M. and Aycard, J. P., *Can. J. Chem.,* **1979**, *57*, 1257. (b) Stolow, R. D. and Giants, T. W., *Tetrahedron Lett*., **1971**, 695. (c) Stolow, R. D. and Giants, T. W., *J. Am. Chem. Soc.,* **1971**, *93*, 3536.
3. Satyanarayana, N. and Nayak, U. R., *Indian J. Chem., Sect. B,* **1985**, *24B*, 799.
4. (a) Trahanovsky, W. S.; Cramer, J. and Brixius, D. W., *J. Am. Chem. Soc.,* **1974**, *96*, 1077. (b) Bacha, J. D. and Kochi, J. K., *J. Org. Chem.,* **1968**, *33*, 83. (c) Kochi, J. K.; Bacha, J. D. and Bethea, T. W., *J. Am. Chem. Soc.,* **1967**, *89*, 6538.
5. Anderson, J. M. and Kochi, J. K., *J. Am. Chem. Soc.,* **1970**, *92*, 2450.
6. Graven, A.; Jørgensen, K. A.; Dahl, S. and Stanczak, A., *J. Org. Chem.,* **1994**, *59*, 3543.
7. Pocker, Y. and Davis, B. C., *J. Am. Chem. Soc.,* **1973**, *95*, 6216.
8. (a) Tanner, D. D. and Osman, S. A. A., *J. Org. Chem.,* **1987**, *52*, 4689. (b) Concepción, J. I.; Francisco, C. G.; Freire, R.; Hernández, R.; Salazar, J. A. and Suárez, E., *J. Org. Chem.,* **1986**, *51*, 402. (c) May, D. D. and Skell, P. S., *J. Am. Chem. Soc.,* **1982**, *104*, 4500. (d) Sheldon, R. A. and Kochi, J. K., *Metal-Catalyzed Oxidations of Organic Compounds,* Academic Press, New York, **1981**. (e) Mannier, M. and Aycard, J. P., *Can. J. Chem.,* **1979**, *57*, 1257. (f) Judhav, P. K. and Nayak, U. R., *Indian J. Chem., Sect. B,* **1978**, *16B*, 947. (g) De Meester, P. and Hodgson, D. J., *J. Am. Chem. Soc.,* **1976**, *98*, 7086. (h) Groves, J. T. and van der Puy, M., *J. Am. Chem. Soc.,* **1975**, *97*, 7118. (i) Pocker, Y. and Davis, B. C., *J. Org. Chem.,* **1975**, *40*, 1625. (j) Fitzpatrick, J. H. and Hopgood, D., *Inorg. Chem.,* **1974**, *13*, 568. (k) Sheldon, R. A. and Kochi, J. K., *Org. React.,* **1972**, *19*, 279. (l) Bartlett, P. D.; Fickes, G. N.; Haupt, F. C. and Helgeson, R., *Acc. Chem. Res.,* **1970**, *3*, 177. (m) Anderson, J. M. and Kochi, J. K., *J. Org. Chem.,* **1970**, *35*, 986. (n) Hertzler, D. V.; Berdahl, J. M. and Eisenbraun, E. J., *J. Org. Chem.,* **1968**, *33*, 2008. (o) Bacha, J. D. and Kochi, J. K., *Tetrahedron,* **1968**, *24*, 2215. (p) Kochi, A. J. and Bacha, J. D., *J. Org. Chem.,* **1968**, *33*, 2746. (q) Starnes, W. H., *J. Am. Chem. Soc.,* **1964**, *86*, 5603. (r) Corey, E. J. and Casanova, J., *J. Am. Chem. Soc.,* **1963**, *85*, 165.

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Koenigs-Knorr Reaction

(Koenigs-Knorr Glycosidation, Koenigs-Knorr Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Koenigs and Knorr in 1901.[1] It is the formation of *O*-glycosides from acetylated glycosyl halides and alcohols or phenols in the presence of a silver or mercury salt that functions as both promoter and halophile. As one of the most widely applied methods for *O*-glycosylation, this reaction has been extensively modified by means of using different promoters (e.g., Ag_2O,[2] Ag_2CO_3,[2] AgOTf,[2] $CdCO_3$,[3] $Hg(CN)_2^4$), different solvents of low polarity (e.g., dichloromethane, cyclohexane and petroleum ether),[4] and various desiccants (Na_2SO_4,[5] $CuSO_4$,[6] $CaCl_2$,[7] Drierite,[8] etc.) to remove the generated water. Therefore, this reaction is generally known as the Koenigs-Knorr method,[2,9] Koenigs-Knorr reaction,[2b,3,9a,10] Koenigs-Knorr synthesis,[2a,3,4b,11] Koenigs-Knorr glycosidation,[12] Koenigs-Knorr glycosylation,[13] or Koenigs-Knorr condensation.[14] Occasionally, this reaction is also referred to as Koenigs-Knorr-Zemplén method[2] or Koenigs-Knorr process.[15]

Under the modified conditions, the Koenigs-Knorr synthesis usually gives only β-*O*-glycosides,[2] except for certain conditions that use mercury salts as promoters.[4b] When carbohydrate itself is applied as an aglycone, the primary OH is considerably more reactive than the secondary OH,[4b] with a relative reactivity on the order of 6-OH >> 3-OH > 4-OH > 2-OH.[4b] For the preparation of alkyl *O*-glycosides, this reaction is generally a solvolysis with an excess amount of alcohol, and the generated water is negligible if compared with the amount of alcohol; therefore, a drying agent is not necessary.[4b] Other modifications of this reaction include the application of glycosyl fluorides as donors[4a] and silver trifluoromethanesulfonate as a promoter for the formation of glycosides from hindered alcohols.[2a]

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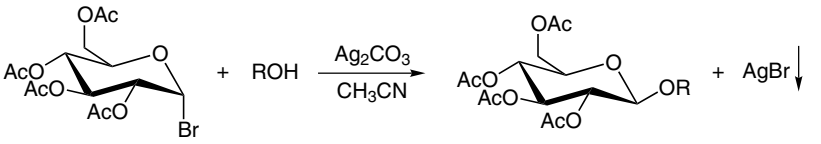
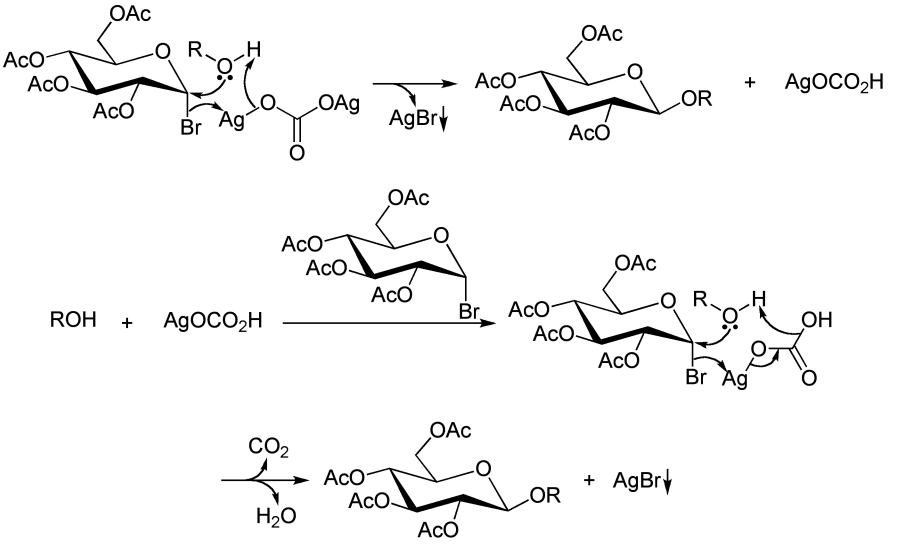
However, because this reaction always requires an excess amount of promoter, it has limited application in large-scale preparations.[2]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been extensively modified to various conditions, including the application of different promoters, solvent systems, and drying agents.

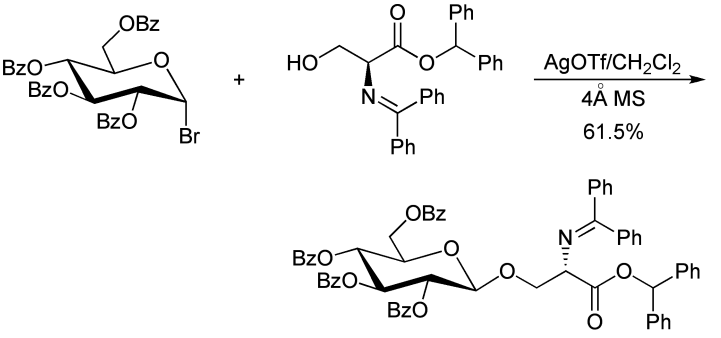
E. APPLICATIONS

This reaction has general application in the preparation of *O*-glycosides.

F. RELATED REACTIONS

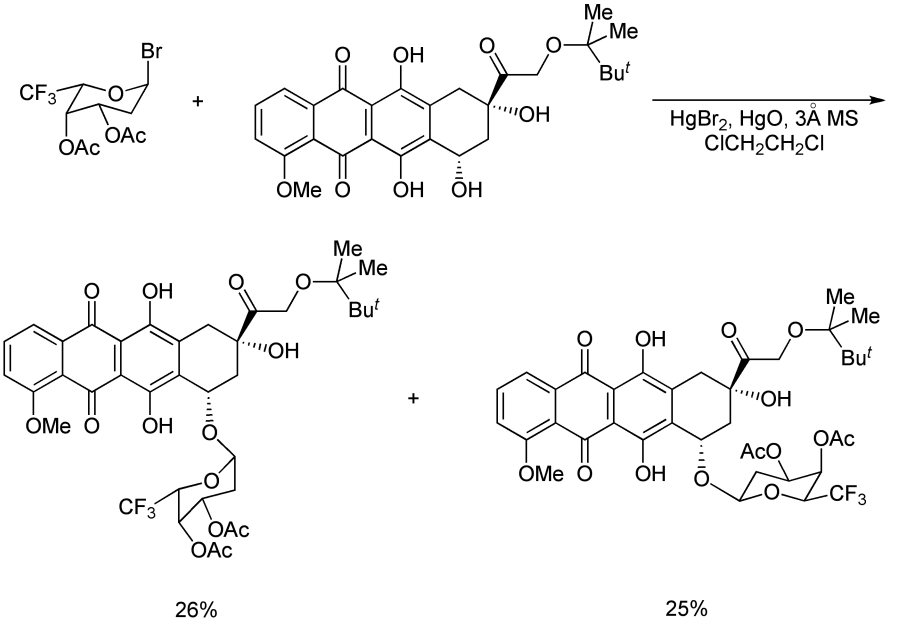
This reaction is related to the *Helferich Glycosylation*, *Hilbert-Johnson Reaction*, and *Kahne Glycosylation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 9a.

A mixture of 1.06 g 2,3,4,6-tetra-*O*-benzoyl-α-bromo-D-glucopyranose (1.61 mmol, 1.40 eq.) and 0.50 g benzhydryl *N*-(diphenylmethylene)-L-serinate (1.15 mmol, 1.0 eq.) was placed in a flame-dried RB flask with 50 mL CH_2Cl_2, along with 1.0 g powdered 4Å molecular sieves under argon and cooled to 0°C. Then 0.45 g AgOTf (1.73 mmol, 1.50 eq.) was added in portions over 45 min. After 14 h, the reaction was complete as monitored by TLC, and the reaction was quenched by the addition of 0.5 mL iPr_2NEt (2.5 eq.) and stirred for an additional 10 min. The solution was filtered through Celite, and the crude solution was washed twice with conc. $Na_2S_2O_3$, twice with conc. Na_2CO_3, and brine and dried over $MgSO_4$. After evaporation on a rotatory evaporator, the crude product was flash chromatographed using 25% EtOAc/hexanes (R_f = 0.33) to obtain 0.72 g diphenylmethyl *N*-diphenylmethylene-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-L-serinate as a white foam, in a yield of 61.5%.



Reference 16.

A mixture of 85 mg 3,4-di-*O*-acetyl-2,6-dideoxy-6,6,6-trifluoro-α-L-*lyxo*-hexopyranosyl bromide (0.24 mmol) and 142 mg 14-*O*-(*tert*-butyldimethylsilyl)adriamycinone

(0.27 mmol) in 4 mL dry 1,2-dichloroethane (freshly distilled from CaH_2) was stirred in the dark in the presence of 498 mg yellow HgO (2.3 mmol), 174 mg $HgBr_2$ (0.48 mmol), and 700 mg 3-Å molecular sieves for 15 h at room temperature. After the addition of $CHCl_3$, the mixture was filtered through a pad of Celite, which was thoroughly washed with $CHCl_3$. The combined filtrates were washed successively with 30% aqueous KI, aqueous $NaHCO_3$, and water; dried over Na_2SO_4; and concentrated. TLC (10:1, toluene/acetone) of the residue showed three spots at $R_f = 0.17$ (an adriamycinone derivative), $R_f = 0.25$ (14-*O*-(*tert*-butyldimethylsilyl)-7-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-6,6,6-trifluoro-β-L-*lyxo*-hexo-pyranosyl)-adriamycinone), and $R_f = 0.28$ (14-*O*-(*tert*-butyldimethylsilyl)-7-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-6,6,6-trifluoro-α-L-*lyxo*-hexo-pyranosyl)-adriamycinone). Separation of the products by column chromatography twice (10:1 toluene/acedtone → 30:1 $CHCl_3$/acetone) gave 50 mg α-anomer (26% yield) and 49 mg β-anomer (25% yield) as red solids.

Other references related to the Koenigs-Knorr reaction are cited in the literature.[17]

H. REFERENCES

1. Koenigs, W. and Knorr, E., *Ber.,* **1901**, *34*, 957.
2. (a) Mastelic, J.; Jerkovic, I.; Vinkovic, M.; Dzolic, Z. and Vikic-Topic, D., *Croat. Chem. Acta,* **2004**, *77*, 491. (b) Fürstner, A.; Radkowski, K.; Grabowski, J.; Wirtz, C. and Mynott, R., *J. Org. Chem.,* **2000**, *65*, 8758.
3. Bernstein, S. and Conrow, R. B., *J. Org. Chem.,* **1971**, *36*, 863.
4. (a) Ali, I. A. I., "Novel Trichloroacetimidates and Their Reactions," Ph.D. dissertation, Suez Canal University, Ismailia, Egypt, **2003**. (b) Bills, A. M., "The Reactivity of the Hydroxyl Groups of Methyl β-D-Glucopyranoside in the Koenigs-Knorr Reaction," Ph.D. dissertation, Institute of Paper Chemistry, Appleton, Wisconsin, USA.
5. Levene, P. A. and Wolfrom, M. L., *J. Biol. Chem*., **1928**, *78*, 525.
6. Schlubach, H. H. and Schroter, G. A., *Ber*., **1928**, *61*, 1216.
7. Helferich, B.; Bohm, E. and Winkler, S., *Ber*., **1930**, *63*, 989.
8. (a) Kreider, L. C. and Evans, W. L., *J. Am. Chem. Soc*., **1936**, *58*, 1661. (b) Reynolds, D. D. and Evans, W. L., *J. Am. Chem. Soc.*, **1938**, *60*, 2559. (c) Kreider, L. C. and Evans, W. L., *J. Am. Chem. Soc*., **1936**, *58*, 797. (d) Kreider, L. C. and Evans, W. L., *J. Am. Chem. Soc*., **1935**, *57*, 229.
9. (a) Mitchell, S. A.; Pratt, M. R.; Hruby, V. J. and Polt, R., *J. Org. Chem.,* **2001**, *66*, 2327. (b) Smits, E.; Engberts, J. B. F. N.; Kellogg, R. M. and van Doren, H. A., *J. Chem. Soc., Perkin Trans. I,* **1996**, 2873. (c) Li, Z. J.; Xiao, G. Q. and Cai, M. S., *Chinese Chem. Lett.,* **1992**, 3, 711. (d) Borrachero Moya, P. and Gomez-Sanchez, A., *Anal. Quim., Ser. C: Quim. Org. Bioquim.,* **1988**, *84*, 55. (e) Schmidt, R. R., *Angew. Chem.,* **1986**, 98, 213. (f) Khokhlov, P. S.; Sokolova, G. D.; Makoveichuk, A. Y. and Chvertkin, B. Y., *Khim. Geterotsiklicheskikh Soedinenii,* **1981**, 1374. (g) Conchie, J. and Levvy, G. A., *Methods Carbohydr. Chem.,* **1963**, 335. (h) Conchie, J. and Levvy, G. A., *Methods Carbohydr. Chem.,* **1963**, 332.
10. (a) Presser, A.; Kunert, O. and Poetschger, I., *Monatsh. Chem.,* **2006**, *137*, 365. (b) Xin, B. W.; Sun, C. J.; Qu, L. Q. and Cao, X. R., *Huaxue Yanjiu Yu Yingyong*, **2003**, *15*, 844. (c) Somsak, L.; Kovacs, L.; Gyollai, V. and Osz, E., *Chem. Commun.,* **1999**, 591. (d) Milovanovic, M. and Stefanovic, M., *J. Serb. Chem. Soc.,* **1993**, *58*, 397. (e) Shimada, K.; Kaji, H. and Kuwabara, K., *J. Chromatograph. Sci.,* **1993**, *31*, 363. (f) Milius, A.; Greiner, J. and Riess, J. G., *New J. Chem.,* **1991**, *15*, 337. (g) Greiner, J.; Milius, A. and Riess, J. G., *Tetrahedron Lett*., **1988**, *29*, 2193.

(h) Weis, A. L.; Brady, R. O. and Shapiro, D., *Chem. Phys. Lipids,* **1985**, *38*, 391. (i) Ricard, A.; Capillon, J. and Quivoron, C., *Poly. Sci. Tech. (Plenum),* **1984**, *24*, 407. (j) Takeo, K.; Kitajima, M. and Fukatsu, T., *Carbohydr. Res.,* **1983**, *112*, 158. (k) Capillon, J.; Ricard, A. and Quivoron, C., *Poly. Preprints,* **1982**, *23*, 168. (l) Koto, S.; Inada, S.; Ogawa, H. and Zen, S., *Carbohydr. Res.,* **1982**, *109*, 276. (m) Temeriusz, A.; Piekarska, B.; Radomski, J. and Stepinski, J., *Carbohydr. Res.,* **1982**, *108*, 298. (n) Liptak, A.; Nanasi, P.; Neszmelyi, A. and Wagner, H., *Carbohydr. Res.,* **1980**, *86*, 133. (o) Takeo, K., *Carbohydr. Res.,* **1980**, *87*, 147. (p) Takeo, K., *Carbohydr. Res.,* **1979**, *77*, 131. (q) Flowers, H. M., *Carbohydr. Res.,* **1979**, *74*, 177. (r) Hirano, S.; Yamasaki, R.; Koto, S. and Iwaki, H., *Carbohydr. Res.,* **1979**, *68*, 147. (s) Igarashi, K., *Adv. Carbohydr. Chem. Biochem.,* **1977**, *34*, 243. (t) Takeo, K., *Carbohydr. Res.,* **1977**, *59*, 258. (u) Wallace, J. E. and Schroeder, L. R., *J. Chem. Soc., Perkin Trans. II,* **1977**, 795. (v) Wallace, J. E. and Schroeder, L. R., *J. Chem. Soc., Perkin Trans. II,* **1976**, 1632. (w) Wallace, J. E. and Schroeder, L. R., *J. Chem. Soc., Perkin Trans. I,* **1976**, 1938. (x) Imperato, F., *J. Org. Chem.,* **1976**, *41*, 3478. (y) Pougny, J. R. and Sinay, P., *Carbohydr. Res.,* **1976**, *47*, 69. (z) Dejter-Juszynski, M. and Flowers, H. M., *Carbohydr. Res.,* **1975**, *41*, 308. (aa) Dejter-Juszynski, M. and Flowers, H. M., *Carbohydr. Res.,* **1974**, *37*, 75. (bb) Knoechel, A.; Rudolph, G. and Thiem, J., *Tetrahedron Lett*., **1974**, 551. (cc) Dejter-Juszynski, M. and Flowers, H. M., *Carbohydr. Res.,* **1973**, 30, 287. (dd) Dejter-Juszynski, M. and Flowers, H. M., *Carbohydr. Res.,* **1973**, *28*, 61. (ee) Dejter-Juszynski, M. and Flowers, H. M., *Carbohydr. Res.,* **1972**, *23*, 41. (ff) Flowers, H. M., *Methods Carbohydr. Chem.,* **1972**, *6*, 474. (gg) Wulff, G. and Roehle, G., *Chem. Ber.,* **1972**, *105*, 1122. (hh) Lloyd, P. F.; Evans, B. and Fielder, R. J., *Carbohydr. Res.,* **1972**, *22*, 111. (ii) Dejter-Juszynski, M. and Flowers, H. M., *Carbohydr. Res.,* **1971**, *18*, 219. (jj) Flowers, H. M., *Carbohydr. Res.,* **1971**, *18*, 211. (kk) Ueno, T.; Kurihara, N.; Hashimoto, S. and Nakajima, M., *Agri. Biol. Chem.,* **1967**, *31*, 1346. (ll) Bills, A. M. and Green, J. W., *J. Chem. Soc. B,* **1967**, 716. (mm) Momose, A.; Iida, R. and Nitta, Y., *Yakugaku Zasshi*, **1965**, *85*, 1032. (nn) Talley, E. A., *Methods Carbohydr. Chem.,* **1963**, 337.

11. (a) Wimmer, Z.; Pechova, L. and Saman, D., *Molecules*, **2004**, *9*, 902. (b) Pavlov, A. E.; Sokolov, V. M. and Zakharov, V. I., *Russ. J. Gen. Chem.,* **2001**, *71*, 1811. (c) Stachulski, A. V. and Lennard, M. S., *J. Chem. Edu.,* **2000**, *77*, 349. (d) Heinkele, G.; Nussbaum, R.; Fischer, P.; Kroemer, H. and Meese, C. O., *Isotopenpraxis,* **1994**, *30*, 213. (e) Banoub, J. and Bundle, D. R., *Can. J. Chem.,* **1979**, *57*, 2091. (f) Baer, H. H.; Rank, W. and Kienzle, F., *Can. J. Chem.,* **1970**, *48*, 1302. (g) Schroeder, L. R. and Green, J. W., *J. Chem. Soc., Org.*, **1966**, 530. (h) Giam, C.-S.; Goldschmid, H. R. and Perlin, A. S., *Can. J. Chem.,* **1963**, *41*, 3074. (i) Allen, P. Z., *Methods Carbohydr. Chem.,* **1962**, *1*, 372. (j) Schmidt, O. Th., *Methods Carbohydr. Chem.,* **1962**, *1*, 349. (k) Finan, P. A. and Warren, C. D., *J. Chem. Soc.,* **1962**, 3089. (l) Goldschmid, H. R. and Perlin, A. S., *Can. J. Chem.,* **1961**, *39*, 2025.
12. (a) Chervin, S. M.; Lowe, J. B. and Koreeda, M., *J. Org. Chem.,* **2002**, *67*, 5654. (b) Seebacher, W.; Haslinger, E. and Weis, R., *Monatsh. Chem.,* **2001**, *132*, 839. (c) Gomez-Sanchez, A.; Garcia-Martin, M. D. G. and Gasch, C., *Carbohdyr. Res.,* **1987**, *164*, 255. (d) Garegg, P. J.; Konradsson, P.; Kvarnström, I.; Norberg, T.; Svensson, S. C. T. and Wigilius, B., *Acta Chem. Scand.,* **1985**, *B39*, 569.
13. (a) Rho, Y. S.; Kim, S. Y.; Kim, W.-J.; Yun, Y. K.; Sin, H. S. and Yoo, D. J., *Synth. Commun.,* **2004**, *34*, 3497. (b) Vidal, S.; Montero, J.-L.; Leydet, A. and Morère, A., *Phosphorus, Sulfur & Silican & Related Elements,* **2002**, *177*, 2363. (c) Bertozzi, C. R. and Kiessling, L. L., *Science,* **2001**, *291*, 2357. (d) Yamada, H. and Nishizawa, M., *J. Org. Chem.,* **1995**, *60*, 386. (e) Plourde, R.; d'Alarcao, M. and Saltiel, A. R., *J. Org. Chem.,* **1992**, *57*, 2606.
14. (a) Temeriusz, A.; Radomski, J.; Stepinski, J. and Piekarska, B., *Carbohydr. Res.,* **1985**, *142*, 146. (b) Magnus, V.; Vikic-Topic, D.; Iskric, S. and Kveder, S., *Carbohydr. Res.,* **1983**, *114*, 209. (c) Temeriusz, A.; Piekarska, B.; Radomski, J. and Stepinski, J., *Pol. J. Chem.,* **1982**, *56*, 141. (d) Hounsell, E. F.; Jones, M. B. and Wright, J. A., *Carbohydr. Res.,* **1978**, *65*, 201.
15. Dong, W.; Li, Y.; Wang, G. and Zhou, Y., *Jiangsu Huagong*, **2005**, *33* (Suppl.), 162.
16. Takagi, Y.; Nakai, K.; Tsuchiya, T. and Takeuchi, T., *J. Med. Chem.,* **1996**, *39*, 1582.

17. (a) Lichtenthaler, F. W.; Lergenmüller, M. and Schwidetzky, S., *Eur. J. Org. Chem.,* **2003**, 3094. (b) Josien-Lefebvre, D. and Le Drian, C., *Helv. Chim. Acta,* **2003**, *86*, 661. (c) Matsumura, S.; Takahashi, S.; Nishikitani, M.; Kubota, K. and Kobayashi, A., *J. Agric. Food Chem.*, **1997**, *45*, 2674. (d) Schmidt, R. R. and Jung, K.-H., "Oligsaccharide Synthesis with Trichloroacetimidates" in *Preparative Carbohydrate Chemistry*, ed. Hanessian, S., Dekker, New York, **1997**, pp. 283–312. (e) Nicolaou, K. C. and Ueno, H., "Oligosaccharide Synthesis from Glycosyl Fluorides and Sulfides" in *Preparative Carbohydrate Chemistry,* ed. Hanessian, S., Dekker, New York, **1997**, pp. 313–338. (f) Hanessian, S., "Glycoside Synthesis Based on the Remote Activation Concept: An Overview" in *Preparative Carbohydrate Chemistry*, ed. Hanessian, S., Dekker, New York, **1997**, pp. 381–388. (g) Tschierske, C.; Joachimi, D.; Müller, H.; Wendorff, J. H.; Schneider, L. and Kleppinger, R., *Angew. Chem. Int. Ed. Engl.,* **1993**, *32*, 1165. (h) Toshima, K. and Tatsuta, K., *Chem. Rev*., **1993**, *93*, 1503. (i) Schmidt, R. R., *Angew. Chem. Int. Ed. Engl.,* **1986**, *25*, 212. (j) Abramson, H. N.; Banning, J. W.; Nachtman, J. P.; Roginski, E. T.; Sardessai, M.; Wormser, H. C.; Wu, J. D.; Nagia, Z.; Schroeder, R. R. and Bernardo, M. M., *J. Med. Chem.,* **1986**, *29*, 1709. (k) Wimmer, Z. and Romanuk, M., *Coll. Czech. Chem. Commun.,* **1982**, *47*, 1878. (l) Paulsen, H., *Angew. Chem. Int. Ed. Engl*., **1982**, *21*, 155. (m) Richmyer, N. K., *Method Carbohydr. Chem.,* **1982**, *1*, 370. (n) Banoub, J. and Bundle, D. R., *Can. J. Chem.,* **1979**, *57*, 2091. (o) Igarashi, K., *Adv. Carbohydr. Chem. Biochem.,* **1977**, *34*, 243.

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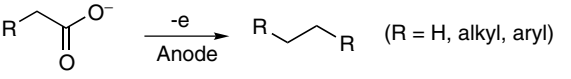
Kolbe Electrolysis

(Kolbe Synthesis, Kolbe Electrosynthesis, Kolbe Electrolytic Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

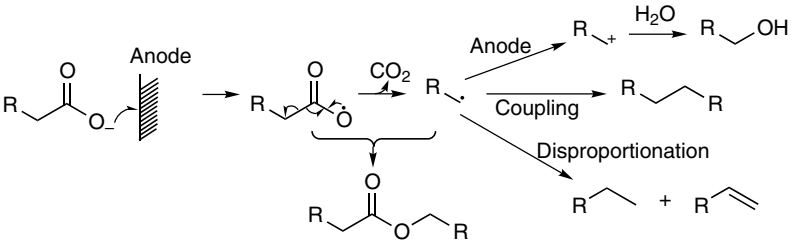
This reaction was first reported by Kolbe in 1849.[1] It is the formation of symmetrical hydrocarbons through the coupling of radicals generated from carboxylic acid at an anode via electrolysis. Therefore, it is generally known as the Kolbe electrolysis,[2] Kolbe synthesis,[3] Kolbe electrosynthesis,[4] or Kolbe electrolytic synthesis.[2aaa,5] Occasionally, this reaction is also referred to as Kolbe hydrocarbon synthesis.[3r,6] It is accepted that this reaction proceeds through a one-electron transfer process at the anode from the carboxylate to form an acyloxy radical, which then undergoes decarboxylation to form an alkyl radical that dimerizes in the end.[3l] In the presence of free radicals, this reaction has been used to initiate the polymerization to prepare low molecular weight polystyrene[7] as well as polymers from vinyl acetate, methyl methacrylate, and vinyl chloride.[2eee] However, under certain conditions, the generated radicals also disproportionate[5i] or lose one more electron to form carbocations; therefore olefins,[8] esters,[3l,5i] ethers[3l] and alcohols[3l] are also formed in this reaction. It is interesting that phenyl 1,2-shift, which occurs frequently for radical intermediates, is not observed during the electrolysis.[2xx]

B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified to occur in liquid ammonia for the electrolysis of ammonium carboxylate.[3q]

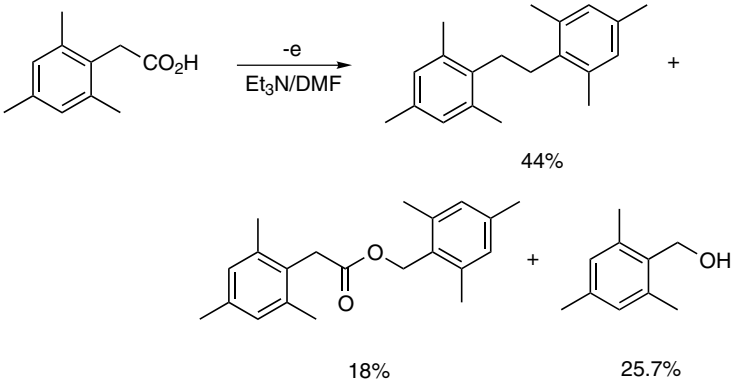
E. APPLICATIONS

This reaction has general application in the preparation of hydrocarbons, especially for the industrial production of special hydrocarbons.

F. RELATED REACTIONS

This reaction is related to the *Hofer-Moest Reaction*.

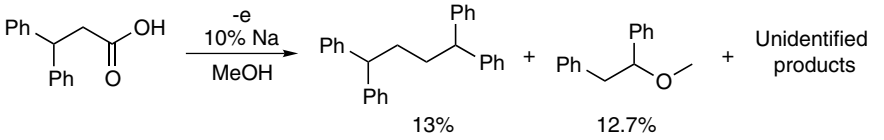
G. CITED EXPERIMENTAL EXAMPLES



Reference 31.

A solution of 3.56 g mesitylacetic acid (20 mmol), 0.6 mL triethylamine, and 30 mL DMF was electrolyzed at 35–50°C at a current density of 16.7–2.5 mA/cm^2 (140–150 V) for 6 h. A total of 0.670 g CO_2 was collected (76%). The solvent was removed under reduced pressure. No acid was recovered by extraction with Na_2CO_3. The reaction mixture was placed on an alumina column and eluted with *n*-hexane to yield 1.17 g 1,2-dimesitylethane,

in a yield of 44%, m.p. 117–119°C. Elution with hexane/benzene (3:2) gave 0.56 g 2,4,6-trimethylbenzyl mesitylacetate, in a yield 18%, m.p. 103–105°C. Further elution with benzene followed by ether gave 0.770 g 2,4,6-trimethylbenzyl alcohol as needles, in a yield of 25.7%, m.p. 89–90°C.



Reference 2xx.

A solution of 2.67 g 3,3-diphenylpropanoic acid in 25 mL absolute methanol containing 27 mg sodium was electrolyzed at 12 F/mol. It was not possible to maintain a constant current since a white precipitate, which obstructed the current flow, formed at the anode. This difficulty was largely overcome by reversing the electrode polarity every 5 min. The electrolysis was continued for a period of 20 h, whereupon the mixture was processed to yield 1.56 g crude syrup. This was chromatographed on 200 g silica gel, using benzene/hexane mixtures gradually enriched in benzene, and finally ether as the eluent. Residues from eluate evaporation, afforded five fractions totaling 97.3% of the charge. Fraction 1 was 1,1,4,4-tetraphenylbutane, which solidified and was recrystallized from hexane as white needles, in a yield of 13%, m.p. 119–122°C. Fraction 2 was an unidentified oil, in a yield of 4.5%. Fraction 3 crystallized and was recrystallized from hexane/benzene to provide a few milligrams of white solid, m.p. 137–139°C, in a yield of 1.1%. The low yield did not provide sufficient material for characterization. Fraction 4 proved to be methyl 1,2-diphenylethyl ether as a clear oil, in a yield of 12.7%. Fraction 5 (68.8% yield) was a crude oil containing at least four components as analyzed from TLC, one of them is similar to 4-phenyl-3,4-dihydrocoumarin, no further identifiable products were isolated from this fraction.

Other references related to the Kolbe electrolysis are cited in the literature.[9]

H. REFERENCES

1. Kolbe, H., *Ann.,* **1849**, *69*, 257.
2. (a) Kurihara, H.; Tajima, T. and Fuchigami, T., *Electrochemistry (Tokyo)*, **2006**, *74*, 615. (b) Ono, Y.; Kim, S.-H.; Yasuda, M. and Nonaka, T., *Electrochemistry (Tokyo)*, **1999**, *67*, 1042. (c) Konig, A., *Praxis Naturwissen., Chem.,* **1999**, *48*, 23. (d) Depecker, C.; Marzouk, H.; Trevin, S. and Devynck, J., *New. J. Chem.,* **1999**, *23*, 739. (e) Goulart, M. O. F. and Schafer, H.-Y., *J. Braz. Chem. Soc.,* **1999**, *10*, 153. (f) Hicks, M. T. and Fedkiw, P. S., *J. Appl. Electrochem.,* **1998**, *28*, 1157. (g) Hicks, M. T. and Fedkiw, P. S., *J. Electrochem. Soc.,* **1998**, *145*, 3728. (h) Fujiwara, H.; Atobe, M.; Nanetsuna, H. and Onaka, T., *J. Chinese Chem. Soc.,* **1998**, *45*, 175. (i) Hiebl, J.; Blanka, M.; Guttman, A.; Kollmann, H.; Leitner, K.; Mayrhofer, G.; Rovenszky, F. and Winkler, K., *Tetrahedron*, **1998**, *54*, 2059. (j) Hiebl, J.; Kollmann, H.; Rovenszky, F. and Winkler, K., *Bioorg. Med. Chem. Lett.,* **1997**, *7*, 2963. (k) Thiemann, T. and Geissler, U., *Naturwissen. Unterricht Chem.,* **1997**, *8*, 22. (l) Schierle, K.; Hopke, J.; Niedt, M.-L.; Boland, W. and Steckhan, E., *Tetrahedron Lett*., **1996**, *37*, 8715. (m) Nuding, G.; Voegtle, F.; Danielmeier, K. and Steckhan, E., *Synthesis*, **1996**, 71.

(n) Harenbrock, M.; Matzeit, A. and Schaefer, H. J., *Liebigs Annalen*, **1996**, 55. (o) Weiguny, J. and Schaefer, H. J., *Liebigs Annalen Chem.*, **1994**, 235. (p) Tashiro, M.; Tsuzuki, H.; Goto, H. and Mataka, S., *Chemistry Express*, **1991**, *6*, 403. (q) Tashiro, M.; Tsuzuki, H.; Goto, H.; Ogasahara, S. and Mataka, S., *J. Labelled Compd. & Radiopharm.,* **1991**, *29*, 475. (r) Sumera, F. C. and Sadain, S., *Philippine J. Sci.,* **1990**, *119*, 333. (s) Tashiro, M.; Tsuzuki, H.; Goto, H.; Ogasahara, S. and Mataka, S., *J. Labelled Compd. & Radiopharm.,* **1990**, *28*, 855. (t) Weiper, A. and Schaefer, H. J., *Angew. Chem.,* **1990**, *102*, 228. (u) Schaefer, H. J., *Top. Curr. Chem.,* **1990**, *152*, 91. (v) Dandge, C. N.; Naik, D. G. and Kapadi, A. H., *Indian J. Chem., Sect. B,* **1988**, *27B*, 854. (w) Becking, L. and Schaefer, H. J., *Tetrahedron Lett*., **1988**, *29*, 2801. (x) Schaefer, H. J., *Studies Org. Chem. (Amsterdam)*, **1987**, *30*, 3. (y) Bestmann, H. J.; Roth, K.; Michaelis, K.; Vostrowsky, O.; Schaefer, H. J. and Michaelis, R., *Liebigs Annalen Chem*., **1987**, 417. (z) Seebach, D. and Renaud, P., *Helv. Chim. Acta,* **1985**, *68*, 2342. (aa) Feldhues, M. and Schafer, H. J., *Tetrahedron*, **1985**, *41*, 4213. (bb) Huhtasaari, M.; Schaefer, H. J. and Becking, L., *Angew. Chem.,* **1984**, *96*, 995. (cc) Levy, P. F.; Sanderson, J. E. and Cheng, L. K., *J. Electrochem. Soc.,* **1984**, *131*, 773. (dd) Huhtasaari, M.; Schaefer, H. J. and Luftmann, H., *Acta Chem. Scand., Ser. B,* **1983**, *B37*, 537. (ee) Sanderson, J. E.; Levy, P. F.; Cheng, L. K. and Barnard, G. W., *J. Electrochem. Soc.,* **1983**, *130*, 1844. (ff) Jensen, U. and Schaefer, H. J., *Chem. Ber.,* **1981**, *114*, 292. (gg) Schaefer, H. J., *Chem. Phys. Lipids,* **1979**, *24*, 321. (hh) Waefler, J. P. and Tissot, P., *Electrochimica Acta*, **1978**, *23*, 899. (ii) Knolle, J. and Schaefer, H. J., *Electrochimica Acta*, **1978**, *23*, 5. (jj) Kluenenberg, H. and Schaefer, H. J., *Angew. Chem.,* **1978**, *90*, 48. (kk) Seidel, W.; Knolle, J. and Schaefer, H. J., *Chem. Ber.,* **1977**, *110*, 3544. (ll) Eberson, L.; Nyberg, K. and Servin, R., *Acta Chem. Scand., Ser. B,* **1976**, *B30*, 906. (mm) Ogumi, Z.; Tari, I.; Takehara, Z. and Yoshizawa, S., *Bull. Chem. Soc. Jpn.,* **1976**, *49*, 841. (nn) Eberson, L.; Nyberg, K.; Servin, R. and Wennerbeck, I., *Acta Chem. Scand., Ser. B,* **1976**, *B30*, 186. (oo) Knolle, J. and Schaefer, H. J., *Angew. Chem.,* **1975**, *87*, 777. (pp) Coleman, J. P.; Lines, R.; Utley, J. H. P. and Weedon, B. C. L., *J. Chem. Soc., Perkin Trans. II,* **1974**, 1064. (qq) Eberson, L. and Ryde-Petterson, G., *Acta Chem. Scand.,* **1973**, *27*, 1159. (rr) Takeda, A.; Moriwake, T.; Torii, S. and Takaki, T., *Bull. Chem. Soc. Jpn.,* **1972**, *45*, 3718. (ss) Schaefer, H. and Pistorius, R., *Angew. Chem. Int. Ed. Engl.,* **1972**, *11*, 841. (tt) Van Zorge, J. A.; Strating, J. and Wynberg, H., *Rec. Trav. Chim. Pays-Bas*, **1970**, *89*, 781. (uu) Haufe, J. and Beck, F., *Chem. Ingen. Technik,* **1970**, *42*, 170. (vv) Smith, W. B. and Yuh, Y. H., *Tetrahedron*, **1968**, *24*, 1163. (ww) Ungureanu, C., *Mater. Plast. (Bucharest),* **1964**, *1*, 193. (xx) Bonner, W. A. and Mango, F. D., *J. Org. Chem.,* **1964**, *29*, 430. (yy) Wilshir, J. F. K., *Aust. J. Chem.,* **1963**, *16*, 432. (zz) Smith, W. B. and Manning, D. T., *J. Poly. Sci.,* **1962**, *59*, S45. (aaa) Eberson, L., *J. Org. Chem.,* **1962**, *27*, 3706. (bbb) Smith, W. B. and Gilde, H. G., *J. Am. Chem. Soc.,* **1961**, *83*, 1355. (ccc) Thiessen, G. W., *Record Chem. Prog.,* **1960**, *21*, 243. (ddd) Finkelstein, M. and Petersen, R. C., *J. Org. Chem.,* **1960**, *25*, 136. (eee) Smith, W. B. and Gilde, H.-G., *J. Am. Chem. Soc.,* **1960**, *82*, 659. (fff) Eberson, L., *Acta Chem. Scand.,* **1959**, *13*, 40. (ggg) Smith, W. B. and Gilde, H. G.,*J. Am. Chem. Soc.,* **1959**, *81*, 5325. (hhh) Overberger, C. G. and Kabasakalian, P., *J. Org. Chem.,* **1956**, *21*, 1124. (iii) Thiessen, G. W. and Miller, R., *J. Am. Chem. Soc.,* **1955**, *77*, 770.

3. (a) Khidirov, Sh. Sh. and Khibiev, Kh. S., *Russ. J. Electrochem.,* **2005**, *41*, 1176. (b) Chechina, O. N.; Tomilov, A. P. and Sokolov, S. V., *Russ. J. Gen. Chem.,* **2005**, *75*, 719. (c) Chechina, O. N.; Sokolov, S. V. and Tomilov, A. P., *Russ. J. Gen. Chem.,* **2004**, *74*, 1714. (d) Chechina, O. N.; Lunin, E. V.; Berenblit, V. V.; Sokolov, S. V.; Zharikova, M. V. and Kim, S. N., *Zh. Prikladnoi Khim.,* **1990**, *63*, 1186. (e) Jensen-Korte, U. and Schaefer, H. J., *Liebigs Annalen Chem.*, **1982**, 1532. (f) Seidel, W. and Schaefer, H. J., *Chem. Ber.,* **1980**, *113*, 3898. (g) Cornelia, R., *Revista Fizica Chim.,* **1980**, *17*, 91. (h) Plzak, V. and Wendt, H., *Ber. Bunsen-Gesellschaft,* **1979**, *83*, 481. (i) Shreider, V. A.; Rozhkov, I. N. and Knunyants, I. L., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1977**, 486. (j) Beck, F., *Electrochimica Acta*, **1973**, *18*, 359. (k) Fleischmann, M.; Mansfield, J. R. and Wynne-Jones, W. F. K., *J. Electroanal. Chem.,* **1965**, *10*, 522. (l) Rand, L. and Hohar, A. F., *J. Org. Chem.,* **1965**, *30*, 3885. (m) Smets, G.; van der Borght, X. and van Haeren, G., *J. Poly. Sci., Part A,* **1964**, *2*, 5187. (n) Karabinos, J. V., *Science Counselor,* **1954**, *17*, 3. (o) Wideqvist, S., *Arkiv. Kemi*, **1954**, *7*, 229. (p) Pasquinelli, E. A., *Anales Asoci. Quim. Argentina,* **1943**, *31*, 181.

(q) Harris, S. and Pierce, J. S., *J. Am. Chem. Soc.,* **1940**, *62*, 2223. (r) Fulton, R. A. and Bergstrom, F. W., *J. Am. Chem. Soc.,* **1934**, *56*, 167. (s) Fichter, F. and Schinde, A., *Helv. Chim. Acta,* **1930**, *13*, 103.

4. (a) Smirnova, N. V.; Neganova, E. G.; Astaf'ev, E. A.; Petrii, O. A.; Tsirlina, G. A. and Beletskaya, I. P., *Russ. J. Electrochem.,* **2001**, *37*, 893. (b) Limaye, P. A.; Kantak, S. M. and Nimse, M. S., *Asian J. Chem.,* **1999**, *11*, 181. (c) Vassil'ev, Y. B. and Grinberg, V. A., *J. Electroanal. Chem.,* **1992**, *336*, 281. (d) Singh, K. N.; Singh, M. and Misra, R. A., *Indian J. Chem., Sect. B,* **1991**, *30B*, 867. (e) Tumanskii, B. L.; Grinberg, V. A.; Vasil'ev, Y. B.; Bubnov, N. N.; Gervits, L. L. and Makarov, K. N., *Elektrokhimiya*, **1990**, 26, 1052. (f) Vasl'ev, Y. B. and Grinberg, V. A., *J. Electroanal. Chem. & Interfacial Electrochem.,* **1990**, *283*, 359. (g) Koval'chuk, E. P. and Tomilov, A. P., *Elektrokhimiya*, **1989**, *25*, 799. (h) Vasil'ev, Y. B.; Skundin, A. M.; Grinberg, V. A.; Zaidenberg, A. Z.; Kazarinov, V. E.; Kalinin, Y. K. and Dyukkiev, E. F., *Elektrokhimiya,* **1986**, *22*, 1529. (i) Lotvin, B. M. and Vasil'ev, Y. B., *Elektrokhimiya*, **1986**, *22*, 1024. (j) Cervino, R. M.; Triaca, W. E. and Arvia, A. J., *J. Electroanal. Chem. & Interfacial Electrochem.,* **1984**, *172*, 255. (k) Rabjohn, N. and Flasch, G. W., *J. Org. Chem.,* **1981**, *46*, 4082. (l) Lushnikov, V. I.; Khazova, O. A.; Gromyko, V. A. and Vasil'ev, Y. B., *Elektrokhimiya,* **1981**, *17*, 176. (m) Lushnikov, V. I.; Kanevskii, L. S. and Vasil'ev, Y. B., *Elektrokhimiya*, **1979**, *15*, 1438. (n) Seko, M.; Yomiyama, A. and Isoya, T., *Chem. Economy & Eng. Rev.,* **1979**, *11*, 48. (o) Gurjar, V. G., *J. Appl. Electrochem.,* **1978**, *8*, 207. (p) Bruno, F. and Dubois, J. E., *Bull. Soc. Chim. Fr,* **1973**, 2270. (q) Bruno, F. and Dubois, J. E., *Electrochimica Acta*, **1972**, *17*, 1161. (r) Dubois, J. E. and Bruno, F., *Compt. Rend.,* **1970**, *271*, 791. (s) Eberson, L., *J. Am. Chem. Soc.,* **1969**, *91*, 2402. (t) Weinberg, N. L. and Weinberg, H. R., *Chem. Rev.,* **1968**, *68*, 449. (u) Toy, M. S., *J. Electrochem. Soc.,* **1967**, *114*, 1042. (v) Vigh, A. K. and Conway, B. E., *Fresen. Zeitsch. Anal. Chem*., **1967**, *230*, 81. (w) Eberson, L., *Electrochem. Tech.*, **1967**, *12*, 1473. (x) Conway, B. E. and Vijh, A. K., *Fresen. Zeitsch. Anal. Chem*., **1967**, *224*, 149. (y) Conway, B. E. and Vijh, A. K., *Electrochimica Acta*, **1967**, *12*, 102. (z) Conway, B. E. and Vijh, A. K., *J. Org. Chem.,* **1966**, *31*, 4283. (aa) Sasaki, K.; Uneyama, K. and Nagaura, S., *Electrochimica Acta*, **1966**, *11*, 891. (bb) Girina, G. P.; Fioshin, M. Y. and Kazarinov, V. E., *Elecktrokhimiya*, **1965**, *1*, 478. (cc) Fioshin, M. Y.; Vasil'ev, Y. B. and Gaginkina, E. G., *Dokl. Akad. Nauk SSSR,* **1960**, *135*, 909. (dd) Nguyen, N. D., *Acta Chem. Scand.,* **1958**, *12*, 585. (ee) Wilson, C. L. and Lippincott, W. T., *J. Electrochem. Soc.,* **1956**, *103*, 672. (ff) Fichter, F. and Stenzl, H., *Helv. Chim. Acta,* **1939**, *22*, 970. (gg) Glasstone, S. and Hickling, A., *Trans. Electrochem. Soc.,* **1939**, *75*, 18.

5. (a) Sugiya, M. and Nohira, H., *Chem. Lett.,* **1998**, 479. (b) Eberson, L.; Granse, S. and Olofsson, B., *Acta Chem. Scand.,* **1968**, *22*, 2462. (c) Eberson, L. and Nilsson, S., *Acta Chem. Scand.,* **1968**, *22*, 2453. (d) Eberson, L. and Sandberg, B., *Acta Chem. Scand.,* **1966**, *20*, 739. (e) Eberson, L. and Nyberg, K., *Acta Chem. Scand.,* **1964**, *18*, 1568. (f) Eberson, L. and Nyberg, K., *Acta Chem. Scand.,* **1964**, *18*, 1567. (g) Eberson, L., *Acta Chem. Scand.,* **1963**, *17*, 2004. (h) Eberso, L., *Svensk Kern. Tidskr.*, **1963**, *75*, 115. (i) Eberson, L, *J. Org. Chem.,* **1962**, *27*, 2329. (j) Weedon, B. C. L., *Adv. Org. Chem. Methods Results,* **1960**, *1*, 1.

6. (a) Fichter, F. and Leupin, O., *Helv. Chim. Acta,* **1938**, *21*, 616. (b) Fichter, F. and Meyer, R. E., *Helv. Chim. Acta,* **1933**, *16*, 1408. (c) Fichter, Fr. and Humpert, K., *Helv. Chim. Acta,* **1926**, *9*, 692.

7. (a) Goldschmidt, S., *Angew. Chem.,* **1957**, *69*, 132. (b) Goldschmidt, S. and Stöckel, E., *Ber.,* **1952**, *85*, 630.

8. Sakata, T.; Kawai, T. and Hashimoto, K., *J. Phys. Chem.,* **1984**, *88*, 2344.

9. (a) Sugiya, M. and Nohira, H., *Bull. Chem. Soc. Jpn*., **2000**, *73*, 705. (b) Sugiya, M. and Noshira, H., *Chem. Lett.,* **1998**, 479. (c) Weiguny, J. and Schäfer, H. J., *Ann.,* **1994**, 225. (d) Vijh, A. K. and Conway, B. E., *Chem. Rev.,* **1967**, *67*, 623. (e) Wilson, C. L. and Lippincott, W. T., *J. Am. Chem. Soc.,* **1956**, *78*, 4290. (f) Weedon, B. C. L., *Quart. Rev.,* **1956**, *6*, 380. (g) Glasstone, S. and Hickling, A., *Trans. Electrochem. Soc.,* **1939**, *75*, 333. (h) Glasstone, S. and Hickling, A., *Ber.,* **1939**, *25*, 425. (i) Hofer, H. and Moest, M., *Ann.,* **1902**, *323*, 284. (j) Crum Brown, A. and Walker, J., *Ann.,* **1891**, *261*, 107.

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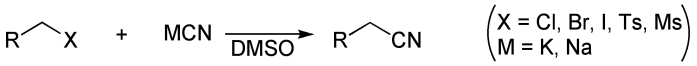
Kolbe Nitrile Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was reported by Kolbe before 1884.[1] It is the synthesis of nitriles via S_N2 substitution between an alkali metal cyanide and an alkyl halide, tosylate, or mesylate and is generally known as the Kolbe nitrile synthesis.[1,2] This reaction works best for primary alkylating agents in a polar aprotic solvent, such as DMSO,[3] HMPA,[4] or NMP.[5] The secondary bromides might give moderate yields of corresponding nitriles as well; however, the tertiary halides may end up with the elimination products, because the alkali metal cyanide functions as a base too. Because cyanide is a bident nucleophile, it can also result in an isonitrile as a by-product, especially when AgCN or CuCN is used as a nucleophile.[2b] This reaction has been modified to use a phase-transfer catalyst[6] and has recently been carried out in various ionic liquids, such as [bmim][BF_4] (1-butyl-3-methyl imidazolium tetrafluoroborate),[5] [bmim][PF_6], [bmim][$N(Tf)_2$] (1-butyl-3-methyl imidazolium bis(trifluoromethylsulfonyl) imide), and [hpyr][$N(Tf)_2$] (1-hexylpyridinium bis(trifluoromethylsulfonyl) imide).[7] This reaction has been applied to extend the carbon chain of carboxylic acid via the reduction of acid to alcohol followed by the hydrolysis of a new nitrile generated through substitution of the corresponding tosylate of the reduced alcohol. It should be pointed out that the configuration of a stereocenter adjacent to the carboxy function is retained in this reaction.[2c]

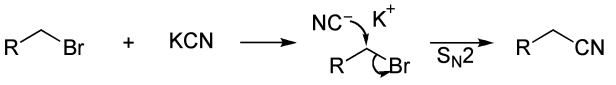
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

The mechanism is represented by the substitution between a primary bromide and potassium cyanide. The potassium cyanide may exist as contact or loose ion pairs or may even dissociate into free cyanide anion, depending on the reaction conditions, but mostly on the chosen solvents.



D. MODIFICATION

This reaction has been modified to occur under the conditions of either an ionic liquid[5,7] or in the presence of a phase-transfer catalyst.[6]

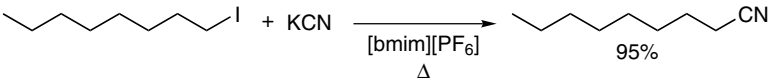
E. APPLICATIONS

This reaction has general application in the preparation of nitriles.

F. RELATED REACTIONS

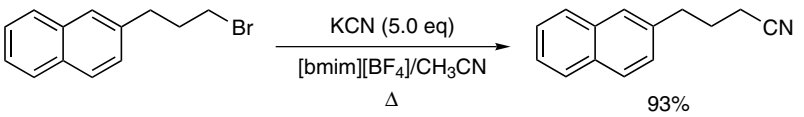
This reaction is related to the S_N2 *Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

Reactions were carried out in a screw cup with Teflon-faced rubber septum vials under magnetic stirring. To a suspension of 3 mmol KCN in 2 mL ionic liquid [bmim][PF_6], stirred overnight at 80°C was added 1 mmol 1-iodo-*n*-octane. The mixture was stirred at 80°C for 7 h, and then the product was extracted with Et_2O (1 mL × 5). The combined organic layers were dried over $MgSO_4$, and concentrated to give 95% 1-nanonitrile.



Reference 5.

Potassium cyanide (325 mg, 5 mmol) was added to a mixture of 249 mg 2-(3-bromopropyl)naphthalene (1.0 mmol) and 3.0 mL [bmim][BF_4] in 3.0 mL acetonitrile. The mixture was stirred at 50°C for 30 min. The reaction mixture was extracted from the ionic liquid phase with Et_2O (7 mL × 3). The ether layers were combined and dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/hexane) to yield 181 mg 2-(3-cyanopropyl)naphthalene (0.93 mmol) as a white solid, in a yield of 93%.

Other references related to the Kolbe nitrile synthesis are cited in the literature.[8]

H. REFERENCES

1. See www.chemie.uni-marburg.de/en/haupt_historie.html.
2. (a) See http://www.organic-chemistry.org/abstracts/literature/545.shtm. (b) See www.organic-chemistry.org/namedreactions/kolbe-nitrile-synthesis.shtm. (c) Zhao, X. Q., "Development of New GABA Uptake Inhibitors Derived from Proline or from Pyrrolidin-2-yl Acetic Acid," Ph.D. dissertation, Fakultät fur Chemie und Pharmazie der Ludwig-Maximilians Universität München, May **2002**.
3. Martin, D.; Weise, A. and Niclas, H., *Angew. Chem. Int. Ed. Engl*., **1967**, *6*, 318.
4. Normant, H., *Angew. Chem. Int. Ed. Engl*., **1967**, *6*, 1046.
5. Kim, D. W.; Song, C. E. and Chi, D. Y., *J. Org. Chem.,* **2003**, *68*, 4281.
6. Varma, R. S. and Naicker, K. P., *Tetrahedron Lett.,* **1998**, *39*, 2915.
7. Chiappe, C.; Pieraccini, D. and Saullo, P., *J. Org. Chem.,* **2003**, *68*, 6710.
8. (a) Detert, H. and Sugiono, E., *Synth. Metals,* **2000**, *115*, 89. (b) Protiva, M.; Polivka, Z.; Licha, I.; Grimova, J. and Maturova, E., *Czech. Pat.*, Jan. 15, **1988**, 254,741. (c) Polivka, Z. and Protiva, M., *Czech. Pat.*, Jan. 15, **1988**, 254,742.

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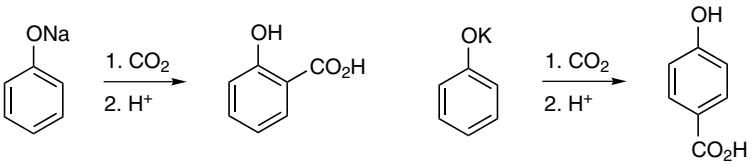
Kolbe-Schmidt Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Kolbe in 1860[1] and subsequently by Schmidt in 1886.[2] It is the preparation of *ortho*- or *para*-hydroxyl benzoic acid from carbon dioxide and sodium or potassium phenolate and is generally known as the Kolbe-Schmidt reaction.[3] In addition, this reaction is also referred to as the Kolbe-Schmidt carboxylation[3c] or Kolbe-Schmidt synthesis.[4] It has been found that heating the mixture of phenol, potassium carbonate, and carbon dioxide also results in the formation of hydroxyl benzoic acid.[3e] It is interesting that the sodium phenolate always leads to the formation of *ortho*-hydroxyl benzoic acid, (i.e., salicylic acid), whereas potassium phenolate often results in the production of *para*-hydroxyl benzoic acid. Even though the mechanism is not quite clear, it is possible that sodium phenolate exists as contact ion pairs, of which sodium cation coordinates with one oxygen of CO_2 that prefers the formation of salicyclic acid; in contrast, potassium phenolate forms dissociated ion pairs and thus attacks CO_2 through the *para*-position. Although in most cases, this reaction is feasible only with the highly activated phenols (with more electron-donating groups), some phenols with electron-withdrawing groups such as CF_3 also undergo this reaction,[3e] and such a reaction even occurs for 3-hydroxy pyridine[3c] and hydroxyl-2(1*H*)-pyridinone.[5]

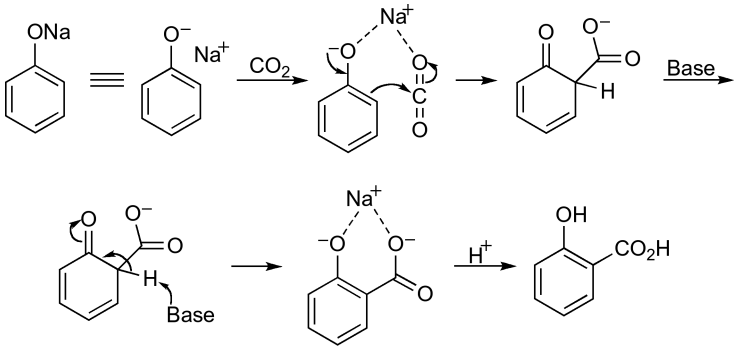
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The mechanism is illustrated by the reaction between sodium phenolate and carbon dioxide to give salicyclic acid.



(Base = phenolate or carboxylate)

D. MODIFICATION

N/A

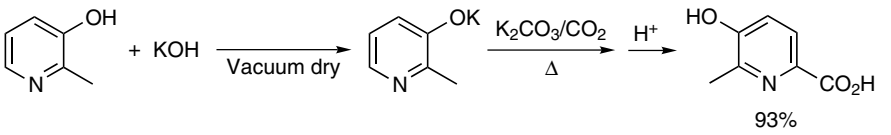
E. APPLICATIONS

This reaction has general application in the preparation of aromatic acids with strong electron-donating group(s).

F. RELATED REACTIONS

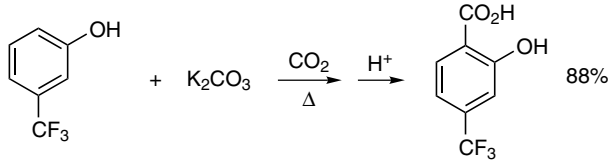
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3c.

The dry potassium salt of 2-methyl-3-hydroxypyridine was prepared by dissolving this compound in an equivalent amount of 2.5 *N* aqueous KOH, concentrating this solution to a thick glass on a steam bath under a nitrogen stream and completing the drying at 70°C in a vacuum oven. A mixture of 27 g of this potassium salt (0.18 mol) and 38 g anhydrous K_2CO_3 (0.28 mol) was thoroughly ground in a ball mill for 1 h. The resulting fine powder was quickly transferred to a hydrogenation bomb, which was charged to a pressure of 500 psi with CO_2 and heated with rocking at 250°C for 9 hours. Rocking was continued as the bomb was allowed to cool to room temperature. In a series of experiments, the pressure drop always amounted to 80–100% of that calculated for the absorption of 1 mol CO_2 per mole of 2-methyl-3-hydroxypyridine. Using 350 mL boiling water in portions, the contents of the bomb were removed, the mixture was heated to boiling and filtered hot, and the filtrate was acidified to pH = 2 with H_2SO_4. The CO_2 was driven off by boiling, and the mixture, cooled to room temperature, was rapidly adjusted to pH 7.3–7.4 with conc. NaOH solution. Filtration at this point gave 23 g 5-hydroxy-6-methylpicolinic acid, and continuous extraction of the filtrate with methylene chloride, maintaining the pH at 7.3, led to a recovery of 3 g 2-methyl-3-hydroxypyridine. The aqueous phase then was acidified to pH = 3 with H_2SO_4 and thoroughly extracted with *n*-butyl alcohol. Concentration of the *n*-butyl alcohol extracts gave an additional 4 g 5-hydroxy-6-methylpicolinic acid, bringing the total to 27 g of material (93% yield, based on consumed 2-methyl-3-hydroxypyridine), melting > 240°C (dec.)



Reference 3e.

The mixture of 48.6 g *m*-trifluoromethylphenol (0.3 mol) and 124.4 g anhydrous K_2CO_3 (0.90 mol) were intimately dispersed in a 250-mL copper bomb, and carbon dioxide gas from a commercial cylinder was introduced at 300 psi at room temperature. The temperature was allowed to rise very slowly over a period of 10 days to 220°C. It was noted that some carbon dioxide was absorbed even at room temperature and that at 140°C the reaction was essentially completed. As CO_2 was taken up, additional gas was introduced. The reaction time can be shortened by raising the temperature much more rapidly. However, there are indications that a fairly slow rise in temperature is beneficial, and an immediate increase of the temperature to > 140°C is not recommended. At the completion of the reaction, the bomb was cooled, vented, and opened. The product was a hard cake, which was dissolved

in hot water. The solution was extracted with ether, decolorized with charcoal, and acidified with concentrated HCl. An 88% yield of 4-trifluoromethylsalicylic acid was isolated with only a trace amount of detectable phenol. Crystallization from alcohol and water yielded pure compound as white needles, m.p. 178–178.5°C.

Other references related to the Kolbe-Schmidt reaction are cited in the literature.[6]

H. REFERENCES

1. Kolbe, H., *Ann.*, **1860**, *113*, 125.
2. Schmidt, R., *J. Prakt. Chem.*, **1885**, *31*, 397.
3. (a) Parales, R. E.; Bruce, N. C.; Schmid, A. and Wackett, L. P., *App. Environ. Microbiol.*, **2002**, *68*, 4699. (b) Braunstein, P.; Matt, D. and Nobel, D., *Chem. Rev.*, **1988**, *88*, 747. (c) Rapoport, H. and Volcheck, E. J., *J. Am. Chem. Soc.*, **1956**, *78*, 2451. (d) Hunt, S. E.; Jones, J. I. and Lindsey, A. S., *Chem. Ind. (London)*, **1955**, 417. (e) Hauptschein, M.; Nodiff, E. A. and Saggiomo, A. J., *J. Am. Chem. Soc.*, **1954**, *76*, 1051. (f) Negoro, K., *J. Soc. Org. Synth. Chem. Jpn.*, **1954**, *12*, 457. (g) Gershzon, G. I., *Zh. Obsh. Khim.*, **1943**, *13*, 68.
4. Silin, N. F. and Moshchinskaya, N. K., *Zh. Obsh. Khim.*, **1938**, *8*, 810.
5. Gorden, A. E. V.; Xu, J. D.; Raymond, K. N. and Durbin, P., *Chem. Rev.*, **2003**, *103*, 4207.
6. (a) Rahim, M. A.; Matsui, Y. and Kosugi, Y., *Bull. Chem. Soc. Jpn.*, **2002**, *75*, 619. (b) Kosugi, Y.; Takahashi, K. and Imaoka, Y., *J. Chem. Res. (S)*, **1999**, 114. (c) Yamaguchi, M.,*Pure & Appl. Chem.*, **1998**, *70*, 1091. (d) Gressier, J. C., *Eur. Polymer J.*, **1989**, *25*, 133. (e) Monastyrskii, V. N.; Tsvetkov, O. N.; Dmitrieva, N. A.; Kazakov, E. I. and Korenev, K. D., *Chemistry and Technology of Fuels and Oils (Hist. Arch.)*, **1970**, *6*, 180. (f) Lindsey, A. S. and Jeskey, H., *Chem. Rev.*, **1957**, *57*, 583. (g) Hales, J. L.; Jones, J. I. and Lindsey, A. S., *J. Chem. Soc.*, **1954**, 3145. (h) Carpenter, A. T. and Hunter, R. F., *J. Appl. Chem.*, **1953**, *3*, 486. (i) Gershzon, G. I., *Zh. Obsh. Khim.*, **1944**, *14*, 447.

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Kondrat'eva Pyridine Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

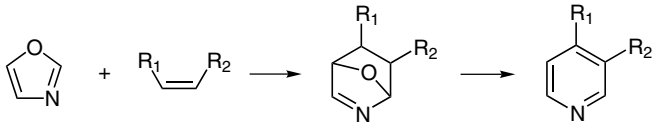
This reaction was first reported by Kondrat'eva in 1957.[1] It is a general method for synthesizing pyridine derivatives involving an inverse demand *Diels-Alder Cycloaddition* between an azadiene (especially the oxazoles) and a dienophile followed by an extrusion of the resulting bridge of the bicyclic intermediate. Thus this reaction is known as the Kondrat'eva pyridine synthesis,[2]Kondrat'eva reaction,[2a] Kondrat'eva cycloaddition,[2,3] or Kondrat'eva approach.[2a,4]

When substituted oxazole is applied as a diene, the dienophiles are usually derived from 2-butene-1,4-diols.[4] In addition, the derivatives of maleic acid and fumaric acid are also good dienophiles.[5] On the other hand, only certain isooxazoles of particular substituted patterns undergo cycloaddition to give pyridine derivatives. For example, 4-methyl-oxazole reacts with either electron-rich or electron-deficient alkenes, and the resulting bicycles can decompose via three different routes: loss of water to pyridine; expelling of a substituent (R) to form 3-pyridinol, depending on the substituent R on alkenes; or oxidative scission to give a different 3-pyridinol.[2b] In addition, an intramolecular version of Kondrat'eva pyridine synthesis between the tethered oxazole and the alkene generally proceeds smoothly.[6]

However, the extremely activated oxazoles, such as 5-amino-oxazole, can undergo different patterns of cycloaddition, including [2 + 4], [2 + 3], and even [2 + 2] cycloaddition, according to the reaction conditions.[7]

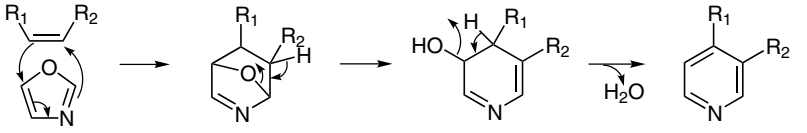
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

In general, the Kondrat'eva pyridine synthesis involves an inverse demand *Diels-Alder Cycloaddition* between an azadiene and a dienophile followed by the extrusion of a part of the resulting bicyclic intermediate to give a pyridine derivative, as illustrated here.



D. MODIFICATION

This reaction has been modified extensively to include the cycloaddition of pyrimidines,[8] pyrazines,[9] 1,2,3-triazene,[10] and 1,2,4-triazenes[11] with dienophiles to give a variety of pyridine derivatives.

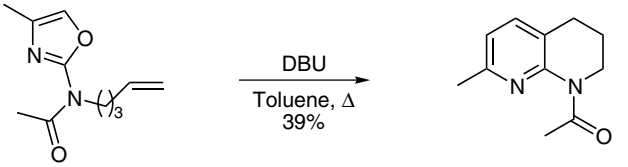
E. APPLICATIONS

This reaction has wide application in the preparation of pyridine derivatives and other heterocycles.

F. RELATED REACTIONS

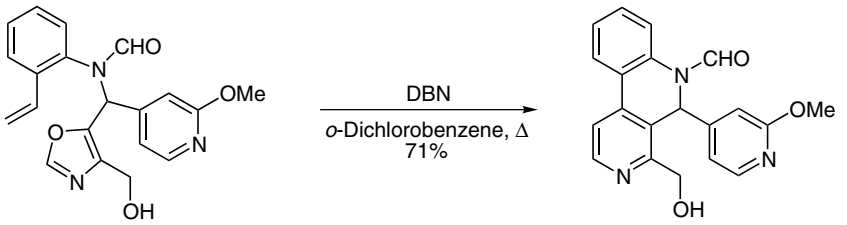
This reaction is related to the *Diels-Alder Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 3.

A solution containing 0.1 g *N*-(4-methyloxazol-2-yl)-*N*-(pent-4-enyl)acetamide (0.5 mmol) and 0.06 g DBU (0.4 mmol) in 2 mL toluene in a sealed tube under an argon atmosphere was heated at 180°C for 20 h. Then the solvent was removed under reduced pressure, and the residue was purified by flash silica gel chromatography to give 0.3 g 1-acetyl-7-methyl-1,2,3,4-tetrahydro-1,8-naphthyridine as a pale yellow oil, in a yield of 39%. (*Note*: It requires 0.842 g starting material to afford 39% naphthyridine derivative in a yield of 39%, but it was stated as 0.1 g in the original article.)



Reference 2a.

A solution of 0.15 g oxazole alcohol (0.41 mmol) and 0.05 g DBN (0.41 mmol) in 60 mL anhydrous *o*-dichlorobenzene was deoxygenated with argon for 45 min. The mixture was heated at 150°C under an argon atmosphere for 1.5 h and then cooled to room temperature. Upon removal of solvent in vacuo, the residue was purified by flash chromatography using MeOH/EtOAc (1:49) as the eluent to afford 0.10 g pyridine alcohol as a pale yellow oil, in a yield of 71%.

Other references related to the Kondrat'eva pyridine synthesis are cited in the literature.[12]

H. REFERENCES

1. Kondrat'eva, G. Ya., *Khim. Nauk. Prom.*, **1957**, *2*, 666.
2. (a) Subramanyam, C.; Noguchi, M. and Weinreb, S. M., *J. Org. Chem.*, **1989**, *54*, 5580. (b) Levin, J. I. and Weinreb, S. M., *J. Org. Chem.*, **1984**, *49*, 4325.
3. Padwa, A.; Brodney, M. A.; Liu, B.; Satake, K. and Wu, T. H., *J. Org. Chem.*, **1999**, *64*, 3595.
4. Dumond, Y. R. and Gum, A. G., *Molecules*, **2003**, *8*, 873.
5. (a) Turchi, I. J. and Dewar, M. J. S., *Chem. Rev.*, **1975**, *75*, 389. (b) Karpeiskii, M. Y. and Florent'ev, V. L., *Russ. Chem. Rev.*, **1969**, *38*, 540. (c) Firestone, R. A.; Harris, E. E. and Reuter, W., *Tetrahedron*, **1967**, *23*, 943. (d) Harris, E. E.; Firestone, R. A.; Pfister, K.; Boettcher, R. R.; Cross, F. J.; Currie, R. B.; Monaco, M.; Peterson, E. R. and Reuter, W., *J. Org. Chem.*, **1962**, *27*, 2705.
6. Levin, J. I. and Weinreb, S. M., *J. Am. Chem. Soc.*, **1983**, *105*, 1397.
7. (a) Shimada, S., *J. Heterocycl. Chem.*, **1987**, *24*, 1237. (b) Bogdanov, V. S.; Kondrat'eva, G. Y. and Aitzhanova, M. A., *Izv. Akad. Nauk. SSSR. Ser. Khim.*, **1980**, 1017. (c) McEwen, W. E.; Grossi, A. V.; MacDonald, R. J. and Stamegna, A. P., *J. Org. Chem.* **1980**, *45*, 1301. (d) Kondrat'eva, G. Y.; Aitzhanova, M. A.; Bogdanov, V. S. and Chizhov, O. S., *Izv. Akad. Nauk. SSSR. Ser. Khim.*, **1979**, 1313. (e) Kondrat'eva, G. Y.; Aitzhanova, M. A. and Bogdanov, V. S., *Izv. Akad. Nauk. SSSR. Ser. Khim.*, **1976**, 2146.
8. (a) Marcelis, A. T. M. and van der Plas, H. C., *J. Org. Chem.*, **1986**, *51*, 67. (b) De Bie, D. A.; Geurten, B. and van der Plas, H. C., *J. Org. Chem.*, **1986**, *51*, 71. (c) Charushin, V. N. and van der Plas, H. C., *J. Org. Chem.*, **1983**, *48*, 2667. (d) van der Plas, H. C. and Charushin, V. N.,

Tetrahedron Lett., **1982**, *23*, 3965. (e) Davies, L. B.; Greenberg, S. G. and Sammes, P. G., *J. Chem. Soc., Perkin Trans. I*, **1981**, 1909. (f) Martin, J. C., *J. Heterocycl. Chem.*, **1980**, *17*, 1111. (g) Neunhoeffer, H. and Lehmann, B., *Ann.*, **1975**, 1113. (h) Neunhoeffer, H. and Werner, G., *Ann.*, **1974**, 1190. (i) Machin, P. J.; Porter, A. E. A. and Sammes, P. G., *J. Chem. Soc., Perkin Trans. I*, **1973**, 404. (j) Kappe, T. and Lube, W., *Angew. Chem. Int. Ed. Engl.*, **1971**, *10*, 925. (k) Porter, A. E. A. and Sammes, P. G., *J. Chem. Soc., Chem. Commun.*, **1970**, 1103.

9. (a) Machin, P. J.; Porter, A. E. A. and Sammes, P. G., *J. Chem. Soc., Perkin Trans. I*, **1973**, 404. (b) Neunhoeffer, H. and Werner, G., *Ann.*, **1972**, *761*, 39.
10. (a) Neunhoeffer, H.; Clausen, M.; Votter, H.-D.; Ohl, H.; Kruger, C. and Angermund, K., *Ann.*, **1985**, 1732. (b) Ohsawa, A.; Arai, H.; Ohnishi, H.; Itoh, T.; Kaihoh, T.; Okado, M. and Igeta, H., *J. Org. Chem.*, **1985**, *50*, 5520. (c) Ohsawa, A.; Arai, H.; Ohnishi, H. and Igeta, H., *J. Chem. Soc., Chem. Commun.*, **1981**, 1174.
11. (a) Boger, D. A. *Chem. Rev.* **1986**, *86*, 781. (b) Boger, D. L., *Tetrahedron*, **1983**, *39*, 2912. (c) Boger, D. L.; Panek, J. S. and Meier, M. M., *J. Org. Chem.*, **1982**, *47*, 895. (d) Metz, H.-J. and Neunhoeffer, H., *Ber.*, **1982**, *114*, 2807. (e) Boger, D. L. and Panek, J. S., *J. Org. Chem.*, **1981**, *46*, 2179. (f) Gockel, U.; Hartmannsgruber, U.; Steigel, A. and Sauer, J., *Tetrahedron Lett.*, **1980**, *595*, 599. (g) Reim, H.; Steigel, A. and Sauer, J., *Tetrahedron Lett.*, **1975**, 2901. (h) Neunhoeffer, H. and Fruhauf, H.-W., *Ann.*, **1972**, *758*, 120. (i) Neunhoeffer, H. and Frey, G., *Ann.*, **1973**, 1963. (j) Steigel, A.; Sauer, J.; Kleier, D. A. and Binsch, G., *J. Am. Chem. Soc.*, **1972**, *94*, 2770. (k) Dittmar, W.; Sauer, J. and Steigel, A., *Tetrahedron Lett.*, **1969**, 5171.
12. (a) Li, J. J. and Corey, E. J., ed. Name Reactions in Heterocyclic Chemistry, John Wiley & Sons, **2005**. (b) Levin, J. I. and Laakso, L. M., *"Oxazole Diels-Alder Reactions,"* in "*The Chemistry of Heterocyclic Compounds, Oxazoles: Synthesis, Reactions, and Spectroscopy*", ed. Taylor, E. C.; Wipf, P. and Weissberger, A., pt. A, vol. 60, John Wiley & Sons, Hoboken, **2003**. (c) Janvier, P.; Sun, X. W.; Bienaymé, H. and Zhu, J. P., *J. Am. Chem. Soc.*, **2002**, *124*, 2560. (d) Voronkov, M. G.; Zefirov, N. S. and Magdesieva, N. N., *Chem. Heterocycl. Compd.*, **1967**, *3*, 753. (e) Huang C. H. and Kondrat'eva, G. Ya., *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **1962**, 525. (f) Kondrat'eva, G. Y., *Dokl. Akad. Nauk SSSR*, **1961**, *141*, 628. (g) Kondrat'eva, G. Ya., *Dokl. Akad. Nauk SSSR*, **1961**, *141*, 861. (h) Kondrat'eva, G. Ya., *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1959**, 484.

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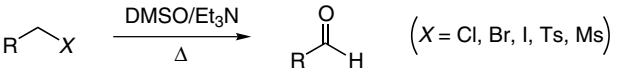
Kornblum Oxidation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Kornblum in 1957.[1] It is the formation of aldehydes by treatment of primary alkyl halides with dimethylsulfoxide and a hydrogen acceptor. Thus it is often known as the Kornblum oxidation.[2] Occasionally, it is also referred to as the Kornblum reaction.[3] In fact, this is the first mild oxidation leading to a carbonyl compound using DMSO.[4] In this reaction, bases such as triethyl amine[2d] and sodium bicarbonate[5] are usually used as the proton acceptor; however, the oxidation of 4-chloro-3-methyl-2-buten-1-ol acetate does not proceed well when sodium bicarbonate is used as the proton scavenger, thus a sodium or potassium phosphate dibasic (Na_2HPO_4 or K_2HPO_4) is used.[3] Generally, this reaction works well for active alkyl halides, such as benzylic or allylic halides or alkyl iodide, because it initially involves the nucleophilic substitution of a halide into an alkoxysulphonium ion that transforms into an aldehyde when treated with a base.[6] Thus those nonactive alkyl halides are often converted into corresponding tosylates and are then treated with DMSO and a base.[1,7] On the other hand, it has been found that a nonnucleophilic silver salt such as $AgBF_4$[8] or zinc sulfide[2b] can assist the nucleophilic substitution that is added to the reaction system. Unfortunately, this reaction is less selective or is uncontrollable for the oxidation of multibenzylic halides[3a] and always requires high temperature treatments.[2a,2c,2d]

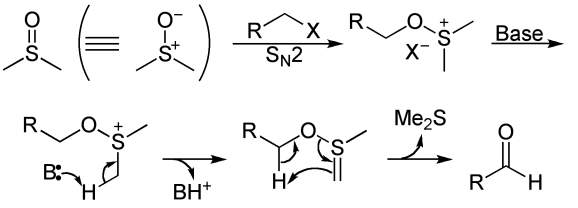
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Illustrated below is the mechanism, in which *B* represents a general base.



D. MODIFICATION

This reaction has been modified by adding nonnucleophilic silver salt[8] or zinc sulfide[2b] to facilitate the initial nucleophilic substitution. In addition, it has been modified to convert α-bromo alcohols into ketones.[2b]

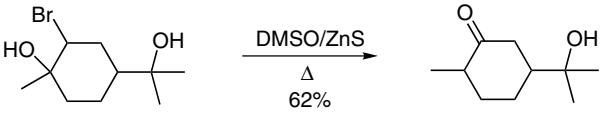
E. APPLICATIONS

This reaction is useful for converting primary alkyl halides into the corresponding aldehydes.

F. RELATED REACTIONS

This reaction is related to the *Swern Oxidation, Dess Martin Oxidation,* and *Moffatt-Swern Oxidation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2b.

To a flask, was added 2.51 g bromohydrin (10 mmol) and 15 mL dry DMSO. To this solution was added 0.97 g dry ZnS (10 mmol), and the mixture was stirred at 70°C. Reaction was monitored by injection of a worked-up aliquot on GC. In the end ($\sim$ 10 h), the reaction mixture was poured into 150 mL water and extracted into CH_2Cl_2 (10 mL $\times$ 3). The organic layer was dried over anhydrous Na_2SO_4, and solvent was evaporated. The residue was chromatographed over SiO_2 using a mixture of EtOAc/hexane (1:9) as the eluent to give 62% ketone.

Other references related to the Kornblum oxidation are cited in the literature.[9]

H. REFERENCES

1. Kornblum, N.; Jones, W. J.; Anderson, G. J.; Powers, J. W.; Larson, H. O.; Levand, O. and Wraver, W. M., *J. Am. Chem. Soc.*, **1957**, *79*, 6562.
2. (a) Paquette, W. D. and Taylor, R. E., *Org. Lett.*, **2004**, *6*, 103. (b) Bettadaiah, B. K.; Gurudutt, K. N. and Srinivas, P., *J. Org. Chem.*, **2003**, *68*, 2460. (c) Iyer, P. S., "Oxonitriles: Cyclizations in Total Synthesis," Master Thesis, Duquesne University, Dec. Pittsburgh, **2003**. (d) Ly, T. W., "Synthetic Studies on Terpenoids. Part 1. Total Synthesis of the Marine Natural Product Nanaimoal. Part 2. Towards the Total Synthesis of Solidago Alcohol via an Intermolecular Diels-Alder Approach," University of Alberta, Edmonton, Canada, **2000**. (e) Ariyoshi, K.; Aso, Y.; Otsubo, T. and Ogura, F., *Chem. Lett.*, **1984**, 891. (f) Kappler, F.; Chawla, R. R. and Hampton, A., *Nucleic Acid Chem.*, **1978**, *2*, 521. (g) Torssell, K., *Acta Chem. Scand.*, **1967**, *21*, 1.
3. (a) Wang, W. Y.; Li, T. C. and Attardo, G., *J. Org. Chem.*, **1997**, 62,6598. (b) Gaylord Chemical Corporation, *Technical Bulletin: Reaction Solvent Dimethyl Sulfoxide (DMSO)*, Slidell, Louisiana.
4. Habib, R.; Husain, M.; Fazal, A. and Husain, M., *Indian J. Chem., Section B*, **1988**, 27*B*,584.
5. Nace, H. R. and Monagle, J. J., *J. Org. Chem.*, **1959**, *24*, 1792.
6. Tidwell, T. T., *Org. React.* **1990**, *39*, 297.
7. (a) Haines, A. H., *Chem. Ind. (London)*, **1976**, 883. (b) Kornblum, N.; Jones, W. J. and Anderson, G. J., *J. Am. Chem. Soc.*, **1959**, *81*, 4113.
8. Ganem, B. and Boeckman, R. K., *Tetrahedron Lett*., **1974**, 917.
9. (a) Katritzky, A. R.; Zhang, D. Z. and Kirichenko, K., *J. Org. Chem.*, **2005**, *70*, 3271. (b) Chandrasekhar, S and Sridhar, M., *Tetrahedron Lett.,* **2000**, *41*, 5423. (c) Fischer, B.; Kabha, E.; Gendron, F. P. and Beaudoin, A. R., *Nucleosides, Nucleotides & Nucleic Acids*, **2000**, *19*, 1033. (d) Hanefeld, W. and Wurtz, S., *J. Prakt. Chem.*, **2000**, *342*, 445. (e) Kobayashi, K.; Itoh, M.; Sasaki, A. and Suginome, H., *Tetrahedron*, **1991**, *47*, 5437. (f) Godfrey, A. G. and Ganem, B., *Tetrahedron Lett*., **1990**, *23*, 4825. (g) Dave, P.; Byun, H. S. and Engel, R., *Synth. Commun.*, **1986**, *16*, 1343. (h) Radominska-Pyrek, A.; Huynh, T.; Lester, R. and St Pyrek, J., *J. Lipid Res.*, **1986**, *27*, 102. (i) Abou-Teim, O.; Jansen, B. R.; McOmie, J. F. W. and Perry, D. H., *J. Chem. Soc., Perkin Trans. 1*, **1980**, 1841. (j) Epstein, W. W. and Sweat, F. W., *Chem. Rev*., **1967**, 67, 247. (k) Kornblum, N. and Frazier, H. W., *J. Am. Chem. Soc.*, **1966**, *88*, 865. (l) Torssell, K., *Tetrahedron Lett*., **1966**, 4445. (m) Traynelis, V. J. and Hergenrother, W. L., *J. Am. Chem. Soc.*, **1964**, *86*, 298. (n) Johnson, A. P. and Pelter, A., *J. Chem. Soc.*, **1964**, 520. (o) Smith, S. G. and Winstein, S., *Tetrahedron*, **1958**, *3*, 317.

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Kornblum-Delamare Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Kornblum and DeLaMare in 1951.[1] It is primarily a base-promoted rearrangement of a peroxide into a ketone and an alcohol and is thus known as the Kornblum-DeLaMare reaction[2] or Kornblum-DeLaMare rearrangement.[3]

In its initial protocol, potassium *tert*-butyl peroxide and 1-phenylethyl bromide are eventually converted into *tert*-butanol and acetophenone in the presence of piperidine, KOH, or NaOEt.[1] However, in the case of symmetric bicyclic endoperoxides, enantioenriched γ-hydroxyenones form via desymmetrization in the presence of a catalytic amount of chiral base, especially for the cinchona, which gives the best results in terms of reactivity and enantioselectivity among the tested amines.[3b] Although organic bases such as trialkylamine (e.g., Et_3N[1,4]) are often used in this reaction, phosphorus ylide[5] and an inorganic base, such as KOH,[1] LiOH,[3c,6] or sodium ethoxide,[1] are also workable for this rearrangement. In addition, even acidic SiO_2 has recently been observed to promote the rearrangement.[3f]

On the other hand, besides the initial S_N2 substitution to form the peroxide,[1] peroxides are normally obtained by 1,4-dioxygenation of conjugated diene with singlet oxygen ($^1O_2$)[3b,3f,4a] or photo-[2+2] cycloaddition between singlet oxygen and alkenes, especially with alkenes activated with an amino or alkoxy group (i.e., enamines or vinyl ethers).[2b] For the special case of *N*-substituted 3-vinylindoles, photo-oxidation with $^1O_2$ occurs efficiently and stereospecifically to afford dioxacarbazole endoperoxides; however, *[2+2] Cycloaddition* would occur preferentially at the 3-vinyl double bond when the s-*cis* conformation is blocked by substituents at the position 2 of indole and the β-position of vinyl moiety.[3f] For *N*-substituted 3-vinylindoles, it is found that both the stability of endoperoxides and the reaction products depend on the *N*- and 3-vinyl β-substituents. For example, an electron-withdrawing group on the nitrogen atom of an indole will stabilize the resulting

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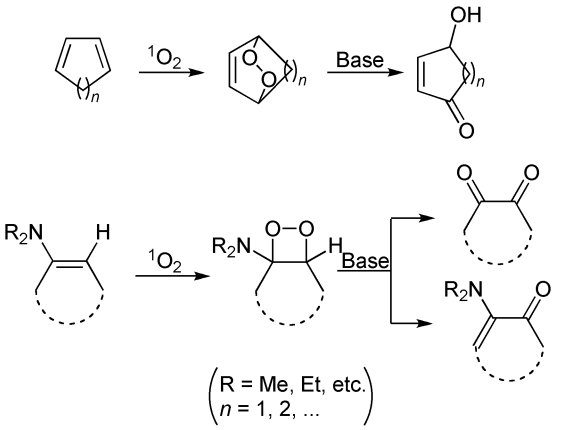
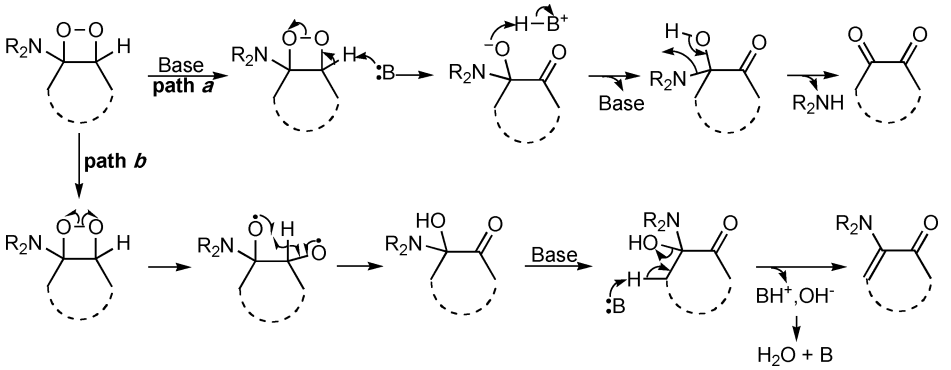
endoperoxide, whereas on the β-carbon of 3-vinyl moiety it will destabilize the endoperoxide and favor the Kornblum-DeLaMare rearrangement. In addition, endoperoxide arising from *N*-methyl 3-vinyl indole is sensitive to acid and will rearrange to dioxetane, which cleaves the 3-vinyl double bond. The β-methoxy group on 3-vinyl moiety has a strong directing effect on the reaction, which accelerates the endoperoxidation when the aromatic double bond is in a *cis*-configuration, while making the *ene* reaction occur exclusively when a *cis*-methyl group is present.[3f]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

In most cases of the Kornblum-DeLaMare rearrangement, an E2 elimination mechanism is involved in the presence of a base, to afford a ketone and an alcohol, as illustrated in path *a*.[2b,3b] However, in the rearrangement of dioxetanes arising from alkenes with electron-donating groups, such as enamines and vinyl ethers, a free-radical process consisting of initial O-O cleavage followed by an internal hydrogen transfer to give α-hydroxy ketones dominates, as shown in path *b*.[2b]



D. MODIFICATION

The enantioselective Kornblum-DeLaMare rearrangement based on the desymmetrization of *meso*-endoperoxides by a chiral base catalyst has recently been developed.[3b]

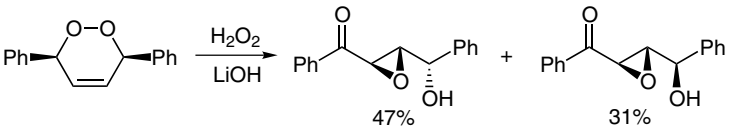
E. APPLICATIONS

This reaction has important applications in the preparation of γ-hydroxyenones.

F. RELATED REACTIONS

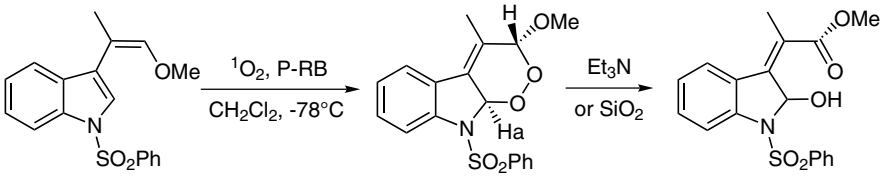
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3c.

To a stirred solution of 0.238 g 1,2-dioxine (1 mmol) in 5 mL THF was added 453 mg 30% aqueous hydrogen peroxide (4 mmol) followed by 23 mg lithium hydroxide (1 mmol). The resulting suspension was stirred vigorously until the reaction was completed as monitored by TLC ($\sim$16 h). A small portion (1–2 mg) of manganese dioxide was added to the mixture and allowed to stir until evolution of gas had ceased. The solution was then diluted with 15 mL water and extracted with CH_2Cl_2 (2 $\times$ 20 mL). The combined organic extracts were dried and evaporated, and the residue was purified by flash chromatography to afford 47% of ($\pm$)-{(2*R*,3*S*)-3-[(*S*)-1-hydroxy-1-phenylmethyl]oxiran-2-yl}(phenyl)methanone as a colorless solid [m.p. 106–107°C, R_f = 0.5 (hexane/EtOAc, 3:2)] and 31% of ($\pm$)-{(2*R*,3*S*)-3-[(*R*)-1-hydroxy-1-phenylmethyl]oxiran-2-yl}(phenyl)methanone as a colorless solid, m.p., 78–80°C, R_f = 0.38 (hexane/EtOAc, 3:2).



Reference 3f.

A solution of 60 mg *N*-phenylsulfonyl-3-(α-methyl-*cis*-β-methoxy)vinylindole (0.18 mmol) and 5 mg polymer-bound rose bengal in 2 mL CH_2Cl_2 was photooxygenated at -78°C for 40 min. After filtration of the polymer-bound rose bengal,

the solution was concentrated to give only *trans*-9,9a-dihydro-3-methoxy-4-methyl-9-(phenylsulfonyl)-3H-1,2-dioxion[3,4-b]indole, which was purified by recrystallization from CH_2Cl_2/hexane (1:1), m.p. 100–102°C. Further treatment of this compound with SiO_2 or Et_3N afforded the final ester compound, which was purified by preparative TLC (petroleum ether/CH_2Cl_2/acetone, 4:2:0.5).

Other references related to the Kornblum-DeLaMare rearrangement are cited in the literature.[7]

H. REFERENCES

1. Kornblum, N. and DeLaMare, H. E., *J. Am. Chem. Soc.*, **1951**, *73*, 880.
2. (a) Mete, E.; Altundas, R.; Secen, H. and Balci, M., *Turk. J. Chem.*, **2003**, *27*, 145. (b) Frimer, A. A., *Chem. Rev.*, **1979**, *79*, 359.
3. (a) McLaughlin, M.; Rubio, S. G.; Tilstam, U.; Antunes, O. A. C.; Laird, T.; Yadav, G. D. and Zlota, A., *Org. Proc. Res. Dev.*, **2007**, *11*, 2. (b) Staben, S. T.; Xin, L. H. and Toste, F. D., *J. Am. Chem. Soc.*, **2006**, *128*, 12658. (c) Greatrex, B. W.; Taylor, D. K. and Tiekink, E. R. T., *J. Org. Chem.*, **2004**, *69*, 2580. (d) Greatrex, B. W.; Jevric, M.; Kimber, M. C.; Krivickas, S. J.; Taylor, D. K. and Tiekink, E. R. T., *Synthesis*, **2003**, 668. (e) Kelly, D. R.; Bansal, H. and Morgan, J. J. G., *Tetrahedron Lett*., **2002**, *43*, 9331. (f) Zhang, X. J.; Khan, S. I. and Foote, C. S., *J. Org. Chem.*, **1993**, *58*, 7839.
4. (a) Akbulut, N. and Balci, M., *J. Org. Chem.*, **1988**, *53*, 3338. (b) Zagorski, M. G. and Salomon, R. G., *J. Am. Chem. Soc.*, **1980**, *102*, 2501.
5. Avery, T. D.; Taylor, D. K. and Tiekink, E. R. T., *J. Org. Chem.*, **2000**, *65*, 5531.
6. Greatrex, B. W.; Kimber, M. C.; Taylor, D. K. and Tiekink, E. R. T., *J. Org. Chem.*, **2003**, *68*, 4239.
7. (a) Mete, E.; Altundas, R.; Secen, H. and Balci, M., *Turk. J. Chem.*, **2003**, *27*, 145. (b) Kelly, D. R.; Bansal, H. and Morgan, J. J. G., *Tetrahedron Lett.*, **2002**, *43*, 9331. (c) Hagenbuch, J. P. and Vogel, P., *J. Chem. Soc., Chem. Commun.*, **1980**, 1062.

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Kostanecki-Robinson Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Kostanecki and Rozycki in 1901.[1] It is the formation of coumarins and chromones from alkyl *o*-hydroxyaryl ketone and aliphatic acid anhydride in the presence of the corresponding aliphatic acid sodium salt, via the *O*-acylation and *Aldol Condensation*. Because this reaction is similar to the *Robinson Annulation*, this reaction is generally known as the Kostanecki-Robinson reaction,[2] Kostanecki-Robinson acylation[2i,3] or Kostanecki-Robinson synthesis.[2i,4] In addition, a specific reaction between alkyl *o*-hydroxyaryl ketone and acetic anhydride is called the Kostanecki-Robinson acetylation;[5] likewise, the corresponding reaction with phenylacetic anhydride is referred to as the Kostanecki-Robinson phenylacetylation.[6] Depending on the actual reaction conditions and substituents, either coumarin or chromone or both can be produced,[2i] and normally, the application of acetic anhydride and sodium acetate gives chromone derivatives.[2b,7] It has been found that the existing α-pyrone ring on the aromatic ketone does not affect the Kostanecki-Robinson reaction.[3g]

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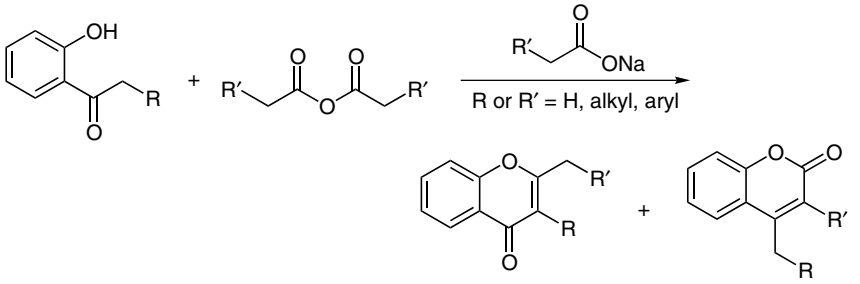
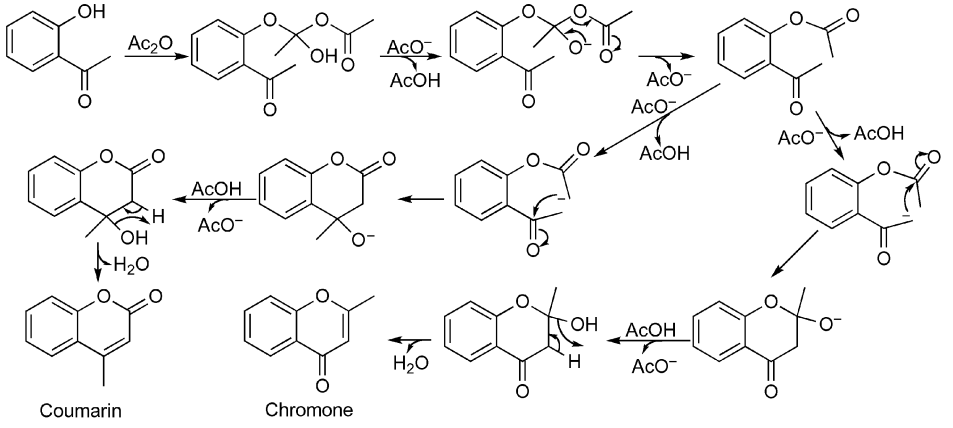
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Shown below is the mechanism of reaction between *o*-hydroxyacetophenone and acetic anhydride in the presence of sodium acetate to form both chromone and coumarin.



D. MODIFICATION

N/A

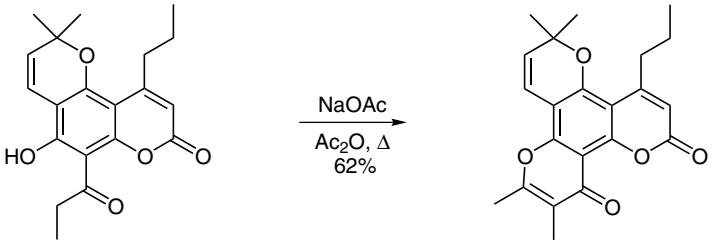
E. APPLICATIONS

This reaction has been used to prepare both coumarin and chromone derivatives.

F. RELATED REACTIONS

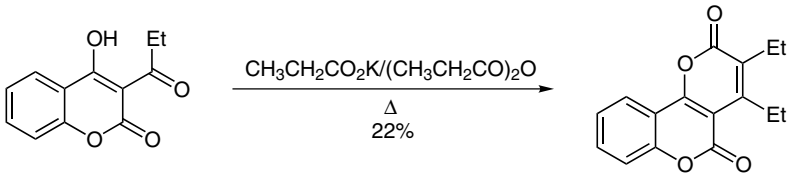
This reaction is related to the *Allan-Robinson Annulation* and *Baker-Venkataraman Rearrangement*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2b.

A mixture of 1.76 g 6,6-dimethyl-9-hydroxy-10-propionyl-4-propyl-2*H*,6*H*-benzo[1,2-*b*:3,4-*b*′]dipyran-2-one (5.11 mmol) and 0.419 g sodium acetate (5.11 mmol) in 12 mL acetic anhydride was refluxed for 4 h, and the solvent was then removed in vacuo. The residue was purified by chromatography on a silica gel column, eluting first with 25% EtOAc/hexane followed by 50% EtOAc/hexane to provide 1.16 g 6,6,10,11-tetramethyl-4-propyl-2*H*,6*H*,12*H*-benzo[1,2-*b*:3,4-*b*′:5,6-*b*″]tripyran-2,12-dione as a yellow solid, in a yield of 62%, m.p. 209–209.5°C after recrystallization from EtOAc.



Reference 2i.

A mixture of 4.0 g aromatic compound, 4.0 g potassium propanate, and 6.6 mL propanic anhydride was refluxed at 135°C for 2 h and then cooled down. The mixture was poured into water. The brown solid was filtered and crystallized from dimethylformamide to give 22% coumarin-product.

Other references related to the Kostanecki-Robinson reaction are cited in the literature.[8]

H. REFERENCES

1. Von Kostanecki, S. and Rozycki, A., *Ber.*, **1901**, *34*, 102.
2. (a) Mamedov, V. A.; Kalinin, A. A.; Gubaidullin, A. T.; Litvinov, I. A. and Levin, Ya. A., *Chem. Heterocycl. Compd.*, **2003**, *39*, 96. (b) Flavin, M. T.; Rizzo, J. D.; Khilevich, A.; Kucherenko, A.; Sheinkman, A. K.; Vilaychack, V.; Lin, L.; Chen, W.; Greenwood, E. M.; Pengsuparp, T.; Pezzuto, J. M.; Hughes, S. H.; Flavin, T. M.; Cibulski, M.; Boulanger, W. A.; Shone, R. L. and Xu, Z.-Q., *J. Med. Chem.*, **1996**, *39*, 1303. (c) Iyer, P. R.; Iyer, C. S. R. and Prasad, K. J. R., *Indian J. Chem., Sect. B,* **1983**, 22*B*, 1055. (d) Rybertt, J. and Valderrama, J., *Revista Latinoamer. Quim.*, **1978**, *9*, 220. (e) Looker, J. H.; McMechan, J. H. and Mader, J. W., *J. Org. Chem.*, **1978**, *43*, 2344. (f) Szell, T. and Eiden, F., *Arch. Pharm. Ber. Deut. Pharm. Gesell.*, **1972**, *305*, 81. (g) Chakravarti, D.; Saha, M. and Das, R., *J. Indian Chem. Soc.*, **1971**, *48*, 765. (h) Szell, T.; Kovacs, K.; Zarandy,

M. S. and Erdohelyi, A., *Helv. Chim. Acta*, **1969**, *52*, 2636. (i) Cook, D. and McIntyre, J. S., *J. Org. Chem.*, **1968**, *33*, 1746. (j) Elliott, K. and Tittensor, E., *J. Chem. Soc.*, **1959**, 484. (k) Trivedi, P. L.; Sethna, S. M. and Shah, R. C., *J. Indian Chem. Soc.*, **1943**, *20*, 171. (l) Sethna, S. M. and Shah, R. C., *J. Indian Chem. Soc.*, **1940**, *17*, 601. (m) Sethna, S. M. and Shah, R. C., *J. Indian Chem. Soc.*, **1940**, *17*, 487. (n) Sethna, S. M. and Shah, R. C., *J. Indian Chem. Soc.*, **1940**, *17*, 239.

3. (a) Pardanani, N. H. and Trivedi, K. N., *J. Indian Chem. Soc.*, **1972**, *49*, 599. (b) Save, S. R. and Trivedi, P. L., *J. Indian Chem. Soc.*, **1972**, *49*, 25. (c) Save, S. R. and Trivedi, P. L., *J. Indian Chem. Soc.,* **1971**, 48, 675. (d) Szell, T.; Dozsai, L.; Zarandy, M. and Menyharth, K., *Tetrahedron*, **1969**, *25*, 715. (e) Re, P. D. and Cimatoribus, L., *Experientia*, **1962**, *18*, 67. (f) Shah, M. V. and Sethna, S., *J. Chem. Soc.*, **1960**, 3899. (g) Shah, D. N. and Shah, N. M., *J. Am. Chem. Soc.*, **1955**, *77*, 1699. (h) Sen, A. B. and Kakaji, T. N., *J. Indian Chem. Soc.*, **1952**, 29, 950. (i) Sen, A. B. and Kakaji, T. N., *J. Indian Chem. Soc.*, **1952**, *29*, 127.
4. (a) Jerzmanowska, Z. and Basinski, W., *Roczniki Chem.*, **1977**, *51*, 2283. (b) Da Re, P.; Colleoni, A. and Verlicchi, L., *Annali Chim. (Italy)*, **1958**, *48*, 762.
5. (a) Ahluwalia, V. K. and Kumar, D., *Indian J. Chem., Sect. B,* **1976**, 14*B*, 326. (b) Ahluwalia, V. K. and Kumar, D., *Indian J. Chem.*, **1975**, *13*, 981. (c) Shaikh, Y. A. and Trivedi, K. N., *J. Indian Chem. Soc.*, **1972**, *49*, 713.
6. (a) Thanawalla, C. B. and Trivedi, P. L., *J. Indian Chem. Soc.*, **1959**, *36*, 49. (b) Thanawalla, C. B. and Trivedi, P. L., *Curr. Sci.*, **1958**, *27*, 20.
7. Re, P. D. and Cimatoribus, L., *J. Org. Chem.*, **1961**, *26*, 3650.
8. (a) Szell, T., *J. Chem. Soc. C*, **1967**, 2041. (b) Hauser, C. R., *Org. React.*, **1954**, *8*, 91. (c) Heilbron, I. M.; Hey, D. H. and Lowe, A., *J. Chem. Soc.*, **1934**, 1311. (d) Baker, W., *J. Chem. Soc.*, **1933**, 1381. (e) Baker, W. and Robinson, R., *J. Chem. Soc.*, **1925**, *127*, 1981. (f) Allan, J. and Robinson, R., *J. Chem. Soc.*, **1924**, *125*, 2192. (g) Blumberg, M. and von Kostanecki, S., *Ber.*, **1903**, *36*, 2191.

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Kowalski Ester Homologation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Kowalski et al. in 1985.[1] It is a one-carbon extension of a carboxylic acid chain of an ester with methylene dibromide by means of strong base treatment at very low temperature and quenched by an alcohol. Thus it is known as the Kowalski homologation,[2] Kowalski chain homologation,[2b,3] or Kowalski ester homologation.[2a,4] The original procedure involves the formation of dibromomethyllithium, to which the ester is added to form a tetrahedron species, which may undergo either of the two paths when treated with an excess amount of a base to form α-bromo-α-keto dianions through either dibromoenolate or bromoenolate; the dianion then rearranges to alkynolate anion, which is quenched by alcohol to give an ester with one more carbon via ketene.[1,5] This reaction has obvious advantages over the *Arndt-Eistert Synthesis* because the latter requires further activation and involves diazomethane and diazoketones.[2a,5] However, this procedure also bears some limitations, such as the moderate yield, small scale (< 2.5 mmol scale), and application of low temperature.[4c,5] On the basis of a mechanism study, this reaction has been modified by first formation of dibromoketone, which is then treated with LHMDS to form bromoenolate or dibromoenolate and further by an excess amount of butyl lithium to give the alkynolate anion. Such two-step modification not only increases the yield but also scales up the reaction to the 25-mmol level, and even 100-mmol level in one case.[5] It has been found that the R group of the carboxylic acid in the ester can be a primary, secondary, or tertiary alkyl group or an aryl, alkenyl, or alkynyl as well as some lactones.[1,5] In addition, the stereochemistry is retained during the migration of the R group.[2a,5]

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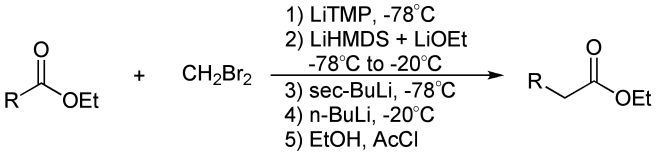
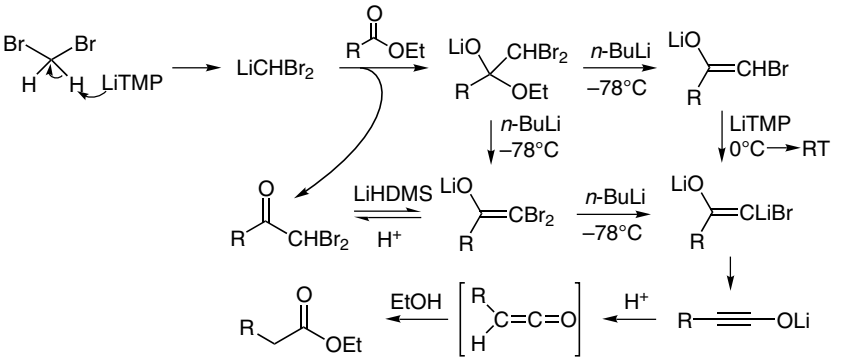
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Displayed below is the modified mechanism proposed by Kowalski.[5]



D. MODIFICATION

This reaction has been modified from a one-pot synthesis to a two-step reaction so that both higher yields and larger reaction scales can be achieved.

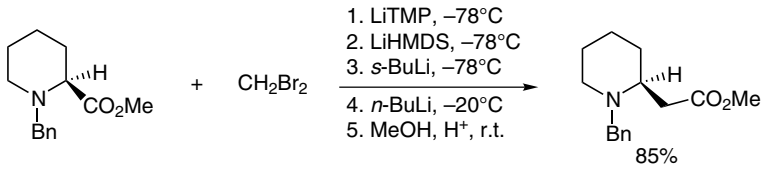
E. APPLICATIONS

Besides the general extension of an ester carbon chain, this reaction has been used to synthesize β-amino acid ester with retention of stereochemistry[2a] and the siloxyacetylene derivatives.[2b]

F. RELATED REACTIONS

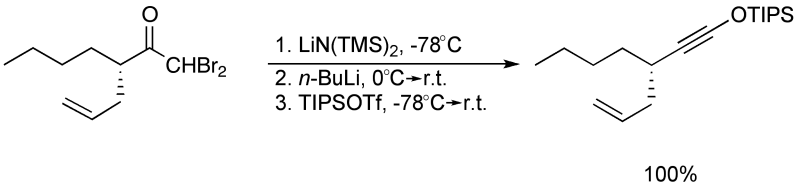
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 2a.

A solution of LiTMP was prepared as follows: 1.1 mL *n*-BuLi in hexanes (3.1 mmol) was added to a stirred, cold (0°C) solution of 0.6 mL TMP (3.3 mmol) in 4.3 mL THF. In a separate flask, a stirred mixture of 216 mg methyl (*S*)-*N*-benzylpipecolinate (0.9 mmol) and 0.2 mL CH_2Br_2 (3.1 mmol) in 4.3 mL THF was cooled to −78°C. After 30 min, the LiTMP solution was cooled to −78°C and added to the ester/CH_2Br_2 mixture dropwise via a double-ended needle. After 15 min, a cold (−78°C) solution of LiHMDS in THF (2.8 mL, 3.1 mmol) was added dropwise via a double-ended needle. The mixture was then allowed to warm to −20°C and was then recooled to −78°C. A solution of *s*-BuLi in hexanes (3.6 mL, 4.7 mmol) was added dropwise. The mixture was then warmed to −20°C, and a solution of *n*-BuLi in hexanes (1.1 mL, 2.8 mmol) was added. The mixture was warmed to room temperature, stirred for 1 h, and then quenched over a 20-min period into 12 mL stirred acidic methanol at 0°C. [Acidic methanol was prepared by the slow addition of acetyl chloride to ice-cooled dry methanol (1:5 volume ratio)]. The mixture was diluted with 150 mL ether and washed with saturated aqueous $NaHCO_3$. The aqueous phase was reextracted with ether (2 × 50 mL), and the combined organic extracts were washed with brine and dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (hexane/EtOAc, 9:1→3:2) gave 195 mg methyl (*S*)-*N*-benzylpiperidin-2-ylacetate, in a yield of 85%, R_f = 0.55 (hexane/EtOAc, 1:1).



Reference 2b.

A solution of 1.50 g dibromoketone (4.78 mmol) in 27 mL THF was cooled to −78°C. In a separate flask, a 1.21-mL solution of hexamethyldisilazane (HMDS) (5.70 mmol) in 27 mL THF was cooled to 0°C and treated with 2.0 mL 2.5 M *n*-BuLi in hexanes (5.0 mmol). This colorless LiHMDS solution was immediately added dropwise via an addition funnel to the dibromoketone solution over a 25-min period. The reaction mixture was stirred for 20 min at −78°C and treated with 4.2 mL 2.5 M *n*-BuLi in hexanes (10.5 mmol) via syringe. After 30 min, 1.39 mL freshly distilled tri-isopropylsilyl trifluoromethylsulfonate (TIPSOTf) (5.18 mmol) was added. The reaction mixture was allowed to warm to 0°C, cooled to −78°C, quenched with 50 mL saturated aqueous $NaHCO_3$, extracted with hexanes (2 × 50 mL), dried over $MgSO_4$, filtered, and concentrated. The product was purified by bulb-to-bulb distillation (0.1 mmHg, oven temperature 80–120°C) to afford 1.48 g siloxyalkyne as a colorless oil, in a yield of 100%.

Other references related to the Kowalski ester homologation was cited in the literature.[6]

H. REFERENCES

1. Kowalski, C. J.; Haque, M. S. and Fields, K. W., *J. Am. Chem. Soc.*, **1985**, *107*, 1429.
2. (a) Gray, D.; Concellón, C. and Gallagher, T., *J. Org. Chem.*, **2004**, *69*, 4849. (b) Smith, A. B.; Adams, C. M.; Kozmin, S. A. and Paone, D. V., *J. Am. Chem. Soc.,* **2001**, *123*, 5925.
3. Chen, P.; Cheng, P. T. W.; Spegel, S. H.; Zahler, R.; Wang, X. B.; Thottathil, J.; Barrish, J. C. and Polniaszek, R. P., *Tetrahedron Lett*., **1997**, *38*, 3175.
4. (a) Bonne, D.; Dekhane, M. and Zhu, J. P., *J. Am. Chem. Soc.*, **2005**, *127*, 6926. (b) Gray, D.; Concellon, C. and Gallagher, T., *J. Org. Chem.,* **2004**, *69*, 4849. (c) Katritzky, A. R.; Zhang, S. M.; Hussein, A. H. M.; Fang, Y. F. and Steel, P. J., *J. Org. Chem.*, **2001**, *66*, 5606.
5. Kowalski, C. J. and Reddy, R. E., *J. Org. Chem.*, **1992**, *57*, 7194.
6. (a) Reddy, R. E. and Kowalski, C. J., *Org. Synth.*, **1992**, 146. (b) Kowalski, C. J. and Lal, G. S., *J. Am. Chem. Soc.*, **1988**, *110*, 3693. (c) Kowalski, C. J.; Lal, G. S. and Haque, M. S., *J. Am. Chem. Soc.*, **1986**, *108*, 7127. (d) Kowalski, C. J. and Haque, M. S., *J. Org. Chem.*, **1985**, *50*, 5140.

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Krapcho Decarboxylation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was studied comprehensively by Krapcho beginning as early as 1967.[1] It is an alkali halide promoted alkylative decarboxylation of active esters (e.g., β-keto esters, β-diesters, α-cyano esters) in polar or dipolar aprotic solvents (e.g., DMF, DMSO, HMPA,)[1e] and is generally known as the Krapcho decarboxylation[2] or Krapcho condition.[3] Occasionally, it is also referred to as the Krapcho decarbalkoxylation.[4] In addition, the corresponding decarboxylation on methyl esters is known as the Krapcho decarbomethoxylation,[5] and the decarboxylation of ethyl esters is referred to as the Krapcho decarboethoxylation.[5a,6]

A few exemplary decarbalkoxylation systems are NaCN/DMSO,[7] LiCl/HMPA/H_2O,[8] LiCl/DMSO/H_2O,[9] LiBr/HMPA/H_2O,[10] LiI/NaCN/DMF/H_2O,[11] NaCl/DMF/H_2O,[12] and tetramethyl-ammonium acetate (Me_4NAc).[13] Among the halides salts, NaCl, NaBr, KCl, and Me_4NBr in solvents such as DMSO and HMPT have been used for the internal alkylative decarboxylation,[14] and LiCl in HMPT has been used for external alkylative decarboxylation.[15] In addition, it has been found that many β-keto esters with an α-hydrogen proceed decarboxylation rapidly in wet DMSO.[1e] Although the common use of iodides in this reaction is due to their prior application for cleavages of methyl ester,[1e] the application of tetramethylammonium acetate can avoid the loss of stereohomogenecity of the double bond; the latter condition is usually superior to the consecutive hydrolysis and decarboxylation.[13a] Among the alkali chlorides, LiCl works better than NaCl due to the difference in solubility of these two salts in DMSO.[1e] It should be pointed out that LiF is ineffective, presumably because LiF exists as contact ion pair in the solution;[1e] in contrast, LiCl or KCN is the most effective salt to remove ethyl ester in wet DMSO.[1e] When LiCl is used, the reaction is accompanied by the formation of lithium carbonate

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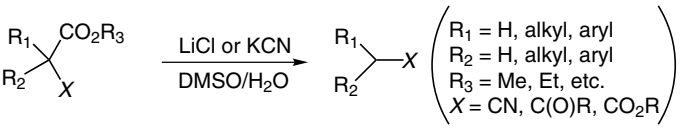
(Li_2CO_3);[1e] in addition, even though the reaction rate depends on the concentration of LiCl, the reaction is not in first-order kinetics in terms of LiCl concentration, since the largest rate increase has been observed in the presence of 5 eq. LiCl, and a much smaller rate enhancement is noticeable afterward.[1e] Other than the listed alkali halides, $MgCl_2$, $Na_3PO_4 \cdot 12H_2O$ and lithium acetate (LiAc) are somewhat effective for the alkylative decarboxylation, and the effectiveness of $Na_3PO_4 \cdot 12H_2O$ is due to its high pH in aqueous solution.[1e]

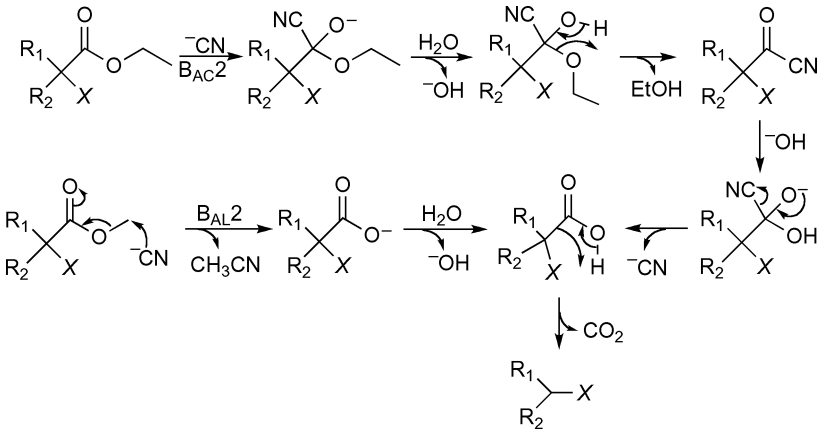
It has also been found that electron-withdrawing substituents facilitate the alkylative decarboxylation, whereas steric hindrance might retard the occurrence of such reaction. For example, diethyl and dimethyl disubstituted malonates do not practically undergo the decarboxylation when heated in $DMSO/H_2O$.[16]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The insensitive isotopic effect observed in the presence of LiCl or KCN indicates a nucleophilic catalytic mechanism.[1e] However, due to steric hindrance, the decarboxylation may proceed via either $B_{AC}2$ or $B_{AL}2$ mechanism, where B_{AC} is for acyl cleavage and B_{AL} is for alkyl cleavage. $B_{AC}2$ mechanism involves a tetrahedral intermediate originating from the attack of a nucleophile on the carbonyl group, while $B_{AL}2$ takes place via a S_N2 pathway on the alkyl moiety.[17] For example, the isolation of ethanol from the reaction of diethyl diethylmalonate indicates that the $B_{AC}2$ mechanism is competitive,



whereas the absence of methanol in the reaction of dimethyl diethylmalonate by $KCN/H_2O/DMSO$ and the 35.1 times rate enhancement are consistent with a dominant $B_{AL}2$ pathway.[1e] Both $B_{AC}2$ and $B_{AL}2$ mechanisms are displayed using ethyl and methyl esters, respectively.

D. MODIFICATION

1,4-Diazabicyclo[2.2.2]octane (DABCO) has been used for the cleavage of β-keto esters.[18]

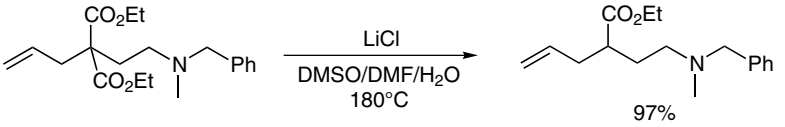
E. APPLICATIONS

This reaction has general application for the mild removal of ester groups from the activated esters.

F. RELATED REACTIONS

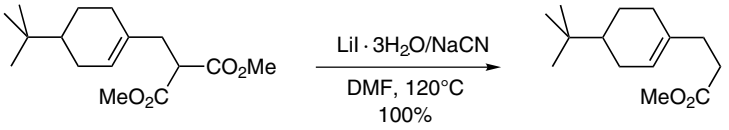
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 5a.

A solution of 12.0 g 6-(*N*-benzyl-*N*-methylamino)-4,4-di(ethoxycarbonyl) hex-1-ene (34.6 mmol) and 3.2 g LiCl (76 mmol) in 32 mL DMSO, 6.5 mL DMF, and 0.5 mL water was heated at 180°C for 6 h under nitrogen. The resulting dark brown reaction mixture was cooled to room temperature and poured into 150 mL water. The mixture was extracted with dichloromethane (5 × 100 mL), and the combined organic phases were washed with ice water (3 × 100 mL) and brine (100 mL). Drying over sodium sulfate and condensation under reduced pressure gave a brown oil, which was purified by flash chromatography on silica gel, using hexane/EtOAc (1:1) as the eluent to afford 9.26 g 6-(*N*-benzyl-*N*-methylamino)-4-ethoxycarbonyl-1-ene, in a yield of 97%. This product was further purified by vacuum distillation at 143–146°C (0.11 mmHg), $R_f = 0.54$ (ether/hexanes, 1:1).



Reference 13a.

A mixture of 83 mg 1-(2′-dicarbomethoxyethyl)-4-*tert*-butylcyclohexene (0.294 mmol), 225 mg lithium iodide trihydrate (1.2 mmol), 13.3 mg NaCN (0.294 mmol), and 5 mL DMF was heated at 120°C for 12 h. After cooling to room temperature, the solution was poured into water and extracted with ether (2 × 75 mL). The combined ethereal solution was washed with water, 10% aqueous HCl solution, and brine. After drying and evaporation in vacuo, the crude oil was purified by preparative TLC using chloroform as the eluent to afford 66 mg 1-(2′-carbomethoxyethyl)-4-*tert*-butylcyclohexene, in a yield of 100%.

Other references related to the Krapcho decarboxylation are cited in the literature.[19]

H. REFERENCES

1. (a) Krapcho, A. P.; Glynn, G. A. and Grenon, B. J., *Tetrahedron Lett.*, **1967**, 215. (b) Fieser, M. and Fieser, L. F., *Reagents for Organic Synthesis*, Wiley-Interscience, New York, vol. *2*, **1969**, p. 381. (c) Krapcho, A. P. and Lovey, A. J., *Tetrahedron Lett.*, **1973**, 957. (d) Krapcho, A. P.; Jahngen, E. G. E.; Lovey, A. J. and Short, F. W., *Tetrahedron Lett.*, **1974**, 1091. (e) Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E.; Lovey, A. J. and Stephens, W. P., *J. Org. Chem.*, **1978**, *43*, 138.
2. (a) Evans, D. A.; Scheidt, K. A. and Downey, C. W., *Org. Lett.*, **2001**, *3*, 3009. (b) Johnson, J. S. and Evans, D. A., *Acc. Chem. Res.*, **2000**, *33*, 325. (c) Brown, S. M.; Bowden, M. C.; Parsons, T. J.; McNeilly, P. and de Fraine, P. J., *Org. Proc. Res. Dev.*, **1997**, *1*, 370.
3. (a) Collins, P. W. and Djuric, S. W., *Chem. Rev.*, **1993**, *93*, 1533. (b) Donaldson, W. A.; Wang, J. K.; Cepa, V. G. and Suson, J. D., *J. Org. Chem.*, **1989**, *54*, 6056.
4. Harmata, M. and Elahmad, S., *Tetrahedron Lett*., **1993**, *34*, 789.
5. (a) Kuehne, M. E.; He, L. W.; Jokiel, P. A.; Pace, C. J.; Fleck, M. W.; Maisonneuve, I. M.; Glick, S. D. and Bidlack, J. M., *J. Med. Chem.*, **2003**, *46*, 2716. (b) Deslongchamps, G.; Mink, D.; Boyle, P. D. and Singh, N., *Can. J. Chem.*, **1994**, *72*, 1162. (c) Lee, W. Y.; Jang, S. Y.; Kim, M. and Park, O. S., *Synth. Commun.*, **1992**, *22*, 1283.
6. Bandarage, U. K.; Kuehne, M. E. and Glick, S. D., *Curr. Med. Chem.: Central Nervous System Agents*, **2001**, *1*, 113.
7. Scott, J. D. and Williams, R. M., *Chem. Rev.*, **2002**, *102*, 1669.
8. Cushing, T. D.; Sanz-Cervera, J. F. and Williams, R. M., *J. Am. Chem. Soc.*, **1996**, *118*, 557.
9. Crimmins, M. T. and Gould, L. D., *J. Am. Chem. Soc.*, **1987**, *109*, 6199.
10. Hansen, T. K.; Lakshmikantham, M. V.; Cava, M. P.; Niziurski-Mann, R. E.; Jensen, F. and Becher, J., *J. Am. Chem. Soc.*, **1992**, *114*, 5035.
11. Trost, B. M.; Weber, L.; Strege, P. E.; Fullerton, T. J. and Dietsche, T. J., *J. Am. Chem. Soc.*, **1978**, *100*, 3416.
12. Paquette, L. A.; Ohkata, K.; Jelich, K. and Kitching, W., *J. Am. Chem. Soc.*, **1983**, *105*, 2800.
13. (a) Trost, B. M.; Weber, L.; Strege, P.; Fullerton, T. J. and Dietsche, T. J., *J. Am. Chem. Soc.*, **1978**, *100*, 3426. (b) Trost, B. M. and Verhoeven, T. R., *J. Am. Chem. Soc.*, **1976**, *98*, 630. (c) Johnson, W. S.; Harbert, C. A.; Ratcliffe, B. E. and Stipanovic, R. D., *J. Am. Chem. Soc.*, **1976**, *98*, 6188.
14. Takei, S. and Kawano, Y., *Tetrahedron Lett.*, **1975**, 4389.
15. Asaoka, M.; Miyake, K. and Takei, H., *Chem. Lett.*, **1975**, 1149.
16. Santosusso, T. M. and Swern, D., *J. Org. Chem.*, **1976**, *41*, 2762.

17. (a) Longo, R. L.; Nunes, R. L. and Bieber, L. W., *J. Braz. Chem. Soc.*, **2001**, *12*, 52. (b) Ingold, C., *Structure and Mechanism in Organic Chemistry*, 2nd ed.; Cornell University Press, Ithaca, N.Y., **1969**.

18. Huang, B.-S.; Parish, E. J. and Miles, D. H., *J. Org. Chem.*, **1974**, *39*, 2647.

19. (a) Brocksom, T. J.; Coelho, F.; Deprés, J.-P.; Greene, A. E.; de Lima, M. E. F.; Hamelin, O.; Hartmann, B.; Kanazawa, A. M. and Wang, Y. Y., *J. Am. Chem. Soc.*, **2002**, *124*, 15313. (b) Ferrier, R. J. and Middleton, S., *Chem. Rev.*, **1993**, *93*, 2779. (c) Bornmann, W. G. and Kuehne, M. E., *J. Org. Chem.*, **1992**, *57*, 1752. (d) Hansen, T. K.; Lakshmikantham, M. V.; Cava, M. P.; Metzger, R. M. and Becher, J., *J. Org. Chem.*, **1991**, *56*, 2720. (e) Schreiber, S. L.; Kelly, S. E.; Porco, J. A.; Sammakia, T. and Suh, E. M., *J. Am. Chem. Soc.*, **1988**, *110*, 6210. (f) Trost, B. M. and Strege, P. E., *J. Am. Chem. Soc.*, **1975**, *97*, 2534. (g) Trost, B. M.; Dietsche, T. J. and Fullerton, T. J., *J. Org. Chem.*, **1974**, *39*, 737. (h) Parish, E. J. and Miles, D. H., *J. Org. Chem.*, **1973**, *38*, 1223. (i) McMurry, J. E. and Wong, G. B., *Synth. Commun.*, **1972**, *2*, 389.

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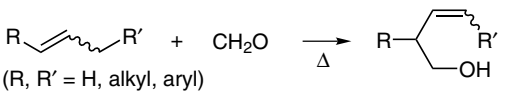
Kriewitz Condensation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Kriewitz in 1899.[1] It is the condensation between formaldehyde and olefins to form unsaturated primary alcohols under conditions of high temperature (e.g., 170°C). In this reaction, water or acetic acid is usually applied as the solvent, and an acid is added as a catalyst, such as sulfuric acid.[2] Under these conditions, formaldehyde and some ketones function as an enophile.[3] The double bond in the new unsaturated alcohol is adjacent to its original position in the starting olefin,[4] with the exception of camphene, which gives an allylic alcohol.[5] For the acylic olefins in this condensation, the isobutylene-type olefins are much more reactive than the monosubstituted olefins or 1,2-disubstituted olefins.[4] The further extension of this reaction involving an intramolecular condensation of an α-alkoxycarbenium ion with a double bond to form a hydropyran derivative is known as the Prins-Kriewitz cyclization.[6]

B. GENERAL REACTION SCHEME



(R, R′ = H, alkyl, aryl)

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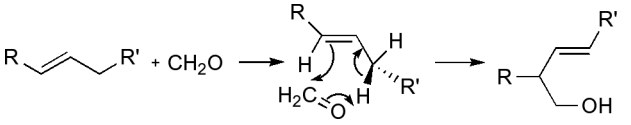
C. PROPOSED MECHANISMS

It is believed that a six-membered ring like transition state is involved in this condensation, as shown here. It is predicted that in the presence of an acid, the carbonyl group would be protonated and even polarized to be more electrophilic, thus the condensation is accelerated. As for the steric hindrance, the major product should be in *trans*-configuration, as in the case of forming *trans*-3-octen-1-ol exclusively from 1-heptene.[4]



D. MODIFICATION

This reaction has been modified to form tetrahydropyran derivatives from the intramolecular condensation of α-alkoxycarbenium ion and internal double bond.[6]

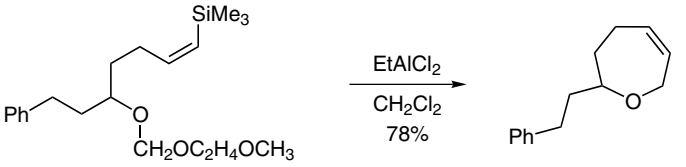
E. APPLICATIONS

This reaction has limited application in organic synthesis. Although it was once used in the production of butadiene or isoprene for the rubber industry, this reaction was found to be less attractive than dehydrogenation and the cracking processes.[2]

F. RELATED REACTIONS

This reaction is related to the *Prins Reaction*.

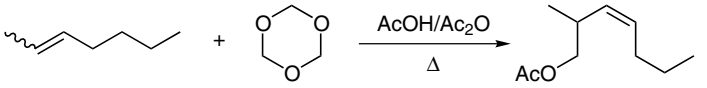
G. CITED EXPERIMENTAL EXAMPLES



Reference 6.

To a solution of 3.0 mL dry CH_2Cl_2 containing 32.3 mg olefin (0.0921 mmol) at -78°C was added 0.10 mL 25.9% $EtAlCl_2$ in heptane (0.28 mmol). The resulting solution was maintained at -78°C for 3 h, allowed to warm to room temperature, maintained there for 2 h, and then cooled to -78°C, and quenched with 5 mL cold (0°C) 2 M NaOH. The two layers were separated, and the aqueous layer was extracted with CH_2C1_2 (2×10 mL).

The combined organic fractions were washed with 10 mL brine, and dried over $MgSO_4$. Purification of the residue on silica gel (hexane/EtOAc 99:1 → 49:1) gave 15 mg of 2-(2-phenylethyl)-2,3,4,7-tetrahydrooxepin as a clear oil, in a yield of 78% with 95% purity by TLC analysis.



Reference 4.

A mixture of 200 g 2-heptene (2.04 mol), 55 g paraformaldehyde (1.83 mol), 96 g acetic acid (1.60 mol), and 18.4 g acetic anhydride (0.20 mol) was heated in a stainless-steel bomb at 180–190°C with agitation for 40 h. The reaction mixture was filtered and separated from 24 g of an aqueous layer. The organic layer was distilled to remove 182.5 g of starting materials, which contained 138.5 g unreacted 2-heptene. Continued distillation gave 62.3 g crude acetate in a yield of 60% (based on 2-heptene consumed), b.p. 98–107°C (30 mmHg).

Other references related to the Kriewitz condensation are cited in the literature.[7]

H. REFERENCES

1. (a) Kriewitz, O., *Ber.*, **1899**, *32*, 57. (b) Kriewitz, O., *J. Chem. Soc.*, **1899**, *76*, 298.
2. Arundale, E. and Mikeska, L. A., *Chem. Rev.*, **1952**, *51*, 505.
3. Dai, S.-H. and Dolbier, W. R., *J. Am. Chem. Soc.*, **1972**, *94*, 3953.
4. Blomquist, A. T.; Passer, M.; Schollenberger, C. S. and Wolinsky, J., *J. Am. Chem. Soc.*, **1957**, *79*, 4972.
5. Langlois, G., *Ann. Chim. (Paris)*, **1919**, *12*, 290.
6. Castañeda, A.; Kucera, D. J. and Overman, L. E., *J. Org. Chem.*, **1989**, *54*, 5695.
7. (a) Blomquist, A. T.; Verdol, J.; Adami, C. L.; Wolinsky, J. and Phillips, D. D., *J. Am. Chem. Soc.,* **1957**, *79*, 4976. (b) Bain, J. P., *J. Am. Chem. Soc.*, **1946**, *68*, 638. (c) Prins, H. J., *Proc. Acad. Sci. Amsterdam*, **1919**, *22*, 51.

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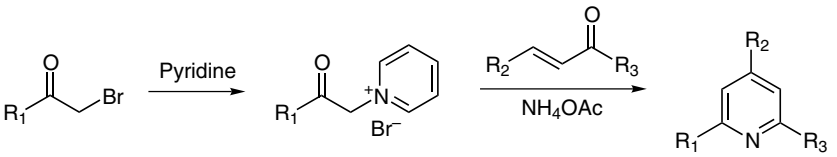
Kröhnke Pyridine Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Kröhnke et al. in 1961.[1] It is the synthesis of 2,4,6-trisubstituted pyridine derivatives involving the formation of pyridinium ylide from pyridine and α-bromoketone, which undergoes the 1,4-Michael addition to an α,β-unsaturated compound to form 1,5-dicarbonyl compounds and cyclizes with ammonium acetate. Therefore, it is generally known as the Kröhnke pyridine synthesis[2] or Kröhnke reaction.[2b,3] In this reaction, the intermediate 1,5-dicarbonyl compounds do not need to be isolated from reaction mixture.[2b,4] Because three different substituents can be introduced into pyridine ring, this reaction becomes the ideal model for combinatorial synthesis,[2b,4,5] and a library pool containing pyridine from 9^5 to over 200^{2b} has been generated by this reaction.

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Illustrated below is the mechanism of the Kröhnke pyridine synthesis in which an ammonium ion attacks the carbonyl group close to R_3. It should be pointed out that the

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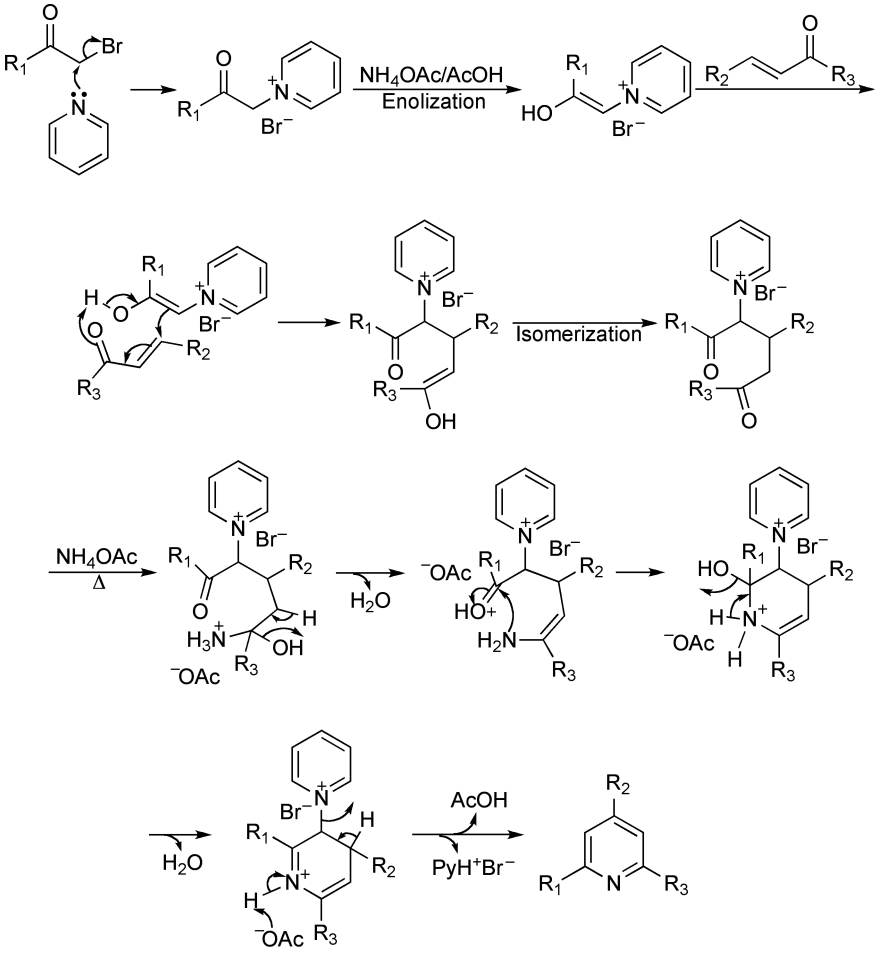
ammonium ion can also attack the carbonyl group adjacent to R_1 as the first step for the cyclization.



D. MODIFICATION

This reaction has been modified to produce 2,4,6-trisubstituted pyridines from isoquinolinium ylide instead of pyridinium ylide.[6]

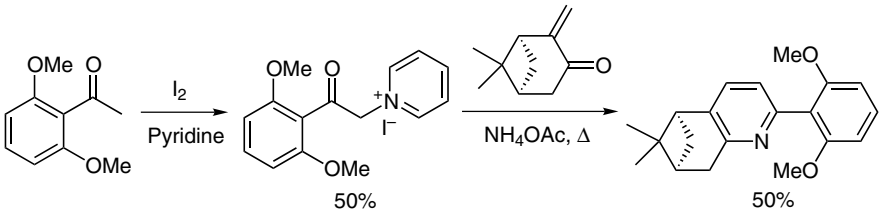
E. APPLICATIONS

This reaction has wide application in the preparation of substituted pyridine derivatives.

F. RELATED REACTIONS

This reaction is related to the *Chichibabin Pyridine Synthesis*, *Guareschi-Thorpe Condensation,* and *Hantzsch Dihydropyridine Synthesis*.

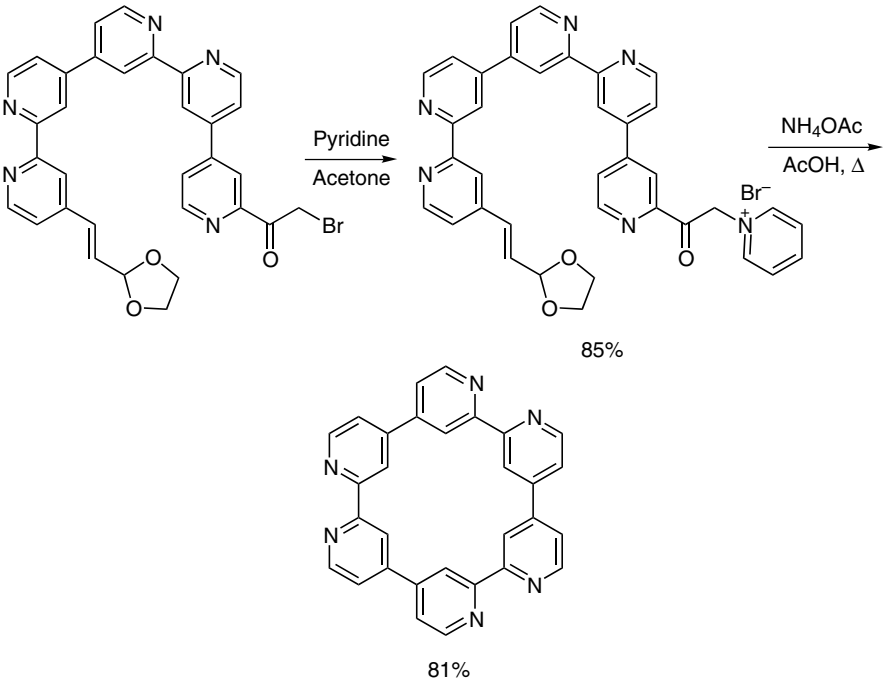
G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

2,6-Dimethoxyacetophenone (48.0 mmol) was heated in 20 mL pyridine until a clear solution was obtained. Crystalline iodine (17.4 g, 57.0 mmol) was added portionwise, and the resulting solution was refluxed for 1 h and then cooled to room temperature. The brownish precipitate was filtered off and successively washed with absolute pyridine (3 × 15 mL) to give 9.29 g 1-[2-(2,6-dimethoxyphenyl)-2-oxo-ethyl]-pyridinium iodide as a pale yellow solid, in a yield of 50%, m.p. 201–203°C (water).

Anhydrous ammonium acetate (110.0 g) was heated in 100 mL acetic acid at 110°C until it dissolved. Then 18.19 g Kröhnke salt (47.0 mmol) was added, and the mixture was left at 110°C until the Kröhnke salt dissolved. (-)-Pinocarvone (43.0 mmol) was added, and the solution was stirred at 110°C for 48 h. Water (20 mL) was then added, and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed successively with water (3 × 50 mL) and 30 mL brine, and dried over $MgSO_4$. The solvent was removed in vacuo to afford an oil that was purified via flash chromatography on 25 g silica gel using petroleum ether, followed by a 9:1 mixture of petroleum ether and EtOAc to give 50% (+)-5-(2,6-dimethoxyphenyl)-10,10-dimethyl-6-aza-tricyclo[7.1.1.$0^{2,7}$]undeca-2(7),3,5-triene.



Reference 8.

A mixture of 0.032 g 2-(bromoacetyl)-4‴″-[2-(1,3-dioxolan-2-yl)ethenyl]-4,4′:2′,2″:4″,4‴:2‴,2‴″-quinquepyridine (0.053 mmol) and 0.010 mL pyridine (0.12 mmol) in 30 mL acetone was stirred at room temperature for 12 h. The solvent was evaporated in vacuo, and the residue was dissolved in $CHCl_3$ and then introduced dropwise to cyclohexane while being stirred. The resulting precipitate was collected by filtration and dried in vacuo to afford 0.031 g 4‴″-[2-(1,3-dioxolan-2-yl)ethenyl]-2-(2-pyridiniumylacetyl)-4,4′:2′,2″:4″,4‴:2‴,2‴″-quinquepyridine bromide as a light brown solid (unstable > 20–25°C) that was used immediately for the final step (85% yield)

A solution of 0.024 g pyridinium salt (0.035 mmol) and 0.170 g ammonium acetate (2.2 mmol) in 50 mL acetic acid was refluxed for 19 h. After cooling, the solvent was evaporated in vacuo and the resulting black solid was washed with $CHCl_3$ and isolated by filtration to give 0.013 g cyclo 2,2′:4′,4″:2″,2‴:4‴,4‴″:2‴″,2‴‴:4‴‴,4-hexipyridine as a dark brown solid, in a yield of 81%.

Other references related to the Kröhnke pyridine synthesis are cited in the literature.[9]

H. REFERENCES

1. (a) Zecher, W. and Kröhnke, F., *Chem. Ber.*, **1961**, *94*, 690. (b) Zecher, W. and Kröhnke, F., *Chem. Ber.*, **1961**, *94*, 698.
2. (a) Sauers, A. L.; Ho, D. M. and Bernhard, S., *J. Org. Chem.*, **2004**, *69*, 8910. (b) Fujimori, T.; Wirsching, P. and Janda, K. D., *J. Comb. Chem.*, **2003**, *5*, 625. (c) Kelly, T. R.; Lee, Y.-J. and Mears, R. J., *J. Org. Chem.*, **1997**, *62*, 2774.
3. Brusotti, G.; Habermann, J.; Azzolina, O. and Collina, S., *Lett. Org. Chem.*, **2006**, *3*, 943.
4. Chiu, C. F.; Tang, Z. L. and Ellingboe, J. W., *J. Comb. Chem.*, **1999**, *1*, 73.
5. Grosche, P.; Holtzel, A.; Walk, T. B.; Trautwein, A. W. and Jung, G., *Synthesis*, **1999**, 1961.
6. (a) Tewari, R. S.; Dubey, A. K.; Misra, N. K. and Dixit, P. D., *J. Chem. Eng. Data*, **1981**, *26*, 106. (b) Tewari, R. S. and Dubey, A. K., *J. Chem. Eng. Data*, **1980**, *25*, 92.
7. Malkov, A. V.; Bell, M.; Castelluzzo, F. and Kocovsky, P., *Org. Lett.*, **2005**, *7*, 3219.
8. Kelly, T. R.; Lee, Y.-J. and Mears, R. J., *J. Org. Chem.*, **1997**, *62*, 2774.
9. (a) Lhoták, P. and Kurfürst, A., *Coll. Czech. Chem. Commun.*, **1992**, *57*, 1937. (b) Maeba, I.; Osaka, K.; Morishit, N.; Fujioka, K. and Ito, C., *J. Chem. Soc., Perkin Trans. I*, **1991**, 939. (c) Gupta, K. C.; Manglum, P. and Saxena, B. K., *J. Chem. Eng. Data*, **1988**, *33*, 390. (d) Newkome, G. R.; Hager, D. C. and Kiefer, G. E., *J. Org. Chem.*, **1986**, *51*, 850. (e) Tewari, R. S. and Dubey, A. K., *Indian J. Chem.*, **1980**, *19B*, 153. (f) Chatterjea, J. N.; Shaw, S. C.; Singh, J. N. and Singh, S. N., *Indian J. Chem.*, **1977**, *15B*, 430. (g) Kröhnke, F., *Synthesis*, **1976**, 1. (h) Tewari, R. S. and Gupta, K. C., *Indian J. Chem.*, **1976**, *14B*, 829. (i) Kendurkar, P. S. and Tewari, R. S., *J. Chem. Eng. Data*, **1974**, *19*, 184. (j) Kendurkar, P. S. and Tewari, R. S., *Z. Naturforsch.*, **1974**, *29B*, 552. (k) Zecher, W. and Kröhnke, F., *Angew. Chem. Int. Ed. Engl.*, **1963**, *2*, 380. (l) Zecher, W. and Kröhnke, F., *Angew. Chem. Int. Ed. Engl.*, **1963**, *2*, 225. (m) Zecher, W. and Kröhnke, F., *Angew. Chem. Int. Ed. Engl.*, **1962**, *1*, 626.

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Kuhn-Roth Oxidation

(Kuhn-Roth C-Methyl Determination, Kuhn-Roth Degradation, Kuhn-Roth Determination)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Kuhn and Roth in 1933.[1] It is a method for quantifying the number of methyl groups attached to the carbon atom in an organic molecule, which involves the oxidation of such an organic compound with chromic acid in the presence of sulfuric acid, followed by steam distillation to collect the generated acetic acid and quantification of the acetic acid via acid/base titration.[2] In addition, the collected acetic acid can be further analyzed by conversion of acetic acid into lithium acetate, pyrolysis of lithium acetate to acetone, and transformation of acetone into iodoform by hypoiodite.[3] Therefore, this reaction is generally known as the Kuhn-Roth C-methyl determination,[4] Kuhn-Roth chromic acid oxidation,[5] Kuhn-Roth degradation,[2b,5,6] Kuhn-Roth determination,[2a,7] or Kuhn-Roth oxidation.[2b–2d,3,6e,8]

Depending on the nature of the organic molecules, the ratio of chromic acid and sulfuric acid varies, such as the use of 4 *N* chromic acid/H_2SO_4 in 4:1 (v/v),[3] or 5 *N* chromic acid/concentrated sulfuric acid (2:1).[7a] After acetic acid is separated from the reaction system by steam distillation, it can be quantified using alkali hydroxide of different concentrations, from as low as 0.07 *N*[2c] to 1.0 *N*.[2b] When 1.0 *N* NaOH is used, phenolphthalein can be applied as the end point indicator.[2b] Besides determining the number of methyl groups, this method can also measure the number of ethyl groups on the cyclic compounds, which will be separated in the form of propionate.[2b] After separation of acetic acid, the excess amount of chromic acid is usually reduced by hydrazine.[5]

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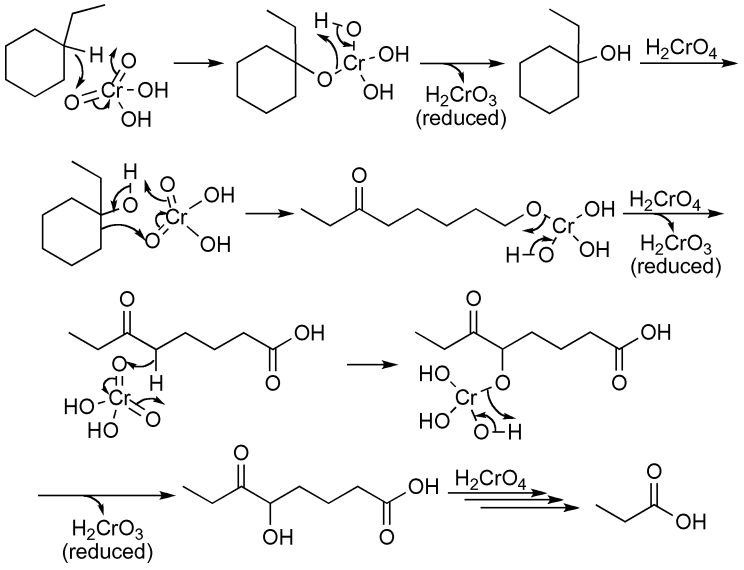
It should be pointed out that the Kuhn-Roth oxidation pertains only to the oxidation at an extra-nuclear carbon atom, with a general reactivity order of $C_6H_5\text{-}CH(R_2) > R_3CH > CH_2(R_2) > RCH_3$ (R = aliphatic chain).[4b] The Kuhn-Roth oxidation can determine the number of methyl groups in monoalkylbenzenes with acceptable accuracy up to 20 carbon atoms on the side chains,[7a] however, it fails in the oxidation of toluene, ethylbenzene, and isopropylbenzene to give the expected amount of acetic acid.[4b] In the case of *t*-butylbenzene, the oxidation occurs exclusively at the ring.[4b]

B. GENERAL REACTION SCHEME

C. PROPOSED MECHANISMS

Although no details of the mechanism are available for Kuhn-Roth oxidation, the reaction is proposed to involve the hydrogen abstraction and hydride abstraction mechanism.[4b] It is reasonable that the oxidation occurs initially at the location carrying the most active hydrogen, such as the tertiary proton in aliphatic compounds or the benzylic proton of alkylbenzenes. After such a proton is abstracted, alcohol is formed. Further oxidation of the resulting alcohol gives ketones, presumably accompanied by the cleavage of an alkyl group in the tertiary alcohol, and finally aliphatic acid is generated. Such an aliphatic acid holding an active α-hydrogen will undergo hydrogen abstraction, decarboxylation, and formation of a new aliphatic acid with a shortened carbon chain, until acetic acid is reached. However, a contradictive conclusion of the oxidation of ethylbenzene would be a potential challenge for this explanation.[4b,7a] An example of Kuhn-Roth oxidation on ethylcyclohexane to form propionic acid[2b] is displayed here.



D. MODIFICATION

N/A

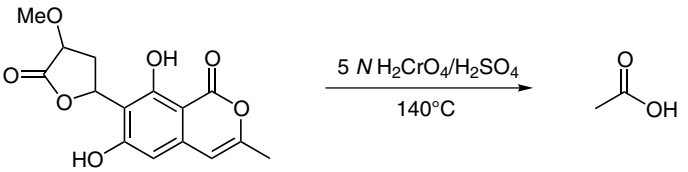
E. APPLICATIONS

This method was extensively used in the structural elucidation of natural products before modern spectroscopy was available.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 8e.

To a 50-mL flask containing 90 mg ^{14}C labeled canescin were added 10 mL 5 *N* chromic acid and 2 mL concentrated sulfuric acid slowly. A slow stream of clinical oxygen was passed, and the flask was heated to 140°C for 4 h with reflux. On cooling, the condenser was washed down with a small amount of distilled water, then 30% hydrazine solution was added dropwise until the color was completely green. After acidification with 4 mL phosphoric acid, the solution was steam distilled, and the distillate was made slightly alkaline with 0.1 *N* NaOH, as indicated by phenolphthalein. Evaporation gave sodium acetate, which was either converted into the *p*-bromophenacyl ester by standard methods or degraded by the Schmidt procedure; the products being measured as barium carbonate and *N*-methyl-2,4-dinitroaniline. In this experiment, 1 equivalent of acetic acid was found.

Other references related to the Kuhn-Roth oxidation are cited in the literature.[9]

H. REFERENCES

1. Kuhn, R. and Roth, H., *Ber.*, **1933**, *66*, 1274.
2. (a) Rangarajan, R. and Eisenbraun, E. J., *J. Org. Chem.*, **1985**, *50*, 2435. (b) Day, L. E.; Chamberlin, J. W.; Gordee, E. Z.; Chen, S.; Gorman, M.; Hamill, R. L.; Ness, T.; Weeks, R. E. and Stroshane, R., *Antimicrobial Agents & Chemotherapy,* **1973**, *4*, 410. (c) Horodysky, A. G.; Waller, G. R. and Eisenbraun, E. J., *J. Biol. Chem.*, **1969**, *244*, 3110. (d) Chaplen, P. and Thomas, R., *Biochem. J.*, **1960**, *77*, 91.

3. Birkinshaw, J. H. and Gowlland, A., *Biochem. J.*, **1962**, *84*, 342.
4. (a) Pansare, V. S. and Dev, S., *Tetrahedron*, **1968**, *24*, 3767. (b) Brandenberger, S. G.; Maas, L. W. and Dvoretzky, I., *J. Am. Chem. Soc.*, **1961**, *83*, 2146. (c) Cope, A. C.; Fournier, A. and Simmons, H. E., *J. Am. Chem. Soc.,* **1957**, *79*, 3905. (d) Urry, W. H.; Kruse, H. W. and McBride, W. R., *J. Am. Chem. Soc.*, **1957**, *79*, 6569. (e) Hochstein, F. A.; Stephens, C. R.; Conover, L. H.; Regna, P. P.; Pasternack, R.; Gordon, P. N.; Pilgrim, F. J.; Brunings, K. J. and Woodward, R. B., *J. Am. Chem. Soc.*, **1953**, *75*, 5455. (f) Hofmann, K.; Lucas, R. A. and Sax, S. M., *J. Biol. Chem.*, **1951**, 473. (g) Petru, F.; Jurecek, M. and Kovar, J., *Chem. Listy Vedu Prumysl*, **1951**, *45*, 300.
5. Wright, A.; Dankert, M.; Fennessey, P. and Robbins, P. W., *Proc. Natl. Acad. Sci. USA*, **1967**, *57*, 1798.
6. (a) Ludwig, S. A. and Villemez, C. L., *Biochem. J.*, **1972**, *128*, 605. (b) Olesch, B. and Boehm, H., *Arch. Pharm. Ber. Deutsch. Pharmazeut. Gesell.*, **1972**, *305*, 222. (c) Rognstad, R.; Woronsberg, J. and Katz, J., *Arch. Biochem. Biophys.*, **1968**, *127*, 429. (d) McMahon, V. and Stumpf, P. K., *Plant Physiol.*, **1966**, *41*, 148. (e) Parson, W. W. and Rudney, H., *Biochemistry*, **1966**, *5*, 1013.
7. (a) Brandenberger, S. G.; Maas, L. W. and Dvoretzky, I., *Anal. Chem.*, **1961**, *33*, 453. (b) Meluch, W. C. and Mislow, K., *J. Org. Chem.*, **1955**, *20*, 1311.
8. (a) Ravn, M. M.; Coates, R. M.; Flory, J. E.; Peters, R. J. and Croteau, R., *Org. Lett.*, **2000**, *2*, 573. (b) Rozzell, J. D. and Benner, S. A., *J. Org. Chem.,* **1983**, *48*, 1190. (c) Rown, C. E.; Katz, J. J. and Shemin, D., *Proc. Nat. Acad. Sci. USA*, **1972**, *69*, 2585. (d) Hollocher, T. C.; You, K.-S. and Conjalka, M., *J. Am. Chem. Soc.*, **1970**, *92*, 1032. (e) Birch, A. J.; Gager, F.; Mo, L.; Pelter, A. and Wright, J. J., *Aust. J. Chem.*, **1969**, *22*, 2429. (f) Bu'Lock, J. D. and Smith, G. N., *Biochem. J.*, **1965**, *96*, 495. (g) Snatzke, G., *Fresenius' Zeitsch. Anal. Chem.,* **1965**, *209*, 412. (h) Dalton, L. K., *Aust. J. Chem.*, **1964**, *17*, 1174. (i) Bentley, R.; Springer, C. M.; Ramsey, V. G.; Dialameh, G. H. and Olson, R. E., *J. Biol. Chem.*, **1963**, *243*, 174. (j) Djerassi, C.; Bowers, A. and Khastgir, H. N., *J. Am. Chem. Soc.*, **1956**, *78*, 1729. (k) Dauben, W. G.; Abraham, S.; Hotta, S.; Chaikoff, I. L.; Bradlow, H. L. and Soloway, A. H., *J. Am. Chem. Soc.*, **1953**, *75*, 3038.
9. (a) Oths, P. J.; Mayer, R. M. and Floss, H. G., *Carbohydr. Res.*, **1990**, *198*, 91. (b) Vleggaar, R., *Pure & Appl. Chem.*, **1986**, *58*, 239. (c) Steyn, P. S., *Pure & Appl. Chem.*, **1979**, *52*, 189. (d) Franck, B. and Knoke, J., *Chem. Ber.*, **1962**, *95*, 579. (e) Weygand, F.; Simon, H.; Bitterlich, W.; Hodge, J. E. and Fisher, B. E., *Tetrahedron*, **1959**, *6*, 123. (f) Birch, A. J.; Ryan, A. J. and Smith, H., *J. Chem. Soc.*, **1958**, 4773. (g) Birch, A. J.; Fitton, P.; Pride, E.; Ryan, A. J.; Smith, H. and Whalley, W. B., *J. Chem. Soc.*, **1958**, 4576. (h) Franzen, V. and Fikentscher, L., *Ann.*, **1958**, 617, 1. (i) Bu'Lock, J. D. and Ryan, A. J., *Proc. Chem. Soc.*, **1958**, 222. (j) Polonsky, J. and Baskevitch, Z., *Bull. Soc. Chim. Fr.*, **1958**, 929. (k) Halpern, O. and Schmid, H., *Helv. Chim. Acta*, **1958**, *41*, 1109. (l) Birch, A. J.; English, R. J.; Massy-Westropp, R. A. and Smith, H., *J. Chem. Soc.*, **1958**, 369. (m) Polonsky, J., *Bull. Soc. Chim. Fr.*, **1957**, 1079. (n) Bentley, R., *Proc. Chem. Soc*., **1957**, 20. (o) Corbaz, R.; Ettlinger, L.; Gaumann, E.; Keller-Schierlein, W.; Kradolfer, F.; Neipp, L.; Prelog, V.; Reusser, P. and Zahner, H., *Helv. Chim. Acta*, **1957**, *40*, 199. (p) Eisenbraun, E. J.; McElvain, S. M. and Aycock, B. F., *J. Am. Chem. Soc.*, **1954**, *76*, 607.

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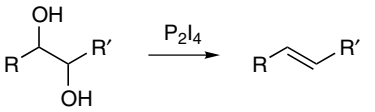
Kuhn-Winterstein Reduction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Kuhn and Winterstein in 1928.[1] It is the conversion of adjacent diols into corresponding olefins by means of a diphosphorus tetraiodide reduction and is known as the Kuhn-Winterstein reduction.[2] This reaction is tolerable for the diols with a terminal acetylene group if the experimental conditions are carefully handled,[3] such as the addition of diol in anhydrous pyridine to the supersaturated solution of diphosphorus tetraiodide in carbon disulfide.[2] In most cases, this reaction gives *trans*-olefins as major products,[3] unless the diol group is a part of a ring.[2]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is known that alcohols can be converted into halides when they are refluxed with red phosphorus and halogen (e.g., Br_2);[4] therefore, it is assumed that the diol is also converted into iodide as an intermediate that then undergoes the elimination in the presence of a base

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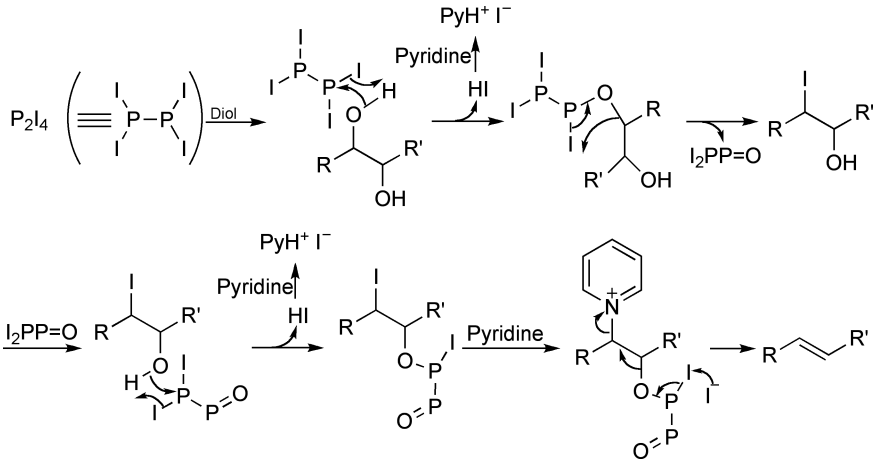
(e.g., pyridine). The brown color indicates the formation of iodine.[2] Shown here is part of the tentative mechanism.



D. MODIFICATION

N/A

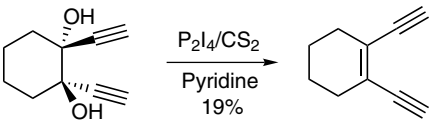
E. APPLICATIONS

This reaction can be used to convert the diols into corresponding olefins.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 2.

Diphosphorus tetraiodide (50 g, 88 mmol) was finely ground in a mortar, and extracted with 2.5 L dry carbon disulfide for 3 h in a Soxhlet extractor. *Trans*-1,2-diethynylcyclohexane-1,2-diol (10 g, 61 mmol) in 500 mL dry pyridine was added with

stirring over 10 min. The solution immediately turned brown and was then stirred at room temperature for 2 h. The carbon disulfide was removed under reduced pressure, and the residue was extracted with ether. The ether extract was washed successively with sodium hydroxide (2 *N*) solution, 12% sodium thiosulfate solution, 1.5 *N* sulfuric acid, water, saturated sodium bicarbonate solution, and saturated sodium chloride solution. The extract was dried over $MgSO_4$ and evaporated. The resulting brown residue (1.8 g) was chromatographed on 200 g silicic acid-Supercel using pentane as the eluent, to afford 1.48 g 1,2-diethynylcyclohexene as a colorless liquid, in a yield of 19%, b.p. 52–53°C (18 mmHg, under nitrogen).

Other references related to the Kuhn-Winterstein reduction are cited in the literature.[5]

H. REFERENCES

1. Kuhn, R. and Winterstein, A., *Helv. Chim. Acta*, **1928**, *11*, 87.
2. Pilling, G. M. and Sondheimer, F., *J. Am. Chem. Soc.*, **1971**, *93*, 1970.
3. Inhoffen, H. H.; Radscheit, K.; Stache, U. and Koppe, V., *Ann.*, **1965**, *684*, 24.
4. (a) Pfander, H., *Pure & Appl. Chem.*, **1985**, *57*, 735. (b) Pfander, H., *Pure & Appl. Chem.*, **1979**, *51*, 565.
5. (a) Rai, R.; Chen, H.-N.; Chang, H. W. and Chang, C.-W, T., *J. Carbohydr. Chem.*, **2005**, *24*, 131. (b) Pilling, G. M. and Sondheimer, F., *J. Am. Chem. Soc.*, **1968**, *90*, 5610. (c) Kuhn, R. and Krauch, H., *Ber.*, **1955**, *88*, 309. (d) Kuhn, R. and Zahn, H., *Ber.*, **1951**, *84*, 566. (e) Sorensen, N. A.; Stene, J. and Samuelsen, E., *Ann.*, **1940**, *543*, 132. (f) Kuhn, R. and Wallenfels, K., *Ber.*, **1938**, *71*, 1510. (g) Clar, E., *Ber.*, **1935**, *68B*, 2066. (h) Smith, J. H. C., *J. Biol. Chem.*, **1931**, *90*, 597.

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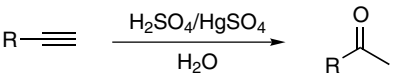
Kutscheroff Acetylene Hydration

A. GENERAL DESCRIPTION OF THE REACTION

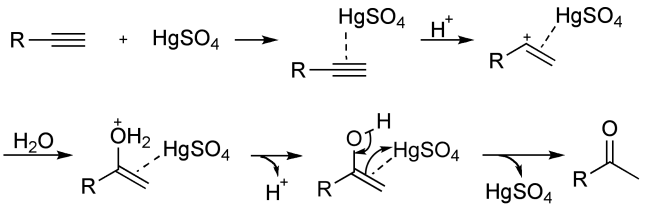
This reaction was first reported by Fittig and Schrohe in 1875[1] and subsequently extended by Kutscheroff in 1881.[2] It is an acid-catalyzed hydration of alkynes into ketones. In this reaction, dilute sulfuric acid and mercuric salt are used as catalysts,[3] and mercuric chloride can form a complex with acetylene in aqueous solution.[4] This reaction has been used to prepare ketones from higher alkynes, such as propyne,[5] and vinylacetylene[6] as well as in commercial production of acetaldehyde from acetylene.[3]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A tentative mechanism is proposed for the hydration of acetylene, as shown below.



D. MODIFICATION

N/A

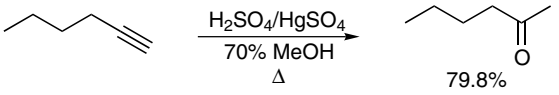
E. APPLICATIONS

This reaction has been used to prepare methyl alkyl ketones and for the commercial production of acetaldehyde.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3.

To a 500-mL three-necked flask equipped with a mercury-sealed stirrer, reflux condenser, and a dropping funnel were added 1.0 g $HgSO_4$, 1.0 g H_2SO_4, and 150.0 g 70% methanol. The mixture was kept at 60 ± 1°C, and 41.0 g 1-hexyne (0.5 mol) was added with good stirring over a period of 1 h. The reaction mixture was then stirred at 60°C for an additional 3 h and cooled to room temperature. The solvent methanol was removed by fractional distillation through an efficient double-jacketed column packed with a single monel wire spiral. The residue was saturated with solid NaCl, and the two layers were separated. The organic layer was washed with brine, Na_2CO_3, and brine again; dried over $CaCl_2$; and distilled from a modified Claisen flask. The portion of the distillate boiling between 124° and 128°C was retained as 2-hexanone, in a yield of 79.8%.

Other references related to the Kutscheroff acetylene hydration are cited in the literature.[7]

H. REFERENCES

1. Fittig, R. and Schrohe, A., *Ber.,* **1875**, *8*, 367.
2. (a) Kutscheroff, M. G., *Ber.*, **1881**, *14*, 1532. (b) Kutscheroff, M. G., *Ber.*, **1881**, *14*, 1540.
3. Thomas, R. J.; Campbell, K. N. and Hennion, G. F., *J. Am. Chem. Soc.*, **1938**, *60*, 718.
4. Kutscheroff, M. G., *J. Russ. Chem. Soc.*, **1893**, *24*, 330.
5. Kutscheroff, M. G., *Ber.*, **1884**, *17*, 13.
6. (a) Conaway, R. F., *U.S. Pat*., Jul 24, **1934**, 1,967,225. (b) Carter, A. S., *U.S. Pat.*, Feb 7, **1933**, 1,896,161.
7. (a) Stang, P. J. and Roberts, K. A., *J. Org. Chem.*, **1987**, *52*, 5213. (b) De la Mare, P. B. D. and Bolton, R., *Electrophilic Additions to Unsaturated Systems*, Elsevier, Amsterdam, **1982**. (c) Patai, S., *The Chemistry of the Carbon-Carbon Triple Bond*, John Wiley & Sons, New York, **1978**. (d) Viehe, H. G., *Chemistry of Acetylenes*, Marcel Dekker, New York, **1969**. (e) Johnson, J. R. and McEwen, W. L., *J. Am. Chem. Soc.*, **1926**, *48*, 469. (f) Grognot, L., *Rev. Gen. Chim.,* **1907**, *10*, 49. (g) Biltz, H. and Mumm, O., *Ber.*, **1904**, *37*, 4417. (h) Peratoner, A., *Gazz. Chim. Ital.*, **1894**, *24*, 36.

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Lander Rearrangement

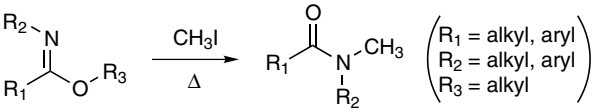
A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Wheeler and Johnson in 1899[1] and was explored extensively by Lander starting in 1900.[2] It is a thermal conversion of alkyl imidates (also known as imino ethers[3]) into *N*-alkyl amides in the presence of an alkylting agent. Therefore, it is generally referred to as the Lander rearrangement.[4]

In this 1,3-shift process,[5] when the alkyl group of the alkylating agent is different from that of the substrate, mixed alkyl amides are obtained;[6] however, when the alkylating agent of a lower alkyl group is used for the pyrolysis of alkyl imidates, the *N*-alkyl amides more likely form, with the alkyl groups substituted by the lower one.[2e] Such trend of alkyl group replacement was postulated as early as in 1897 for the conversion of 2-methoxyquinoline or 2-ethoxyquinoline into *N*-methyl-2-quinolone with excess methyl iodide.[7]

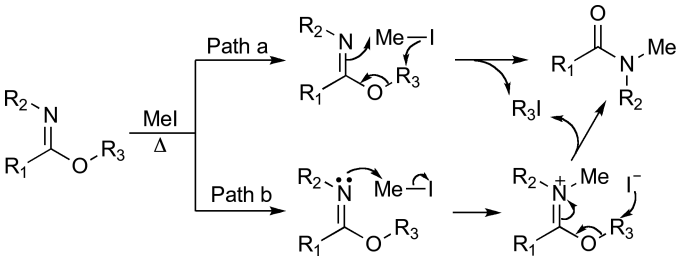
It should be pointed out that this rearrangement also occurs smoothly in the absence of an alkylting agent, as shown in the transformation of *N*-substitued imidates to *N*,*N*-disubstituted amides during the distillation in vacuo,[5] and the reaction under such condition is now known as the *Chapman Rearrangement*.[8]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Different mechanisms have been proposed for this reaction, including a radical process,[4b,8] an ionic proces[9] and even a concerted rearrangement.[10] In addition, experimental evidence indicates that this rearrangement is an intramolecular process.[5] An illustration of such rearrangement by two possible pathways is displayed below.



D. MODIFICATION

This reaction has been extended to the thermal conversion of 2-methylthiobenzthiazole to 2,3-dihydro-3-methylthiobenzthiazole-2-thione in the presence of a methiodide salt.[11] In addition, the *Chapman Rearrangement* and *Hilbert-Johnson Reaction* can be considered as the extensions of the Lander rearrangement.

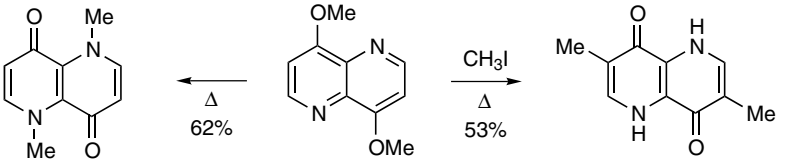
E. APPLICATIONS

This reaction is often used to convert methoxypyridines into *N*-methylpyridones.[12]

F. RELATED REACTIONS

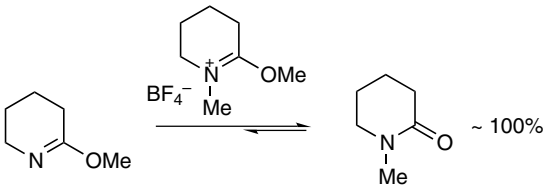
This reaction is closely related to the *Chapman Rearrangement* and *Hilbert-Johnson Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4a.

A mixture of 140 mg 4,8-dimethoxy-1,5-naphthyridine and 34 mg methyl iodide (molar ratio = 3:1) was heated at 220°C for 12 h. The resulting crude product was boiled with benzene to remove any 1,5-dimethyl-1,5-naphthyridine-4(1*H*),8(5*H*)-dione present and then gradient sublimed at 275°C. The white crystalline sublimate was dissolved in warm dilute aqueous NaOH, and the resulting violet solution was adjusted to pH 2 with concentrated HCl. The precipitate was collected and recrystallized from a large volume of water to afford 74 mg pure 3,7-dimethyl-1,5-naphthyridine-4(1*H*),8(5*H*)-dione, in a yield of 53%, m.p. > 300°C. However, when 280 mg pure 4,8-dimethoxy-1,5-naphthyridine was heated at 226°C for 10 h, and the crude product was dissolved in boiling benzene and filtered hot through a thin pad of Norit A on Celite, 174 mg 1,5-dimethyl-1,5-naphthyridine-4(1*H*),8(5*H*)-dione was obtained as a white crystalline after cooling and filtration, in a yield of 62%, m.p. 268.5–272°C.



Reference 4c.

A sealed tube containing 0.138 g *O*-methylvalerolactim and 0.029 g *N*-methyl-2-methoxy-3,4,5,6-tetrahydropyridinium fluoroborate was heated at 130°C for 2 h. After the reaction, the mixture was taken up by 1.2 mL CH_2Cl_2, and 0.019 g *N*-methyl-2-methoxy-3,4,5,6-tetrahydropyridinium fluoroborate was precipitated by the addition of 8.0 mL Et_2O. GLPC analysis of the solution using phenyl ether as an internal standard indicated a 104 ± 5% yield of *N*-methylvalerolactam.

Other references related to the Lander rearrangement are cited in the literature.[13]

H. REFERENCES

1. Wheeler, H. L. and Johnson, T. B., *Amer. Chem. J.*, **1899**, *21*, 185.
2. (a) Lander, G. D., *J. Chem. Soc., Trans.*, **1900**, *77*, 729. (b) Lander, G. D., *J. Chem. Soc., Trans.*, **1901**, *79*, 701. (c) Lander, G. D., *J. Chem. Soc., Trans.*, **1902**, *81*, 591. (d) Lander, G. D. and Jewson, F. T., *J. Chem. Soc., Trans.*, **1903**, *83*, 766. (e) Lander, G. D., *J. Chem. Soc., Trans.*, **1903**, *83*, 406. (f) Lander, G. D., *J. Chem. Soc., Trans.*, **1903**, *83*, 320. (g) Lander, G. D., *J. Chem. Soc., Trans.*, **1904**, *85*, 984.
3. Huston, R. C. and Allen, W. F., *J. Am. Chem. Soc.*, **1934**, *56*, 1358.
4. (a) Brown, S. B. and Dewar, M. J. S., *J. Org. Chem.*, **1978**, *43*, 1331. (b) McNamee, G. M.; Willett, B. C.; La Perriere, D. M. and Peters, D. G., *J. Am. Chem. Soc.*, **1977**, *99*, 1831. (c) Beak, P.; Bonham, J. and Lee, J. T., *J. Am. Chem. Soc.*, **1968**, *90*, 1569.
5. Roger, R. and Neilson, D. G., *Chem. Rev.*, **1961**, *61*, 179.
6. Roberts, R. M. and Vogt, P. J., *J. Am. Chem. Soc.*, **1956**, *78*, 4778.
7. Knorr, L. and Rabbe, P., *Ber.*, **1897**, *30*, 927.
8. Wiberg, K. B.; Shryne, T. M. and Kintner, R. R., *J. Am. Chem. Soc.*, **1957**, *79*, 3160.

9. (a) Brown, D. J. and Foster, R. V., *J. Chem. Soc.*, **1965**, 4911. (b) Taguchi, T.; Kawazoe, Y.; Yoshihira, Y.; Kawayama, H.; Mori, M.; Tabata, K. and Harano, K., *Tetrahedron Lett.*, **1965**, 2717.
10. Cohen, L. A. and Witkop, B., "Rearrangements in the Chmistry of Amino Acids and Peptides" in *Molecular Rearrangements,* 2, ed. de Mayo, P., Interscience Publishers, New York, **1964**, p. 981.
11. Fry, D. J. and Kendall, J. D., *J. Chem. Soc.*, **1951**, 1716.
12. (a) Paquette, L. A. and Nelson, N. A., *J. Org. Chem.,* **1962**, *27*, 1085. (b) Sidgwick, N. V., *The Organic Chemistry of Nitrogen*, Clarendon Press, Oxford, **1937**, p. 531.
13. (a) Brown, S. B. and Dewar, M. J. S., *J. Chem. Soc., Chem. Commun.*, **1977**, 87. (b) Golfier, M. and Milcent, R., *Tetrahedron Lett.*, **1974**, 3871. (c) Golfier, M. and Milcent, R., *Bull. Soc. Chim. Fr.*, **1973**, 254. (d) Oesper, R. E. and Cook, W. A., *J. Am. Chem. Soc.*, **1925**, *47*, 422. (e) Wislicenus, W. and Goldschmidt, M., *Ber.*, **1900**, *33*, 1467.

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Larock Indole Synthesis
(Larock Heteroannulation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Larock et al. in 1991.[1] It is a palladium-catalyzed chemoselective and "ligandless" heteroannulation between *ortho*-iodoanilines and disubstituted alkynes to form substituted indole derivatives. Therefore, this reaction is generally known as the Larock heteroannulation[2] or Larock indole synthesis.[3]

This reaction is affected by various factors, including an added base, lithium halide and its stoichiometry, the presence or absence of ligand PPh_3, and the reaction temperature.[1,4] Specifically, for the reaction of 0.25 mmol *ortho*-iodoaniline with 0.75 mmol alkyne (3 eq.), using 5 mol % of $Pd(OAc)_2$ as the catalyst and 5 eq. of base in 10 mL DMF, it is not at all necessary to have a ligand (e.g., PPh_3) present.[4] The bases tested for this reaction are KOAc, NaOAc, K_2CO_3, and Na_2CO_3; the potassium salts are obviously better than the sodium salts, and KOAc is always superior to K_2CO_3, except when no other reagent is added, such as LiCl.[4] For example, when KOAc is used as the base, only 1 eq. of LiCl is needed, and an excess amount of LiCl will result in a lower reaction rate, lower yield, and contamination from further insertion. Under these conditions, the reaction must be carried out at temperature $> 120^{\circ}C$ and the addition of 5 mol % of ligand will lower the yield.[4] However, when K_2CO_3 is used as a base, LiBr or LiI can be used as the LiCl substitute, and ligand has no effect on this reaction; in contrast, in the presence of 1 eq. LiCl, the reaction temperature can be lowered to $100^{\circ}C$. Therefore, the best condition for the Larock indole synthesis is to use 5 mol % $Pd(OAc)_2$ and either KOAc or K_2CO_3 as the base, with 1 eq. LiCl and 2–5 eq. alkynes.[4] On the other hand, this reaction is very versatile, as indicated by its tolerance of diversified substituents on the alkynes and nitrogen atom of anilines. For example, the substituents on the nitrogen atom of anilines can be methyl, acetyl, tosyl, etc.,[1]

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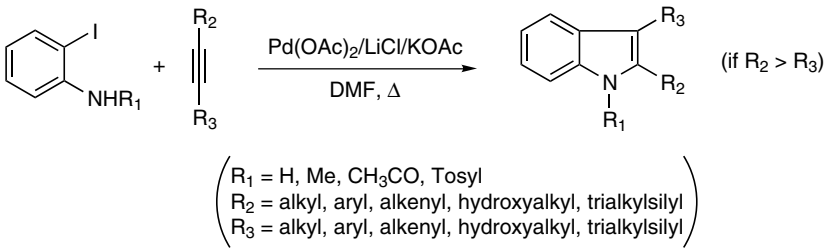
and the alkynes can bear alkyl, aryl, alkenyl, hydroxyl, and silyl groups.[1] Even bulky tertiary alkyl or trimethylsilyl groups are readily accommodated by this reaction.[4] In addition, this reaction is highly regioselective, whereas the more sterically bulky group ends up at the 2-position.[1,4] However, for the case of diethyl acetal of 2-butynal, no regioselectivity was observed that may have been caused by an electronic effect.[4] It has been found that for the reaction between *o*-iodoacetylaniline and alkynes with hindered or unhindered hydroxyalkyl group, the migration of the *N*-acetyl group from nitrogen to the alcohol group does sometimes occur, which may arise from the base-catalyzed intramolecular transfer of acetyl group.[4]

B. GENERAL REACTION SCHEME

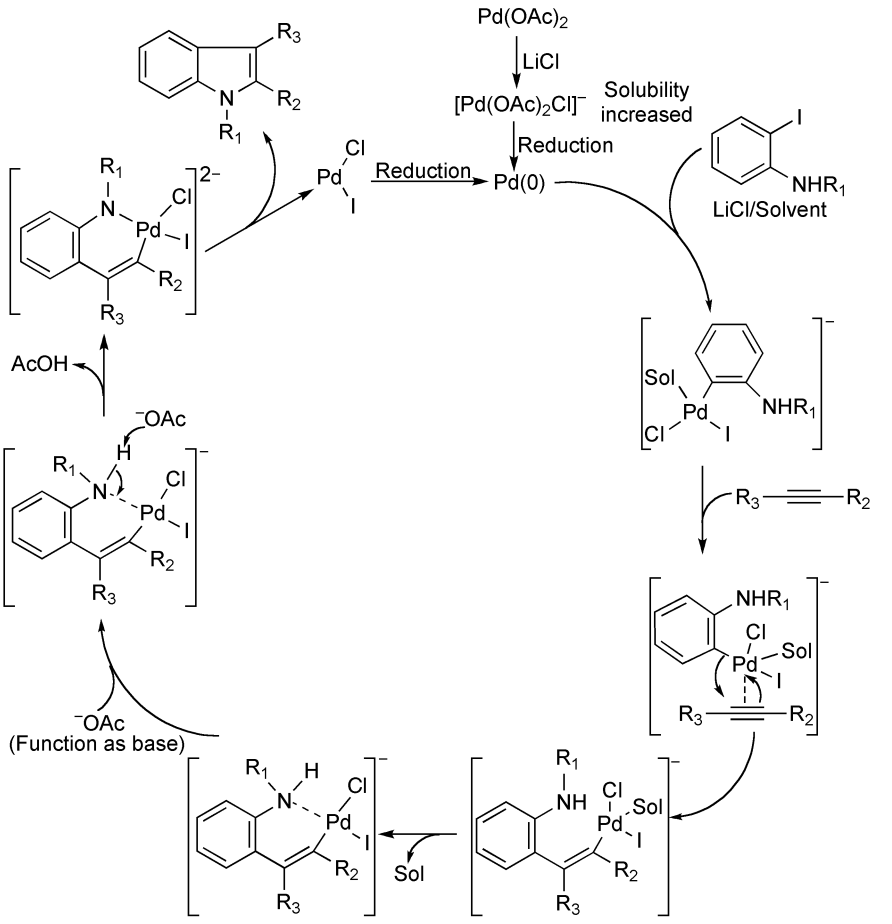


C. PROPOSED MECHANISMS

Although a mechanism has been proposed to rationalize the reaction that contains a several steps for the catalytic cycle,[1,4,5] a different mechanism is proposed here. The original mechanism includes the following steps in the catalytic cycle: (*a*) reduction of $Pd(OAc)_2$ to Pd(0) to initiate the catalytic cycle, (*b*) coordination of chloride to palladium, (*c*) oxidative addition of aryl iodide to Pd(0), (*d*) coordination of alkyne to palladium atom and subsequent regioselective *syn*-insertion into the arylpalladium bond, (*e*) nitrogen displacement of the halide in the resulting vinylic palldium intermediate to form a palladacycle, and (*f*) reductive elimination to form indole and the regenerated Pd(0) reenters the catalytic cycle.

As mentioned, this ligandless reaction proceeds in the presence of a base, 1 eq. LiCl, using a catalytic amount of $Pd(OAc)_2$. The presence of LiCl may have two effects: coordination with palladium and enhancement of solubility. In addition, the catalytic amount of $Pd(OAc)_2$ can be reduced to Pd(0) by any reducing reagent in the reaction solution, which then inserts into *o*-iodoaniline. At this stage, one or two solvent molecules may coordinate with palladium to stabilize the complex, and the role of the solvent in the complex can be replaced by ligand if a ligand presents. After that, an alkyne coordinates with the complex, and an alkenyl palladium species forms. When an *ortho* amino group coordinates with palladium, the proton on the nitrogen atom is more acidic than it's used to be, which can be deprotonated by the existing base. Finally, reductive elimination affords the substituted indole molecule, and Pd(II) species can be reduced to Pd(0) and enter the catalytic cycle again. This new mechanism is displayed here.

Carbonate is a stronger base than acetate, so when acetate is used as the base, the reaction occurs $> 120^{\circ}C$; whereas when K_2CO_3 is used as base, the reaction temperature can be lowered to $100^{\circ}C$.



D. MODIFICATION

This reaction has been modified to occur between *o*-iodoaniline and allene to form 3-methyleneindolines,[6] and between *o*-alkynylhaloarene and amines to form indole derivatives.[7] More importantly, this reaction has been successfully extended to *ortho*-bromoanilines or *ortho*-chloroanilines by carefully choosing ligand, base, solvent, and concentration.[5] For example, 1,1′-bis(di-*tert*-butylphosphino)ferrocene or tricyclohexylphosphine has been used as a ligand; the former is the best ligand discovered so far, whereas the latter does not result in normal by-products.[5]

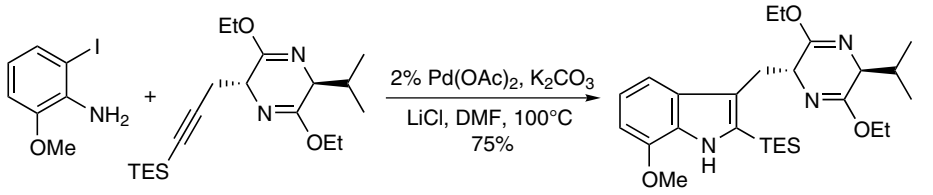
E. APPLICATIONS

This reaction has been used to prepare a variety of heterocycles, including 5-aza-indoles;[8] 5-,6-, and 7-aza-indoles;[9] pyrrolo[3,2-*c*]quinolines;[10] 12-methoxy-N_a-methyl-vellosimine;[2c] (+)-12-methoxyaffinisine;[2c] and (-)-fuchsiaefoline.[2c]

F. RELATED REACTIONS

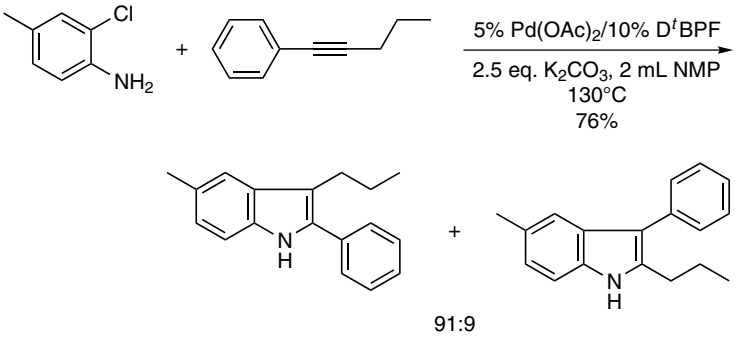
This reaction is related to the *Hegedus Indole Synthesis*, *Castro Indole Synthesis*, and *Mori-Ban Indole Synthesis.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 2b.

To a 2-L round-bottomed flask were added 102 g 2-iodo-6-methoxyaniline (0.41 mol), 179 g Schöllkopf derivative (0.49 mol), 17.4 g LiCl (0.41 mol), 141.3 g K_2CO_3 (1.02 mol); 1.84 g $Pd(OAc)_2$ (8.2 mmol), and 700 mL anhydrous DMF. The mixture was then degassed with a vacuum pump three times at room temperature (with argon). The suspension that resulted was heated for 36 h at 100°C under an atmosphere of argon. After the consumption of iodoaniline, as monitored by TLC, the reaction mixture was cooled to room temperature and diluted with EtOAc. The mixture was washed with H_2O (5 × 20 mL) to remove DMF. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography over silica gel (2% EtOAc/hexane) provided 149 g (5*R*,2*S*)-3,6-diethoxy-2-isopropyl-5-[7-methoxy-2-(triethylsilyl)-3-indolyl]methyl-2,5-dihydropyrazine as a yellow oil, in a yield of 75%.



Reference 5.

To an oven-dried reaction vial were added 11 mg $Pd(OAc)_2$ (0.05 mmol), 47 mg 1,1′-bis(di-*t*-butylphosphino)ferrocene (0.1 mmol), and 346 mg potassium carbonate (2.5 mmol). The vial was purged with argon. Then 123 μL 2-chloro-4-methylaniline (1 mmol), 192 μL 1-phenyl-1-pentyne (1.2 mmol), and 2 mL NMP were added via syringe. The reaction was heated to 130°C, stirred at the same temperature; and monitored by HPLC. The reaction was complete after 4 h. The ratio of the regioisomer was 91:9. The mixture

was filtered through a pad of Celite. The cake was washed with EtOAc. The organic solvent was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to give a brown residue. The product was purified via column chromatography.

Other references related to the Larock indole synthesis are cited in the literature.[11]

H. REFERENCES

1. Larock, R. C. and Yum, E. K., *J. Am. Chem. Soc.*, **1991**, *113*, 6689.
2. (a) Ma, J.; Yin, W. Y.; Zhou, H. and Cook, J. M., *Org. Lett.*, **2007**, *9*, 3491. (b) Zhou, H.; Liao, X. B.; Yin, W. Y.; Ma, J. and Cook, J. M., *J. Org. Chem.*, **2006**, *71*, 251. (c) Zhou, H.; Liao, X. B. and Cook, J. M., *Org. Lett.*, **2004**, *6*, 249.
3. (a) Kálai, T.; Balog, M.; Jeko, J.; Hubbell, W. L. and Hideg, K., *Synthesis*, **2002**, 2365. (b) Walsh, T. F.; Toupence, R. B.; Ujjainwalla, F.; Young, J. R. and Goulet, M. T., *Tetrahedron*, **2001**, *57*, 5233. (c) Nishikawa, T.; Ishikawa, M.; Wada, K. and Isobe, M., *Synlett*, **2001**, 945.
4. Larock, R. C.; Yum, E. K. and Refvik, M. D., *J. Org. Chem.*, **1998**, *63*, 7652.
5. Shen, M.; Li, G. S.; Lu, B. Z.; Hossain, A.; Roschangar, F.; Farina, V. and Senanayake, C. H., *Org. Lett.*, **2004**, *6*, 4129.
6. (a) Zenner, J. M. and Larock, R. C., *J. Org. Chem.*, **1999**, *64*, 7312. (b) Larock, R. C. and Zenner, J. M., *J. Org. Chem.*, **1995**, *60*, 482.
7. Ackermann, L., *Org. Lett.*, **2005**, *7*, 439.
8. Xu, L.; Lewis, I. R.; Davidsen, S. K. and Summers, J. B., *Tetrahedron Lett.*, **1998**, *39*, 5159.
9. Ujjainwalla, F. and Warner, D., *Tetrahedron Lett.*, **1998**, *39*, 5355.
10. Kang, S. K.; Park, S. S.; Kim, S. S.; Choi, J.-K. and Yum, E. K., *Tetrahedron Lett.*, **1999**, *40*, 4379.
11. (a) Charrier, N.; Demont, E.; Dunsdon, R.; Maile, G.; Naylor, A.; O'Brien, A.; Redshaw, S.; Theobald, P.; Vesey, D. and Walter, D., *Synthesis*, **2006**, 3467. (b) Humphrey, G. R. and Kuethe, J. T., *Chem. Rev.*, **2006**, *106*, 2875. (c) King, A. O. and Yasuda, N., *Topics Organomet. Chem.*, **2004**, *6*, 205. (d) Konno, T.; Chae, J. H.; Ishihara, T. and Yamanaka, H., *J. Org. Chem.*, **2004**, *69*, 8258. (e) Nishikawa, T.; Wada, K. and Isobe, M., *Biosci. Biotechnol. Biochem.*, **2002**, *66*, 2273. (f) Gribble, G. W., *J. Chem. Soc*., *Perkin Trans. I*, **2000**, 1045. (g) Takeda, A.; Kamijo, S. and Yamamoto, Y., *J. Am. Chem. Soc.*, **2000**, *122,* 5662.

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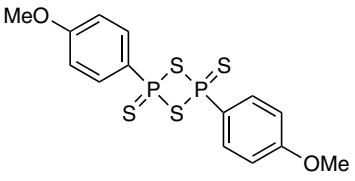
Lawesson's Reagent

A. GENERAL DESCRIPTION OF THE REACTION

The full name of this reagent is 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (or -disulphide),[1] 2,4-bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane,[2] 4-methoxy-phenylthionophosphine sulphide dimmer,[2] or (*p*-methoxyphenyl)thionophosphine sulfide.[3] Although it was not initially invented by Lawesson,[4] it is known as the Lawesson's reagent (LR)[5] after Lawesson who extensively studied the reactivities of this reagent and made it a popular chemical reagent.[1a,6] Lawesson's reagent is a powerful, mild, and versatile[7] thiation[1a,8] (also called thionation[1b,3,9] or sulfuration[10]) agent that efficiently converts oxygen functionalities into their *thio*-analogs. First, it converts the carbonyl group into thiocarbonyl group, as shown in the transformation of ketone into thioketone,[6b,11] amide to thioamide,[11,12] ester to thioester,[13] urea to thiourea,[14] trimethylsilyl ferrocenoketone to analgous thioketone,[12b] enaminoaldehyde to enaminothioaldehyde,[9a] enaminoketone to enaminothioketone,[9a] oxalamide to oxala-thioamide,[10,15] flavones to thioflavones,[11] isoflavones to thioisoflavones,[11] lactones to thiolactone,[11] and coumarin to 2*H*-chromene-2-thione.[6d,16] Second, the Lawesson reagent also converts the carbon-oxygen single bond into a carbon-sulfur single bond, as indicated in the transformation of benzylic and related alcohols into corresponding thiols;[9e,17] β-lactone to β-thio lactone;[18] and orthoesters, acetals, or epoxides to their thio-analogues.[19] Third, because of the versatility in replacing oxygen functionalities, this reagent has been used for the cyclization of compounds containing at least two oxygen functionalities. This type of reaction includes the conversion of 1,4-dicarbonyl compounds into 2,5-disubstituted thiophenes;[20] 4-hydroxy enone[17a] or 4-keto enol[8a] into thiophene derivatives; α-keto amide into 1,3-thiazoles;[20a,21] nonenolizable 1,4-, 1,5-, 1,6-, and 1,7-diketones into 1,3-dithietanes;[22] and β-keto esters in combination with sulfur to dithiolethiones.[9c] More importantly, this reagent has been

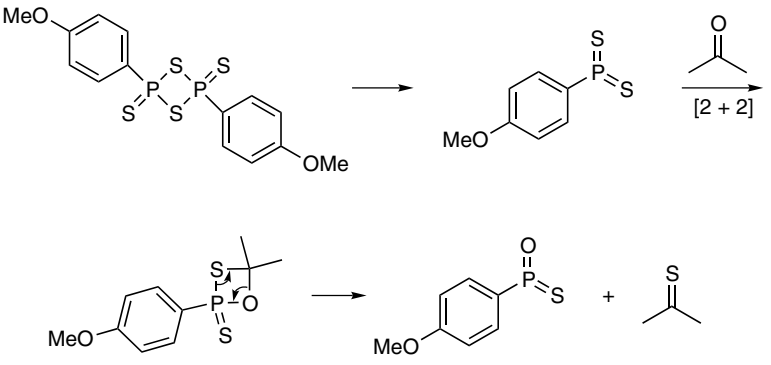
used to convert two ester groups into an olefinic bond in combination with 1,1,3,3-tetramethylthiourea, as demonstrated by the synthesis of hemibrevitoxin B and brevitoxin B.[13a,13b] If two oxygen functionalities coexist within a molecule, it has been found that the hydroxyl group is superior to amido group toward the Lawesson's reagent;[9e] similarly, an amido group is superior to an ester group in terms of reactivity.[23] This is parallel to the electron density on those groups, in which the oxygen functionality with more enriched electron should react faster with the Lawesson's reagent.[14] In some cases, the steric hindrance also influences the selectivity.[9d] It is interesting that the thionation of dibenzyl ketone ends up with styrenyl thiol as the major product.[24] Other applications of Lawesson's reagent are indicated by the reductive coupling of phenalenone to peropyrene,[25] the thionation of phosphonamidate oxygen (i.e., converting P=O bond to P=S bond),[9d] thionation of S-oxide in thioketene to form thiirane-2-thione,[26] thionation of S-oxide in thioketone to give dithiirane,[27] synthesis of β-lactams in combination with a Schiff base,[1b] and thionation on organometallic compounds[3,9b] such as converting the W=O bond to W=S.[28] Nevertheless, it is believed that the Lawessons reagent $(ArPS_2)_2$ breaks into 2 eq. active species ($ArPS_2$), which is involved in all the functional transformation.[8b] Although this reagent is very versatile, it does have some disadvantages during functional group transformation. For example, due to its relatively high molecular weight, this reagent is normally used for small-scale reactions.[9c] In addition, the by-products derived from this reagent generally cannot be separated by simple extraction but usually by column chromatography.[9c]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Only the mechanism for the formation of thioketone from ketone is illustrated here.



D. MODIFICATION

The thionation from the Lawesson's reagent has been improved by using P_4S_{10} and hexamethyldisiloxane as the thionation reagent, from which the by-products can be easily removed by extraction and column chromatography after the thionation.[9c]

E. APPLICATIONS

Besides the extensive applications of the Lawesson's reagent as already mentioned, this reagent has been used to synthesize many five- and six-membered phosphorus heterocycles,[9e] and sulfur-containing heterocycles;[9e] in addition, this compound has also been used as the racemization-free coupling reagent in peptide synthesis,[29] and the 1,3-dipole indicator.[8b]

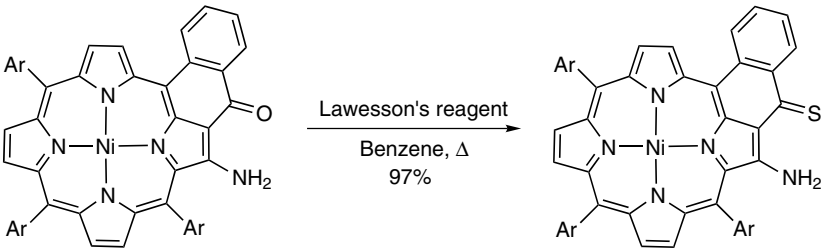
F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES

Reference 8a.

To a solution of 0.834 g 1,2-C_5H_3(CTpOH)(COTp) (2.92 mmol) in 90 mL dry toluene was added 1.59 g Lawesson's reagent (3.94 mmol). The solution was refluxed for 8 h under stirring. After cooling to room temperature, the solution was concentrated to an oil via rotary evaporation and further dried on the Schlenk line for 2 h. The oil was cooled over liquid nitrogen, then extracted using cold pentane. The organics were filtered, and the volatiles were removed via rotary evaporation, giving an oil. The crude oil was purified by silica gel column chromatography (30:70, toluene/pentane) to yield 1,3-dithienyl-4*H*-cyclopenta[*c*]thiophene as a cream-colored solid. Rechromatographing the second fluorescent fraction, containing a mixture of 1,3-dithienyl-4*H*-cyclopenta[*c*]thiophene and an unknown compound (96:4, hexane/Et_2O) yielded another batch of 1,3-dithienyl-4*H*-cyclopenta[*c*]thiophene, in total amount of 0.125 g, in a yield of 15.0%. m.p. 98–101°C (MeOH).



Reference 9a.

A solution of 273 mg nickel enaminocetone (0.26 mmol) and 152 mg Lawesson's reagent (2.66 mmol) in 150 mL benzene was refluxed until consumption of all starting material (∼2 h). After evaporation of the solvent, the residue was chromatographed on a silica gel column (dichloromethane/hexane, 1:1). After crystallization from dichloromethane/methanol, 270 mg green nickel enaminothioketone (0.254 mmol) was isolated, in a yield of 97%.

Other references related to the Lawesson's reagent are cited in the literature.[30]

H. REFERENCES

1. (a) Thomsen, I.; Clausen, K.; Scheibye, S. and Lawesson, S. O., *Org. Synth.*, **1984**, *62*, 158. (b) Sharma, S. D. and Kanwar, S., *Org. Proc. Res. Dev.*, **2004**, *8*, 658.
2. Lancaster Research Chemicals, **2004-2005** catalog windham, NH, p. 1025.
3. Weng, Z. Q. and Goh, L. Y., *Acc. Chem. Res.*, **2004**, *37*, 187.
4. Lecher, H. Z.; Greenwood, R. A.; Whitehouse, K. C. and Chao, T. H., *J. Am. Chem. Soc.*, **1956**, *78*, 5018.
5. (a) Romero, N.; Gnecco, D.; Teran, J.; Juarez, J. and Galindo, A., *J. Sulfur Chem.*, **2007**, *28*, 239. (b) Nagano, T.; Kimoto, H.; Nakatsuji, H.; Motoyoshiya, J.; Aoyama, H.; Tanabe, Y. and Nishii, Y., *Chem. Lett.*, **2007**, *36*, 62. (c) Kanwar, S. and Sharma, S. D., *Bull. Chem. Soc. Jpn.*, **2006**, *79*, 1748. (d) Przychodzen, W., *Heteroatom Chem.*, **2006**, *17*, 676. (e) Peesapati, V. and Rupavani, G., *Indian J. Chem., Sect. B,* **2006**, *45B*, 1034. (f) Kaleta, Z.; Makowski, B. T.; Soos, T. and Dembinski, R., *Org. Lett.*, **2006**, *8*, 1625. (g) Brayton, D.; Jacobsen, F. E.; Cohen, S. M. and Farmer, P. J., *Chem. Commun.*, **2006**, 206. (h) El-Kateb, A. A. and Abd El-Rahman, N. M., *Phosphorus, Sulfur & Silicon & Related Elements*, **2006**, *181*, 249. (i) Poeylaut Palena, A. A. and Mata, E. G., *ARKIVOC*, **2005**, (*xii)*, 282. (j) Valette, L.; Poulain, S.; Fernandez, X. and Lizzani-Cuvelier, L., *J. Sulfur Chem.*, **2005**, *26*, 155. (k) Gierczyk, B. and Zalas, M., *Org. Prep. Proc. Int.*, **2005**, *37*, 213. (l) Kodama, Y.; Ori, M. and Nishio, T., *Helv. Chim. Acta*, **2005**, *88*, 187. (m) Wu, X. Y.; Mahalingam, A. K. and Alterman, M., *Tetrahedron Lett*., **2005**, *46*, 1501. (n) Mohamed, N.; El-Saidi, M. M.; Abdallah, T. and Nada, A., *Phosphorus, Sulfur & Silicon & Related Elements*, **2004**, *179*, 2387. (o) Przychodzen, W., *Phosphorus, Sulfur & Silicon & Related Elements*, **2004**, *179*, 1621. (p) Liu, H.-L.; Mao, H.-Y.; Xu, C.; Zhang, H.-Y.; Hou, H.-W.; Wu, Q.-A.; Zhu, Y.; Ye, B.-X. and Yuan, L.-J., *Polyhedron*, **2004**, *23*, 1799. (q) Huang, H.-M.; Yu, H.-T.; Chen, P.-L.; Han, J. and Meng, J.-B., *Youji Huaxue*, **2004**, *24*, 502. (r) Mohamed, N. R.; El-Saidi, M. M. T.; Hassaneen, H. M. and Erian, A. W., *Phosphorus, Sulfur & Silicon & Related Elements*, **2004**, *179*, 521. (s) Rafiqul, I. M.; Shimada, K.; Aoyagi, S.; Fujisawa, Y. and Takikawa, Y., *Heteroatom Chem*., **2004**, *15*, 208. (t) Ertas, E. and Ozturk, T., *Tetrahedron Lett*., **2004**, *45*, 3405. (u) Venkateswarlu, P. and Venkata, S. C., *Tetrahedron Lett*., **2004**, *45*, 3207. (v) Abdel-Malek, H. A., *Heterocycl. Commun*., **2003**, *9*, 457. (w) Mohamed, N. R.; Kamel, E. M.; Erian, A. W. and Nada, A. A., *Egypt. J. Chem.*, **2003**, *46*, 873. (x) Mohamed, N. R.; Elmegeed, G. A. and Younis, M., *Phosphorus, Sulfur & Silicon & Related Elements*, **2003**, *178*, 2003. (y) Markovic, R.; Baranac, M. and Jovetic, S., *Tetrahedron Lett*., **2003**, *44*, 7087. (z) Bethke, J.; Karaghiosoff, K. and Wessjohann, L. A., *Tetrahedron Lett*., **2003**, *44*, 6911. (aa) Butler, I. R.; Caballero, A. G. and Kelly, G. A., *Inorg. Chem. Commun.*, **2003**, *6*, 639. (bb) Peyrane, F.; Fourrey, J.-L. and Clivio, P., *Chem. Commun.*, **2003**, 736. (cc) Deng, S.-L. and Chen, R.-Y., *Phosphorus, Sulfur & Silicon & Related Elements*, **2003**, *178*, 211. (dd) He, L. N.; Luo, Y. P.; Li, K.; Yang, G. F.; Ding, M. W.; Liu, X. P. and Wu, T. J., *Phosphorus, Sulfur & Silicon & Related Elements*, **2002**, *177*, 2675. (ee) Liu, S. T.; Hu, X.; Zhao, Z. R. and Zhang, J., *Huaxue Shiji*, **2002**, *24*, 290. (ff) He, L. N.; Luo, Y. P.; Li, K.; Ding, M. W.; Lu, A. H.; Liu, X. P.; Wu, T. J. and Cai, F., *Synth. Commun.*, **2002**, *32*, 1415. (gg) Ju, J. Y. and McKenna, C. E., *Bioorg. Med. Chem. Lett.*, **2002**, *12*, 1643.

(hh) Nishio, T. and Ori, M., *Helv. Chim. Acta*, **2001**, *84*, 2347. (ii) Nishio, T.; Konno, Y.; Ori, M. and Sakamoto, M., *Eur. J. Org. Chem.*, **2001**, 3553. (jj) Luo, Y. P.; He, L. N.; Ding, M. W.; Yang, G. F.; Luo, A. H.; Liu, X. P. and Wu, T. J., *Heterocycl. Commun.*, **2001**, *7*, 37.

6. (a) Perregaard, J.; Thomsen, I. and Lawesson, S. O., *Bull. Soc. Chim. Belg.*, **1977**, *86*, 321. (b) Pedersen, B. S.; Scheibye, S.; Nilsson, N. H. and Lawesson, S. O., *Bull. Soc. Chim. Belg.*, **1978**, *87*, 223. (c) Scheibye, S.; Pedersen, B. S. and Lawesson, S. O., *Bull. Soc. Chim. Belg.*, **1978**, *87*, 229. (d) Pedersen, B. S.; Scheibye, S.; Clausen, K. and Lawesson, S. O., *Bull. Soc. Chim. Belg.*, **1978**, *87*, 293. (e) Scheibye, S.; Pedersen, B. S. and Lawesson, S. O., *Bull. Soc. Chim. Belg.*, **1978**, *87*, 299. (f) Fritz, H.; Hug, P.; Lawesson, S. O.; Logemann, E.; Pedersen, B. S.; Sauter, H.; Scheibye, S. and Winkler, T., *Bull. Soc. Chim. Belg.*, **1978**, *87*, 525. (g) Scheibye, S.; Kristensen, J. and Lawesson, S. O., *Tetrahedron*, **1979**, *35*, 1339. (h) Pedersen, B. S. and Lawesson, S. O., *Tetrahedron*, **1979**, *35*, 2433. (i) Scheibe, S.; Shabana, R. and Lawesson, S. O. *Tetrahedron* **1982**, *38*, 993. (j) Clausen, K.; Spatola, A. F.; Lenieux, C.; Schiller, P. W. and Lawesson, S. O., *Biochem. Biophys. Res. Commun.*, **1984**, *120*, 305. (k) Jensen, D. E. and Lawesson, S. O., *Tetrahedron*, **1985**, *41*, 5595. (l) Lawesson, S. O.; Perregaard, J.; Scheibye, S.; Meyer, H. J. and Thomsen, I., *Bull. Soc. Chim. Belg.*, **1997**, *86*, 679.
7. Wu, C.-Y.; Lin, H.-C.; Wang, Z. Y. and Wu, H.-J., *J. Org. Chem.*, **2001**, *66*, 4610.
8. (a) Snyder, C. A.; Selegue, J. P.; Tice, N. C.; Wallace, C. E.; Blankenbuehler, M. T.; Parkin, S.; Allen, K. D. E. and Beck, R. T., *J. Am. Chem. Soc.*, **2005**, *127*, 15010. (b) Dubau-Assibat, N.; Baceiredo, A. and Bertrand, G., *J. Org. Chem.*, **1995**, *60*, 3904.
9. (a) Richeter, S.; Jeandon, C.; Gisselbrecht, J.-P.; Graff, R.; Ruppert, R. and Callot, H. J., *Inorg. Chem.,* **2004**, *43*, 251. (b) Weng, Z. Q.; Leong, W. K.; Vittal, J. J. and Goh, L. Y., *Organometallics*, **2003**, *22*, 1645. (c) Curphey, T. J., *J. Org. Chem.*, **2002**, *67*, 6461. (d) Karp, G. M., *J. Org. Chem.*, **1999**, *64*, 8156. (e) Nishio, T., *J. Org. Chem.*, **1997**, *62*, 1106. (f) Cava, M. P. and Levinson, M. I., *Tetrahedron*, **1985**, *41*, 5061.
10. Aragoni, M. C.; Arca, M.; Demartin, F.; Devillanova, F. A.; Garau, A.; Isaia, F.; Lelj, F.; Lippolis, V. and Verani, G., *J. Am. Chem. Soc.*, **1999**, *121*, 7098.
11. Varma, R. S. and Kumar, D., *Org. Lett.*, **1999**, *1*, 697.
12. (a) No, K. H.; Lee, J. H.; Yang, S. H.; Yu, S. H.; Cho, M. H.; Kim, M. J. and Kim, J. S., *J. Org. Chem.*, **2002**, *67*, 3165. (b) Miletin, M.; Hartl, J.; Dolezal, M.; Odlerova, Z.; Kralova, K. and Machacek, M., *Molecules*, **2000**, *5*, 208. (c) Moody, C. J. and Roffey, J. R. A., *ARKIVOC*, **2000**, *1*, 393. (d) Olsson, R.; Hansen, H. C. and Andersson, C.-M., *Tetrahedron Lett.*, **2000**, *41*, 7947. (e) Thomsen, I.; Clausen, K.; Scheibye, S. and Lawesson, S.-O., *Org. Synth. Coll.*, **1990**, *7*, 7372.
13. (a) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Nugiel, D. A.; Abe, Y.; Reddy, K. B.; DeFrees, S. A.; Reddy, D. R.; Awartani, R. A.; Conley, S. R.; Rutjes, F. P. J. T. and Theodorakis, E. A., *J. Am. Chem. Soc.*, **1995**, *117*, 10227. (b) Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Sato, F.; Xiao, X.-Y. and Hwang, C.-K., *J. Am. Chem. Soc.*, **1993**, *115*, 3558.
14. Cow, C. N. and Harrison, P. H. M., *J. Org. Chem.*, **1997**, *62*, 8834.
15. Bigoli, F.; Deplano, P.; Devillanova, F. A.; Ferraro, J. R.; Lippolis, V.; Lukes, P. J.; Mercuri, M. L.; Pellinghelli, M. A.; Trogu, E. F. and Williams, J. M., *Inorg. Chem.*, **1997**, *36*, 1218.
16. Ibrahim, N. M., *Phosphorus, Sulfur & Silicon & Related Elements*, **2006**, *181*, 1773.
17. (a) Lin, S.-C.; Yang, F.-D.; Shiue, J.-S.; Yang, S.-M. and Fang, J.-M., *J. Org. Chem.,* **1998**, *63*, 2909. (b) Nishio, T., *J. Chem. Soc., Perkin Trans. I*, **1993**, 1113. (c) Nishio, T., *J. Chem. Soc., Chem. Commun.*, **1989**, 205.
18. Adam, W.; Albert, R.; Hasemann, L.; Salgado, V. O. N.; Nestler, B.; Peters, E.-M.; Peters, K.; Prechtl, F. and von Schnering, H. G., *J. Org. Chem.*, **1991**, *56*, 5782.
19. El-Barbary, A. A., *Monatsch. Chem.*, **1984**, *115*, 769.
20. (a) Kiryanov, A. A.; Sampson, P. and Seed, A. J., *J. Org. Chem.*, **2001**, *66*, 7925. (b) Hempenius, M. A.; Langeveld-Voss, B. M. W.; van Haare, J. A. E. H.; Janssen, R. A. J.; Sheiko, S. S.; Spatz,

J. P.; Müller, M. and Meijer, E. W., *J. Am. Chem. Soc.*, **1998**, *120*, 2798. (c) Shridhar, D. R.; Jogibhukta, M.; Rao, P. S. and Handa, V. K., *Synthesis*, **1982**, 1061.

21. Li, W. W. and Lam, Y. L., *J. Comb. Chem.*, **2005**, *7*, 644.
22. Ishii, A.; Hoshino, M. and Nakayama, J., *Pure & Appl. Chem.*, **1996**, *68*, 869.
23. Wang, L. and Phanstiel, O., *J. Org. Chem.,* **2000**, *65*, 1442.
24. Selzer, T. and Rappoport, Z., *J. Org. Chem.,* **1996**, *61*, 5462.
25. Pogodin, S. and Agranat, I., *J. Am. Chem. Soc.*, **2003**, *125*, 12829.
26. Okuma, K.; Shigetomi, T.; Nibu, Y.; Shioji, K.; Yoshida, M. and Yokomori, Y., *J. Am. Chem. Soc.*, **2004**, *126*, 9508.
27. Ishii, A.; Yamashita, R.; Saito, M. and Nakayama, J., *J. Org. Chem.*, **2003**, *68*, 1555.
28. Partyka, D. V.; Staples, R. J. and Holm, R. H., *Inorg. Chem.*, **2003**, *42*, 7877.
29. Bartsch, H. and Erker, T., *Tetrahedron Lett*., **1992**, *33*, 199.
30. (a) Okuma, K.; Shigetomi, T.; Shibata, S. and Shioji, K., *Bull. Chem. Soc. Jpn.*, **2004**, *77*, 187. (b) Lopin, C.; Gouhier, G.; Gautier, A. and Piettre, S. R., *J. Org. Chem.*, **2003**, *68*, 9916. (c) Zong, Z.-M.; Peng, Y.-L.; Liu, Z.-G.; Zhou, S.-L.; Wu, L.; Wang, X.-H.; Wei, X.-Y. and Lee, C. W., *Korean J. Chem. Eng.*, **2003**, *20*, 235. (d) Jesberger, M.; Davis, T. P. and Barner, L., *Synthesis*, **2003**, 1929. (e) Curphey, T. J., *Tetrahedron Lett.*, **2002**, *43*, 371. (f) Curphey, T. J., *Tetrahedron Lett.*, **2000**, *41*, 9963. (g) Foreman, and Wollins, *J. Chem. Soc., Dalton Trans.*, **2000**, 1533. (h) Pandey, R. K.; Isaac, M.; MacDonald, I.; Medforth, C. J.; Senge, M. O.; Dougherty, T. J. and Smith, K. M., *J. Org. Chem.*, **1997**, *62*, 1463. (i) Baeuerle, P.; Goetz, G.; Emerle, P.; and Port, H., *Adv. Mater.*, **1992**, *4*, 564. (j) Xie, M. Q. and Lightner, D. A., *J. Heterocyclic Chem.*, **1991**, *28*, 1753.

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Lebedev Process

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Lebedev in 1928.[1] It is a one-step industrial production of butadiene from ethanol at temperature of 400–450°C in the presence of a catalyst with both dehydration and dehydrogenation processes. Therefore, this reaction is generally known as the Lebedev process.[2] Occasionally, it is also referred to as the Lebedev contact process,[3] Lebedev method,[4] Lebedev reaction,[2f] or Lebedev synthesis.[5] The butadiene produced by this process is used for production of synthetic rubber.[2f] The best catalyst for this process is a silica gel impregnated with tantalum oxide (SiO_2-Ta_2O_5),[2d] silica-magnesium-tantalum, and silica-magnesium-chromium.[6] Furthermore, it has been found that the addition of copper gives good results if sufficient acetaldehyde is maintained.[2d] On the other hand, it has been reported that diethyl acetal, vinyl ethyl ether, diethyl ether, *n*-butanol, *n*-butanediols, *n*-butyraldehyde, ethylene, acetylene, and tetrahydrofuran are not major intermediates in this process,[7] even though some of these chemicals have been proposed in the mechanism to rationalize this process. For example, Lebedev proposed a radical mechanism and claimed that acetaldehyde and ethylene were the intermediates to form 1,3-butadiene.[8] Some other mechanisms proposed are the dehydrogenation and dehydration of ethanol to both ethylene and acetylene, which form butadiene;[2f] the formation of butanediols from ethanol and acetaldehyde, which dehydrates to give butadiene;[9] and the formation of diethyl ether, which gives butadiene.[10] However, none of these mechanisms make sense from the advanced organic chemistry point of view, and the most important evidence for the real mechanism is that conversion of crotonaldehyde and ethanol to butadiene is easier than that of ethanol and acetaldehyde, and acetaldehyde is produced by the time the

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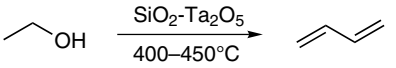
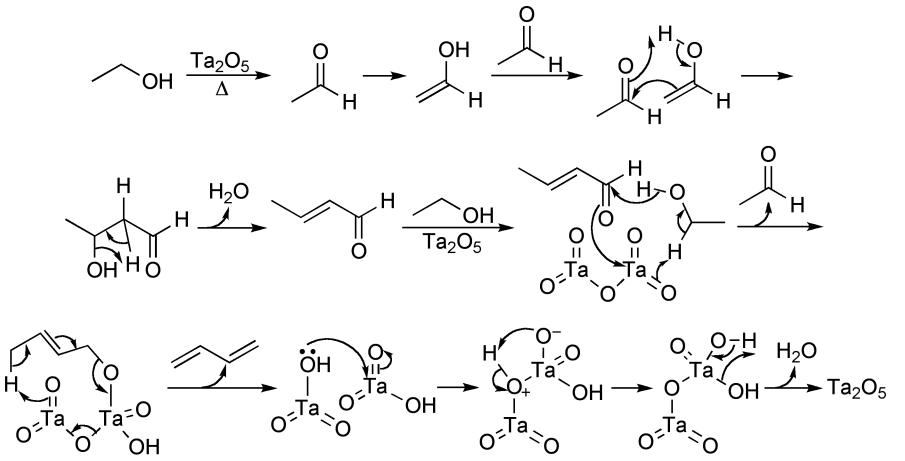
crotonaldehyde is converted into butadiene.[2d,2e] It has been found that the silica component in the catalyst facilitates the condensation of acetaldehyde to crotonaldehyde, whereas tantalum promotes the deoxygenation of crotonaldehyde using ethanol as the hydrogen donor.[7]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is believed[2e] that this reaction involves the following consecutive steps: dehydrogenation of ethanol to acetaldehyde, condensation of acetaldehyde into acetaldol, dehydration of aldol product to crotonaldehyde, and deoxygenation of crotonaldehyde. This mechanism is illustrated here.



D. MODIFICATION

N/A

E. APPLICATIONS

This process was used for the production of butadiene for synthetic rubber by both the former Soviet Union and Germany during World War II.

F. RELATED REACTIONS

This reaction is closely related to the *Ostromislensky Reaction*.

G. CITED EXPERIMENTAL EXAMPLES

Because this is an industrial production process, no preparative experimental procedure is provided here.

Other references related to this reaction are cited in the literature.[9]

H. REFERENCES

1. Lebedev, S. V., *Fr. Pat*., Dec. 15, **1928**, 665,917.
2. (a) Bukala, M. and Dul, M., *Przemysl Chem*., **1967**, *46*, 600. (b) Zavgorodnii, S. V. and Gonsovskaya, T. B., *Izv. Vysshikh Uchebnykh Zavedenii, Khim. Khim. Tekh.,* **1961**, *4*, 128. (c) Nesvizhskii, M. P., *Sbornik Trudov Voronezk. Otdel. Vsesoyuz. Khim. Obshchestva Mendeleeva*, **1957**, 27. (d) Toussaint, W. J.; Dunn, J. T. and Jackson, D. R., *Ind. Eng. Chem.,* **1947**, *39*, 120. (e) Quattlebaum, W. M.; Toussaint, W. J. and Dunn, J. T., *J. Am. Chem. Soc.,* **1947**, *69*, 593. (f) Egloff, G. and Hulla, G., *Chem. Rev.,* **1945**, *36*, 63. (g) Talalay, A. and Talalay, L., *Rubber Chem. Technol.,* **1942**, *15*, 403.
3. Frolov, A. F.; Makhnin, A. A.; Aronovich, K. A. and Rabotnov, V. V., *Prom. Sint. Kauch., Nauchno-Tekh. Sb.*, **1973**, 3.
4. Gorin, Yu. A. and Kalinicheva, N. A., *Zh. Obsh. Khim.,* **1952**, *22*, 1256.
5. Gorin, Yu. A. and Ivanov, V. S., *Kataliz Vysshei Shkole, Min. Vysshego Srednego Spets. Obrazov. SSSR, Mezhvuz. Soveshch. Katalizu,* **1962**, *1958* (1, Pt. 2), 268.
6. Corson, B. B.; Jones, H. E.; Welling, C. E.; Hinckley, J. A. and Stahly, E. E., *Ind. Eng. Chem.,* **1950**, *42*, 359.
7. Jones, H. E.; Stahly, E. E. and Corson, B. B., *J. Am. Chem. Soc.,* **1949**, *71*, 1822.
8. Lebedev, S. V., *J. Gen. Chem. USSR,* **1933**, *3*, 698.
9. (a) Balandin, A. A., *J. Phys. Chem. USSR,* **1935**, *6*, 357. (b) Balandin, A. A., *Acta Physicochim. USSR,* **1935**, *2*, 345. (c) Balandin, A. A., *Acta Physicochim. USSR,* **1935**, *2*, 363.
10. Ipatieff, V. N., *Catalytic Reactions at High Pressures and Temperatures,* Macmillan, New York, **1936**, pp. 119–20.
11. (a) Kovarik, B., *Chemicky Prumysl*, **1961**, *11*, 472. (b) Gorin, Yu. A.; Ivanov, V. S.; Pushnova, T. G. and Zlatogurskaya, V. V., *Zh. Obsh. Khim.,* **1959**, *29*, 1104. (c) Natta, G. and Rigamonti, R., *Chim. Ind. (Milan),* **1947**, *29*, 195. (d) Egloff, G. and Hulla, G., *Chem. Rev.,* **1944**, *35*, 279. (e) Tallalay, A. and Tallalay, L., *Rubber Chem. Technol.,* **1942**, *15*, 403. (f) Lebedev, S. V., *Brit. Pat.,* June 30, **1930,** 331,482. (g) Abramovich, L. A., *Vestnik Dermatologii Venerologii*, **1939**, 32. (h) Shorygin, P. P. and Guseva, A. R., *Zh. Obsh. Khim.,* **1936**, *6*, 1569. (i) Lebedev, S. V., *Chim. Ind. (Paris),* **1933**, *32*, 1150. (j) Lebedev, S. V., *Sotzialist. Rekonstruktziya Nauka*, **1933**, *3*, 127.

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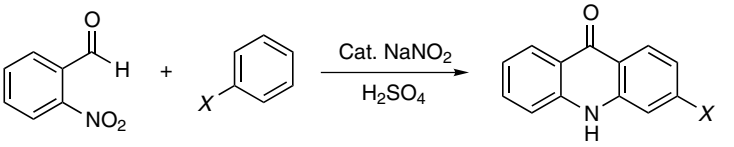
Lehmstedt-Tanasescu Reaction

A. GENERAL DESCRIPTION OF THE REACTION

Although acridone was not first synthesized by Lehmstedt,[1] it was Lehmstedt who extensively explored the methods for the preparation of acridones, including the reaction between anthranilic acid and chloro-nitrobenzene,[2] desulfurization of thioacridone by copper,[3] and treatment of *ortho*-nitro benzaldehyde with chloro-nitrobenzene and sulfuric acid.[4] Among these methods, the one between *o*-nitrobenzaldehyde and halobenzene is known as the Lehmstedt-Tanasescu method[5] or Lehmstedt-Tanasescu reaction.[5,6] In addition, this preparation of acridone is also referred to as the Tanasescu synthesis.[7]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

As limited mechanistic information is available, only a tentative mechanism is proposed here, although it may not correctly explain the experimental results. In this mechanism, sodium nitrite is converted into nitrous acid under acidic conditions, which reduces the

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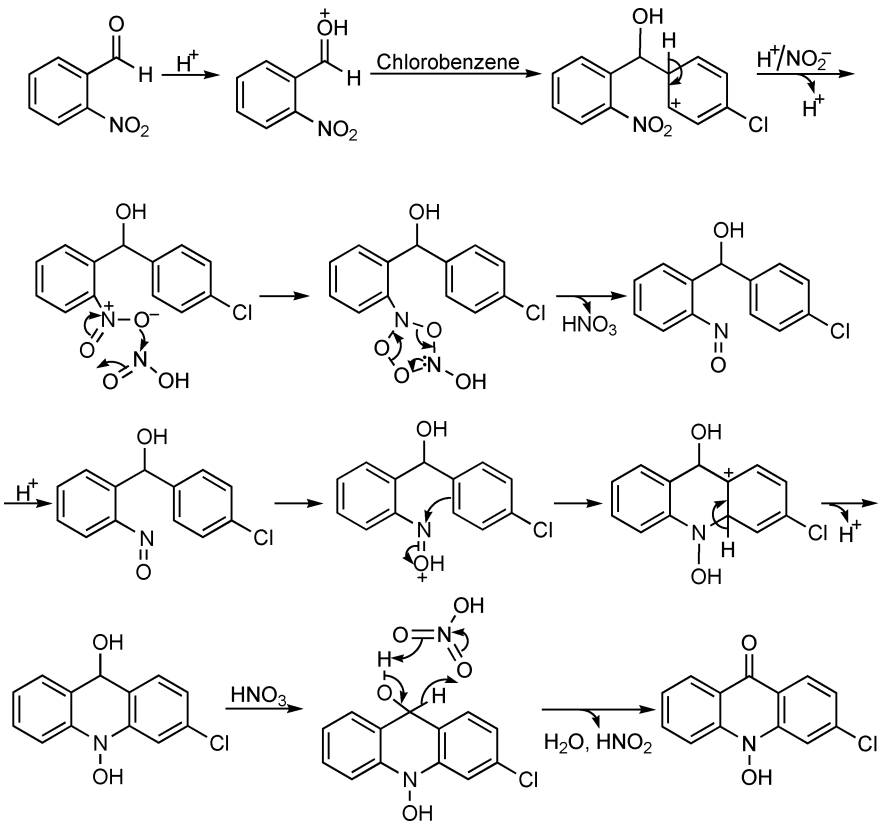
nitro group to a nitroso group, and the nitrous acid itself is oxidized to nitric acid. The nitric acid then oxidizes the alcohol into a ketone. A part of this mechanism is outlined here.



D. MODIFICATION

This method has been extended to the reaction between anthranilic acid and chlorobenzene.[2]

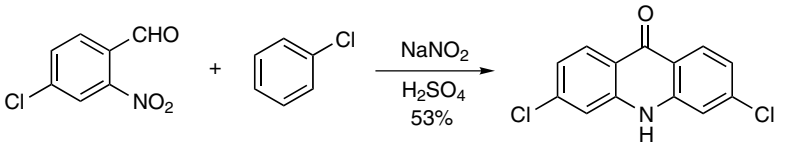
E. APPLICATIONS

This reaction has limited application in the preparation of acridone derivatives.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 5.

A mixture of 18.5 g crude 2-nitro-4-chlorobenzaldehyde (0.1 mol) prepared from the oxidation of 2-nitro-4-chloro-toluene by concentrated sulfuric acid in acetic anhydride, 78.8 g chlorobenzene (0.7 mol), 37.5 mL conc. H_2SO_4, and 0.35 g $NaNO_2$ was treated for 6 days by alternating 9 h of shaking and 15 h of standing. At the end of each 2-day period (except the last) 10 mL conc. H_2SO_4 containing 0.1 g $NaNO_2$ was added to the reaction mixture. The mixture was poured into 500 mL water and steam distilled until no further aldehyde solidified in the condenser. The residue from the steam distillation was filtered and digested twice with benzene, leaving 14 g 3,9-dichloroacridone as a dark yellow solid, in a yield of 53%, m.p. $> 315^{\circ}$C.

Other references related to the Lehmstedt-Tanasescu reaction and acridone synthesis are cited in the literature.[8]

H. REFERENCES

1. (a) Kliegl, A., *Ber.*, **1908**, *41*, 1845. (b) Kliegl, A., *Ber.*, **1909**, *42*, 591. (c) Bamberger, E., *Ber.*, **1909**, *42*, 1707. (d) Tanasescu, I., *Bull. Soc. Chim. Fr.*, **1927**, *41*, 528.
2. Lehmstedt, K. and Schrader, K., *Ber.*, **1937**, *70B*, 1526.
3. Lehmstedt, K. and Hundertmark, H., *Ber.*, **1930**, *63B*, 1229.
4. (a) Lehmstedt, K., *Ber.*, **1932**, *65B*, 834. (b) Lehmstedt, K., *Ber.*, **1932**, *65B*, 999.
5. Spalding, D. P.; Moersch, G. W.; Mosher, H. S. and Whitmore, F. C., *J. Am. Chem. Soc.*, **1946**, *68*, 1596.
6. (a) Silberg, A.; Frenkel, Z. and Bauer, E., *Studia Univ. Babes-Bolyai, Chem.*, **1965**, *10*, 31. (b) Silberg, A. and Frenkel, Z., *Studii Cercetari Chim.*, **1965**, *13*, 1071. (c) Silberg, A. and Frenkel, Z., *Revue Roumaine Chim.*, **1965**, *10*, 1035. (d) Frenkel, Z., *Studia Univ. Babes-Bolyai, Chem.*, **1964**, *9*, 25. (e) Silberg, A. and Frenkel, Z., *Studia Univ. Babes-Bolyai, Chem.*, **1962**, *7*, 53.
7. Panea, I.; Hopirtean, I. and Ionescu, M., *Studii Cercetari Chim.*, **1974**, 22, 29.
8. (a) Cholody, W. M.; Hernandez, L.; Hassner, L.; Scudiero, D. A.; Djurickovic, D. B. and Michejda, C. J., *J. Med. Chem.*, **1995**, *38*, 3043. (b) Capps, D. B.; Dunbar, J.; Kesten, S. R.; Shillis, J.; Werbel, L. M.; Plowman, J. and Ward, D. L., *J. Med. Chem.*, **1992**, *35*, 4770. (c) White, E. H.; Roswell, D. F.; Dupont, A. C. and Wilson, A. A., *J. Am. Chem. Soc.*, **1987**, *109*, 5189. (d) Cain, B. F.; Atwell, G. J. and Denny, W. A., *J. Med. Chem.*, **1975**, *18*, 1110. (e) Silberg, and Frenkel, *Rev. Roumaine Chim.*, **1965**, *10*, 1035. (f) Fryer, R. I.; Earley, J. V. and Sternbach, L. H., *J. Org. Chem.*, **1965**, *30*, 521. (g) Fryer, R. I.; Earley, J. V. and Sternbach, L. H., *J. Chem. Soc.*, **1963**, 4979. (h) Tanasescu, I. and Frenkel, *Bull. Soc. Chim. Fr.*, **1960**, 693. (i) Bachman, G. B. and Cowen, F. M., *J. Org. Chem.*, **1948**, *13*, 89. (j) Lehmstedt, K. and Dostal, F., *Ber.*, **1939**, *72*, 804. (k) Matsumura, K., *J. Am. Chem. Soc.*, **1939**, *61*, 2247. (l) Tanasescu, I., *Bull. Soc. Chim.*, **1933**, *53*, 381. (m) Lehmstedt, K. and Hundertmark, H., *Ber.*, **1931**, *64B*, 2381. (n) Lehmstedt, K. and Wirth, E., *Ber.*, **1928**, *61B*, 2044.

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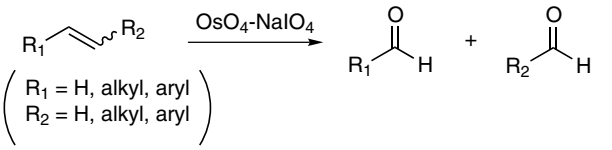
Lemieux-Johnson Oxidation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Lemieux and Johnson in 1956.[1] It is a conversion of an olefin into two individual aldehydes by means of an oxidative cleavage of a carbon-carbon double bond with osmium tetraoxide-sodium periodate. Therefore, it is known as the Lemieux-Johnson oxidative cleavage,[2] Lemieux-Johnson reaction,[3] or simply Lemieux-Johnson oxidation.[4] In addition, the combination of osmium tetraoxide and sodium periodate is referred to as Lemieux-Johnson reagent.[5] It should be pointed out that a lactol may be obtained directly from the oxidation of the olefin with a hydroxyl group near the olefinic bond.[4a]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Without added sodium periodate, olefins are converted only into *cis*-diols by OsO_4 upon workup, therefore, it is plausible that sodium periodate further oxidizes osmium species and triggers the cleavage of carbon-carbon bond, as shown here.

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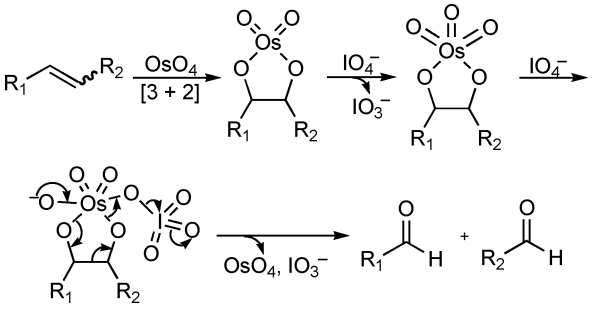


D. MODIFICATION

This reaction has been improved by addition of 2,6-lutidine to suppress the side reactions and increase the yields of aldehydes.[6] In addition, this oxidation has been modified by using osmium tetraoxide and oxone as oxidants, which directly convert 1,2-disubstituted olefins into two individual carboxylic acids.[3] On the basis of this modification, osmium tetraoxide has been made to be a three-dimensional networked nanomaterial that, in combination with oxone, forms a superior heterogeneous catalyst, which even oxidizes alkynes into carboxylic acids.[7]

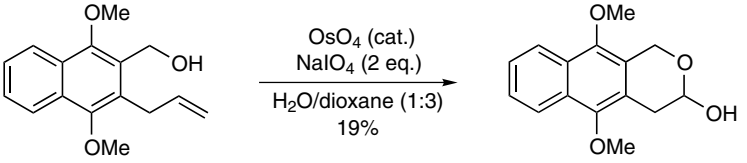
E. APPLICATIONS

This reaction is very useful for the conversion of olefins into aldehydes.

F. RELATED REACTIONS

N/A

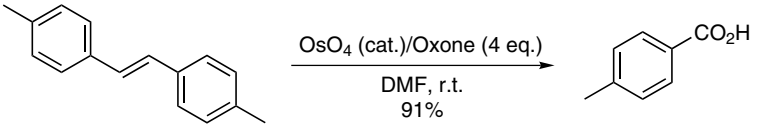
G. CITED EXPERIMENTAL EXAMPLES



Reference 4a.

To a solution of 100 mg 2-allyl-3-hydroxymethyl-1,4-dimethoxynaphthalene (0.4 mmol) in 5 mL water and 15 mL dioxane was first added a catalytic amount of osmium tetroxide (10 mg), and then 170 mg sodium periodate (0.8 mmol) was added portionwise over a period of 1 h. The suspension formed was stirred for 3 days, poured into water, extracted with ether, washed with brine, dried over $MgSO_4$, and evaporated at reduced pressure. Flash

chromatography on silica gel with 40% EtOAc in hexane gave 20 mg 3,4-dihydro-5,10-dimethoxy-1*H*-naphtho[2,3-*c*]pyran-3-ol, in a yield of 19%.



Reference 3.

To a 0.2 M DMF solution of 4,4′-dimethyl *trans*-stilbene was added 0.01 eq. of OsO_4 (2.5% in *t*-BuOH) under stirring; 5 min later, 4 eq. Oxone was added in one portion, and the solution was stirred at room temperature until the solution became colorless. This usually marked the completion of the reaction which was verified by TLC. Na_2SO_3 (6 eq. w/w) was added to reduce the remaining oxidant, and the solution was stirred for an additional hour. EtOAc was added to extract the products and 1 N HCl was used to dissolve the salts. The organic extract was washed with 1 N HCl (3 ×) and brine and dried over Na_2SO_4; the solvent was removed under reduced pressure to obtain the crude product, which was purified by silica gel column chromatography to give 91% *p*-toluic acid.

Other references related to the Lemieux-Johnson oxidation are cited in the literature.[8]

H. REFERENCES

1. Pappo, R.; Allen, D. S.; Lemieux, R. U. and Johnson, W. S., *J. Org. Chem.*, **1956**, *21*, 478.
2. de Fátima, Â. And Pilli, R. A., *ARKIVOC*, **2003**, 118.
3. Travis, B. R.; Narayan, R. S. and Borhan, B., *J. Am. Chem. Soc.*, **2002**, *124*, 3824.
4. (a) Kesteleyn, B.; de Kimpe, N. and van Puyvelde, L., *J. Org. Chem.,* **1999**, *64*, 1173. (b) Vorbrüggen, H. and Bennua, B., *Synthesis*, **1985**, 925.
5. Yang, D. and Zhang, C., *J. Org. Chem.*, **2001**, *66*, 4814.
6. Yu, W. S.; Mei, Y.; Kang, Y.; Hua, Z. M. and Jin, Z. D., *Org. Lett.*, **2004**, *6*, 3217.
7. Lee, K. Y.; Kim, Y.-H.; Han, S. B.; Kang, H. K.; Park, S. Y.; Seo, W. S.; Park, J. T.; Kim, B. S. and Chang, S. B., *J. Am. Chem. Soc.*, **2003**, *125*, 6844.
8. (a) Nielsen, T. E. and Meldal, M., *Org. Lett.*, **2005**, *7*, 2695. (b) De Fátima, A.; Lapis, A. A. M. and Pilli, R. A., *J. Braz. Chem. Soc.*, **2005**, *16*, 495. (c) Frunzke, J.; Loschen, C. and Frenking, G., *J. Am. Chem. Soc.*, **2004**, *126*, 3642. (d) Storm, J. P. and Andersson, C.-M., *Org. Lett.*, **1999**, *1*, 1451. (e) Markó, I. E.; Mekhalfia, A.; Murphy, F.; Bayston, D. J.; Bailey, M.; Janousek, Z. and Dolan, S., *Pure & Appl. Chem.*, **1997**, *69*, 565. (f) Wolfe, S.; Ingold, C. F. and Lemieux, R. U., *J. Am. Chem. Soc.*, **1981**, *103*, 938.

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Leuckart Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Leuckart in 1885.[1] It is the reductive amination of carbonyl compounds (i.e., aldehydes and ketones) with ammonium formate or the combination of formic acid and formamides to give primary, secondary, or tertiary amines. Therefore, it is generally known as the Leuckart reaction.[2,3] Occasionally, it is also referred to as the Leuckart reductive amination,[2b] Leuckart alkylation,[4] Leuckart synthesis,[5] or Leuckart reduction.[6] This reaction occurs between a carbonyl compound and formamide, or ammonium formate, or a combination of formic acid and formamide,[3m,3o,3p] from which the primary and secondary amines are obtained as the formyl derivatives; tertiary amines are produced as the formates.[3m] Although it has been reported that higher yields might be obtained if formamide rather than ammonium formate is used in this reaction,[5d] more evidence has indicated that ammonium formate is the actual reactant.[3q] For example, benzophenone condenses with ammonium formate only in diethylene glycol solution at 120–130°C and does not react with formamide.[3q] In this reaction, formic acid and formates function as reducing reagents or hydride donors,[2hh,3c,7] so that tertiary amine can be prepared either from the reaction between aldehyde and a formamide (or a monoalkylformamide) or from the reaction between an aldehyde (or a ketone) and a dialkylformamide.[3o] Interestingly, it has been found that ammonium formate, ammonium sulfate, and magnesium chloride can catalyze the condensation between carbonyl compounds and dialkylformamides to form tertiary amines.[3o,3q] Even though the Leuckart reaction is not a moisture-sensitive reaction,[3b] it has been proved that if water is removed from the reaction, the yields of the corresponding amines will be increased for any reagents other than formamide, in the following order: formamide < ammonium formate ~ combination of formamide and ammonium formate < combination of formamide and formic acid.[3m] However, if water is not removed,

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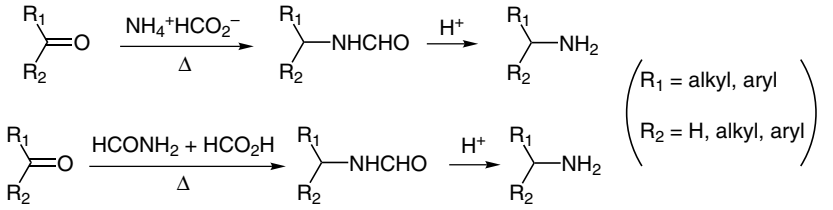
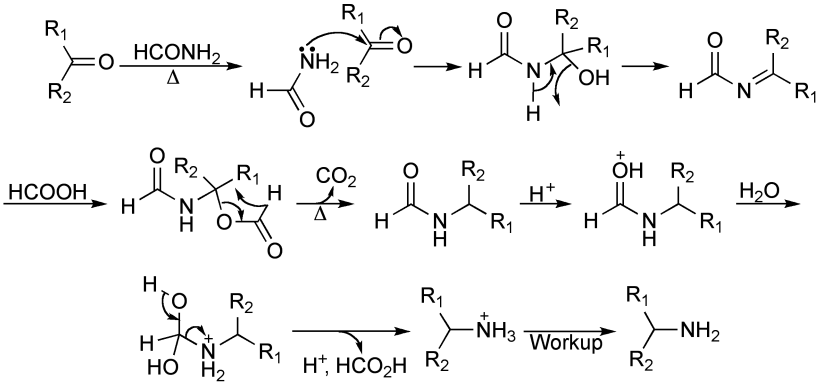
then the combination of formamide and ammonium formate give the best yields at low temperature.[3m] When the reaction is carried out at a temperature $<100^{\circ}C$, it has been found that the higher the reaction temperature, the higher the yield of tertiary amines and the lower the yield of secondary amines. Likewise, at a lower reaction temperature, the reaction with a higher concentration of formic acid gives higher yield of secondary amines. However, the concentration effect of formic acid at a high reaction temperature is not as effective as that at low temperature.[3m]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The mechanism of this reaction has already been studied.[2tt,3m] Therefore, the mechanism is illustrated by the formation of a primary amine from a ketone and the combination of formamide and formic acid, as shown below.



D. MODIFICATION

This reaction has been modified to occur in the presence of an excess amount of formic acid by Wallach,[8] thus the reaction under such conditions is known as Leuckart-Wallach alkylation[9] or Leuckart-Wallach reaction.[10] In addition, this reaction has been modified

to produce primary amines in high yield using ammonium formate ($NH_4^+HCO_2^-$) as a reducing agent and Cp*Rh(III) as a catalyst at relative low reaction temperatures.[10a]

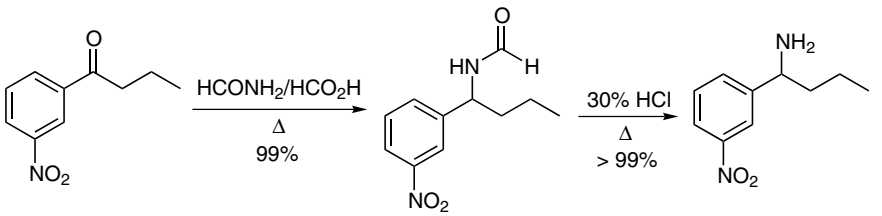
E. APPLICATIONS

This reaction has wide application in the preparation of primary, secondary, and tertiary amines.

F. RELATED REACTIONS

This reaction is related to the *Eschweiler-Clarke Methylation.*

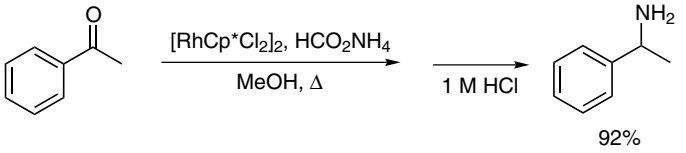
G. CITED EXPERIMENTAL EXAMPLES



Reference 2b.

A mixture of 25.0 g 1-(3-nitrophenyl)-1-butanone (129 mmol), 77 mL formamide, and 35 mL formic acid was refluxed until the reaction was complete (followed by ^1H NMR spectroscopy). After cooling to ambient temperature, 200 mL water was added, and the mixture was extracted with Et_2O (3×100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to furnish 28.7 g (±)-1-butyl-1-(3-nitrophenyl)formamide as a red oil, in a yield of 99%.

A mixture of the formamide and 100 mL 30% HCl was refluxed for overnight. After cooling to ambient temperature, 200 mL water was added. The reaction mixture was carefully adjusted to pH 10 with 33% aqueous NaOH and extracted with Et_2O (3×100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to furnish >99% (±)-1-butyl-1-(3-nitrophenyl)amine as a red oil.



Reference 9a.

To a 1000-mL Schlenk tube containing 257 mg $[RhCp^*Cl_2]_2$ (0.416 μmol) and 26.2 g $HCOONH_4$ (416 mmol) was added 9.71 mL acetophenone (83.2 mmol) and 83.2 mL MeOH. The reddish brown mixture was frozen, and the whole system was evacuated. The

system was closed and then stirred at 70°C for 7 h. After the resulting dark green solution was cooled to room temperature, 160 mL 1 M HCl was added, and the mixture was washed with CH_2Cl_2 (2×20 mL) to remove the neutral compounds. After the addition of 15 mL cold 12 M NaOH solution to the aqueous layer, the mixture was extracted with CH_2Cl_2 (6×50 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Filtration and evaporation under reduced pressure gave 9.3 g α-amino ethylbenzene, in a yield of 92% with $> 99\%$ purity as determined by ^{1}H NMR and GC analyses. Further distillation at 83°C (44 mmHg) afforded 8.6 g α-amino ethylbenzene, in a yield of 85%.

Other references related to the Leuckart reaction are cited in the literature.[11]

H. REFERENCES

1. Leuckart, R., *Ber.*, **1885**, *18*, 2341.
2. (a) Tournier, L. and Zard, S. Z., *Tetrahedron Lett*., **2005**, *46*, 971. (b) Dalmolen, J.; van der Sluis, M.; Nieuwenhuijzen, J. W.; Meetsma, A.; de Lange, B.; Kaptein, B.; Kellogg, R. M. and Broxterman, Q. B., *Eur. J. Org. Chem.*, **2004**, 1544. (c) Garcia Martinez, A.; Teso Vilar, E.; Garcia Fraile, A. and Martinez-Ruiz, P., *Tetrahedron*, **2003**, *59*, 1565. (d) Garcia Martinez, A.; Teso Vilar, E.; Garcia Fraile, A. and Martinez-Ruiz, P., *Tetrahedron: Asymmetry*, **2001**, *12*, 2153. (e) Garcia Martinez, A.; Teso Vilar, E.; Garcia Fraile, A. and Martinez-Ruiz, P., *Eur. J. Org. Chem.*, **2001**, 2805. (f) Martinez, A. G.; Vilar, E. T.; Fraile, A. G.; Ruiz, P. M.; San Antonio, R. M. and Alcazar, M. P. M., *Tetrahedron: Asymmetry*, **1999**, *10*, 1499. (g) Lejon, T. and Helland, I., *Acta Chem. Scand.*, **1999**, *53*, 76. (h) Sharma, M. L.; Talwar, K. K.; Gupta, A. and Kishore, L., *J. Indian Chem. Soc.*, **1997**, *74*, 233. (i) Bhatt, B. M.; Gitu, P. M. and Yusuf, A. O., *Int. J. BioChemPhys.*, **1993**, *2*, 60. (j) Carlson, R.; Lejon, T.; Lundstedt, T. and Le Clouerec, E., *Acta Chem. Scand.*, **1993**, *47*, 1046. (k) Laporterie, A. and Manuel, G., *Bull. Union Phys.*, **1991**, *85*, 751. (l) Awachie, P. I. and Agwada, V. C., *Tetrahedron*, **1990**, *46*, 1899. (m) Romero Maldonado, I. C. A. and Nikiforov, G. A., *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1987**, 2356. (n) Fulop, F.; Pihlaja, K.; Mattinen, J. and Bernath, G., *Tetrahedron Lett*., **1987**, *28*, 115. (o) Villa, M. J.; Dominguez, E. and Lete, E., *Heterocycles*, **1986**, *24*, 1943. (p) Bannikov, G. F.; Nikiforov, G. A. and Ershov, V. V., *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1985**, 1408. (q) Dominguez, E.; Lete, E.; Jesus, V. M. and Iriondo, C., *Heterocycles*, **1984**, *22*, 1217. (r) Patel, S. B., *J. Inst. Chem. (India)*, **1983**, *55*, 77. (s) Tatsugi, J. and Okumura, M., *Nippon Kagaku Kaishi*, **1982**, 876. (t) Agwada, V. C. and Awachie, P. I., *Tetrahedron Lett*., **1982**, *23*, 779. (u) Patel, S. B., *J. Inst. Chem. (India)*, **1981**, *53*, 274. (v) Irismetov, M. P.; Goryaev, M. I.; Bazalitskaya, V. S. and Kairgalieva, A. K., *Izv. Akad. Nauk Kazakhskoi SSR, Ser. Khim.*, **1980**, 81. (w) Galin, F. Z.; Lerman, B. M. and Tolstikov, G. A., *Zh. Org. Khim.*, **1979**, *15*, 758. (x) Tatsugi, J. and Okumura, M., *Bull. Chem. Soc. Jpn.*, **1978**, *51*, 1227. (y) Thiagarajan, S.; Srinivasan, M. and Krishnamoorthy, K. V., *Indian J. Chem., Sect. B*, **1976**, *14B*, 633. (z) Srinivasan, M. and Rampal, J. B., *Tetrahedron Lett*., **1974**, 2883. (aa) Kim, H.-O.; Goryaev, M. I.; Irismetov, M. P. and Alibaeva, K. A., *Izv. Akad. Nauk Kazakhskoi SSR, Ser. Khim.*, **1972**, *22*, 86. (bb) Breuer, E. and Melumad, D., *J. Org. Chem.*, **1972**, *37*, 3949. (cc) Semenov, V. A. and Skorovarov, D. I., *Zh. Org. Khim.*, **1969**, *5*, 41. (dd) Breuer, E. and Stein, Y., *Isr. J. Chem.*, **1968**, *6*, 901. (ee) Smith, H. E. and Rajevsky, V., *J. Heterocycl. Chem.*, **1968**, *5*, 715. (ff) Balog, A.; Beu, L. and Gonczi, F., *Revistade Chim. (Bucharest)*, **1968**, *19*, 360. (gg) Coe, P. F.; Uff, B. C. and Lewis, J. W., *J. Chem. Soc. C*, **1968**, 2265. (hh) Bach, R. D., *J. Org. Chem.*, **1968**, *33*, 1647. (ii) Hey, D. G.; Meakins, G. D. and Whateley, T. L., *J. Chem. Soc. C*, **1967**, 1509. (jj) Kalamar, J. and Ryban, B., *Chemicke Zvesti*, **1966**, *20*, 79. (kk) Dauksas, V. and Lastauskas, A., *Biol. Aktivn. Soedin., Akad. Nauk SSSR*, **1965**, 136. (ll) Volodina, M. A.; Kiryushkina, G. V. and Terent'ev, A. P., *Dokl. Akad. Nauk SSSR*, **1965**, *162*, 90. (mm) Panouse, J. J.; Schmitt, J.;

Cornu, P. J.; Hallot, A.; Pluchet, H. and Comoy, P., *Bull. Soc. Chim. Fr.*, **1963**, 1753. (nn) Potapov, V. M.; Terent'ev, A. P. and Dem'yanovich, V. M., *Zh. Obsh. Khim.*, **1960**, *30*, 1043. (oo) Lukes, R. and Janda, M., *Coll. Czech. Chem. Commun.*, **1960**, *25*, 1612. (pp) Cavallini, G.; Massarani, E. and Nardi, D., *Farmaco, Edizione Sci.*, **1956**, *11*, 805. (qq) Terent'ev, A. P.; Potapov, V. M. and Semion, I. Z., *Zh. Obsh. Khim.*, **1956**, *26*, 3263. (rr) Rekasheva, A. F. and Miklukhin, G. P., *Zh. Obsh. Khim.,* **1956**, *26*, 2407. (ss) Terent'ev, A. P.; Potapov, V. M. and Semion, I. Z., *Zh. Obsh. Khim.*, **1956**, *26*, 2934. (tt) Kost, A. N. and Grandberg, I. I., *Zh. Obsh. Khim.*, **1955**, *25*, 1432. (uu) Chubb, F.; Hay, A. S. and Sandin, R. B., *J. Am. Chem. Soc.*, **1953**, *75*, 6042. (vv) Quelet, R. and Frainnet, E., *Compt. Rend.*, **1953**, *236*, 492. (ww) Lukes, R. and Veceea, M., *Coll. Czech. Chem. Commun.*, **1953**, *18*, 243. (xx) Walter, C. R., *J. Am. Chem. Soc.*, **1952**, *74*, 5185. (yy) Noyce, D. S. and Bachelor, F. W., *J. Am. Chem. Soc.*, **1952**, *74*, 4577. (zz) Horii, Z.; Tamura, Y. and Murakami, Y., *Yakugaku Zasshi*, **1952**, *72*, 1206. (aaa) Tomita, M.; Uyeo, S.; Inoue, H.; Watanabe, O.; Makino, H.; Mori, Y.; Kuwabara, T. and Kitsutaka, T., *Yakugaku Zasshi*, **1951**, *71*, 850. (bbb) Tomita, M.; Uyeo, S. and Otaya, H., *Yakugaku Zasshi*, **1951**, *71*, 849. (ccc) Tomita, M.; Uyeo, S. and Mori, Y., *Yakugaku Zasshi*, **1951**, *71*, 846. (ddd) Tomita, M.; Uyeo, S. and Otaya, H., *Yakugaku Zasshi*, **1951**, *71*, 849. (eee) Metayer, M.; Mastagli, P. and Bricard, A., *Bull. Soc. Chim. Fr.*, **1950**, 1054. (fff) Metayer, M.; Mastagli, P. and Larramona, H., *Bull. Soc. Chim. Fr.*, **1950**, 1052. (ggg) Metayer, M., *Bull. Soc. Chim. Fr.,* **1950**, 1050. (hhh) Smith, P. A. S. and Macdonald, A. J., *J. Am. Chem. Soc.*, **1950**, *72*, 1037. (iii) Lewis, K. G., *J. Chem. Soc.,* **1950**, 2249. (jjj) Metayer, M., *Bull. Soc. Chim. Fr.,* **1948**, 1097. (kkk) Goodson, L. H.; Wiegand, C. J. W. and Splitter, J. S., *J. Am. Chem. Soc.,* **1946**, *68*, 2174. (lll) Crossley, F. S. and Moore, M. L., *J. Org. Chem.*, **1944**, *9*, 529.

3. (a) Howie, R. A. and Wardell, S. M. S. V., *Acta Cryst.*, **2005**, *E61*, 1686. (b) Korotkikh, N. I.; Shvaika, O. P.; Rayenko, G. F.; Kiselyov, A. V.; Knishevitsky, A. V.; Cowley, A. H.; Jones, J. N. and MacDonald, C. L. B., *ARKIVOC*, **2005**, 10. (c) Terasaki, M.; Nomoto, S.; Mita, H. and Shimoyama, A., *Viva Origino*, **2004**, *32*, 53. (d) Blachut, D.; Maurin, J. K.; Starosta, W.; Wojtasiewicz, K. and Czarnocki, Z., *Z. Naturforsch.*, **2002**, *57b*, 593. (e) Akimova, T. I.; Ivanenko, Z. A.; Gerasimenko, A. V. and Vysotskii, V. I., *Russ. J. Org. Chem.*, **2001**, *37*, 1232. (f) Slavikova, B.; Kasal, A. and Kohout, L., *Coll. Czech. Chem. Commun.*, **1998**, *63*, 655. (g) Sindelar, K.; Kmon icek, V.; Hrubantova, M. and Polivka, Z., *Coll. Czech. Chem. Commun.*, **1992**, *57*, 194. (h) Carlsen, L. and Andnesen, K., *Euro. J. Nucl. Med. Mol. Imaging*, **1982**, *7*, 280. (i) Meinters, A. F.; Bolze, C.; Scherer, A. L. and Morriss, F. V., *J. Org. Chem.*, **1958**, *23*, 1122. (j) Horii, Z.; Sakai, T. and Tamura, Y., *Pharm. Bull.*, **1957**, *5*, 132. (k) Horii, Z.; Sakai, T. and Inoi, T., *Pharm. Bull.*, **1955**, *3*, 159. (l) Burckhalter, J. H. and Johnson, S. H., *J. Am. Chem. Soc.*, **1951**, *73*, 4830. (m) Pollard, C. B. and Young, D. C., *J. Org. Chem.*, **1951**, *16*, 661. (n) Moore, M. L., *Org. React.*, **1949**, *5*, 301. (o) Bunnett, J. F. and Marks, J. L., *J. Am. Chem. Soc.*, **1949**, *71*, 1587. (p) Alexander, E. R. and Wildman, R. B., *J. Am. Chem. Soc.*, **1948**, *70*, 1187. (q) Webers, V. J. and Bruce, W. F., *J. Am. Chem. Soc.*, **1948**, *70*, 1422.
4. Ruby, P. and DeBenneville, P. L., *J. Am. Chem. Soc.*, **1953**, *75*, 3027.
5. (a) Bunnett, J. F.; Marks, J. L. and Moe, H., *J. Am. Chem. Soc.*, **1953**, *75*, 985. (b) Bruce, W. F. and Webers, V. J., *U.S. Pat.*, Jul. 15, **1952**, 2,603,661. (c) Novell, A., *J. Am. Chem. Soc.*, **1939**, *61*, 520. (d) Ingersoll, A. W.; Brown, J. H.; Kim, C. K.; Beauchamp, W. D. and Jennings, G., *J. Am. Chem. Soc.*, **1936**, *58*, 1808.
6. Sauers, R. R., *J. Am. Chem. Soc.*, **1958**, *80*, 4721.
7. Johnstone, R. A. W.; Wilby, A. H. and Entwistle, I. D., *Chem. Rev.*, **1985**, *85*, 129.
8. Wallach, O., *Ann.,* **1892**, *272*, 99.
9. Franzen, V., *Chemiker-Zeitung*, **1956**, *80*, 779.
10. (a) Kitamura, M.; Lee, D. H.; Hayashi, S.; Tanaka, S. and Yoshimura, M., *J. Org. Chem.*, **2002**, *67*, 8685. (b) Mousseron, M.; Jacquier, R. and Zagdoun, R., *Bull. Soc. Chim. Fr.,* **1953**, 974. (c) Mousseron, M.; Jacquier, R. and Zagdoun, R., *Bull. Soc. Chim. Fr.*, **1952**, 197. (d) DeBenneville, P. L. and Macartney, J. H., *J. Am. Chem. Soc.*, **1950**, *72*, 3073.

11. (a) Blachut, D.; Maurin, J. K.; Starosta, W.; Wojtasiewicz, K. and Czarnocki, Z., *Zeitsch. Naturforsch., B: Chem. Sci.*, **2002**, *57*, 593. (b) Martinez, A. G., Vilar, E. T.; Fraile, A. G.; Ruiz, P. M.; San Antonio, R. M. and Alcazar, M. P. M., *Tetrahedron: Asymmetry*, **1999**, *10*, 1499. (c) Helland, I. and Lejon, T., *Hetereocycles*, **1999**, *51*, 611. (d) Adger, B. M.; Dyer, U. C.; Lennon, I. C.; Tifflon, P. D. and Ward, S. E., *Tetrahedron Lett.*, **1997**, *38*, 2153. (e) Loupy, A.; Monteux, D.; Petit, A.; Aizpurua, J. M.; Dominguez, E. and Palomo, C., *Tetrahedron Lett.*, **1996**, *37*, 8177. (f) Carlson, R.; Lejon, T.; Lundstedt, T. and Le Clouerec, E., *Acta Chem. Scand.*, **1993**, *47*, 1046. (g) Bellini, A. M.; Mencini, E.; Quaglio, M. P.; Guarneri, M. and Fini, A., *Steroids*, **1991**, *56*, 395. (h) Awachie, P. I. and Agwada, V. C., *Tetrahedron*, **1990**, *46*, 1899. (i) Kolycheva, M. T.; Gerus, I. I. and Kukhar, V. P., *Zh. Org. Khim.*, **1989**, *25*, 2367. (j) Fülöp, F.; Pihlaja, K.; Mattinen, J. and Bernáth, G., *Tetrahedron Lett.*, **1987**, *28*, 115. (k) Villa, M. J.; Dominguez, E. and Lete, E., *Heterocycles*, **1986**, *24*, 1943. (l) Solomons, W. E. and Doorenbos, N. J., *J. Pharm. Sci.*, **1974**, *63*, 19. (m) Lednicer, D. and Hauser, C. R., *J. Org. Chem.*, **1959**, *24*, 43. (n) Marcus, E. and Fitzpatrick, J. T., *J. Org. Chem.*, **1959**, *24*, 1031. (o) Staple, E. and Wagner, E. C., *J. Org. Chem.*, **1949**, *14*, 559. (p) Crossley, F. S. and Moore, M. L., *J. Org. Chem.*, **1945**, *10*, 529. (q) Novelli, A. and Somaglino, J. C., *Anal. Asoc. Quim. Argentina*, **1943**, *31*, 147.

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Leuckart Thiophenol Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Leuckart in 1890.[1] It is the synthesis of thiophenol involving the reaction between a diazonium salt and potassium ethylxanthate to form diazonium ethylxanthate, which decomposes upon heating to both diarylthiocarbonate and aryl xanthate that then afford thiophenol upon alkaline hydrolysis. Therefore, this reaction is simply known as the Leuckart thiophenol synthesis[2] or Leuckart synthesis.[2,3] It has been found that aryl xanthate, diarylthiocarbonate, and ethyl ethylxanthate all are produced in this reaction, and the yield of diarylthiocarbonate is slightly higher than that of ethyl ethylxanthate.[2] It is clear that aryl xanthate is not the intermediate in the formation of diarylthiocarbonate. Even though the decomposition of diazonium salt may produce a free radical, the formation of diarylthiocarbonate presumably involves a heterolytic mechanism, since the yield of diarylthiocarbonate is lower in methanol than that in water. Further evidence for the heterolytic mechanism is the detection of phenol arising from aryl carbonium and the absence of biaryl in reaction mixture. Although the presence of a large group at the *ortho*-position of diazonium salt can increase the yield of diarylthiocarbonate and the ratio of diarylthiocarbonate over aryl xanthate, there is no significant electronic effect from the substituent at the *para*-position, because diazonium salt with either a methoxy or a nitro group at the *para*-position gives similar yields of diarylthiocarbonate, and the orientation of substituents in both diarylthiocarbonate and aryl xanthates is the same as those in the initial diazonium salt. In comparison, the replacement of ethyl group by isopropyl or benzyl group in potassium ethylxanthate does not significantly affect the yield of diarylthiocarbonate. It has been found that the best yield of diarylthiocarbonate can be obtained when a 1:1 ratio

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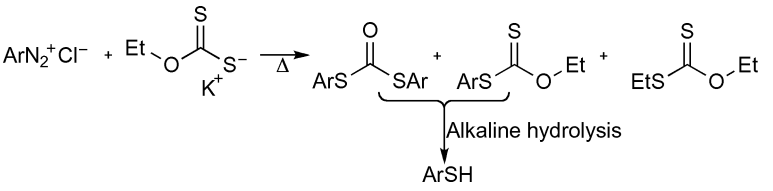
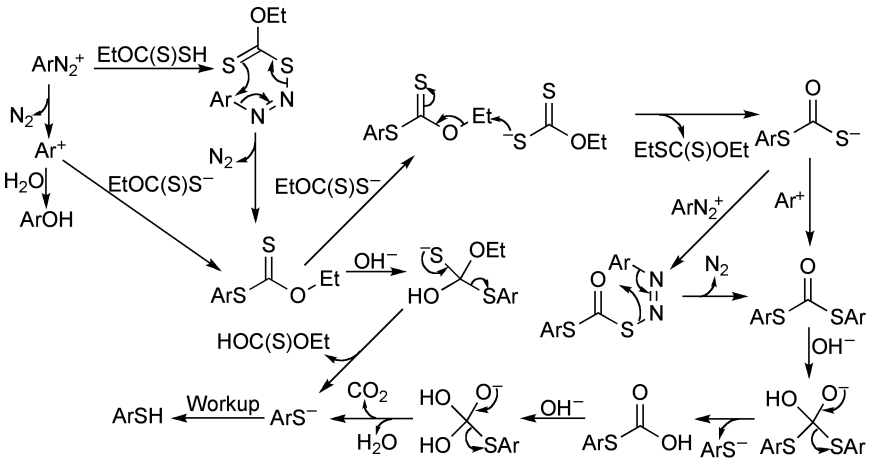
of diazonium salt and potassium ethyl xanthate are used, and the increase of acidity definitely lowers the yield of diarylthiocarbonate.[2] It is believed that the ethyl xanthate anion exists in the mesomeric form, which attacks the diazonium salt followed by loss of ethanol, giving the intermediate of $ArSC(O)S^-$ that then attacks the second diazonium ion to form diarylthiocarbonate.[4]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Even though a fragmental mechanism has been provided in the literature, a new mechanism is proposed here considering all the experimental results, including the rationalization on the 1:1 ratio between diazonium salt and potassium ethyl xanthate, and the pathway to form diarylthiocarbonate.



D. MODIFICATION

N/A

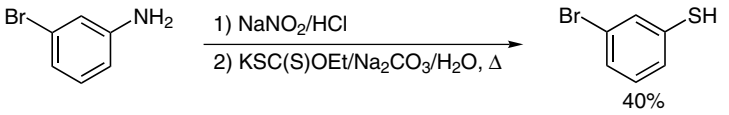
E. APPLICATIONS

This reaction provides a general method to prepare thiophenols.

F. RELATED REACTIONS

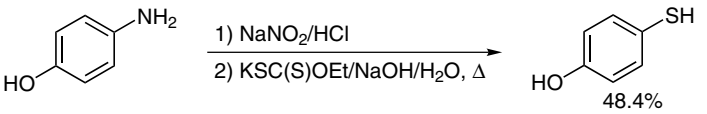
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 5.

m-Bromoaniline (43 g, 0.25 mol) was diazotized at 5°C with 49 mL conc. HCl and 17.2 g $NaNO_2$ (0.25 mol) in 110 mL water. The solution of the diazonium salt was added over a 1.5-h period to a solution of 40 g potassium ethyl xanthate (0.25 mol) and 33.0 g Na_2CO_3 (0.3 mol) in 250 mL water at 70°C. The mixture was maintained at this temperature for an additional hour, the resulting oil was separated, the aqueous phase was extracted twice with ether, and the ether layers were combined with the oil. The ether was removed on a steam bath in a stream of nitrogen, and the residual oil was added to a solution of 40 g NaOH in 250 mL MeOH and 40 mL water. The mixture was refluxed for 2 h under nitrogen, diluted with 4 L water, and acidified with hydrochloric acid. The resulting oil was separated, the aqueous phase was washed with methylene chloride, and the latter was combined with the oil and dried over anhydrous Na_2SO_4. Distillation at 100–104°C (10 mmHg) yielded 19.1 g *m*-bromothiopheno1, in a yield of 40%. The *m*-bromothiophenol was redistilled at 123–124°C (40 mmHg) for further purification.



Reference 6.

p-Aminophenol (110 g, 1.0 mol) was mixed with excess of 10% HCl (2.25 mol). The solution was cooled <15°C and diazotized by the gradual addition of 70 g $NaNO_2$ (1.0 mol) while the temperature was maintained between 1.5° and 20°C by means of ice. The diazo solution was then run slowly beneath the surface of a hot solution of 224 g potassium ethyl xanthate (1.4 mol) in 650 g water, and the reaction mixture was stirred vigorously and kept at 70 –75°C to ensure complete decomposition of the intermediate diazo combination. When all the diazo solution was in, the temperature was raised to 90°C and maintained for 30 min. The xanthate ester was then decomposed by adding 160 g solid NaOH (4 mol) and refluxing for several hours, the mixture was then strongly acidified with an excess of 50% H_2SO_4 and further refluxed in the presence of zinc and benzene to reduce any disulfide that may have been formed. The crude thiohydroquinone was separated as an oil, washed with dilute hydrochloric acid and water, and distilled in vacuo to afford 61.0 g thiohydroquinone as a clear colorless liquid, in a yield of 48.4%, b.p. 133–137°C at 11.0 mmHg.

Other references related to the Leuckart thiophenol synthesis are cited in the literature.[17]

H. REFERENCES

1. Leuckart, R., *J. Prakt. Chem.*, **1890**, *41*, 179.
2. Cox, J. R.; Gladys, C. L.; Field, L. and Pearson, D. E., *J. Org. Chem.*, **1960**, *25*, 1083.
3. Biamonte, M. A.; Shi, J. D.; Hurst, D.; Hong, K.; Boehm, M. F. and Kasibhatla, S. R., *J. Org. Chem.*, **2005**, *70*, 717.
4. Hölzle, K., *Helv. Chim. Acta*, **1946**, *29*, 1883.
5. Bordwell, F. G. and Andersen, H. M., *J. Am. Chem. Soc.*, **1953**, *75*, 6019.
6. Miller, E. and Read, R. R., *J. Am. Chem. Soc.*, **1933**, *55*, 1224.
7. (a) Weinstein, A. H.; Pierson, R. M.; Wargotz, B. and Yen, T. F., *J. Org. Chem.*, **1958**, *23*, 363. (b) Overberger, C. G. and Lebovits, A., *J. Am. Chem. Soc.*, **1956**, 78, 4792. (c) Tarbell, D. S. and Fukushima, D. K., *Org. Syn. Coll.*, **1955**, *3*, 809. (d) Tarbell, D. S. and McCall, M. A., *J. Am. Chem. Soc.*, **1952**, *74*, 48. (e) Hunter, W. H. and Kohlhase, A. H., *J. Am. Chem. Soc.*, **1932**, *54*, 2425. (f) Clifford, A. M. and Lichty, J. G., *J. Am. Chem. Soc.*, **1932**, *54*, 1163. (g) Bass, S. L. and Johnson, T. B., *J. Am. Chem. Soc.*, **1930**, *52*, 1146. (h) Bennett, G. M. and Berry, W. A., *J. Chem. Soc.*, **1927**, 1669. (i) Mauthner, F., *Ber.*, **1906**, *39*, 1347. (j) Leuckart, R. and Holtzapfel, W., *J. Prakt. Chem.*, **1890**, *41*, 197.

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Levinstein Process

A. GENERAL DESCRIPTION OF THE REACTION

This reaction presumably was first reported by Levinstein. It is the preparation of bis(2-chloroethyl)sulfide by bubbling dry ethylene gas through sulfur monochloride at 35°C and distilling the remaining material.[1] This reaction is generally known as the Levinstein process[2] and is occasionally referred to as the Levinstein reaction.[3] The product produced from this process normally contains up to 70% of bis(2-chloroethyl)sulfide, and another 30% of bis(2-chloroethyl)polysulfides,[2h,2i] ranging from trisulfide to nonasulfide,[2h] depending on the conditions under which the reaction was carried out, including the temperature, degree of agitation, the rate of addition of ethylene, and the nature of sulfur monochloride used.[2i] The product of bis(2-chloroethyl)sulfide is often known as mustard gas.[1,2e,2g,2h,3,4] In addition, it is also called Levinstein mustard gas,[5] which has been applied as vesicant agent on the battlefield.[2a] As a result, this compound also gained other names, such as "H," the compound made from the Levinstein process;[2c,6] "HD," the distilled or nearly pure mustard,[2b,6] containing about 5% of impurity[2b] (e.g., 2-chloroethyl 2-chlorovinyl sulfide[2g]); "sulfur mustard," also called "LOST" or "S-LOST" after the two German chemists (Lommell and Steinkopf) who suggested its use as a chemical weapon;[7] "yellow cross" for its identifying mark during World War I;[6,7] "yperite," for the site of its first use;[6,7] and "HT," for the 60:40 mixture of HD and bis(2-chloroethylthio)ethyl ether.[2b] Interestingly, it has been found that ethylene does not react with pure sulfenyl chloride, but this reaction proceeds extremely fast in carbon tetrachloride, probably due to the low solubility of ethylene in sulfenyl chloride.[1] The formation of polysulfide is due to the disproportionation of sulfur monochloride to sulfur dichloride and trisulfurdichloride; the latter then reacts with ethylene

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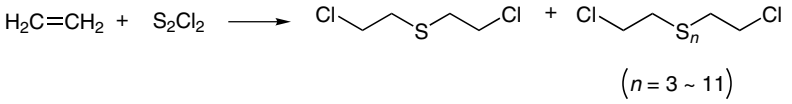
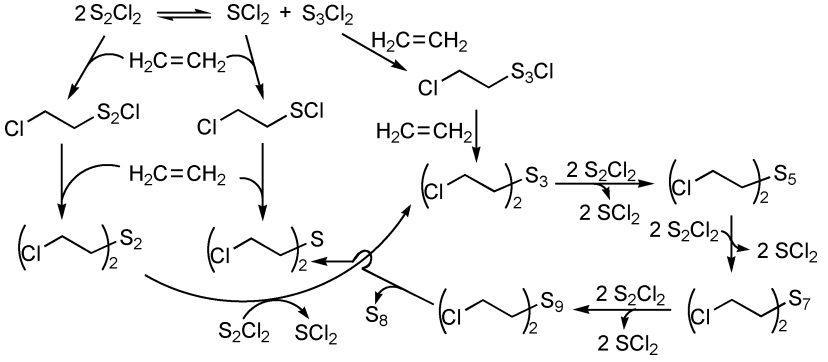
to form bis(2-chloroethyl)trisulfide and higher-order sulfides.[1] At higher reaction temperatures (e.g., 60°C), the yield of mustard gas is increased up to 80%, and sulfur deposits immediately; at lower temperatures (e.g., 20°C), the yield of mustard gas is lowered to 61%, and sulfur appears in the mustard gas in a few weeks.[2i]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Shown below is the mechanism for the interchanges between sulfides.



D. MODIFICATION

The production of mustard gas has been improved by the chlorination of thiodiglycol, which does not precipitate solid after distillation.[8]

E. APPLICATIONS

The reaction has been used for the production of the mustard gas for military usage.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES

Because this reaction is primarily for the industrial production of mustard gas, no laboratory preparation is provided here.

Other references related to the Levinstein process are cited in the literature.[9]

H. REFERENCES

1. Fuson, R. C.; Price, C. C.; Bauman, R. A.; Bullitt, O. H.; Hatchard, W. R. and Maynert, E. W., *J. Org. Chem.*, **1949**, 14, 469.
2. (a) U.S. Army Medical Research Institute of Chemical Defense, See detail at: https://ccc.apgea.army.mil/products/Info/products.htm (b) Colorado Deapartment of bublic Health and Environment, no publiction city. See detail at: http://www.cdphe.state.co.us/HM/hwid.pdf (c) Bunnett, J. F., *Pure & Appl. Chem.*, **1995**, *67*, 841. (d) Kinnear, A. M. and Harley-Mason, J., *J. Soc. Chem. Ind., London, Trans. & Commun.*, **1948**, *67*, 107. (e) Macy, R.; Jarman, G. N.; Morrison, A. and Emmet Reid, E., *Science*, **1947**, *106*, 355. (f) Fuson, R. C.; Price, C. C. and Burness, D. M., *J. Org. Chem.*, **1946**, *11*, 475. (g) Fuson, R. C. and Parham, W. E., *J. Org. Chem.*, **1946**, *11*, 482. (h) Fuson, R. C.; Price, C. C.; Burness, D. M.; Foster, R. E.; Hatchard, W. R. and Lipscomb, R. D., *J. Org. Chem.*, **1946**, *11*, 487. (i) Fuson, R. C.; Foster, R. E. and Lipscomb, R. D., *J. Org. Chem.*, **1946**, *11*, 504.
3. Fuson, R. C; Burness, D. M.; Foster, R. E. and Lipscomb, R. D., *J. Org. Chem.*, **1946**, *11*, 499.
4. (a) Pernot, R., *Ann. Chim.*, **1946**, *1*, 625. (b) Felsing, W. A. and Arenson, S. B., *J. Ind. Eng. Chem.*, **1920**, *12*, 1065. (c) Green, A. G., *J. Soc. Chem. Ind., London*, **1919**, *39*, 363. (d) Pope, W. J., *J. Soc. Chem. Ind., London*, **1919**, *38*, 344.
5. Fuson, R. C.; Price, C. C.; Burness, D. M.; Foster, R. E.; Hatchard, W. R. and Lipscomb, R. D., *J. Org. Chem.*, **1946**, *11*, 487.
6. See www.inchem.org/documents/pims/chemical/mustardg.htm.
7. Sidell, F. R.; Urbanetti, J. S.; Smith, W. S. and Hurst, C. G., "Vesicants," in *Medical Aspects of Chemical and Biological Warfare*, ed. Sidell, F. R.; Takafuji, E. T. and Franz, D. R., Walter Reed Army Medical Center, Washington, D.C., **1997**, ch. 7.
8. See www.fas.org/nuke/intro/cw/produce.htm.
9. Sartori, M., *The War Gases: Chemistry and Analysis*, Van Nostrand , New York, **1939**.

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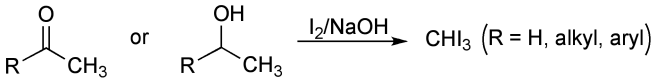
Lieben Iodoform Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Lieben in 1870.[1] It is an alkaline degradation of compounds with acetyl or methylcarbinol groups by means of iodine treatment to form volatile iodoform. This reaction has been widely used to test the presence of acetyl or methylcarbinol groups and is known as the Lieben reaction,[2] Lieben iodoform reaction,[2d,3] iodoform test of Lieben,[4] or Lieben test.[5] It is believed that the positive test of methylcarbinol group is because of the oxidation of such groups by hypoiodite generated *in situ* from the alkaline disproportionation of iodine.[2d] Similarly, other compounds that can generate the acetyl group under the test conditions also give a positive result,[2a] such as the retro *Aldol Reaction* of α,β-unsaturated compounds.[6] In addition, compounds with groups capable of exerting excessively high steric hindrance have also been reported to be positive toward the Lieben test.[2d] Unfortunately, some ketones, such as α-chloroacetophenone, acetomesitylene, propiophenone,[5b] pinacolone, and similar compounds involving steric hindrance[7] result in a negative test. While the original procedure involves the treatment of compounds with iodine and excess of base[5b] and can detect compounds at concentrations as low as 1 part in 2000,[1] it often gives ambiguous results because of the anesthetic action of the iodoform on the olfactory nerve.[8]

B. GENERAL REACTION SCHEME



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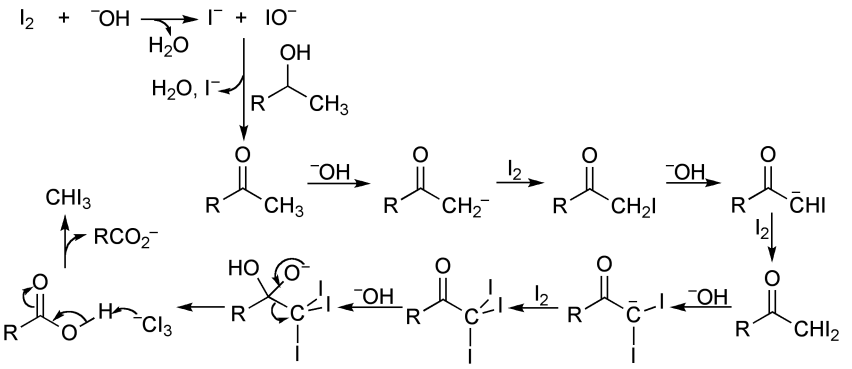
C. PROPOSED MECHANISMS

A mechanism including the disproportionation of iodine, oxidation of methylcarbinol into acetyl group, and the final formation of iodoform is illustrated below.



D. MODIFICATION

Because of the importance of this reaction for structural identification in the early days, it has been modified to occur in dioxane with a slight excess of iodine-potassium iodide solution at 60°C to test water-insoluble compounds.[4a] In addition, this test has been improved from being an older test to a color test by the addition of pyridine, quinoline, or their homologs to the alkali hypochlorite or hypobromite solution, by which a carmine red or pink color develops immediately if an acetyl or methylcarbinol group exists.[8] Further improvement has been done to differentiate between the acetyl and the methylcarbinol groups by the addition of *ortho*-nitrobenzaldehyde in the alkaline solution, by which methyl ketone can undergo the *Baeyer-Drewson Indigo Synthesis*, whereas compounds with methylcarbinol groups won't. Under these conditions, the negative Lieben test indicates the absence of acetyl and methylcarbinol groups, whereas a positive Lieben test but negative indigo reaction shows the presence of methylcarbinol group, and both positive tests from Lieben iodoform reaction and the indigo reaction implies the presence of methyl ketones.[2d]

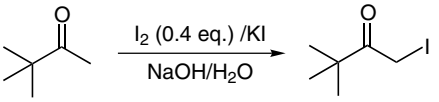
E. APPLICATIONS

This reaction had wide application in the structural elucidation of organic compounds before the modern spectroscopy. In addition, this reaction has been used to prepare α-monoiodo and α-diiodoketones by using a less than theoretical amount of iodine.[9]

F. RELATED REACTIONS

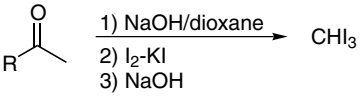
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 9.

A mixture of 80 g pinacolone and 800 mL 5% NaOH solution was cooled in an ice and salt mixture, and 80 g iodine, dissolved in aqueous potassium iodide, was added through a rapidly revolving hollow stirrer. The addition was complete in 2 h. The solution was immediately shaken with ether, and the resulting ether solution was washed with water. The solution was dried over Na_2SO_4, and the ether was removed. The strongly lachrymatory liquid thus obtained was distilled at 92–98°C (20 mmHg) to afforded 6 mL α-iodopinacolone as a liquid, which was shaken with mercury to remove the iodine color and redistilled twice at 48–49°C (2 mmHg). (No yield was given for the original experiment.)



Reference 2d.

About 100 mg of the compound being tested was dissolved in 5 mL dioxane in a 150 × 16 mm test tube, followed by the addition of 1 mL 10% NaOH. The iodine reagent was added dropwise with shaking until a slight excess of iodine caused a definite dark color that did not disappear on standing. The test tube was then placed in a water bath maintained at 60°C, and the dropwise addition of the iodine reagent was continued until the definite dark color persisted as before; but the warming at 60°C should not last $>$ 2 min. The excess of iodine was removed with a few drops of 10% NaOH solution, and the test tube was filled with cold water, allowed to stand for 15 min, and filtered. The characteristic odor of iodoform was readily distinguishable. As a confirmation, the crystals collected on the filter paper were dried at 100°C for 1 h and identified by their melting point. (Iodoform melts at 114–121°C).

Other references related to the Lieben iodoform reaction are cited in the literature.[10]

H. REFERENCES

1. Lieben, A., *Ann. (Suppl.)*, **1870**, *7*, 218.
2. (a) Gillis, B. T., *J. Org. Chem.*, **1959**, *24*, 1027. (b) Kamen, K., *Chemicky Prumysl*, **1957**, 7, 472. (c) Poggi, A. R.; Biffoli, R. and Stella, C., *Gazz. Chim. Ital.*, **1947**, *77*, 536. (d) Kamlet, J., *Ind. Eng. Chem.*, **1944**, *16*, 362. (e) Poggi, R., *Gazz. Chim. Ital.*, **1940**, *70*, 328. (f) Lorber, L., *Biochem. Zeitsch.*, **1927**, *181*, 375.
3. van der Haar, A. W., *Rec. Trav. Chim. Pays-Bas Belg.*, **1922**, *41*, 784. Kunz, R., *Zeitsch. Anal. Chem.*, **1920**, *59*, 302.

4. (a) Fuson, R. C. and Tullock, C. W., *J. Am. Chem. Soc.*, **1934**, *56*, 1638. (b) Baskerville, C. and Hamor, W. A., *J. Ind. Eng. Chem.*, **1912**, 362.
5. (a) Asahina, Y. and Ukita, T., *Ber.*, **1941**, *74B*, 952. (b) Fuson, R. C. and Bull, B. A., *Chem. Rev.*, **1935**, *15*, 275.
6. Esafov, V. I. and Stafeeva, N. M., *Zh. Anal. Khim.*, **1951**, *6*, 195. [*Chem. Abstr.*, **1951**, *45*, 8404].
7. Delange, L., *Bull. Soc. Chim.*, **1908**, [*4*]*3*, 910.
8. Adachi, J., *Anal. Chem.*, **1951**, *23*, 1491.
9. Johnson, R. and Fuson, R. C., *J. Am. Chem. Soc.*, **1935**, *57*, 919.
10. (a) Seelye, R. N. and Turney, T. A., *J. Chem. Edu.*, **1959**, *36*, 572. (b) McElvain, S. M., *The Characterization of Organic Compounds*, Macmillan., New York, **1949**, p. 137. (c) Hans, M., *Analyse und Konstitutionsermittlung Organischer Verbindungen*, Julius Springer, Berlin, **1938**, pp. 305–306. (d) Baskerville, C. and Hamor, W. A., *J. Ind. Eng. Chem.*, **1912**, 499. (e) Porcher, C. and Hervieux, C., *Compt. Rend. Seances Soc. Biol. Ses Filiales*, **1907**, *62*, 651. (f) Lieben, A., *Ann. (Suppl.)*, **1870**, *7*, 377.

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Liebeskind-Srögl Cross-Coupling

A. GENERAL DESCRIPTION OF THE REACTION

This reaction can be traced back to 1996 when Liebeskind used copper (I) 2-thiophenecarboxylate as a mediator for the coupling between alkyl tributyltin and alkyl halides.[1] This reaction had been extensively investigated by Liebeskind, in collaboration with Srögl,[2] and became a very useful palladium-catalyzed coupling reaction between an aryl boronic acid and a general sulfur containing molecules to form a variety of compounds, including ketones, thioethers, alkynes, and biaryls. Therefore, it is known as the Liebeskind-Srögl coupling,[3] Liebeskind-Srögl cross coupling,[2f,2g,4] or Liebeskind-Srögl thiol ester-boronic acid cross-coupling.[5] It should be pointed out that this reaction occurs under very mild, nonbasic conditions. For the coupling between aryl boronic acid and 4-halo-*n*-butylthiol esters, the presence of a catalytic amount of sodium iodide is crucial to facilitate the alkylation-activated coupling to form phenyl ketones. Among the tested palladium catalysts, *trans*-di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)-benzyl]dipalladium(II) is the most efficient catalyst for this coupling.[2d] Other types of thioesters can also couple with aryl boronic acid to form ketones in the presence of a stoichiometric amount of copper(I) thiophene-2-carboxylate (CuTC) and a catalytic amount of palladium catalyst,[4b] where Cu(I) carboxylate activates both the carbon-sulfur bond for oxidative addition of palladium and the transmetalation by coordinative delivery of the carboxylate to the boron atom.[2e,2h] Under these conditions, sodium iodide is not necessary. In contrast to the *Suzuki Coupling*, aryl boronic acid can also couple with aryl or alkenyl iodide under nonbasic conditions in the presence of a palladium catalyst and Cu(I) carboxylate, so that the base-labile groups can tolerate this coupling condition.[2d] In addition, the coupling between the protected methyl thiopseudourea and phenyl boronic acid catalyzed by palladium in the presence of copper (I) thiophenecarboxylate provides a method for benzamidine derivatives.[2g] However, it has

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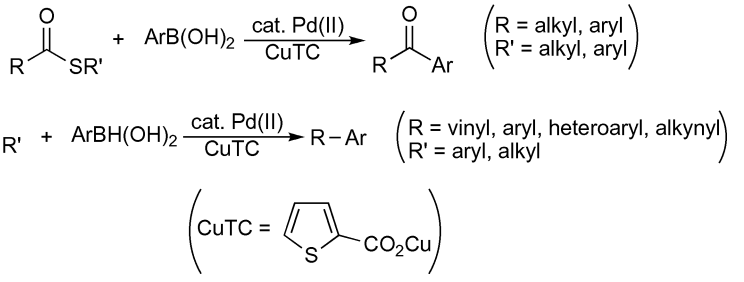
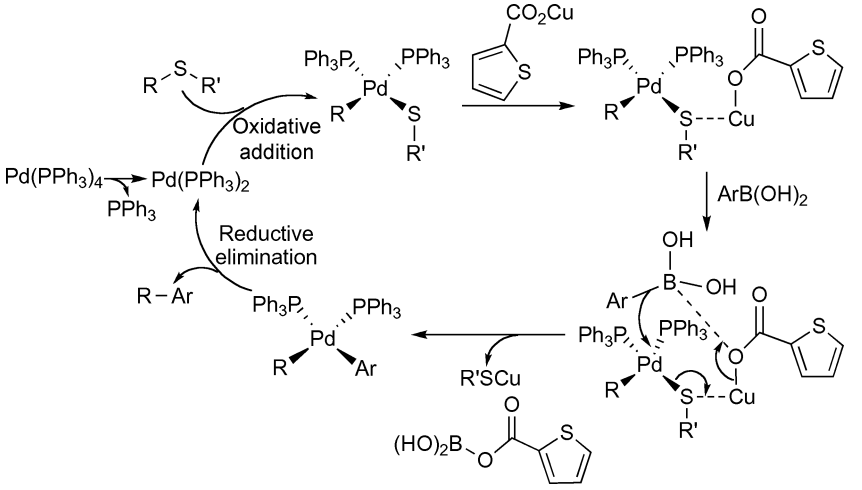
been found that the solvent is very crucial for the coupling between heteroaryl vinyl ether and aryl boronic acid, by which amide-based solvents, including DMF, DMA, and DMI (1,3-dimethyl-2-imidazolidinone), are the best solvents, and $Pd(PPh_3)_4$ is the best palladium catalyst.[4a] In addition, the π-electron-deficient heteroaryl thioether can also couple either with aryl boronic acid under similar conditions (palladium catalyst and Cu(I) carboxylate)[2f] or with aryl, alkenylstannanes in the presence of a catalytic amount of palladium catalyst and more than a stoichiometric amount of Cu(I) carboxylate—For example, CuTc or copper(I) 3-methylsalicylate (CuMeSal)[6] or copper(I) bromide dimethylsulfide complex.[7] Even thiourea can similarly couple with aryl boronic acid with the help of microwave irradiation.[3] For the preparation of alkynes from the coupling between alkynyl thioether and aryl boronic acid, it has been found that the reagent (e.g., CuCl, CuBr, CuI) and base (K_2CO_3, NaOAc) in the *Sonogashira Coupling* are not very effective. For this special case, dioxane and THF are found to be the best solvents, and any palladium catalyst and readily available copper (I) carboxylate are good for this coupling.[2e] The thioethers used for this coupling can easily be prepared from the coupling between aryl boronic acid and alkyl, heteroaryl, and alkyl *N*-thioimide in the presence of catalytic copper (I) carboxylate.[8]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A general mechanism for the coupling between thioether and aryl boronic acid is illustrated below, using $Pd(PPh_3)_4$ as the catalyst, in the presence of a stoichiometric amount of copper (I) 2-thiophenecarboxylate as the transmetalation agent.



D. MODIFICATION

This reaction has been modified to occur efficiently under microwave irradiation.[3] Besides copper (I) 2-thiophenecarboxylate, Cu(I)-3-methylsalicylate (CuMeSal)[6,8,9] and copper diphenylphosphinate[10] have also been developed as mediators.

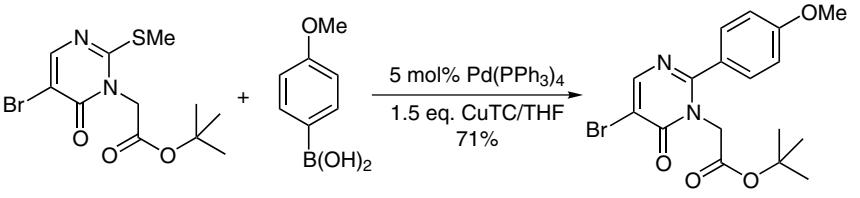
E. APPLICATIONS

This reaction, like other coupling methods has wide application in organic synthesis.

F. RELATED REACTIONS

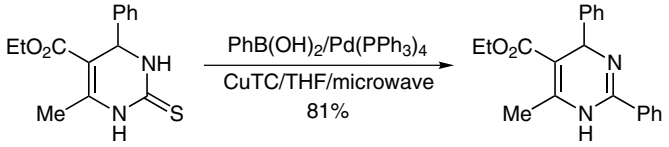
This reaction is related to the *Suzuki Coupling* and *Sonogashira Coupling*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2h.

A mixture of 415 mg 4-methoxyphenylboronic acid (2.73 mmol), 446 mg CuTC (2.34 mmol), 523 mg *tert*-butyl [5-bromo-2-(methylthio)-6-oxopyrimidin-1(6H)-yl]acetate (1.56 mmol), and 5 mol % $Pd(PPh_3)_4$ was placed in a flask. After three vacuum/argon cycles, 15 mL dry and degassed THF was added. The reaction was stirred for 12–18 h at 50–60°C and monitored by LC/MS. When the reaction was complete, the mixture was cooled to ambient temperature, EtOAc was added, and the mixture was filtered through a medium frit sintered glass funnel. The filtrate was washed with 1 N $NaHSO_4$, saturated $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to a viscous solid. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 200:1) to afford 439 mg *tert*-butyl [5-bromo-2-(4-methoxyphenyl)-6-oxopyrimidin-1(6H)-yl]acetate as a pale yellow solid, in a yield of 71%.



Reference 3.

A microwave process vial was charged with a stir bar. To this vessel were added DHPM (69.1 mg, 0.25 mmol), 45.7 mg $PhB(OH)_2$ (0.375 mmol), 142.9 mg Cu(I) thiophene-2-carboxylate (CuTC) (0.75 mmol), and 8.7 mg $Pd(PPh_3)_4$ (3.0 mol %). The reaction vessel was flushed with argon and sealed. Through the septum was added 5 mL anhydrous THF, and the reaction vessel was irradiated at 100°C for 25 min. After cooling, the mixture was transferred to a round-bottomed flask and was adsorbed on silica gel. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 3:1) to yield 81% dihydropyrimidine as a semisolid.

Other references related to the Liebeskind-Srögl cross-coupling are cited in the literature.[11]

H. REFERENCES

1. Allred, G. D. and Liebeskind, L. S., *J. Am. Chem. Soc.*, **1996**, *118*, 2748.
2. (a) Zhang, S. J.; Zhang, D. W. and Liebeskind, L. S., *J. Org. Chem.*, **1997**, *62*, 2312. (b) Liebeskind, L. S. and Srögl, J., *J. Am. Chem. Soc.,* **2000**, 122, 11260. (c) Savarin, C.; Srögl, J. and Liebeskind, L. S., *Org. Lett.*, **2000**, *2*, 3229. (d) Savarin, C. and Liebeskind, L. S., *Org. Lett.*, **2001**, *3*, 2149. (e) Savarin, C.; Srögl, J. and Liebeskind, L. S., *Org. Lett.*, **2001**, *3*, 91. (f) Liebeskind, L. S. and Srögl, J., *Org. Lett.*, **2002**, *4*, 979. (g) Kusturin, C. L.; Liebeskind, L. S. and Neumann, W. L., *Org. Lett.*, **2002**, *4*, 983. (h) Kusturin, C.; Liebeskind, L. S.; Rahman, H.; Sample, K.; Schweitzer, B.; Srögl, J. and Neumann, W. L., *Org. Lett.*, **2003**, *5*, 4349. (i) Yu, Y. and Liebeskind, L. S., *J. Org. Chem*., **2004**, 69, 3554. (j) Zhang, Z. H. and Liebeskind, L. S., *Org. Lett.*, **2006**, *8*, 4331. (k) Yang, H. and Liebeskind, L. S., *Org. Lett.*, **2007**, *9*, 2993.
3. Lengar, A. and Kappe, C. O., *Org. Lett.*, **2004**, *6*, 771.
4. (a) Muraoka, N.; Mineno, M.; Itami, K. and Yoshida, J.-I., *J. Org. Chem.*, **2005**, *70*, 6933. (b) Rodríguez-Cendejas, C. G.; Liebeskind, L. S. and Peña-Cabrera, E., *ARKIVOC*, **2005**, 250. (c) Lory, P. and Gilbertson, S. R., *Chemtracts*, **2005**, 18, 569.
5. Prokopcova, H.; Pisani, L. and Kappe, C. O., *Synlett*, **2007**, 43.
6. Egi, M. and Liebeskind, L. S., *Org. Lett.*, **2003**, *5*, 801.
7. Alphonse, F.-A.; Suzenet, F.; Keromnes, A.; Lebret, B. and Guillaumet, G., *Org. Lett.*, **2003**, *5*, 803.
8. Savarin, C.; Srögl, J. and Liebeskind, L. S., *Org. Lett.*, **2002**, *4*, 4309.
9. Yu, Y.; Srögl, J. and Liebeskind, L. S., *Org. Lett.*, **2004**, *6*, 2631.
10. Wittenberg, R.; Srögl, J.; Egi, M. and Liebeskind, L. S., *Org. Lett*., **2003**, 5, 3033.
11. (a) Kaval, N.; Singh, B. K.; Ermolat'ev, D. S.; Claerhout, S.; Parmar, V. S.; van der Eycken, J. and van der Eycken, E., *J. Comb. Chem.*, **2007**, *9*, 446. (b) Pisani, L.; Prokopcova, H.; Kremsner, J. M. and Kappe, C. O., *J. Comb. Chem.*, **2007**, 9, 415. (c) Fukuyama, T. and Tokuyama, H., *Aldrichimica Acta*, **2004**, *37*, 87. (d) Zeysing, B.; Gosch, C. and Terfort, A., *Org. Lett.*, **2000**, *2*, 1843. (e) Tokuyama, H.; Yokoshima, S.; Yamashita, T. and Fukuyama, T., *Tetrahedron Lett.*, **1998**, *39*, 3189.

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Lindlar Hydrogenation
(Lindlar Reduction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported in 1947[1] and optimized by Lindlar in 1952.[2] It is a stereoselective reduction of alkynes to *cis*-alkenes by hydrogen in the presence of palladium that is impregnated onto calcium carbonate and then deactivated by lead acetate and quinoline. Therefore, this reaction is often known as the Lindlar reduction[3] or Lindlar hydrogenation,[3a–3c,3e] and the palladium on calcium carbonate poisoned with lead acetate and quinoline is referred to as the Lindlar catalyst.[1,3d,4] The Lindlar catalyst exists as a slurry mixture resulting in a heterogeneous hydrogenation.[1,4a] It has been found that palladium coated on $BaSO_4$ is superior to $CaCO_3$, presumably because of the stability of the solid support toward acid.[5] This catalyst is prepared by reduction of $PdCl_2$ with $CaCO_3$ slurry followed by the addition of lead acetate and 0.05–1 eq. quinoline.[4d] It has been found that the addition of quinoline lowers the reduction rate[6] but efficiently enhances the selectivity by inhibiting alkene surface interaction.[7] Although the addition of lead acetate has been suggested to block the most active catalyst sites and prevent overreduction of alkenes to alkanes,[1] it has been found that lead acetate does not block certain active sites but rather acts to modify the surface structure of the catalyst, such as the formation of the Pd_3Pb alloy particle.[1,4d] Such modifications on the catalyst surface also increase the selectivity.[4d] It is believed that the stereoselective reduction of alkynes to only *cis*-alkenes is because one face of the triple bond is shielded by the Lindlar catalyst so that hydrogen is restricted to approach the triple bond from the other side. In this reduction, the solvent also plays an important role. It has been reported that the *cis*/*trans* ratio was dramatically enhanced from 10:1 to 25:1 by changing the solvent from MeOH to hexane/EtOAc (1:1), and the *cis*/*trans* ratio was further increased to 86:1 by the addition of quinoline in hexane/EtOAc (1:1).[3d]

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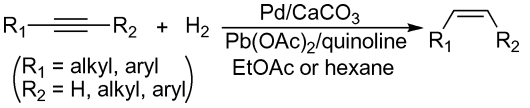
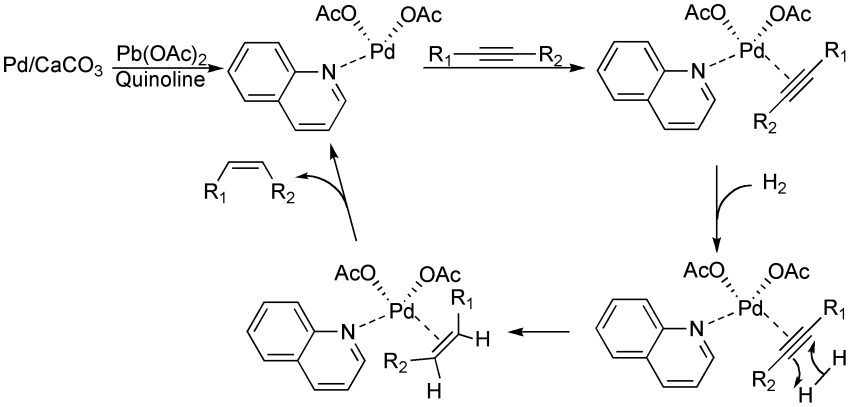
Even though the palladium in the Lindlar catalyst is known to be reduced to zero valence, it has been found that the palladium in Lindlar catalyst is still electron-deficient with a bond energy ~2.1 eV higher than that of Pd(0).[4a] Because of such an electron deficiency, alkynes are more strongly absorbed onto the catalyst, and once they are reduced to alkenes, the alkenes are released from the catalyst without overreduction to alkanes because of the relatively weaker interaction between catalyst and alkenes. However, an unprotected amino group sitting near the alkyne group will accelerate the overreduction of alkenes and reduce the selectivity,[4b] simply because of the strong electron-donating ability. In this case, the addition of 1 eq. of ethylenediamine in the reaction mixture will reduce the overreduction to a minimal level.[4b]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A possible mechanism for the hydrogenation is illustrated here, where acetate and quinoline all coordinate with palladium.



D. MODIFICATION

This reaction has been modified by the addition of $MnCl_2$ to enhance the selectivity during hydrogenation.[8] In addition, it has been found that palladium on Al_2O_3 is superior to the Lindlar catalyst operating under same conditions (e.g., temperature, hydrogen pressure, and Pd/substrate ratio).[4a]

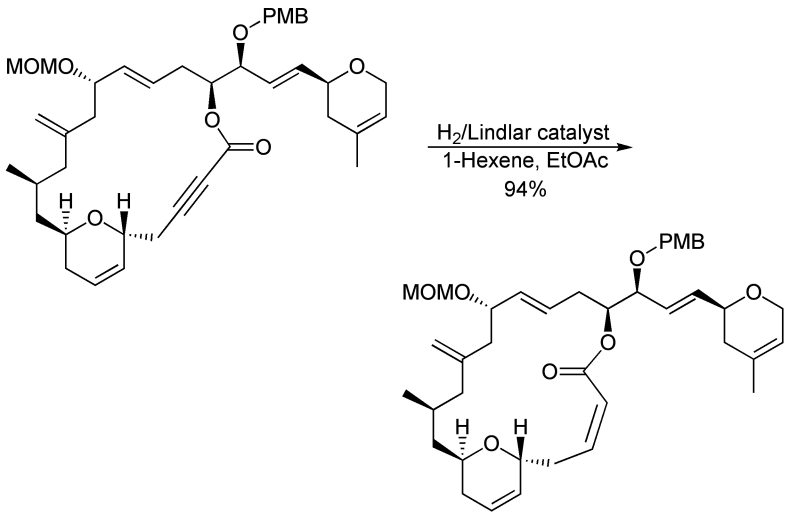
E. APPLICATIONS

This reaction has broad application in natural product synthesis.

F. RELATED REACTIONS

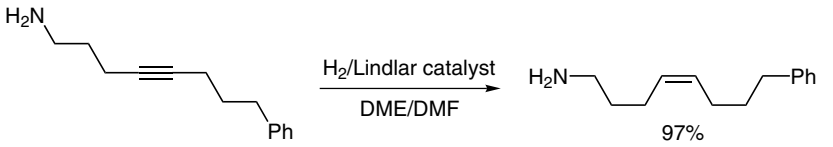
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 9.

To a solution of 8.5 mg lactone (0.013 mmol) in 1 mL 1-hexene and 1 mL EtOAc was added 2 mg Lindlar catalyst. The resulting suspension was vigorously stirred under a hydrogen balloon for 1.5 h. The mixture was filtered through a pad of Celite and washed with EtOAc. Concentration of the filtrate gave a residue, that was purified by silica gel chromatography (20% EtOAc/hexane) to afford 8.0 mg *cis*-macrolactone, in a yield of 94%.



Reference 4b.

To a solution of 2.5 g alkyne (12.4 mmol) in 25 mL DMF was added 1.0 mL ethylenediamine (15 mmol) followed by 100 mg Lindlar catalyst. The reaction flask was evacuated, purged with hydrogen five times, and then stirred under a hydrogen atmosphere for 4 h. The reaction mixture was filtered over Celite and washed with 25 mL isopropyl acetate. The resulting solution was washed with 37 mL 2 wt % NH_4Cl and water (2×25 mL). The organic solution was concentrated to yield 2.45 g *cis*-aminoalkene as an oil, contaminated with 2.5% *trans*-aminoalkene and 0.5% aminoalkane in a yield of 97%.

Other references related to the Lindlar hydrogenation are cited in the literature.[10]

H. REFERENCES

1. McEwen, A. B.; Guttieri, M. J.; Maier, W. F.; Laine, R. M. and Shvo, Y., *J. Org. Chem.*, **1983**, *48*, 4436.
2. Lindlar, H., *Helv. Chim. Acta*, **1952**, *35*, 446.
3. (a) Fürstner, A.; Grela, K.; Mathes, C. and Lehmann, C. W., *J. Am. Chem. Soc.,* **2000**, *122*, 11799. (b) Hauser, F. M. and Ganguly, D., *J. Org. Chem.*, **2000**, *65* 1842. (c) Fürstner, A. and Dierkes, T., *Org. Lett.*, **2000**, *2*, 2463. (d) Qin, D. H.; Byun, H.-S. and Bittman, R., *J. Am. Chem. Soc.*, **1999**, *121*, 662. (e) Fürstner, A.; Guth, O.; Rumbo, A. and Seidel, G., *J. Am. Chem. Soc.*, **1999**, *121*, 11108.
4. (a) Lederhos, C. R.; L'Argentière, P. C. and Fígoli, N. S., *Ind. Eng. Chem. Res.*, **2005**, *44*, 1752. (b) Campos, K. R.; Cai, D. W.; Journet, M.; Kowal, J. J.; Larsen, R. D. and Reider, P. J., *J. Org. Chem.*, **2001**, *66*, 3634. (c) Stachurski, J. and Thomas, J. M., *Catal. Lett.*, **1988**, *1*, 67. (d) Ulan, J. G.; Kuo, E.; Maier, W. F.; Rai, R. S. and Thomas, G., *J. Org. Chem.*, **1987**, *52*, 3126. (e) Cerveny, L.; Franzova, P. and Ruzicka, V., *Chemicky Prumysl*, **1986**, *36*, 592.
5. Fukuda, T., *Bull. Chem. Soc. Jpn.*, **1958**, *31*, 343.
6. Maier, W. F.; Chettle, S. B.; Rai, R. S. and Thomas, G., *J. Am. Chem. Soc.*, **1986**, *108*, 2608.
7. (a) Steenhoek, A.; van Wijngaarden, B. H. and Pabon, H. J. J., *Recl. Trav. Chim. Pays-Bas*, **1971**, *90*, 961. (b) Bond, G. C. and Wells, P. B., *Adv. Catal.*, **1964**, *15*, 155.
8. Rajaram, J.; Narula, A. P. S.; Chawla, H. P. S. and Dev. S., *Tetrahedron*, **1983**, *39*, 2315.
9. Ghosh, A. K.; Wang, Y. and Kim, J. T., *J. Org. Chem.*, **2001**, *66*, 8973.
10. (a) Kirsch, S. F.; Overman, L. E. and White, N. S., *Org. Lett.*, **2007**, *9*, 911. (b) Dos Santos, A. A. and Francke, W., *Tetrahedron: Asymmetry*, **2006**, *17*, 2487. (c) Kraft, P.; Popaj, K. and Abate, A., *Synthesis*, **2005**, 2798. (d) Moormann, A. E.; Wang, J. L.; Palmquist, K. E.; Promo, M. A.; Snyder, J. S.; Scholten, J. A.; Massa, M. A.; Sikorski, J. A. and Webber, R. K., *Tetrahedron*, **2004**, *60*, 10907. (e) Shin, Y.; Fournier, J.-H.; Fukui, Y.; Brueckner, A. M. and Curran, D. P., *Angew. Chem. Int. Ed.*, **2004**, *43*, 4634. (f) Yokokawa, F.; Sugiyama, H.; Aoyama, T. and Shioiri, T., *Synthesis*, **2004**, 1476. (g) Paterson, I. and Tudge, M., *Tetrahedron*, **2003**, *59*, 6833. (h) Furstner, A.; Mathes, C. and Lehmann, C. W., *Chem. Eur. J.*, **2001**, *7*, 5299. (i) Krause, N. and Ebert, S., *Eur. J. Org. Chem.*, **2001**, 3837. (j) Marshall, J. A. and Johns, B. A., *J. Org. Chem.*, **1998**, *63*, 7885. (k) Jin, J. and Weinreb, S. M., *J. Am. Chem. Soc.*, **1997**, *119*, 5773. (l) Arnold, W. and Mohr, P., *Synlett*, **1996**, 1215. (m) Vasiljeva, L. L.; Manukina, T. A.; Demin, P. M.; Lapitskaja, M. A. and Pivnitsky, K. K., *Tetrahedron*, **1993**, *49*, 4099. (n) Luthria, D. L. and Sprecher, H., *Lipids*, **1993**, *28*, 853. (o) Chapuis, C., *Tetrahedron Lett*., **1992**, *33*, 2461. (p) Robins, M. J.; Manfredini, S.; Wood, S. G.; Wanklin, R. J.; Rennie, B. A. and Sacks, S. L., *J. Med. Chem.,* **1991**, *34*, 2275. (q) Nicolaou, K. C.; Marron, B. E.; Veale, C. A.; Webber, S. E. and Serhan, C. N., *J. Org. Chem.*, **1989**, *54*, 5527. (r) Nicolaou, K. C.; Marron, B. E.; Veale, C. A.; Webber, S. E.; Dahlen, S. E.; Samuelsson, B. and Serhan, C. N., *Biochim. Biophys. Acta, Lipids & Lipid Metabolism*, **1989**, *1003*, 44. (s) Hahn, S.; Stoilov, I. L.; Ha, T. B. T.; Raederstorff, D.; Doss, G. A.; Li, H. T. and Djerassi, C., *J. Am. Chem. Soc.*, **1988**, *110*, 8117. (t) Roush, W. R.; Straub, J. A. and Brown, R. J., *J. Org. Chem.*, **1987**, *52*, 5127. (u) Corey, E. J.; Shih, C.; Shih, N. Y. and Shimoji, K., *Tetrahedron Lett*., **1984**, *25*, 5013. (v) Hermeling, D. and Schaefer, H. J., *Angew. Chem.*, **1984**, *96*, 238. (w) Rosenberger, M.; Newkom, C. and Aig, E. R., *J. Am. Chem. Soc.*, **1983**, *105*, 3656. (x) Cohen, N.; Banner, B. L.; Lopresti, R. J.; Wong, F.; Rosenberger, M.; Liu, Y.-Y.; Thom, E. and Liebman, A. A., *J. Am. Chem. Soc.,* **1983**, *105*, 3661. (y) Priebe, H. and Hopf, H., *Angew. Chem.*, **1982**, *94*, 299. (z) Baker, R. and Rao, V. B., *J. Chem. Soc., Perkin Trans. I*, **1982**, 67. (aa) Lang, R. W. and Djerassi, C., *J. Org. Chem.*, **1982**, *47*, 625. (bb) Roush, W. R.; Gillis, H. R. and Hall, S. E., *Tetrahedron Lett*., **1980**, *21*, 1023. (cc) L'vova, S. D.; Kozlov, Yu. P. and Gunar, V. I., *Zh. Obsh. Khim.*, **1977**, *47*, 1251. (dd) Meyer, H. H., *Tetrahedron Lett*., **1975**, 3221. (ee) Stork, G.; Kowalski, C. and Garcia, G., *J. Am. Chem. Soc.*, **1975**, *97*, 3258. (ff) Lindlar, H. and Dubuis,

R., *Org. Synth. Coll. 5*, **1973**, 880. (gg) Corey, E. J.; Fleet, G. W. J. and Kato, M., *Tetrahedron Lett.*, **1973**, 3963. (hh) Murray, R. D. H.; Hogg, T. C.; Ballantyne, M. M. and McCabe, P. H., *Tetrahedron Lett*., **1971**, 3317. (ii) Stork, G. and Raucher, S., *J. Am. Chem. Soc.*, **1970**, *92*, 1583. (jj) Gutmann, H. and Lindlar, H., "Partial Catalytic Hydrogenation of Autylenes," ed. Viele, H.G., Marcle Dekker, New York, **1969**, pp. 355–364. (kk) Hubert, A. J., *J. Chem. Soc.*, **1965**, 6669. (ll) Dobson, N. A.; Eglinton, G.; Krishnamurti, M.; Raphael, R. A. and Willis, R. G., *Tetrahedron*, **1961**, *16*, 16. (mm) Isler, O.; Ronco, A.; Guex, W.; Hindley, N. C.; Huber, W.; Dialer, K. and Kofler, M., *Helv. Chim. Acta*, **1949**, *32*, 489.

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Lobry de Bruyn-Alberda van Ekenstein Transformation

(Lobry de Bruyn-van Ekenstein Transformation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Lobry de Bruyn in 1895,[1] and explored extensively by Lobry de Bruyn and Alberda van Ekenstein.[2] It is the reciprocal interconversion of carbohydrates into their isomers in an alkaline solution through the enediolic intermediate. The name of reaction given here is probably the only one time the full name of the people who discovered such reaction. It is known as the Lobry de Bruyn-Alberda van Ekenstein rearrangement,[3] Lobry de Bruyn-Alberda van Ekenstein transformation,[3f,4] Lobry de Bruyn-Albreda van Ekenstein C-2 epimerization,[5] or Lobry de Bruyn-van Ekenstein transformation.[6]

It is a very general glycochemical reaction[3b] catalyzed by hydroxide, regardless of the counterions, and depends only on the base concentration and temperature.[7] For example, the treatment of glucose by either KOH, NaOH, NH_4OH, $Mg(OH)_2$, Na_2CO_3, or K_2CO_3 will end up with the same equilibrium between glucose, mannose, and fructose.[7] Likewise, galactose can form an equilibrium with tagatose and talose.[8] It is found that such interconversion catalyzed by a base is essentially similar to the group transfer reaction of glucose-6-phosphate catalyzed by isomerase.[3b,9] It is interesting that sorbose does not occur in such a transformation;[10] and under treatment of lead hydroxide, glucose yields only mannose, and fructose gives neither of its corresponding aldose isomers (i.e., glucose and mannose).[7] In addition, it has been found that carbohydrates may degrade under basic conditions to lower analogs via retro-aldol condensation.[4c,8]

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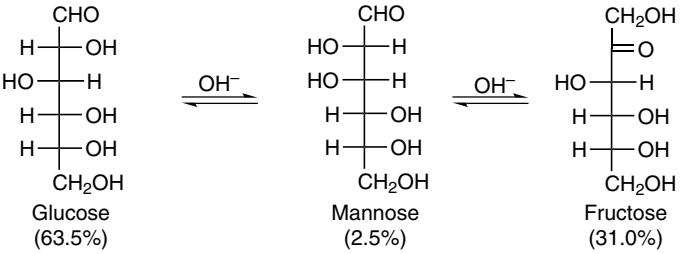
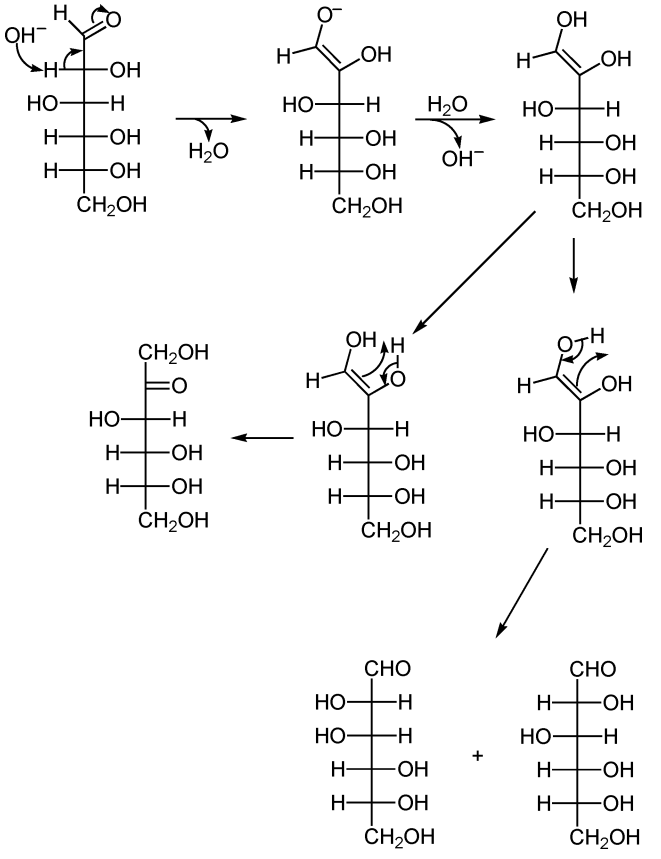
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

An interchange from glucose to mannose and fructose is illustrated here; a similar conversion from fructose or mannose to glucose can be depicted likewise.



D. MODIFICATION

N/A

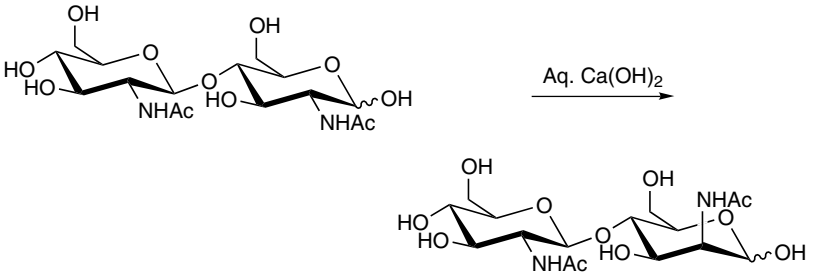
E. APPLICATIONS

This reaction can be used to prepare carbohydrate isomers on the basis of available carbohydrate molecules.

F. RELATED REACTIONS

This reaction is related to the *Aldol Condensation*.

G. CITED EXPERIMENTAL EXAMPLES



23% conversion; starting material was then degraded by β-*N*-acetylhexosaminidase, and the mixture was separated by gel filtration column with 18% yield

Reference 5.

N,*N*′-Diacetylchitobiose (500 mg, 1.18 mmol) was dissolved in 25 mL saturated lime solution and left overnight at laboratory temperature. Dowex 50WX2 in H^+ form was used for the neutralization and the removal of Ca^{2+} ions. The mixture was evaporated and dissolved in 25 mL 50 mM citrate-phosphate buffer (pH 5.3) and the *β*-*N*-acetylhexosaminidase from *Aspergillus oryzae* (20 U) was added. The mixture was incubated at 37°C (typically 2 h) until all *N*,*N*′-diacetylchitobiose had disappeared (TLC). The enzyme was then deactivated by 5 min boiling, and the mixture was evaporated to 1–2 mL. The sample was loaded onto a Bio Gel P2 column (2.6 × 80 cm, flow rate 12 mL/h, void volume 190 mL) and eluted with H_2O to afforded 18% 4-*O*-(2-acetamido-2-deoxy-*β*-D-glucopyranosyl)-2-acetamido-2-deoxy-D-mannopyranose.

Other references related to the Lobry de Bruyn-Alberda van Ekenstein transformation are cited in literature.[11]

H. REFERENCES

1. de Bruyn, L., *Rec. Trav. Chim.*, **1895**, *14*, 156.
2. (a) de Bruyn, L. and van Ekenstein, A., *Rec. Trav. Chim.*, **1895**, *14*, 203. (b) de Bruyn, L. and van Ekenstein, A., *Rec. Trav. Chim.,* **1896**, *15*, 92. (c) de Bruyn, L. and van Ekenstein, A., *Rec. Trav. Chim.,* **1897**, *16*, 257. (d) de Bruyn, L. and van Ekenstein, A., *Rec. Trav. Chim.,* **1897**, *16*, 262. (e) de Bruyn, L. and van Ekenstein, A., *Rec. Trav. Chim.,* **1897**, *16*, 282. (f) de Bruyn, L. and van

Ekenstein, A., *Rec. Trav. Chim.,* **1899**, *18*, 147. (g) de Bruyn, L. and van Ekenstein, A., *Rec. Trav. Chim.,* **1900**, *19*, 1.

3. (a) Schimpf, S.; Louis, C. and Claus, P., *Appl. Catal. A: General*, **2007**, *318*, 45. (b) Hirabayashi, J., *Trends Glycosci. Glycotech.*, **2004**, *16*, 63. (c) Rada-Mendoza, M.; Villamiel. M. and Olano, A., *Lait*, **2002**, *82*, 629. (d) Sedmera, P.; Prikrylová, V.; Bezouška, K.; Rajnochová, E.; Thiem, J. and Kren, V., *J. Carbohydr. Chem.*, **1998**, *17*, 1351. (e) Koell, P. and Papert, G., *Liebigs Annalen Chem.*, **1986**, 1568. (f) Tilley, B. E.; Porter, D. W. and Gracy, R. W., *Carbohydr. Res.*, **1973**, *27*, 289. (g) Mizuno, T., *Kagaku Ryoiki*, **1972**, *26*, 762.
4. (a) Ekeberg, D.; Morgenlie, S. and Stenstrom, Y., *Carbohydr. Res.*, **2005**, *340*, 373. (b) Paquette, L. A. and Hofferberth, J. E., *Org. React.,* **2003**, *62*, 477. (c) Kabyemela, B. M.; Adschiri, T.; Malaluan, R. M. and Arai, K., *Ind. Eng. Chem. Res.* **1999**, *38*, 2888. (d) Yaylayan, V. A.; Ismail, A. A. and Huyghues-Despointes, Al., *Special Pub. - Royal Soc. Chem.*, **1994**, *151*, 69. (e) Walker, T. E.; Unkefer, C. J. and Ehler, D. S., *J. Carbohydr. Chem.*, **1988**, *7*, 115. (f) Andrews, G. R. and Prasad, S. K., *J. Dairy Res.*, **19**87, *54*, 207. (g) Hatt, B. W., *Chem. Ind. (London)*, **1975**, 617. (h) Brooks, R. D., "A Kinetic Study of the Rate of Cleavage of the Glycosidic Bond of Methyl-b-Glucopyranoside in an Alkaline Medium," doctoral thesis, the Institute of Paper Chemistry, Appleton Wisconsin, Jan. **1966**. (i) Sumere, C. F. van and Kint, J., *Mededel. Vlaanse Chem. Ver.*, **1964**, *26*, 63. (j) Siddiqui, I. R. and Purves, C. B., *Can. J. Chem.*, **1963**, *41*, 382.
5. Hušáková, L.; Herkommerová-Rajnochová, E.; Semenuk, T.; Kuzma, M.; Rauvolfová, J.; Prikrylová, V.; Ettrich, R.; Plíhal, O.; Bezouška, K. and Křen, V., *Adv. Synth. Catal.*, **2003**, *345*, 735.
6. (a) Sauerbrei, B.; Niggemann, J.; Groeger, S.; Lee, S. and Floss, H. G., *Carbohydr. Res.*, **1996**, *280*, 223. (b) Adachi, S., *Nippon Nogei Kagaku Kaishi*, **1959**, *33*, 809. (c) Gottfried, J. B. and Benjamin, D. G., *J. Ind. Eng. Chem.,* **1952**, *44*, 141. (d) Mathews, J. A. and Jackson, R. F., *Bur. Standards J. Res*., **1933**, *11*, 619. (e) Hibbert, H.; Platt, M. E. and Carter, N. M., *J. Am. Chem. Soc.*, **1929**, *51*, 3644. (f) Groot, J., *Biochem. Zeitsch.*, **1924**, *146*, 72.
7. Evans, W. L., *Chem. Rev.*, **1942**, *31*, 537.
8. Evans, W. L., *Chem. Rev.*, **1929**, *6*, 281.
9. de Raadt, A.; Ekhart, C. W. and Stuetz, A. E., *Adv. Detailed React. Mech.*, **1995**, *4*, 175. [*Chem. Abstr.*, **1996**, *124*, 146594].
10. Hirabayashi, J., *Viva Origino*, **2001**, *29*, 119.
11. (a) Peters, S.; Lichtenthaler, F. W. and Lindner, H. J., *Tetrahedron: Assymetry*, **2003**, *14*, 2475. (b) Shashikala, V. and Rangappa, K. S., *J. Carbohydr. Chem.*, **2002**, *21*, 219. (c) Petruš, L.; Petrušová, M. and Hricovíniová, Z., *Top. Curr. Chem.*, **2001**, *215*, 15. (d) Angyal, S. J., *Top. Curr. Chem*., **2001**, *215*, 1. (e) Campa, C.; Donati, I.; Vetere, A.; Gamini, A. and Paoletti, S., *J. Carbohydr. Chem.,* **2001**, *20*, 263. (f) Nath, N. and Singh, M. P., *J. Phys. Chem.*, **1965**, *69*, 2038. (g) Schaffer, R., *J. Org. Chem*., **1964**, *29*, 1473. (h) Richards, E. L. and Chandrasekhara, M. R., *J. Dairy Res*., **1960**, *27*, 59. (i) Sowden, J. C. and Thompson, R. R., *J. Am. Chem. Soc*., **1958**, *80*, 1435. (j) Speck, J. C., *Adv. Carbohydr. Chem*., **1953**, *13*, 63. (k) Sowden, J. C. and Schaffer, R., *J. Am. Chem. Soc*., **1952**, *74*, 499. (l) Sowden, J. C. and Schaffer, R., *J. Am. Chem. Soc*., **1952**, *74*, 505. (m) Gardner, T. S., *J. Org. Chem.*, **1943**, *8*, 111. (n) Kreider, L. C. and Evans, W. L., *J. Am. Chem. Soc.*, **1936**, *58*, 1661. (o) Simons, J. H. and Struck, H. C., *J. Am. Chem. Soc.*, **1934**, *56*, 1947. (p) Wolfrom, M. L. and Lewis, W. L., *J. Am. Chem. Soc.*, **1928**, *50*, 837. (q) Evans, W. L. and Cornthwaite, W. R., *J. Am. Chem. Soc.*, **1928**, *50*, 486. (r) Evans, W. L. and O'Donnell, D. C., *J. Am. Chem. Soc*., **1928**, *50*, 2543. (s) Evans, W. L.; Edgar, R. H. and Hoff, G. P., *J. Am. Chem. Soc.*, **1926**, *48*, 2665. (t) Evans, W. L. and Hass, H. B., *J. Am. Chem. Soc.*, **1926**, *48*, 2703. (u) Evans, W. L.; Buehler, C. A.; Looker, C. D.; Crawford, R. A. and Holl, C. W., *J. Am. Chem. Soc.*, **1925**, *47*, 3085. (v) Nef, J. U., *Ann.*, **1914**, *403*, 204. (w) Nef, J. U., *Ann.*, **1907**, *357*, 214.

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Lombardo Methylenation
(Lombardo Olefination, Lombardo Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Lombardo in 1982.[1] It is a modification of the *Takai-Nozaki Methylenation*[2] (also known as the *Nozaki-Hayashe Methylenation*[3]) to convert ketones/aldehydes into alkenes using the "low temperature aged" carbenoid reagent generated from zinc, dibromomethane, and $TiCl_4$. Therefore, this reaction is known as the Lombardo methylenation,[2,4] Lombardo olefination[5] or Lombardo reaction;[2,6] and the combination of $Zn/CH_2Br_2/TiCl_4$ is known as the Lombardo reagent[4a,4e,5b,6a,7] or Lombardo's reagent.[8] However, because this reaction is closely related to the condition reported by Takai, Oshima and co-workers in 1978,[9] this reaction is also referred to as the Lombardo-Oshima methylenation,[7b,10] Lombardo-Takai olefination[11] or Takai/Oshima-Lombardo methylenation;[12] and the Lombardo reagent is also referred to as the Lombardo-Oshima reagent.[10]

The Lombardo reagent is usually prepared by addition of $TiCl_4$ to a precooled suspension of zinc dust in a solution of dibromomethane in dry THF at very low temperature (e.g., $-40^\circ C$), and aged for 2 days at $4^\circ C$ before the methylenation.[4a] Different from the *Wittig Reaction*, the Lombardo methylenation is highly selective and occurs under nonbasic conditions.[13] This reaction is especially valuable for the methylenation of keto ester, for which the *Wittig Reaction* fails,[14] and for the olefination of β,γ-unsaturated enones without enolization.[15] Thus the Lombardo methylenation is an alternative olefination method when *Wittig Reaction* or *Tebbe Olefination* is not applicable.[3,10,11b,13,16] However, it also

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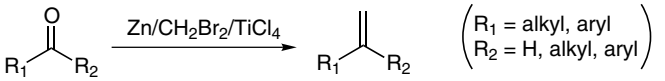
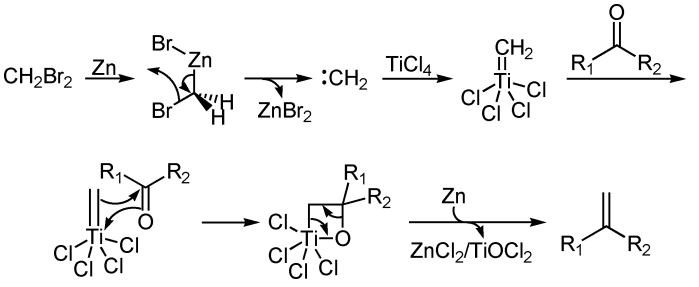
has some disadvantages, such as the lengthy preparation of the reagent,[6a] the heterogenous nature of the reaction condition,[6a] the need for a large excess of reagent,[11] and the low yield in conversion of ketene into allene.[6a] An excess amount of reagent makes the workup and isolation very difficult.[11]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is plausible that the Lombardo methylenation proceeds via an analogous pathway of *Tebbe Olefination*, as illustrated below.



D. MODIFICATION

N/A

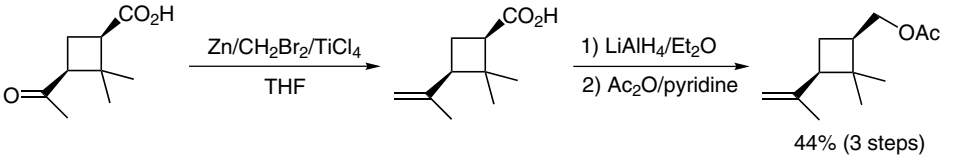
E. APPLICATIONS

This reaction has been widely used for the methylenation of carbonyl functionality.

F. RELATED REACTIONS

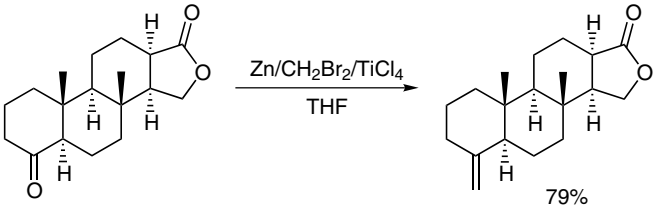
This reaction is related to the *Takai Olefination* and *Tebbe Olefination*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 17.

To a suspension of 24.9 g activated zinc (381 mmol, 10.9 eq.) in 150 mL anhydrous THF with 10 mL dibromomethane (142.5 mmol, 4.1 eq.) cooled at −45°C, was added 12.0 mL $TiCl_4$ (109 mmol, 3.1 eq.) dropwise. When the formation of yellow smoke had subsided, the mixture was warmed to 0°C and maintained with good stirring for 2 days. Anhydrous CH_2Cl_2 (40 mL) was added, followed by the dropwise addition of 5.97 g (+)-(1*R*)-*cis*-2,2-dimethyl-3-acetyl-cyclobutanecarboxylic acid (35.1 mmol) in 35 mL CH_2Cl_2. The mixture was stirred for 30 min and then at room temperature for 3 h. To this reaction mixture was then added 100 mL hexane and 1.5 *N* HCl (slow initially, total 140 mL). The mixture was stirred for 30 min and then separated. The aqueous layer was extracted with hexane twice, and the combined extracts were dried over Na_2SO_4, filtered, and evaporated to afford (+)-(1*R*)-*cis*-2,2-dimethyl-3-isopropenyl-cyclobutanecarboxylic acid. The acid was immediately taken up by Et_2O and reduced with $LiAlH_4$ to prevent epimerization and finally transformed into corresponding acetic acid ester: (+)-(1*R*)-*cis*-2,2-dimethyl-3-isopropenyl-cyclobutane-methyl acetate, in a total of 44% yield, b.p. 83–86°C.



Reference 7a.

A 10 mL 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (10 mmol) was added dropwise over 10 min to a vigorously stirred suspension of 2.87 g activated zinc dust (44.0 mmol) and dibromethane (1.01 mL, 2.43 g, 14.0 mmol) in 25 mL THF at −40°C. The mixture was warmed to 0°C, and then stirred in a cold room at 0°C for 18 h. A portion (0.5 mL) of this Lombardo reagent was added dropwise over 5 min to a solution of 10 mg (5b,13a)- and (5a,13a)-8-methyl-18-nor-16-oxaandrostan-4,17-dione (0.0344 mmol) in 1 mL CH_2Cl_2 at 0°C, and the reaction was then stirred at 0°C for 30 min. The mixture was poured into 15 mL saturated aqueous $NaHCO_3$ and then extracted with 20 mL Et_2O. The separated organic phase was washed with 20 mL water, and both separated aqueous layers were then

extracted with 20 mL Et_2O. The combined organic extracts were dried over $MgSO_4$ and then evaporated in vacuo. Chromatography of the residue on silica gel using EtOAc/light petroleum (b.p. 40–60°C) (3:17) as the eluent gave 7.8 mg (5a,13a)-8-methyl-4-methylene-18-nor-16-oxaandrostan-17-one as white needles, m.p. 130–135°C, in a yield of 79%.

Other references related to the Lombardo methylenation are cited in the literature.[18]

H. REFERENCES

1. Lombardo, L., *Tetrahedron Lett.*, **1982**, *23*, 4293.
2. Mander, L. N., *Nat. Prod. Rep.*, **2003**, *20*, 49.
3. King, G. R.; Mander, L. N.; Monck, N. J. T.; Morris, J. C. and Zhang, H. B., *J. Am. Chem. Soc.*, **1997**, *119*, 3828.
4. (a) Morrison, J. P.; Read, J. A.; Coleman, W. G. and Tanner, M. E., *Biochemistry,* **2005**, **44**, 5907. (b) Wengel, J.; Svendsen, M. L.; Joergensen, P. N. and Nielsen, C., *Nucleosides & Nucleotides*, **1995**, *14*, 1465. (c) Curran, D. P. and Shen, W., *Tetrahedron*, **1993**, *49*, 755. (d) Nemoto, H.; Nagamochi, M. and Fukumoto, K., *J. Chem. Soc., Chem. Commun.*, **1992**, 1695. (e) Plamondon, L. and Wuest, J. D., *J. Org. Chem.*, **1991**, *56*, 2076.
5. (a) Giacomini, R. A.; Miranda, P. C. M. de L.; Baptistella, L. H. B. and Imamura, P. M., *ARKIVOC*, **2003**, (*x*), 314. (b) Vedejs, E.; Dent, W. H.; Kendall, J. T. and Oliver, P. A., *J. Am. Chem. Soc.*, **1996**, *118*, 3556.
6. (a) Marsden, S. P. and Ducept, P. C., *Beilstein J. Org. Chem.*, **2005**, *1*, 5. (b) Hodgson, D. M. and Boulton, L. T., *Preparation of Alkenes*, **1996**, 81.
7. (a) Pattenden, G.; Roberts, L. and Blake, A. J., *J. Chem. Soc., Perkin Trans. I*, **1998**, 863. (b) Pour, M.; Kraft-Klaunzer, P.; Furber, M.; Mander, L. N.; Twitchin, B.; Oyama, N.; Murofushi, N.; Yamane, H. and Yamauchi, T., *Aust. J. Chem.*, **1997**, *50*, 289. (c) Huang, H. and Forsyth, C. J., *J. Org. Chem.*, **1995**, *60*, 5746. (d) Mlinaric-Majerski, K.; Vinkovic, M. and Fry, J. L., *J. Org. Chem.*, **1994**, *59*, 664. (e) Mlinaric-Majerski, K.; Pavlovic, D. and Sindler-Kulyk, M., *J. Org. Chem.*, **1993**, *58*, 252. (f) Plamondon, L. and Wuest, J. D., *J. Org. Chem.*, **1991**, *56*, 2066. (g) Magnus, P.; Mugrage, B.; DeLuca, M. R. and Cain, G. A., *J. Am. Chem. Soc.*, **1990**, *112*, 5220. (h) Udodong, U. E. and Fraser-Reid, B., *J. Org. Chem.*, **1989**, *54*, 2103.
8. (a) Lebel, H. and Paquet, V., *J. Am. Chem. Soc.*, **2004**, *126*, 320. (b) Shook, C. A.; Romberger, M. L.; Jung, S.-H.; Xiao, M. C.; Sherbine, J. P.; Zhang, B. R.; Lin, F.-T. and Cohen, T., *J. Am. Chem. Soc.*, **1993**, *115*, 10754. (c) Jasperse, C. P. and Curran, D. P., *J. Am. Chem. Soc.*, **1990**, *112*, 5601.
9. Takai, K.; Hotta, Y.; Oshima, K. and Nozaki, H., *Tetrahedron Lett.*, **1978**, 2417.
10. Furber, M.; Kraft-Klaunzer, P.; Mander, L. N.; Pour, M.; Yamauchi, T.; Murofushi, N.; Yamane, H. and Schraudolf, H., *Aust. J. Chem.*, **1995**, *48*, 427.
11. (a) Pérez-Hernández, N.; Febles, M.; Pérez, C.; Pérez, R.; Rodríguez, M. L.; Foces-Foces, C. and Martín, J. D., *J. Org. Chem.*, **2006**, *71*, 1139. (b) Urbanek, R. A.; Sabes, S. F. and Forsyth, C. J., *J. Am. Chem. Soc.*, **1998**,*120*, 2523.
12. Zhang, L. M. and Koreeda, M., *Org. Lett.*, **2004**, *6*, 537.
13. Stoermer, D.; Caron, S. and Heathcock, C. H., *J. Org. Chem.*, **1996**, **61**, 9115.
14. Srikrishna, A.; Nagamani, S. A. and Jagadeesh, S. G., *Tetrahedron: Asymmetry*, **2005**, *16*, 1569.
15. Rigby, J. H. and Senanayake, C., *J. Am. Chem. Soc.*, **1987**, *109*, 3147.
16. Jamison, T. F.; Shambayati, S.; Crowe, W. E. and Schreiber, S. L., *J. Am. Chem. Soc.*, **1997**, *119*, 4353.
17. Passaro, L. C. and Webster, F. X., *J. Agric. Food Chem.*, **2004**, **52**, 2896.

18. (a) Colby, E. A.; O'Brien, K. C. and Jamison, T. F., *J. Am. Chem. Soc.*, **2005**, *127*, 4297. (b) Reddy, P. G. and Baskaran, S., *J. Org. Chem.*, **2004**, *69*, 3093. (c) Normant, J. F., *Acc. Chem. Res.*, **2001**, *34*, 640. (d) Laird, T. and Hermitage, S. A., *Org. Proc. Res. Dev.*, **2001**, *5*, 544. (e) Lebel, H.; Paquet, V. and Proulx, C., *Angew. Chem. Int. Ed.*, **2001**, *40*, 2887. (f) Wirth, T. and Fragale, G., *Synthesis*, **1998**, 162. (g) Iwasaki, T.; Suzuki, M.; Furukawa, T.; Tsushima, K.; Ishiwatari, T. and Tsuchiya, T., *U.S. Pat*., Aug. 27, **1996**, 5,550,258. (h) Ward, D. E.; Gai, Y. Z. and Kaller, B. F., *J. Org. Chem.*, **1996**, *61*, 5498. (i) Lombardo, L., *Org. Synth. Coll,* **1993**, *31*, 386. (j) Sorensen, T. S. and Whitworth, S. M., *J. Am. Chem. Soc.*, **1990**, *112*, 8135. (k) Furber, M.; Mander, L. N. and Patrick, G. L., *J. Org. Chem.*, **1990**, *55*, 4860. (l) Takai, K.; Fujimura, O.; Kataoka, Y. and Utimoto, K., *Tetrahedron Lett.*, **1989**, *30*, 211. (m) Ekhato, I. V. and Robinson, C. H., *J. Org. Chem.*, **1989**, *54*, 1327. (n) Magnus, P.; Slater, M. J. and Principe, L. M., *J. Org. Chem.*, **1989**, *54*, 5148. (o) Furber, M. and Mander, L. N., *J. Am. Chem. Soc.*, **1988**, *110*, 4084. (p) Shelly, K. P. and Weiler, L., *Can. J. Chem.*, **1988**, *66*, 1359. (q) Rigby, J. H. and Wilson, J. A. Z., *J. Org. Chem.*, **1987**, *52*, 34. (r) Hibino, J.; Okazoe, T.; Takai, K. and Nozaki, H., *Tetrahedron Lett*., **1985**, *26*, 5579. (s) Lombardo, L. and Mander, L. N., *J. Org. Chem.*, **1983**, *48*, 2298. (t) Lombardo, L.; Mander, L. N. and Turner, J. V., *J. Am. Chem. Soc.*, **1980**, *102*, 6626.

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Lossen Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Lossen in 1872.[1] It is a thermal or alkaline conversion of hydroxamic acid into an isocyanate via the intermediacy of its *O*-acyl, sulfonyl, or phosphoryl derivative. In the presence of water, amine, or alcohol, the isocyanate is converted into amine, urea or urethane, respectively. Therefore, this reaction is generally known as the Lossen rearrangement.[2,3] Occasionally, it is also referred to as the Lossen reaction,[4] Lossen degradation,[5] or Lossen transformation.[6]

Initially, this reaction was thought to occur via a similar mechanism of *Curtius Rearrangement* or *Hofmann Rearrangement*[7] by means of the formation of an univalent nitrogen intermediate (known as nitrene), from which the alkyl group migrates from the carbon to the nitrogen atom to form isocyanate.[7] However, such idea of the reaction mechanism is challenged on the basis of the modern valence theory, thus a few mechanisms are proposed to rationalize the Lossen rearrangement,[2k,2n,3bb,4c,4f] including the one proposed by Jones and Hurd.[8] In addition, the recently accepted mechanism[2k,2n,3bb,4c,4f] involves the deprotonation of N-H from a base, followed by the concurrent migration of an alkyl group and release of a carboxylate (or sulfonate or phosphonate) if the hydroxamic acid is activated by an acyl group (or correspondingly by a sulfonyl or phosphoryl group[2n]). It has been found that the rearrangement rate is directly proportional to the acidity of the leaving group or the conjugate acid of the leaving group if the leaving group is an anion;[2h] in addition, in the case of *O*-benzoyl phenylhydroxamic acid, the electron-donating group on the phenyl and electron-withdrawing group on the benzoyl moiety will facilitate the rearrangement, especially when these substituents are in the *meta*- or *para*-positions.[4c] It has been

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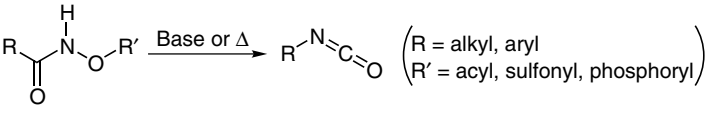
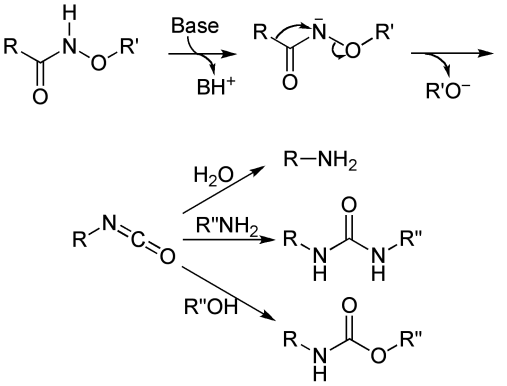
found that the stereochemistry of the migrating group is retained after the migration.[2l,3bb] Unfortunately, because of the intrinsic self-condensation reaction between the hydroxamic acid and the isocyanate, and the general unavailability of hydroxamic acid,[2b] this reaction had not been widely used in organic synthesis until recent modifications.[2f] In fact, the desired hydroxamic acid can easily be prepared from the reaction between hydroxamine and acyl halide, ester, or anhydride.[3bb] The Lossen rearrangement has been modified by the addition of a water-soluble carbodiimide,[2j] application of lithium aluminum hydride as base and reducing reagent,[2m] or protection of hydroxamic acid with a *t*-butylcarboxyl group[2b] as well as carrying out the reaction in the presence of formamide[2f] and using an enzyme to catalyze the reaction.[2e,3x]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A simple mechanism is depicted here for this rearrangement, including the formation of isocyanate derivatives.



D. MODIFICATION

This reaction has been modified to occur under different conditions, such as the addition of carbodiimide, and formamide, as described in Section A.

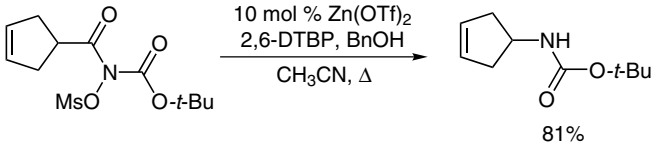
E. APPLICATIONS

This reaction has general application in the preparation of amine, urea, and urethane derivatives.

F. RELATED REACTIONS

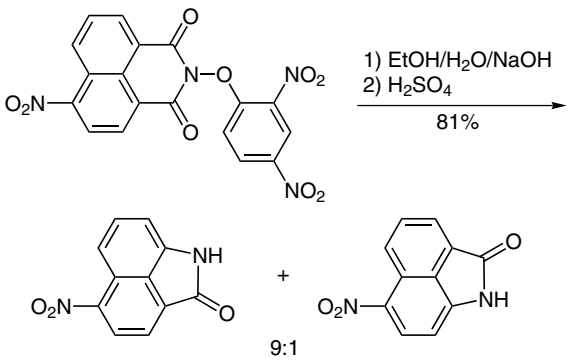
This reaction is related to the *Curtius Rearrangement* and *Hofmann Rearrangement*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2b.

To a solution of 610 mg *N*-(*t*-butyloxycarbonyl)-*N*-(methanesulfonyloxy)cyclopent-3-enylcarboxamide (2.0 mmol) in 10 mL CH_3CN were added 238 mg benzyl alcohol (2.2 mmol), 382 mg 2,6-di-*t*-butylpyridine (2.0 mmol), and 72 mg zinc triflate (0.2 mmol). The mixture was heated with stirring at 85°C for 16 h and then cooled to room temperature. It was then diluted with 50 mL EtOAc, washed with water, 1 M H_3PO_4, and brine (50 mL each). The combined aqueous layers were back extracted with ethyl acetate (2 × 50 mL); the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was flash chromatographed (4:1, hexanes/EtOAc) to afford 352 mg *N*-(benzyloxycarbonyl)cyclopent-3-enylamine as a colorless solid, in a yield of 81%, m.p. 50–52°C.



Reference 9.

To a 22-L, of clean, three-necked flask were added 4.650 L deionized water and 10.75 L absolute ethanol. To this solution was added 236 g NaOH (5.9 mol, 4.04 eq.). The resultant solution was cooled to 10°C, and 620 g *N*-(2,4-dinitrophenoxy)-4-nitronaphthalimide (1.46 mol, 1.0 eq.) was added. The mixture was stirred for 44 h at ambient temperature until the completion was detected by TLC ($CHCl_3$/MeOH, 95:5). The pH was adjusted to 3 with 175 mL conc. H_2SO_4, and the mixture was cooled to < 10°C and filtered. The wet filter cake was reslurried in 3 L deionized water, and the pH was adjusted to 7–8 by the addition of saturated aqueous $NaHCO_3$ solution. The mixture was filtered, washed with water and 95% ethanol, and dried under vacuum to yield 254 g 5-nitrobenz[*cd*]indol-2(1*H*)-one, in a yield of 81%. ^{1}HNMR analysis of the product showed that the product was contaminated with ~10% of the regioisomer 6-nitrobenz[*cd*]indol-2(1*H*)-one.

Other references related to the Lossen rearrangement are cited in the literature.[10]

H. REFERENCES

1. Lossen, W., *Ann.*, **1872**, *161*, 347.
2. (a) Zalipsky, S., *Chem. Commun.*, **1998**, 69. (b) Stafford, J. A.; Gonzales, S. S.; Barrett, D. G.; Suh, E. M. and Feldman, P. L., *J. Org. Chem.,* **1998**, *63*, 10040. (c) Hirrlinger, B. and Stolz, A., *Appl. Environ. Microbio.*, **1997**, *63*, 3390. (d) Salomon, C. J. and Breuer, E., *J. Org. Chem.*, **1997**, *62*, 3858. (e) Groutas, W. C.; Stanga, M. A. and Brubaker, M. J., *J. Am. Chem. Soc.*, **1989**, *111*, 1931. (f) Eckstein, Z.; Jadach, T. and Lipczynska-Kochany, E., *J. Chem. Eng. Data*, **1983**, *28*, 279. (g) Tserng, K.-Y. and Bauer, L., *J. Org. Chem.,* **1973**, *38*, 3498. (h) Swenson, J. S.; Davis, A. M.; Deyo, R. A.; Graham, B. W.; Jahn, E. P. and Mattice, J. D., *J. Org. Chem.*, **1973**, *38*, 3956. (i) Zvilichovsky, G., *J. Org. Chem.,* **1969**, *34*, 486. (j) Hoare, D. G.; Olson, A. and Koshland, D. E., *J. Am. Chem. Soc.*, **1968**, *90*, 1638. (k) Berndt, D. C. and Adams, W. J., *J. Org. Chem.*, **1966**, *31*, 976. (l) Bauer, L. and Miarka, S. V., *J. Org. Chem.*, **1959**, *24*, 1293. (m) Bauer, L., *J. Am. Chem. Soc.*, **1956**, *78*, 1945. (n) Stolberg, M. A.; Tweit, R. C.; Steinberg, G. M. and Wagner-Jauregg, T., *J. Am. Chem. Soc.*, **1955**, *77*, 765. (o) Hurd, C. D.; Bauer, L. and Klotz, I. M., *J. Am. Chem. Soc.*, **1953**, *75*, 624. (p) Franklin, E. C., *Chem. Rev.*, **1934**, 219.
3. (a) Yagupolskii, L. M.; Shelyazhenko, S. V.; Maletina, I. I.; Sokolenko, L. V.; Chernega, A. N.; Rusanov, E. B. and Tsymbal, I. F., *J. Fluor. Chem.*, **2007**, *128*, 515. (b) Needs, P. W.; Rigby, N. M.; Ring, S. G. and MacDougall, A. J., *Carbohydr. Res.*, **2001**, *333*, 47. (c) Abbady, M. S.; Kandeel, M. M. and Youssef, M. S. K., *Phosphorus, Sulfur & Silicon & Related Elements*, **2000**, *163*, 55. (d) Podlaha, J.; Cisarova, I.; Soukupova, L.; Schraml, J. and Exner, O., *J. Chem. Res. (S)*, **1998**, 520. (e) Casteel, D. A.; Gephart, R. S. and Morgan, T., *Heterocycles*, **1993**, *36*, 485. (f) Fawcett, J.; Harger, M. J. P. and Sreedharan-Menon, R., *J. Chem. Soc., Chem. Commun.*, **1992**, 227. (g) Adams, G. W.; Bowie, J. H. and Hayes, R. N., *J. Chem. Soc., Perkin Trans. II*, **1991**, 689. (h) Harger, M. J. P. and Smith, A., *J. Chem. Soc., Perkin Trans. I*, **1990**, 1447. (i) Pihuleac, J. and Bauer, L., *Synthesis*, **1989**, 61. (j) Groutas, W. C.; Giri, P. K.; Crowley, J. P.; Castrisos, J. C. and Brubaker, M. J., *Biochem. Biophys. Res. Commun.*, **1986**, *141*, 741. (k) Harger, M. J. P., *J. Chem. Soc., Perkin Trans. I*, **1983**, 2699. (l) Harris, R. B. and Wilson, I. B., *J. Biol. Chem.*, **1983**, *258*, 1357. (m) Van Verst, M. E.; Bell, C. L. and Bauer, L., *J. Heterocycl. Chem.*, **1979**, *16*, 1329. (n) Harger, M. J. P., *J. Chem. Soc., Chem. Commun.*, **1979**, 930. (o) Fahmy, A. F. M.; Aly, N. F.; Nada, A. and Aly, N. Y., *Bull. Chem. Soc. Jpn.*, **1977**, *50*, 2678. (p) Bergman, J.; Lindstroem, J. O.; Abrahamsson, J. and Hadler, E., *Tetrahedron Lett.*, **1976**, 3615. (q) Bittner, S.; Grinberg, S. and Kartoon, I., *Tetrahedron Lett.*, **1974**, 1965. (r) Dell, D.; Boreham, D. R. and Martin, B. K., *J. Pharm. Sci.*, **1971**, *60*, 1368. (s) Beck, W. and Lindenberg, B., *Angew. Chem. Int. Ed. Engl.*, **1970**, *9*, 735. (t) BeMiller, J. N. and Wisely, G. T., *Trans. Illinois State Acad. Sci.*, **1967**, *60*, 117.

(u) Bauer, L. and Mahajanshetti, C. S., *J. Heterocycl. Chem.*, **1967**, *4*, 325. (v) Gallop, P. M.; Seifter, S.; Lukin, M. and Meilman, E., *J. Biol. Chem.*, **1960**, *235*, 2619. (w) Behringer, H. and Meier, H., *Ann.*, **1957**, *607*, 67. (x) Ettlinger, M. G. and Lundeen, A. J., *J. Am. Chem. Soc.*, **1957**, *79*, 1764. (y) Andersen, W., *Acta Chem. Scand.*, **1954**, *8*, 1721. (z) Hurd, C. D. and Bauer, L., *J. Am. Chem. Soc.*, **1951**, *73*, 4387. (aa) Bright, R. D. and Hauser, C. R., *J. Am. Chem. Soc.*, **1939**, *61*, 618. (bb) Wallis, E. S. and Dripps, R. D., *J. Am. Chem. Soc.*, **1933**, *55*, 1701.

4. (a) Chandrasekhar, S. and Sridhar, M., *Tetrahedron: Asymmetry*, **2000**, *11*, 3467. (b) Knobler, Y.; Frydman, N. and Eliasoff, H., *Isr. J. Chem.*, **1971**, *9*, 165. (c) Berndt, D. C. and Shechter, H., *J. Org. Chem.*, **1964**, *29*, 916. (d) Snyder, H. R. and Elston, C. T., *J. Am. Chem. Soc.*, **1954**, *76*, 3039. (e) Wieland, T. and Fritz, H., *Chem. Ber.*, **1953**, *86*, 1186. (f) Renfrow, W. B. and Hauser, C. R., *J. Am. Chem. Soc.,* **1937**, *59*, 2308.
5. (a) Joensson, N. A. and Moses, P., *Acta Chem. Scand., Ser. B*, **1974**, *28*, 441. (b) Feinstein, G.; Bodlaender, P. and Shaw, E., *Biochemistry*, **1969**, *8*, 4949. (c) Holm, A., *Acta Chem. Scand.*, **1968**, *22*, 2019. (d) Bauer, L. and Mahajanshetti, C. S., *J. Heterocycl. Chem.*, **1968**, *5*, 331. (e) Lund, H., *Acta Chem. Scand.*, **1960**, *14*, 359.
6. Anilkumar, R.; Chandrasekhar, S. and Sridhar, M., *Tetrahedron Lett.*, **2000**, *41*, 5291.
7. (a) Stieglitz, J. and Leech, P. N., *J. Am. Chem. Soc.*, **1914**, *36*, 272. (b) Stieglitz, J., *Am. Chem. J.*, **1903**, *29*, 49. (c) Stieglitz, J., *Am. Chem. J.*, **1896**, *18*, 751.
8. Jones, L.W. and Hurd, C.D. *J. Am. Chem. Soc.*, **1921**, *43*, 2422. Jones, L.W. and Hurd, C.D.
9. Marzoni, G. and Varney, M. D., *Org. Proc. Res. Dev.*, **1997**, *1*, 81.
10. (a) Simanenko, Y. S.; Prokopeva, T. M.; Popov, A. F.; Bunton, C. A.; Karpichev, E. A.; Savelova, V. A. and Ghosh, K. K., *Russ. J. Org. Chem.*, **2004**, *40*, 1337. (b) Burungule, A. S.; Bondge, S. P.; Munde, S. B.; Bhingolikar, V. E. and Mane, R. A., *Synth. Commun.*, **2003**, *33*, 1923. (c) Dadd, M. R.; Claridge, T. D. W.; Pettman, A. J. and Knowles, C. J., *Biotechnology Lett.*, **2001**, *23*, 221. (d) Hecht, S. S., *Drug Metabol. Rev.*, **2000**, *32*, 395. (e) Shikita, M.; Fahey, J. W.; Golden, T. R.; Holtzclaw, W. D. and Talalay, P., *Biochem. J.*, **1999**, *341*, 725. (f) Horspool, K. R.; Stevens, M. F. G.; Newton, C. G.; Lunt, E.; Walsh, R. J. A.; Pedgrift, B. L.; Baig, G. U.; Lavelle, F. and Fizames, C., *J. Med. Chem.*, **1990**, *33*, 1393. (g) Lwowski, W.; de Mauriac, R. A.; Thompson, M.; Wilde, R. E. and Chen, S.-Y., *J. Org. Chem.*, **1975**, *40*, 2608. (h) Bauer, L. and Exner, O., *Angew. Chem. Int. Ed. Engl.*, **1974**, *13*, 376. (i) Linke, S.; Tisue, G. T. and Lwowski, W., *J. Am. Chem. Soc.*, **1967**, *89*, 6308. (j) Lwowski, W. and Scheiffele, E., *J. Am. Chem. Soc.*, **1965**, *87*, 4359. (k) Cohen, L. A. and Witkop, B., *Angew. Chem.*, **1961**, *73*, 260. (l) Walling, C. and Naglieri, A. N., *J. Am. Chem. Soc.*, **1960**, *82*, 1820. (m) Popp, F. D. and McEwen, W. E., *Chem. Rev.*, **1958**, *58*, 374. (n) Hurd, C. D.; Buess, C. M. and Bauer, L., *J. Org. Chem.*, **1952**, *17*, 865. (o) Hauser, C. R. and Kantor, S. W., *J. Am. Chem. Soc.*, **1950**, *72*, 4284. (p) Yale, H. L., *Chem. Rev.*, **1943**, *33*, 209. (q) Bright, R. D. and Hauser, C. R., *J. Am. Chem. Soc.*, **1939**, *61*, 618.

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Luche Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Luche in 1985.[1] It is the modification of the initial aqueous allylation of carbonyl compounds (in 1983) via the intermediacy of tin in the presence of a catalytic amount of hydrobromic acid (HBr),[2] to the zinc mediated allylation of carbonyl compounds using ultrasonic irradiation in saturated aqueous NH_4Cl/THF solution.[1] Thus the new reaction condition is referred to as the Luche reaction.[3] In parallel, Li[4] and Chan[5] extended the Barbier-Grignard-type reaction to successfully proceed in aqueous media and contributed to the new area called "green chemistry."[6]

As a weak acid, ammonium chloride is often added to the reaction media to activate the metal surface[1a] so that the yield can be dramatically enhanced.[7] However, it is intriguing that under acidic conditions, zinc reduces proton to hydrogen; in addition, the expected allylzinc intermediate reacts violently with water,[3b] but these strong trends do not burden the process of the Luche reaction. When 1,3-dichloropropene, preferably 3-iodo-1-chloropropene is used in this reaction, 1,3-butadienes are obtained; however, when this reaction is interrupted by base treatment after the initial allylation to carbonyl group, vinyloxiranes are obtained as final products.[8] It has been found that when both ketone and aldehyde groups exist, aldehyde reacts in preference;[1b] likewise, aromatic aldehyde prevails in this reaction in the presence of an aliphatic aldehyde.[4c] For the reaction between aldehyde and bromopropenyl methylcarbonate to give the rearranged allyl methylcarbonate, it has been found that a mixture of diastereomers are obtained, and the ratio of *syn*/*anti* depends on the nature of the aldehyde. For example, *syn* adducts are preferentially formed from the conjugated aldehydes whereas the *anti* adducts prevail when nonconjugated aldehydes are used.[9] Moreover, as Luche pointed out, in the presence of a catalytic amount of nickel acetylacetone [$Ni(acac)_2$], allylzinc bromide undergoes conjugate addition with α,β-unsaturated

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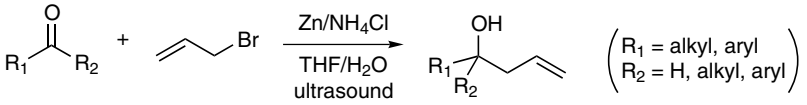
carbonyl compounds.[1c] However, the corresponding branched allylzinc chloride (e.g., 2-methyl allylzinc chloride) adds only to the carbonyl group of α,β-unsaturated compounds, even in the presence of nickel and a variety of ligands,[10] presumably due to the steric hindrance of the side chain. In addition, when a zinc-copper couple is used, alkyl halide reacts with α,β-unsaturated carbonyl compounds and nitriles via a conjugate addition under the conditions of the Luche reaction.[11,12] It is interesting that the allylation of carbonyl compounds with allyl bromide with terminal substituents undergoes γ-allylation rather than α-allylation, affording carbon skeleton rearranged products.[6a]

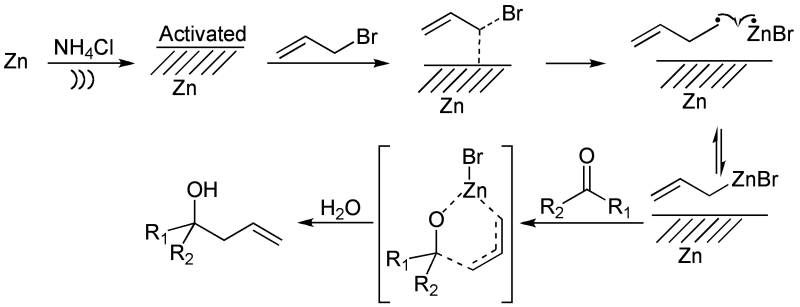
Besides zinc, some other metals have also been applied to facilitate the aqueous allylation of carbonyl compounds. It has been found that the combination of manganese and copper, even only a catalytic amount of copper in any oxidation state [e.g., Cu(0), Cu(I), or Cu(II)], is a highly regioselective mediator for the allylation of aromatic aldehydes in the presence of aliphatic aldehdyes, and this reaction is highly effective when combined with a catalytic amount of acetic acid or in aqueous NH_4Cl. The high regioselectivity is attributed to the difference in reductive potentials of the two types of aldehydes.[13] On the other hand, the metal indium—due to its lower first ionization potential than that of zinc, tin, and even magnesium and its insensitivity to boiling water or alkali—has been found to be the ideal mediator for the allylation of carbonyl compounds in aqueous solution. For example, the indium mediated allylation proceeds smoothly at room temperature without any other promoters; in addition, only a catalytic amount is needed in combination with zinc.[7]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Although the details of the mechanism are still under debate,[1a,14] the Luche reaction probably proceeds via radical mechanism,[3b,5a,15] similar to that of Barbier-Grignard-type reaction occurring in aqueous solution,[4d] as outlined here.



D. MODIFICATION

This reaction has been modified to proceed in aqueous solution using reverse-phase silica gel to substitute the co-solvent THF so that the slurry of zinc, C-18 silica gel, allyl bromide, and aldehyde are stirred in a saturated aqueous NH_4Cl solution at room temperature in an open vessel, affording comparable yields of products.[3b] In addition, when the combination of zinc and indium trichloride are used as the mediator, much cheaper allyl chloride is an effective allylation agent.[16] Moreover, other types of aqueous allylation protocols have been developed, including the application of gold,[4b] manganese,[4c,5b] magnesium,[4d] tin,[17] and indium.[18] Especially for the case of indium, acetylene can directly add to aldehyde in the presence of an indium salt;[6c] it is worth pointing out that the indium mediated reaction between the aldehydes and a propargyl bromide with a terminal aliphatic or aromatic substituent gives the allenylation products exclusively.[4e]

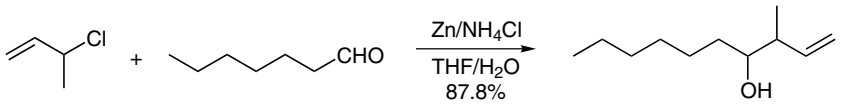
E. APPLICATIONS

This reaction has important application in modern organic synthesis, especially with respect to increasing environmental concerns.

F. RELATED REACTIONS

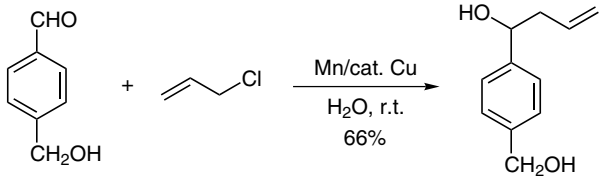
This reaction is related to the *Barbier Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 3b.

To a solution of 2.27 g heptaldehyde (19.9 mmol) in 20 mL saturated aqueous NH_4Cl and 4 mL THF, was added 1.56 g zinc (24 mmol) and 2.36 mL crotyl chloride (24 mmol). The reaction mixture exposed to the air was stirred overnight at room temperature, and the suspension (containing zinc salts) was then extracted with Et_2O, and the ether layer was dried over $MgSO_4$. Upon evaporation of Et_2O, the residue was quickly passed through a silica gel pad to afford 2.97 g 3-methyl-1-decen-4-ol as a 1:1 mixture of *erythro* to *threo* products, in a yield of 87.8%, $R_f = 0.5$ (EtOAc/hexane, 1:9).



Reference 5b.

To a 25-mL flask were added 136 mg 4-(hydroxylmethyl)benzaldehyde (1 mmol), allyl chloride (230 mg, 3 mmol), 165 mg manganese (3 mmol), 6.4 mg copper (0.1 mmol), and 2 mL water. The flask was stoppered and stirred vigorously at room temperature for 8 h followed by quenching with 1 *N* HCl and extracted with Et_2O. The combined ethereal solution was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography using hexanes/EtOAc (2:1) as the eluent to give 117 mg 1-(4-(hydroxymethyl) phenyl)-3-buten-1-ol, in a yield of 66%.

Other references related to the Luche reaction are cited in the literature.[19]

H. REFERENCES

1. (a) Pétrier, C. and Luche, J.-L., *J. Org. Chem.*, **1985**, *50*, 910. (b) Pétrier, C.; Einhorn, C. and Luche, J.-L., *Tetrahedron Lett.*, **1985**, *26*, 1449. (c) Pétrier, C.; Souza-Barbosa, J. C.; Dupuy, C. and Luche, J.-L., *J. Org. Chem.*, **1985**, *50*, 5761.
2. Nokami, J.; Otera, J.; Sudo, T. and Okawara, R., *Organometallics*, **1983**, *2*, 191.
3. (a) Tanaka, K.; Kishigami, S. and Toda, F., *J. Org. Chem.*, **1991**, *56*, 4333. (b) Wilson, S. R. and Guazzaroni, M. E., *J. Org. Chem.*, **1989**, *54*, 3087.
4. (a) Keh, C. C. K.; Wei, C. M. and Li, C.-J., *J. Am. Chem. Soc.*, **2003**, *125*, 4062. (b) Wei, C. M. and Li, C.-J., *J. Am. Chem. Soc.*, **2003**, *125*, 9584. (c) Li, C.-J., *Acc. Chem. Res.*, **2002**, *35*, 533. (d) Zhang, W.-C. and Li, C-J., *J. Org. Chem.*, **1999**, *64*, 3230. (e) Yi, X.-H.; Meng, Y.; Hua, X.-G. and Li, C.-J., *J. Org. Chem.*, **1998**, *63*, 7472.
5. (a) Chan, T. H.; Yang, Y. and Li, C.-J., *J. Org. Chem.*, **1999**, *64*, 4452. (b) Li, C.-J.; Meng, Y.; Yi, X.-H.; Ma, J. H. and Chan, T.-H., *J. Org. Chem.*, **1998**, *63*, 7498. (c) Li, C.-J. and Chan, T.-H., *Organometallics*, **1991**, *10*, 2548.
6. (a) Li, C.-J. and Chen, L., *Chem. Soc. Rev.*, **2006**, *35*, 68. (b) Li, C.-J., *Green Chem.*, **2002**, *4*, 1. (c) Wei, C. M. and Li, C.-J., *Green Chem.*, **2002**, *4*, 39.
7. Li, C.-J., *Chem. Rev.*, **1993**, *93*, 2023.
8. Chan, T. H. and Li, C.-J., *Organometallics*, **1990**, *9*, 2649.
9. Lombardo, M.; Pasi, F. and Trombini, C., *Eur. J. Org. Chem.*, **2006**, 3061.
10. Durandetti, S.; Sibille, S. and Périchon, J., *J. Org. Chem.*, **1989**, *54*, 2198.
11. (a) Luche, J.-L. and Allavena, C., *Tetrahedron Lett.*, **1988**, *29*, 5369. (b) Pétrier, C.; Dupuy, C. and Luche, J.-L., *Tetrahedron Lett.*, **1986**, *27*, 3149.
12. Pietrusiewicz, K. M. and Zablocka, M., *Tetrahedron Lett.*, **1988**, *29*, 937.
13. Li, C.-J.; Meng, Y.; Yi, X. H.; Ma, J. H. and Chan, T. H., *J. Org. Chem.*, **1997**, *62*, 8632.
14. (a) Sjöholm, R.; Rairama, R. and Ahonen, M., *J. Chem. Soc., Chem. Commun.*, **1994**, 1217. (b) Waldmann, H., *Synlett*, **1990**, 627.
15. Molle, G. and Baner, P., *J. Am. Chem. Soc.*, **1982**, *104*, 3481.
16. Hui, A. L.; Xu, X. L.; Zha, Z. G.; Zhou, C. L. and Wang, Z. Y., *ARKIVOC*, **2004**, (*ix*), 52.
17. (a) Wu, S. H.; Houng, B. Z.; Zhu, T. M.; Yiao, D. Z. and Chu, Y. L., *Acta Chim. Sinica*, **1990**, *48*, 372. (b) Wu, S.; Huang, B. and Gao, X., *Synth. Commun.*, **1990**, *20*, 1279.
18. Araki, S.; Jin, S. J.; Idou, Y. and Butsugan, Y., *Bull. Chem. Soc. Jpn.*, **1992**, *65*, 1736.
19. (a) Lombardo, M.; Pasi, F.; Tiberi, C. and Trombini, C., *Synthesis*, **2005**, 2609. (b) Keltjens, R.; Vadivel, S. K.; de Gelder, R.; Klunder, A. J. H. and Zwanenburg, B., *Eur. J. Org. Chem.*, **2003**, 1749.

(c) Lombardo, M.; Morganti, S.; d'Ambrosio, F. and Trombini, C., *Tetrahedron Lett.*, **2003**, *44*, 2823. (d) Luche, J.-L. and Sarandeses, L. A., "Zinc-mediated Barbier Reactions" in *Organozinc Reagents: A Practical Approach*; ed. Knochel, P. and Jones, P., Oxford University Press, Oxford, **1999**, p. 307. (e) Hyldtoft, L.; Poulsen, C. S. and Madsen, R., *Chem. Commun.*, **1999**, 2101. (f) Einhorn, C. and Luche, J.-L., *J. Organomet. Chem.*, **1987**, *322*, 177. (g) Uneyama, K.; Kamaki, N.; Moriya, A. and Torii, S., *J. Org. Chem.*, **1985**, *50*, 5396.

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Luche Reduction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Luche in 1978.[1] It is a reduction of carbonyl group into an alcohol using the combination of sodium borohydride ($NaBH_4$) and cerium chloride ($CeCl_3$) in methanol as the reducing reagent. Therefore, it is generally known as the Luche reduction,[2,3] and the combination of $NaBH_4$ and $CeCl_3$ is referred to as the Luche reagent.[4] This reaction occurs under very mild conditions, and can tolerate a variety of functional groups within the same substrates, including the azido (N_3),[5] peroxide (-OO-),[5] ester,[6] α-halocarbonyl,[5,7] cyano,[5] epoxide,[8] lactone,[6a,9] cyclopropanyl,[4e] vinyl ester,[5] *t*-butoxycarbamido,[5] phenoxycarbamido,[10] acetal,[2j] ketal,[6c,11] and carbonate[12]. More importantly, this reduction always gives 1,2-addition[3i,5,13] products if the carbonyl group is conjugated to an alkenyl,[2g,2i,2j,4,6,8–10,11a,12,14] aryl,[2d] or alkynyl[2a,5,15] group. In addition, this reduction also demonstrates chemoselectivity between ketone and aldehyde groups, and often the ketone is reduced in the presence of an aldehyde group;[5] if both conjugated aldehyde and isolated aldehyde group exist in the same substrate, then the conjugated aldehyde group is often reduced. This is because $CeCl_3$ functions as a Lewis acid that catalyzes the acetalization of the aldehyde group with methanol, and the isolated aldehyde group forms the acetal first and will remain during the reduction.[5] Similarly, the isolated ketone will not be reduced if a conjugated aldehyde or ketone group coexist. In addition, this reduction also provides a certain level of stereoselectivity and diastereoselectivity.[2a] Generally speaking, the selectivity at lower temperatures would be higher than that of the reduction conducted at higher temperatures;[2d] for the reduction of cyclohexanone series, the Luche reduction affords cyclohexanol with the hydroxyl group at the equatorial position via the axial attack.[2g,2j,5] Besides cerium chloride, other lanthallides are also suitable for such reduction,[16] and it has been found that the stereoselectivity is in a bell-shape

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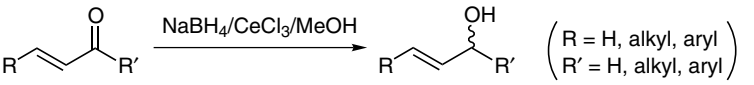
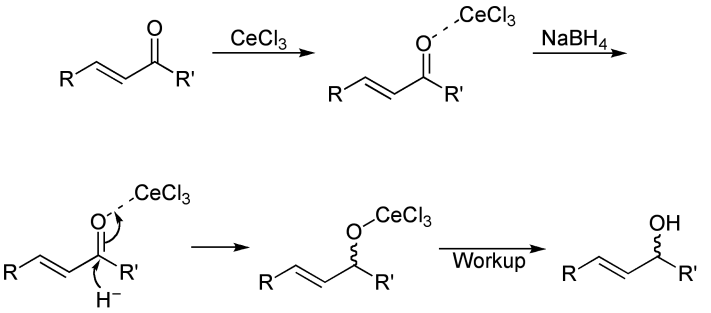
correlation with the size of lanthallides, in the order of $TbCl_3 > EuCl_3 \sim HoCl_3 > CeCl_3 \sim ErCl_3 > LaCl_3$.[2e]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is believed that the coordination between cerium and the oxygen atom of the carbonyl group further polarizes the carbonyl group so that the 1,2-reduction is favored, as displayed below.



D. MODIFICATION

The combination of $LiAlH_4$ and $CeCl_3$ has been used for similar reduction conditions but with less 1,2-reduction selectivity.[5]

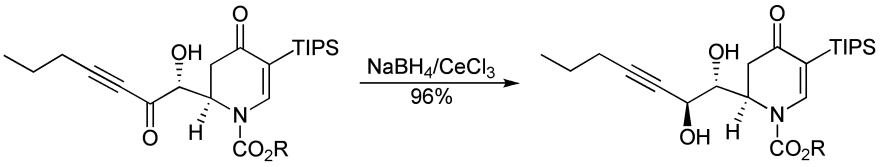
E. APPLICATIONS

This reaction has very broad application in organic synthesis.

F. RELATED REACTIONS

N/A

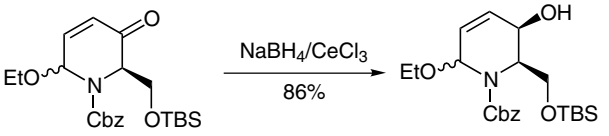
G. CITED EXPERIMENTAL EXAMPLES



R = *trans*-2-(α-cumyl)-cyclohexyl

Reference 2a.

To a solution of 100 mg (2*R*)-2-((1*R*)-hydroxy-1-hept-3-yn-2-one)-1-[((1*S*,2*R*)-2-(1-methyl-1-phenylethyl) cyclohexyoxy) carbonyl]-5-(triisopropylsilyl)-2,3-dihydro-4-pyridone (0.161 mmol) in 7 mL methanol was added 66 mg cerium(III) chloride heptahydrate ($CeCl_3 \cdot 7H_2O$, 0.177 mmol) in one portion. After being stirred for 10 min, the mixture was cooled to -50°C, and 9 mg sodium borohydride (0.241 mmol) was added. The reaction mixture was stirred for an additional 10 min, quenched with 10 mL water, and extracted with CH_2Cl_2 (3 $\times$ 10 mL). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by radial PLC (silica gel, 30% EtOAc/hexanes) to give 96 mg (2*R*)-2-((1*R*,2*S*)-dihydroxy-hept-3-yne)-1-[((1*S*,2*R*)-2-(1-methyl-1-phenylethyl)-cyclohexyloxy)carbonyl]-5-(triisopropylsilyl)-2,3-dihydro-4-pyridone as a colorless oil, in a yield of 96%.



Reference 2b.

A 100-mL flask was charged with 555 mg (2*R*)-2-(*tert*-butyldimethylsilyloxymethyl)-6-ethoxy-3-oxo-3,6-dihydro-2*H*-pyridine-1-carboxylic acid benzyl ester (1.32 mmol), a magnetic stir bar and 6 mL CH_2Cl_2. The mixture was cooled to -78°C in a dry ice–acetone bath under a nitrogen atmosphere. To this solution was added a 10 mL 0.4 M $CeCl_3$ solution in methanol. After additional stirring and continued cooling, 75 mg $NaBH_4$ (1.98 mmol, 1.5 eq.) was added. The reaction was stirred at -78°C until only alcohol was visible by TLC ($\sim$2 h). The reaction mixture was diluted with 15 mL ether and quenched at -78°C by the addition of 4 mL 1 M $NaHSO_4$. This mixture was stirred for 20 min and separated. The aqueous layer was extracted with ether (4 $\times$ 10 mL), and the combined organic layers were washed with brine and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography provided 477 mg (2*R*,3*R*)-2-(*tert*-butyldimethylsilyloxymethyl-6-ethoxy-3-hydroxy-3,6-dihydro-2*H*-pyridine-1-carboxylic acid benzyl ester as a colorless oil, in a yield of 86%, $R_f = 0.36$ (EtOAc /hexanes, 1:4).

Other references related to the Luche reduction are cited in the literature.[17]

H. REFERENCES

1. (a) Luche, J.-L., *J. Am. Chem. Soc.*, **1978**, *110*, 2226. (b) Luche, J.-L.; Rodriguez-Hahn, L.; and Crabbe, P., *J. Chem. Soc., Chem. Commun.*, **1978**, 601.
2. (a) Kuethe, J. T. and Comins, D. L., *J. Org. Chem.*, **2004**, *69*, 5219. (b) Haukaas, M. H. and O'Doherty, G. A., *Org. Lett.*, **2001**, *3*, 401. (c) Hale, K. J.; Frigerio, M. and Manaviazar, S., *Org. Lett.*, **2001**, *3*, 3791. (d) Flavin, M. T.; Rizzo, J. D.; Khilevich, A.; Kucherenko, A.; Sheinkman, A. K.; Vilaychack, V.; Lin, L.; Chen, W.; Greenwood, E. M.; Pengsuparp, T.; Pezzuto, J. M.; Hughes, S. H.; Flavin, T. M.; Cibulski, M.; Boulanger, W. A.; Shone, R. L. and Xu, Z.-Q., *J. Med. Chem.*, **1996**, *39*, 1303. (e) Cha, J. K. and Kim, N.-S., *Chem. Rev.*, **1995**, *95*, 1761. (f) Norcross, R. D. and Paterson, I., *Chem. Rev.,* **1995**, *95*, 2041. (g) Williams, D. R.; Benbow, J. W.; McNutt, J. G. and Allen, E. E., *J. Org. Chem.*, **1995**, *60*, 833. (h) Paquette, L. A. and Watson, T. J., *J. Org. Chem.*, **1994**, *59*, 5708. (i) Ireland, R. E.; Wipf, P. and Xiang, J.-N., *J. Org. Chem.*, **1991**, *56*, 3572. (j) Abelman, M. M.; Overman, L. E. and Tran, V. D., *J. Am. Chem. Soc.*, **1990**, *112*, 6959. (k) Ishihara, M.; Tsuneya, T.; Shiota, H.; Shiga, M. and Nakatsu, K., *J. Org. Chem.*, **1986**, *51*, 491.
3. (a) Guo, H. B. and O'Doherty, G. A., *Org. Lett.*, **2006**, *8*, 1609. (b) Mandal, A. K.; Schneekloth, J. S.; Kuramochi, K. and Crews, C. M., *Org. Lett.*, **2006**, *8*, 427. (c) Kennedy, A.; Nelson, A. and Perry, A., *Beilstein J. Org. Chem.*, **2005**, 2. (d) Ng, F. W.; Lin, H. and Danishefsky, S. J., *J. Am. Chem. Soc.*, **2002**, *124*, 9812. (e) Bazin, H. G.; Wolff, M. W. and Linhardt, R. J., *J. Org. Chem.*, **1999**, *64*, 144. (f) O'Leary, D. J.; Blackwell, H. E.; Washenfelder, R. A.; Miura, K. and Grubbs, R. H., *Tetrahedron Lett.*, **1999**, *40*, 1091. (g) Constantino, M. G.; de Oliveira Matias, L. G.; José da Silva, G. V.; Barbieri, E. and do Prado Gambardella, M. T., *Quim. Nova*, **1998**, *21*, 719. (h) Hutton, G.; Jolliff, G.; Mitchell, H. and Warren, S., *Tetrahedron Lett*., **1995**, *36*, 7905. (i) Burke, S. D.; Piscopio, A. D.; Kort, M. E.; Matulenko, M. A.; Parker, M. H.; Armistead, D. M. and Shankaran, K., *J. Org. Chem.*, **1994**, *59*, 332. (j) Li, K. Q.; Hamann, L. G. and Koreeda, M., *Tetrahedron Lett*., **1992**, *33*, 6569. (k) Tanaka, K.; Kishigami, S. and Toda, F., *J. Org. Chem*., **1991**, *56*, 4333.
4. (a) Jin, C. Y.; Burgess, J. P.; Rehder, K. S. and Brine, G. A., *Synthesis*, **2007**, 219. (b) Rozek, T.; Tiekink, E. R. T.; Taylor, D. K. and Bowie, J. H., *Aust. J. Chem.*, **1998**, *51*, 1057. (c) Leclaire, M. and Jean, P., *Bull. Soc. Chim. Fr.*, **1996**, *133*, 801. (d) Krief, A. and Surleraux, D., *Synlett*, **1991**, 273. (e) Paquette, L. A. and Ham, W. H., *J. Am. Chem. Soc.*, **1987**, *109*, 3025.
5. Molander, G. A., *Chem. Rev.*, **1992**, *92*, 29.
6. (a) Kawada, K.; Dolence, E. K.; Morita, H.; Kometani, T.; Watt, D. S.; Balapure, A.; Fitz, T. A.; Orlicky, D. J. and Gerschenson, L. E., *J. Med. Chem.*, **1989**, *32*, 256. (b) Danishefsky, S. J.; DeNinno, M. P. and Chen, S.-H., *J. Am. Chem. Soc.*, **1988**, *110*, 3929. (c) Zoretic, P. A.; Chambers, R. J.; Marbury, G. D. and Riebiro, A. A., *J. Org. Chem.*, **1985**, *50*, 2981.
7. Turner, D. and Vogel, P., *Synlett*, **1998**, 304.
8. Wipf, P. and Kim, Y. T., *J. Org. Chem.*, **1994**, *59*, 3518.
9. Hart, D. J.; Li, J.; Wu, W.-L. and Kozikowski, A. P., *J. Org. Chem.*, **1997**, *62*, 5023.
10. Comins, D. L. and Mantlo, N. B., *J. Org. Chem.*, **1986**, *51*, 5456.
11. (a) Kim, S. K. and Fuchs, P. L., *J. Am. Chem. Soc.*, **1993**, *115*, 5934. (b) DeShong, P.; Waltermire, R. E. and Ammon, H. L., *J. Am. Chem. Soc.*, **1988**, *110*, 1901.
12. Young, W. B.; Masters, J. J. and Danishefsky, S., *J. Am. Chem. Soc.*, **1995**, *117*, 5228.
13. Kende, A. S.; Liu, K.; Kaldor, I.; Dorey, G. and Koch, K., *J. Am. Chem. Soc.*, **1995**, *117*, 8258.
14. Paquette, L. A.; Waykole, L.; Jendralla, H. and Cottrell, C. E., *J. Am. Chem. Soc.*, **1986**, *108*, 3739.
15. Boutin, R. H. and Rapoport, H., *J. Org. Chem.*, **1986**, *51*, 5320.
16. Gemal, A. L. and Luche, J.-L., *J. Am. Chem. Soc.*, **1981**, *103*, 5454.

17. (a) De la Torre, M. C.; Garcia, I. and Sierra, M. A., *Chem. Eur. J.*, **2005**, *11*, 3659. (b) Sha, C.-K.; Huang, S.-J. and Zhan, Z.-P., *J. Org. Chem.*, **2002**, *67*, 831. (c) Wipf, P.; Kim, Y. T. and Goldstein, D. M., *J. Am. Chem. Soc.*, **1995**, *117*, 11106. (d) Wovkulich, P. M.; Tang, P. C.; Chadha, N. K.; Batcho, A. D.; Barrish, J. C. and Uskokovic, M. R., *J. Am. Chem. Soc.,* **1989**, *111*, 2596. (e) Sardina, F. J.; Howard, M. H.; Koskinen, A. M. P. and Rapoport, H., *J. Org. Chem.*, **1989**, *54*, 4654. (f) Hua, D. H.; Venkataraman, S.; Chan-Yu-King, R. and Paukstelis, J. V., *J. Am. Chem. Soc.*, **1988**, *110*, 4741. (g) Leblanc, Y.; Fitzsimmons, B. J.; Adams, J.; Perez, F. and Rokach, J., *J. Org. Chem.*, **1986**, *51*, 789. (h) Fukuzawa, S. I.; Fujinami, T.; Yamaguchi, S. and Sakai, S., *J. Chem. Soc., Perkin Trans. I*, **1986**, 1929.

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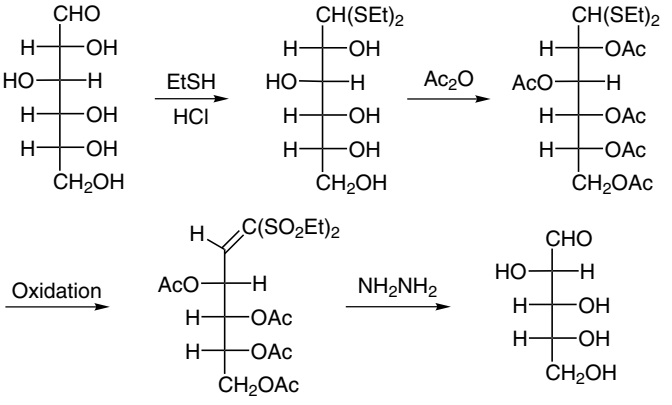
MacDonald-Fischer Degradation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by MacDonald and Fischer in 1952.[1] It is the degradation of hexoses into pentoses involving the steps of formation of dithioacetal, oxidation to unsaturated disulfone by means of perphthalic acid, hydrazine treatment, and benzaldehyde splitting of the corresponding hydrazone. Therefore, the whole process is known as the MacDonald-Fischer degradation.[2] In addition, when the unsaturated disulfone is dissolved in aqueous ammonia or methanol saturated with ammonia, 2-deoxy-2-amino sugar is resolved.[1] This reaction in combination with mass spectroscopy was used to study the structure and stereochemistry of carbohydrates.[2c,2d,3]

B. GENERAL REACTION SCHEME



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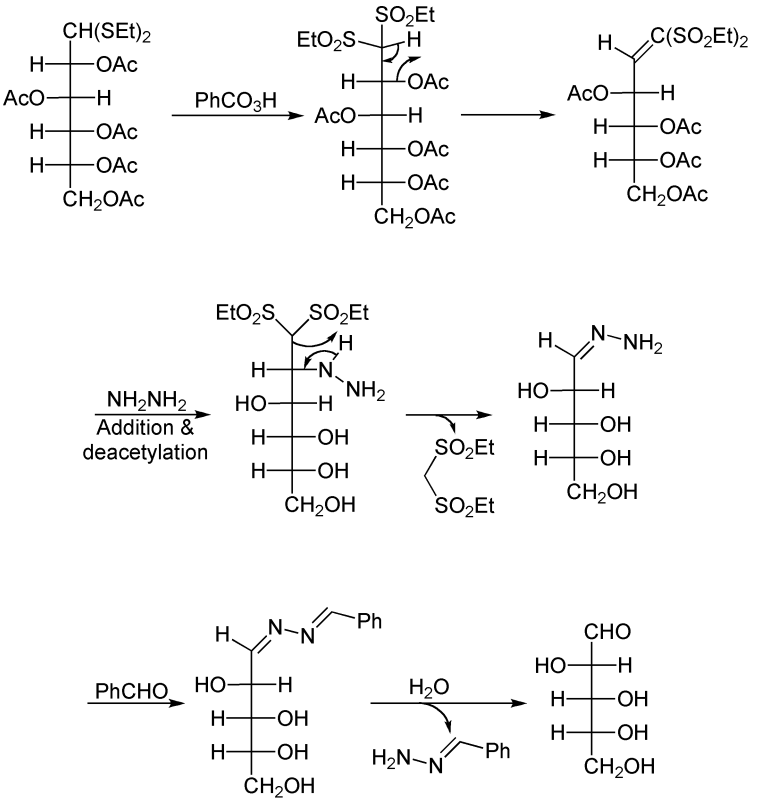
C. PROPOSED MECHANISMS

A tentative mechanism is proposed here to rationalize the degradation of disulfones.



D. MODIFICATION

N/A

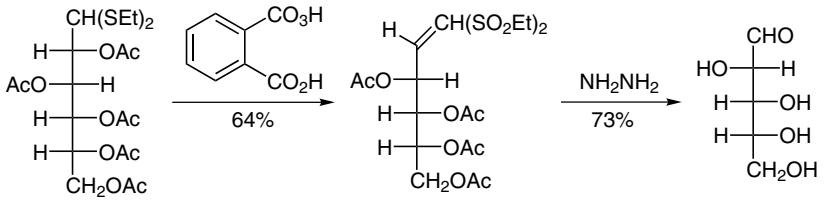
E. APPLICATIONS

This reaction has been used to degrade the carbohydrates and study the structure and stereochemistry of carbohydrates.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 1.

To an ice cold solution of 20.0 g D-glucose diethyl mercaptal pentaacetate in 200 mL dry ether was added 35.21 g monoperphthalic acid in ether (4.8 eq.). The solution was cooled in ice for 1 h and then allowed to stand at room temperature for an additional 16 h. The ether was removed under reduced pressure, and the residue was extracted with $CHCl_3$ (4×75 mL). The chloroform was washed with saturated aqueous $NaHCO_3$ and then with water and was dried over Na_2SO_4. Then $CHCl_3$ was removed under reduced pressure to give 19.9 g D-arabo-3,4,5,6-tetraacetoxy-1,1-bis-(ethanesulfonyl)-hexene-1 as a crystalline material, m.p., 134–146°C. Two recrystallizations from diisobutyl ketone followed by one from isopropyl alcohol and one from methyl ethyl ketone by addition of petroleum ether (b.p. 35–60°C), gave 12.9 g pure product with a constant melting point of 160–162°C, in a yield of 64%.

D-arabo-3,4,5,6-tetraacetoxy-1,1-bis-(ethanesulfony1)-hexene-1(5g) was added to 100 mL methanol; to this was added 4.5 mL 85% hydrazine hydrate in water. The material dissolved rapidly and, after 4 h at room temperature, the solvent was removed at reduced pressure, then 50 mL water was added, and the mixture was extracted with $CHCl_3$ (4×20 mL). To the aqueous layer was added 35 mL benzaldehyde, 0.5 g benzoic acid, and 40 mL ethanol. The mixture was refluxed for 3 h. After cooling, the mixture was extracted with $CHCl_3$ (3×20 mL) and then 20 mL ether. The mixture was washed with 400 mL water, and concentrated to 10 mL. Charcoal was added, and water was removed from the filtered solution in a vacuum oven at 40°C. Then 5 mL hot methanol was added; after 24 h at 4°C, the crystalline residue was washed twice with cold methanol and dried in vacuum over $CaCl_2$ to give 1.10 g D-arabinose, in a yield of 73%.

Other references related to the MacDonald-Fischer degradation are cited in the literature.[4]

H. REFERENCES

1. MacDonald, D. L. and Fischer, H. O. L., *J. Am. Chem. Soc.,* **1952**, *74*, 2087.
2. (a) Follmann, H. and Hogenkamp, H. P. C., *J. Am. Chem. Soc.*, **1970**, *92*, 671. (b) Hanessian, S., *J. Org. Chem.*, **1967**, *32*, 163. (c) DeJongh, D. C. and Hanessian, S., *J. Am. Chem. Soc.*, **1966**, *88*, 3114. (d) DeJongh, D. C. and Hanessian, S., *J. Am. Chem. Soc.*, **1965**, *87*, 3774.

3. (a) Hanessian, S. and Haskell, T. H., *J. Heterocycl. Chem.*, **1964**, *1*, 57. (b) Haskell, T. H. and Hanessian, S., *J. Org. Chem.*, **1963**, *28*, 2598. (c) Hough, L. and Taha, M., *J. Chem. Soc.*, **1957**, 3654.
4. (a) Buchanan, J. G.; Edgar, A. R. and Hutchison, R. J., *Carbohydr. Res.*, **1987**, *164*, 403. (b) Hough, L. and Richardson, A. C., *J. Chem. Soc.,* **1962**, 1019. (c) Hough, L. and Richardson, A. C., *J. Chem. Soc.,* **1962**, 1024. (d) Hough, L. and Richardson, A. C., *J. Chem. Soc.*, **1961**, 5561. (e) Barker, R. and MacDonald, D. L., *J. Am. Chem. Soc.*, **1960**, *82*, 2297. (f) Hough, L. and Taylor, T. J., *J. Chem. Soc.*, **1955**, 3544. (g) MacDonald, D. L. and Fischer, H. O. L., *Biochim. et Biophys. Acta*, **1953**, *12*, 203. (h) Wolfrom, M. L. and Anno, K., *J. Am. Chem. Soc.*, **1952**, *74*, 6150.

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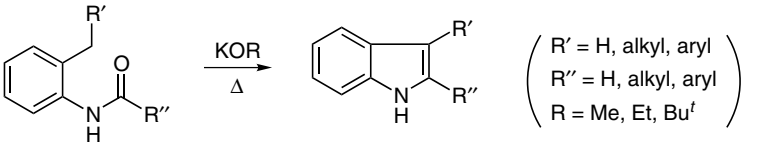
Madelung Indole Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Madelung in 1912.[1] It is a synthesis of indole derivatives by means of the treatment of *ortho*-alkyl *N*-acylaniline with a strong base (e.g., potassium alkoxide) at high temperature (e.g., 300–400°C). Therefore, this reaction is known as the Madelung indole synthesis,[2] Madelung synthesis,[2b,2c,3] Madelung cyclization,[4] or Madelung reaction.[2b,5] It has been improved by using sodium amide or lithium amide as a base to substitute for potassium alkoxide,[5c] so that the reaction can occur at a relatively lower temperature. In addition, it has been reported that when butyl lithium is used as base, the reaction can take place at room temperature.[3a,6] In addition, *ortho*-alkyl *N*-benzoyl anilines react at relatively lower temperatures.[7] However, this method is difficult for the preparation of nitro- or halogen-substituted indoles.[8]

B. GENERAL REACTION SCHEME



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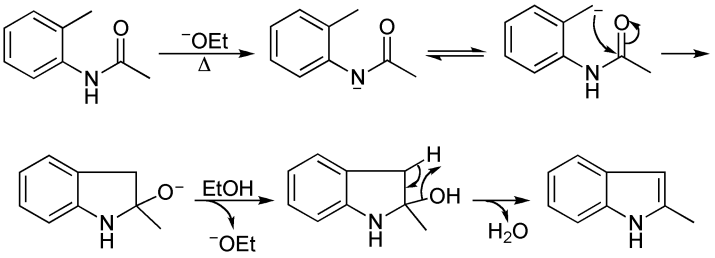
C. PROPOSED MECHANISMS

It is believed that the removal of a benzylic proton to form a benzylic anion is the important step in this reaction. As potassium alkoxide or sodium alkoxide is not strong enough to deprotonate benzylic proton, thus a very high temperature is required for this reaction to proceed. However, if sodium amide, a even stronger base, is used, the reaction can occur at a relatively lower temperature; similarly, if amino group of aniline is protected by benzoyl group, a stronger electron-withdrawing group, then the acidity of benzylic proton is enhanced, thus a lower temperature is good enough for the Madelung indole synthesis. An illustrative mechanism is shown below.



D. MODIFICATION

This reaction has been modified by using lithium amide[5c] or butyl lithium[3a,6] as base so that the reaction can take place at milder conditions.

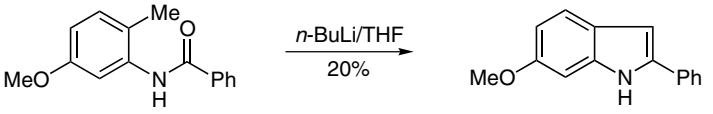
E. APPLICATIONS

This reaction is useful for the preparation of unsubstituted indole and indoles with substitutents at 2-position.

F. RELATED REACTIONS

N/A

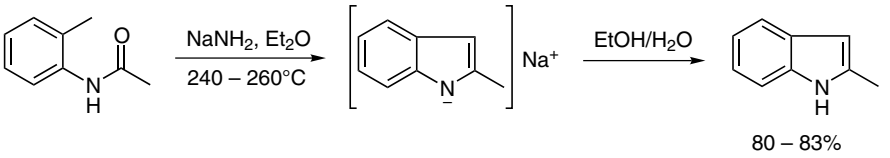
G. CITED EXPERIMENTAL EXAMPLES



Reference 3a.

To an ice-cooled solution of 2.41 g *N*-(2-methyl-5-methoxyphenyl) benzamide (10 mmol) in 20 mL dry THF was added 13.75 mL 1.6 M *n*-butyllithium in hexane (22 mmol) dropwise under a nitrogen atmosphere. This mixture was stirred at room temperature for

20 h, then cooled to 0°C and treated dropwise with 11 mL 2 N HCl. The organic layer was separated, and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to obtain a black residue, which was then purified by flash chromatography (silica gel, toluene as the eluent) and crystallization from toluene to give 0.45 g 6-methoxy-2-phenylindole as a white solid, in a yield of 20%, m.p. 177–178°C.



Reference 9.

To a 1-L flask was added a mixture of 64 g finely pulverized $NaNH_2$, 100 g acetyl-*o*-toluidine, and ~50 mL dry ether. Then the flask was swept out with dry nitrogen, followed by a slow current of dry nitrogen passing through the mixture. The flask was heated in a metal bath to 240–260°C over a 30-min period and was maintained at this temperature for 10 min. A vigorous evolution of gas occurred, the cessation of which indicated the completion of this reaction. The metal bath was removed to allow the flask to cool, then 50 mL 95% ethanol and 250 mL warm water (~50°) were added successively. The decomposition of the sodium derivative of 2-methylindole and of any excess $NaNH_2$ were completed by warming the mixture gently with a Bunsen burner. The cooled reaction mixture was extracted with ether (2 × 200 mL), and the combined ether extracts were filtered, and concentrated to ~125 mL. The solution was then transferred to a 250-mL Claisen flask and distilled at 119–126°C (3–4 mmHg) as a water-white liquid, which rapidly solidified in the receiver to a white crystalline mass and weighed 70–72 g, in a yield of 80–83%, m.p., 56–57°C. This product could be further purified by dissolving it in 100 mL methanol, adding 30 mL water, and allowing the solution to stand in the ice chest for 5 h.

Other references related to the Madelung indole synthesis are cited in the literature.[10]

H. REFERENCES

1. Madelung, W., *Ber.*, **1912**, *45*, 1128.
2. (a) Quintanilla-Licea, R.; Colunga-Valladares, J. F.; Caballero-Quintero, A.; Rodríguez-Padilla, C.; Tamez-Guerra, R.; Gómez-Flores, R. and Waksman, N., *Molecules*, **2002**, *7*, 662. (b) Houlihan, W. J.; Parrino, V. A. and Uike, Y., *J. Org. Chem.*, **1981**, *46*, 4511. (c) Houlihan, W. J.; Uike, Y. and Parrino, V. A., *J. Org. Chem.*, **1981**, *46*, 4515. (d) Tyson, F. T., *J. Am. Chem. Soc.*, **1941**, *63*, 2024.
3. (a) Tarzia, G.; Dikamantini, G.; Giacomo, B. D.; Spadoni, G.; Esposti, D.; Nonno, R.; Lucini, V.; Pannacci, M.; Fraschini, F. and Stankov, B. M., *J. Med. Chem.*, **1997**, *40*, 2003. (b) Verboom, W.; Berga, H. J.; Trompenaars, W. P. and Reinhoudt, D. N., *Tetrahedron Lett.*, **1985**, *26*, 685. (c) Piozzi, F. and Langella, M. R., *Gazz. Chim. Ital.*, **1963**, *93*, 1392. (d) Piozzi, F. and Langella, M. R., *Gazz. Chim. Ital.*, **1963**, *93*, 1392. (e) Piozzi, F. and Casnati, G., *Atti Accad. Nazl. Lincei. Rend., Classe Sci., Fis., Mat. Nat.*, **1956**, *20*, 629.

4. (a) Cacchi, S. and Fabrizi, G., *Chem. Rev.*, **2005**, *105*, 2873. (b) Herz, W. and Murty, D. R. K., *J. Org. Chem.*, **1960**, *25*, 2242.
5. (a) Orlemans, E. O. M.; Schreuder, A. H.; Conti, P. G. M.; Verboom, W. and Reinhoudt, D. N., *Tetrahedron*, **1987**, *43*, 3817. (b) Verboom, W.; Orlemans, E. O. M.; Berga, H. J.; Scheltinga, M. W. and Reinhoudt, D. N., *Tetrahedron*, **1986**, *42*, 5053. (c) Augustine, R. L.; Gustavsen, A. J.; Wanat, S. F.; Pattison, I. C.; Houghton, K. S. and Koletar, G., *J. Org. Chem.*, **1973**, *38*, 3004. (d) Piozzi, F. and Langella, M. R., *Gazz. Chim. Ital.*, **1963**, *93*, 1382.
6. Haseltine, J.; Visnick, M. and Smith, A. B., *J. Org. Chem.* **1988**, 53,6160.
7. Chen, H. Z.; Jin, Y. D.;Xu, R. S.; Peng, B. X.; Desseyn, H.; Janssens, J.; Heremans, P.; Borghs, G. and Geise, H. J., *Synthetic Metals*, **2003**, *139*, 529.
8. (a) Noland, W. E. and Reich, C., *J. Org. Chem.*, **1967**, *32*, 828. (b) Noland, W. E.; Smith, L. R. and Rush, K. R., *J. Org. Chem.*, **1965**, *30*, 3457.
9. Allen, C. F. H. and VanAllan, J., *Org. Synth. Coll., Vol.*, **1955**, 3597.
10. (a) Wacker, D. A. and Kasireddy, P., *Tetrahedron Lett*., **2002**, *43*, 5189. (b) Smith, A. B.; Haseltine, J. N. and Visnick, M., *Tetrahedron*, **1989**, *45*, 2431. (c) Verboom, W.; Reinhoudt, D. N.; Lammerink, B. H. M.; Orlemans, E. O. M.; Van Veggel, F. C. J. M. and Lelieveld, P., *Anti-Cancer Drug Design*, **1987**, *2*, 271. (d) Ghini, A. A.; Burton, G. and Gros, E. G., *Anales Asoc. Quim. Argentina*, **1982**, *70*, 1079. (e) Wu, A. and Snieckus, V., *Tetrahedron Lett*., **1975**, 2057. (f) Remers, W. A. and Brown, R. K., "Indoles," in *The Chemistry of Heterocyclic Compounds, Vol. 25*, Part I, ed. Houlihan, W. J., John Wiley & Sons, New York, **1972**, pp. 385–396. (g) Willette, R. E., *Adv. Heterocycl. Chem.*, **1968**, *9*, 27. (h) Casnati, G.; Langella, M. R.; Piozzi, F.; Ricca, A. and Umani-Ronchi, A., *Tetrahedron Lett*., **1964**, 1597. (i) Merchant, J. R.; Vaghani, D. D. and Kallianpur, C. S., *J. Indian Chem. Soc.*, **1963**, *40*, 315. (j) Keglevic, D.; Stojanac, N. and Desaty, D., *Croat. Chem. Acta*, **1961**, *33*, 83. (k) Robison, M. M. and Robison, B. L., *J. Am. Chem. Soc.*, **1955**, *77*, 457. (l) Tyson, F. T., *Org. Synth. Coll.*, **1955**, 3479. (m) Galat, A. and Friedman, H. L., *J. Am. Chem. Soc*., **1948**, *70*, 1280. (n) Madelung, W., *Ann.*, **1914**, *405*, 58.

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Maillard Reaction

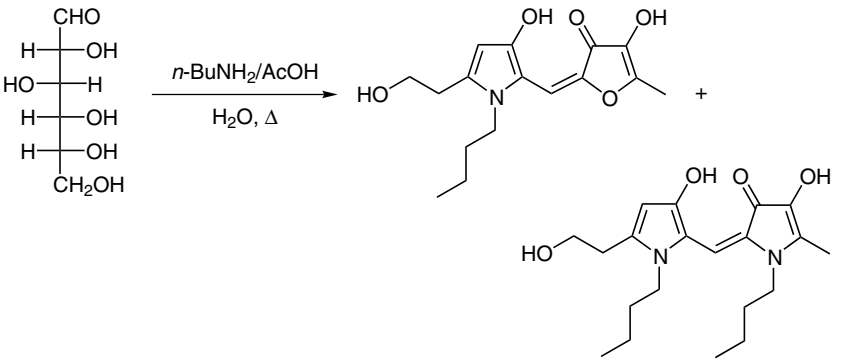
A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Ling and Malting in 1908 who studied the color formation in beer from sugars and amino groups.[1] Because the color is generally brown-like, this reaction is sometimes called nonenzymatic browning reaction.[2] However, it was Maillard who reported the coloring reaction between reducing sugars and amino groups in 1912[3] and initially realized the significance of this reaction in plant pathology, geology, and medicine; therefore, this reaction is generally known as the Maillard reaction.[4,5] In fact, this reaction is probably the most complicated organic reaction that involves any reaction between a reducing sugar and molecules with a free amino group (e.g., amino acids, peptides, and proteins). Depending on the source of reducing sugars and amino compounds, the products formed show different colors and flavors.[2b] Nonetheless, the end products are nitrogenous heterocyclic molecules with different substituents on nitrogen that give the brown-like colors.[4b] Generally speaking, this reaction involves three stages: the nucleophilic addition of an amino group to the aldehyde group of reducing sugar leads to glycosylamine, which then undergoes the *Amadori Rearrangement* to yield ketosyl compounds irreversibly and give different products via various reaction pathways, such as enolization, *Aldol Condensation*, dehydration, fragmentation of amino acid, and polymerization.[2a,6] The overall outcome of this reaction is the browning, fluorescence (by advanced glycation end products, AGEs[2a]), and cross-linking of protein.[4e] The products of the Maillard reaction are generally known as the Maillard reaction products (MRPs)[4a] or melanoidins.[4f] Among these products, some are reported to have antimutagenic[7] and antioxidant[8] activity, whereas other products are undesired, such as those in milk powder. It has been found that the activity of water, pH, reaction duration, and temperature all affect the extent of this reaction.[4d] Further information about this reaction can be located in the relevant books.[9]

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

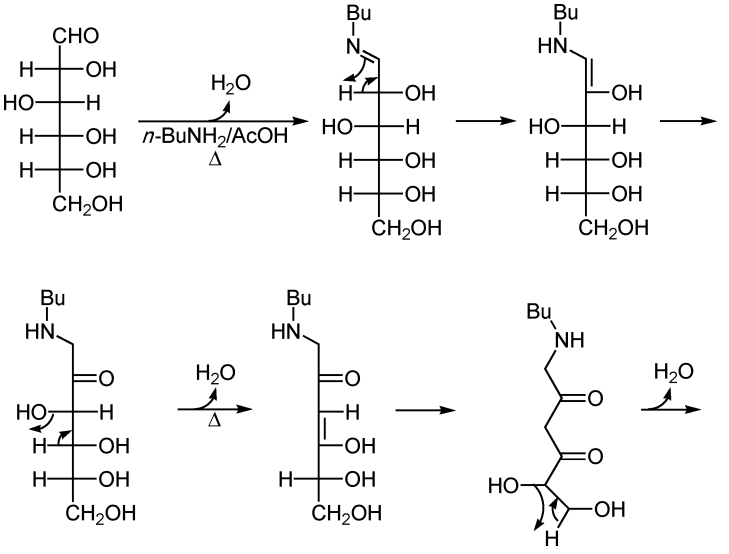
B. GENERAL REACTION SCHEME

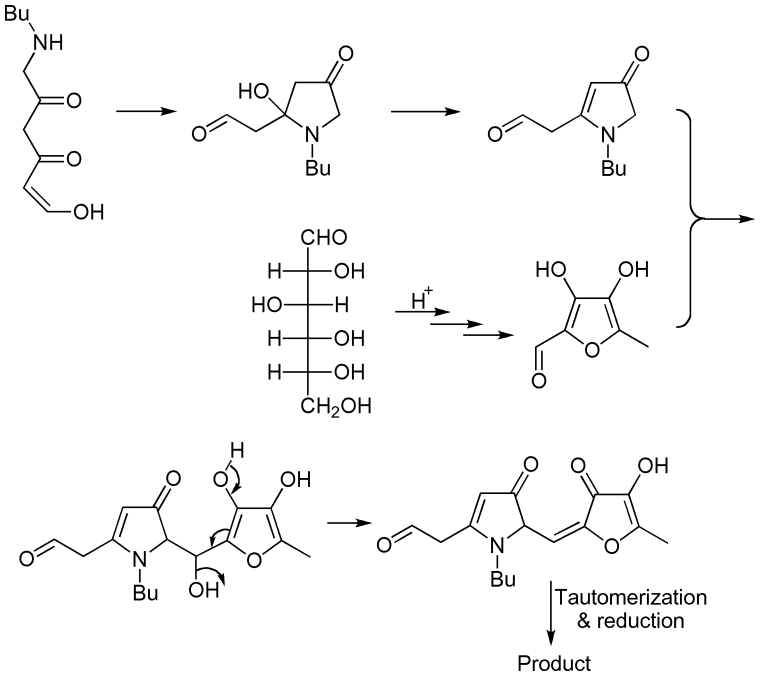
Shown below is a specific reaction between D-glucose and *n*-butylamine.[4b,4c]



C. PROPOSED MECHANISMS

It is assumed that the isolated products are correct as shown in the reaction scheme, and a tentative mechanism (partially) is outlined here to indicate the possible route for the formation of such product.[4c]





D. MODIFICATION

N/A

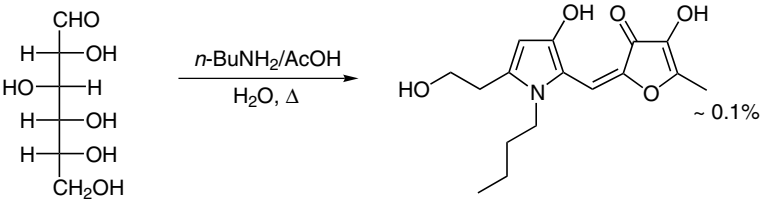
E. APPLICATIONS

This reaction has important application in sitology.

F. RELATED REACTIONS

This reaction is related to the *Amadori Rearrangement*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4c.

A mixture of 36.0 g D-glucose (0.2 mol), 30 mL *n*-butylamine (0.3 mol), and 21.0 mL acetic acid (0.35 mol) in 150 mL water was refluxed for 30 min. After it was cooled, the solution was extracted with 250 mL EtOAc. The organic layer was washed with 150 mL water and concentrated under reduced pressure. The mixture was separated by column chromatography on silica gel (20 cm × 5.5 cm (i.d.), EtOAc/MeOH, 100:3). A dark brown fraction (Fraction A, 30 mL) was followed by a light yellow fraction (Fraction B, 20 mL) and an intense yellow-orange fraction (Fraction C, 50 mL) in front of a light yellow fraction and a broad brown zone. Fraction C was further separated by thin-layer chromatography, using acetone/$CHCl_3$ (5:4) as the eluent. An intense yellow zone of $R_f = 0.65$ was extracted with acetonitrile/methanol (6:1) and concentrated under reduced pressure to afford 4-hydroxy-5-methyl-2-(*N*-butyl-3-hydroxy-5-(2-hydroxyethyl) pyrrolyl-2-methylidene)-2*H*-furan-3-one as a yellow-orange oil, in a very poor yield (0.1%).

Because this reaction has been studied extensively, it is impossible to collect all the references here; additional citations can be found in the literature.[10]

H. REFERENCES

1. Ling, A. R. and Malting, J., *J. Inst. Brew.*, **1908**, *14*, 494.
2. (a) Matsuura, N.; Aradate, T.; Sasaki, C.; Kojima, H.; Ohara, M.; Hasegawa, J. and Ubukata, M., *J. Health Sci.*, **2002**, *48*, 520. (b) Wang, M. F.; Jin, Y.; Li, J. G. and Ho, C.-T., *J. Agri. Food Chem.*, **1999**, *47*, 48. (c) Seaver, J. L. and Kertesz, Z. I., *J. Am. Chem. Soc.*, **1946**, *68*, 2178.
3. Maillard, L. C., *Compt. Rend.*, **1912**, *54*, 66.
4. (a) Billaud, C.; Maraschin, C.; Peyrat-Maillard, M.-N. and Nicolas, J., *Ann. N. Y. Acad. Sci.*, **2005**, *1043*, 876. (b) Lerche, H.; Pischetsrieder, M. and Severin, T., *J. Agri. Food Chem.*, **2003**, *51*, 4424. (c) Lerche, H.; Pischetsrieder, M. and Severin, T., *J. Agri. Food Chem.*, **2002**, *50*, 2984. (d) del Castillo, M. D.; Corzo, N. and Olano, A., *J. Agri. Food Chem.*, **1999**, *47*, 4388. (e) Wells-Knecht, K. J.; Brinkmann, E. and Baynes, J. W., *J. Org. Chem.*, **1995**, *60*, 6246. (f) Farmar, J. G.; Ulrich, P. C. and Cerami, A., *J. Org. Chem.*, **1988**, *53*, 2346. (g) Chichester, C. O.; Stadtman, F. H. and MacKinney, G., *J. Am. Chem. Soc.*, **1952**, *74*, 3418.
5. (a) Zhao, M.-M.; Zeng, X.-F.; Cui, C. and Wang, J.-S., *Sichuan Daxue Xuebao, Gongcheng Kexueban*, **2007**, *39*, 77. (b) Dai, Z. Y.; Nemet, I.; Shen, W. and Monnier, V. M., *Arch. Biochem. Biophys.*, **2007**, *463*, 78. (c) Zhang, Y. and Zhang, Y., *Critic. Rev. Food Sci. & Nutri.*, **2007**, *47*, 521. (d) Yan, W. Q. and Tang, B. J., *Shipin Kexue (Beijing)*, **2006**, *27*, 272. (e) Davidek, T.; Robert, F.; Devaud, S.; Vera, F. A. and Blank, I., *J. Agri. Food Chem.*, **2006**, *54*, 6677. (f) Davidek, T.; Devaud, S.; Robert, F. and Blank, I., *J. Agri. Food. Chem.*, **2006**, *54*, 6667. (g) Gerrard, J. A., *Trends Food Sci. Technol.*, **2006**, *17*, 324. (h) Sun, Y. X.; Hayakawa, S.; Chuamanochan, M.; Fujimoto, M.; Innun, A. and Izumori, K., *Biosci. Biotechnol. Biochem.*, **2006**, *70*, 598. (i) Hu, K.; Fang, S. Y.; Wang, X. X.; Ye, W. Y. and Qiu, C. L., *Shipin Gongye Keji*, **2005**, *26*, 72. (j) Morgan, F.; Appolonia Nouzille, C.; Baechler, R.; Vuataz, G. and Raemy, A., *Lait*, **2005**, *85*, 315. (k) Cardelle-Cobas, A.; Moreno, F. J.; Corzo, N.; Olano, A. and Villamiel, M., *J. Agri. Food Chem.*, **2005**, *53*, 9078. (l) Sandwick, R.; Johanson, M. and Breuer, E., *Ann. N. Y. Acad. Sci.*, **2005**, *1043*, 85. (m) Davidek, T.; Devaud, S.; Robert, F. and Blank, I., *Ann. N. Y. Acad.Sci.*, **2005**, *1043*, 73. (n) Yilmaz, Y. and Toledo, R., *Food Chem.,* **2005**, *93*, 273. (o) Hiramoto, S.; Itoh, K.; Shizuuchi, S.; Kawachi, Y.; Morishita, Y.; Nagase, M.; Suzuki, Y.; Nobuta, Y.; Sudou, Y.; Nakamura, O.; Kagaya, I.; Goshima, H.; Kodama, Y.; Icatro, F. C.; Koizumi, W.; Saigenji, K.; Miura, S.; Sugiyama, T. and Kimura, N., *Helicobacter*, **2004**, *9*, 429. (p) Chen, Y.; Chin, C.-K. and Ho, C.-T., *Adv. Expert. Med. Biology*, **2004**, *542*, 327. (q) Saito, A.; Nakajima, N.; Matsuura, N.;

Tanaka, A. and Ubukata, M., *Heterocycles*, **2004**, *62*, 479. (r) Ai, P. and Zhang, W. M., *Zhongguo Tiaoweipin*, **2002**, 32.

6. Namiki, M., *Adv. Food Res.*, **1988**, *32*, 116.
7. Yen, G. C., *J. Agri. Food Chem*., **1992**, *40*, 1034.
8. (a) Yen, G. C. and Hsieh, P. P., *J. Sci. Food Agri*., **1995**, *67*, 415. (b) Bedinghaus, A. J. and Ockerman, H. W., *J. Food Sci*., **1995**, *60*, 992. (c) Lingnert, H.; Waller, G. R., *J. Agri. Food Chem*., **1983**, *31*, 27.
9. (a) Nursten, H. E., *The Maillard Reaction, Chemistry, Biology and Implications*,Springer-Verlag, New York, **2005**. (b) Fayle, S. E. and Gerrard, J. A., *The Maillard Reaction*, Royal Society of Chemistry: Cambridge, U.K., **2002**.
10. (a) Seifert, S. T.; Krause, R.; Gloe, K. and Henle, T., *J. Agri. Food Chem.*, **2004**, *52*, 2347. (b) Cerny, C. and Davidek, T., *J. Agri. Food Chem.,* **2004**, *52*, 958. (c) Marko, D.; Habermeyer, M.; Kemeny, M.; Weyand, U.; Niederberger, E.; Frank, O. and Hofmann, T., *Chem. Res. Toxicol.*, **2003**, *16*, 48. (d) Stadler, R. H.; Verzegnassi, L.; Varga, N.; Grigorov, M.; Studer, A.; Riediker, S. and Schilter, B., *Chem. Res. Toxicol.*, **2003**, *16*, 1242. (e) Rizzi, G. P., *J. Agri. Food Chem.*, **2003**, *51*, 1728. (f) Pollien, P.; Lindinger, C.; Yeretzian, C. and Blank, I., *Anal. Chem.,* **2003**, *75*, 5488. (g) French, S. J.; Harper, W. J.; Kleinholz, N. M.; Jones, R. B. and Green-Church, K. B., *J. Agri. Food Chem.;* **2002**, *50*, 820. (h) Manini, P.; d'Ischia, M. and Prota, G., *J. Org. Chem.*, **2001**, *66*, 5048. (i) Patel, S.; Rabone, J.; Russell, S.; Tissen, J. and Klaffke, W., *J. Chem. Inf. Comput. Sci.*, **2001**, *41*, 926. (j) Mastrocola, D. and Munari, M., *J. Agri. Food Chem.,* **2000**, *48*, 3555. (k) Shimamura, T.; Ukeda, H. and Sawamura, M., *J. Agri. Food Chem.,* **2000**, *48*, 6227. (l) del Castillo, M. D.; Villamiel, M.; Olano, A. and Corzo, N., *J. Agri. Food Chem.*, **2000**, *48*, 4217. (m) Antony, S. M.; Han, I. Y.; Rieck, J. R. and Dawson, P. L., *J. Agri. Food Chem.,* **2000**, *48*, 3985. (n) Ikeda, K.; Higashi, T.; Sano, H.; Jinnouchi, Y.; Yoshida, M.; Araki, T.; Ueda, S. and Horiuchi, S., *Biochemistry*, **1996**, *35*, 8075. (o) Ledl, F. and Schleicher, E., *Angew. Chem. Int. Ed. Engl.*, **1990**, *29*, 565. (p) Handwerk, R. L. and Coleman, R. L., *J. Agri. Food Chem.*, **1988**, *36*, 231.

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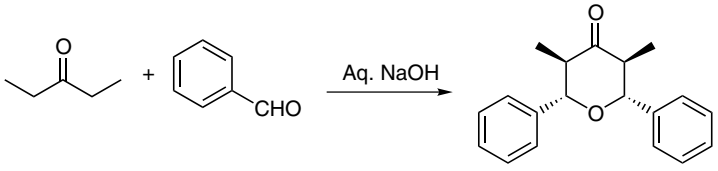
Maitland-Japp Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Japp and Maitland in 1904.[1] It is a one-pot three-component condensation to form multisubstituted tetrahydropyran-4-ones involving a ketone and 2 equivalent of aldehydes. According to the tradition of naming a reaction, such condensation should be known as the Japp-Maitland reaction, but it is generally referred to as the Maitland-Japp reaction.[2] When this reaction was carried out in a basic medium, a mixture of stereoisomers were obtained in low yields,[3] as shown in the original preparation of 2,6-diphenylmethyltetrahydro-4-pyranones from benzaldehyde and 2-butanone by Japp and Maitland.[1] Such reaction was not known for many years due to its long reaction time (e.g., > 7 days), use of excess aqueous reagents, low yield, and lack of generality.[2b] In contrast, when the reaction is promoted by a Lewis acid, the enantioenriched aldol products can be transformed into enantioenriched tetrahydropyran-4-ones without the loss of enantiomeric integrity.[2c] In fact, enantiomerically pure 2,6-*cis*-disubstituted tetrahydropyran-4-ones can be obtained in high yields.[2c]

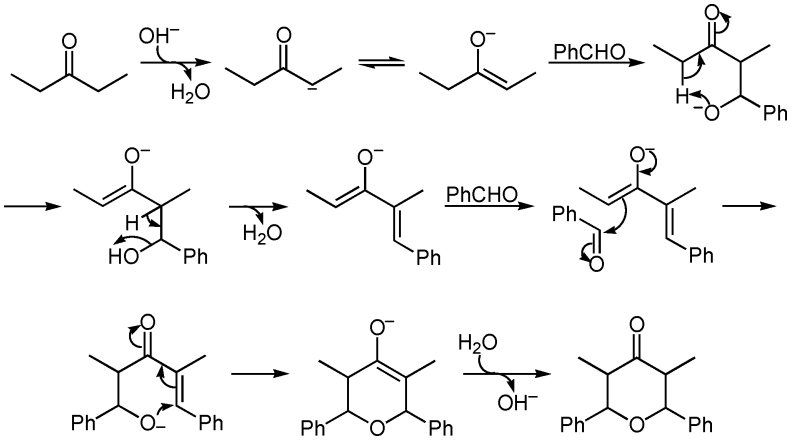
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

This reaction consists of an *Aldol Condensation*, a *Knoevenagel Condensation*, and a *Michael Reaction*.[2c] In addition, it may involve an olefinic intermediate, as evidenced in the condensation between a triethylcarbinol and a benzaldehyde to give 2,6-diphenyl-3,5-dimethyl-4-ethyl-4-tetrahydropyranol.[4] An illustration of the reaction route is provided here.



D. MODIFICATION

This reaction has been extended to use the dienolates of β-ketoesters,[2a,2c,2d] in which two different substituents can be mounted to the 2- and 6-positions of tetrahydropyran-4-ones due to the marked difference in the reactivity of the two enolate carbons by reacting with different aldehydes.[2d]

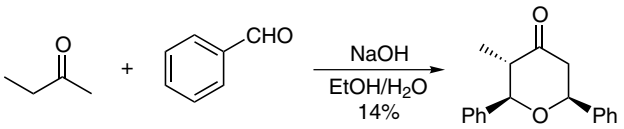
E. APPLICATIONS

N/A

F. RELATED REACTIONS

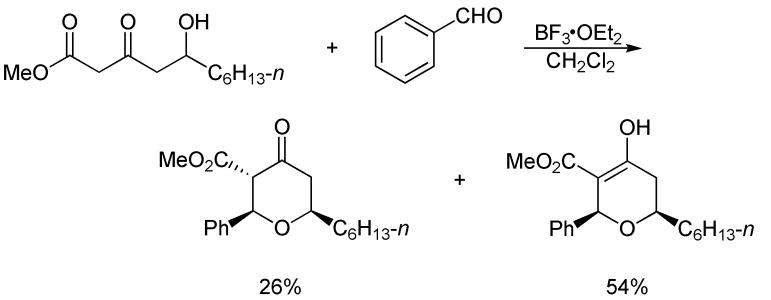
This reaction is related to the *Aldol Condensation* and *Michael Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 3.

A mixture of 223 g benzaldehyde (2.1 mol), 72 g 2-butanone (1 mol), 575 g 66% ethanol (12.5 mol), 1080 g water (60 mol), and 80 mL 10% NaOH (2 mol) was vigorously stirred for 8 days. The thick yellow oily layer was washed with water and taken up in ether, and the ethereal solution was dried over Na_2SO_4. Evaporation of the solvent gave a residue that was fractionated under reduced pressure (2–3 mmHg). The final fraction (b.p. 186–192°C) solidified upon standing, which was purified by crystallization in methanol to give 38 g *r-2*,*cis*-6-diphenyl-*trans*-3-methyltetrahydro-4-pyranone as shining crystals, in a yield of 14%, m.p. 82–83°C.



Reference 2d.

To a stirred solution of 53 mg 3-keto-5-hydroxyl undecanoic acid methyl ester (0.23 mmol), 29.7 mg benzaldehyde (0.28 mmol) in 2 mL CH_2Cl_2 was added 44 μL boron trifluoride etherate (0.35 mmol). The yellowish reaction mixture was stirred at room temperature for 90 min and then diluted with 30 mL ethyl acetate. This solution was washed with saturated aqueous $Na_2S_2O_3$ ($\times$ 3), brine ($\times$ 1) and dried over anhydrous $MgSO_4$. Upon removal of solvent, the residue was purified by flash column chromatography using petroleum ether/EtOAc (20:1) as the eluent to afford 80% pyran derivative in a 1:2 ratio, as shown.

Other references related to the Maitland-Japp reaction are cited in the literature.[4]

H. REFERENCES

1. Japp, F. R. and Maitland, W., *J. Chem. Soc.*, **1904**, *85*, 1473.
2. (a) Clarke, P. A. and Martin, W. H. C., *Tetrahedron,* **2005**, *61*, 5433. (b) Clarke, P. A.; Martin, W. H. C.; Hargreaves, J. M.; Wilson, C. and Blake, A. J., *Org. Biomol. Chem.,* **2005**, *3*, 3551. (c) Clarke, P. A.; Martin, W. H. C.; Hargreaves, J. M.; Wilson, C. and Blake, A. J., *Chem. Commun.*, **2005**, 1061. (d) Clarke, P. A. and Martin, W. H. C., *Org. Lett.*, **2002**, *4*, 4527.
3. Sivakumar, R.; Satyamurthy, N.; Ramalingam, K.; O'Donnell, D. J.; Ramarajan, K. and Berlin, K. D., *J. Org. Chem.*, **1979**, *44*, 1559.
4. (a) Clarke, P. A. and Martin, W. H. C., *Tetrahedron Lett.*, **2004**, *45*, 9061. (b) Duke, F. R. and Freeland, M. Q., *J. Am. Chem. Soc.,* **1955**, *77*, 1675.

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Majetich Annulation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Majetich in 1985.[1] It is a Lewis acid or fluoride promoted intramolecular cyclization of allylsilanes with their intrinsic olefinic group. Thus it is generally called the Majetich annulation. The special case of a 7-trialkylsilyl-1,5-diene system forming vinyl cyclobutanes when promoted by fluoride is known as the Majetich cyclobutane annulation or Majetich reaction, whereas cyclopentanes or cyclohexanes may form if a Lewis acid is used to promote the reaction.[2] This is because the fluoride ion confers an *anti*-orientation of the silyl alkene through kinetic control, and the Lewis acid prefers the synclinal orientation.[3] This reaction is especially useful for the preparation of bicyclic ring systems, such as 5-5, 6-5, 5-7, and 6-7 ring systems, via the intramolecular addition of allylsilanes to cycloalkenones.[4] It has been found that the formation of cyclohexane in a bicyclic ring system promoted by the Lewis acid is not sensitive to the size of the existing cycloalkenone, and the regioselectivity is not affected by the silicon ligand either. This particular reaction prefers an excess amount of Lewis acid and may lead to silyl dienol ethers if no acidic hydrolysis or incomplete hydrolysis is applied during the workup process.[3] Comparably, when a corresponding annulation is promoted by fluoride, it is better to carry out the reaction in DMF in the presence of three equivalent of HMPA, rather than the conventional solvent of THF.[3]

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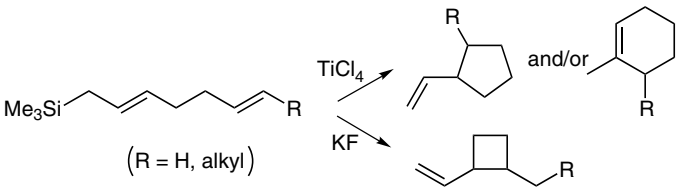
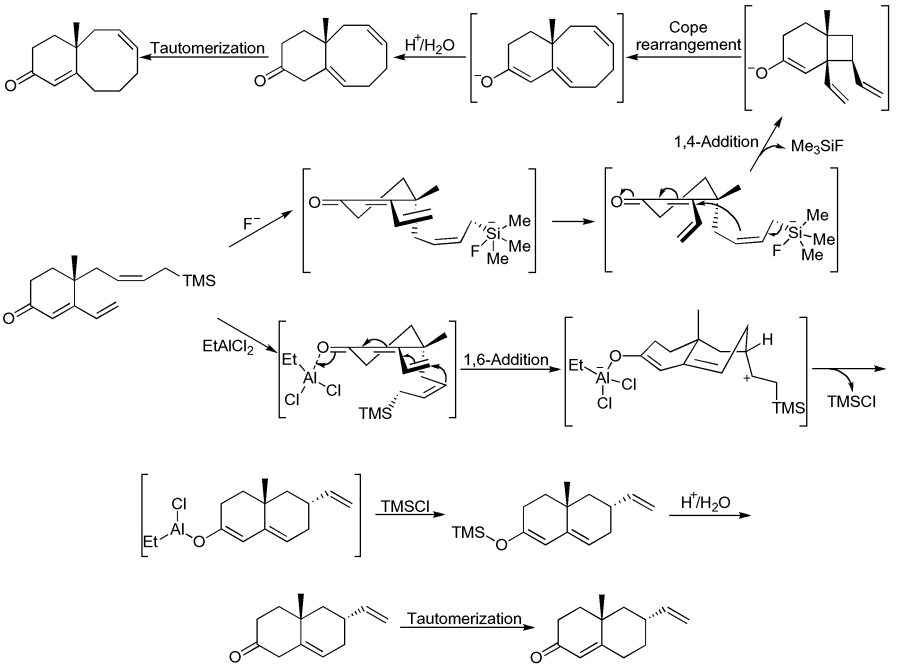
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A mechanism modified from Majetich is illustrated below to demonstrate the formation of a 6-membered ring and a 6-membered ring in a bicyclic system when promoted by a Lewis acid and fluoride, respectively.



D. MODIFICATION

N/A

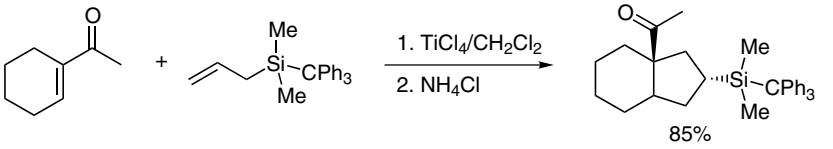
E. APPLICATIONS

This reaction has general application in the preparation of bicyclic systems.

F. RELATED REACTIONS

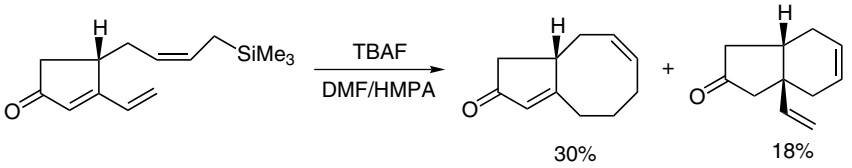
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 5.

To 3 mL CH_2Cl_2 solution containing 37.2 mg 1-acetyl cyclohexene (0.3 mmol) at –78°C was added 0.36 mL 1.0 M $TiCl_4$ in CH_2Cl_2 dropwise via syringe. After the mixture was vigorously stirred for 5 min, 0.12 g allyltrityldimethylsilane (0.36 mmol) was added dropwise as a solution in CH_2Cl_2. The reaction temperature was slowly allowed to reach 0°C over 4 h. The reaction was monitored by TLC (1:4, EtOAc/hexanes) and quenched by the addition of saturated aqueous NH_4Cl, resulting in a colorless mixture. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. The residue was purified via flash chromatography (9:1, hexanes/EtOAc) to afford 0.11 g *trans*-1-acetyl-8-(dimethyltritylsilyl)bicyclo[4.3.0]-nonane as a colorless solid, in a yield of 85%, m.p. 152–153°C.



Reference 3.

A reaction vessel containing 4-Å molecular sieves was flame dried under vacuum for 5 min and placed under nitrogen. A DMF solution (3 mL) containing 35 mg anhydrous TBAF (0.13 mmol) was added to the flask and stirred for 20 min, followed by the addition of HMPA (0.54 mL, 3.0 mmol). A solution of 150 mg (*Z*)-4-[4-(trimethylsilyl)-2-butenyl]-3-vinyl-2-cyclopenten-1-one (0.64 mmol) in 2.0 mL DMF was added dropwise via syringe pump at room temperature over a 2-h period. The resulting mixture was stirred for an additional 12 h. Standard ethereal workup afforded 112 mg crude oily residue. Purification on silica gel (hexane/EtOAc, 10:1) provided 18 mg *cis*-3a,4,7,7a-tetrahydro-3a-ethenyl-2-indanone, in a yield of 18%, $R_f = 0.72$ (hexane/EtOAc, 1:1). Further elution provided 32 mg 1,2,4,5,9,9a-hexahydro-6H-cyclopentacycloocten-2-one, in a yield of 30%, $R_f = 0.50$ (hexane/EtOAc, 1:1).

Other references related to the Majetich annulation are cited in the literature.[6]

H. REFERENCES

1. Majetich, G.; Defauw, J.; Hull, K. and Shawe, T., *Tetrahedron Lett*., **1985**, *39*, 4711.
2. May, S. A.; Grieco, P. A. and Lee, H.-H., *Synlett*, **1997**, 493.
3. Majetich, G.; Hull, K.; Casares, A. M. and Khetani, V., *J. Org. Chem*., **1991**, *56*, 3958.
4. Majetich, G.; Defauw, J. and Ringold, C., *J. Org. Chem*., **1988**, *53*, 50.
5. Groaning, M. D.; Brengel, G. P. and Meyers, A. I., *J. Org. Chem*., **1998**, *63*, 5517.
6. (a) Mehta, G. and Srikrishna, A., *Chem. Rev*., **1997**, *97*, 671. (b) May, S. A.; Grieco, P. A. and Lee, H. H., *Synlett*, **1997**, 493. (c) Brengel, G. P.; Rithner, C. and Meyers, A. I., *J. Org. Chem*., **1994**, *59*, 5144. (d) Majetich, G.; Song, J.-S.; Ringold, C.; Nemeth, G. A. and Newton, M. G., *J. Org. Chem*., **1991**, *56*, 3973. (e) Majetich, G. and Defauw, *J., Tetrahedron*, **1988**, *44*, 3833.

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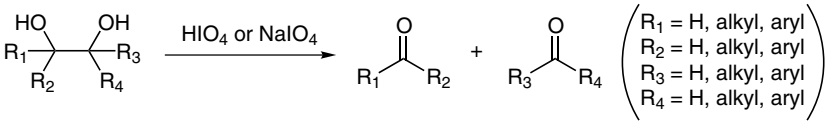
Malaprade Reaction
(Malaprade Oxidation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Malaprade in 1928.[1] It is an oxidation of adjacent diols with periodic acid or its salt in aqueous solution. Thus it is generally known as the Malaprade reaction.[2,3] Occasionally, it is also referred to as the Malaprade oxidation.[4] In this oxidation, solvents such as methanol, ethanol, and acetic acid, can be added to the reaction solution to increase the solubility of organic substrates. Similar to the *Criegee Glycol Oxidation*, this reaction is also assumed to involve an acidic cyclic ester intermediate that decomposes to yield aldehyde and/or ketone.[5] This reaction has been extended to the cleavage of α-hydroxy carbonyl compounds, 1,2-dicarbonyl compounds, α-amino alcohols, α-amino acids,[6] and polyhydroxy alcohols.[7] In these oxidations, the hydroxyl group is oxidized to an aldehyde or a ketone group, the carbonyl group is oxidized to a carboxyl group, and the amino group is converted into an aldehyde group and ammonia (or a substituted amine in the case of a secondary amine). In the case of an adjacent polyhydroxyl alcohol, the reaction occurs at the terminal hydroxyl group, and middle hydroxyl groups are converted into formic acid.[7a] It has been found that this reaction proceeds faster under acidic conditions than that in neutral or basic solutions.[8] This reaction has been successfully used for the degradation of carbohydrates and in structural analysis.[2h,9]

B. GENERAL REACTION SCHEME



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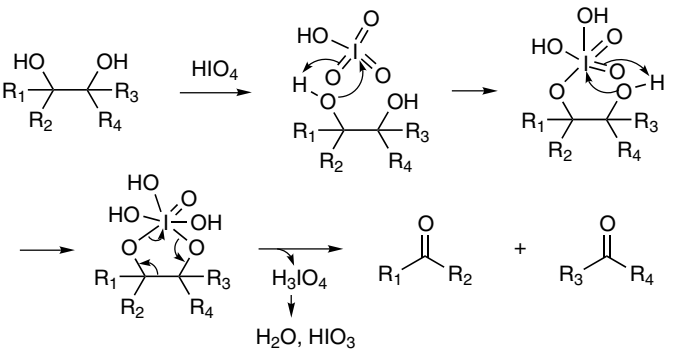
C. PROPOSED MECHANISMS



D. MODIFICATION

N/A

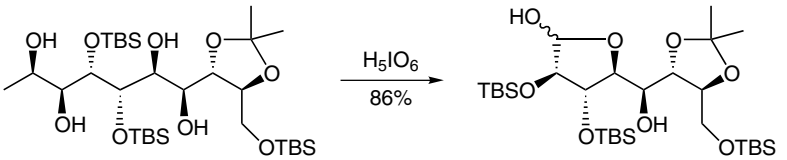
E. APPLICATIONS

This reaction has general application in the oxidation of vicinal diols, amino alcohols, and similar structures.

F. RELATED REACTIONS

This reaction is related to the *Criegee Glycol Oxidation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 10.

To a solution of 500 mg (2*R*,3*S*,4*S*,5*R*,6*R*,7*R*,8*R*,9*S*)-4,5,10-tris[(*tert*-butyldimethylsilyl)oxy]-8,9-*O*-(l-methylethylidene)-2,3,6,7-decanetetrol (0.75 mmol) in 15 mL THF at 0°C was added 188 mg periodic acid (0.82 mmol). After being stirred at 0°C for

1 h, the reaction mixture was diluted with 50 mL Et_2O; washed with saturated $NaHCO_3$ (10 mL), H_2O (10 mL), and brine (10 mL); and dried over Na_2SO_4. Flash chromatography on silica gel (4:l, hexanes/Et_2O) afforded 400 mg lactol as a colorless oil, in a yield of 86%.

Other references related to the Malaprade reaction are cited in the literature.[11]

H. REFERENCES

1. (a) Malaprade, L., *Bull. Soc. Chim. Fr.*, **1928**, *43*, 683. (b) Malaprade, L., *Compt. Rend.*, **1928**, *186*, 382.
2. (a) Pumera, M.; Jelinek, I.; Jindrich, J.; Coufal, P. and Horsky, J., *J. Chromatogr. A.*, **2000**, *891*, 201. (b) Kuotsu, B.; Tiewsoh, E.; Debroy, A. and Mahanti, M. K., *J. Org. Chem.*, **1996**, *61*, 8875. (c) Chen, K. P., *J. Pharm. Sci.*, **1984**, *73*, 681. (d) Mikhailov, B. M.; Aronovich, P. M. and Kiselev, V. G., *Russ. Chem. Bull.*, **1968**, *17*, 137. (e) Kirby, J. R.; Baldwin, A. J. and Heidner, R. H., *Anal. Chem.*, **1965**, *37*, 1306. (f) Marder, H. L. and Schuerch, C., *J. Org. Chem.*, **1959**, *24*, 1977. (g) Nogare, S. D. and Oemler, A. N., *Anal. Chem.*, **1952**, *24*, 902. (h) Moe, O. A.; Miller, S. E. and Iwen, M. H., *J. Am. Chem. Soc.*, **1947**, *69*, 2621.
3. (a) Gupta, M.; Jain, A. and Verma, K. K., *Talanta*, **2007**, *71*, 1039. (b) Zhang, B. and Beck, H. P., *J. Flow. Inject. Anal.*, **2004**, *21*, 37. (c) Afkhami, A. and Mosaed, F., *J. Anal. Chem.*, **2003**, *58*, 588. (d) Afkhami, A. and Mosaed, F., *Microchem. J.*, **2001**, *68*, 35. (e) Jie, N. Q.; Yang, D. L.; Zhang, Q.; Yang, J. H. and Song, Z. Q., *Anal. Chim. Acta*, **1998**, *359*, 87. (f) Guillen-Sans, R. and Guzman-Chozas, M., *Critic. Rev. Food Sci. & Nutri.*, **1998**, *38*, 315. (g) Liu, W. X. and Tan, H. L., *Yaowu Shengwu Jishu*, **1996**, *3*, 112. (h) Bystryakov, V. P.; Polevkov, Ya. V. and Dragun, S. K., *Farmatsiya (Moscow)*, **1992**, *41*, 72. (i) Berzas Nevado, J. J. and Valiente Gonzalez, P., *Analyst (Cambridge)*, **1989**, *114*, 989. (j) Berzas Nevado, J. J. and Valiente Gonzalez, P., *Analyst (Cambridge)*, **1989**, *114*, 243. (k) Verma, K. K.; Gupta, D.; Sanghi, S. K. and Jain, A., *Analyst (Cambridge)*, **1987**, *112*, 1519. (l) Velich, V. and Stehlik, F., *J. Therm. Anal.*, **1982**, *24*, 299. (m) Al-Zamil, I. Z.; Al-Hajjaji, M. A. and Aziz-Alrahman, A. M., *Anal. Lett.*, **1982**, *15*, 831. (n) Durrani, A. A.; Sun, G. C. and Tyman, J. H. P., *Lipids*, **1982**, *17*, 561. (o) Mochon, M. C. and Munoz Leyva, J. A., *Anal. Chim. Acta*, **1982**, *140*, 271. (p) Belcher, R.; Dryhurst, G. and MacDonald, A. M. G., *J. Chem. Soc.*, **1965**, 3964. (q) Shimizu, S., *Bull. Agri. Chem. Soc. Jpn.*, **1956**, *20*, 84. (r) Fleury, P. F., *Bull. Soc. Chim. Fr.*, **1955**, 1126. (s) Lorenzini, P., *Endocrinol. Sci. Costituz.*, **1952**, *21*, 131. (t) Head, F. S. H. and Hughes, G., *J. Chem. Soc.*, **1952**, 2046.
4. (a) Moulines, J.; Bats, J.-P.; Lamidey, A.-M. and da Silva, N., *Helv. Chim. Acta*, **2004**, *87*, 2695. (b) Lillie, R. D., *Anatomical Record*, **1950**, *108*, 239.
5. Wittcoff, H.; Moe, O. A. and Iwen, M. H., *J. Am. Chem. Soc.*, **1948**, *70*, 742.
6. Nicolet, B. H. and Shinn, L. A., *J. Am. Chem. Soc.*, **1939**, *61*, 1615.
7. (a) Hurd, C. D.; Baker, P. J.; Holysz, R. P. and Saunders, W. H., *J. Org. Chem.*, **1953**, *18*, 186. (b) Brockmann, M. C. and Werkman, C. H., *Anal. Chem.*, **1933**, *5*, 206.
8. Price, C. C. and Kroll, H., *J. Am. Chem. Soc.*, **1938**, *60*, 2726.
9. (a) Hullar, T. L. and Smith, F., *J. Org. Chem.*, **1966**, *31*, 1657. (b) Hamilton, J. K. and Smith, F., *J. Am. Chem. Soc.*, **1956**, *78*, 5907. (c) Michell, J. H. and Purve, C. B., *J. Am. Chem. Soc.*, **1942**, *64*, 585.
10. Marshall, J. A. and Beaudoin, S., *J. Org. Chem.*, **1994**, *59*, 6614.
11. (a) Evans, B. J.; Doi, J. T. and Musker, W. K., *J. Org. Chem.*, **1990**, *55*, 2580. (b) König, H. and Walldorf, E., *Anal. Bioanal. Chem.*, **1989**, *335*, 216. (c) Bunton, C. A. and Shine, V. J., *J. Chem.*

Soc., **1960**, 1593. (d) Buist, G. J.; Bunton, C. A. and Miles, J. H., *J. Chem. Soc.*, **1957**, 4567. (e) Buist, G. J.; Bunton, C. A. and Miles, J. H., *J. Chem. Soc.*, **1957**, 4575. (f) Goldstein, I. J.; Hamilton, J. K.; Montgomery, R. and Smith, F., *J. Am. Chem. Soc.*, **1957**, *79*, 6469. (g) Jones, L. R. and Riddick, J. A., *Anal. Chem.*, **1957**, *29*, 1214. (h) Rankin, J. C. and Jeanes, A., *J. Am. Chem. Soc.*, **1954**, *76*, 4435. (i) Jackson, E. L., *Org. React.*, **1944**, *2*, 341. (j) Jackson, E. L. and Hudson, C. S., *J. Am. Chem. Soc.*, **1939**, *61*, 1530. (k) Fleury, P. and Lange, J., *Compt. Rend.*, **1932**, *195*, 1395. (l) Fleury, P. and Paris, R., *Compt. Rend.*, **1933**, *196*, 1416. (m) Malaprade, L., *Ann. Chim.*, **1929**, *11*, 104.

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Malonic Ester Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

It is a general reaction using dialkyl malonates, mostly diethyl malonate, as starting material, and is commonly known as malonic ester synthesis.[1] In general, being activated by two electron-withdrawing ester groups, the α-methylene protons of dialkyl malonates are relatively acidic with a pKa $\sim$13 and can be readily deprotonated by sodium ethoxide to form the corresponding carbanions, which then participate in the reactions that other carbanions usually undergo, such as the nucleophilic substitutions and nucleophilic additions. For the nucleophilic substitution, mostly via the S_N2 mechanism, alkyl halides,[1j,2] sulfates,[2b] carbonates,[3] and mesylates[1b] are all suitable alkylating reagents. It has been found that the alkylation rate is related to the acidity of α-proton,[4] and in the presence of an excess amount of malonic acid ester, the yield of monosubstitution is improved.[2a] On the other hand, when the substitution on the secondary mesylate proceeds under almost neutral conditions, it results in a complete inversion of stereochemistry.[1a] In addition, malonic acid ester can function as an acid to facilitate the inversion of chirality without the occurrence of substitution.[5] Meanwhile, the fast alkylation of preformed enolate from alkyl malonic acid ester can afford the vinyl malonic acid ester.[6] During the alkylation of malonic acid ester, the reversible cleavage of formed alkyl malonic acid ester or dialkyl malonic acid ester gives a simple alkyl ester;[3b,3c] furthermore, the cleavage of the dialkyl malonic acid ester is faster than that of monosubstituted or unsubstituted malonic acid ester.[3c] For the reaction between sodium malonic acid ester and 2-bromo-2-nitropropane or 2-chloro-2-nitropropane, only the reaction with 2-chloro-2-nitropropane undergoes the expected substitution, whereas sodium 2-nitropropane and ethyl bromomalonate are generated from the reaction with 2-bromo-2-nitropropane.[7] These alkylated malonic acid esters are used to synthesize barbiturates[8] with urea or α-amino acid ester or α-amino acid and

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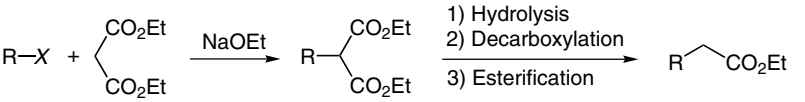
alkyl nitrite.[9] It is interesting that the allyl group can be applied as the protecting group of α-proton, which can be removed by $Ti(OPr)_4$; therefore, monosubstituted malonic acid ester can be easily obtained from allylic malonic acid ester.[10]

On the other hand, the sodium malonic acid ester enolate also undergoes nucleophilic addition reaction. For example, the addition to epoxide in the presence of $AlCl_3$ results in the formation of γ-hydroxy carboxylate[11] and γ-butyrolactone;[12] the addition of enolate to α-carbonyl acetylene yields 2-pyrone ester,[13] of which the alkyl group is from the solvent, regardless of the starting malonic acid ester.[13a] Similarly, the addition of sodium malonic acid ester enolate to imino acetylene gives 2-pyridones.[14] The addition of acyl halide leads to the formation of β-ketoester.[15] In the presence of $Mn(OAc)_3$, malonic acid ester adds to cyclopropylidene involving a free radical.[16] In a special case, the malonic acid ester enolate can undergo either nucleophilic substitution or nucleophilic addition when it reacts with α-chloro-aldehyde, depending on the aprotic solvent (e.g., THF) or protic solvent (e.g., H_2O).[17] The malonic ester synthesis has been modified for traceless synthesis on solid support.[18] After the desired reaction, one of the ester groups can be removed via hydrolysis, decarboxylation, and reesterification; however, the ester group can also be removed through pyrolysis at temperatures $\sim 470^{\circ}C$.[19]

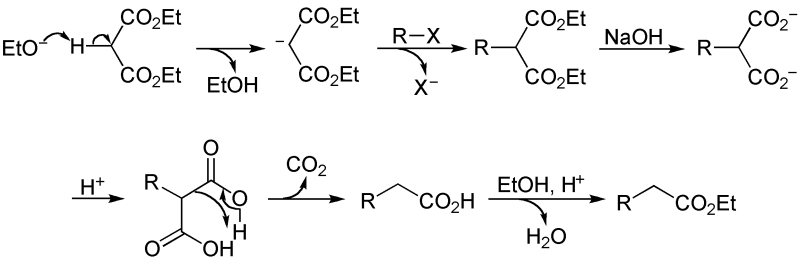
In general, malonic acid ester can be prepared from (*a*) α-chloroacetic acid and NaCN,[8] (*b*) carboxylation of aliphatic acid enolate then esterification with diazomethane,[20] and (*c*) aliphatic acid enolate with diethyl carbonate.[3c]

B. GENERAL REACTION SCHEME



(R–*X* = halide, tosylate, mesylate, carbonate)

C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified for traceless synthesis via solid support.[18]

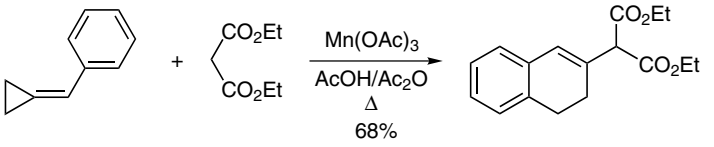
E. APPLICATIONS

This reaction has very general application in organic synthesis.

F. RELATED REACTIONS

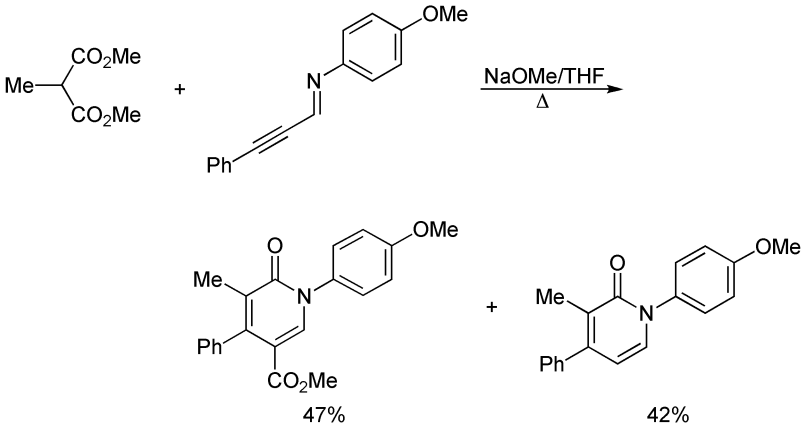
This reaction is related to *Acetoacetic Ester Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 16.

The mixture of 130 mg benzylidenecyclopropane (1.0 mmol), 530 mg $Mn(OAc)_3 \cdot 2H_2O$ (2.0 mmol), and 160 mg diethyl malonate (1.0 mmol) in 5 mL $AcOH/Ac_2O$ (9:1) was stirred at 65°C under a nitrogen atmosphere for 10 h. The mixture was diluted with 40 mL brine and extracted three times with EtOAc. The organic phases were combined, dried over $MgSO_4$, and concentrated. The residue was purified via silica gel chromatography (*n*-hexane/ EtOAc, 10:1) to afford 196 mg 2-(3,4-dihydro-naphthalen-2-yl)-malonic acid diethyl ester as a oil, in a yield of 68%.



Reference 14.

To a THF solution of 0.4 mmol sodium methoxide was added 0.5 mmol dimethyl methylmalonate in 2 mL THF at room temperature, followed by 2 mL THF solution containing 0.2 mmol alkynyl imine. The mixture was refluxed for 7 h and then cooled to room temperature. Brine (10 mL) was added to quench the reaction, and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by preparative TLC to give 47% 2-pyridone and 42% decarboxylated 2-pyridone, respectively.

Other references related to the malonic ester synthesis are cited in the literature.[21]

H. REFERENCES

1. (a) Ogawa, K.; Sasaki, M. and Nozaki, T., *Appl. Radiation Isotopes*, **1997**, *48*, 623. (b) Sato, T. and Otera, J., *J. Org. Chem.*, **1995**, *60*, 2627. (c) Hoogenboom, B. E.; Ihrig, P. J.; Langsjoen, A. N.; Linn, C. J. and Mulder, S. D., *J. Chem. Edu.,* **1991**, *68*, 689. (d) Obaza, J. and Smith, F. X., *Synth. Commun.*, **1982**, *12*, 19. (e) Casadei, M. A.; Galli, C. and Mandolini, L., *J. Org. Chem.*, **1981**, 46, 3127. (f) Padgett, H. C.; Csendes, I. G. and Rapoport, H., *J. Org. Chem.*, **1979**, *44*, 3492. (g) Sasamura, Y. and Morita, S., *Tomakomai Kogyo Koto Senmon Gakko Kiyo*, **1979**, 83. (h) Verbrugge, P. A.; Tieleman, J. H.; Van der Jagt, P. J. and Bickelhaupt, F., *Synth. Commun.*, **1977**, *7*, 1. (i) Hunter, D. H. and Perry, R. A., *Synthesis*, **1977**, *37*. (j) McMurry, J. E. and Musser, J. H., *J. Org. Chem.*, **1975**, *40*, 2556. (k) Black, D. S. C.; Brown, R. F. C. and Wade, A. M., *Aust. J. Chem.*, **1972**, *25*, 2155. (l) Creger, P. L., *J. Am. Chem. Soc.*, **1970**, *92*, 1397. (m) Mamedov, S.; Khydyrov, D. N.; Gevorkyan, A. N.; Rustamov, V. R. and Ismailov, R. G., *Dokl. Akad. Nauk Azerbaidzhanskoi SSR*, **1969**, *25*, 10. (n) Shimo, K. and Wakamatsu, S., *J. Org. Chem.*, **1963**, *28*, 504. (o) Tschudy, D. P. and Collins, A., *J. Org. Chem.*, **1959**, *24*, 556. (p) Mizuno, Y.; Adachi, K. and Ikeda, K., *Pharm. Bull.*, **1954**, *2*, 225. (q) Ghosh, A.; Mukherjee, R. B. and Raha, C. R., *Sci. Culture*, **1954**, *20*, 95. (r) Sommer, L. H.; Goldberg, G. M.; Barnes, G. H. and Stone, L. S., *J. Am. Chem. Soc.*, **1954**, *76*, 1609. (s) Sommer, L. H.; Goldberg, G. M.; Barnes, G. H. and Stone, L. S., *J. Am. Chem. Soc.*, **1954**, *76*, 1609. (t) Gol'mov, V. P., *Zh. Obsh. Khim.*, **1953**, *23*, 1169. (u) Gol'mov, V. P. and Afanas'ev, N. M., *Zh. Obsh. Khim.*, **1953**, *23*, 1188.
2. (a) Grigsby, W. E.; Hind, J.; Chanley, J. and Westheimer, F. H., *J. Am. Chem. Soc.*, **1942**, *64*, 2606. (b) Cope, A. C. and Hancock, E. M., *J. Am. Chem. Soc.*, **1938**, *60*, 2644.
3. (a) Wallingford, V. H. and Jones, D. M., *J. Am. Chem. Soc.*, **1942**, *64*, 578. (b) Wallingford, V. H.; Homeyer, A. H. and Jones, D. M., *J. Am. Chem. Soc.*, **1941**, *63*, 2056. (c) Cope, A. C. and McElvain, S. M., *J. Am. Chem. Soc.*, **1932**, *54*, 4319.
4. Pearson, R. G., *J. Am. Chem. Soc.*, **1949**, *71*, 2212.
5. Kubo, A.; Kubota, H.; Takahashi, M. and Nunami, K.-I., *J. Org. Chem.*, **1997**, *62*, 5830.
6. Cope, A. C.; Hartung, W. H.; Hancock, E. M. and Crossley, F. S., *J. Am. Chem. Soc.*, **1940**, *62*, 314.
7. Van Tamelen, E. E. and van Zyl, G., *J. Am. Chem. Soc.*, **1950**, *72*, 2979.
8. Ross, A. A. and Bibbins, F. E., *Ind. Eng. Chem.*, **1937**, *29*, 1341.
9. Shivers, J. C. and Hauser, C. R., *J. Am. Chem. Soc.*, **1947**, *69*, 1264.
10. Yamazaki, T.; Kasatkin, A.; Kawanaka, Y. and Sato, F., *J. Org. Chem.*, **1996,** *61*, 2266.
11. Raha, C., *J. Am. Chem. Soc.*, **1953**, *75*, 4098.
12. (a) Hart, H. and Curtis, O. E., *J. Am. Chem. Soc.*, **1955**, *77*, 3138. (b) van Tamelen, E. E.; van Zyl, G. and Zuidema, G. D., *J. Am. Chem. Soc.*, **1950**, *72*, 488. (c) Russell, R. R. and VanderWerf, C. A., *J. Am. Chem. Soc.*, **1947**, *69*, 11.
13. (a) Bickel, C. L., *J. Am. Chem. Soc.*, **1950**, *72*, 1022. (b) Kohler, E. P., *J. Am. Chem. Soc.*, **1922**, *44*, 379.
14. Hachiya, I.; Ogura, K. and Shimizu, M., *Org. Lett.*, **2002**, *4*, 2755.
15. Riegel, B. and Lilienfeld, W. M., *J. Am. Chem. Soc.*, **1945**, *67*, 1273.
16. Zhou, H. W.; Huang, X. and Chen, W. L., *J. Org. Chem.*, **2004**, *69*, 5471.
17. Takeda, A.; Tsuboi, S. and Oota, Y., *J. Org. Chem.*, **1973**, *38*, 4148.
18. Huang, X. and Liu, Z. X., *J. Org. Chem.*, **2002**, *67*, 6731.
19. Bailey, W. J. and Daly, J. J., *J. Org. Chem.*, **1964**, *29*, 1249.
20. Hauser, C. C.; Levine, R. and Kibler, R. F., *J. Am. Chem. Soc.*, **1946**, *68*, 26.
21. (a) Zambito, A. J. and Howe, E. E., *Org. Synth.*, **1960**, *40*, 21. (b) Blomquist, A. T. and Wolinsky, J., *J. Org. Chem.*, **1956**, *21*, 1371. (c) Pratt, E. F. and Boehme, W. E., *J. Am. Chem. Soc.*, **1951**, *73*, 444.

(d) Bachmann, W. E. and Fornefeld, E. J., *J. Am. Chem. Soc.*, **1950**, *72*, 5529. (e) Kepner, R. E.; Winstein, S. and Young, W. G., *J. Am. Chem. Soc.*, **1949**, *71*, 115. (f) Cope, A. C.; Hofmann, C. M.; Wyckoff, C. and Hardenbergh, E., *J. Am. Chem. Soc.*, **1941**, *63*, 3452. (g) Roland, J. R. and McElvain, S. M., *J. Am. Chem. Soc.*, **1937**, *59*, 132. (h) Smith, L. I. and Webster, I. M., *J. Am. Chem. Soc.*, **1937**, *59*, 662. (i) Smith, L. I. and Johnson, K. C., *J. Am. Chem. Soc.*, **1937**, *59*, 673. (j) Michael, A., *J. Org. Chem.*, **1937**, *2*, 303. (k) Wojcik, B. and Adkins, H., *J. Am. Chem. Soc.*, **1934**, *56*, 2424. (l) Dunn, M. S.; Redemann, C. E. and Lauritsen, S., *J. Am. Chem. Soc.*, **1932**, *54*, 4335. (m) Michael, A. and Ross, J., *J. Am. Chem. Soc.*, **1930**, *52*, 4598.

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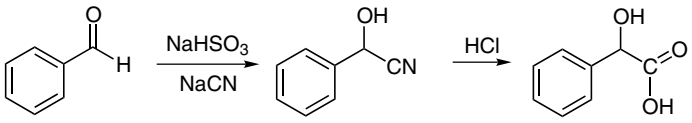
Mandelic Acid Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

Mandelic acid is α-hydroxyl phenyl acetic acid. Mandelic acid and its derivatives are very useful in medicinal chemistry;[1] some of them have been used in pharmaceutical applications.[2] A few methods have been developed to synthesize mandelic acid and even optically pure mandelic acid. Shown here is the general method for the preparation of mandelic acid from benzaldehyde and sodium cyanide.

B. GENERAL REACTION SCHEME



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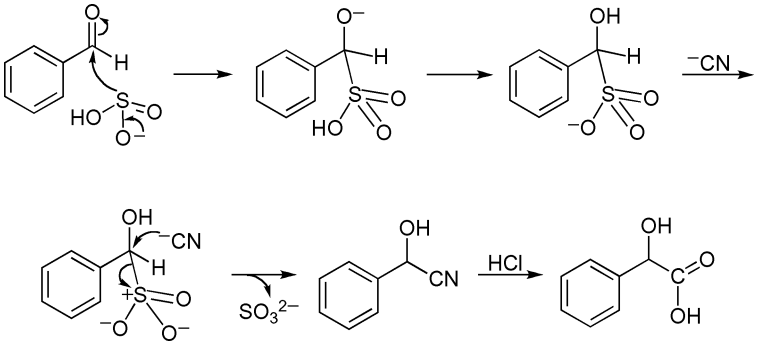
C. PROPOSED MECHANISMS



D. MODIFICATION

Because NaCN is extremely poisonous, other methods have been developed to prepare mandelic acid and its derivatives, as shown in Section G.

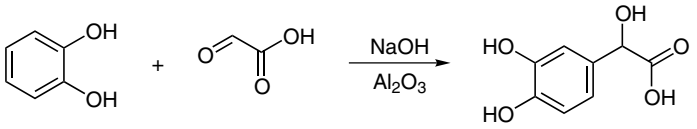
E. APPLICATIONS

Mandelic acid and its derivatives have found wide application in the pharmaceutical industry.[3]

F. RELATED REACTIONS

N/A

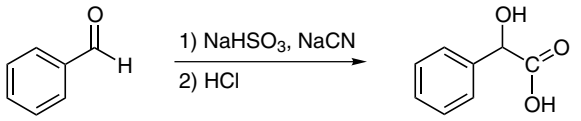
G. CITED EXPERIMENTAL EXAMPLES



Reference 4.

Catechol (5.00 g, 45.41 mmol) was dissolved in aqueous NaOH prepared from 3.21 g NaOH (80.3 mmol) and 55.0 mL water; then 2.04 g Al_2O_3 (20 mmol) was added. After 5 min, 50% aqueous solution containing 7.10 g glyoxylic acid (48.0 mmol) was added to the reaction mixture, and the resulting mixture was heated at 60°C for 24 h under vigorous stirring. The reaction mixture was then allowed to precipitate for 10 min and Al_2O_3 was removed by filtration. The filter cake was washed with 20 mL 1 M NaOH. The combined

aqueous solution was acidified to pH 3-4 with 6.0 mL 37% HCl and extracted with ethyl acetate to recover the unreacted catechol (1.2 g). The aqueous solution was further acidified to pH 1 by 2 mL concentrated HCl and extracted with ethyl acetate to isolate 5.1 g mandelic acid derivative (28.08 mmol) with 77.5% conversion, and 90.5% selectivity.



Reference 5.

In a 4-L wide-mouthed glass jar fitted with a mechanical stirrer was placed a solution of 150 g sodium cyanide (3 mol) in 500 mL water and 318 g benzaldehyde (3 mol). The stirrer was started, and 850 mL saturated sodium bisulfite solution was added to the mixture, slowly at first and then in a thin stream. The time of addition was 10–15 min. During the addition of the first half of the solution, 900 g cracked ice was added to the reaction mixture, a handful at a time. The layer of mandelonitrile, which appeared during the addition of the sulfite solution was separated from the water in a separatory funnel. The water was extracted once with ∼150 mL benzene, the benzene was evaporated, and the residual mandelonitrile was added to the main portion.

The crude nitrile (∼ 290 mL) was placed at once in a 25-cm evaporating dish, and conc. HCl (425 mL) was added. The hydrolysis was allowed to proceed in the cold for ∼12 h, after which the mixture was heated on a steam bath to remove the water and excess hydrochloric acid. After being heated for 5–6 h, the mixture was cooled and the ammonium chloride and mandelic acid mixture that separated was filtered. The filtrate was then evaporated to dryness. This residue was added to the solid material obtained earlier. The product was deeply colored and had to be dried in the air and light for at least 24 h. The total yield of the crude mandelic acid–ammonium chloride mixture was 370–390 g, depending on the amount of moisture. The mixture of ammonium chloride and mandelic acid was ground in a mortar, transferred to a 2-L flask, and washed twice with 750-mL portions of cold benzene. The insoluble portion was transferred to a suction funnel and sucked dry.

The mandelic acid was separated from the ammonium chloride by extraction with hot benzene. This was best done by dividing the solid mixture into 10 approximately equal parts. One of these portions was placed in a flask with 1 L boiling benzene. After a few minutes, the hot benzene solution was decanted through a suction funnel. The filtrate was cooled in an ice bath, and the mandelic acid that crystallized was filtered with suction. The benzene was returned to the extraction flask containing the residue from the first extraction, and a new portion of the ammonium chloride–mandelic acid mixture was added and extracted as before. The process was repeated until the mandelic acid was completely removed from the ammonium chloride. The amount of pure white mandelic acid, melting at 118°C, was 229–235 g, with a corresponding 50–52% yield.

Other references related to the mandelic acid synthesis are cited in the literature.[6]

H. REFERENCES

1. (a) Khalaj, A.; Shadnia, H. and Sharifzadeh, M., *Pharm. Pharmacol. Commun*., **1998**, *4*, 373. (b) Miersch, O.; Kramell, R.; Parthier, B. and Wasternack, C., *Phytochemistry*, **1999**, *50*, 353. (c) El-Nimr, A. E.; Salama, H. A.; Khalil, R. M. and Kassem, M. A., *Pharmazie*, **1983**, *38*, 728. (d) Nishihata, T.; Takahagi, H.; Yamamoto, M.; Tomida, H.; Rytting, J. H. and Higuchi T., *J. Pharm. Sci*., **1984**, *73*, 109. (e) Yoshioka, M.; Yoshida, A.; Ichihashi, Y. and Saito, H., *Chem. Pharm. Bull*., **1985**, *33*, 2145.
2. Grover, P. T.; Bhongle, N. N.; Wald, S. A. and Senanayake, C. H., *J. Org. Chem.*, **2000**, *65*, 6283.
3. Hof, R. P. and Kellogg, R. M., *J. Org. Chem.*, **1996**, *61*, 3423.
4. Bjørsvik, H.-R.; Liguori, L. and Minisci, F., *Organic Process Research & Development,* **2000**, *4*, 534.
5. Corson, B. B.; Dodge, R. A.; Harris, S. A. and Yeaw, J. S., *Org. Synth. Coll. Vol. I,* **1941**, 336.
6. (a) Ling, S. M. and Long, J. Q., *Huaxue Shijie*, **2005**, *46*, 551. (b) Mateo, C.; Chmura, A.; Rustler, S.; van Rantwijk, F.; Stolz, A. and Sheldon, R. A., *Tetrahedron: Asymmetry*, **2006**, *17*, 320. (c) Jian, Z.; Wang, Z. J. and Wu, Y. Z., *Jingxi Huagong Zhongjianti*, **2005**, *35*, 50. (d) Bolm, C.; Zani, L.; Rudolph, J. and Schiffers, I., *Synthesis*, **2004**, 2173. (e) Chen, H.-B.; Lin, Y.-B. and Liu, Z.-P., *Hecheng Huaxue*, **2002**, *10*, 186. (f) Li, X.-R.; Chen, S.-H.; Zhang, J.-F. and Liu, J.-J., *Hecheng Huaxue*, **2001**, *9*, 241. (g) Yang, W. M. and Zhang, Y. B., *Shanghai Huagong*, **2000**, *25*, 22. (h) Gathergood, N.; Zhuang, W. and Jørgensen, K. A., *J. Am. Chem. Soc.*, **2000**, *122*, 12517. (i) Li, Q. J. and Li, X. R., *Zhongnan Gongye Daxue Xuebao*, **1999**, *30*, 273. (j) Zhang, G.-S. and Gong, H., *Synth. Commun.*, **1999**, *29*, 3149. (k) Maeda, K. and Okamoto, Y., *Macromolecules*, **1998**, *31*, 1046. (l) Lee, D. G. and Chen, T., *J. Am. Chem. Soc*., **1993**, *115*, 11231. (m) Markey, S. P.; Powers, K.; Dubinsky, D. and Kopin, I. J., *J. Labelled Compd. Radiopharm.*, **1980**, *17*, 103. (n) Merz, A., *Synthesis*, **1974**, 724.

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Mannich Reaction

(Mannich Condensation, Mannich Aminomethylation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Mannich and Kroesche in 1912.[1] It is a multicomponent condensation between an amine (1°, 2° amine or ammonia), an enolizable carbonyl compound (donor),[2] and a nonenolizable carbonyl compound (acceptor) to form a β-amino carbonyl compound[3] (ketone or ester[4]), with the concomitant formation of both carbon-carbon and carbon-nitrogen bonds, known as the Mannich base.[2,4,5] Thus this reaction is generally known as the Mannich reaction,[6,7] or Mannich condensation.[8] For the special case of condensation in which the nonenolizable carbonyl compound is formaldehyde, a methylamino group is introduced onto the enolizable carbonyl compound. This special condensation is commonly referred to as the Mannich aminomethylation.[6e,9,10] In addition, the Mannich reaction has been extended to different variants, such as the aza-Mannich reaction,[11] halo-Mannich reaction,[12] azido-Mannich reaction process,[2] (or azido ketone Mannich reaction),[13] vinylogous Mannich reaction,[14,15] nitro-Mannich reaction,[16] borono-Mannich reaction,[17] and List-Barbas-Mannich reaction.[6c,18] The aza-Mannich reaction is the condensation between imines,[11b] the halo-Mannich reaction is the one accompanied by the formation of a haloalkyl group,[12b] and the azido-Mannich reaction generates an imine *in situ* from the degradation of an azido group in the presence of triflic acid.[19] Similarly, the vinylogous Mannich reaction is the condensation between imine and conjugated enolate to form 6-amino-α,β-unsaturated carbonyl compound,[15] the nitro-Mannich reaction is the condensation between imine and nitro-alkane,[16g–16j,16o] and the List-Barbas-Mannich reaction is the proline-catalyzed stereoselective Mannich reaction.[6c] The Mannich reaction

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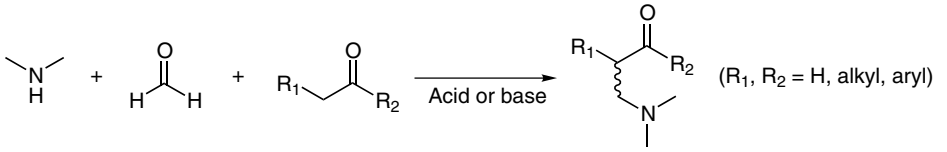
can also be divided into direct and indirect Mannich reactions: aldehyde (as acceptor), unmodified ketone (as donor), and amines are used directly in the direct Mannich reaction;[20] in the indirect Mannich reaction, either the ketone is converted into a preformed enolate or its equivalent (such as enolate, enol ether, or enamine), or the acceptor carbonyl compound is transformed into an imine intermediate.[21] In addition, besides the enolate equivalent undergoing the Mannich reaction, the electron-rich phenols also undergo the Mannich reaction with an imine component,[6b,6e,22] whereas an electron-deficient phenol such as 2,6-dinitrophenol fails for this reaction.[6e]

The Mannich reaction is one of the most popular reactions in modern organic synthesis because it generally occurs under very simple conditions and gives desired compounds in high yields with two potential chiral centers.[6e] Consequently, it has been extensively modified beside the variants already noted, including the coupling of (*a*) aldimines, such as the reaction between aldimine and silyl enol ether[4] or silicon enolate,[23] aldimine and fluorovinyl ether,[24] chiral aldimines and silyloxydienes,[25] and fluorinated aldimines with aliphatic aldehydes;[26] (*b*) iminium ions, such as the reaction between cyclic iminium ions and enol derivatives (enol silane, vinyloxytrimethylsilane),[27] and cyclic *N*-alkoxycarbonyl pyrrolinium ion and 2-trimethylsilyloxyfuran;[15b] (*c*) hydrozones, such as the coupling between chiral *N*-acylhydrazones and silyl enolates,[28] hydrazones with ketene silyl acetal,[29] and hydrazone ester and silicon enolates;[30] (*d*) imino esters, such as the reaction between α-imino ester and aldehydes,[3a] *N*-PMP-protected α-imino glyoxylate and α,α-disubstituted aldehyde,[31] α-imino ester and a glycinated Schiff base,[32] and *N*-acylimino ester and silyl enol ethers or vinyl ethers.[33] Furthermore, the Mannich reaction also occurs between the coupling of acetate enolate equivalent and α-amido sulfones or PMP-imines,[34] glyoxylate imines and ketene acetals,[35] alkynyl imine and silylketene acetals,[36] and phosphonylimine and hydroxyketones.[37] Moreover, the direct Mannich reaction has also been modified to occur between aldehydes, ketones, and carbamtes;[3b] between aldehydes, secondary amines, and methoxytris-(pentafluorophenyl)silane (i.e., $MeOSi(C_6F_5)_3$).[38]

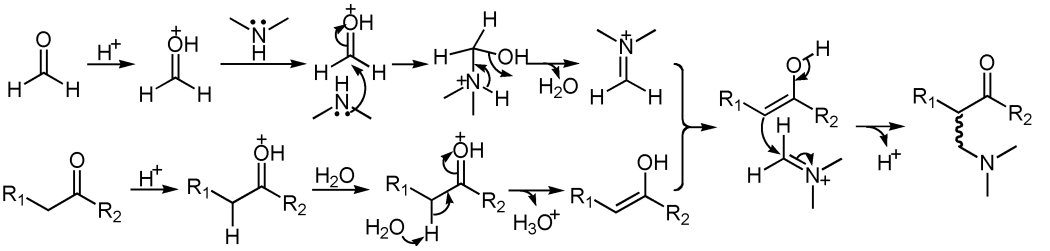
It is interesting that the condensation between electron-rich phenol, amine, and a chiral α-*N*,*N*-dibenzylamino aldehyde has been reported to be temperature sensitive, with high *syn* selectivity at high reaction temperatures while high *anti* selectivity is observed at low reaction temperatures.[22a] Similar to the *Aldol Condensation*, the Mannich reaction can be promoted or catalyzed by either acid or base. Furthermore, different protic acids or Lewis acid alone or in combination with a different chiral ligand or auxiliary group is used to enhance the stereoselectivity of the Mannich reaction, such as proline,[20,26,31,39] (*S*)-amino sulfonamide,[3a] BINOL phosphate,[40] *N*-spiro chiral quaternary ammonium bromide,[32] and dodecylbenzenesulfonic acid[41] as well as Lewis acids, such as $Cu(OAc)_2$,[9b] $CuClO_4$,[33,42] $Cu(OTf)_2$-chiral diamine complexes,[16i,16j,42,43] ZnX_2,[44] $ZnCl_2$,[28] $Zn(OTf)_2 \cdot H_2O$,[25] ZnF_2 with diamine complex,[30] Et_2Zn with (*S*, *S*)-linked BINOL,[45] dinuclear zinc catalyst,[46] chiral zirconium catalyst[4] (e.g., Zr(O-*t*-Bu)$_4$, (*S*)-6,6-BINOL[23]), $Bi(OTf)_3 \cdot 4H_2O$,[47] $Sc(OTf)_3$,[29] $InCl_3$ in MeOH,[48] $Y[N(SiMe_3)_2]_3$/TMS linked BINOL,[37] $AuCl_3$-PPh_3,[3b] $RuCl_2(PPh_3)_3$,[49] and AgOAc with ligand.[36,50] On the other hand, chiral basic molecules such as pyrrolidines with substituents at the 2- and 4-positions (or 3- and 5-positions) are also good catalysts for the Mannich reaction.[51] Finally, the Mannich reaction has also been modified to occur under various conditions, such as microwave irradiation,[6a] phase-transfer reaction,[32,52] in ionic liquid,[49] in aqueous solution without organic co-solvent,[30] $VO(acac)_2$ catalyzed reaction via the generation of iminium ions *in situ* from amine oxides,[22c] and immobilization of chiral ligand onto silica surface.[2d] This reaction is very useful in organic synthesis.

B. GENERAL REACTION SCHEME

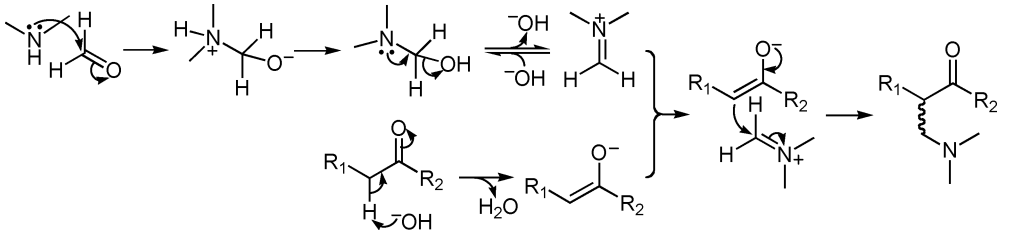


C. PROPOSED MECHANISMS

The mechanism of Mannich reaction under both acidic (Scheme 1) and basic (Scheme 2) conditions are outlined, using formaldehyde, dimethylamine, and a general ketone as example.



SCHEME 1. *Mannich reaction under acidic conditions.*



SCHEME 2. *Mannich reaction under basic conditions.*

D. MODIFICATION

This reaction has been extensively modified as described in Section A.

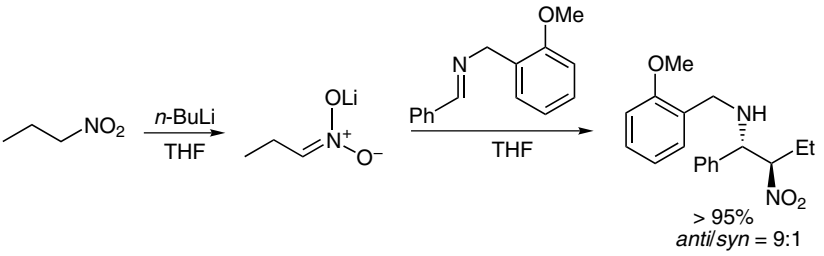
E. APPLICATIONS

This reaction has very broad application in organic synthesis, especially for the preparation of stereoselective compounds under catalytic conditions.

F. RELATED REACTIONS

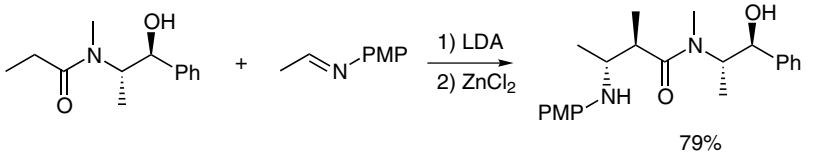
This reaction is related to the *Betti Reaction* and *Robinson-Schöpf Condensation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 16h.

A solution of 0.56 mL 2.5 M *n*-butyllithium in hexanes (1.40 mmol) was added to 20 mL THF solution containing 0.13 mL 1-nitropropane (1.40 mmol) over 10 min at −78°C under nitrogen. The mixture was stirred for 10 min. A solution of 10 mL THF containing 1.0 mmol *N*-(*o*-methoxy)benzyl benzaldimine was then added, and the mixture was stirred at −78°C for 10 min. Then 0.14 mL AcOH (2.4 mmol) was added, and the mixture was stirred for an additional 20 min before being allowed to warm to 25°C over 30 min. Saturated aqueous $NaHCO_3$ (10 mL) and 20 mL Et_2O were then added, and the organic phase was separated, washed with 10 mL saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and evaporated to yield crude β-nitroamine, in a yield of 95% with a *syn/anti* ratio of 1:9.



Reference 53.

At −78°C, a solution of 1 mmol propionamide in 10 mL THF was slowly added to 20 mL THF containing 2 mmol LDA. After being stirred for 1 h at this temperature, the mixture was allowed to reach room temperature and was stirred for another 15 min. The reaction was then cooled to −78°C, and a solution of 2 mmol $ZnCl_2$ in 10 mL THF was added. The reaction was stirred for 1 h at −78°C and then allowed to warm to 0°C, at which time a solution of 4 mmol imine was slowly added. The mixture was stirred until TLC analysis indicated full conversion, and water (2 mmol) was then added. The resulting ZnO precipitate was filtered off and washed with CH_2Cl_2, and 40 mL saturated aqueous Na_2CO_3 was added to the filtrate. The crude reaction mixture was extracted with CH_2Cl_2. The combined organic fractions were collected, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (hexanes/EtOAc, 2:8) to afford 79% (2*R*,3*R*,1′*S*,2′*S*)-(+)-3-(4-methoxyphenylamino)-*N*,2-dimethyl-*N*-(2′-phenyl-2′-hydroxy-1′-methylethyl)butanamide, m.p. 86–89°C (Et_2O).

Other references related to the Mannich reaction are cited in the literature.[54]

H. REFERENCES

1. Mannich, C. and Kroesche, W., *Arch. Pharm.*, **1912**, *250*, 647.
2. Desai, P.; Schildknegt, K.; Agrios, K. A.; Mossman, C.; Milligan, G. L. and Aubé, J., *J. Am. Chem. Soc.*, **2000**, *122*, 7226.
3. (a) Kano, T.; Yamaguchi, Y.; Tokuda, O. and Maruoka, K., *J. Am. Chem. Soc.*, **2005**, *127*, 16408. (b) Xu, L.-W.; Xia, C.-G. and Li, L., *J. Org. Chem.*, **2004**, *69*, 8482. (c) Manabe, K. and Kobayashi, S., *Org. Lett.*, **1999**, *1*, 1965.
4. Ishitani, H.; Ueno, M. and Kobayashi, S., *J. Am. Chem. Soc.*, **2000**, *122*, 8180.
5. (a) Comanita, E.; Roman, G.; Popovici, I. and Comanita, B., *J. Serb. Chem. Soc.*, **2001**, *66*, 9. (b) Belyaev, V. F. and Grushevich, V. I., *Vestsi Akad. Navuk BSSR, Ser. Khim. Navuk*, **1977**, 137.
6. (a) Kidwai, M.; Thakur, R. and Mohan, R., *Acta Chim. Slov.*, **2005**, *52*, 88. (b) D'Hardemare, A. du M.; Jarjayes, O. and Mortini, F., *Synth. Commun.*, **2004**, *34*, 3975. (c) Hayashi, Y.; Tsuboi, W.; Shoji, M. and Suzuki, N., *J. Am. Chem. Soc.*, **2003**, *125*, 11208. (d) Belinelo, V. J.; Reis, G. T.; Stefani, G. M.; Ferreira-Alves, D. L. and Piló-Veloso, D., *J. Braz. Chem. Soc.*, **2002**, *13*, 830. (e) Habata, Y.; Akabori, S.; Bradshaw, J. S. and Izatt, R. M., *Ind. Eng. Chem. Res.*, **2000**, *39*, 3465. (f) Belyaev, N. A. and Mokrushin, V. S., *Chem. Heterocycl. Compd.*, **1989**, *25*, 165.
7. (a) Liu, Z.-G.; Chen, Z.-H. and Wang, D.-Z., *Zhongguo Zaozhi Xuebao*, **2007**, *22*, 104. (b) Sharifi, A.; Mirzaei, M. and Naimi-Jamal, M. R., *J. Chem. Res.*, **2007**, 129. (c) Prukala, D., *Tetrahedron Lett*., **2006**, *47*, 9045. (d) Gao, P.; Liu, Y. Q.; Zhang, L.; Xu, P.-F.; Wang, S. W.; Lu, Y.; He, M. Y. and Zhai, H. B., *J. Org. Chem.*, **2006**, *71*, 9495. (e) Hui, B.; Meng, N.; Chen, F.-H.; Ding, X.; Xiao, M.-L.; Chen, Z.-J.; Guo, B.-S. and Tang, W.-M., *Huaxue Shiji*, **2006**, *28*, 323. (f) Song, J.; Wang, Y. and Deng, L., *J. Am. Chem. Soc.*, **2006**, *128*, 6048. (g) Catino, A. J.; Nichols, J. M.; Nettles, B. J. and Doyle, M. P., *J. Am. Chem. Soc.*, **2006**, *128*, 5648. (h) Janey, J. M.; Hsiao, Y. and Armstrong, J. D., *J. Org. Chem.*, **2006**, *71*, 390. (i) Dotsenko, V. V.; Krivokolysko, S. G. and Litvinov, V. P., *Russ. Chem. Bull.*, **2005**, *54*, 2692. (j) Wei, R. Q.; Zhu, J. X.; Liu, X. N. and He, X. J., *Xiandai Huagong*, **2005**, *25*, 30. (k) Frolov, K. A.; Dotsenko, V. V.; Krivokolysko, S. G. and Litvinov, V. P., *Russ. Chem. Bull.*, **2005**, *54*, 2226. (l) Lou, S.; Taoka, B. M.; Ting, A. and Schaus, S. E., *J. Am. Chem. Soc.*, **2005**, *127*, 11256. (m) Brocke, C.; Brimble, M. A.; Lin, D. S.-H. and McLeod, M. D., *Synlett*, **2004**, 2359. (n) Xu, L.-W.; Wang, Z.-T.; Xia, C.-G.; Li, L. and Zhao, P.-Q., *Helv. Chim. Acta*, **2004**, *87*, 2608. (o) Lehmann, F.; Pilotti, A. and Luthman, K., *Molecular Diversity*, **2003**, *7*, 145. (p) Dornyei, G.; Incze, M.; Kajtar-Peredy, M. and Szantay, C., *Coll. Czech. Chem. Commun.*, **2002**, *67*, 1669.
8. (a) Huang, Z. G., *Huagong Shikan*, **2006**, *20*, 58. (b) Bian, X. X.; Zhang, D.; Huang, Z. Y. and Qin, Y., *Synlett*, **2006**, 3419. (c) Higham, C. S.; Dowling, D. P.; Shaw, J. L.; Cetin, A.; Ziegler, C. J. and Farrell, J. R., *Tetrahedron Lett*., **2006**, *47*, 4419. (d) Kabalka, G. W.; Zhou, L.-L.; Wang, L. and Pagni, R. M., *Tetrahedron*, **2006**, *62*, 857. (e) Koval'skaya, S. S.; Kozlov, N. G. and Tkachev, A. V., *Russ. J. Org. Chem.*, **2005**, *41*, 1836. (f) Yakunina, I. E.; Shakhkel'dyan, I. V.; Atroshchenko, Yu. M.; Rybakova, A. S.; Troitskii, N. A. and Shuvalova, E. V., *Russ. J. Org. Chem.*, **2005**, *41*, 1238. (g) Li, P.-H. and Wang, L., *Chinese J. Chem.*, **2005**, *23*, 1076. (h) Takahashi, I.; Nishiuchi, K.; Miyamoto, R.; Hatanaka, M.; Uchida, H.; Isa, K.; Sakushima, A. and Hosoi, S., *Lett. Org. Chem.*, **2005**, *2*, 40. (i) Takahashi, I.; Miyamoto, R.; Nishiuchi, K.; Hatanaka, M.; Yamano, A.; Sakushima, A. and Hosoi, S., *Heterocycles*, **2004**, *63*, 1267. (j) Driessen, W. L.; Rehorst, D.; Reedijk, J.; Mutikainen, I. and Turpeinen, U., *Inorg. Chim. Acta*, **2003**, *355*, 64. (k) Barnes, D. M.; Bhagavatula, L.; DeMattei, J.; Gupta, A.; Hill, D. R.; Manna, S.; McLaughlin, M. A.; Nichols, P.; Premchandran, R.; Rasmussen, M. W.; Tian, Z. P. and Wittenberger, S. J., *Tetrahedron: Asymmetry*, **2003**, *14*, 3541. (l) Wang, L. and Li, P.-H., *Chinese J. Chem.*, **2003**, *21*, 710. (m) Durran, S. E.; Elsegood, M. R. J.; Hawkins, N.; Smith, M. B. and Talib, S., *Tetrahedron Lett*., **2003**, *44*, 5255. (n) Koval'skaya, S. S. and Kozlov, N. G., *Russ. J. Org. Chem.*, **2002**, *38*, 662. (o) Ebraheem, K. A. K.; Mubarak, M. S. and Al-Gharabli, S. I., *J. Macromol. Sci.,*

Pure & Appl. Chem., **2002**, *A39*, 217. (p) Tshuva, E. Y.; Gendeziuk, N. and Kol, M., *Tetrahedron Lett*., **2001**, *42*, 6405. (q) Kabalka, G. W.; Wang, L. and Pagni, R. M., *Tetrahedron Lett*., **2001**, *42*, 6049. (r) Youngman, M. A. and Dax, S. L., *J. Comb. Chem.*, **2001**, *3*, 469. (s) Leonova, O. V.; Shakhkel'dyan, I. V.; Grudtsyn, Yu. D.; Atroshchenko, Yu. M.; Alifanova, E. N.; Gitis, S. S.; Chudakov, P. V.; Nikiforova, E. G.; Alekhina, N. N. and Kaminskii, A. Ya., *Russ. J. Org. Chem.*, **2001**, *37*, 395. (t) Kabalka, G. W.; Wang, L. and Pagni, R. M., *Synlett*, **2001**, 676. (u) Katritzky, A. R.; Cui, X. L.; Long, Q. H.; Mehta, S. and Steel, P. J., *ARKIVOC*, **2000**, 1 (*iv*), 471. (v) Zhang, Y. J.; Zhou, W. L. and Wen, J. Q., *Proc. Int. Pyrotech. Seminar*, **1997**, *23*, 999. (w) Takahashi, I.; Kawakami, T.; Hirano, E.; Yokota, H. and Kitajima, H., *Synlett*, **1996**, 353. (x) Miksovsky, D. and Vojtech, A., *Propellants, Explosives, Pyrotechnics*, **1995**, *20*, 138. (y) Qiu, Y. S.; Wang, X. T. and Wang, Z. L., *Lubrication Eng.*, **1994**, *50*, 937. (z) Wei, Y. Y.; Lu, C. X.; Lu, M.; Wang, Y. and Li, Z. P., *Yingyong Huaxue*, **1994**, *11*, 104. (aa) Takahashi, I.; Tsuzuki, M.; Yokota, H.; Kitajima, H. and Isa, K., *Heterocycles*, **1994**, *37*, 933. (bb) Smith, G. S.; Berlin, K. D.; Zisman, S. A.; Holt, E. M.; Green, V. A. and van der Helm, D., *Phosphorus & Sulfur & Related Elements*, **1988**, *39*, 91. (cc) Soellhuber-Kretzer, M.; Troschuetz, R. and Roth, H. J., *Arch. Pharm.*, **1982**, *315*, 199. (dd) Anwar, M.; El-Barbary, A. A.; Ghattas, A. A. G. and Hashem, A. F., *Pol. J. Chem.*, **1981**, *55*, 599. (ee) Gaudry, M.; Jasor, Y. and Trung, B. K., *Org. Synth.*, **1980**, *59*, 153. (ff) Troschuetz, R., *Arch. Pharm.*, **1979**, *312*, 455. (gg) Boehme, H. and Clement, B., *Arch. Pharm.,* **1979**, *312*, 527. (hh) Misiti, D.; Settimj, G.; Mantovani, P. and Chiavarelli, S., *Gazz. Chim. Ital.*, **1970**, *100*, 495. (ii) Pauson, P. L.; Kelly, P. B. and Porter, R. J., *J. Chem. Soc. C*, **1970**, 1323. (jj) Bobbitt, J. M. and Dutta, C. P., *J. Org. Chem.*, **1969**, *34*, 2001. (kk) Atavin, A. S.; Dmitrieva, Z. T. and Trofimov, B. A., *Zh. Obsh. Khim.*, **1968**, *38*, 1024. (ll) Novikov, S. S.; Dudinskaya, A. A.; Makarov, N. V. and Khmel'nitskii, L. I., *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1967**, 1839. (mm) Makarov, N. V.; Dudinskaya, A. A.; Novikov, S. S. and Khmel'nitskii, L. I., *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1967**, 1837. (nn) Novikov, S. S.; Dudinkaya, A. A.; Makarov, N. V. and Khmel'nitskii, L. I., *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1967**, 1833. (oo) Graefe, G., *Arch. Pharm. Ber. Deut. Pharm. Gesell.*, **1967**, *300*, 111. (pp) Olijnsma, T.; Engberts, J. B. F. N. and Strating, J., *Rec. Trav. Chim. Pays-Bas*, **1967**, *86*, 463. (qq) Engberts, J. B. F. N.; Olijnsma, T. and Strating, J., *Rec. Trav. Chim. Pays-Bas*, **1966**, *85*, 1211. (rr) Varma, R. S. and Nobles, W. L., *J. Pharm. Sci.*, **1966**, *55*, 1451. (ss) Engberts, J. B. F. N. and Strating, J., *Rec. Trav. Chim. Pays-Bas*, **1965**, *84*, 942. (tt) Engberts, J. B. F. N. and Strating, J., *Rec. Trav. Chim. Pays-Bas*, **1964**, *83*, 733. (uu) Sipos, Gy.; Dobo, I. and Matkovics, B., *Acta Phys. Chem.*, **1963**, *9*, 43. (vv) Lazar, J.; Matkovics, B. and Gondos, Gy., *Chem. Ind. (London)*, **1963**, 913. (ww) Varela, R. and Kinel, F. A., *Ciencia (Mex.)*, **1962**, *21*, 213. (xx) Baum, K. and Maurice, W. T., *J. Org. Chem.*, **1962**, *27*, 2231. (yy) Muhlstadt, M., *Chem. Ber.*, **1960**, *93*, 2638. (zz) Stetter, H.; Schafer, J. and Dieminger, K., *Chem. Ber.*, **1958**, *91*, 598. (aaa) Stetter, H.; Schafer, J. and Dieminger, K., *Angew. Chem.*, **1958**, *70*, 52. (bbb) Bombardieri, C. C. and Taurins, A., *Can. J. Chem.*, **1955**, *33*, 923. (ccc) Rosenmund, K. W., *Pharm. Zeit.-Nach.*, **1952**, *88*, 856. (ddd) Vystreil, A. and Dasek, J., *Chem. Listy Vedu Prumysl*, **1951**, *45*, 139. (eee) Karbe, H., *Arch. Pharm.*, **1950**, *283*, 48. (fff) Reichert, B., *Pharm. Ind.*, **1942**, *9*, 379.

9. (a) Aime, S.; Cavallotti, C.; Gianolio, E.; Giovenzana, G. B.; Palmisano, G. and Sisti, M., *Org. Lett.*, **2004**, *6*, 1201. (b) Cassino, C.; Gabano, E.; Ravera, M.; Cravotto, G.; Palmisano, G.; Vessieres, A.; Jaouen, G.; Mundwiler, S.; Alberto, R. and Osella, D., *Inorg. Chim. Acta*, **2004**, *357*, 2157. (c) Song, H.-C.; Bradshaw, J. S.; Chen, Y.-W.; Xue, G.-P.; Chiara, J. A.;Krakowiak, K. E.; Savage, P. B.; Xue, Z.-L. and Izatt, R. M., *ARKIVOC*, **2001**, 25. (d) Levina, I. S., *Russ. Chem. Rev.*, **1998**, *67*, 975. (e) Grinev, A. N. and Zotova, S. A., *Pharm. Chem. J.*, **1974**, *8*, 588.

10. (a) Barge, A.; Cravotto, G.; Robaldo, B.; Gianolio, E. and Aime, S., *J. Inclusion Phenomena & Macrocycl. Chem.*, **2007**, *57*, 489. (b) Glushchenko, O. V.; Yanovska, E. S.; Kichkiruk, O. Yu. and Tertykh, V. A., *Functional Mater.,* **2006**, *13*, 265. (c) Ng, C. H.; Lin, C. M.; Chang, T. M.; Teoh, S. G.; Yap, S. Y. and Ng, S. W., *Polyhedron*, **2006**, *25*, 1287. (d) Ibrahem, I.; Zou, W. B.; Casas, J.; Sunden, H. and Cordova, A., *Tetrahedron*, **2006**, *62*, 357. (e) Ng, C. H.; Chong, T. S.; Teoh, S. G. and Ng, S. W., *J. Coord. Chem.*, **2005**, *58*, 1455. (f) Biava, M.; Porretta, G. C.; Giorgi,

G. and Sleiter, G., *ARKIVOC*, **2004**, (*v*), 325. (g) Ng, C. H.; Chong, T. S.; Teoh, S. G.; Adams, F. and Ng, S. W., *J. Chem. Soc., Dalton Trans.*, **2002**, 3361. (h) Ng, C.-H.; Teo, S.-B.; Teoh, S.-G.; Declercq, J.-P. and Ng, S. W., *Aust. J. Chem.,* **2001**, *54*, 743. (i) Bradshaw, J. S.; Bordunov, A. V.; Zhang, X. X.; Pastushok, V. N. and Izatt, R. M., *ACS Symposium Ser.*, **1999**, *716*, 133. (j) Teo, S.-B.; Ng, C.-H.; Teoh, S.-G. and Wei, C., *Polyhedron*, **1994**, *13*, 2537. (k) Miocque, M., *Ann. Pharm. Fr.*, **1969**, *27*, 381. (l) Bataev, P. S. and Lopushinskaya, T. I., *Zh. Org. Khim.*, **1967**, *3*, 1785.

11. (a) Shimizu, M.; Tanaka, M.; Itoh, T. and Hachiya, I., *Synlett*, **2006**, 1687. (b) Lanter, J. C.; Chen, H. F.; Zhang, X. Q. and Sui, Z. H., *Org. Lett.*, **2005**, *7*, 5905.
12. (a) Koseki, Y.; Fujino, K.; Takeshita, A.; Sato, H. and Nagasaka, T., *Tetrahedron: Asymmetry*, **2007**, *18*, 1533. (b) Timmons, C.; Guo, L.; Liu, J. Y.; Cannon, J. F. and Li, G. G., *J. Org. Chem.*, **2005**, *70*, 7634. (c) Williams, A. L. and Day, A. R., *J. Am. Chem. Soc.*, **1952**, *74*, 3875.
13. Chowdari, N. S.; Ahmad, M.; Albertshofer, K.; Tanaka, F. and Barbas, C. F., *Org. Lett.*, **2006**, *8*, 2839.
14. (a) Niess, B. and Joergensen, K. A., *Chem. Commun.*, **2007**, 1620. (b) Liu, T.-Y.; Cui, H.-L.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S. and Chen, Y.-C., *J. Am. Chem. Soc.*, **2007**, *129*, 1878. (c) Carswell, E. L.; Snapper, M. L. and Hoveyda, A. H., *Angew. Chem. Int. Ed.*, **2006**, *45*, 7230. (d) Bayon, P.; Busque, F. and Figueredo, M., *Targets Heterocycl. Systems*, **2005**, 9, 281. (e) Oudeyer, S.; Dudot, B. and Royer, J., *Heterocycles*, **2005**, *65*, 823. (f) Spanedda, M. V.; Ourevitch, M.; Crousse, B.; Begue, J.-P. and Bonnet-Delpon, D., *Tetrahedron Lett.*, **2004**, *45*, 5023. (g) Winter, A. and Risch, N., *Synlett*, **2003**, 1959. (h) Deiters, A.; Chen, K.; Eary, C. T. and Martin, S. F., *J. Am. Chem. Soc.*, **2003**, *125*, 4541. (i) Reichelt, A.; Bur, S. K. and Martin, S. F., *Tetrahedron*, **2002**, *58*, 6323. (j) Martin, S. F., *Acc. Chem. Res.*, **2002**, *35*, 895. (k) Kawecki, R., *Tetrahedron*, **2001**, *57*, 8385. (l) Bur, S. K. and Martin, S. F., *Tetrahedron*, **2001**, *57*, 3221. (m) Martin, S. F. and Lopez, O. D., *Tetrahedron Lett.*, **1999**, *40*, 8949. (n) Martin, S. F. and Bur, S. K., *Tetrahedron*, **1999**, *55*, 8905. (o) Martin, S. F.; Chen, K. X. and Eary, C. T., *Org. Lett.*, **1999**, *1*, 79. (p) Martin, S. F. and Barr, K. J., *J. Am. Chem. Soc.*, **1996**, *118*, 3299. (q) Martin, S. F. and Liras, S., *J. Am. Chem. Soc.*, **1993**, *115*, 10450.
15. (a) Liras, S.; Lynch, C. L.; Fryer, A. M.; Vu, B. T. and Martin, S. F., *J. Am. Chem. Soc.*, **2001**, *123*, 5918. (b) Bur, S. K. and Martin, S. F., *Org. Lett.*, **2000**, *2*, 3445. (c) Martin, S. F.; Barr, K. J.; Smith, D. W. and Bur, S. K., *J. Am. Chem. Soc.*, **1999**, *121*, 6990. (d) Martin, S. F., *Pure & Appl. Chem.*, **1997**, *69*, 571.
16. (a) Handa, S.; Gnanadesikan, V.; Matsunaga, S. and Shibasaki, M., *J. Am. Chem. Soc.*, **2007**, *129*, 4900. (b) Bode, C. M.; Ting, A. and Schaus, S. E., *Tetrahedron*, **2006**, *62*, 11499. (c) Mahasneh, A. S., *Zeit. Naturforsch., B: Chem. Sci.*, **2006**, *61*, 1162. (d) Shibasaki, M.; Kanai, M. and Matsunaga, S., *TCIMeru*, **2006**, *131*, 2. (e) Tsuritani, N.; Yamada, K.-I.; Yoshikawa, N. and Shibasaki, M., *Chem. Lett.*, **2005**, *34*, 452. (f) Yoon, T. P. and Jacobsen, E. N., *Angew. Chem. Int. Ed.*, **2005**, *44*, 466. (g) Li, Z. P. and Li, C.-J., *J. Am. Chem. Soc.*, **2005**, *127*, 3672. (h) Anderson, J. C.; Blake, A. J.; Howell, G. P. and Wilson, C., *J. Org. Chem.*, **2005**, *70*, 549. (i) Anderson, J. C.; Howell, G. P.; Lawrence, R. M. and Wilson, C. S., *J. Org. Chem.*, **2005**, *70*, 5665. (j) Lee, A.; Kim, W. S.; Lee, J. W.; Hyeon, T. H. and Kim, B. M., *Tetrahedron: Asymmetry*, **2004**, *15*, 2595. (k) Tsuritani, N.; Yamada, K.-I.; Yoshikawa, N. and Shibasaki, M., *Chem. Lett.*, **2002**, 276. (l) Yamada, K.-I.; Moll, G. and Shibasaki, M., *Synlett*, **2001**, 980. (m) Qian, C.; Gao, F. and Chen, R., *Tetrahedron Lett.*, **2001**, *42*, 4673. (n) Yamada, K.-I.; Harwood, S. J.; Groger, H. and Shibasaki, M., *Angew. Chem. Int. Ed.*, **1999**, *38*, 3504. (o) Adams, H.; Anderson, J. C.; Peace, S. and Pennell, A. M. K., *J. Org. Chem.*, **1998**, *63*, 9932.
17. (a) Au, C. W. G. and Pyne, S. G., *J. Org. Chem.,* **2006**, *71*, 7097. (b) Gravel, M.; Thompson, K. A.; Zak, M.; Berube, C. and Hall, D. G., *J. Org. Chem.*, **2002**, *67*, 3.
18. Kiyota, H., *Kagaku (Kyoto)*, **2004**, *59*, 59,
19. Wrobleski, A. and Aubé, J., *J. Org. Chem.*, **2001**, *66*, 886.

20. List, B., *J. Am. Chem. Soc.*, **2000**, *122*, 9336.
21. (a) Wenzel, A. G. and Jacobsen, E. N., *J. Am. Chem. Soc.*, **2002**, *124*, 12964. (b) Miyabe, H.; Fujii, K.; Goto, T. and Naito, T., *Org. Lett.*, **2000**, *2*, 4071.
22. (a) Rondot, C. and Zhu, J. P., *Org. Lett.*, **2005**, *7*, 1641. (b) Joshi, N. S.; Whitaker, L. R. and Francis, M. B., *J. Am. Chem. Soc.*, **2004**, *126*, 15942. (c) Hwang, D.-R. and Uang, B.-J., *Org. Lett.*, **2002**, *4*, 463. (d) Leigh, D. A. and Linnane, P., *Tetrahedron Lett.*, **1993**, *34*, 5639.
23. Ihori, Y.; Yamashita, Y.; Ishitani, H. and Kobayashi, S., *J. Am. Chem. Soc.*, **2005**, *127*, 15528.
24. Chung, W. J.; Omote, M. and Welch, J. T., *J. Org. Chem.*, **2005**, *70*, 7784.
25. Ishimaru, K. and Kojima, T., *J. Org. Chem.*, **2003**, *68*, 4959.
26. Fustero, S.; Jiménez, D.; Sanz-Cervera, J. F.; Sánchez-Roselló, M.; Esteban, E. and Simón-Fuentes, A., *Org. Lett.*, **2005**, *7*, 3433.
27. Tomazela, D. M.; Moraes, L. A. B.; Pilli, R. A.; Eberlin, M. N. and D'Oca, M. G. M., *J. Org. Chem.*, **2002**, *67*, 4652.
28. Jacobsen, M. F.; Ionita, L. and Skrydstrup, T., *J. Org. Chem.*, **2004**, *69*, 4792.
29. Manabe, K.; Oyamada, H.; Sugita, K. and Kobayashi, S., *J. Org. Chem.*, **1999**, *64*, 8054.
30. Hamada, T.; Manabe, K. and Kobayashi, S., *J. Am. Chem. Soc.*, **2004**, *126*, 7768.
31. Chowdari, N. S.; Suri, J. T. and Barbas, C. F., *Org. Lett.*, **2004**, *6*, 2507.
32. Ooi, T.; Kameda, M.; Fujii, J.-i. and Maruoka, K., *Org. Lett.*, **2004**, *6*, 2397.
33. Kobayashi, S.; Matsubara, R.; Nakamura, Y.; Kitagawa, H. and Sugiura, M., *J. Am. Chem. Soc.*, **2003**, *125*, 2507.
34. Palomo, C.; Oiarbide, M.; Landa, A.; González-Rego, M. C.; García, J. M.; González, A.; Odriozola, J. M.; Martín-Pastor, M. and Linden, A., *J. Am. Chem. Soc.*, **2002**, *124*, 8637.
35. Jacobsen, M. F. and Skrydstrup, T., *J. Org. Chem.*, **2003**, *68*, 7112.
36. Josephsohn, N. S.; Carswell, E. L.; Snapper, M. L. and Hoveyda, A. H., *Org. Lett.*, **2005**, *7*, 2711.
37. Sugita, M.; Yamaguchi, A.; Yamagiwa, N.; Handa, S.; Matsunaga, S. and Shibasaki, M., *Org. Lett.*, **2005**, *7*, 5339.
38. Dilman, A. D.; Belyakov, P. A.; Korlyukov, A. A.; Struchkova, M. I. and Tartakovsky, V. A., *Org. Lett.*, **2005**, *7*, 2913.
39. (a) Cordova, A. and Barbas, C. F., *Tetrahedron Lett*., **2003**, *44*, 1923. (b) Cordova, A. and Barbas, C. F., *Tetrahedron Lett.*, **2002**, *43*, 7749. (c) Watanabe, S.; Cordova, A.; Tanaka, F. and Barbas, C. F. *Org. Lett.*, **2002**, *4*, 4519. (d) Cordova, A.; Notz, W.; Zhong, G.; Betancort, J. M. and Barbas, C. F., *J. Am. Chem. Soc*., **2002**, *124*, 1842. (e) Cordova, A.; Watanabe, S.; Tanaka, F.; Notz, W. and Barbas, C. F., *J. Am. Chem. Soc*., **2002**, *124*, 1866. (f) List, B.; Pojarliev, P.; Biller, W. T. and Martin, H., *J. Am. Chem. Soc*., **2002**, *124*, 827. (g) List, B., *Tetrahedron*, **2002**, *58*, 5573. (h) List, B., *Synlett*, **2001**, 1675. (i) Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G. and Barbas, C. F., *Tetrahedron Lett*., **2001**, *42*, 199.
40. Uraguchi, D. and Terada, M., *J. Am. Chem. Soc.*, **2004**, *126*, 5356.
41. (a) Manabe, K.; Mori, Y. and Kobayashi, S., *Tetrahedron*, **2001**, *57*, 2537. (b) Manabe, K. and Kobayashi, S., *Org. Lett.*, **1999**, *1*, 1965.
42. Kobayashi, S.; Matsubara, R. and Kitagawa, H., *Org. Lett.*, **2002**, *4*, 143.
43. Nakamura, Y.; Matsubara, R.; Kiyohara, H. and Kobayashi, S., *Org. Lett.*, **2003**, *5*, 2481.
44. Kobayashi, S.; Hamada, T. and Manabe, K., *J. Am. Chem. Soc.*, **2002**, *124*, 5640.
45. Matsunaga, S.; Kumagai, N.; Harada, S. and Shibasaki, M., *J. Am. Chem. Soc.*, **2003**, *125*, 4712.
46. Trost, B. M. and Terrell, L. R., *J. Am. Chem. Soc.*, **2003**, *125*, 338.
47. Ollevier, T. and Nadeau, E., *J. Org. Chem.*, **2004**, *69*, 9292.
48. Loh, T.-P. and Chen, S.-L., *Org. Lett.*, **2002**, *4*, 3647.
49. Yang, X.-F.; Wang, M. W.; Varma, R. S. and Li, C.-J., *Org. Lett.*, **2003**, *5*, 657.

50. Josephsohn, N. S.; Snapper, M. C. and Hoveyda, A. H., *J. Am. Chem. Soc.*, **2004**, *126*, 3734.
51. Mitsumori, S.; Zhang, H. L.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F. and Barbas, C. F., *J. Am. Chem. Soc.*, **2006**, *128*, 1040.
52. Okada, A.; Shibuguchi, T.; Ohshima, T.; Masu, H.; Yamaguchi, K. and Shibasaki, M., *Angew. Chem. Int. Ed.*, **2005**, *44*, 4564.
53. Vicario, J. L.; Badía, D. and Carrillo, L., *J. Org. Chem.*, **2001**, *66*, 9030.
54. (a) Tremblay-Morin, J.-P.; Raeppel, S. and Gaudette, F., *Tetrahedron Lett.*, **2004**, *45*, 3471. (b) Raman, N.; Esthar, S. and Thangaraja, C., *J. Chem. Sci.*, **2004**, *116*, 209. (c) Hata, S.; Iguchi, M.; Iwasawa, T.; Yamada, K.-i. and Tomioka, K., *Org. Lett.*, **2004**, *6*, 1721. (d) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M. and Sakai, K., *Angew. Chem.*, **2003**, *115*, 3805. (e) Evans, G. B.; Furneaux, R. H.; Tyler, P. C. and Schramm, V. L., *Org. Lett.*, **2003**, *5*, 3639. (f) Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H. and Fukuyama, T., *Pure & Appl. Chem.*, **2003**, *75*, 29. (g) Kubota, H.; Lim, J. W.; Depew, K. M. and Schreiber, S. L., *Chem. & Biol.*, **2002**, *9*, 265. (h) Vicario, J. L.; Badía, D. and Carrillo, L., *Org. Lett.*, **2001**, *3*, 773. (i) Davis, F. A.; Chao, B. and Rao, A., *Org. Lett.*, **2001**, *3*, 3169. (j) Shibasaki, M. and Kanai, M., *Chem. Pharm. Bull.*, **2001**, *49*, 511. (k) Saito, S.; Hatanaka, K. and Yamamoto, H., *Org. Lett.*, **2000**, *2*, 1891. (l) Takaya, J.; Kagoshima, H. and Akiyama, T., *Org. Lett.*, **2000**, *2*, 1577. (m) El-Masry, A. H.; Fahmy, H. H. and Abdelwahed, S. H. A., *Molecules*, **2000**, *5*, 1429. (n) Incze, M.; Dornyei, G.; Kajtar-Peredy, M. and Szantay, C., *Coll. Czech. Chem. Commun.*, **1999**, *64*, 408. (o) McNally, J. J.; Youngman, M. A. and Dax, S. L., *Tetrahedron Lett.*, **1998**, *39*, 967. (p) Dyatkin, A. and Rivero, R. A., *Tetrahedron Lett.*, **1998**, *39*, 3647. (q) Arend, M.; Westermann, B. and Risch, N., *Angew. Chem. Int. Ed.*, **1998**, *37*, 1045. (r) Krawezyk, H., *Synth. Commun.*, **1994**, *24*, 2263. (s) Tramontini, M. and Angiolini, L., *Tetrahedron*, **1990**, *46*, 1791. (t) Smiley, R. A., *J. Org. Chem.*, **1958**, *23*, 1115. (u) Bombardieri, C. C. and Taurins, A., *Can. J. Chem.*, **1955**, *33*, 923. (v) Wheatley, W. B.; Fitzgibbon, W. E. and Cheney, L. C., *J. Am. Chem. Soc.*, **1954**, *76*, 4490. (w) Meinwald, J. and Hutto, F. B., *J. Am. Chem. Soc.*, **1953**, *75*, 485. (x) Grillot, G. F. and Bashford, R. I., *J. Am. Chem. Soc.*, **1951**, *73*, 5598. (y) Blicke, F. F., *Org. React.*, **1942**, *1*, 303.

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Marckwald Asymmetric Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Marckwald in 1904.[1] It is the synthesis of chiral L-valeric acid (α-methyl propanoic acid) from the pyrolysis of brucine salt of racemic α-methyl-α-ethylmalonic acid.[1,2] Therefore, it is generally known as the Marckwald asymmetric synthesis.[3] Occasionally, it is also referred to as the Marckwald method.[4] In this reaction, the brucine salts of racemic α-methyl-α-ethylmalonic acid essentially exist as a pair of diastereomers that are separated by fractional crystallization; the one with lower solubility is isolated. Upon pyrolysis of such crystalline salt at 170°C, the corresponding brucine salt of L-valeric acid forms upon decarboxylation, resulting in a 10% e.e.[2c] In addition, Marckwald defined the asymmetric synthesis as reactions that produce optically active molecules from symmetrically constituted compounds with the use of optically active materials and exclusion of any analytical processes, such as resolution.[5] However, this work was challenged as not being a true asymmetric synthesis because the procedure was similar to that of Pasteur.[3d] In fact, the fractional crystallization of the diastereomers is a resolution process. This process is used as base for many other preparations of chiral molecules, such as tartaric acid;[6] and under its influence, the kinetic resolution and true asymmetric synthesis have been developed in modern organic synthesis.[7] The asymmetric synthesis has been redefined by Morrison and Mosher as the reaction by which an achiral unit of the substrate is converted into a chiral unit in such a manner that the two resulting stereoisomers are produced in unequal amounts.[8]

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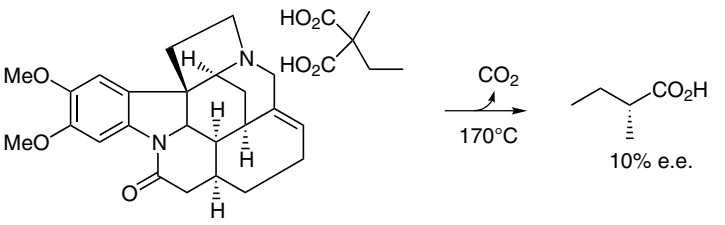
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

For achiral molecules that, when coupling with a chiral molecule (mostly alkaloids, such as brucine, cinchonidine, and sparteine), form a pair of diastereomers with different physical properties that can be separated by the methods of fractional crystallization, column chromatography, etc., resulting in the enantiomeric resolution. No actual mechanism is necessary for this reaction.

D. MODIFICATION

The original asymmetric synthesis has been extensively improved in modern organic synthesis, such as in the *Sharpless Epoxidation*, asymmetric hydrogenation, and enzymatic hydrolysis.

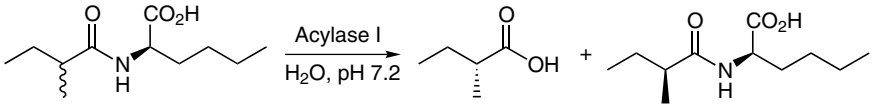
E. APPLICATIONS

The original procedure has some application in the preparation of chiral molecules.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 9.

A solution of 54 g DL-α-methylbutyryl-L-norleucine (0.25 mol) was treated with lithium hydroxide to pH 7.2 and then diluted to a volume of 10 L. After the addition of 1.5 g acylase I powder, the mixture was incubated at 37°C. After 40% completion of the hydrolysis, as determined by the manometric ninhydrin-CO_2 method on aliquots withdrawn periodically over a period of ~14 h, the pH of solution was adjusted to 5 by 2 *N* HCl. After the addition of Norit A, the digest was filtered to remove the major portion of the protein. After the readjustment of the pH to 8.5, the solution was concentrated in vacuo to a volume of ~500 mL, then acidified to pH 1.7 by concentrated HCl, and extracted twice with ether. The organic layers were combined and dried over anhydrous sodium sulfate. Removal of the solvent left a thick oily residue, which was a mixture of the free α-methylbutyric acid and residual α-methylbutyryl-L-norleucine. These were separated by dissolving the residue in a small amount of dry ether and adding a large excess of petroleum ether. The free acid remained in solution, whereas the acylated amino acid was separated as a white, oily mass. The residue was again dissolved in ether and again precipitated with excess petroleum ether. Both supernatant solutions were combined, and the solvent was removed by a stream of air. The residual oil was twice fractionated by distillation at 10 mmHg to yield 4.3 g of the final product, b.p. 69°C; α_D at 25°C was + 11.25° for a 2-d.cm tube. Using a d_{25} value of 0.94, the calculated $[\alpha]_{25}^{D} = +6.0°$.

The residual α-methylbutyryl-L-norleucine that had been precipitated from ether solution by excess petroleum ether was refluxed with 200 mL 2 *N* HCl for 2.5 h. After cooling to 25°C, the solution was extracted with ether as above, and the residual oil was subjected to fractional distillation at 10 mmHg. The clear liquid boiled at 69–69.5°C, and after the second distillation amounted to 6.2 g. The α_D at 28°C was −5.5° for a 2-d.cm tube, and using a d_{25} value of 0.94, the calculated $[\alpha]_{25}^{D}$ was –3.0°. The original α-methylbutyryl-L-norleucine when treated in the same fashion, did not yield any optical activity.

Other references related to the Marckwald asymmetric synthesis are cited in the literature.[10]

H. REFERENCES

1. Marckwald, W., *Ber.*, **1904**, *37*, 349.
2. (a) Blaser, H.-U., *Chem. Rev.*, **1992**, *92*, 935. (b) Fuji, K.; Node, M.; Terada, S.; Murata, M.; Nagasawa, H.; Taga, T. and Machida, K., *J. Am. Chem. Soc.,* **1985**, *107*, 6404. (c) Jones, L. W., *J. Am. Chem. Soc.*, **1905**, *27*, 1553.
3. (a) Kenyon, J. and Ross, W. A., *J. Chem. Soc.,* **1952**, 2307. (b) Eisenlohr, F. and Meier, G., *Ber.*, **1938**, *71B*, 997. (c) Tijmstra, S., *Proc. Koninklijke Nederlandse Akad. Wetenschappen*, **1904**, *7*, 465. (d) Cohen, J. B. and Patterson, T. S., *Ber.*, **1904**, *37*, 1012.
4. Ives, D. J. G. and Nettleton, M. R., *J. Chem. Soc.*, **1948**, 1085.
5. Marckwald, W., *Ber.*, **1904**, *37*, 1368.
6. (a) Williams, O. F. and Bailar, J. C., *J. Am. Chem. Soc.*, **1959**, *81*, 4464. (b) Richtmyer, N. K. and Hudson, C. S., *J. Am. Chem. Soc.*, **1936**, *58*, 2540.
7. Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M. and Sharpless, K. B., *J. Am. Chem. Soc.*, **1981**, *103*, 6237.
8. Morrison, J. D. and Mosher, H. S., *Asymmetric Organic Reaction*, Prentice Hall, Englewood Cliffs, N.J., **1971**.
9. Winitz, M.; Birnbaum, S. M. and Greenstein, J. P., *J. Am. Chem. Soc.*, **1955**, *77*, 3106.

10. (a) Mikami, K. and Yamanaka, M., *Chem. Rev.*, **2003**, *103*, 3369. (b) Prelog, V. and Scherrer, H., *Helv. Chim. Acta*, **1959**, *42*, 2227. (c) Kenyon, J. and Ross, W. A., *J. Chem. Soc.,* **1951**, 3407. (d) Kenyon, J. and Ross, W. A., *J. Chem. Soc.*, **1948**, 1085. (e) Baker, R. H. and Linn, L. E., *J. Am. Chem. Soc.*, **1948**, *70*, 3721. (f) Eisenlohr, F. and Meier, G., *Ber.*, **1938**, *71*, 1004. (g) Wallis, E. S. and Adams, F. H., *J. Am. Chem. Soc.*, **1933**, *55*, 3838. (h) Ebel, F. and Freudenberg, K., *Stereochemie*, **1933**, *2*, 581. (i) Erlenmeyer, E. and Landsberger, F., *Biochem. Zeitsch.*, **1914**, *64*, 366. (j) Marckwald, W. and Meth, R., *Ber.*, **1905**, *38*, 801.

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Markownikoff Rule and Anti-Markownikoff Rule

(Markovnikov Rule and Anti-Markovnikov Rule)

A. GENERAL DESCRIPTION OF THE REACTION

The Markownikoff rule[1] or Markovnikov rule[2] was first formulated by Markownikoff in 1870,[3] and specifies the orientation of the electrophilic addition of hydrogen halides to asymmetrical alkenes or alkynes in which hydrogen itself attaches to the least-substituted carbon atom in a double bond (or triple bond). This rule has been extended to the heterolytic addition of a polar molecule to an alkene or alkyne, of which the more electronegative atom (or group) of the polar molecule attaches to the carbon with more substituents. However, in the presence of peroxide, the order of addition for hydrogen bromide to alkene is reversed.[4] Furthermore, during the hydroboration of alkene or alkyne, hydrogen also attaches to the carbon atom with more substituents.[5] Such a reverse addition order to alkene or alkyne is known as the *anti*-Markownikoff rule[1d,1f,6] (or *anti*-Markovnikov rule[2b,7]) or *contra*-Markownikoff rule.[8] Likewise, the addition reaction that follows the Markownikoff rule is referred to as the Markownikoff addition[6f,9] or Markovnikov addition,[10] and the addition reaction against the Markownikoff rule is called *anti*-Markownikoff addition.[6f] In general, Markownikoff rule is followed when an electron-withdrawing or partially positive group exists on the double bond, in spite of steric hindrance.[6f] For example, the hydroboration of 1,1,1-trifluoropropene yields 74% secondary alcohol;[11] similarly, 87–92% of Markownikoff addition products were observed for 1-(trimethylsilyl)cyclopentene and 1-(trimethylsilyl)cyclohexene under kinetic conditions.[12] Similarly, dimethylchlorosilylethylene, methyldichlorosilylethylene, trichloromethylsilylethylene,[13] and vinyl halide[14]

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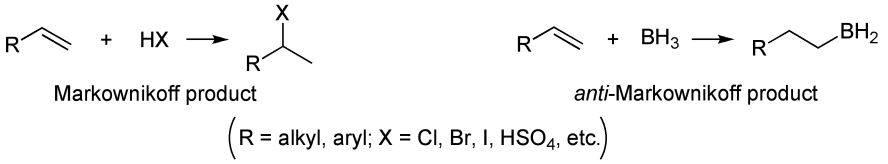
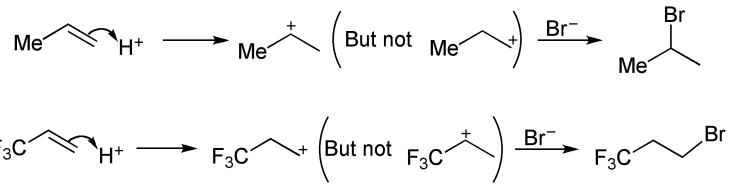
all give the Markownikoff products in addition reactions. Moreover, the ozonolysis of 1,2-dibenzoylpropene is found to follow the Markownikoff rule as well.[15] It is interesting that the acid-promoted cleavage of the cyclopropane ring also follows a modified version of the Markownikoff rule in that the ring opens between the carbons with the most and least alkyl substituents.[16] On the other hand, the hydroboration of an alkene with an alkyl group (or electron-donating group) often yields the *anti*-Markownikoff product.[5] For example, the hydroboration of alkylethylenes give 93–94% terminal alcohol, while 1,1-dialkylethylene and trialkylethylene yield 98–99% terminal alcohols.[6f] Even the addition of alkyl nitrite to styrenes in the presence of a cobalt complex and tetrahydroborate ion exclusively gives the *anti*-Markownikoff product.[6c] It is interesting that the addition of alkyl dichlorocarbamates to vinylsilanes always gives [2-chloro-2-(trialkylsilyl)ethyl]carbamates as the *anti*-Markownikoff product, either through an ionic or a radical mechanism.[6e]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

For the addition of hydrogen halide to asymmetrical alkenes, the proton first adds to the least-substituted carbon atom of the double bond, so that a more stable carbocation can form as an intermediate, then the halide attacks the carbocation to give the Markownikoff product. However, if a strong electron-withdrawing group exists on a carbon atom of the double bond, then the attachment of the proton to such a carbon atom will result in a relatively stable carbocation intermediate, and *anti*-Markownikoff product may predominate in such addition, as shown here by the addition of hydrobromide to propene and 1,1,1-trifluoropropene.



D. MODIFICATION

The acid-promoted cleavage of the cyclopropane ring similarly follows the Markownikoff rule.

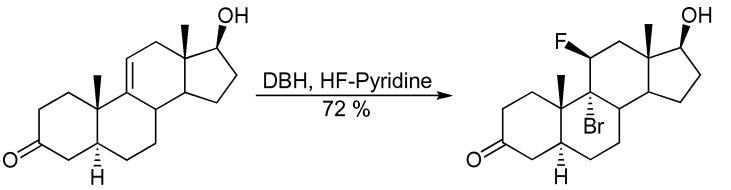
E. APPLICATIONS

This rule is normally used to rationalize the addition products.

F. RELATED REACTIONS

N/A

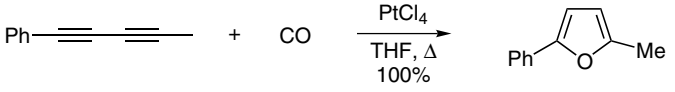
G. CITED EXPERIMENTAL EXAMPLES



Anti-Markownikoff product

Reference 6b.

1,3-Dibromo-5,5-dimethylhydantoin (DBH) (114 mg, 0.4 mmol) was placed in a polyethy1ene vial, followed by a few milliliters of CH_2Cl_2. A substantial amount of DBH was not soluble until 62 μL HF-pyridine (2.17 mmol) was added. Then 208 mg 17β-hydroxy-9(11)-androsten-3-one (0.72 mmol) was added, and the solution was stirred at room temperature for 1.5 h. Product was isolated in CH_2Cl_2 and then purified by column chromatography (benzene/EtOAc, 4:1) to afford 202 mg 9α-bromo-11β-fluoro-17β-hydroxyandrostan-3-one as a white solid, m.p. 138–140°C.



Reference 17.

A solution of 50.5 mg $PtCl_4$ (0.15 mmol) in 2.0 mL THF containing 5% H_2O was placed in a mini autoclave equipped with a magnetic bar and was stirred for 20 min at 100°C under 200 psi CO. To this green solution was added 1.05 g 1-phenyl-1,4-pentadiyne (7.5 mmol). The CO pressure was reduced to 20 psi, and stirring was continued at 80°C for 3 h. Then the reaction mixture was dried over $MgSO_4$, evaporated, and chromatographed on silica gel (hexan/ether) to afford 100% 1-phenyl-4-methyl furan. (*Note:* 2.0 mL THF in original procedure might not be enough to dissolve 1.05 g of the alkyne.)

Other references related to the Markownikoff rule and *anti*-Markownikoff rule are cited in literature. [18]

H. REFERENCES

1. (a) Ananikov, V. P.; Malyshev, D. A. and Beletskaya, I. P., *Russ. J. Org. Chem.*, **2002**, *38*, 1475. (b) Keiko, N. A.; Funtikova, E. A.; Stepanova, L. G.; Chuvashev, Yu. A.; Albanov, A. I. and Voronkov, M. G., *Russ. J. Org. Chem.*, **2001**, *37*, 1693. (c) Barluenga, J.; Martinez-Gallo, J. M.; Najera, C. and Yus, M., *Synthesis*, **1987**, 582. (d) Bruening, H., *Praxis Naturwissen., Chem.*, **1983**, *32*, 21. (e) Fischli, A. and Mueller, P. M., *Helv. Chim. Acta*, **1980**, *63*, 529. (f) Okamoto, H.; Adachi, S. and Iwai, T., *J. Macromol. Sci., Chem.*, **1977**, *A11*, 1949.
2. (a) Adimurthy, S.; Ramachandraiah, G. and Ghosh, P. K., *Synth. Commun.*, **2007**, *37*, 1579. (b) Mukbaniani, O.; Titvinidze, G.; Tatrishvili, T.; Mukbaniani, N.; Brostow, W. and Pietkiewicz, D., *J. Appl. Poly. Sci.*, **2007**, *104*, 1176. (c) Yan, H.; Noll, B. C.; Fehlner, T. P., *J. Organomet. Chem.*, **2006**, *691*, 5060. (d) Martynov, A. V.; Makhaeva, N. A. and Amosova, S. V., *Russ. J. Org. Chem.*, **2006**, *42*, 954. (e) French, G.; Hughes, P.; Gore-Randall, E. and Troiano, S., *Edu. Chem.*, **2006**, *43*, 80. (f) Madhavi, N.; Sundar, B. S. and Radhakrishnamurti, P. S., *J. Inst. Chem. (Indi(a)*, **2005**, *77*, 46. (g) Aizman, A.; Contreras, R.; Galvan, M.; Cedillo, A.; Santos, J. C. and Chamorro, E., *J. Phys. Chem. A*, **2002**, *106*, 7844. (h) Gooch, E. E., *J. Chem. Edu.*, **2001**, *78*, 1358. (i) White, A. D., *School Sci. Rev.*, **1981**, *63*, 111. (j) Haugen, G. R. and Benson, S. W., *J. Phys. Chem.*, **1970**, *74*, 1607. (k) Isenberg, N. and Grdinic, M., *J. Chem. Edu.*, **1969**, *46*, 601. (l) Andreevskii, D. N., *Zh. Fizicheskoi Khimii*, **1967**, *41*, 980. (m) Jones, G., *J. Chem. Edu.*, **1961**, *38*, 297. (n) Batuev, M. I., *Zh. Obsh. Khim.*, **1957**, *27*, 953. (o) Shostakovskii, M. F.; Prilezhaeva, E. N. and Shapiro, E. S., *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1955**, 734.
3. (a) Markownikoff, W., *Ann.*, **1870**, *153*, 256. (b) Kuppermann, A., *J. Phys. Chem. A*, **2001**, *105*, 2129.
4. Cartas-Rosado, R.; Santoyo, M. E. R.; Alvarez-Idaboy, J. R. and Vivier-Bunge, A., *J. Phys. Chem. A*, **2001**, *105*, 9222.
5. See *Brown Hydroboration* herein (P. 536).
6. (a) Jun, C.-H.; Lee, H. and Hong, J.-B., *J. Org. Chem.*, **1997**, *62*, 1200. (b) Choe, Y. S.; Lidström, P. J.; Chi, D. Y.; Bonasera, T. A.; Welch, M. J. and Katzenellenbogen, J. A., *J. Med. Chem.*, **1995**, *38*, 816. (c) Okamoto, T.; Kobayashi, K.; Oka, S. and Tanimoto, S., *J. Org. Chem.*, **1988**, *53*, 4897. (d) Iyer, R. S. and Rowland, F. S., *J. Phys. Chem.*, **1985**, *89*, 3730. (e) Lukevics, E.; Dirnens, V. V.; Goldberg, Y. S.; Liepinsh, E. E.; Gavars, M. P.; Kalvinsh, I. Y. and Shymanska, M. V., *Organometallics*, **1985**, *4*, 1648. (f) Graham, G. D.; Freilich, S. C. and Lipscomb, W. N., *J. Am. Chem. Soc.*, **1981**, *103*, 2546.
7. (a) Arnold, D. R.; Chan, M. S. W. and McManus, K. A., *Can. J. Chem.*, **1996**, *74*, 2143. (b) Kutyrev, G. A.; Kapura, A. A.; Sadykova, L. A.; Nikanorov, V. A.; Cherkasov, R. A. and Pudovik, A. N., *Zh. Obsh. Khim.*, **1987**, *57*, 56. (c) Tedder, J. M., *J. Chem. Edu.*, **1984**, *61*, 237. (d) Brown, H. C. and Ravindran, N., *J. Org. Chem.*, **1973**, *38*, 182. (e) Prilezhaeva, E. N.; Petukhova, N. P. and Shostakovskii, M. F., *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1962**, 728.
8. (a) Pérez-Casany, M. P.; Sánchez-Marín, J. and Nebot-Gil, I., *J. Am. Chem. Soc.*, **2000**, *122*, 11585. (b) Pérez-Casany, M. P.; Nebot-Gil, I. and Sánchez-Marín, J., *J. Phys. Chem. A*, **2000**, *104*, 6277. (c) Pérez-Casany, M. P.; Nebot-Gil, I. and Sánchez-Marín, J., *J. Phys. Chem. A*, **2000**, *104*, 11340.
9. Atta-ur-Rehman; Waheed, N. and Ghazala, M., *Z. Naturforsch., Teil B: Anorg. Chem., Org. Chem.*, **1976**, *31B*, 264.
10. (a) Brisbois, R. G.; Batterman, W. G. and Kragerud, S. R., *J. Chem. Edu.*, **1997**, *74*, 834. (b) Beverly, G. M. and Hogg, D. R., *Chem. Commun. (Londo(n)*, **1966**, 138.
11. Phillips, J. R. and Stone, F. G. A., *J. Chem. Soc.*, **1962**, 94.
12. DeJesus, M.; Rosario, O. and Larson, G. L., *J. Organomet. Chem.*, **1977**, *132*, 301.
13. Lin, T. F. O.; Myers, J. K.; Rogers, G. T. and Jones, P. R., *J. Organomet. Chem.*, **1977**, *135*, 249.

14. Pasto, D. J. and Snyder, R., *J. Org. Chem.*, **1966**, *31*, 2773.

15. Bailey, P. S. and Bath, S. S., *J. Am. Chem. Soc.*, **1957**, *79*, 3120.

16. Zimmerman, M. P.; Li, H.-T.; Duax, W. L.; Weeks, C. M. and Djerassi, C., *J. Am. Chem. Soc.*, **1984**, *106*, 5602.

17. Baidossi, W.; Lahav, M. and Blum, J., *J. Org. Chem.*, **1997**, *62*, 669.

18. (a) Jun, C.-H.; Lee, D.-Y.; Kim, Y.-H. and Lee, H., *Organometallics*, **2001**, *20*, 2928. (b) Kirpichenko, S. V.; Abrosimova, A. T.; Albanov, A. I. and Voronkov, M. G., *Russ. J. Gen. Chem.*, **2001**, *71*, 1874. (c) Golden. D. M., *J. Phys. Chem. A*, **1998**, *102*, 8439. (d) Kalasinsky, V. F. and Pechsiri, S., *J. Phys. Chem.*, **1982**, *86*, 5110. (e) Stacey, F. W. and Harris, J. H., *Org. React.*, **1963**, *13*, 155. (f) Mayo, F. R. and Walling, C., *Chem. Rev.*, **1940**, *27*, 351. (g) Kharasch, M. S. and Mayo, F. R., *J. Am. Chem. Soc.*, **1933**, *55*, 2468.

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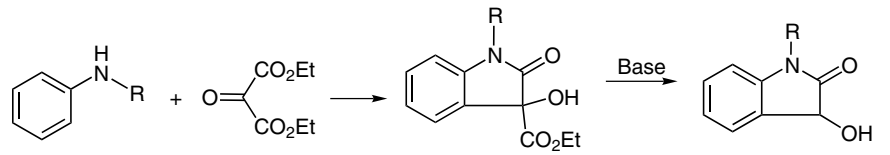
Martinet Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Martinet in 1913.[1] It is a synthesis of dioxindole derivatives by alkali treatment of the condensation products from substituted anilines and ethyl or methyl ester of oxomalonic acid in the absence of oxygen.[2] Thus it is known as the Martinet reaction.[3] In the presence of oxygen, the dioxindoles are further oxidized into isatins.[2] This reaction has been extended to the preparation of α- and β-naphthisatins.[4]

B. GENERAL REACTION SCHEME



(R = H, alkyl, aryl)

C. PROPOSED MECHANISMS

A detailed mechanism is illustrated here for the reaction between aniline and ethyl oxomalonate.

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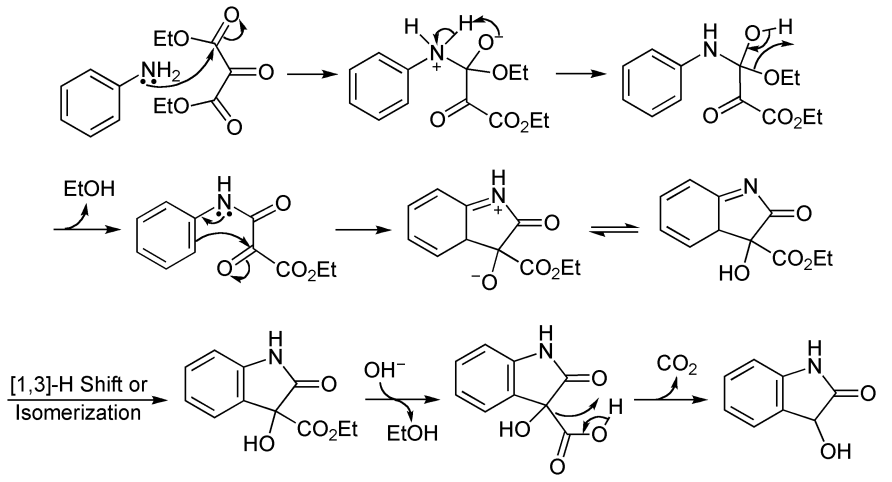


D. MODIFICATION

N/A

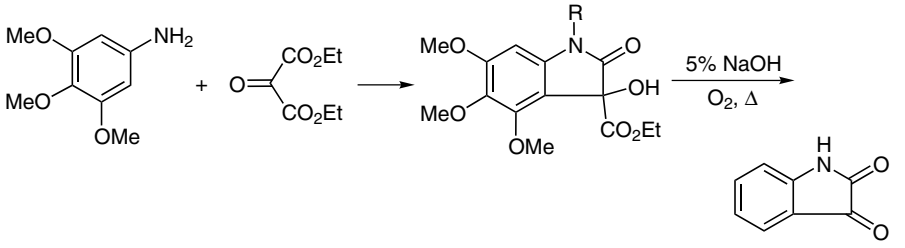
E. APPLICATIONS

This reaction is useful for the preparation of oxindole derivatives.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3.

A solution of 1.8 g 3,4,5-trimethoxyaniline in 10 mL glacial acetic acid was treated with 1.9 g ethyl oxomalonate (dihydrate). The resulting olive green solution was heated on the steam bath for 10 min and then kept for 2 h at room temperature. Diluting the solution with 125 mL water and then adding solid ammonium carbonate to give a final pH of 8 caused the precipitation of 2.7 g 4,5,6-trimethoxy-3-hydroxy-3-carbethoxyoxindole as a light tan

solid, in a yield of 86.8%. Recrystallization from a mixture of ether-benzene-petroleum ether afforded pure product as colorless prisms, m.p. 189–190 °C. A solution of 450 mg above oxindole in 5.0 mL 5% NaOH solution was heated on a water bath, and a stream of air was passed through the solution for 10 min. The resulting light yellow solution was brought to pH 4 by the dropwise addition of 95% formic acid. The orange microcrystalline solid separated was collected and washed with water. Recrystallization from ethanol-water afforded 100 mg orange platelets, m.p. 194–195 °C(dec).

Other references related to the Martinet reaction are cited in the literature.[5]

H. REFERENCES

1. Guyot, A. and Martinet, J., *Compt. Rend.*, **1913**, *156*, 1625.
2. (a) Sumpter, W. C., *Chem. Rev.*, **1945**, *37*, 443. (b) Sumpter, W. C., *Chem. Rev.*, **1944**, 34393.
3. Benington, F.; Morin, R. D. and Clark, L. C., *J. Org. Chem.*, **1955**, *20*, 1454.
4. (a) Langenbeck, W.; Hellrung, F. and Juttemann, R., *Ann.*, **1934**, *512*, 276. (b) Langenbeck, W.; Hellrung, F. and Juttemann, R., *Ann.*, **1932**, *499*, 201. (c) Martinet, J., *Ann. Chim.*, **1919**, *11*, 85. (d) Martinet, J., *Compt. Rend.*, **1918**, *166*, 851.
5. (a) Raileanu, D. and Nenitzescu, C. D., *Acad. Rep. Populare Romine Studii Cercetari Chim.*, **1963**, *11*, 19. (b) Kalb, L. and Berrer, E., *Ber.*, **1924**, *57B*, 2105. (c) Martinet, J. and Vacher, F., *Bull. Soc. Chim. Fr.*, **1922**, *31*, 435. (d) Bonnefoy, J. and Martinet, J., *Compt. Rend.*, **1921**, *172*, 220. (e) Halberkann, J., *Ber.*, **1921**, *54B*, 3079. (f) Martinet, J., *Compt. Rend.*, **1918**, *166*, 851. (g) Martinet, J., *Compt. Rend.*, **1918**, *166*, 998.

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Martin's Sulfurane

A. GENERAL DESCRIPTION OF THE REACTION

Martin's sulfurane[1] was first reported by Martin in 1971.[2] It is a ketal analog[3] of diarylsulfoxide with 2-phenyl-2-hexafluoropropanol prepared either from the treatment of diarylsulfide with one equivalent of 2-phenyl-hexafluoro-2-propyl hypochlorite followed by one equivalent potassium alkoxide of 2-phenyl-hexafluoro-2-propanol,[4] or from the treatment of diarylsulfide with two equivalents potassium alkoxide of 2-phenyl-hexafluoro-2-propanol with one equivalent of chlorine at -78°C.[2b,4] The second procedure is especially useful for the preparation of symmetrical sulfurane in high yield.[4] During the preparation, moisture must be avoided at all stages because of the high sensitivity toward moisture.[2b] As a result, the Martin's sulfurane is a very powerful dehydration reagent and can be applied to efficiently dehydrate alcohols under very mild conditions.[5] In general, dehydration of tertiary alcohols takes place via an E1 mechanism,[5b,5c] whereas dehydration of secondary alcohols occurs by a mechanism with considerable E2 character with a strong preference for the formation of *trans*-olefin[5b,5c] (>95% selectivity).[6] However, dehydration of primary alcohols without active β-hydrogen often results in asymmetrical ethers.[5b,5c] In addition, the Martin's sulfurane can also dehydrate the diols, by which epoxide can be prepared from *trans*-1,2-diol[5a,7] and oxetane and tetrahydrofuran can be formed from the treatment of 1,3-diol[5a] and 1,4-diol,[5a] respectively. In contrast, the dehydration of 1,4-hydroquinone from Martin's sulfurane results in 1,4-quinone.[3] More importantly, the dehydration by Martin's sulfurane can complete in seconds[5c] at a very low temperature (e.g., -50°C),[5c] which often provides advantages over other dehydrating reagents. For example, both sulfuric acid and phosphorus pentoxide fail to yield any olefin from tricyclopropylcarbinol, whereas 32% olefin is produced from the dehydration by the Martin's sulfurane.[5c] However, it should be pointed out that the Martin's sulfurane, together with the Burgess

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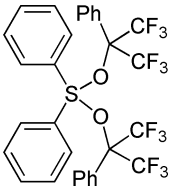
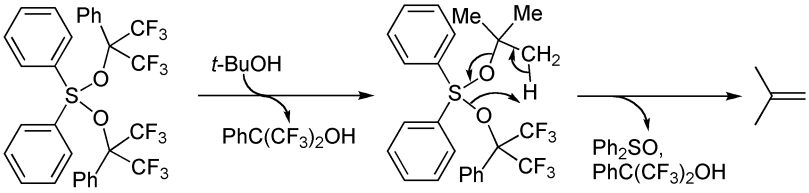
reagent and DAST, fails to dehydrate a tertiaryl alcohol to form an *exo*-double bond.[8] It is interesting that the spirosulfuranes, also developed by Martin, have been found much less reactive than the acyclic sulfuranes.[9] Other sulfuranes, such as tetraoxysulfurane,[10] 5-bis [α,α-bis(trifluoromethyl)-benzenemethanolato]-10-phenylphenothiazine, 5-bis-[α,α-bis(trifluoromethyl)benzenemethanolato]-10-phenoxathiin, and 5-bis[α,α-bis(trifluoromethyl)-benz-enemethanolato]thianthrene,[11] have also been developed for the dehydration of alcohols.

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Although the dehydration of tertiary alcohol shows strong E1 elimination character, an alternative mechanism for the dehydration of *t*-BuOH is presented here.



D. MODIFICATION

Other sulfurane derivatives have been developed for the hydration of alcohols.[10,11]

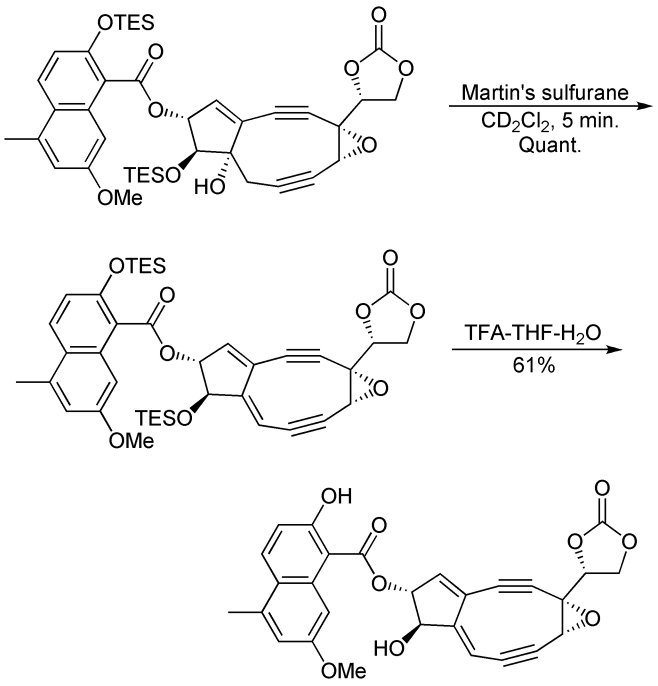
E. APPLICATIONS

This reagent is very useful for the dehydration of alcohols and the formation of olefins and cyclic ethers (e.g., epoxides, oxetanes, and THF).

F. RELATED REACTIONS

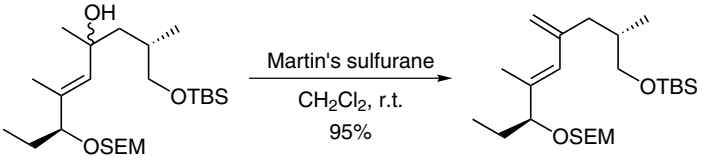
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 12.

To an 1.2 mL CH_2Cl_2 solution containing 3.9 mg alcohol (0.0052 mmol) was added 23.0 mg Martin's sulfurane dehydrating reagent (0.0340 mmol). The mixture was stirred for 10 min at room temperature and concentrated to 0.1 mL. A solution of trifluoroacetic acid/THF/water (1:10:5) was added, and the mixture was stirred for 35 min at 0°C. Et_2O (10 mL); 5 mL saturated $NaHCO_3$ was added, and the resulting mixture was stirred for 1 h at 0°C. The aqueous phase was extracted with Et_2O-EtOAc, and the combined organic layer was dried over anhydrous $MgSO_4$. After filtration, the solution was concentrated to 0.3 mL and exposed to flash column chromatography (silica gel, hexane/EtOAc). The fractions containing aglycon were pooled, concentrated to 0.2 mL, and then subjected to HPLC (Mightysil Si 60, 250–10 [5 μm], flow rate 4 mL/min, hexane/EtOAc as the eluent). The fractions, including pure aglycon (retention time 10 min 15 s), were concentrated to 0.2 mL, diluted with 3 mL MeOH, and then concentrated to 0.2 mL. This process was repeated, and the concentrate was taken up by 5 mL MeOH. In the end, 2.3 mg aglycon was obtained (0.0032 mmol), with a total yield of 61% for the two steps.



Reference 6b.

To a solution of 20 g alcohol (43.5 mmol) in 400 mL CH_2Cl_2 at room temperature was added Martin's sulfurane reagent until the completion of the reaction as monitored by TLC

analysis. The mixture was then concentrated in vacuo and chromatographed to give 18.26 g diene (95% yield) and its isomer (95:5). A small amount was further purified by PTLC to give an analytically pure sample.

Other references related to the Martin's sulfurane are cited in the literature.[13]

H. REFERENCES

1. (a) Wensley, A. M.; Hardy, A. O.; Gonsalves, K. M. and Koviach, J. L., *Tetrahedron Lett.*, **2007**, *48*, 2431. (b) Yokokawa, F. and Shioiri, T., *Tetrahedron Lett*., **2002**, *43*, 8679.
2. (a) Martin, J. C. and Arhart, R. J., *J. Am. Chem. Soc.*, **1971**, *93*, 2339. (b) Martin, J. C. and Arhart, R. J., *J. Am. Chem. Soc.*, **1971**, *93*, 2341.
3. Kaplan, L. J. and Martin, J. C., *J. Am. Chem. Soc.*, **1973**, *95*, 793.
4. Arhart, R. J. and Martin, J. C., *J. Am. Chem. Soc.*, **1972**, *94*, 4997.
5. (a) Martin, J. C.; Franz, J. A. and Arhart, R. J., *J. Am. Chem. Soc.*, **1974**, *96*, 4604. (b) Arhart, R. J. and Martin, J. C., *J. Am. Chem. Soc.*, **1972**, *94*, 5003. (c) Martin, J. C. and Arhart, R. J., *J. Am. Chem. Soc.*, **1971**, *93*, 4327.
6. (a) Evans, D. A.; Cee, V. J.; Smith, T. E. and Santiago, K. J., *Org. Lett.*, **1999**, *1*, 87. (b) Tse, B., *J. Am. Chem. Soc.*, **1996**, *118*, 7094.
7. (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Fong, K. C. and Choi, H.-S., *J. Am. Chem. Soc.*, **2002**, *124*, 2190. (b) Bartlett, P. D.; Aida, T.; Chu, H.-K. and Fang, T.-S., *J. Am. Chem. Soc.*, **1980**, *102*, 3515.
8. Donohoe, T. J.; Sintim, H. O.; Sisangia, L.; Ace, K. W.; Guyo, P. M.; Gowley, A. and Harling, J. D., *Chem. Eur. J.*, **2005**, *11*, 4227.
9. Martin, J. C. and Perozzi, E. F., *J. Am. Chem. Soc.*, **1974**, *96*, 3155.
10. Wilson, G. E. and Belkind, B. A., *J. Org. Chem.*, **1977**, *42*, 765.
11. Perozzi, E. F. and Martin, J. C., *J. Org. Chem.*, **1977**, *42*, 3222.
12. Kobayashi, S.; Hori, M.; Wang, G. X. and Hirama, M., *J. Org. Chem.*, **2006**, *71*, 636.
13. (a) Geng, X. D. and Danishefsky, S. J., *Org. Lett.*, **2004**, *6*, 413. (b) Usami, Y.; Hatsuno, C.; Yamamoto, H.; Tanabe, M. and Numata, A., *Chem. Pharm. Bull.*, **2004**, *52*, 1130. (c) Begum, L.; Box, J. M.; Drew, M. G. B.; Harwood, L. M.; Humphreys, J. L.; Lowes, D. J.; Morris, G. A.; Redon, P. M.; Walker, F. M. and Whitehead, R. C., *Tetrahedron*, **2003**, *59*, 4827. (d) Myers, A. G.; Hogan, P. C.; Hurd, A. R. and Goldberg, S. D., *Angew. Chem. Int. Ed.*, **2002**, *41*, 1062. (e) Nicolaou, K. C. and Baran, P. S., *Angew. Chem. Int. Ed*., **2002**, *41*, 2678. (f) Myers, A. G.; Glatthar, R.; Hammond, M.; Harrington, P. M.; Kuo, E. Y.; Liang, J.; Schaus, S. E.; Wu, Y. S. and Xiang, J.-N., *J. Am. Chem. Soc.*, **2002**, *124*, 5380. (g) Yokokawa, F. and Shioiri, T., *Tetrahedron Lett*., **2002**, *43*, 8673. (h) Box, J. M.; Harwood, L. M.; Humphreys, J. L.; Morris, G. A.; Redon, P. M. and Whitehead, R. C., *Synlett*, **2002**, 358. (i) Ho, Z.-C.; Livant, P.; Lott, W. B. and Webb, T. R., *J. Org. Chem.*, **1999**, *64*, 8226. (j) Rao, P. N. and Wang, Z., *Steroids*, **1997**, *62*, 487. (k) Wood, J. L.; Stoltz, B. M.; Goodman, S. N. and Onwueme, K., *J. Am. Chem. Soc.*, **1997**, *119*, 9652. (l) Atarashi, S.; Choi, J.-K.; Ha, D.-C.; Hart, D. J.; Kuzmich, D.; Lee, C.-S.; Ramesh, S. and Wu, S. C., *J. Am. Chem. Soc.*, **1997**, *119*, 6226. (m) Furukawa, N.; Ogawa, S.; Matsumura, K.; Shibutani, T. and Fujihara, H., *Chem. Lett.*, **1990**, 979. (n) Engel, P. S.; Keys, D. E. and Kitamura, A., *J. Am. Chem. Soc.*, **1985**, *107*, 4964. (o) Majewski, M. and Snieckus, V., *Tetrahedron Lett*., **1982**, *23*, 1343. (p) Kitazume, T. and Shreeve, J. M., *Inorg. Chem.*, **1978**, *17*, 2173. (q) Adzima, L. J. and Martin, J. C., *J. Org. Chem.*, **1977**, *42*, 4006. (r) Astrologes, G. W. and Martin, J. C., *J. Am. Chem. Soc.*, **1975**, *97*, 6909. (s) Franz, J. A. and Martin, J. C., *J. Am. Chem. Soc.*, **1975**, *97*, 583. (t) Paul, I. C.; Martin, J. C. and Perozzi, E. F., *J. Am. Chem. Soc.*, **1972**, *94*, 5010.

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Mattox-Kendall Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Mattox and Kendall in 1948.[1] It is a synthesis of α,β-unsaturated ketones by means of dehydrobromination of phenylhydrazone of a semicarbazone derivative of the corresponding α-bromoketone. Therefore, it is often known as the Mattox-Kendall reaction.[2] Occasionally, it is also referred to as the Kendall synthesis[3] or Mattox-Kendall dehydrobromination.[4] Although this reaction is primarily used for the transformation of steroids—such as the conversion of 2-bromo-3-ketoallo-steroids,[2b] 4-bromo-3-ketosteroid,[2b] 2,2-dibromo-3-ketoallosteroids,[2b] and 6-bromo-3-ketosteroids[2b]—into corresponding conjugated ketones, it is also applicable for other cyclic α-bromo ketones[5] or alicyclic ketones.[5] The dehydrobromination of intermediate hydrazone can be achieved using either pyruvate,[6] or pyruvic acid.[7] However, it has been reported that the rigorous purification of α-bromo ketone is essential for a high yield of corresponding conjugated ketone.[6] On the other hand, even though the α-bromo ketones can also be dehydrobrominated directly by a base such as collidine,[8] such dehydrobromination does not give conjugated enone under these conditions. It should be pointed out that the Mattox-Kendall reaction does not work for 2-bromo-1-tetralone and 2-bromo-1-keto-1,2,3,4-tetrahydrophenanthrene,[5] from which the bromo is replaced by a methoxy group upon boiling with methanol. In addition, this reaction does not work for methyl 4β-bromo-3-ketocholanate.[9]

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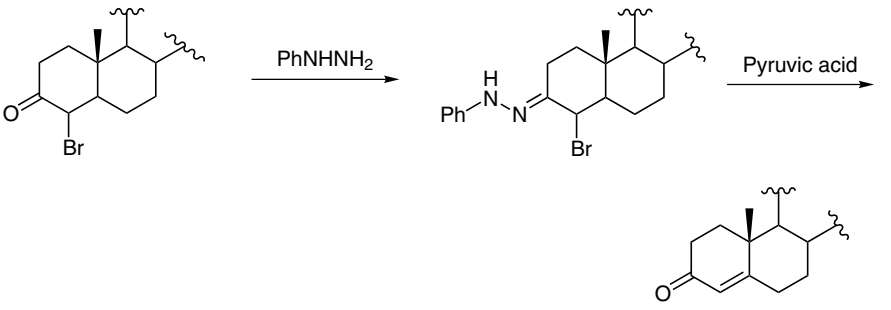
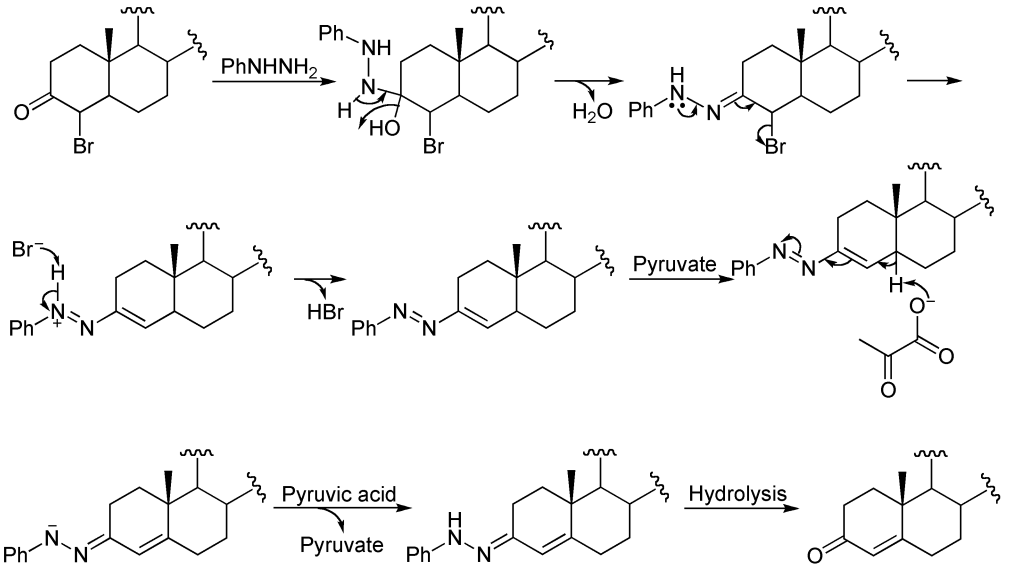
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The mechanism is illustrated here using pyruvate as a base.



D. MODIFICATION

This reaction has been extended to directly eliminate hydrogen bromide by using collidine as a base.

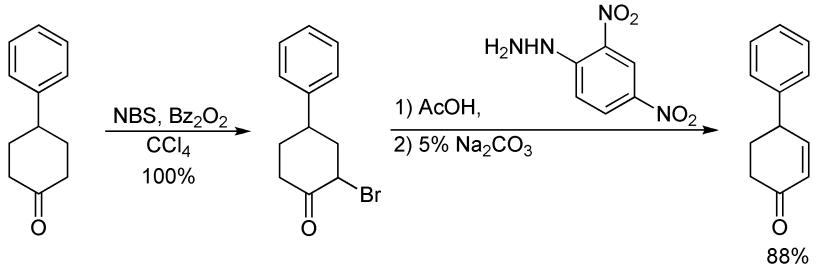
E. APPLICATIONS

This reaction is very useful in the preparation of conjugated enones, especially in steroids.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 8.

A mixture of 30 g 4-phenylcyclohexanone, 27.3 g *N*-bromosuccinimide, 0.05 g benzoyl peroxide, and 150 mL carbon tetrachloride was cautiously heated on a water bath. When the exothermic reaction had subsided, the mixture was refluxed for 20 min, cooled, filtered, and concentrated in vacuo. The remaining solution was deposited on ice and gave 48 g 2-bromo-4-phenylcyclohexanone in a quantitative yield that was recrystallized from cyclohexane and melted at 104–105°C.

To a hot solution of 1.0 g 2-bromo-4-phenylcyclohexanone in 30 mL acetic acid was added 0.52 g 2,4-dinitrophenylhydrazine, and the mixture was refluxed for 2 min. The corresponding dinitrophenyl hydrazone precipitated initially dissolved, and no crystals appeared upon cooling. The mixture was therefore diluted with $CHCl_3$, and the solution was washed with 5% Na_2CO_3 solution and water, dried over Na_2SO_4, and concentrated. The dark solid that remained was recrystallized from butanol. In addition to some amorphous insoluble material, 1.0 g brown-red crystals was obtained, in a yield of 88%, m.p., 122°C

Alternatively, a solution of 1.0 g *anti*-2,4-dinitrophenyl hydrazone in 30 mL acetic acid was refluxed for 2 min in an atmosphere of nitrogen. Water was added, and the precipitate formed was recrystallized from butanol to give 0.6 g 4-phenylcyclohex-2-en-1-one, in a yield of 83%, m.p., 122°C.

Other references related to the Mattox-Kendall reaction are cited in the literature.[10]

H. REFERENCES

1. Mattox, V. R. and Kendall, E. C., *J. Am. Chem. Soc.,* **1948**, *70*, 882.
2. (a) Kritchevsky, T. H.; Garmaise, D. L. and Gallagher, T. F., *J. Am. Chem. Soc.,* **1952**, *74*, 483. (b) Djerassi, C., *J. Am. Chem. Soc.,* **1949**, *71*, 1003.
3. Hershberg, E. B.; Herzog, H. L.; Coan, S. B.; Weber, L. and Jevnik, M., *J. Am. Chem. Soc.,* **1952**, *74*, 2585.
4. Djerassi, C. and Marshall, D., *J. Am. Chem. Soc.,* **1958**, *80*, 3986.

5. Ramirez, F. and Kirby, A. F., *J. Am. Chem. Soc.,* **1953**, *75*, 6026.
6. Koechlin, B. A.; Kritchevsky, T. H. and Gallagher, T. F., *J. Am. Chem. Soc.,* **1951**, *73*, 189.
7. Yanagita, M. and Yamakawa, K., *J. Org. Chem.,* **1956**, *21*, 500.
8. Bergmann, E. D. and Yaroslavsky, S., *J. Am. Chem. Soc.,* **1959**, *81*, 2772.
9. Fieser, L. F. and Ettorre, R., *J. Am. Chem. Soc.,* **1953**, *75*, 1700.
10. (a) Warnhoff, E. W., *J. Org. Chem.,* **1963**, *28*, 887. (b) Djerassi, C.; Geller, L. E. and Eisenbraun, E. J., *J. Org. Chem.,* **1960**, *25*, 1. (c) Engel, C. R., *J. Am. Chem. Soc.,* **1956**, *78*, 4727. (d) Magerlein, B. J.; Lyttle, D. A. and Levin, R. H., *J. Org. Chem.,* **1955**, *20*, 1709. (e) Beereboom, J. J.; Djerassi, C.; Ginsberg, D. and Fieser, L. F., *J. Am. Chem. Soc.,* **1953**, *75*, 3500. (f) Constantin, J. M.; Haven, A. C. and Sarett, L. H., *J. Am. Chem. Soc.,* **1953**, *75*, 1716. (g) Djerassi, C. and Nussbaum, A. L., *J. Am. Chem. Soc.,* **1953**, *75*, 3700. (h) Kendall, E. C. and McGuckin, W. F., *J. Am. Chem. Soc.,* **1952**, *74*, 5811. (i) Samuels, L. T. and Reich, H., *Ann. Rev. Biochem.,* **1952**, *21*, 129. (j) Ramirez, F. and Kirby, A. F., *J. Am. Chem. Soc.,* **1952**, *74*, 4331. (k) Mattox, V. R. and Kendall, E. C., *J. Biol. Chem.,* **1951**, *188*, 287. (l) Wendler, N. L.; Huang, M. L. and Tishler, M., *J. Am. Chem. Soc.,* **1951**, *73*, 3818. (m) Kritchevsky, T. H. and Gallagher, T. F., *J. Am. Chem. Soc.,* **1951**, *73*, 184. (n) Mattox, V. R. and Kendall, E. C., *J. Am. Chem. Soc.,* **1950**, *72*, 2290. (o) Koechlin, B. A.; Kritevsky, T. H. and Gallagher, T. F., *J. Biol. Chem.,* **1950**, *184*, 393. (p) Rinne, W. W.; Deutsch, H. R.; Bowman, M. I. and Joffe, I. B., *J. Am. Chem. Soc.,* **1950**, *72*, 5759.

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McCormack Cycloaddition
(McCormack Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by McCormack in 1953.[1] It is a synthesis of phospholene oxides involving the cycloaddition of dihalophosphines with 1,3-dienes and subsequent hydrolysis. Therefore, it is generally known as the McCormack reaction[2] or McCormack cycloaddition.[2f,2i,3] Occasionally, this reaction is also referred to as the McCormack synthesis.[4] The resulting products are called the McCormack adducts[3k] or McCormack cycloadducts.[3b,5] In general, this reaction is performed neatly[2a] without any solvent added. In addition, this reaction is often sluggish[2e,2g] and takes days or weeks to complete for less reactive dienes.[2e,2g,2h,3h] In contrast, the cycloaddition of phosphenium ion with 1,3-diene is much faster,[2e,2h,3a] taking as little as 15 min[2g] because of the highly electrophilic nature of phosphenium;[2h] the actual reaction time is depends on steric and electronic factors.[2e] It is interesting that even though 1,3-cycloheptadiene reacts with methyldichlorophosphine to give the corresponding adduct, 1,3-cyclohexadiene fails to undergo such cycloaddition.[2f,3b] This reaction has been modified to react with ethylene chlorophosphite (2-chloroethyl dichlorophosphite) to produce chlorophosphine oxide[2a] and react with phosphorus tribromide to form bromophosphine.[2b] Besides the general preparation of phospholene oxides, this reaction has been used to prepare bicyclic phospholene oxides, including hexahydrophosphindole 1-oxide,[3e] hexahydrophosphindole,[3b] and 7-phenyldinaphtho[2,1-b:1,2-d]phosphole.[2c] In addition, the corresponding phospholene sulfides can be prepared by addition of hydrogen sulfide to the McCormack cycloadducts.[3k] Similar to the *Diesl-Alder Cycloaddition*, the McCormack cycloaddition is also reversible,[2f] and has been applied to the preparation of dioxyphosphoranes,[6] for example.

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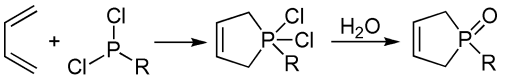
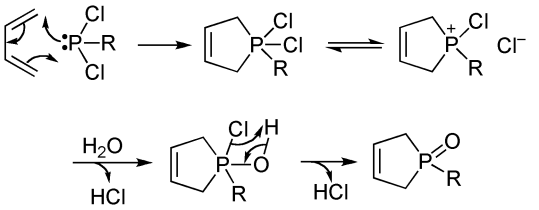
B. GENERAL REACTION SCHEME



(R = alkyl, alkoxyl, aryl, halogen)

C. PROPOSED MECHANISMS

It is believed that the lone-pair electrons of phosphorus in dihalophosphine is involved in the cycloaddition, as demonstrated below.



D. MODIFICATION

This reaction has been modified to react with 2-chloroethyl dichlorophosphite and phosphorus tribromide.

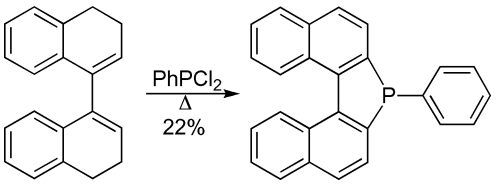
E. APPLICATIONS

This reaction has very general application in the preparation of phospholene oxides.

F. RELATED REACTIONS

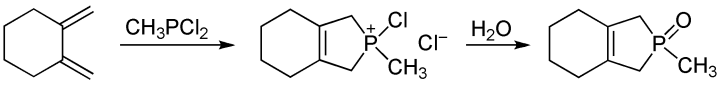
This reaction is related to the *Diels-Alder Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2c.

A mixture of 1.11 mL $PhPCl_2$ (8.17 mmol) and 0.4 g bis-dialin (1.54 mmol) was refluxed at 220°C for 3 h under nitrogen. After cooling to room temperature, the solution was poured carefully into 20 mL 15% KOH aqueous solution. The resulting yellow solid was filtered off, washed with 10 mL 15% KOH aqueous solution, and dissolved in CH_2C1_2. The organic phase was washed with water and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude product was purified by flash chromatography (n-hexane/CH_2Cl_2, 8:1) and recrystallized from CH_2Cl_2/petroleum ether to afford 22% 7-phenyldinaphtho[2,l-b:l′, 2′-d] phosphole, m.p. 157–8°C.



82%

Reference 3c.

Methylphosphorous dichloride (37.4 g, 0.32 mol) was added to a mixture of 29.3 g 1,2-dimethylenecyclohexane (0.27 mol), 400 mg copper stearate, and 100 mL hexane in a wide-mouthed brown bottle with a Teflon-lined cap. The bottle was loosely capped until the initial exothermic reaction had subsided. As the solid cycloadduct formed, additional solvent was added (three 25-mL portions) to keep the adduct covered. The bottle was tightly sealed and allowed to stand for 13 days. The solid cycloadduct was filtered off, washed with petroleum ether (35–60°C, 3 × 50 mL), and added cautiously to 150 mL ice-cold, saturated $NaHCO_3$ solution. The resulting solution was extracted continuously with chloroform for 48 h. The chloroform extract was dried, filtered, and concentrated to give a brown solid residue. Distillation at 106–107°C (0.03 mmHg) gave 37.6 g phospholene oxide as a colorless oil, in a yield of 82%, which quickly solidified to a white, hygroscopic solid.

Other references related to the McCormack cycloaddition are cited in the literature.[7]

H. REFERENCES

1. (a) McCormack, W. B., *U.S. Pat*., Dec. 22, **1953**, 2,663,737. (b) McCormack, W. B., *U.S. Pat.,* Dec. 22, **1953**, 2,663,738.
2. (a) Hum, G., "The Design and Synthesis of Strained Transition State Analogues for Phosphotriester Hydrocysis," *Master Thesis*, University of Toronto, Toronto, Ontario, Canada, **1997**. (b) Gruneich, J. A. and Wisian-Neilson, P., *Macromolecules*, **1996**, *29*, 5511. (c) Gladiali, S.; Dore, A.; Fabbri, D.; Lucchi, O. D. and Valle, G., *J. Org. Chem.,* **1994**, *59*, 6363. (d) Cowley, A. H.; Kemp, R. A.; Lasch, J. G.; Norman, N. C.; Stewart, C. A.; Whittlesey, B. R. and Wright, T. C., *Inorg. Chem.*, **1986**, *25*, 740. (e) Cowley, A. H. and Kemp, R. A., *Chem. Rev.*, **1985**, *85*, 367. (f) Quin, L. D.; Caster, K. C.; Kisalus, J. C. and Mesch, K. A., *J. Am. Chem. Soc.*, **1984**, *106*, 7021. (g) SooHoo, C. K. and Baxter, S. G., *J. Am. Chem. Soc.*, **1983**, *105*, 7443. (h) Cowley, A. H.; Kemp, R. A.; Lasch, J. G.; Norman, N. C. and Stewart, C. A., *J. Am. Chem. Soc.*, **1983**, *105*, 7444. (i) Symmes, C. and Quin, L. D., *J. Org. Chem.*, **1979**, *44*, 1048.
3. (a) Allen, D. W., *Organophospnhorus Chemistry*, **2005**, *34*, 1. (b) Quin, L. D.; Caster, K. C. and Soloway, S. B., *J. Org. Chem.*, **1984**, *49*, 2627. (c) Quin, L. D.; Middlemas, E. D.; Rao, N. S.; Miller, R. W. and McPhail, A. T., *J. Am. Chem. Soc.*, **1982**, *104*, 1893. (d) Quin, L. D. and MacDiarmid, J. E., *J. Org. Chem.*, **1982**, *47*, 3248. (e) Quin, L. D. and MacDiarmid, J. E., *J. Org. Chem.*, **1981**, *46*, 461. (f) MacDiarmid, J. E. and Quin, L. D., *J. Org. Chem.*, **1981**, *46*,

1451. (g) Middlemas, E. D. and Quin, L. D., *J. Org. Chem.*, **1979**, *44*, 2587. (h) Quin, L. D. and Middlemas, E. D., *J. Am. Chem. Soc.*, **1977**, *99*, 8370. (i) Symmes, C.; Morris, J. and Quin, L. D., *Tetrahedron Lett*., **1977**, 335. (j) Symmes, C. and Quin, L. D., *J. Org. Chem.*, **1976**, *41*, 238. (k) Symmes, C. and Quin, L. D., *J. Org. Chem.*, **1976**, *41*, 1548. (l) Marsi, K. L.; Burns, F. B. and Clark, R. T., *J. Org. Chem.*, **1972**, *37*, 238.

4. Boukherroub, R.; Garrigues, E. and Manuel, G., *Phosphorus, Sulfur & Silicon & Related Elements*, **1995**, *105*, 101.
5. Quin, L. D.; Borleske, S. G. and Engel, J. F., *J. Org. Chem.*, **1973**, *38*, 1858.
6. (a) Scott, G.; Hammond, P. J.; Hall, C. D. and Bramblett, J. D., *J. Chem. Soc., Perkin Trans. II*, **1977**, 882. (b) Chang, L. L.; Denney, D. Z.; Denney, D. B. and Hsu, Y. F., *Phosphorus*, **1974**, *4*, 265.
7. (a) Hum, G.; Wooler, K.; Lee, J. and Taylor, S. D., *Can. J. Chem.*, **2000**, *78*, 642. (b) Gladiali, S.; Dore, A.; Fabbri, D.; De Lucchi, O. and Valle, G., *J. Org. Chem.*, **1994**, *59*, 6363. (c) Toda, M.; Miyahara, I.; Hirotsu, K.; Yamaguchi, R.; Kozima, S. and Matsumoto, K., *Chem. Lett.*, **1991**, 1677. (d) Quin, L. D., *Heterocyclic Chemistry of Phosphorus*, John Wiley & Sons, New York, **1981**. (e) Quin, L. D.; Symmes, C.; Middlemas, E. D. and Lawson, H. F., *J. Org. Chem.*, **1980**, *45*, 4688. (f) Quin, L. D. and Middlemas, E. D., *Pure & Appl. Chem.*, **1980**, *52*, 1013. (g) Baccolini, G. and Todesco, P. E., *J. Org. Chem.*, **1974**, *39*, 2650. (h) Quin, L. D., "Trivalent Phosphorus Compounds as Dienophiles," in *1,4-Cycloaddition Reaction*, ed. Hamer, J., Academic Press, New York, **1967**, pp. 47–96. (i) Quin, L. D.; Bryson, J. G. and Moreland, C. G., *J. Am. Chem. Soc.*, **1969**, *91*, 3308. (j) Quin, L. D.; Gratz, J. P. and Barket, T. P., *J. Org. Chem.*, **1968**, *33*, 1034. (k) Quin, L. D. and Barket, T. P., *J. Chem. Soc., Chem. Commun.*, **1967**, 914.

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McFadyen-Stevens Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by McFadyen and Stevens in 1936.[1] It is a synthesis of aromatic or heterocyclic aldehydes from base-catalyzed thermal decomposition of acylbenzenesulfonylhydrazides in ethylene glycol. Therefore, it is generally known as the McFadyen-Stevens reaction.[2] Occasionally, it is also referred to as the McFadyen-Stevens reduction,[2g] McFadyen-Stevens synthesis,[3] or McFadyen-Stevens aldehyde synthesis.[2i,4] The general procedure of this reaction is to add 5 equivalents of solid sodium carbonate to the solution of acylbenzenesulfonylhydrazides in ethylene glycol at 160°C for a short time (1.25 min) then rapidly cooled it to obtain 70% of the corresponding aldehydes.[2i] However, the optimal condition for this reaction is to pyrolyze the acylbenzenesulfonylhydrazides in an aprotic solvent in the presence of an equivalent of base and solid powder;[2e] the aprotic solvent can be DMSO, DMF, or dimethylacetamide (DMA),[2e] and solids include "charcoal, copper, zinc, diatomaceous earth (Super Cel), glass wool (Pyrex), powdered soft glass, sodium carbonate, barium carbonate and barium hydroxide."[2i] It has been found that this decomposition is accelerated by electron-donating groups and retarded by electron-withdrawing substituents with a slop of -1.38 (ρ) for the Hammett plot.[2e] It is plausible that the decomposition of acylbenzenesulfonylhydrazide of aliphatic carboxylic acids to aldehydes holds similar mechanistic characters, in which the failure to yield corresponding aldehydes is attributed to the successive reaction of aliphatic aldehydes under basic conditions,[2e] whereas the aldehydes without α-protons, such as pivalaldehyde[2g] and apocamphane-1-carboxaldehyde,[2g] or cyclopropanecarboxaldehyde, due to the "unsaturation" properties of the cyclopropane ring,[5] can be obtained accordingly.

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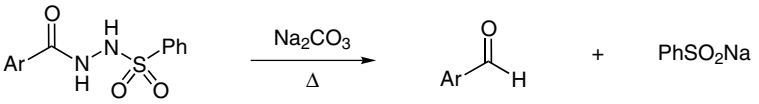
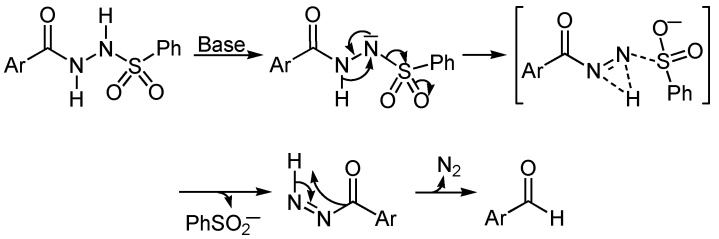
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified to occur with only one equivalent of base in the presence of a solid powder.

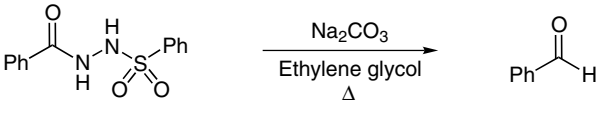
E. APPLICATIONS

This reaction has general application in the conversion of carboxylic acid into corresponding aldehydes.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



73%

Reference 2i.

To a stirred hot mixture of 0.5 g *N*-benzenesulfonylbenzhydrazide, 0.2 g powdered soft glass (finer than 30 mesh), and 5 mL ethylene glycol in a test tube was added anhydrous

sodium carbonate. The mixture was stirred at 160°C with a wad of glass wool. At the end of the reaction period, the test tube was quickly transferred from the heating bath to an ice bath. The reaction mixture was then washed through a sintered glass filter with methanol into a 0.05 M solution of 2,4-dinitrophenylhydrazine in 0.5% of methanolic hydrochloric acid. After several hours, the precipitate was washed with 5–10 mL acidic methanol and dried to a constant weight. The yield of this reaction was 73%.

Other references related to the McFadyen-Stevens reaction are cited in the literature.[6]

H. REFERENCES

1. McFadyen, J. S. and Stevens, T. S., *J. Chem. Soc.*, **1936**, 584.
2. (a) Jaisankar, P.; Pal, B. and Giri, V. S., *Synth. Commun.*, **2002**, *32*, 2569. (b) Bu, T. H. and Xie, S. J., *Jinan Liyi Xuebao*, **1986**, 70. (c) Graboyes, H.; Anderson, E. L.; Levinson, S. H. and Resnick, T. M., *J. Heterocycl. Chem.*, **1975**, *12*, 1225. (d) Shirai, H.; Oda, N.; Amano, R. and Ishida, E., *Nagoya-Shiritsu Daigaku Yakugakubu Kiyo*, **1975**, *5*, 61. (e) Matin, S. B.; Craig, J. C. and Chan, R. P. K., *J. Org. Chem.*, **1974**, *39*, 2285. (f) Baltazzi, E., *Compt. Rend.*, **1962**, *254*, 702. (g) Sprecher, M.; Feldkimel, M. and Wilchek, M., *J. Org. Chem.*, **1961**, *26*, 3664. (h) Jensen, K. A. and Holm, A., *Acta. Chem. Scand.*, **1961**, *15*, 1787. (i) Newman, M. S. and Caflisch, E. G., *J. Am. Chem. Soc.*, **1958**, *80*, 862.
3. Babad, H.; Herbert, W. and Stiles, A. W., *Tetrahedron Lett*., **1966**, 2927.
4. (a) Dudman, C. C.; Grice, P. and Reese, C. B., *Tetrahedron Lett*., **1980**, *21*, 4645. (b) Nair, M. and Shechter, H., *J. Chem. Soc., Chem. Commun.*, **1978**, 793.
5. Roberts, J. D., *J. Am. Chem. Soc.*, **1951**, *73*, 2959.
6. (a) Lin, M.-R. and Liao, L.-A., *Zhongguo Xinyao Zazhi*, **2005**, *14*, 1318. (b) Ukhin, L. Yu. and Kuz'mina, L. G., *Russ. Chem. Bull.*, **2004**, *53*, 2262. (c) Manna, R. K.; Jaisankar, P. and Giri, V. S., *Synth. Commun.*, **1998**, *28*, 9. (d) Santini, A.; Pedone, C.; Benedetti, E.; Silipo, C.; Vittoria, A.; Caliendo, G. and Greco, G., *Struct. Chem.*, **1994**, *5*, 183. (e) Crow, W. D. and McNab, H., *Aust. J. Chem.*, **1979**, *32*, 99. (f) Eichler, E.; Rooney, C. S. and Williams, H. W. R., *Aust. J. Chem.*, **1976**, *13*, 841. (g) Eichler, E.; Rooney, C. S. and Williams, H. W. R., *J. Heterocycl. Chem.*, **1976**, *13*, 43. (h) Toda, T.; Ryu, S.; Hagiwara, Y. and Nozoe, T., *Bull. Chem. Soc. Jpn.*, **1975**, *48*, 82. (i) Cacchi, S. and Paolucci, G., *Gazz. Chim. Ital.*, **1974**, *104*, 221. (j) Siddappa, S. and Bhat, G. A., *J. Chem. Soc. C*, **1971**, 178. (k) Spasov, A. and Demirov, G., *Chem. Ber.*, **1970**, *103*, 3867. (l) van Es, T.; Backeberg, O. G. and Morrison, I., *J. South Afri. Chem. Inst.*, **1964**, *17*, 95. (m) Toan, L. Q. and Tefas, D., *Farmacia (Bucharest)*, **1962**, *10*, 19. (n) Campaigne, E.; Thompson, R. L. and van Werth, J. E., *J. Med. Pharm. Chem.*, **1959**, *1*, 577. (o) Woodcock, D. and Davies, B. L., *J. Chem. Soc.*, **1958**, 4723. (p) Brown, U., M.; Carter, P. H. and Tomlinson, M., *J. Chem. Soc.*, **1958**, 1843. (q) Kulka, K., *Amer. Perfumer & Aromatics*, **1957**, *70*, 54. (r) Holland, D. O. and Nayler, J. H. C., *Chem. Ind. (London)*, **1954**, 224. (s) Mosettig, E., *Org. React.*, **1954**, *8*, 232. (t) Cauquil, G. and Casadevall, A., *Compt. Rend.*, **1954**, *238*, 908. (u) Mulholland, T. P. C. and Ward, G., *J. Chem. Soc.*, **1954**, 4676. (v) Huisgen, R. and Nakaten, H., *Ann.*, **1954**, *586*, 84. (w) Linnel, W. H.; Mathieson, D. W. and Modi, D. T., *J. Chem. Soc.*, **1953**, 3257. (x) Baker, J. W.; Barrett, G. F. C. and Tweed, W. T., *J. Chem. Soc.*, **1952**, 2831. (y) Kushner, S.; Dalalian, H.; Sanjurjo, J. L.; Bach, F. L.; Safir, S. R.; Smith, V. K. and Williams, J. H., *J. Am. Chem. Soc.*, **1952**, *74*, 3617.

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McLafferty Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported from mass spectroscopy of butyric acid by Happ and Stewart in 1952,[1] but it was McLafferty who initially worked out the cyclic transition state and indicated the importance of such fragmentation pattern for the ionized organic molecules in mass spectroscopy beginning in 1956.[2] Thus this reaction is generally known as the McLafferty rearrangement[3,4] and is occasionally referred to as the McLafferty reaction[3j,5] as well. This reaction is generally defined as the rearrangement of monounsaturated molecular ion or radical ion with the cleavage of α,β-bond of the unsaturated system along with the concomitant transfer of a γ-hydrogen via a six-membered transition state by the formation of a pair of unsaturated fragments, regardless of which fragment holds the charge. This reaction, though without practical value in synthetic organic chemistry, is one of the most common fragmentations and studied most extensively in the field of mass spectroscopy.

It has been found that, during the fragmentation, the structural, steric, and electronic factors determine the actual fragmentation paths.[3j] Taking carbonyl compounds as an example, the critical activation barrier is in the range of 0.2–0.8 eV,[3c] corresponding to 4.61–18.45 Kcal/mol in energy. It has been found that the attachment of an electron-withdrawing group to a carbonyl group and an electron-donating group to the carbon with γ-hydrogen will enhance the McLafferty rearrangement.[3m] On the other hand, the ionization potential of enol is generally lower than that of olefin; thus the enolic ion and olefin are formed through the fragmentation; unless the charged olefin is more stable, in this case the neutral enol and charged olefin will be the fragmentation products, as shown by the fragmentation of aliphatic aldehydes.[3j] The latter case is known as the reverse McLafferty rearrangement,[6] complementary McLafferty rearrangement[3m] or McLafferty rearrangement with charged olefinic product.[3j] The special rearrangement of alkyl formate for the formation of

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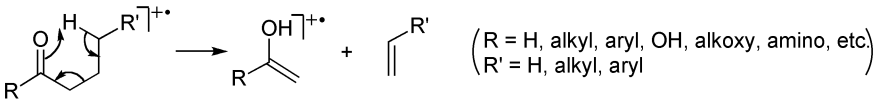
$HC(OH)_2^+$ (m/z = 47) ion is called the [R-2H] loss reaction or McLafferty + 1 rearrangement.[3g] In addition, as γ-hydrogen migrates through the overlapping of the orbitals of hydrogen and the oxygen of the carbonyl group, it is anticipated that the distance between the migrating γ-hydrogen and the oxygen, as well as the angle τ between the plane of carbonyl group and the γ-hydrogen, will be as small as possible.[3j] It is hypothesized that if the distance between γ-hydrogen and oxygen were >1.8Å, then no McLafferty rearrangement would be expected.[3j] In addition, the angle τ can be in the range of 0–90°, and it has been reported that when the angle is ~ 45°, the activation energy is ~ 76 Kcal/mol.[7] No McLafferty rearrangement is reported with a τ value > 50°.[3k] However, in the case of 12-keto steroids possessing a C-17 side chain with a C-20 hydrogen atom (e.g., 12-ketopregnanes, 12-ketoergostanes, and 12-ketocholanates), there is a very strong peak exhibited at m/z = 233 through the McLafferty rearrangement, though the distance between hydrogen and oxygen is predicted to be 3Å.[3m] Such a rearrangement is believed to occur after the cleavage of a ring. It should be pointed out that other functional groups, such as deuterium,[3j] phenyl,[8] trimethylsilyl[3n] and trimethylstannyl,[9] can also migrate. In general, hydrogen has a higher migrating tendency over deuterium, with an isotopic effect in the range of 0.5–1.0 for ketones, esters, and aromatic and heterocyclic substrates;[3j] secondary hydrogen is easier to migrate than the primary hydrogen.[3k]

In contrast to the migration of hydrogen, which has an analogous photochemical reaction (i.e., *Norrish Type II Reaction*[3j,10]), the migration of the trimethylsilyl group does not have a similar analogue in corresponding photochemistry.[3n] Different from the migration of hydrogen, almost all molecular ions of aldehydes, ketones, thioketones, carboxylic acids, and acetates that contain a δ-silyl group can undergo a silyl group migration through a seven-membered transition state, with a higher migration ability for a small silyl group in acyclic carbonyl compounds than that for a larger silyl group in cyclic carbonyl compounds.[3d] However, if the molecule contains a site or group of lower ionization potential than carbonyl,[3j] as in the case of amino ester,[10] amino ketone,[11] ω-amino ester,[12] isopropyl pyruvate,[13] and α-hydroxy ketones,[14] no McLafferty rearrangement is observed, because those groups will be first ionized.

Mechanistically, the McLafferty rearrangement can be either concerted with "simultaneous hydrogen transfer and β-cleavage," or stepwise with the "initial hydrogen transfer being followed by β-cleavage,"[3j] More and more experimental evidence supports the stepwise mechanism rather than the concerted one,[3e,3g,3h] although they cannot be differentiated from theoretical studies.[15] Furthermore, the infrared multiple photon (IRMP) activated dissociation of the butyrophenone molecular cation shows the involvement of a distonic ion as the intermediate, which provides solid support for the stepwise mechanism.[3h]

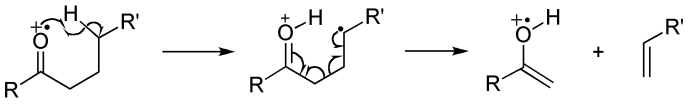
Besides the carbonyl compounds, organic molecules with other types of multiple bonds also undergo similar rearrangements, such as hydrazones, oximes, and semicarbazones.[3j] Even the molecules of epoxides without a double bond, undergo the MaLafferty rearrangement but in two distinct pathways: "inside" and "outside."[16]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Shown here is a stepwise mechanism for the McLafferty rearrangement of a carbonyl compound, including a hydrogen transfer to oxygen and the subsequent β-cleavage of the α,β-bond. In this mechanism, n-bonding carbonyl group is the highest occupied molecular orbital (HOMO) in carbonyl compounds, so that it is often excited, losing one electron to form a radical cation, which undergoes the β-cleavage to afford the two fragments.



D. MODIFICATION

N/A

E. APPLICATIONS

This rearrangement has very wide application in structural elucidation using mass spectroscopy as the tool.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES

No practical experiment is available for synthetic purposes. More references related to the McLafferty rearrangement are cited in the literature.[17]

H. REFERENCES

1. Happ, G. P. and Stewart, D. W., *J. Am. Chem. Soc.*, **1952**, *74*, 4404.
2. (a) McLafferty, F. W., *Anal. Chem.*, **1956**, *28*, 306. (b) Gilpin, J. A. and McLafferty, F. W., *Anal. Chem.*, **1957**, *29*, 990. (c) McLafferty, F. W., *Anal. Chem.*, **1959**, *31*, 82.
3. (a) Hosamani, K. M. and Sattigeri, R. M., *Ind. Eng. Chem. Res.*, **2005**, *44*, 254. (b) Chaves, M. H.; Roque, N. F. and Ayres, M. C. C., *J. Braz. Chem. Soc.*, **2004**, *15*, 608. (c) Fagerquist, C. K.; Hellerstein, M. K.; Faubert, D. and Bertrand, M. J., *J. Am. Soc. Mass Spect.*, **2001**, *12*, 754. (d) Hwu, J. R.; Wu, I.-F.; Shiao, S.-S.; Tseng, W. N.; Huang, J.-J. and Chen, B.-L., *Organometallics*, **1999**, *18*, 2314. (e) Oh, S. T.; Choe, J. C. and Kim, M. S., *J. Phys. Chem.*, **1996**, *100*, 13367. (f) Todd, J. F. J., *Pure & Appl. Chem.*, **1991**, *63*, 1541. (g) Zha, Q. M.; Hayes, R. N.; Nishimura, T.; Meisels, G. G. and Gross, M. L., *J. Phys. Chem.*, **1990**, *94*, 1286. (h) Osterheld, T. H. and Brauman, J. I., *J. Am. Chem. Soc.*, **1990**, *112*, 2014. (i) Litton, J. F.; Kruger, T. L. and Cooks, R. G., *J. Am. Chem. Soc.*, **1976**, *98*, 2011. (j) Kingston, D. G. I.; Bursey, J. T. and Bursey, M. M., *Chem. Rev.*, **1974**, *74*, 215. (k) Henion, J. D. and Kingston, D.

G. I., *J. Am. Chem. Soc.*, **1974**, *96*, 2532. (l) Grunwell, J. R. and Kochan, A., *J. Org. Chem.*, **1973**, *38*, 1610. (m) Dias, J. R.; Sheikh, Y. M. and Djerassi, C., *J. Am. Chem. Soc.*, **1972**, *94*, 473. (n) Weber, W. P.; Felix, R. A. and Willard, A. K., *J. Am. Chem. Soc.*, **1970**, *92*, 1420. (o) MacLeod, J. K. and Djerassi, C., *J. Am. Chem. Soc.*, **1967**, *89*, 5182. (p) Djerassi, C. and Tokis, L., *J. Am. Chem. Soc.*, **1966**, *88*, 536.

4. (a) Klyba, L. V.; Nedolya, N. A.; Shlyakhtina, N. I. and Zhanchipova, E. R., *Russ. J. Org. Chem.*, **2005**, *41*, 1544. (b) Loos, J.; Schroeder, D.; Schwarz, H.; Thissen, R. and Dutuit, O., *Int. J. Mass Spect.*, **2005**, *240*, 121. (c) van der Rest, G.; Jensen, L. B.; Azeim, S. A.; Mourgues, P. and Audier, H. E., *J. Am. Soc. Mass Spect.*, **2004**, *15*, 966. (d) Olah, G. A.; Mathew, T.; Goeppert, A.; Rasul, G.; Prakash, G. K. S. and Esteves, P. M., *J. Am. Soc. Mass Spect.*, **2004**, *15*, 959. (e) Nibbering, N. M. M., *J. Am. Soc. Mass Spect.*, **2004**, *15*, 956. (f) Alvarez, R. M.; Fernandez, A. H.; Chioua, M.; Perez, P. R.; Vilchez, N. V. and Torres, F. G., *Rapid Commun. Mass Spect*, **1999**, *13*, 2480. (g) Oprean, R.; Roman, L. and Sandulescu, R., *J. Pharm. Biomed. Anal.*, **1996**, *14*, 1031. (h) Takayama, M., *Int. J. Mass Spect. Ion Proc.*, **1995**, *144*, 199. (i) Dohmeier-Fischer, S.; Kraemer, N. and Gruetzmacher, H.-F., *Eur. Mass Spect.*, **1995**, *1*, 3. (j) Stringer, M. B.; Underwood, D. J.; Bowie, J. H.; Allison, C. E.; Donchi, K. F. and Derrick, P. J., *Org. Mass Spect.,* **1992**, *27*, 270. (k) Liu, R. F. and Pulay, P., *J. Compt. Chem.*, **1992**, *13*, 183.
5. (a) Loos, J.; Schröder, D. and Schwarz, H., *J. Org. Chem.*, **2005**, *70*, 1073. (b) Loos, J.; Schröder, D.; Zummack, W.; Schwarz, H.; Thissen, R. and Dutuit, O., *Int. J. Mass Spect.*, **2002**, *214*, 105. (c) Kuck, D., *Org. Mass Spect.*, **1989**, *24*, 1077. (d) Zollinger, M. and Seibl, J., *Org. Mass Spect.*, **1985**, *20*, 649.
6. Harpp, D. N. and Gleason, J. G., *J. Org. Chem.*, **1971**, *36*, 73.
7. Boer, F. P.; Shannon, T. W. and McLafferty, F. W., *J. Am. Chem. Soc.*, **1968**, *90*, 7239.
8. Webster, B. R., *J. Chem. Soc., Chem. Commun.*, **1966**, 124.
9. Kuivila, H. G.; Tsai, K.-H. and Kingston, D. G. I., *J. Organometal. Chem.*, **1970**, *23*, 129.
10. Bruderer, M.; Richter, W. and Vetter, W., *Helv. Chim. Acta*, **1967**, *50*, 1917.
11. (a) Highet, R. J. and Highet, D. F., *Tetrahedron Lett.*, **1970**, 1803. (b) Stermitz, F. R. and McMurtrey, K. D., *J. Org. Chem.*, **1968**, *33*, 1140.
12. Wolff, R. E. and Caspar, A., *Tetrahedron Lett.*, **1970**, 1807.
13. Turro, N. J.; Weiss, D. S.; Haddon, W. F. and McLafferty, F. W., *J. Am. Chem. Soc.*, **1967**, *89*, 3379.
14. Brown, C. and Djerassi, C., *J. Chem. Soc., C*, **1969**, 2550.
15. Ha, T.-K.; Radloff, C. and Nguyen, M. T., *J. Phys. Chem.*, **1986**, *90*, 2991.
16. Brown, P.; Kossanyi, J. and Djerassi, C., *Tetrahedron, Suppl.*, **1966**, *8*, 241.
17. (a) Simionato, A. V. C.; Santos da Silva, D.; Lambais, M. R. and Carrilho, E., *J. Mass Spect.*, **2007**, *42*, 490. (b) Yang, S.-Z.; Wei, D.-Z. and Mu, B.-Z., *J. Biochem. Biophy. Methods*, **2007**, *70*, 519. (c) Hudson, C. E. and McAdoo, D. J., *J. Am. Soc. Mass Spect.*, **2007**, *18*, 270. (d) Kasai, H. F.; Tsubuki, M. and Honda, T., *Anal. Sci.*, **2006**, *22*, 921. (e) Grossert, J. S.; Cook, M. C. and White, R. L., *Rapid Commun. Mass Spect.,* **2006**, *20*, 1511. (f) Wang, X. and Holmes, J. L., *Int. J. Mass Spect.*, **2006**, *249–250*, 222. (g) Li, Q.-R.; Xue, S. and Yin, H., *Chem. Res. Chinese Univ.*, **2006**, *22*, 40. (h) Bulleigh, K.; Howard, A.; Do, T.; Wu, Q.; Anbalagan, V. and Van Stipdonk, M., *Rapid Commun. Mass Spect.*, **2006**, *20*, 227. (i) Dunbar, R. C. and Klein, R., *J. Am. Chem. Soc.*, **1977**, *99*, 3744. (j) Diekman, J.; MacLeod, J. K.; Djerassi, C. and Bladeschwieler, J. D., *J. Am. Chem. Soc.*, **1969**, *91*, 2069. (k) Stermitz, F. R. and Wei, C. C., *J. Am. Chem. Soc.*, **1969**, *91*, 3103. (l) Eadon, G.; Diekman, J. and Djerassi, C., *J. Am. Chem, Soc.*, **1969**, *91*, 3986. (m) Djerassi, C.; von Mutzenbecher, G.; Fajkos, J.; Williams, D. H. and Budzikiewicz, H., *J. Am. Chem. Soc.*, **1965**, *87*, 817.

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McMurry Coupling
(McMurry Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

Although the initial study on the reductive coupling of carbonyl compounds to olefins by a low-valent titanium reagent had been conducted concurrently by Tyrlik ($TiCl_4$-Mg)[1] and Mukaiyama ($TiCl_4$-Zn)[2] by 1973, it was McMurry who pioneered in the application of using low-valent titanium as a reducing reagent for a variety of functional groups (e.g., nitro, oxime)[3] and extensively studied the scope of the coupling of carbonyl compounds begining in 1974, using $LiAlH_4$, $LiBH_4$, LiH, CaH_2, etc. in combination with $TiCl_3$ or $TiCl_4$.[4] Therefore, this reaction is generally known as the McMurry coupling,[5,6] or McMurry reaction.[5e,5f,7,8] Occasionally, it is also referred to as the McMurry condensation,[7e] McMurry cross-coupling,[5a,5t,8b,9] McMurry reductive coupling,[5f,10] McMurry pinacol coupling,[7c,11] McMurry synthesis,[7d] McMurry olefination,[12] or McMurry olefin synthesis.[13] The combination of $TiCl_3$ and Zn/Cu couple in DME[7h] or $TiCl_3$-Li in DME[14] is known as the McMurry reagent, which is usually in colloidal status.[14] It has been reported that the active reducing species in the McMurry coupling is Ti^{n+} ($0<n<3$) rather than Ti(0),[7g] as supported by a similar reactivity of TiO_2 single crystal after sputtering off the terminal oxygen by Ar^+ bombardment.[15]

In general, this reaction gives *trans*-olefins in preference,[5o,5t,7h,14] but sometimes contaminated with pinacol.[14] However, the formation of the predominant *cis*-stilbene from acetophenone under the McMurry coupling condition is because of the π-π preassociation.[5t] In addition, the *cis*-olefins are formed in the case of intramolecular cyclization to form macrocycles, such as zearalenone[5k] and helicene.[5p] On the other hand, this reaction primarily works for the coupling of aromatic carbonyl compounds,[3,14] and generally requires high temperatures and prolonged time for deoxygenation.[7f,14] The inability to effectively couple aliphatic carbonyl compounds into olefins is probably due to the strong alkyl-oxygen bond in the intermediate pinacolates.[14] In mechanistic terms, the McMurry coupling has

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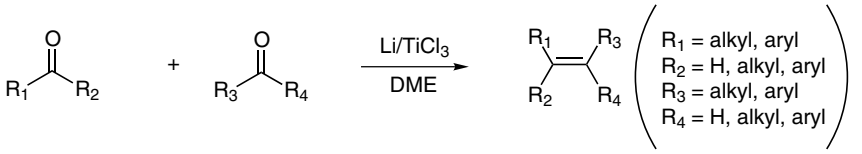
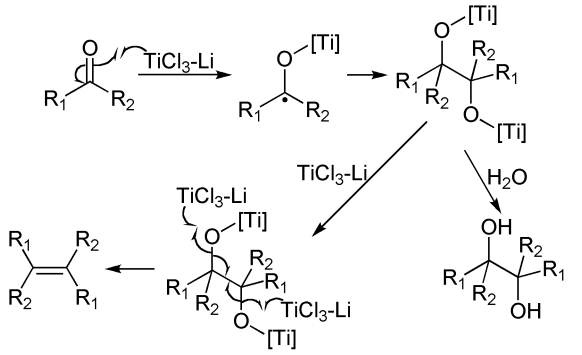
been proposed to involve the metallocarbenoid species to account for the formation of alkanes/olefins through direct deoxygenation of the carbonyl compounds.[8j,8l] However, the widely accepted mechanism consists of two defined steps: the pinacol reaction and the deoxygenation of pinacol to form olefin.[5s,5t,7b,7e,14] In this reaction, the reducing species donates an electron to the carbonyl compound to generate a radical anion, which dimerizes to form a pinacol product; the coupling of pinacol with low-valent titanium followed by deoxygenation results in the olefins. Because of the versatility of this reaction in the formation of olefins, especially in macrocycles, the McMurry coupling has been extensively modified to enhance the chemoselectivity and diastereoselectivity and shorten the reaction time. Some of the modifications are (*a*) the pretreatment of commercial titanium powder with chlorosilanes for the coupling of carbonyl compounds in THF, DME, EtOAc, or pyridine but not MeCN;[7g] (*b*) the addition of 10 equivalents of pyridine with respect to $TiCl_3$ to the THF-solvated low-valent titanium reagent;[5s] (*c*) the addition of a substoichiometric amount of iodine to a low-valent titanium reagent ($TiCl_3$-Li-THF);[7f] and (*d*) refluxing a mixture of a substoichiometric amount (0.25 eq.) of arenes (e.g., naphthalene), $TiCl_3$, and Li (or Mg) in THF or DME.[14] In addition, in the presence of a ligand (e.g., catechol), the McMurry coupling can be used to prepare pinacols with diastereoselectivity.[7c]

B. GENERAL REACTION SCHEME

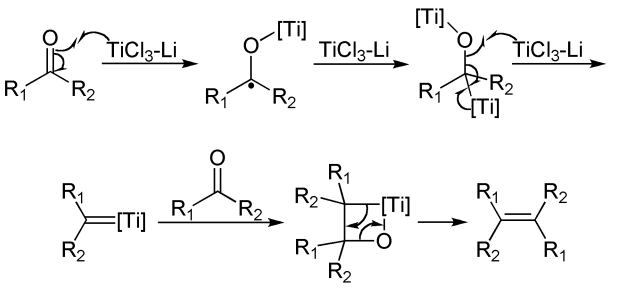


C. PROPOSED MECHANISMS

Two mechanisms involving the intermediate of either pinacol or metallocarbenoid are outlined in Scheme 1 and Scheme 2.



SCHEME 1. *McMurry coupling involving a pinacol intermediate.*



SCHEME 2. *McMurry coupling involving a metallocarbenoid intermediate.*

D. MODIFICATION

This reaction has been modified by the addition of pyridine[5s] or a substoichiometric amount of iodine[7f] or arenes[14] to the reaction solution and by treatment of the titanium powder with chlorosilane.[7g]

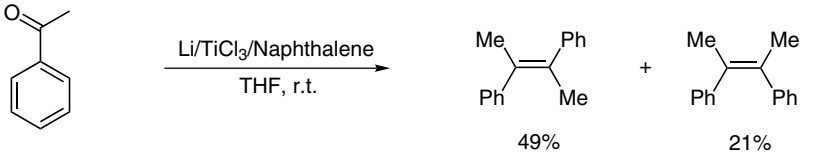
E. APPLICATIONS

This reaction has wide application in the preparation of olefins.

F. RELATED REACTIONS

This reaction is related to the *Barton-Kellogg Reaction.*

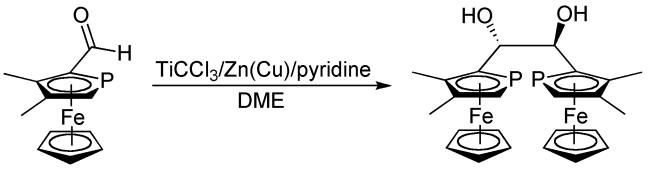
G. CITED EXPERIMENTAL EXAMPLES



Reference 14.

To a stirred suspension of 0.23 g lithium (33 mmol) in 20 mL dry THF under argon was successively added 1.55 g $TiCl_3$ (10 mmol) in 20 mL THF and 0.32 g naphthalene (2.5 mmol) at room temperature. After the mixture was refluxed for 3 h, a thick dense homogeneous black mass of activated Ti species was obtained and was cooled to ambient temperature. To this solution was added 0.3 g acetophenone (2.5 mmol) in 5 mL THF under stirring. After the mixture was stirred at room temperature for 3 h, acetophenone disappeared as shown by TLC. Then the reaction mixture was diluted with hexane and quenched with

aqueous saturated NH_4Cl solution. The supernatant was passed through a bed of Celite. The eluent was removed by evaporation, and the naphthalene in the residue was separated by vacuum sublimation (50°C/10 mmHg). The remainder was subjected to preparative TLC (EtOAc/hexane, 5:95) to afford 70% 2,3-dimethylstilbene with an *E*/*Z* ratio of 7:3.



Reference 7e.

To a mixture of 1.09 g [$TiCl_3 \cdot DME_{1.5}$] (3.8 mmol), 1.076 g Zn(Cu) (15.1 mmol), and 0.31 mL pyridine (3.8 mmol) in 15 mL dry DME at 0°C was added 261.3 mg (*Rp*)-formylphosphaferrocene (1.05 mmol). The mixture was stirred at 0°C for 1 h and quenched by the addition of 10 mL saturated aqueous K_2CO_3. The mixture was filtered, and the solid residue was washed once with EtOAc. The organic layer was separated, and the aqueous phase was extracted once with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered, and evaporated to dryness, giving an orange powder, which was further purified by chromatography on alumina with CH_2Cl_2/MeOH (100:1) to afford 67% *threo*-pinacol as an orange powder.

Other references related to the McMurry coupling are cited in the literature.[16]

H. REFERENCES

1. Tyrlik, S. and Wolochowicz, I., *Bull. Soc. Chim. Fr.,* **1973**, 2147.
2. Mukaiyama, T.; Sato, T. and Hanna, J., *Chem. Lett.,* **1973**, 1041.
3. McMurry, J. E., *Acc. Chem. Res.,* **1974**, *7*, 281.
4. (a) McMurry, J. E. and Fleming, M. P., *J. Am. Chem. Soc.,* **1974**, *96*, 4708. (b) McMurry, J. E.; Fleming, M. P.; Kees, K. L. and Krepski, L. R., *J. Org. Chem.,* **1978**, *43*, 3255. (c) McMurry, J. E., *Acc. Chem. Res.,* **1983**, *16*, 405. (d) McMurry, J. E., *Chem. Rev.,* **1989**, *89*, 1513.
5. (a) Pigeon, P.; Top, S.; Vessières, A.; Huché, M.; Hillard, E. A.; Salomon, E. and Jaouen, G., *J. Med. Chem.,* **2005**, *48*, 2814. (b) Vessières, A.; Top, S.; Pigeon, P.; Hillard, E.; Boubeker, L.; Spera, D. and Jaouen, G., *J. Med. Chem.,* **2005**, *48*, 3937. (c) Ephritikhine, M. and Villiers, C., "The McMurry Coupling and Related Reactions," in *"Modern Carbonyl Olefination*," ed. Takeda, T., Wiley-VCH, Weinheim, **2004**. (d) Heo, R. W.; Park, J.-S.; Goodson, J. T.; Claudio, G. C.; Takenaga, M.; Albright, T. A. and Lee, T. R., *Tetrahedron,* **2004**, *60*, 7225. (e) Maiorana, S.; Papagni, A.; Licandro, E.; Annunziata, R.; Paravidino, P.; Perdicchia, D.; Giannini, C.; Bencini, M.; Clays, K. and Persoons, A., *Tetrahedron,* **2003**, *59*, 6481. (f) Yu, D. D. and Forman, B. M., *J. Org. Chem.,* **2003**, *68*, 9489. (g) Honda, T.; namiki, H.; Nagase, H. and Mizutani, H., *ARKIVOC,* **2003**, (*viii*), 188. (h) Touleec, P.; Ricard, L. and Mathey, F., *Organometallics,* **2002**, *21*, 2635. (i) Kotha, S.; Lahiri, K. and Kashinath, D., *Tetrahedron,* **2002**, *58*, 9633. (j) Agbaria, K. and Biali, S. E., *J. Org. Chem.,* **2001**, *66*, 5482. (k) Fürstner, A.; Thiel, O. R.; Kindler, N. and Bartkowska, B., *J. Org. Chem.,* **2000**, *65*, 7990. (l) Gleiter, R.; Fritzsche, G.; Borzyk, O.; Oeser, T.; Rominger, F. and Irngartinger, H., *J. Org. Chem.,* **1998**, *63*, 2878. (m) Jan, S.-T.; Rogan, E. G. and Cavalieri, E. L., *Chem. Res. Toxicol.,* **1998**, *11*, 408. (n) Eguchi, T.; Ibaragi, K. and Kakinuma, K., *J. Org.*

Chem., **1998**, *63*, 2689. (o) Eguchi, T.; Arakawa, K.; Terachi, T. and kakinuma, K., *J. Org. Chem.,* **1997**, *62*, 1924. (p) Tanaka, K.; Suzuki, H. and Osuga, H., *J. Org. Chem.,* **1997**, *62*, 4465. (q) Kataoka, Y.; Akiyama, H.; Makihira, I. and Tani, K., *J. Org. Chem.,* **1997**, *62*, 8109. (r) Buretea, M. A. and Tilley, T. D., *Organometallics,* **1997**, *16*, 1507. (s) Balu, N.; Nayak, S. K. and Banerji, A., *J. Am. Chem. Soc.,* **1996**, *118*, 5932. (t) Paolesse, R.; Pandey, R. K.; Forsyth, T. P.; Jaquinod, L.; Gerzevske, K. R.; Nurco, D. J.; Senge, M. O.; Licoccia, S.; Boschi, T. and Smith, K. M., *J. Am. Chem. Soc.,* **1996**, *118*, 3869. (u) Kozaki, M.; Parakka, J. P. and Cava, M. P., *J. Org. Chem.,* **1996**, *61*, 3657. (v) Aggarwal, V. K.; Jones, D.; Turner, M. L. and Adams, H., *J. Organomet. Chem.,* **1996**, *524*, 263.

6. (a) Halvorsen, H.; Skramstad, J. and Hope, H., *Synth. Commun.,* **2007**, *37*, 1179. (b) Duan, X.-F.; Zeng, J.; Lu, J.-W. and Zhang, Z.-B., *Synthesis*, **2007**, 713. (c) Gupta, A.; Dwivedy, A.; Keshri, G.; Sharma, R.; Balapure, A. K.; Singh, M. M. and Ray, S., *Bioorg. Med. Chem. Lett.,* **2006**, *16*, 6006. (d) Rajakumar, P.; Swaroop, M. G.; Jayavelu, S. and Murugesan, K., *Tetrahedron,* **2006**, *62*, 12041. (e) Some, S.; Dutta, B. and Ray, J. K., *Tetrahedron Lett*., **2006**, *47*, 1221. (f) Rajakumar, P. and Gayatri Swaroop, M., *Tetrahedron Lett.,* **2005**, *46*, 8543. (g) Ephritikhine, M. and Villiers, C., *Modern Carbonyl Olefination*, **2004**, 223. (h) Rajakumar, P. and Gayatri Swaroop, M., *Tetrahedron Lett*., **2004**, *45*, 6165. (i) Mayekar, N. V.; Chattopadhyay, S. and Nayak, S. K., *Synthesis*, **2003**, 2041. (j) Top, S.; El Bachir, K.; Vessieres, A.; Leclercq, G.; Laios, I.; Ourevitch, M.; Deuschel, C.; McGlinchey, M. J. and Jaouen, G., *ChemBioChem*, **2003**, *4*, 754. (k) Schultz, A.; Diele, S.; Lschat, S. and Nimuz, M., *Adv. Functional Mater.,* **2001**, *11*, 441. (l) Gupta, S.; Kar, G. K. and Ray, J. K., *Synth. Commun.,* **2000**, *30*, 2393. (m) Markl, G.; Sauer, H.; Kreitmeier, P.; Burgemeister, T. and Kastner, F., *Tetrahedron,* **1999**, *55*, 13407. (n) Hong, B.-C. and Chin, S.-F., *Synth. Commun.,* **1999**, *29*, 3097. (o) Daik, R.; Feast, J. W.; Batsanov, A. S. and Howard, J. A. K., *New J. Chem.,* **1998**, *22*, 1047. (p) Harter, P.; Latzel, K.; Spiegler, M. and Herdtweck, E., *Polyhedron*, **1998**, *17*, 1141. (q) Arduini, A.; Fanni, S.; Pochini, A.; Sicuri, A. R. and Ungaro, R., *Tetrahedron*, **1995**, *51*, 7951. (r) Andersson, P. G., *Tetrahedron Lett*., **1994**, *35*, 2609. (s) Eguchi, T.; Terachi, T. and Kakinuma, K., *Tetrahedron Lett*., **1993**, *34*, 2175.

7. (a) Cao, X.-Y.; Zhang, W.; Zi, H. and Pei, J., *Org. Lett.,* **2004**, *6*, 4845. (b) Kingston, J. V.; Ozerov, O. V.; Parkin, S.; Brock, C. P. and Ladipo, F. T., *J. Am. Chem. Soc.,* **2002**, *124*, 12217. (c) Agustsson, S. O.; Hu, C. H.; Englert, U.; Marx, T.; Wesemann, L. and Ganter, C., *Organometallics,* **2002**, *21*, 2993. (d) Caselli, A.; Solari, E.; Scopelliti, R. and Floriani, C., *J. Am. Chem. Soc.,* **1999**, *121*, 8296. (e) Gies, A.-E. and Pfeffer, M., *J. Org. Chem.,* **1999**, *64*, 3650. (f) Talukdar, S.; Nayak, S. K. and Banerji, A., *J. Org. Chem.,* **1998**, *63*, 4925. (g) Fürstner, A. and Tesche, B., *Chem. Mater.,* **1998**, *10*, 1968. (h) Xie, H.; Lee, D. A.; Wallace, D. M.; Senge, M. O. and Smith, K. M., *J. Org. Chem.,* **1996**, *61*, 8508. (i) Lectka, T., The McMurry Reaction, in *Active Metals, Preparation, Characterization, Applications*, ed. Fürstner, A., VCH Publishers, New York, **1995**, pp. 85–131.

8. (a) Duan, X.-F.; Zeng, J.; Lue, J.-W. and Zhang, Z.-B., *J. Org. Chem.,* **2006**, *71*, 9873. (b) Ishiduka, T.; Tsukayama, M. and Kawamura, Y., *Int. J. Modern Phys. B,* **2006**, *20*, 4595. (c) Brenna, E.; Fronza, G.; Fuganti, C.; Magnone, G. A. and Pellegatta, C., *Pharmaz. Indust.,* **2005**, *67*, 1214. (d) Stuhr-Hansen, N., *Tetrahedron Lett*., **2005**, *46*, 5491. (e) Fuerstner, A., *Trans. Metal Org. Synth.,* **2004**, *1*, 449. (f) Ortin, Y.; Grealis, J.; Scully, C.; Mueller-Bunz, H.; Manning, A. R. and McGlinchey, M. J., *J. Organomet. Chem.,* **2004**, *689*, 4683. (g) Lhotak, P.; Zieba, R.; Hromadko, V.; Stibor, I. and Sykora, J., *Tetrahedron Lett*., **2003**, *44*, 4519. (h) Kawase, T.; Ueda, N.; Tanaka, K.; Seirai, Y. and Oda, M., *Tetrahedron Lett*., **2001**, *42*, 5509. (i) Gauthier, S.; Sanceau, J.-Y.; Mailhot, J.; Caron, B. and Cloutier, J., *Tetrahedron,* **2000**, *56*, 703. (j) Ephritikhine, M., *Chem. Commun.,* **1998**, 2549. (k) Talukdar, S.; Nayak, S. K. and Banerji, A., *Synth. Commun.,* **1998**, *28*, 2325. (l) Villiers, C. and Ephritikhine, M., *Angew. Chem. Int. Ed. Engl.,* **1997**, *36*, 2380. (m) Stahl, M.; Pidun, U. and Frenking, G., *Angew. Chem. Int. Ed. Engl.,* **1997**, *36*, 2234. (n) Rucker, M. and Bruckner, R., *Tetrahedron Lett*., **1997**, 38, 7353. (o) Top, S.; Dauer, B.; Vaissermann, J. and Jaouen, G., *J. Organomet. Chem.,* **1997**, *541*, 355. (p) Lectka, T., *Active Metals*, **1996**, 85. (q) Jaquinod, L.; Nurco, D. J.; Medforth, C. J.; Pandey, R. K.; Forsyth, T. P.; Olmstead, M. M.

and Smith, K. M., *Angew. Chem. Int. Ed. Engl.,* **1996**, *35*, 1013. (r) Gauthier, S.; Mailhot, J. and Labrie, F., *J. Org. Chem.,* **1996**, *61*, 3890. (s) Laatsch, H.; Talvitie, A.; Kral, A.; Ernst, B.-P. and Motemeyer, M., *J. Prakt. Chem./Chemiker-Zeit.,* **1996**, *338*, 140. (t) Lhotak, P. and Shinkai, S., *Tetrahedron Lett*., **1996**, *37*, 645. (u) Bogdanovic, B. and Bolte, A., *J. Organomet. Chem.,* **1995**, *502*, 109. (v) Fuerstner, A.; Seidel, G.; Gabor, B.; Kopiske, C.; Krueger, C. and Mynott, R., *Tetrahedron*, **1995**, *51*, 8875. (w) Aleandri, L. E.; Becke, S.; Bogdanovic, B.; Jones, D. J. and Roziere, J., *J. Organomet. Chem.,* **1994**, *472*, 97. (x) Aleandri, L. E.; Bogdanovic, B.; Gaidies, A.; Jones, D. J.; Liao, S.; Michalowicz, A.; Roziere, J. and Schott, A., *J. Organomet. Chem.,* **1993**, *459*, 87. (y) Burger, P. and Brintzinger, H. H., *J. Organomet. Chem.,* **1991**, *407*, 207. (z) Paek, K. S. and Cram, D. J., *Bull. Korean Chem. Soc.,* **1989**, *10*, 572. (aa) Gruetzmacher, H. F.; Neumann, E.; Ebmeyer, F.; Albrecht, K. and Schelenz, P., *Chem. Ber.,* **1989**, *122*, 2291. (bb) Coe, P. L. and Scriven, C. E., *J. Chem. Soc., Perkin Trans. I,* **1986**, 475. (cc) Dormagen, W. and Breitmaier, E., *Chem. Ber.,* **1986**, *119*, 1734. (dd) Auderset, P. C.; Gartenmann, T. C. C. and Gesing, E. R. F., *Kontakte (Darmstadt),* **1985**, 14. (ee) Welzel, P., *Nachrichten Chem., Tech. Laborat.,* **1983**, *31*, 814. (ff) Dams, R.; Malinowski, M. and Geise, H. J., *Trans. Metal Chem.,* **1982**, *7*, 37.

9. (a) Top, S.; Vessieres, A.; Leclercq, G.; Quivy, J.; Tang, J.; Vaissermann, J.; Huche, M. and Jaouen, G., *Chem. Eur. J.,* **2003**, *9*, 5223. (b) Sabelle, S.; Hydrio, J.; Leclerc, E.; Mioskowski, C. and Renard, P.-Y., *Tetrahedron Lett*., **2002**, *43*, 3645.
10. (a) Pavlik, M.; Pfleger, J.; Jossifov, C. and Vohlidal, J., *Macromol. Symposia,* **2004**, *212*, 555. (b) Cacciapaglia, R.; Di Stefano, S. and Mandolini, L, *J. Org. Chem.,* **2002**, *67*, 521. (c) Villiers, C.; Vandais, A. and Ephritikhine, M., *J. Organomet. Chem.,* **2001**, *617–618*, 744. (d) Kawase, T.; Hosokawa, Y.; Kurata, H. and Oda, M., *Chem. Lett.,* **1999**, 745. (e) Kataoka, Y.; Takai, K.; Oshima, K. and Utimoto, K., *Tetrahedron Lett*., **1990**, *31*, 365.
11. Nicolaou, K. C.; Yang, Z.; Sorensen, E. J. and Nakada, M., *J. Chem. Soc., Chem. Commun.,* **1993**, 1024.
12. (a) Chung, M.-K.; Fancy, P. and Stryker, J. M., *Can. J. Chem.,* **2006**, *84*, 1250. (b) Moreau, A.; Rao, P. N. P. and Knaus, E. E., *Bioorg. Med. Chem.,* **2006**, *14*, 5340. (c) Chung, M.-K.; Qi, G. Z. and Stryker, J. M., *Org. Lett.,* **2006**, *8*, 1491. (d) Uddin, M. J.; Rao, P. N. P. and Knaus, E. E., *Synlett*, **2004**, 1513. (e) Mayekar, N. V.; Chattopadhyay, S. and Nayak, S. K., *Lett. Org. Chem.,* **2004**, *1*, 203. (f) Li, W.-D. Z.; Li, Y. and Li, Y. L., *Tetrahedron Lett*., **1999**, *40*, 965.
13. Richardson, W. H., *Synth. Commun.,* **1981**, *11*, 895.
14. Rele, S.; Talukdar, S.; Banerji, A. and Chattopadhyay, S., *J. Org. Chem.,* **2001**, *66*, 2990.
15. (a) Barteau, M. A., *Chem. Rev*., **1996**, *96*, 1413. (b) Rekoske, J. E. and Barteau, M. A., *Ind. Eng. Chem. Res*., **1995**, *34*, 2931.
16. (a) Zheng, L. F.; Wei, Q. Y.; Zhou, B.; Yang, L. and Liu, Z.-L., *Anti-Cancer Drugs*, **2007**, *18*, 1039. (b) Huang, L.-F.; Chen, C.-W. and Luh, T.-Y., *Org. Lett.,* **2007**, *9*, 3663. (c) Rajakumar, P. and Selvam, S., *Tetrahedron*, **2007**, *63*, 8891. (d) Iyoda, M., *Heteroatom Chem*., **2007**, *18*, 460. (e) Walko, M. and Feringa, B. L., *Chem. Commun.,* **2007**, 1745. (f) Wang, H. J. H.; Jaquinod, L.; Olmstead, M. M.; Vicente, M. G. H.; Kadish, K. M.; Ou, Z. P. and Smith, K. M., *Inorg. Chem.,* **2007**, *46*, 2898.

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Meerwein Arylation
(Meerwein Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Meerwein et al. in 1939.[1] It is a copper salt-initiated reaction between an aryl diazonium salt and an alkene (or an alkyne, arene) that is activated by an electron-withdrawing group. Therefore, it is generally known as the Meerwein arylation[2,3] or Meerwein reaction.[2b,2f,2h,2j,4] The final products are the mixtures resulting from aryl addition and substitution.[2j] It is known that this reaction involves a single-electron transfer[2a] reductive cleavage of aryl diazonium salt by CuCl to form an aryl radical, which normally adds to the β-position of the activated alkenes to form a more stable radical.[2i,4bb] Subsequently, the new formed radical couples with a halide to form the addition product, or undergoes proton abstraction to give the substituted product. It is interesting that for the reaction between *p*-chlorobenzenediazonium chloride and maleic or fumaric acid, the resulting mixture of substituted fumaric acid and maleic acid are in an approximately ratio of 2:1, indicating the intermediate from aryl radical attack is unable to retain its configuration.[2j] It should be pointed out that a few factors strongly influence this reaction, such as the substrate, solvent, temperature, pH, and catalyst. On the one hand, the alkenes are generally activated by either the electron-withdrawing groups (e.g., halogens) or by conjugation with unsaturated functional groups (e.g., aryl, vinyl, cyano, and carbonyl groups).[2g] On the other hand, the aryl diazonium salt with an electron-donating group, especially at the *ortho*-position, often depresses the yield of the Meerwein reaction.[2g] Among the suitable solvents, acetone is the best followed by acetonitrile.[4dd] These unsaturated solvents may be involved in some fundamental way in this reaction.[4dd] To produce a high yield of product, this reaction is often carried out at a very low temperature[2e] in a buffer with pH regulated between 2 and 4.[4dd] At low pH, the competition from that *Sandmeyer Reaction* of the aryl diazonium salt becomes important, whereas at high pH, various side reactions start to take place to form resinous products.[4dd] Although zinc, cadmium, and

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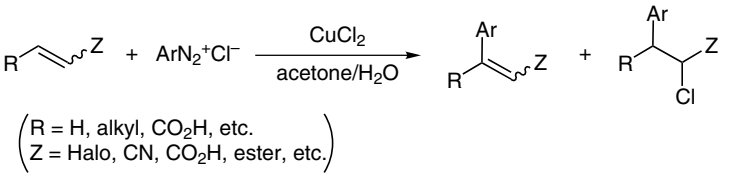
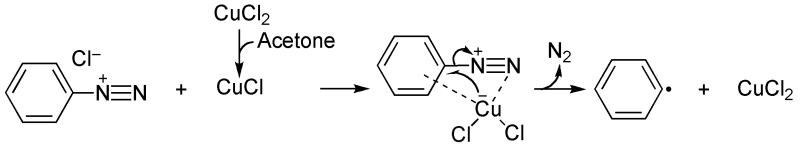
mercuric salts as well as copper powder have shown certain levels of catalytic activity, cupric chloride is the most effective catalyst.[3f] However, with increasing cupric salt concentration, the corresponding yield of the reaction decreases.[4bb] Overall, this reaction is best carried out in 65:35 acetone/water (v/v) at 0–25°C in the presence of 1–2 mol % $CuCl_2$, 2 eq. of LiCl, and an excess amount of alkene at pH ~ 2 under an oxygen-free atmosphere; CaO rather than NaOAc is added in some cases to neutralize the generated HCl.[2e] This reaction so far has been used to react with vinyl ferrocene,[2d] fluorinated olefins,[2g] benzene,[4cc] nitrobenzene[4cc] and chlorobenzene.[4cc] In addition, the reaction with vinyl sulfones forms α-halo-β-arylsulfones;[2i] likewise, the reaction with anthracene yields 9-aryl and 9,10-diaryl anthracenes;[2h] and the reaction with vinyl acetate or vinyl bromide forms 6- and 4-substituted indoles,[2e] respectively. Furthermore, this reaction has been modified to generate the aryldiazonium salt from arylamine and alkylnitrite.[2f] The ionic analogue of Meerwein arylation has been conducted photochemically by irradiation of aryl halide or diazonium salt with alkene present.[2a,2b]

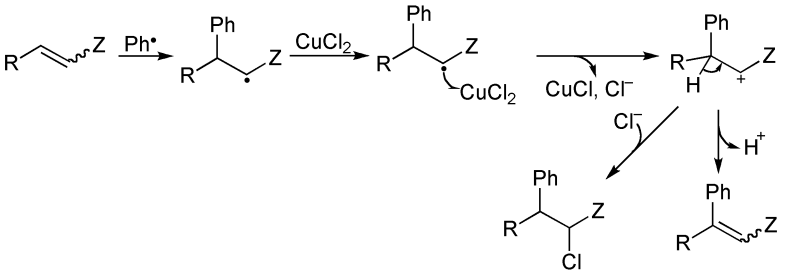
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is known that cupric chloride can be reduced by acetone to cuprous chloride,[2h] thus a novel mechanism is proposed here by which cuprous chloride can form a coordination complex in which the cuprous atom not only receives two pairs of electrons from nitrogen and chloride but also donates an electron pair to an electron-deficient aromatic ring, attaching to a strong electron-withdrawing diazo group. Single-electron transfer from a cuprous atom to an aromatic ring, and concomitant evolving nitrogen generates the aryl radical; at the same time, cuprous chloride is oxidized to cupric chloride again. The addition of an aryl radical to an electron-deficient alkene produces a new radical, which is then oxidized by cupric chloride to form carbocation and cuprous chloride. The coupling of a carbocation with chloride results in the addition product, whereas the β-elimination of a proton from carbocation yields the aryl-substituted product. The details of the mechanism are outlined here.





D. MODIFICATION

This reaction has been modified by using alkyl nitrite to produce the aryldiazonium salt.[2f] In addition, an ionic analogue of Meerwein arylation has been developed in which an aryl cation is generated photochemically.[2a,2b]

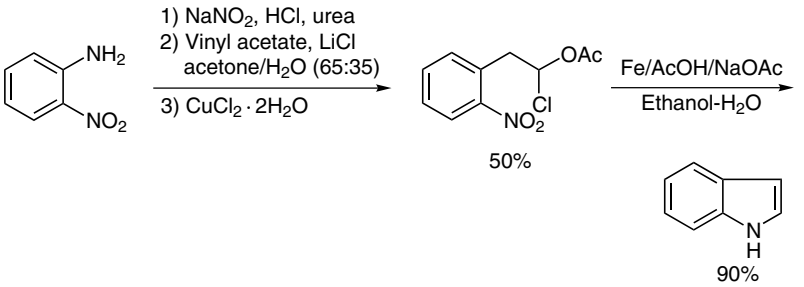
E. APPLICATIONS

This reaction has general application in the preparation of substituted styrene derivatives and aryl derivatives, especially for substituted indoles that are difficult to make by the traditional *Fischer Indole Synthesis*.[2e]

F. RELATED REACTIONS

This reaction is related to the *Sandmeyer Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2e.

2-Nitroaniline hydrochloride, prepared by heating a mixture of 1.38 g 2-nitroaniline (10.0 mol) and 2.50 mL conc. HCl (12 M, 30.0 mmol) for several minutes, was cooled to −5°C in an ice-salt bath, and a 3-mL cold aqueous solution of 725 mg $NaNO_2$ (10.5 mmol) was added over 15 min under stirring, while the temperature of the mixture was held between −5° and 2°C. The mixture was stirred for an additional 15 min, and 30 mg urea (0.60 mmol) in 5 mL cold water was added. This cold solution was added over 10 min to a stirred mixture

of 2.77 mL vinyl acetate (30.0 mmol) and 0.85 g LiCl (20.0 mmol) in 50 mL 65:35 (v/v) acetone/water in a 100-mL two-necked flask fitted with a gas bubbler that was cooled to −5°C under an atmosphere of argon. A cold solution of 0.26 g $CuCl_2 \cdot 2H_2O$ (1.5 mmol) in 5 mL water was then added over 10 min, and the evolution of nitrogen commenced. The temperature of the reaction mixture was held between 3° and 10°C for 2 h and then warmed to room temperature over 2 h. After an additional 2 h, nitrogen evolution had ceased, and acetone was evaporated. The reaction mixture was poured into 50 mL water and extracted with dichloromethane (3 × 30 mL). The combined extracts were washed successively with water and brine and dried over anhydrous magnesium sulfate. Evaporation of the solvent and purification by flash column chromatography in 70 g silica gel (35% dichloromethane in hexanes) gave 1.21 g 1-acetoxy-1-chloro-2-(2-nitrophenyl)ethane as a light yellow oil, in a yield of 50%.

In a 250-mL one-necked flask, fitted with a reflux condenser, were placed 1.21 g l-acetoxy-l-chloro-2-(2-nitrophenyl)ethane (5.00 mmol), 0.98 g 200 mesh iron powder (17.5 mmol), 2.10 g acetic acid (35.0 mmol), 0.68 g sodium acetate dihydrate (5.0 mmol), and 100 mL 80:20 (v/v) ethanol/water. The mixture was refluxed for 2 h under an atmosphere of argon. The reaction mixture was cooled, the ethanol was evaporated, and the residue was extracted with dichloromethane (3 × 30 mL). The combined extracts were washed successively with water and brine and dried over potassium carbonate. Evaporation of the solvent and purification by flash column chromatography on 50 g silica gel (dichloromethane /hexanes, 50:50) gave 0.53 g indole, in a yield of 90%, m.p. 52–53°C.

Other references related to the Meerwein arylation are cited in the literature.[5]

H. REFERENCES

1. Meerwein, H.; Buchner, E. and van Emster, K., *J. Prakt. Chem.,* **1939**, *152*, 237.
2. (a) Milanesi, S.; Fagnoni, M. and Albini, A., *J. Org. Chem.,* **2005**, *70*, 603. (b) Mella, M.; Coppo, P.; Guizzardi, B.; Fagnoni, M.; Freccero, M. and Albini, A., *J. Org. Chem.,* **2001**, *66*, 6344. (c) Guizzardi, B.; Mella, M.; Fagnoni, M.; Freccero, M. and Albini, A., *J. Org. Chem.,* **2001**, *66*, 6353. (d) Nock, H. and Schottenberger, H., *J. Org. Chem.,* **1993**, *58*, 7045. (e) Raucher, S. and Koolpe, G. A., *J. Org. Chem.,* **1983**, *48*, 2066. (f) Doyle, M. P.; Siegfried, B.; Elliott, R. C. and Dellaria, J. F., *J. Org. Chem.,* **1977**, *42*, 2431. (g) Rondestvedt, C. S., *J. Org. Chem.,* **1977**, *42*, 2618. (h) Dickerman, S. C.; Felix, A. M. and Levy, L. B., *J. Org. Chem.,* **1964**, *29*, 26. (i) Truce, W. E.; Breiter, J. J. and Tracy, J. E., *J. Org. Chem.,* **1964**, *29*, 3009. (j) Vogl, O. and Rondestvedt, C. S., *J. Am. Chem. Soc.,* **1956**, *78*, 3799.
3. (a) Molinaro, C.; Mowat, J.; Gosselin, F.; O'Shea, P. D.; Marcoux, J.-F.; Angelaud, R. and Davies, I. W., *J. Org. Chem.,* **2007**, *72*, 1856. (b) Karpyak, V. V.; Obushak, M. D. and Ganushchak, M. I., *Molecules*, **2003**, *8*, 263. (c) Brunner, H.; Bluchel, C. and Doyle, M. P., *J. Organomet. Chem.,* **1997**, *541*, 89. (d) Takahashi, I.; Muramatsu, O.; Fukuhara, J.; Hosokawa, Y.; Takeyama, N.; Morita, T. and Kitajima, H., *Chem. Lett.,* **1994**, 465. (e) Takahashi, I.; Nishimura, H.; Takeyama, N.; Muramatsu, O.; Fukuhara, J. and Kitajima, H., *Chem. Express,* **1993**, *8*, 585. (f) Takahashi, I.; Takeyama, N.; Morita, T.; Mori, H.; Yamamoto, M.; Nishimura, H. and Kitajima, H., *Chem. Express,* **1993**, *8*, 289. (g) Takahashi, I.; Takeyama, N.; Mori, H.; Yamamoto, M.; Nishimura, H. and Kitajima, H., *Chem. Express,* **1992**, *7*, 709. (h) Polishchuk, O. P.; Buzo, A.; Ganushchak, N. I. and Koval'chuk, E. P., *Zh. Org. Khim.,* **1991**, *27*, 2244. (i) Schmidt, A. H.; Schmitt, G. and Diedrich, H., *Synthesis*, **1990**, 579. (j) Weis, C. D., *Dyes & Pigments*, **1988**, *9*, 1. (k) Hu, H. W.; Pan, Y. and Xu, J. H., *Gaodeng Xuexiao Huaxue Xuebao*, **1987**, *8*, 819. (l) Sutter, P. and Weis, C.

D., *J. Heterocycl. Chem.,* **1987**, *24*, 69. (m) Bhavsar, M. D. and Saraiya, P. N., *Man-Made Textiles in India*, **1986**, *29*, 485. (n) Ganushchak, N. I.; Obushak, N. D. and Luka, G. Y., *Zh. Org. Khim.,* **1981**, *17*, 870. (o) Farinas, S.; Rodriguez Palacio, C. R. and Ramos Raimundo, I., *CENTRO, Ser.: Quim. Tecnologia Quim.*, **1977**, *5*, 75. (p) Astik, R. R.; Undavia, N. K. and Thaker, K. A., *J. Inst. Chemists (India),* **1977**, *49*, 48. (q) Rondestvedt, C. S., *Org. React.,* **1976**, *24*, 225. (r) Filler, R.; White, A. B.; Taqui-Khan, B. and Gorelic, L., *Can. J. Chem.,* **1967**, *45*, 329. (s) Filler, R.; Gorelic, L. and Taqui-Khan, B., *Proc. Chem. Soc.*, **1962**, 117. (t) Rondestvedt, C. S., *Org. React.,* **1960**, *11*, 189. (u) Dickerman, S. C.; Levy, L. B. and Schwartz, A. W., *Chem. Ind. (London),* **1958**, 360.

4. (a) Naidan, V. M. and Naidan, G. D., *Russ. J. Gen. Chem.,* **2006**, *76*, 1844. (b) Fagnoni, M. and Albini, A., *Acc. Chem. Res.,* **2005**, *38*, 713. (c) Naidan, V. M. and Fesak, A. Yu., *Russ. J. Gen. Chem.,* **2003**, *73*, 1419. (d) Kudrevich, S. V.; Ali, H. and van Lier, J. E., *J. Chem. Soc., Perkin Trans. I,* **1994**, 2767. (e) Obushchak, N. D.; Lyakhovich, M. B. and Gamushchak, N. I., *Zh. Org. Khim.,* **1993**, *29*, 731. (f) Dombrovskii, A. V., *Uspekhi Khim*., **1984**, *53*, 1625. (g) Olah, G. A.; Doggweiler, H. and Felberg, J. D., *J. Org. Chem.,* **1984**, *49*, 2116. (h) Fritz, H.; Rihs, G.; Sutter, P. and Weis, C. D., *J. Heterocycl. Chem.,* **1981**, *18*, 1571. (i) Ganushchak, N. I., *Vestn. L'vov. Politekhn. In-ta*, **1980**, 53. (j) Balasubramaniam, A., *Indian J. Chem. Edu.,* **1979**, *6*, 8. (k) Naidan, V. M. and Naidan, G. D., *Zh. Obsh. Khim.,* **1978**, *48*, 2787. (l) Naidan, V. M.; Naidan, G. D. and Litvin, G. V., *Zh. Org. Khim.,* **1978**, *14*, 2622. (m) Oleinik, A. F.; Modnikova, G. A.; Novitskii, K. Y. and Novitskaya, N. A., *Khim.-Farmatsevticheskii Zh.,* **1978**, *12*, 38. (n) Cleland, G. H., *J. Chem. Edu.,* **1978**, *55*, 814. (o) Naidan, V. M.; Naidan, G. D. and Litvin, G. V., *Zh. Org. Khim.,* **1978**, *14*, 2010. (p) Al Adel, I.; Adeoti Salami, B.; Levisalles, J. and Rudler, H., *Bull. Soc. Chim. Fr.,* **1976**, 934. (q) Al Adel, I.; Adeoti Salami, B.; Levisalles, J. and Rudler, H., *Bull. Soc. Chim. Fr.,* **1976**, 930. (r) Markova, I. G.; Polievktov, M. K.; Oleinik, A. F. and Modnikova, G. A., *Khim. Geterotsiklicheskikh Soedinenii*, **1976**, 598. (s) Oleinik, A. F.; Modnikova, G. A.; Vozyakova, T. I.; Burgova, E. N. and Novitskii, K. Y., *Khim. Geterotsiklicheskikh Soedinenii*, **1975**, 452. (t) Naidan, V. M. and Naidan, G. D., *Zh. Org. Khim.,* **1974**, *10*, 664. (u) Mondon, A.; Schattka, K. and Krohn, K., *Chem. Ber.,* **1972**, *105*, 3748. (v) Allard, M. and Levisalles, J., *Bull. Soc. Chim. Fr.,* **1972**, 1926. (w) Cleland, G. H., *J. Org. Chem.,* **1969**, *34*, 744. (x) Bell, F. and Oliver, C. J., *Chem. Ind. (London),* **1965**, 1558. (y) Cleland, G. H., *J. Org. Chem.,* **1961**, *26*, 3362. (z) Minisci, F. and Pallini, U., *Gazz. Chim. Ital.,* **1960**, *90*, 1318. (aa) Dickerman, S. C.; Weiss, K. and Ingberman, A. K., *J. Am. Chem. Soc.,* **1958**, *80*, 1904. (bb) Kochi, J. K., *J. Am. Chem. Soc.,* **1957**, *79*, 2942. (cc) Dickerman, S. C. and Weiss, K., *J. Org. Chem.,* **1957**, *22*, 1070. (dd) Rondestvedt, C. S. and Vogl, O., *J. Am. Chem. Soc.,* **1955**, *77*, 3401.

5. (a) Obushak, N. D.; Karpyak, V. V.; Ganushchak, N. I. and Lemeshev, A. N., *Zh. Org. Khim.*, **1994**, *30*, 631. (b) Noland, W. E. and Sellstedt, J. H., *J. Org. Chem.,* **1966**, *31*, 345. (c) Schrauzer, G. N., *Ber.,* **1961**, *94*, 1891. (d) Clendinning, R. A. and Rauscher, W. H., *J. Org. Chem.,* **1961**, *26*, 2963. (e) Rondestvedt, C. S., *Org. React.,* **1960**, *11*, 189. (f) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J. and Kierstead, R. W., *Tetrahedron,* **1958**, *2*, 1. (g) Rondestvedt, C. S.; Kalm, M. J. and Vogl, O., *J. Am. Chem. Soc.,* **1956**, *78*, 6115. (h) Rondestvedt, C. S. and Vogl, O., *J. Am. Chem. Soc.,* **1955**, *77*, 2313. (i) Franzen, V. and Krauch, H., *Chem. Ztg.,* **1952**, *79*, 101.

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Meerwein-Ponndorf-Verley Reduction

(Meerwein-Ponndorf-Verley Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported concurrently by Meerwein and Schmidt[1] and Verley[2] in 1925, and by Ponndorf[3] in 1926, respectively. It is an aluminum alkoxide-catalyzed reduction of carbonyl compounds (ketones and aldehydes) to corresponding alcohols using another alcohol (e.g., isopropanol) as the reducing agent or hydride source. Therefore, it is generally known as the Meerwein-Ponndorf-Verley reduction (MPV)[4,5] or Meerwein-Ponndorf-Verley reaction.[6] Occasionally, it is also referred to as the Meerwein-Ponndorf reduction,[7] Meerwein-Ponndorf reaction,[8] or Meerwein-Schmidt-Ponndorf-Verley reaction.[9] About 12 years later, Oppenauer reported the reversion of this reaction in which alcohols were reversely oxidized into carbonyl compounds.[10] Since then, the interchanges between carbonyl compounds and alcohols in the presence of aluminum alkoxide are generally called the Meerwein-Ponndorf-Oppenauer-Verley reduction[11] or Meerwein-Ponndorf-Verley-Oppenauer reaction.[4e,4k,6e,11,12]

The formation of equilibrium between carbonyl compounds and alcohols is general for this reaction, except for the reduction of trifluoromethyl phenyl ketone.[13] The Meerwein-Ponndorf-Verley reduction has advantages of chemoselectivity, mild reaction conditions, operational simplicity, low cost, and scalability.[4a,14] In addition, this reaction does not affect other double bonds or triple bonds as well as other enolizable carbonyl compounds (e.g., β-keto ester, β-diketone). The catalysts suitable for this reaction include aluminum alkoxide and some transition-metal alkoxides (e.g., zirconium,[4g,4h,15] iron,[15a]

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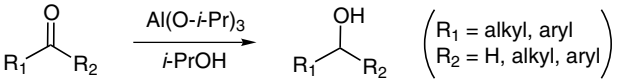
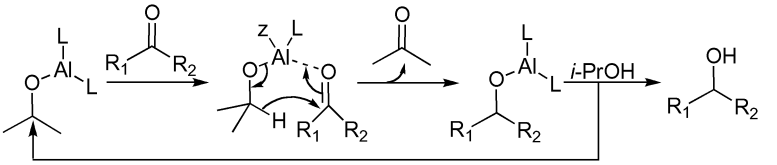
titanium,[4d] and lanthanide[4f]), which are used as homogenous catalysts; in addition, Al-, Ti- and Sn-β zeolites[4d] are also found to be efficient catalysts for this reduction. It is known that this reaction involves the following steps: (*a*) coordination of a carbonyl compound to the metal atom of the alkoxide catalyst, typically Al(*O*-*i*-Pr)$_3$, to increase the positive character of the carbonyl group;[16] (*b*) internal hydride transfer from an alkoxide ligand to the carbonyl group coordinating to the metal atom through a six-membered transition state,[6e,9,11,15a,16,17] to generate a new alkoxide ligand and carbonyl compound; and (*c*) dissociation of the new carbonyl compound and alcoholysis of the mixed metal alkoxide to release the alcohol and regenerate the catalyst.[15a] The increased positive character of the carbonyl compound during coordination is supported by the Hammett ρ constant of 1.296 for the equilibrium between substituted benzophenones and the secondary alcohol,[4l] and the internal hydride transfer is evidenced by the fact that such transfer takes place in the absence of any alcohol.[6m] The alcoholysis is found to be the rate-determining step.[18] The advantage of using Al(*O*-*i*-Pr)$_3$ as a catalyst is that acetone formed can easily be removed by heating to shift the equilibrium toward the alcohol,[18] although the removal of acetone is not necessary for most reactions.[19] It has been reported that when an acid in half equivalent amount of aluminum was added, the reduction rate was remarkably enhanced, especially when CF_3CO_2H was added.[4k] It is interesting that the reduction of carbonyl compounds by lithium alkoxide involves a radical intermediate.[4j]

Because the reaction often forms equilibrium, it has been modified to enhance the yields of reduction by using freshly prepared nonaggregated aluminum alkoxide[9] or by a slow addition of carbonyl compounds into the aluminum alkoxide solution.[19] In addition, this reaction has been modified to reduce carbonyl compounds enantioselectively by application of a chiral diol as auxiliary (e.g., 1,2:5,6-di-*O*-isopropylidene-D-mannitol,[4g,20] enantiopure 2,2′-dihydroxy-1,1′-binaphthyl[9]) or a chiral samarium catalyst.[4i,21] Moreover, the tandem Michael addition–MPV reduction and subsequent desulfurization can convert α,β-unsaturated ketones into saturated secondary alcohols or allyl alcohols in high enantioselectivity (e.g., 95% e.e.).[22] It is interesting that the reduction of α-amino aromatic ketone by catalytic Al(*O*-*i*-Pr)$_3$ resulted in an alcohol with high *anti* selectivity through the chelation of nitrogen to aluminum, whereas a similar reduction of an α-hydroxy ketone produced the alcohol with high *syn* selectivity.[4a]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been extensively modified by the application of different catalysts or the addition of a chiral ligand as described in Section A.

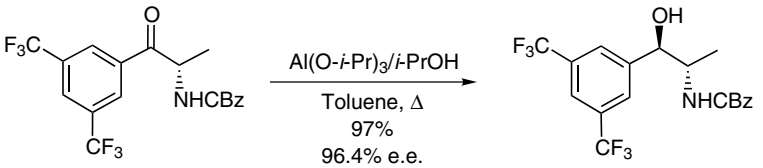
E. APPLICATIONS

This reaction has wide application in the reduction of carbonyl compounds.

F. RELATED REACTIONS

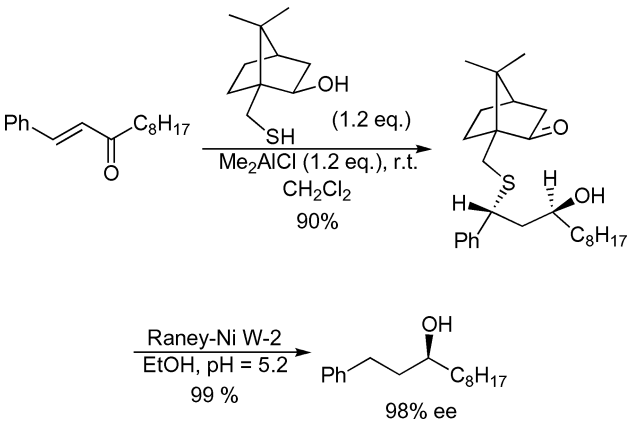
This reaction is closely related to the *Oppenauer Oxidation* as well as *Cannizzaro Reaction* and *Tishchenko Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4a.

A mixture of 267 mg (S)-α'-*N*-carboxylbenylamino-ethyl-3,5-ditrifluoromethyl-phenylketone (0.637 mmol, 1 eq.), 26 mg Al(*O*-*i*-Pr)$_3$ (0.2 eq.), and 0.536 mL *i*-PrOH (11 eq.) in 0.8 mL toluene (1.3 mL/mmol) was heated at 50°C under nitrogen for 15 h. The reaction was cooled and quenched with 4 mL 1 N HCl and 4 mL EtOAc. The organic layer was washed with 4 mL water and concentrated. The crude product was further purified by a hexane tituration to give 260 mg (1*R*,2*S*)-1-(3′,5′-bistrifluoromethylphenyl)-2-benzyloxycarbonylamino-1-propanol as a white solid, in a yield of 97% with > 99% enantiomeric excess (ChiralPak AD-H (4.6 × 150 mm) column, 0.1:10:90 of TFA/*i*-PrOH/heptane, 1.5 mL/min at 30°C; retention times for desired 1*R*,2*S* enantiomers: 2.6 min and for undesired: 4.7 min, m.p., 141–142°C.



Reference 5p.

To a 20 mL dichloromethane solution of 100 mg (-)-10-mercaptoisoborneol (0.54 mmol) was added 0.57 mL 0.94 M dimethylaluminum chloride (0.55 mmol) dropwise at room temperature. After the mixture was stirred for 1 h, a 5 mL dichloromethane solution of 2-*trans*-nanoyl styrene (0.45 mmol) was added dropwise, and the mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with a saturated NH_4Cl solution, and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc, 10:1 to 7:1) to afford (3S)-1-[(1S,4R)-2-oxobornane-10-sulfenyl]-1-phenyl-3-undecanol as a colorless oil, in a yield of 90%. To the ethanol solution of the compound was added 2 mL Raney Ni W-2 suspension in ethanol, and the mixture was stirred for 40 min at room temperature. The mixture was filtered with Celite and concentrated in vacuo. A preparative TLC afforded 99% of alcohol with 98% e.e.

Other references related to the Meerwein-Ponndorf-Verley reduction are cited in the literature. [23]

H. REFERENCES

1. Meerwein, H. and Schmidt, R., *Ann.*, **1925**, *444*, 221.
2. (a) Verley, A., *Bull. Soc. Chim.*, **1925**, *37*, 537. (b) Verley, A., *Bull. Soc. Chim.*, **1925**, *37*, 871.
3. Ponndorf, W., *Angew. Chem.*, **1926**, *39*, 138.
4. (a) Yin, J. J.; Huffman, M. A.; Conrad, K. M. and Armstrong, J. D., *J. Org. Chem.*, **2006**, *71*, 840. (b) Dong, S. Z. and Paquette, L. A., *J. Org. Chem.*, **2005**, *70*, 1580. (c) Schrekker, H. S.; de Bolster, M. W. G.; Orru, R. V. A. and Wessjohann, L. A., *J. Org. Chem.*, **2002**, *67*, 1975. (d) Corma, A.; Domine, M. E.; Nemeth, L. and Valencia, S., *J. Am. Chem. Soc.*, **2002**, *124*, 3194. (e) Wilk, B. K.; Helom, J. L. and Coughlin, C. W., *Org. Proc. Res. Dev.*, **1998**, *2*, 407. (f) Hu, X. M. and Kellogg, R. M., *Recl. Trav. Chim. Pays-Bas*, **1996**, *115*, 410. (g) Krohn, K. and Knauer, B., *Rec. Trav. Chim. Pays-Bas*, **1996**, *115*, 140. (h) Knauer, B and Krohn, K., *Ann.*, **1995**, 677. (i) Evans, D. A.; Nelson, S. G.; Gagné, M. R. and Muci, A. R., *J. Am. Chem. Soc.*, **1993**, *115*, 9800. (j) Ashby, E. C. and Argyropoulos, J. N., *J. Org. Chem.*, **1986**, *51*, 3593. (k) Kow, R.; Nygren, R. and Rathke, M. W., *J. Org. Chem.*, **1977**, *42*, 826. (l) Snyder, C. H., *J. Org. Chem.*, **1967**, *32*, 2904.
5. (a) Chuah, G. K.; Jaenicke, S.; Zhu, Y. Z. and Liu, S. H., *Curr. Org. Chem.*, **2006**, *10*, 1639. (b) Zhu, Y. Z.; Chuah, G.-K. and Jaenicke, S., *J. Catal.*, **2006**, *241*, 25. (c) Zhu, Y. Z.; Liu, S. H.; Jaenicke, S. and Chuah, G., *Catal. Today*, **2004**, *97*, 249. (d) Kellogg, R. M., *Chemtracts*, **2004**, *17*, 250. (e) Cheralathan, K. K.; Palanichamy, M. and Murugesan, V., *Appl. Catal., A: Gen.,* **2004**, *263*, 219. (f) Nishide, K.; Ozeki, M.; Kunishige, H.; Shigeta, Y.; Patra, P. K.; Hagimoto, Y. and Node, M., *Angew. Chem. Int. Ed.*, **2003**, *42*, 4515. (g) Zhu, Y. Z.; Jaenicke, S. and Chuah, G. K., *J. Catal.,* **2003**, *218*, 396. (h) Lermontov, S. A.; Shkavrov, S. V. and Kuryleva, N. V., *J. Fluor. Chem.*, **2003**, *121*, 223. (i) Nishide, K. and Node, M., *Chirality*, **2002**, *14*, 759. (j) Aramendia, M. A.; Borau, V.; Jimenez, C.; Marinas, J. M.; Ruiz, J. R. and Urbano, F. J., *J. Chem. Soc., Perkin Trans. II*, **2002**, 1122. (k) Liu, S. H.; Jaenicke, S. and Chuah, G. K., *J. Catal.,* **2002**, *206*, 321. (l) Creyghton, E. J. and Van der Waal, J. C., *Fine Chemicals through Heterogeneous Catalysis*, **2001**, 438. (m) Ooi, T.; Ichikawa, H. and Maruoka, K., *Angew. Chem. Int. Ed.,* **2001**, *40*, 3610. (n) Bartosova, M.; Cerveny, L. and Wichterlova, B., *Chemicke Listy*, **2001**, *95*, 278. (o) Aremo, N. and Hase, T., *Tetrahedron Lett*., **2001**, *42*, 3637. (p) Node, M.; Nishide, K.; Shigeta, Y.; Shiraki, H. and Obata, K., *J. Am. Chem. Soc.*, **2000**, *122*, 1927. (q) Ooi, T.; Itagaki, Y.; Miura, T. and Maruoka, K., *Tetrahedron Lett*., **1999**, *40*, 2137. (r) Ooi, T.; Miura, T. and Maruoka, K., *Angew. Chem. Int. Ed.*, **1998**, *37*, 2347. (s) Kumbhar, P. S.; Sanchez-Valente, J.; Lopez, J. and Figueras,

F., *Chem. Commun.,* **1998**, 535. (t) Van der Waal, J. C.; Creyghton, E. J.; Kunkeler, P. J.; Tan, K. and van Bekkum, H., *Top. Catal.*, **1998**, *4*, 261. (u) Fujita, M.; Takarada, Y.; Sugimura, T. and Tai, A., *Chem. Commun.*, **1997**, 1631. (v) Ding, Z.-B. and Wu, S.-H., *Huaxue Xuebao*, **1997**, *55*, 351. (w) Ding, Z.-B.; Cheng, K.-J. and Wu, S.-H., *Chinese J. Chem.*, **1996**, *14*, 561. (x) Okano, T.; Matsuoka, M.; Konishi, H. and Kiji, J., *Chem. Lett.*, **1987**, 181. (y) Horner, L. and Kaps, U. B., *Liebigs Annalen Chem.*, **1980**, 192. (z) Jones, R. A. and Webb, T. C., *Tetrahedron*, **1972**, *28*, 2877. (aa) Snyder, C. H. and Micklus, M. J., *J. Org. Chem.*, **1970**, *35*, 264. (bb) Csuros, Z.; Kalman, V.; Lengyel-Meszaros, A. and Petro. J., *Periodic. Polytech., Chem. Eng.*, **1968**, *12*, 161. (cc) Bezuglyi, V. L.; Dovgosheya, M. I. and Kotok, L. A., *Monokrist., Stsintill. Org. Lyuminofory*, **1967**, 118. (dd) Hoffsommer, R. D.; Taub, D. and Wendler, N. L., *Chem. Ind.,* **1964**, 482. (ee) Mislow, K. and McGinn, F. A., *Magyar Kemiai Folyoirat*, **1958**, *63*, 5. (ff) Simonyi, I.; Tokar, G. and Gal, G., *Acta Chim. Acad. Sci. Hungaricae*, **1956**, *10*, 217. (gg) Gal, Gy.; Simonyi, I. and Tokar, G., *Acta Chim. Acad. Sci. Hungaricae*, **1955**, *8*, 163. (hh) Gal, G.; Tokar, G. and Simonyi, I., *Magyar Kemiai Folyoirat*, **1955**, *61*, 268. (ii) Franzen, V. and Krauch, H., *Chemiker-Zeit.*, **1955**, *79*, 243.

6. (a) Ruiz, J. R.; Jimenez-Sanchidrian, C. and Hidalgo, J. M., *Catal. Commun.*, **2007**, *8*, 1036. (b) Ramanathan, A.; Klomp, D.; Peters, J. A. and Hanefeld, U., *J. Mol. Cata. A: Chem.*, **2006**, *260*, 62. (c) Jimenez-Sanchidrian, C.; Hidalgo, J. M. and Ruiz, J. R., *Appl. Cata., A: Gen.,* **2006**, *303*, 23. (d) Akata, B.; Warzywoda, J. and Sacco, A., *J. Catal.*, **2004**, *222*, 397. (e) Klomp, D.; Maschmeyer, T.; Hanefeld, U. and Peters, J. A., *Chem. Eur. J.*, **2004**, *10*, 2088. (f) Zhu, Y. Z.; Chuah, G. and Jaenicke, S., *Chem. Commun.*, **2003**, 2734. (g) Aramendia, M. A.; Borau, V.; Jimenez, C.; Marinas, J. M.; Ruiz, J. R. and Urbano, F. J., *Appl. Cata., A: Gen.*, **2003**, *244*, 207. (h) Aramendia, M. A.; Borau, V.; Jimenez, C.; Marinas, J. M.; Ruiz, J. R. and Urbano, F. J., *J. Colloid Interface Sci.*, **2001**, *238*, 385. (i) Sugunan, S. and Sherly, K. B., *React. Kinet. Catal. Lett.*, **1993**, *51*, 533. (j) Baramee, A.; Chaichit, N.; Intawee, P.; Thebtaranonth, C. and Thebtaranonth, Y., *J. Chem. Soc., Chem. Commun.*, **1991**, 1016. (k) Rodionov, N. P.; Mairanovskii, S. G.; Gul'tyai, V. P. and Proskurovskaya, I. V., *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1976**, 1327. (l) Zimakova, E. A. and Chernyshev, E. A., *Zh. Obsh. Khim.*, **1975**, *45*, 1132. (m) Williams, E. D.; Krieger, K. A. and Day, A. R., *J. Am. Chem. Soc.*, **1953**, *75*, 2404. (n) Scipioni, A. and Borsetto, V., *Gazz. Chim. Ital.*, **1951**, *81*, 654.
7. (a) Hrnciar, P. and Podany, V., *Chemicke Zvesti*, **1961**, *15*, 713. (b) Jackman, L. M.; Mills, J. A. and Shannon, J. S., *J. Am. Chem. Soc.*, **1950**, *72*, 4814.
8. Andreeva, I. V.; Koton, M. M.; Madorskaya, L. Y.; Pokrovskii, E. I. and Lyubimova, G. V., *Vysokomolekulyarnye Soedineniya, Ser. A*, **1972**, *14*, 1565.
9. Cohen, R.; Graves, C. R.; Nguyen, S. T.; Martin, J. M. L. and Ratner, M. A., *J. Am. Chem. Soc.*, **2004**, *126*, 14796.
10. Oppenauer, R. V., *Recl. Trav. Chim. Pays-Bas*, **1937**, *56*, 137.
11. Sominsky, L.; Rozental, E.; Gottlieb, H.; Gedanken, A. and Hoz, S., *J. Org. Chem.*, **2004**, *69*, 1492.
12. (a) Aramendia, M. A.; Borau, V.; Jimenez, C.; Marinas, J. M. and Romero, F. J., *Catal. Lett.*, **1999**, *58*, 53. (b) Otvos, L.; Gruber, L. and Meisel-Agoston, J., *Acta Chim. Acad. Sci. Hungaricae*, **1965**, *43*, 149.
13. Morrison, J. D. and Ridgway, R. W., *J. Org. Chem.*, **1974**, *39*, 3107.
14. Ooi, T.; Miura, T. and Maruoka, K., *J. Am. Chem. Soc.*, **1998**, *120*, 10790.
15. (a) Strickler, J. R.; Bruck, M. A.; Wexler, P. A. and Wigley, D. E., *Organometallics*, **1990**, *9*, 266. (b) Nakano, T.; Umano, S.; Kino, Y.; Ishii, Y. and Ogawa, M., *J. Org. Chem.*, **1988**, *53*, 3752.
16. Moulton, W. N.; van Atta, R. E. and Ruch, R. R., *J. Org. Chem.*, **1961**, *26*, 290.
17. (a) Liu, Y.-C.; Ko, B.-T.; Huang, B.-H. and Lin, C.-C., *Organometallics*, **2002**, *21*, 2066. (b) Ko, B.-T.; Wu, C.-C. and Lin, C.-C., *Organometallics*, **2000**, *19*, 1864.

18. Shiner, V. J. and Whittaker, D., *J. Am. Chem. Soc.*, **1963**, *85*, 2337.
19. Truett, W. L. and Moulton, W. N., *J. Am. Chem. Soc.*, **1951**, *73*, 5913.
20. Huskens, J.; de Graauw, C. F.; Peters, J. A. and van Bekkum, H., *Recl. Trav. Chim. Pays-Bas*, **1994**, *113*, 488.
21. Molander, G. A. and McKie, J. A., *J. Am. Chem. Soc.*, **1993**, *115*, 5821.
22. Nishide, K.; Shigeta, Y.; Obata, K. and Node, M., *J. Am. Chem. Soc.*, **1996**, *118*, 13103.
23. (a) Fukuzawa, S.-I.; Nakano, N. and Saitoh, T., *Eur. J. Org. Chem.*, **2004**, 2863. (b) Ishii, Y.; Nakano, T.; Inada, A.; Kishigami, Y.; Sakurai, K. and Ogawa, M., *J. Org. Chem.*, **1986**, *51*, 240. (c) Namy, J. L.; Souppe, J.; Collin, J. and Kagan, H. B., *J. Org. Chem.*, **1984**, *49*, 2045. (d) Hach, V., *J. Org. Chem.*, **1973**, *38*, 293. (e) Shiner, V. J. and Whittaker, D., *J. Am. Chem. Soc.*, **1969**, *91*, 394. (f) Yager, B. J. and Hancock, C. K., J. Org. Chem., **1965**, *30*, 1174. (g) Mislow, K. and McGinn, F. A., *J. Am. Chem. Soc.*, **1958**, *80*, 6036. (h) Doering, W. von E. and Young, R. W., *J. Am. Chem. Soc.*, **1950**, *72*, 631. (i) Jackson, L. M. and Mills, J. A., *Nature*, **1949**, *164*, 789. (j) Wilds, A. L., *Org. React.*, **1944**, *2*, 178. (k) Lund, H., *Ber.*, **1937**, *70*, 1520.

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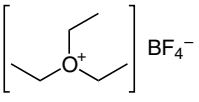
Meerwein's Salt
(Meerwein's Reagent)

A. GENERAL DESCRIPTION OF THE REACTION

This salt was first reported by Meerwein et al. in 1937.[1] Generally speaking, any combination of a trialkyloxonium[2] with a strong Lewis acid could be called Meerwein's salt,[3] such as triethyloxonium hexachloroantimonate (V) ($Et_3O^+SbCl_6^-$),[4] and triethyloxonium hexafluorophosphate ($Et_3O^+PF_6^-$).[5] However, Meerwein's salt, or known as Meerwein's reagent,[6] specifically means triethyloxonium tetrafluoroborate ($Et_3O^+BF_4^-$),[3a,6e,7] which can easily be prepared from diethyl ether, BF_3, and epichlorohydrin.[8] This reagent has been widely used as an alkylating agent for heteroatom nucleophiles, such as amides, lactams[9] (for *O*-alkylation to form amide acetals[7f,9b]), amines (for *N*-alkylation until quaternization),[7e] α-pyridones (for both *N*- and *O*-alkylation),[10] thiocarbonyl compounds (for *S*-alkylation),[7b] etc. In the presence of a superacid,[2] especially the magic acid ($FSO_3H + SbF_5$),[11] Meerwein's salt can even react with a carbon nucleophile, such as benzene and toluene. It should be pointed out that triethyloxonium hexachloroantimonate has been identified as the only Meerwein's salt used to prepare crystalline aromatic radical cations from any aromatic compounds with an oxidation potential <1.5 V.[4]

B. GENERAL REACTION SCHEME



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C. PROPOSED MECHANISMS

No mechanism is needed for this reagent.

D. MODIFICATION

Other combinations of trialkyloxonium and Lewis acid are added to this group of salts, including triethyloxonium hexachloroantimonate ($Et_3O^+SbCl_6^-$)[4] and triethyloxonium hexafluorophosphate ($Et_3O^+PF_6^-$).[5]

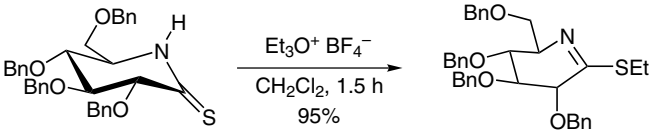
E. APPLICATIONS

This reagent has been widely used as an alkylating agent.

F. RELATED REACTIONS

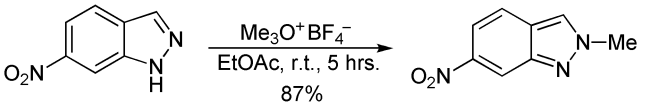
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 7b.

To a solution of 300 mg gluconothiolactam (0.54 mmol) in 13 mL dry CH_2Cl_2 at 0°C was added 112 mg triethyloxonium tetrafluoroborate (0.59 mmol). The mixture was stirred at 0°C for 1.5 h, then the solvent was removed under vacuum to afford 298 mg ethyl 2,3,4,6-tetra-*O*-benzyl-D-gluconoiminothioether, in a yield of 95%.



Reference 12.

To a stirred mixture of 163 mg 6-nitro-1*H*indazole (1 mmol) and 3 mL EtOAc was added 192 mg trimethyloxonium tetrafluoroborate (1.3 mmol). The mixture was stirred at room temperature for 5 h under nitrogen and then diluted with 20 mL EtOAc and washed with 20 mL saturated $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was extracted with EtOAc (20 mL × 2). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by column

chromatography (1:1, EtOAc/hexane) to afford 154 mg 2-methyl-6-nitro-2*H*-indazole as a yellow solid, in a yield of 87%, mp 158–160°C (EtOAc).

Other references related to the Meerwein's salt are cited in the literature.[13]

H. REFERENCES

1. Meerwein, H.; Hinz, G.; Hoffman, P.; Kroning, E. and Pfeil, E., *J. Prakt. Chem.*, **1937**, *147*, 257.
2. Hartz, N.; Rasul, G. and Olah, G. A., *J. Am. Chem. Soc.*, **1993**, *115*, 1277.
3. (a) Pichlmair, S., *Synlett*, **2004**, 195. (b) Crich, D. and Dyker, H., *Tetrahedron Lett*., **1989**, *30*, 475. (c) Barcza, S.; Eberle, M. K.; Engstrom, N. and Kahle, G. G., *J. Org. Chem.*, **1976**, *41*, 1244.
4. Rathore, R.; Kumar, A. S.; Lindeman, S. V. and Kochi, J. K., *J. Org. Chem.*, **1998**, *63*, 5847.
5. Bergeron, R. J.; Wiegand, J.; Wollenweber, M.; McManis, J. S.; Algee, S. E. and Ratliff-Thompson, K., *J. Med. Chem.*, **1996**, *39*, 1575.
6. (a) Kiessling, A. J. and McClure, C. K., *Synth. Commun.*, **1997**, *27*, 923. (b) Motorina, I. A.; Fowler, F. W. and Grierson, D. S., *J. Org. Chem.*, **1997**, *62*, 2098. (c) Chen, F. M. F. and Benoiton, N. L., *Can. J. Chem.*, **1977**, *55*, 1433. (d) Baker, P. F. and Rubinson, K. A., *J. Physiology*, **1977**, *266*, 3. (e) McMinn, D. G., *Synthesis*, **1976**, 824. (f) Alhaique, F.; Cozzani, R. G. E. and Riccieri, F. M., *Farmaco, Edizione Sci.*, **1976**, *31*, 845. (g) Baum, J. S. and Viehe, H. G., *J. Org. Chem.*, **1976**, *41*, 183.
7. (a) Moonen, K.; Laureyn, I. and Stevens, C. V., *Chem. Rev.*, **2004**, *104*, 6177. (b) Heck, M.-P.; Vincent, S. P.; Murray, B. W.; Bellamy, F.; Wong, C.-H. and Mioskowski, C., *J. Am. Chem. Soc.*, **2004**, *126*, 1971. (c) Namyslo, J. C. and Kaufmann, D. E., *Chem. Rev.*, **2003**, *103*, 1485. (d) Yan, Y.-Y. and RajanBabu, T. V., *J. Org. Chem.*, **2001**, *66*, 3277. (e) Diem, M. J.; Burow, D. F. and Fry, J. L., *J. Org. Chem.*, **1977**, *42*, 1801. (f) Howe, R. K., *J. Org. Chem.*, **1969**, *34*, 230.
8. (a) Meerwein, H., *Org. Synth. Coll.*, **1973**, *5*, 1080. (b) Meerwein, H., *Org. Synth.*, **1966**, *46*, 113.
9. (a) Weintraub, L.; Oles, S. R. and Kalish, N., *J. Org. Chem.*, **1968**, *33*, 1679. (b) Meerwein, H.; Florian, W.; Schön, N. and Stopp, G., *Ann.,* **1961**, *641*, 1. (c) Meerwein, H.; Borner, P.; Fuchs, O.; Sasse, H. J.; Schrodt, H. and Spille, J., *Chem. Ber.*, **1956**, *89*, 2060. (d) Meerwein, H.; Bhattenberg, E.; Pfeil, E. and Willfang, G., *J. Prakt. Chem.*, **1939**, *154*, 83.
10. (a) Kornblum, N. and Coffey, G. P., *J. Org. Chem.*, **1966**, *31*, 3447. (b) Kornblum, N. and Coffey, G. P., *J. Org. Chem.*, **1966**, *31*, 3449.
11. Olah, G. A.; DeMember, J. R.; Mo, Y. K.; Svoboda, J. J.; Schilling, P. and Olah, J. A., *J. Am. Chem. Soc.*, **1974**, *96*, 884.
12. Cheung, M.; Boloor, A. and Stafford, J. A., *J. Org. Chem.*, **2003**, *68*, 4093.
13. (a) Paterson, I.; Britton, R.; Ashton, K.; Knust, H. and Stafford, J., *Proc. Nat. Acad. Sci., USA*, **2004**, *101*, 11986. (b) Göschke, R.; Stutz, S.; Heinzelmann, W. and Maibaum, J., *Helv. Chim. Acta*, **2003**, *86*, 2848. (c) Mättner, M. and Neunhoeffer, H., *Synthesis*, **2003**, 413. (d) Gall, E. L.; Hurvois, J.-P. and Sinbandhit, S., *Eur. J. Org. Chem.*, **1999**, 2645. (e) Fry, S. E. and Pienta, N. J., *J. Org. Chem.*, **1984**, *49*, 4877. (f) Sheehan, J. C. and Nafissi-V, M. M., *J. Org. Chem.,* **1970**, *35*, 4246. (g) Borch, R. F., *J. Org. Chem.*, **1969**, *34*, 627. (h) Donaruma, L. G., *J. Org. Chem.*, **1957**, *22*, 1024.

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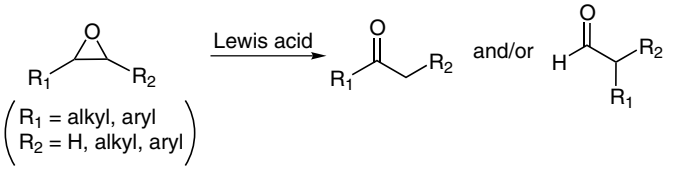
Meinwald Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Meinwald in 1963.[1] It is a Lewis acid-promoted conversion of epoxide to carbonyl compounds (ketones or aldehydes).[2] Therefore, it is generally known as the Meinwald rearrangement.[2,3] The Lewis acids used for this reaction include $BF_3{\cdot}Et_2O$,[4] $ZnBr_2$,[3b] $MgBr_2$,[4] $InCl_3$,[5] and methylaluminium bis(4-bromo-2, 6-di-*tert*-butylphenoxide).[6] In addition, protic acid is also found to be suitable for this rearrangement.[3b] It should be pointed out that this reaction is generally carried out under anhydrous conditions in the presence of a stoichiometric or an excess amount of Lewis acid with protection by an inert atmosphere.[2] The nature of the products is determined by the migratory aptitude of the substituents attached to the epoxide moiety, the solvent and Lewis acid used. Recently, this reaction was carried out using a catalytic amount of Lewis acid.[2,7]

B. GENERAL REACTION SCHEME



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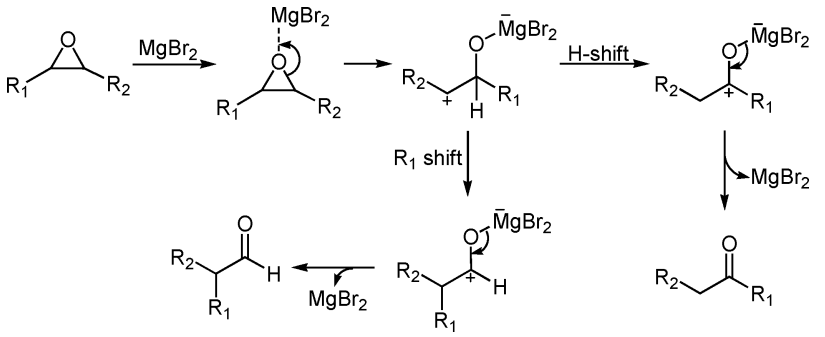
C. PROPOSED MECHANISMS

Demonstrated below is the reaction mechanism using the Lewis acid $MgBr_2$.



D. MODIFICATION

This reaction has been modified to take place in the presence of a catalytic amount of Lewis acid.[2,7]

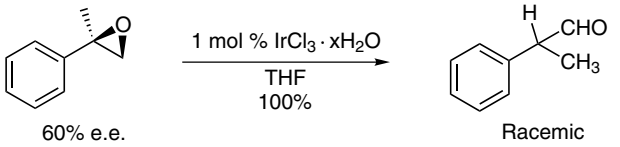
E. APPLICATIONS

This reaction has general application in the conversion of epoxides into aldehydes and ketones.

F. RELATED REACTIONS

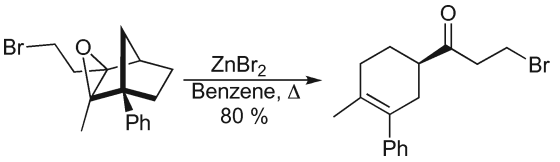
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 2.

To 1 mL THF solution containing 1 mg $IrCl_3 \cdot xH_2O$ (3.35×10^{-3} mmol) was added 45 mg (*R*)-α-methylstyrene oxide (0.335 mmol). The reaction mixture was stirred at 50°C and monitored by GC. After about 2 h, the reaction completed, and the solvent was removed to afford 100% racemic α-methylphenylacetaldehyde.



Reference 3b.

To a solution of 35 mg epoxide (0.11 mmol) in 3 mL benzene was added 117 mg anhydrous zinc bromide (0.52 mmol), and the mixture was stirred at 70 °C for ∼10 min. After cooling to room temperature, the mixture was diluted with ether, washed with water and brine, and dried over $MgSO_4$. Upon removal of the solvent, the residue was purified by column chromatography to afford 27 mg ketone as a colorless oil, in a yield of 80%.

Other references related to Meinwald rearrangement are cited in the literature.[8]

H. REFERENCES

1. Meinwald, J.; Labana, S. S. and Chadha, M. S., *J. Am. Chem. Soc.*, **1963**, *85*, 582.
2. Karame, I.; Tommasino, M. L. and Lemaire, M., *Tetrahedron Lett.*, **2003**, *44*, 7687.
3. (a) Robinson, M. W. C.; Pillinger, K. S. and Graham, A. E., *Tetrahedron Lett*., **2006**, *47*, 5919. (b) Li, W.-D. Z. and Yang, Y.-R., *Org. Lett.*, **2005**, *7*, 3107. (c) Niwayama, S.; Noguchi, H.; Ohno, M. and Kobayashi, S., *Tetrahedron Lett*., **1993**, *34*, 665. (d) Niwayama, S.; Kobayashi, S. and Ohno, M., *Tetrahedron Lett*., **1988**, *29*, 6313.
4. Kita, Y.; Kitagaki, S.; Yoshida, Y.; Mihara, S.; Fang, D.-F.; Kondo, M.; Okamoto, S.; Imai, R.; Akai, S. and Fujioka, H., *J. Org. Chem.*, **1997**, *62*, 4991.
5. Ranu, B. C. and Jana, U., *J. Org. Chem.*, **1998**, *63*, 8212.
6. Maruoka, K.; Ooi, T. and Yamamoto, H., *Tetrahedron*, **1992**, *48*, 3303.
7. (a) Leonard, N. M.; wieland, L. C. and Mohan, R. S., *Tetrahedron*, **2002**, *58*, 8373. (b) Bhatia, K. A.; Eash, K. J.; Leonard, N. M.; Oswald, M. C. and Mohan, R. S., *Tetrahedron Lett.*, **2001**, *42*, 8129. (c) Anderson, A. M.; Blazek, J. M.; Garg, P.; Payne, B. J. and Mohan, R. S., *Tetrahedron Lett.*, **2000**, *41*, 1527. (d) Kulasegaram, S. and Kulawiec, R. J., *Tetrahedron*, **1998**, *54*, 1361. (e) Kulasegaram, S. and Kulawiec, R. J., *J. Org. Chem.*, **1997**, *62*, 6547.
8. (a) Sun, H.; Yang, J.; Amaral, K. E. and Horenstein, B. A., *Tetrahedron Lett*., **2001**, *42*, 2451. (b) Rhee, H.; Yoon, D.-O. and Jung, M. E., *Nucleosides, Nucleotides & Nucleic Acids*, **2000**, *19*, 619. (c) Kim, W.; Kim, H. and Rhee, H., *Heterocycles*, **2000**, *53*, 219. (d) Niwayama, S.; Kobayashi, S. and Ohno, M., *J. Am. Chem. Soc.*, **1994**, *116*, 3290. (e) Bell, T. W. and Ciacciot, J. A., *J. Org. Chem.*, **1993**, *58*, 5153. (f) Garin, D. L., *J. Org. Chem.*, **1971**, *36*, 1697. (g) Garin, D. L., *J. Org. Chem.*, **1969**, *34*, 2355. (h) Williamson, K. L.; Coburn, J. I. and Herr, M. F., *J. Org. Chem.*, **1967**, *32*, 3934. (i) Meinwald, J.; Seidel, M. C. and Cadoff, B. C., *J. Am. Chem. Soc.*, **1958**, *80*, 6303.

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Meisenheimer Complexes
(Anionic σ Complexes)

A. GENERAL DESCRIPTION OF THE REACTION

Although this type of structure was first reported by Jackson et al. in 1900 for the reaction between picryl ether and potassium alkoxide,[1] it was Meisenheimer who actually isolated and characterized the structure of such molecule for the first time in 1902.[2] Since then, the stable or transient anionic σ complexes[3] formed from electron-deficient aromatic compounds and a variety of organic and inorganic bases[4] are generally called the Meisenheimer complexes.[5] Occasionally, this type of molecule is also referred to as the Meisenheimer adducts,[6] Meisenheimer compounds,[7] Meisenheimer σ-adducts,[8] Meisenheimer σ complexes,[9] Jackson-Meisenheimer adducts,[10] or Jackson-Meisenheimer complexes.[5z,11]

The Meisenheimer complexes are the intermediates of most nucleophilic aromatic substitution (S_NAr) reactions,[5c,5z,12] which consist of two-step mechanisms:[5z,13] the formation of Meisenheimer complexes and the expelling of a leaving group to resume the aromaticity of the products. It is known that the aprotic solvent,[5z,14] especially DMSO, is best for the formation of such σ complexes,[15] and the addition of a nucleophile to the aromatic ring is the rate-limiting step.[13a,15] In general, only aromatic compounds that contain at least one strong electron-withdrawing group can form Meisenheimer complexes,[16] and the activating groups can be nitro,[5i,17] cyano,[18] carbonyl,[19] sulfonyl,[19] fluoroalkyl,[19] and many different heterocycles (including oxadiazole,[19,20] triazole,[19] and benzazole[19]). These activating groups have two obvious features during the formation of the Meisenheimer complexes: to reduce the electron density on the aromatic ring and to stabilize the formed complexes after the addition of the nucleophiles.[19] The nucleophiles involved in the formation of the Meisenheimer complexes can be categorized as *H*-, *C*-, *O*-, *N*- and *S*-nucleophiles, which attack the electron-deficient aromatics through the corresponding atoms. Among the Meisenheimer complexes studied so far, almost half the complexes are generated

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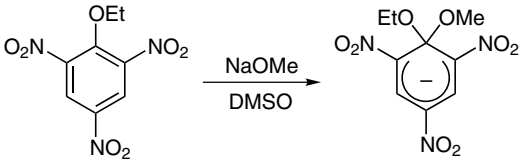
through the attack of *O*-nuclephiles, primarily the alkoxide nucleophiles,[5z] except for a few cases of aryloxide nucleophiles.[12c] The *C*-nucleophiles known include the carbanions generated from nitromethanes[21] and carbonyl compounds (ketones and aldehydes) with α-hydrogen;[12b] the *N*-nucleophiles are primary and secondary amines[5c,22] and anilines.[23] Specifically, hydride-Meisenheimer complexes from *H*-nucleophiles are generated from enzymatic reduction and are important intermediates for the biodegradation of high explosives (e.g., TNT).[17a,17c,17e] In addition, some bidentate nucleophiles, such as enolate and phenoxide, can add to the aromatic ring through either an *O*- or a *C*-attack,[12b,14a] and pyrrolide and indolide anions can function as either *C*- or *N*-nucleophiles.[14a] It is interesting that anion generated from solvent DMSO (dimsyl dianion) is a tridentate, attacking the aromatic ring through the *O*-, *S*-, and *C*- atom.[14a] On the other hand, even though it has been predicted that the *O*-attack is preferred over *C*-attack for the enolate nucleophiles,[24] most of the Meisenheimer complexes from enolates are actually the *C*-attack ones. This is because that the *O*-attack is a kinetic controlled process whereas *C*-attack of enolate is under thermodynamical control.[12b] The formation of σ complexes from the *C*-attack of enolate, known as the *Janovsky Reaction*, has been widely applied in pharmaceutical tests.[12b] Besides the benzene derivatives, other substituted aromatics such as naphthalenes[5y,13b] and phenanthrenes[25] can also form corresponding Meisenheimer complexes. Kinetically, the nucleophile would preferentially add to the *meta*-position of the leaving group; in contrast, for the case of 2,4,6-trinitrofluorobenzene, the dominant Meisenheimer complex is the one formed by addition at position 1. This regioselectivity is referred to as K3T1 ("kinetic preference for reaction at the 3-position but thermodynamic preference for formation of the C-1 adduct").[12a] The formation of the Meisenheimer complexes has been used in the Sanger protein sequence[5c] as well as in many other synthetic applications.[17d,19,20,25] The formation of the Meisenheimer complexes has been modified using a micellar catalyst[13a] or an electrochemical reduction via a charge-transfer complex between trinitrofluorenone and electron-donating molecules (e.g., pyrrole, indole, and carbazole).[5i]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

N/A

D. MODIFICATION

The formation of the Meisenheimer complexes has been modified to take place under electrochemical reduction conditions through a charge-transfer complex between electron-deficient aromatics and electron-donative heterocycles.[5i]

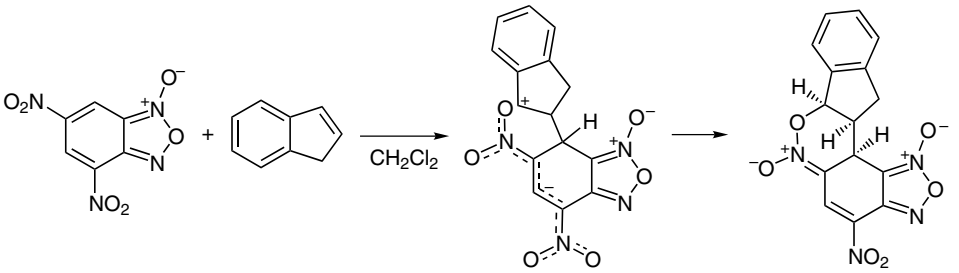
E. APPLICATIONS

The Meisenheimer complexes have been widely observed in nucleophilic aromatic substitution reactions.

F. RELATED REACTIONS

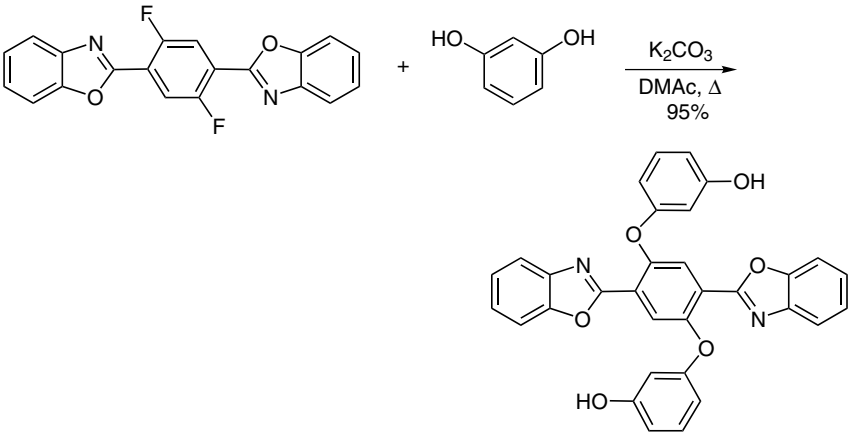
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 26.

To a stirred solution of 128 mg indene in 2 mL CH_2Cl_2 was added 226 mg 4,6-dinitrobenzofuroxan (1 mmol) at room temperature. The solution turned orange, and some precipitate was formed after 2 h. After 24 h at room temperature, the resulting yellow crystals were filtered, washed with diethyl ether, and dried over P_2O_5 under vacuum to afford the oxazine *N*-oxide, m.p. 165°C (dec.)



Reference 19.

To a three-necked reaction flask equipped with a nitrogen inlet and Dean-Stark trap fitted with a condenser and a nitrogen outlet, were added 0.576 g K_2CO_3 (4.17 mmol) and 0.410 g *m*-cresol (3.79 mmol) in a mixture of 8 mL DMAc and 12 mL toluene under stirring. The mixture was heated to 150°C to remove moisture via an azeotrope with toluene. After 4–6 h, the mixture was dehydrated and cooled to $\sim$ 60°C, then 0.6 g 1,4-bis(2-benzoxazolyl)-2,5-difluorobenzene (1.72 mmol) in 8 mL DMAc was added and stirred at 155°C for 20 h. The mixture was poured into 250 mL water containing 1% AcOH, and the yellow precipitate was filtered, washed, and dried at 80°C under vacuum for 24 h. The crude product was purified by flash column chromatography (CH_2Cl_2) to afford 95% 1,4-bis(2-benzoxazolyl)-2,5-bis(3-methylphenoxy)benzene as a light yellow crystalline, m.p., 274°C (DSC).

Other references related to the Meisenheimer complexes are cited in the literature.[27]

H. REFERENCES

1. Jackson, C. J. and Gazzolo, F. H., *Am. Chem. J.*, **1900**, *23*, 376.
2. Meisenheimer, J., *Ann.*, **1902**, *323*, 205.
3. (a) Demeter, A.; Weber, C.; Brlik, J.; Veszpremi, T. and Nemeth, B., *Acta Pharm. Hungarica*, **2004**, *74*, 29. (b) Alifanova, E. N.; Kalninsh, K. K.; Kaminsky, A. J.; Atroshchenko, Y. M.; Gitis, S. S.; Kutzenko, A. D.; Chudakov, P. V. and Tarasova, E. Y., *J. Mol. Liquids*, **2001**, *91*, 115. (c) Borbulevych, O. Y.; Antipin, M. Y.; Shishkin, O. V. and Knyazev, V. N., *J. Mol. Struct.*, **2000**, *520*, 141. (d) Shishkin, O. V.; Borbulevych, O. Y.; Blokhin, V.; Atroschenko, Y. M. and Gitis, S. S., *Russ. Chem. Bull.*, **1998**, *47*, 2074. (e) Gitis, S. S. and Stempin, N. D., *Zh. Obsh. Khim.*, **1996**, *66*, 1516. (f) Knyazev, V. N. and Drozd, V. N., *Zh. Org. Khim.*, **1995**, *31*, 3. (g) Blokhin, I. V.; Antroshchenko, Y. M.; Kaninskii, A. Y. and Gitis, S. S., *Zh. Org. Khim.*, **1993**, *29*, 2065. (h) Stempin, N. D.; Gitis, S. S.; Glaz, A. I. and Shakhkel'dyan, I. V., *Zh. Obsh. Khim.*, **1991**, *61*, 563.
4. Strauss, M. J. and Bard, R. R., *J. Org. Chem.*, **1978**, *43*, 3600.
5. (a) Chiavarino, B.; Crestoni, M. E.; Fornarini, S.; Lanucara, F.; Lemaire, J. and Maitre, P., *Angew. Chem. Int. Ed.,* **2007**, *46*, 1995. (b) Herance, J. R.; Concepcion, P.; Domenech, A.; Bourdelande, J. L.; Marquet, J. and Garcia, H., *Chem. Eur. J.*, **2005**, *11*, 6491. (c) Lakshman, M. K., *Curr. Org. Synth.*, **2005**, *2*, 83. (d) Al-Kaysi, R. O.; Creed, D. and Valente, E. J., *J. Chem. Cryst.*, **2004**, *34*, 685. (e) Chen, H.; Chen, H. W. and Cooks, R. G., *J. Am. Soc. Mass. Spect*., **2004**, *15*, 998. (f) Buncel, E.; Dust, J. M.; Manderville, R. A. and Tarkka, R. M., *Can. J. Chem.*, **2003**, *81*, 443. (g) Borbulevych, O. Y.; Shishkin, O. V. and Antipin, M. Y., *J. Phys. Chem. A*, **2002**, *106*, 8109. (h) Dong, J.; Carey, P. R.; Wei, Y. S.; Luo, L. S.; Lu, X. F.; Liu, R.-Q. and Dunaway-Mariano, D., *Biochemistry*, **2002**, *41*, 7453. (i) Ozawa, N.; Seki, H.; Kitamura, T.; Kokado, H.; Ishikawa, T. and Hoshino, K., *Chem. Mater.*, **2002**, *14*, 1067. (j) Knyazev, V. N.; Borbulevich, O. Y. and Shishkin, O. V., *Russ. J. Org. Chem.*, **2000**, *36*, 1634. (k) Knyazev, V. N.; Borbulevich, O. Y. and Shishkin, O. V., *Russ. J. Org. Chem.*, **2000**, *36*, 706. (l) Borbulevych, O. Y.; Antipin, M. Y.; Shishkin, O. V. and Knyazev, V. N., *Russ. Chem. Bull.*, **2000**, *49*, 452. (m) Behrend, C. and Heesche-Wagner, K., *Appl. Environ. Microbio.*, **1999**, *65*, 1372. (n) Weiss, R.; Schwab, O. and Hampel, F., *Chem. Eur. J.*, **1999**, *5*, 968. (o) Sepulcri, P.; Goumont, R.; Halle, J.-C.; Buncel, E. and Terrier, F., *Chem. Commun.*, **1997**, 789. (p) Knyazev, V. N. and Drozd, V. N., *Zh. Org. Khim.*, **1996**, *32*, 1394. (q) Bakry, R. S.; El Walily, A. F. and Belal, S. F., *Anal. Lett.*, **1995**, *28*, 2503. (r) Knyazev, V. N. and Drozd, V. N., *Zh. Org. Khim.*, **1995**, *31*, 121. (s) Drozd, V. N.; Knyazev, V. N.; Khilkova, N. L.; Yufit, D. S.; Struchkov, Y. T.; Stankevich, I. V. and Chistyakov, A. L., *Zh. Org. Khim.*, **1993**, *29*, 770. (t) Drozd, V. N.;

Knyazev, V. N.; Nam, N. L.; Lezina, V. P.; Mozhaeva, T. Y. and Savel'ev, V. L., *Zh. Org. Khim.*, **1993**, *29*, 782. (u) Mozhaeva, T. Y.; Lezina, V. P.; Savel'ev, V. L.; Knyazev, V. N. and Drozd, V. N., *Zh. Org. Khim.*, **1991**, *27*, 1733. (v) Knyazev, V. N.; Drozd, V. N.; Patalakha, N. S.; Yufit, D. S. and Struchkov, Y. T., *Zh. Org. Khim.*, **1991**, *27*, 192. (w) Drozd, V. N.; Knyazev, V. N.; Mozhaeva, T. Y.; Savel'ev, V. L. and Lezina, V. P., *Zh. Org. Khim.,* **1991**, *27*, 175. (x) Clark, A. G. and Sinclair, M., *Biochem. Pharmacol.*, **1988**, *37*, 259. (y) Sekiguchi, S.; Aizawa, T. and Tomoto, N., *J. Org. Chem.*, **1984**, *49*, 93. (z) Terrier, F., *Chem. Rev.*, **1982**, *82*, 77.

6. Snyder, S. E.; Carey, J. R.; Shvets, A. B. and Pirkle, W. H., *J. Org. Chem.*, **2005**, *70*, 4073.
7. Gallardo, I. and Guirado, G., *Electrochem. Commun.*, **2007**, *9*, 173.
8. Kustov, A. V.; Alifanova, E. N.; Lapina, O. Y. and Korolev, V. P., *Thermochimica Acta*, **2003**, *406*, 185.
9. Blokhin, I. V.; Atroshchenko, Y. M.; Alifanova, E. N.; Kurenkova, Y. V.; Kaminskii, A. Y.; Gitis, S. S. and Blokhina, N. I., *Russ. J. Gen. Chem.*, **1999**, *69*, 1793.
10. Chudek, J. A. and Foster, R., *Gazz. Chim. Ital.*, **1987**, *117*, 629.
11. Beletskaya, I. P.; Artamkina, G. A. and Reutov, O. A., *J. Organomet. Chem.*, **1972**, *42*, C16.
12. (a) Manderville, R. A. and Buncel, E., *J. Org. Chem.*, **1997**, *62*, 7614. (b) Buncel, E.; Dust, J. M. and Manderville, R. A., *J. Am. Chem. Soc.*, **1996**, *118*, 6072. (c) Bernasconi, C. F. and Muller, M. C., *J. Am. Chem. Soc.*, **1978**, *100*, 5530.
13. (a) Broxton, T. J. and Chung, R. P.-T., *J. Org. Chem.*, **1990**, *55*, 3886. (b) Sekiguchi, S.; Aizawa, T. and Aoki, M., *J. Org. Chem.*, **1981**, *46*, 3657.
14. (a) Buncel, E.; Park, K.-T.; Dust, J. M. and Manderville, R. A., *J. Am. Chem. Soc.*, **2003**, *125*, 5388. (b) Larsen, J. W.; Amin, K. and Fendler, J. H., *J. Am. Chem. Soc.*, **1971**, *93*, 2910.
15. Bernasconi, C. F. and Gehriger, C. L., *J. Am. Chem. Soc.*, **1974**, *96*, 1092.
16. Wubbles, G. G.; Ota, N. and Crosier, M. L., *Org. Lett.*, **2005**, *7*, 4741.
17. (a) Lewis, T. A.; Newcombe, D. A. and Crawford, R. L., *J. Environ. Manag.*, **2004**, *70*, 291. (b) Boyd, E. and Bruce, N., *Microbiology Today*, **2002**, *29*, 72. (c) Nivinskas, H.; Koder, R. L.; Anusevicius, Z.; Sarlauskas, J.; Miller, A.-F. and Cenas, N., *Arch. Biochem. Biophys.*, **2001**, *385*, 170. (d) Padwa, A. and Waterson, A. G., *ARKIVOC,* **2001**, 29. (e) Rieger, P.-G.; Sinnwell, V.; Preuβ, A.; Francke, W. and Knackmuss, H.-J., *J. Bacteriology*, **1999**, *181*, 1189.
18. Fendler, J. H. and Larsen, J. W., *J. Org. Chem.*, **1972**, *37*, 2608.
19. Kim, J.-H.; Bang, S. W. and Kim, Y. J., *Bull. Korean Chem. Soc.*, **2000**, *21*, 896.
20. Sava, I.; Iosip, M.-D.; Bruma, M.; Hamciuc, C.; Robison, J.; Okrasa, L. and Pakula, T., *Eur. Polym. J.*, **2003**, *39*, 725.
21. Popov, I. A.; Chen, H.; Kharybin, O. N.; Nikolaev, E. N. and Cooks, R. G., *Chem. Commun.*, **2005**, 1953.
22. Bernasconi, C. F., *J. Org. Chem.*, **1970**, *35*, 1214.
23. Strauss, M. J.; Renfrow, R. A. and Buncel, E., *J. Am. Chem. Soc.*, **1983**, *105*, 2473.
24. Houk, K. N. and Paddon-Row, M. N., *J. Am. Chem. Soc.*, **1988**, *110*, 2706.
25. Sekiguchi, S.; Hirai, M.; Ota, E.; Hiratsuka, H.; Mori, Y. and Tanaka, S., *J. Org. Chem.*, **1985**, *50*, 5105.
26. MacCormack, P.; Halle, J.-C.; Pouet, M.-J. and Terrier, F., *J. Org. Chem.*, **1988**, *53*, 4407.
27. (a) Williams, R. E.; Rathbone, D. A.; Scrutton, N. S. and Bruce, N. C., *Appl. Environ. Microbio.*, **2004**, *70*, 3566. (b) Onyidoa, I.; Hamaguchi, M. and Buncel, E., *ARKIVOC*, **2003**, (*xii*) 197. (c) Holden, H. M.; Benning, M. M.; Haller, T. and Gerlt, J. A., *Acc. Chem. Res.*, **2001**, *34*, 145. (d) Nückel, S. and Burger, P., *Organometallics*, **2000**, *19*, 3305. (e) Adam, W.; Makosza, M.; Zhao, C.-G. and Surowiec, M., *J. Org. Chem.*, **2000**, *65*, 1099. (f) Chang, G.-G.; Huang, T.-M. and Hung, H.-C., *Proc. Natl. Sci. Counc. ROC(B)*, **2000**, *24*, 89. (g) Hoshino, K.; Ozawa, N.; Kokado, H.; Seki, H.; Tokunaga, T. and Ishikawa, T., *J. Org. Chem.*, **1999**, *64*, 4572. (h) Lindkvist, B.;

Weinander, R.; Engman, L.; Koetse, M.; Engberts, J. B. F. N. and Morgenstern, R., *Biochem. J.*, **1997**, *323*, 39. (i) Bernasconi, C. F.; Flores, F. X. and Kittredge, K. W., *J. Am. Chem. Soc.*, **1997**, *119*, 2103. (j) Sachs, W.; Knoche, W. and Herrmann, C., *J. Chem. Soc., Perkin Trans. II*, **1991**, 701. (k) Blakeley, R. L. and Zerner, B., *J. Am. Chem. Soc.*, **1980**, *102*, 6586. (l) Ah-Kow, G.; Terrier, F.; Pouet, M.-J. and Simonnin, M.-P., *J. Org. Chem.*, **1980**, *45*, 4399. (m) Terrier, F.; Chatrousse, A.-P.; Paulmier, C. and Schaal, R., *J. Org. Chem.*, **1975**, *40*, 2911. (n) Farnham, S. and Taylor, R., *J. Org. Chem.*, **1974**, *39*, 2446. (o) Taylor, R. P. and Vatz, J. B., *J. Am. Chem. Soc.*, **1973**, *95*, 5819. (p) Terrier, F.; Chatrousse, A.-P. and Schaal, R., *J. Org. Chem.*, **1972**, *37*, 3010. (q) Larsen, J. W.; Amin, K.; Ewing, S. and Magid, L. L., *J. Org. Chem.*, **1972**, *37*, 3857. (r) Taylor, R. P., *J. Org. Chem.*, **1970**, *35*, 3578. (s) Larsen, J. W.; Fendler, J. H. and Fendler, E. J., *J. Am. Chem. Soc.*, **1969**, *91*, 5903. (t) Servis, K. L., *J. Am. Chem. Soc.*, **1965**, *87*, 5495.

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Meisenheimer Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Meisenheimer in 1919.[1] It is a thermal transformation of tertiary aliphatic amine oxides (tertiary *N*-oxides) into substituted *N*-alkoxylamines[2] or *N*-hydroxylamines,[3] and is generally known as the Meisenheimer rearrangement.[2–4] Occasionally, it is also referred to as the Meisenheimer *N*-oxide rearrangement,[5] Meisenheimer reaction,[6] or Meisenheimer transformation.[7] In addition, depending on the location of the migrating group attached, this reaction is specifically called [1,2]-Meisenheimer rearrangement,[8] or [2,3]-Meisenheimer rearrangement[9] (or [2,3]-sigmatropic Meisenheimer rearrangement[10]). It is known that this reaction occurs through a radical mechanism involving a homolytic cleavage of a nitrogen-carbon bond and the migration of an alkyl group to form the *N*-alkoxylamine.[3c,4i,4pp] The migrating entity should be capable of stabilizing the generated radical, although a case of unlikely migration of a tertiary group has been reported (i.e., 3-homoadamantyl[3c]). However, this reaction does not apply to aromatic *N*-oxides.[2] It has been found that the aryl allyl *N*-oxides undergo a [2,3]-sigmatropic rearrangement through a cyclic transition state.[4m] In contrast, the rearrangement of *N*-propargylmorpholine *N*-oxide depends on the nature of the solvent, although such rearrangement is reported to take place through a similar cyclic transition state.[3a] For example, in aprotic solvents, *N*-propargylmorpholine *N*-oxide undergoes a regular Meisenheimer rearrangement; whereas in protic solvents (e.g., C_1-C_4 alcohols), the rate of Meisenheimer rearrangement is reduced, and the protonation results in the formation of an enaminoaldehyde.[3a] This reaction has been used to differentiate the *N*-oxides from isomerically hydroxylated metabolites through mass spectroscopy and to determine the position of *N*-oxides.[2] In addition, this reaction has been used for both the degradation of polyamines,[4d]

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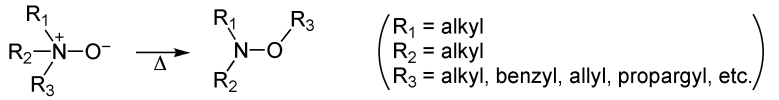
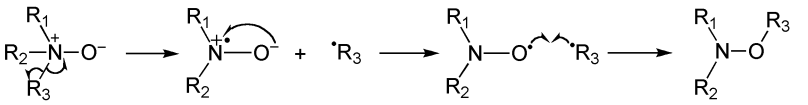
and the living radical polymerization to produce a polymer with a narrow molecular weight distribution.[4i]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

N/A

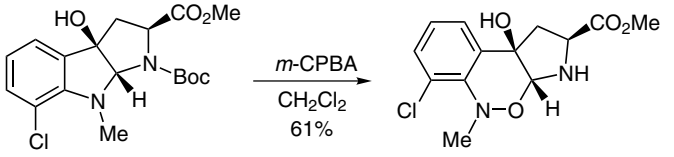
E. APPLICATIONS

This reaction has general application in organic synthesis, as well as in polymer chemistry by either initiation of living radical polymerization[4i] or degradation of polyamines.[4d]

F. RELATED REACTIONS

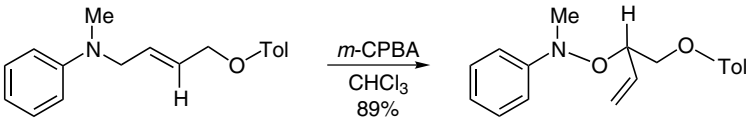
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 4e.

To a solution of 100 mg methyl (2*S*,3a*R*,8a*S*)-7-chloro-3a-hydroxy-8-methyl-3,3a,8,8a-tetrahydro-2*H*-pyrrolo[2,3-*b*]indole-1,2-dicarboxylate (0.35 mmol) in 2 mL CH_2Cl_2 was added 61 mg *m*-CPBA (0.33 mmol, 1.0 eq.) in 1 mL CH_2Cl_2 dropwise under stirring at 0°C. After 30 min, an additional 61 mg *m*-CPBA (0.35 mmol, 1.0 eq.) in 1 mL CH_2Cl_2 was added dropwise, and stirring was continued at 0°C for a further 30 min. The solution was diluted with 5 mL CH_2Cl_2, washed with 10% aqueous Na_2CO_3, dried over Na_2SO_4, and rotary evaporated. HCl in EtOAc (1 M, 5 mL) was added with stirring to the residue. After 1 h, the solution was concentrated under reduced pressure, and saturated aqueous $NaHCO_3$ was added to adjust the pH to 8. The mixture was extracted with CH_2Cl_2 (2×10 mL), and the organic layer was dried over Na_2SO_4. Rotary evaporation and chromatography (hexanes/EtOAc, 1:1) gave 64 mg methyl (2*S*,3a*R*,9b*R*)-6-chloro-9b-hydroxy-5-methyl-1,2,3,3a,5,9b-hexahydro-4-oxa-3,5-diazacyclopenta[*a*]naphthalene-2-carboxylate as a yellow oil, in a yield of 61%, $R_f = 0.13$ (hexanes/EtOAc, 1:1).



Reference 4m.

To a well-stirred solution of 10 mmol tertiary amine in 50 mL $CHCl_3$, was added 3.44 g *m*-CPBA (10 mmol, 50%) in 50 mL $CHCl_3$ at 0–5°C over a period of 20 min. The reaction mixture was stirred for additional 10 h. The reaction mixture was washed with an aqueous solution of K_2CO_3 and dried over Na_2SO_4. The solvent was removed, and the residue was purified by column chromatography over silica gel with petroleum ether to afford 89% *O*-[2-(2-methylbut-3-enyl)]-*N*-methyl-*N*-phenylhydroxylamine as a viscous liquid.

Other references related to the Meisenheimer rearrangement are cited in the literature.[11]

H. REFERENCES

1. Meisenheimer, J., *Ber.*, **1919**, *52*, 1667.
2. Ma, S. G.; Chowdhury, S. K. and Alton, K. B., *Anal. Chem.*, **2005**, *77*, 3676.
3. (a) Mucsi, Z.; Szabó, A.; Hermecz, I.; Kucsman, A. and Csizmadia, I. G., *J. Am. Chem. Soc.*, **2005**, *127*, 7615. (b) Molina, J.; M.; El-Bergmi, R.; Dobado, J. A. and Portal, D., *J. Org. Chem.*, **2000**, *65*, 8574. (c) Adams, B. L. and Kovacic, P., *J. Am. Chem. Soc.*, **1974**, *96*, 7014. (d) Maricich, T. J. and Harrington, C. K., *J. Am. Chem. Soc.*, **1972**, *94*, 5115.
4. (a) Majumdar, K. C.; Roy, B.; Basu, P. K. and Biswas, P., *Indian J. Chem., Sect. B*, **2006**, *45B*, 719. (b) Malpass, J. R.; Skerry, P. S. and Rimmington, S. L., *Heterocycles*, **2004**, *63*, 1529. (c) Malpass, J. R.; Skerry, P. S. and Rimmington, S. L., *Heterocycles*, **2004**, *62*, 679. (d) Kabanov, V. A., *Pure & Appl. Chem.*, **2004**, *76*, 1659. (e) Didier, C.; Critcher, D. J.; Walshe, N. D.; Kojima, Y.; Yamauchi, Y. and Barrett, A. G. M., *J. Org. Chem.*, **2004**, *69*, 7875. (f) Guarna, A.; Occhiato, E. G.; Pizzetti, M.; Scarpi, D.; Sisi, S. and van Sterkenburg, M., *Tetrahedron: Asymmetry*, **2000**, *11*, 4227. (g) Buston, J. E. H.; Coldham, I. and Mulholland, K. R., *J. Chem. Soc., Perkin Trans. I*, **1999**, 2327. (h) Buston, J. E. H.; Coldham, I. and Mulholland, K. R., *Tetrahedron: Asymmetry*, **1998**, *9*, 1995. (i) Bergbreiter, D. E. and Walchuk, B., *Macromolecules*, **1998**, *31*, 6380.

(j) Majumdar, K. C. and Jana, G. H., *Can. J. Chem.*, **1998**, *76*, 297. (k) Yoneda, R.; Araki, L.; Harusawa, S. and Kurihara, T., *Chem. Pharm. Bull.*, **1998**, *46*, 853. (l) Walchuk, B. and Bergbreiter, D. E., *Polymer Preprints*, **1998**, *39*, 296. (m) Majumdar, K. C. and Jana, G. H., *J. Org. Chem.*, **1997**, *62*, 1506. (n) Davies, S. G. and Smyth, G. D., *J. Chem. Soc., Perkin Trans. I*, **1996**, 2467. (o) Kurihara, T.; Sakamoto, Y.; Kimura, T.; Ohishi, H.; Harusawa, S.; Yoneda, R.; Suzutani, T. and Azuma, M., *Chem. Pharm. Bull.*, **1996**, *44*, 900. (p) Davies, S. G. and Smyth, G. D., *Tetrahedron: Asymmetry*, **1996**, *7*, 1001. (q) Bremner, J. B.; Smith, R. J. and Tarrant, G. J., *Tetrahedron Lett*., **1996**, *37*, 97. (r) Kurihara, T.; Sakamoto, Y.; Takai, M.; Ohishi, H.; Harusawa, S. and Yoneda, R., *Chem. Pharm. Bull.*, **1995**, *43*, 1089. (s) Thiele, S. and Otto, H. H., *Scientia Pharmaceutica*, **1994**, *62*, 17. (t) Kurihara, T.; Sakamoto, Y.; Matsumoto, H.; Kawabata, N.; Harusawa, S. and Yoneda, R., *Chem. Pharm. Bull.*, **1994**, *42*, 475. (u) Kurihara, T.; Sakamoto, Y.; Takai, M.; Tsukamoto, K.; Sakai, T.; Harusawa, S. and Yoneda, R., *Chem. Pharm. Bull.*, **1994**, *42*, 31. (v) Kurihara, T.; Sakamoto, Y.; Takai, M.; Ohuchi, K.; Harusawa, S. and Yoneda, R., *Chem. Pharm. Bull.*, **1993**, *41*, 1221. (w) Bailey, T. S. and Bremner, J. B., *Aust. J. Chem.*, **1993**, *46*, 1965. (x) Kurihara, T.; Sakamoto, Y.; Tsukamoto, K.; Ohishi, H.; Harusawa, S. and Yoneda, R., *J. Chem. Soc., Perkin Trans. I*, **1993**, 81. (y) Kurihara, T.; Ohuchi, K.; Kawamoto, M.; Harusawa, S. and Yoneda, R., *Chem. Lett.*, **1991**, 1781. (z) Kurihara, T.; Doi, M.; Hamaura, K.; Ohishi, H.; Harusawa, S. and Yoneda, R., *Chem. Pharm. Bull.*, **1991**, *39*, 811. (aa) Bremner, J. B.; Browne, E. J.; Engelhardt, L. M.; Gunawardana, I. W. K. and White, A. H., *Aust. J. Chem.*, **1988**, *41*, 293. (bb) Khuthier, A.-H.; Al-Rawi, J. M. A.; Al-Kazzaz, A. K. and Al-Iraqi, M. A., *Org. Magnet. Reson.*, **1982**, *18*, 104. (cc) Banks, R. E.; Brown, A. K.; Haszeldine, R. N.; Kenny, A. and Tipping, A. E., *J. Fluor. Chem.*, **1981**, *17*, 85. (dd) Al-Iraqi, M. A.; Al-Rawi, J. M. A. and Khuthier, A. H., *Org. Magnet. Reson.*, **1980**, *14*, 161. (ee) Bremner, J. B.; Browne, E. J.; Davies, P. E.; Raston, C. L. and White, A. H., *Aust. J. Chem.*, **1980**, *33*, 1323. (ff) Bremner, J. B.; Browne, E. J. and Davies, P. E., *Aust. J. Chem.*, **1980**, *33*, 1335. (gg) Bremner, J. B.; Browne, E. J.; Davies, P. E. and Van Thuc, L., *Aust. J. Chem.,* **1980**, *33*, 833. (hh) Khuthier, A. H.; Ahmed, T. Y. and Jallo, L. I., *J. Chem. Soc., Chem. Commun.*, **1976**, 1001. (ii) Rautenstrauch, V., *Helv. Chim. Acta*, **1973**, *56*, 2492. (jj) Lorand, J. P.; Grant, R. W.; Samuel, P. A.; O'Connel, E. M.; Zaro, J.; Pilotte, J. and Wallace, R. W., *J. Org. Chem.*, **1973**, *38*, 1813. (kk) Castagnoli, N.; Cymerman C., John; M., Armen, P. and Roy, S. K., *J. Chem. Soc. D*, **1970**, 1327. (ll) Hubert, A. J., *Bull. Soc. Chim. Belg.*, **1970**, *79*, 195. (mm) Johnstone, R. A. W., *Mech. Mol. Migr.*, **1969**, *2*, 249. (nn) Tabushi, I.; Hamuro, J. and Oda, R., *Nippon Kagaku Zasshi*, **1969**, *90*, 197. (oo) Schöllkopf, U. and Ludwig, U., *Ber.*, **1968**, *101*, 2224. (pp) Schöllkopf, U.; Patsch, M. and Schaefer, H., *Tetrahedron Lett.*, **1964**, 2515.

5. Williams, E. J.; Kenny, P. W.; Kettle, J. G. and Mwashimba, P. G., *Tetrahedron Lett*., **2004**, *45*, 3737.
6. (a) Paudler, W. W. and Pokorny, D. J., *J. Org. Chem.*, **1971**, *36*, 1720. (b) Brown, E. V. and Plasz, A. C., *J. Org. Chem.,* **1971**, *36*, 1331. (c) Brown, E. V. and Plasz, A. C., *J. Heterocycl. Chem.*, **1971**, *8*, 303.
7. LaLonde, R. T.; Woolever, J. T.; Auer, E. and Wong, C. F., *Tetrahedron Lett*., **1972**, 1503.
8. (a) Yoneda, R.; Kimura, T.; Kinomoto, J.; Harusawa, S. and Kurihara, T., *J. Heterocycl. Chem.*, **1996**, *33*, 1909. (b) Yoneda, R.; Sakamoto, Y.; Oketo, Y.; Harusawa, S. and Kurihara, T., *Tetrahedron*, **1996**, *52*, 14563. (c) Yoneda, R.; Sakamoto, Y.; Oketo, Y.; Minami, K.; Harusawa, S. and Kurihara, T. *Tetrahedron Lett*., **1994**, *35*, 3749.
9. (a) Blanchet, J.; Bonin, M.; Micouin, L. and Husson, H.-P., *Tetrahedron Lett*., **2000**, *41*, 8279. (b) Buston, J. E. H.; Coldham, I. and Mulholland, K. R., *Synlett*, **1997**, 322.
10. Enders, D. and Kempen, H., *Synlett*, **1994**, 969.
11. (a) Fulop, F. and Bernath, G., *Curr. Org. Chem.*, **1999**, *3*, 1. (b) Arnone, A.; Metrangolo, P.; Novo, B. and Resnati, G., *Tetrahedron*, **1998**, *54*, 7831. (c) Castagnoli, N.; Craig, J. C.; Melikian, A. P. and Roy, S. K., *Tetrahedron*, **1970**, *26*, 4319. (d) Wragg, A. H.; Stevens, T. S. and Ostle, D. M., *J. Chem. Soc.*, **1958**, 4057.

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Menke Nitration

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Menke in 1925.[1] It is a nitration of aromatic compounds with cupric nitrate and acetic anhydride. Therefore, it is known as the Menke nitration.[2] This reaction is generally suitable for the aromatics with an electron-donating substituent (activating group), such as amino, hydroxyl, and gives the highest ratio of *ortho*-product.[3] For example, the nitration of phenol with cupric nitrate in acetic acid yields only *othro*-nitrophenol, whereas picric acid is produced in acetic anhydride;[4] likewise, the nitration of aniline gives only *ortho*-nitroaniline.[4] Under the Menke condition, it has been found that the nitrate salts of iron,[4,5] manganese,[4] cobalt,[4,5] nickel,[4,5] copper,[4,5] mercury,[4] lithium,[4] aluminum,[5] cerium,[5] and uranium[5] are all effective for the nitration of aromatics. Among these inorganic nitrates, cupric nitrate is the most effective reagent.[4] It is believed that under these conditions, diacetyl *ortho*-nitric acid and acetyl nitrate might be generated, which are efficient nitrating agents;[4–6] in addition, the excess of humidity would be scavenged by acetic anhydride.[7] Although chloroform is the mostly used solvent, other solvents, such as hexane, cyclohexane, nitromethane, acetonitrile, methylene chloride, and nitrobenzene are also suitable for this reaction.[6] It should be pointed out that the nitration rate is faster in the solvent with a higher dielectric constant than that of a lower dielectric constant.[6] The original protocol has been improved to use acidic monmorillonite clay supported cupric nitrate, known as "claycop" as the nitrating agent in acetic anhydride, so that toluene can be quantitatively converted into nitrotoluene isomers.[8] It is interesting that the application of a clay (e.g., H-ZSM-5 zeolite) impregnated with cupric nitrate or ferric nitrate—containing large number of active sites in the interior regions of the channels—produces > 90% of *para*-nitro isomer during nitration of toluene.[9] In addition, by the use of excess amounts of such claycop (e.g., 48-fold) and small amounts of fuming nitric acid, polynitrated aromatics

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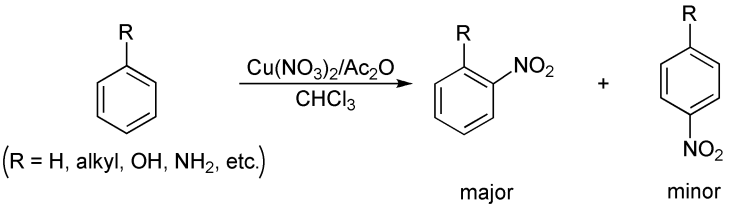
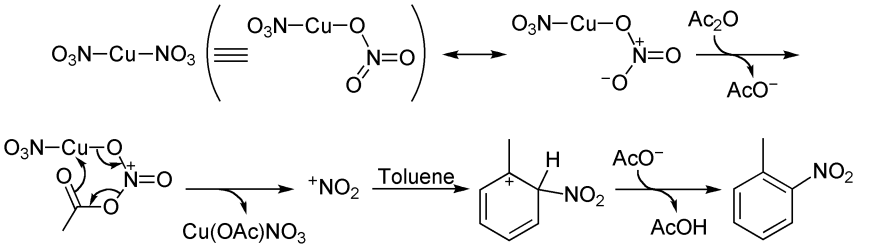
will be yielded. Under these conditions, not only the aromatics with an activating group will be nitrated but also those aromatics with deactivating groups, such as chlorobenzene and benzaldehyde, can be nitrated.[9] This reaction has been further extended to occur in trifluoroacetic anhydride to enhance the nitration yields.[6]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Although it has been reported that diacetyl *ortho*-nitric acid and acetyl nitrate might be the nitrating agents, it is proposed here that the reaction of cupric nitrate and acetic anhydride yields the nitronium ion as the real nitration agent, which adds preferably at the *ortho*-position of the aromatic, resulting in the *ortho*-nitrated product, as shown by the example of toluene. This is because the newly generated carbocation is a tertiary carbocation, which is closest to the electron-donating group.



D. MODIFICATION

The acidic monmorillonite clay-supported cupric nitrate has been applied to improve the yield;[8] in addition, the application of cupric nitrate impregnated on H-ZSM-5 zeolite with a large number of internal active regions has altered the regioselectivity of nitration.[9] Further modifications have adapted the combination of cupric nitrate and trifluoroacetic anhydride as the nitrating agent.[6]

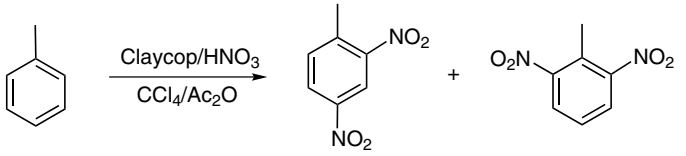
E. APPLICATIONS

This reaction has general application in the preparation of nitroaromatics with high *ortho*-selectivity.

F. RELATED REACTIONS

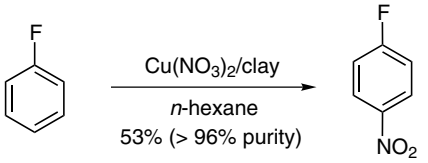
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 9.

To a suspension of 4.8 g claycop in 30 mL CCl_4 and 15 mL acetic anhydride was added 1.07 mL toluene (10 mmol). The mixture was stirred vigorously at room temperature and followed by GLC. The reaction mixture was then cooled in an ice bath, and 7.5 mL fuming nitric acid was added dropwise. After the addition, the reaction mixture was kept at room temperature with vigorous stirring until completion (∼4 h) and then filtered. The filter cake was washed with CCl_4, and the combined organic portions were washed with water and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to afford 95% dinitrotoluene with a 86:13 ratio of 2,4-dinitrotoluene to 2,6-dinitrotoluene.



Reference 10.

In a 1-L pear-shaped evaporating flask, were added 26 g cupric nitrate trihydrate and 400 mL acetone, and the mixture was vigorously stirred for ∼5 min. K10 clay (30 g) was then added, and stirring was continued for another 5 min. Then acetone was removed by rotary evaporation on a water bath at 50°C. After a dry solid crust adhered to the walls of the flask was flaked off with a spatula, and the rotary drying under vacuum was resumed for 30 min at the same temperature. This yielded the clay-supported cupric nitrate as a blue free-flowing powder.

To a solution of 0.96 g fluorobenzene (10 mmol) in 50 mL *n*-hexane was added 5 g clay-supported cupric nitrate and 9.4 mL acetic anhydride (100 mmol). The mixture was stirred vigorously at room temperature for 48 h, and then filtered under reduced pressure. The filter cake was washed with *n*-hexane, and the organic solvent was combined, dried, and evaporated. The residue was purified by silica gel column chromatography (cyclohexane/EtOAc, 9:1) to afford 53% nitrofluorobenzene, with 25:1 of *ortho*/*para* selectivity.

Other references related to Menke nitration are cited in the literature.[11]

H. REFERENCES

1. (a) Menke, J. B., *Brit. Pat.*, **1925**, June 25, 235,698. (b) Menke, J. B., *Recl. Trav. Chim. Pays-Bas*, **1925**, *44*, 141. (c) Menke, J. B., *Recl. Trav. Chim. Pays-Bas*, **1925**, *44*, 269. (d) Menke, J. B., *Recl. Trav. Chim. Pays-Bas*, **1925**, *44*, 270.
2. (a) Peng, X. H. and Lu, C. X., *Hanneng Cailiao*, **1995**, *3*, 27. (b) Velikorodov, A. V.; Maksimova, T. N. and Mochalin, V. B., *Izv. Vysshikh Uchebnykh Zavedenii, Khim. Khim. Tekh.,* **1992**, *35*, 16. (c) Ferlan, M., *Vestnik Slovenskega Kemijskega Drustva*, **1955**, *2*, 17.
3. Soeda, Y.; Takiguchi, D.; Kosaka, S. and Noguchi, T., *J. Agri. Food Chem.*, **1972**, *20*, 940.
4. Bacharach, G., *J. Am. Chem. Soc.*, **1927**, *49*, 1522.
5. Lacher, J. R.; Schwarz, J. and Park, J. D., *J. Org. Chem.*, **1961**, *26*, 2536.
6. Crivello, J. V., *J. Org. Chem.*, **1981**, *46*, 3056.
7. Delaude, L.; Laszlo, P. and Smith, K., *Acc. Chem. Res.*, **1993**, *26*, 607.
8. Kwok, T. J.; Jayasuriya, K.; Damavarapu, R. and Brodman, B. W., *J. Org. Chem.*, **1994**, *59*, 4939.
9. Gigante, B.; Prazeres, A. O.; Marcelo-Curto, M. J.; Cornelis, A. and Laszlo, P., *J. Org. Chem.*, **1995**, *60*, 3445.
10. Laszlo, P. and Pennetreau, P., *J. Org. Chem.*, **1987**, *52*, 2407.
11. (a) Varlamov, A. V.; Borisova, T. N. and Voskressensky, L. G., *Synthesis*, **2002**, 155. (b) Laszlo, P. and Vandormael, J., *Chem. Lett.*, **1988**, 1843. (c) Shine, H. J.; Park, K. H.; Brownawell, M. L. and Filippo, J. S., *J. Am. Chem. Soc.*, **1984**, *106*, 7077. (d) Williams, K. I. H.; Cremer, S. E.; Kent, F. W.; Sehm, E. J. and Tarbell, D. S., *J. Am. Chem. Soc.*, **1960**, *82*, 3982. (e) Paul, M. A., *J. Am. Chem. Soc.*, **1958**, *80*, 5332. (f) McKee, R. H. and Wilhelm, R. H., *Ind. Eng. Chem.*, **1936**, *28*, 662.

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Menschutkin Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Menschutkin in 1890.[1] It is a synthesis of a quaternary ammonium salt from a tertiary amine and an alkylating agent and is generally known as the Menschutkin reaction.[2,3] Occasionally, it is also called the Menschutkin alkylation.[4] Essentially, this reaction is a type of nucleophilic substitution and can occur via either an S_N1 or an S_N2 mechanism, thus it is widely used as a model reaction to study the substituent and solvent effects on the reaction mechanism.[2a,2f,2g,2i] For example, the reactions of benzylic systems with pyridine and *N*,*N*-dimethylanilines have been found to take place through an S_N2 mechanism with looser cationic transition states when the benzylic systems bear electron-donating groups, whereas an S_N1 mechanism is dominant for a comparable reaction of benzylic systems carrying electron-withdrawing groups. However, such reactions between benzylic systems and aromatic tertiary amines actually undergo independent S_N1 and S_N2 simultaneously.[5] For comparison, the reaction between pyridine derivatives and chloromethyl alkyl ethers or sulfides proceeds the S_N1 mechanism.[2b] On the other hand, the reaction rate is very sensitive to the polarity of the solvent, which varies by orders of magnitude among the solvents with different dielectric constants.[2a] In general, the reaction is fast in the solvents of high dielectric constants.[2k] In addition, it has been found that the "catalytic effect of small amount of 'active' co-solvents dissolved in 'inert' solvent is much larger than" predicted on the basis of purely dielectric constants.[2g] This reaction is highly endothermic, with free energy change in the range of 103–105 Kcal/mol.[6]

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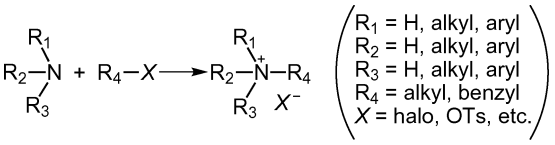
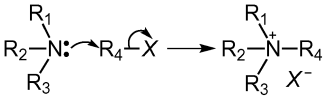
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Depending on the nature of alkylating agents, the reaction might take place via either an S_N1 or an S_N2 mechanism or both. Shown below is an S_N2 mechanism.



D. MODIFICATION

N/A

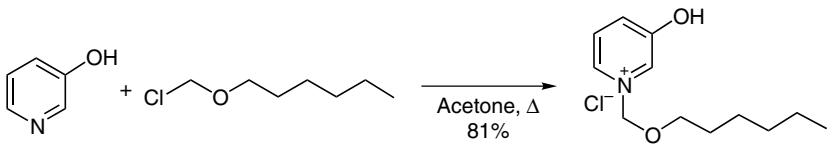
E. APPLICATIONS

This reaction is generally used for the preparation of quaternary ammonium salt.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 2b.

To 25 mL anhydrous acetone was added 20 mmol 3-hydroxypyridine and 22 mmol chloromethyl hexyl ether. The mixture was stirred and heated for 15 min and then kept at 0–5°C for 2 h, and filtered. The filtrate was dried by rotary evaporation at ∼ 45°C and

20 mmHg, washed with dry hexane, and then recrystallized from acetone. The hygroscopic product was dried overnight at 50°C and 8 mmHg.

Other references related to the Menschutkin reaction are cited in the literature.[7]

H. REFERENCES

1. (a) Menschutkin, N., *Z. Phys. Chem.*, **1890**, *5*, 58. (b) Menschutkin, N., *Z. Phys. Chem.*, **1890**, *5*, 589. (c) Menschutkin, N., *Z. Phys. Chem.*, **1890**, *6*, 41.
2. (a) Purse, B. W.; Gissot, A. and Rebek, J., *J. Am. Chem. Soc.*, **2005**, *127*, 11222. (b) Pernak, J. and Branicka, M., *Ind. Eng. Chem. Res.*, **2004**, *43*, 1966. (c) Lee, H.-S.; Cheong, D.-Y.; Yoh, S.-D.; Kim, W.-S.; Kwak, Y.-W.; Park, Y.-T. and Lee, J.-K., *Bull. Korean Chem. Soc*., **2001**, *22*, 633. (d) Kim, S. H.; Yoh, S.-D.; Kim, C.; Mishima, M.; Fujio, M. and Tsuno, Y., *J. Phys. Org. Chem.,* **1998**, *11*, 254. (e) Calado, A. R. T.; Pinheiro, L. M. V.; Albuquerque, L. M. P. C.; Goncalves, R. M. C.; Roses, M.; Rafols, C. and Bosch, E., *Coll. Czech. Chem. Commun.*, **1994**, *59*, 898. (f) Alemany, M. T.; Diez, M. T.; Arin, M. J. and Abboud, J.-L. M., *J. Phys. Chem.*, **1990**, *94*, 4491. (g) Abboud, J.-L. M.; Douhal, A.; Arin, M. J.; Diez, M. T.; Homan, H. and Guiheneuf, G., *J. Phys. Chem.*, **1989**, *93*, 214. (h) Sawada, M.; Takai, Y.; Chong, C.; Hanafusa, T. and Misumi, S., *Anal. Chem.*, **1986**, *58*, 231. (i) Schug, J. C.; Viers, J. W. and Seeman, J. I., *J. Org. Chem.*, **1983**, *48*, 4892. (j) Barnard, P. W. C. and Smith, B. V., *J. Chem. Edu.*, **1981**, *58*, 282. (k) Reinheimer, J. D.; Harley, J. D. and Meyers, W. W., *J. Org. Chem.*, **1963**, *28*, 1575. (l) Harman, D.; Stewart, T. D. and Ruben, S., *J. Am. Chem. Soc.*, **1942**, *64*, 2294.
3. (a) Yoh, S.-D.; Cheong, D.-Y. and Lee, O.-S., *J. Phys. Org. Chem.*, **2003**, *16*, 63. (b) Markgraf, J. H.; Sangani, P. K.; Manalansan, R. J.; Snyder, S. A. and Thummel, R. P., *J. Chem. Res. (S)*, **2000**, 561. (c) Hossain, D. and Morshed, M. M., *J. Bangladesh Acad. Sci.*, **1998**, *22*, 39. (d) Lim, C.; Kim, S.-H.; Yoh, S.-D.; Fujio, M. and Tsuno, Y., *Tetrahedron Lett*., **1997**, *38*, 3243. (e) Pinheiro, L. M. V.; Calado, A. R. T. and Viana, C. A. N., *AIP Conference Proceedings*, **1994**, *309*, 1329. (f) Jenkins, H. D. B.; Kelly, E. J. and Samuel, C. J., *Tetrahedron Lett*., **1994**, *35*, 6543. (g) Awwal, A.; Miah, A. S.; Kabir, M. and Muslim, M., *J. Bangladesh Acad. Sci.*, **1993**, *17*, 231. (h) Goncalves, R. M. C.; Calado, A. R. T.; Pinheiro, L. M. V.; Albuquerque, L. M. P. C. and Macedo, E. A., *J. Phys. Org. Chem.*, **1993**, *6*, 595. (i) Kang, S. G.; Jung, S. K.; Kim, M. S.; Park, J. H. and Yoh, S. D., *Bull. Chem. Soc. Jpn.*, **1993**, *66*, 972. (j) Viana, C. A. N.; Calado, A. R. T. and Pinheiro, L. M. V., *J. Chem. Res. (S)*, **1992**, 6. (k) Chen, L. P. and Han, S. J., *Huaxue Wuli Xuebao*, **1991**, *4*, 170. (l) Pillay, M. K.; Jeyaraman, R. and Nallu, M., *Indian J. Chem., Sect. A*, **1991**, *30A*, 432. (m) Kondo, Y.; Kambe, H. and Kusabayashi, S., *J. Chem. Soc., Perkin Trans. II*, **1990**, 915. (n) Alemany, M. T.; Diez, M. T.; Arin, M. J. and Abboud, J. L. M., *J. Phys. Chem.*, **1990**, *94*, 4491. (o) Kohjiya, S.; Ohtsuki, T. and Yamashita, S., *Makromol. Chem.*, **1990**, *191*, 397. (p) Yoh, S.-D. and Kim, J. H., *Taehan Hwahakhoe Chi*, **1989**, *33*, 413. (q) Abboud, J. L. M.; Douhal, A.; Arin, M. J.; Diez, M. T.; Homan, H. and Guiheneuf, G., *J. Phys. Chem.*, **1989**, *93*, 214. (r) Kondo, Y.; Uematsu, R.; Nakamura, Y. and Kusabayashi, S., *J. Chem. Soc., Perkin Trans. II*, **1988**, 1219. (s) Yoh, S. D.; Park, J. H.; Lee, K. A. and Han, I. S., *Bull. Chem. Soc. Jpn.*, **1987**, *60*, 1149. (t) Elshafie, S. M. M., *Egypt. J. Chem.*, **1986**, *29*, 659. (u) Ando, T.; Yamataka, H. and Wada, E., *Isr. J. Chem.*, **1985**, *26*, 354. (v) Sawada, M.; Takai, Y.; Chong, C.; Hanafusa, T.; Misumi, S. and Tsuno, Y., *Tetrahedron Lett*., **1985**, *26*, 5065. (w) Yoh, S. D.; Tsuno, Y. and Yukawa, Y., *Taehan Hwahakhoe Chi*, **1984**, *28*, 433. (x) Viers, J. W.; Schug, J. C.; Stovall, M. D. and Seeman, J. I., *J. Compt. Chem.*, **1984**, *5*, 598. (y) Kondo, Y.; Ogasa, M. and Kusabayashi, S., *J. Chem. Soc., Perkin Trans. II*, **1984**, 2093. (z) Matsumoto, K.; Hashimoto, S.; Ikemi, Y. and Otani, S., *Heterocycles*, **1984**, *22*, 1417. (aa) Balmares, H. and Ernesto Castillo, Y. J., *Revista Soc. Quim. Mexico*, **1981**, *25*, 541. (bb) Claramunt, R. M.; Gallo, R.; Elguero, J.; Mathieu, D. and Phan Tan Luu, R., *J. Chim. Phys. Phys. –Chim. Biol.*, **1981**, *78*, 805. (cc) Abraham, M. H. and Nasehzadeh, A., *J.*

Chem. Soc., Chem. Commun., **1981**, 905. (dd) Kevill, D. N., *J. Chem. Soc., Chem. Commun.*, **1981**, 421. (ee) Schaper, K. J., *Arch. Pharm.*, **1978**, *311*, 650. (ff) Schaper, K. J., *Arch. Pharm.,* **1978**, *311*, 641. (gg) Seeman, J. I.; Secor, H. V.; Whidby, J. F. and Bassfield, R. L., *Tetrahedron Lett*., **1978**, 1901. (hh) Saheki, Y.; Kimura, M. and Negoro, K., *Nippon Kagaku Kaishi*, **1978**, 1123. (ii) Abraham, M. H. and Abraham, R. J., *J. Chem. Soc., Perkin Trans. II*, **1975**, 1677. (jj) Yamataka, H. and Ando, T., *Tetrahedron Lett*., **1975**, 1059. (kk) Pankova, M.; Krupicka, J. and Zavada, J., *Coll. Czech. Chem. Commun.*, **1974**, *39*, 167. (ll) Ottenbrite, R. M. and Myers, G. R., *Can. J. Chem.*, **1973**, *51*, 3631. (mm) Tamura, K.; Ogo, Y. and Imoto, T., *Bull. Chem. Soc. Jpn.*, **1973**, *46*, 2988. (nn) Leffek, K. T. and Matheson, A. F., *Can. J. Chem.*, **1972**, *50*, 986. (oo) Brauer, H. D. and Kelm, H., *Zeit. Phys. Chem.*, **1971**, *76*, 98. (pp) Undheim, K. and Groenneberg, T., *Acta Chem. Scand*., **1971**, *25*, 18. (qq) Matsui, T. and Tokura, N., *Bull. Chem. Soc. Jpn.*, **1970**, *43*, 1751. (rr) Abraham, M. H., *J. Chem. Soc. D*, **1969**, 1307. (ss) Hartmann, H. and Schmidt, A. P., *Zeit. Phys. Chem.*, **1968**, *62*, 312. (tt) Pozharskii, A. F.; Chegolya, T. N. and Simonov, A. M., *Khim. Geterotsiklicheskikh Soedinenii*, **1968**, 503. (uu) Sicher, J.; Tichy, M.; Zavada, J. and Krupicka, J., *Coll. Czech. Chem. Commun.*, **1968**, *33*, 1438. (vv) Okamoto, K.; Fukui, S.; Nitta, I. and Shingu, H., *Bull. Chem. Soc. Jpn.*, **1967**, *40*, 2354. (ww) Okamoto, K.; Fukui, S.; Nitta, I. and Shingu, H., *Bull. Chem. Soc. Jpn.,* **1967**, *40*, 2350. (xx) Heydtmann, H., *Zeit. Phys. Chem.*, **1967**, 54, 237. (yy) Leffek, K. T. and MacLean, J. W., *Can. J. Chem.*, **1965**, *43*, 40. (zz) Fischer, A.; Galloway, W. J. and Vaughan, J., *J. Chem. Soc.*, **1964**, 3596. (aaa) Tokura, N. and Kondo, Y., *Bull. Chem. Soc. Jpn.*, **1963**, *36*, 200. (bbb) Stewart, J. M. and Weale, K. E., *Proc. Chem. Soc.*, **1961**, 389. (ccc) Harris, A. P. and Weale, K. E., *J. Chem. Soc.*, **1961**, 146. (ddd) Popovici, S. and Pop, M., *Compt. Rend.*, **1957**, *244*, 351. (eee) Li, T.-C.; Li, W.-C. and Sun, C.-E., *Huaxue Xuebao*, **1956**, *22*, 386. (fff) Hamann, S. D., *Aust. J. Chem.*, **1956**, *9*, 533. (ggg) Petrachkov, F. A. and Gol'tschmidt, V. A., *Zh. Fizicheskoi Khim.*, **1954**, *28*, 1213. (hhh) Bunton, C. A.; Greenstreet, C. H.; Hughes, E. D. and Ingold, C. K., *J. Chem. Soc.*, **1954**, 647.

4. Fountain, K. R.; Hutchinson, L. K.; Mulhearn, D. C. and Xu, Y. B., *J. Org. Chem.*, **1993**, *58*, 7883.
5. Yoh, S.D.; Lee, M.-K.; Son, K.-J.; Cheong, D.-Y.; Han, I.-S. and Shim, K.-T., *Bull. Korean Chem. Soc.*, **1999**, *20*, 466.
6. Shaik, S.; Ioffe, A.; Reddy, A. C. and Pross, A., *J. Am. Chem. Soc.*, **1994**, *116*, 262.
7. (a) Mineva, T.; Russo, N. and Sicilia, E., *J. Comput. Chem.*, **1998**, *19*, 290. (b) Levillain, J. and Vazeux, M., *Synthesis*, **1995**, 56. (c) Abboud, J.-L. M.; Notario, R.; Bertrán, J. and Solà, M. *Prog. Phys. Org. Chem.*, **1993**, *19*, 1. (d) Azzaro, M. and Metztzger, J., *Bull. Soc. Chim. Fr.*, **1964**, 1575. (e) Henderson, W. A. and Schultz, C. J., *J. Org. Chern.,* **1962**, *27*, 4643. (f) Watanabe, M. and Fuoss, R. M., *J. Am. Chem. Soc.*, **1956**, *78*, 527. (g) Brown, H. C. and Cahn, A., *J. Am. Chem. Soc*., **1955**, *77*, 1715.

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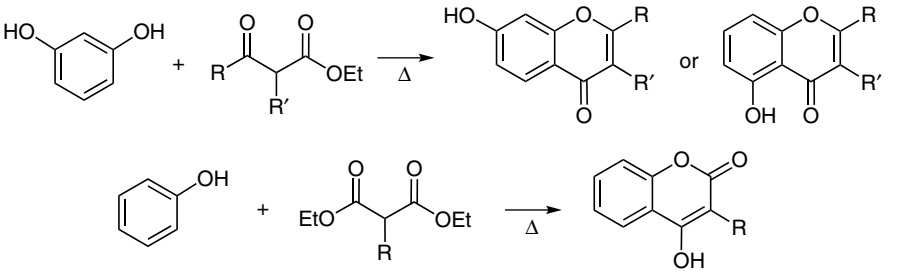
Mentzer Pyrone Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Mentzer et al. in 1946.[1] It is a synthesis of pyrone or flavone derivatives from the reaction between phenols and β-ketoesters[2] or malonates.[3] This reaction is normally carried out by cooking the mixture at high temperature for a long period.[2]

B. GENERAL REACTION SCHEME



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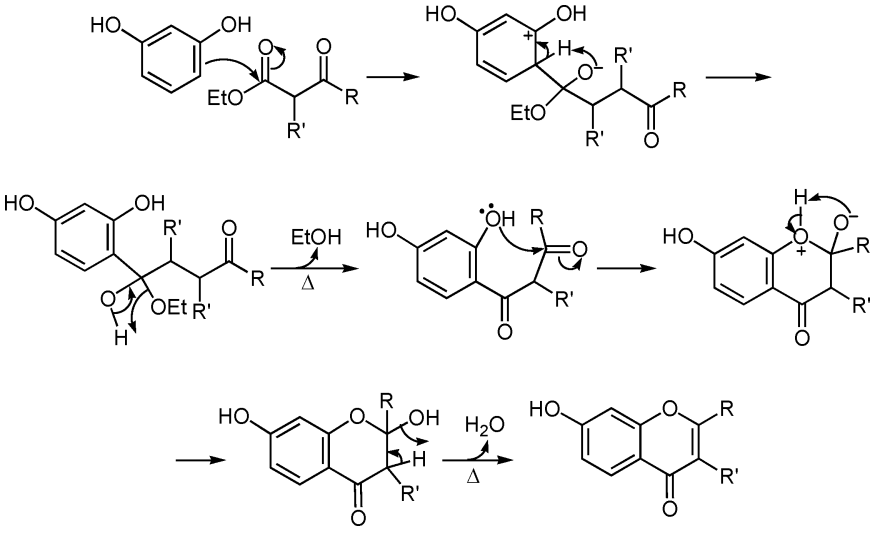
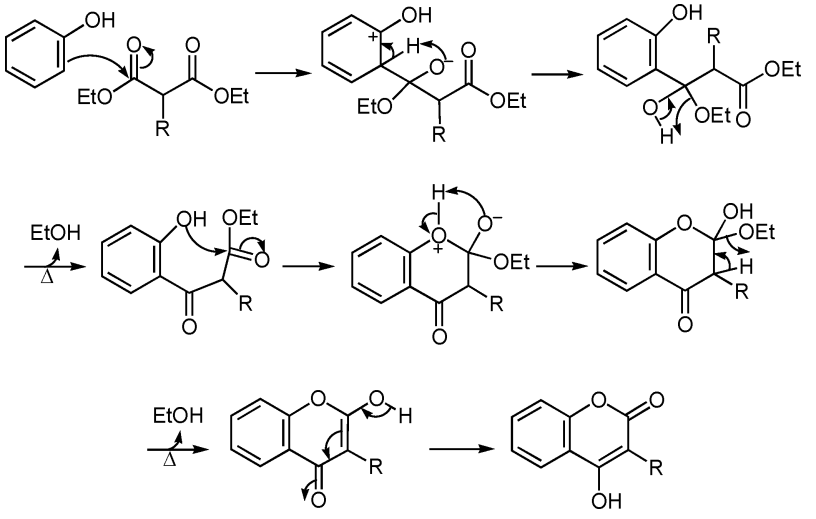
C. PROPOSED MECHANISMS

The mechanism for the reaction between a phenol and a β-ketoester is demonstrated in Scheme 1, and the reaction between a phenol and a dialkyl malonate is outlined in Scheme 2.



SCHEME 1. *Reaction mechanism between phenol and β-ketoester.*



SCHEME 2. *Reaction mechanism between phenol and dialkyl malonate.*

D. MODIFICATION

This reaction has been modified to occur under microwave irradiation.[2]

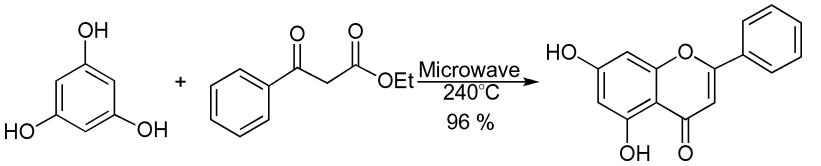
E. APPLICATIONS

This reaction can be used to prepare pyrone and flavone derivatives.

F. RELATED REACTIONS

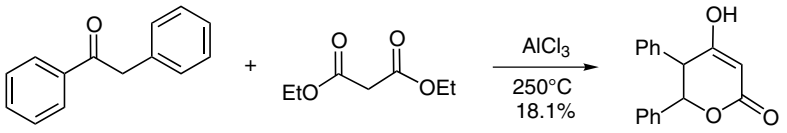
This reaction is related to the *Pechman Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2.

A mixture of 384 mg ethyl benzoyl acetate (2 mmol) and 126 mg phloroglucinol (1 mmol) was irradiated with microwaves (ETHOS D, Millestone, at 80% of a total output of 1000 W or with the temperature control set to 240°C) for 3 min. The crude was dissolved in 20 mL 10% aqueous NaOH solution and washed with Et_2O (2 × 20 mL). Then the aqueous layer was acidified with conc. HCl. The precipitate was filtered, washed with water, and vacuum dried to give 243 mg chrysin, in a yield of 96%, m.p., 288–290°C (dichloromethane-methanol).



Reference 3.

A mixture of 8.0 g diethyl malonate and 9.8 g deoxybenzoin in the presence of 500 mg anhydrous aluminum chloride was heated at 250°C for 1 h. The cold reaction mixture was poured onto water, and NaOH was added. The aqueous solution was washed with ether, and the aqueous layer was acidified with HCl. The aqueous acid solution was extracted with ether, and the organic layers were combined, dried over Na_2SO_4, and concentrated to afford 2.4 g 4-hydroxy-5,6-diphenyl-2-pyrone as an oil that solidified upon standing, in a yield of 18.1%. The solid was triturated with ether to remove soluble impurities and recrystallized from methanol to give a white solid, m.p. 187–188°C.

Other references related to the Mentzer pyrone synthesis are cited in the literature.[4]

H. REFERENCES

1. Molho, D. and Mentzer, C., *Compt. Rend.,* **1946**, *223*, 1141.
2. Seijas, J. A.; Vazquez-Tato, M. P. and Carballido-Reboredo, R., *J. Org. Chem.,* **2005**, *70*, 2855.
3. Padwa, A. and Hartman, R., *J. Am. Chem. Soc.,* **1966**, *88*, 3759.
4. (a) Gotschel, C. and Mentzer, C., *Bull. Soc. Chim. Fr.,* **1962**, 365. (b) Gowan, J. E.; Riogh, S. P. M.; McMahon, G. J.; O'Farrell, B. R.; O'Cleirigh, S.; Philbin, E. M. and Wheeler, T. S., *Chem. Ind.,* **1955**, 1672. (c) Lacey, R. N., *J. Chem. Soc.,* **1954**, 856. (d) Pillon, D., *Bull. Soc. Chim. Fr.,* **1954**, 9. (e) Mentzer, C. and Vercier, P., *Compt. Rend.,* **1952**, *232*, 1674. (f) Pillon, D., *Compt. Rend.,* **1952**, *234*, 444. (g) Mentzer, C.; Molho, D. and Vercier, P., *Compt. Rend.,* **1951**, *232*, 1488. (h) Djerassi, C., *Chem. Rev.,* **1948**, *43*, 271.

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Merrifield Solid-Phase Peptide Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Merrifield in 1963.[1] It is a synthesis of peptides and small proteins in which the resinous polymer supported amino acid and succeeding peptide repeatedly reacts with *N*-protected amino acids followed by deprotection until the desired peptide or protein is assembled. Therefore, it is generally referred to as the Merrifield solid-phase peptide synthesis[2] (or SPPS[3]), and the polymeric resin—that is, 1% divinylbenzene cross-linked polystyrene resin—is known as the Merrified resin.[4] This reaction, essentially because of the macroscopical insolubility of the resin in the chosen solvent,[2d] has made peptide synthesis economical, simple, and rapid, which can be automatically carried out due to its repetitive, stepwise nature.[2d] The initial protocol using *N*-benzyloxycarbonyl-protected amino acid has been improved and developed into two complementary methods. In the first method,[3] the *N*-*t*-butyloxycarbonyl (Boc) protected amino acid is attached to the solid phase via a linker moiety, the Boc group is then cleaved by trifluoroacetic acid, and the resin is neutralized by a tertiary amine; subsequently, the second *N*-Boc amino acid is added and linked to the resin in the presence of an activator. After the reaction completes, the resin containing the peptide is washed thoroughly with solvent to remove the unreacted material, and Boc is removed again in a similar manner to start a new coupling cycle until the desired sequence of peptide (or small protein) is reached, and the peptide (or small protein) is cleaved off from the resin by HF. By the same time, other protecting groups on the side chains of amino acids are also removed. The second protocol uses 9-fluorenylmethyloxycarbonyl (Fmoc) as the amino protecting group, which can be easily cleaved by piperidine in DMF or *N*-methylpyrrolidone. After the peptide synthesis, the small protein or peptide is released from the solid linker by the use of trifluoroacetic acid. However, it has been found that the ongoing peptide chain may stop growing or lead to a low

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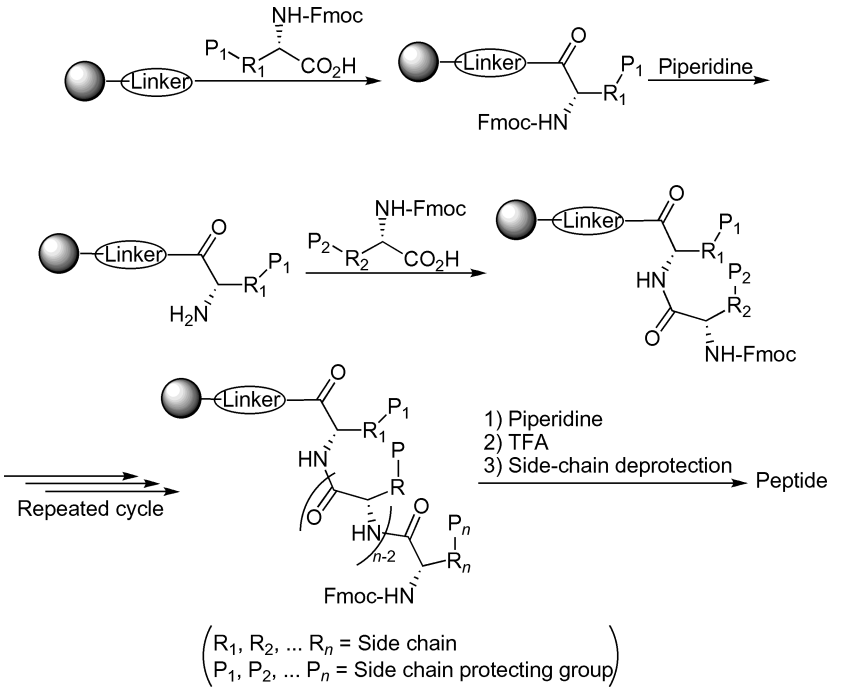
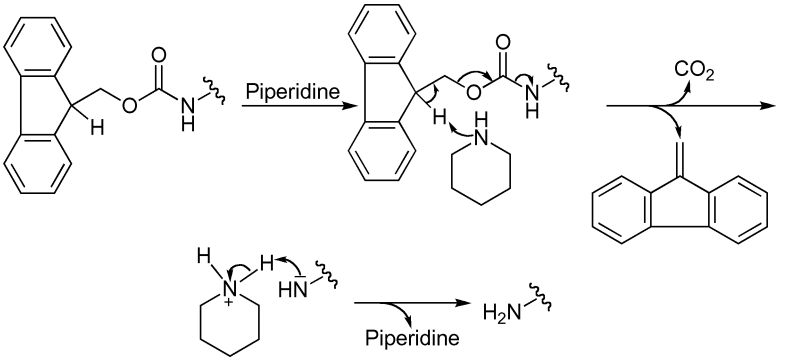
yield of peptide,[2i] due to the association of the peptide chain, the swelling problem of the resin, etc.;[2d] in this case, the application of a mixed solvent of CH_2Cl_2 and DMF apparently enhances the result.[2i] This method has been extended to oligonucleotide synthesis.[5]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The deprotection of Fmoc group by piperidine is displayed here.



D. MODIFICATION

This reaction has been modified extensively by application of different linkers, side chain protecting groups, and different solvent systems.

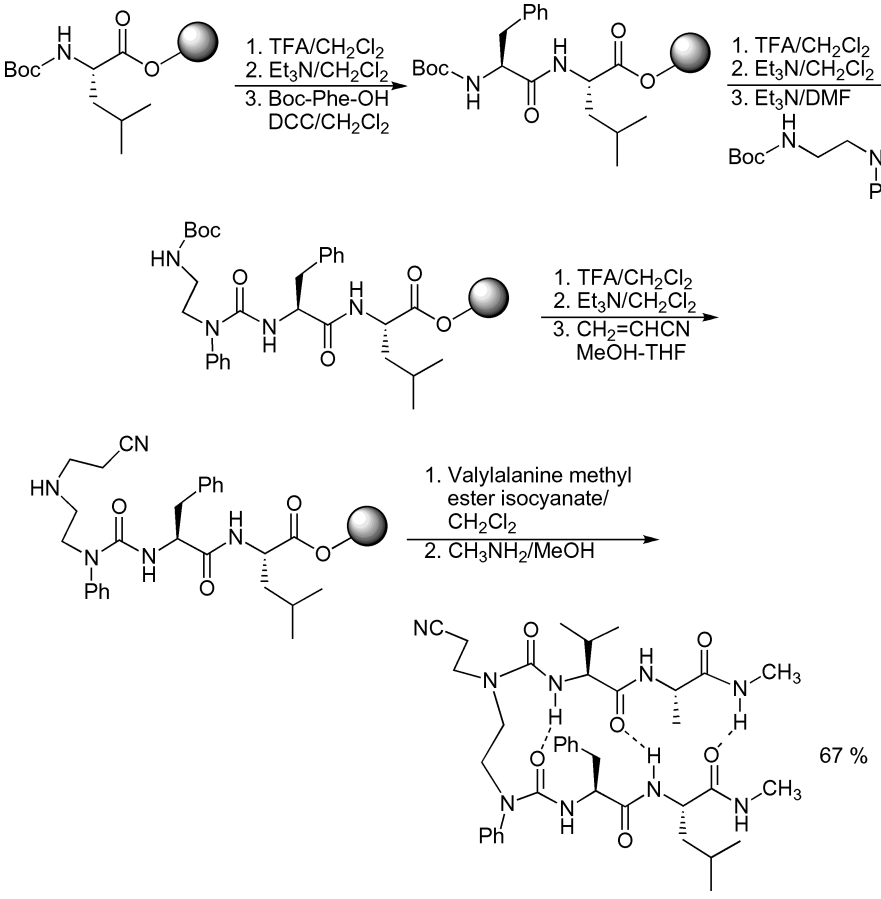
E. APPLICATIONS

This reaction has been widely used for the synthesis of peptides and small proteins.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 4.

A 50-mL solid-phase reaction vessel was charged with 1.50 g Boc-leucine Merrified resin (0.80 mmol/g, 1.20 mmol). The resin was washed with CH_2Cl_2 (6 × 20 mL) and 20 mL of CH_2Cl_2/TFA/indole solution and was then shaken with 20 mL CH_2Cl_2/TFA/indole solution for 30 min. The solution was drained, and the resin was washed with CH_2Cl_2 (6 × 20 mL), CH_2Cl_2/Et_3N (10:1, v/v) (2 × 20 mL) and CH_2Cl_2 (6 × 20 mL). The resin was shaken with 796 mg *N*-Boc-Phe-OH (3.00 mmol), 3.0 mL 1.0 M DCC in CH_2Cl_2 (3.0 mmol), and 15 mL CH_2Cl_2 for 2 h. The resulting white suspension was filtered, and the residue was washed with 20 mL CH_2Cl_2 and EtOH (3 × 20 mL) to afford white beads.

These white resin beads were washed with CH_2Cl_2 (6 × 20 mL) and 20 mL of CH_2Cl_2/TFA/indole solution, and then shaken with 20 mL CH_2Cl_2/TFA/indole for 30 min. The solution was drained, the resin was washed with CH_2Cl_2 (6 × 20 mL) and CH_2Cl_2/Et_3N (10:1, v/v) (2 × 20 mL), CH_2Cl_2 (6 × 20 mL), and EtOH (3 × 20 mL). The resin was dried in vacuo and transferred to a 25-mL, round-bottomed flask, and gently stirred with 20 mL DMF, 1.20 mL Et_3N (8.61 mmol), and 1.08 g carbamoyl chloride at 50°C for 2 h. The suspension was transferred back to the 50-mL solid-phase reaction vessel and filtered, and the resin was washed with 20 mL DMF and CH_2Cl_2 (3 × 20 mL) to give pale tan beads.

The pale tan resin was washed with CH_2Cl_2 (3 × 20 mL) and 20 mL CH_2Cl_2/TFA/indole solution, and then shaken with 20 mL CH_2Cl_2/TFA/indole solution for 30 min. The solution was drained, and the resin was washed with CH_2Cl_2 (6 × 20 mL), CH_2Cl_2/Et_3N (10:1, v/v) (2 × 20 mL), and CH_2Cl_2 (6 × 20 mL). The resin was washed with THF (3 × 20 mL) and shaken with a solution of THF/MeOH/acrynitrile (15 mL, 5 mL, 5 mL) for 12 h. The solution was drained, and the resin was washed with CH_2Cl_2 (3 × 20 mL) to yield a new pale tan resin, which was shaken with 20 mL CH_2Cl_2 and 488 mg valylalanine methyl ester isocyanate (1.4 mmol) for 3.5 h. The solution was drained, and the resin was washed with CH_2Cl_2 (3 × 20 mL), and shaken with 20 mL 10 M methylamine in MeOH for 17 h. The solution was collected, the resin was washed with MeOH (2 × 20 mL), and the combined methylamine solution and MeOH washes were concentrated by rotary evaporation. The methylamine treatment and MeOH washing of the resin were repeated, and the combined residue from both treatments were concentrated by rotary evaporation to afford 769 mg of a white solid. Silica gel column chromatography (MeOH-$CHCl_3$) followed by radial-thin layer chromatography (*i*-PrOH-$CHCl_3$, 1:20) afforded 587 mg artificial β-sheet as a white foam, in a total yield of 67%.

Other references related to the Merrifield solid-phase peptide synthesis are cited in the literature.[6]

H. REFERENCES

1. Merrifield, R. B., *J. Am. Chem. Soc.*, **1963**, *85*, 2149.
2. (a) Lipinski, C. A., *Drug Delivery Today*, **2003**, *8*, 12. (b) Felix, A. M., *Kobunshi*, **2002**, *51*, 630. (c) Kahn, M. and Bertenshaw, S., *Tetrahedron Lett*., **1989**, *30*, 2317. (d) Ludwick, A. G.; Jelinski, L. W.; Live, D.; Kintanar, A. and Dumais, J. J., *J. Am. Chem. Soc.,* **1986**, *108*, 6493. (e) Sallay, S. I. and Oroszlan, S., *Chromatographic Sci. Ser.*, **1979**, *10*, 199. (f) Badawi, M. M.; Abdel Kader, M. M. and Madkour, M. K., *J. Drug Res.*, **1974**, *6*, 157. (g) Monahan, M. W. and Gilon, C., *Biopolymers*, **1973**, *12*, 2513. (h) Westall, F. C.; Scotchler, J. and Robinson, A. B., *J. Org. Chem.*, **1972**, *37*, 3363. (i) Westall, F. C. and Robinson, A. B., *J. Org. Chem.*, **1970**, *35*, 2842. (j) Lenard, J. and Robinson, A. B., *J. Am. Chem. Soc.*, **1967**, *89*, 181.

3. Borgia, J. A. and Fields, G. B., *TIBTECH*, **2000**, 18, 243.
4. Holmes, D. L.; Smith, E. M. and Nowick, J. S., *J. Am. Chem. Soc.*, **1997**, *119*, 7665.
5. Caruthers, M., *Science*, **1985**, *230*, 281.
6. (a) Roussa, E.; Nastainczyk, W. and Thevenod, F., *Biochem. Biophys. Res. Commun.*, **2004**, *314*, 382. (b) Basharov, M. A., *J. Cell. Mol. Med.*, **2003**, *7*, 223. (c) Cruz, B. H.; Diaz-Cruz, J. M.; Sestakova, I.; Velek, J.; Arino, C. and Esteban, M., *J. Electroanal. Chem.*, **2002**, *520*, 111. (d) Roychoudhury, S.; Blondelle, S. E.; Collins, S. M.; Davis, M. C.; McKeever, H. D.; Houghten, R. A. and Parker, C. N., *Molecular Diversity*, **1998**, *4*, 173. (e) O'Donnell, M. J.; Zhou, C. Y. and Scott, W. L., *J. Am. Chem. Soc.*, **1996**, *118*, 6070. (f) Merrifield, R. B., "Solid-Phase Peptide Synthesis," in *Peptides: Synthesis, Structures and Applications*, ed. Gutte, B., Academic Press, San Diego, **1995**, pp. 93–169. (g) Smith, D. D.; Conlon, J. M.; Petzel, J.; Chen, L.; Murphy, R. F. and Morley, B. J., *Int. J. Peptide Protein Res.*, **1994**, *44*, 183. (h) Larsen, B. D.; Christensen, D. H.; Holm, A.; Zillmer, R. and Nielsen, O. F., *J. Am. Chem. Soc.*, **1993**, *115*, 6247. (i) Merrifield, R. B., *Science*, **1986**, *232*, 341. (j) Tam, J. P.; Heath, W. F. and Merrified, R. B., *J. Am. Chem. Soc.*, **1983**, *105*, 6442. (k) Bhargava, K. K.; Sarin, V. K.; Trang, N. L.; Cerami, A. and Merrifield, R. B., *J. Am. Chem. Soc.*, **1983**, *105*, 3247. (l) Rebek, J. and Trend, J. E., *J. Am. Chem. Soc.*, **1979**, *101*, 737. (m) Farrall, M. J. and Frechet, J. M. J., *J. Am. Chem. Soc.*, **1978**, *100*, 7998. (n) Leznoff, C. C., *Chem. Soc. Rev.*, **1974**, *3*, 65. (o) Carpino, L. A. and Han, G. Y., *J. Org. Chem.*, **1972**, *37*, 3404. (p) Gutte, B. and Merrifield, R. B., *J. Biol. Chem.*, **1971**, *246*, 1722. (q) Stewart, J. M. and Young, J. D., *Solid Phase Peptide Synthesis*, W. H. Freeman, New York, **1969**. (r) Marshall, G. R. and Merrifield, R. B., *Biochemistry*, **1965**, *4*, 2394. (s) Merrifield, R. B., *J. Am. Chem. Soc.*, **1964**, *86*, 304. (t) Merrifield, R. B., *Biochemistry*, **1964**, *3*, 1385.

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Meyer-Hartmann Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Hartmann and Meyer in 1894.[1] It is the formation of diaryliodonium salt from the reaction between iodosobenzene (PhIO) and iodoxybenzene ($PhIO_2$) in the presence of silver (I) oxide, known as the Meyer-Hartmann reaction.[2] It has been reported that the mixture of an equal amount of iodosobenzene and iodoxybenzene is converted into diphenyliodonium hydroxide in the presence of alkali,[3] and the resulting diaryliodonium salt shows the chemical properties of ammonium hydroxide, thus termed a diaryliodonium salt.[4] In addition, iodoxybenzene itself could be converted to diphenyliodonium hydroxide under similar conditions.[5] Therefore, it is believed that silver (I) oxide, when mixed with water or moisture, hydrates and causes basicity. What is more, this reaction even takes place in the presence of a catalytic amount of silver (I) oxide.[6] It is the iodine atom in iodosobenzene that enters into the diphenyliodonium ion, whereas the iodine atom in iodoxybenzene is oxidized to iodate.[2] Although this reaction is time-consuming,[7] it is still the major method for preparing diaryliodonium salt, from which other iodonium salts can be prepared.[8] The diaryliodonium salt has wide application in industry. For example, it is commonly used for lithography and as a polymerization initiator.[9] A similar reaction for preparing *p*-iodophenyl phenyliodonium bisulfate has also been developed by Meyer and Hartman through the treatment of iodosobenzene with concentrated sulfuric acid.[10]

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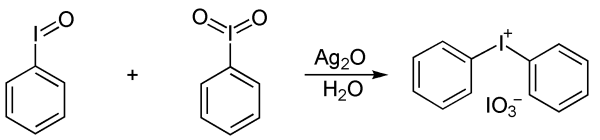
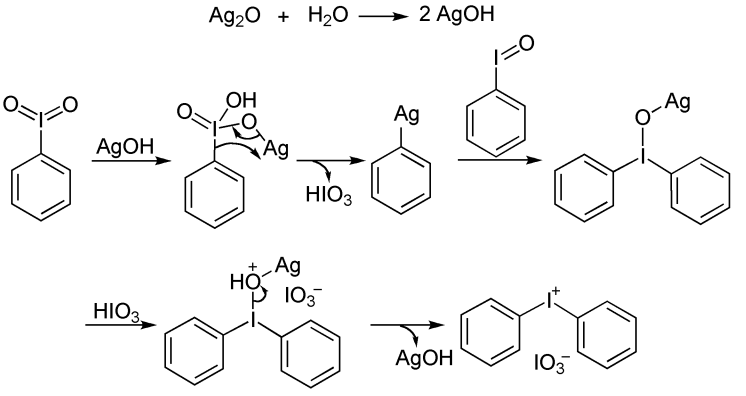
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A tentative mechanism is proposed here, which explains that only a catalytic amount of silver (I) oxide is required. Between iodosobenzene and iodoxybenzene, the latter has a higher tendency for silver hydroxide to attack because of its higher valent iodine atom. Upon cleavage of hydrogen iodate, phenyl silver forms, which then adds to iodosobenzene. Successive protonation from hydrogen iodate facilitates the formation of diphenyliodonium iodate and the cleavage of silver hydroxide, which enters another catalytic cycle. The slow reaction rate might arise from the gradual hydration of Ag_2O and the slow addition of silver hydroxide to iodoxybenzene.



D. MODIFICATION

This reaction has been modified by the replacement of Ag_2O with sodium hydroxide.[3]

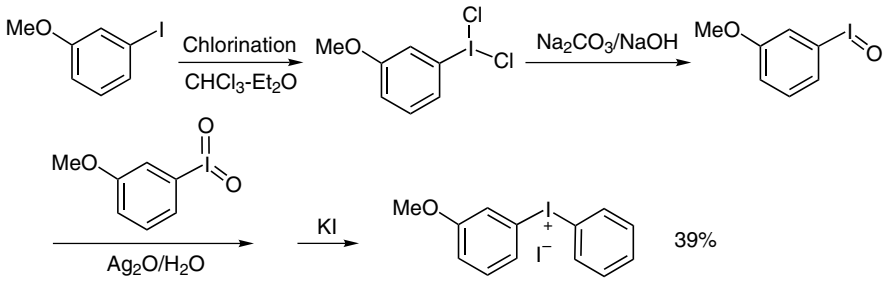
E. APPLICATIONS

This reaction can be applied to the preparation of diaryliodonium salts.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 11.

3-Iodoanisole (20 g, 85.5 mmol) was chlorinated in a chilled chloroform-ether mixture. Chilling with dry ice was necessary to precipitate the dichloride, which was air dried and weighed 15.7 g (51.6 mmol, 60%), m.p. 62–64°C. It was then hydrolyzed with 13 g Na_2CO_3 and 35 mL 5 *N* NaOH, washed with water and acetone, and dried at 50°C under vacuum to afford 7.3 g 3-methoxyiodosobenzene (29.2 mmol, 52%). This compound was shaken in an amber jar for 40 h with 7 g iodoxybenzene, 1 L water and Ag_2O freshly precipitated from 15 g $AgNO_3$. After filtration and clarification of the resultant solution, addition of a KI solution yielded 5 g 3-methoxydiphenyliodonium iodide (11.4 mmol), in a yield of 39%, m.p. 176–177°C (Fisher-Johns apparatus, inserted at 100°C).

Other references related to the Meyer-Hartmann reaction are cited in the literature.[12]

H. REFERENCES

1. Hartmann, C. and Meyer, V., *Ber.*, **1894**, *27*, 502.
2. Bothner-By, A. A. and Vaughan, C. W., *J. Am. Chem. Soc.*, **1952**, *74*, 4400.
3. Lucas, H. J. and Kennedy, E. R., *Org. Synth.*, **1942**, *22*, 52.
4. Tsarevsky, N.; Slaveykova, V.; Manev, S. and Lazarov, D., *J. Chem. Edu.*, **1997**, *74*, 734.
5. Masson, I.; Race, E. and Pounder, F. E., *J. Chem. Soc.*, **1935**, 1669.
6. Lucas, H. J.; Kennedy, E. R. and Wilmot, C. A., *J. Am. Chem. Soc.*, **1936**, *58*, 157.
7. Beringer, F. M.; Drexler, M.; Gindler, E. M. and Lumpkin, C. C., *J. Am. Chem. Soc.*, **1953**, *75*, 2705.
8. Banks, D. F., *Chem. Rev.*, **1966**, *66*, 243.
9. Stang, P. J. and Zhdankin, V. V., *Chem. Rev.*, **1996**, *96*, 1123.
10. Hartmann, C. and Meyer, V., *Ber.*, **1894**, *27*, 426.
11. Beringer, F. M. and Lillien, I., *J. Am. Chem. Soc.*, **1960**, *82*, 725.
12. (a) Beringer, F. M. and Nathan, R. A., *J. Org. Chem.*, **1969**, *34*, 685. (b) Aten, J. B. Th. And Aten, A. H. W., *J. Am. Chem. Soc.*, **1952**, *74*, 2411. (c) Bothner-By, A. A. and Medalia, A. I., *J. Am. Chem. Soc.*, **1952**, *74*, 4402. (d) Sandin, R. B., *Chem. Rev.*, **1943**, *32*, 249. (e) Hartmann, C. and Meyer, V., *Ber.*, **1894**, *27*, 1592.

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Meyers Aldehyde Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Meyers in 1969.[1] It is a 4,4,6-trimethyl-5,6-dihydro-1,3-oxazines-based aldehyde synthesis involving the steps of deprotonation, alkylation, reduction, and hydrolytic cleavage of the 1,3-oxazine ring. Therefore, it is known as the Meyers aldehyde synthesis.[2] During this process, the 5,6-dihydro-1,3-oxazines can be readily prepared from the condensation of 2-methyl-2,4-pentanediol and nitrile in concentrated sulfuric acid at 0°C.[3] The resulting 5,6-dihydro-1,3-oxazine is deprotonated by a lithium reagent, and then alkylated with an alkyl halide. The alkylated product is subsequently reduced by sodium borohydride or deuterium borohydride to tetrahydro-1,3-oxazine, which is then hydrolyzed in dilute oxalic acid solution.[4] It has been found that *t*-butyl lithium is the best suitable reagent for the purpose of deprotonation, followed by *n*-butyl lithium and phenyl lithium; other bases such as Grignard reagent, alkoxide, hydride, and dimethylsulfinyl reagent all fail for deprotonation.[3b] On the other hand, alkyl bromides and iodides are all good alkylating reagents, whereas alkyl tosylates do not work in this reaction.[3b] It has been reported that a considerable quantity of amino alcohol is also produced during the reduction from sodium borohydride,[3b] and such side reactions can be suppressed by reduction under basic conditions (pH = 9) instead of acidic conditions (pH = 5).[3b] However, as shown in Section C, an equivalent of amino alcohol will be naturally generated from the acidic hydrolysis of the tetrahydro-1,3-oxazine. The aldehydes produced in this reaction can be obtained by steam distillation from oxalic acid solution[1,3b,4a] if they are volatile enough, leaving the side product (e.g., amino alcohol) in the solution; otherwise they can be extracted after refluxing the oxalic acid solution for 1–2 h.[3b] This reaction can be used to prepare α,β-unsaturated aldehyde if the lithiated carbanion is allowed to react with a carbonyl compound, especially with β,β-disubstituted acroleins;[4a] silimarly, cycloalkyl

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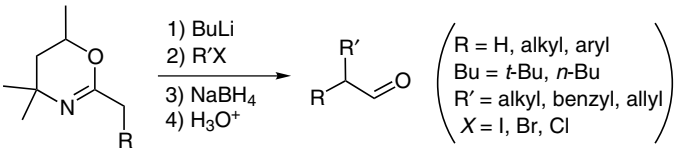
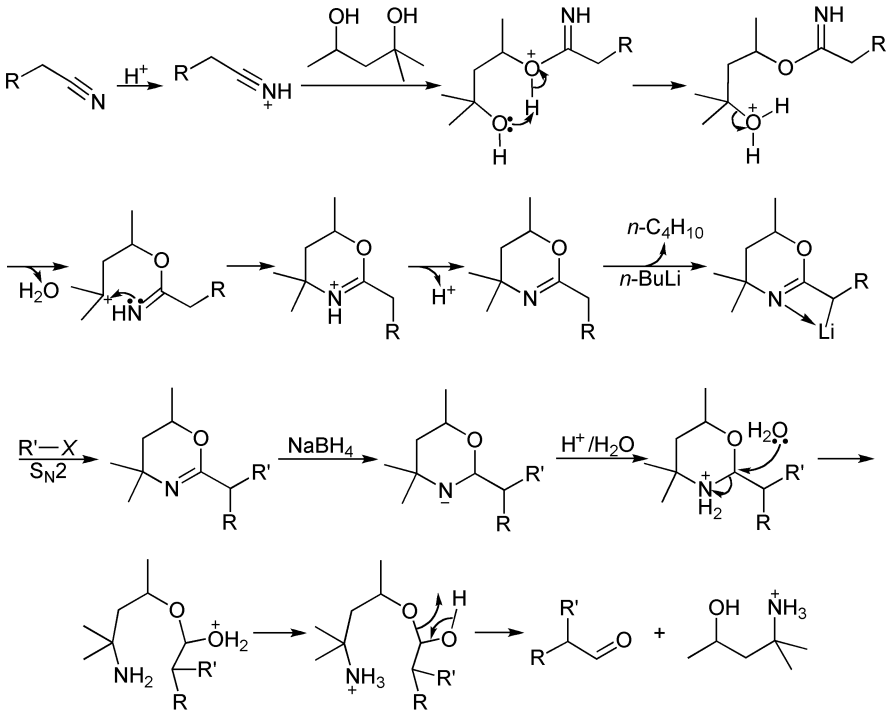
aldehyde[4b] and γ-hydroxy or γ-oxo aldehyde[5] can also be produced from this reaction by reacting lithiated carbanion with α,ω-dihaloalkane and epoxides, respectively. In addition, this reaction can also be used for the synthesis of ketones[6] by treatment of an excess amount of lithium reagent or from 2-alkenylozaxine using Grignard reagent followed by lithium reagent, etc.

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Shown here is the mechanism of the Meyers aldehyde synthesis, including the formation of 5,6-dihydro-1,3-oxazine.



D. MODIFICATION

N/A

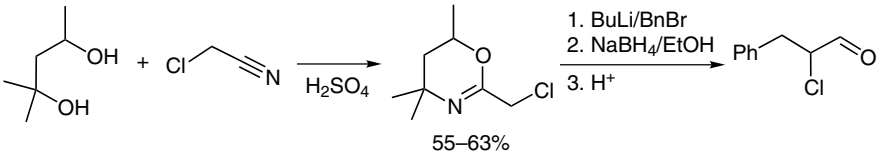
E. APPLICATIONS

This reaction has general application in the preparation of aldehydes and ketones.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3a.

To a 500-mL flask equipped with a thermometer, a stirrer, and a 125-mL addition funnel was added 100 mL concentrated sulfuric acid. The acid was cooled to 0–5°C in an ice-acetone bath, and 41.6 g of chloroacetonitrile (0.55 mol) was added at such a rate that the temperature was maintained at 0–5°C. After the addition of the nitrile was completed, 59.0 g 2-methyl-2,4-pentanediol (0.4 mol) was added at such a rate that the same temperature was maintained. The mixture was stirred for an additional 1 h and then poured onto 400 g crushed ice. The aqueous solution was washed with CH_2Cl_2 (4 × 50 mL), and the CH_2Cl_2 extracts were discarded. The cold aqueous acidic solution was carefully poured into a beaker cooled at 0°C, containing 400 g $NaHCO_3$ and 300 mL Et_2O. Upon becoming neutral, a red-yellow oil appeared, which was taken up in the ether layer. The aqueous layer was extracted with Et_2O (4 × 200 mL) (water was added as needed), and the combined ether extracts were dried over anhydrous K_2CO_3. The ether was removed by rotary evaporation, and the residue was distilled through a 20-cm fractioning column to give 47–57 g 2-chloromethyl-4,4,6-trimethyl-5,6-dihydro-l,3-oxazine as a colorless liquid, in a yield of 55–63%, b.p. 41°C at 1.0 mmHg.

To 40 mL THF at –78°C under nitrogen was added 11 mmol *t*-butyllithium in pentane, followed by 1.76 g 2-chloromethyl-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (10 mmol) in 10 mL THF. The mixture was stirred for 30 min, and 10 mmol benzyl bromide was added via syringe. The mixture was allowed to stir for 2 h, and quenched at –30°C with cold 1 N HCl, then washed with pentane. The pentane extracts were discarded. The aqueous acid solution was neutralized with $NaHCO_3$, extracted with ether, and concentrated. Vacuum distillation of the residue at 0.15 mmHg afforded 72% of 2-(1-chloro-2-phenylethyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine, b.p. 98°C (0.15 mmHg), which solidified from pentane,

m.p., 65–66.5°C. This oxazine was dissolved in 10 mL 95% ethanol to which 0.5 mL 40% NaOH was added. To this solution was added more than one equivalent of $NaBH_4$ dissolved in a minimum amount of water, and the mixture was stirred for 1 h at 25°C. Excess amounts of sodium borohydride were destroyed at –45°C with 3 N HCl to avoid halogen removal. The alcohol was removed by rotary evaporation, and the residue was diluted with saturated salt solution. Ether extraction was followed by washing the ethereal extracts with brine, and drying over Na_2SO_4. Concentration afforded the tetrahydro-1,3-oxazine. This tetrahydro-1,3-oxazine was hydrolyzed in diluted oxalic acid solution, and steam distillation afforded 2-chloro-3-phenylpropanal, b.p. 112°C at 13 mmHg.

Other references related to the Meyers aldehyde synthesis are cited in the literature.[7]

H. REFERENCES

1. Meyers, A. I.; Nabeya, A.; Adickes, H. W. and Politzer, I. R., *J. Am. Chem. Soc.*, **1969**, *91*, 763.
2. Nabeya, A., *Yuki Gosei Kagaku Kyokaishi*, **1976**, *34*, 49.
3. (a) Malone, G. R. and Meyers, A. I., *J. Org. Chem.*, **1974**, *39*, 618. (b) Meyers, A. I.; Nabeya, A.; Adickes, H. W.; Politzer, I. R.; Malone, G. R.; Kovelesky, A. C.; Nolen, R. L. and Portnoy, R. C., *J. Org. Chem.*, **1973**, *38*, 36.
4. (a) Meyers, A. I.; Nabeya, A.; Adickes, H. W.; Fitzpatrick, J. M.; Malone, G. R. and Politzer, I. R., *J. Am. Chem. Soc.*, **1969**, *91*, 764. (b) Meyers, A. I.; Adickes, H. W.; Politzer, I. R. and Beverung, W. N., *J. Am. Chem. Soc.*, **1969**, *91*, 765.
5. Adickes, H. W.; Politzer, I. R. and Meyers, A. I., *J. Am. Chem. Soc.*, **1969**, *91*, 2155.
6. (a) Meyers, A. I.; Kovelesky, A. C. and Jurjevich, A. F., *J. Org. Chem.*, **1973**, *38*, 2136. (b) Meyers, A. I.; Smith, E. M. and Ao, M. S., *J. Org. Chem.*, **1973**, *38*, 2129. (c) Meyers, A. I. and Smith, E. M., *J. Am. Chem. Soc.*, **1970**, *92*, 1084. (d) Meyers, A. I. and Kovelesky, A. C., *J. Am. Chem. Soc.*, **1969**, *91*, 5887.
7. (a) Malone, G. R. and Meyers, A. I., *J. Org. Chem.*, **1974**, *39*, 623. (b) Narwid, T. A. and Meyers, A. I., *J. Org. Chem.*, **1974**, *39*, 2572. (c) Meyers, A. I. and Nazarenko, N., *J. Org. Chem.*, **1973**, *38*, 175.

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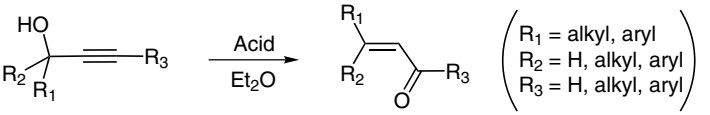
Meyer-Schuster Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Meyer and Schuster in 1922.[1] It is an acid-catalyzed transformation of secondary or tertiary α-acetylenic alcohols into α,β-unsaturated carbonyl compounds, and is generally known as the Meyer-Schuster rearrangement[2] or Meyer-Schuster reaction.[2h,3] When the acetylenic group is terminal, the resulting product is an aldehyde.[2n] This reaction can be carried out either in acidic nonaqueous media or in highly acidic aqueous solutions;[3b] the former conditions include the application of ether saturated with dry HCl,[2m,2n] acetic anhydride,[2m,2n] acetyl chloride,[2m,2n] vanadium (V) salt,[4] or polyphosphoric acid trimethylsilyl ester;[2e] the latter conditions use the mixture of acetic acid and concentrated sulfuric acid.[2m,2n] The reaction involves three consecutive steps as follows: protonation of hydroxy group, 1,3-shift of the protonated hydroxy group, and enol/keto tautomerization.[2h,3b] Alternatively, this reaction may take place through an allenic carbonium ion intermediate, from which the nucleophilic attack by water ends up with α,β-unsaturated carbonyl compound.[2p,5] Thus electron-donating solvent can electrostatically solvate the intermediate cation and facilitate this reaction.[2h,2m,3b] Because intermediate alkynyl cation cannot expel a proton from an adjacent carbon atom,[2n] tertiary α-acetylenic alcohols exclusively undergo the Meyer-Schuster rearrangement.[2m]

B. GENERAL REACTION SCHEME



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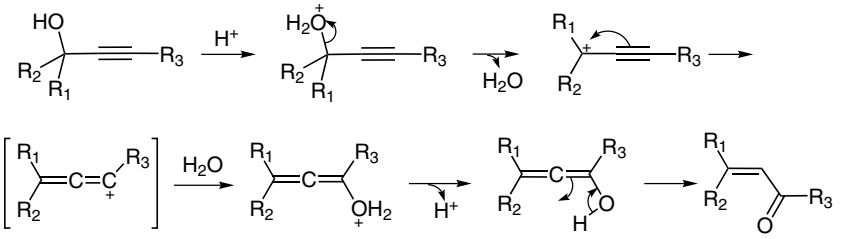
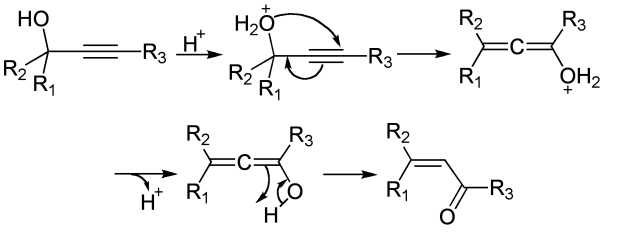
C. PROPOSED MECHANISMS

This reaction may proceed via an allenic cation intermediate generated by acidic dehydration, as shown in Scheme 1, or through a 1,3-shift of the protonated hydroxy group as shown in Scheme 2.



SCHEME 1. *Meyer-Schuster rearrangement involving an allenic cation intermediate.*



SCHEME 2. *Meyer-Schuster rearrangement involving a 1,3-shift of protonated hydroxyl group.*

D. MODIFICATION

This reaction has been adapted to primary acetylenic alcohol by treatment of the mixture of propargyl acetate and water with mercury(II) trifluoromethanesulfonate [mercuric triflate, $Hg(Tf)_2$] to give vinyl ketones under very mild conditions.[6] In addition, this reaction has been carried out at high temperatures without the addition of an acid catalyst.[7]

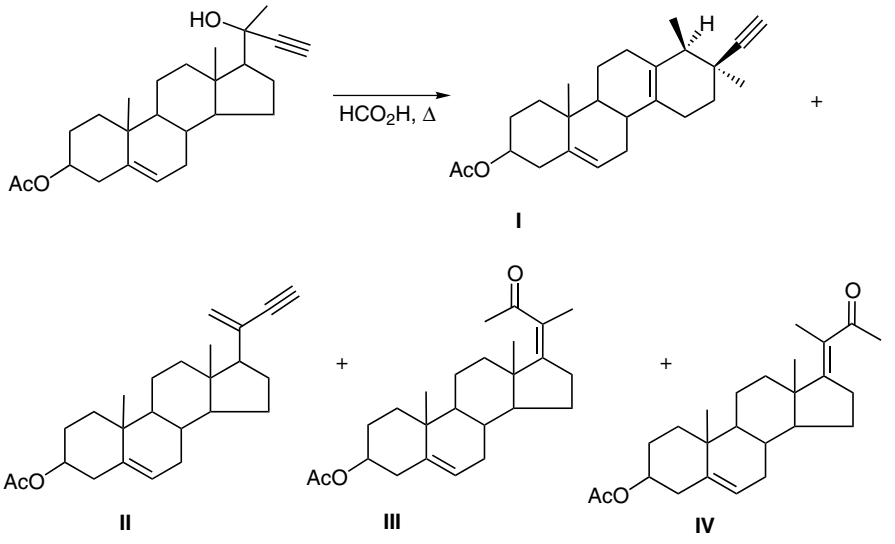
E. APPLICATIONS

This reaction is useful for the preparation of α,β-unsaturated carbonyl compounds.

F. RELATED REACTIONS

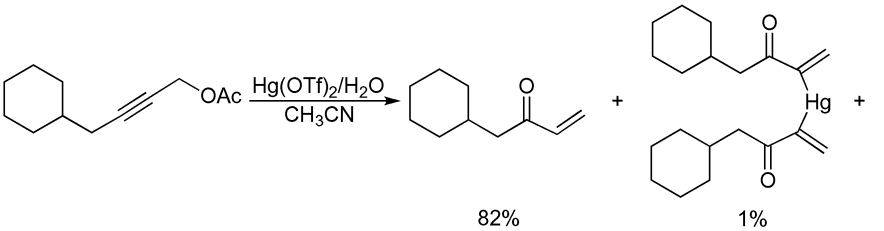
This reaction is related to the *Rupe Rearrangement*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 5.

A mixture of 5 g 20α-ethynylpregn-5-ene-3β,20β-diol 3-acetate and 25 mL 97% formic acid was heated with stirring on a steam bath for 3–4 min. When everything went into solution and a deep violet color developed, the solution was then poured over ice and extracted with CH_2Cl_2, washed with 2 N Na_2CO_3 and water, and dried over Na_2SO_4. After the solvent was evaporated, a brown residue was obtained, which solidified on standing. Four spots were identified by TLC. The residue was dissolved in 10 mL benzene and diluted with 10 mL hexane. The solution was then put on a column of 200 g alumina prepared in hexane, and the material was chromatographically separated into various fractions. The first fraction, in a total amount of 1 g, was eluted from the column with a 1:1 mixture of benzene and hexane, m.p., 141–142°C (methanol) (**I**). The second fraction was solely eluted with benzene that weighed 300 mg and contained two compounds, which were further separated by column chromatography using 30 g alumina to give 200 mg compound **I** and 50 mg **II**, m.p., 125–127°C (methanol). The third fraction in an amount of 1.1 g was eluted from the column with 2–5% ether in benzene and was identified as **III**, m.p. 176–178°C (methanol). The fourth fraction in an amount of 650 mg was eluted from the column with 4–10% EtOAc in benzene as oil, which was further purified by column chromatography using 50 g alumina, to afford 100 mg **III** and 450 mg compound **IV**, m.p., 119–121°C (methanol).



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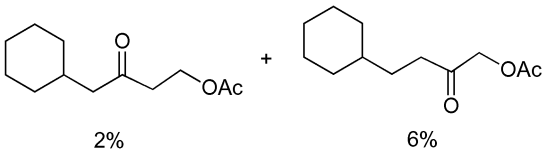

Reference 6.

To a stirred solution of 194 mg 4-cyclohexylbut-2-ynyl acetate (1.0 mmol) and 27 mg water (1.5 mmol, 1.5 eq.) in 9.5 mL acetonitrile was added 0.5 mL 0.1 M $Hg(OTf)_2$ (5 mol%) in acetonitrile at room temperature under argon. The mixture was allowed to stir at the same temperature for 4 h. After the addition of aqueous $NaHCO_3$, the organic material was extracted with ether. Dried and concentrated material was subjected to a column chromatography on silica gel using pentane and ether as eluents to give 128 mg 1-cyclohexylbut-3-en-2-one (82%) and a mixture of bis(4-cyclohexyl-3-oxobut-1-en-2-yl) mercury (1%), 4-cyclohexyl-3-oxobutyl acetate (2%), and 4-cyclohexyl-2-oxobutyl acetate (6%). (All yields are based on NMR measurements.)

Other references related to the Meyer-Schuster rearrangement are cited in the literature.[8]

H. REFERENCES

1. Meyer, K. H. and Schuster, K., *Ber.*, **1922**, *55*, 819.
2. (a) Lopez, S. S.; Engel, D. A. and Dudley, G. B., *Synlett*, **2007**, 949. (b) Engel, D. A. and Dudley, G. B., *Org. Lett.*, **2006**, *8*, 4027. (c) Yamabe, S.; Tsuchida, N. and Yamazaki, S., *J. Chem. Theory & Compt.*, **2006**, *2*, 1379. (d) Lorber, C. Y. and Osborn, J. A., *Tetrahedron Lett.*, **1996**, *37*, 853. (e) Yoshimatsu, M.; Naito, M.; Kawahigashi, M.; Shimizu, H. and Kataoka, T., *J. Am. Chem. Soc.*, **1995**, *60*, 4798. (f) Erman, M. B.; Gulyi, S. E. and Aulchenko, I. S., *Mendeleev Commun.*, **1994**, 89. (g) Omar, E. A.; Tu, C.; Wigal, C. T. and Braun, L. L., *J. Heterocycl. Chem.*, **1992**, *29*, 947. (h) Andres, J.; Cardenas, R.; Silla, E. and Tapia, O., *J. Am. Chem. Soc.*, **1988**, *110*, 666. (i) Andres, J.; Silla, E. and Tapia, O., *THEOCHEM*, **1983**, *14*, 307. (j) Andres, J.; Silla, E. and Tapia, O., *Chem. Phys. Lett.*, **1983**, *94*, 193. (k) Cachia, P.; Darby, N.; Mak, T. C. W.; Money, T. and Trotter, J., *Can. J. Chem.*, **1980**, *58*, 1172. (l) Branca, S. J.; Lock, R. L. and Smith, A. B., *J. Org. Chem.*, **1977**, *42*, 3165. (m) Edens, M.; Boerner, D.; Chase, C. R.; Nass, D. and Schiavelli, M. D., *J. Org. Chem.*, **1977**, *42*, 3403. (n) Swaminathan, S. and Narayanan, K. V., *Chem. Rev.*, **1971**, *71*, 429. (o) Kagawa, M., *Chem. Pharm. Bull.*, **1959**, *7*, 306. (p) Smissman, E. E.; Johnsen, R. H.; Carlson, A. W. and Aycock, B. F., *J. Am. Chem. Soc.*, **1956**, *78*, 3395. (q) McEntee, M. E.; Pinder, A. R.; Smith, H. and Thornton, R. E., *J. Chem. Soc.*, **1956**, 4699. (r) Clapperton, E. T. and MacGregor, W. S., *J. Am. Chem. Soc.*, **1950**, *72*, 2501.
3. (a) Sakharov, B. N.; Lipkin, M. A. and Markevich, V. S., *Zh. Org. Khim.*, **1992**, *28*, 930. (b) Tapia, O.; Lluch, J. M.; Cargenas, R. and Andres, J., *J. Am. Chem. Soc.*, **1989**, *111*, 829. (c) Andres, J.; Pascual-Ahuir, J. L.; Silla, E. and Bertran, J., *Anales Quim., Ser. A: Quim. Fisica Ing. Quim.*, **1988**, *84*, 159. (d) Tapia, O. and Andres, J., *Chem. Phys. Lett.*, **1984**, *109*, 471. (e) Andres, J.; Arnau, A.; Silla, E.; Bertran, J. and Tapia, O., *THEOCHEM*, **1983**, *14*, 49.

4. (a) Erman, M. B.; Gulyi, S. E. and Aulchenko, I. S., *Mendeleev Commun.*, **1994**, 89. (b) Olson, G. L.; Cheung, H. C.; Morgan, K. D.; Borer, R. and Saucy, G., *Helv. Chim. Acta*, **1976**, *59*, 567. (c) Pauling, H.; Andrews, D. A. and Hindley, N. C., *Helv. Chim. Acta*, **1976**, *59*, 1233.
5. Chaudhuri, N. K. and Gut, M., *J. Am. Chem. Soc.*, **1965**, *87*, 3737.
6. Imagawa, H.; Asai, Y.; Takano, H.; Hamagaki, H. and Nishizawa, M., *Org. Lett.*, **2006**, *8*, 447.
7. An, J. Y.; Bagnell, L.; Cablewski, T.; Strauss, C. R. and Trainor, R. W., *J. Org. Chem.*, **1997**, *62*, 2505.
8. Buser, D.; Pauling, H.; Thum, A. and bonrath, W., *Molecules*, **2002**, *7*, 341.

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Michael Addition

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Michael in 1887.[1] It is generally defined as the 1,4-addition (or conjugated addition) of a nucleophile to an electron-deficient alkene or alkyne. Thus this reaction is generally referred to as the Michael addition[2,3] or Michael reaction.[4,5] The nucleophiles are generally called the Michael donors,[6] while the electron-deficient alkenes or alkynes are known as the Michael acceptors,[5d,7] and the addition products are named the Michael adducts.[5h,8] Generally speaking, the more electron-rich the nucleophile is and the more electron-deficient the acceptor is, the easier the Michael addition occurs. Thus some Michael additions can proceed in neutral media[9] and even at room temperature without any catalyst.[10] Because both nucleophile and Michael acceptor become a part of the Michael adduct, this reaction is one of the most atom-efficient reactions[5e] and has been widely explored in many aspects. A part of the known nucleophiles include compounds containing heteroatoms of lone-pair electrons, such as primary and secondary amines,[7b] thiols,[7e,8c,11] and fullerenol;[12] neutral carbon-nucleophiles such as indoles,[5e,13] (*tert*-butyldimethylsiloxy) pyrrole,[5h] silyl ketene acetals, and enolsilanes;[14] carbon-nucleophiles with α-active protons, such as malonates,[5b,5c,5f,5g] β-ketoesters,[7d] silyl nitronates,[15] and nitroalkanes;[16] and anionic carbon-nucleophiles, such as enolates,[6,9,17] chiral Fischer aminocarbene complexes,[18] α-lithiated vinylic sulfoxide,[19] and enantio-enriched allenyltitaniums;[20] lithium eneselenolates generated from selenoamides;[21] and acylperoxy radicals.[22] Accordingly, the Michael addition involving noncarbon nucleophiles is generally referred to as hetero-Michael addition,[7e,11e,23] such as the *aza*-Michael addition,[24] *oxo*-Michael addition,[25] and *phospha*-Michael addition.[26] Specifically, the Lewis acid-promoted addition of silyl ketene acetals or enolsilanes to α,β-unsaturated carbonyl compounds to generate 1,5-dicarbonyl compounds is referred to as the *Mukaiyama-Michael Addition*.[14]

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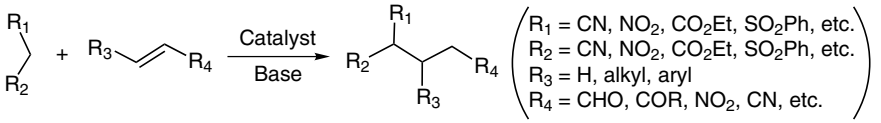
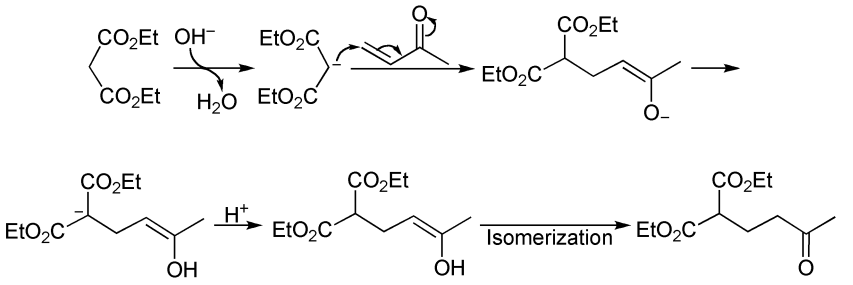
On the other hand, the initial Michael acceptors, such as α,β-unsaturated carbonyl compounds[7b] (e.g., acrylates[17,24b,27] and ethyl vinyl ketone[28]), have been extended to a variety of electron-deficient alkenes or alkynes, such as 2-*oxo*-3-butynoate,[7b] 2-*oxo*-3-pentynoate,[7b] cyclic enones[5c,5f] (e.g., cyclohexenone[5g]), chalcone,[5b,11b] acrynitrile,[29] alkylidene malonates,[13b,20] α,β-unsaturated imides,[30] nitroalkenes,[5c,31] nitrostyrene,[5c] α-methylene lactones,[5h] 1,4-benzoquinones,[5h] 3-alkylidene-3*H*-indole 1-oxide,[11d] 3-(*E*-enoyl)-4-phenyl-1,3-oxazolidin-2-ones,[7f,32] and α,β-unsaturated iodonium salt.[33] Although α,β-unsaturated aldehydes often give 1,2-addition products,[15] they also undergo regular Michael addition under certain conditions, such as in the reaction with 2-alkoxypropenals.[15,34] Furthermore, the carbon nucleophiles with α-active proton are often treated with base before the Michael addition. The bases used for this reaction range from strong bases such as butyl lithium to weak bases such as piperidine, quaternary ammonium hydroxide, and tertiary amines.[35] However, the Michael addition sometimes still requires a prolonged reaction time,[5f] thus different catalysts have been used or developed to facilitate the reaction or to enhance the diastereoselectivity and enantioselectivity of the Michael adducts. Some such catalysts are the organometallic complexes: chiral (salen)-aluminum complex,[30] Ru[(*S*, *S*)-Msdpen](η^6-hexamethylbenzene)((*S*, *S*)-MsDPEN) = (1*S*,2*S*)-*N*-(methanesulfonyl)-1,2-diphenylethylenedi-amine),[5c] *N*-spiro C_2-symmetric chiral quaternary ammonium bifluoride,[15] chiral Ni(II) complex of the Schiff base of glycine with (S)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone,[36] $Cu(SbF_6)_2$-AdamBox,[9] $Cu(OTf)_2$-trisoxazoline,[13b,37] copper(II) bis-(5-*tert*-butylsalicylaldehydate),[9] $Yb(OTf)_3$-TMEDA,[38] and late transition metal complexes of BINOL-derived salens;[5g] Lewis acids such as $BF_3{\cdot}OEt_2$,[5h] $Cu(ClO_4)_2{\cdot}6H_2O$,[13b] $Hf(OTf)_4$,[5i] $InBr_3$,[13a] and $CeCl_3{\cdot}7H_2O$-NaI;[5e] chiral amines such as DBU,[16c] (*S*)-2-[bis(3,5-dimethylphenyl)methyl]pyrrolidine,[39] C_2-symmetric (2*S*,5*S*)-2,5-diphenylpyrrolidine,[39] (-)-quinine,[25] and proline;[31b] polymer catalysts such as antibody 38C2[40] and polymer-anchored chiral catalysts;[41] and solid base catalysts such as MgO[42] and Mg-Al-O-*t*-Bu hydrotalcite.[43] Furthermore, the solvent-free Michael addition has been established by application of $CeCl_3{\cdot}7H_2O$-NaI as catalyst[5e] or microwave irradiation of reactants on $BiCl_3$ or CdI_2,[44] $EuCl_3$,[45] $CeCl_3{\cdot}5H_2O$,[46] and alumina surfaces.[47] It is interesting that the thermal treatment or microwave irradiation of 1,5-ketodiesters or 1,5-diketones in DMSO in the presence of Na*X* (*X* = Cl, Br, I) results in the *retro*-Michael addition.[8a]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Shown here is the mechanism of reaction between ethyl malonate and vinyl methyl ketone using NaOH as a base.



D. MODIFICATION

This reaction has been extensively modified by application of different bases and catalysts to enhance the diastereoselectivities and enantioselectivities.

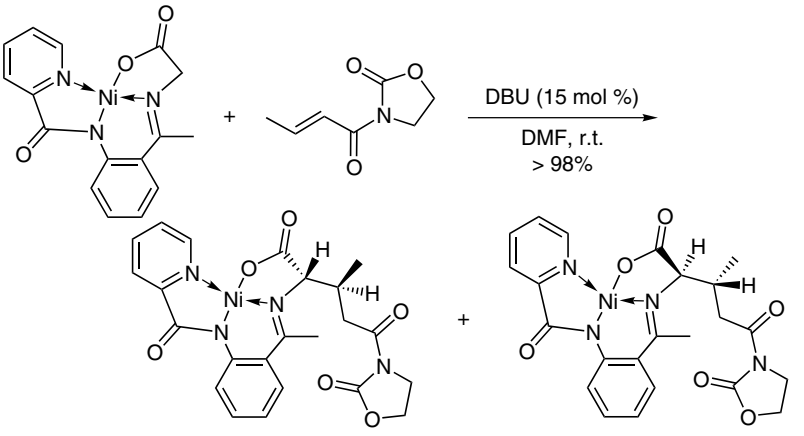
E. APPLICATIONS

This reaction has wide application in organic synthesis and is probably one of the most known organic reactions.

F. RELATED REACTIONS

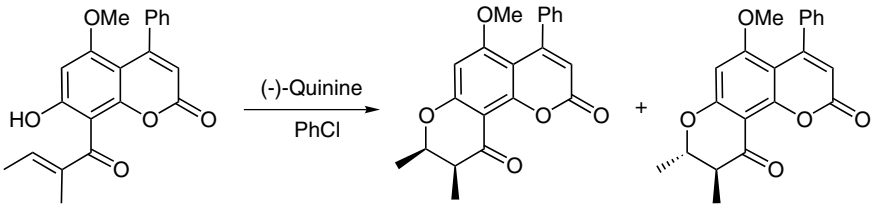
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 7c.

To a suspension of 0.5 mmol Ni(II) complex of Schiff base arising from glycine and (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]-benzophenone in 2.0 mL DMF was added 0.525 mmol 3-(*trans*-3′-methylpropenoyl)oxazolidin-2-one; the mixture was stirred at ambient temperature for 10 min. Then 10 μL DBU (0.07 mmol) was added, and the reaction was monitored by TLC. After the reaction completed ($\sim$ 15 min), the mixture was poured into 80 mL icy 5% aqueous acetic acid and stirred with a glass bar to initiate crystallization of the product. The crystalline product was filtered off, thoroughly washed with water, and dried in vacuo to afford $>$ 98% of the addition products. The diastereomeric isomers were isolated by silica gel column chromatography (acetone/chloroform, 1/4), in a ratio of 2.4 to 1.



Reference 17.

A suspension of 0.140 g 7-hydroxy-5-methoxy-4-phenyl-8-tigloylcoumarin (0.40 mmol) in 2.5 mL chlorobenzene in the presence of 0.013 g (-)-quinine (0.041 mmol) was stirred at 4°C for 33 h under argon. After evaporation of solvent, 5 mL water was added. The aqueous mixture was extracted with $CHCl_3$ (3 $\times$ 20 mL). The organic solution was successively washed with 20 mL 10% HCl, 20 mL water, 20 mL brine and dried over $MgSO_4$. Upon evaporation of solvent, the residue was purified by silica gel column chromatography (benzene/EtOAc, 10:1) to afford 0.032 g (8*S*,9*S*)-8,9-dihydro-8,9-dimethyl-5-methoxy-4-phenyl-2*H*,10*H*−benzo[1,2-*b*;5,6-*b*′]dipyran-2,10-dione (23%, m.p. 193–194°C) and 0.098 g (8*R*,9*S*)-8,9-dihydro-8,9-dimethyl-5-methoxy-4-phenyl-2*H*,10*H*-benzo[1,2-*b*;5,6-*b*′]dipyran-2,10-dione as colorless prisms, in a yield of 70%, m.p., 219–221°C.

Other references related to the Michael addition are cited in the literature.[48]

H. REFERENCES

1. Michael, A., *J. Prakt. Chem.*, **1887**, *35*, 379.
2. (a) Guo, R. W.; Morris, R. H. and Song, D. T., *J. Am. Chem. Soc.*, **2005**, *127*, 516. (b) Thompson, A. J.; Hart, S. R.; Franz, C..; Barnouin, K.; Ridley, A. and Cramer, R., *Anal. Chem.*, **2003**, *75*, 3232. (c) Rocchetti, M. T.; Fino, V.; Capriati, V.; Florio, S. and Luisi, R., *J. Org. Chem.*, **2003**, *68*, 1394. (d) Naidu, B. N.; Sorenson, M. E.; Connolly, T. P. and Ueda, Y., *J. Org. Chem.*, **2003**, *68*, 10098. (e) Patil, N. T.; Tilekar, J. N. and Dhavale, D. D., *J. Org. Chem.*, **2001**, *66*, 1065. (f) Hassner, A.; Ghera, E.; Yechezkel, T.; Kleiman, V.; Balasubramanian, T. and Ostercamp, D., *Pure & Appl. Chem.*, **2000**, *72*, 1671. (g) Takasu, K.; Mizutani, S.; Noguchi, M.; Makita, K. and Ihara, M., *J. Org. Chem.*, **2000**, *65*, 4112. (h) Russell, R. J.; Sirkar, K. and Pishko, M. V., *Langmuir*, **2000**, *16*, 4052. (i) Davies, S. C., *Pure & Appl. Chem.*, **1988**, *60*, 13.
3. (a) Hu, Q. S.; Wang, C.; Li, D. Z. and Xi, Z. F., *Org. Biomol. Chem.*, **2007**, *5*, 2114. (b) Batterjee, S.; Hassan, M. A. and Taib, L. A., *J. Saudi Chem. Soc.*, **2007**, *11*, 131. (c) Zu, L. S.; Li, H.; Xie, H.

X.; Wang, J.; Jiang, W.; Tang, Y. and Wang, W., *Angew. Chem. Int. Ed.*, **2007**, *46*, 3732. (d) Grigg, R.; Inman, M.; Kilner, C.; Koeppen, I.; Marchbank, J.; Selby, P. and Sridharan, V., *Tetrahedron*, **2007**, *63*, 6152. (e) An, L.-T.; Zou, J.-P.; Zhang, L.-L. and Zhang, Y., *Tetrahedron Lett*., **2007**, *48*, 4297. (f) Qu, G.-R.; Zhang, Z.-G.; Geng, M.-W.; Xia, R.; Zhao, L. and Guo, H.-M., *Synlett*, **2007**, 721. (g) Nagao, H.; Yamane, Y. and Mukaiyama, T., *Heterocycles*, **2007**, *72*, 553. (h) Bialk, H. M.; Hedman, C.; Castillo, A. and Pedersen, J. A., *Environ. Sci. Technol.*, **2007**, *41*, 3593. (i) Matsuo, J.-I.; Kawai, H. and Ishibashi, H., *Tetrahedron Lett*., **2007**, *48*, 3155. (j) Murthy, A. S. K.; Rambabu, C.; Vijeender, K.; Bhusan, P. B. and Chandrasekhar, S., *Synlett*, **2007**, 668. (k) Chaturvedi, D.; Mishra, N. and Mishra, V., *J. Sulfur Chem.*, **2007**, *28*, 39. (l) Choudary, B. M.; Rajasekhar, C. V.; Krishna, G. G. and Reddy, K. R., *Synth. Commun.*, **2007**, *37*, 91. (m) Li, H.; Zu, L. S.; Xie, H. X.; Wang, J.; Jiang, W. and Wang, W., *Org. Lett.*, **2007**, *9*, 1833.

4. (a) Shibuguchi, T.; Mihara, H.; Kuramochi, A.; Ohshima, T. and Shibasaki, M., *Chem. Asian J.*, **2007**, *2*, 794. (b) Fukushima, M.; Morii, A.; Hoshi, T.; Suzuki, T. and Hagiwara, H., *Tetrahedron*, **2007**, *63*, 7154. (c) Uria, U.; Vicario, J. L.; Badia, D. and Carrillo, L., *Chem. Commun.*, **2007**, 2509. (d) Torihata, M.; Nakahata, T. and Kuwahara, S., *Org. Lett.*, **2007**, *9*, 2557. (e) Yadav, J. S.; Reddy, B. V. S.; Singh, A. P. and Basak, A. K., *Tetrahedron Lett*., **2007**, *48*, 4169. (f) Gu, Y. L.; Ogawa, C. and Kobayashi, S., *Org. Lett.*, **2007**, *9*, 175. (g) Wang, S.-Y.; Ji, S.-J. and Loh, T.-P., *J. Am. Chem. Soc.*, **2007**, *129*, 276. (h) Park, D. Y.; Lee, M. J.; Kim, T. H. and Kim, J. N., *Tetrahedron Lett*., **2005**, *46*, 8799.
5. (a) Okino, T.; Hoashi, Y.; Fukukawa, T.; Xu, X. and Takemoto, Y., *J. Am. Chem. Soc.*, **2005**, *7*, 119. (b) Ooi, T.; Ohara, D.; Fukumoto, K. and Maruoka, K., *Org. Lett.*, **2005**, *7*, 3195. (c) Watanabe, M.; Ikagawa, A.; Wang, H.; Murata, K. and Ikariya, T., *J. Am. Chem. Soc.*, **2004**, *126*, 11148. (d) Smith, P. L.; Keane, J. M.; Shankman, S. E.; Chordia, M. D. and Harman, W. D., *J. Am. Chem. Soc.*, **2004**, *126*, 15543. (e) Bartoli, G.; Bartolacci, M.; Bosco, M.; Foglia, G.; Giuliani, A.; Marcantoni, E.; Sambri, L. and Torregiani, E., *J. Org. Chem.*, **2003**, *68*, 4594. (f) Narasimhan, S. and Velmathi, S., *Molecules*, **2003**, *8*, 256. (g) Annamalai, V.; DiMauro, E. F.; Carroll, P. J. and Kozlowski, M. C., *J. Org. Chem.*, **2003**, *68*, 1973. (h) Arroyo, Y.; de Paz, M.; Rodriguez, J. F.; Sanz-Tejedor, M. A. and Garcia Ruano, J. L., *J. Org. Chem.*, **2002**, *67*, 5638. (i) Kobayashi, S.; Ogawa, C.; Kawamura, M. and Sugiura, M., *Synlett*, **2001**, 983. (j) Paquette, L. A.; Tae, J. S.; Arrington, M. P. and Sadoun, A. H., *J. Am. Chem. Soc.* **2000**, *122*, 2742.
6. Yasuda, M.; Chiba, K.; Ohigashi, N.; Katoh, Y. and Baba, A., *J. Am. Chem. Soc.*, **2003**, *125*, 7291.
7. (a) Peelen, T. J.; Chi, Y. G. and Gellman, S. H., *J. Am. Chem. Soc.*, **2005**, *127*, 11598. (b) Brik, A.; Dawson, P. E. and Keinan, E., *Bioorg. Med. Chem.*, **2002**, *10*, 3891. (c) Cai, C. Z.; Soloshonok, V. A. and Hruby, V. J., *J. Org. Chem.*, **2001**, *66*, 1339. (d) Bensa, D.; Brunel, J.-M.; Buono, G. and Rodriguez, J., *Synlett*, **2001**, 715. (e) Reuter, C.; Schmieder, R. and Vögtle, F., *Pure & Appl. Chem.*, **2000**, *72*, 2233. (f) Soloshonok, V. A.; Cai, C. Z. and Hruby, V. J., *Org. Lett.*, **2000**, *2*, 747.
8. (a) Rao, H. S. P. and Jothilingam, S., *J. Chem. Sci.*, **2005**, *117*, 27. (b) Ishii, T.; Fujioka, S.; Sekiguchi, Y. and Kotsuki, H., *J. Am. Chem. Soc.*, **2004**, *126*, 9558. (c) Nishide, K.; Ohsugi, S.-I.; Shiraki, H.; Tamakita, H. and Node, M., *Org. Lett.*, **2001**, *3*, 3121.
9. Comelles, J.; Moreno-Mañas, M.; Pérez, E.; Roglans, A.; Sebastián, R. M. and Vallribera, A., *J. Org. Chem.*, **2004**, *69*, 6834.
10. Yamamoto, K.; Higuchi, M.; Takai, H. and Nishiumi, T., *Org. Lett.*, **2001**, *3*, 131.
11. (a) Metters, A. and Hubbell, J., *Biomacromolecules*, **2005**, *6*, 290. (b) Ranu, B. C.; Dey, S. S. and Samanta, S., *ARKIVOC*, **2005**, 44. (c) Heggli, M.; Tirelli, N.; Zisch, A. and Hubbell, J. A., *Bioconjugate Chem.*, **2003**, *14*, 967. (d) Myers, A. G. and Herzon, S. B., *J. Am. Chem. Soc.*, **2003**, *125*, 12080. (e) Reuter, C. and Vögtle, F., *Org. Lett.*, **2000**, *2*, 593.
12. Goswami, T. H.; Singh, R.; Alam, S. and Mathur, G. N., *Chem. Mater.*, **2004**, *16*, 2442.
13. (a) Agnusdei, M.; Bandini, M.; Melloni, A. and Umani-Ronchi, A., *J. Org. Chem.*, **2003**, *68*, 7126. (b) Zhou, J. and Tang, Y., *J. Am. Chem. Soc.*, **2002**, *124*, 9030.

14. Harada, T.; Iwai, H.; Takatsuki, H.; Fujita, K.; Kubo, M. and Oku, A., *Org. Lett.*, **2001**, *3*, 2101.
15. Ooi, T.; Doda, K. and Maruoka, K., *J. Am. Chem. Soc.*, **2003**, *125*, 9022.
16. (a) Itoh, K. and Kanemasa, S., *J. Am. Chem. Soc.*, **2002**, *124*, 13394. (b) Halland, N.; Hazell, R. G. and Jørgensen, K. A., *J. Org. Chem.*, **2002**, *67*, 8331. (c) Ballini, R.; Bosica, G.; Fiorini, D.; Gil, M. V. and Petrini, M., *Org. Lett.*, **2001**, *3*, 1265. (d) Corey, E. J. and Zhang, F.-Y., *Org. Lett.*, **2000**, *2*, 4257. (e) Funabashi, K.; Saida, Y.; Kanai, M.; Arai, T.; Sasi, H. and Shibasaki, M., *Tetrahedron Lett.*, **1998**, *39*, 7557.
17. Ley, S. V. and Massi, A., *J. Comb. Chem.*, **2000**, *2*, 104.
18. Licandro, E.; Maiorana, S.; Capella, L.; manzotti, R.; Papagni, A.; Vandoni, B.; Albinati, A.; Chuang, S. H. and Hwu, J.-R., *Organometallics*, **2001**, *20*, 485.
19. Maezaki, N.; Sawamoto, H.; Yuyama, S.; Yoshigami, R.; Suzuki, T.; Izumi, M.; Ohishi, H. and Tanaka, T., *J. Org. Chem.*, **2004**, *69*, 6335.
20. Song, Y. C.; Okamoto, S. and Sato, F., *Org. Lett.*, **2001**, *3*, 3543.
21. Murai, T.; Suzuki, A.; Ezaka, T. and Kato, S., *Org. Lett.*, **2000**, *2*, 311.
22. Balamraju, Y. N.; Sun, M. J. and Salomon, R. G., *J. Am. Chem. Soc.*, **2004**, *126*, 11522.
23. Aiguade, J.; Hao, J. L. and Forsyth, C. J., *Org. Lett.*, **2001**, *3*, 979.
24. (a) Volonterio, A.; de Arellano, C. R. and Zanda, M., *J. Org. Chem.*, **2005**, *70*, 2161. (b) Colantoni, D.; Fioravanti, S.; Pellacani, L. and Tardella, P. A., *Org. Lett.*, **2004**, *6*, 197.
25. Sekino, E.; Kumamoto, T.; Tanaka, T.; Ikeda, T. and Ishikawa, T., *J. Org. Chem.*, **2004**, *69*, 2760.
26. Tedeschi, L. and Enders, D., *Org. Lett.*, **2001**, *3*, 3515.
27. Walker, E. H.; Apblett, A. W.; Walker, R. and Zachary, A., *Chem. Mater.*, **2004**, *16*, 5336.
28. Colombo, M. I.; Zinczuk, J.; Mischne, M. P. and Rúveda, E. A., *Pure & Appl. Chem.*, **2001**, *73*, 623.
29. Hou, Z. M.; Koizumi, T.-a.; Fujita, A.; Yamazaki, H. and Wakatsuki, Y., *J. Am. Chem. Soc.*, **2001**, *123*, 5812.
30. Taylor, M. S. and Jacobsen, E. N., *J. Am. Chem. Soc.*, **2003**, *125*, 11204.
31. (a) Evans, D. A. and Seidel, D., *J. Am. Chem. Soc.*, **2005**, *127*, 9958. (b) List, B.; Pojarliev, P. and Martin, H. J., *Org. Lett.*, **2001**, *3*, 2423.
32. Soloshonok, V. A.; Ueki, H.; Tiwari, R.; Cai, C. Z. and Hruby, V. J., *J. Org. Chem.*, **2004**, *69*, 4984.
33. Fujita, M.; Kim, W. H.; Fujiwara, K. and Okuyama, T., *J. Org. Chem.*, **2005**, *70*, 480.
34. Keiko, N. A.; Funtikova, E. A.; Stepanova, L. G.; Chuvashev, Y. A. and Larina, L. I., *ARKIVOC*, **2001**, 67.
35. Rao, H. S. P. and Jothilingam, S., *J. Chem. Sci.*, **2005**, *117*, 323.
36. Soloshonok, V. A.; Cai, C. Z.; Yamada, T.; Ueki, H.; Ohfune, Y. and Hruby, V. J., *J. Am. Chem. Soc.*, **2005**, *127*, 15296.
37. Ye, M.-C.; Li, B.; Zhou, J.; Sun, X.-L. and Tang, Y., *J. Org. Chem.*, **2005**, *70*, 6108.
38. Ding, R.; Katebzadeh, K.; Roman, L.; Bergquist, K.-E. and Lindström, U. M., *J. Org. Chem.*, **2006**, *71*, 352.
39. Melchiorre, P. and Jørgensen, K. A., *J. Org. Chem.*, **2003**, *68*, 4151.
40. Weinstain, R.; Lerner, R. A.; Barbas, C. F. and Shabat, D., *J. Am. Chem. Soc.*, **2005**, *127*, 13104.
41. Sundararajan, G. and Prabagaran, N., *Org. Lett.*, **2001**, *3*, 389.
42. Kabashima, H.; Tsuji, H. and Hattori, H., *Appl. Catal., A*, **1997**, *165*, 319.
43. Choudary, B. M.; Kantam, M. L.; Reddy, C. V. and Figueras, F., *Tetrahedron*, **2000**, *56*, 9357.
44. Baruah, B.; Boruah, A.; Prajapati, D. and Sandhu, J. S., *Tetrahedron Lett.*, **1997**, *38*, 1449.
45. Soriente, A.; Spinella, A.; Rosa, M. D.; Giordano, M. and Scettri, A., *Tetrahedron Lett.*, **1997**, *38*, 289.

46. Boruah, A.; Baruah, M.; Prajapati, D. and Sandhu, J. S., *Synth. Commun.*, **1998**, *28*, 653.

47. (a) Patonay, T.; Varma, R. S.; Vass, A.; Lévai, A. and Dudás, J., *Tetrahedron Lett.*, **2001**, *42*, 1403. (b) Ranu, B. C.; Guchhait, S. K.; Ghosh, K. and Patra, A., *Green Chem.*, **2000**, 5.

48. (a) Yamazaki, S. and Iwata, Y., *J. Org. Chem.*, **2006**, *71*, 739. (b) Ranu, B. C. and Banerjee, S., *Org. Lett.*, **2005**, *7*, 3049. (c) Chi, Y. and Gellman, S. H., *Org. Lett.*, **2005**, *7*, 4253. (d) Willis, M. C.; Chauhan, J. and Whittinham, W. G., *Org. Biomol. Chem.*, **2005**, *3*, 3094. (e) Zheng, J.-C.; Liao, W.-W.; Tang, Y.; Sun, X.-L. and Dai, L.-X., *J. Am. Chem. Soc.*, **2005**, *127*, 12222. (f) Scriban, C.; Kovacik, I. and Glueck, D. S., *Organometallics*, **2005**, *24*, 4871. (g) Kraus, G. A. and Jeon, I., *Tetrahedron*, **2005**, *61*, 2111. (h) Madjarova, G.; Tadjer, A.; Cholakova, T. P.; Dobrev, A. A. and Mineva, T., *J. Phys. Chem. A*, **2005**, *109*, 387. (i) Wu, D. C.; Liu, Y.; He, C. B.; Chung, T. S. and Goh, S. T., *Macromolecules*, **2004**, *37*, 6763. (j) Dixon, D. J.; Horan, R. A.; Monck, N. J. T. and Berg, P., *Org. Lett.*, **2004**, *6*, 4427. (k) Lutolf, M. P. and Hubbell, J. A., *Biomacromolecules*, **2003**, *4*, 713. (l) Oe, T.; Matsumoto, S. and Toyo'oka, T., *J. Health Sci.*, **2001**, *47*, 339. (m) Zhang, J. Z.; Flippen-Anderson, J. L. and Kozikowski, A. P., *J. Org. Chem.*, **2001**, *66*, 7555. (n) Krause, N. and Hoffmann-Röder, A., *Synthesis*, **2001**, 171. (o) Müh, E.; Marquardt, J.; Klee, J. E.; Frey, H. and Mülhaupt, R., *Macromolecules*, **2001**, *34*, 5778. (p) Dixon, D. J.; Ley, S. V. and Rodriguez, F., *Org. Lett.*, **2001**, *3*, 3753. (q) Jang, D.-P.; Chang, J.-W. and Uang, B.-J., *Org. Lett.*, **2001**, *3*, 983. (r) Mikoshiba, H.; Mikami, K. and Nakai, T., *Synlett*, **2001**, 989. (s) Soloshonok, V. A.; Cai, C. Z.; Hruby, V. J.; Meervelt, L. V. and Yamazaki, T., *J. Org. Chem.*, **2000**, *65*, 6688. (t) Bunce, R. A.; Herron, D. M. and Ackerman, M. L., *J. Org. Chem.*, **2000**, *65*, 2847. (u) Maeda, H. and Kraus, G. A., *J. Org. Chem.*, **1997**, *62*, 2314. (v) Wu, J.-C. and Chattopadhyaya, J., *Tetrahedron*, **1989**, *45*, 855. (w) Bergmann, E. D.; Gingberg, D. and Pappo, R., *Org. React.*, **1959**, *10*, 179.

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Michaelis-Arbuzov Rearrangement

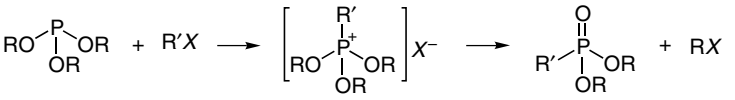
(Arbuzov Rearrangement, Arbuzov Reaction, Arbuzov Transformation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially discovered by Michaelis in 1898[1] and explored in great detail by Arbuzov and several subsequent investigators.[2] It is one of the most versatile routes to form alkyl phosphonates containing one phosphorus-carbon bond from the reaction of an ester of trivalent phosphorus (i.e., trialkyl phosphite) and alkyl halides. Therefore, this reaction is generally known as the Michaelis-Arbuzov rearrangement,[3] Arbuzov rearrangement,[4] or Arbuzov reaction.[5] Occasionally, it is also referred to as the Arbuzov dealkylation[6] or Arbuzov transformation.[7] Besides the rearrangement of phosphites, a similar reaction is also observed for dialkyl sulfite,[8] sulfenate ester,[9] alkoxysulfanes,[10] and other thio-derivatives,[11] and such an analogous rearrangement is referred to as the thio-Arbuzov reaction.[5s,9,10] It has been found that the Michaelis-Arbuzov rearrangement can be promoted by metal-centered radicals,[4f] anode oxidation,[4g] or photo irradiation, and the Arbuzov reaction occurring under photochemical illumination is generally called the photo-Arbuzov rearrangement.[4a,4e,12] In addition, this reaction can also be catalyzed by ruthenium.[4k] This reaction has been used in the synthesis of phosphonates, phosphinic acid esters, and phosphine oxides.

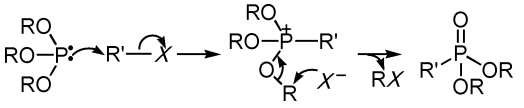
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

At least three mechanisms have been proposed for this reaction. The first one, originally postulated by Arbuzov,[2d] consists of an alkylation reaction that yields an alkoxyphosphonium ion and a nucleophilic substitution from the conjugate nucleophile (X^-), as shown here. The second mechanism, suggested initially by Rumpf,[13] is an autocatalyzed process, in which the species that attacks the alkoxyphosphonium ion is the ester of trivalent phosphorus (i.e., phosphite) rather than the conjugate nucleophile X^-. Although the majority of experimental results support the first type mechanism, the autocatalyzed mechanism is clearly favored in a few experiments, in which an ester of trivalent phosphorus reacts with dimethyl sulfate or methyl triflate rather than alkyl halides.[14] In addition, a radical mechanism was also proposed in 1982.[15] According to the first two mechanisms, if R′ = R as shown in Section B, only a catalytic amount of R′*X* is needed for the transformation of trialkyl phosphite into phosphonate. In addition, it has been found that haloalkyl phosphites can undergo an internal rearrangement upon heating.[16]



D. MODIFICATION

This reaction has been extensively modified. Besides the ruthenium-catalyzed, metal-centered radical or photo-Arbuzov rearrangements as described earlier, alkyl halides have been replaced by metal halides (e.g., $NiCl_2$),[17] trimethylsilyl chloride (TMSCl),[18] and organometallics.[19]

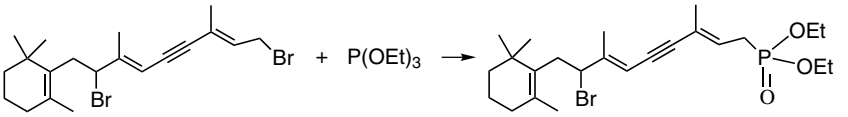
E. APPLICATIONS

The Arbuzov rearrangement has been widely used for the synthesis of a variety of phosphorus related compounds, including phosphonates,[20] phosphinates,[21] tertiary phosphine oxides,[22] phosphonyl, and phosphonyl halides.[23] Some of these products can be used for the *Wittig Reactions*, such as in the synthesis of carotene.[24]

F. RELATED REACTIONS

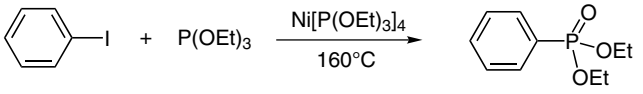
The reaction between alkyl halides and the anion of diethyl phosphonate, made by the ionization of the P-H bond by a very strong base, such as BuLi, to form a new carbon-phosphorus bond is known as the Michaelis-Becker reaction.

G. CITED EXPERIMENTAL EXAMPLES



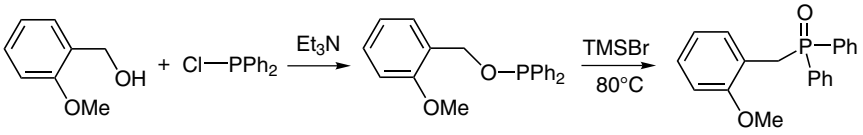
Reference 24.

To a distillation flask were added 107 g 1,8-dibromo-3,7-dimethyl-9-(2,6,6-trimethyl-l-cyclohexen-l-yl)-2,6-nonadien-4-yne, 100 mL toluene, and 83 g triethyl phosphite. The resulting mixture was heated at 145°C for 4 h. Upon removal of the solvent, the residue was distilled through a centrifugal molecular still to give 80.9 g 3,7-dimethyl-9-(2,5,6-trimethyl-l-cyclohexen-1-yl)-2,6,8-nonatrien-4-yn-1-ylphosphonic acid diethyl ester, in a yield of 70%, m.p. 28°C.



Reference 17.

To a flask equipped with a dropping funnel and refluxing condenser were added 10 g iodobenzene and 10 mg nickel tetra(triethyl phosphite). When the solution was heated to 160°C, 9.37 g triethyl phosphite (56.4 mmol) was added in small portions (∼ 5 drops). The solution became deep red upon each addition of phosphite. The color rapidly faded to yellow, ethyl iodide was distilled into a cold trap, and an exotherm was observed. When the reaction was completed (monitored by GLC), 9.88 g diethyl phenylphosphonate was obtained via distillation at 0.1 mmHg, b.p. 94–101°C, in a yield of 94%.



Reference 18.

In a nitrogen-flushed reaction vessel was added a solution of 100 μL chloro diphenyl phosphinite (0.56 mmol) in 5 mL dry THF, followed by 100 μL triethyl amine (0.8 mmol) and 81 μL 2-methoxybenzyl alcohol (0.6 mmol) successively. After overnight stirring at room temperature, triethyl ammonium salts were filtered off under nitrogen (glove box), and

rinsed with dry Et_2O. Solvents and remaining starting material were removed under vacuum. The crude reaction mixture was transferred to a flame-dried, nitrogen-flushed pressure-resistant reaction vessel, and 7 μL TMSBr was added. The reaction vessel was then made airtight with a Teflon stopper, and after being stirred for 2 h at 80°C, the crude reaction mixture was submitted to silica gel column chromatography (acetone/dichloromethane, 1:9), to afford 139 mg 2-methoxybenzyl diphenylphosphine oxide, in a yield of 77%.

Other references to the Arbuzov rearrangement are cited in the literature.[26]

H. REFERENCES

1. Michaelis, A. and Kaehne, R., *Ber.,* **1898**, *31*, 1048.
2. (a) Arbuzov, B. A., *Pure & Appl. Chem.*, **1964**, *9*, 307. (b) Harvey, R. G. and Sombre, E. R. De. "The Michaelis-Arbuzov and Related Reactions" in *Topics in Phosphorus Chemistry*, vol. I, ed. Grayson, M. and Griffth, E. J. Interscience, New York, **1964**, p. 57. (c) Koeolapoff, G., *Organophosphorus Compounds*, Wiley, New York, **1950**, ch. 7. (d) Arbuzov, A. E., *J. Russ. Phys. Chem. Soc.,* **1906**, *38*, 687.
3. (a) Prasad, G. S.; Manjunath, M.; Reddy, K. R. K. K.; Reddy, O. V. S. and Reddy, C. S., *ARKIVOC*, **2006**, (*xvi*), 128. (b) Matveeva, E. V.; Odinets, I. L.; Kozlov, V. A.; Shaplov, A. S. and Mastryukova, T. A., *Tetrahedron Lett*., **2006**, *47*, 7645. (c) Erker, T. and Handler, N., *Synthesis*, **2004**, 668. (d) Renard, P.-Y.; Vayron, P.; Leclerc, E.; Valleix, A. and Mioskowski, C., *Angew. Chem. Int. Ed.*, **2003**, *42*, 2389. (e) Baldwin, L. C. and Fink, M. J., *J. Organomet. Chem.*, **2003**, *646*, 230. (f) Kato, T.; Tejima, M.; Ebiike, H. and Achiwa, K., *Chem. Pharm. Bull.*, **1996**, *44*, 1132. (g) Jin, G. Y.; Wu, H. K. and Ni, Y. H., *Youji Huaxue*, **1993**, *13*, 278. (h) Procopio, A.; Sindona, G. and Uccella, N., *Synth. Commun.*, **1992**, *22*, 289. (i) Brunner, H. and Zettlmeier, W., *Bull. Soc. Chim. Belg.*, **1991**, *100*, 247. (j) Juge, S. and Genet, J. P., *Tetrahedron Lett*., **1989**, *30*, 2783. (k) Bhattacharya, A. K. and Thyagarajan, G., *Chem. Rev.*, **1981**, *81*, 415. (l) Berlin, K. D.; Hellwege, D. M.; Nagabhushanam, M. and Gaudy, E. T., *Tetrahedron*, **1966**, *22*, 2191. (m) Berlin, K. D.; Hildebrand, C.; South, A.; Hellwege, D. M.; Peterson, M.; Pier, E. A. and Verkade, J. G., *Tetrahedron*, **1964**, *20*, 323. (n) Aksnes, G. and Aksnes, D., *Acta Chem. Scand.*, **1963**, *17*, 2121. (o) Berlin, K. D.; Hildebrand, C.; Verkade, J. G. and Dermer, O. C., *Chem. Ind. (London)*, **1963**, 291.
4. (a) Bhanthumnavin, W. and Bentrude, W. G., *J. Org. Chem.*, **2005**, *70*, 4643. (b) Shipov, A. E.; Genkina, G. K.; Petrovskii, P. V. and Mastryukova, T. A., *Russ. Chem. Bull.*, **2004**, *53*, 1996. (c) Sa, M. M.; Silveira, G. P.; Bortoluzzi, A. J. and Padwa, A., *Tetrahedron*, **2003**, *59*, 5441. (d) Kaboudin, B. and Balakrishna, M. S., *Synth. Commun.*, **2001**, *31*, 2773. (e) Bhanthumnavin, W.; Ganapathy, S.; Arif, A. M. and Bentrude, W. G., *Heteroatom Chem.*, **1998**, *9*, 155. (f) Kuksis, I. and Baird, M. C., *J. Organomet. Chem.*, **1996**, *512*, 253. (g) Yasui, S.; Shioji, K.; Tsujimoto, M. and Ohno, A., *Tetrahedron Lett*., **1996**, *37*, 1625. (h) Lavastre, O.; Bonnet, G.; Leblanc, J. C. and Moise, C., *Polyhedron*, **1995**, *14*, 307. (i) El-Khazandar, A. N., *Sci. Phys. Sci*., **1993**, *5*, 34. (j) Wang, W. M.; Liu, L. P. and Li, X. L., *Huaxue Shiji*, **1992**, *14*, 65. (k) Ji, H. L.; Nelson, J. H.; De Cian, A. and Fischer, J., *Organometallics*, **1992**, *11*, 1618. (l) Gverdtsiteli, M.; Gamziani, G. and Gverdtsiteli, I., *Soobshcheniya Akademii Nauk Gruzii*, **1991**, *144*, 273. (m) Sindona, A. P. G. and Uccella, N., *Nucleosides & Nucleotides*, **1991**, *10*, 615. (n) No, B. I.; Zotov, Y. L. and Karev, V. N., *Zh. Obsh. Khim.*, **1990**, *60*, 1428. (o) Juge, S.; Wakselman, M.; Stephan, M. and Genet, J. P., *Tetrahedron Lett*., **1990**, *31*, 4443. (p) Niedermann, H. P.; Eckes, H. L. and Meier, H., *Tetrahedron Lett*., **1989**, *30*, 155. (q) Danchenko, M. N. and Sinitsa, A. D., *Zh. Obsh. Khim.*, **1987**, *57*, 1919. (r) Dvorak, D.; Saman, D.; Budesinsky, M. and Arnold, Z., *Coll. Czech. Chem. Commun.*, **1987**, *52*, 2926. (s) Livantsov, M. V.; Prishchenko, A. A. and Lutsenko, I. F., *Zh. Obsh. Khim.*, **1987**,

57, 1042. (t) Livantsov, M. V.; Prishchenko, A. A. and Lutsenko, I. F., *Zh. Obsh. Khim.*, **1986**, *56*, 2427. (u) Landon, S. J. and Brill, T. B., *Inorg. Chem.*, **1984**, *23*, 4177. (v) Landon, S. J. and Brill, T. B., *J. Am. Chem. Soc.*, **1982**, *104*, 6571.

5. (a) Grunlan, M. A. and Weber, W. P., *PMSE Preprints*, **2003**, *89*, 470. (b) Yarkevich, A. N. and Tsvetkov, E. N., *Russ. J. Gen. Chem.*, **2002**, *72*, 486. (c) Mugrage, B.; Diefenbacher, C.; Somers, J.; Parker, D. T. and Parker, T., *Tetrahedron Lett.*, **2000**, *41*, 2047. (d) Cherkasov, R. A.; Polezhaeva, N. A. and Galkin, V. I., *Phosphorus, Sulfur & Silicon & Related Elements*, **1999**, *144-146*, 333. (e) Abalonin, B. E., *Russ. J. Gen. Chem.*, **1999**, *69*, 26. (f) Pergament, I. and Srebnik, M., *Tetrahedron Lett.*, **1999**, *40*, 3895. (g) Villemin, D.; Simeon, F.; Decreus, H. and Jaffres, P.-A., *Phosphorus, Sulfur & Silicon & Related Elements*, **1998**, *133*, 209. (h) Kolodyazhnyi, O. I.; Neda, E. V.; Neda, I. and Schmutzler, R., *Russ. J. Gen. Chem.*, **1998**, *68*, 1159. (i) Salamonczyk, G.; Rehnberg, N.; Krawiecka, B. and Michalski, J., *Tetrahedron Lett.*, **1997**, *38*, 647. (j) Chen, Z.; Jablonski, C. and Bridson, J., *Can. J. Chem.*, **1996**, *74*, 2083. (k) Pevzner, L. M.; Ignat'ev, V. M. and Ionin, B. I., *Zh. Obsh. Khim.*, **1996**, *66*, 763. (l) Polezhaeva, N. A.; Loginova, I. V.; Galkin, V. I.; Ovechkina, E. V.; Sakhibullina, V. G. and Cherkasov, R. A., *Zh. Obsh. Khim.*, **1996**, *66*, 798. (m) Pevzner, L. M.; Ignat'ev, V. M. and Ionin, B. I., *Zh. Obsh. Khim.*, **1995**, *65*, 965. (n) Montchamp, J.-L.; Tian, F. and Frost, J. W., *J. Org. Chem.*, **1995**, *60*, 6076. (o) Chen, R. Y.; Chen, X. R. and Li, H., *Chinese Chem. Lett.*, **1995**, *6*, 23. (p) Yasui, S.; Shioji, K.; Yoshihara, M.; Maeshima, T. and Ohno, A., *Bull. Chem. Soc. Jpn.*, **1993**, *66*, 2077. (q) Zhou, Z. X.; Jablonski, C. and Bridson, J., *Organometallics*, **1993**, *12*, 3677. (r) El-Khazandar, A. N., *Sci. Phys. Sci.*, **1993**, *5*, 34. (s) Wenschuh, E. and Kersten, M., *Sulfur Lett.*, **1992**, *14*, 233. (t) Liang, L.; Stevens, E. D. and Nolan, S. P., *Organometallics*, **1992**, *11*, 3459. (u) Phadtare, S. and Zemlicka, J., *Nucleosides & Nucleotides*, **1991**, *10*, 275. (v) Sentemov, V. V.; Krasil'nikova, E. A. and Berdnik, I. V., *Zh. Obsh. Khim.*, **1991**, *61*, 374. (w) Sentemov, V. V.; Krasil'nikova, E. A. and Berdnik, I. V., *Zh. Obsh. Khim.*, **1989**, *59*, 2692. (x) Sahni, S. K. and Cabasso, I., *J. Poly. Sci., Part A: Poly. Chem.*, **1988**, *26*, 3251. (y) Makarov, A. M.; Matevosyan, G. L. and Zavlin, P. M., *Zh. Obsh. Khim.*, **1986**, *56*, 341.
6. (a) Nakazawa, H.; Fujita, T.; Kubo, K. and Miyoshi, K., *J. Organomet. Chem.*, **1994**, *473*, 243. (b) Boone, B. J.; Jablonski, C. R.; Jones, P. G.; Newlands, M. J. and Yu, Y. F., *Organometallics*, **1993**, *12*, 3042. (c) Jablonski, C. R.; Ma, H. Z.; Chen, Z.; Hynes, R. C.; Bridson, J. N. and Bubenik, M. P., *Organometallics*, **1993**, *12*, 917. (d) Liang, L.; Stevens, E. D. and Nolan, S. P., *Organometallics*, **1992**, *11*, 3459. (e) Nakazawa, H.; Yamaguchi, M.; Kubo, K. and Miyoshi, K., *J. Organomet. Chem.*, **1992**, *428*, 145. (f) Nakazawa, H.; Kadoi, Y. and Miyoshi, K., *Organometallics*, **1989**, *8*, 2851.
7. (a) Mazurkiewicz, R. and Kuznik, A., *Tetrahedron Lett.*, **2006**, *47*, 3439. (b) Natchev, I., *Izvestiya Khimiya*, **1989**, *22*, 224. (c) Schleman, E. V. and Brill, T. B., *J. Organomet. Chem.*, **1987**, *323*, 103. (d) Sullivan, R. J.; Bao, Q. B.; Landon, S. J.; Rheingold, A. L. and Brill, T. B., *Inorg. Chim. Acta*, **1986**, *111*, 19.
8. Narula, S. P.; Kaur, S.; Shankar, R.; Verma, S.; Venugopalan, P.; Sharma, S. K. and Chadha, R. K., *Inorg. Chem.*, **1999**, *38*, 4777.
9. Brown, C. and Evans, G. R., *Tetrahedron Lett.*, **1996**, *37*, 9101.
10. Kersten, M. and Wenschuh, E., *Phosphorus, Sulfur & Silicon & Related Elements*, **1995**, *102*, 205.
11. (a) Shankar, R.; Singh, A. P. and Upreti, S., *Inorg. Chem.*, **2006**, *45*, 9166. (b) Kumar, R. C.; Kinkead, S. A. and Shreeve, J. M., *Inorg. Chem.*, **1984**, *23*, 3112.
12. (a) Landis, M. S.; Turro, N. J.; Bhanthumnavin, W.; Bentrude, W. G., *J. Organomet. Chem.*, **2002**, *646*, 239. (b) Bhanthumnavin, W. and Bentrude, W. G., *J. Org. Chem.*, **2001**, *66*, 980. (c) Ganapathy, S.; Sekhar, B. B. V. S.; Cairns, S. M.; Akutagawa, K. and Bentrude, W. G., *J. Am. Chem. Soc.,* **1999**, *121*, 2085. (d) Bhanthumnavin, W.; Arif, A. and Bentrude, W. G., *J. Org. Chem.*, **1998**, *63*, 7753. (e) Mullah, K. B. and Bentrude, W. G., *Nucleosides & Nucleotides*, **1994**, *13*, 127. (f) Mullah, K. B. and Bentrude, W. G., *J. Org. Chem.,* **1991**, *56*, 7218.

13. Rumpf, P., *Bull. Soc. Chin. Fr.*, **1951**, *18*, 128.
14. Lewis, E. S. and Hamp, D., *J. Org. Chem.,* **1983**, *48*, 2025.
15. Bentrude, W. *G., Acc. Chem. Res.*, **1982**, *15*, 117.
16. Kabachnik, M. I. and Rossijskaja, P. A., *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1946**, 403 [*Chem. Abstr.*, **1948**, *42*, 7242].
17. Balthazor, T. M. and Grabiak, R. C., *J. Org. Chem.*, **1980**, *45*, 5425.
18. Renard, P. Y.; Vayron, P. and Mioskowski, C., *Org. Lett.,* **2003**, *5*, 1661.
19. Brill, T. E. and Landon, S. J., *Chem. Rev.*, **1984**, *84*.577.
20. (a) Kosolapoff, G. M., *Org. React.*, **1951**, *6*, 273. (b) Kosolapoff, G. M., *J. Am. Chem. Soc.*, **1945**, *67*, 2259.
21. (a) Aksnes, G. and Bernesen, K., *Acta. Chem. Scand.*, **1966**, *20*, 2508. (b) Helferich, B. and Aufderhaar, E., *Ann.*, **1962**, *658*, 100.
22. Razumov, A. I., *Zh. Obsh. Khim.*, **1959**, *29*, 1635 [*Chem. Abstr*., **1960**, *54*, 8608b].
23. Kosolapoff, G. M., *J. Am. Chem. Soc.*, **1949**, *71*, 369.
24. Surmatis, J. D. and Thommen, R., *J. Org. Chem.,* **1969**, *34*, 559.
25. Michaelis, A. and Becker, T., *Ber*., **1897**, *30*, 1003.
26. (a) Anderson, N. G.; Ciaramella, B. M.; Feldman, A. F.; Lust, D. A.; Moniot, J. L.; Moran, L.; Polomski, R. E. and Wang, S. S. Y., *Org. Proc. Res. Dev.*, **1997**, *1*, 211. (b) Megati, S.; Phadtare, S. and Zemlicka, J., *J. Org. Chem.,* **1992**, *57*, 2320. (c) Nielsen, J. and Caruthers, M. H., *J. Am. Chem. Soc.,* **1988**, *110*, 6275. (d) Omelanzcuk, J.; Sopchik, A. E.; Lee, S.-G.; Akutagawa, K.; Cairns, S. M. and Bentrude, W. G., *J. Am. Chem. Soc.*, **1988**, *110*, 6908. (e) Bao, Q.-B. and Brill, T. B., *Organometallics,* **1987**, *6*, 2588. (f) Spears, L. G.; Liao, A.; Minsek, D. and Lewis, E. S., *J. Org. Chem.*, **1987**, *52*, 61. (g) Bhattacharya, A. K. and Thyagarajan, G., *Chem. Rev.*, **1981**, *81*, 415. (h) Colle, K. S. and Lewis, E. S., *J. Org. Chem.*, **1978**, *43*, 571. (i) Fujii, A. and Miller, S. I., *J. Am. Chem. Soc.*, **1971**, *93*, 3694. (j) Gordon, M. and Griffin, C. E., *J. Org. Chem.,* **1966**, *31*, 333. (k) Buck, F. C. and Yoke, J. T., *J. Org. Chem.,* **1962**, *27*, 3675. (l) Harwood, H. J. and Grisley, D. W., *J. Am. Chem. Soc.*, **1960**, *82*, 423. (m) Garner, A. Y.; Chapin, E. C. and Scaslon, P. M., *J. Org. Chem.*, **1959**, *24*, 532. (n) Michaelis, A., *Ann.*, **1903**, *326*, 139.

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Michael-Stetter Reaction
(Stetter Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Stetter et al. in 1973.[1] It is a thiazolium-catalyzed nucleophilic conjugate addition of an aldehyde to an electron-deficient alkene to form a 1,4-bifunctional compound and is generally known as the Stetter reaction.[2,3] Occasionally, it is also referred to as the Stetter condensation.[4] Furthermore, since this reaction is analogous to the well-known *Michael Addition*, it is also called the Michael-Stetter reaction.[5] Besides thiazolium, imidazole and triazolium can also catalyze this reaction in a same way.[2b,2f,5c,5d] In this reaction, it is suggested that the addition of a catalyst to aldehyde changes the carbonyl group into an acyl anion equivalent,[2c] which then adds to an α,β-unsaturated compound (ketone, ester, nitrile, etc.) to form the 1,4-dicarbonyl compound.[5d] In addition, this reaction generally offers high enantioselectivity and diastereoselectivity,[2c] especially in the presence of a chiral triazolium salt;[2b,2c,2e] moreover, the intramolecular reaction is capable of forming tertiary ether, thioether, and quaternary stereocenters with very high enantioselectivity.[2e] However, the catalytic activity of thiazolium, as well as triazolium salt, is generally low for the Michael-Stetter reaction. Because the addition of acyl anion equivalent to α,β-unsaturated compound produces a relatively stable adduct,[2f] thiazolium or triazolium salt would not cleave from the adduct efficiently and resume another catalytic cycle.

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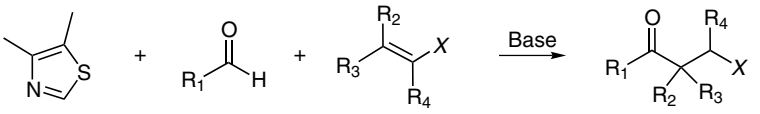
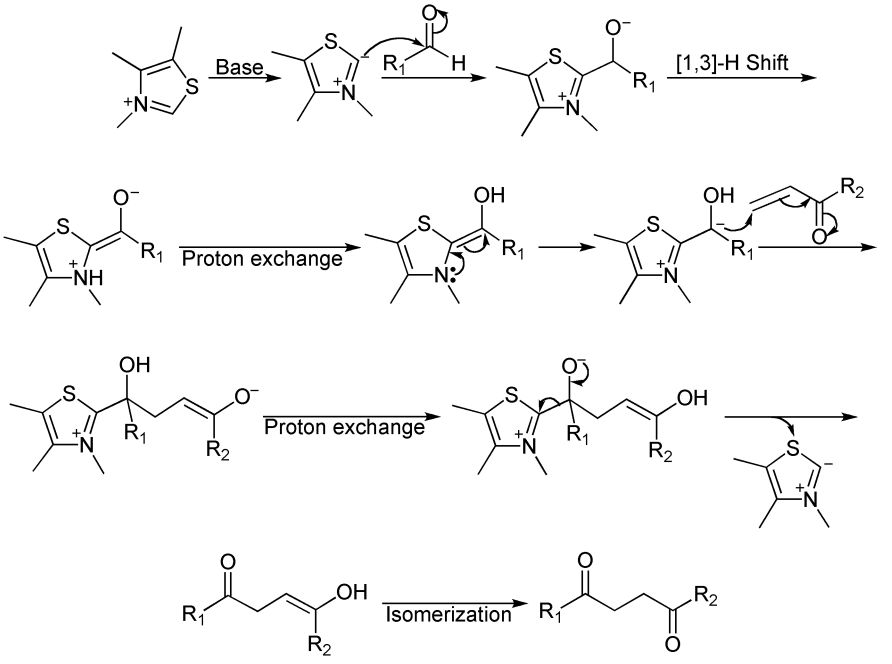
B. GENERAL REACTION SCHEME



(R_1 = H, alkyl, aryl
R_2 = H, alkyl
R_3 = H, alkyl, aryl
R_4 = H, alkyl, aryl
X = COR, CO_2R, CN, NO_2, SO_2R, etc.)

C. PROPOSED MECHANISMS

As the mechanism of this reaction is not very clear, a tentative mechanism between an aldehyde and an α,β-unsaturated ketone catalyzed by a thiazolium salt is displayed here.



D. MODIFICATION

N/A

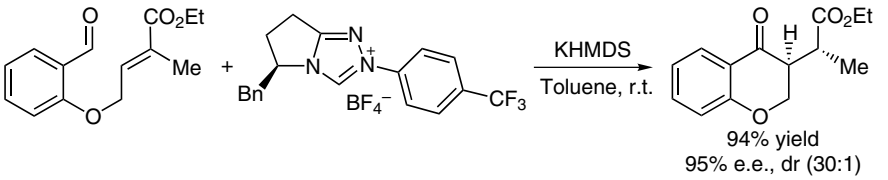
E. APPLICATIONS

This reaction has general application in the preparation of 1,4-bifunctional molecules starting from aldehydes.

F. RELATED REACTIONS

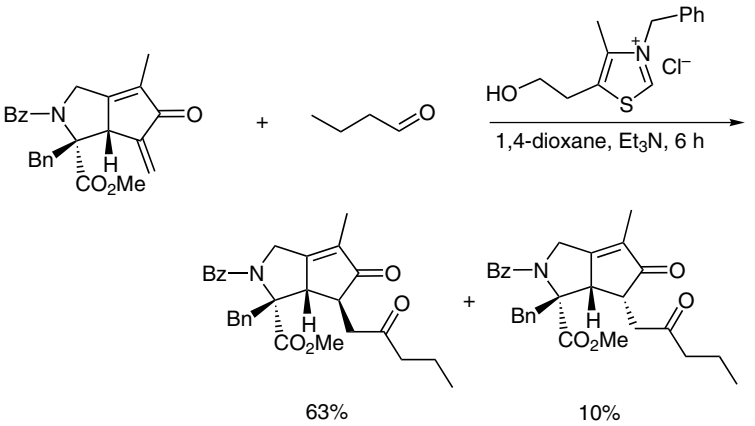
This reaction is related to the *Michael Addition*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2c.

To a flame-dried, round-bottomed flask was added 13.0 mg triazolium salt (0.031 mmol) and 2 mL toluene. To this solution was added 61 μL 0.5 M KHMDS solution (0.031 mmol) via syringe, and the solution was stirred at ambient temperature for 5 min. Toluene and HMDS were removed in vacuo by placement under high vacuum for 1 h. Then 3 mL toluene was added, followed by a solution of 38.0 mg substrate in 2 mL toluene, and the resulting solution was allowed to stir at ambient temperature for 24 h. The reaction was quenched with 2 mL 15% AcOH/toluene and concentrated. The residue was purified by flash column chromatography using mixture of hexane and EtOAc (6:1) as the eluent to afford 35.7 mg (2*R*,3′*S*)-(4-oxo-chroman-3-yl)-propionic acid ethyl ester as a white solid, in a yield of 94%. The product was tested to be pure enough with 95% e.e. and 30:1 dr, $R_f = 0.7$ (hexane/EtOAc, 1:1).



Reference 6.

To a solution of 163 mg 1-benzyl-2-benzoyl-4-methyl-5-oxo-6-methylene-1,2,3,5,6,6a-hexahydrocyclopenta[c]pyrrole-1-carboxylic acid methyl ester (0.403 mmol) in 2 mL 1,4-dioxane were added 42 μL Et_3N (0.30 mmol), 184 μL butyraldehyde (2.03 mmol), and 22 mg 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (0.080 mmol). The reaction vessel was sealed with a rubber septum and heated to 70°C for 6 h. The reaction mixture was then poured into 50 mL water, and the aqueous layer was extracted with Et_2O (3 $\times$ 25 mL). The combined organic layers were washed with 20 mL brine, dried over $MgSO_4$, and concentrated under vacuum. After the addition of 5 mL hexanes to the residue, a white precipitate formed. The precipitate was collected by decantation and purified by flash chromatography (hexanes/EtOAc, 9:1 to 2:1, v/v) to afford 121 mg of the major diastereomer of 2-benzoyl-1-benzyl-4-methyl-5-oxo-6-(2-oxopentyl)-1,2,3,5,6,6a-hexahydrocyclopenta[*c*]pyrrole-1-carboxylic acid methyl ester (63% yield) and 19 mg of the minor diastereomer (10% yield).

Other references related to the Michael-Stetter reaction are cited in the literature.[7]

H. REFERENCES

1. Stetter, H. and Schreckenberg, M., *Angew. Chem. Int. Ed. Engl.*, **1973**, *12*, 81.
2. (a) Nahm, M. R.; Potnick, J. R.; White, P. S. and Johnson, J. S., *J. Am. Chem. Soc.*, **2006**, *128*, 2751. (b) Liu, Q. and Rovis, T., *J. Am. Chem. Soc.*, **2006**, *128*, 2552. (c) de Alaniz, J. R. and Rovis, T., *J. Am. Chem. Soc.*, **2005**, *127*, 6284. (d) Ye, W.; Cai, G. L.; Zhuang, Z. Y.; Jia, X. S. and Zhai, H. B., *Org. Lett.*, **2005**, *7*, 3769. (e) Kerr, M. S. and Rovis, T., *J. Am. Chem. Soc.*, **2004**, *126*, 8876. (f) Enders, D. and Balensiefer, T., *Acc. Chem. Res.*, **2004**, *37*, 534. (g) Bhasin, M.; Billinsky, J. L. and Palmer, D. R. J., *Biochemistry*, **2003**, *42*, 13496.
3. (a) Liu, Q. and Rovis, T., *Org. Proc. Res. Dev.*, **2007**, *11*, 598. (b) Webber, P. and Krische, M. J., *Chemtracts*, **2006**, *19*, 262. (c) Moore, J. L.; Kerr, M. S. and Rovis, T., *Tetrahedron*, **2006**, *62*, 11477. (d) Zhou, Z.-Z.; Ji, F.-Q.; Cao, M. and Yang, G.-F., *Adv. Synth. Catal.*, **2006**, *348*, 1826. (e) Matsumoto, Y. and Tomioka, K., *Tetrahedron Lett.*, **2006**, *47*, 5843. (f) Nemoto, T.; Fukuda, T. and Hamada, Y., *Tetrahedron Lett.*, **2006**, *47*, 4365. (g) Reynolds, N. T. and Rovis, T., *Tetrahedron*, **2005**, *61*, 6368. (h) Christmann, M., *Angew. Chem. Int. Ed.*, **2005**, *44*, 2632. (i) Nakamura, T.; Hara, O.; Tamura, T.; Makino, K. and Hamada, Y., *Synlett*, **2005**, 155. (j) Mennen, S.; Blank, J.; Tran-Dube, M. B.; Imbriglio, J. E. and Miller, S. J., *Chem. Commun.*, **2005**, 195. (k) Anjaiah, S.; Chandrasekhar, S. and Gree, R., *Adv. Synth. Catal.*, **2004**, *346*, 1329. (l) Barrett, A. G. M.; Love, A. C. and Tedeschi, L., *Org. Lett.*, **2004**, *6*, 3377. (m) Gacem, B. and Jenner, G., *High Pressure Res.*, **2004**, *24*, 233. (n) Pesch, J.; Harms, K. and Bach, T., *Eur. J. Org. Chem.*, **2004**, 2025. (o) Mattson, A. E.; Bharadwaj, A. R. and Scheidt, K. A., *J. Am. Chem. Soc.*, **2004**, *126*, 2314. (p) Kerr, M. S. and Rovis, T., *Synlett*, **2003**, 1934. (q) Kerr, M. S.; Read de Alaniz, J. and Rovis, T., *J. Am. Chem. Soc.*, **2002**, *124*, 10298. (r) Gong, J. H.; Im, Y. J.; Lee, K. Y. and Kim, J. N., *Tetrahedron Lett.*, **2002**, *43*, 1247. (s) Enders, D.; Breuer, K.; Runsink, J. and Teles, J. H., *Helv. Chim. Acta*, **1996**, *79*, 1899. (t) Ciganek, E., *Synthesis*, **1995**, 1311. (u) Pouwer, K. L.; Vries, T. R.; Havinga, E. E.; Meijer, E. W. and Wynberg, H., *J. Chem. Soc., Chem. Commun.*, **1988**, 1432. (v) Stetter, H.; Kuhlmann, H. and Haese, W., *Org. Synth.*, **1987**, *65*, 26. (w) Parfenov, E. A.; Bekker, A. R. and Kosterova, G. F., *Zh. Org. Khim.*, **1981**, *17*, 885.
4. Ho, T. L. and Liu, S. H., *Synth. Commun.*, **1983**, *13*, 1125.
5. (a) Zhou, Z.-Z.; Ji, F.-Q. and Yang, G.-F., *Youji Huaxue*, **2006**, *26*, 906. (b) Nair, V.; Sreekumar, V.; Bindu, S. and Suresh, E., *Org. Lett.*, **2005**, *7*, 2297. (c) Nair, V.; Bindu, S.; Sreekumar, V. and Rath, N. P., *Org. Lett.*, **2003**, *5*, 665. (d) Bourissou, D.; Guerret, O.; Gabbaï, F. P. and Bertrand,

G., *Chem. Rev.*, **2000**, *100*, 39. (e) Powell, P. and Sosabowski, M. H., *J. Chem. Res. (S)*, **1995**, 306. (f) Phillips, R. B.; Herbert, S. A. and Robichaud, A. J., *Synth. Commun.*, **1986**, *16*, 411.

6. Brummond, K. M.; Curran, D. P.; Mitasev, B. and Fischer, S., *J. Org. Chem.*, **2005**, *70*, 1745.
7. (a) Mattson, A. E.; Bharadwaj, A. R. and Scheidt, K. A., *J. Am. Chem. Soc.*, **2004**, *126*, 2314. (b) Enders, D. and Kallfass, U., *Angew. Chem. Int. Ed.*, **2002**, *41*, 1743. (c) Davis, J. H. and Forrester, K., *Tetrahedron Lett.*, **1999**, *40*, 1621. (d) Woo, P. W. K.; Hartman, J.; Huang, Y.; Nanninga, T.; Bauman, K.; Butler, D. E.; Rubin, J. R.; Lee, H. T. and Huang, C. C., *J. Labelled Compd. & Radiopharm.*, **1999**, *42*, 121. (e) Enders, D.; Breuer, K.; Runsink, J. and Teles, J. H., *Helv. Chim. Acta,* **1996**, *79*, 1899. (f) Teles, J. H.; Melder, J. P.; Ebel, K.; Schneider, R.; Gehrer, E.; Harder, W.; Brode, S.; Enders, D.; Breuer, K. and Rabbe, G., *Helv. Chim. Acta*, **1996**, *79*, 1271. (g) Stetter, H. and Kuhlmann, H., *Org. React*., **1991**, *40*, 407. (h) Stetter, H. and Skobel, H., *Ber*., **1987**, *120*, 643. (i) Stetter, H. and Haese, W., *Ber*., **1984**, *117*, 682. (j) Stetter, H., *Angew. Chem*., **1976**, *88*, 695. (k) Stetter, H., *Angew. Chem. Int. Ed. Engl*., **1976**, *15*, 639. (l) Stetter, H. and Huhlmann, H., *Ber.*, **1976**, *109*, 2890.

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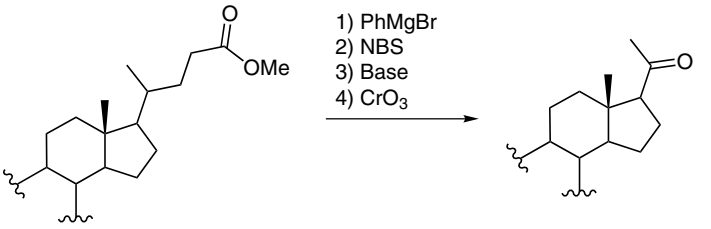
Miescher Degradation
(Meystre-Miescher Degradation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Meystre and Miescher et al. in 1944.[1] It is a multistep cleavage of the side chain of steroid, such as bile acid methyl ester, to the stage of methyl ketone by sequential reactions with the phenyl Grignard reagent, dehydration of resulting tertiary alcohol to alkene, α-bromination by *N*-succinimide bromide, dehydrobromination of allyl bromide to form a conjugated diene, and oxidation of the diene by chromium trioxide. Thus it is known as the Miescher degradation[2] or Meystre-Miescher degradation.[3]

B. GENERAL REACTION SCHEME



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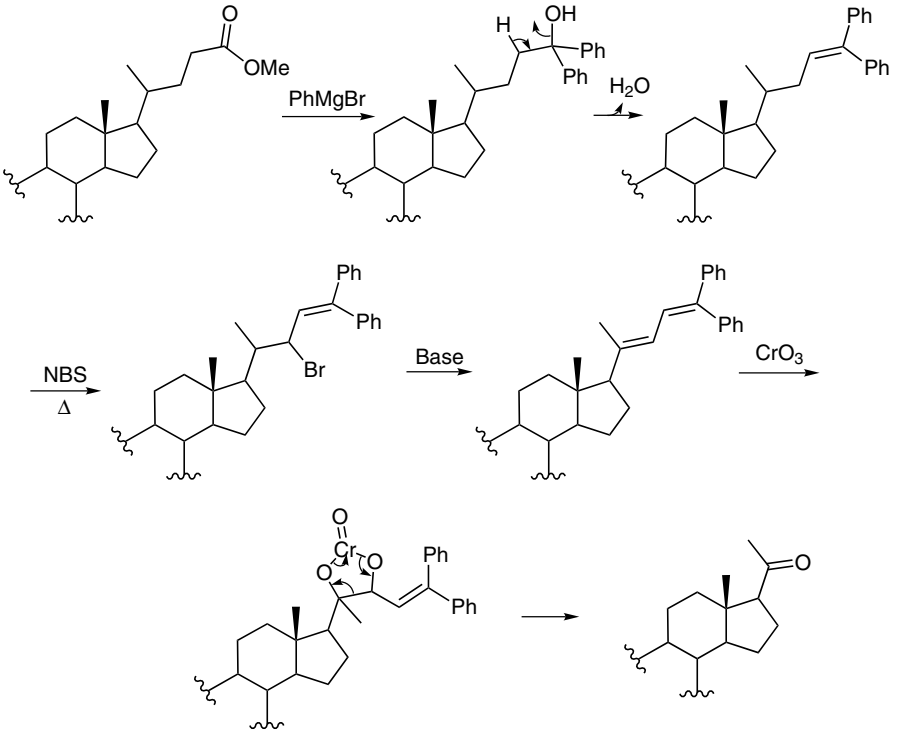
C. PROPOSED MECHANISMS

This reaction is a multistep process, and the reaction scheme displayed here illustrates the mechanism.



D. MODIFICATION

N/A

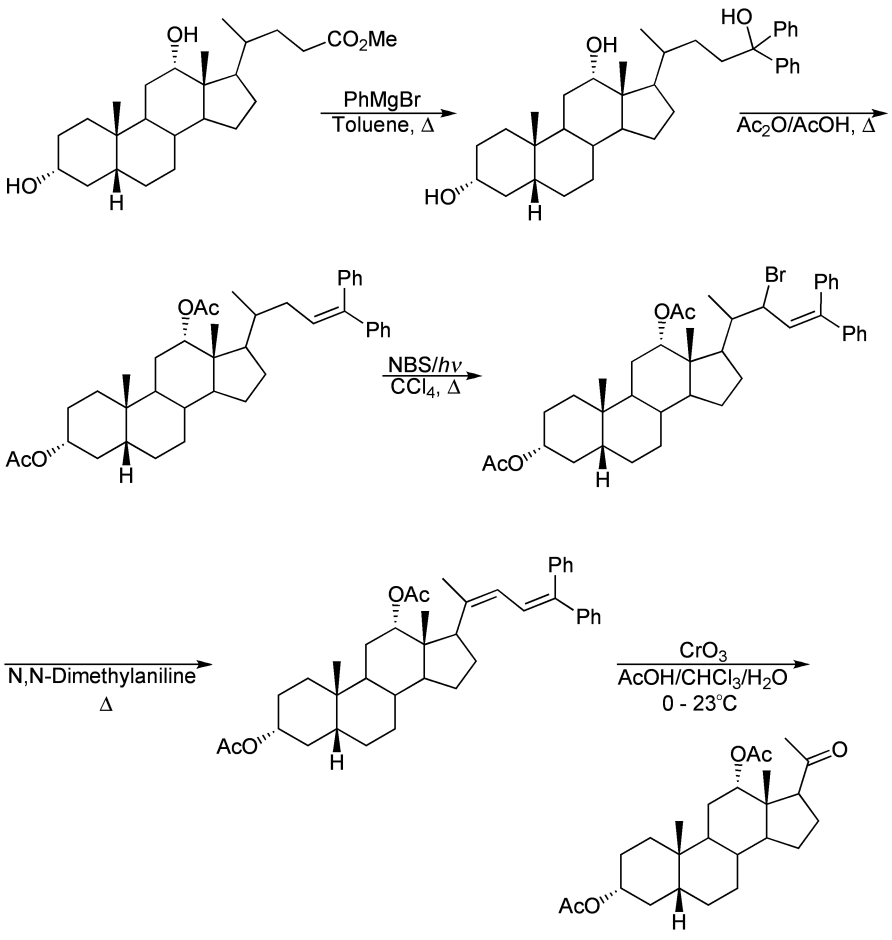
E. APPLICATIONS

This reaction has limited application in organic synthesis but is used primarily in steroid chemistry.

F. RELATED REACTIONS

This reaction is related to the *Barbier-Wieland Degradation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4.

Preparation of 3α,6β-Dihydroxy-*nor*-cholanyldiphenylcarbinol

A solution of 1 Kg methyl hyodesoxycholate in 12 L hot toluene was added to 7 L dry ether containing 39 mol PhMgBr. The ether was distilled off during the addition, and the reaction mixture was refluxed overnight. The mixture was worked up in the usual way to afford 1035 g crude 3α,6β-dihydroxy-*nor*-cholanyldiphenylcarbino1, m.p. 203–205°C (recrystallized twice from benzene).

Formation of 3α,6β-Dihydroxy-*bis*-*nor*-cholanyldiphenylethylene

3α,6β-Dihydroxy-*nor*-cholanyldiphenylcarbino1 (5 g) in a mixture of 100 mL acetic acid and 5 mL acetic anhydride was refluxed for 4 h. The solution was concentrated and poured into cold water. The suspended solid was coagulated by warming and dissolved in 300 mL methanol. NaOH (12 g) in 20 mL water was added, and the solution was

refluxed for 1 h, filtered, and diluted with water to afford 4.7 g 3α,6β-dihydroxy-*bis-nor*-cholanyldiphenylethylene as solid, m.p. 181–183°C. Recrystallization from 80% methanol gave needles, m.p., 184–186°C. (*Note*: The deacetylation is not necessary in this preparation, so that the next step of acetylation can be skipped.)

Preparation of 3α,6β-Diacetoxy-*bis-nor*-cholanyldiphenylethylene

A solution of 68.7 g 3α,6β-dihydroxy-*bis-nor*-cholanyldiphenyl-ethylene in 360 mL acetic acid and 36 mL acetic anhydride was refluxed for 3.5 h, cooled, filtered, and concentrated in vacuo. Petroleum ether (b.p. 100°C) was added and distilled off under reduced pressure to remove the last traces of acetic anhydride. The residue was crystallized from CCl_4 from which it separated with 31% of solvent which could be removed only by fusion; weight 82.5 g, m.p. 80–92°C. A sample of the glass remaining after drying in vacuo at 100°C was crystallized first from acetone and then from methanol to afford white crystals, m.p. 121.5–124°C.

Formation of 3α,6β-Diacetoxy-pregnan-20-one

To a solution of 54.2 g 3α,6β-diacetoxy-*bis-nor*-cholanyldiphenylethylene in 800 mL CCl_4 was added 17.8 g NBS. The flask was illuminated with a 150-W reflector floodlight and heated to reflux for 15 min. After cooling, the succinimide and excess *N*-bromosuccinimide were removed by filtration. To this solution was added 81 mL dimethylaniline; the solvent (CCl_4) was distilled off, and the residue was heated at reflux temperature for 10 min. After cooling, 300 mL 10% HCl was added and the mixture was shaken with ether and benzene. The ether-benzene layer was separated, washed with water, and dried over Na_2SO_4. The solvent was removed, and the residue was reacetylated by refluxing for 2 h with acetic acid (100 mL) and 25 mL acetic anhydride. After removing the solvent in vacuo, 62 g crude 1-(3,6-diacetoxy-*etio*-cholanyl)-1-methyl-4,4-diphenyl-1,3-butadiene was obtained. This crude butadiene was mixed with 125 mL acetic acid, 125 mL $CHCl_3$, and 25 mL H_2O and maintained at the temperature between 0° and 23°C. Then the solution of 40 g CrO_3 in 130 mL H_2O and 640 mL acetic acid was added while maintaining at the same temperature. After the oxidation, the excess CrO_3 was destroyed with SO_2, and the solvent was removed in vacuo. The residue was shaken with water and extracted with a mixture of $CHCl_3$ and ether, which was washed with 5% $NaHCO_3$ solution, water, dried over Na_2SO_4. Removal of the solvent left 57 g residue, which was subjected to a ketone separation with Girard's reagent P. The ketone-containing fraction weighed 14 g and was crystallized from methanol containing a little water, giving 3α,6β-diacetoxy-pregnan-20-one, m.p. 120–122°C. Further column chromatography on alumina afforded a fraction that after crystallization from petroleum ether (b.p. 69°C) and then from methanol melted at 131–133°C.

Other references related to the Miescher degradation are cited in the literature.[5]

H. REFERENCES

1. Meystre, C.; Frey, H.; Wettstein, A. and Miescher, K., *Helv. Chim. Acta,* **1944**, *27*, 1815.
2. Pines, S. H., *Org. Proc. Res. Dev.,* **2004**, *8*, 708.

3. (a) Shimizu, K.; Yamaga, N. and Kohara, H., *Steroids,* **1988**, *51*, 283. (b) Brown, K. S. and Kupchan, S. M., *J. Am. Chem. Soc.,* **1962**, *84*, 4592. (c) Bharucha, K. R., *Experientia*, **1958**, *14*, 5.
4. Moffett, R. B.; Stafford, J. E.; Linsk, J. and Hoehn, W. M., *J. Am. Chem. Soc.,* **1946**, *68*, 1857.
5. (a) Fieser, L. F. and Fieser, M., *Steroids,* Reinhold Publishing: New York, **1959**, p. 645. (b) Sarel, S. and Yanuka, Y., *J. Org. Chem.,* **1959**, *24*, 2018. (c) Wettstein, A. and Anner, G., *Experientia,* **1954**, *10*, 397. (d) Turner, R. B.; Mattox, V. R.; McGuckin, W. F. and Kendall, E. C., *J. Am. Chem. Soc.,* **1952**, *74*, 5814. (e) Gallagher, T. F. and Elisberg, E., *J. Am. Chem. Soc.,* **1951**, *73*, 194. (f) Spring, F. S., *J. Chem. Soc.,* **1950**, 3355. (g) MacPhillamy, H. B. and Scholz, C. R., *J. Org. Chem.,* **1949**, *14*, 643. (h) Shoppee, C. W., *Ann. Repts. (Chem. Soc. London),* **1947**, *44*, 187. (i) Miescher, K. and Schmidlin, *Helv. Chim. Acta,* **1947**, *30*, 1405. (j) Meystre, C. and Miescher, K., *Helv. Chim. Acta,* **1946**, *29*, 33.

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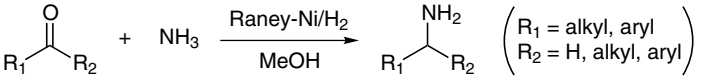
Mignonac Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Mignonac in 1921.[1] It is a direct synthesis of primary amines from catalytic hydrogenation of aldehydes or ketones over nickel in liquid ammonia or in alcohol saturated with ammonia and is known as the Mignonac reaction.[2] In addition, this reaction can also be applied to the hydrogenation of an oxime for the preparation of corresponding amine.[3] It has been found that the yield of amines can be enhanced if the intermediates from aldehydes or ketones with ammonia are isolated and the subsequent hydrogenation is carried out in an organic solvent.[3] In addition, this reaction has been improved by reduction of aldehydes or ketones over Raney nickel with a hydrogen pressure of 20–150 atms at temperatures ranging from 40° to 150°C.[4] However, this modification often requires high-pressure equipment.[5] An additional modification of this reaction is to carry out the reduction of aldehydes or ketones over platinum oxide in the presence of an excess amount of ammonium chloride in methanol that is saturated with ammonia, so that the newly generated primary amine is protonated immediately from ammonium chloride and can not further attack the rest of carbonyl compound.[5]

B. GENERAL REACTION SCHEME



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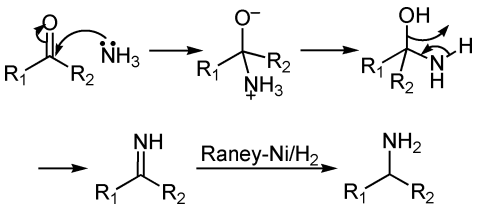
C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified by the addition of an excess amount of ammonium chloride in alcohol during the catalytic hydrogenation.

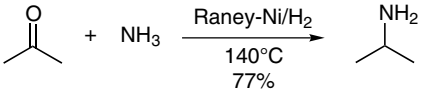
E. APPLICATIONS

This reaction has general application in the conversion of aldehydes or ketones into primary amines.

F. RELATED REACTIONS

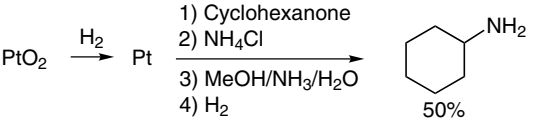
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 6.

A mixture of 696 g acetone (12.0 mol) and 204 g ammonia (12 mol) was hydrogenated in a stirred autoclave over 50 g Raney nickel at 140°C and 740 psi of hydrogen. After the reaction completed, the mixture was distilled to afford 545 g isopropylamine, in a yield of 77%, b.p. 31.5–32.5°C.



Reference 5.

In a 300-mL reduction bottle were added 10 mL distilled water and 0.2 g platinum oxide, and platinum oxide was reduced to platinum by shaking in an atmosphere of hydrogen for ~ 10 min. Then 29.4 g cyclohexanone (0.3 mol), 20.0 g NH_4Cl (0.37 mol), 225 mL absolute MeOH saturated with ammonia, and 25 mL aqueous ammonia were added to the reduction bottle. The mixture was reduced by shaking with hydrogen at 1–3 atms. Hydrogenation was continued until a constant pressure reading indicated the completion of the reduction. The shaker was then stopped, the bottle was vented, and the catalyst was allowed to settle. The platinum was removed by filtering the mixture through a Hirsch funnel into a 1-L round-bottomed flask, and any salt that collected on the filter was rinsed down with water. The flask and contents were then removed to a hood and refluxed under a condenser for 1 h to remove the excess ammonia. The solution was cooled, acidified to congo red paper with concentrated hydrochloric acid, and evaporated to about half of its volume under vacuum. Then 200 mL water was added, and the solution was washed with benzene (3×25 mL). The benzene extracts were discarded. The aqueous solution was then made strongly basic with 50% NaOH, the two layers formed were separated, and the water layer was extracted three or four times with ether. The ether extracts and the oily layer were then combined, washed with water, and dried over KOH. The cyclohexylamine was purified by distillation through a 13-cm. column packed with glass helices, in a yield of 50%.

Other references related to the Mignonac reaction are cited in the literature.[7]

H. REFERENCES

1. Mignonac, G., *Compt. Rend.,* **1921**, *172*, 223.
2. Sen, D. J. and Pandya, D., *Pharma Times,* **2004**, *36*, 22.
3. Winans, C. F. and Adkins, H., *J. Am. Chem. Soc.,* **1933**, *55*, 2051.
4. (a) Schwoegler and Adkins, H., *J. Am. Chem. Soc.,* **1939**, *61*, 3499. (b) Winans, C. F., *J. Am. Chem. Soc.,* **1939**, *61*, 3566.
5. Alexander, E. R. and Misegades, A. L., *J. Am. Chem. Soc.,* **1948**, *70*, 1315.
6. Norton, D. G.; Haury, V. E.; Davis, F. C.; Mitchell, L. J. and Ballard, S. A., *J. Org. Chem.,* **1954**, *19*, 1054.
7. (a) Lawrence, S. A., *Amines, Synthesis, Properties and Applications,* Cambridge University Press, Cambridge, **2004**. (b) Randvere, F., *Anal. Farm. Bioquim.,* **1948**, *19*, 81. (c) Winans, C. F. and Adkins, H., *J. Am. Chem. Soc.,* **1932**, *54*, 306. (d) Mignonac, G., *Compt. Rend.,* **1921**, *172*, 275.

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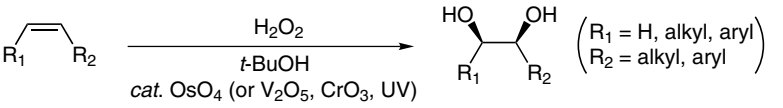
Milas Hydroxylation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Milas and Sussman in 1936.[1] It is a transformation of olefins into *cis*-diols by the oxidation with anhydrous hydrogen peroxide (H_2O_2) in *tert*-butyl or *tert*-amyl alcohol in the presence of a catalytic amount of osmium tetroxide (OsO_4). Therefore, this reaction is known as the Milas hydroxylation, and hydrogen peroxide is referred to as the Milas reagent.[2] In the absence of OsO_4, the hydroxylation of olefin by H_2O_2 is not likely to occur.[1] However, OsO_4 is not the only reagent to trigger this hydroxylation, other transition metal oxides such as vanadium pentoxide and chromium trioxide are also effective under similar conditions,[3] even ultraviolet light can initiate the hydroxylation.[4] It has been found that this reaction exclusively affords the *cis*-diols;[3,5] although in some cases, it further converts the diols into other products due to overoxidation. For example, the hydroxylation of cyclohexene results in a large quantity of adipic acid,[3] while the oxidation of stilbene gives benzaldehyde quantitatively.[4] It has been found that solvents have a very important role in this reaction. For instance, the hydroxylation of alkene in the presence of OsO_4 in diethyl ether gives aldehyde predominantly.[6] It is interesting that the hydroxylation of conjugate dienes, as in the case of cyclopentadiene, affords *cis*-1,4-diols.[7] This reaction has been extended by Sharpless using *tert*-buyl peroxide as the oxidation agent under basic conditions to suppress the by-products,[2] such as the application of tetraethylammonium hydroxide as the base in *t*-BuOH or tetraethylammonium acetate as the base in acetone.[8]

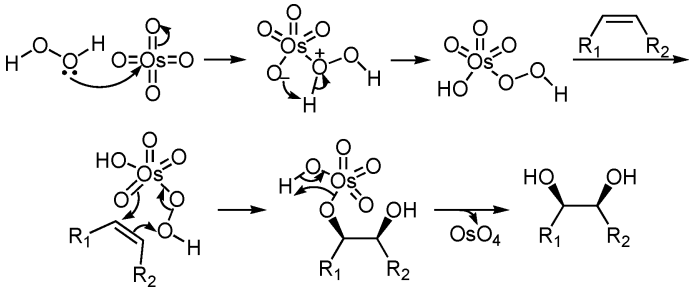
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Although a mechanism has been proposed for this reaction,[9] it does not correctly present the real reaction path. Thus a tentative mechanism is outlined here. In the current mechanism, the peroxide bond in H_2O_2 is weakened through the bonding with osmium tetroxide, functioning as a strong electron-withdrawing group, so that the peroxide can easily add to the C=C double bond through a six-membered transition state, resulting in *cis*-diol. In addition, osmium tetroxide leaves the catalytic cycle upon the formation of *cis*-diol. There would be no reduction of osmium tetroxide by olefin to the Os(VI) complex, which is then oxidized by H_2O_2 to OsO_4.



D. MODIFICATION

This reaction has been modified by Sharpless to take place under basic conditions using *tert*-butyl peroxide as a hydroxylation agent.[2,8]

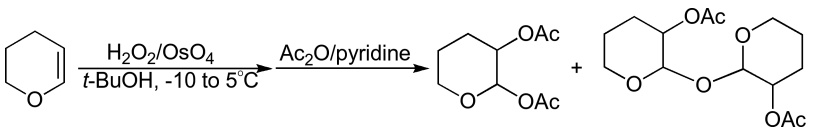
E. APPLICATIONS

This reaction is very useful for the preparation of *cis*-diols from olefins.

F. RELATED REACTIONS

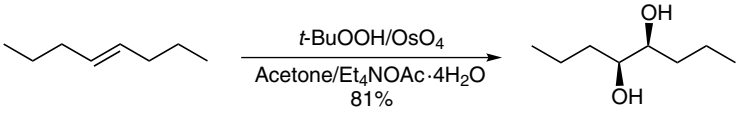
This reaction is related to the *Sharpless Dihydroxylation* and *Prévost Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 10.

To a 2-L three-necked flask was added 196 g 3,4-dihydro-2H-pyran (2.3 mol) and 5 mL osmium tetroxide catalyst prepared from 0.5 g OsO_4 in 100 mL *t*-BuOH. While the flask was cooled to −10° to 5°C, 1320 mL 6% hydrogen peroxide in *t*-BuOH was added dropwise under stirring over a period of 4 h. An additional 3 mL catalyst solution was added after 2 hours and after all of the peroxide solution had been added. The reaction is highly exothermic, and care must be exercised not to add the peroxide at too fast a rate. The solution was allowed to stand overnight. The solvent was removed under reduced pressure at a bath temperature of 60°C or below. The residue (255 g) was acetylated by dissolving it in 600 mL pyridine and adding 750 mL acetic anhydride at 10°C. The solution was allowed to warm to room temperature and stand overnight. After destruction of the unused acetic anhydride by addition of excess 75% EtOH, the solvent was removed at reduced pressure. The residue (335 g) was allowed to stand overnight, whereupon some crystallization was noted, leading to 53 g 2-acetyl-3,4-dideoxyaldopentosyl 2-acetyl-3,4-dideoxyaldopentoside, which was collected on a filter. The solid was recrystallized from MeOH, m.p. 132–133°C. The filtrate, after separation of the disaccharide, was distilled at 1 mmHg to afford 135 g crude 2,3-diacetoxytetrahydropyran, b.p. 96–115°C. Redistillation of this material gave 115 g 2,3-diacetoxytetrahedropyran collected at 108–120°C and 2–5 mmHg.



Reference 8.

A 1-L Erlenmeyer flask equipped with magnetic stirrer was charged with 200 mL acetone, 11.2 g (*E*)-4-octene (100 mmol), 6.5 g $Et_4NOAc{\cdot}4H_2O$(25 mmol), and 18 mL (∼162 mmol) 90+% *tert*-butyl hydroperoxide. The mixture was stirred at room temperature until the Et_4NOAc had dissolved. The resulting solution was cooled in an ice bath and 10 mL (i.e., 50 mg or 0.2 mmol of OsO_4) of the catalyst solution containing OsO_4 in *tert*-butyl alcohol was added in one portion. The solution immediately became brownish purple. After 1 h, the ice bath was removed and the reaction mixture was allowed to warm to room temperature, stoppered loosely, and stirred overnight. Ether (400 mL) was added, and the resulting mixture was cooled by stirring in an ice bath. Then 50 mL of freshly prepared 10% $NaHSO_3$ solution was added in one portion. The ice bath was removed, and stirring was continued for 1 h, at which point the organic layer had become almost colorless. Solid NaCl was added until the aqueous layer was saturated, and stirring of the two-phase mixture was continued for several minutes. The organic layer was separated and washed with 50 mL brine. The combined aqueous layers were extracted with ether (2 × 100 mL). The combined organic layers were dried over Na_2SO_4 and when concentrated afforded an oil that,

upon distillation, gave 11.8 g *threo*-4,5-dihydroxyoctane, in a yield of 81%, b.p. 87–90°C (3 mmHg).

Other references related to the Milas hydroxylation are cited in the literature.[11]

H. REFERENCES

1. Milas, N. A. and Sussman, S., *J. Am. Chem. Soc.,* **1936**, *58*, 1302.
2. Sharpless, K. B. and Akashi, K., *J. Am. Chem. Soc.,* **1976**, *98*, 1986.
3. Milas, N. A., *J. Am. Chem. Soc.,* **1937**, *59*, 2342.
4. (a) Milas, N. A., *J. Am. Chem. Soc.,* **1937**, *59*, 543. (b) Milas, N. A. and Sussman, S., *J. Am. Chem. Soc.,* **1937**, *59*, 2345.
5. Daniels, R. and Fischer, J. L., *J. Org. Chem.,* **1963**, *28*, 320.
6. Criegee, R., *Ann.,* **1936**, *522*, 75.
7. Milas, N. A. and Maloney, L. S., *J. Am. Chem. Soc.,* **1940**, *62*, 1841.
8. (a) See *Sharpless Dihydroxylation* herein (P. 2574). (b) Akashi, K.; Palermo, R. E. and Sharpless, K. B., *J. Org. Chem.,* **1978**, *43*, 2063.
9. Milas, N. A.; Trepagnier, J. H.; Nolan, J. T. and Iliopulos, M. I., *J. Am. Chem. Soc.,* **1959**, *81*, 4730.
10. Hurd, C. D. and Kelso, C. D., *J. Am. Chem. Soc.,* **1948**, *70*, 1484.
11. (a) Jonsson, S. Y.; Färnegårdh, K. and Bäckvall, J.-E., *J. Am. Chem. Soc.,* **2001**, *123*, 1365. (b) Kolb, H. C.; VanNieuwenhze, M. S. and Sharpless, K. B., *Chem. Rev.,* **1994**, *94*, 2483. (c) Minato, M.; Yamamoto, K. and Tsuji, J., *J. Org. Chem.,* **1990**, *55*, 766. (d) Holder, N. L., *Chem. Rev.,* **1982**, *82*, 287. (e) Schroder, M., *Chem. Rev.,* **1980**, *80*, 187. (f) Eastham, J. F.; Milas, G. B. and Krauth, C. A., *J. Am. Chem. Soc.,* **1959**, *81*, 3114. (g) Cook, J. W. and Schoental, R., *J. Chem. Soc.,* **1950**, 47. (h) Milas, N. A.; Sussman, S. and Mason, H. S., *J. Am. Chem. Soc.,* **1939**, *61*, 1844.

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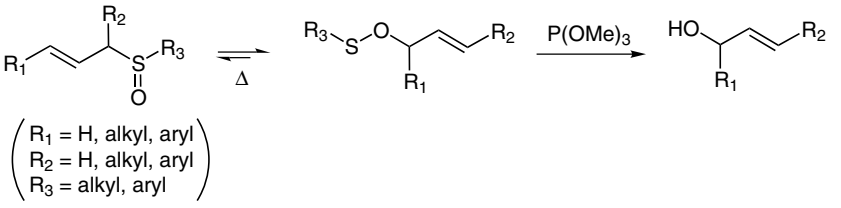
Mislow-Evans Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

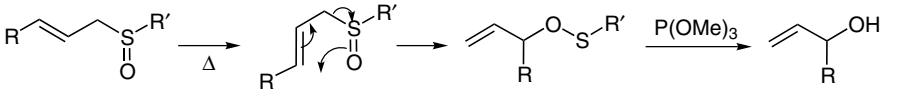
This reaction was first reported by Mislow et al. in 1968,[1] and was subsequently developed by Evans into a valuable method for the synthesis of allylic alcohols.[2] It is a base-promoted [2,3]-sigmatropic rearrangement of allyl sulfoxide into relatively unstable allyl sulfenate, which then decomposes into the corresponding allylic alcohol in the presence of a thiophilic reagent. Therefore, this reaction is generally known as the Mislow-Evans rearrangement.[3] Occasionally, this reaction is also referred to as the Mislow-Evans reaction,[3j] Mislow-Evans-Braverman rearrangement[4] or Mislow-Evans sulfenate-sulfoxide rearrangement.[5] This reaction is highly stereoselective[3g,3k,3l] and always gives *trans*-allylic alcohol predominately if a bulky substituent presents on the allyl sulfoxide. Whereas allyl sulfoxide without a bulky group yields the thermodynamically controlled mixture of allylic alcohols.[3m] On the other hand, this reaction is also sensitive to solvation.[3j] For example, the rearrangement rate of allyl *p*-tolyl sulfoxide is reduced by factors of 29 or 332 at 67°C in ethanol and 2,2,3,3-tetrafluoro-1-propanol, respectively, if compared with the reaction in methylcyclohexane.[1] This is rationalized by the further stabilization of allyl sulfoxide by solvation from a polar solvent, which increases the activation energy for the transformation of allyl sulfoxide to sulfenate, a less polar structure than sulfoxide.[3j]

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

N/A

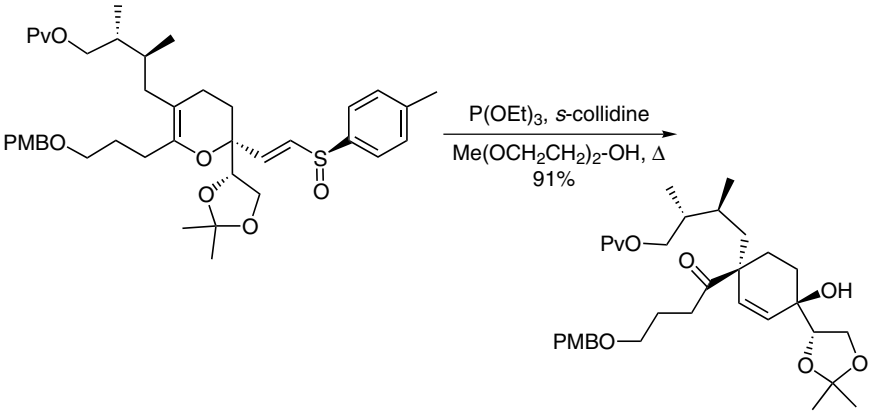
E. APPLICATIONS

This reaction has general application in the preparation of *trans*-allylic alcohols.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3e.

A solution of 0.154 g vinylic sulfoxide (0.217 mmol), 0.18 mL triethyl phosphite (1.05 mmol), and 0.14 mL *s*-collidine (1.05 mmol) in 2.7 mL $MeOCH_2CH_2OCH_2CH_2OH$ was heated at 150°C for 15 h in a sealed vial under argon. After cooling, the reaction mixture was diluted with EtOAc and washed with saturated aqueous NH_4Cl and then water three times. The combined aqueous layers were extracted with EtOAc. The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexanes, 2:3) to yield 0.117 g allyl alcohol after drying in high vacuum at 50°C to remove the residual *s*-collidine, in a yield of 92%. (*Note*: The whole process involves a [3,3]-Claisen rearrangement and subsequent Mislow-Evans rearrangement.)

Other references related to the Mislow-Evans rearrangement are cited in the literature.[6]

H. REFERENCES

1. Bickart, P.; Carson, F. W.; Jacobus, J.; Miller, E. G. and Mislow, K., *J. Am. Chem. Soc.,* **1968**, *90*, 4869.
2. (a) Evans, D. A.; Andrews, G. C. and Sims, C. L., *J. Am. Chem. Soc.,* **1971**, *93*, 4956. (b) Evans, D. A. and Andrews, G. C., *Acc. Chem. Res.,* **1974**, *7*, 147.
3. (a) Pelc, M. J. and Zakarian, A., *Tetrahedron Lett*., **2006**, *47*, 7519. (b) Hagiwara, H.; Isobe, K.; Numamae, A.; Hoshi, T. and Suzuki, T., *Synlett*, **2006**, 1601. (c) Charest, M. G.; Lerner, C. D.; Brubaker, J. D.; Siegel, D. R. and Myers, A. G., *Science,* **2005**, *308*, 395. (d) Yeung, K.-S. and Paterson, I., *Chem. Rev.,* **2005**, *105*, 4237. (e) Pelc, M. J. and Zakarian, A., *Org. Lett.,* **2005**, *7*, 1629. (f) Repasky, M. P.; Guimarães, C. R. W.; Chandrasekhar, J.; Tirado-Rives, J. and Jorgensen, W. L., *J. Am. Chem. Soc.,* **2003**, *125*, 6663. (g) Fokin, A. A.; Kushko, A. O.; Kirij, A. V.; Yurchenko, A. G. and Schleyer, P. V. R., *J. Org. Chem.,* **2000**, *65*, 2984. (h) Jenson, C. and Jorgensen, W. L., *J. Am. Chem. Soc.,* **1997**, *119*, 10846. (i) Lim, D. and Jorgensen, W. L., *J. Phys. Chem.,* **1996**, *100*, 17490. (j) Jones-Hertzog, D. K. and Jorgensen, W. L., *J. Am. Chem. Soc.,* **1995**, *117*, 9077. (k) Sato, T.; Shima, H. and Otera, J., *J. Org. Chem.,* **1995**, *60*, 3936. (l) Jones-Hertzog, D. K. and Jorgensen, W. L., *J. Org. Chem.,* **1995**, *60*, 6682. (m) Sato, T.; Otera, J. and Nozaki, H., *J. Org. Chem.,* **1989**, *54*, 2779. (n) Masaki, Y.; Sakuma, K. and Kaji, K., *Chem. Pharm. Bull.,* **1985**, *33*, 2531. (o) Bartlett, P. A. and McQuaid, L. A., *J. Am. Chem. Soc.,* **1984**, *106*, 7854.
4. (a) Satoh, T. and Miyagawa, T., *Tetrahedron Lett*., **2006**, *47*, 1981. (b) Alameda-Angulo, C.; Quiclet-Sire, B.; Schmidt, E. and Zard, S. Z., *Org. Lett.,* **2005**, *7*, 3489.
5. (a) Smith, A. B. and Adams, C. M., *Acc. Chem. Res.*, **2004**, *37*, 365. (b) Zhou, Z. H. S.; Flohr, A. and Hilvert, D., *J. Org. Chem.,* **1999**, *64*, 8334.
6. (a) Aubele, D. L.; Wan, S. Y. and Floreancig, P. E., *Angew. Chem. Int. Ed.,* **2005**, *44*, 3485. (b) Shinada, T.; Fuji, T.; Ohtani, Y.; Yoshida, Y. and Ohfune, Y., *Synlett*, **2002**, 1341. (c) Prilezhaeva, E. N., *Russ. Chem. Rev.,* **2001**, *70*, 897. (d) Hartley, R. C.; Richards, I. C. and Warren, S., *J. Chem. Soc., Perkin Trans. I,* **1996**, 359. (e) Jursic, B. S., *THEOCHEM,* **1995**, *358*, 131. (f) Jorgensen, W. L.; Blake, J. F.; Lim D. and Severance, D. L., *Trans. Faraday Soc.,* **1994**, *90*, 1727. (g) Sato, T. and Otera, J., *Tetrahedron Lett*., **1994**, *35*, 6701. (h) Majetich, G.; Song, J. C.; Ringold, C.; Nemeth, G. A. and Newton, M. G., *J. Org. Chem.,* **1991**, *56*, 3973. (i) Tang, R. and Mislow, K., *J. Am. Chem. Soc.,* **1970**, *92*, 2100.

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Mitsunobu Reaction

(Mitsunobu Coupling, Mitsunobu Esterification)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Mitsunobu in 1967.[1] It is the alkylation of compounds with active protons by using primary or secondary alcohols as the alkylating agents in combination with triphenylphosphine and diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD), to form molecules like esters, ethers, thioethers, and amines. Therefore, this reaction is generally known as the Mitsunobu reaction[2] or Mitsunobu coupling.[3] In addition, the specific reaction for forming esters by means of DEAD (or DIAD) and PPh_3 is generally referred to as the Mitsunobu esterification.[4] Occasionally, the Mitsunobu reaction is also called the Mitsunobu transformation (for the conversion of alcohol into amines)[5] or Mitsunobu cyclization (for the formation of cyclic compounds).[6] Because of its intrinsic features of stereospecificity,[7] as well as its occurrence in neutral media and at room temperature[8] without a prerequisite activation of alcohol,[8b] this reaction has been extensively studied and used to synthesize a variety of compounds since 1970.

It is known that this reaction begins with the formation of a relatively stable betaine,[4b,4f,9] called the Morrison-Brunn-Huisgen intermediate,[9a,9c,10] through the irreversible Michael-type nucleophilic addition of triphenylphosphine on the N=N double bond of DEAD.[4f,9b,9d] Then the betaine intermediate abstracts a hydrogen atom from the nucleophile carrying an active proton,[9a] and alkoxy phosphonium salt[4i,4j,9a,9d,11] or alkoxyphosphorane[4i,4j,7c,9d,11c,12] forms, which then undergoes a normal S_N2 displacement from nucleophile to give the corresponding product. It has been found that both

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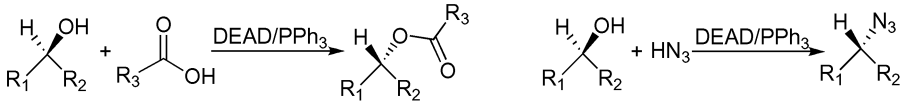
alkoxy phosphonium salt and alkoxy phosphorane should be involved as the intermediates in this reaction,[4i,4j] depending on the order of the addition and the pKa of the nucleophile. In addition, the position of equilibrium between these intermediates depends on the pKa of the nucleophile and the polarity of the solvent.[4j] For example, only alkoxy phosphonium salt is observed when strong acid with low pKa, such as trifluoroacetic acid, is used as a nucleophile,[4j] and dioxytriphenylphosphorane can be detected only when the nucleophilic acid is added last.[4k,11c] In addition, this reaction is also evidenced to undergo through a radical mechanism,[4f,13] because a nitrogen radical has been detected when triphenylphosphine and an alkyl azodicarboxylate are mixed.[4f] Although this reaction takes place smoothly in neutral media at room temperature, due to the strong affinity of triphenylphsophine for oxygen and DEAD for hydrogen, the nucleophiles employed must be acidic enough—generally with a pKa of less than 11,[14] preferably < 10[8b]—to protonate the betaine intermediate, which prevents the formation of other side products. The compounds of carboxylic acid,[4b,4c,4e,4f,4i] phenol,[3c,3g,15] phosphate,[16] phosphonic acid,[16] and *N*-hydroxyimide[11b] are suitable oxygen nucleophiles; and phthalimide[9d,17] and hydrogen azide[11b] are suitable nitrogen nucleophiles. Other nucleophiles include hydrogen halide[11b] and activated carbon acid.[18]

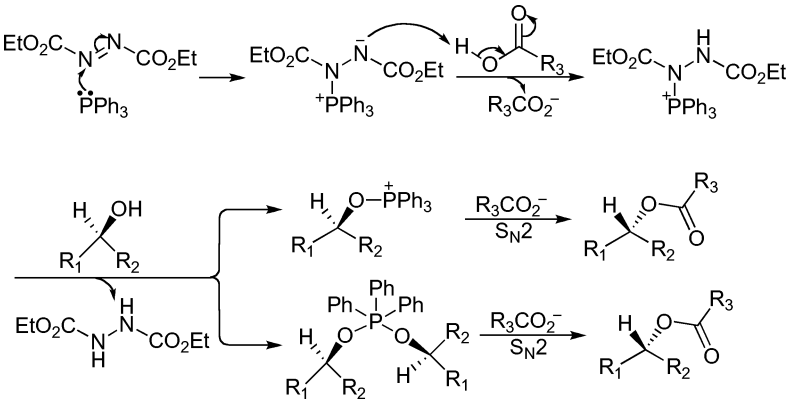
When secondary alcohols are used as alkylating agents, the stereochemistry is generally inverted via the *Walden Inversion*, because of the nature of S_N2 displacement.[3f,7b,7c,9a,11d,14,15] However, examples with partial retention of stereochemistry have also been reported.[15] Especially for the intramolecular version of the Mitsunobu reaction for the hindered alcohols, the products are formed with an exclusive retention of configuration.[11a] The overall result of this reaction is the alkylation of nucleophiles by alcohols, the simultaneous oxidation of triphenylphosphine to an oxide, and reduction of DEAD to hydrazinedicarboxylate. Thus triphenylphosphine oxide and dialkyl hydrazinedicarboxylate cannot be avoided in this reaction, which often prevents the desired products from being isolated. Therefore, this reaction has been extensively modified to ease the separation and purification of products. These modifications include the fixation of either triphenylphosphine[17] or dialkyl azodicarboxylate[19] to polymers, thus the resulting side products can be removed by simple filtration. In addition, phosphines with a basic moiety, such as 2-pyridyl[4l] and 4-dimethylaminophenyl,[20] are also used to improve the reaction, and the corresponding phosphine oxide can easily be washed away by acid. Furthermore, the nucleophile is also anchored to a fluorous reagent, to purify the product by extraction.[2r,8a]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A general mechanism containing the formation of phosphonium salt and phosphorane intermediates are displayed here.



D. MODIFICATION

This reaction has been extensively modified, including the fixation of phosphine and dialkyl azodicarboxylate onto a polymer or fluorous reagent and the introduction of a basic moiety to a phenylphosphine.[2r] In addition, bis(2-(1-adamantyl)ethyl) azodicarboxylate (BadEAD),[10] bis(1-adamantylmethyl) azodicarboxylate (BadMAD),[10] bis(5-norbornen-2-ylmethyl) azodicarboxylate (DNAD),[17] di-*tert*-butyl azodicarboxylate (DBAD),[21] fluorous azodicarboxylate (FDEAD),[22] *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD),[23] and 1,1′-(azodicarbonyl)dipiperidine (ADDP),[23] have also been developed for the Mitsunobu reaction.

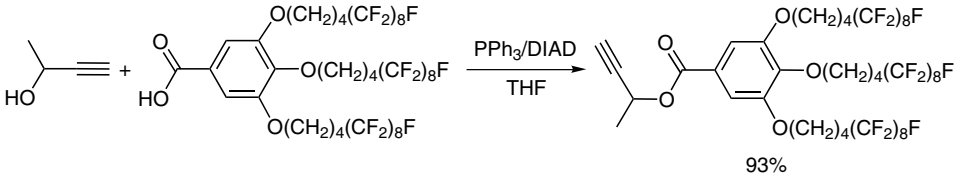
E. APPLICATIONS

This reaction has very wide application in organic synthesis, including the preparation of esters, ethers, thioethers, amines, and azides.

F. RELATED REACTIONS

This reaction is related to the *Appel Reaction, Staudinger Reaction*, and *Michaelis-Arbuzov Rearrangement*.

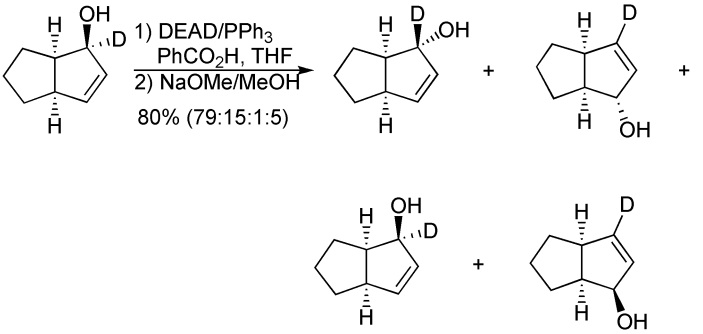
G. CITED EXPERIMENTAL EXAMPLES



93%

Reference 8a.

To a round-bottomed flask was added 0.478 g 3,4,5-tris(5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-heptadecafluorododecan-1-yloxy)benzoic acid (0.30 mmol), 10 mL THF, and 0.211 g triphenylphosphine (0.804 mmol). The mixture was stirred under a nitrogen atmosphere at room temperature. Then 0.30 mL 10% 3-butyn-2-ol (v/v) in THF (0.38 mmol) was added to the reaction mixture, followed by 0.15 mL DIAD (0.76 mmol). The reaction mixture was stirred for 40 h. The solvent was evaporated by rotary evaporation, and the residue was recrystallized from $CHCl_3$/MeOH (1:1). A white solid was isolated by filtration and dried over P_2O_5 under an oil pump vacuum to afford 0.458 g ester, in a yield of 93%.



Reference 9d.

To a 2 mL THF solution of 0.120 g *endo*-2-deuterio-2-hydroxy-1R,5R-bicyclo[3.3.0]oct-3-ene (0.96 mmol) at 0°C, were added 0.30 g triphenylphosphine (1.14 mmol, 1.2 eq.), 0.20 gram DEAD (1.15 mmol, 1.2 eq.), and 0.14 g benzoic acid (1.14 mmol, 1.2 eq.). The resultant solution was stirred for 1 h at this temperature, and then the solvent was removed under reduced pressure, followed by the addition of 10 mL hexane/EtOAc (2:1). The solution was filtered, the solvent was removed under reduced pressure, and the crude product was purified by silica gel chromatography (petroleum ether). The purified benzoate mixture was then hydrolyzed by addition of 5 mL 5% NaOMe/methanol, and the resulting mixture was stirred for 3 h. The solvent was removed under reduced pressure, and the crude mixture was dissolved in 10 mL ether, washed once with 5 mL water and 5 mL brine, dried over Na_2SO_4, filtered, and concentrated to provide 80% of alcohols, with 79% of inversion.

Other references related to the Mitsunobu reaction are cited in the literature.[24]

H. REFERENCES

1. (a) Mitsunobu, O.; Yamada, M. and Mukaiyama, T., *Bull. Chem. Soc. Jpn.,* **1967**, *40*, 935. (b) Mitsunobu, O. and Yamada, M., *Bull. Chem. Soc. Jpn.,* **1967**, *40*, 2380.
2. (a) Kelleher, F. and Proinsias, K. O., *Tetrahedron Lett*., **2007**, *48*, 4879. (b) Fitzjarrald, V. P. and Pongdee, R., *Tetrahedron Lett*., **2007**, *48*, 3553. (c) Manivel, P.; Rai, N. P.; Jayashankara, V. P. and

Arunachalam, P. N., *Tetrahedron Lett*., **2007**, *48*, 2701. (d) Mishra, J. K. and Panda, G., *J. Comb. Chem.,* **2007**, *9*, 321. (e) Jeon, H. S.; Yoo, J. H.; Kim, J. N. and Kim, T. H., *Tetrahedron Lett*., **2007**, *48*, 439. (f) Teodorovic, P.; Slaettegard, R. and Oscarson, S.,*Org. Biomol. Chem.,* **2006**, *4*, 4485. (g) Banfi, L.; Guanti, A. B. G.; Lecinska, P. and Riva, R., *Org. Biomol. Chem.,* **2006**, *4*, 4236. (h) Curran, D. P.; Bajpai, R. and Sanger, E., *Adv. Synth. Catal.,* **2006**, *348*, 1621. (i) Fleckenstein, C. A. and Plenio, H., *Adv. Synth. Catal.,* **2006**, *348*, 1058. (j) Proctor, A. J.; Beautement, K.; Clough, J. M.; Knight, D. W. and Li, Y. F., *Tetrahedron Lett*., **2006**, *47*, 5151. (k) Ludek, O. R. and Meier, C., *Synlett*, **2005**, 3145. (l) Ohtani, T.; Kawano, Y.; Kitano, K.; Matsubara, J.; Komatsu, M.; Uchida, M.; Tabusa, F. and Nagao, Y., *Heterocycles*, **2005**, *66*, 481. (m) Grab, T. and Braese, S., *Adv. Synth. Catal.,* **2005**, *347*, 1765. (n) Polchow, K. and Voss, J., *Phosphorus, Sulfur & Silicon & Related Elements*, **2005**, *180*, 1755. (o) Hovinen, J. and Sillanpaeae, R., *Tetrahedron Lett*., **2005**, *46*, 4387. (p) Hernandez Linares, A.; Fourmy, D.; Fourrey, J.-L. and Loukaci, A., *Org. Biomol. Chem.,* **2005**, *3*, 2064. (q) Robinson, D. E.; Seth, P. P. and Jefferson, E. A., *Synth. Commun.,* **2004**, *34*, 2743. (r) Dembinski, R., *Eur. J. Org. Chem.,* **2004**, 2763. (s) Grun, A.; Koszegi, E. and Bitter, I., *Tetrahedron*, **2004**, *60*, 5041. (t) Sugimura, H.; Koizumi, A. and Kiyohara, W., *Nucleosides, Nucleotides & Nucleic Acids*, **2003**, *22*, 727. (u) Cravotto, G.; Nano, G. M.; Palmisano, G. and Tagliapietra, S., *Heterocycles*, **2003**, *60*, 1351. (v) Hubert, C.; Alexandre, C.; Aubertin, A.-M. and Huet, F., *Tetrahedron*, **2003**, *59*, 3127. (w) Shi, Y.-J.; Hughes, D. L. and McNamara, J. M., *Tetrahedron Lett*., **2003**, *44*, 3609. (x) Goksu, S.; Secen, H. and Sutbeyaz, Y., *Synthesis*, **2002**, 2373. (y) Hughes, D. L., *Org. Prep. Proc. Int.,* **1996**, *28*, 127. (z) Hughes, D. L., *Org. React.,* **1992**, *42*, 335. (aa) Wipf, P. and Miller, C. P., *Tetrahedron Lett.,* **1992**, *33*, 6267.

3. (a) Lu, W. B.; Sengupta, S.; Petersen, J. L.; Akhmedov, N. G. and Shi, X. D., *J. Org. Chem.,* **2007**, *72*, 5012. (b) Yin, X.-Q.; Li, W.-K. and Schneller, S. W., *Tetrahedron Lett*., **2006**, *47*, 9187. (c) Lepore, S. D. and He. Y. J., *J. Org. Chem.,* **2003**, *68*, 8261. (d) Ganguly, N. C.; Sukai, A. K.; Dutta, S. and De, P., *J. Indian Chem. Soc.,* **2001**, *78*, 380. (e) Miller, R. D.; Hawker, C. and Lee, V. Y., *Tetrahedron Lett*., **1995**, *36*, 4393. (f) Perez-Perez, M.-J.; Rozenski, J.; Busson, R. and Herdewijn, P., *J. Org. Chem.,* **1995**, *60*, 1531. (g) Roush, W. R. and Lin, X.-F., *J. Org. Chem.,* **1991**, *56*, 5740. (h) Lipshutz, B. H. and Miller, T. A., *Tetrahedron Lett*., **1990**, *31*, 5253.
4. (a) Bouzemi, N.; Aribi-Zouioueche, L. and Fiaud, J.-C., *Tetrahedron: Asymmetry*, **2006**, *17*, 797. (b) Harned, A. M.; He, H. S.; Toy, P. H.; Flynn, D. L. and Hanson, P. R., *J. Am. Chem. Soc.,* **2005**, *127*, 52. (c) Batovska, D. I.; Kishimoto, T.; Bankova, V.; Kamenarska, Z. G. and Ubukata, M., *Molecules,* **2005**, *10*, 552. (d) Liu, H.-L. and Anthonsen, T., *Chirality*, **2002**, *14*, 25. (e) Hughes, D. L. and Reamer, R. A., *J. Org. Chem.,* **1996**, *61*, 2967. (f) Camp, D.; Hanson, G. R. and Jenkins, I. D., *J. Org. Chem.,* **1995**, *60*, 2977. (g) Warmerdam, E. G. J. C.; Brussee, J.; Kruse, C. G. and van der Gen, A., *Phosphorus, Sulfur & Silicon & Related Elements*, **1993**, *75*, 3. (h) Warmerdam, E. G. J. C.; Brussee, J.; Kruse, C. G. and van der Gen, A., *Tetrahedron*, **1993**, *49*, 1063. (i) Camp, D. and Jenkins, I. D., *J. Org. Chem.,* **1989**, *54*, 3049. (j) Camp, D. and Jenkins, I. D., *J. Org. Chem*., **1989**, *54*, 3045. (k) Hughes, D. L.; Reamer, R. A.; Bergan, J. J. and Grabowski, E. J. J., *J. Am. Chem. Soc*., **1988**, *110*, 6487. (l) Camp, D. and Jenkins, I. D., *Aust. J. Chem.,* **1988**, *41*, 1835.
5. Krchnak, V., *J. Comb. Chem.,* **2005**, *7*, 507.
6. Hughes, A. B. and Sleebs, M. M., *J. Org. Chem.,* **2005**, *70*, 3079.
7. (a) Charette, A. B.; Janes, M. K. and Boezio, A. A., *J. Org. Chem.,* **2001**, *66*, 2178. (b) Persky, R. and Albeck, A., *J. Org. Chem.,* **2000**, *65*, 3775. (c) Crich, D.; Dyker, H. and Harris, R. J., *J. Org. Chem.,* **1989**, *54*, 257.
8. (a) Markowicz, M. W. and Dembinski, R., *Org. Lett.,* **2002**, *4*, 3785. (b) Itôt, S. and Tsunoda, T., *Pure & Appl. Chem.,* **1999**, *71*, 1053.
9. (a) Swamy, K. C. K.; Kumar, K. P. and Kumar, N, N, B., *J. Org. Chem.,* **2006**, *71*, 1002. (b) Schenk, S.; Weston, J. and Anders, E., *J. Am. Chem. Soc.,* **2005**, *127*, 12566. (c) Kumar,

N. S.; Kumar, K. P.; Kumar, K. V. P. P.; Kommana, P.; Vittal, J. J. and Swamy, K. C. K., *J. Org. Chem.,* **2004**, *69*, 1880. (d) Shull, B. K.; Sakai, T.; Nichols, J. B. and Koreeda, M., *J. Org. Chem.,* **1997**, *62*, 8294.

10. Kumar, N. S.; Kommana, P.; Vittal, J. J. and Swamy, K. C. K., *J. Org. Chem.,* **2002**, *67*, 6653.
11. (a) Ahn, C. and DeShong, P., *J. Org. Chem.,* **2002**, *67*, 1754. (b) Sebesta, D. P.; O'Rourke, S. S. and Pieken, W. A., *J. Org. Chem.,* **1996**, *61*, 361. (c) Varasi, M.; Walker, K. A. M. and Maddox, M. L., *J. Org. Chem.,* **1987**, *52*, 4235. (d) Grochowski, E.; Hilton, B. D.; Kupper, R. J. and Michejda, C. J., *J. Am. Chem. Soc.,* **1982**, *104*, 6876.
12. Pautard-Cooper, A. and Evans, S. A., *J. Org. Chem.,* **1989**, *54*, 2485.
13. (a) Sung, D. D.; Choi, M. J.; Ha, K. M. and Uhm, T. S., *Bull. Korean Chem. Soc.,* **1999**, *20*, 935. (b) Eberson, L.; Persson, O. and Svensson, J. O., *Acta Chem. Scand.,* **1998**, *52*, 1293.
14. Arnold, L. D.; Assil, H. I. and Vederas, J. C., *J. Am. Chem. Soc.,* **1989**, *111*, 3973.
15. Freedman, J.; Vaal, M. J. and Huber, E. W., *J. Org. Chem.,* **1991**, *56*, 670.
16. Campbell, D. A., *J. Org. Chem.,* **1992**, *57*, 6331.
17. Barrett, A. G. M.; Roberts, R. S. and Schröder, J., *Org. Lett.,* **2000**, *2*, 2999.
18. Takacs, J. M.; Xu, Z. R.; Jiang, X.-T.; Leonov, A. P. and Theriot, G. C., *Org. Lett.,* **2002**, *4*, 3843.
19. Lan, P.; Porco, J. A.; South, M. S. and Parlow, J. J., *J. Comb. Chem.,* **2003**, *5*, 660.
20. von Itzstein, M. and Mocerino, M., *Synth. Commun.,* **1990**, *20*, 2049.
21. (a) Ruhland, T.; Holm, P. and Andersen, K., *J. Comb. Chem.,* **2003**, *5*, 842. (b) Gentles, R. G.; Wodka, D.; Park, D. C. and Vasudevan, A., *J. Comb. Chem.,* **2002**, *4*, 442. (c) Kiankarimi, M.; Lowe, R.; McCarthy, J. R. and Whitten, J. P., *Tetrahedron Lett.,* **1999**, *40*, 4497. (d) Flynn, D. L., *Med. Res. Rev.,* **1999**, *19*, 408. (e) Starkey, G. W.; Parlow, J. J. and Flynn, D. L., *Bioorg. Med. Chem. Lett.,* **1998**, *8*, 2385.
22. (a) Dandapani, S. and Curran, D. P., *Tetrahedron*, **2002**, *58*, 3855. (b) Dobbs, A. P. and McGregor-Johnson, C., *Tetrahedron Lett.,* **2002**, *43*, 2807.
23. Kosower, E. M. and Kanety-Londner, H., *J. Am. Chem. Soc.,* **1976**, *98*, 3001.
24. (a) Chaturvedi, D. and Ray, S., *Tetrahedron Lett*., **2007**, *48*, 149. (b) Maillard, L. T.; Benohoud, M.; Durand, P. and Badet, B., *J. Org. Chem.,* **2005**, *70*, 6303. (c) Dandapani, S. and Curran, D. P., *J. Org. Chem.,* **2004**, *69*, 8751. (d) Leonetti, F.; Cappa, A.; Maccallini, C. and Carotti, A., *ARKIVOC,* **2004**, (*v*), 272. (e) Dandapani, S. and Curran, D. P., *Chem. Eur. J.,* **2004**, *10*, 3130. (f) Dinsmore, C. J. and Mercer, S. P.,*Org. Lett.,* **2004**, *6*, 2885. (g) Nune, S. K., *Synlett,* **2003**, 1221. (h) Glatz, H. and Bannwarth, W., *Tetrahedron Lett.,* **2003**, *44*, 149. (i) Ahn, C.; Correia, R. and DeShong, P., *J. Org. Chem.,* **2002**, *67*, 1751. (j) Ko, S. Y., *J. Org. Chem.,* **2002**, *67*, 2689. (k) Olofsson, B.; Wijtmans, R. and Somfai, P., *Tetrahedron*, **2002**, *58*, 5979. (l) Moravcova, J.; Spilova, L.; Capkova, J.; Chery, F.; and Rollin, P., *Coll. Czech. Chem. Commun.,* **2000**, *65*, 1745. (m) He, L. L.; Wanunu, M.; Byun, H.-S. and Bittman , R., *J. Org. Chem.,* **1999**, *64*, 6049. (n) Bach, T.; Kather, K. and Kramer, O., *J. Org. Chem.,* **1998**, *63*, 1910. (o) Gao, Y.; Lane-Bell, P. and Vederas, J. C., *J. Org. Chem.,* **1998**, *63*, 2133. (p) Yamada, K.; Sakata, S. and Yoshimura, Y., *J. Org. Chem.,* **1998**, *63*, 6891. (q) Nikam, S. S.; Kornberg, B. E. and Rafferty, M. F., *J. Org. Chem.,* **1997**, *62*, 3754. (r) Pasto, M.; Moyano, A.; Pericas, M. A. and Riera, A., *J. Org. Chem.,* **1997**, *62*, 8425. (s) Nicolaou, K. C.; Boddy, C. N. C.; Natarajan, S.; Yue, T.-Y.; Li, H.; Bräse, S. and Ramanjulu, J. M., *J. Am. Chem. Soc.,* **1997**, *119*, 3421. (t) Keinan, E.; Sinha, A.; Yazbak, A.; Sinhaa, S. C. and Sinhaa, S. C., *Pure & Appl. Chem.,* **1997**, *69*, 423. (u) Charette, A. B.; Côté, B.; Monroc, S. and Prescott, S., *J. Org. Chem.,* **1996**, *60*, 6888. (v) Cherney, R. J. and Wang, L., *J. Org. Chem.,* **1996**, *61*, 2544. (w) Anderson, N. G.; Lust, D. A.; Colapret, K. A.; Simpson, J. H.; Malley, M. F. and Gougoutas, J. Z., *J. Org. Chem.,* **1996**, *61*, 7955. (x) Alexandratos, S. D. and Miller, D. H. J., *Molecules,* **1996**, *29*, 8025. (y) Sen, S. E. and Roach, S. L., *Synthesis*, **1995**, 756. (z) Roush, W. R. and Lin, X. F., *J. Am. Chem. Soc.,* **1995**, *117*, 2236. (aa) Dodge, J. A.; Trujillo,

J. I. and Presnell, M., *J. Org. Chem.,* **1994**, *59*, 234. (bb) Campbell, J. A. and Hart, D. J., *J. Org. Chem.,* **1993**, *58*, 2900. (cc) Koppel, I.; Koppel, J.; Degerbeck, F.; Grehn, L. and Ragnarsson, U., *J. Org. Chem.,* **1991**, *56*, 7172. (dd) Strijteen, B. and Kellog, R. M., *Recl. Trav. Chim. Pays-Bas,* **1987**, *106*, 539. (ee) Walker, M. A., *J. Org. Chem.,* **1986**, *60*, 5352. (ff) Adam, W.; Narita, N. and Nishizawat, Y., *J. Am. Chem. Soc.,* **1984**, *106*, 1843. (gg) Hughes, D. L., *Org. React.,* **1983**, *29*, 1. (hh) Amos, R. A.; Emblidge, R. W. and Havens, N., *J. Org. Chem.,* **1983**, *48*, 3598. (ii) Mitsunobu, O., *Synthesis,* **1981**, 1. (jj) Mitsunobu, O.; Wada, M. and Sano, T., *J. Am. Chem. Soc.,* **1972**, *94*, 679.

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Moffatt-Swern Oxidation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Moffatt in 1965[1] and subsequently modified by Swern in 1978,[2] who introduced oxalyl chloride and triethylamine to the reaction system. It is the oxidation of primary and secondary alcohols to carbonyl compounds (aldehydes and ketones) from dimethyl sulfoxide (DMSO) in combination with oxalyl chloride and triethylamine under anhydrous conditions. Therefore, it is generally known as the Moffatt-Swern oxidation[3] or simply the Swern oxidation.[4] Occasionally, it is also referred to as the Swern-Moffatt oxidation,[3o] or Moffatt oxidation.[5] The combination of oxalyl chloride, DMSO, and triethylamine is called the Swern-Moffatt reagent[6] or Moffatt reagent.[7] It is known that this reaction involves the formation of an ylide through an alkoxydimethylsulfonium ion; if it is impossible to form the ylide, then there would be no such oxidation.[8] Compared to chromium-based oxidation reagents, such as PCC[9] and PDC,[10] the Swern-Moffatt reagent is less toxic. In addition, this reaction is also superior[11] to the PCC and *Dess-Martin Periodinane Oxidation* in some cases. On the other hand, this reaction does not cleave the adjacent di-carbonyl functionality. For example, the Moffatt-Swern oxidation converts terminal 1,2-diol into α-hydroxy aldehyde but not into an α-keto aldehyde,[3o] whereas the modification using the combination of DMSO/EDC/Cl_2CHCO_2H can transform α-hydroxyamide to α-ketoamide.[4b] Because this reaction is very mild and selective, it has been widely used in organic synthesis, even for the preparation of some very unstable aldehydes, which are subjected to subsequent transformation directly.[12] For ketones that are sensitive to triethylamine, they can be prepared by substituting triethylamine with the Hunig's base.[6] However, this reaction also has some flaws. For example, it must be carried out under anhydrous conditions because of oxalyl chloride; the reaction temperature is often very low to avoid the *Pummerer Rearrangement*.[13] In addition, this reaction may

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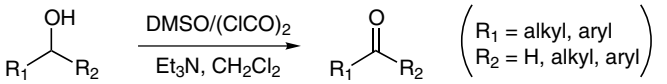
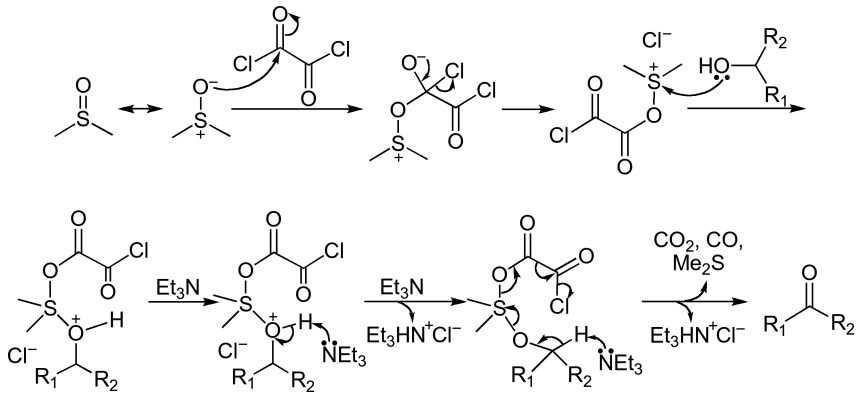
leave trace impurities that cannot be detected by spectroscopy or combustion analysis but could affect some subsequent reactions, such as palladium catalyzed reactions.[14] Moreover, this reaction may cause the racemization of chiral molecules.[3m]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified to use the combination of DMSO/EDC/Cl_2CHCO_2H to oxidize α-hydroxyamide to α-ketoamide;[4b] in addition, Hunig's base has been substituted for triethylamine for the preparation of ketones, which are sensitive to triethylamine.[6]

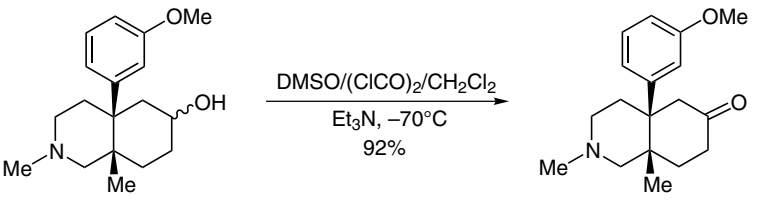
E. APPLICATIONS

This reaction has wide application in the preparation of ketones and aldehydes.

F. RELATED REACTIONS

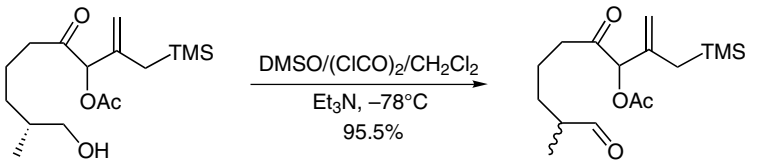
This reaction is related to the *Corey-Kim Oxidation* and *Pfitzner-Moffatt Oxidation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 3c.

Into a dry flask containing 3.45 mL oxalyl chloride in 15 mL CH_2Cl_2 (6.9 mmol, 2.0 M) cooled to −70°C was added 0.83 mL DMSO (11.7 mmol) in 10 mL CH_2Cl_2 over 10 min. The solution was stirred for an additional 10 min at −70°C, and 1.54 g *N*-methyl-4a-(3-methoxyphenyl)-8a-methyloctahydroisoquinoline-6-ol (5.32 mmol) in CH_2Cl_2 was added over 30 min. After an additional 30 min at −70°C, 1.11 mL Et_3N (7.98 mmol) was added, and the solution was warmed to room temperature, washed with 100 mL saturated aqueous $NaHCO_3$, dried over Na_2SO_4, concentrated, and purified via flash chromatography (4% MeOH-$CHCl_3$) to afford 1.40 g *N*-Methyl-4a-(3-methoxyphenyl)-8a-methyl-6-oxooctahydroisoquinoline, in a yield of 92%.



Reference 3m.

To a solution of 0.894 g oxalyl chloride (0.05 mmol) in 25 mL dichloromethane was added a solution of 1.0 g DMSO (12.8 mmol) in 4.0 mL dichloromethane at −78°C. A solution of 2.02 g (+)-3-acetoxy-9-hydroxy-8(*R*)-methyl-2-((trimethylsilyl)methyl)-non-1-en-4-one (6.41 mmol) in 6.0 mL dichloromethane was added, the solution was stirred for 20 min, and then 2.41 g triethylamine (17.1 mmol) was added. The cloudy white mixture was allowed to warm to −20°C, whereupon the mixture was poured into a vigorously stirred mixture of water (80 mL), ether (40 mL), and hexanes (40 mL). The organic layer was extracted with 40 mL ether. The organic layers were washed with aqueous 10% sodium bisulfate (2 × 40 mL) and brine (40 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford 1.91 g racemic 3-acetoxy-8-methyl-9-oxo-2-((trimethylsilyl)methyl)non-1-en-4-one as a light yellow oil, in a yield of 95.5%. (*Note*: The racemization might arise from the enolization after the formation of aldehyde under basic conditions.)

Other references related to the Moffatt-Swern oxidation are cited in the literature.[15]

H. REFERENCES

1. Pfitzner, K. E. and Moffatt, J. G., *J. Am. Chem. Soc.,* **1965**, *87*, 5661.
2. (a) Mancuso, A. J.; Juang, S. L. and Swern, D., *J. Org. Chem.,* **1978**, *41*, 2480. (b) Omura, K. and Swern, D., *Tetrahedron,* **1978**, *34*, 1651.
3. (a) Trost, B. M. and Fandrick, D. R., *Org. Lett.,* **2005**, *7*, 823. (b) Trost, B. M.; Dong, L. and Schroeder, G. M., *J. Am. Chem. Soc.,* **2005**, *127*, 10259. (c) Carroll, F. I.; Chaudhari, S.; Thomas, J. B.; Mascarella, S. W.; Gigstad, K. M.; Deschamps, J. and Navarro, H. A., *J. Med. Chem.,* **2005**, *48*, 8182. (d) Trost, B. M.; Wrobleski, S. T.; Chisholm, J. D.; Harrington, P. E. and Jung, M., *J. Am. Chem. Soc.,* **2005**, *127*, 13589. (e) Trost, B. M. and Papillon, J. P. N., *J. Am. Chem. Soc.,* **2004**, *126*, 13618. (f) Jellerichs, B. G.; Kong, J.-R. and Krische, M. J., *J. Am. Chem. Soc.,* **2003**, *125*, 7758. (g) Scheidt, K. A.; Bannister, T. D.; Tasaka, A.; Wendt, M. D.; Savall, B. M.; Fegley, G. J. and Roush, W. R., *J. Am. Chem. Soc.,* **2002**, *124*, 6981. (h) Wallace, G. A. and Heathcock, C. H., *J. Org. Chem.,* **2001**, *66*, 450. (i) Wilson, M. S. and Dake, G. R., *Org. Lett.,* **2001**, *3*, 2041. (j) Turner, S. C.; Zhai, H. B. and Rapoport, H., *J. Org. Chem.,* **2000**, *65*, 861. (k) Trost, B. M.; Haffner, C. D.; Jebaratnam, D. J.; Krische, M. J. and Thomas, A. P., *J. Am. Chem. Soc.,* **1999**, *121*, 6183. (l) Denhart, D. J.; Griffith, D. A. and Heathcock, C. H., *J. Org. Chem.,* **1998**, *63*, 9616. (m) Trost, B. M. and Higuchi, R. I., *J. Am. Chem. Soc.,* **1996**, *118*, 10094. (n) Isaacs, N. S. and Laila, A. H., *J. Phys. Org. Chem.,* **1991**, *4*, 639. (o) Magnus, P.; Katoh, T.; Matthews, I. R. and Huffman, J. C., *J. Am. Chem. Soc.,* **1989**, *111*, 6707. (p) Trost, B. M. and Lee, D. C., *J. Org. Chem.,* **1989**, *54*, 2271.
4. (a) Jadhav, S. B. and Ghosh, U., *Tetrahedron Lett*., **2007**, *48*, 2485. (b) Brewer, M., *Tetrahedron Lett*., **2006**, *47*, 7731. (c) He, X. and Chan, T. H., *Tetrahedron*, **2006**, *62*, 3389. (d) Gilsing, H.-D.; Angerer, J. and Prescher, D., *Monatsh. Chem.,* **2003**, *134*, 1207. (e) Choi, M. K. W. and Toy, P. H., *Tetrahedron,* **2003**, *59*, 7171. (f) Yamato, T.; Hironaka, T.; Saisyo, T.; Manabe, T. and Okuyama, K.-I., *J. Chem. Res. (S),* **2003**, 63. (g) Firouzabadi, H.; Hassani, H. and Hazarkhani, H., *Phosphorus, Sulfur & Silicon & Related Elements*, **2003**, *178*, 149. (h) Bisai, A; Chandrasekhar, M. and Singh, V. K., *Tetrahedron Lett*., **2002**, *43*, 8355. (i) Cole, D. C.; Stock, J. R. and Kappel, J. A., *Bioorg. Med. Chem. Lett.*, **2002**, *12*, 1791. (j) De Luca, L.; Giacomelli, G. and Porcheddu, A., *J. Org. Chem.,* **2001**, *66*, 7907. (k) Izumi, H. and Futamura, S., *J. Org. Chem.,* **1999**, *64*, 4502. (l) Bailey, P. D.; Cochrane, P. J.; Irvine, F.; Morgan, K. M.; Pearson, D. P. J. and Veal, K. T., *Tetrahedron Lett*., **1999**, *40*, 4593. (m) Harris, J. M.; Liu, Y.; Chai, S.; Andrews, M. D. and Vederas, J. C., *J. Org. Chem.,* **1998**, *63*, 2407. (n) Nakajima, N. and Ubukata, M., *Tetrahedron Lett*., **1997**, *38*, 2099. (o) Chrisman, W. and Singaram, B., *Tetrahedron Lett*., **1997**, *38*, 2053. (p) Bourlot, A.-S.; Guillaumet, G. and Merour, J.-Y., *J. Heterocycl. Chem.,* **1996**, *33*, 191. (q) Gilbert, J. C. and Selliah, R. D., *Res. Chem. Intermediates,* **1996**, *22*, 91. (r) Liu, Y. and Vederas, J. C., *J. Org. Chem.,* **1996**, *61*, 7856. (s) Gentilucci, L.; Grijzen, Y.; Thijs, L. and Zwanenburg, B., *Tetrahedron Lett*., **1995**, *36*, 4665. (t) Hofmann, B. and Reissig, H.-U., *Chem. Ber.,* **1994**, *127*, 2327. (u) Kawada, K.; Gross, R. S. and Watt, D. S., *Synth. Commun.,* **1989**, *19*, 777. (v) Richardson, S. K. and Ife, R. J., *J. Chem. Soc., Perkin Trans. I,* **1989**, 1172. (w) Bird, C. W. and Lewis, A. E., *Chem. Ind. (London),* **1989**, 146. (x) Smith, A. B.; Leenay, T. L.; Liu, H. J.; Nelson, L. A. K. and Ball, R. G., *Tetrahedron Lett*., **1988**, *29*, 49. (y) Keirs, D. and Overton, K., *J. Chem. Soc., Chem. Commun.,* **1987**, 1660. (z) Marx, M. and Tidwell, T. T., *J. Org. Chem.,* **1984**, *49*, 788.
5. (a) Chen, K. X.; Njoroge, F. G.; Arasappan, A.; Venkatraman, S.; Vibulbhan, B.; Yang, W. Y.; Parekh, T. N.; Pichardo, J.; Prongay, A.; Cheng, K.-C.; Butkiewicz, N.; Yao, N. H.; Madison, V. and Girijavallabhan, V., *J. Med. Chem.,* **2006**, *49*, 995. (b) Chen, K. X.; Njoroge, F. G.; Pichardo, J.; Prongay, A.; Butkiewicz, N.; Yao, N. H.; Madison, V. and Girijavallabhan, V., *J. Med. Chem.,* **2006**, *49*, 567. (c) Wigfield, D. C.; Feiner, S. and Phelps, D. J., *Steroids*, **1972**, *20*, 435.
6. Trost, B. M.; Seoane, P.; Mignani, S. and Acemoglu, M., *J. Am. Chem. Soc.,* **1989**, *111*, 7487.

7. Singh, S.; Nambiar, S.; Porter, R. A.; Sander, T. L.; Taylor, K. G. and Doyle, R. J., *J. Org. Chem.,* **1989**, *54*, 2300.
8. Shine, H. J. and Yueh, W., *J. Org. Chem.,* **1994**, *59*, 3553.
9. See *Corey-Suggs Oxidation* herein (P. 742).
10. See *Corey-Schmidt Oxidation* herein (P. 738).
11. Trost, B. M. and Li, Y., *J. Am. Chem. Soc.,* **1996**, *118*, 6625.
12. (a) Linderman, R. J. and Suhr, Y., *J. Org. Chem.,* **1988**, *53*, 1569. (b) Ireland, R. E. and Norbeck, D. W., *J. Org. Chem.,* **1985**, *50*, 2198.
13. Nguyen, H. M.; Chen, Y. N.; Duron, S. G. and Gin, D. Y., *J. Am. Chem. Soc.,* **2001**,*123*, 8766.
14. Trost, B. M.; Grese, T. A. and Chan, D. M. T., *J. Am. Chem. Soc.,* **1991**, *113*, 7350.
15. (a) Trost, B. M.; Chisholm, J. D.; Wrobleski, S. T. and Jung, M., *J. Am. Chem. Soc.,* **2002**, *124*, 12420. (b) Trost, B. M.; Probst, G. D. and Schoop, A., *J. Am. Chem. Soc.,* **1998**, *120*, 9228. (c) Tidwell, T. T., *Org. React.,* **1990**, *39*, 297. (d) Tidwell, T. T., *Synthesis,* **1990**, *10*, 857. (e) Mancuso, A. J. and Swern, D., *Synthesis,* **1981**, 165. (f) Mancuso, A. J.; Brownfain, D. S. and Swern, D., *J. Org. Chem.,* **1979**, *44*, 4148. (g) Jenkins, I. D.; Verheyden, J. P. H. and Moffatt, J. G., *J. Am. Chem. Soc.,* **1971**, *93*, 4223.

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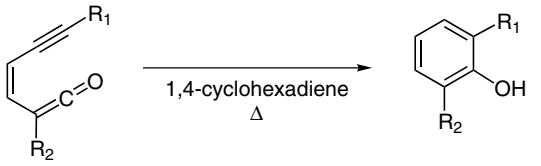
Moore Cyclization

A. GENERAL DESCRIPTION OF THE REACTION

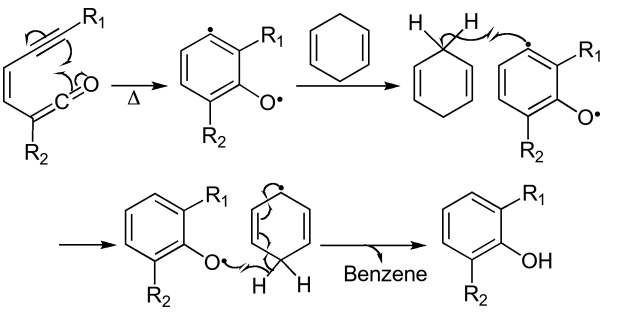
This reaction was first reported by Moore in 1985.[1] It is a synthesis of phenol (or quinone) derivatives by means of the thermal cyclization of enyne-ketenes between C_2 and C_7 via an aryl/phenoxy biradical intermediate. Therefore, it is generally known as the Moore cyclization.[2] Occasionally, it is directly referred to as the Moore reaction.[2d,3] It has been found that the biradical intermediate sometimes also shows the character of zwitterions.[2b,2d,2j] Although the cyclization between C_2 and C_7 is strongly favored in kinetics and thermodynamics,[2d] the formation of a five-membered fulvene biradical via C_2-C_6 cyclization is also known, especially for the enyne-ketenes with a phenyl or other radical-stabilizing group at the alkynyl terminus.[1,ba,2d,4] For example, the thermal decomposition of 4-phenylacetylenyl-2,3-dimethoxy-4-(trimethylsiloxy)-cyclobutenone in *p*-xylene at 135°C affords 52% cyclopenten-1,3-dione derivative but only 13% quinone.[1] The formation of a biradical intermediate via C_2-C_7 cyclization has been evidenced in the formation of spiroepoxide through the *exo* addition of an aryl radical to the proximal alkyne moiety and subsequent proton abstraction from an adjacent methoxy group by the resulting vinyl radical[5]and the partial cleavage of DNA during the decomposition of cyclobutenone.[6]

B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been extended to the cyclization of ketenimine.[7]

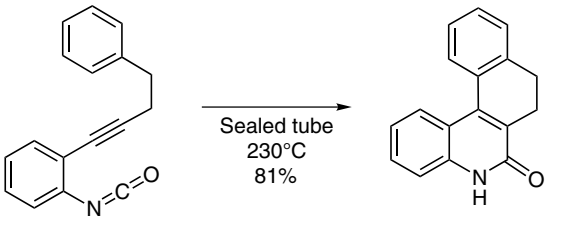
E. APPLICATIONS

This reaction has special application in formation of phenol and related derivatives.

F. RELATED REACTIONS

This reaction is related to the *Bergmann Cyclization* and *Myers-Saito Cyclization.*

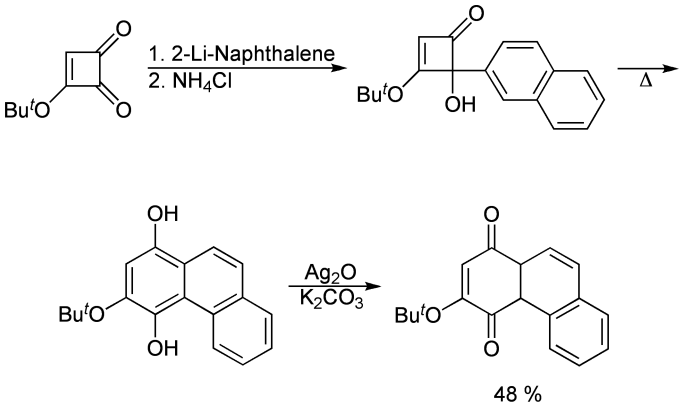
G. CITED EXPERIMENTAL EXAMPLES



Reference 2b.

A solution of 0.186 g enyne-isocyanate (0.75 mmol) in 10 mL 1,2-dichlorobenzene was refluxed for 14 days. The solvent was removed in vacuo, and the residue was purified by column chromatography to afford 0.050 g 7,8-dihydrobenzo[*k*]phenanthridin-6(5*H*)-one as brown crystals, in a yield of 27%. Similarly, a solution of 0.100 g same enyne-isocyanate

(0.40 mmol) in 2 mL 1,2-dichlorobenzene in a sealed glass tube was heated at 230°C for 24 h to afford 0.081 g 7,8-dihydrobenzo[*k*]phenanthrid in-6(5*H*)-one, in a yield of 81%, m.p. 245–246°C.



Reference 7.

To a solution of 180 μL 2-bromonaphthalene (1.3 mmol) in 8 mL dry THF cooled to −78°C under argon was added 0.74 mL 1.6 M *n*-BuLi in hexane (1.2 mmol). The solution was stirred for 30 min, the anion was added via cannula to a −78°C solution of 170 mg 3-*tert*-butoxy-3-cyclobutene-l,2-dione (1.1 mmol) in 30 mL dry THF. After being stirred for another 30 min, the reaction mixture was poured into 20 mL 1% NH_4Cl solution. The aqueous layer was extracted with EtOAc (2 × 30 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and evaporated. The resulting alcohol was purified by flash column chromatography on silica gel (2:l, hexane/EtOAc) to give a white powder, which was used without characterization. The alcohol was dissolved in 80 mL dry *p*-xylene and refluxed under argon for 25 min. Upon cooling to room temperature, 550 mg Ag_2O (2.4 mmol) and 330 mg K_2CO_3 (2.4 mmol) were added, and the suspension was stirred at room temperature for 1.75 h. The reaction mixture was then filtered through Celite and evaporated to a bright yellow oil. The oil was purified by flash column chromatography on silica gel (10:1, hexane/EtOAc) to give 140 mg 2-*tert*-butoxy-l,4-phenanthrenedione as a bright yellow powder, in a yield of 48%.

Other references related to the Moore cyclization are cited in the literature.[8]

H. REFERENCES

1. Karlsson, J. O.; Nguyen, N. V.; Foland, L. D. and Moore, H. W., *J. Am. Chem. Soc.,* **1985**, *107*, 3392.
2. (a) Schreiner, P. R. and Bui, B. H., *Eur. J. Org. Chem.,* **2006**, 1162. (b) Li, H. B.; Yang, H.; Petersen, J. L. and Wang, K. K., *J. Org. Chem.,* **2004**, *69*, 4500. (c) Lu, X. L.; Petersen, J. L. and Wang, K. K., *Org. Lett.,* **2003**, *5*, 3277. (d) Musch, P. W.; Remenyi, C.; Helten, H. and Engels, B., *J. Am. Chem. Soc.,* **2002**, *124*, 1823. (e) Shi, C. S.; Zhang, Q. and Wang, K. K., *J. Org. Chem.,* **1999**, *64*, 925. (f) Shi, C. S. and Wang, K. K., *J. Org. Chem.,* **1998**, *63*, 3517. (g) Herndon, J. W. and Wang, H. X., *J. Org. Chem.,* **1998**, *63*, 4562. (h) Tarli, A. and Wang, K. K., *J. Org. Chem.,*

1997, *62*, 8841. (i) Rahm, A. and Wulff, W. D., *J. Am. Chem. Soc.,* **1996**, *118*, 1807. (j) Wang, K. K., *Chem. Rev.,* **1996**, *96*, 207.

3. McComas, C. C.; Perales, J. B. and van Vranken, D. L., *Org. Lett.,* **2002**, *4*, 2337.
4. Pollart, D. J. and Moore, H. W., *J. Org. Chem.,* **1989**, *54*, 5444.
5. Xia, H. J. and Moore, H. W., *J. Org. Chem.,* **1992**, *57*, 3765.
6. Sullivan, R. W.; Coghlan, V. M.; Munk, S. A.; Reed, M. W. and Moore, H. W., *J. Org. Chem.,* **1994**, *59*, 2276.
7. Heerding, J. M. and Moore, H. W., *J. Org. Chem.,* **1991**, *56*, 4048.
8. (a) Rahm, A. and Wulff, W. D., *J. Am. Chem. Soc.,* **1996**, *118*, 1807. (b) Moore, H. W. and Yerxa, M. R., *Chemtracts,* **1992**, 273. (c) Xu, S. L.; Taing, M. and Moore, H. W., *J. Org. Chem.,* **1991**, *56*, 6104. (d) Chow, K.; Nguyen, N. V. and Moore, H. W., *J. Org. Chem.,* **1990**, *55*, 3876. (e) Foland, L. D.; Karlsson, J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S. and Moore, H. W., *J. Am. Chem. Soc.,* **1989**, *111*, 975.

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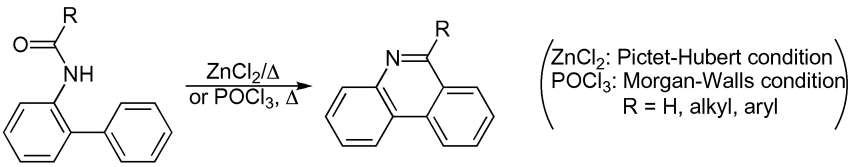
Morgan-Walls Cyclization

(Pictet-Hubert Phenanthridine Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Pictet and Hubert in 1896[1] and subsequently modified by Morgan and Walls.[2] It is the synthesis of phenanthridine derivatives by means of the treatment of *N*-acyl *ortho*-aminobiphenyls with $ZnCl_2$ at high temperature[1] or with $POCl_3$.[2] Therefore, it is known as the Pictet-Hubert phenanthridine synthesis.[3] Due to the intrinsic disadvantages of the original protocol, including the long reaction time and low yield,[4] the modification by Morgan and Walls using $POCl_3$ as the dehydrating agent is often used to prepare phenanthridine, even though such modification was unsuccessful for the transformation of *ortho*-formamidobiphenyl itself to the parent phenanthridine scaffold.[4] This modification is referred to as the Morgan-Walls cyclization[5] or Morgan-Walls reaction.[4,6] Under these reaction conditions, it is best to use a high-boiling solvent, such as nitrobenzene.[7] In addition, HBF_4 has been found to be able to catalyze such a cyclization.[6a]

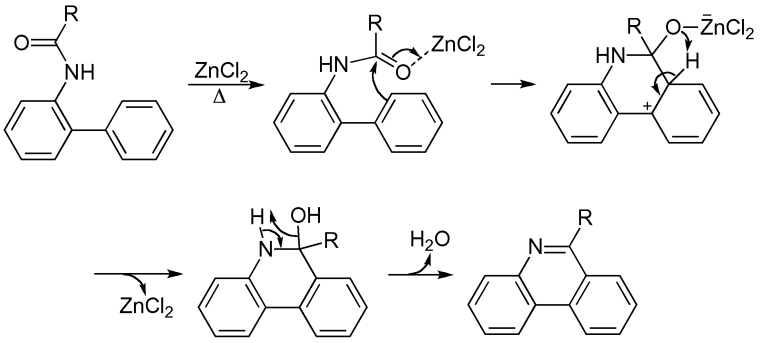
B. GENERAL REACTION SCHEME



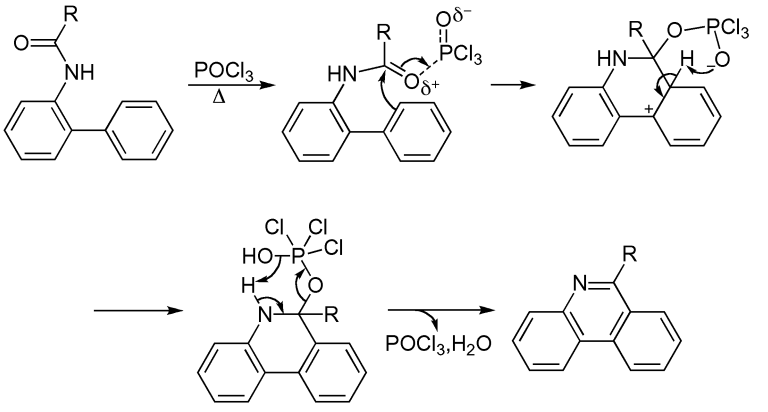
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

The reaction mechanism under the initial Pictet-Hubert condition is displayed in Scheme 1 and the modified Morgan-Wall condition is outlined in Scheme 2. It is believed that the complexation of Lewis acid (e.g., $ZnCl_2$) with oxygen polarizes the carbonyl group, which facilitates the electrophilic substitution as shown below.



SCHEME 1. *Mechanism under Pictet-Hubert condition.*



SCHEME 2. *Mechanism under Morgan-Walls condition.*

D. MODIFICATION

The phenanthridine can be obtained from the reduction and dehydration of phenanthridone, which is easily prepared from the cyclization of *o*-biphenyl isocyanante with $AlCl_3$. In addition, the coupling between nitrile and biphenyl carbocation generated from *ortho*-diazonium biphenyl salt is also a good method for phenanthridine (i.e., the *Ritter Reaction*)[8].

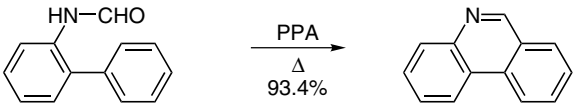
E. APPLICATIONS

This reaction is useful for the preparation of phenanthridine derivatives, especially for 6-substituted phenanthridines.[5b]

F. RELATED REACTIONS

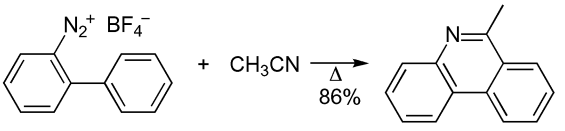
This reaction is related to the *Bischler-Napieralski Isoquinoline Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 8.

A mixture of 20 mL polyphosphoric acid and 2.0 g 2-formamidobiphenyl in a 100-mL round-bottomed flask was heated at 140–160°C for 1 h with constant stirring. The viscous reaction mixture was then poured into 200 mL cold water. The resulting milky solution was basified to pH 10 with a strong NaOH solution and allowed to stand several hours at room temperature. The light pink solid was filtered, washed extensively with water, and dried to give 1.70 g phenanthridine, in a yield of 93.4%, m.p. 104.5–106°C. The product can be further purified by recrystallization from ligroin to colorless needles, m.p. 106–107°C.



Reference 6a.

A solution of 1.07 g 2-biphenyldiazonium tetrafluoroborate in 25 mL anhydrous CH_3CN was refluxed for 12 h under conditions without moisture. Nitrogen evolution was complete in a few minutes. After cooling, the unreacted CH_3CN was evaporated, and the solid residue was treated with 15 mL $CHCl_3$ and 5% aqueous NaOH. The organic layer was extracted with 8% H_3PO_4 (3×15 mL). The combined extracts were washed with $CHCl_3$, neutralized with NaOH, and then extracted with $CHCl_3$. The combined $CHCl_3$ was dried over Na_2SO_4, and 0.66 g 6-methylphenanthridine was obtained after the evaporation of $CHCl_3$, in a yield of 86%, m.p. 84°C. GLPC analysis indicated that this product was contaminated by 4.5% 2-fluorobiphenyl.

Other references related to the synthesis of phenanthridine are cited in the literature.[9]

H. REFERENCES

1. Pictet, A. and Hubert, A., *Ber.,* **1896**, *29*, 1182.
2. Morgan, C. T. and Walls, L. P., *J. Chem. Soc.,* **1931**, 2447.
3. Buntrock, R. E. and Taylor, E. C., *Chem. Rev.,* **1967**, *67*, 209.
4. Theobald, R. S. and Schofield, K., *Chem. Rev.,* **1950**, *46*, 171.
5. (a) Nagarajan, K. and Shah, R. K., *Indian J. Chem.,* **1972**, *10*, 450. (b) Gilman, H. and Eisch, J., *J. Am. Chem. Soc.,* **1957**, *79*, 4423.
6. (a) Petterson, R. C.; Bennett, J. T.; Lankin, D. C.; Lin, G. W.; Mykytka, J. P. and Troendle, T. G., *J. Org. Chem.,* **1974**, *39*, 1841. (b) Matvelashvili, G. S.; Belevskii, S. F.; Fedotova, O. Y. and Kolesnikov, G. S., *Chem. Heterocycl. Compd.,* **1972**, *5*, 788. (c) Ritchie, E., *J. Proc. Royal Soc. New South Wales,* **1945**, *78*, 147.
7. (a) Walls, L. P., *J. Chem. Soc.,* **1945**, 294. (b) Morgan, G. T. and Walls, L. P., *Brit. Pat.,* **1940**, Apr. 18, 520,273.
8. Taylor, E. C. and Kalenda, N. W., *J. Am. Chem. Soc.,* **1954**, *76*, 1699.
9. (a) Churruca, F.; Martin, R. S.; Carril, M.; Urtiaga, M. K.; Solans, X.; Tellitu, I. and Domínguez, E., *J. Org. Chem.,* **2005**, *70*, 3178. (b) Eisch, J. and Gilman, H., *Chem. Rev.,* **1957**, *57*, 525. (c) Walls, L. P., *Heterocycl. Compd.,* **1952**, *4*, 574. (d) Finkelstein, J. and Linder, S. M., *J. Am. Chem. Soc.,* **1951**, *73*, 302. (e) Cymerman, J. and Short, W. F., *J. Chem. Soc.,* **1949**, 703. (f) Butler, J. M., *J. Am. Chem. Soc.,* **1949**, *71*, 2578. (g) Stepan, A. H. and Hamilton, C. S., *J. Am. Chem. Soc.,* **1949**, *71*, 2438. (h) Gilman, H. and Nelson, R. D., *J. Am. Chem. Soc.,* **1948**, *70*, 3316. (i) Walls, L. P., *J. Chem. Soc.,* **1947**, 67. (j) Pinck, L. A. and Hilbert, G. E., *J. Am. Chem. Soc.,* **1937**, *59*, 8. (k) Koelsch, C. F., *J. Am. Chem. Soc.,* **1936**, *58*, 1325. (l) Morgan, C. T. and Walls, L. P., *J. Chem. Soc.,* **1932**, 2225. (m) Moore, F. J. and Huntress, E. H., *J. Am. Chem. Soc.,* **1927**, *49*, 1324.

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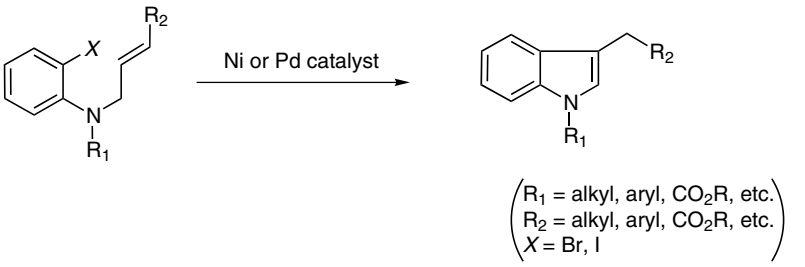
Mori-Ban Indole Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Mori and Ban in 1976.[1] It is a synthesis of indole derivatives by an intramolecular *Heck Reaction* of *o*-halo-*N*-allylanilines catalyzed by a low-valent metal complex and is known as the Mori-Ban indole synthesis.[2] In this reaction, the low-valent metal can be nickel[1] or palladium,[3] but the *ortho* halogen must be bromine or iodine.[4] Often the *o*-iodo-*N*-allylaniline is more reactive than corresponding *o*-bromo substrate.[5] In addition, it has been found that the catalyst can be deactivated under the reaction conditions, thus a periodic provision of fresh catalyst normally gives higher overall yields than that using the same total amount of catalyst at once.[5]

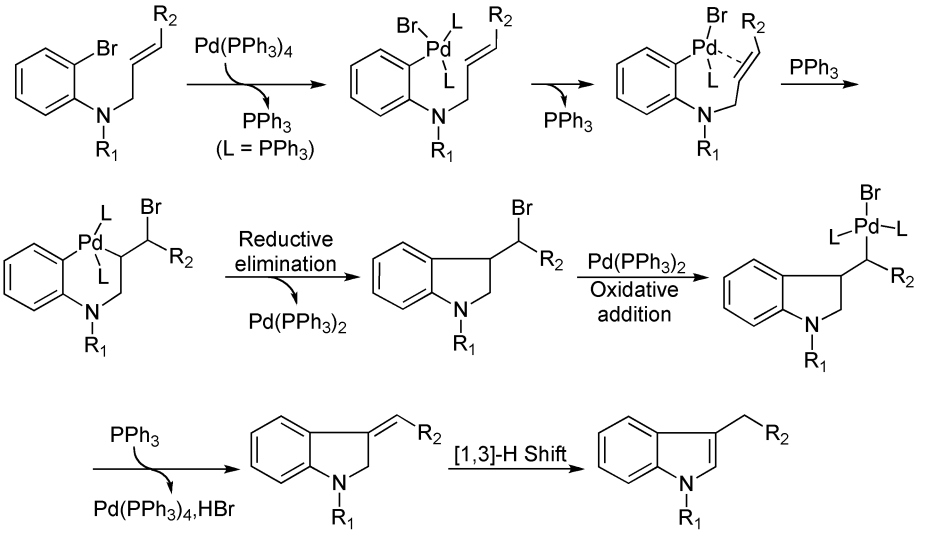
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

A general mechanism for this reaction is displayed below, using *o*-bromo-*N*-allylaniline as the substrate and $Pd(PPh_3)_4$ as a catalyst.



D. MODIFICATION

This reaction has been modified by using a zirconocene complex as a catalyst;[6] in addition, a solid-phase supported substrate has been used in this reaction.[7]

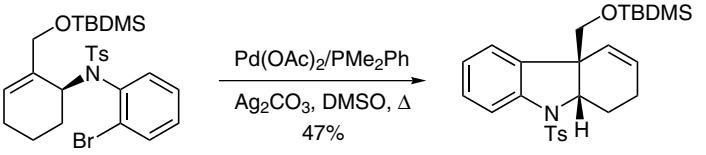
E. APPLICATIONS

This reaction has general application for the synthesis of indole and indoline derivatives.

F. RELATED REACTIONS

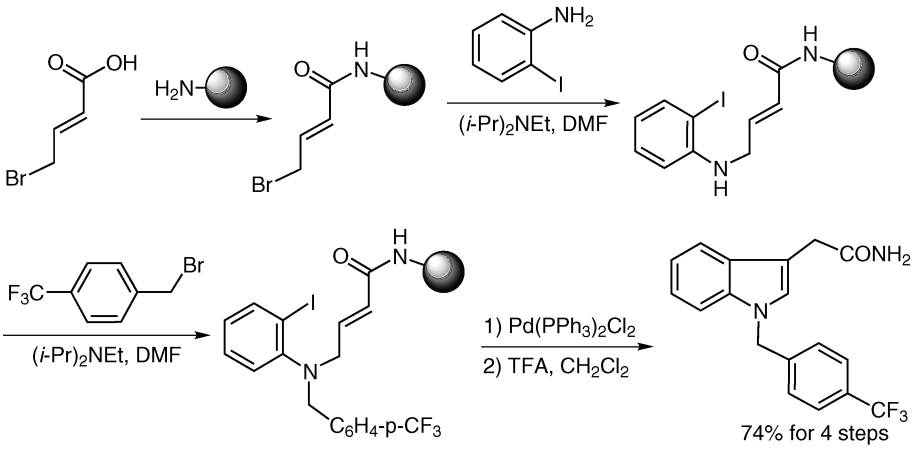
This reaction is related to the *Larock Indole Synthesis.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 8.

A solution of 763 mg (*S*)-*N*-(2-bromophenyl)-*N*-(2-[(2-*tert*-butyldimethylsilanyloxymethyl-2-cyclohexenyl)-4-methyl-benzenesulfonamide (1.39 mmol), 15.6 mg $Pd(OAc)_2$ (69.3 μmol), 20.0 μL Me_2PPh (139 μmol), and 382 mg Ag_2CO_3 (1.39 mmol) in 14 mL DMSO was heated at 120°C for 24 h. After cooling to room temperature, the mixture was filtered through the pad of Celite. Then EtOAc was added, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography using hexane/CH_2Cl_2 (1:1) as the eluent to afford 306.9 mg (4a*S*,9a*S*)-4a-(*tert*-butyldimethylsilanyloxymethyl)-9-(4-methylbenzenesulfonyl)-2,4a,9,9a-tetrahydro-1*H*-carbazole as a white solid, in a yield of 47%.



Reference 7.

Rink amid resin (7.5 g, 0.48 mmol/g, 3.6 mmol) was deprotected with 100 mL 20% piperidine in DMF at room temperature for 1.5 h and then filtered and washed with DMF, MeOH, and CH_2Cl_2. The deprotected resin was suspended in 36 mL DMF and treated with 2.73 g DIC (21.6 mmol), followed by 3.56 g γ-bromocrotonic acid (21.6 mmol). The mixture was stirred at room temperature for 30 min and then filtered and washed with CH_2Cl_2 and DMF. The resulting resin was retreated with 36 mL DMF, 2.73 g DIC, and 3.56 g γ-bromocrotonic acid at room temperature for 30 min; it was then washed with DMF, MeOH, CH_2Cl_2, and Et_2O. It was dried in vacuo to give 7.41 g resin with a loading level of 0.32 mmol/g, which was determined by cleaving an aliquot with 30% TFA in CH_2Cl_2 at room temperature for 80 min. Then 1.2 g of this resin (0.38 mmol) was suspended in 10 mL DMF and treated with 387 mg *N*,*N*-diisopropylethylamine (3.0 mmol), followed by 420 mg 2-iodoaniline (1.9 mmol). The reaction mixture was stirred at 80°C for 18 h and then filtered and washed with CH_2Cl_2, MeOH, and CH_2Cl_2. It was dried in vacuo to give 1.25 g *o*-iodo-*N*-allylanlinide. A mixture of 230 mg of this *o*-iodo-anilide (0.070 mmol), 90 mg *N*,*N*-diisopropylethylamine (0.70 mmol), and 167 mg α'-bromo-α,α,α-trifluoro-*p*-xylene (0.70 mmol) in 2.5 mL DMF was stirred at 80°C for 22 h and then filtered, washed sequentially with MeOH and CH_2Cl_2, and dried in vacuo to give *o*-iodo-*N*-benzyl-allylanilide. The resulting resin was then suspended in 4 mL DMF-H_2O mixture (9:1) and treated with 29 mg tetrabutylammonium chloride (0.11 mmol), 21 mg triethylamine (0.21 mmol), and 4.9 mg bis-(triphenylphosphine)palladium(II) chloride (0.007 mmol). The suspension was stirred at 80°C for 8 h, at which time TLC indicated that the reaction was complete. The dark brown

reaction mixture was filtered; washed sequentially with CH_2Cl_2, MeOH, and CH_2Cl_2; and then dried in vacuo. The resulting resin was cleaved with 8 mL 30% TFA in CH_2Cl_2 at room temperature for 1.5 h. The crude cleaved product obtained was dissolved in 25 mL EtOAc, washed with 5 mL water to remove contaminated Et_3N-TFA salt, and then washed with 5 mL brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting product showed 85% purity by reversed-phase HPLC (2 mL/min, 7:3 H_2O/CH_3CN (0.2% TFA), linear gradient to 5:95 in 30 min; $R_f = 18.5$ min). After purification by preparative TLC using EtOAc/MeOH (95:5), 17.2 mg 2-[1-[4-(trifluoromethyl) benzyl]-1*H*-indol-3-yl]acetamide was obtained as a colorless solid, in a total yield of 74% for four steps.

Other references related to the Mori-Ban indole synthesis are cited in the literature.[9]

H. REFERENCES

1. (a) Mori, M. and Ban, Y., *Tetrahedron Lett.,* **1976**, *17*, 1803. (b) Mori, M. and Ban, Y., *Tetrahedron Lett.,* **1976**, *17*, 1807.
2. Li, J. J. and Gribble, G. W., *Palladium in Heterocyclic Chemistry: A Guide for the Synthetic Chemist* [Tetrahedron Organic Chemistry Series], Elsevier, Oxford, **2000**.
3. (a) Mori, M.; Kanda, N.; Oda, I. and Ban, Y., *Tetrahedron,* **1985**, *41*, 5465. (b) Mori, M.; Chiba, K. and Ban, Y., *Tetrahedron Lett.,* **1977**, *18*, 1037.
4. Cacchi, S. and Fabrizi, G., *Chem. Rev.,* **2005**, *105*, 2873.
5. Odle, R.; Blevins, B.; Ratcliff, M. and Hegedus, L. S., *J. Org. Chem.,* **1980**, *45*, 2709.
6. Tidwell, J. H.; Senn, D. R. and Buchwald, S. L., *J. Am. Chem. Soc.,* **1991**, *113*, 4685.
7. Zhang, H.-C. and Maryanoff, B. E., *J. Org. Chem.,* **1997**, *62*, 1804.
8. Mori, M.; Nakanishi, M.; Kajishima, D. and Sato, Y., *Org. Lett.,* **2001**, *3*, 1913.
9. (a) Mori, M.; Nakanishi, M.; Kajishima, D. and Sato, Y., *J. Am. Chem. Soc.,* **2003**, *125*, 9801. (b) Kamijo, S. and Yamamoto, Y., *J. Org. Chem.,* **2003**, *68*, 4764. (c) Tidwell, J. H. and Buchwald, S. L., *J. Am. Chem. Soc.,* **1994**, *116*, 11797. (d) Mori, M.; Kubo, Y. and Ban, Y., *Tetrahedron,* **1988**, *44*, 4321. (e) Ohnuma, T.; Tabe, M.; Shiiya, K.; Ban, Y. and Date, T., *Tetrahedron Lett.,* **1983**, *24*, 4249. (f) Mori, M.; Oda, I. and Ban, Y., *Tetrahedron Lett.,* **1982**, *23*, 5315. (g) Mori, M.; Hashimoto, Y. and Ban, Y., *Tetrahedron Lett.,* **1980**, *21*, 631. (h) Mori, M.; Kudo, S. and Ban, Y., *J. Chem. Soc., Perkin Trans. I,* **1979**, 771. (i) Mori, M. and Ban, Y., *Tetrahedron Lett.,* **1977**, *18*, 1133.

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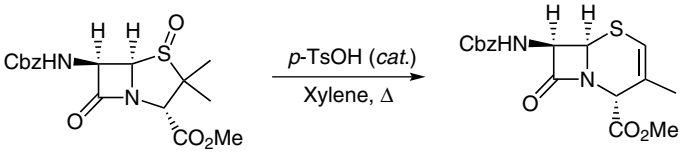
Morin Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Morin et al. in 1963.[1] It is an acid-promoted stereospecific transformation of penicillin sulfoxides into corresponding desacetoxycephalosporins[2] and is generally known as the Morin rearrangement[2,3] or Morin reaction.[4] Occasionally, this reaction is also referred to as the Morin process.[5] This reaction involves the following steps: (*a*) activation of sulfoxide by an acid, (*b*) generation of azetidinone sulfenic acid[2] via stereospecifically sigmatropic opening of the thiazolidine ring without concomitant rupture of the β-lactam[6] by abstracting a proton from the C-2 methyl group *cis* to the sulfoxide S-O bond,[2] (*c*) protonation of sulfenic acid, and (*d*) cyclization of protonated sulfenic acid with the adjacent π-bond and the final deprotonation.[5] This rearrangement is found to be general for penicillin[4a] and hetacillin sulfoxides.[4a] Further evidence for the protonation of sulfenic acid that cyclizes to adjacent π-bond has been demonstrated by the capture of putative cationic intermediate by carbon nucleophiles, such as indole, furan, and anisole.[3b] This reaction has clearly indicated the existence of a thermal equilibrium between the sulfoxide and the sulfenic acid.[7] In addition, it provides the first direct chemical correlation between the penicillins and cephalosporins and a practical preparation of important antibiotics containing deacetoxycephalosporin moiety.[8]

B. GENERAL REACTION SCHEME



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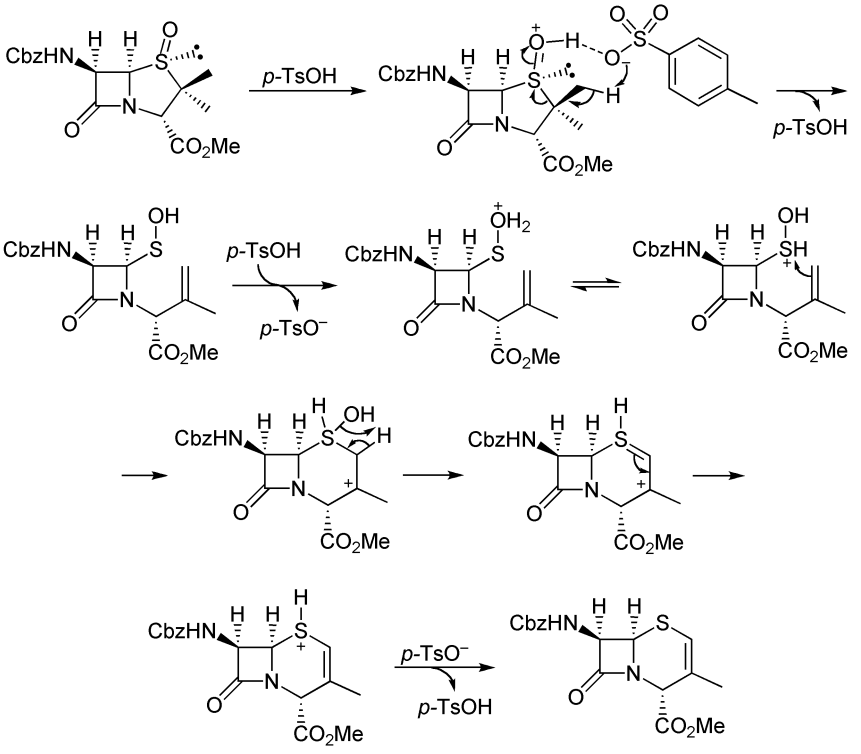
C. PROPOSED MECHANISMS

Although it is assumed that the reaction involves the activation of sulfoxide by an acid, formation of sulfenic acid, and cyclization with adjacent π-bond,[2] no detailed mechanism has been provided in literature. A tentative mechanism in full details is displayed here.



D. MODIFICATION

N/A

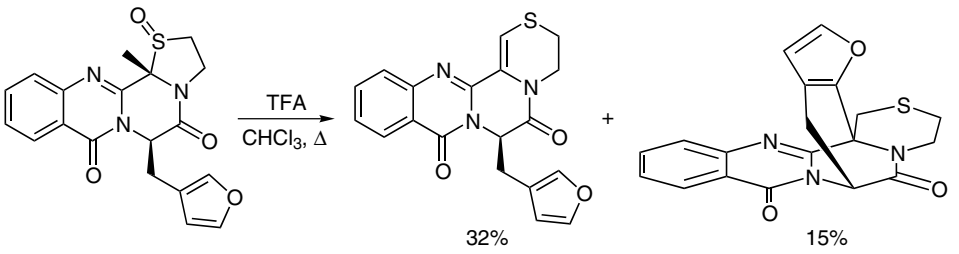
E. APPLICATIONS

This reaction has important application in the preparation of antibiotics containing deacetoxy-cephalosporin moiety.

F. RELATED REACTIONS

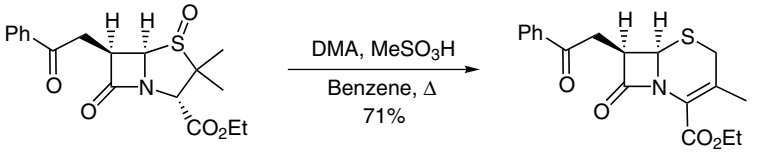
This reaction is related to the *Pummerer Reaction.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 3b.

To a 250-mL round-bottomed flask fitted with a reflux condenser and magnetic stirrer were added 680 mg sulfoxide (1.8 mmol), 90 mL $CHCl_3$, and 10 mL trifluoroacetic acid (130 mmol). The resulting rose-colored solution was refluxed for 18 h. The reaction mixture was then transferred to a separation funnel and washed successively with two 125-mL portions of 1 M Na_2CO_3 and 75 mL water. The aqueous washes were back extracted with $CHCl_3$, and the organic extracts were combined, dried over $MgSO_4$, filtered, and evaporated to give an amorphous solid residue. The residue was chromatographed using MPLC over silica gel (hexanes/EtOAc, 4:3) to afford a white foam. Then the foam was fractionally recrystallized from EtOAc/hexanes to afford 210 mg high pure thioether, in a yield of 32%, m.p. 189–192°C (EtOAc/hexanes). The mother liquor was concentrated to give a solid residue, which was recrystallized from EtOAc/hexanes to give 100 mg furan fused thioether, in a yield of 15%, m.p. 249–251°C (EtOAc/hexanes).



Reference 9.

A solution of 963 mg β,β,β-trichloroethyl 6β-(phenylcarbothio)penicillanate 1-oxide (α and β isomers, 1.98 mmol), 32 mL dry benzene, 24 mL *N*,*N*-dimethylacetamide, and 3 drops methanesulfonic acid were refluxed for 19 h under a Dean-Stark trap, protected from moisture with a drying tube (temperature of external heating bath was maintained between 110° and 120°C). Removal of the solvent by distillation under reduced pressure (temperature of bath ~ 50°C, 2–3 mmHg) and silica gel chromatography of the dark brown residue using CH_2Cl_2 as an eluent gave 659 mg β,β,β-trichloroethyl 7β-(phenylcarbothio)-deacetoxycephalosporanate as a white solid, in a yield of 71%. Recrystallization from CH_2Cl_2/petroleum ether gave an analytically pure sample as thin, white needles, m.p. 175.5–176.0°C.

Other references related to the Morin rearrangement are cited in literature.[10]

H. REFERENCES

1. Morin, R. B.; Jackson, B. G.; Mueller, R. A.; Lavagnino, E. R.; Scanlon, W. B. and Andrews, S. L., *J. Am. Chem. Soc.,* **1963**, *85*, 1896.
2. Micetich, R. G.; Singh, R. and Shaw, C. C., *J. Org. Chem.,* **1986**, *51*, 1811.
3. (a) Michael, J. P., *Nat. Prod. Rep.,* **2002**, *19*, 742. (b) Freed, J. D.; Hart, D. J. and Magomedov, N. A., *J. Org. Chem.,* **2001**, *66*, 839. (c) Hart, D. J. and Magomedov, N., *J. Org. Chem.,* **1999**, *64*, 2990. (d) Kant, J.; Roth, J. A.; Fuller, C. E.; Walker, D. G.; Benigni, D. A. and Farina, V., *J. Org. Chem.,* **1994**, *59*, 4956. (e) Cooper, R. D. G.; DeMarco, P. V.; Cheng, J. C. and Jones, N. D., *J. Am. Chem. Soc.,* **1969**, *91*, 1408.
4. (a) Sammes, P. G., *Chem. Rev.,* **1976**, *76*, 113. (b) San Martin, C. R.; Mosqueira, A. and Garcia, B. L., *Farmacognosia, Anales Instituto Jose Celestino Mutis*, **1950**, *10*, 185. (c) Neelakantam, K. and Row, L. R., *Proc. Indian Acad. Sci., Sect. A,* **1941**, *14A*, 307. (d) Sandell, E. B., *Ind. Eng. Chem., Anal. Ed.,* **1940**, *12*, 762.
5. Bur, S. K. and Padwa, A., *Chem. Rev.,* **2004**, *104*, 2401.
6. Cooper, R. D. G. and José, F. L., *J. Am. Chem. Soc.,* **1970**, *92*, 2575.
7. Cooper, R. D. G., *J. Am. Chem. Soc.,* **1970**, *92*, 5010.
8. Kukolja, S.; Lammert, S. R.; Gleissner, M. R. B. and Ellis, A. I., *J. Am. Chem. Soc.,* **1976**, *98*, 5040.
9. Sheehan, J. C.; Commons, T. J. and Lo, Y. S., *J. Org. Chem.,* **1977**, *42*, 2224.
10. (a) Farina, V. and Kant, J., *Synlett,* **1994**, 565. (b) Tsushima, T. and Tanida, H., *J. Org. Chem.,* **1980**, *45*, 3205. (c) Brian, E. G.; Eglington, A. J.; Nayler, J. H. C.; Osborne, N. F.; Pearson, M. J.; Smale, T. C.; Southgate, R.; Tolliday, P.; Basker, M. J. and Sutherland, R., *J. Med. Chem.,* **1977**, *20*, 1082. (d) Cooper, R. D. G.; Hatfield, L. D. and Spry, D. O., *Acc. Chem. Res.,* **1973**, *6*, 32. (e) Cooper, R. D. G., *J. Am. Chem. Soc.,* **1972**, *94*, 1018. (f) Spry, D. O., *J. Org. Chem.,* **1972**, *37*, 793. (g) Spry, D. O., *J. Am. Chem. Soc.,* **1970**, *92*, 5006. (h) Morin, R. B.; Jackson, B. G.; Mueller, R. A.; Lavagnino, E. R.; Scanlon, W. B. and Andrews, S. L., *J. Am. Chem. Soc.,* **1969**, *91*, 1401.

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Mosher's Acid

A. GENERAL DESCRIPTION OF THE REACTION

This compound was first applied by Mosher et al. as early as 1968 to determine the enantiomeric excess (% e.e.) of chiral molecules.[1] It is α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA), made from the reaction between α,α,α-trifluoroacetophenone and sodium cyanide in DME followed by alkylation with Me_2SO_4 and subsequent hydrolysis.[2] This molecule has a boiling point of 105–110°C at 1 mmHg,[3] and 90–93°C at 0.3 mmHg,[2a] and has been widely used in the determination of enantiomeric excess of chiral molecules. Therefore, MTPA is referred to as the Mosher's acid,[2a,4] its derivative (i.e., acyl chloride) for the preparation of ester or amide from primary or secondary alcohol or amine is known as Mosher's reagent,[5] and the corresponding ester is called the Mosher ester.[4c,6] Unlike the preparation of mandelate or *O*-methylmandelate derivatives,[7] the racemization is impossible during the derivatization of Mosher's acid[2b,8] because no α-proton exists in this acid.[5b] In addition, both ^{1}H NMR[9] and ^{19}F NMR[10] can be used to determine the % e.e. value of enantiomeric compounds, although it has been reported that ^{1}H NMR is superior to ^{19}F NMR.[5b] It has been found that the % e.e. obtained from this method is very consistent with the result determined from chiral HPLC (e.g., $< 1\%$ error).[4c] In addition, this acid can also be used to determine the diastereomeric excess (% d.e.).[6i] More importantly, not only can MTPA be used to determine the absolute configuration (R or S) of alcohol by comparing the NMR signals of natural and synthetic alcohols,[11] but it has also been successfully used for the determination of stereochemistry of alcohols when there is no available basis for comparison.[6h,12] It has been found that while the chemical shift of one group attached to the carbinyl location in (R)-(+)-MTPA ester moves upfield, the chemical shift of the other group exclusively goes downfield; the reverse movement of chemical shifts are observed for the same carbinol in (S)-(-)-MTPA ester.[8a] As demonstrated in Section C,

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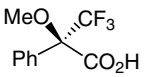
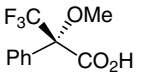
1A and 1B are the diastereomeric esters prepared from (R)-(+)-MTPA and (S)-(-)-MTPA, in which the (R)-(+)-MTPA ester always shows an upfield signal for the group L_2 and a downfield signal for the group L_3, compared to the alternate diastereomer—that is the (S)-(-)-MTPA ester.[8a] This is because the electron-withdrawing α-trifluoromethyl group, more or less, eclipses the carbonyl group in the ester, and one of the group (L_2 or L_3) will yield different time-weighted average preferential shieldings from the π-cloud of the α-phenyl group, resulting in a different chemical shift movement, even though the carbinyl proton is still located in the same relative position in each diastereomer.[8a] As shown in Section C in the case of (R)-(+)-MTPA ester, L_2 is juxtaposed with the phenyl group, which will be deshielded from such phenyl group and move upfield; similarly, in the case of (S)-(-)-MTPA ester, L_3 is juxtaposed with phenyl group and will go upfield too.[8a] To determine the absolute configuration of a given alcohol, both (R)-(+)-MTPA and (S)-(-)-MTPA esters are prepared, and different NMR spectra are measured, including ^{1}H NMR, COSY, and TOCSY, to assign the chemical shifts for every proton; the critical chemical shifts of protons on the groups attached to the carbinyl location are then used to calculate the difference of the chemical shift, and the absolute configuration of that chiral center is determined according to the layouts shown by 1A and 1B.[7,8a] For some alcohols, of which the chemical shift changes very small, the corresponding (R)- and (S)-2-naphthylmethoxyacetic acid (2-NMA) esters are employed to determine the configuration, due to their improved long-range anisotropic effects.[12b]

B. GENERAL REACTION SCHEME



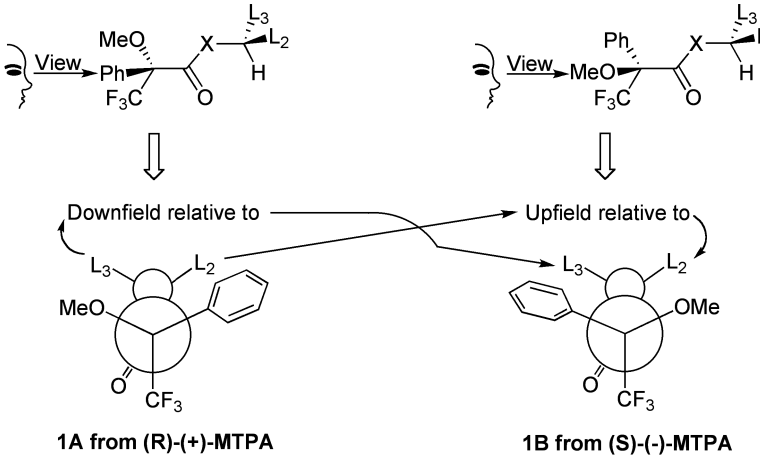
(R)-(+)-MTPA



(S)-(-)-MTPA

C. PROPOSED MECHANISMS

The correlation between the movement of chemical shift and the shielding/deshielding of the carbinyl group from the phenyl group of Mosher's acid is demonstrated here.



1A from (R)-(+)-MTPA **1B from (S)-(-)-MTPA**

D. MODIFICATION

Several analogues of Mosher's acid have been developed for determining the stereochemistry.[12b,13] In addition, a modified Mosher's method has been used to determined the absolute configuration of some natural products.[14] Moreover, the preparation of MTPA has been improved to one-pot synthesis by the addition of trimethylsilyl trichloroacetate to α,α,α-trifluoroacetophenone and subsequent hydrolysis.[2a]

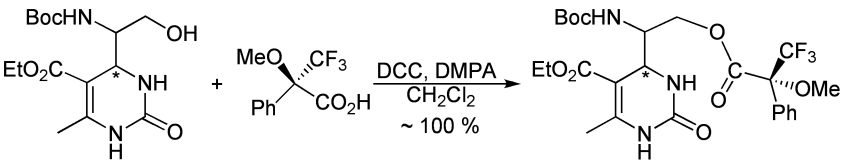
E. APPLICATIONS

This compound has wide application in determination of enantiomeric excess and the absolute configuration of chiral compounds.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 10.

To a stirred solution of 0.1 mmol (4*R*,1′*S*)- and (4*S*,1′*S*)-4-(1′-*tert*-butoxycarbonylamino-2′-hydroxyethyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester in 1 mL anhydrous CH_2Cl_2 were added 29 mg (R)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (0.12 mmol), 25 mg 1,3-dicyclohexylcarbodiimide (0.12 mmol), and a catalytic amount of 4-*N*,*N*-(dimethylamino)pyridine. The mixture was stirred for an additional 12 h at room temperature, then concentrated. The residue was taken into EtOAc, washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The residue was purified by preparative TLC, affording the corresponding Mosher ester in almost quantitative yield.

Other references related to the Mosher's acid are cited in the literature.[15]

H. REFERENCES

1. Dale, J. A. and Mosher, H. S., *J. Am. Chem. Soc.,* **1968**, *90*, 3732.
2. (a) Goldberg, Y. and Alper, H., *J. Org. Chem.,* **1992**, *57*, 3731. (b) Dale, J. A.; Dull, D. L. and Mosher, H. S., *J. Org. Chem.,* **1969**, *34*, 2543.

3. Hall, W. E.; Seeholzer, K.; Baumeister, M. and Ugi, I., *Tetrahedron,* **1986**, *42*, 547.
4. (a) Cravotto, G.; Bicchi, C.; Tagliapietra, S.; Costa, L.; Di Carlo, S. and Nervi, C., *Chirality,* **2004**, *16*, 526. (b) Buszek, K. R. and Sato, N., *Org. Prep. Proc. Int.,* **2000**, *32*, 488. (c) Riedl, R.; Tappe, R. and Berkessel, A., *J. Am. Chem. Soc.,* **1998**, *120*, 8994. (d) Matthews, D. B.; Hinton, R. H.; Wright, B.; Wilson, I. D. and Stevenson, D., *J. Chromat., B: Biomed. Sci. Appl.,* **1997**, *695*, 279. (e) Matthews, D. B.; Hinton, R. H.; Wright, B.; Wilson, I. D. and Stevenson, D., *J. Chromat., B: Biomed. Sci. Appl.,* **1997**, *695*, 279. (f) Benanni, Y. L.; Vanhessche, K. P. M. and Sharpless, K. B., *Tetrahedron: Asymmetry*, **1994**, *5*, 1473. (g) Chong, J. M. and Loewith, R., *Synth. Commun.,* **1993**, *23*, 2145. (h) Berger, B.; de Raadt, A.; Griengl, H.; Hayden, W.; Hechtberger, P.; Klempier, N. and Faber, K., *Pure & Appl. Chem.,* **1992**, *64*, 1085. (i) Ward, D. E. and Rhee, C. K., *Tetrahedron Lett*., **1991**, *32*, 7165. (j) Koenig, W. A.; Nippe, K. S. and Mischnick, P., *Tetrahedron Lett*., **1990**, *31*, 6867. (k) Jeanneret-Gris, G. and Pousaz, P., *Tetrahedron Lett*., **1990**, *31*, 75. (l) Fleming, I., *Pure & Appl. Chem.,* **1988**, *60*, 71. (m) Hull, W. E.; Seeholzer, K.; Baumeister, M. and Ugi, I., *Tetrahedron*, **1986**, *42*, 547.
5. (a) Linhart, I.; Gut, I.; Smejkal, J. and Novák, J., *Chem. Res. Toxicol.,* **2000**, *13*, 36. (b) Jackson, P. T.; Kim, T.-Y. and Carr, P. W., *Anal. Chem.,* **1997**, *69*, 5011.
6. (a) Brand, D. J.; Steenkamp, J. A.; Brandt, E. V. and Takeuchi, Y., *Tetrahedron Lett*., **2007**, *48*, 2769. (b) Curran, D. P.; Zhang, Q. S.; Lu, H. J. and Gudipati, V., *J. Am. Chem. Soc.,* **2006**, *128*, 9943. (c) Guilet, D.; Guntern, A.; Ioset, J.-R.; Queiroz, E. F.; Ndjoko, K.; Foggin, C. M. and Hostettmann, K., *J. Nat. Prod.,* **2003**, *66*, 17. (d) Su, B.-N.; Park, E. J.; Mbwambo, Z. H.; Santarsiero, B. D.; Mesecar, A. D.; Fong, H. H. S.; Pezzuto, J. M. and Kinghorn, A. D., *J. Nat. Prod.,* **2002**, *65*, 1278. (e) Colman de Saizarbitoria, T.; Tillett, S. and Malaughlin, J. L., *Boletin Soc. Chilena Quim.,* **2000**, *45*, 521. (f) Joshi, B. S. and Pelletier, S. W., *Heterocycles*, **1999**, *51*, 183. (g) Duret, P.; Waechter, A.-I.; Figadère, B.; Hocquemiller, R. and Cave, A., *J. Org. Chem.,* **1998**, *63*, 4717. (h) Spinella, A.; Zubía, E.; Martînez, E.; Ortea, J. and Cimino, G., *J. Org. Chem.,* **1997**, *62*, 5471. (i) Rodríguez R., G. H. and Biellmann, J.-F., *J. Org. Chem.,* **1996**, *61*, 1822. (j) Nishioka, S.; Araya, H.; Murasaki, C.; Sahai, M. and Fujimoto, Y., *Nat. Prod. Lett.,* **1994**, *5*, 117. (k) Hoye, T. R.; Hanson, P. R.; Hasenwinkel, L. E.; Ramirez, E. A. and Zhuang, Z. P., *Tetrahedron Lett*., **1994**, *35*, 8529. (l) Gu, Z.; Zeng, L.; Fang, X.; Colman-Saizarbitoria, T.; Huo, M. and McLaughlin, J. L., *J. Org. Chem.,* **1994**, *59*, 5162. (m) Hammerschmidt, F. and Li, Y.-F., *Tetrahedron,* **1994**, *50*, 10253. (n) Rieser, M. J.; Hui, Y. H.; Rupprecht, J. K.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L.; Hanson, P. R.; Zhuang, Z. P. and Hoye, T. R., *J. Am. Chem. Soc.,* **1992**, *114*, 10203. (o) Theil, F.; Costisella, B. and Schick, H., *J. Prakt. Chem./Chemiker-Zeit.,* **1992**, *334*, 85.
7. Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L. and Springer, J. P., *J. Org. Chem.,* **1986**, *51*, 2370.
8. (a) Dale, J. A. and Mosher, H. S., *J. Am. Chem. Soc.,* **1973**, *95*, 512. (b) Sullivan, G. R.; Dale, J. A. and Mosher, H. S., *J. Org. Chem.,* **1973**, *38*, 2143.
9. Marotta, E.; Baravelli, M.; Maini, L.; Righi, P. and Rosini, G., *J. Org. Chem.,* **1998**, *63*, 8235.
10. Dondoni, A.; Massi, A.; Minghini, E.; Sabbatini, S. and Bertolasi, V., *J. Org. Chem.,* **2003**, *68*, 6172.
11. Coffey, D. S.; Overman, L. E. and Stappenbeck, F., *J. Am. Chem. Soc.,* **2000**, *122*, 4904.
12. (a) Bashyal, B. P.; Wijeratne, E. M. K.; Faeth, S. H. and Gunatilaka, A. A. L., *J. Nat. Prod.,* **2005**, *68*, 724. (b) Ishii, H.; Krane, S.; Itagaki, Y.; Berova, N.; Nakanishi, K. and Weldon, P. J., *J. Nat. Prod.,* **2004**, *67*, 1426. (c) Okamoto, S.; Hosoe, T.; Itabashi, T.; Nozawa, K.; Okada, K.; de Campos Takaki, G. M.; Chikamori, M.; Yaguchi, T.; Fukushima, K.; Miyaji, M. and Kawai, K.-I., *J. Nat. Prod.,* **2004**, *67*, 1580. (d) Marshall, J. A.; Piettre, A.; Paige, M. A. and Valeriote, F., *J. Org. Chem.,* **2003**, *68*, 1780. (e) de Napoli, L.; Messere, A.; Palomba, D.; Piccialli, V.; Evidente, A. and Piccialli, G., *J. Org. Chem.,* **2000**, *65*, 3432. (f) Rasmussen, H. B.; Christensen, S. B.; Kvist, L. P.; Kharazmi, A. and Huansi, A. G., *J. Nat. Prod.,* **2000**, *63*, 1295. (g) Qureshi,

A.; Salvá, J.; Harper, M. K. and Faulkner, D. J., *J. Nat. Prod.,* **1998**, *61*, 1539. (h) Ondeyka, J. G.; Helms, G. L.; Hensens, O. D.; Goetz, M. A.; Zink, D. L.; Tsipouras, A.; Shoop, W. L.; Slayton, L.; Dombrowski, A. W.; Polishook, J. D.; Ostlind, D. A.; Tsou, N. N.; Ball, R. G. and Singh, S. B., *J. Am. Chem. Soc.,* **1997**, *119*, 8809. (i) Rosa, S. D.; Milone, A.; Crispino, A.; Jaklin, A. and Giulio, A. D., *J. Nat. Prod.,* **1997**, *60*, 462. (j) Barrett, A. G. M.; Peña, M. and Willardsen, J. A., *J. Org. Chem.,* **1996**, *61*, 1082.

13. (a) Vodicka, P.; Streinz, L.; Vavra, J.; Koutek, B.; Budesinsky, M.; Ondracek, J. and Cisarova, I., *Chirality*, **2005**, *17*, 378. (b) Kawano, Y.; Kaneko, N. and Mukaiyama, T., *Chem. Lett.,* **2006**, *35*, 304. (c) Prakash, G. K. S.; Yan, P.; Torok, B. and Olah, G. A., *Synlett*, **2003**, 527.
14. (a) Kusumi, T.; Hamada, T.; Ishitsuka, M. O.; Ohtani, I. and Kakisawa, H., *J. Org. Chem.,* **1992**, *57*, 1033. (b) Kusumi, T.; Fujita, Y.; Ohtani, I. and Kakisawa, H., *Tetrahedron Lett*., **1991**, *32*, 2923.
15. (a) Cordero, F. M.; Pisaneschi, F.; Salvati, M.; Valenza, S.; Faggi, C. and Brandi, A., *Chirality*, **2005**, *17*, 149. (b) Torres-Valencia, J. M.; Leon, G. I.; Villagomez-Ibarra, J. R.; Suarez-Castillo, O. R.; Cerda-Garcia-Rojas, C. M. and Joseph-Nathan, P., *Phytochem. Anal.,* **2002**, *13*, 329. (c) Shimona, F.; Kusaka, H.; Wada, K.; Azami, H.; Yasunami, M.; Suzuki, T.; Hagiwara, H. and Ando, M., *J. Org. Chem.,* **1998**, *63*, 920. (d) Bueno, A. B.; Carreño, M. C.; Ruano, J. L. G.; Arrayáas, R. G. and Zarzuelo, M. M., *J. Org. Chem.,* **1997**, *62*, 2139. (e) Shi, G. E.; He, K.; Liu, X. X.; Ye, Q.; MacDougal, J. M. and McLaughlin, J. L., *Nat. Prod. Lett.,* **1997**, *10*, 125. (f) Shi, G. E.; Gu, Z.-M.; He, K.; Wood, K. V.; Zeng, L.; Ye, Q.; MacDougal, J. M. and McLaughlin, J. L., *Bioorg. Med. Chem.,* **1996**, *4*, 1281. (g) Kusumi, T.; Ohtani, I.; Inouye, Y. and Kakisawa, H., *Tetrahedron Lett*., **1988**, *29*, 4731.

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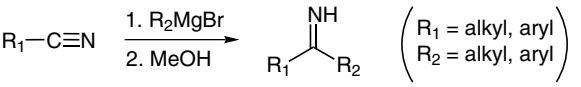
Moureau-Mignonac Ketimine Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Blaise in 1901,[1] and subsequently explored by Moureau and Mignonac extensively since 1913.[2] It is a direct synthesis of ketimine involving the reaction between a nitrile and a Grignard reagent and careful hydrolysis at low temperature with hydrogen chloride and finally with ammonia. Therefore, it is known as the Moureau-Mignonac ketimine synthesis. It is found that the ratio of Grignard reagent to nitrile from 4.85 to 2 has almost no effect on the yield of ketimine.[3] Although many of the resulting ketimines can be hydrolyzed to ketones[4] or reduced to amines,[5] some of the synthesized ketimines are fairly stable toward hydrolysis, such as 2,2,6-trimethylcyclohexyl phenyl ketimine,[6] *t*-butyl-*o*-tolyl ketimine,[7] and isopropyl 1-methyl-3-isopropylcyclopentyl ketimine.[3] The latter ketimine in particular can survive refluxing with 6 N HCl for a period of 2 days.[3] In addition, it has been found that the hydrolysis of ketimine depends on the ketimine-enamine tautomerization (and/or resonance) and the steric hindrance.[8] For the monosubstituted aryl ketimine, the hydrolysis rate is in the order of *meta* > *ortho* > *para*.[8] The reaction has been improved to decompose the nitrile-Grignard complex in a toluene solution with anhydrous ammonia.[9] In addition, this reaction has also been improved by using a copper (I) salt to catalyze the addition of a Grignard reagent to nitrile[5] and by the decomposition of nitrile-Grignard complex in anhydrous methanol.[7]

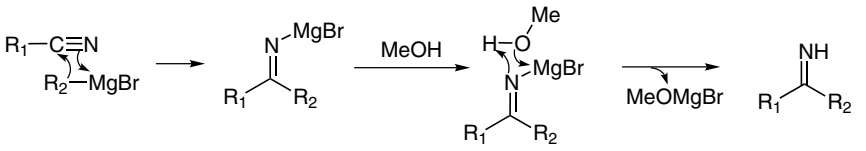
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Displayed below is the reaction mechanism to hydrolyze the nitrile-Grignard complex in anhydrous methanol.



D. MODIFICATION

This reaction has been modified to use copper (I) salt to accelerate the reaction[5] and anhydrous methanol to hydrolyze the nitrile-Gringard complex.[7]

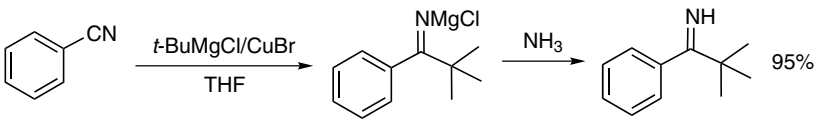
E. APPLICATIONS

This reaction is one of the best reactions for the preparation of ketimines.

F. RELATED REACTIONS

This reaction is related to the *Grignard Reaction*.

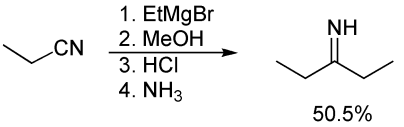
G. CITED EXPERIMENTAL EXAMPLES



Reference 5.

To a mixture of 2.0 g benzonitrile (19.4 mmol), 10.7 mL 2 M *tert*-butylmagnesium chloride in THF (21.4 mmol) and 40 mL THF, was added 50 mg CuBr (0.34 mmol), and the mixture was refluxed under nitrogen for 14 h. After cooling to 0–5°C (ice water bath), the nitrogen inlet tube attached to the condenser was replaced by a soda lime trap

and 10 mL anhydrous ammonia was condensed into the vessel. After allowing the mixture to warm to ambient temperature, it was filtered through Celite and the filtrate was concentrated at water-aspirator pressure on a rotary evaporator to afford 3.52 g α-(1,1-dimethylethyl)-benzenemethanimine as a colorless oil, which was further purified through Kugelrohr distillation to collect 2.97 g product, in a yield of 95%, b.p. 80–84°C at 0.6 mmHg.



Reference 7.

To the anhydrous diethyl ether solution containing 0.5 mol ethylmagnesium bromide was added 16 g propionitrile (0.285 mol) dropwise, and the mixture was refluxed for 4 h. After cooling to room temperature, the stirred complex was decomposed by the dropwise addition of 3 mol anhydrous methanol. Reaction was vigorous, and completion of the decomposition gave a white slurry, crystalline solid that could be easily filtered, although at the intermediate stage the mixture was sometimes gummy. Immediately following the decomposition, the slurry was filtered, and the filtrate was treated with hydrogen chloride. Then the diethyl ketimine hydrochloride (m.p. 104°C) was isolated by filtration, and the diethyl ketimine was regenerated with anhydrous ammonia and purified by distillation, in a yield of 50.5%, b.p. 86.5°C at 730 mmHg.

Other references related to the Moureau-Mignonac ketimine synthesis are cited in the literature.[10]

H. REFERENCES

1. Blaise, E. E., *Compt. Rend.,* **1901**, *132*, 38.
2. (a) Moureu, C. and Mignonac, G., *Compt. Rend.,* **1913**, *156*, 1801. (b) Moureau, C. and Mignonac, G., *Compt. Rend.,* **1914**, *158*, 1395. (c) Moureau, C. and Mignonac, G., *Compt. Rend.,* **1914**, *159*, 149. (d) Mignonac, G., *Compt. Rend.,* **1919**, *169*, 237. (e) Mignonac, G., *Compt. Rend.,* **1920**, *170*, 936. (f) Moureau, C. and Mignonac, G., *Ann. Chim.,* **1920**, *14*, 322. (g) Moureau, C. and Mignonac, G., *Compt. Rend.,* **1920**, *170*, 1353.
3. Pickard, P. L. and Engles, E. F., *J. Am. Chem. Soc.,* **1952**, *74*, 4607.
4. Layer, R. W., *Chem. Rev.,* **1962**, *62*, 489.
5. Weiberth, F. J. and Hall, S. S., *J. Org. Chem.,* **1987**, *52*, 3901.
6. Lochte, H. L.; Horeczy, J.; Pickard, P. L. and Barton, A. D., *J. Am. Chem. Soc.,* **1948**, *70*, 2012.
7. Pickard, P. L. and Tolbert, T. L., *J. Org. Chem.,* **1961**, *26*, 4886.
8. Culbertson, J. B., *J. Am. Chem. Soc.,* **1951**, *73*, 4818.
9. Pickard, P. L. and Vaughan, D. J., *J. Am. Chem. Soc.,* **1950**, *72*, 876.
10. (a) Culbertson, J. B.; Butterfield, D.; Kolewe, O. and Shaw, R., *J. Org. Chem.,* **1962**, *27*, 729. (b) Pickard, P. L. and Polly, G. W., *J. Am. Chem. Soc.,* **1954**, *76*, 5169. (c) Pickard, P. L. and Engles, E. F., *J. Am. Chem. Soc.,* **1953**, *75*, 2148. (d) Pickard, P. L. and Young, C. W., *J. Am. Chem. Soc.,* **1951**, *73*, 42. (e) Cheney, L. C.; Smith, R. R. and Binkley, S. B., *J. Am. Chem. Soc.,* **1949**, *71*, 53. (f) Campbell, K. N., *J. Am. Chem. Soc.,* **1937**, *59*, 2058.

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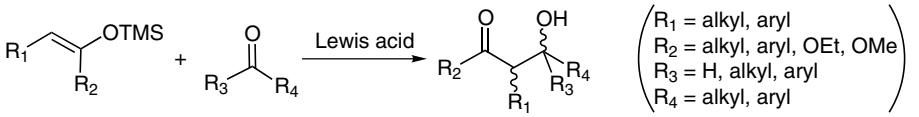
Mukaiyama Aldol Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Mukaiyama et al. in 1974.[1] It is a Lewis acid-catalyzed nucleophilic addition of silyl enol ether to carbonyl compounds and is one of the most important carbon-carbon bond-forming reactions in current organic synthesis.[2] Therefore, this reaction is generally known as the Mukaiyama aldol reaction.[3,4] In addition, it is also referred to as the Mukaiyama reaction,[5] Mukaiyama aldol coupling,[6] or Mukaiyama aldolization.[7] It has been reported that the configuration of the silyl ether will determine the relative stereochemistry of the concomitantly forming vicinal stereocenters, while the inherent chirality of the carbonyl compounds primarily will determine the carbonyl facial selectivity.[6a] The stereoselectivity can be enhanced by the application of a chiral catalyst[3d,5b] or by the unbalanced one face shielding from a remote substituent.[3f] Some of the Lewis acid catalysts used in this reaction are $BF_3{\cdot}Et_2O$,[3a] $InCl_3$,[3f] $TiCl_4$,[5n] $Cu(OTf)_2$,[5b] and chiral (acyloxy) borane.[3d] This reaction has been extended to several different types of nucleophiles, including the Danishefsky's diene,[3g] ketene silyl acetals,[3d] imines,[8] and vinylogous silyl enol ether.[5b]

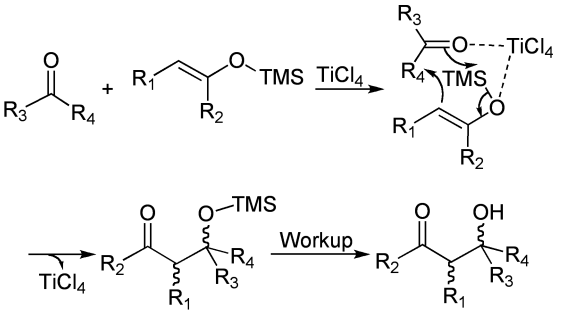
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

Displayed here is a general Mukaiyama aldol reaction catalyzed by Lewis acid $TiCl_4$.



D. MODIFICATION

This reaction has been extended to use different Lewis acids as the catalysts and the application of a variety of nucleophiles.

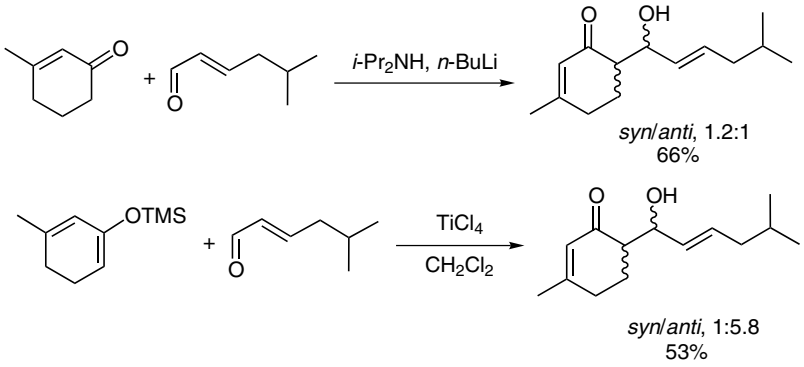
E. APPLICATIONS

This reaction has very broad application in organic synthesis.

F. RELATED REACTIONS

This reaction is related to the *Aldol Reaction* and *Mukaiyama-Michael Reaction.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 3d.

To a cooled (0°C) and stirred solution of 2.8 mL *i*-Pr_2NH (20 mmol) in 20 mL THF was added 11.5 mL 1.54 M *n*-BuLi in hexane under argon. After being stirred at 0°C for 30 min, the solution was cooled to −78°C, and 2.10 mL 3-methyl-2-cyclohexenone (18.1 mmol) was added. The mixture was stirred at −78°C for 30 min and then warmed to −18°C; a solution of 2.03 g 5-methyl-2-en-hexaldehyde (18.1 mmol) in 20 mL THF was added. After being stirred at −18°C for 15 min, the mixture was quenched with 3 mL saturated aqueous NH_4Cl, diluted with 200 mL EtOAc, and washed with saturated aqueous NH_4Cl (3 × 200 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:8) to provide 2.64 g rel-(6*R*)-6-[(1*S*,2*E*)-1-hydroxy-5-methyl-2-hexenyl]-3-methyl-2-cyclohexen-1-one and rel-(6*R*)-6-[(1*R*,2*E*)-1-hydroxy-5-methyl-2-hexenyl]-3-methyl-2-cyclohexen-1-one as an inseparable mixture (1.2:1), in a yield of 66%, $R_f = 0.35$ (EtOAc/hexane, 1:3).

For comparison, a solution of 666 mg (2*R*,3*R*)-2-*O*-(2,6-diisopropoxybenzoyl)tartaric acid (1.80 mmol), 382 mg *o*-phenoxyphenylboronic acid (1.79 mmol), and 3-methyl-2-cyclohexenone in 24 mL propionitrile was stirred for 30 min under argon to prepare 1-methyl-3-trimethylsiloxyl-cyclohex-1,3-diene. A solution of 1.0 g 5-methyl-2-en-hexaldehyde (8.92 mmol) and 2.46 g 1-methyl-3-trimethylsiloxyl-cyclohex-1,3-diene (13.4 mmol) in CH_2Cl_2 was cooled to −78°C, and a catalytic amount of $TiCl_4$ was added and stirred at the same temperature for 2.5 h; the mixture was quenched with 10 mL 0.2 M HCl, warmed to room temperature, and stirred for an additional 1 h. The resulting mixture was diluted with 100 mL EtOAc and washed with H_2O (3 × 50 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:5) to provide 2.61 g crude mixture (10:1) of the above product as a pale yellow oil, which was contaminated with *o*-phenoxyphenylboronic acid but used in the next step without further purification.

Other references related to the Mukaiyama aldol reaction are cited in the literature.[9]

H. REFERENCES

1. Narasaki, K.; Soai, K. and Mukaiyama, T., *Chem. Lett.,* **1974**, 1223.
2. Ishii, A.; Kojima, J. and Mikami, K., *Org. Lett.,* **1999**, *1*, 2013.
3. (a) Engers, D. W.; Bassindale, M. J. and Pagenkopf, B. L.; *Org. Lett.,* **2004**, *6*, 663. (b) Savall, B. M.; Blanchard, N. and Roush, W. R., *Org. Lett.,* **2003**, *5*, 377. (c) Dakin, L. A. and Panek, J. S., *Org. Lett.,* **2003**, *5*, 3995. (d) Takao, K.-I.; Tsujita, T.; Hara, M. and Tadano, K.-i., *J. Org. Chem.,* **2002**, *67*, 6690. (e) Wallace, G. A.; Scott, R. W. and Heathcock, C. H., *J. Org. Chem.,* **2000**, *65*, 4145. (f) Loh, T.-P.; Huang, J.-M.; Goh, S.-H. and Vittal, J. J., *Org. Lett.,* **2000**, *2*, 1291. (g) Yao, S. L.; Roberson, M.; Reichel, F.; Hazell, R. G. and Jørgensen, K. A., *J. Org. Chem.,* **1999**, *64*, 6677.
4. (a) Costantino, U.; Fringuelli, F.; Nocchetti, M. and Piermatti, O., *Appl. Catal., A: Gen.,* **2007**, *326*, 100. (b) Iwata, S.; Hamura, T.; Matsumoto, T. and Suzuki, K., *Chem. Lett.,* **2007**, *36*, 538. (c) Downey, C. W. and Johnson, M. W., *Tetrahedron Lett.,* **2007**, *48*, 3559. (d) Kalesse, M. and Hassfeld, J., *Asymmetric Synthesis,* **2007**, 105. (e) Shirokawa, S.; Shinoyama, M.; Ooi, I.; Hosokawa, S.; Nakazaki, A. and Kobayashi, S., *Org. Lett.,* **2007**, *9*, 849. (f) Wong, C. T. and Wong, M. W., *J. Org. Chem.,* **2007**, *72*, 1425. (g) Naruse, Y.; Fukasawa, S.; Ota, S.; Deki, A. and Inagaki, S., *Tetrahedron Lett*., **2007**, *48*, 817. (h) Desimoni, G.; Faita, G.; Piccinini, F. and Toscanini, M., *Eur. J. Org. Chem.,* **2006**, 5228. (i) Isoda, T.; Akiyama, R.; Oyamada,

H. and Kobayashi, S., *Adv. Synth. Catal.,* **2006**, *348*, 1813. (j) McGilvra, J. D.; Unni, A. K.; Modi, K. and Rawal, V. H., *Angew. Chem. Int. Ed.,* **2006**, *45*, 6130. (k) Zeitouni, J.; Norsikian, S.; Merlet, D. and Lubineau, A., *Adv. Synth. Catal.,* **2006**, *348*, 1662. (l) Appel, B.; Rotzoll, S.; Kranich, R.; Reinke, H. and Langer, P., *Eur. J. Org. Chem.,* **2006**, 3638. (m) Jankowska, J.; Paradowska, J. and Mlynarski, J., *Tetrahedron Lett*., **2006**, *47*, 5281. (n) Fu, F.; Teo, Y.-C. and Loh, T.-P., *Tetrahedron Lett*., **2006**, *47*, 4267. (o) Hiraiwa, Y.; Ishihara, K. and Yamamoto, H., *Eur. J. Org. Chem.,* **2006**, 1837. (p) Itsuno, S.; Arima, S. and Haraguchi, N., *Tetrahedron*, **2005**, *61*, 12074. (q) Gondi, V. B.; Gravel, M. and Rawal, V. H., *Org. Lett.,* **2005**, *7*, 5657. (r) Langner, M.; Remy, P. and Bolm, C., *Chem. Eur. J.,* **2005**, *11*, 6254. (s) Li, H.-J.; Tian, H.-Y.; Wu, Y.-C.; Chen, Y.-J.; Liu, L.; Wang, D. and Li, C.-J., *Adv. Synth. Catal.,* **2005**, *347*, 1247. (t) Acocella, M. R.; Massa, A.; Palombi, L.; Villano, R. and Scettri, A., *Tetrahedron Lett*., **2005**, *46*, 6141. (u) Adhikari, S.; Caille, S.; Hanbauer, M.; Ngo, V. X. and Overman, L. E., *Org. Lett.,* **2005**, *7*, 2795. (v) Lopez, C. S.; Alvarez, R.; Vaz, B.; Faza, O. N. and De Lera, A. R., *J. Org. Chem.,* **2005**, *70*, 3654. (w) Mlynarski, J. and Jankowska, J., *Adv. Synth. Catal.,* **2005**, *347*, 521. (x) Mizugaki, T.; Hetrick, C. E.; Murata, M.; Ebitani, K.; Amiridis, M. D. and Kaneda, K., *Chem. Lett.,* **2005**, *34*, 420. (y) Angell, P.; Zhang, J.; Belmont, D.; Curran, T. and Davidson, J. G., *Tetrahedron Lett*., **2005**, *46*, 2029. (z) Wong, C. T. and Wong, M. W., *J. Org. Chem.,* **2005**, *70*, 124. (aa) Ishihara, K. and Yamamoto, H., *Modern Aldol Reactions*, **2004**, *2*, 25. (bb) Zhou, D.-Y. and Chen, Q.-Y., *Chinese J. Chem.,* **2004**, *22*, 953. (cc) Phukan, P., *Synth. Commun.,* **2004**, *34*, 1065. (dd) Shimada, Y.; Matsuoka, Y.; Irie, R. and Katsuki, T., *Synlett*, **2004**, 57. (ee) Chen, S.-L.; Ji, S.-J. and Loh, T.-P., *Tetrahedron Lett*., **2004**, *45*, 375. (ff) Mikami, K.; Yamanaka, M.; Islam, M. N.; Kudo, K.; Seino, N. and Shinoda, M., *Tetrahedron*, **2003**, *59*, 10593. (gg) Chaperon, A.; Bertschy, H.; Franz-schrumpf, A.-L.; Hugelet, B.; Neels, A.; Stoeckli-evans, H. and Neier, R., *Chimia*, **2003**, *57*, 601. (hh) Mikami, K.; Yamanaka, M.; Islam, M. N.; Kudo, K.; Seino, N. and Shinoda, M., *Tetrahedron Lett.,* **2003**, *44*, 7545. (ii) Wadamoto, M.; Ozasa, N.; Yanagisawa, A. and Yamamoto, H., *J. Org. Chem.,* **2003**, *68*, 5593. (jj) Zhang, X. X.; Li, W. D. and Tang, B. C., *Chinese Chem. Lett.,* **2003**, *14*, 225. (kk) Du, X. H.; Chu, H. F. V. and Kwon, O., *Org. Lett.,* **2003**, *5*, 1923. (ll) Cain, M. J.; Cawley, A.; Sum, V.; Brown, D.; Thornton-Pett, M. and Kee, T. P., *Inorg. Chim. Acta,* **2003**, *345*, 154. (mm) Munoz-Muniz, O.; Quintanar-Audelo, M. and Juaristi, E., *J. Org. Chem.,* **2003**, *68*, 1622. (nn) Imashiro, R. and Kuroda, T., *J. Org. Chem.,* **2003**, *68*, 974.

5. (a) Saraber, F. C. E.; Baranovsky, A.; Jansen, B. J. M.; Posthumus, M. A. and De Groot, A., *Tetrahedron*, **2006**, *62*, 1726. (b) Moreau, X.; Bazán-Tejeda, B. and Campagne, J.-M., *J. Am. Chem. Soc.,* **2005**, *127*, 7288. (c) Bazan-Tejeda, B.; Georgy, M. and Campagne, J.-M., *Synlett*, **2004**, 720. (d) Mandoli, A.; Pini, D.; Orlandi, S.; Mazzini, F. and Salvadori, P., *Tetrahedron: Asymmetry*, **1998**, *9*, 1479. (e) Angert, H.; Czerwonka, R. and Reissig, H. U., *Liebigs Annalen/Recueil*, **1997**, 2215. (f) Chen, J.-X. and Otera, J., *Tetrahedron,* **1997**, *53*, 14275. (g) Kim, S. B. and Han, J. S., *J. Korean Chem. Soc.,* **1995**, *39*, 818. (h) Bach, T.; Fox, D. N. A. and Reetz, M. T., *J. Chem. Soc., Chem. Commun.,* **1992**, 1634. (i) Angert, H.; Kunz, T. and Reissig, H. U., *Tetrahedron,* **1992**, *48*, 5681. (j) Stevens, D. R.; Till, C. P. and Whiting, D. A., *J. Chem. Soc., Perkin Trans. I,* **1992**, 185. (k) Otera, J.; Wakahara, Y.; Kamei, H.; Sato, T.; Nozaki, H. and Fukuzumi, S., *Tetrahedron Lett*., **1991**, *32*, 2405. (l) Demnitz, F. W. J., *Tetrahedron Lett*., **1989**, *30*, 6109. (m) Bellassoued, M.; Dubois, J. E. and Bertounesque, E., *Tetrahedron Lett*., **1988**, *29*, 1275. (n) Gennari, C.; Colombo, L.; Bertolini, G. and Schimperna, G., *J. Org. Chem.,* **1987**, *52*, 2754.
6. (a) Panek, J. S. and Jain, N. F., *J. Org. Chem.,* **2001**, *66*, 2747. (b) Delas, C.; Szymoniak, J.; Lefranc, H. and Moise, C., *Tetrahedron Lett*., **1999**, *40*, 1121.
7. (a) Ruland, Y.; Noereuil, P. and Baltas, J., *Tetrahedron,* **2005**, *61*, 8895. (b) Sugisaki, C. H.; Ruland, Y.; Le Clezio, I. and Baltas, M., *Synlett*, **2001**, 1905. (c) Hutchinson, J. H.; Pattenden, G. and Myers, P. L., *Tetrahedron Lett*., **1987**, *28*, 1313.

8. Cainelli, G. F.; Contento, M.; Drusiani, A.; Panunzio, M. and Plessi, L., *J. Chem. Soc., Chem. Commun.,* **1985**, 240.

9. (a) Ooi, T.; Takahashi, M.; Yamada, M.; Tayama, E.; Omoto, K. and Maruoka, K., *J. Am. Chem. Soc.,* **2004**, *126*, 1150. (b) Heathcock, C. H., "The Aldol Addition Reaction" in *Asymmetric Synthesis*, ed. Morrison, J. D., Academic Press, Orlando, Fla, **1984**, *3*. pp. 111–212. (c) Mukaiyama, T. and Iwasawa, N., *Chem. Lett*., **1984**, 753. (d) Mukaiyama, T., *Org. React.,* **1982**, *28*, 203. (e) Evans, D. A.; Nelson, J. V. and Taber, T. R., *Topics in Stereochemistry*, Vol. 13, Interscience, New York, **1982**.

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Mukaiyama-Michael Reaction

(Mukaiyama-Michael Addition, Mukaiyama-Michael Conjugate Addition)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Mukaiyama et al. in 1974.[1] It is a Lewis acid-catalyzed Michael conjugate addition of silyl enol ether to α,β-unsaturated compounds. Therefore, it is generally referred to as the Mukaiyama-Michael reaction.[2,3] Because this reaction is essentially a conjugate addition, it is also known as the Mukaiyama-Michael addition[2a,4] or Mukaiyama-Michael conjugate addition.[5] This reaction is a mechanistic complement for the base-catalyzed Michael addition,[2j,2l] and often occurs at much milder conditions and affords superior regioselectivity.[2g] Besides silyl enol ether, silyl ketene acetals are also suitable nucleophiles in this reaction.[2d,2i,2j,2k,4c] For the hindered ketene silyl acetals, the Lewis acid actually mediates the electron transfer from the nucleophiles to α,β-unsaturated carbonyl molecules.[2j,2k] On the other hand, the α,β-unsaturated compounds, such as 3-crotonoyl-2-oxazolidinone,[6] alkylidene malonates,[2f,7] and α-acyl-α,β-unsaturated phosphonates[2i] are often applied as the Michael acceptors. It has been found that the enantioselectivity is very sensitive to the reactant structures[2g]—for example, α-acyl-α,β-unsaturated phosphonates especially prefers the unique *syn*- vs *anti*-diastereoselectivity in this reaction.[2i] In addition,

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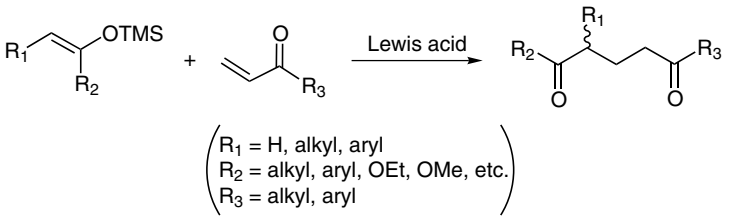
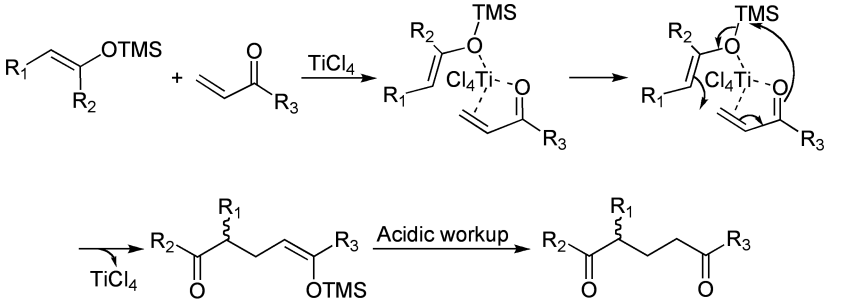
the stereochemistry is improved in the presence of a chiral Lewis acid, such as [Cu(*S*, *S*)-*t*-Bu-box](SbF$_6$)$_2$,[7,8] titanium-BINOL complex (*R*)-L50,[9] C_2-symmetric bis(oxazoline)-Cu(II) complexes,[2g,7] and oxazaborolidinone.[2b,4b] Moreover, the recently developed chiral imidazolidinone is also an effective catalyst for this reaction.[2a,3d]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is believed that the coordination of α,β-unsaturated carbonyl compounds to Lewis acid facilitates this reaction, as illustrated by the tentative mechanism given here.



D. MODIFICATION

This reaction has been extensively modified by application of different types of chiral Lewis acid catalysts.

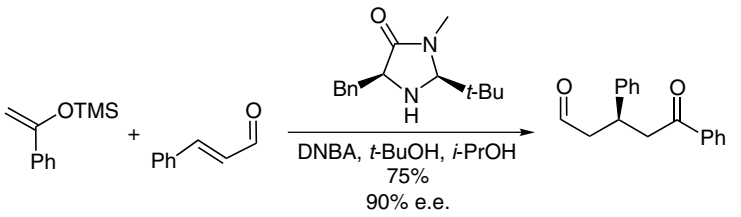
E. APPLICATIONS

This reaction has very wide application in organic synthesis.

F. RELATED REACTIONS

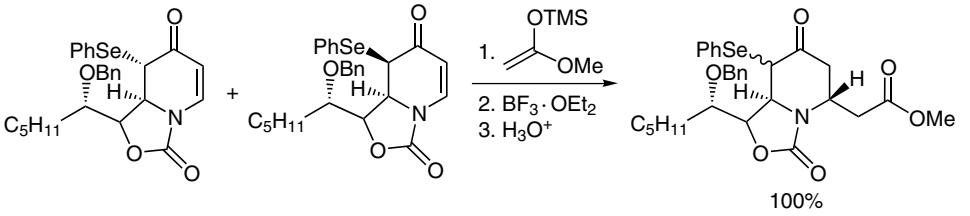
This reaction is related to the *Michael Addition* and *Mukaiyama Aldol Reaction.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 2a.

A mixture of 1 mmol *trans*-cinnamaldehyde, 0.3 mmol chiral 1-*N*-methyl-3-benzyl-5-*t*-butyl-imidazolidinone, and 0.3 mmol 2,4-dinitrobenzenesulfonic acid (DNBA) in 0.5 mL *t*-BuOH and *i*-PrOH (v/v, 5:1) was stirred at room temperature for 10 min. Then 5 mmol 1-(trimethylsilylox)ethylene was added, and the mixture was stirred for 4 h at room temperature. The solution was concentrated in vacuo. The resulting residue was then purified by silica gel chromatography to afford 75% (R)-5-oxo-3,5-diphenyl-pentanal, with 90% e.e.



Reference 2c.

To a solution of 70 mg (1*R*,1′*S*,8*S*,9*R*)-1′-((1-phenylmethoxy)hexane)-1,2,8-tetrahydro-8-phenylselenyl-2-oxaindolizine-3,7-dione (0.140 mmol) and 103 mg 1-methoxy-1-trimethylsiloxyethene (0.704 mmol) in 15 mL CH_2Cl_2 at −78°C was added dropwise 22 mg boron trifluoride etherate (0.154 mmol). The reaction mixture was allowed to stir at −78°C for 30 min and then quenched with saturated aqueous $NaHCO_3$. The organic layer was separated and concentrated under reduced pressure. The crude residue was redissolved in 7 mL THF, and then 1 mL H_2O followed by 2 drops 5% HCl were added. After 1 h, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel radial PLC (20% EtOAc/hexanes) to give 79 mg (1*R*,1′*S*,5*R*,8*S*,9*S*)-1-((1′-phenylmethoxy)hexane)-8-phenylselenyl-1,2,5,6,6a,8-hexahydro-2-oxaindolizine-3,5-dione acetic acid methyl ester as a clear oil, which was an inseparable mixture of diastereomers.

Other references related to the Mukaiyama-Michael reaction are cited in the literature.[10]

H. REFERENCES

1. Narasaki, K.; Soai, K. and Mukaiyama, T., *Chem. Lett.,* **1974**, 1223.
2. (a) Wang, W.; Li, H. and Wang, J., *Org. Lett.,* **2005**, *7*, 1637. (b) Harada, T.; Adachi, S. and Wang, X. W., *Org. Lett.,* **2004**, *6*, 4877. (c) Kuethe, J. T. and Comins, D. L., *J. Org. Chem.,*

2004, *69*, 5219. (d) Wang, X. W.; Adachi, S.; Iwai, H.; Takatsuki, H.; Fujita, K.; Kubo, M.; Oku, A. and Harada, T., *J. Org. Chem.,* **2003**, *68*, 10046. (e) Towers, M. D. K. N.; Woodgate, P. D. and Brimble, M. A., *ARKIVOC,* **2003**, 43. (f) Wang, X. W.; Harada, T.; Iwai, H. and Oku, A., *Chirality,* **2003**, *15*, 28. (g) Evans, D. A.; Scheidt, K. A.; Johnston, J. N. and Willis, M. C., *J. Am. Chem. Soc.,* **2001**, *123*, 4480. (h) Kuethe, J. T. and Comins, D. L., *Org. Lett.,* **1999**, *1*, 1031. (i) Telan, L. A.; Poon, C.-D. and Evans, S. A., *J. Org. Chem.,* **1996**, *61*, 7455. (j) Otera, J.; Fujita, Y.; Sakuta, N.; Fujita, M. and Fukuzumi, S., *J. Org. Chem.,* **1996**, *61*, 2951. (k) Sato, T.; Wakahara, Y.; Otera, J.; Nozaki, H. and Fukuzumi, S., *J. Am. Chem. Soc.,* **1991**, *113*, 4028. (l) Heathcock, C. H.; Norman, M. H. and Uehling, D. E., *J. Am. Chem. Soc.,* **1985**, *107*, 2797.

3. (a) Saraber, F. C. E.; Dratch, S.; Bosselaar, G.; Jansen, B. J. M. and De Groot, A., *Tetrahedron*, **2006**, *62*, 1717. (b) Barluenga, J.; de Prado, A.; Santamaria, J. and Tomas, M., *Angew. Chem. Int. Ed.,* **2005**, *44*, 6583. (c) Shen, Z.-L.; Ji, S.-J. and Loh, T.-P., *Tetrahedron Lett*., **2005**, *46*, 507. (d) Brown, S. P.; Goodwin, N. C. and MacMillan, D. W. C., *J. Am. Chem. Soc.,* **2003**, *125*, 1192. (e) Desimoni, G.; Faita, G.; Filippone, S.; Mella, M.; Zampori, M. G. and Zema, M., *Tetrahedron*, **2001**, *57*, 10203. (f) Borah, H. N.; Boruah, R. C. and Sandhu, J. S., *Indian J. Chem., Sect. B,* **1997**, *36B*, 384. (g) Fujita, Y.; Fukuzumi, S. and Otera, J., *Tetrahedron Lett*., **1997**, *38*, 3655. (h) Fujita, Y.; Fukuzumi, S. and Otera, J., *Tetrahedron Lett*., **1997**, *38*, 2121. (i) Fujita, Y.; Fukuzumi, S. and Otera, J., *Tetrahedron Lett*., **1997**, *38*, 2117. (j) Fujita, Y.; Otera, J. and Fukuzumi, S., *Tetrahedron*, **1996**, *52*, 9419. (k) Otera, J.; Fujita, Y. and Fukuzumi, S., *Tetrahedron*, **1996**, *52*, 9409. (l) Berl, V.; Helmchen, G. and Preston, S., *Tetrahedron Lett*., **1994**, *35*, 233.
4. (a) Gnaneshwar, R.; Wadgaonkar, P. P. and Sivaram, S., *Tetrahedron Lett*., **2003**, *44*, 6047. (b) Harada, T.; Iwai, H.; Takatsuki, H.; Fujita, K.; Kubo, M. and Oku, A., *Org. Lett.,* **2001**, *3*, 2101. (c) Krause, N. and Hoffmann-Röder, A., *Synthesis,* **2001**, 171. (d) Ranu, B. C.; Saha, M. and Bhar, S., *J. Chem. Soc., Perkin Trans. I,* **1995**, 183. (e) Ranu, B. C.; Saha, M. and Bhar, S., *J. Chem. Soc., Perkin Trans. I*, **1994**, 2197. (f) Ranu, B. C.; Saha, M. and Bhar, S., *Tetrahedron Lett*., **1993**, *34*, 1989.
5. (a) Grzywacz, P.; Marczak, S. and Wicha, J., *J. Org. Chem.,* **1997**, *62*, 5293. (b) Marczak, S.; Michalak, K. and Wicha, J., *Tetrahedron Lett*., **1995**, *36*, 5425. (c) Marczak, S. and Wicha, J., *Tetrahedron Lett*., **1993**, *34*, 6627.
6. Suga, H.; Kitamura, T.; Kakehi, A. and Baba, T., *Chem. Commun.,* **2004**, 1414.
7. Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, C. W. and Tedrow, J. S., *J. Am. Chem. Soc.,* **2000**, *122*, 9134.
8. Evans, D. A.; Rovis, T. and Johnson, J. S., *Pure & Appl. Chem.,* **1999**, *71*, 1407.
9. Kobayashi, S.; Suda, S.; Yamada, M. and Mukaiyama, T., *Chem. Lett.,* **1994**, 97.
10. (a) Giuseppone, N. and Collin, J., *Tetrahedron*, **2001**, *57*, 8089. (b) Evans, D. A.; Wills, M. C. and Johnston, J. N., *Org. Lett.*, **1999**, *1*, 865. (c) Paulsen, H.; Antons, S.; Brandes, A.; Logers, M.; Muller, S. N.; Naab, P.; Schmeck, C.; Schneider, S. and Stoltefuss, J., *Angew. Chem. Int. Ed. Engl.,* **1999**, *38*, 3373. (d) Giuseppone, N.; Courtaux, Y. and Collin, J., *Tetrahedron Lett.,* **1998**, *39*, 7874. (e) Iwasawa, N.; Yura, T. and Mukaiyama, T., *Tetrahedron,* **1989**, *45*, 1197. (f) Yura, T.; Iwasawa, N.; Narasaka, K. and Mukaiyama, T., *Chem. Lett.,* **1988**, 1025. (g) Mukaiyama, T. and Kobayashi, S., *Heterocycles,* **1987**, *25*, 245.

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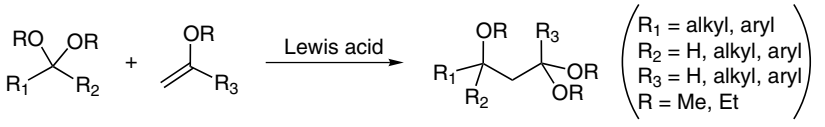
Müller-Cunradi-Pieroh Process

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Müller-Cunradi and Pieroh in 1939.[1] It is a Lewis acid-catalyzed reaction between acetal and enol ether to form 3-alkoxy acetals via carbocationic intermediate, and is known as the Müller-Cunradi-Pieroh process.[2] The resulting 3-alkoxyacetals can be easily converted into 3-alkoxy aldehyde by treatment of formic acid/sodium formate.[2] However, this reaction often gives a mixture of products resulting from the further reaction between 3-alkoxyacetal and enol ether.[3] It is believed that the formation of 1:1 adduct (i.e., 3-alkoxyacetal) depends on the relative reactivity of the initial acetal and 3-alkoxyacetal,[3] and only when the former reacts much faster than 3-alkoxyacetal with enol ether would this reaction be a practical method for organic synthesis. It has been found that if the acetal is much more labile toward acid-promoted hydrolysis than 3-alkoxyacetal, then 3-alkoxyacetal can be feasibly obtained by this method.[3] The reaction rate for acetals toward enol ether are found in the following order: saturated acetals < aromatic acetals = ortho esters < α,β-unsaturated acetals.[4]

B. GENERAL REACTION SCHEME



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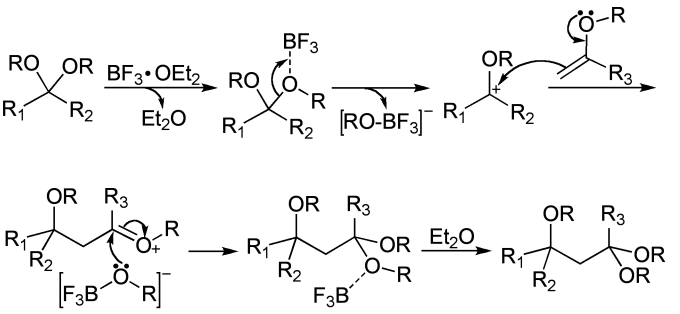
C. PROPOSED MECHANISMS

Because no mechanistic details are available for this reaction, a tentative mechanism is provided here.



D. MODIFICATION

N/A

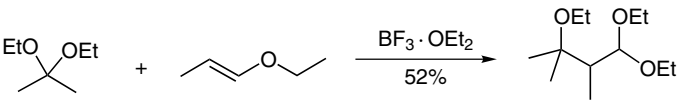
E. APPLICATIONS

This reaction is useful for the preparation of β-alkoxyl acetals, aldehydes and ketones.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 2.

To a stirred mixture of 233 g 2,2-diethoxypropane (1.77 mol, 3 eq.) and 1.2 mL boron trifluoride-etherate (9.5 mmol, 0.016 eq.) cooled at -10°C was added 51.5 g ethyl propenyl ether (0.6 mol, 1 eq.) slowly under nitrogen ($\sim$30 min). The resulting mixture was stirred at 0°C for 3 h and then at room temperature for 2 h. Powdered K_2CO_3 was then added with stirring until the solution turned orange. The reaction mixture was filtered through sintered glass and distilled over K_2CO_3. Unreacted 2,2-diethoxypropane was collected first (91 g, 0.69 mol) followed by 67.7 g 1,1,3-triethoxy-2,3-dimethylbutane, in a yield of 52%, b.p. 110–115°C at 110 mmHg.

Other references related to the Müller-Cunradi-Pieroh process are cited in the literature.[5]

H. REFERENCES

1. Müller-Cunradi, M. and Pieroh, M., *U.S. Pat.,* **1939**, July 11, 2,165,962 [*Chem. Abstr.,* **1939**, *33*, 8210].
2. Gosselin, P.; Bourdy, C.; Mille, S. and Perrotin, A., *J. Org. Chem.,* **1999**, *64*, 9557.
3. von der Brüggen, U.; Lammers, R. and Mayr, H., *J. Org. Chem.,* **1988**, *53*, 2920.
4. Povarov, L. S., *Russ. Chem. Rev.,* **1965**, *34*, 639.
5. (a) Makin, S. M., *Pure & Appl. Chem.,* **1976**, *47*, 173. (b) Effenberger, F., *Angew. Chem.,* **1969**, *81*, 374. (c) Effenberger, F., *Angew. Chem. Int. Ed. Engl.,* **1969**, *8*, 295. (d) Makin, S. M., *Russ. Chem. Rev.,* **1969**, *38*, 237. (e) Hoaglin, R. I. and Hirsch, D. H., *J. Am. Chem. Soc.,* **1949**, *71*, 3468.

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Myers-Saito Cyclization

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Myers et al.[1] and Saito et al.[2] concurrently in 1989. It is a thermal intramolecular cyclization of eneyne-allene via a σ,π-biradical intermediate generated by the bonding between C_2 and C_7. Therefore, it is generally known as the Myers-Saito cyclization[3]. In addition, this reaction is also sometimes referred to as the Myers-Saito reaction[3h,3m,4] or Myers-Saito enyne-allene cycloaromatization reaction.[5] Compared to the *Bergman Cyclization*, this reaction takes place smoothly even below room temperature,[6] benefiting from a cyclic electron delocalization.[7] Similarly, the partially conjugated σ,π-biradical is less reactive than the σ,σ-biradical in the *Bergman Cyclization*.[8] This reaction has been reported to be an exothermic reaction,[3i,3m,7,8] and its enthalpy is estimated to be -13.5 Kcal/mol[9] (or -9.7 Kcal/mol[3i]), its corresponding activation energy is $\sim 23.3 \pm 0.5$ Kcal/mol[9] at 25°C. Besides the thermal initiation, this reaction can also be triggered by light,[10] acid,[11] or base;[12] however, the reaction rate is sensitive to the substituents on alkyne and allene moieties.[6] For example, when the hydrogen at the alkyne terminus is replaced by an aryl or a sterically bulky group (e.g., *t*-Bu, $SiMe_3$), the easily occurring C_2-C_7 cyclization is switched to the *Schmittel Cyclization* by formation of a bond between C_2-C_6.[3m] This reaction is very useful for building up polycyclic aromatic ring systems and developing potential anticancer drugs,[3m] such as neocarzinostatin.[9,13]

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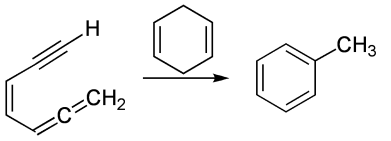
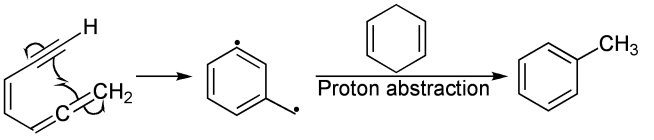
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The mechanism of this reaction is illustrated here by the simplest enyne-allene via the formation of a biradical intermediate.



D. MODIFICATION

This reaction has been extended to azaenyne-allene cyclization, the so-called *aza*-Myers-Saito cyclization.[14]

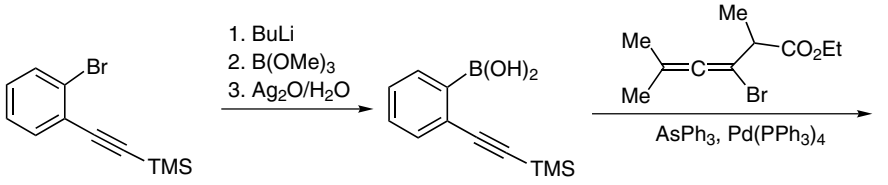
E. APPLICATIONS

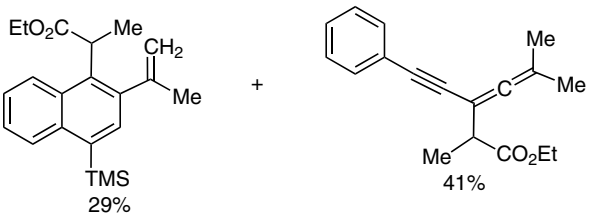
This reaction is very useful in the preparation of polycyclic aromatic ring systems.

F. RELATED REACTIONS

This reaction is related to the *Bergman Cyclization* and *Schmittel Cyclization*.

G. CITED EXPERIMENTAL EXAMPLES





Reference 5.

To a stirred solution of 1.01 g (2-bromophenylethynyl)trimethylsilane (4 mmol) in 20 mL dry THF was added 3.25 mL 1.6 M *n*-BuLi in hexane (5.2 mmol) at −95°C. After the mixture was stirred for 10 min, 0.54 g trimethylborate (5.2 mmol) was added. The solution was allowed to warm to −5°C, and 3.71 g Ag_2O in 16 mL water, 0.23 g tetrakis(triphenylphosphine)-palladium (0.2 mmol), 0.49 g triphenylarsine (1.6 mmol), and 0.99 g bromoallene (4 mmol) were added successively. The reaction was stirred at 25°C for 24 h. Ag_2O was removed by filtration, and the crude product was diluted in 40 mL Et_2O. The organic layer was washed with 50 mL distilled water, 50 mL saturated $NaHCO_3$, and 50 mL brine and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure, and the residue was purified by column chromatography with hexane/Et_2O (10:1) to afford 0.39 g naphthalene (29%) and 0.44 g yne-allene (41%) as pale yellow oils.

Other references related to the Myers-Saito cyclization are cited in the literature [15].

H. REFERENCES

1. (a) Myers, A. G.; Kuo, E. Y. and Finney, N. S., *J. Am. Chem. Soc*., **1989**, *111*, 8057. (b) Myers, A. G. and Dragovich, P. S., *J. Am. Chem. Soc*., **1989**, *111*, 9130.
2. Nagata, R.; Yamanaka, H.; Okazaki, E. and Saito, I., *Tetrahedron Lett*., **1989**, *30*, 4995.
3. (a) Alabugin, I. V. and Manoharan, M., *J. Am. Chem. Soc.,* **2005**, *127*, 12583. (b) Li, H. B.; Yang, H.; Petersen, J. L. and Wang, K. K., *J. Org. Chem.,* **2004**, *69*, 4500. (c) Dai, W. X.; Petersen, J. L. and Wang, K. K., *Org. Lett.,* **2004**, *6*, 4355. (d) Chen, W.-C.; Zou, J.-W. and Yu, C.-H., *J. Org. Chem.,* **2003**, *68*, 3663. (e) Yang, Y. H.; Petersen, J. L. and Wang, K. K., *J. Org. Chem.,* **2003**, *68*, 8545. (f) Basak, A.; Mandal, S. and Bag, S. S., *Chem. Rev.,* **2003**, *103*, 4077. (g) Bui, B. H. and Schreiner, P. R., *Org. Lett.,* **2003**, *5*, 4871. (h) Musch, P. W.; Remenyi, C.; Helten, H. and Engels, B., *J. Am. Chem. Soc.,* **2002**, *124*, 1823. (i) Stahl, F.; Moran, D.; Schleyer, P. V. R.; Prall, M. and Schreiner, P. R., *J. Org. Chem.,* **2002**, *67*, 1453. (j) Cramer, C. J. and Thompson, J., *J. Phys. Chem. A,* **2001**, *105*, 2091. (k) McMahon, R. J.; Halter, R. J.; Fimmen, R. L.; Wilson, R. J.; Peebles, S. A.; Kuczkowski, R. L. and Stanton, J. F., *J. Am. Chem. Soc.,* **2000**, *122*, 939. (l) Hrovat, D. A.; Duncan, J. A. and Borden, W. T., *J. Am. Chem. Soc.,* **1999**, *121*, 169. (m) Engels, B. and Hanrath, M., *J. Am. Chem. Soc.,* **1998**, *120*, 6356. (n) Schmittel, M.; Keller, M.; Kiau, S. and Strittmatter, M., *Chem. Eur. J.,* **1997**, *3*, 807.
4. (a) Schmittel, M.; Mahajan, A. A. and Bucher, G., *J. Am. Chem. Soc.,* **2005**, *127*, 5324. (b) Schmittel, M.; Steffen, J.-P. and Auer, D. M., *Tetrahedron Lett*., **1997**, *38*, 6177. (c) Schmittel, M.; Kiau, S.; Siebert, T. and Strittmatter, M., *Tetrahedron Lett*., **1996**, *37*, 7691.
5. Saalfrank, R. W.; Haubner, M.; Deutscher, C.; Bauer, W. and Clark, T., *J. Org. Chem.,* **1999**, *64*, 6166.
6. Sydnes, L. K., *Chem. Rev.,* **2003**, *103*, 1133.

7. Wenk, H. H.; Winkler, M. and Sander, W., *Angew. Chem. Int. Ed.,* **2003**, *42*, 502.
8. Schreiner, P. R. and Prall, M., *J. Am. Chem. Soc.,* **1999**, *121*, 8615.
9. Cramer, C. J.; Kormos, B. L.; Seierstad, M.; Sherer, E. C. and Winget, P., *Org. Lett.,* **2001**, *3*, 1881.
10. Nakatani, K.; Isoe, S.; Maekawa, S. and Saito, I., *Tetrahedron Lett*., **1994**, *35*, 605.
11. Scheuplein, S. W.; Machinek, R.; Suffert, J. and Brückner, R., *Tetrahedron Lett*., **1994**, *34*, 6549.
12. Toshima, K.; Ohta, K.; Ohtake, T. and Tatsuta, K., *Tetrahedron Lett*., **1991**, *32*, 391.
13. Schreiner, P. R.; Navarro-Vázquez, A. and Prall, M., *Acc. Chem. Res.*, **2005**, *38*, 29.
14. Feng, L. P.; Kumar, D.; Birney, D. M. and Kerwin, S. M., *Org. Lett.,* **2004**, *6*, 2059.
15. (a) Navarro-Vázquez, A.; Prall, M. and Schreiner, P. R., *Org. Lett.,* **2004**, *6*, 2981. (b) Lu, X. L.; Petersen, J. L. and Wang, K. K., *Org. Lett.,* **2003**, *5*, 3277. (c) Musch, P. W. and Engels, B., *J. Am. Chem. Soc.,* **2001**, *123*, 5557. (d) Prall, M.; Wittkopp, A. and Schreiner, P. R., *J. Phys. Chem. A,* **2001**, *105*, 9265. (e) König, B., *Eur. J. Org. Chem.,* **2000**, 381. (f) Wenthold, P. G. and Lipton, M. A., *J. Am. Chem. Soc.,* **2000**, *122*, 9265.

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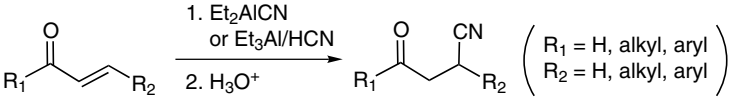
Nagata Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Nagata et al. in 1962.[1] It is a conjugate hydrocyanation of an α,β-unsaturated carbonyl compound from diethylaluminum cyanide[2] or the combination of hydrogen cyanide and diethylaluminum chloride[3] (or triethylaluminum[4]) in an inert solvent. Therefore, it is generally known as the Nagata reaction.[2d,5] The solvents that are suitable for such reaction include ether, THF, and benzene.[4] Although the enol intermediate in a conjugate addition can be trapped when α,β-unsaturated ketones are treated with trimethylsilyl cyanide and dimethylaluminum chloride,[6] it is not always the case. For example, the enols resulting from the addition of diethylaluminum cyanide to some of the steroids could not be trapped through the formation of silyl enol ether or enol acetate; however, they could be trapped by further reaction with bromine.[2d] Furthermore, for the addition of Et_2AlCN to α,β-unsaturated silyl oxonium, both 1,2- and 1,4-adduct are obtained in CH_2Cl_2, whereas only 1,4-conjugate addition product is obtainable in THF.[7] It has been found that diethylaluminum cyanide will not add to the simple 3-substituted cyclohex-2-enone[2c] and α-sulfinyl quinone,[8] probably because of steric hindrance. This reaction has been extended to the hydrocyanation of an isolated carbonyl group of β-keto sulfoxide by the addition of Et_2AlCN to β-keto sulfoxide,[8] and the hydrocyanation of epoxide functionality by cleavage of the epoxide ring of an α-carbonyl epoxide.[5]

B. GENERAL REACTION SCHEME



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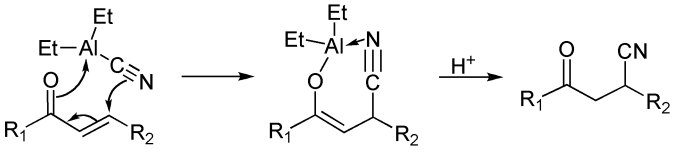
C. PROPOSED MECHANISMS



D. MODIFICATION

Other hydrocyanation reagents, such as KCN/Et_2AlCN/18-crown-6,[9] TMSCN,[8] and acetone cyanohydrin in combination with a catalytic amount of $Cp_2Sm(THF)_2$[4] have been used as the complements to Et_2AlCN.

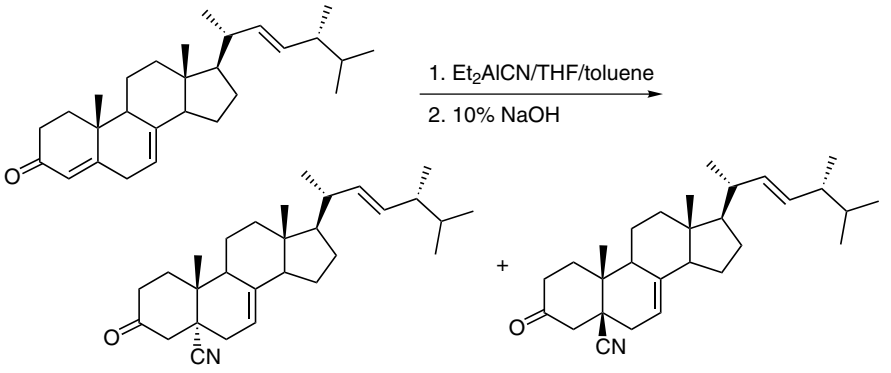
E. APPLICATIONS

This reaction is very useful for the introduction of a cyano group into the organic compounds.

F. RELATED REACTIONS

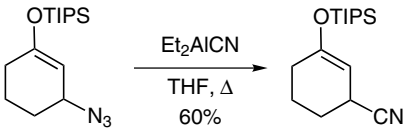
This reaction is related to the *Michael Addition.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 2b.

To a solution of 1.5 g 4,7,22(*E*)-ergostatrien-3-one (3.8 mmol) in 300 mL anhydrous THF was added 11.4 mL 1.0 M Et_2AlCN in toluene (11.4 mmol), and the solution turned dark red. After being stirried for 3.5 h, the mixture was washed with an ice-cold 10% NaOH solution (2 × 40 mL). (*Caution*! When the reaction is performed on a large scale, add the aqueous components dropwise to avoid a violent exotherm.) The aqueous layer was exhaustively extracted with CH_2Cl_2, the combined organic layers were dried with anhydrous $MgSO_4$ and filtered, and the solvent was evaporated in vacuo. The residue was purified by flash chromatography using an eluent of hexane/EtOAc (from 8:1 to 0:1) to afford 1.3 g 5α-cyano-7,22(*E*)-ergostadien-3-one (82%) and 0.2 g 5β-cyano-7,22(*E*)-ergostadien-3-one(13%). The α-isomer was recrystallized from EtOH to give white plates, m.p., 280–282°C, $R_f = 0.30$ (hexane/EtOAc, 3:1), and the β isomer was isolated as a white solid, m.p., 120–123°C, $R_f = 0.15$ (hexane/EtOAc, 3:1).



Reference 7.

To a 4-mL THF solution containing 74 mg triisopropylsilyl 3-azido-cyclohexenyl ether (0.25 mmol, 1.0 eq.) was added 500 μL 1.0 M Et_2AlCN in toluene. The mixture was refluxed for 60 h and then cooled to 25°C. Saturated aqueous $NaHCO_3$ (20 mL) and 40 mL Et_2O were added, and the mixture was filtered through Celite. The phases were separated. The extracts were washed with brine (2 × 10 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by silica gel flash chromatography using an eluent of hexane/EtOAc (4:1) to afford 42 mg 3-cyano-1-triisopropylsilyloxy-cyclohexan-1-ene as a colorless oil, in a yield of 60%.

Other references related to the Nagata reaction are cited in the literature.[10]

H. REFERENCES

1. Nagata, W.; Yoshioka, M. and Hirai, S., *Tetrahedron Lett.*, **1962**, 461.
2. (a) Gregory, R. J. H., *Chem. Rev.,* **1999**, *99*, 3649. (b) Goldstein, A. S., *J. Med. Chem.,* **1996**, *39*, 5092. (c) Callis, D. J.; Thomas, N. F.; Pearson, D. P. J. and Potter, B. V. L., *J. Org. Chem.,* **1996**, *61*, 4634. (d) Gallagher, T. F. and Adams, J. L., *J. Org. Chem.,* **1992**, *57*, 3347.
3. Hernández, R.; Suárez, E. and Melián, D., *J. Org. Chem.,* **1994**, *59*, 2766.
4. Kawasaki, Y.; Fujii, A.; Nakano, Y.; Sakaguchi, S. and Ishii, Y., *J. Org. Chem.,* **1999**, *64*, 4214.
5. (a) Pellissier, H.; Michellys, P.-Y. and Santelli, M., *Steroids*, **2007**, *72*, 297. (b) Moss, D. K.; Olmstead, M. M. and Nantz, M. H., *J. Org. Chem.,* **1998**, *63*, 5259.
6. Utimoto, K.; Obayashi, M.; Shishiyama, Y.; Inoue, M. and Nozaki, H., *Tetrahedron Lett.,* **1980**, *21*, 3389.
7. Magnus, P.; Lacour, J.; Evans, P. A.; Rigollier, P. and Tobler, H., *J. Am. Chem. Soc.,* **1998**, *120*, 12486.
8. Luis, J.; Ruano, G. and Alemparte, C., *J. Org. Chem.,* **2004**, *69*, 1405.

9. Barrero, A. F.; Alvarez-Manzaneda, E. J.; Alvarez-Manzaneda, R.; Chahboun, R.; Meneses, R.; Cuerva, J. M.; Aparicio, M. and Romera, J. L., *Org. Lett.,* **2001**, *3*, 647.

10. (a) Watanabe, S.-i.; Córdova, A.; Tanaka, F. and Barbas, C. F., *Org. Lett.,* **2002**, *4*, 4519. (b) Nicolaou, K. C.; Vassilikogiannakis, G.; Kranich, R.; Baran, P.; Zhong, Y.-L. and Natarajan, S., *Org. Lett.,* **2000**, *2*, 1895. (c) Ruano, J. L. G.; Paredes, C. G. and Hamdouchi, C., *Tetrahedron: Asymmetry,* **1999**, *10*, 2935. (d) Garcia, M. M. C.; Ruano, J. L. G.; Castro, A. M. M.; Ramos, J. H., R. and Fernandez, I., *Tetrahedron: Asymmetry,* **1998**, *9*, 859. (e) Bryans, J. S.; Davies, N.; Gee, N. S.; Dissanayake, V. U. K.; Ratcliffe, G. S.; Horwell, D. C.; Kneen, C. O.; Morrell, A. I.; Oles, R. J.; O'Toole, J. C.; Perkins, G. M.; Singh, L.; Suman-Chauhan, N. and O'Neill, J. A., *J. Med. Chem.,* **1998**, *41*, 1838. (f) Davis, F. A.; Portonovo, P. S.; Reddy, R. E. and Chiu, Y.-h., *J. Org. Chem.,* **1996**, *61*, 440. (g) Ruano, J. L. G.; Castro, A. M. M. and Rodriguez, J. H., *J. Org. Chem.,* **1992**, *57*, 7235. (h) Nagata, W.; Yoshioka, M and Murakami, M., *Org. Synth. Coll.,* **1988**, 6, 307. (i) Nagata, W. and Yoshioka, M., *Org. React.,* **1977**, *25*, 255. (j) Nagata, W.; Yoshioka, M. and Murakami, M., *J. Am. Chem. Soc.,* **1972**, *94*, 4654. (k) Nagata, W.; Yoshioka. and Hirai, S., *J. Am. Chem. Soc.,* **1972**, *94*, 4635. (l) Nagata, W.; Yoshioka, M. and Murakami, M., *J. Am. Chem. Soc*., **1972**, *94*, 4644. (m) Nagata, W.; Yoshioka, M. and Terasawa, T., *J. Am. Chem. Soc.,* **1972**, *94*, 4672. (n) Nagata, W. and Yoshioka, M., *Tetrahedron Lett.,* **1966**, 1913. (o) Nagata, W.; Yoshioka, M. and Okumura, T., *Tetrahedron Lett.,* **1966**, 847.

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Nazarov Cyclization
(Nazarov Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Nazarov et al. in 1942.[1] It is an acid-promoted cationic pericyclic reaction that transforms a divinyl ketone into 2-cyclopentenone. Therefore, it is generally known as the Nazarov cyclization,[2] or Nazarov reaction.[2bb,3] In general, this reaction requires 1 eq. of strong Brønsted acid or Lewis acid[2q,4] and undergoes a 4-π electrocyclic, conrotatory cyclization[2q,2u,2v,3m,3n,5] via a 3-oxy-pentadienylic cation.[2q,5] Although this reaction gives a thermodynamically favored cyclopentenone with more substituents,[2tt,6] the classical reaction protocol generally lacks control over the position of the endocyclic double bond (Scheme 1).[6,7] It has been found that the presence of an electron-donating group such as alkoxy on a vinyl group,[8] or the presence of a bridge-headed proton on the endocyclic intermediate[2w] facilitates the protic acid-promoted cyclization. Besides the conventional Lewis acid catalysts, such as $BF_3{\cdot}Et_2O$,[2q,4,9] $SnCl_4$,[2q,4] $TiCl_4$,[2q,4,9] and $AlCl_3$,[2q,4] more complicated Lewis acids have also been used for this reaction, such as TMSOTf,[3s,7a] $Cu(OTf)_2$,[2q,3s,4] $PdCl_2(MeCN)_2$,[10] Sc(pybox)$(OTf)_3$,[2u] Cu(pybox)$(OTf)_2$,[2v] dicationic Ir(III) complex [IrMe(CO)(dppe)-(DIB)]$(BARF)_2$ (where dppe = bis(diphenylphosphino)ethane, DIB = *o*-diiodobenzene, and BARF = [B(3,5-$C_6H_3(CF_3)_2)_4$]),[2q] and montmorillonite clay K10.[11] In addition, $MeSO_3H$ was found to be a superior protic acid for the Nazarov reaction.[3s]

It should be pointed out that this reaction has been carried out photochemically[2v] (i.e., the photo-Nazarov cyclization[2x,2y,12]), or under near-critical water conditions.[3m] More importantly, it has been improved to occur in a controllable fashion, through a *directed* Nazarov cyclization or an *interrupted* Nazarov reaction.[2zz,3h,3k,3u,3v] It is worth noting that two practically directed Nazarov cyclizations have been developed, one by Denmark by using the β-cation stabilizing effect and electrofuge of silicon (Scheme 2),[2oo,2tt,6,13] and the other from Ichikawa by application of a β-cation destabilizing effect and the

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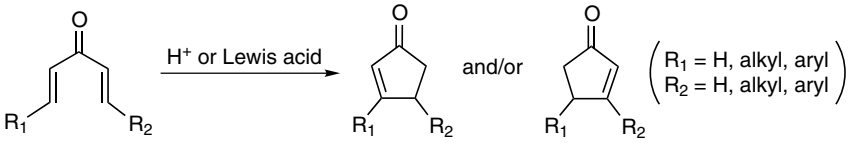
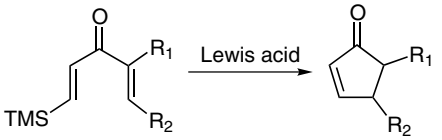
α-electron-donating effect of fluorine[2ii,7] to control the regiochemistry (Scheme 3). Analogous to silicon, tin is also used to direct the Nazarov cyclization.[14] The interrupted Nazarov reaction has been developed by West et al. to extend the reaction of the cationic endocyclic intermediate with carbon nucleophiles.[3l,9,15] Furthermore, this reaction has been extended to imino-Nazarov cyclization of vinyl allenyl imine.[12,16]

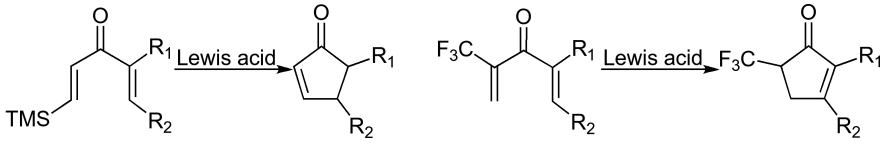
B. GENERAL REACTION SCHEME



SCHEME 1. *Classical Nazarov cyclization.*



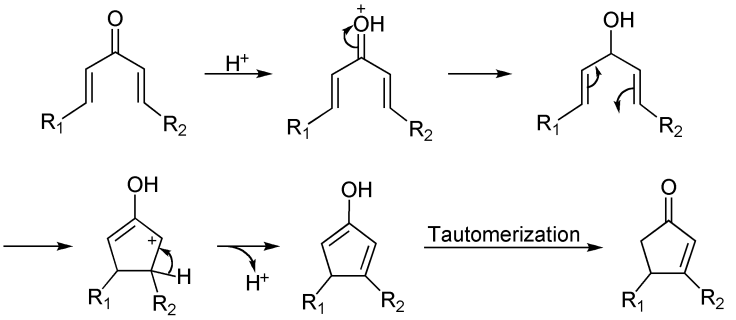
SCHEME 2. *Silicon-directed Nazarov cyclization.*



SCHEME 3. *Fluorine-directed Nazarov cyclization.*

C. PROPOSED MECHANISMS

A general mechanism catalyzed by a protic acid is illustrated here.



D. MODIFICATION

This reaction has been extensively modified by the application of different Lewis acids as catalysts.

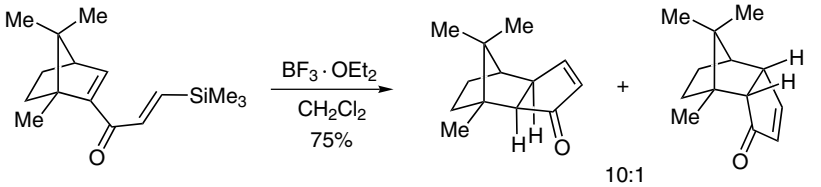
E. APPLICATIONS

This reaction has very broad application in organic synthesis.

F. RELATED REACTIONS

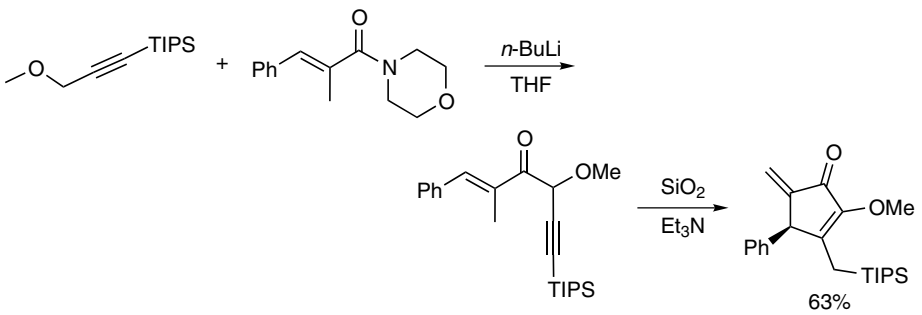
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3l.

A solution of 50 mg dienone (0.19 mmol) in 19 mL CH_2Cl_2 was cooled to $-78^{\circ}C$, and 94 μL $BF_3{\cdot}OEt_2$ (0.76 mmol) was added. After 10 min, the reaction was allowed to warm to $0^{\circ}C$ and was stirred for 8 h. Water (10 mL) was added, and the phases were separated. The aqueous layer was washed with Et_2O (2 $\times$ 15 mL), and the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to give a colorless oil. Silica gel radial chromatography (2 mm rotor; 9:1, hexanes/EtOAc) furnished 25 mg mixed cyclopentenone in a ratio of 10:1, in a yield of 75%. Careful chromatography of this mixture produced pure *exo*-diastereomer as a colorless oil, $R_f = 0.37$ (hexane/EtOAc, 9:1), and *endo*-diastereomer, $R_f = 0.34$ (hexane/EtOAc, 9:1).



Reference 3k.

To a solution of 147 mg 3-methoxy-1-triisopropylsilyl propyne (0.65 mmol) in 3 mL THF at −78°C was added 0.25 mL 2.5 M *n*-BuLi in hexanes (0.63 mmol). After 30 min, a solution of 125 mg enamide (0.54 mmol) in 1 mL THF was added dropwise via cannula. The reaction was stirred at −78°C for 1 h, quenched with 1 M HCl, and diluted with ether. The aqueous phase was extracted with Et_2O three times, and the combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Removal of a trace solvent was done under high vacuum for 1 h. The crude product was transferred to a 4-dram vial charged with two glass beads. To a separate 4-dram vial containing 540 mg activated silica gel (9.0 mmol) was added 90 μL triethylamine (0.65 mmol). The mixture was stirred for 10 min and then transferred to the vial that contained the crude enone. The reaction was stirred at room temperature for 3 h. Direct purification of the reaction mixture by silica gel flash column chromatography with 5% EtOAc in hexanes gave cyclopentenone (126 mg) as a colorless oil, in a yield of 63%, $R_f = 0.33$ (5% EtOAc in hexanes).

Other references related to the Nazarov cyclization are cited in the literature.[17]

H. REFERENCES

1. Nazarov, I. N.; Torgov, I. B. and Terekhova, L. N., *Izv. Akad. Nauk. SSSR Otd. Khim. Nauk.,* **1942**, 200.
2. (a) Huang, J. and Frontier, A. J., *J. Am. Chem. Soc.,* **2007**, *129*, 8060. (b) Shindo, M.; Yaji, K.; Kita, T. and Shishido, K., *Synlett,* **2007**, 1096. (c) Dhoro, F.; Kristensen, T. E.; Stockmann, V.; Yap, G. P. A. and Tius, M. A., *J. Am. Chem. Soc.,* **2007**, *129*, 7256. (d) Banaag, A. R. and Tius, M. A., *J. Am. Chem. Soc.,* **2007**, *129*, 5328. (e) Rueping, M.; Ieawsuwan, W.; Antonchick, A. P. and Nachtsheim, B. J., *Angew. Chem. Int. Ed.,* **2007**, *46*, 2097. (f) He, W.; Huang, J.; Sun, X. F. and Frontier, A. J., *J. Am. Chem. Soc.,* **2007**, *129*, 498. (g) Malona, J. A.; Colbourne, J. M. and Frontier, A. J., *Org. Lett.,* **2006**, *8*, 5661. (h) De los Santos, D. B.; Banaag, A. R. and Tius, M. A., *Org. Lett.,* **2006**, *8*, 2579. (i) Janka, M.; He, W.; Haedicke, I. E.; Fronczek, F. R.; Frontier, A. J. and Eisenberg, R., *J. Am. Chem. Soc.,* **2006**, *128*, 5312. (j) Lawrence, N. J.; Armitage, E. S. M.; Greedy, B.; Cook, D.; Ducki, S. and McGown, A. T., *Tetrahedron Lett.,* **2006**, *47*, 1637. (k) Giese, S.; Mazzola, R. D.; Amann, C. M.; Arif, A. M. and West, F. G., *Angew. Chem. Int. Ed.,* **2005**, *44*, 6546. (l) Janka, M.; He, W.; Frontier, A. J.; Flaschenriem, C. and Eisenberg, R., *Tetrahedron*, **2005**, *61*, 6193. (m) Douelle, F.; Tal, L. and Greaney, M. F., *Chem. Commun.,* **2005**, 660. (n) Berger, G. O. and Tius, M. A., *Org. Lett.,* **2005**, *7*, 5011. (o) Frontier, A. J. and Collison, C., *Tetrahedron,* **2005**, *61*, 7577. (p) Biermann, U. and Metzger, J. O., *Topics Catal.,* **2004**, *27*, 119. (q) Janka, M.; He, W.; Frontier, A. J. and Eisenberg, R., *J. Am. Chem. Soc.,* **2004**, *126*, 6864. (r) Barluenga, J.; Barrio, P.; Vicente, R.; Lopez, L. A. and Tomas, M., *J. Organomet. Chem.,* **2004**, *689*, 3793. (s) Schwartz, K. D.; White, J. D.; Tosaki, S.-y. and Shibasaki, M., *Org. Synth.,* **2006**, *83*, 49. (t) Zimmermann, M.; Wibbeling, B. and Hoppe, D., *Synthesis,* **2004**, 765. (u) Liang, G. X.; Gradl, S. N. and Trauner, D., *Org. Lett.,* **2003**, *5*, 4931. (v) Aggarwal, V. K. and Belfield, A. J., *Org. Lett.,* **2003**, *5*, 5075. (w) Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A.; Deagostino, A. and Venturello, P., *J. Org. Chem.,* **2002**, *67*, 7144. (x) Leitich, J.; Heise, I.; Rust, J. and Schaffner, K., *Eur. J. Org. Chem.,* **2001**, 2719. (y) Leitich, J.; Heise, I. and Schaffner, K., *J. Photochem. Photobiol., A: Chem.,* **2001**, *140*, 207. (z) Clive, D. L. J.; Sannigrahi, M. and Hisaindee, S., *J. Org. Chem.,* **2001**, *66*, 954. (aa) Quayle, P., *Ann. Rep. Prog. Chem., Sect. B,* **2000**, *96*, 259. (bb) Balczewski, P. and Mikolajczyk, M., *Org. Lett.,* **2000**, *2*, 1153. (cc) Kim, S.-H. and Cha, J. K., *Synthesis,* **2000**, 2113. (dd) Kuroda, C.; Koshio, H.; Koito, A.; Sumiya, H.; Murase, A. and Hirono, Y., *Tetrahedron*, **2000**, *56*, 6441. (ee) Pridgen, L. N.; Huang, K.; Shilcrat, S.; Tickner-Eldridge, A.; DeBrosse,

C. and Haltiwanger, R. C., *Synlett*, **1999**, 1612. (ff) Buchholz, H. A. and De Meijere, A., *Eur. J. Org. Chem.,* **1998**, 2301. (gg) Giese, S. and West, F. G., *Tetrahedron Lett*., **1998**, *39*, 8393. (hh) Hashmi, A. S. K.; Bats, J. W.; Choi, J.-H. and Schwarz, L., *Tetrahedron Lett*., **1998**, *39*, 7491. (ii) Ichikawa, J.; Fujiwara, M.; Okauchi, T. and Minami, T., *Synlett,* **1998**, 927. (jj) Zakharkin, L. I.; Guseva, V. V. and Petrovskii, P. V., *Russ. Chem. Bull.,* **1997**, *46*, 1269. (kk) Kuroda, C.; Sumiya, H.; Murase, A. and Koito, A., *Chem. Commun.,* **1997**, 1177. (ll) Halterman, R. L. and Tretyakov, A., *Tetrahedron*, **1995**, *51*, 4371. (mm) Habermas, K. L.; Denmark, S. E. and Jones, T. K., *Org. React.,* **1994**, *45*, 1. (nn) Bond, C. S.; Leonard, G. A.; Regan, A. C.; Hunter, W. N. and Andrews, J. F. P., *Acta Cryst., Sect. C,* **1994**, *C50*, 133. (oo) Smith, D. A. and Ulmer, C. W., *J. Org. Chem.,* **1993**, *58*, 4118. (pp) Andrews, J. F. P.; Regan, A. C.; Wallis, J. D. and Povey, D. C., *Acta Cryst., Sect. C,* **1992**, *C48*, 2196. (qq) Smith, D. A. and Ulmer, C. W., *Tetrahedron Lett*., **1991**, *32*, 725. (rr) Andrews, J. F. P. and Regan, A. C., *Tetrahedron Lett*., **1991**, *32*, 7731. (ss) Leitich, J.; Heise, I.; Werner, S.; Krueger, C. and Schaffner, K., *J. Photochem. Photobiol., A: Chem.,* **1991**, *57*, 127. (tt) Smith, D. A. and Ulmer, C. W., *J. Org. Chem.,* **1991**, *56*, 4444. (uu) Hudlicky, T. and Price, J. D., *Chem. Rev.,* **1989**, *89*, 1467. (vv) Denmark, S. E.; Habermas, K. L. and Hite, G. A., *Helv. Chim. Acta,* **1988**, *71*, 168. (ww) Denmark, S. E. and Klix, R. C., *Tetrahedron,* **1988**, *44*, 4043. (xx) Denmark, S. E. and Hite, G. A., *Helv. Chim. Acta,* **1988**, *71*, 195. (yy) Wada, E.; Fujiwara, I.; Kanemasa, S. and Tsuge, O., *Bull. Chem. Soc. Jpn.,* **1987**, *60*, 325. (zz) Denmark, S. E.; Habermas, K. L.; Hite, G. A. and Jones, T. K., *Tetrahedron,* **1986**, *42*, 2821. (aaa) Chenard, B. L.; Van Zyl, C. M. and Sanderson, D. R., *Tetrahedron Lett*., **1986**, *27*, 2801. (bbb) Jacobson, R. M. and Lahm, G. P., *J. Org. Chem.,* **1979**, *44*, 462. (ccc) Braude, E. A. and Coles, J. A., *J. Chem. Soc.,* **1952**, 1430.

3. (a) Williams, D. R.; Robinson, L. A.; Nevill, C. R. and Reddy, J. P., *Angew. Chem. Int. Ed.,* **2007**, *46*, 915. (b) Polo, V. and Andres, J., *J. Chem. Theory & Compt.,* **2007**, *3*, 816. (c) Dieker, J.; Froehlich, R. and Wuerthwein, E.-U., *Eur. J. Org. Chem.,* **2006**, 5339. (d) Grant, T. N. and West, F. G., *J. Am. Chem. Soc.,* **2006**, *128*, 9348. (e) Cavalli, A.; Masetti, M.; Recanatini, M.; Prandi, C.; Guarna, A. and Occhiato, E. G., *Chem. Eur. J.,* **2006**, *12*, 2836. (f) Zhang, L. M. and Wang, S. Z., *J. Am. Chem. Soc.,* **2006**, *128*, 1442. (g) Prandi, C.; Deagostino, A.; Venturello, P. and Occhiato, E. G., *Org. Lett.,* **2005**, *7*, 4345. (h) White, T. D. and West, F. G., *Tetrahedron Lett*., **2005**, *46*, 5629. (i) Occhiato, E. G.; Prandi, C.; Ferrali, A. and Guarna, A., *J. Org. Chem.,* **2005**, *70*, 4542. (j) Harmata, M.; Lee, D. R. and Barnes, C. L., *Org. Lett.,* **2005**, *7*, 1881. (k) Dhoro, F. and Tius, M. A., *J. Am. Chem. Soc.,* **2005**, *127*, 12472. (l) Mazzola, R. D.; White, T. D.; Vollmer-Snarr, H. R. and West, F. G., *Org. Lett.,* **2005**, *7*, 2799. (m) Leikoski, T.; Kaunisto, J.; Alkio, M.; Aaltonen, O. and Yli-Kauhaluoma, J., *Org. Proc. Res. Dev.,* **2005**, *9*, 629. (n) Chiu, P. and Li, S. L., *Org. Lett.,* **2004**, *6*, 613. (o) Harmota, M., *Chemtracts*, **2004**, *17*, 416. (p) Prandi, C.; Ferrali, A.; Guarna, A.; Venturello, P. and Occhiato, E. G., *J. Org. Chem.,* **2004**, *69*, 7705. (q) Harmata, M.; Schreiner, P. R.; Lee, D. R. and Kirchhoefer, P. L., *J. Am. Chem. Soc.,* **2004**, *126*, 10954. (r) Liang, G. X. and Trauner, D., *J. Am. Chem. Soc.,* **2004**, *126*, 9544. (s) Kerr, D. J.; Metje, C. and Flynn, B. L., *Chem. Commun.,* **2003**, 1380. (t) Harmata, M. and Lee, D. R., *J. Am. Chem. Soc.,* **2002**, *124*, 14328. (u) Zuev, D. and Paquette, L. A., *Chemtracts*, **1999**, *12*, 1019. (v) Bender, J. A.; Blize, A. E.; Browder, C. C.; Giese, S. and West, F. G., *J. Org. Chem.,* **1998**, *63*, 2430. (w) Oda, M.; Yamazaki, T.; Kajioka, T.; Miyatake, R. and Kuroda, S., *Liebigs Ann./Rec.,* **1997**, 2563. (x) Suzuki, T.; Ohwada, T. and Shudo, K., *J. Am. Chem. Soc.,* **1997**, *119*, 6774. (y) Motoyoshiya, J.; Mizuno, K.; Tsuda, T. and Hayashi, S., *Synlett,* **1993**, 237. (z) Motoyoshiya, J.; Yazaki, T. and Hayashi, S., *J. Org. Chem.,* **1991**, *56*, 735. (aa) Santelli-Rouvier, C. and Santelli, M., *Synthesis,* **1983**, 429. (bb) Jones, T. K. and Denmark, S. E., *Helv. Chim. Acta,* **1983**, *66*, 2377. (cc) Jones, T. K. and Denmark, S. E., *Helv. Chim. Acta,* **1983**, *66*, 2397. (dd) Hirano, S.; Takagi, S.; Hiyama, T. and Nozaki, H., *Bull. Chem. Soc. Jpn.,* **1980**, *53*, 169.
4. He, W.; Sun, X. F. and Frontier, A. J., *J. Am. Chem. Soc.,* **2003**, *125*, 14278.
5. Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A. and Venturello, P., *J. Org. Chem.,* **2003**, *68*, 9728.

6. Denmark, S. E. and Jones, T. K., *J. Am. Chem. Soc.,* **1982**, *104*, 2642.
7. (a) Ichikawa, J., *Pure & Appl. Chem.*, **2000**, *72*, 1685. (b) Ichikawa, J.; Miyazaki, S.; Fujiwara, M. and Minami, T., *J. Org. Chem.,* **1995**, *60*, 2320.
8. (a) Casson, S. and Kocienski, P., *J. Chem. Soc., Perkin Trans. I,* **1994**, 1187. (b) Tius, M. A.; Kwok, C.-K.; Gu, X.-Q. and Zhao, C. *Synth. Commun.,* **1994**, *24*, 871.
9. Browder, C. C.; Marmsalter, F. P. and West, F. G., *Org. Lett.,* **2001**, *3*, 3033.
10. Bee, C.; Leclerc, E. and Tius, M. A., *Org. Lett.,* **2003**, *5*, 4927.
11. Metzger, J. O. and Biermann, U., *Fett/Lipid,* **1998**, *100*, 2.
12. Tius, M. A.; Chu, C. C. and Nieves-Colberg, R., *Tetrahedron Lett.,* **2001**, *42*, 2419.
13. (a) Habermas, K. L.; Denmark, S. E. and Jones, T. K., *Org. React.,* ed., Paquette, L. A., John Wiley & Sons, New York, **1994**, *45*, pp. 1–158. (b) Denmark, S. E.; Wallace, M. A. and Walker, C. B., *J. Org. Chem.,* **1990**, *55*, 5543.
14. Peel, M. R. and Johnson, C. R., *Tetrahedron Lett.,* **1986**, *27*, 5947.
15. (a) Browder, C. C.; Marmsäter, F. P. and West, F. G., *Can. J. Chem.,* **2004**, *82*, 375. (b) Yungai, A. and West, F. G., *Tetrahedron Lett.,* **2004**, *45*, 5445. (c) Wang, Y.; Schill, D. D.; Arif, A. M. and West, F. G., *Org. Lett.* **2003**, *5*, 2747. (d) Giese, S.; Kastrup, L.; Stiens, D. and West, F. G., *Angew. Chem. Int. Ed.,* **2000**, *39*, 1970. (e) Giese, S. and West, F. G., *Tetrahedron,* **2000**, *56*, 10221. (f) Bender, J. A.; Arif, A. M. and West, F. G., *J. Am. Chem. Soc.,* **1999**, *121*, 7443.
16. Tius, M. A., *Acc. Chem. Res.,* **2003**, *36*, 284.
17. (a) Song, C. J.; Knight, D. W. and Whatton, M. A., *Org. Lett.,* **2006**, *8*, 163. (b) Batson, W. A.; Sethumadhavan, D. and Tius, M. A., *Org. Lett.,* **2005**, *7*, 2771. (c) Belardi, J. K.; Curtis, L. A.; Clareen, S. S.; Shimp, H. L.; Leimkuhler, C. E.; Simonowicz, N. L. and Casillas, E., *Synth. Commun.,* **2005**, *35*, 1633. (d) Pellissier, H., *Tetrahedron,* **2005**, *61*, 6479. (e) Kuroda, C. and Suzuki, H., *Curr. Org. Chem.,* **2003**, *7*, 115. (f) Padwa, A.; Heidelbaugh, T. M.; Kuethe, J. T.; McClure, M. S. and Wang, Q., *J. Org. Chem.,* **2002**, *67*, 5928. (g) Rupert, K. C.; Liu, C. C.; Nguyen, T. T.; Whitener, M. A. and Sowa, J. R., *Organometallics,* **2002**, *21*, 144. (h) Sugimoto, Y.; Wigchert, S. C. M.; Thuring, J. W. J. F. and Zwanenburg, B., *J. Org. Chem.,* **1998**, *63*, 1259. (i) Halterman, R. L.; Tretyakov, A.; Combs, D.; Chang, J. and Khan, M. A., *Organometallics,* **1997**, *16*, 3333. (j) Baddeley, G.; Taylor, H. T. and Pickles, W., *J. Chem. Soc.,* **1953**, 124. (k) Braude, E. A. and Forbes, W. F., *J. Chem. Soc.,* **1953**, 2208.

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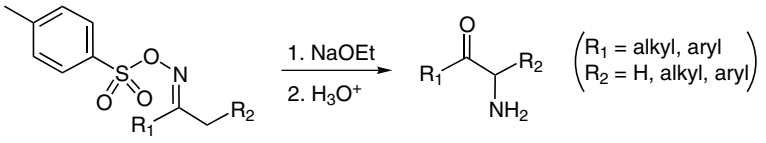
Neber Rearrangement
(Neber Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Neber et al. in 1926.[1] It is the transformation of a ketoxime *O*-arylsulfonate into an α-amino ketone involving the deprotonation of an α-methylene hydrogen by a base and the subsequent acidic hydrolysis of the resulting azirine intermediate. Therefore, this reaction is generally known as the Neber rearrangement[2] or Neber reaction.[2u,3] Different from the *Beckmann Rearrangement*,[4] in which the configuration of oxime controls the reaction direction, the Neber rearrangement does not hold such stereospecificity.[2u,2x] In addition, the amino group is generally introduced to the α-position with a higher acidic hydrogen in ketoxime *O*-arylsulfonate.[2u,2x] This rearrangement is generally carried out in ethanol by treatment of the ketoxime tosylate with sodium ethoxide, followed by the acidic hydrolysis.[2c] For cyclic ketones, the amino group is generally introduced at the equatorial positions at the α-carbon.[5] For 2,4-dinitrophenylacetone, even a weak base, like pyridine, is enough to trigger the rearrangement, as demonstrated in the isolation of the resulting azirine-pyridine hydrochloride complex.[6] It is interesting that the aldoxime tosylate usually results in the formation of corresponding nitrile or isonitrile under similar conditions.[2x,7] It should be pointed out that the starting material is usually prepared by the treatment of oxime with *p*-toluenesulfonyl chloride in pyridine.[2u]

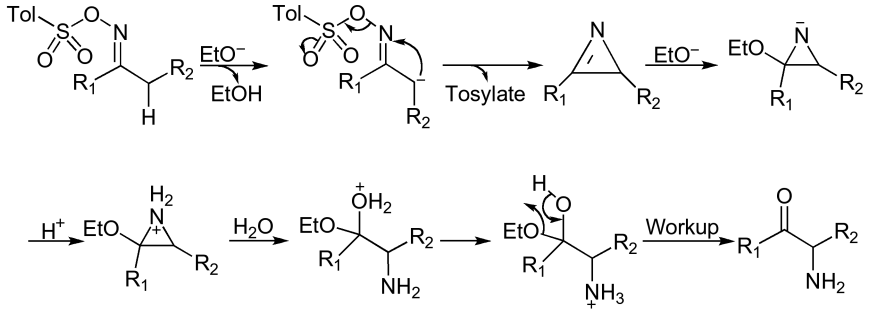
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Although it has been proposed that this reaction is initiated by an alkoxide addition to C=N double bond followed by the loss of tosyloxy group to form a nitrene intermediate, which inserts to the α-carbon to form an alkoxy ethylenimine,[2u] more experimental evidence indicates that the Neber rearrangement involves an initial base-induced elimination of the more acidic α-proton accompanied by the loss of the tosyloxy group to give azirine ring.[2c,2x]



D. MODIFICATION

This reaction has been modified by using a liquid-liquid phase transfer catalyst.[2c]

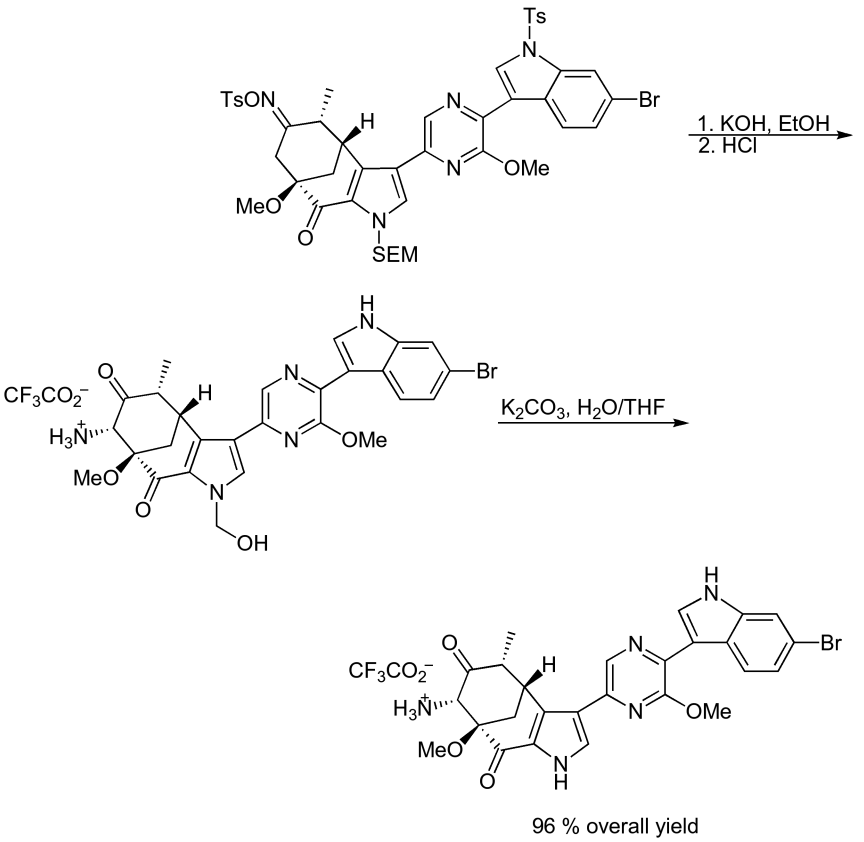
E. APPLICATIONS

This reaction has general application in the preparation of α-amino ketones.

F. RELATED REACTIONS

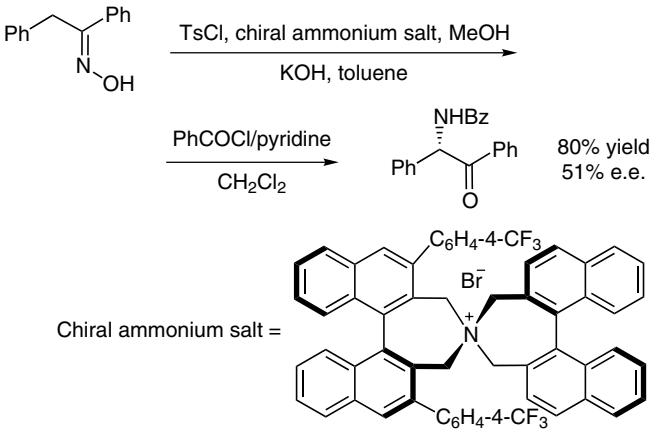
This reaction is related to the *Beckmann Rearrangement*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2b.

To a stirred solution of 23.3 mg tosyl oxime (0.0236 mmol) in 3.5 mL EtOH at 0°C was added 450 μL 50% aqueous KOH dropwise over 1 min. The reaction mixture was stirred at 0°C for 3 h; then 5 mL 6 N aqueous HCl was added. The reaction mixture was heated to 60°C for 10 h, cooled to 23°C, and purified by loading to a reversed-phase Sep-Pak column with water containing 0.1% TFA (w/v) and by washing with 15% acetonitrile in water containing 0.1% TFA (w/v) to remove salts and then in 70% acetonitrile in water containing 0.1% TFA (w/v) to collect the crude product. The solvents were removed under reduced pressure to afford the hemiaminal intermediate, which was immediately mixed with 60 mg K_2CO_3 (0.434 mmol) in 2 mL THF; 200 μL H_2O was added at 23°C. The reaction mixture was stirred for 10 min and purified by a similar procedure for the hemiaminal intermediate to afford the crude product. After the solvents were removed under reduced pressure, the crude material was further purified by reversed-phased HPLC. Concentration under reduced pressure provided 15.0 mg amino ketone as an orange/red oil, in a yield of 96%.



Reference 2c.

cis-Benzyl phenyl ketoxime (63 mg, 0.3 mmol), 69 mg *p*-toluenesulfonyl chloride (0.36 mmol), 14 mg chiral quaternary ammonium salt (0.015 mmol, 5 mol %), and 123 μL MeOH (3 mmol, 10 eq.) were dissolved in 3 mL toluene. Then 1 mL 50% aqueous KOH was added to the mixture dropwise at 0°C. This mixture was stirred vigorously at 0°C for 48 hours. The resulting mixture was diluted with cooled water, and the organic layer was separated. The aqueous layer was extracted with ether. The combined organic layers were dried over $MgSO_4$. Upon removal of solvent, the residue was dissolved in 3 mL CH_2Cl_2. Pyridine (485 μL, 6 mmol) and 174 μL benzoyl chloride (1.5 mmol) were added sequentially, and the mixture was stirred at room temperature. After several hours, ~6 mL 6 N HCl was added, and the biphasic mixture was stirred vigorously for 3 h. The mixture was extracted with ether and dried over Na_2SO_4. After removal of the solvent, the residue was purified by silica gel column chromatography (ether/CH_2Cl_2/hexane, 1:30:20) to afford 76 mg α-benzamidylbenzyl phenyl ketone, in a yield of 80% and 51% e.e.

Other references related to the Neber rearrangement are cited in the literature.[8]

H. REFERENCES

1. Neber, P. W. and Friedolsheim, A., *Ann.,* **1926**, *449*, 109.
2. (a) Garg, N. K.; Caspi, D. D. and Stoltz, B. M., *J. Am. Chem. Soc.,* **2005**, *127*, 5970. (b) Garg, N. K.; Caspi, D. D. and Stoltz, B. M., *J. Am. Chem. Soc.,* **2004**, *126*, 9552. (c) Ooi, T.; Takahashi, M.; Doda, K. and Maruoka, K., *J. Am. Chem. Soc.,* **2002**, *124*, 7640. (d) Forns, P.; Rubiralta, M. and Díez, A., *Contributions to Science,* **2001**, *2*, 63. (e) Mphahlele, M. J.; Gheevarghese, O. and Makhubela, N. F. H., *Phosphorus, Sulfur & Silicon & Related Elements*, **2000**, *166*, 303. (f) Oldfield, M. F. and Botting, N. P., *J. Labelled Compd. & Radiopharm.,* **1998**, *41*, 29. (g) Mphahlele, M. J. and Modro, T. A., *Phosphorus, Sulfur & Silicon & Related Elements,* **1997**, *127*, 131. (h) Moldvai, I.; Szantay, C. and Szantay, C., *Heterocycles*, **1996**, *43*, 2377. (i) Hyatt, J. A., *J. Org. Chem.,* **1981**, *46*, 3953. (j) Parcell, R. F. and Sanchez, J. P., *J. Org. Chem.,* **1981**, *46*, 5229. (k) LaMattina, J. L. and Suleske, R. T., *Synthesis*, **1980**, 329. (l) Friis, P.; Larsen, P. O. and Olsen, C. E., *J. Chem. Soc., Perkin Trans. I,* **1977**, 661. (m) Lap, B. V. and Williams, L. R., *Aust. J. Chem.,* **1977**, *30*, 2205. (n) Grouiller, A.; Pacheco, H. and Carret, G., *J. Heterocycl. Chem.,*

1976, *13*, 853. (o) Tamura, Y.; Fujiwara, H.; Sumoto, K.; Ikeda, M. and Kita, Y., *Synthesis*, **1973**, 215. (p) Parvu, D., *Revista Fizica Chim*., *Ser. A*, **1969**, *6*, 287. (q) Renfrow, W. B.; Witte, J. F.; Wolf, R. A. and Bohl, W. R., *J. Org. Chem.,* **1968**, *33*, 150. (r) Henery-Logan, K. R. and Fridinger, T. L., *J. Am. Chem. Soc.,* **1967**, *89*, 5724. (s) Dudykina, N. V. and Zagorevskii, V. A., *Zh. Org. Khim.,* **1966**, *2*, 2222. (t) Morrow, D. F. and Butler, M. E., *J. Heterocycl. Chem.,* **1964**, *1*, 53. (u) O'Brien, C., *Chem. Rev.,* **1964**, *64*, 81. (v) Parcell, R. F., *Chem. Ind. (London),* **1963**, 1396. (w) House, H. O. and Berkowitz, W. F., *J. Org. Chem.,* **1963**, *28*, 307. (x) Hatch, M. J. and Cram, D. J., *J. Am. Chem. Soc.,* **1953**, *75*, 38.

3. (a) Verstappen, M. M. H.; Ariaans, G. J. A. and Zwanenburg, B., *J. Am. Chem. Soc.,* **1996**, *118*, 8491. (b) Corkins, H. G.; Storace, L. and Osgood, E., *J. Org. Chem.,* **1980**, *45*, 3156. (c) Kakehi, A.; Ito, S.; Manabe, T.; Maeda, T. and Imai, K., *J. Org. Chem.,* **1977**, *42*, 2514. (d) Garst, M. E.; Cox, D. D.; Harper, R. W. and Kemp, D. S., *J. Org. Chem.,* **1975**, *40*, 1169.
4. See *Beckmann Rearrangement* and *Beckmann Fragmentation* herein (P. 288).
5. Drefahl, G. and Martin, D., *Ber.,* **1960**, *93*, 2497.
6. Neber, P. W. and Burgard, A., *Ann.,* **1932**, *493*, 281.
7. Mueller, E. and Narr, B., *Z. Naturforsch.,* **1961**, *16B*, 845.
8. (a) Chung, J. Y. L.; Ho, G.-J.; Chartrain, M.; Roberge, C.; Zhao, D.; Leazer, J.; Farr, R.; Robbins, M.; Emerson, K.; Mathre, D. J.; McNamara, J. M.; Hughes, D. L.; Grabowski, E. J. J. and Reider, P. J., *Tetrahedron Lett*., **1999**, *40*, 6739. (b) Diez, A.; Voldoire, A.; Lopez, I.; Rubiralta, M.; Segarra, V.; Pages, L. I. and Palacios, J. M., *Tetrahedron,* **1995**, *51*, 5143. (c) Padwa, A. and Woolhouse, A. D., *Aziridines and Fused Ring Derivatives* in *Comprehensive Heterocyclic Chemistry*, ed., Lowowski, W., Pergamon Press, New York, **1984**, *7*, chapter 5.04. (d) Nair, V., *Small Ring Heterocycles* in *The Chemistry of Heterocyclic Compounds*, ed., Hassner, A., John Wiley & Sons, New York, **1983**, *42.1*, chapter 2. (e) Morrow, D. F.; Butler, M. E. and Huang, E. C. Y., *J. Org. Chem.,* **1965**, *30*, 579. (f) House, H. O. and Berkowitz, W. F., *J. Org. Chem.,* **1963**, *28*, 2271. (g) Heldt, W. Z., *J. Am. Chem. Soc.,* **1958**, *80*, 5880. (h) Cram, D. J. and Hatch, M. J., *J. Am. Chem. Soc.,* **1953**, *75*, 33. (i) Neber, P. W.; Burgard, A. and Their, W., *Ann.,* **1936**, *526*, 277. (j) Neber, P. W. and Huh, G., *Ann.,* **1935**, *515*, 283.

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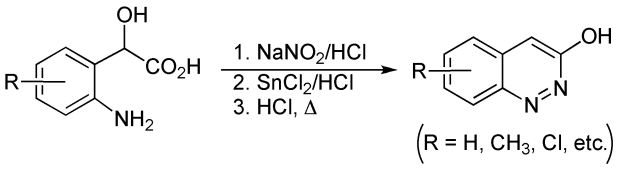
Neber-Bössel Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first described in 1929 by Bössel,[1] who was a student of Neber. This reaction was subsequently extended by Neber and co-workers.[2] It is the transformation of an *o*-amino mandelic acid into a 3-hydroxy-cinnoline involving the diazotization of the *o*-amino mandelic acid, reduction by stannous chloride, and subsequent acidic cyclization. Therefore, this reaction is generally known as the Neber-Bössel synthesis.[3]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A general mechanism is shown here for the formation of 3-hydroxycinnoline.

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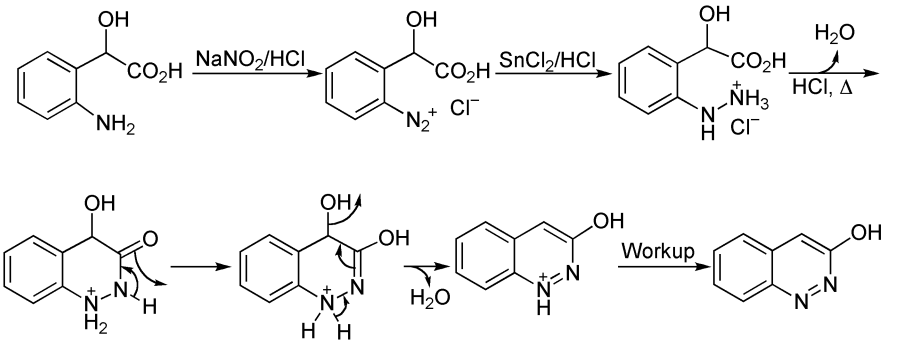


D. MODIFICATION

This reaction has been modified by treatment of isatin with Grignard reagent to form α-substituted *o*-amino mandelic acid, from which 4-substituted 3-hydroxycinnoline can be prepared.[3b]

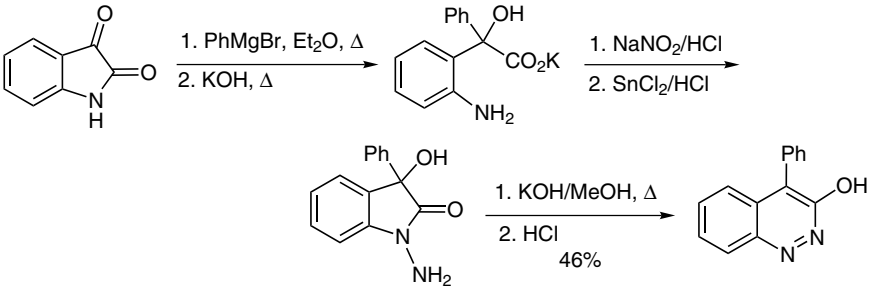
E. APPLICATIONS

This reaction provides a general synthesis of cinnoline derivatives.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3b.

To the flask equipped with a dropping funnel and a Soxhlet extracter (modified for constant return of the extract) and protected by a drying tube was added 5.0 g magnesium turnings and 50 mL dry ether, followed by a crystal of iodine and a few drops of a

solution of 32.0 g bromobenzene in 50 mL dry ether. When the reaction started, the remainder of the bromobenzene was added at such a rate so as to maintain the moderate reflux (30–45 min). When all of the bromobenzene had been added, the ether solution was refluxed for an additional 15 min, then 300 mL dry benzene was introduced through the dropping funnel, and the Soxhlet thimble was charged with 10.0 g isatin. The benzene solution was refluxed for 24 h. To the mixture was added 100 g 10% H_2SO_4, and the mixture was steam distilled to remove the biphenyl; 1.5–2 L of distillate was collected. After the residue in the still pot had been cooled to 10–15°C in the ice bath, the solid formed was collected and digested with 200 g 10% NaOH. After the basic solution had been treated with charcoal and filtered, the pH of the solution was adjusted to 2 by 6 N H_2SO_4. The solid formed was collected and washed liberally with water to remove the Na_2SO_4 which separated with the product. The 3-phenyldioxindole remaining was recrystallized from 75 mL 50% EtOH or 50% acetic acid to give 8.5 g nearly colorless needles, m.p. 209–211°C.

A mixture of 10.0 g 3-phenyldioxindole (0.044 mol) and 100 g 5% KOH (0.088 mol) solution was refluxed for 3–4 h. After the solution had been cooled, 3.1 g $NaNO_2$ (0.044 mol) was added, and the resulting solution was added dropwise with stirring to 90 mL cold conc. HCl. A solution of diazotized α-phenylmandelic acid was added to a precooled (0–5°C), vigorously stirred solution of 28.8 g $SnCl_2 \cdot 2H_2O$ in 80 mL conc. HCl. A pale yellow solid, thought to be a tin salt, began to separate well before the addition of the diazonium solution was complete. The final mixture was stored overnight in the refrigerator, during which time the solid coagulated. The resultant solid was collected and washed thoroughly with water. After drying, the crude product weighed 8.1 g, m.p., 153–220°C. Recrystallization from benzene gave 3.8 g 1-amino-3-phenyldioxindole, m.p. 168.5–169.5°C.

A mixture of 1.0 g 1-amino-3-phenyldioxindole (4.2 mmol), 8.42 mL 1.984 N KOH solution and 10 mL MeOH was refluxed for 2 h. The hot solution was neutralized by the dropwise addition of 8.46 mL 1.974 N HCl, which effected the immediate separation of the canary yellow product along with some of the starting material. After the mixture had been cooled, the solid was collected, washed thoroughly with water, and recrystallized from 150 mL 95% EtOH, giving 0.42 g 4-phenyl-3-cinnolinol as yellow blades, m.p., 294–302°C (dec.)

No further references related to the Neber-Bössel synthesis are found in the literature.

H. REFERENCES

1. Bössel, G., *Chem. Zentr.*, **1929**, *100*, 3015.
2. Neber, P. W.; Knoller, G.; Herbst, K. and Trissler, A., *Ann.,* **1929**, *471*, 113.
3. (a) Baumgarten, H. E.; Creger, P. L. and Zey, R. L., *J. Am. Chem. Soc.,* **1960**, *82*, 3977. (b) Baumgarten, H. E. and Creger, P. L., *J. Am. Chem. Soc.,* **1960**, *82*, 4634. (c) Djerassi, C.; Donovan, F. W.; Burstein, S. and Mauli, R., *J. Am. Chem. Soc.,* **1958**, *80*, 1972. (d) Alford, E. J. and Schofield, K., *J. Chem. Soc.,* **1952**, 2102.

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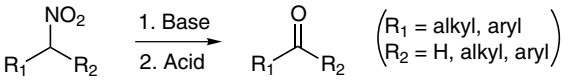
Nef Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Konovalov in 1893[1] and subsequently by Nef in 1894.[2] It is the transformation of a primary or secondary nitroalkane into the corresponding carbonyl compound (i.e, an aldehyde or a ketone)[3] by means of deprotonation of the nitroalkane to an *aci*-nitro compound followed by hydrolysis with a strong acid. Therefore, this reaction is generally known as the Nef reaction.[4] Occasionally, it is also referred to as the Nef transformation[5] or Nef conversion.[6] It should be pointed out that the primary nitroalkanes can also be converted into carboxylic acids under similar conditions,[4j,4ee] depending on the proton donating capability of the acid.[4ee] For example, 4-nitrobenzyl nitronate when treated with 4 *N* H_2SO_4 gives 93% of 4-nitrophenyl nitromethane, whereas it forms 86% 4-nitrobenzhydroxamic acid in 31 *N* H_2SO_4 (i.e., 85% H_2SO_4).[4ee] Moreover, it has been found that the yield of a ketone is generally low if the alkaline solution of a nitroalkane is added to the acid or exposed to an excess amount of acid.[4oo] However, this does not mean that the Nef reaction will occur only at low proton concentration.[4x] Furthermore, if there exists a considerable resonance stabilization in nitroalkane,[4ee,4rr] such as the conjugation with an olefinic moiety,[4uu] or a steric hindrance,[4rr] the Nef reaction will proceed with difficulty or not at all. It is very easy to monitor the reaction because of its characteristic transitory blue color.[4tt]

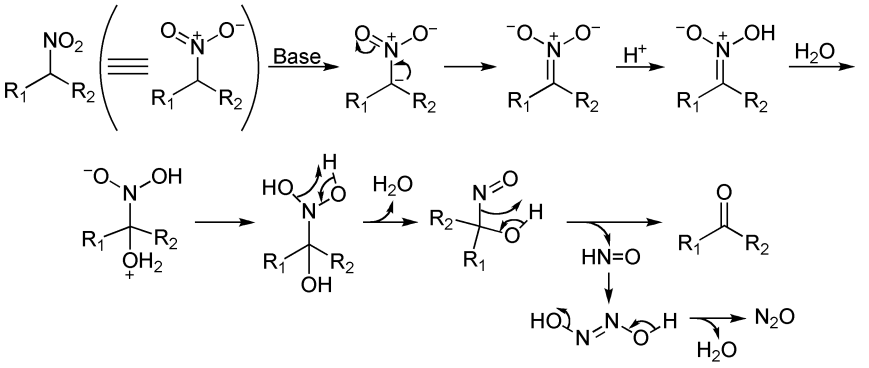
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

A revised scheme based on a reported mechanism[4nn] is shown here.



D. MODIFICATION

Being anionic carbonyl synthons, the nitroalkanes have been explored extensively for their conversion into the corresponding carbonyl compounds. For example, the embedment of a nitroalkane onto an activated basic silica gel[4x] or the blockage of the C-protonation of nitronate with a protonated concave pyridine.[4m] The reaction under the latter condition is called the soft Nef reaction.[4m] In addition, the introduction of a γ-trimethylsilyl group is proved to smooth the Nef reaction.[4n] Moreover, when a primary nitroalkane is treated with nitrite/acetic acid, a carboxylic acid is resolved.[7] Furthermore, the oxidative Nef reaction has successfully converted the nitro cyclohexadienes into the substituted phenols via a nucleophilic addition.[4c,4g,4j]

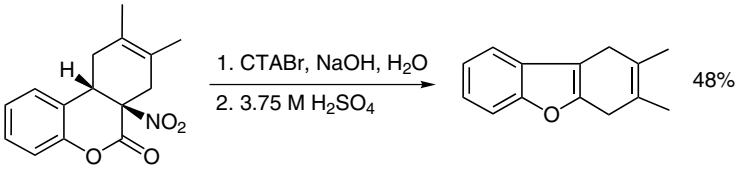
E. APPLICATIONS

This reaction has general application in the synthesis of aldehydes and ketones, especially for 1,4-diketones[8] and dihydrofurans.[9] The 1,4-diketones can be prepared by the combination of a Michael reaction between a nitroalkane and an α,β-unsaturated ketone followed by a Nef reaction, whereas dihydrofurans can be synthesized by the Nef reaction followed by cyclohydration.

F. RELATED REACTIONS

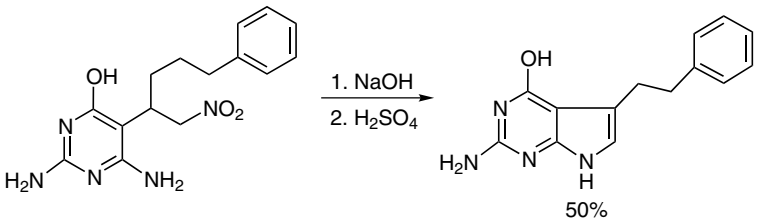
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 9.

To a 50-mL flask were added 0.147 g cetyltrimethylammonium bromide (CTABr, 0.4 mmol), 3.6 g NaOH (90 mmol), and 30 mL water; the resulting solution was warmed to 50°C. Then 0.546 g rel(6a*R*,10a*S*)-8,9-dimethyl-6a-nitro-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromen-6-one (2.0 mmol) was added rapidly, and the alkaline solution was stirred for 1 h. The final orange mixture was cooled to 0°C and added dropwise to a 100-mL flask at 0°C containing 15 mL 3.75 M H_2SO_4 solution. The heterogeneous mixture was left under stirring at this temperature for 5 min and then warmed to room temperature for 1 h. The mixture was transferred into a 250-mL separatory funnel, saturated with NaCl, and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The gummy solid obtained was purified by column chromatography to give 0.190 g 2,3-dimethyl-1,4-dihydrodibenzo[*b*,*d*]furan as a white solid, in a yield of 48%, m.p., 91–93°C (petroleum ether).



Reference 4d.

To an aqueous solution of 0.34 g NaOH (8.5 mmol) in 5 mL water was added 0.148 g 2,6-diamino-5-(1-nitromethyl)-3-phenylpropyl)-3*H*-pyrimidin-4-one (1.58 mmol) at room temperature. The mixture was stirred for 2 h and then was slowly added to a cold aqueous solution prepared from 1.37 g 98% H_2SO_4 (14 mmol) and 5 mL water. The resulting mixture was stirred at 0°C for 1 h and at room temperature for an additional hour. The color of the mixture changed to gray. Concentrated NH_4OH was added at 0°C to adjust the pH to 7. The precipitated solid was collected and purified by silica gel column chromatography (EtOAc/MeOH, 9:1) to give 0.2 g 2-amino-5-phenethyl-3,7-dihydropyrrolo[2,3-*d*]pyrimidin-4-one as a light yellow solid, in a yield of 50%.

Other references related to the Nef reaction are cited in the literature.[10]

H. REFERENCES

1. Konovalov, M., *J. Russ. Phys. Chem. Soc.,* **1893**, *25*, 509.
2. Nef, J. U., *Ann.,* **1894**, *280*, 263.
3. Ballini, R. and Petrini, M., *Tetrahedron*, **2004**, *60*, 1017.
4. (a) Krawczyk, H.; Albrecht, L.; Wojciechowski, J. and Wolf, W. M., *Tetrahedron,* **2006**, *62*, 9135. (b) Petrusova, M.; Vojtech, M.; Pribulova, B.; Lattova, E.; Matulova, M.; Polakova, M.; BeMiller, J. N.; Kren, V. and Petrus, L., *Carbohydr. Res.,* **2006**, *341*, 2019. (c) Makosza, M.; Surowiec, M. and Paszewski, M., *ARKIVOC,* **2004**, 172. (d) Taylor, E. C. and Liu, B., *J. Org. Chem.,* **2003**, *68*, 9938. (e) Hughes, C. C. and Trauner, D., *Angew. Chem. Int. Ed.,* **2002**, *41*, 4556. (f) Ballini, R.; Bosica, G.; Fiorini, D. and Petrini, M., *Tetrahedron Lett.*, **2002**, *43*, 5233. (g) Adam, W.; Makosza, M.; Zhao, C.-G. and Surowiec, M., *J. Org. Chem.,* **2000**, *65*, 1099. (h) Gil, M. V.; Roman, E. and Serrano, J. A., *Tetrahedron Lett*., **2000**, *41*, 10201. (i) Shahi, S. P. and Vankar, Y. D., *Synth.*

Commun., **1999**, *29*, 4321. (j) Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Epifano, F. and Rosati, O., *Synth. Commun.,* **1998**, *28*, 3057. (k) Adam, W.; Makosza, M.; Saha-Moeller, C. R. and Zhao, C.-G., *Synlett*, **1998**, 1335. (l) Denmark, S. E. and Thorarensen, A., *Chem. Rev.,* **1996**, *96*, 137. (m) Lüning, U.; Baumstark, R.; Wangnick, C.; Müller, M.; Schyja, W.; Gerst, M. and Gelbert, M., *Pure & Appl. Chem.,* **1993**, *65*, 527. (n) Hwu, J. R. and Gilbert, B. A., *J. Am. Chem. Soc.,* **1991**, *113*, 5917. (o) Pinnick, H. W., *Org. React.,* **1990**, *38*, 655. (p) Luening, U.; Baumstark, R.; Mueller, M.; Wangnick, C. and Schillinger, F., *Chem. Ber.,* **1990**, *123*, 221. (q) Aizpurua, J. M.; Oiarbide, M. and Palomo, C., *Tetrahedron Lett.,* **1987**, *28*, 5361. (r) Chikashita, H.; Morita, Y. and Itoh, K., *Synth. Commun.,* **1987**, *17*, 677. (s) Akhtar, M. S.; Sharma, V. L. and Bhaduri, A. P., *J. Heterocycl. Chem.,* **1987**, *24*, 23. (t) Lou, J. D. and Lou, W. X., *Kexue Tongbao*, **1985**, *30*, 426. (u) Boberg, F.; Ruhr, M. and Garming, A., *Liebigs Ann. Chem*., **1984**, 223. (v) Barton, D. H. R.; Motherwell, W. B. and Zard, S. Z., *Tetrahedron Lett*., **1983**, *24*, 5227. (w) Lagrenee, M., *Compt. Rend.,* **1977**, *284*, 153. (x) Keinan, E. and Mazur, Y., *J. Am. Chem. Soc.,* **1977**, *99*, 3861. (y) Ranganathan, S.; Ranganathan, D. and Mehrotra, A. K., *J. Am. Chem. Soc.,* **1974**, *96*, 5261. (z) Mikhailovskii, D. I.; Mikhailovskaya, V. N. and Favorskaya, T. A., *Zh. Org. Khim.,* **1973**, *9*, 1804. (aa) Bagli, J. and Bogri, T., *Tetrahedron Lett*., **1972**, 3815. (bb) Black, D. St. C., *Tetrahedron Lett*., **1972**, 1331. (cc) Sun, S.-F. and Folliard, J. T., *Tetrahedron*, **1971**, *27*, 323. (dd) Boberg, F.; Marei, A. and Kirchhoff, K., *Ann*., **1967**, *708*, 142. (ee) Kornblum, N. and Brown, R. A., *J. Am. Chem. Soc.,* **1965**, *87*, 1742. (ff) Noland, W. E. and Libers, R., *Tetrahedron*, **1963**, *19*, 23. (gg) Larson, H. O. and Wat, E. K. W., *J. Am. Chem. Soc.,* **1963**, *85*, 827. (hh) Feuer, H. and Nielsen, A. T., *J. Am. Chem. Soc.,* **1962**, *84*, 688. (ii) Colonge, J. and Pouchol, J. M., *Bull. Soc. Chim. Fr.,* **1962**, 832. (jj) Weinstein, B. and Fenselau, A. H., *J. Org. Chem.,* **1962**, *27*, 4094. (kk) Boberg, F.; Marei, A. and Schultze, G. R., *Ann.*, **1962**, *655*, 102. (ll) Boberg, F. and Kieso, A., *Ann.,* **1959**, *626*, 71. (mm) Boberg, F. and Schultze, G. R., *Chem. Ber.,* **1957**, *90*, 1215. (nn) Hawthorne, M. F., *J. Am. Chem. Soc.,* **1957**, *79*, 2510. (oo) Noland, w. E.; Baker, M. S. and Freeman, H. I., *J. Am. Chem. Soc.,* **1956**, *78*, 2233. (pp) Noland, W. E., *Chem. Rev.,* **1955**, *55*, 137. (qq) Leitch, L. C., *Can. J. Chem.,* **1955**, *33*, 400. (rr) Wildman, W. C. and Saunders, D. R., *J. Org. Chem.,* **1954**, *19*, 381. (ss) Wildman, W. C. and Saunders, D. R., *J. Org. Chem.,* **1953**, *18*, 381. (tt) Gilsdorf, R. T. and Nord, F. F., *J. Am. Chem. Soc.,* **1952**, *74*, 1837. (uu) van Tamelen, E. E. and Thiede, R. J., *J. Am. Chem. Soc.,* **1952**, *74*, 2615. (vv) Wildman, W. C. and Hemminger, C. H., *J. Org. Chem.,* **1952**, *17*, 1641. (ww) Wildman, W. C. and Wildman, R. B., *J. Org. Chem.,* **1952**, *17*, 581. (xx) Oroshnik, W. and Mebane, A. D., *J. Am. Chem. Soc.,* **1949**, *71*, 2062.

5. (a) Clark, J. H.; Cork, D. G. and Gibbs, H. W., *J. Chem. Soc., Perkin Trans. I,* **1983**, 2253. (b) Chapas, R. B.; Knudsen, R. D.; Nystrom, R. F. and Snyder, H. R., *J. Org. Chem.,* **1975**, *40*, 3746.
6. Ballini, R.; Fiorini, D.; Maggi, R.; Oro, C.; Palmieri, A. and Sartori, G., *Synlett*, **2006**, 1849.
7. Mioskowski, C. and Matt, C., *J. Org. Chem.,* **1997**, *62*, 234.
8. Lahmar, N.; Ayed, T. B.; Bellassoued, M. and Amri, H., *Beilstein J. Org. Chem.,* **2005**, *I*, 11.
9. Amantini, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F. and Vaccaro, L., *J. Org. Chem.,* **2003**, *68*, 9263.
10. (a) Luchaco-Cullis, C. A. and Hoveyda, A. H., *J. Am. Chem. Soc.*, **2002**, *124*, 8192. (b) Wang, J.; Brower, K. R. and Naud, D. L., *J. Org. Chem.,* **1997**, *62*, 9048. (c) Hergovich, E. and Speier, G., *Chem. Lett.,* **1996**, 573. (d) Lawrance, G. A.; O'Leary, M. A.; Skelton, B. W.; Woon, F.-H. and White, A. H., *Aust. J. Chem.,* **1988**, *41*, 1533. (e) Seebach, D. and Colvin, E., *Chemia,* **1979**, *33*, 1. (f) Hass, H. B. and Riley, E. F., *Chem. Rev.,* **1943**, *32*, 398.

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Negishi Cross-Coupling

(Negishi Coupling, Negishi Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Negishi et al. in 1977.[1] It is a palladium or nickel-catalyzed coupling between an aryl or alkenylzinc, zirconium or aluminum reagent[2] and an alkenyl or aryl halide or triflate; specifically, it is an organozinc reagent-mediated coupling with an alkenyl or aryl halides/triflates. Therefore, it is generally known as the Negishi cross-coupling,[2,3] Negishi coupling,[3m,3y,3z,3aa,3ll,4] or Negishi reaction.[3p,3dd,3nn,4x,4z,4ee,5] In addition, the zirconium based coupling is known as the zirconium-Negishi reaction.[6]

The Negishi cross-coupling can tolerate a variety of functional groups that include olefin,[3dd] ether,[3aa,3dd] nitrile,[3aa,3dd] ester,[3dd] nitro,[3aa] and amino[3aa] groups. The aryl zinc reagents can be prepared from aryl bromides (or iodides) by insertion of an activated Rieke zinc,[3y,7] or prepared through transmetallation by treatment of an *ortho*-aryl halide with lithium base (e.g., LDA) followed by $ZnBr_2$ or $ZnCl_2$.[3jj] Generally speaking, if the desired alkenyl zinc reagent are readily accessible via hydrometallation or carbometallation, the aryl electrophile (e.g., halide/triflate) can be added to the organozinc reagent as one-pot synthesis.[2] However, the common alkenyl electrophiles, such as vinyl bromide, vinylidene bromide, and especially the alkenyl triflates or phosphates prepared from corresponding carbonyl compounds, prefer the coupling with arylzinc reagents.[2] This reaction is commonly catalyzed by a transition metal of palladium or nickel with triaryl or trialkyl phosphines as ligands, such as $PdCl_2(dppf)_2$,[3al] $Pd[P(t\text{-}Bu)_3]_2$,[3aa,3nn,4bb,4cc] ($Pd_2(dba)_3/PCy_3$/NMI),[3dd] 4% $Ni(cod)_2$/8% *s*-Bu-Pybox,[3p,4x] or $Pd_2(dba)_3$/P(2-furyl)$_3$.[4cc] It has been found that the ligand has a substantial impact on the course of the Negishi cross-coupling.[3dd] For example, the decrease of the ratio of phosphine to palladium lowers the yield of the desired compound,[3dd] whereas the application of an electron-enriched ligand such as

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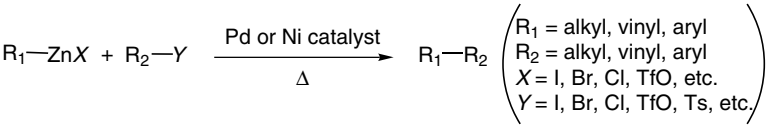
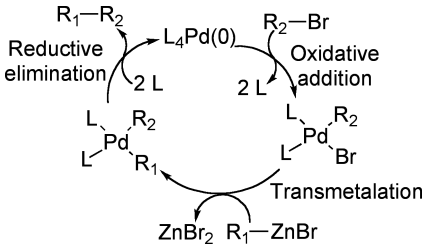
$P(t\text{-Bu})_3$[3aa,3nn,4bb,4cc] or especially dicyclohexyl *o*-(2,6-diisopropylphenyl)phenyl phosphine allows the coupling of two bulkyl aryl moieties,[3aa] with a load of palladium of $< 0.01\%$. In addition, Pd-*N*-heterocyclic carbene (NHC) catalyst facilitates the coupling at room temperature,[3o,3p] whereas the normal Negishi cross-coupling requires high temperature and long reaction time.[3y]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A general modified mechanism is shown here, based on References 3z and 5a.



D. MODIFICATION

This reaction has been modified for various conditions, such as the application of microwave irradiation[3b,3y] and the application of phosphine-containing polymer prepared from the ruthenium-catalyzed ring-opening metathesis polymerization of the norbornene.[3t,5h] Most importantly, this reaction has been extended to the coupling of primary or secondary alkyl halides with aryl, vinyl, and even alkyl halide (or tosylate).[3l,3o,3p,3y,3dd,3nn,4v,4x,6]

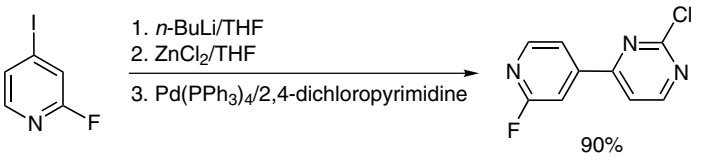
E. APPLICATIONS

This reaction has very general application in the formation of C-C bonds, including biaryls, aryl alkenes, alkanes, and even ketones.[8]

F. RELATED REACTIONS

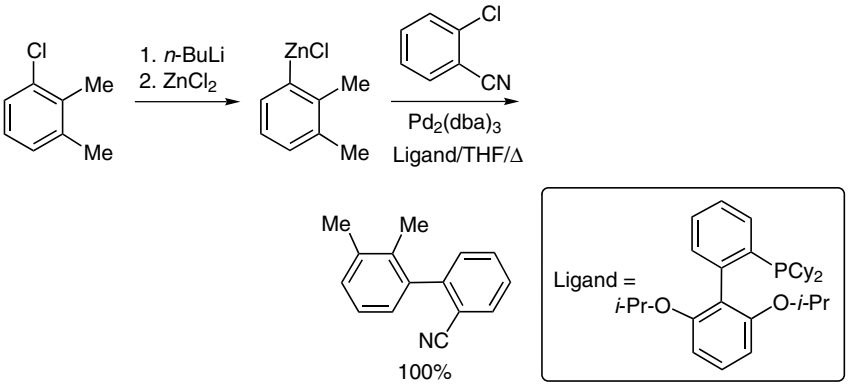
This reaction is related to the *Heck Reaction*, *Stille Coupling*, and *Suzuki Coupling*, etc.

G. CITED EXPERIMENTAL EXAMPLES



Reference 3q.

4-Iodo-2-fluoropyridine (15.52 g, 69.60 mmol, 1 eq.) was dissolved in 150 mL dry THF and cooled to −70°C. Then *n*-BuLi (73.08 mmol, 1.05 eq.) was added, and the reaction mixture was stirred at −70°C for 20 min. Subsequently, 10.44 g dry $ZnCl_2$ (76.61 mmol, 1.1 eq.) was added as a solution in 60 mL dry THF while kept at temperature < −60°C. The reaction mixture was then warmed to room temperature, and 0.40 g $Pd(PPh_3)_4$ (0.35 mmol, 0.005 eq.) and 7.26 g 2,4-dichloropyrimidine (48.73 mmol, 0.75 eq.) in 100 mL dry THF were added. The reaction mixture was refluxed until complete conversion. Then the reaction mixture was poured onto a 10% aqueous EDTA solution, basified with saturated aqueous Na_2CO_3 solution, and extracted with CH_2Cl_2. Upon removal of the solvent, the residue was purified by flash column chromatography using petroleum ether/EtOAc (10:1) as the eluent to afford 9.17 g 2-chloro-4-(2-fluoropyridin-4-yl)pyrimidine as beige crystals, in a yield of 90%, m.p. 157–159°C.



Reference 3aa.

An oven-dried resealable Schlenk tube containing a magnetic stir bar was capped with a rubber septum and then evacuated and backfilled with argon (this sequence was repeated for three times). The Schlenk tube was charged with 0.75 mmol 2,3-dimethylphenyl chloride (1.5 eq.) and 1.0 mL dry THF. The resulting solution was cooled to −78°C; then 0.825 mmol *n*-butyllithium (1.65 eq.) in THF was added dropwise via syringe through the septum, and the resulting solution was stirred at −78°C for 1 h. $ZnCl_2$ (0.9 mmol, 1.8 eq.) was added in one solid portion by removal of the septum. After 30 min at −78°C, the Schlenk tube was removed from the cooling bath, and the resulting solution was stirred at room temperature for 1 h. Then 2.3 mg $Pd_2(dba)_3$ (0.5 mol %), 4.7 mg dicyclohexyl (2,6-diisopropylphenyl)phenyl phosphine (2.0 mol %), and 0.5 mmol 2-chlorobenzonitrile (1.0 eq.) were added with the

aid of 0.5 mL THF, which was used to rinse the walls of the tube. The septum was replaced with a Teflon screw cap, and the Schlenk tube was sealed. The reaction mixture was placed in a preheated oil bath at 70°C and magnetically stirred until the aryl halide had been completely consumed as judged by GC analysis. The reaction mixture was then cooled to room temperature, diluted with 1 mL water, and extracted with diethyl ether (4 × 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material obtained was purified by flash chromatography on silica gel to afford 100% 2,3-dimethyl-2′-cyano-biphenyl.

Other references related to the Negishi cross-coupling are cited in the literature.[9]

H. REFERENCES

1. (a) Negishi, E.-i.; King, A. O. and Okukado, N., *J. Org. Chem.,* **1977**, *42*, 1821. (b) King, A. O.; Okukado, N. and Negishi, E.-i., *J. Chem. Soc., Chem. Commun.,* **1977**, 683.
2. Negishi, E.-i.; Hu, Q.; Huang, Z. H.; Qian, M. X. and Wang, G. W., *Aldrichimica Acta,* **2005**, *38*, 71.
3. (a) Kiehne, U.; Bunzen, J.; Staats, H. and Luetzen, A., *Synthesis*, **2007**, 1061. (b) Genov, M.; Almorin, A. and Espinet, P., *Tetrahedron: Asymmetry*, **2007**, *18*, 625. (c) Perez-Balado, C.; Willemsens, A.; Ormerod, D.; Aelterman, W. and Mertens, N., *Org. Proc. Res. Dev.,* **2007**, *11*, 237. (d) Gong, H. G.; Sinisi, R. and Gagne, M. R., *J. Am. Chem. Soc.,* **2007**, *129*, 1908. (e) Kondolff, I.; Doucet, H. and Santelli, M., *Organometallics*, **2006**, *25*, 5219. (f) Gavryushin, A.; Kofink, C.; Manolikakes, G. and Knochel, P., *Tetrahedron*, **2006**, *62*, 7521. (g) Alves, D.; Schumacher, R. F.; Brandao, R.; Nogueira, C. W. and Zeni, G., *Synlett*, **2006**, 1035. (h) Ousmer, M.; Boucard, V.; Lubin-Germain, N.; Uziel, J. and Auge, J., *Eur. J. Org. Chem.,* **2006**, 1216. (i) Stanetty, P.; Roehrling, J.; Schnuerch, M. and Mihovilovic, M. D., *Tetrahedron*, **2006**, *62*, 2380. (j) Kruppa, M.; Imperato, G. and Koenig, B., *Tetrahedron*, **2006**, *62*, 1360. (k) Commeiras, L.; Bourdron, J.; Douillard, S.; Barbier, P.; Vanthuyne, N.; Peyrot, V. and Parrain, J.-L., *Synthesis,* **2006**, 166. (l) Xie, M. H.; Wang, J. L.; Gu, X. X.; Sun, Y. and Wang, S. W., *Org. Lett.,* **2006**, *8*, 431. (m) Denni-Dischert, D.; Marterer, W.; Bänziger, M.; Yusuff, N.; Batt, D.; Ramsey, T.; Geng, P.; Michael, W.; Wang, R.-M. B.; Taplin, F.; Versace, R.; Cesarz, D. and Perez, L. B., *Org. Proc. Res. Dev.,* **2006**, *10*, 70. (n) Jacobsen, M. F.; Moses, J. E.; Adlington, R. M. and Baldwin, J. E., *Org. Lett.,* **2005**, *7*, 641. (o) Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J. and Organ, M. G., *Org. Lett.,* **2005**, *7*, 3805. (p) Hadei, N.; Kantchev, A. B.; O'Brien, C. J. and Organ, M. G., *J. Org. Chem.,* **2005**, *70*, 8503. (q) Stanetty, P.; Hattinger, G.; Schnürch, M. and Mihovilovic, M. D., *J. Org. Chem.,* **2005**, *70*, 5215. (r) Chen, D. J.; Kotti, S. and Li, G. G., *Chemtracts,* **2005**, *18*, 193. (s) Solano, C.; Svensson, D.; Olomi, Z.; Jensen, J.; Wendt, O. F. and Waernmark, K., *Eur. J. Org. Chem.,* **2005**, 3510. (t) Fischer, C. and Fu, G. C., *J. Am. Chem. Soc.,* **2005**, *127*, 4594. (u) Tews, D. and Escarpa Gaede, P., *Tetrahedron Lett*., **2004**, *45*, 9029. (v) Sapountzis, I.; Dube, H. and Knochel, P., *Adv. Synth. Catal.,* **2004**, *346*, 709. (w) Zeni, G.; Alves, D.; Braga, A. L.; Stefani, H. A. and Nogueira, C. W., *Tetrahedron Lett*., **2004**, *45*, 4823. (x) Miyasaka, M. and Rajca, A., *Synlett*, **2004**, 177. (y) Walla, P. and Kappe, C. O., *Chem. Commun.,* **2004**, 564. (z) Anderson, T. J. and Vicic, D. A., *Organometallics,* **2004**, *23*, 623. (aa) Milne, J. E. and Buchwald, S. L., *J. Am. Chem. Soc.,* **2004**, *126*, 13028. (bb) Kaae, B. H.; Krogsgaard-Larsen, P. and Johansen, T. N., *J. Org. Chem.,* **2004**, *69*, 1401. (cc) Nguyen, T.; Wicki, M. A. and Snieckus, V., *J. Org. Chem.,* **2004**, *69*, 7816. (dd) Zhou, J. R. and Fu, G. C., *J. Am. Chem. Soc.,* **2003**, *125*, 12527. (ee) Luetzen, A.; Hapke, M.; Staats, H. and Bunzen, J., *Eur. J. Org. Chem.,* **2003**, 3948. (ff) Cotton, H. K.; Huerta, F. F. and Baeckvall, J.-E., *Eur. J. Org. Chem.,* **2003**, 2756. (gg) Fang, Y.-Q.; Polson, M. I. J. and Hanan, G. S., *Inorg. Chem.,* **2003**, *42*, 5. (hh) Smith, A. P.; Savage, S. A.; Love, J. C. and Fraser,

C. L., *Org. Synth.,* **2002**, *78*, 51. (ii) Bach, T. and Heuser, S., *J. Org. Chem.,* **2002**, *67*, 5789. (jj) Lotz, M.; Kramer, G. and Knochel, P., *Chem. Commun.,* **2002**, 2546. (kk) Russell, J. M.; Sabat, M. and Grimes, R. N., *Organometallics,* **2002**, *21*, 4113. (ll) Littke, A. F. and Fu, G. C., *Angew. Chem. Int. Ed.,* **2002**, *41*, 4176. (mm) Lutzen, A. and Hapke, M., *Eur. J. Org. Chem.,* **2002**, 2292. (nn) Dai, C. Y. and Fu, G. C., *J. Am. Chem. Soc.,* **2001**, *123*, 2719. (oo) Nshimyumukiza, P.; Cahard, D.; Rouden, J.; Lasne, M.-C. and Plaquevent, J.-C., *Tetrahedron Lett*., **2001**, *42*, 7787. (pp) Yus, M. and Gomis, J., *Tetrahedron Lett*., **2001**, *42*, 5721. (qq) Sonoda, M.; Inaba, A.; Itahashi, K. and Tobe, Y., *Org. Lett.,* **2001**, *3*, 2419. (rr) Jensen, J.; Skjaerbaek, N. and Vedso, P., *Synthesis,* **2001**, 128. (ss) Banwell, M.; Hockless, D.; Jarrott, B.; Kelly, B.; Knill, A.; Longmore, R. and Simpson, G., *J. Chem. Soc*., *Perkin Trans. I*, **2000**, 3555. (tt) Savage, S. A.; Smith, A. P. and Fraser, C. L., *J. Org. Chem.,* **1998**, *63*, 10048.

4. (a) Bowling, N. P. and McMahon, R. J., *J. Org. Chem.,* **2006**, *71*, 9602. (b) Berkowitz, D. B.; Wu, B. and Li, H. J., *Org. Lett.,* **2006**, *8*, 971. (c) Shimizu, H. and Manabe, K., *Tetrahedron Lett.,* **2006**, *47*, 5927. (d) Hlavinka, M. L. and Hagadorn, J. R., *Tetrahedron Lett*., **2006**, *47*, 5049. (e) Dutheuil, G.; Paturel, C.; Lei, X. S.; Couve-Bonnaire, S. and Pannecoucke, X., *J. Org. Chem.,* **2006**, *71*, 4316. (f) Martinez-Esperon, M. F.; Rodriguez, D.; Castedo, L. and Saa, C., *Tetrahedron,* **2006**, *62*, 3843. (g) Walters, I. A. S., *Tetrahedron Lett*., **2006**, *47*, 341. (h) Mutule, I. and Suna, E., *Tetrahedron*, **2005**, *61*, 11168. (i) Holub, N.; Neidhöfer, J. and Blechert, S., *Org. Lett.,* **2005**, *7*, 1227. (j) Lipshutz, B. H.; Clososki, G. C.; Chrisman, W.; Chung, D. W.; Ball, D. B. and Howell, J., *Org. Lett.,* **2005**, *7*, 4561. (k) Gómez-Reino, C.; Vitale, C.; Maestro, M. and Mouriño, A., *Org. Lett.,* **2005**, *7*, 5885. (l) Kuo, G.-H.; DeAngelis, A.; Emanuel, S.; Wang, A. H.; Zhang, Y.; Connolly, P. J.; Chen, X.; Gruninger, R. H.; Rugg, C.; Fuentes-Pesquera, A.; Middleton, S. A.; Jolliffe, L. and Murray, W. V., *J. Med. Chem.,* **2005**, *48*, 4535. (m) Cai, S. P.; Dimitroff, M.; McKennon, T.; Reider, M.; Robarge, L.; Ryckman, D.; Shang, X. and Therrien, J., *Org. Proc. Res. Dev.,* **2004**, *8*, 353. (n) Negishi, E.-I.; Zeng, X. Z.; Tan, Z.; Qian, M. X.; Hu, Q. and Huang, Z. H., *Palladium- or Nickel-Catalyzed Cross-Coupling with Organometals Containing Zinc, Aluminum, and Zirconium: The Negishi Coupling* in *Metal-Catalyzed Cross-Coupling Reactions*, ed. De Meijere, A. and Diederich, F., Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, **2004** *2*, pp. 815–889. (o) Corley, E. G.; Conrad, K.; Murry, J. A.; Savarin, C.; Holko, J. and Boice, G., *J. Org. Chem.,* **2004**, *69*, 5120. (p) Mutule, I. and Suna, E., *Tetrahedron Lett*., **2004**, *45*, 3909. (q) Lessene, G., *Aust. J. Chem.,* **2004**, *57*, 107. (r) Peyrat, J.-F.; Thomas, E.; L'Hermite, N.; Alami, M. and Brion, J.-D., *Tetrahedron Lett*., **2003**, *44*, 6703. (s) Arvanitis, A. G.; Arnold, C. R.; Fitzgerald, L. W.; Frietze, W. E.; Olson, R. E.; Gilligan, P. J. and Robertson, D. W., *Bioorg. Med. Chem. Lett.,* **2003**, *13*, 289. (t) Ragan, J. A.; Raggon, J. W.; Hill, P. D.; Jones, B. P.; McDermott, R. E.; Munchhof, M. J.; Marx, M. A.; Casavant, J. M.; Cooper, B. A.; Doty, J. L. and Lu, Y., *Org. Proc. Res. Dev.,* **2003**, *7*, 676. (u) Duffey, M. O.; Tiran, A. L. and Morken, J. P., *J. Am. Chem. Soc.,* **2003**, *125*, 1458. (v) Ma, S. M.; Ren, H. J. and Wei, Q., *J. Am. Chem. Soc.,* **2003**, *125*, 4817. (w) Aïssa, C.; Riveiros, R.; Ragot, J. and Fürstner, A., *J. Am. Chem. Soc.,* **2003**, *125*, 15512. (x) Zhou, J. R. and Fu, G. C., *J. Am. Chem. Soc.,* **2003**, *125*, 14726. (y) Manley, P. W.; Acemoglu, M.; Marterer, W. and Pachinger, W., *Org. Proc. Res. Dev.,* **2003**, *7*, 436. (z) Stadler, A.; Yousefi, B. H.; Dallinger, D.; Walla, P.; der Eycken, E. V.; Kaval, N. and Kappe, C. O., *Org. Proc. Res. Dev.,* **2003**, *7*, 707. (aa) Novák, Z. and Kotschy, A., *Org. Lett.,* **2003**, *5*, 3495. (bb) Pei, J.; Ni, J.; Zhou, X.-H.; Cao, X.-Y. and Lai, Y.-H., *J. Org. Chem.,* **2002**, *67*, 4924. (cc) Feldman, K. S.; Eastman, K. J. and Lessene, G., *Org. Lett.,* **2002**, *4*, 3525. (dd) Su, M.; Kang, Y.; Yu, W. S.; Hua, Z. M. and Jin, Z. D., *Org. Lett.,* **2002**, *4*, 691. (ee) Arefolov, A.; Langille, N. F. and Panek, J. S., *Org. Lett.,* **2001**, *3*, 3281. (ff) Wang, F.; Wilson, M. S.; Rauh, R. D.; Schottland, P. and Reynolds, J. R., *Macromolecules,* **1999**, *32*, 4272. (gg) Pihko, P. M. and Koskinen, A. M. P., *Synlett,* **1999**, 1966. (hh) Klein, M. and Boche, G., *Synthesis*, **1999**, 1246. (ii) Palmgren, A.; Thorarensen, A. and Bäckvall, J.-E., *J. Org. Chem.,* **1998**, *63*, 3764.

5. (a) Casares, J. A.; Espinet, P.; Fuentes, B. and Salas, G., *J. Am. Chem. Soc.,* **2007**, *129*, 3508. (b) Akao, A.; Tsuritani, T.; Kii, S.; Sato, K.; Nonoyama, N.; Mase, T. and Yasuda, N., *Synlett*,

2007, 31. (c) Genov, M.; Fuentes, B.; Espinet, P. and Pelaz, B., *Tetrahedron: Asymmetry,* **2006**, *17*, 2593. (d) Organ, M. G.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J. and Valente, C., *Chem. Eur. J.,* **2006**, *12*, 4749. (e) Arp, F. O. and Fu, G. C., *J. Am. Chem. Soc.,* **2005**, *127*, 10482. (f) Rau, S.; Lamm, K.; Goerls, H.; Schoeffel, J. and Walther, D., *J. Organomet. Chem.,* **2004**, *689*, 3582. (g) Wang, N.-X., *Synth. Commun.,* **2003**, *33*, 2119. (h) Yang, Y.-C. and Luh, T.-Y., *J. Org. Chem.,* **2003**, *68*, 9870.

6. (a) Andrei, D. and Wnuk, S. F., *J. Org. Chem.,* **2006**, *71*, 405. (b) Wiskur, S. L.; Korte, A. and Fu, G. C., *J. Am. Chem. Soc.,* **2004**, *126*, 82.
7. See *Rieke Metal* herein (P. 2388).
8. Wang, D. H. and Zhang, Z. G., *Org. Lett.,* **2003**, *5*, 4645.
9. (a) Jacobsen, M. F.; Moses, J. E.; Adlington, R. M. and Baldwin, J. E., *Org. Lett.,* **2005**, *7*, 2473. (b) Sicre, C. and Cid, M. M., *Org. Lett.,* **2005**, *7*, 5737. (c) Sutherland, A.; Gallagher, T.; Sharples, C. G. V. and Wonnacott, S., *J. Org. Chem.,* **2003**, *68*, 2475. (d) Przezdziecka, A.; Kurek-Tyrlik, A. and Wicha, J., *Coll. Czech. Chem. Commun.,* **2002**, *67*, 1658. (e) Pedersen, H. and Johannsen, M., *Chem. Commun.*, **1999**, 2517. (f) Knochel, P. and Singer, R. D., *Ber.,* **1997**, *130*, 1021. (g) Larsen, M. and Jørgensen, M., *J. Org. Chem.,* **1997**, *62*, 4171. (h) Knochel, P. and Singer, R. D., *Chem. Rev.,* **1993**, *93*, 2117. (i) Negishi, E.-I.; Takahashi, T. and King, A. O., *Org. Synth.,* **1987**, *66*, 67. (j) Negishi, E.-I., *Acc. Chem. Res.*, **1982**, *15*, 340. (k) Negishi, E.-I.; Valente, L. F. and Kobayashi, M., *J. Am. Chem. Soc.*, **1980**, *102*, 3298.

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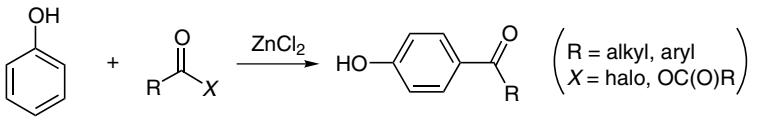
Nencki Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Nencki et al. in 1881.[1] It is the preparation of an acyl phenol derivative by zinc chloride-activated acylation between a phenol and an acyl chloride, anhydride, or even a carboxylic acid. Therefore, this reaction is generally known as the Nencki reaction.[2] The Nencki reaction generally takes place with at least one equivalent of zinc chloride;[3] however, it does not involve the formation of a complex between zinc chloride and acyl chloride or anhydride in a manner similar to that of aluminum chloride.[3] It has been found that the regioselectivity in preference of *para*-acylation decreases when the size of the acylating reagent increases.[4]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A new mechanism is proposed here to illustrate the Nencki reaction from acyl anhydride, with the preference of *para*-acylation and the requirement of at least one equivalent of $ZnCl_2$.

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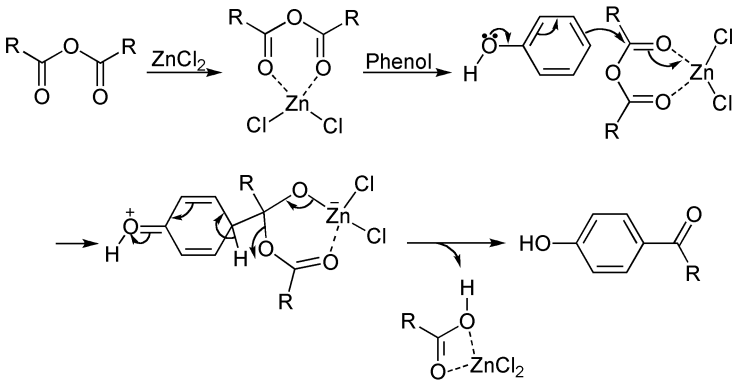


D. MODIFICATION

This reaction has been modified by using a catalytic amount of $ZnCl_2$ for the acylation of heterocycles.[3]

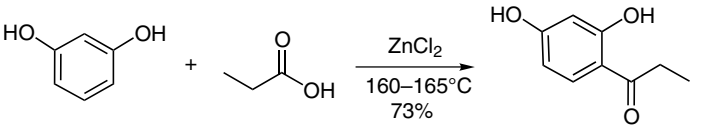
E. APPLICATIONS

This reaction is useful for the preparation of acyl phenol derivatives.

F. RELATED REACTIONS

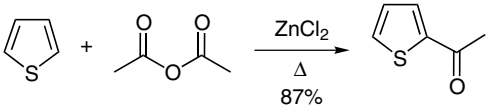
This reaction is related to the *Friedel-Crafts Acylation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 5.

To a hot mixture of 80 g propionic acid and 80 g fused $ZnCl_2$ was added 50 g resorcinol. The mixture was refluxed to an intense bubbling of the solution, which occurred between 160 and 165°C. The solution was then allowed to cool slowly; it was then poured into a water and ice mixture and acidified with HCl. The dark brown oil solidified on standing, which was crystallized from alcohol by decolorizing from charcoal to afford 73% 4-propanoyl resorcinol.



Reference 3.

To a mixture of 168 g thiophene (2 mol) and 107 g 95% Ac_2O (1 mol) was added 4.0 g anhydrous $ZnCl_2$ (0.03 mol) pulverized under thiophene. The reaction mixture was maintained at a reflux temperature of 94–103°C over a period of 4 h, and then cooled to 50°C. Water (200 mL) was added. The material was thoroughly washed with water and finally neutralized with Na_2CO_3 solution. Water and unreacted thiophene were removed by distillation from a Vigreux-modified Claisen flask. The residue was vacuum distillated to afford 109 g 2-acetylthiophene, in a yield of 87%, b.p. 77–78°C at 4 mmHg.

Other references related to the Nencki reaction are cited in the literature.[6]

H. REFERENCES

1. (a) Nencki, M. and Sieber, N., *J. Prakt. Chem.,* **1881**, *23*, 147. (b) Nencki, M. and Sieber, N., *J. Prakt. Chem.,* **1881**, *23*, 150.
2. (a) Bhattacharya, I., *Asian J. Chem.,* **2001**, *13*, 581. (b) Shakil, N. A.; Singh, A.; Prasad, A. K.; Kumar, V.; Olsen, C. E.; Jain, S. C.; Cholli, A. L.; Watterson, A. C. and Parmar, V. S., *J. Macromolecular Sci., Pure & Appl. Chem.,* **2001**, *A38*, 1275. (c) Lakshmi, G. S. P. B.; Murthy, Y. L. N.; Anjaneyulu, A. S. R. and Santhamma, C., *Dyes & Pigments,* **1995**, *29*, 211. (d) Anjaneyulu, A. S. R.; Rani, G. S.; Mallavadhani, U. V. and Murthy, Y. L. N., *Indian J. Chem. Sect. B,* **1994**, *33*, 847. (e) Merchant, J. R. and Shah, N. J., *Indian J. Chem.,* **1974**, *12*, 994. (f) Feigl, F. and Gentil, V., *Publ. Inst. Invest. Microquim., Univ. Nacl. Litoral (Rosario, Arg.)*, **1965**, *26*, 93. (g) Pankajamani, K. S. and Seshadri, T. R., *J. Sci. Ind. Res.,* **1954**, *13B*, 396. (h) Beri, R. M.; Gakhar, K. L. and Rao, P. S., *Proc. Indian Acad. Sci., Sect. A,* **1951**, *33A*, 88. (i) Woods, L. L., *J. Am. Chem. Soc.,* **1948**, *70*, 2608. (j) Desai, R. D. and Waravdekar, W. S., *Curr. Sci.,* **1941**, *10*, 524.
3. Hartough, H. D. and Kosak, A. I., *J. Am. Chem. Soc.,* **1947**, *69*, 1012.
4. Ralston, A. W. and Bauer, S. T., *J. Org. Chem.,* **1940**, *5*, 165.
5. Brewster, C. M. and Harris, J. C., *J. Am. Chem. Soc.,* **1930**, *52*, 4866.
6. (a) Badhwar, I. C. and Venkataraman, K., *Org. Synth. Coll.,* **1943**, 2, 304. (b) Hart, M. C. and Woodruff, E. H., *J. Am. Chem. Soc.,* **1936**, *58*, 1957. (c) Dohme, A. R. L.; Cox, E. H. and Miller, E., *J. Am. Chem. Soc.,* **1926**, *48*, 1688. (d) Ward, C. F., *J. Chem. Soc.,* **1921**, *119*, 850. (e) Johnson, T. B. and Lane, F. W., *J. Am. Chem. Soc.,* **1921**, *43*, 348. (f) Nencki, M., *Monatsh.,* **1889**, *10*, 906. (g) Nencki, M., *J. Prakt. Chem.,* **1882**, *25*, 273. (h) Nencki, M. and Stoeber, E., *Ber.,* **1897**, *30*, 1768.

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Nenitzescu Synthesis
(Darzens-Nenitzescu Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Nenitzescu in 1931.[1] It is the formation of an α,β-unsaturated ketone directly by aluminum chloride-promoted acylation of alkenes with acyl halides. Therefore, it is generally known as the Nenitzescu synthesis.[2] Occasionally, it is also referred to as the Nenitzescu acylation,[2d] or Nenitzescu reductive acylation (or Darzens-Nenitzescu reaction).[3] Under such reaction conditions, Nenitzescu prepared 2-butenyl methyl ketone from acetyl chloride and 1-butene,[4] and dimethylacetylcyclohexene from acetyl chloride and cyclooctene.[5] However, in the presence of benzene or hexane, the saturated ketones are often resolved, as supported by the preparation of 4-phenyl cyclohexyl methyl ketone from the reaction of cyclohexene and acetyl chloride in benzene[6] and the synthesis of 3- or 4-methylcyclohexyl methyl ketone by refluxing the mixture of cycloheptene and acetyl chloride in cyclohexane or isopentane.[5b,7] The formation of the saturated ketones is probably caused by the intermolecular hydrogen transfer from the solvent.[8] In addition, owing to its intrinsic strain, cyclopropyl group reacts in a manner similar to an olefinic functionality so that it can be readily acylated too.[9] It should be pointed out that under various reaction conditions, the Nenitzescu synthesis is often complicated with the formation of β-halo ketones, β,γ-enones, or β-acyloxy ketones.[8,10] This complication can be overcome by an aluminum chloride-promoted acylation with vinyl mercuric chloride, resulting in a high purity of stereochemistry.[11]

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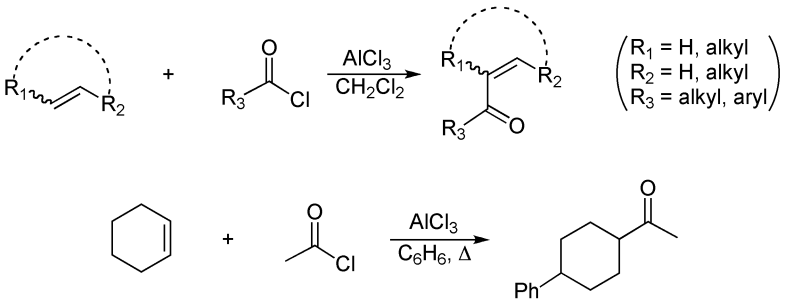
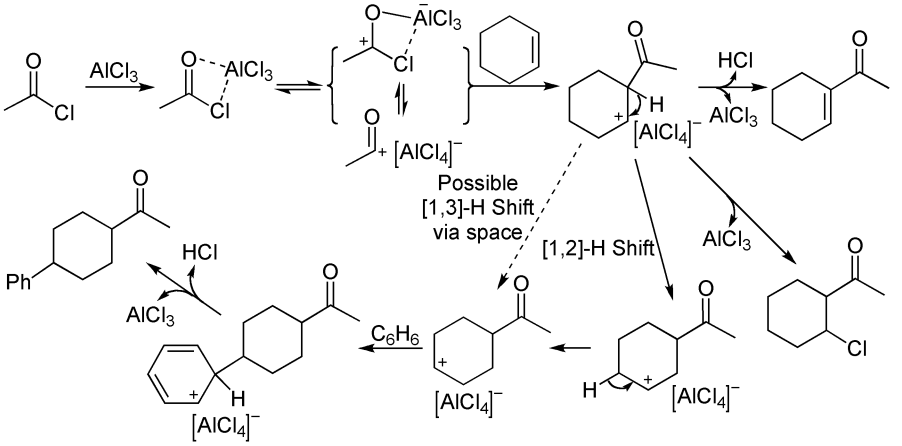
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Although the mechanism for the formation of acetylcyclohexane is known,[3] an alternative mechanism is proposed here for the acylation of cyclohexene with acetyl chloride. In this reaction, after the acyl cation is added to double bond, the elimination of the α-proton gives an α,β-unsaturated ketone, whereas the attack of chloride produces a β-chloroketone. Because acetyl is an electron-withdrawing group, it is plausible that the positive charge migrates to form a more stable carbocation, which electrophilically alkylates with benzene.



D. MODIFICATION

The formation of α,β-unsaturated ketones has been modified by the acylation of vinyl mercuric chloride.[11] In addition, this reaction has been extended to the acylation of alkynes,[10] and a zinc chloride-promoted acylation of olefins.[12]

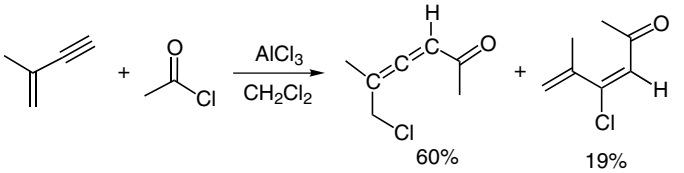
E. APPLICATIONS

This reaction has general application in the preparation of α,β-unsaturated ketones.

F. RELATED REACTIONS

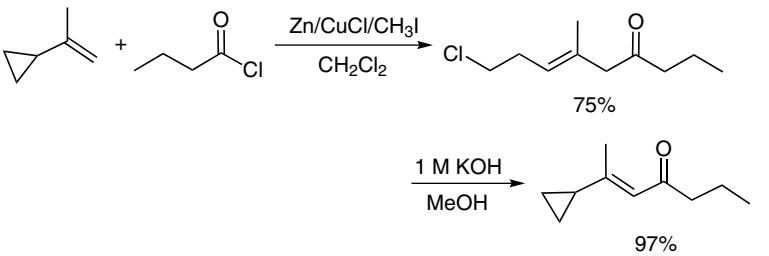
This reaction is related to the *Friedel-Crafts Acylation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 10.

A mixture of 3.33 g $AlCl_3$ (25 mmol), 1.96 mL acetyl chloride (27.5 mmol, 1.1 eq.), and 45 mL anhydrous CH_2Cl_2 was stirred until dissolution. The resulting solution was stirred for 3 min at 20 mmHg and then cooled to −90°C; 2.86 mL 2-methyl-1-buten-3-yne (30 mmol, 1.2 eq.) in 30 mL anhydrous CH_2Cl_2 was slowly added over 2 h. The solution was allowed to warm to −60°C, the mixture was stirred until the completion of reaction as monitored by TLC, and then it was transferred to a vigorously stirred mixture of crushed ice and Et_2O. The organic layer was quickly stirred with a saturated solution of $NaHCO_3$ and dried using $MgSO_4$ and stored in a refrigerator. After filtration and concentration in vacuo at room temperature, the crude product was quickly flash chromatographed on silica gel, eluting with a gradient of pentane-ether to afford 60% 5-methyl-6-chloro-3,4-hexadien-2-one, and 19% 5-methyl-4-chloro-3,5-hexadien-2-one, which were stored in refrigerator.



Reference 12.

A mixture of 6.54 g zinc dust (0.10 mol) and 0.99 g cuprous chloride (0.01 mol) in 30 mL CH_2Cl_2 was refluxed with stirring under nitrogen for 30 min. After the mixture was cooled to room temperature, 7.1 g iodomethane (0.05 mol) was added, and the mixture was then refluxed for an additional hour. Into the solution of the freshly prepared active zinc compounds was added 4.11 g 2-cyclopropyl-propene (0.05 mol) in 10 mL CH_2Cl_2 at 0–5°C under nitrogen with stirring. After a short period, 10 mL CH_2Cl_2 solution containing 1.07 g butyryl chloride (0.010 mol) was added dropwise into the stirred mixture over 15 min at 15–20°C with external cooling. An exothermic reaction took place, and the mixture

gradually turned red-brown. The reaction mixture was stirred at room temperature for 2 h and then was refluxed for another 2 h. After that, 30 mL10% H_2SO_4 was carefully added into the mixture under cooling with an ice water bath. The reaction mixture was filtered with suction and extracted with ether (3 × 50 mL). The combined ethereal solution was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated to give a mixture of products, which was purified to give 75% 9-chloro-6-methyl-6-en-4-nanone. This product upon treatment with 1 M KOH in methanol gave 97% 1-cyclopropyl-2-en-hept-4-one.

Other references related to the Nenitzescu synthesis are cited in the literature.[13]

H. REFERENCES

1. Nenitzescu, C. D. and Ionescu, C. N., *Finn.,* **1931**, *491*, 189.
2. (a) Borisov, A. M.; Kamanina, N. A. and Velikorodov, A. V., *Russ. J. Org. Chem.,* **2007**, *43*, 414. (b) Lyubchanskaya, V. M.; Sarkisova, L. S.; Alekseyeva, L. M.; Kuleshova, Ye. F.; Sheinker, Yu. N. and Granik, V. G., *Khim.-Farmatsevticheskii Zh.,* **1992**, *26*, 108. (c) Palaghita, M. and Raileanu, D., *Revue Roumaine Chim.,* **1988**, *33*, 953. (d) Patrick, J. B. and Saunders, E. K., *Tetrahedron Lett*., **1979**, 4009. (e) Raileanu, D.; Palaghita, M. and Nenitzescu, C. D., *Tetrahedron*, **1971**, *27*, 5031.
3. Otvos, L.; Tudos, H. and Szabolcs, A., *Acta Chim. Acad. Sci. Hungaricae,* **1972**, *71*, 193.
4. Nenitzescu, C. D. and Gavat, I. G., *Ann.,* **1935**, *519*, 260.
5. (a) Nenitzescu, C. D., *Aliphatic Acylation* in *Friedel-Crafts and Related Reactions*, ed. Olah, G. A., Interscience Publishers, New York, **1964**, *3*, p. 1125. (b) Nenitzescu, C. D., Pogany, I. and Mihai, G., *Acad. Rep. Populare Romine, Studii Cercetari Chim.,* **1958**, *6*, 375 [*Chem. Abstr.,* **1950**, *53*, 18885o].
6. Johnson, W. S. and Offenhauer, R. D., *J. Am. Chem. Soc.,* **1945**, *67*, 1045.
7. Friess, S. L. and Pinson, R., *J. Am. Chem. Soc.,* **1951**, *73*, 3512.
8. Rand, L. and Dolinski, R. J., *J. Org. Chem.,* **1966**, *31*, 3063.
9. Doyle, M. P.; Elliott, R. C. and Dellaria, J. F., *J. Org. Chem.,* **1978**, *43*, 4459.
10. Santelli-Rouvier, C.; Lefrère, S. and Santelli, M., *J. Org. Chem.,* **1996**, *61*, 6678.
11. Larock, R. C. and Bernhardt, J. C., *J. Org. Chem.,* **1978**, *43*, 710.
12. Shono, T.; Nishiguchi, I.; Sasaki, M.; Ikeda, H. and Kurita, M., *J. Org. Chem.,* **1983**, *48*, 2503.
13. (a) Morel-Fourrier, C.; Dulcere, J.-P. and Santelli, M., *J. Am. Chem. Soc.,* **1991**, *113*, 8062. (b) Snider, B. B. and Jackson, A. C., *J. Org. Chem.,* **1982**, *47*, 5393. (c) Hoffmann, H. M. R. and Tsushima, T., *J. Am. Chem. Soc.,* **1977**, *99*, 6008. (d) Cantrell, T. S., *J. Org. Chem.,* **1967**, *32*, 1669. (e) Rand, L. and Dolinski, R. J., *J. Org. Chem.,* **1966**, *31*, 4061. (f) Stevens, C. L. and Farkas, E., *J. Am. Chem. Soc.,* **1953**, *75*, 3306. (g) Nenitzescu, C. D. and Gavat, I. G., *Ber.,* **1937**, *70*, 1883. (h) Nenitzescu, C. D. and Cioranescu, E., *Ber.,* **1936**, *69*, 1820. (i) Nenitzescu, C. D. and Chicos, I., *Ber.,* **1935**, *68*, 1584. (j) Nenitzescu, C. D. and Cantuniari, I. P., *Ann.,* **1934**, *510*, 269.

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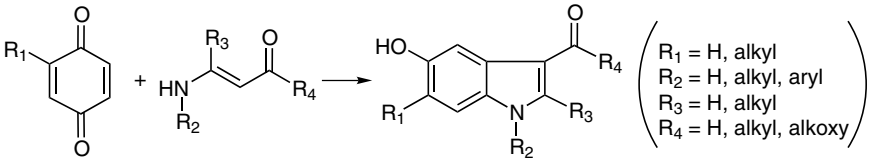
Nenitzescu Indole Synthesis

(Nenitzescu Reaction, Nenitzescu Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Nenitzescu in 1929.[1] It is the synthesis of a 5-hydroxyindole derivative involving the condensation between a 1,4-benzoquinone and a β-amino-α,β-unsaturated compound and subsequent cyclization. Therefore, this reaction is generally known as the Nenitzescu indole synthesis,[2] Nenitzescu reaction,[2e,2g,2i,2j,3] or Nenitzescu synthesis.[2g,2j,4] Occasionally, it is also referred to as the Nenitzescu cyclization,[5] Nenitzescu condensation,[2g,2l] or Nenitzescu process.[6] It should be pointed out that the synthesized indole derivatives by this reaction are restricted to those with an electron-withdrawing group at position 3, such as an ester or a carbonyl group.[6] In addition, the completion of this reaction requires an appropriate oxidizing agent to convert the initial adduct into the indole derivative.[2g,2j] From monosubstituted quinone, 4-, 6- and 7-substituted 5-hydroxyindole derivatives all are possible products, but 6-substituted isomer is the one normally obtained.[2k]

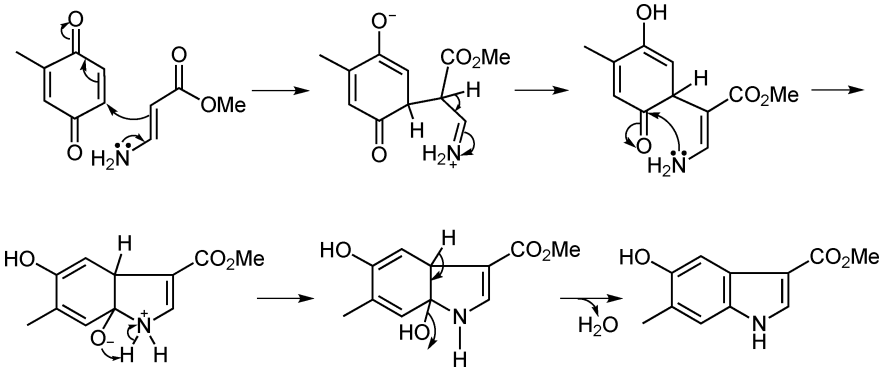
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

Two kinds of mechanisms are possible for the Nenitzescu indole synthesis, depending on the order of carbon-carbon bond and carbon-nitrogen bond formation.[2g,2l,2m,3u,3v] However, the one involving the initial carbon-carbon condensation is more plausible as illustrated here for the reaction between 2-methyl 1,4-benzoquinone and β-amino methyl crotonate.[2g]



D. MODIFICATION

This reaction has been modified by using quinone mono-ketals to control the regioselectivity.[2e] In addition, an *aza*-Nenitzescu reaction involving the condensation between quinones and hydrazones has been developed for the synthesis of indazole derivatives.[7]

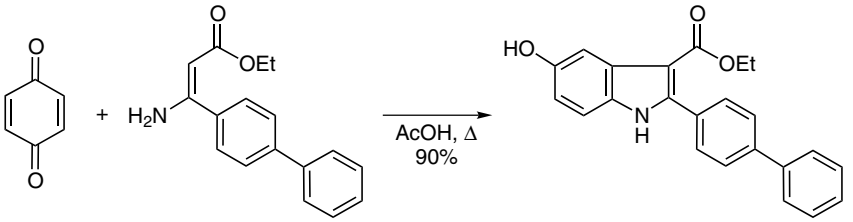
E. APPLICATIONS

This reaction is particularly useful for the preparation of 5-hydroxyindole derivatives.

F. RELATED REACTIONS

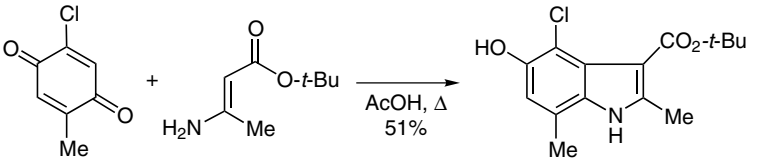
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 8.

1,4-Benzoquinone (1.71 g, 15.8 mmol) and 3.5 g ethyl 3-amino-3-(4-biphenylyl)-propenoate (9.8 mmol) in 50 mL acetic acid were refluxed for 1 h. After cooling, the crude product was precipitated out with light petroleum ether and filtered off, which was purified by column chromatography (EtOAc) and recrystallization (EtOAc) to yield 4.21 g ethyl 2-(4-biphenylyl)-5-hydroxyindole-3-carboxylate as a colorless solid, in a yield of 90%, m.p., 260–262°C.



Reference 2i.

To a hot solution of 3.12 g 5-chloro-2-methyl-l,4-*p*-benzoquinone (19.9 mmol) in 15 mL acetic acid, was added 3.14 g *t*-butyl-3-aminocrotonate (20 mmol). After 30 min without the application of heat, the solution was cooled, and the resulting pink precipitate was filtered and washed with chilled acetic acid to give 2.99 g *t*-butyl 4-chloro-5-hydroxy-2,7-dimethylindole-3-carboxylate, in a yield of 51%, m.p. 178–180°C (dec.)

Other references related to the Nenitzescu indole synthesis are cited in the literature.[9]

H. REFERENCES

1. Nenitzeecu, C. D., *Bull. Soc. Chim. Romania,* **1929**, *11*, 37 [*Chem. Abstr.,* **1930**, *24*, 110].
2. (a) Velezheva, V. S.; Kornienko, A. G.; Topilin, S. V.; Turashev, A. D.; Peregudov, A. S. and Brennan, P. J., *J. Heterocycl. Chem.,* **2006**, *43*, 873. (b) Ketcha, D. M.; Wilson, L. J. and Portlock, D. E., *Tetrahedron Lett*., **2000**, *41*, 6253. (c) Mayadeo, M. S. and Gandhi, S. A., *J. Indian Chem. Soc.,* **1994**, *71*, 281. (d) Luly, J. R. and Rapoport, H., *J. Am. Chem. Soc.,* **1983**, *105*, 2859. (e) Coates, R. M. and MacManus, P. A., *J. Org. Chem.,* **1982**, *47*, 4822. (f) Aggarwal, V.; Kumar, A.; Ila, H. and Junjappa, H., *Synthesis*, **1981**, 157. (g) Littell, R.; Morton, G. O. and Allen, G. R., *J. Am. Chem. Soc.,* **1970**, *92*, 3740. (h) Littell, R.; Morton, G. O. and Allen, G. R., *J. Am. Chem. Soc.,* **1970**, *92*, 3740. (i) Poletto, J. F. and Weiss, M. J., *J. Org. Chem.,* **1970**, *35*, 1190. (j) Allen, G. R. and Weiss, M. J., *J. Org. Chem.,* **1968**, *33*, 198. (k) Littell, R. and Allen, G. R., *J. Org. Chem.,* **1968**, *33*, 2064. (l) Allen, G. R.; Pidacks, C. and Weiss, M. J., *J. Am. Chem. Soc.,* **1966**, *88*, 2536. (m) Allen, G. R. and Weiss, M. J., *Chem. Ind. (London),* **1966**, 117. (n) Allen, G. R.; Pidacks, C. and Weiss, M. J., *Chem. Ind. (London),* **1965**, 2096.
3. (a) Lyubchanskaya, V. M.; Panisheva, E. K.; Savina, S. A.; Alekseeva, L. M.; Shashkov, A. S. and Granik, V. G., *Russ. Chem. Bull.,* **2005**, *54*, 1690. (b) Landwehr, J. and Troschuetz, R., *Synthesis*, **2005**, 2414. (c) Mukhanova, T. I.; Alekseeva, L. M.; Shashkov, A. S. and Granik, V. G., *Chem. Heterocycl. Compd.,* **2005**, *41*, 221. (d) Shefali, S. K. S.; Husbands, S. M. and Lewis, J. W., *J. Med. Chem.,* **2005**, *48*, 635. (e) Lyubchanskaya, V. M.; Savina, S. A.; Alekseeva, L. M.; Shashkov, A. S.; Chernyshev, V. V. and Granik, V. G., *Russ. Chem. Bull.,* **2004**, *53*, 2834. (f) Mukhanova, T. I.; Alekseeva, L. M.; Shashkov, A. S. and Granik, V. G., *Chem. Heterocycl. Compd.,* **2004**, *40*, 16. (g) Dotzauer, B. and Troschuetz, R., *Synlett*, **2004**, 1039. (h) Lyubchanskaya, V. M.; Alekseeva, L. M.; Savina, S. A.; Shashkov, A. S. and Granik, V. G., *Chem. Heterocycl. Compd.,* **2003**, *39*, 872. (i) Lyubchanskaya, V. M.; Alekseeva, L. M.; Savina, S. A. and Granik, V. G., *Chem. Heteroccyl. Compd.,* **2000**, *36*, 1276. (j) Kucklander, U. and Lessel, U., *J. Prakt. Chem.,* **2000**, *342*, 17.

(k) Alekseeva, L. M.; Lyubchanskaya, V. M.; Mukhanova, T. I.; Panisheva, E. K. and Granik, V. G., *Chem. Heterocycl. Compd.,* **1997**, *33*, 282. (l) Mukhanova, T. I.; Panisheva, E. K.; Lyubchanskaya, V. M.; Alekseeva, L. M.; Sheinker, Y. N. and Granik, V. G., *Tetrahedron*, **1997**, *53*, 177. (m) Kinugawa, M.; Arai, H.; Nishikawa, H.; Sakaguchi, A.; Ogasa, T.; Tomioka, S. and Kasai, M., *J. Chem. Soc., Perkin Trans. I,* **1995**, 2677. (n) Kucklaender, U. and Lessel, U., *Arch. Pharm.,* **1994**, *327*, 143. (o) Kucklaender, U.; Kuna, K.; Zerta, G. and Poll, W., *Zeitsch. Naturforsch., B,* **1992**, *47*, 1403. (p) Kucklaender, U.; Herweg-Wahl, U. and Kuna, K., *Arch. Pharm.,* **1991**, *324*, 7. (q) Kucklaender, U.; Ulmer, P. and Zerta, G., *Chem. Ber.,* **1989**, *122*, 1493. (r) Bernier, J.-L. and Hénichart, J.-P., *J. Org. Chem.,* **1981**, *46*, 4197. (s) Hiremath, S. P.; Goudar, N. N. and Purohit, M. G., *Indian J. Chem., Sect. B,* **1980**, *19B*, 848. (t) Kucklaender, U. and Edoho, E. J., *Arch. Pharm.,* **1980**, *313*, 582. (u) Kucklaender, U. and Huehnermann, W., *Arch. Pharm.,* **1979**, *312*, 515. (v) Kucklaender, U., *Ann.,* **1978**, 129. (w) Allen, G. R., *Org. React.,* **1973**, *20*, 337. (x) Kucklaender, U., *Arch. Pharm. & Ber. Deutsch. Pharm. Gessellsch.,* **1971**, *304*, 602. (y) Eiden, F. and Kucklaender, U., *Arch. Pharm. & Ber. Deutsch. Pharm. Gessellsch.,* **1971**, *304*, 57. (z) Kucklaender, U., *Tetrahedron Lett*., **1971**, 157.

4. (a) Borisov, A. M.; Kamanina, N. A. and Velikorodov, A. V., *Russ. J. Org. Chem.,* **2007**, *43*, 414. (b) Sheinker, Yu. N. and Granik, V. G., *Khim.-Farmatsevticheskii Zh*., **1992**, *26*, 108. (c) Lyubchanskaya, V. M.; Sarkisova, L. S.; Alekseyeva, L. M.; Kuleshova, Ye. F.; Palaghita, M. and Raileanu, D., *Revue Roumaine Chim.,* **1988**, *33*, 953. (d) Patrick, J. B. and Saunders, E. K., *Tetrahedron Lett*., **1979**, 4009. (e) Raileanu, D.; Palaghita, M. and Nenitzescu, C. D., *Tetrahedron,* **1971**, *27*, 5031.
5. Kondo, Y.; Kojima, S. and Sakamoto, T., *J. Org. Chem.,* **1997**, *62*, 6507.
6. (a) Satomura, M., *J. Org. Chem.,* **1993**, *58*, 6936. (b) Satomura, M., *J. Org. Chem.,* **1993**, *58*, 3757.
7. Lyubchanskaya, V. M.; Alekseeva, L. M. and Granik, V. G.,*Chem. Heterocycl. Compd.,* **1999**, *35*, 570.
8. Beall, H. D.; Winski, S.; Swann, E.; Hudnott, A. R.; Cotterill, A. S.; O'Sullivan, N.; Green, S. J.; Bien, R.; Siegel, D.; Ross, D. and Moody, C. J., *J. Med. Chem.,* **1998**, *41*, 4755.
9. (a) Gribble, G. W., *J. Chem. Soc*., *Perkin Trans. I*, **2000**, 1045. (b) Pawlak, J. M.; Khau, V. V.; Hutchison, D. R. and Martinelli, M. J., *J. Org. Chem.*, **1996**, *61*, 9055. (c) Kamat, A. G.; Joshi, R. G. and Gadaginamath, G. S., *Proc. Indian Acad. Sci., Chem. Sci.,* **1993**, *105*, 189. (d) Lyubchanskaya, V. M.; Alekseeva, L. M. and Granik, V. G., *Chem. Heterocycl. Compounds,* **1992**, *28*, 34. (e) Peter, M. G. and Speckenbach, F., *Helv. Chim. Acta,* **1982**, *65*, 1279. (f) Yamada, Y. and Matsui, M., *Agri. Biol. Chem.,* **1971**, *35*, 282. (g) Raileanu, D. and Nenitzescu, C. D., *Rev. Roumaine Chim.,* **1965**, *10*, 339. (h) Steck, E. A.; Brundage, R. P. and Fletcher, L. T., *J. Org. Chem.,* **1959**, *24*, 1750. (i) Beer, R. J. S.; Davenport, H. F. and Robertson, A., *J. Chem. Soc.,* **1953**, 1262. (j) Beer, R. J. S.; Clark, K.; Davenport, H. F. and Robertson, A., *J. Chem. Soc.,* **1951**, 2029.

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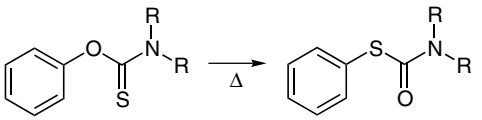
Newman-Kwart Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially and concurrently reported by Newman[1] and Kwart[2] in 1966. It is a thermal transformation of *N*,*N*-dialkyl *O*-arylthiocarbamate into *N*,*N*-dialkyl *S*-arylcarbamate. Therefore, it is generally known as the Newman-Kwart rearrangement.[3] Occasionally, it is also referred to as the Newman-Kwart reaction,[3g,4] Newman-Kwart synthesis,[5] or Miyazaki-Newman-Kwart rearrangement.[6] It has been found that the *ortho*-substituent in the migrating aromatic ring may enhance the rearrangement rate, the effect known as the steric acceleration due to hindered rotation (SAHR).[3m] In addition, for the rearrangement of *O*-binaphthol thiocarbamate into dithiol derivative, the stereochemistry is retained.[7]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Similar to the *Barton Decarboxylation* and *Barton Deoxygenation*, it is assumed that this reaction also involves a free radical mechanism, as proposed below.

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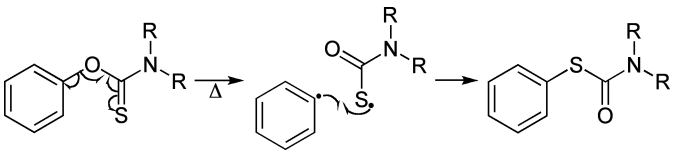


D. MODIFICATION

N/A

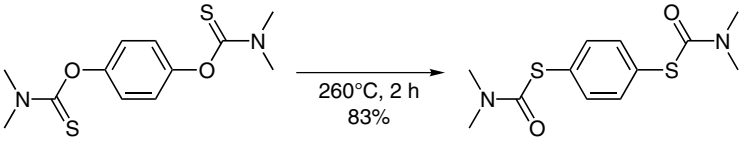
E. APPLICATIONS

This reaction has been used to prepare thio-analogs of binaphthol[7] and 1,4-dithiophenol[3g] derivatives.

F. RELATED REACTIONS

This reaction is related to the *Schönberg Rearrangement*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 3g.

The bis-(*N*,*N*′-dimethylthiocarbamate) (10.0 g, 0.035 mol) was heated in the bulk at 260°C under nitrogen for 2 h. After cooling, the remaining material was crystallized from chloroform/methanol and further recrystallized from methyl ethyl ketone to afford 8.3 g bis-(*N*,*N*′-dimethyl-*S*-carbamate), in a yield of 83%, m.p. 201–203°C.

Other references related to the Newman-Kwart rearrangement are cited in the literature.[8]

H. REFERENCES

1. Newman, M. S. and Karnes, H. A., *J. Org. Chem.,* **1966**, *31*, 3980.
2. Kwart, H. and Evans, E. R., *J. Org. Chem.,* **1966**, *31*, 410.
3. (a) Moseley, J. D. and Lenden, P., *Tetrahedron*, **2007**, *63*, 4120. (b) Jacobsen, H. and Donahue, J. P., *Can. J. Chem.,* **2006**, *84*, 1567. (c) Moseley, J. D.; Sankey, R. F.; Tang, O. N. and Gilday, J. P.,

Tetrahedron, **2006**, *62*, 4685. (d) Kusch, D., *Speciality Chem. Mag.,* **2003**, *23*, 41. (e) Prabhakar, S.; Kar, P.; Mirza, S. P.; Lakshmi, V. V. S.; Nagaiah, K. and Vairamani, M., *Rapid Commun. Mass Spect.,* **2001**, *15*, 2127. (f) Lin, S.; Moon, B.; Porter, K. T.; Rossman, C. A.; Zennie, T. and Wemple, J., *Org. Prep. Proc. Int.,* **2000**, *32*, 547. (g) Ding, Y.; Hlil, A. R.; Hay, A. S.; Tsuchida, E. and Miyatake, K., *Macromolecules,* **1999**, *32*, 315. (h) Cossu, S.; De Lucchi, O.; Fabbri, D.; Valle, G.; Painter, G. F. and Smith, R. A. J., *Tetrahedron*, **1997**, *53*, 6073. (i) de Lucchi, O., *Pure & Appl. Chem.,* **1996**, *68*, 945. (j) Hanefeld, W.; Von Goesseln, H. J., *Liebigs Ann. Chem*., **1991**, 405. (k) Wagenaar, A. and Engberts, J. B. F. N., *Rec. J. Royal Netherlands Chem. Soc.,* **1982**, *101*, 91. (l) Kurth, H. J.; Kraatz, U. and Korte, F., *Chem. Ber.,* **1973**, *106*, 2419. (m) Relles, H. M. and Pizzolato, G., *J. Org. Chem.,* **1968**, *33*, 2249.

4. Kane, V. V.; Gerdes, A.; Grahn, W.; Ernst, L.; Dix, I.; Jones, P. G. and Hopf, H., *Tetrahedron Lett*., **2001**, *42*, 373.
5. Besserer, K.; Koehler, H. and Rundel, W., *Chem. Ber.,* **1982**, *115*, 3678.
6. Zonta, C.; De Lucchi, O.; Volpicelli, R. and Cotarca, L., *Top. Curr. Chem.,* **2007**, *275*, 131.
7. Fabbri, D.; de Lucchi, O. and Delogu, G., *J. Org. Chem.,* **1993**, *58*, 1748.
8. (a) Li, P. K.; Pillai, R.; Young, B. L.; Bender, W. H.; Martino, D. M. and Lin, F. T., *Steroids*, **1993**, *58*, 106. (b) Garcia, C.; Andraud, C. and Collet, A., *Supramolecular Chem*., **1992**, *1*, 31. (c) Kajino, M.; Mizuno, K.; Tawada, H.; Shibouta, Y.; Nishikawa, K. and Meguro, K., *Chem. Pharm. Bull.,* **1991**, *39*, 2888. (d) Lau, C. K.; Belanger, P. C.; Dufresne, C. and Scheigetz, J., *J. Org. Chem.,* **1987**, *52*, 1670. (e) Hori, M.; Ban, M.; Imai, E.; Iwata, N.; Suzuki, Y.; Baba, Y.; Morita, T.; Fujimura, H.; Nozaki, M. and Niwa, M., *J. Med. Chem.,* **1985**, *28*, 1656. (f) Hori, M.; Ban, M.; Imai, E.; Iwata, N.; Baba, Y.; Fujimura, H.; Nozaki, M. and Niwa, M., *Heterocycles*, **1983**, *20*, 2359. (g) Rahman, L. K. A. and Scrowston, R. M., *J. Chem. Soc., Perkin Trans. I,* **1983**, 2973. (h) Kurth, H. J.; Kraatz, U. and Korte, F., *Ann.,* **1976**, 1313. (i) Kurth, H. J.; Kraatz, U. and Korte, F., *Chem. Ber.,* **1976**, *109*, 2164. (j) Rundel, W. and Koehler, H., *Chem. Ber.,* **1972**, *105*, 1087.

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Nicholas Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Nicholas et al. in 1971.[1] It is a nucleophilic substitution on a propargylic alcohol, ether or ester by a carbon or heteroatom nucleophile involving the generation of a carbocation by a strong Lewis acid, stabilization of the propargylic cation via the formation of hexacarbonyldicobalt alkyne complex, and final liberation of alkyne moiety by oxidation with cerium ammonium nitrate or *N*-methylmorpholine *N*-oxide.[2] Therefore, this reaction is generally known as the Nicholas reaction.[2,3] Occasionally, it is also referred to as the Nicholas cyclization,[3i,3l,3x] or Nicholas propargylic substitution.[4] In this reaction, the propargylic cation can be generated by the treatment of a propargylic alcohol[3e,3i–3l,3p,3cc,3qq,5] ether,[3e,3j,3p,3q,3cc,3qq] or ester[3j,3q,3aa] (including acetate[3m,3q]) from a strong Lewis acid, such as $BF_3{\cdot}OEt_2$,[3e] $TiCl_4$,[3e] or $GeCl_4$.[3e] Among these Lewis acids, $BF_3{\cdot}OEt_2$ is the most commonly used acid for the Nicholas reaction.[3e] While some milder Lewis acids such as $MgBr_2$, LiCl, LiBr, and $ZnBr_2$, are not strong enough for this reaction,[3e] the mild acid of Montmorillonite K-10 is found to be an effective promoter.[6] In addition, the nucleophile can be either a carbon-nucleophile (such as an enolate,[3cc,5] arene,[3q] or a heterocycle[3m]) or a hetero-atom nucleophile (e.g., an alcohol,[3l,3aa] epoxide,[3i] or a carboxylic acid).[3f] Beacuse the cobalt-mediated cyclization is reversible,[3l] there exists an equilibrium at the propargylic center through a fluxional cationic intermediate; thus the original stereochemistry of the substrate is usually lost upon treatment by a Lewis acid.[3bb] It should be pointed out that the application of an Evans's oxazoline enolate in coupling with a propargylic cation to generate high stereoselectivity (i.e., in favor of the *syn*-adduct) is specifically referred to as the Nicholas-Schreiber reaction.[3cc]

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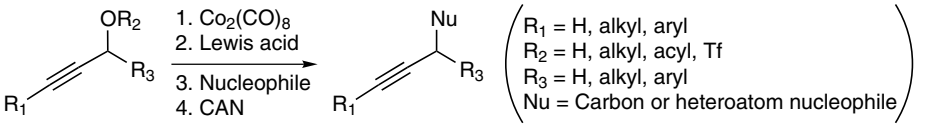
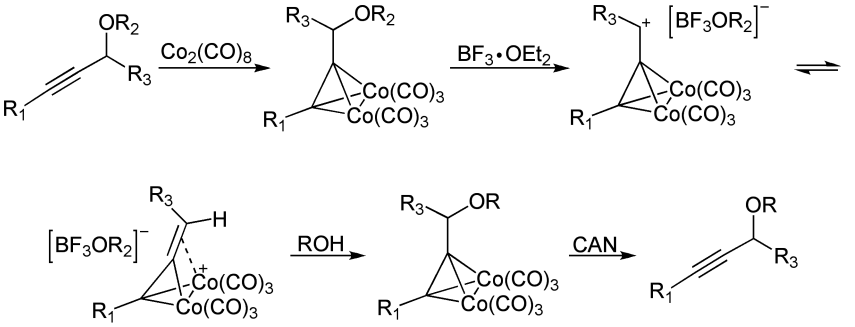
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A general mechanism is illustrated below to demonstrate the stabilization of propargylic cation from the cobalt complex, in which a general alcohol is used as a representative nucleophile.



D. MODIFICATION

Some of the modifications for the Nicholas reaction include the fixation of a propargylic substrate onto a solid phase,[3e] application of montmorillonite K-10 as acid to generate the propargylic cation,[6] complexation of alkyne with a ruthenium complex,[3d] and application of tetrabutylammonium fluoride for decomplexation.[3aq]

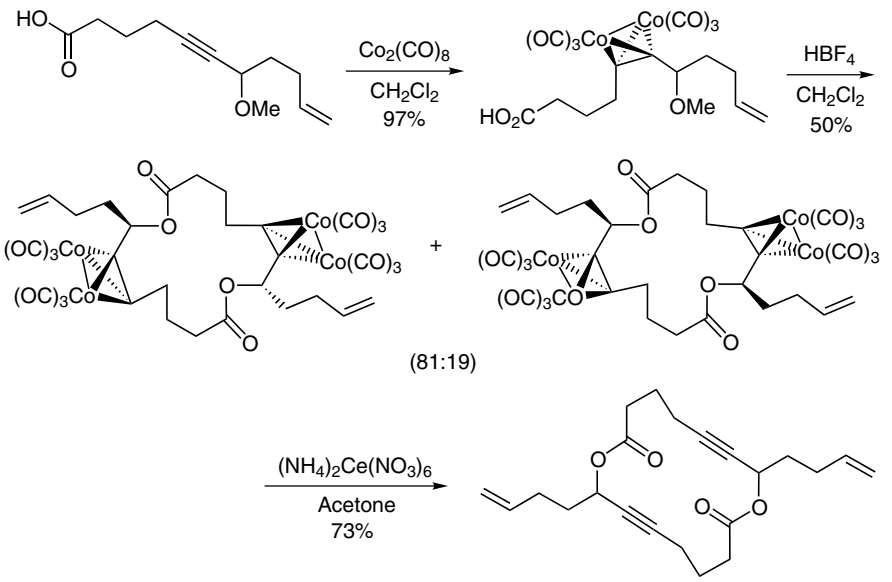
E. APPLICATIONS

This reaction is especially useful for the formation of cyclic ethers,[3i,3l,3aa] and macrocycles.[3m,3q,5]

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3f.

A flame-dried, round-bottomed flask equipped with a septum and gas inlet needle was charged with 253 mg 7-methoxyundec-10-en-5-ynoic acid (1.20 mmol) and placed under a nitrogen atmosphere. Then 2.5 mL CH_2Cl_2 was added followed by 494 mg $Co_2(CO)_8$ (1.44 mmol, 1.2 eq.) to yield a dark red/black solution that was stirred at room temperature for 30 min. A second portion of $Co_2(CO)_8$ (165 mg, 0.481 mmol, 0.4 eq.) was added and the reaction was allowed to stir at room temperature for an additional 30 min. The reaction mixture was added directly to a 60-g silica gel column eluting with 10–35% ether in petroleum ether to afford 577 mg 7-methoxyundec-10-en-5-ynoic acid hexacarbonyl dicobalt complex as a thick red oil, in a yield of 97%.

A flame-dried, round-bottomed flask equipped with a septum and gas inlet adapter was charged with 577 mg cobalt complex (1.16 mmol) and placed under a nitrogen atmosphere. CH_2Cl_2 was added, and the resulting dark red/black solution was cooled at 0°C. Then 0.16 mL 54% HBF_4 in ether (1.16 mmol) was added, and the reaction mixture was stirred at 0°C for 1 h. The reaction was quenched while still cold by the addition of 15 mL saturated $NaHCO_3$. The aqueous layer was removed, and the organic phase was dried over $MgSO_4$ and added to a sintered glass funnel packed with silica gel. Rinsing with 400 mL CH_2Cl_2 furnished 269 mg 8,16-dibut-3-enyl-1,9-dioxacyclohexadeca-6,14-diyne-2,10-dione hexacarbonyl dicobalt complex as a bright red/orange solid, in a yield of 50%, m.p. 124–125°C (dec).

A round-bottomed flask was charged with 53 mg 8,16-dibut-3-enyl-1,9-dioxacyclohexadeca-6,14-diyne-2,10-dione hexacarbonyl dicobalt complex (0.0534 mmol) and 12 mL acetone to yield a red suspension. The reaction flask was cooled at 0°C, and 472 mg cerium ammonium nitrate (CAN) (0.86 mmol) was added in eight portions (59 mg/portion) over 5 min. The cooling bath was removed, and the reaction was allowed to stir at room

temperature for 4 h. The resulting yellow-orange suspension was concentrated to yield a yellow solid that was transferred to a flask containing CH_2Cl_2 and water. The organic layer was separated, dried over $MgSO_4$, and concentrated to yield 21 mg yellow oil that was deposited on 40 mg silica gel and added to a 2-g silica gel column eluting with 5% ether in petroleum ether to afford 14 mg 8,16-dibut-3-enyl-1,9-dioxacyclohexadeca-6,14-diyne-2,10-dione as a white film, in a yield of 73%.

Other references related to the Nicholas reaction are cited in the literature.[7]

H. REFERENCES

1. Nicholas, K. M. and Pettit, R., *Tetrahedron Lett.,* **1971**, *37*, 3475.
2. Fischer, S., *Synlett,* **2002**, 1558.
3. (a) Diaz, D. D.; Betancort, J. M. and Martin, V. S., *Synlett*, **2007**, 343. (b) Konno, T.; Nagai, G. and Ishihara, T., *J. Fluor. Chem.,* **2006**, *127*, 510. (c) DiMartino, J. and Green, J. R., *Tetrahedron*, **2006**, *62*, 1402. (d) Ortega, N.; Martín, T. and Martín, V. S., *Org. Lett.,* **2006**, *8*, 871. (e) Gachkova, N.; Cassel, J.; Leue, S. and Kann, N., *J. Comb. Chem.,* **2005**, *7*, 449. (f) Shea, K. M.; Closser, K. D. and Quintal, M. M., *J. Org. Chem.,* **2005**, *70*, 9088. (g) Ding, Y. and Green, J. R., *Synlett,* **2005**, 271. (h) Guo, R.; Gibe, R. and Green, J. R., *Can. J. Chem.,* **2004**, *82*, 366. (i) Crisóstomo, F. R. P.; Martín, T. and Martín, V. S., *Org. Lett.,* **2004**, *6*, 565. (j) Quintal, M. M.; Closser, K. D. and Shea, K. M., *Org. Lett.,* **2004**, *6*, 4949. (k) Cadierno, V.; Díez, J.; Carcía-Garrido, S. E. and Gimeno, J., *Chem. Commun.,* **2004**, 2716. (l) Takase, M.; Morikawa, T.; Abe, H. and Inouye, M., *Org. Lett.,* **2003**, *5*, 625. (m) Gibe, R.; Green, J. R. and Davidson, G., *Org. Lett.,* **2003**, *5*, 1003. (n) Álvaro, E.; de la Torre, M. C. and Sierra, M. A., *Org. Lett.,* **2003**, *5*, 2381. (o) Teobald, B. J., *Tetrahedron*, **2002**, *58*, 4133. (p) Cassel, J. A.; Leue, S.; Gachkova, N. I. and Kann, N. C., *J. Org. Chem.,* **2002**, *67*, 9460. (q) Gibe, R. and Green, J. R., *Chem. Commun.,* **2002**, 1550. (r) Montana, A. M. and Cano, M., *Magnet. Res. Chem.,* **2002**, *40*, 261. (s) Mukai, C.; Yamashita, H.; Sassa, M. and Hanaoka, M., *Tetrahedron*, **2002**, *58*, 2755. (t) Tyrrell, E.; Skinner, G. A. and Bashir, T., *Synlett*, **2001**, 1929. (u) Montana, A. M. and Cano, M., *Tetrahedron Lett*., **2001**, *42*, 7961. (v) Diaz, D. and Martin, V. S., *Tetrahedron Lett*., **2000**, *41*, 743. (w) Montana, A. M. and Fernandez, D., *Tetrahedron Lett*., **1999**, *40*, 6499. (x) Hosokawa, S. and Isobe, M., *J. Org. Chem.,* **1999**, *64*, 37. (y) Mann, A.; Muller, C. and Tyrrell, E., *J. Chem. Soc., Perkin Trans. I,* **1998**, 1427. (z) Berge, J.; Claridge, S.; Mann, A.; Muller, C. and Tyrrell, E., *Tetrahedron Lett*., **1997**, *38*, 685. (aa) Isobe, M.; Tsuboi, K.; Hosokawa, S.; Bamba, M.; Kira, K.; Shibuya, S.; Ohtani, I. I.; Nishikawa, T. and Ichikawa, Y., *Pure & Appl. Chem.,* **1997**, *69*, 401. (bb) Jamison, T. F.; Shambayati, S.; Crowe, W. E. and Schreiber, S. L., *J. Am. Chem. Soc.,* **1997**, *119*, 4353. (cc) Jacobi, P. A.; Murphree, S.; Rupprecht, F. and Zheng, W. J., *J. Org. Chem.,* **1996**, *61*, 2413. (dd) Tyrrell, E.; Claridge, S.; Davis, R.; Lebel, J. and Berge, J., *Synlett*, **1995**, 714. (ee) Tanaka, S. and Isobe, M., *Synthesis*, **1995**, 859. (ff) Muehldorf, A. V.; Guzman-Perez, A. and Kluge, A. F., *Tetrahedron Lett*., **1994**, *35*, 8755. (gg) Tanaka, S.; Tatsuta, N.; Yamashita, O. and Isobe, M., *Tetrahedron*, **1994**, *50*, 12883. (hh) Tyrrell, E.; Heshmati, P. and Sarrazin, L., *Synlett*, **1993**, 769. (ii) Maier, M. E. and Brandstetter, T., *Liebigs Ann. Chem*., **1993**, 1009. (jj) Jacobi, P. A. and Zheng, W. J., *Tetrahedron Lett*., **1993**, *34*, 2581. (kk) Jacobi, P. A. and Zheng, W. J., *Tetrahedron Lett*., **1993**, *34*, 2585. (ll) Roth, K. D. and Mueller, U., *Tetrahedron Lett*., **1993**, *34*, 2919. (mm) Takano, S.; Sugihara, T. and Ogasawara, K., *Synlett,* **1992**, 70. (nn) Turuta, A. M.; Kamernitskii, A. V.; Luu, D. H. and Fadeeva, T. M., *Izv. Akad. Nauk SSSR, Ser. Khim*., **1991**, 1180. (oo) Jeong, N.; Yoo, S. E.; Lee, S. J.; Lee, S. H. and Chung, Y. K., *Tetrahedron Lett*., **1991**, *32*, 2137. (pp) Nakagawa, M.; Ma, J. and Hino, T.,*Heterocycles*, **1990**, *30*, 451. (qq) Schreiber, S. L.; Sammakia, T. and Crowe, W. E., *J. Am. Chem. Soc.,* **1986**, *108*, 3128.
4. Soleilhavoup, M.; Saccavini, C.; Lepetit, C.; Lavigne, G.; Maurette, L.; Donnadieu, B. and Chauvin, R., *Organometallics,* **2002**, *21*, 871.

5. Magnus, P. and Fortt, S. M., *J. Chem. Soc., Chem. Commun.,* **1991**, 544.

6. Crisóstomo, F. R. P.; Carrillo, R.; Martín, T. and Martín, V. S., *Tetrahedron Lett.,* **2005**, *46*, 2829.

7. (a) Díaz, D. D.; Ramírez, M. A. and Martín, V. S., *Chem. Eur. J.,* **2006**, *12*, 2593. (b) Bustelo, E. and Dixneuf, P. H., *Adv. Synth. Catal.,* **2005**, *347*, 393. (c) Montaña, A. M. and Grima, P. M., *Synth. Commun.,* **2003**, *33*, 265. (d) Kira, K.; Tanda, H.; Hamajima, A.; Baba, T.; Takai, S. and Isobe, M., *Tetrahedron,* **2002**, *58*, 6485. (e) Marco-Contelles, J. and de Opazo, E., *J. Carbohydr. Chem.,* **2002**, *21*, 201. (f) Montana, A. M. and Cano, M., *Tetrahedron,* **2002**, *58*, 933. (g) Green, J. R., *Curr. Org. Chem.,* **2001**, *5*, 809. (h) Lu, Y. and Green, J. R., *Synlett,* **2001**, 243. (i) Müller, T. J. J., *Eur. J. Org. Chem.,* **2001**, 2021. (j) Guo, R. and Green, J. R., *Synlett,* **2000**, 746. (k) Castro, J.; Moyano, A.; Pericàs, M. A.; Riera, A.; Maestro, M. A. and Mahía, J., *Organometallics,* **2000**, *19*, 1704. (l) Mukai, C.; Yamaguchi, S.; Sugimoto, Y.; Miyakoshi, N.; Kasamatsu, E. and Hanaoka, M., *J. Org. Chem.,* **2000**, *65*, 6761. (m) Patel, M. M. and Green, J. R., *Chem. Commun.,* **1999**, 509. (n) Guo, R. and Green, J. R., *Chem. Commun.,* **1999**, 2503. (o) Green, J. R., *Chem. Commun.,* **1998**, 1751. (p) Kuhn, O.; Rau, D. and Mayr, H., *J. Am. Chem. Soc.,* **1998**, *120*, 900. (q) Nicholas, K. M., *Acc. Chem. Res.,* **1987**, *20*, 207. (r) Nicholas, K. M. and Siegel, J., *J. Am. Chem. Soc.,* **1985**, *107*, 4999. (s) Nicholas, K. M.; Mulvaney, M. and Bayer, M., *J. Am. Chem. Soc.,* **1980**, *102*, 2508. (t) Hodes, H. D. and Nicholas, K. M., *Tetrahedron Lett.,* **1978**, 4349. (u) Lockwood, R. F. and Nicholas, K. M., *Tetrahedron Lett.,* **1977**, 4163.

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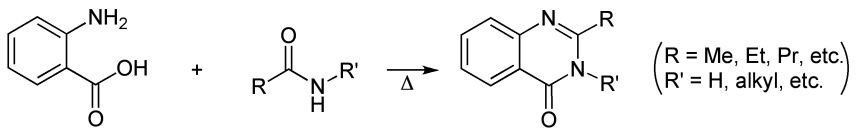
Niementowski Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Niementowski in 1895.[1] It is the thermal transformation of an anthranilic acid into 4-keto-3,4-dihydroquinazoline by the condensation with an amide. Therefore, it is generally referred to as the Niementowski reaction.[2] Occasionally, this reaction is also referred to as the von Niementowski synthesis,[2l,3] Niementowski condensation,[4] or Niementowski 4-oxoquinazoline synthesis.[5] Although the formation of 4-keto-3,4-dihydroquinazoline, also known as benzoylene urea,[6] appears to involve a simultaneous condensation between the amino group of anthranilic acid and the carbonyl group of an amide and the condensation between the carboxyl group of anthranilic acid and the amido group of the amide,[7] it actually proceeds via the formation of an intermediate of the anthranilate salt, which can be isolated as a crystal when the reaction mixture is dissolved in an alcohol.[2l] In addition, this reaction usually requires a high temperature and long reaction time; and a high yield is expected when a formamide or acetamide reacts with an anthranilic acid, whereas the yield decreases when a higher order of amide is used in this reaction.[2l,7,8] This general trend is caused by the thermal decarboxylation of the anthranilic acid.[2l]

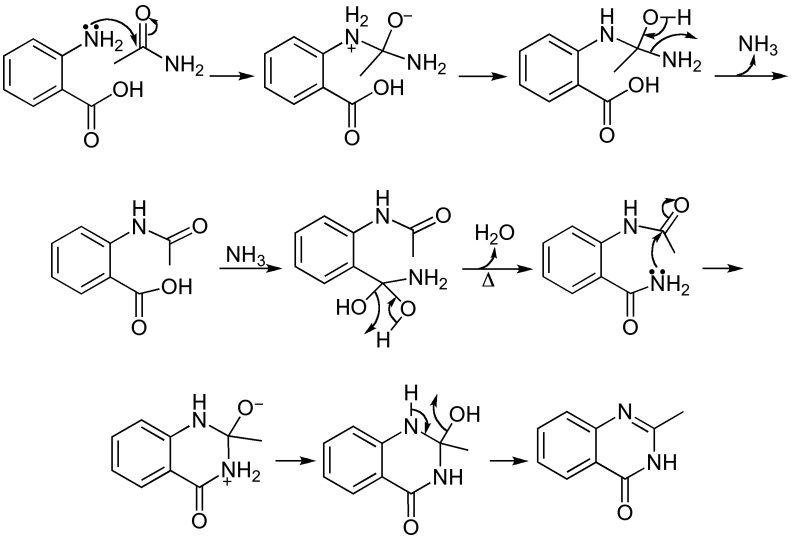
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

A detailed mechanism for the reaction between anthranilic acid and acetamide is illustrated here, according to the proposed reaction path.[9]



D. MODIFICATION

This reaction has been extended to occur between an anthranilic acid and a thiobenzamide.[10] In addition, different anthranilic acid derivatives—including *o*-acylaminobenzamides,[2l] ammonium *o*-acylaminobenzoates,[2l] *o*-acetaminobenzonitrile,[2l] acetanthranil[2l] and anthranilic ester[2l]—have been used successfully in this reaction. Moreover, efficient reaction conditions have been established under microwave irradiation.[2a,2b,2d,2g,3a,4b]

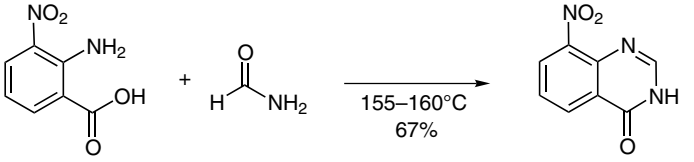
E. APPLICATIONS

This reaction is generally used for the preparation of quinazoline derivatives.

F. RELATED REACTIONS

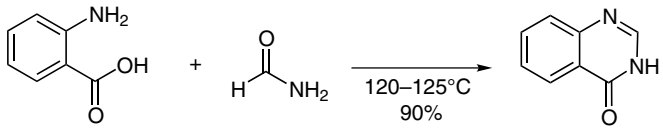
This reaction is related to the *Friedländer Condensation* and *Pfitzinger Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2k.

3-Nitroanthranilic acid (60 g) and 120 g freshly distilled formamide were heated in an open beaker in an oil bath at an inside temperature of 155–160°C for 6 h. The dark residue, after cooling, was pulverized and washed with 5% $NaHCO_3$ solution, then with water, and dried to afford 42 g crude 8-nitroquinazolone-4, in a yield of 67%, m.p. 240–248°C. The crude product was then recrystallized from nitrobenzene (100 mL per 15 g product) with a liberal use of charcoal for decolorization. The crystal was washed with ether to remove residual nitrobenzene, and pale yellow needles were obtained, which melted at 250–251°C.



Reference 10.

Anthranilic acid (137.1 g, 1.0 mol) was heated with 75.6 g formamide (1.68 mol) at 120–125°C for 4 h. The product was filtered and recrystallized from ethanol to afford 131.5 g 4-quinazolone, in a yield of 90%, m.p., 215.5–216.5°C.

Other references related to the Niementowski reaction are cited in the literature.[11]

H. REFERENCES

1. Von Niementowski, S., *J. Prakt. Chem.,* **1895**, *51*, 564.
2. (a) Desai, K. R. and Desai, A. R., *Chemistry (India),* **2005**, *2*, 216. (b) Desai, A. R. and Desai, K. R., *ARKIVOC,* **2005**, (*xiii*), 98. (c) Kidwai, M.; Rastogi, S.; Mohan, R. and Venkataramanan, R., *Croat. Chem. Acta,* **2003**, *76*, 365. (d) Alexandre, F.-R.; Berecibar, A. and Besson, T., *Tetrahedron Lett.,* **2002**, *43*, 3911. (e) Liu, Z.-H.; Sun, X.-L. and Zhang, S.-Y., *Youji Huaxue*, **2001**, *21*, 1161. (f) Son, J. K.; Kim, S. and Jahng, Y. D., *Heterocycles*, **2001**, *55*, 1981. (g) Khajavi, M. S.; Afshani, P. and Rad Moghadam, K., *Indian J. Chemistry Chem. Eng.,* **1998**, *17*, 29. (h) Showalter, H. D. H.; Sun, L.; Sercel, A. D.; Winters, R. T.; Denny, W. A. and Palmer, B. D., *J. Org. Chem.,* **1996,** *61*, 1155. (i) Buyuktimkin, S. and Buyuktimkin, N., *J. Faculty Pharm. Istanbul Univ.,* **1985**, *21*, 53. (j) Moszew, J. and Kusmierczyk, S., *Zeszyty Naukowe Uniwersytetu Jagiellonskiego, Prace Chemiczne*, **1968**, *13*, 31. (k) Baker, B. R.; Joseph, J. P.; Schaub, R. E.; McEvoy, F. J. and Williams, J. H., *J. Org. Chem.,* **1953**, *18*, 138. (l) Elderfield, R. C.; Williamson, T. A.; Gensler, W. J. and Kremer, C. B., *J. Org. Chem.,* **1947**, *12*, 405. (m) Meyer, J. F. and Wagner, E. C., *J. Org. Chem.,* **1943**, *8*, 239.
3. (a) Domon, L.; Coeur, C.; Grelard, A.; Thiery, V. and Besson, T., *Tetrahedron Lett.,* **2001**, *42*, 6671. (b) Feldman, J. R. and Wagner, E. C., *J. Org. Chem.,* **1942**, *7*, 31.
4. (a) Laird, T.; Hermitage, S. A. and Tilstam, U., *Org. Proc. Res. Dev.,* **2003**, *7*, 226. (b) Alexandre, F.-R.; Berecibar, A.; Wrigglesworth, R. and Besson, T., *Tetrahedron Lett.,* **2003**, *59*, 1413. (c) Dael, A.; Tomasik, P.; Kappe, T. and Gheath, A. H., *Pol. J. Chem.,* **1996**, *70*, 302.
5. (a) Bures, M. G. and Jorgensen, W. L., *J. Org. Chem.,* **1988**, *53*, 2504. (b) Mehta, H. J.; Patel, B. M. and Patel, S. R., *J. Indian Chem. Soc.,* **1972**, *49*, 407. (c) Patel, V. S. and Patel, S. R., *J. Indian Chem. Soc.,* **1968**, *45*, 167. (d) Patel, V. S. and Patel, S. R., *J. Indian Chem. Soc.*, **1965**, *42*, 531.
6. Bogert, M. T. and Scatchard, G., *J. Am. Chem. Soc.,* **1920**, *42*, 2052.
7. Bogert, M. T. and Gotthelf, A. H., *J. Am. Chem. Soc.,* **1900**, *22*, 129.
8. Bogert, M. T. and Hand, W. F., *J. Am. Chem. Soc.,* **1906**, *28*, 94.

9. Bogert, M. T. and Gotthelf, A. H., *J. Am. Chem. Soc.,* **1900**, *22*, 522.
10. Endicott, M. M.; Wick, E.; Mercury, M. L. and Sherrill, M. L., *J. Am. Chem. Soc.,* **1946**, *68*, 1299.
11. (a) Marzaro, G.; Chilin, A.; Pastorini, G. and Guiotto, A., *Org. Lett.,* **2006**, *8*, 255. (b) Foster, R. H. and Leonard, N. J., *J. Org. Chem.,* **1980**, *45*, 3072. (c) Irwin, W. J. and Wibberley, D. G., *Pyridopyrimidines: 1,3,5-, 1,3,6-, 1,3,7-, and 1,3,8- Triazanaphthalenes* in *Advances in Heterocyclic Chemistry*, ed, Katritzky, A. R. and Boulton, A. J., Academic Press, New York, **1969**, *10*, pp. 149–198. (d) Armarego, W. L. F., *J. Appl. Chem.,* **1961**, *11*, 70. (e) Bogert, M. T. and Kropff, A. H., *J. Am. Chem. Soc.,* **1909**, *31*, 1071. (f) Bogert, M. T.; Wiggin, J. D. and Sinclair, J. E., *J. Am. Chem. Soc.,* **1907**, *29*, 82. (g) Bogert, M. T. and Dox, A. W., *J. Am. Chem. Soc.,* **1906**, *28*, 1127. (h) Bogert, M. T. and Hoffman, A., *J. Am. Chem. Soc.,* **1906**, *28*, 1293. (i) Bogert, M. T. and Chambers, V. J., *J. Am. Chem. Soc.,* **1905**, *27*, 649.

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Nierenstein Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Staudinger in 1914,[1] subsequently by Clibbens and Nierenstein in 1915,[2] and extensively studied by Nierenstein.[3] It is the synthesis of α-chloromethyl ketone by treatment of an aliphatic or aromatic acyl chloride with diazomethane. Therefore, it is generally known as the Nierenstein reaction.[4] Occasionally, it is also referred to as the Clibbens-Nierenstein reaction[5] or Nierenstein chloromethylation.[6]

Besides α-chloromethyl ketones, this reaction can be used to make other reactive halides carrying different elements (e.g., mercury)[7] and even molecules containing a halogen sensitive group, such as Si-H link.[8] It should be pointed out that α-chloromethyl ketone is not the only product from the reaction between an acyl chloride and a diazomethane; in fact, the direct product from such reaction is a diazoketone. For example, benzoyl chloride when reacting with diazomethane is quickly and completely transformed into diazoacetophenone, accompanied by the evolution of nitrogen.[9] The *in situ* generated diazoketones then decompose and produce a variety of products. For example, diazoketones lose nitrogen when decomposed catalytically; if no protic reagent is present, the resulting product is an ethylenic compound coupled from two diazoketone molecules;[10] when acyl chloride is added to more than two equivalents of diazomethane, the diazoketone can be obtained, purified, and further converted into corresponding acid, ester, amide or substituted amide.[11] However, when α-chloromethyl ketone is the desired product, the reversed process should be used so that the total amount of diazomethane is restricted to the minimum needed, in a way that an excess amount of diazomethane is quickly added into the acyl chloride solution.[9,11] Unfortunately, this reaction works poorly for preparing α-bromomethyl ketone, probably because the bromine atom is less mobile.[12] Under certain conditions, the dihalogenated dioxanes are also produced,[4a] as shown in the reaction between benzoyl bromide and

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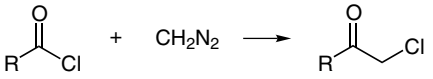
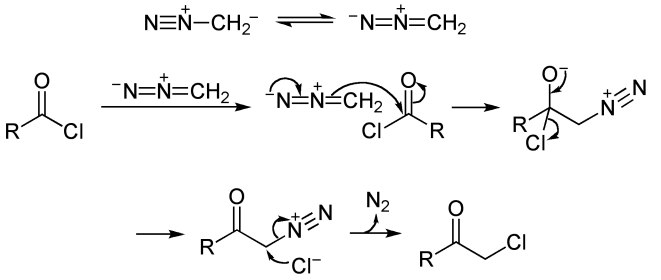
diazomethane, in which 62% 2,5-dibromo-2,5-diphenyl-1,4-dioxane is obtained, whereas only 28% ω-bromoacetophenone is yielded.[3a] Similarly, when the mobility of chlorine atom is reduced, the yield of the corresponding α-chloromethyl ketone decreases too. Examples are the reactions between diazomethane and phenylacetyl chloride, diphenylacetyl chloride, or triphenylacetyl chloride, by which the former two acetyl chlorides give 87% and 82% of the corresponding α-chloro-γ-phenyl-acetone, and α-chloro-γ,γ-diphenyl-acetone, respectively, and the latter yields 92% dioxane derivative.[3a] This reaction has been extended to a one-pot preparation of terminal olefins.[6]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Displayed below is a simple illustration of the reaction mechanism.



D. MODIFICATION

N/A

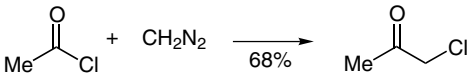
E. APPLICATIONS

This reaction has a general application in the preparation of α-chloromethyl ketones; in addition, the α-chloromethyl ketones can be converted into terminal olefins by treatment with a Grignard reagent, and these two steps can be combined into a one-pot process.[4a]

F. RELATED REACTIONS

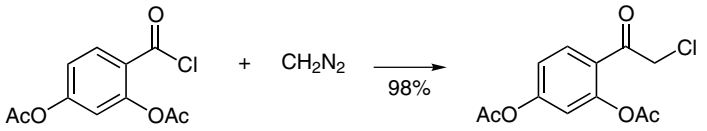
This reaction is related to the *Arndt-Eistert Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



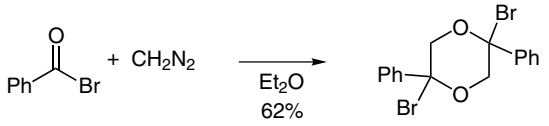
Reference 13.

To a 1-L three-necked flask containing 0.5 mol diazomethane and ~500 mL dried ether was added 0.25 mol acetyl chloride slowly from a dropping funnel with constant stirring of the solution, which was maintained at a temperature not greater than 5°C. The reaction mixture was allowed to stand for 2 h after the addition of the acetyl chloride and was then saturated with dry hydrogen chloride over a period of 2 h. The bulk of the ether was removed by distillation, and the residual solution was fractionated through a small column. The fraction boiling at 118–119°C at 736 mmHg was collected and weighed 15.8 g, in a yield of 68%.



Reference 3b.

An ether solution of 6 g diacetyl-β-resorcoyl chloride was treated with an excess of diazomethane. The solid left on evaporating crystallizes from dry benzene in prismatic needles, in a yield of 98%, m.p. 73°C.



Reference 3a.

Benzoyl bromide dissolved in anhydrous ether (dried over the Grignard reagent) was allowed to react with an excess amount of diazomethane. After evaporation of the solvent, the solid left was pulverized, mixed with dry sand (purified by washing with HCl) and extracted in a Soxhlet apparatus with ligroin (b.p. 50–60°C) and then with benzene (dried over sodium). The first extraction, which dissolved only bromoacetophenone, was concluded when no solid was left on evaporation of a little of the overflowing liquid. The benzene, which was dried in the same manner, dissolved 2,5-dibromo-2,5-diphenyl-1,4-dioxane, which was crystallized as long needles from benzene, in a yield of 62%, m.p. 159°C.

Other references related to the Nierenstein reaction are cited in the literature.[14]

H. REFERENCES

1. Staudinger, H., *Chem. Ztg.,* **1914**, 758.
2. Clibbens, D. A. and Nierenstein, M., *J. Chem. Soc., Trans.,* **1915**, *107*, 1491.
3. (a) Lewis, H. H.; Nierenstein, M. and Rich, E. M., *J. Am. Chem. Soc.,* **1925**, *47*, 1728. (b) Nierenstein, M.; Wang, D. G. and Warr, J. C., *J. Am. Chem. Soc.,* **1924**, *46*, 2551. (c) Nierenstein, M.; Wang, D. G. and Warr, J. C., *J. Am. Chem. Soc.,* **1924**, *46*, 2554. (d) Kahil, A. I. M. and Nierenstein, M., *J. Am. Chem. Soc.,* **1924**, *46*, 2556. (e) Nierenstein, M., *J. Chem. Soc.,* **1920**, *117*, 1153.
4. (a) Malkin, T. and Nierenstein, M., *J. Am. Chem. Soc.,* **1952**, *74*, 1504. (b) Bachman, W. E. and Struve, W. S., *Org. React.,* **1942**, *1*, 38. (c) Bradley, W. and Robinson, R., *Nature,* **1928**, *122*, 130. (d) Nierenstein, M., *Nature,* **1928**, *122*, 313. (e) Nierenstein, M., *Nature,* **1928**, *121*, 940.
5. (a) Misiti, D.; Marchi, F. D. and Rosnati, V., *Annali dell'Instituto Superiore di Sanita,* **1965**, *1*, 209. (b) Misiti, D.; Marchi, F. D. and Rosnati, V., *Gazz. Chim. Ital.,* **1963**, *93*, 1044.
6. Barluenga, J.; Yus, M.; Concellõn, J. M. and Bernad, P., *J. Org. Chem.,* **1983**, *48*, 3116.
7. Hellerman, L. and Newman, M. D., *J. Am. Chem. Soc.,* **1932**, *54*, 2859.
8. Seyferth, D., *Chem. Rev.,* **1955**, *55*, 1155.
9. Bradley, W. and Robinson, R., *J. Am. Chem. Soc.,* **1930**, *52*, 1558.
10. Grundmann, C., *Ann.,* **1938**, *536*, 29.
11. Sonntag, N. O. V., *Chem. Rev.,* **1953**, *52*, 237.
12. Clibbens, D. A. and Nierenstein, M., *J. Chem. Soc.,* **1915**, *107*, 1492.
13. van Atta, R. E.; Zook, H. D. and Elving, P. J., *J. Am. Chem. Soc.,* **1954**, *76*, 1185.
14. (a) Pusino, A.; Rosnati, V. and Saba, A., *Tetrahedron,* **1984**, *40*, 1893. (b) Erickson, J. L. E.; Dechary, J. M. and Kesling, M. R., *J. Am. Chem. Soc.,* **1951**, *73*, 5301. (c) Catch, J. R.; Elliott, D. F.; Hey, D. H. and Jones, E. R. H., *J. Chem. Soc.,* **1948**, 278. (d) McPhee, W. D. and Klingsberg, E., *Org. Synth.,* **1946**, *26*, 13. (e) Wolfrom, M. L.; Weisblat, D. I.; Zophy, W. H. and Waisbrot, S. W., *J. Am. Chem. Soc.,* **1941**, *63*, 201. (f) Bradley, W. and Robinson, R., *J. Chem. Soc.,* **1928**, 1310. (g) Bradley, W. and Schwarzenbach, G., *J. Chem. Soc.,* **1928**, 2904. (h) Malkin, T. and Nierenstein, M., *Ber.,* **1928**, *61*, 797. (i) Dale, R. T. and Nierenstein, M., *Ber.,* **1927**, *60*, 1026. (j) Staudinger, H. and Mächling, C., *Ber.,* **1916**, *49*, 1973.

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Norrish Type I Reaction

(Norrish Type I Process, Norrish Type I Cleavage)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Norrish in 1932.[1] It is a light-initiated carbon-carbon bond cleavage between the α-carbon and the carbonyl of a ketone or an aldehyde to form an alkyl and an acyl radical pairs, from which a variety of products can be formed, including alkane,[2] alkene,[2] cyclic acetal,[3] decarbonyl compound,[3] and oxetane.[4] In order to differentiate this reaction from other common photoreactions of ketones and aldehydes, it is generally known as the Norrish type I reaction.[4,5] In addition, it is also referred to as the Norrish type I process,[2,6] Norrish type I α-cleavage,[5c,7] Norrish type I photocleavage,[8] Norrish type I cleavage,[2,6a,9] and Norrish type I photochemical reaction.[8a] This reaction is initiated by a n-π^* excitation,[5b,6b,10] from the ground state (S_0) to its first excited singlet state (S_1),[5b] followed by an α-cleavage to form an acyl and an alkyl radical pairs. Alternatively, the first excited singlet may convert itself into the first excited triplet state through an intersystem crossing, which then undergoes the α-cleavage.[5a,6b] The α-cleavage taking place from the triplet excited state is sometimes called the *reluctant* Norrish type I reaction.[9h] This reaction is influenced by both the structure of the substrate and the reaction conditions, as evidenced in the different product distributions between the reactions in the gas phase and in the solution phase.[2] Even the product distribution in the solution phase is different from that when cyclodextrin is present, which often results in a cage effect.[5m,10] Similarly, the product distribution also differs from that occurring in the solid state,[9c,10] or in zeolite.[2,5m,9a,11] It has been found that aliphatic cyclic imides[5r] and small cyclic ketones up to cycloheptanone[5m] undergo only the Norrish type I reaction, from both singlet and triplet excited states;[5m] whereas acetophenone and benzophenone do not undergo the Norrish type I reaction, so that they are often used as the Norrish type I photosensitizers.[12]

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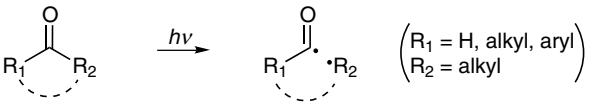
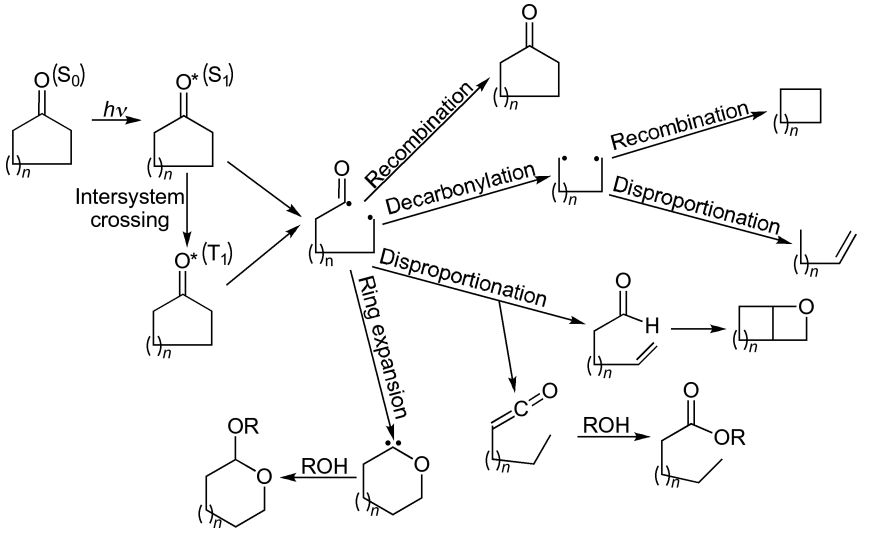
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A general mechanism for the Norrish type I reaction is displayed below, including all the possible products.



D. MODIFICATION

This reaction has been carried out in the presence of zeolite[2,5m,9a,11] and cyclodextrin[5m,10] and in the solid state.[9i,10]

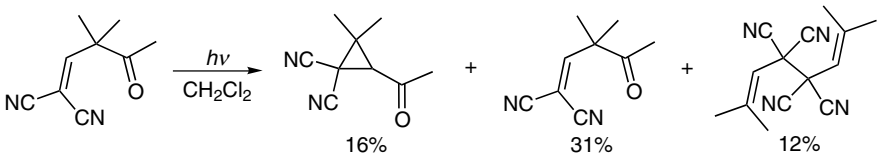
E. APPLICATIONS

This reaction provides a convenient source of hydrocarbon radicals.[13] In addition, it has been used extensively in organic synthesis and photochemistry.

F. RELATED REACTIONS

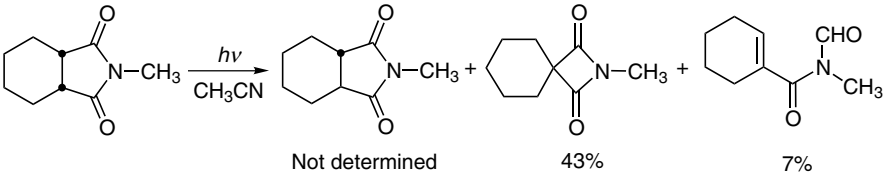
This reaction is related to the *Norrish Type II Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 14.

To a quartz immersion well apparatus were added 128 mg 3,3-dimethyl-5,5-dicyano-pent-4-en-2-one (0.79 mmol) and 270 mL CH_2Cl_2. The solution was purged with argon for 1 h, then the apparatus together with a Pyrex filter was irradiated with six 9-W low-pressure mercury arc lamps with a maximum emission at 254 nm for 12 h. After completion of the irradiation, the solvent was removed under reduced pressure. The residue was separated by silica gel column chromatography using hexane/EtOAc (95:5) as the eluent to afford 22 mg 2,7-dimethyl-4,4,5,5-tetracyano-2,6-octadiene as a colorless oil (12% yield), 39 mg starting material (31% recovery) and 20 mg cyclopropylketone as a colorless oil, in a yield of 16%. Further elution with EtOAc afforded 29 mg highly polar material.



Reference 15.

A solution of 500 mg *N*-methylcyclohexane-*cis*-1,2-dicarboxyimide in 25 mL CH_3CN was purged with nitrogen and irradiated for 7 h. After removal of the solvent, the residue was separated by column chromatography to afford 298 mg of a mixture of starting material and *N*-methylcyclohexane-*trans*-1,2-dicarboxyimide, 88 mg *N*-methylcyclohexane-1,1-dicarboxyimide (43%, colorless crystal, m.p. 96–97°C), and 14 mg *N*-formyl-*N*-methyl-1-cyclohexene-1-carboxamide (7%).

Other references related to the Norrish Type I reaction are cited in the literature.[16]

H. REFERENCES

1. (a) Norrish, R. G. W. and Kirkbride, F. W., *J. Chem. Soc.,* **1932**, 1518. (b) Norrish, R. G. W. and Bamford, C. H., *Nature,* **1936**, *138*, 1016.
2. Yamashita, H.; Takada, S.; Hada, M.; Nakatsuji, H. and Anpo, M., *J. Photochem. Photobiol. A: Chem.,* **2003**, *160*, 37.
3. Bohne, C., "Norrish Type I Processes of Ketones: Basic Concepts," in *CRC Handbook of Organic Photochemistry and Photobiology*, ed., Horspool, W. M. and Song, P.-S., CRC Press, Boca Raton, Fla., **1995**, pp. 416–429.
4. Adam, W.; Arnold, M. A. and Saha-Möller, C. R., *J. Org. Chem.,* **2001**, *66*, 597.

5. (a) Ruzicka, R.; Baráková, L. and Klán, *J. Phys. Chem. B,* **2005**, *109*, 9346. (b) He, H.-Y.; Fang, W.-H. and Phillips, D. L., *J. Phys. Chem. A,* **2004**, *108*, 5386. (c) Lapinski, L.; Rostkowska, H.; Khvorostov, A.; Fausto, R. and Nowak, M. J., *J. Phys. Chem. A,* **2003**, *107*, 5913. (d) Nishino, H.; Kosaka, A.; Hembury, G. A.; Aoki, F.; Miyauchi, K.; Shitomi, H.; Onuki, H. and Inoue, Y., *J. Am. Chem. Soc.,* **2002**, *124*, 11618. (e) Solling, T. I.; Diau, E. W.-G.; Kotting, C.; De Feyter, S. and Zewail, A. H., *ChemPhysChem*, **2002**, *3*, 79. (f) López, D.; Quiñoá, E. and Riguera, R., *J. Org. Chem.,* **2000**, *65*, 4671. (g) Sakurai, H. and Kato, S., *THEOCHEM*, **1999**, 461. (h) Suzuki, I.; Tanaka, R.; Yamaguchi, A.; Maki, S.-i.; Misawa, H.; Tokumaru, K.; Nakagaki, R. and Sakuragi, H., *Bull. Chem. Soc. Jpn.,* **1999**, *72*, 103. (i) Tanaka, R.; Kuriyama, Y.; Itoh, H.; Sakuragi, H. and Tokumaru, K., *Chem. Lett.,* **1993**, 1447. (j) Tanaka, R.; Suzuki, I.; Yamaguchi, A.; Misawa, H.; Sakuragi, H. and Tokumaru, K., *Tetrahedron Lett*., **1992**, *33*, 3651. (k) De Keukeleire, D. and He, S. L., *J. Chem. Soc., Chem. Commun.,* **1992**, 419. (l) Netto-Ferreira, J. C.; Wintgens, V. and Scaiano, J. C., *J. Photochem. Photobiol., A: Chem.,* **1991**, *57*, 153. (m) Ramamurthy, V.; Lei, X.-G.; Turro, N. J.; Lewis, T. J. and Scheffer, J. R., *Tetrahedron Lett.,* **1991**, *32*, 7675. (n) Carroll, F. A.; Strouse, G. F. and Hain, J. M., *J. Chem. Edu.,* **1987**, *64*, 84. (o) Weir, D. and Scaiano, J. C., *Chem. Phys. Lett.,* **1985**, *118*, 526. (p) Weiss, D. S., *Org. Photochem.,* **1981**, *5*, 347. (q) Muthuramu, K. and Ramamurthy, V., *J. Chem. Soc., Chem. Commun.,* **1980**, 243. (r) Kanaoka, Y.; Okajima, H. and Hatanaka, Y., *J. Org. Chem.,* **1979**, *44*, 1749. (s) Morizur, J. P.; Bidan, G. and Kossanyi, J., *Tetrahedron Lett*., **1975**, 4167.
6. (a) Winter, P. R.; Rowland, B.; Hess, W. P.; Radziszewski, J. G.; Nimlos, M. R. and Ellison, G. B., *J. Phys. Chem. A,* **1998**, *102*, 3238. (b) Martin, X.; Moreno, M. and Lluch, J. M., *J. Phys. Chem.,* **1993**, *97*, 12186. (c) Ramamurthy, V.; Corbin, D. R.; Turro, N. J. and Sato, Y., *Tetrahedron Lett.,* **1989**, *30*, 5829. (d) Burchill, P. J.; Kelso, A. G. and Power, A. J., *Aust. J. Chem.,* **1976**, *29*, 2477.
7. Burns, C. S.; Heyerick, A.; Keukeleire, D. D. and Forbes, M. D. E., *Chem. Eur. J.,* **2001**, *7*, 4553.
8. (a) Anderson, A. S.; Hwang, J.-T. and Greenberg, M. M., *J. Org. Chem.,* **2000**, *65*, 4648. (b) Körner, S.; Bryant-Friedrich, A. and Giese, B., *J. Org. Chem.,* **1999**, *64*, 1559. (c) Greenberg, M. M.; Barvian, M. R.; Cook, G. P.; Goodman, B. K.; Matray, T. J.; Tronche, C. and Venkatesan, H., *J. Am. Chem. Soc.,* **1997**, *119*, 1828. (d) Adam, W. and Oestrich, R. S., *J. Am. Chem. Soc.,* **1992**, *114*, 6031. (e) Adam, G. and Sung, T. V., *Tetrahedron Lett*., **1976**, 247. (f) Dominh, T., *Ind. Chim. Belg.,* **1971**, *36*, 1080.
9. (a) Clennan, E. L. and Pan, G.-l., *Org. Lett.,* **2003**, *5*, 4979. (b) Hwu, J. R. and King, K.-Y., *Curr. Sci.,* **2001**, *81*, 1043. (c) Kang, T. and Scheffer, J. R., *Org. Lett.,* **2001**, *3*, 3361. (d) Muraoka, O.; Okumura, M.; Maeda, T.; Wang, L. C. and Tanabe, G., *Chem. Pharm. Bull.,* **1995**, *43*, 517. (e) Person, M. D.; Kash, P. W. and Butler, L. J., *J. Phys. Chem.,* **1992**, *96*, 2021. (f) Hwu, J. R.; Gilbert, B. A.; Lin, L. C. and Liaw, B. R., *J. Chem. Soc., Chem. Commun.,* **1990**, 161. (g) McGimpsey, W. G. and Scaiano, J. C., *J. Am. Chem. Soc.,* **1987**, *109*, 2179. (h) Johnston, L. J. and Scaiano, J. C., *J. Am. Chem. Soc.,* **1987**, *109*, 5487. (i) Murray, R. K. and Ford, T. M., *J. Am. Chem. Soc.,* **1980**, *102*, 3194.
10. Reddy, G. D.; Usha, G.; Ramanathan, K. V. and Ramamurthy, V., *J. Org. Chem.,* **1986**, *51*, 3085.
11. Corbin, D. R.; Eaton, D. F. and Ramamurthy, V., *J. Am. Chem. Soc.,* **1988**, *110*, 4848.
12. Adam, W.; Arnold, M. A.; Nau, W. M.; Pischel, U. and Saha-Möller, C. R., *J. Am. Chem. Soc.,* **2002**, *124*, 3893.
13. Kim, S. K. and Zewail, A. H., *Chem. Phys. Lett.,* **1996**, *250*, 279.
14. Armesto, D.; Ortiz, M. J.; Agarrabeitia, A. R. and Martín-Fontecha, M., *Org. Lett.,* **2005**, *7*, 2687.
15. Maruyama, K.; Ishitoku, T. and Kubo, Y., *J. Org. Chem.,* **1981**, *46*, 27.
16. (a) Arumugam, S.; Vutukuri, D. R.; Thayumanavan, S. and Ramamurthy, V., *J. Am. Chem. Soc.,* **2005**, *127*, 13200. (b) Goldsmith, M. R.; Rogers, P. J.; Cabral, N. M.; Ghiggino, K. P. and Roddick, F. A., *J. Am. Soc. Brew. Chem.,* **2005**, *63*, 177. (c) Conforti, P. F. and Garrison, B. J., *Chem. Phys. Lett.,* **2005**, *406*, 294. (d) Carroccio, S.; Puglisi, C. and Montaudo, G., *Macromolecules,* **2004**, *37*, 6037. (e) Capouet, M.; Peeters, J.; Nozìere, B. and Müller, J.-F., *Atmos. Chem. Phys.,* **2004**, *4*,

2285. (f) Sarpong, R.; Su, J. T. and Stoltz, B. M., *J. Am. Chem. Soc.,* **2003**, *125*, 13624. (g) Font-Sanchis, E.; Miranda, M. A.; Pérez-Prieto, J. and Scaiano, J. C., *J. Org. Chem.,* **2002**, *67*, 6131. (h) Tadić, J.; Juranić, I. and Moortgat, G. K., *Molecules,* **2001**, *6*, 287. (i) Tadić, J.; Juranić, I. and Moortgat, G. K., *J. Photochem. Photobiol. A: Chem.,* **2001**, *143*, 169. (j) Morozova, O. B.; Yurkovskaya, A. V.; Tsentalovich, Y. P.; Sagdeev, R. Z.; Wu, T. N. and Forbes, M. D. E., *J. Phys. Chem. A,* **1997**, *101*, 8803. (k) Horspool, W. M., *Photochemistry,* **1994**, *25*, 67. (l) Ramamurthy, V.; Corbin, D. R. and Eaton, D. F., *J. Org. Chem.,* **1990**, *55*, 5269. (m) Singh, S.; Usha, G.; Tung, C.-H.; Turro, N. J. and Ramamurthy, V., *J. Org. Chem.,* **1986**, *51*, 941. (n) Chapman, O. L. and Weiss, D. S., *Org. Photochem.,* **1973**, *3*, 197. (o) Coyle, J. D. and Carless, H. A., *Chem. Soc. Rev.,* **1972**, *1*, 465. (p) Norrish, R. G. W. and Bamford, C. H., *Nature,* **1937**, *140*, 195.

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Norrish Type II Reaction

(Norrish Type II Process, Norrish Type II Photoreaction, Yang Cyclization)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Norrish in 1934.[1] It is a light initiated intramolecular abstraction of a δ-hydrogen of an excited ketone or aldehyde to generate a 1,4-biradical, from which different products can form, including alkene, enol, and cyclobutanol. Therefore, this reaction is generally known as the Norrish type II reaction,[2] Norrish type II process,[2z,3] or Norrish type II photoreaction.[4] Occasionally, this reaction is also referred to as the Norrish type II photochemical reaction,[2d,2h] Norrish type II cleavage,[5] Norrish type II photolysis,[6] Norrish type II photoelimination,[7] Norrish type II rearrangement,[8] or Norrish type II photofragmentation.[2f,9] *Type II* is used to differentiate this reaction from another type of photoreaction that ketone and aldehyde undergo, the *Norrish Type I Reaction.* In addition, because Yang at the University of Chicago extensively extended this reaction,[10] the Norrish type II reaction is also called the Yang reaction,[11] Yang cyclization,[2d,12] Norrish/Yang type II reaction,[13] Norrish-Yang type II reaction,[2h,14] or Norrish-Yang photocyclisation.[14a]

This reaction is influenced by both environmental and structural factors.[2h,2r,14b] For example, the solvent polarity affects the lifetime of the 1,4-biradical in a solution-phase reaction,[6a] although the solvent dynamics barely affects the intersystem crossing rate.[15] In addition, the behavior of a triplet ketone and 1,4-biradical is controlled by the interior size and shape when a ketone is encapsulated inside the zeolites.[2r] In addition, it is known that both the excited singlet (S_1) and triplet (T_1) state of a dialkyl ketone can undergo such reaction,[16] whereas an aryl alkyl thioketone proceeds from the excited triplet

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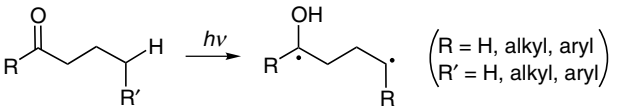
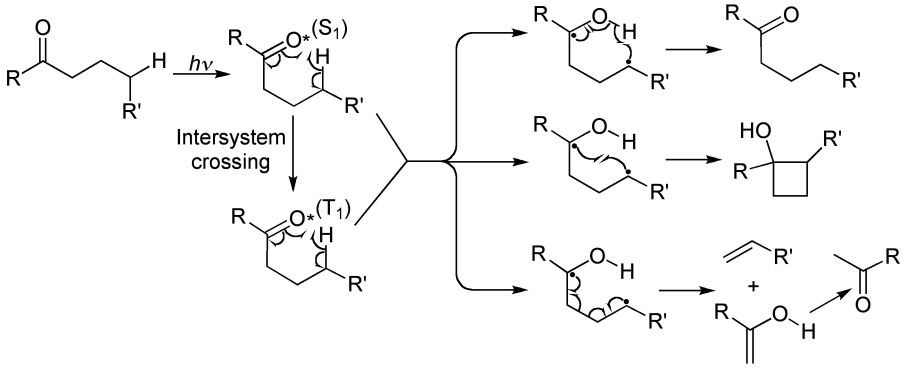
state (T_1),[16a] and the reaction of an ester primarily involves the excited triplet (T_1).[2n] For aliphatic or benzylic hydrogen abstraction, ketones with a lowest π-π^* triplet state are much less reactive than those with the lowest n-π^* triplet state.[17] The lifetime of the triplet is generally on the order of 10–100 ns,[14b,15] because of the small spin-orbit coupling.[15] For an aryl ketone, a skew 1,4-biradical is generated initially from the excited triplet state, which isomerizes to either a *cis*-biradical or a *trans*-biradical; after the intersystem crossing, the singlet *trans*-biradical leads to the fragmentation product, whereas the *cis*-biradical cyclizes to cyclobutanol.[14b] For special ketones like α-allylbutyrophenone and γ-cyclopropylbutyrophenone, the light-generated 1,4-biradicals undergo both rearrangement and a normal Norrish type II reaction.[4f] It is interesting that the light-initiated δ-hydrogen abstraction can also take place on an allylic alcohol from which the alcoholic hydrogen is abstracted from the olefinic moiety to yield an aldehyde, a process also known as the inverse Norrish type II rearrangement.[8a]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A general mechanism for the generation of a 1,4-biradical and all possible products arising from such 1,4-biradical are displayed here.



D. MODIFICATION

This reaction has been extended by Yang to the condition known as Yang cyclization.

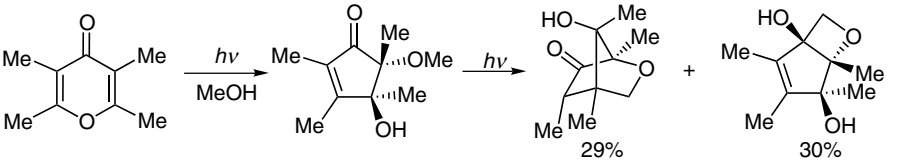
E. APPLICATIONS

This reaction has wide application in organic synthesis, especially for the generation of free radicals.[2z]

F. RELATED REACTIONS

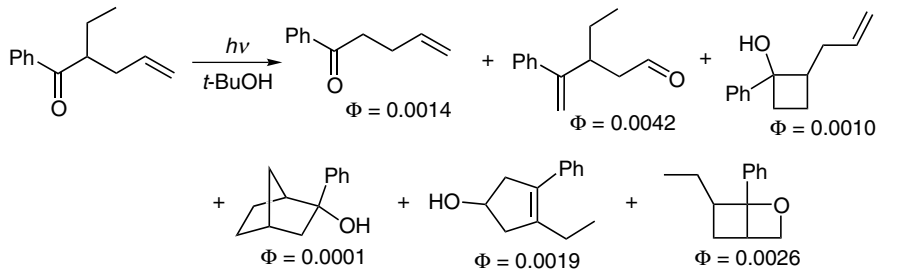
This reaction is related to the *Norrish Type I Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 18.

To a polished quartz tube were added 100 mL MeOH and 100 mg 2,3,5,6-tetramethylpyran-4-one (0.67 mmol), and the solution was deoxygenated for 15 min with a slow stream of dry nitrogen. Then the tube was placed at ~10 cm from the outside of the lamp's water jacket and irradiated until consumption of the pyran-4-one as detected by TLC. Upon removal of solvent under reduced pressure, the residue was purified via silica gel flash column chromatography with CH_2Cl_2/Et_2O/hexane (2:1:1) as the eluent to give 36 mg tetrahydrofuran-like derivative as a colorless oil, $R_f = 0.30$ (CH_2Cl_2/Et_2O/hexane, 2:1:1), in a yield of 29%. Further eluting the column with hexane/EtOAc (1:19) afforded 37 mg diol as a white waxy solid, in a yield of 30%, $R_f = 0.33$ (EtOAc), m.p., 153–156°C (dec).



Reference 4f.

A solution of 16.0 g α-allylbutyrophenone in 180 mL *tert*-butyl alcohol was irradiated under nitrogen in an immersion well with a Pyrex-filtered 450-W Hanovia mercury arc until < 10% of the starting ketone remained. GC analysis showed six products, but none of products was identified as 3-methyl-l-benzoylcyclopentane. After stripping of the solvent, the residue was chromatographed on neutral alumina with cyclohexane/$CHCl_3$ (1:1) as the eluent to afford five components, of which the first three were further purified by GC through a column packed with 15% QF-1 and 3% Carbowax. These compounds were 1-phenyl-3-penten-1-one, 4-phenyl-3-ethyl-4-pentenal, 1-phenyl-2-allylcyclobutanol, 2-phenylbicyclo[2.2.1]heptanol-2, and 3-phenyl-4-ethyl-3-cyclopentenol.

Other references related to the Norrish type II reaction are cited in the literature[19].

H. REFERENCES

1. (a) Norrish, R. G. W. and Appleyard, M. E. S., *J. Chem. Soc.,* **1934**, 874. (b) Norrish, R. G. W. and Bamford, C. H., *Nature,* **1936**, *138*, 1016. (c) Norrish, R. G. W. and Bamford, C. H., *Nature,* **1937**, *140*, 195.
2. (a) Stark, M. and Thiem, J., *Carbohydr. Res.,* **2006**, *341*, 1543. (b) Aumont, B.; Szopa, S. and Madronich, S., Atmos. Chem. Phys., **2005**, *5*, 2497. (c) Herrmann, A., *Spectrum,* **2004**, *17*, 10. (d) Saphier, S.; Sinha, S. C. and Keinan, E., *Angew. Chem. Int. Ed.,* **2003**, *42*, 1378. (e) Müller, P.; Klán, P. and Církva, V., *J. Photochem. Photobiol. A: Chem.,* **2003**, *158*, 1. (f) Levrand, B. and Herrmann, A., *Photochem. & Photobiol. Sci.,* **2002**, *1*, 907. (g) Seebach, D.; Beck, A. K. and Heckel, A., *Angew. Chem. Int. Ed.,* **2001**, *40*, 92. (h) Kell, A. J.; Stringle, D. L. B. and Workentin, M. S., *Org. Lett.,* **2000**, *2*, 3381. (i) De Feyter, S.; Diau, E. W.-G. and Zewail, Ahmed H., *Angew. Chem. Int. Ed.,* **2000**, *39*, 260. (j) Ihmels, H. and Scheffer, J. R., *Tetrahedron*, **1999**, *55*, 885. (k) Griesbeck, A. G.; Henz, A.; Kramer, W.; Wamser, P.; Peters, K. and Peters, E.-M., *Tetrahedron Lett*., **1998**, *39*, 1549. (l) Takagi, K.; Harata, E.; Shichi, T.; Kanoh, T. and Sawaki, Y., *J. Photochem. Photobiol., A: Chem.,* **1997**, *105*, 47. (m) Bhattacharyya, A. and Subramanian, S., *THEOCHEM*, **1996**, *361*, 145. (n) Niu, Y. P.; Christophy, E. and Hossenlopp, J. M., *J. Am. Chem. Soc.,* **1996**, *118*, 4188. (o) Nuss, J. M. and Murphy, M. M., *Tetrahedron Lett*., **1994**, *35*, 37. (p) Sengupta, D. and Chandra, A. K., *J. Photochem. Photobiol., A: Chem.,* **1993**, *75*, 151. (q) Ramamurthy, V. and Sanderson, D. R., *Tetrahedron Lett*., **1992**, *33*, 2757. (r) Ramamurthy, V.; Corbin, D. R. and Johnston, L. J., *J. Am. Chem. Soc.,* **1992**, *114*, 3870. (s) Vicens, J., *Mol. Cryst. Liquid Crystals,* **1990**, *187*, 375. (t) Ramamurthy, V.; Corbin, D. R. and Eaton, D. F., *J. Chem. Soc., Chem. Commun.,* **1989**, 1213. (u) Oda, K.; Yoshida, E.; Ohno, K.; Machida, M. and Kanaoka, Y., *Chem. Pharm. Bull.,* **1989**, *37*, 642. (v) Reddy, G. D.; Jayasree, B. and Ramamurthy, V., *J. Org. Chem.,* **1987**, *52*, 3107. (w) Ariel, S.; Evans, S.; Omkaram, N.; Scheffer, J. R. and Trotter, J., *J. Chem. Soc., Chem. Commun.,* **1986**, 375. (x) Ariel, S.; Askari, S. H.; Scheffer, J. R. and Trotter, J., *Tetrahedron Lett*., **1986**, *27*, 783. (y) Machida, M.; Oda, K. and Kanaoka, Y., *Tetrahedron Lett*., **1985**, *26*, 5173. (z) Small, R. D. and Scaiano, J. C., *J. Phys. Chem.,* **1978**, *82*, 2662.
3. (a) Chandra, A. K. and Sreedhara Rao, V., *Chem. Phys. Lett.,* **1997**, *270*, 87. (b) Sreedhara Rao, V. and Chandra, A. K., *Chem. Phys.,* **1997**, *214*, 103. (c) Oda, K.; Fukuzawa, Y.; Ohno, K.; Machida, M. and Kanaoka, Y., *Heterocycles*, **1993**, *36*, 71. (d) Sengupta, D.; Sumathi, R. and Chandra, A. K., *J. Photochem. Photobiol., A: Chem.,* **1991**, *60*, 149. (e) O'Neal, H. E.; Miller, R. G. and Gunderson, E., *J. Am. Chem. Soc.,* **1974**, *96*, 3351. (f) Pacifici, J. G. and Hyatt, J. A., *Mol. Photochem.,* **1971**, *3*, 271. (g) Pacifici, J. G. and Hyatt, J. A., *Mol. Photochem.,* **1971**, 3, 267. (h) Evans, T. R. and Leermakers, P. A., *J. Am. Chem. Soc.,* **1968**, *90*, 1840.
4. (a) Marciniak, B., *J. Chem. Edu.,* **1988**, *65*, 832. (b) Osuka, A.; Shimizu, H.; Suzuki, H. and Maruyama, K., *Chem. Lett.,* **1987**, 1061. (c) Hasegawa, T.; Arata, Y. and Kageyama, A., *Tetrahedron Lett*., **1983**, *24*, 1995. (d) Osuka, A.; Shimizu, H.; Suzuki, H. and Maruyama, K., *Chem. Lett.,* **1982**, 329. (e) Osuka, A., *J. Org. Chem.,* **1982**, *47*, 3131. (f) Wagner, P. J.; Liu, K.-C. and Noguchi, Y., *J. Am. Chem. Soc.,* **1981**, *103*, 3837. (g) Kaptein, R.; De Kanter, F. J. J. and Rist, G. H., *J. Chem. Soc., Chem. Commun.,* **1981**, 499.
5. (a) Charette, A. B.; Chong, K. C. W.; Fournier, J.-F.; Patrick, B. and Scheffer, J. R., *Photochem. Photobiol. Sci.,* **2003**, *2*, 1052. (b) Henne, A. and Fischer, H., *Angew. Chem.,* **1976**, *88*, 445.
6. (a) Zimmt, M. B.; Doubleday, C. and Turro, N. J., *Chem. Phys. Lett.,* **1987**, *134*, 549. (b) Doubleday, C., *Chem. Phys. Lett.,* **1982**, *85*, 65.
7. (a) Dalby, K. N., *Annu. Rep. Prog. Chem., Sect. B,* **2002**, *98*, 253. (b) Bishop, R., *J. Chem. Soc., Chem. Commun.,* **1972**, 1388. (c) Kumler, P. L.; Pedersen, C. and Buchardt, O., *Acta Chem. Scand.,* **1968**, *22*, 2719.

8. (a) Studebaker, J.; Srinivasan, R.; Ors, J. A. and Baum, T., *J. Am. Chem. Soc.,* **1980**, *102*, 6872. (b) DeBoer, C. D.; Herkstroeter, W. G.; Marchetti, A. P.; Schultz, A. G. and Schlessinger, R. H., *J. Am. Chem. Soc.,* **1973**, *95*, 3963.
9. (a) Rochat, S.; Minardi, C.; De Saint Laumer, J.-Y. and Herrmann, A., *Helv. Chim. Acta,* **2000**, *83*, 1645. (b) DeCosta, D. P.; Bennett, A. K. and Pincock, J. A., *J. Am. Chem. Soc.,* **1999**, *121*, 3785.
10. Yang, N. C. and Yang, D. H., *J. Am. Chem. Soc.,* **1958**, *80*, 2913.
11. (a) Griesbeck, A. G. and Heckroth, H., *Res. Chem. Intermediates,* **1999**, *25*, 599. (b) Niu, Y. P.; Christophy, E.; Pisano, P. J.; Zhang, Y. and Hossenlopp, J. M., *J. Am. Chem. Soc.,* **1996**, *118*, 4181.
12. (a) Moorthy, J. N.; Koner, A. L.; Samanta, S.; Singhal, N.; Nau, W. M. and Weiss, R. G., *Chem. Eur. J.,* **2006**, *12*, 8744. (b) Singhal, N.; Koner, A. L.; Mal, P.; Venugopalan, P.; Nau, W. M. and Moorthy, J. N., *J. Am. Chem. Soc.,* **2005**, *127*, 14375. (c) Natarajan, A.; Mague, J. T. and Ramamurthy, V., *J. Am. Chem. Soc.,* **2005**, *127*, 3568. (d) Saphier, S.; Hu, Y. F.; Sinha, S. C.; Houk, K. N. and Keinan, E., *J. Am. Chem. Soc.,* **2005**, *127*, 132. (e) Moorthy, J. N. and Mal, P., *Tetrahedron Lett*., **2003**, *44*, 2493. (f) Griesbeck, A. G.; Heckroth, H. and Lex, J., *Chem. Commun.,* **1999**, 1109.
13. (a) Kresge, A. J., *Chemtracts*, **1997**, *10*, 292. (b) Gudmundsdottir, A. D.; Lewis, T. J.; Randall, L. H.; Scheffer, J. R.; Rettig, S. J.; Trotter, J. and Wu, C.-H., *J. Am. Chem. Soc.,* **1996**, *118*, 6167.
14. (a) Griesbeck, A. G.; Cygon, P. and Lex, J., *Lett. Org. Chem.,* **2004**, *1*, 313. (b) Kell, A. J. and Workentin, M. S., *Langmuir,* **2001**, *17*, 7355.
15. Morita, A. and Kato, S., *J. Phys. Chem.,* **1993**, *97*, 3298.
16. (a) Lu, Y. L.; Carlson, D. and Morrison, H., *J. Am. Chem. Soc.,* **1993**, *115*, 6446. (b) Casey, C. P. and Boggs, R. A., *J. Am. Chem. Soc.,* **1972**, *94*, 6457.
17. Leigh, W. J.; Lathioor, E. C. and Pierre, M. J. S., *J. Am. Chem. Soc.,* **1996**, *118*, 12339.
18. Fleming, M.; Basta, R.; Fisher, P. V.; Mitchell, S. and West, F. G., *J. Org. Chem.,* **1999,** *64*, 1626.
19. (a) Rodilla, J. M. L.; Díez, D.; Urones, J. G. and Rocha, P. M., *Molecules,* **2004**, *9*, 300. (b) Adam, W.; Arnold, M. A.; Nau, W. M.; Pischel, U. and Saha-Möller, C. R., *Nucleic Acids Res.,* **2001**, *29*, 4955. (c) De Feyter, S.; Diau, E. W. and Zewail, A. H., *Angew. Chem. Int. Ed. Engl.,* **2000**, *39*, 260. (d) Sauers, R. R. and Edberg, L. A., *J. Org. Chem.,* **1994**, *59*, 7061. (e) Evans, S. V.; Garcia-Garibay, M.; Omkaram, N.; Scheffer, J. R.; Trotter, J. and Wireko, F., *J. Am. Chem. Soc.,* **1986**, *108*, 5648. (f) Aoyama, H.; Sakamoto, M.; Kuwabara, K.; Yoshida, K. and Omote, Y., *J. Am. Chem. Soc.,* **1983**, *105*, 1958. (g) Kumar, C. V.; Chattopadhyay, S. K. and Das, P. K., *J. Am. Chem. Soc.,* **1983**, *105*, 5143. (h) Ariel, S.; Ramamurthy, V.; Scheffer, J. R. and Trotter, J., *J. Am. Chem. Soc.,* **1983**, *105*, 6959. (i) Scaiano, J. C., *Acc. Chem. Res.,* **1982**, *15*, 252. (j) Ito, Y.; Matsuura, T. and Yokoya, H., *J. Am. Chem. Soc.,* **1979**, *101*, 4010. (k) Dewar, M. J. S. and Doubleday, C., *J. Am. Chem. Soc.,* **1978**, *100*, 4935. (l) Wagner, P. J., *Top. Curr. Chem.,* **1976**, *66*, 1. (m) Stephenson, L. M. and Gibson, T. A., *J. Am. Chem. Soc.,* **1974**, *96*, 5624. (n) Wagner, P. J., *Acc. Chem. Res.,* **1971**, *4*, 168. (o) Brainard, R. and Morrison, H., *J. Am. Chem. Soc.,* **1971**, *93*, 2685. (p) Neckers, D. C.; Kellogg, R. M.; Prins, W. L. and Schoustra, B., *J. Org. Chem.,* **1971**, *36*, 1838. (q) Siqal, P., *J. Phys. Chem.,* **1963**, *67*, 2660.

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Noyori Hydrogenation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Ikariya[1a] and Noyori[1b] concurrently in 1985. It is a ruthenium or rhodium complex-catalyzed reduction of the carbonyl or alkenyl group by hydrogen with high efficiency and excellent enantioselectivity. Therefore, it is generally known as the Noyori hydrogenation[2] or Noyori reduction.[3] Occasionally, it is also referred to as the Noyori transfer hydrogenation[3i,4] or Noyori hydrogen transfer reaction.[3f] The ruthenium complex of [$RuCl_2$\{(R)-BINAP\}\{(R,R)-DPEN\}], where BINAP = 2,2-bis(diphenylphosphino)-1,1-binaphthyl and DPEN = 1,2-diphenylethylene-diamine,[5] is known as the Noyori catalyst[2d,6] or Noyori/Ikariya catalyst.[7] This catalyst is generally prepared in isopropanol by mixing $RuCl_2$ with an excess amount of strong base, such as $KOBu^t$, under hydrogen atmosphere to neutralize the HCl that is formed during the catalyst activation.[8] In this reaction, hydrogen is activated by binding to the ruthenium atom and subsequent attacking from a Brønsted base, such as alkoxide.[6b] During the reduction of ketone, the amino group is crucial to the activity of the catalyst,[8] of which the NH-proton interacts with the oxygen atom of ketone and a hydride bound to ruthenium is transferred to carbon atom of the carbonyl group through a six-membered transition state.[6b] It has been reported that the enantioselectivity arises from the specific recognition of the *re* or *si* face of the carbonyl group,[2d] and the combination of HCO_2H/Et_3N or $HCO_2Na/n\text{-}Bu_4NBr$ in H_2O/CH_2Cl_2 can be used as the hydrogen source.[7a] However, this reaction is not suitable for the compounds with functionalities that could be reduced during the high-pressure hydrogenation.[2d]

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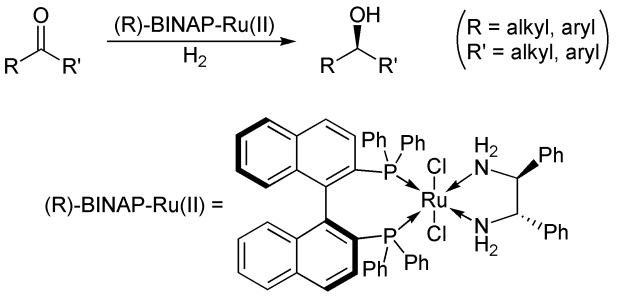
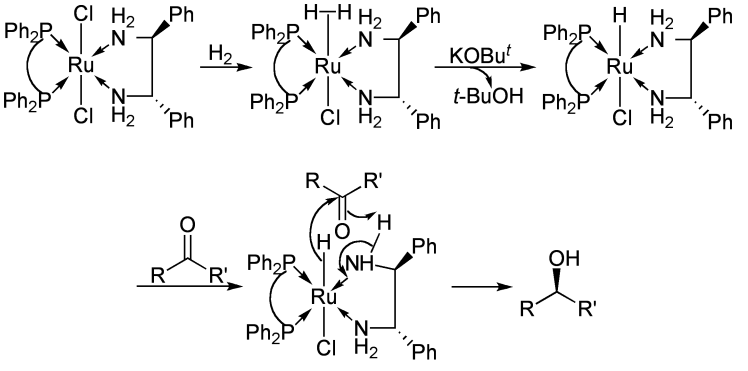
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A part of the mechanism for the catalyzed hydrogenation is shown below.



D. MODIFICATION

This reaction has been modified to use a self-supported catalyst.[5]

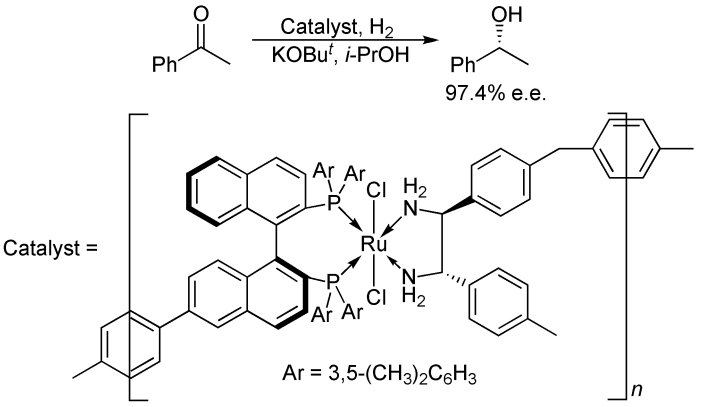
E. APPLICATIONS

This reaction is very useful for the enantiomeric hydrogenation of ketones and olefins.

F. RELATED REACTIONS

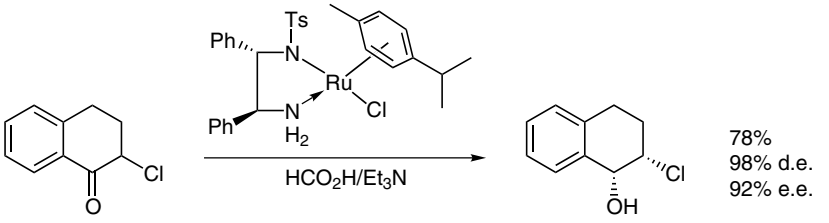
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 5.

To a test tube were added 4.6 mg ruthenium complex (3.0 μmol), 6.8 mg KO-*t*-Bu (60 μmol), 0.36 g acetophenone (3.0 mmol), and 2 mL anhydrous isopropanol under argon. Then the test tube was placed in a stainless-steel autoclave, purged with hydrogen six times, and then sealed. The autoclave was charged with hydrogen (40 atm), and the mixture was stirred at room temperature for 20 h. The remaining hydrogen was release, and the catalyst was recovered by filtration through a cannula under nitrogen. The alcohol was tested with 97.4% e.e.



Reference 7a.

To a solution of 10 μmol catalyst (*S*,*S*)-[RuCl(TsDPEN)(*p*-cymene)] in HCO_2H/Et_3N was added 2 mmol 2-chlorotetralone; the mixture was stirred at room temperature until completion of hydrogenation (5 days). The reaction mixture was then diluted with 20 mL CH_2Cl_2 and washed with a saturated solution of $NaHCO_3$ (2 $\times$ 15 mL). The organic layer was dried and concentrated, and the residue was purified by flash chromatography to afford 78% (1*R*,2*S*)-1-hydroxy-2-chloro-tetralin, with 98% d.e. and 92% e.e.

Other references related to the Noyori hydrogenation are cited in the literature.[9]

H. REFERENCES

1. (a) Ikariya, T.; Ishii, Y.; Kawano, H.; Arai, T.; Saburi, M.; Yoshikawa, S. and Akutagawa, S., *J. Chem. Soc., Chem. Commun.,* **1985**, 922. (b) Inoue, S.; Osada, M.; Koyano, K.; Takaya, H. and Noyori, R., *Chem. Lett.,* **1985**, 1007.
2. (a) Reiff, E. A.; Nair, S. K.; Reddy, B. S. N.; Inagaki, J.; Henri, J. T.; Greiner, J. F. and Georg, G. I., *Tetrahedron Lett*., **2004**, *45*, 5845. (b) Hartmann, R. and Chen, P., *Angew. Chem. Int. Ed.,* **2001**, *40*, 3581. (c) Yang, H. W. and Romo, D., *Tetrahedron,* **1999**, *55*, 6403. (d) Hudlicky, T.; Tsunoda, T.; Gadamasetti, K. G.; Murry, J. A. and Keck, G. E., *J. Org. Chem.,* **1991**, *56*, 3619.
3. (a) Ferrié, L.; Reymond, S.; Capdevielle, P. and Cossy, J., *Org. Lett.,* **2007**, *9*, 2461. (b) Shan, M. D. and O'Doherty, G. A., *Org. Lett.,* **2006**, *8*, 5149. (c) Guo, H. B. and O'Doherty, G. A., *Org. Lett.,* **2006**, *8*, 1609. (d) Maki, K.; Motoki, R.; Fujii, K.; Kanai, M.; Kobayashi, T.; Tamura, S. and Shibasaki, M., *J. Am. Chem. Soc.,* **2005**, *127*, 17111. (e) Guo, H. B. and O'Doherty, G. A., *Org. Lett.,* **2005**, *7*, 3921. (f) Santos, L. S.; Pilli, R. A. and Rawal, V. H., *J. Org. Chem.,* **2004**, *69*, 1283. (g) Marshall, J. A. and Bourbeau, M. P., *Org. Lett.,* **2003**, *5*, 3197. (h) Herb, C. and Maier, M. E., *J. Org. Chem.,* **2003**, *68*, 8129. (i) Vedejs, E.; Trapencieris, P. and Suna, E., *J. Org. Chem.,* **1999**, *64*, 6724.
4. (a) Huckins, J. R. and Rychnovsky, S. D., *J. Org. Chem.,* **2003**, *68*, 10135. (b) Cossrow, J. and Rychnovsky, S. D., *Org. Lett.,* **2002**, *4*, 147.
5. Liang, Y. X.; Jing, Q.; Li, X.; Shi, L. and Ding, K. L., *J. Am. Chem. Soc.,* **2005**, *127*, 7694.
6. (a) Hartmann, R. and Chen, P., *Adv. Synth. Catal.,* **2003**, *345*, 1353. (b) Berkessel, A.; Schubert, T. J. S. and Müller, T. N., *J. Am. Chem. Soc.,* **2002**, *124*, 8693. (c) Chung, J. Y. L.; Zhao, D. L.; Hughes, D. L.; Mcnamara, J. M.; Grabowski, E. J. J. and Reider, P. J., *Tetrahedron Lett*., **1995**, *36*, 7379.
7. (a) Ros, A.; Magriz, A.; Dietrich, H.; Fernández, R.; Alvarez, E. and Lassaletta, J. M., *Org. Lett.,* **2006**, *8*, 127. (b) Li, X. G.; Wu, X. F.; Chen, W. P.; Hancock, F. E.; King, F. and Xiao, J. L., *Org. Lett.,* **2004**, *6*, 3321.
8. Abdur-Rashid, K.; Clapham, S. E.; Hadzovic, A.; Harvey, J. N.; Lough, A. J. and Morris, R. H., *J. Am. Chem. Soc.,* **2002**, *124*, 15104.
9. (a) Wisman, R. V.; de Vries, J. G.; Deelman, B.-J. and Heeres, H. J., *Org. Proc. Res. Dev.,* **2006**. *10*, 423 (b) Santos, L. S.; Fernandes, S. A.; Pilli, R. A. and Marsaioli, A. J., *Tetrahedron: Asymmetry,* **2003**, *14*, 2515. (c) Noyori, R.; Yamakawa, M. and Hashiguchi, S., *J. Org. Chem.,* **2001**, *66*, 7931. (d) Noyori, R. and Ohkuma, T., *Angew. Chem.,* **2001**, *113*, 41. (e) Noyori, R. and Ohkuma, T., *Angew. Chem. Int. Ed.,* **2001**, *40*, 40. (f) Kaldor I.; Feldman, P. L.; Mook, R. A.; Ray, J. A.; Samano, V.; Sefler, A. M.; Thompson, J. B.; Travis, B. R. and Boros, E. E., *J. Org. Chem.,* **2001**, *66*, 3495. (g) Ohkuma, T.; Koizumi, M.; Ikehira, H.; Yokozawa, T. and Noyori, R., *Org. Lett.,* **2000**, *2*, 659. (h) Tietze, L. F.; Zhou, Y. F. and Topken, E., *Eur. J. Org. Chem.,* **2000**, 2247. (i) Meuzelaar, G. J.; van Vliet, M. C. A.: Maat, L. and Sheldon, R. A., *Eur. J. Org. Chem.,* **1999**, 2315. (j) Samano, V.; Ray, J. A.; Thompson, J. B.; Mook, R. A.; Jung, D. K.; Koble, C. S.; Martin, M. T.; Bigham, E. C.; Regitz, C. S.; Feldman, P. L. and Boros, E. E., *Org. Lett.,* **1999**, *1*, 1993. (k) Kitamura, M.; Hsiao, Y.; Ohta, M.; Tsukamoto, M.; Ohta, T.; Takaya, H. and Noyori, R., *J. Org. Chem.,* **1994**, *59*, 297. (l) Noyori, R.; Ohta, M.; Hsiao, Y.; Kitamura, M.; Ohta, T. and Takaya, H., *J. Am. Chem. Soc.,* **1986**, *108*, 7117.

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Nozaki-Hiyama-Kishi Reaction

(Nozaki-Hiyama-Kishi Coupling)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Hiyama and Nozak in 1977[1] and extended by Kishi in 1986.[2] It is a chromium-promoted coupling between a halide and a carbonyl compound. Therefore, it is often known as the Nozaki-Hiyama-Kishi reaction,[3] Nozaki-Hiyama-Kishi coupling,[3n,4] or Nozaki-Hiyama reaction.[3q,5] Occasionally, this reaction is also referred to as the Hiyama-Nozaki reaction,[6] Kishi-Nozaki reaction,[7] or Nozaki-Hiyama-Kishi Ni(II)/Cr(II) coupling.[4f] In addition, an intramolecular version of this reaction to afford a cyclic product is generally called the Nozaki-Hiyama-Kishi cyclization,[3f,3j,3k,8] and the special version of the Nozaki-Hiyama-Kishi reaction involving an allylic nucleophile is termed the Nozak-Hiyama allylation.[5d,9] Overall, this reaction has special features of high aldehyde chemoselectivity,[3t,3u] occurrence under mild conditions[6,10] and the compatibility with a wide range of nucleophiles, such as allyl, propargyl, aryl, and alkenyl halides, alkenyl triflates, allyl sulphonates and phosphates.[3n,3t,3u] However, this reaction does have some weaknesses, such as the high toxicity of chromium (II),[3m,3t,3u] the need of an excess amount of chromium (2 to 16 equivalents),[3t,3u] and the lack of facial selectivity.[3t,4g] It has been suggested that the nucleophile first reacts with Cr^{2+} via an oxidative insertion, the resulting complex then adds to the carbonyl group, and the nickel salt catalyzes the formation of C-Cr bond.[3t] It has been reported that when a bromofluoroalkene is applied as the nucleophile, only (*E*)-bromofluoroalkene couples with the aldehyde, giving moderate to good yields;[10] whereas for the coupling between an aryl bromide and an aromatic aldehyde, the aldehyde with an electron-donating group proceeds ordinarily, but the one with an electron-withdrawing group gives a predominant product of pinacol.[3m] When γ-monosubstituted

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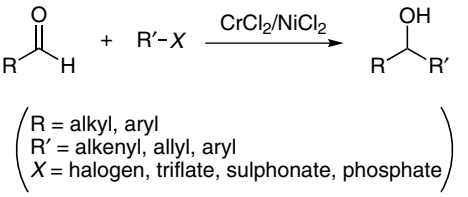
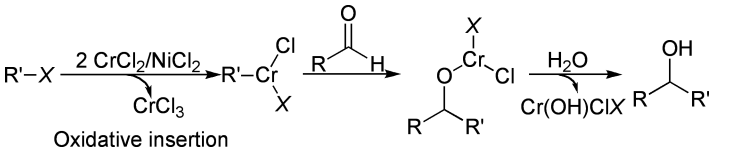
allylhalides are used as the nucleophiles, the corresponding homoallyl alcohols form with an excellent *anti* selectivity, regardless of the original configuration of the allyl halides.[3u] Usually, alkenyl halides or triflates completely retain their double-bond geometry during this coupling.[3u] In addition, this coupling reaction can also occur catalytically with only 7–15% of Cr^{2+} present, which is constantly recycled by the nontoxic manganese powder in the presence of trimethylchlorosilane.[3t,3u] Other catalytic conditions include the regeneration of Cr^{2+} by aluminum[11] or via an electrochemical reduction.[12] Recent development has made this reaction proceed with the control of enantioselectivity in the presence of some chiral ligands, such as salen,[5d] tridentate bis(oxazolinyl)carbazole,[5d] and DIANANE (*endo,endo*-2,5-diaminonorborane).[13]

B. GENERAL REACTION SCHEME

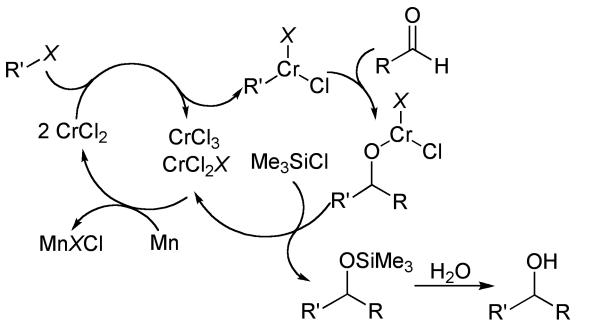


C. PROPOSED MECHANISMS

Although it has been reported that this reaction involves a radical intermediate,[9e] nonradical mechanisms are proposed here, including a stoichiometric Nozaki-Hiyama-Kishi reaction in Scheme 1, and a catalytic version of such reaction in the presence of manganese and trimethylchlorosilane in Scheme 2.



SCHEME 1. *Mechanism of regular Nozaki-Hiyama-Kishi reaction.*



SCHEME 2. *Mechanism of Nozaki-Hiyama-Kishi reaction with manganese and TMSCl present.*

D. MODIFICATION

This reaction has been modified to proceed catalytically,[3t,3u,11,12] by reducing Cr^{3+} back to Cr^{2+}. In addition, it is also made enantioselectively with a chiral ligand present.[5d,13]

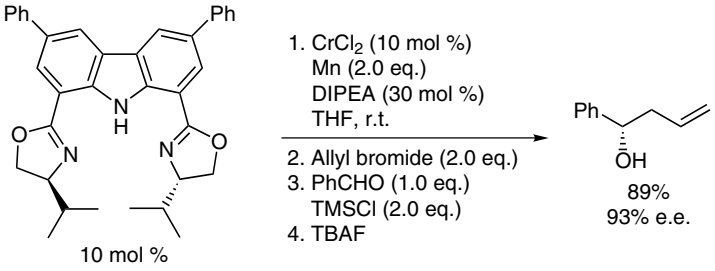
E. APPLICATIONS

This reaction has wide application in organic synthesis, especially for the synthesis of natural products.

F. RELATED REACTIONS

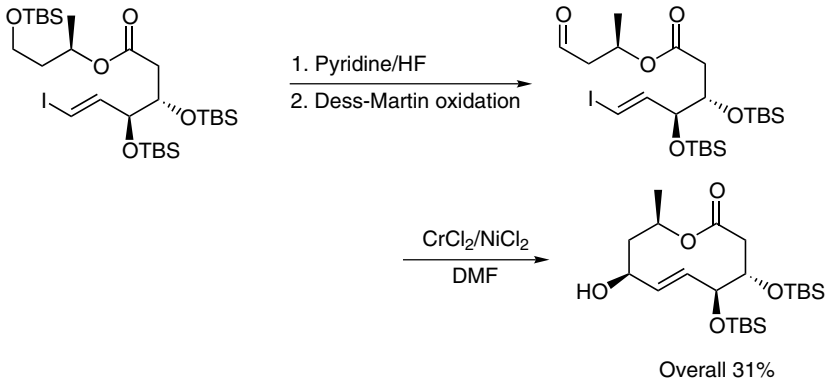
This reaction is related to the *Negishi Cross-Coupling*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 5d.

A mixture of 27.1 mg 1,8-bis[4-(*S*)-isopropyloxazolin-2-yl]-3,6-diphenyl carbazole (0.05 mmol), 6.3 mg $CrCl_2$ (0.051 mmol), and 53.8 mg maganese (0.979 mmol) was azeotroped three times with toluene, dried under high vacuum, and suspended in 2 mL THF. The color of the suspension immediately turned to brown. To the stirred suspension was added 0.026 mL DIEPA (0.15 mmol), and after 5 min to the resulting mixture was added 0.086 mL allylbromide (0.99 mmol). After the mixture was stirred for another 30 min, the color turned to greenish brown. To this stirred mixture was added 0.05 mL benzaldehyde (0.49 mmol), and 0.125 mL TMSCl (0.985 mmol) successively at 0°C. After 12 h the color of the reaction mixture turned to reddish brown. The reaction was quenched with 1 mL saturated $NaHCO_3$ aqueous solution, filtered through Celite, and evaporated under vacuum. The crude product was dissolved in 2 mL THF, and the stirred mixture was treated with 1 mL 1 M TBAF solution. The reaction was quenched with 2 mL saturated NH_4Cl solution, extracted with Et_2O (10 mL $\times$ 4), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 10:1) to afford 64.7 mg (*S*)-1-phenyl-3-butene-1-ol, in a yield of 89% with 93% e.e.



Reference 3j.

This preparation started from 0.0503 g (*R*)-3-(*tert*-butyldimethylsilyloxy)-1-methylpropyl (3*S*,4*S*,5*E*)-3,4-bis-(*tert*-butyldimethylsilyloxy)-6-iodo-5-hexenoate (0.073 mmol), which was deprotected and oxidized to aldehyde using the Dess-Martin periodinane. To a suspension of 0.130 g $CrCl_2$ (1.06 mmol) containing 0.5 mol % $NiCl_2$ in 12 mL degassed DMF was added via cannula the above aldehyde in 2.6 mL degassed DMF (predried with 2 × 0.5 mL benzene). The reaction mixture was stirred overnight at room temperature, and the solvent was distilled off under vacuum (0.1 mmHg). The residue was dissolved in 10 mL saturated NH_4Cl and extracted with Et_2O (4 × 10 mL) and EtOAc (2 × 10 mL). The organic layer was washed with brine (40 mL) and dried over $MgSO_4$. The crude product was purified by flash chromatography (EtOAc/hexane, 10:90, v/v) to yield 10 mg (*4S,5S,8S,10R*)-8-hydroxy-4,5-bis-(*tert*-butyldimethylsilyloxy)-10-methyl-3,4,5,8,9,10-hexahydro-2H-2-oxecinone, in an overall yield of 31% for three steps.

Other references related to the Nozaki-Hiyama-Kishi reaction are cited in the literature.[14]

H. REFERENCES

1. (a) Okude, Y.; Hirano, S.; Hiyama, T. and Nozaki, H., *J. Am. Chem. Soc.*, **1977**, *99*, 3179. (b) Okude, Y.; Hiyama, T. and Nozaki, H., *Tetrahedron Lett.*, **1977**, 3829.
2. Jin, H.; Uenishi, J.; Christ, W. J. and Kishi, Y., *J. Am. Chem. Soc.*, **1986**, *108*, 5644.
3. (a) Ramana, G. V. and Rao, B. V., *Tetrahedron Lett*., **2005**, *46*, 3049. (b) Wang, M. and Shen, J.-K., *Hecheng Huaxue*, **2004**, *12*, 445. (c) Kato, N.; Shimamura, S.; Kikai, Y. and Hirama, M., *Synlett,* **2004**, 2107. (d) Dai, W.-M.; Tachi, Y.; Nishimoto, S.-i.; Zhong, X. and Guo, Z., *Lett. Drug Design & Discovery*, **2004**, *1*, 69. (e) Berkessel, A.; Menche, D.; Sklorz, C. A.; Schröder, M. and Paterson, I., *Angew. Chem. Int. Ed.*, **2003**, *42*, 1032. (f) Bekele, T.; Brunette, S. R. and Lipton, M. A., *J. Org. Chem.*, **2003**, *68*, 8471. (g) Sabino, A. A. and Pilli, R. A., *Tetrahedron Lett.*, **2002**, *43*, 2819. (h) Pilli, R. A. and Victor, M. M., *Tetrahedron Lett.*, **2002**, *43*, 2815. (i) Shaughnessy, K. H. and Huang, R. C., *Synth. Commun.*, **2002**, *32*, 1923. (j) Pilli, R. A. and Victor, M. M., *J. Braz. Chem. Soc.*, **2001**, *12*, 373. (k) MacMillan, D. W. C.; Overman, L. E. and Pennington, L. D., *J. Am. Chem. Soc.*, **2001**, *123*, 9033. (l) Maezaki, N.; Kojima, N.; Sakamoto, A.; Iwata, C. and Tanaka, T., *Org. Lett.*, **2001**, *3*, 429. (m) Durandetti, M.; Médélec, J.-Y. and Périchon, J., *Org. Lett.*, **2001**, *3*, 2073. (n) Blaauw, R. H.; Brière, J.-F.; de Jong, R.; Benningshof, J. C.; van Ginkel, A. E.; Fraanje, J.; Goubitz, K.; Schenk, H.; Rutjes, F. P. J. T. and Hiemstra, H., *J. Org. Chem.*, **2001**, *66*, 233. (o) Dai, W.-M.; Wu, A. and Hamaguchi, W., *Tetrahedron Lett*., **2001**, *42*, 4211. (p) Bandini, M.; Cozzi, P. G. and Umani-Ronchi, A., *Polyhedron*, **2000**, *19*, 537. (q) Baati, R.; Gouverneur, V. and Mioskowski, C., *J. Org. Chem.*, **2000**, *65*, 1235. (r) Yang, H.; Sheng, X. N.

C.; Harrington, E. M.; Ackermann, K.; Garcia, A. M. and Lewis, M. D., *J. Org. Chem.*, **1999**, *64*, 242. (s) Pilli, R. A. and Victor, M. M., *Tetrahedron Lett.*, **1998**, *39*, 4421. (t) Fürstner, A. and Shi, N. Y., *J. Am. Chem. Soc.*, **1996**, *118*, 2533. (u) Fürstner, A. and Shi, N. Y., *J. Am. Chem. Soc.,* **1996**, *118*, 12349.

4. (a) Blakemore, P. R.; Browder, C. C.; Hong, J.; Lincoln, C. M.; Nagornyy, P. A.; Robarge, L. A.; Wardrop, D. J. and White, J. D., *J. Org. Chem.*, **2005**, *70*, 5449. (b) Venkatraman, L.; Aldrich, C. C.; Sherman, D. H. and Fecik, R. A., *J. Org. Chem.*, **2005**, *70*, 7267. (c) Gu, Y. H. and Snider, B. B., *Org. Lett.*, **2003**, *5*, 4385. (d) Nicolaou, K. C.; Namoto, K.; Ritzén, A.; Ulven, T.; Shoji, M.; Li, J.; D'Amico, G.; Liotta, D.; French, C. T.; Wartmann, M.; Altmann, K.-H. and Giannakakou, P., *J. Am. Chem. Soc.*, **2001**, *123*, 9313. (e) Taylor, R. E. and Chen, Y., *Org. Lett.*, **2001**, *3*, 2221. (f) Mi, B. Y. and Maleczka, R. E., *Org. Lett.*, **2001**, *3*, 1491. (g) Pilli, R. A.; Victor, M. M. and de Meijere, A., *J. Org. Chem.*, **2000**,*65*, 5910. (h) Pilli, R. A.; de Andrade, C. K. Z.; Souto, C. R. O. and de Meijere, A., *J. Org. Chem.*, **1998**, *63*, 7811.
5. (a) Inoue, M. and Nakada, M., *Heterocycles*, **2007**, *72*, 133. (b) Iwamoto, M.; Miyano, M.; Utsugi, M.; Kawada, H. and Nakada, M., *Tetrahedron Lett*., **2004**, *45*, 8653. (c) Schrekker, H. S.; Micskei, K.; Hajdu, C.; Patonay, T.; De Bolster, M. W. G. and Wessjohann, L. A., *Adv. Synth. Catal.*, **2004**, *346*, 731. (d) Inoue, M.; Suzuki, T. and Nakada, M., *J. Am. Chem. Soc.*, **2003**, *125*, 1140. (e) Micskei, K.; Kiss-Szikszai, A.; Gyarmati, J. and Hajdu, C., *Tetrahedron Lett*., **2001**, *42*, 7711. (f) Bandini, M.; Cozzi, P. G.; Melchiorre, P. and Umani-Ronchi, A., *Angew. Chem. Int. Ed.*, **1999**, *38*, 3357. (g) Maguire, R. J.; Mulzer, J. and Bats, J. W., *Tetrahedron Lett*., **1996**, *37*, 5487. (h) Eckhardt, M. and Brueckner, R., *Liebigs Ann.*, **1996**, 473. (i) Wipf, P. and Lim, S.,*J. Chem. Soc., Chem. Commun.*, **1993**, 1654. (j) Cintas, P., *Synthesis*, **1992**, 248.
6. Schrekker, H. S.; de Bolster, M. W. G.; Orru, R. V. A. and Wessjohann, L. A., *J. Org. Chem.*, **2002**, *67*, 1975.
7. (a) Inoue, M. and Nakada, M., *Org. Lett.*, **2004**, *6*, 2977. (b) Drouet, K. E. and Theodorakis, E. A., *Chem. Eur. J.*, **2000**, *6*, 1987.
8. (a) Bian, J. W.; Van Wingerden, M. and Ready, J. M., *J. Am. Chem. Soc.*, **2006**, *128*, 7428. (b) Crominboeuf, O.; Overman, L. E. and Pennington, L. D., *J. Am. Chem. Soc.*, **2003**, *125*, 6650. (c) Elliott, M. R.; Dhimane, A.-L.; Hamon, L. and Malacria, M., *Eur. J. Org. Chem.*, **2000**, 155.
9. (a) McManus, H. A.; Cozzi, P. G. and Guiry, P. J., *Adv. Synth. Catal.*, **2006**, *348*, 551. (b) Xia, G. Y. and Yamamoto, H., *J. Am. Chem. Soc.*, **2006**, *128*, 2554. (c) Rozners, E. and Fontanez, J., *Lett. Org. Chem.*, **2005**, *2*, 524. (d) Breitenstein, K.; Llebaria, A. and Delgado, A., *Tetrahedron Lett.*, **2004**, *45*, 1511. (e) Mulzer, J.; Strecker, A. R. and Kattner, L., *Tetrahedron Lett*., **2004**, *45*, 8867. (f) Suzuki, T.; Kinoshita, A.; Kawada, H. and Nakada, M., *Synlett*, **2003**, 570.
10. Dutheuil, G.; Lei, X. S.; Pannecoucke, X. and Quirion, J.-C., *J. Org. Chem.*, **2005**, *70*, 1911.
11. Kurobashi, M.; Tanaka, M.; Kishimoto, S.; Goto, K.; Tanaka, H. and Torii, S., *Tetrahedron Lett.*, **1999**, *40*, 2785.
12. (a) Kurobashi, M.; Tanaka, M.; Kishimoto, S.; Tanaka, H. and Torii, S., *Synlett*, **1999**, 69. (b) Grigg, R.; Putnikovic, B. and Urch, C. J., *Tetrahedron Lett.*, **1997**, *38*, 6307.
13. Berkessel, A.; Schröder, M.; Sklorz, C. A.; Tabanella, S.; Vogl, N.; Lex, J. and Neudörfl, J. M., *J. Org. Chem.*, **2004**, *69*, 3050.
14. (a) Lee, J.-Y.; Miller, J. J.; Hamilton, S. S. and Sigman, M. S., *Org. Lett.*, **2005**, *7*, 1837. (b) Berkessel, A.; Menche, D.; Sklorz, C. A.; Schroeder, M. and Paterson, I., *Angew. Chem.*, **2003**, *115*, 1062. (c) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Morganti, S. and Umani-Ronchi, A., *Org. Lett.*, **2001**, *3*, 1153. (d) Comins, d. L.; Hiebel, A.-C. and Huang, S. L., *Org. Lett.*, **2001**, *3*, 769. (e) Gyarmati, J.; Hajdu, C.; Dinya, Z.; Micskei, K.; Zucchi, C. and Palyi, G., *J. Organomet. Chem.*, **1999**, *586*, 106. (f) Fürstner, A., *Chem. Eur. J.*, **1998**, *4*, 567. (g) McCauley, J. A.; Nagasawa, K.; Lander, P. A.; Mischke, S. G.; Semones, M. A. and Kishi, Y., *J. Am. Chem. Soc.*, **1998**, *120*, 7647. (h) Brimble, M. A.; Fares, F. A. and Turner, P., *J. Chem. Soc., Perkin Trans. I*, **1998**, 677. (i) Kishi, Y., *Pure & Appl. Chem*., **1992**, *64*, 343.

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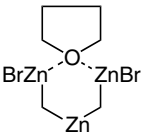
Nysted Reagent
(Nysted Methylenation)

A. GENERAL DESCRIPTION OF THE REACTION

This reagent was first reported by Nysted in 1975.[1] It is the cyclo-dibromo-di-*m*-methylene-(*m*-tetrahydrofuran)-trizinc[2] prepared by treatment of dibromomethane with activated zinc-lead couple[3] or hydrogen chloride-activated zinc dust[3b] in THF and is generally known as the Nysted reagent.[2–4] This reagent, in combination with $TiCl_4$ in THF or CH_2Cl_2, is very useful for converting a carbonyl group,[2b,2c,4c,4e] especially the sterically hindered oxo group, into a methylene group,[2b] and such transformation is known as the Nysted methylenation[5] or Nysted olefination.[2a] In some cases, this reagent is superior to the *Tebbe Reagent* in conversion of a carbonyl group into a methylene group.[6] In addition, during the workup process the protecting group such as MOM acetal can be removed simultaneously.[2b]

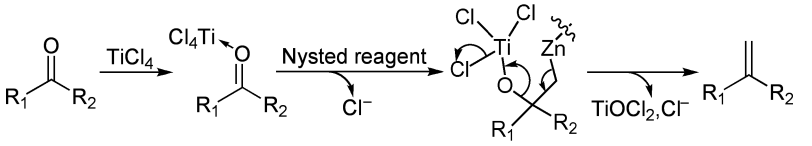
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A part of the mechanism for the olefination of a carbonyl compound is illustrated here.

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang



D. MODIFICATION

N/A

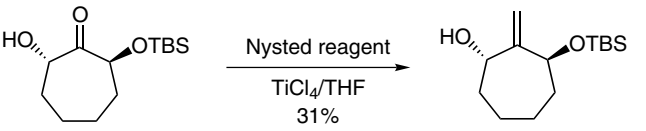
E. APPLICATIONS

This reagent is very useful for the conversion of the carbonyl groups into methylene groups.

F. RELATED REACTIONS

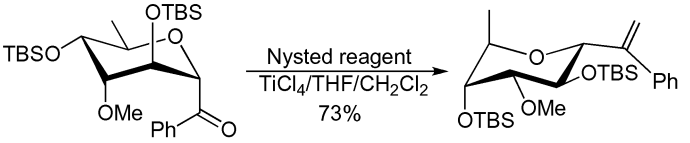
This reagent is related to the *Tebbe Reagent*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4d.

To a flame-dried flask equipped with a stirring bar and a nitrogen-filled balloon was added a 20% suspension of the Nysted reagent (4.23 g in THF, 1.9 mmol) and 3.5 mL THF. The suspension was cooled to 0°C, and 0.21 mL neat titanium tetrachloride (1.9 mmol) was introduced dropwise followed by 0.32 g *trans*-2-(*tert*-butyldimethylsilylox)-7-hydroxy-cycloheptanone (1.24 mmol) in 2.4 mL THF. The mixture was stirred at room temperature for 24 h, quenched with 100 mL 10% HCl, and transferred to a separatory funnel. The product was extracted with ether (3 × 100 mL), and the combined organic phases were dried and concentrated. The residue was purified via silica gel column chromatography using hexane/EtOAc (10:1) as the eluent to afford 74 mg *trans*-2-(*tert*-butyldimethylsilyloxy)-7-hydroxymethylenecycloheptane as a colorless oil, in a yield of 31%.



Reference 4f.

To a slurry of Nysted reagent (20 wt % suspension in THF, 320 mg, 0.7 mmol) and 74 mg 2,6-anhydro-1-phenyl-1-keto-3,5-bis-*O*-*tert*-butyldimethylsilyl-4-*O*-methyl-7-deoxy-α-D-altro-heptitol (0.15 mmol) in 2 mL dry THF at -78°C under nitrogen was added 0.6 mL 1 M $TiCl_4$ in CH_2Cl_2 dropwise. The mixture turned yellow and was warmed to room temperature and stirred overnight ($\sim$14 h). The resulting dark slurry was then cooled in an ice bath, and 0.5 mL Et_3N was added, followed by silica gel. The mixture was warmed to room temperature and was filtered through a plug of silica gel using EtOAc as a wash. The filtrate was concentrated, and the residue was isolated by silica gel column chromatography using petroleum ether/EtOAc (1:19) as eluent to afford 54 mg 3,7-anhydro-1,2,8-trideoxy-2-phenyl-4,6-bis-*O*-*tert*-butyldimethylsilyl-5-*O*-methyl-α-D-altro-oct-1-enitol as an oil, in a yield of 73%.

Other references related to the Nysted reagent are cited in the literature.[7]

H. REFERENCES

1. Nysted, L. N., *U. S. Pat.,* **1975**, Feb. 11, 3,865,848 [*Chem. Abstr.*, **1975**, *83*, 10406q].
2. (a) Ericsson, A.; Marinier, A. and Zusi, F., *U. S. Pat.,* **2004**, Nov. 30, 6,825,233. (b) Aïssa, C.; Riveiros, R.; Ragot, J. and Fürstner, A., *J. Am. Chem. Soc.,* **2003**, *125*, 15512. (c) Tarraga, A.; Molina, P.; López, J. L.; Velasco, M. D.; Bautista, D. and Jones, P. G., *Organometallics,* **2002**, *21*, 2055.
3. (a) Marek, I. and Normant, J.-F., *Chem. Rev.,* **1996**, *96*, 3241. (b) Takai, K.; Kakiuchi, T.; Kataoka, Y. and Utimoto, K., *J. Org. Chem.,* **1994**, *59*, 2668.
4. (a) Chacko, S. A. and Wenthold, P. G., *J. Org. Chem.,* **2007**, *72*, 494. (b) Crich, D. and Banerjee, A., *Org. Lett.,* **2005**, *7*, 1395. (c) Clark, J. S.; Fessard, T. C. and Wilson, C., *Org. Lett.,* **2004**, *6*, 1773. (d) Paquette, L. A.; Hartung, R. E.; Hofferberth, J. E.; Vilotijevic, I. and Yang, J., *J. Org. Chem.,* **2004**, *69*, 2454. (e) Clark, J. S.; Marlin, F.; Nay, B. and Wilson, C., *Org. Lett.,* **2003**, *5*, 89. (f) Pasetto, P. and Franck, R. W., *J. Org. Chem.,* **2003**, *68*, 8042. (g) Matsubara, S.; Sugihara, M. and Utimoto, K., *Synlett,* **1998**, 313. (h) Franck, R. W. and Marzabadi, C. H., *J. Org. Chem.,* **1998**, *63*, 2197. (i) Tochtermann, W.; Bruhn, S.; Meints, M.; Wolff, C.; Peters, E.-M.; Peters, K. and von Schnering, H. G., *Tetrahedron*, **1995**, *51*, 1623.
5. Namyslo, J. C. and Kaufmann, D. E., *Chem. Rev.,* **2003**, *103*, 1485.
6. Watson, A. T.; Park, W. Y.; Wiemer, D. F. and Scott, W. J., *J. Org. Chem.,* **1995**, *60*, 5102.
7. (a) Provoost, O. Y.; Hedley, S. J.; Hazelwood, A. J. and Harrity, J. P. A., *Tetrahedron Lett.,* **2006**, *47*, 331. (b) Tarraga, A.; Molina, P.; Lopez, J. L. and Velasco, M. D., *Tetrahedron Lett*., **2001**, *42*, 8989. (c) Tanaka, M.; Imai, M.; Fujio, M.; Sakamoto, E.; Takahashi, M.; Eto-Kato, Y.; Wu, X. M.; Funakoshi, K.; Sakai, K. and Suemune, H., *J. Org. Chem*., **2000**, *65*, 5806. (d) Tochtermann, W.; Panitzsch, T.; Petroll, M.; Habeck, T.; Schlenger, A.; Wolff, C.; Peters, E.-M.; Peters, K. and von Schnering, H. G., *Eur. J. Org. Chem.,* **1998**, 2651. (e) Zhang, W. and Dowd, P., *Tetrahedron Lett.,* **1995**, *36*, 8539. (f) Nysted, L. N., *Aldrichimica Acta,* **1993**, *26*, 14. (g) Nysted, L. N., *U. S. Pat.,* **1976**, June 1, 3,960,904 [*Chem. Abstr.,* **1976**, *85*, 94618n].

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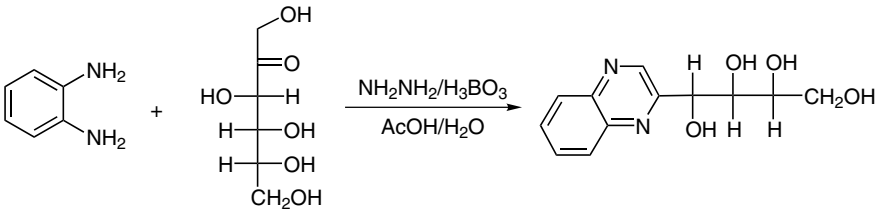
Ohle Quinoxaline Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first studied by Griess and Harrow in 1887,[1] then reported by Hinsberg in 1893,[2] and extensively explored by Ohle since 1934.[3] It is the preparation of 2-tetrahydroxybutyl-quinoxaline from the condensation between a monosaccharide and *o*-phenylenediamine.[4] Unfortunately, the yields are generally low, such as in the range of 15–30%.[5] The most feasible protocol is the one developed by Ohle by reacting monosaccharide, such as fructose, with hydrazine, *o*-phenylenediamine, and boric acid in a dilute acetic acid with bubbling of oxygen into the solution.[6] In addition, the hydrazone/osazone of the sugar is also used to react with *o*-phenylenediamine to give a moderate yield of the quinoxaline derivative.[5,7] Although atmospheric oxygen is the hydrogen acceptor, hydrazine is believed to be a better acceptor because a higher yield of quinoxaline is obtained in the presence of hydrazine.[8] Thus it is assumed that quinoxaline is formed from the reaction between *o*-phenylenediamine and the osazone of the monosaccharide, arising from hydrazine and the monosaccharide in the presence of oxygen. It has been found that the use of other oxidation reagents, such as hydrogen peroxide, benzoyl peroxide, hydroxylamine, methylhydrazine, phenylhydrazine, and semicarbazide provides no obvious advantages over Ohle's protocol.[9] It should be pointed out that hydroxylamine, methylhydrazine, phenylhydrazine, and semicarbazide may not function as the oxidation reagents under these conditions. The generated tetrahydroxybutyl quinoxaline can be converted into flavazole derivatives when refluxed with an excess amount of hydrazine or phenylhydrazine.[3c,3e] In addition, the side chain of quinoxaline can be modified or removed by oxidation.[6a]

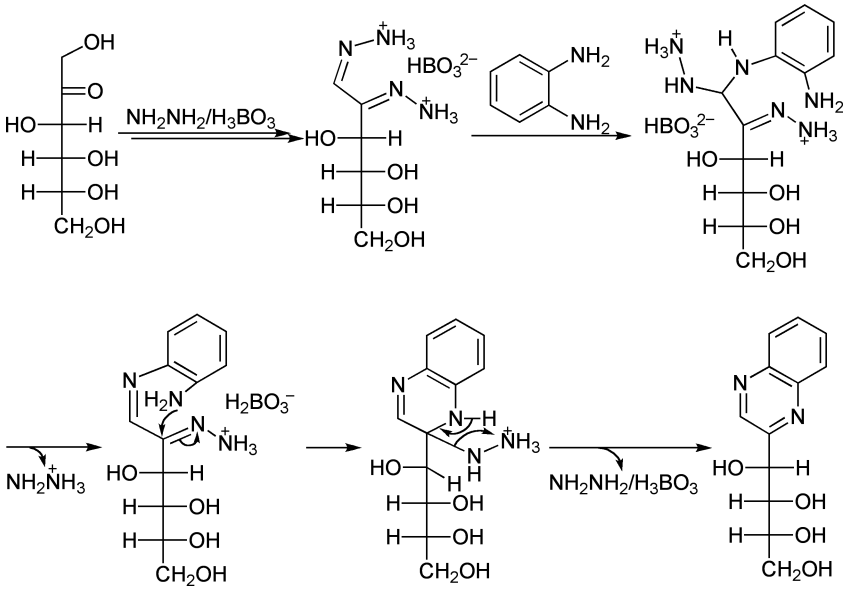
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The mechanism for the formation of hydrazone or osazone of carbohydrate with hydrazine or phenylhydrazine was described in detail for the *Fischer Phenylhydrazone and Osazone Synthesis*, so only a part of the mechanism for the preparation of quinoxaline derivative is illustrated here. The presence of boric acid and acetic acid may help the formation of hydrazone.



D. MODIFICATION

N/A

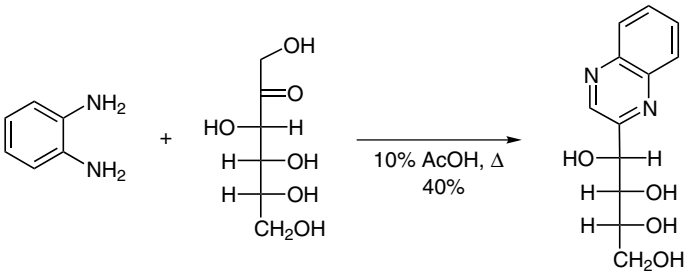
E. APPLICATIONS

This reaction is useful for the formation of quinoxaline derivatives.

F. RELATED REACTIONS

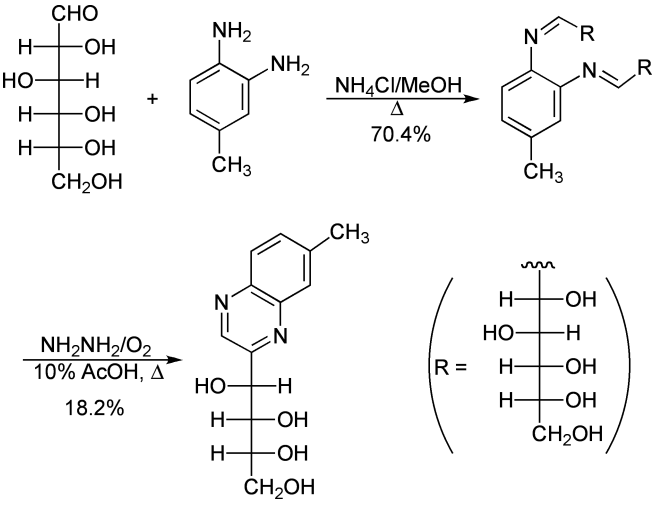
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 5.

1,2-Phenylenediamine (450 g, 4.16 mol) was placed in a 5-L, three-necked, round-bottomed flask equipped with a mechanical stirrer and thermocouple. Aqueous acetic acid (2.0 L, 10% solution) was added to the reactor, and the mixture was stirred for 30 min. Then 750 g D-fructose (4.16 mol) was added portionwise over 20 min. The mixture was heated at 80°C under stirring for 18 h. The reaction mixture was cooled to 10°C for 5 h. The solids were filtered through shark skin filter paper using a Büchner funnel. The solids were washed with water (2 × 500 mL). A rubber dam was placed over the funnel, and the funnel was kept under vacuum for 3 h. The light brown solids were placed in a vacuum oven for 18 h at an oven temperature of 60°C at 1 mmHg to afford 400 g 2-tetrahydroxybutyl-quinoxaline, in a yield of 40%, m.p., 181–184°C.



Reference 8.

A mixture of 36 g D-glucose, 12 g 3,4-diaminotoluene, 0.2 g NH_4Cl, and 800 mL MeOH were refluxed for 30 min. After cooling, the crystalline product was promptly separated by filtration to yield 33.8 g *N*,*N*-di-D-glucosyl-3,4-diaminotoluene, in a yield of 70.4%. This compound was further purified by recrystallization from a large volume of aqueous methanol, m.p., 142–143°C.

The mixture of 4.5 g of *N*,*N*-di-D-glucosyl-3,4-diaminotoluene and 50 mL 10% acetic acid was refluxed for 30 min. Under an ordinary atmosphere, no separable amount of the crystalline product was obtained, but under vigorous passing of oxygen through the solution, 0.35 g 2-D-*arabino*-tetrahydroxybutyl-6-methylquinoxaline was obtained after cooling, in a yield of 7.8%. However, when an equal molar amount of hydrazine was added to the reaction system under ordinary atmosphere, 0.82 g of the quinoxaline derivative was obtained, in a yield of 18.2%, m.p. 177–178°C.

Other references related to the Ohle quinoxaline synthesis are cited in the literature.[10]

H. REFERENCES

1. Griess, P. and Harrow, G., *Ber*., **1887**, *20*, 2205.
2. Hinsberg, O., *Ber*., **1893**, *26*, 3092.
3. (a) Ohle, H., *Ber.,* **1934**, *67*, 155. (b) Erlbach, H. and Ohle, H., *Ber.,* **1934**, *67*, 555. (c) Ohle, H. and Melkonian, G. A., *Ber.,* **1941**, *74*, 279. (d) Ohle, H. and Hielscher, M., *Ber.,* **1941**, *71*, 13. (e) Ohle, H. and Iltgen, A., *Ber.,* **1943**, *76*, 1. (f) Ohle, H. and Kruyff, J. J., *Ber.,* **1944**, *77*, 507.
4. (a) Hall, A. N.; Kulka, D. and Walker, T. K., *Biochem. J.,* **1955**, *60*, 271. (b) Stubbs, J. J.; Lockwood, L. B.; Roe, E. T.; Tabenkin, B. and Ward, G. E., *Ind. Eng. Chem.,* **1940**, *32*, 1626. (c) Muller, A. and Varga, I., *Ber.,* **1939**, *72*, 1993. (d) Maurer, K. and Boettger, B., *Ber.,* **1938**, *71*, 1183.
5. Harms, A. E., *Org. Proc. Res. Dev.,* **2004**, *8*, 666.
6. (a) Lichtenthaler, F. W., *Acc. Chem. Res.,* **2002**, *35*, 728. (b) Lichtenthaler, F. W., *Carbohydrates in Ullmann's Encyclopedia of Industrial Chemistry*, 6th ed. Bailey, J.E.; Brinker.C. J. and Cornils,B., Wiley-VCH Verlag, Weinheim, **2002**, *1*, pp. 1–47.
7. Moore, S. and Link, K. P., *J. Org. Chem.,* **1940**, *5*, 637.
8. Kitaoka, S. and Onodera, K., *J. Org. Chem.,* **1963**, *28*, 231.
9. Petering, H. G. and Schmitt, J. A., *J. Am. Chem. Soc.,* **1949**, *71*, 3977.
10. (a) Chilton, W. S. and Krahn, R. C., *J. Am. Chem. Soc.,* **1968**, *90*, 1318. (b) Chilton, W. S. and Krahn, R. C., *J. Am. Chem. Soc.,* **1967**, *89*, 4129. (c) Towne, J. C. and Spikner, J. E., *Anal. Chem.,* **1963**, *35*, 211. (d) Forrest, H. S. and Walker, J., *J. Chem. Soc.,* **1949**, 79. (e) Forrest, H. S. and Walker, J., *Nature,* **1948**, *161*, 308. (f) Weygand, F. and Bergmann, A., *Ber.,* **1947**, *80*, 255. (g) Lohmar, R. and Link, K. P., *J. Biol. Chem.,* **1943**, *150*, 351. (h) Ohle, H. and Hielscher, M., *Ber.,* **1941**, *74B*, 18. (i) Moore, S. and Link, K. P., *J. Org. Chem.,* **1940**, *5*, 637. (j) Haskins, W. T. and Hudson, C. S., *J. Am. Chem. Soc.,* **1939**, *61*, 1266. (k) Haworth, W. N. and Hirst, E. L., *Ann. Rev. Biochem.,* **1936**, *5*, 81. (l) Maurer, K.; Schiedt, B. and Schroeter, H., *Ber*., **1935**, *68*, 1716.

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Oppenauer Oxidation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Oppenauer in 1937.[1] It is the Lewis acid, primarily aluminum tri-isopropanoxide (i.e., Al(O-*i*-Pr)$_3$), catalyzed oxidation of secondary alcohols into ketones using another ketone or an aldehyde as the oxidant, which in turn is reduced to the corresponding alcohol. Therefore, it is generally known as the Oppenauer oxidation.[2] Because it is the reverse reaction of the *Meerwein-Ponndorf-Verley Reduction*, the interchange between alcohols and ketones in the presence of an aluminum catalyst is referred to as the MPVO reaction.[2h] Compared to other oxidation methods for alcohols, the Oppenauer oxidation is much more benign for the environment[2k] and is tolerated by many other functional groups, including carbon-carbon double and triple bonds, amino groups, aldehyde groups, halogens, and sulfur-containing groups.[2u] In addition, this reaction shows high selectivity[2k] and does not produce carboxylic acid from the overoxidation of a primary alcohol. Thus it is a very common method for the preparation of ketones.[2k] However, the Oppenauer oxidation also has problems in the oxidation of primary alcohols[2k,2u,3] and α-amino alcohols.[2aa,2dd,2ff] The unsuccessful oxidation of primary alcohol probably arises from the further *Aldol Condensation* between aldehyde and ketone, deactivation of the moisture-sensitive catalyst (i.e., deactivation of aluminum alkoxide by water),[2k] and the accompanying *Tishchenko Reaction*.[2m] As a result, an aldehyde such as benzaldehyde is often used as an oxidant in the Oppenauer oxidation.[2j,2m] The failure for oxidation of α-amino alcohol is probably due to the formation of a stable cyclic complex between α-amino alcohol and aluminum alkoxide,[2dd] which does not undergo further reaction. Therefore, some α-amino ketones have been used as oxidants for the Oppenauer oxidation too,[4] such as 1-methyl-4-piperidone.[5] The application of aluminum *t*-butoxide as catalyst is sufficient for the oxidation of an α-amino alcohol to an α-amino ketone at

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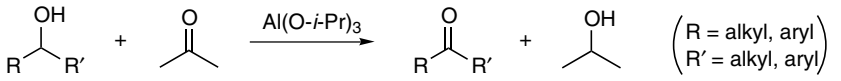
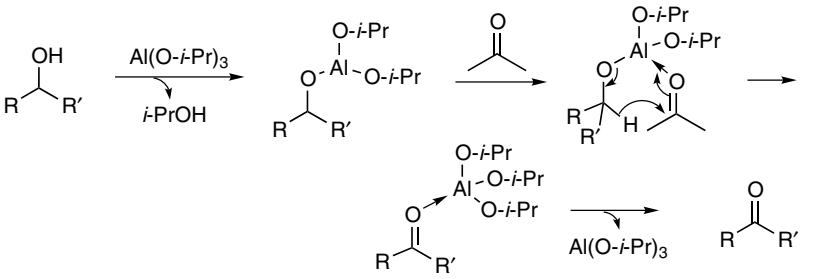
high temperature.[2aa] In addition, cyclohexanone can also be used as oxidant because of its high oxidation potential.[2cc–2ff,4] The Oppenauer oxidation has been extensively modified by the application of different transition metal compounds as catalysts to substitute for aluminum alkoxide, including chromium(III) alkoxide,[2m] magnesium alkoxide,[2a,2c] zirconium alkoxide,[2v] seven-membered oxazirconacycle,[2i] lanthanoid triisopropoxide,[2x] samarium(II) iodide,[2y] Cp*Ir(III) complex,[3,6] $RuCl_2(PPh_3)_3^3$, and heterobimetallic Ir(I)-Ru(II) catalyst.[3] Among these modifications, the Cp*Ir(III) complex can catalyze the oxidation of primary alcohol to aldehyde using 2-butanone as the oxidant,[2k] and the introduction of *N*-heterocyclic carbene ligand can effectively enhance the turnover number for the oxidation of secondary alcohols.[6]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is assumed that the alcohol displaces one of the alcoholic components of aluminum alkoxide to form a new aluminum alkoxide, which then forms a complex with oxidative ketone. The hydrogen transfer occurs through a six-membered transition state to give a new ketone and aluminum alkoxide. The mechanistic details are shown here.



D. MODIFICATION

This reaction has been extensively modified by the use of different transition metal compounds as catalysts, as described in section A.

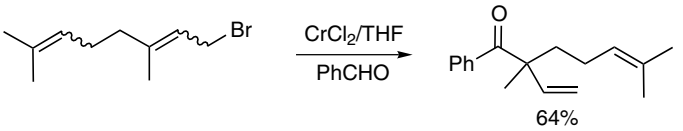
E. APPLICATIONS

This reaction is very useful in the preparation of ketones.

F. RELATED REACTIONS

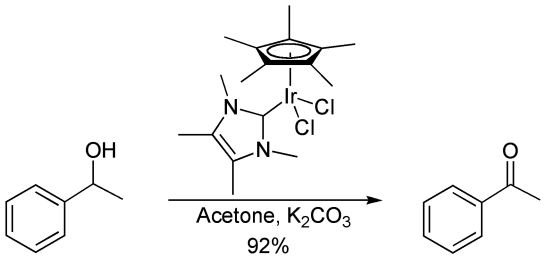
This reaction is closely related to the *Meerwein-Ponndorf-Verley Reduction* and is also related to the *Cannizzaro Reaction* and *Tishchenko Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2m.

To a flask was added 200 mg chromium(II) chloride (1.63 mmol, 2.5 eq.); then 2.5 mL THF was added under vigorous stirring. After a few minutes, 229 mg benzaldehyde (2.16 mmol, 3.0 eq.) and 156.3 mg 3,7-dimethyl-1-bromo-oct-2,6-diene (0.72 mmol, 1.0 eq.) were added. The resulting mixture was stirred for 3 h at 55°C, and the reaction was quenched with brine. The aqueous layer was extracted three times with diethyl ether, and the combined organic fractions were washed twice with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography using diethyl ether as the eluent, to afford 64% 2,6-dimethyl-1-phenyl-2-vinyl-hept-5-en-1-one as a colorless oil, in a yield of 64%, R_f = 0.64 (hexane/EtOAc, 98:2).



Reference 6a.

To a flask were added 20 μmol Cp*Ir(IMeMe)Cl_2 catalyst, 20 μmol K_2CO_3, and 8.0 mL acetone. To another flask were added 20.0 mmol 1-phenylethanol and 8.0 mL acetone. Then the alcohol solution was transferred to the solution containing the iridium catalyst and base, and the resulting mixture was stirred at 40°C for 4 h. After removal of the solvent, the product was analyzed with GC, indicating a 95% conversion of 1-phenylethanol to acetophenone with a yield of 92%, and a turnover number of 920 for such a catalyst.

Other references related to the Oppenauer oxidation are cited in the literature.[7]

H. REFERENCES

1. Oppenauer, R. V., *Rec. Trav. Chim.,* **1937**, *56*, 137.
2. (a) Kloetzing, R. J.; Krasovskiy, A. and Knochel, P., *Chem. Eur. J.,* **2007**, *13*, 215. (b) Gabrielsson, A.; Van Leeuwen, P. and Kaim, W., *Chem. Commun.,* **2006**, 4926. (c) Xin, L. H.; Satterfield, A. D. and Johnson, J. S., *J. Am. Chem. Soc.,* **2006**, *128*, 9302. (d) Letondor, C.; Humbert, N. and Ward, T. R., *Proc. Natl. Acad. Sci.,* **2005**, *102*, 4683. (e) Schroeter, M., *Synth. Commun.,* **2005**, *35*, 2203. (f) Liu, S. H.; Chuah, G. K. and Jaenicke, S., *J. Mol. Catal. A: Chem.,* **2004**, *220*, 267. (g) Hon, Y.-S.; Chang, C.-P. and Wong, Y.-C., *Tetrahedron Lett*., **2004**, *45*, 3313. (h) Klomp, D.; Maschmeyer, T.; Hanefeld, U. and Peters, J. A., *Chem. Eur. J.,* **2004**, *10*, 2088. (i) Zhao, C. J.; Yan, J. and Xi, Z. F. *J. Org. Chem.,* **2003**, *68*, 4355. (j) Schulze, V.; Nell, P. G.; Burton, A. and Hoffmann, R. W., *J. Org. Chem.,* **2003**, *68*, 4546. (k) Suzuki, T.; Morita, K.; Tsuchida, M. and Hiroi, K., *J. Org. Chem.,* **2003**, *68*, 1601. (l) Quan, H.-J.; Koyanagi, J.; Ohmori, K.; Uesato, S.; Tsuchido, T. and Saito, S., *Eur. J. Med. Chem.,* **2002**, *37*, 659. (m) Schrekker, H. S.; de Bolster, M. W. G.; Orru, R. V. A. and Wessjohann, L. A., *J. Org. Chem.,* **2002**, *67*, 1975. (n) Creyghton, E. J. and van der Waal, J. C., *Meerwein-Ponndorf-Verley Reduction Oppenauer Oxidation, and Related Reactions* in Fine Chemicals through Heterogeneous Catalysis, ed. Sheldon, R.A. and van Bekkum, H., Wiley-VCH Verlag GmbH, Weinheim, **2001**, pp. 438–448. (o) Bartosova, M.; Cerveny, L. and Wichterlova, B., *Chem. Listy,* **2001**, *95*, 278. (p) Laxmi, Y. R. S. and Bäckvall, J.-E., *Chem. Commun.*, **2000**, 611. (q) Ciocan-Tarta, I.; Vlassa, M.; Silberg, I. A. and Oprean, I., *Revue Roumaine Chim*., **1999**, *44*, 45. (r) Raja, T.; Jyothi, T. M.; Sreekumar, K.; Talawar, M. B.; Santhanalakshmi, J. and Rao, B. S., *Bull. Chem. Soc. Jpn.,* **1999**, *72*, 2117. (s) Akamanchi, K. G. and Chaudhari, B. A., *Tetrahedron Lett*., **1997**, *38*, 6925. (t) Fujita, M.; Takarada, Y.; Sugimura, T. and Tai, A., *Chem. Commun.,* **1997**, 1631. (u) Ishihara, K.; Kurihara, H. and Yamamoto, H., *J. Org. Chem.,* **1997**, *62*, 5664. (v) Krohn, K.; Knauer, B.; Kuepke, J.; Seebach, D.; Beck, A. K. and Hayakawa, M., *Synthesis,* **1996**, 1341. (w) Tassignon, P.; de Rijk, T.; de Wit, D. and de Buyck, L., *Chem. Phys. Lipids,* **1994**, *74*, 39. (x) Okano, T.; Matsuoka, M.; Kinoshita, M. and Kiji, J., *Nippon Kagaku Kaishi,* **1993**, 487. (y) Molander, G. A. and McKie, J. A., *J. Am. Chem. Soc.,* **1993**, *115*, 5821. (z) Rosenfeld, R. S.; Paul, I. and Zumoff, B., *J. Lipid Res.,* **1983**, *24*, 781. (aa) Warnhoff, E. W. and Reynolds-Warnhoff, P., *J. Org. Chem.,* **1963**, *28*, 1431. (bb) Michel, R. H. and Murphey, W. A., *J. Poly. Sci.,* **1962**, *60*, S45. (cc) Ringold, H. J.; Löken, B.; Rosenkranz, G. and Sondheimer, F., *J. Am. Chem. Soc.,* **1956**, *78*, 816. (dd) Lutz, R. E. and Wayland, R. L., *J. Am. Chem. Soc.,* **1951**, *73*, 1639. (ee) Gleason, C. H. and Holden, G. W., *J. Am. Chem. Soc.,* **1950**, *72*, 1751. (ff) Lutz, R. E.; Jordan, R. H. and Truett, W. L., *J. Am. Chem. Soc.,* **1950**, *72*, 4085. (gg) Rapoport, H.; Naumann, R.; Bissell, E. R. and Bonner, R. M., *J. Org. Chem.,* **1950**, *15*, 1103.
3. Gauthier, S.; Scopelliti, R. and Severin, K., *Organometallics,* **2004**, *23*, 3769.
4. Almeida, M. L. S.; Kocovsky, P. and Bäckvall, J.-E., *J. Org. Chem.,* **1996**, *61*, 6587.
5. (a) Kirk, D. N.; Rajagopalan, M. S. and Varley, M. J., *J. Chem. Soc., Perkin Trans. I,* **1983**, 2225. (b) Keana, J. F. W. and Reich, R., *Synth. Commun.,* **1972**, *2*, 323.
6. (a) Hanasaka, F.; Fujita, K.-i. and Yamaguchi, R., *Organometallics,* **2005**, *24*, 3422. (b) Hanasaka, F.; Fujita, K.-I. and Yamaguchi, R., *Organometallics,* **2004**, *23*, 1490.
7. (a) Bunnell, A.; O'Yang, C.; Petrica, A. and Soth, M. J., *Synth. Commun.,* **2006**, *36*, 285. (b) Ooi, T.; Otsuka, H.; Miura, T.; Ichikawa, H. and Maruoka, K., *Org. Lett.,* **2002**, *4*, 2669. (c) Zheng, B. and Srebnik, M., *J. Org. Chem.,* **1995**, *60*, 3278. (d) Jones, R. A. Y. and Bunnett, J. F., *Pure & Appl. Chem.,* **1989**, *61*, 725. (e) Ishii, Y.; Nakano, T.; Inada, A.; Kishigami, Y.; Sakurai, K. and Ogawa, M., *J. Org. Chem.,* **1986**, *51*, 240. (f) Kamernitskii, A. V.; Reshetova, I. G. and Chernyuk, K. Y., *Pharm. Chem. J.,* **1977**, *11*, 1501. (g) Oppenauer, R. V., *Org. Synth. Coll.*, **1955**, 3, 207.

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Orton Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Bender in 1886,[1] subsequently by Armstrong in 1890,[2] and was extensively explored by Orton et al. beginning in 1899.[3] It is the rearrangement of an *N*-chloro acyl anilide into an *N*-acyl *p*-chloroanilide in the presence of an acid such as HCl. Therefore, it is generally known as the Orton rearrangement.[4] This reaction is assumed to proceed via a multistep processes, including the liberation of chlorine and subsequent electrophilic substitution,[4i,5] as suggested by Orton.[3a] The former step is reversible, whereas the electrophilic substitution is irreversible.[4i,5] Although hypochlorous acid has been proposed as the intermediate during the chlorination at the aromatic ring[3e] because the Orton rearrangement occurs readily in a chlorinating solution in which HClO is the major species,[4b] this mechanism was abandoned by Orton.[3p] It is known that the Orton rearrangement is promoted simultaneously by proton (i.e., H^+) and chloride.[5b] The rearrangement of acetyl *N*-chloroanilide in acetic acid containing NaCl and sodium acetate buffer is a first-order reaction, and the reaction rate is accelerated by the addition of acetanilide or *N*-acetonaphthalide, with a maximal rate limit.[5c] It has been found that both solvent composition[5a] and substrate influence this rearrangement.[4i] For example, in acetic acid, no hydrogen chloride is detected,[5a] and no chlorination products are formed by the treatment of tertiary acyl anilides such as *N*-methyl benzanilide and *N*-phenyl benzanilide.[6] In addition, the Orton rearrangement can be triggered by a Lewis acid, such as $AgBF_4$,[7] as well as by light,[8] such as irradiation from a mercury-vapor lamp even in solid state.[9] Furthermore, the chlorination of acyl anilide from chlorine can proceed by two paths: the normal Orton rearrangement via *N*-chlorination or the direct chlorination of the aromatic ring, which may take place independently and simultaneously.[4i]

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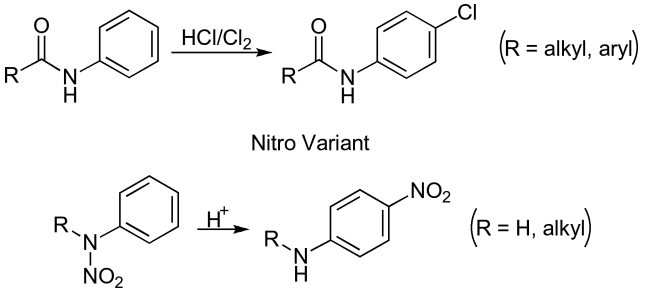
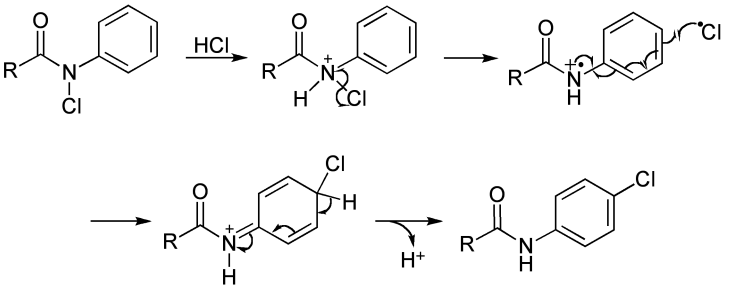
Similar to the migration of chlorine, the nitro group has also been found to rearrange in a similar fashion when *N*-nitro-anilides are treated with a strong acid.[10] During these rearrangements, when the *para* position of the aniline moiety is occupied by an electron-donating group (such as Me, F, Cl, Br, Ph, and PhO), the *ortho*-nitroanilides are formed. In one case, the *para*-bromo group is found to be replaced by a nitro group. However, when the *para*-position is occupied by an electron-withdrawing group, such as a nitro, cyano, or sulfonyl group, then the rearrangement is relatively suppressed.[10c] It has been found that both the rearrangement yield and the *ortho*/*para* ratio of isomers increase when the solvent viscosity is increased.[10a] It is interesting that in the presence of HNO_3, H_2SO_4, HCl, or $HClO_4$, *N*-nitro-2,4-dichloroaniline is converted into 2-nitro-4,6-dichloroaniline,[11] whereas 2,4-dichlorobenzenediazonium bromide is obtained quantitatively in the presence of HBr.[12]

B. GENERAL REACTION SCHEME

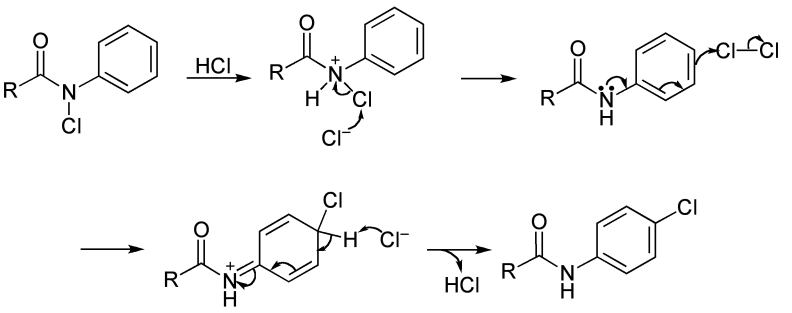


C. PROPOSED MECHANISMS

Although a mechanism involving the formation of chlorine and subsequent electrophilic substitution has been proposed, it is possible that the N-Cl bond in the protonated *N*-chloro acyl anilide cleaves homolytically to form a chloro radical and an anilide radical, and the chloro radical adds to the *para*-position of the aniline moiety to form a conjugated iminium cation, followed by the elimination of the *para*-proton to give the rearranged product (Scheme 1). Alternatively, it is possible that after the protonation of *N*-chloro acyl anilide, chloride undergoes a halophilic substitution to form chlorine, then chlorine undergoes the electrophilic substitution (Scheme 2).



SCHEME 1. *Orton rearrangement involving a radical mechanism.*



SCHEME 2. *Orton rearrangement involving the chlorination by chlorine.*

D. MODIFICATION

N/A

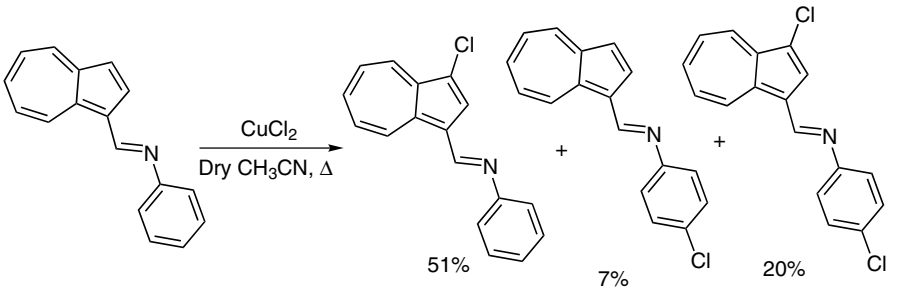
E. APPLICATIONS

This reaction is useful for the preparation of *para*-halo anilides.

F. RELATED REACTIONS

N/A

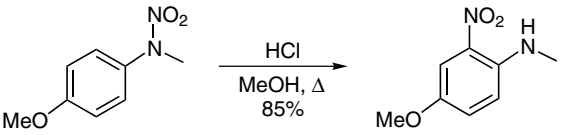
G. CITED EXPERIMENTAL EXAMPLES



Reference 4e.

Anhydrous copper chloride (0.121 g, 0.9 mmol) was dissolved in 10 mL boiling MeCN (distilled on CaH_2), and a yellow solution was obtained. Then 0.3 mmol *N*-(azulen-1-ylmethylene)aniline was added, and the color of the solution turned to red. The solution was vigorously refluxed for 5 h, then MeCN was evaporated to ~5 mL. After cooling to room temperature, 50 mL benzene and 50 mL saturated $NaHCO_3$ solution were

added, and the color of the organic layer turned to green. The organic layer was washed with water and dried over Na_2SO_4. The solvent was evaporated in vacuo to give 51% *N*-(3-chloroazulen-1-ylmethylene)aniline, 7% *N*-(azulen-1-ylmethylene)-4-chloroaniline, and 20% *N*-(3-chloroazulen-1-ylmethylene)-4-chloroaniline.



Reference 10c.

A mixture of 1.0 g *p*-methoxy-*N*-nitro-*N*-methylaniline, 50 mL methanol, and 50 mL conc. HCl was refluxed for 2 h and then allowed to stand for 20 h at 25°C. The solution was cooled to 0°C, and the solid product was collected by suction filtration. The solid was purified by neutral alumina column chromatography using benzene as the eluent to afford 85% 2-nitro-4-methoxyl-*N*-methylaniline, m.p. 98–99°C.

Other references related to the Orton rearrangement are cited in the literature.[13]

H. REFERENCES

1. Bender, G., *Ber.,* **1886**, *19*, 2272.
2. Armstrong, H. E., *J. Chem. Soc., Trans.,* **1900**, *77*, 1047.
3. (a) Chattaway, F. D. and Orton, K. J. P., *J. Chem. Soc.,* **1899**, *75*, 1046. (b) Chattaway, F. D.; Orton, K. J. P. and Hurtley, W. H., *J. Chem. Soc., Trans.,* **1900**, *77*, 800. (c) Chattaway, F. D. and Orton, K. J. P., *J. Chem. Soc., Trans.,* **1900**, *77*, 797. (d) Chattaway, F. D. and Orton, K. J. P., *J. Chem. Soc., Trans.,* **1900**, *77*, 787. (e) Chattaway, F. D. and Orton, K. J. P., *J. Chem. Soc., Trans.,* **1900**, *77*, 134. (f) Chattaway, F. D. and Orton, K. J. P., *J. Chem. Soc., Trans.,* **1901**, *79*, 816. (g) Orton, K. J. P., *Proc. Chem. Soc.,* (London), **1902**, *18*, 200. (h) Orton, K. J. P. and Smith, A. E., *J. Chem. Soc.,* **1905**, *87*, 389. (i) Orton, K. J. P. and Smith, A. E., *Proc. Chem. Soc.,* **1905**, *21*, 91. (j) Kipping, F. S.; Orton, K. J. P.; Ruhemann, S.; Lapworth, A. and Hewitt, J. T., *Brit. Assoc. Rep.,* **1905**, 103. (k) Reed, W. W. and Orton, K. J. P., *J. Chem. Soc., Trans.,* **1907**, *91*, 1543. (l) Smith, A. E. and Orton, K. J. P., *Proc. Chem. Soc.,* **1907**, 23, 14. (m) Orton, K. J. P. and Pearson, C., *J. Chem. Soc., Trans.,* **1908**, *93*, 725. (n) Smith, A. E. and Orton, K. J. P., *Proc. Chem. Soc.,* **1908**, *24*, 27. (o) Kipping, F. S.; Orton, K. J. P.; Rhemann, S.; Lapworth, A. and Hewitt, J. T., *Chem. News & J. Ind. Sci.,* **1908**, *96*, 85. (p) Orton, K. J. P. and Jones, W. J., *J. Chem. Soc., Trans.,* **1909**, *95*, 1456. (q) Orton, K. J. P. and Jones, W. J., *Proc. Chem. Soc.,* **1909**, *25*, 196. (r) Jones, W. J. and Orton, K. J. P., *J. Chem. Soc., Trans.,* **1909**, *95*, 1056.
4. (a) Madhavi, N.; Sundar, B. S. and Radhakrishnamurti, P. S., *Oxidation Commun.,* **2006**, *29*, 908. (b) Soice, N. P.; Maladono, A. C.; Takigawa, D. Y.; Norman, A. D.; Krantz, W. B. and Greenberg, A. R., *J. Appl. Poly. Sci.,* **2003**, *90*, 1173. (c) Medina, I. C. R. and Hanson, J. R., *J. Chem. Res.,* **2003**, 428. (d) Ghosh, S. and Baul, S., *Synth. Commun.,* **2001**, *31*, 2783. (e) Razus, A. C.; Nitu, C.; Carvaci, S.; Birzan, L.; Razus, S. A.; Pop, M. and Tarko, L., *J. Chem. Soc*., *Perkin Trans. 1*, **2001**, 1227. (f) Kannan, P.; Venkatachalaphathy, C. and Pitchumani, K., *Indian J. Chem., Sect. B,* **1999**, *38B*, 384. (g) Yamamoto, J.; Tada, M. and Isoda, Y., *Nihon Yukagakkaishi*, **1999**, *48*, 607. (h) Yamamoto, J.; Tada, M.; Kojima, H. and Isoda, Y., *Nihon Yukagakkaishi*, **1999**, *48*, 463. (i) Glater, J.; Hong, S.-k and Elimelech, M., *Desalination,* **1994**, *95*, 325. (j) Yamamoto, J. and Matsumoto, H., *Chem. Express,* **1988**, *3*, 419. (k) Jayaram, B. and Mayanna, S. M., *React. Kinetics*

Catal. Lett., **1983**, *24*, 379. (l) Golding, P. D.; Reddy, S.; Scott, J. M. W.; White, V. A. and Winter, J. G., *Can. J. Chem.,* **1981**, *59*, 839. (m) Mahadevappa, D. S.; Rangappa, K. S. and Gowda, N. M. M., *React. Kinetics Catal. Lett.,***1980**, *15*, 13. (n) Scott, J. M. W. and Martin, J. G., *Can. J. Chem.,* **1966**, *44*, 2901. (o) Verma, S. M. and Srivastava, R. C., *Indian J. Chem.,* **1965**, *3*, 266. (p) Scott, J. M. W. and Martin, J. G., *Can. J. Chem.,* **1965**, *43*, 732. (q) Scott, J. M. W., *Can. J. Chem.,* **1960**, *38*, 2441. (r) Dewar, M. J. S. and Scott, J. M. W., *J. Chem. Soc.,* **1957**, 2676. (s) Dewar, M. J. S. and Scott, J. M. W., *J. Chem. Soc.,* **1957**, 1445. (t) Dewar, M. J. S. and Scott, J. M. W., *J. Chem. Soc.,* **1955**, 1845.

5. (a) Olson, A. R. and Hornel, J. C., *J. Org. Chem.,* **1939**, *4*, 76. (b) Percival, J. O. and La Mer, V. K., *J. Am. Chem. Soc.,* **1936**, *58*, 2413. (c) Barnes, C. D. and Porter, C. W., *J. Am. Chem. Soc.,* **1930**, *52*, 2973.
6. Kawaguchi, T. and Tamura, H., *J. Appl. Poly. Sci.,* **1984**, *29*, 3359.
7. Loeppky, R. N. and Rotman, M., *J. Org. Chem.,* **1967**, *32*, 4010.
8. Naumov, P.; Sakurai, K.; Tanaka, M. and Hara, H., *J. Phys. Chem. B,* **2007**, *111*, 10373.
9. Porter, C. W. and Wilbur, P., *J. Am. Chem. Soc.,* **1927**, *49*, 2145.
10. (a) White, W. N.; White, H. S. and Fentiman, A., *J. Org. Chem.,* **1976**, *41*, 3166. (b) White, W. N.; Hathaway, C. and Huston, D., *J. Org. Chem.,* **1970**, *35*, 737. (c) White, W. N. and Klink, J. R., *J. Org. Chem.,* **1970**, *35*, 965. (d) White, W. N. and White, H. S., *J. Org. Chem.,* **1970**, *35*, 1803.
11. Orton, K. J. P., *Chem. News,* **1912**, *106*, 236.
12. Orton, K. J. P., *Brit. Assoc. Advan. Sci. Rep.,* **1908**, 115.
13. (a) Rhee, E. S. and Shine, H. J., *J. Am. Chem. Soc.,* **1986**, *108*, 1000. (b) White, W. N. and Golden, J. T., *J. Org. Chem.,* **1970**, *35*, 2759. (c) Bieron, J. F. and Dinan, F. J., "Rearrangement and Elimination of the Amido Group," in *The Chemistry of Amides*, ed., Zabicky, J., Wiley Interscience, New York, **1970**, pp. 263–266. (d) Orton, K. J. P.; Soper, F. G. and Williams, G., *J. Chem. Soc.,* **1928**, 998. (e) Kipping, F. S.; Orton, K. J. P.; Ruhemann, S.; Hewitt, J. T. and Grey, W. H., *Chem. News,* **1913**, *108*, 155. (f) Orton, K. J. P. and Jones, W. J., *J. Chem. Soc.,* **1909**, *95*, 1456.

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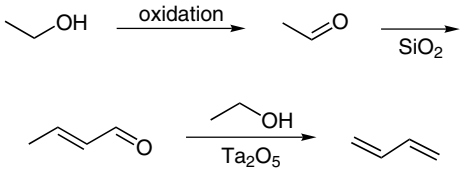
Ostromislensky Process

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Ostromislensky in 1915.[1] It is a two-step process for the manufacturing of 1,3-butadiene from ethanol, involving the dehydrogenation of ethanol to acetaldehyde and the deoxygenation of crotonaldehyde. Therefore, it is known as the Ostromislensky process[2] or Ostromislensky reaction.[2] The crucial step in this process is the conversion of acetaldehyde into crotonaldehyde.[2] For the industrial production of 1,3-butadiene, a mixture of ~69 wt % of ethanol, 24 wt % of acetaldehyde, and 7 wt % of water is passed over a tanta catalyst (Ta_2O_5) supported on silica gel (2% Ta_2O_5/98% SiO_2) at 350°C.[3] This process provided > 60% of the emergency need of 1,3-butadiene for rubber during World War II in the United States.[4] It is known that silica gel is critical for the condensation of acetaldehyde, while Ta_2O_5 catalyzes the deoxygenation of crotonaldehyde in the presence of ethanol.[3] Alternatively, Zirconia can be used as catalyst for this reaction.[2]

B. GENERAL REACTION SCHEME



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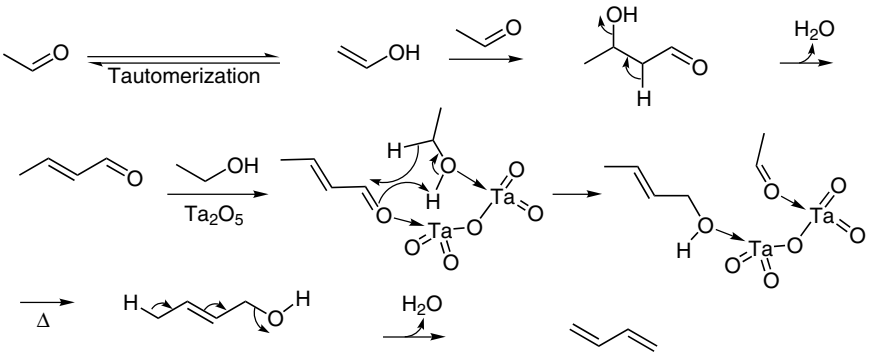
C. PROPOSED MECHANISMS

Only a part of the mechanism for this industrial process is given here.



D. MODIFICATION

N/A

E. APPLICATIONS

This process has very important industrial application in the production of 1,3-butadiene for rubber.

F. RELATED REACTIONS

This reaction is related to the *Lebedev Process*.

G. CITED EXPERIMENTAL EXAMPLES

Because this is an industrial process for the production of 1,3-butadiene and no experiment at the laboratorial scale is available, no experimental protocol is provided for this reaction.

Other references related to the Ostromislensky process are cited in the literature.[5]

H. REFERENCES

1. Ostromislensky, L. I., *J. Russ. Phys. Chem. Soc.,* **1915**, *47*, 1494.
2. Toussaint, W. J.; Dunn, J. T. and Jackson, D. R., *Ind. Eng. Chem.,* **1947**, *39*, 121.
3. Jones, H. E.; Stahly, E. E. and Corson, B. B., *J. Am. Chem. Soc.,* **1949**, *71*, 1822.

4. Corson, B. B.; Jones, H. E.; Welling, C. E.; Hinckley, J. A. and Stahly, E. E., *Ind. Eng. Chem.,* **1950**, *42*, 359.

5. (a) Fisher, H. L., *Ind. Eng. Chem.,* **1954**, *46*, 2067. (b) Fisher, H. L., *Ind. Eng. Chem.,* **1951**, *43*, 290. (c) Kampmeyer, P. M. and Stahly, E. E., *Ind. Eng. Chem.,* **1949**, *41*, 550. (d) Quattlebaum, W. M.; Toussaint, W. J. and Dunn, J. T., *J. Am. Chem. Soc.,* **1947**, *69*, 593. (e) Egloff, G. and Hulla, G., *Chem. Rev.,* **1945**, *36*, 73.

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Overman Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Overman in 1974.[1] It is a thermal or Hg(II) or Pd(II) promoted rearrangement of an allyl trichloroacetimidate into an allyl trichloroacetamide. Therefore, it is generally known as the Overman rearrangement.[2] Occasionally, it is also referred to as the *aza-oxa*-Cope rearrangement[2c] or the Overman imidate rearrangement.[3] In this reaction, allyl trichloroacetimidate, readily available by the treatment of allyl alcohol with trichloroacetonitrile in the presence of a catalytic amount of potassium hydride,[3] undergoes a [3,3]-sigmatropic rearrangement with an excellent regiochemical[2c] and geometrical control[2c] as well as the complete retention of stereochemistry.[2d] The resulting allylic trichloroacetamides can be hydrolyzed or degraded into a wide variety of nitrogen-containing products, including amino sugars, nucleosides, peptides, amino acids, and many nitrogen heterocycles.[2b] The Overman rearrangement is generally carried out in a dry and nonnucleophilic solvent to minimize the hydrolysis of allyl trichloroacetimidate.[2b] It has been found that the substitution of potassium hydride with a catalytic amount of DBU (20 mol %) improves the yield from a substrate with an aromatic group at the terminal carbon of the allylic moiety.[2n,3] This reaction is especially useful for the preparation of the sterically hindered allylic amines that are difficult to obtain from conventional methods.[4] However, when the allylic double bond is a part of α,β-unsaturated carbonyl system or is attached with a strong electron-withdrawing group, such as dienyl ester, the Overman rearrangement is unsuccessful.[5] In addition, this rearrangement is problematic for the unsaturated pyranose substrates with axial hydroxy groups at the 1 and 4 positions.[6]

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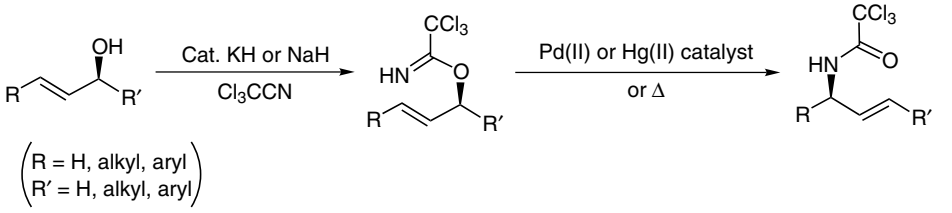
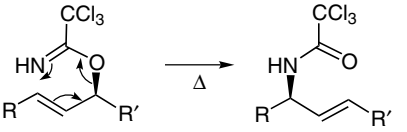
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

This reaction is believed to undergo a [3,3]-sigmatropic rearrangement, as shown below for the thermal rearrangement.



D. MODIFICATION

This reaction has been modified by using a chiral Pd(II) catalyst to yield allylic trichloroacetamides with good enantioselectivity.[7] In addition, a [3,3]-sigmatropic rearrangement of alloxy iminodiaza-phospholidines has been implemented recently for the preparation of different nitrogen-containing molecules.[2c]

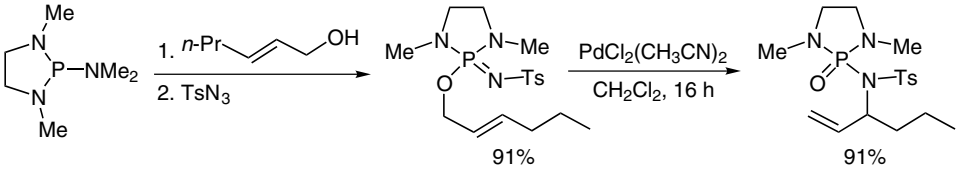
E. APPLICATIONS

This reaction has wide application in organic synthesis for the preparation of a wide variety of nitrogen-containing compounds.

F. RELATED REACTIONS

This reaction is related to the *Cope Rearrangement, Claisen Rearrangement*, etc.

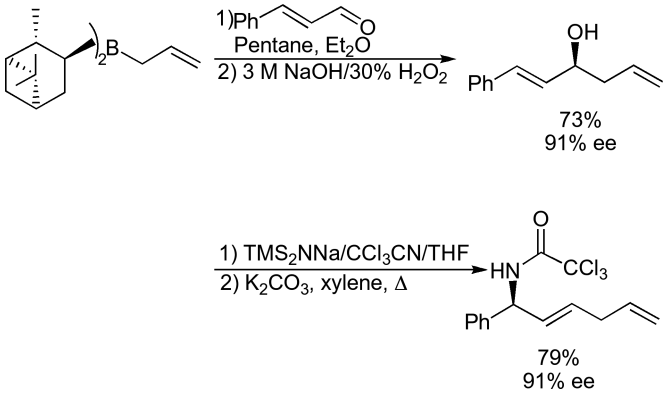
G. CITED EXPERIMENTAL EXAMPLES



Reference 2c.

To a flame-dried round-bottomed flask containing 0.6 mmol diazophospholidinyl dimethylamine in 6 mL benzene, was added 0.6 mmol hex-2-en-1-ol under nitrogen. The mixture was stirred for 6 h under a dynamic atmosphere of nitrogen and then checked for completion by ^{31}P NMR. Tosyl azide (0.6 mmol) was then slowly added to the stirring solution, resulting in rapid effervescence. After the complete addition of tosyl azide, the solution was stirred for 15 min and concentrated in vacuo to yield a crude syrup. The crude syrup was then dissolved in a minimum amount of CH_2Cl_2 and purified by flash column chromatography (EtOAc/hexanes, 1.5:1 + 5% NEt_3) to afford 91% (*E*)-*N*-(2-hex-2-enyloxy-1,3-dimethyl-2λ^5-[1,3,2]diazaphospholidin-2-ylidene)-4-methylbenzene-sulfonamide as a clear oil, $R_f = 0.38$ (EtOAc/hexanes, 2:1).

To a flame-dried round-bottomed flask under nitrogen, was added 8 mg bis(acetonitrile)dichloropalladium(II) (5 mol %) and 0.67 mmol iminodiazophospholidine in 5 mL CH_2Cl_2; the resulting solution was stirred for 16 h under a dynamic atmosphere of nitrogen and then checked for completion by ^{31}P NMR. The solution was then concentrated in vacuo. The residue was dissolved in a minimum amount CH_2Cl_2 and purified by flash column chromatography (EtOAc/hexanes, 2:1) to afford 91% *N*-(1,3-dimethyl-2-oxo-2λ^5-[1,3,2]diazaphospholidin-2-yl)-4-methyl-*N*-(1-vinyl-butyl)-benzenesulfonamide as a clear oil, $R_f = 0.36$ (EtOAc/hexanes, 2:1).



Reference 2d.

To a cooled solution of 6 mmol α-pinene-allyl borane in 6 mL pentane mixed with 3 mL Et_2O at $-100°$C was added a precooled solution of 0.7 g (2*E*)-3-phenylbut-2-enal in 6 mL Et_2O at $-78°$C. The mixture was stirred for 3 h, and then warmed to $-78°$C. To this solution was added 1.6 mL 3 M NaOH (slowly) and 1.3 mL 30% H_2O_2, and the solution was stirred for 14 h under positive nitrogen pressure while it slowly warmed to room temperature. The reaction mixture was then extracted with Et_2O (3 $\times$ 20 mL); the combined organic layers were washed with brine and dried over $MgSO_4$. Upon removal of the solvent, the residue was purified by silica gel flash column chromatography (hexanes/EtOAc, 200:1) to furnish 0.66 g (4*S*,5*E*)-6-phenylhepta-1,5-dien-4-ol, in a yield 73% with 91% e.e.

To a precooled solution of 0.5 g (4*S*,5*E*)-6-phenylhepta-1,5-dien-4-ol (2.7 mmol) in 13 mL THF at $-42°$C, was added 0.27 mL 1 M sodium bis(trimethylsilyl)amide in THF (0.27 mmol); the solution was stirred for 0.5 h, then 0.3 mL trichloroacetonitrile (2.9 mmol) was added. The reaction mixture was then allowed to warm to room temperature, and the solvent was removed under reduced pressure. The residue was diluted with 6 mL xylenes,

and 0.4 g K_2CO_3 (2.9 mmol) was added; the mixture was refluxed for 10 h (150°C). The mixture was then filtered through Celite, concentrated under reduced pressure, and purified by silica gel flash column chromatography (hexanes/EtOAc, 99:1) to afford 0.76 g 2,2,2-trichloro-*N*-[(1*S*,2*E*)-1-methyl-1-phenylhexa-2,5-dienyl]acetamide as an oily substance, in a yield of 79% with 91% e.e.

Other references related to the Overman rearrangement are cited in the literature.[8]

H. REFERENCES

1. Overman, L. E., *J. Am. Chem. Soc.,* **1974**, *96*, 597.
2. (a) Jaunzeme, I.; Jirgensons, A.; Kauss, V. and Liepins, E., *Tetrahedron Lett*., **2006**, *47*, 3885. (b) Overman, L. E. and Carpenter, N. E., *Org. React.,* **2005**, *66*, 1. (c) Lee, E. E. and Batey, R. A., *J. Am. Chem. Soc.,* **2005**, *127*, 14887. (d) Ramachandran, P. V.; Burghardt, T. E. and Reddy, M. V. R., *J. Org. Chem.,* **2005**, *70*, 2329. (e) Jaunzeme, I. and Jirgensons, A., *Synlett*, **2005**, 2984. (f) Ramachandran, P. V.; Burghardt, T. E. and Reddy, M. V. R., *Tetrahedron Lett*., **2005**, *46*, 2121. (g) Montero, A.; Mann, E. and Herradon, B., *Tetrahedron Lett*., **2005**, *46*, 401. (h) Sato, H.; Oishi, T. and Chida, N., *Yuki Gosei Kagaku Kyokaishi*, **2004**, *62*, 693. (i) Singh, O. V. and Han, H. S., *Org. Lett.,* **2004**, *6*, 3067. (j) Donohoe, T. J.; Logan, J. G. and Laffan, D. D. P., *Org. Lett.,* **2003**, *5*, 4995. (k) Kriek, N. M. A. J.; van der Hout, E.; Kelly, P.; van Meijgaarden, K. E.; Geluk, A.; Ottenhoff, T. H. M.; van der Marel, G. A.; Overhand, M.; van Boom, J. H.; Valentijn, A. R. P. M. and Overkleeft, H. S., *Eur. J. Org. Chem.,* **2003**, 2418. (l) Ohyabu, N.; Nishikawa, T. and Isobe, M., *J. Am. Chem. Soc.,* **2003**, *125*, 8798. (m) Donohoe, T. J.; Blades, K.; Moore, P. R.; Waring, M. J.; Winter, J. J. G.; Helliwell, M.; Newcombe, N. J. and Stemp, G., *J. Org. Chem.,* **2002**, *67*, 7946. (n) Oishi, T.; Ando, K.; Inomiya, K.; Sato, H.; Iida, M. and Chida, N., *Org. Lett.,* **2002**, *4*, 151. (o) Oishi, T.; Ando, K.; Inomiya, K.; Sato, H.; Iida, M. and Chida, N., *Bull. Chem. Soc. Jpn.,* **2002**, *75*, 1927. (p) Oishi, T.; Ando, K.; Inomiya, K.; Sato, H.; Iida, M. and Chida, N., *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu*, **2001**, *43*, 157. (q) Cho, C.-G.; Lim, Y.-K.; Lee, K.-S.; Jung, I.-H. and Yoon, M.-Y., *Synth. Commun.,* **2000**, *30*, 1643. (r) Nishikawa, T.; Asai, M.; Ohyabu, N. and Isobe, M., *J. Org. Chem*., **1998**, *63*, 188. (s) Eguchi, T.; Koudate, T. and Kakinuma, K., *Tetrahedron*, **1993**, *49*, 4527. (t) Isobe, M.; Fukuda, Y.; Nishikawa, T.; Chabert, P.; Kawai, T. and Goto, T., *Tetrahedron Lett*., **1990**, *31*, 3327.
3. Lurain, A. E. and Walsh, P. J., *J. Am. Chem. Soc.,* **2003**, *125*, 10677.
4. Chen, Y. K.; Lurain, A. E. and Walsh, P. J., *J. Am. Chem. Soc.,* **2002**, *124*, 12225.
5. Felix, C.; Laurent, A.; Lebideau, F. and Mison, P., *J. Chem. Res. (S),* **1993**, 389.
6. Campbell, M. M.; Floyd, A. J.; Lewis, T.; Mahon, M. F. and Ogilvie, R. J., *Tetrahedron Lett.,* **1989**, *30*, 1993.
7. (a) Kirsch, S. F.; Overman, L. E. and Watson, M. P., *J. Org. Chem.,* **2004**, *69*, 8101. (b) Anderson, C. E. and Overman, L. E., *J. Am. Chem. Soc.,* **2003**, *125*, 12412. (c) Overman, L. E.; Owen, C. E.; Pavan, M. M. and Richards, C. J., *Org. Lett.,* **2003**, *5*, 1809.
8. (a) Kim, S. H.; Lee, T. H.; Lee, E. J.; Lee, J. K.; Fan, G.-j.; Lee, S. K. and Kim, D. J., *J. Org. Chem.,* **2004**, *69*, 3144. (b) O'Brien, P. and Pilgram, C. D., *Org. Biomol. Chem.,* **2003**, *1*, 523. (c) Allmendinger, T.; Felder, E. and Hungerbuehler, E., *Tetrahedron Lett.,* **1990**, *31*, 7301. (d) Overman, L. E., *Acc. Chem. Res.,* **1980**, *13*, 218. (e) Overman, L. E., *J. Am. Chem. Soc.,* **1976**, *98*, 2901.

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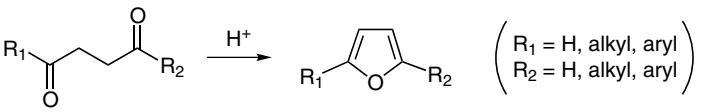
Paal-Knorr Furan Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Paal and Knorr in 1885.[1] It is an acid-catalyzed transformation of 1,4-dicarbonyl compounds into furan derivatives and is generally known as the Paal-Knorr reaction[2] or Paal-Knorr synthesis.[2b,3] The acidic catalysts reported in the literature include P_2O_5 (in ethanol),[4] *p*-TsOH or $ZnCl_2$ (in Ac_2O)[5] and polyphosphoric acid.[6] It has been found that the *meso*-diastereomers with substituents between two carbonyl groups cyclize faster when the substituents are electron-donating methyl groups, whereas the *dl*-isomers cyclize faster with bulky substituents.[2b] This reaction is believed to involve the protonation of the carbonyl group that tautomerizes to enol, which attacks the second protonated carbonyl group.[2b,3a] Although it is an important reaction for the preparation of furan derivatives, it is not widely applied in organic synthesis because of the generally low availability of suitable 1,4-dicarbonyl compounds.[2b,3a]

B. GENERAL REACTION SCHEME



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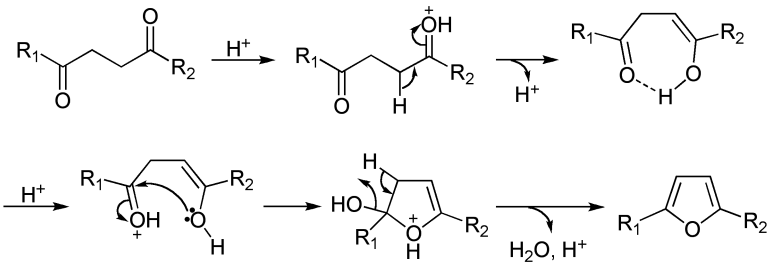
C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified by the cyclization of 2-ene-1,4-diones or 2-yne-1,4-diones under microwave irradiation in PEG-200 in the presence of formic acid and palladium on carbon.[3a]

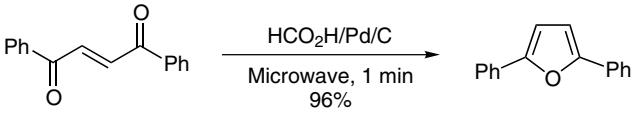
E. APPLICATIONS

This reaction is generally applicable for the preparation of furan derivatives.

F. RELATED REACTIONS

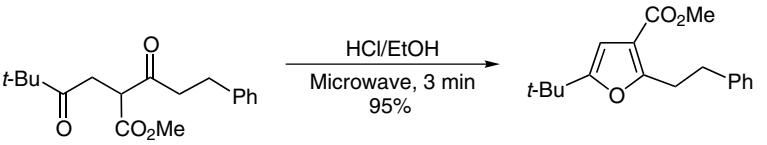
This reaction is related to the *Paal-Knorr Pyrrole Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 3a.

To a 25-mL conical flask, were added 118 mg 1,4-diphenyl enedione (0.5 mmol), 1 mL formic acid, 2 mg 5% palladium on carbon, and 2 mL PEG-200. The reaction mixture was irradiated in the microwave oven at 400 W for 1 min, then cooled to room temperature, loaded on a filter silica gel column (100–200 mesh; 1 cm $\times$ 9 cm) using 1 mL CH_2Cl_2, and eluted with a hexane/CH_2Cl_2 solution to afford 105 mg 2,5-diphenylfuran as a white solid, in a yield of 96%, m.p. 86–88°C (recrystallized from CH_2Cl_2/hexanes, 2:98), $R_f = 0.68$ (hexanes/CH_2Cl_2, 1:1).



Reference 2a.

To a 50-mL round-bottomed flask equipped with a stir bar and a refluxing condenser were added 0.5 g 2,2-dimethyl-4-(methoxycarbo)-8-phenyl-oct-3,6-dione (1.64 mmol), 2 mL EtOH, and 0.1 mL 37% HCl. The flask was inserted into the cavity of a Discovery microwave system apparatus (from CEM) and heated at 150 W for 4 min with an internal temperature of 100°C. The mixture was diluted with EtOAc and washed several times with a saturated solution of $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography, eluting with hexane/EtOAc (8:1, $R_f = 0.75$) to afford 0.49 g methyl 5-*tert*-butyl-2-(2-phenyethyl)furane-3-carboxylate, in a yield of 95%.

Other references related to the Paal-Knorr furan synthesis are cited in the literature.[7]

H. REFERENCES

1. (a) Paal, C., *Ber.,* **1885**, *18*, 367. (b) Knorr, L., *Ber.,* **1885**, *18*, 299.
2. (a) Minetto, G.; Raveglia, L. F. and Taddei, M., *Org. Lett.,* **2004**, *6*, 389. (b) Amarnath, V. and Amarnath, K., *J. Org. Chem.,* **1995**, *60*, 301. (c) Newkome, G. R.; Sauer, J. D.; Roper, J. M. and Hager, D. C., *Chem. Rev.,* **1977**, *77*, 513.
3. (a) Rao, H. S. P. and Jothilingam, S., *J. Org. Chem.,* **2003**, *68*, 5392. (b) Kretchmer, R. A. and Laitar, R. A., *J. Org. Chem.,* **1978**, *43*, 4596.
4. (a) Nozaki, H.; Koyama, T. and Mori, T., *Tetrahedron,* **1969**, *25*, 5357. (b) Nozaki, H.; Koyama, T.; Mori, T. and Noyori, R., *Tetrahedron Lett.,* **1968**, 2181.
5. Wolthuis, E.; Bossenbrock, B.; DeWall, G.; Geels, E. and Leedwater, A., *J. Org. Chem.,* **1963**, *28*, 148.
6. Nowlin, G., *J. Am. Chem. Soc.,* **1950**, *72*, 5754.
7. (a) Mortensen, D. S.; Rodriguez, A. L.; Carlson, K. E.; Sun, J.; Katzenellenbogen, B. S. and Katzenellenbogen, J. A., *J. Med. Chem.,* **2001**, *44*, 3838. (b) Stauffer, F. and Neier, R., *Org. Lett.,* **2000**, *2*, 3535. (c) Gilchrist, T. L., *J. Chem. Soc., Perkin Trans. I*, **1999**, 2849. (d) Hou, X. L.; Cheung, H. Y.; Hon, T. U.; Kwan, P. L.; Lo, T. H.; Tong, S. Y. and Wong, H. N. C., *Tetrahedron,* **1998**, *54*, 1955. (e) Truel, I.; Mohamed-Hachi, A.; About-Jaudet, E. and Collignon, N., *Synth. Commun.,* **1997**, *27*, 1165. (f) Dean, F. M. and Sargent, M. V., *Furans and Their benzo Derivatives* in *Comprehensive Heterocyclic Chemistry*, ed. Katritzky, A. R.; Rees, C. W. and Scriven, E. F. V., Pergamon, New York, **1984**, *3*, p. 531. (g) Dean. F. M., *Adv. Heterocycl. Chem.,* **1982**, *30*, 167. (h) Hirano, S.; Hiyama, T.; Fujita, S.; Kawaguti, T.; Hayashi, Y. and Nozaki, H., *Tetrahedron,* **1974**, *30*, 2633.

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Paal-Knorr Pyrrole Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported concurrently by Paal[1] and Knorr[2] in 1884. It is the acid-catalyzed formation of pyrrole derivatives from 1,4-dicarbonyl compounds and ammonia or primary amines. Therefore, it is generally known as the Paal-Knorr pyrrole synthesis,[3] Paal-Knorr synthesis,[4] Paal-Knorr reaction,[4b,4e–4h,5] or Paal-Knorr condensation.[4e–4g,6] Occasionally, it is also referred to as the Paal-Knorr cyclization,[5d,5e] Paal-Knorr cyclocondensation,[7] Paal-Knorr 1H-pyrrole synthesis,[3g] or Paal-Knorr pyrrole reaction.[7] This reaction provides a general route for pyrrole derivatives from a variety of 1,4-dicarbonyl compounds and primary amines,[4g,8] which can be catalyzed by either a Brønsted acid or Lewis acid, by which the latter is especially useful for molecules with acid-sensitive/epimerizable functionalities. In this reaction, the 1,4-dicarbonyl compounds provide the four carbons of the pyrrole ring through double condensation with the amines that contribute the nitrogen to the ring. However, the primary amines with an alkyl substituent at the α-position do not undergo this reaction. For example, no pyrrole was observed from the reaction of cyclohexyl amine.[4b] The mechanistic study demonstrates that *dl*-diastereomers of 3,4-dimethyl or 3,4-diethyl-2,5-hexanediones are 1.3–57.0 times faster than their corresponding *meso*-diastereomers to form pyrroles in aprotic solvents or aqueous solutions near neutrality, indicating a rate-limiting step in the hemiaminal cyclization.[4g] This reaction has been catalyzed by iodine,[5c] Fe^{3+}- montmorillonite,[3b] montmorillonite KSF-clay,[5c] and bulky Lewis acids such as titanium (IV) tetra-isopropoxide.[4e] Recently, this reaction was improved to finish in seconds under microwave radiation.[5b,5e,9]

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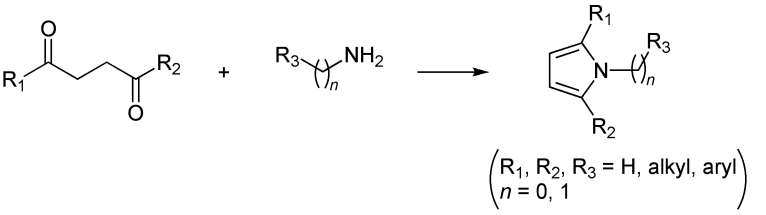
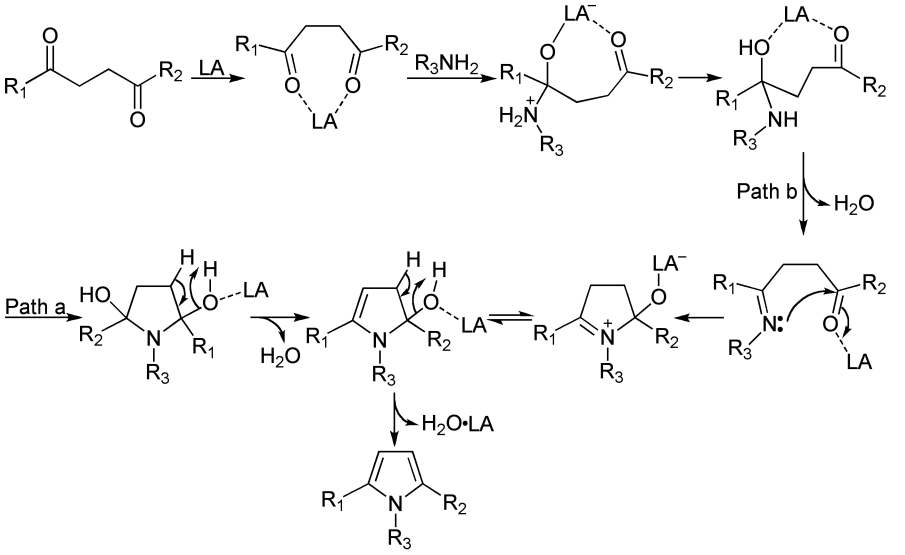
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The mechanism is modified from that of Amarnath et al.[4g] under the catalysis of a general Lewis acid (LA), as illustrated here.



D. MODIFICATION

This reaction has been modified to proceed under solvent-free conditions[3e] and microwave irradiation.[5b,5e,9] In addition, this reaction has been catalyzed by various Lewis acids.

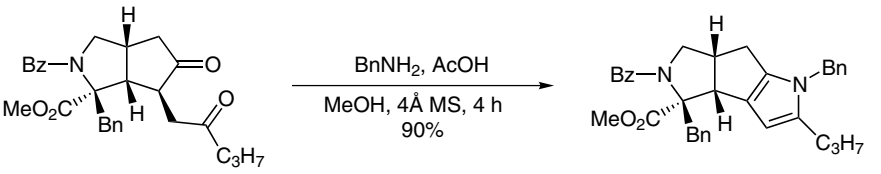
E. APPLICATIONS

This reaction has a general application in the synthesis of pyrrole derivatives.

F. RELATED REACTIONS

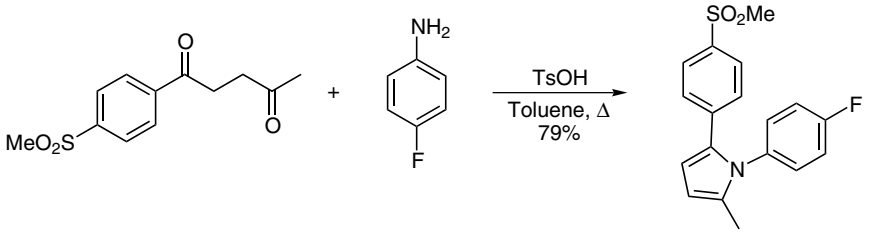
This reaction is related to the *Hantzsch Pyrrole Synthesis* and *Knorr Pyrrole Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4b.

To a solution of 10 mg 1,4-dione (0.021 mmol) in 0.5 mL methanol were added 23 μL benzylamine (0.21 mmol), 12 μL acetic acid (0.21 mmol), and 30 mg 4Å molecular sieves activated by flame drying under vacuum. The reaction mixture was stirred at 70°C for 1–4 h. Upon completion, the reaction mixture was diluted with 50 mL EtOAc and washed with 1 M HCl (2 × 20 mL). The organic layer was then dried over $MgSO_4$, and the solvents were removed in vacuo. The crude material was purified by flash chromatography (gradient elution; hexanes/EtOAc, 19:1–3:1, v/v) to afford 10 mg 5-benzoyl-1,4-dibenzyl-2-propyl-3b,4,5,6,6a,7-hexahydro-1*H*-1,5-diaza-cyclopenta[*a*]pentalene-4-carboxylic acid methyl ester, in a yield of 90%.



Reference 5f.

A mixture of 580 mg 1-[4-(methylsulfonyl)phenyl]pentane-1,4-dione (2.28 mmol), 0.24 mL 4-fluoroaniline (2.5 mmol), and 30 mg *p*-toluenesulfonic acid in 50 mL toluene was refluxed for 20 h using a Dean-Stark apparatus. The reaction mixture was cooled, filtered, and concentrated. The crude mixture (820 mg) was chromatographed (silica gel, hexane/EtOAc, 7:3) to give 595 mg pure 1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)-phenyl]-1*H*-pyrrole as a white solid, in a yield of 79%, m.p. (DSC) 157°C.

Other references related to the Paal-Knorr pyrrole synthesis are cited in the literature.[10]

H. REFERENCES

1. (a) Paal, C., *Ber.,* **1884**, *17*, 2756. (b) Paal, C., *Ber.,* **1885**, *18*, 367.
2. (a) Knorr, L., *Ber.,* **1884**, *17*, 2863. (b) Knorr, L., *Ber.,* **1885**, *18*, 299.
3. (a) Mothana, B. and Boyd, R. J., *THEOCHEM*, **2007**, *811*, 97. (b) Song, G. Y.; Wang, B.; Wang, G.; Kang, Y. R.; Yang, T. and Yang, L. M., *Synth. Commun.,* **2005**, *35*, 1051. (c) Salamone, S. G. and Dudley, G. B., *Org. Lett.,* **2005**, *7*, 4443. (d) Quiclet-Sire, B.; Quintero, L.; Sanchez-Jimenez, G. and Zard, S. Z., *Synlett*, **2003**, 75. (e) Taghavi-Moghadam, S.; Kleemann, A. and Golbig, K.

G., *Org. Proc. Res. Dev.,* **2001**, *5*, 652. (f) Dreier, T.; Erker, G.; Fröhlick, R. and Wibbeling, B., *Organometallics,* **2000**, *19*, 4095. (g) Chiu, P. K.; Lui, K. H.; Maini, P. N. and Sammes, M. P., *J. Chem. Soc., Chem. Commun.,* **1987**, 109.

4. (a) Zamora, R. and Hidalgo, F. J., *Synlett*, **2006**, 1428. (b) Brummond, K. M.; Curran, D. P.; Mitasev, B. and Fischer, S., *J. Org. Chem.,* **2005**, *70*, 1745. (c) Park, S.-Y.; Chun, M.-S.; Song, J.-S. and Kim, H.-J., *Bull. Korean Chem. Soc.,* **2005**, *26*, 575. (d) Banik, B. K.; Banik, I.; Renteria, M. and Dasgupta, S. K., *Tetrahedron Lett*., **2005**, *46*, 2643. (e) Dong, Y.; Pai, N. N.; Ablaza, S. L.; Yu, S.-X.; Bolvig, S.; Forsyth, D. A. and Le Quesne, P. W., *J. Org. Chem.,* **1999**, *64*, 2657. (f) Amarnath, V.; Amarnath, K.; Valentine, W. M.; Eng, M. A. and Graham, D. G., *Chem. Res. Toxicol.,* **1995**, *8*, 234. (g) Amarnath, V.; Anthony, D. C.; Amarnath, K.; Valentine, W. M.; Wetterau, L. A. and Graham, D. G., *J. Org. Chem.,* **1991**, *56*, 6924. (h) Szakd-Quin, G.; Graham, D. G.; Millington, D. S.; Maltby, D. A. and McPhail, A. T., *J. Org. Chem.,* **1986**, *51*, 621.
5. (a) Kidwai, M.; Singhal, K. and Rastogi, S., *J. Heterocycl. Chem.,* **2006**, *43*, 1231. (b) Minetto, G.; Raveglia, L. F.; Sega, A. and Taddei, M., *Eur. J. Org. Chem.,* **2005**, 5277. (c) Banik, B. K.; Samajdar, S. and Banik, I., *J. Org. Chem.,* **2004**, *69*, 213. (d) Bharadwaj, A. R. and Scheidt, K. A., *Org. Lett.,* **2004**, *6*, 2465. (e) Minetto, G.; Raveglia, L. F. and Taddei, M., *Org. Lett.,* **2004**, *6*, 389. (f) Khanna, I. K.; Weier, R. M.; Yu, Y.; Collins, P. W.; Koboldt, C. M.; Veenhuizen, A. W.; Currie, J. L.; Seibert, K. and Isakson, P. C., *J. Med. Chem.,* **1997**, *40*, 1619. (g) Yu, S.-X. and Le Quesne, P. W., *Tetrahedron Lett.,* **1995**, *36*, 6205. (h) Chiu, P. K. and Sammes, M. P., *Tetrahedron,* **1990**, *46*, 3439. (i) Lui, K. H. and Sammes, M. P., *J. Chem. Soc., Perkin Trans. I,* **1990**, 457. (j) Maini, P. N.; Sammes, M. P. and Katritzky, A. R., *J. Chem. Soc., Perkin Trans. I,* **1988**, 161. (k) Subba, N. V.; Rao, K. S. and Ratnam, C. V., *Proc. Indian Acad. Sci., Sect. A,* **1971**, *73*, 59.
6. (a) Zhang, J.; Fan, X. D.; Liu, Y. F. and Li, H., *Xiandai Huagong*, **2006**, *26*, 47. (b) Du, Y. Y.; Tian, F. L.; Zhao, W. Z. and Fang, L., *Huaxue Tongbao*, **2006**, *69*, 306. (c) Wang, B.; Gu, Y. L.; Luo, C.; Yang, T.; Yang, L. M. and Suo, J. S., *Tetrahedron Lett*., **2004**, *45*, 3417. (d) Robertson, J.; Hatley, R. J. D. and Watkin, D. J., *J. Chem. Soc., Perkin Trans. I,* **2000**, 3389. (e) Kobierski, M. E.; Kim, S.; Murthi, K. K.; Iyer, R. S. and Salomon, R. G., *J. Org. Chem.,* **1994**, *59*, 6044. (f) Katritzky, A. R.; Yousaf, T. I.; Chen, B. C. and Zeng, G. Z., *Tetrahedron,* **1986**, *42*, 623. (g) Hori, I. and Igarashi, M., *Bull. Chem. Soc. Jpn.,* **1971**, *44*, 2856.
7. Braun, R. U.; Zeitler, K. and Müller, T. J. J., *Org. Lett.,* **2001**, *3*, 3297.
8. Joule, J. A. and Mills, K., *Heterocyclic Chemistry,* 4th ed., Blackwell Science, Cambridge **2000**.
9. Danks, T. N., *Tetrahedron Lett.,* **1999**, *40*, 3957.
10. (a) Martyn, D. C.; Vernall, A. J.; Clark, B. M. and Abell, A. D., *Org. Biomol. Chem*., **2003**, *1*, 2103. (b) Arrowsmith, J.; Jennings, S. A.; Clark, A. S. and Stevens, M. F. G., *J. Med. Chem*., **2002**, *45*, 5458. (c) Wurtz, N. R.; Turner, J. M.; Baird, E. E. and Dervan, P. B., *Org. Lett.,* **2001**, *3*, 1201. (d) Ballini, R.; Bosica, G.; Fiorini, G. and Giarlo, G., *Synthesis,* **2001**, 2003. (e) Ballini, R.; Barboni, L.; Bosica, G. and Petrini, M., *Synlett,* **2000**, 391. (f) Haubmann, C.; Huebner, H. and Gmeiner, P., *Bioorg. Med. Chem. Lett.,* **1999**, *9*, 3143. (g) Korostova, S. E.; Mikhaleva, A. I.; Vasil'tsov, Am. M. and Trofimov, B. A., *Russ. J. Org. Chem.,* **1998**, *34*, 1691. (h) Meth-Cohn, O. and Wang, M.-X., *Tetrahedron Lett*., **1995**, *36*, 9561. (i) Amarnath, K. and Amarnath, K., *J. Org. Chem.,* **1995**, *60*, 301. (j) Jousseaume, B.; Kwon, H.; Verlhac, J.-B.; Denat, F. and Dubac, J., *Synlett,* **1993**, 117. (k) Wassermann, H. H.; Gosselink, E.; Keith, D. D.; Nadelson, J. and Sykes, R. J., *Tetrahedron,* **1976**, *32*, 1863. (l) Buu-Hoi, N. P.; Xuong, Ng. D. and Gazave, J. M., *J. Org. Chem.,* **1955**, *20*, 639. (m) Buu-Hoi, N. P. and Xuong, Ng. D., *J. Org. Chem.,* **1955**, *20*, 850. (n) Young, D. M. and Allen, C. F. H., *Org. Synth.,* **1936**, *16*, 25.

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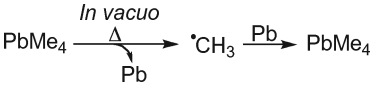
Paneth Technique

A. GENERAL DESCRIPTION OF THE REACTION

It was first reported by Paneth et al. in 1929.[1] It is a preparation of alkyl or aryl radicals, primarily methyl radical by thermal decomposition of organolead compounds under a vacuum system and is generally referred to as the Paneth technique.[2] In this process, tetramethyl lead is decomposed at 1–2 mmHg of pressure in a glass tube heated either by a mobile Bensen burner or by an electric furnace. The generated methyl radical is carried by hydrogen gas at a speed of 16 m/s down the tube to eliminate the deposited lead mirror by formation of tetramethyl lead again.[2a] Under these conditions, no diffusion against the flow of methyl radical occurs.[2a] Through the thermal decomposition, the methyl radical is clearly generated from tetramethyl lead, as evidenced by the disappearance of deposited lead mirror as far as 40 cm from the heated zone by reacting with the continual flowing of the methyl radical; even the space between the heated zone and deposited lead mirror is cooled by water.[2a,3] It has been found that tetraethyl lead reacts in the same fashion, whereas other higher order alkyl lead compounds give a mixture of radicals upon thermal decomposition.[4] Besides lead, other metals have been found to react with methyl radicals too, including arsenic,[5] antimony,[5] zinc,[5] cadmium,[5] and tellurium.[6]

B. GENERAL REACTION SCHEME



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C. PROPOSED MECHANISMS

This is a simple decomposition of an organolead compound; therefore, it is not necessary to provide a mechanism for this obvious reaction.

D. MODIFICATION

N/A

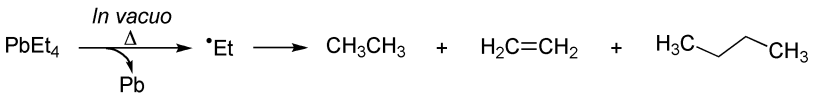
E. APPLICATIONS

This technique provides a convenient method for the production of radicals. In addition, this fast flowing technique is also useful for studying many unstable species in vacuo.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

A 50-mL round-bottomed flask equipped with a 50-cm long refluxing condenser was flushed with nitrogen and filled with 5 mL tetraethyl lead. Then the tetraethyl lead was pumped out, and the flask was filled with nitrogen several times to eliminate oxygen from the system. The flask was then fitted with a delivery tube extending under water into a 2-L bottle, which served to collect the gases. The flask was heated gently with a luminous Bunsen flame so that tetraethyl lead was kept just at the boiling point with no visible refluxing. The heating must be done very carefully to avoid the explosion. After the decomposition completed, a deposit of finely divided lead was left in the flask. This deposit was easily removed with nitric acid; no evidence of carbon was detected. It was apparent that most of the ethyl radicals reacted to form ethane and ethylene, with only a small amount of butane. Details of a fast-flowing decomposition of tetraethyl lead were also provided in the reference.[7]

Other references related to the Paneth technique are cited in the literature.[8]

H. REFERENCES

1. Paneth, F. and Hofeditz, W., *Ber.,* **1929**, *62*, 1335.
2. (a) Steacie, E. W. R. and Le Roy, D. J., *Chem. Rev.,* **1942**, *31*, 227. (b) Calingaert, G. and Soroos, H., *J. Org. Chem.,* **1938**, *3*, 535.

3. Rice, F. O., *J. Am. Chem. Soc.,* **1931**, *53*, 1959.
4. Leeper, R. W.; Summers, L. and Gilman, H., *Chem. Rev.,* **1954**, *54*, 102.
5. Paneth, F. and Lautsch, W., *Ber.,* **1931**, *64*, 2702.
6. Paneth, F. and Lautsch, W., *Ber.,* **1931**, *64*, 2708.
7. Meinert, R. N., *J. Am. Chem. Soc.,* **1933**, *55*, 979.
8. (a) Steacie, E. W. R. and Lossing, F. P., *Ann. Rev. Phys. Chem.,* **1953**, *4*, 323. (b) Leighton, P. A. and Mortensen, R. A., *J. Am. Chem. Soc.,* **1936**, *58*, 448. (c) Paneth, F. and Lautsch, W., *J. Chem. Soc.,* **1935**, 381. (d) Rice, F. O., *J. Am. Chem. Soc.,* **1934**, *56*, 488. (e) Simons, J. H. and Dull, M. F., *J. Am. Chem. Soc.,* **1933**, *55*, 2696. (f) Rice, F. O.; Johnston, W. R. and Evering, B. L., *J. Am. Chem. Soc.,* **1932**, *54*, 3529. (g) Paneth, F. and Herzfeld, K., *Z. Electrochem.,* **1931**, *37*, 577. (h) Geddes, R. L. and Mack, E., *J. Am. Chem. Soc.,* **1930**, *52*, 4372.

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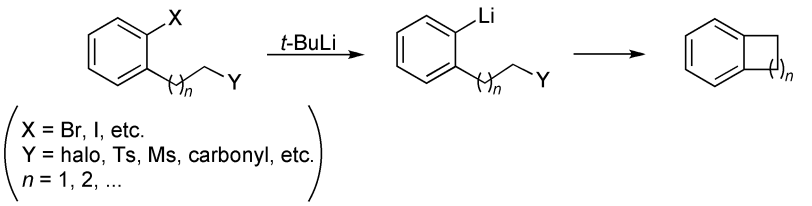
Parham Cyclization

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially developed by Parham in 1975[1] and extended primarily by Bradsher after Parham's death in 1976.[2] It is the synthesis of aryl or heteroaryl ring fused carbocylces or heterocycles through the intramolecular reaction between a side chain electrophile and an aryl or heteroaryllithium generated from lithium-halogen exchange.[3] Therefore, this reaction is generally known as the Parham cyclization.[3a,3b,4] Occasionally, it is also referred to as the Parham reaction.[4j,4l,5] This reaction is very useful for the synthesis of alkaloids.[4a,4b,4l]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

This is a very general reaction between aryl or heteroaryllithium and intramolecular electrophiles, and cannot be represented by a simple reaction. Thus a specific reaction is

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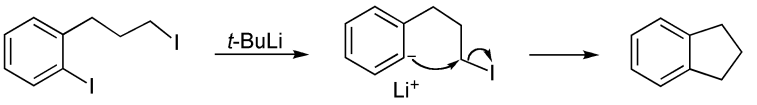
given here to demonstrate the mechanism. When the electrophile is a carbonyl group, a cyclic carbinol will form; a carboxylic group will result in the formation of a cyclic ketone.



D. MODIFICATION

This reaction has many variants because of the number of different intramolecular electrophiles.

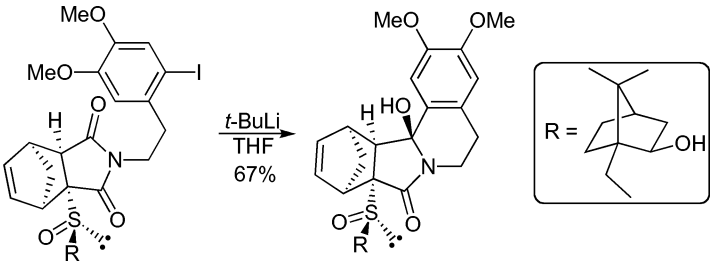
E. APPLICATIONS

This reaction is very useful for the preparation of aryl or heteroaryl fused carbocycles or heterocycles, especially for alkaloids.

F. RELATED REACTIONS

N/A

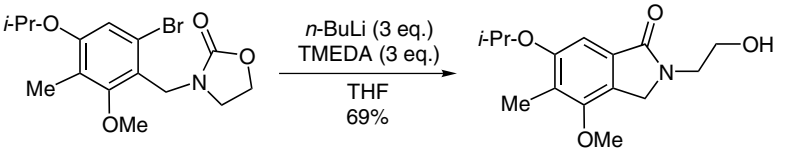
G. CITED EXPERIMENTAL EXAMPLES



Reference 3a.

To a solution of 121 mg iodo imide (0.18 mmol) in 15 mL dry THF was added 0.63 mL 1.17 M *t*-BuLi in pentane (0.74 mmol) at −78°C. The resulting mixture was stirred at this temperature for 5 h, quenched by 5 mL saturated NH_4Cl, and allowed to warm to room temperature. The organic layer was separated, and the aqueous phase was extracted with Et_2O (2 × 5 mL) and CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was crystallized from Et_2O to afford 66 mg (8a*R*,9*S*,12*R*,12a*S*,12b*S*)-(+)-8a-[(1*S*,2*R*,4*R*,S*R*)-(2-hydroxy-7,7-dimethylbicyclo[2.2.1]-heptan-1-yl)methylsulfinyl]-12b-hydroxy-2,3-dimethoxy-5,6,

8a,9,12,12ahexahydro-9,12-methaneisoindolin[2,3-*a*]isoquinolin-8-one, in a yield of 67%, m.p. 198–200°C.



Reference 4a.

A mixture of 2.0 mL 2.0 M *n*-BuLi in pentane (4 mmol) and 465 mg TMEDA (4 mmol) in 5 mL dry THF was carefully degassed by three freeze–thaw cycles and stirred at −78°C under dry deoxygenated argon. Then 0.47 g 3-(6-bromo-4-isopropoxy-2-methoxy-3-methylbenzyl)oxazolidin-2-one (1.31 mmol) in 15 mL degassed THF was added dropwise through a cannula. The mixture was stirred for 30 min at −78°C, quenched with 5 mL saturated NH_4Cl solution, and diluted with 30 mL water. The resulting mixture was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. The solid residue was purified by flash column chromatography on silica gel using acetone/hexanes (80:20) as the eluent to afford 0.23 g 2-(2-hydroxyethyl)-6-isopropoxy-4-methoxy-5-methyl-2,3-dihydro-1*H*-isoindol-1-one, in a yield of 69%, m.p., 113–114°C (white crystals from hexane/toluene).

Other references related to the Parham cyclization are cited in the literature.[6]

H. REFERENCES

1. Parham, W. E.; Jones, L. D. and Sayed, Y., *J. Org. Chem.,* **1975**, *40*, 2394.
2. Parham, W. E. and Bradsher, C. K., *Acc. Chem. Res.,* **1982**, *15*, 300.
3. (a) González-Temprano, I.; Osante, I.; Lete, E. and Sotomayor, N., *J. Org. Chem.,* **2004**, *69*, 3875. (b) Mehta, G. and Kotha, S., *Tetrahedron,* **2001**, *57*, 625. (c) Collado, M. I.; Manteca, I.; Sotomayor, N.; Villa, M.-S. and Lete, E., *J. Org. Chem.,* **1997**, *62*, 2080.
4. (a) Moreau, A.; Lorion, M.; Couture, A.; Deniau, E. and Grandclaudon, P., *J. Org. Chem.,* **2006**, *71*, 3303. (b) Couture, A.; Lamblin, M.; Moreau, A.; Deniau, E.; Lebrun, S. and Grandclaudon, P., *New Developments of the Pahram Cyclization Process. Applications in Natural Products Synthesis in 9th Int. Electronic Conference on Synth. Org. Chem*., *ECSOC-9-1-30*, A021, November **2005**. (c) Moreau, A.; Couture, A.; Deniau, E. and Grandclaudon, P., *Eur. J. Org. Chem.,* **2005**, 3437. (d) Ruiz, J.; Ardeo, A.; Ignacio, R.; Sotomayor, N. and Lete, E., *Tetrahedron,* **2005**, *61*, 3311. (e) Osante, I.; Lete, E. and Sotomayor, N., *Tetrahedron Lett*., **2004**, *45*, 1253. (f) Osante, I.; Garcia, E.; Ardeo, A.; Arrasate, S.; Lete, E. and Sotomayor, N., *Recent Res. Dev. Org. Chem.,* **2002**, *6*, 103. (g) Ardeo, A.; Collado, M. I.; Osante, I.; Ruiz, J.; Sotomayor, N. and Lete, E., *Recent Advances in the Parham Cyclization for the synthesis of Heterocyclic Systems* in *Targets in Heterocyclic Systems*, ed. Atanassi, O. and Spinelli, D., Italian Society of Chemistry, Rome, **2001**, *5*, pp. 393–418. (h) Osante, I.; Collado, M. I.; Lete, E. and Sotomayor, N., *Synlett,* **2000**, 101. (i) Collado, M. I.; Sotomayor, N.; Villa, M.-J. and Lete, E., *Tetrahedron Lett.,* **1996**, *37*, 6193. (j) Sibi, M. P.; Shankaran, K.; Alo, B. I.; Hahn, W. R. and Snieckus, V., *Tetrahedron Lett*., **1987**, *28*, 2933. (k) Ruiz, J.; Sotomayor, N. and Lete, E., *Org. Lett.,* **2003**, *5*, 1115. (l) Shklyaev, Y. V., *Chem. Comput. Simulation, Butlerov Commun.,* **2002**, *2*, 21. (m) Quallich, G. J.; Fox, D. E.; Friedmann, R. C. and Murtiashaw, C. W., *J. Org. Chem.,* **1992**, *57*, 761.

5. (a) Saeki, S., *Yuki Gosei Kagaku Kyokaishi*, **1992**, *50*, 213. (b) Alabaster, R. J.; Cottrell, I. F.; Marley, H. and Wright, S. H. B., *Synthesis,* **1988**, 950.

6. (a) De la Fuente, M. C. and Dominguez, D., *Tetrahedron*, **2004**, *60*, 10019. (b) Sotomayor, N. and Lete, E., *Curr. Org. Chem.,* **2003**, *7*, 275. (c) Nájera, C.; Sansano, J. M. and Yus, M., *Tetrahedron,* **2003**, *59*, 9255. (d) Kraus, G. A. and Kim, I., *Org. Lett*., **2003**, *5*, 1191. (e) Clayden, J., *Organolithiums: Selectivity for Synthesis*, Elsevier Science, Oxford, **2002**. (f) Mealy, M. J. and Bailey, W. F., *J. Organomet. Chem*., **2002**, *646*, 59. (g) Ardeo, A.; Lete, S. and Sotomayor, N., *Tetrahedron Lett.,* **2000**, *41*, 5211. (h) Larsen, S. D., *Synlett,* **1997**, 1013. (i) Suemitsu, R.; Ohnishi, K.; Morikawa, Y. and Nagatomo, S., *Phytochemistry,* **1995**, *38*, 495. (j) Couture, A.; Deniau, E. and Grandclaudon, P., *J. Chem. Soc., Chem. Commun.,* **1994**, 1329. (k) Bradsher, C. K. and Edgar, K. J., *J. Org. Chem*., **1981**, *46*, 4600. (l) Bradsher, C. K. and Hunt, D. A., *J. Org. Chem*., **1981**, *46*, 4608. (m) Bradsher, C. K. and Reames, D. C., *J. Org. Chem.,* **1978**, *43*, 3800. (n) Parham, W. E.; Bradsher, C. K. and Hunt, D. A., *J. Org. Chem.,* **1978**, *43*, 1606. (o) Parham, W. E.; Jones, L. D. and Sayed Y. A., *J. Org. Chem.,* **1976**, *41*, 1184.

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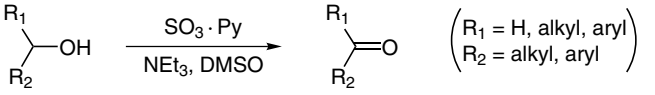
Parikh-Doering Oxidation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Parikh and Doering in 1967.[1] It is to oxidize primary and secondary alcohols into aldehydes and ketones at room temperature using sulfur trioxide-pyridine complex in combination with dimethylsulfoxide and triethylamine. Therefore, this reaction is called the Parikh-Doering oxidation. In addition, this reaction is also known as the Parikh-Doering protocol[2] or Doering oxidation.[3] The attractive features of this oxidation include the fast reaction rate (usually completed within minutes),[1] convenient working conditions (room temperature instead of cryogenic reaction temperature),[1,4] functional group tolerance, negligible side products (methyl thiomethyl ether derivative of alcohol),[1] easy-to-handle reagents,[4] and flexibility to charge with more reagent if necessary.[4] The functional group tolerance is clearly demonstrated by the fact that double bond,[2,5] epoxide,[6] acetals,[3] etc. are not affected, even under the conditions for oxidizing alcohol in tosylate salt.[4] The Parikh-Doering oxidation is especially feasible for the oxidation of alcohols mounted onto polymer[7] and in the preparation of α,β-unsaturated carbonyl compounds,[1,5] by which the former situation has often been recognized as problematic under other conditions.[7] The oxidation has been proven to be superior to TPAP/NMO oxidation[3] but not as good as the *Moffatt-Swern Oxidation* and *Corey-Suggs Oxidation* for the oxidation of long-chain alcohols.[8] In addition, this reaction is not good for the highly strained alcohols.[9]

B. GENERAL REACTION SCHEME



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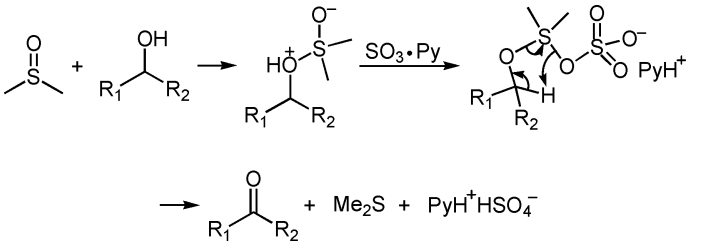
C. PROPOSED MECHANISMS



D. MODIFICATION

N/A

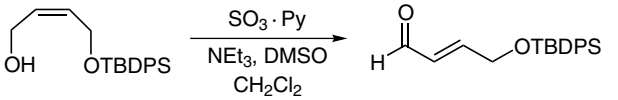
E. APPLICATIONS

This reaction is generally useful for the conversion of primary and secondary alcohols into carbonyl compounds.

F. RELATED REACTIONS

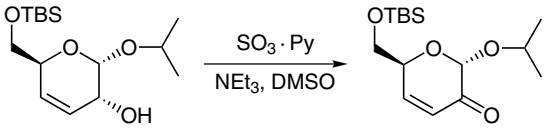
This reaction is related to the *Moffatt-Swern Oxidation.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 10.

To a solution of 10.2 g 1-*tert*-butyldiphenylsilyloxy-*cis*-2-butene-4-ol (31.2 mmol), 18.0 mL Et_3N (129 mmol), and 20 mL DMSO in 200 mL CH_2Cl_2 at 0°C, was added 9.75 g SO_3-pyridine complex (61.3 mmol). The reaction was warmed to room temperature, stirred for 2 h then poured onto 200 mL water and extracted with 200 mL Et_2O (three times). The combined organic layers were washed with 100 mL saturated aqueous NH_4Cl, 50 mL 10% aq. $CuSO_4$, 100 mL water (three times), and 100 mL brine; they were dried over Na_2SO_4. Concentration in vacuo gave an orange oil. ^1H NMR analysis of the unpurified mixture showed a 2:1 mixture of the isomeric *cis*- and *trans*-aldehydes. The orange oil was allowed to stand at room temperature under high vacuum (<1 mmHg) for 24 h, whereupon complete isomerization to the *trans*-aldehyde was observed by TLC. The oil was then subjected to silica gel chromatography (20:1; hexanes/EtOAc) to give 6.35 g (2*E*)-4-(2,2-dimethyl-1,1-diphenyl-1-silaprop-oxy)but-2-enal as a colorless solid, in a yield of 63%, $R_f = 0.35$ (4:1, hexanes/ EtOAc).



Reference 5a.

To a mixture of 80.68 g allyl alcohol (266.7 mmol) and 223 mL Et_3N (1.60 mol) in 700 mL DMSO was added dropwise a solution of 127 g SO_3·Py (798 mmol) in 500 mL DMSO over 10 min at room temperature. After being stirred at that temperature for 40 min, the reaction mixture was diluted with Et_2O, and the resulting solution was poured into an ice-cold saturated NH_4Cl solution. The mixture was extracted with Et_2O (three times). The combined organic layers were washed with saturated NH_4Cl solution (twice) and brine (twice), and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel 1.0 kg, ether/hexane, 1:60–1:10) to give 74.41 g enone as a colorless oil, in a yield of 93%.

Other references related to the Parikh-Doering oxidation are cited in the literature.[11]

H. REFERENCES

1. Parikh, J. P. and Doering, W. v. E., *J. Am. Chem. Soc.,* **1967**, *89*, 5505.
2. Wipf, P. and Spencer, S. R., *J. Am. Chem. Soc.,* **2005**, *127*, 225.
3. Ott, M. M. and Little, R. D., *J. Org. Chem.,* **1997**, *62*, 1610.
4. Ripin, D. H. B.; Abele, S.; Cai, W. L.; Blumenkopf, T.; Casavant, J. M.; Doty, J. L.; Flanagan, M.; Koecher, C.; Laue, K. W.; McCarthy, K.; Meltz, C.; Munchhoff, M.; Pouwer, K.; Shah, B.; Sun, J. M.; Teixeira, J.; Vries, T.; Whipple, D. A. and Wilcox, G., *Org. Proc. Res. Dev.,* **2003**, *7*, 115.
5. (a) Ohyabu, N.; Nishikawa, T. and Isobe, M., *J. Am. Chem. Soc.,* **2003**, *125*, 8798. (b) Uwai, K.; Ohashi, K.; Takaya, Y.; Ohta, T.; Tadano, T.; Kisara, K.; Shibusawa, K.; Sakakibara, R. and Oshima, Y., *J. Med. Chem.,* **2000**, *43*, 4508.
6. (a) Wills, A. J.; Krishnan-Ghosh, Y. and Balasubramanian, S., *J. Org. Chem.,* **2002**, *67*, 6646. (b) Cheng, W.-C. and Kurth, M. J., *J. Org. Chem.,* **2002**, *67*, 4387.
7. Groth, T. and Meldal, M. *J. Comb. Chem.,* **2001**, *3*, 34.
8. Mancuso, A. J.; Huang, S.-L. and Swern, D., *J. Org. Chem.,* **1978**, *43*, 2480.
9. Huang, S. L.; Omura, K. and Swern, D., *J. Org. Chem.,* **1976**, *41*, 3329.
10. Evans, D. A. and Starr, J. T., *J. Am. Chem. Soc.,* **2003**, *125*, 13531.
11. (a) Mickel, S. J.; Sedelmeier, G. H.; Niederer, D.; Schuerch, F.; Seger, M.; Schreiner, K.; Daeffler, R.; Osmani, A.; Bixel, D.; Loiseleur, O.; Cercus, J.; Stettler, H.; Schaer, K.; Gamboni, R.; Bach, A.; Chen, G.-P.; Chen, W. C.; Geng, P.; Lee, G. T.; Loeser, E.; McKenna, J.; Kinder, F. R.; Konigsberger, K.; Prasad, K.; Ramsey, T. M.; Reel, N.; Repje, O.; Rogers, L.; Shieh, W.-C.; Wang, R.-M.; Waykole, L.; Xue, S.; Florence, G. and Paterson, I., *Org. Proc. Res. & Dev.,* **2004**, *8*, 113. (b) Smith, A. B.; Lee, D.; Adams, C. M. and Kozlowski, M. C., *Org. Lett.,* **2002**, *4*, 4539. (c) Yokokawa, F.; Asano, T. and Shioiri, T., *Org. Lett.,* **2000**, *2*, 4169. (d) Tori, M.; Toyada, N. and Sono, M., *J. Org. Chem.,* **1998**, *63*, 306. (e) Panek, J. S. and Masse, C. E., *J. Org. Chem.,* **1997** , *62*, 8290. (f) Ihara, M.; Tokunaga, Y.; Taniguchi, N.; Fukumoto, K. and Kabuto, C., *J. Org. Chem.,* **1991**, *56*, 5281. (g) Martin, S. F.; Dappen, M. S.; Dupré, B.; Murphy, C. J. and Colapret, J. A., *J. Org. Chem.,* **1978**, *43*, 2480. (h) Goh, S. H. and Harvey, R. G., *J. Am. Chem. Soc.,* **1973**, *95*, 242.

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Passerini Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Passerini in 1921.[1] It is an atom-economical three-component condensation among isonitrile (i.e., isocyanide), carboxylic acid, and aldehyde (or ketone) to form α-acyloxy amide through acyl rearrangement and tautomerization. Therefore, it is generally known as the Passerini reaction.[2,3] Occasionally, this reaction is also referred to as the Passerini multicomponent condensation,[2i,2p,4] Passerini multicomponent reaction,[5] Passerini 3CC condensation,[2i] Passerini condensation,[2o,4,6] Passerini three-component condensation,[2p,3i,3s,7] and Passerini three-component coupling.[2d,8] Kinetically, this reaction is on the third order—that is, the first order in each of the reactants.[2u] Owing to its multicomponent nature and atom efficiency, the Passerini reaction has been used extensively in combinatorial chemistry.[2o,9] However, it still has a few drawbacks. For instance, aryl ketone and aryl isonitriles are not suitable for this reaction;[2t] in addition, the reaction is often sluggish[2d,2m] and results in low yields, unless either highly acidic carboxylic acid or electrophilic carbonyl compounds are used.[2d] This reaction has been modified to occur in aqueous solution with obvious advantages of a high reaction rate and easy separation.[2b] In addition, Lewis base,[2a] such as pyridine-trifluoroacetic acid[2q,2s] has been used to promote this reaction. On the other hand, Lewis acid has also been used to promote the Passerini reaction, such as $TiCl_4$,[2r,10] and $Zn(OTf)_2$/TMSCl.[2m] In particular, the use of a catalytic amount of tridentate indan(pybox) Cu(II) Lewis acid complex has shown the potential for asymmetric synthesis.[2d] Similarly, 1,2,3,4-tetra-*O*-acetyl-α-D-galacturonic acid has been used as an asymmetric inducer.[2e]

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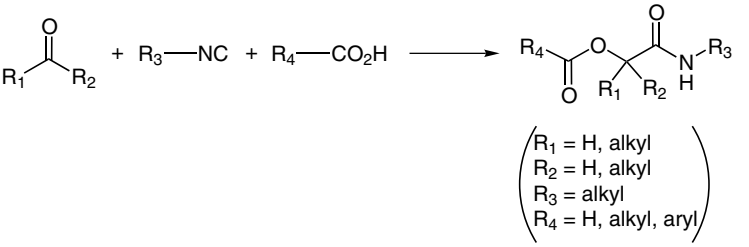
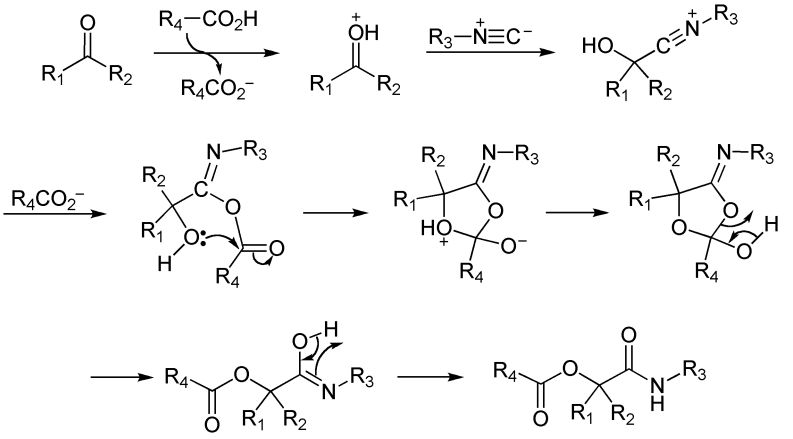
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Initially, Passerini proposed that the reaction involved an addition of carboxylic acid to carbonyl compound, giving acyloxy hemiacetal, which then reacted with isonitrile to form the final product.[1] However, current views about this reaction favor the following consecutive processes: the protonation of the carbonyl compound from carboxylic acid, followed by the attack of isonitrile to give a nitrilium ion, the nucleophilic addition of carboxylate, acyl group transfer, and the final amide tautomerization. A general mechanism for this reaction is shown here.[2a,2b]



D. MODIFICATION

This reaction has been modified to occur in aqueous solution[2b,3f] and ionic liquid (e.g., [bmim]BF_4).[3i] In addition, different Lewis acids have been used to promote this reaction.

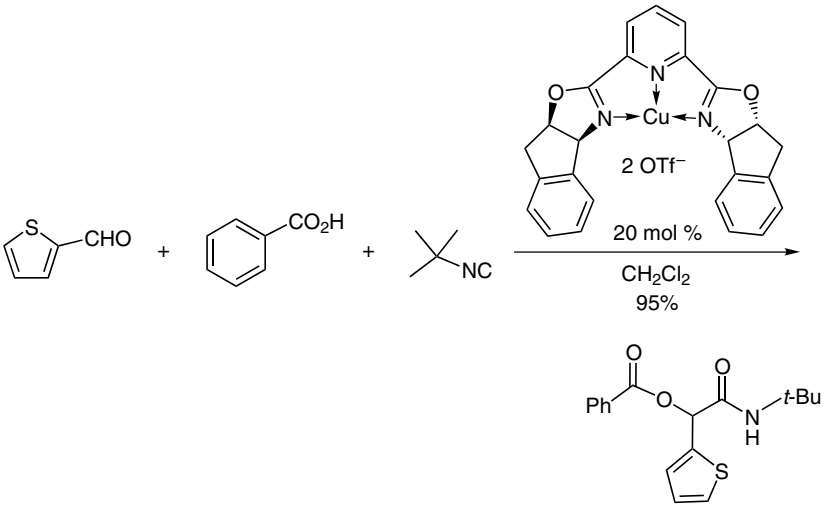
E. APPLICATIONS

This reaction has wide applications in combinatorial synthesis.

F. RELATED REACTIONS

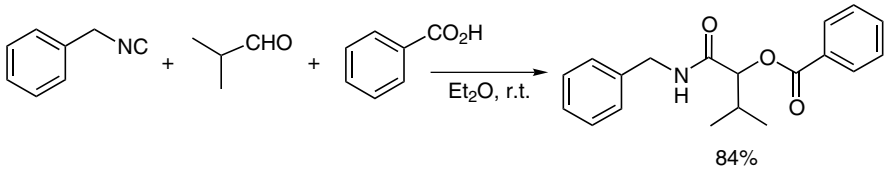
This reaction is related to the *Ugi Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2d.

To a 25-mL round-bottomed flask equipped with a stir bar and dried under argon with flame was added 7.0 mL CH_2Cl_2, 20 mol % $Cu(OTf)_2$, and 20 mol % indane (pybox) ligand. The mixture was stirred at 38°C until the components were completely dissolved. Then 2-thiophenecarboxyl (64 mg, 77 μL, 0.57 mmol, 1.05 eq.) was added, and the solution was cooled to 0°C and allowed to stand for 30 min, at which time 400 mg molecular sieves (AW-300) were added. In a separate flame-dried round-bottomed flask under argon were added 69 mg benzoic acid (0.57 mmol, 1.05 eq.) and 45 mg *t*-butyl isonitrile (61 μL, 0.54 mmol, 1.0 eq.), 3.0 mL CH_2Cl_2, and 100 mg AW-300 molecular sieves. This mixture was shaken for 30 min and then was drawn into a gas syringe and delivered to the first solution via a syringe pump over 4 h. The reaction was stirred for 24 h, during which time TLC analysis was conducted with EtOAc/hexanes (1:1) as the eluent. After the reaction completed, 2.0 mL saturated NaOCl solution was added, and the mixture was allowed to stir for an additional hour; solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography with hexane/EtOAc (9:1–1:3) to afford 162 mg *t*-butylcarbamoyl(thiophen-2-yl)methyl benzoate as a white solid, in a yield of 95%, $R_f = 0.45$ (hexane/EtOAc, 2:1).



Reference 2h.

To a 10-mL Et_2O solution containing 610 mg benzoic acid (5 mmol) were added 360 mg isobutyric aldehyde (5 mmol) and 586 mg benzyl isocyanide (5 mmol). The resulting mixture was stirred overnight at room temperature. The crystallized product was filtered off, washed with cold Et_2O, and dried under high vacuum to give 1.30 g 1-benzylcarbamoyl-2-methyl propyl benzoate as a solid, in a yield of 84%.

Other references related to the Passerini reaction are cited in the literature.[11]

H. REFERENCES

1. (a) Passerini, M., *Gazz. Chim. Ital.,* **1921**, *51*, 126. (b) Passerini, M., *Gazz. Chim. Ital.,* **1921**, *51*, 181.
2. (a) Denmark, S. E. and Fan, Y., *J. Org. Chem.,* **2005**, *70*, 9667. (b) Pirrung, M. C. and Sarma, K. D., *J. Am. Chem. Soc.,* **2004**, *126*, 444. (c) Zakrzewski, J.; Jezierska, J. and Hupko, J., *Org. Lett.,* **2004**, *6*, 695. (d) Andreana, P. R.; Liu, C. C. and Schreiber, S. L., *Org. Lett.,* **2004**, *6*, 4231. (e) Blaser, H.-U., *Chimia,* **2004**, *58*, 76. (f) Marcaccini, S.; Miguel, D.; Torroba, T. and García-Valverde, M., *J. Org. Chem.,* **2003**, *68*, 3315. (g) Beck, B.; Larbig, G.; Mejat, B.; Magnin-Lachaux, M.; Picard, A.; Herdtweck, E. and Dömling, A., *Org. Lett.,* **2003**, *5*, 1047. (h) Kusebauch, U.; Beck, B.; Messer, K.; Herdtweck, E. and Dömling, A., *Org. Lett.,* **2003**, *5*, 4021. (i) Ostaszewski, R.; Portlock, D. E.; Fryszkowska, A. and Jeziorska, K., *Pure & Appl. Chem.,* **2003**, *75*, 413. (j) Costa, S. P. G.; Maia, H. L. S. and Pereira-Lima, S. M. M. A., *Org. Biomol. Chem.,* **2003**, *1*, 1475. (k) Denmark, S. E. and Fan, Y., *J. Am. Chem. Soc.,* **2003**, *125*, 7825. (l) Janezic, D.; Hodoscek, M. and Ugi, I., *Internet Electron. J. Mol. Des*., **2002**, *1*, 293. (m) Xia, Q. and Ganem, B., *Org. Lett.,* **2002**, *4*, 1631. (n) Owens, T. D. and Semple, J. E., *Org. Lett.,* **2001**, *3*, 3301. (o) Banfi, L.; Guanti, G. and Riva, R., *Chem. Commun.*, **2000**, 985. (p) De Nooy, A. E. J.; Capitani, D.; Masci, G. and Crescenzi, V., *Biomacromolecules*, **2000**, *1*, 259. (q) Semple, J. E.; Owens, T. D.; Nguyen, K. and Levy, O. E., *Org. Lett.,* **2000**, *2*, 2769. (r) Carofiglio, T.; Cozzi, P. G.; Floriani, C.; Chiesi-Villa, A. and Rizzoli, C., *Organometallics,* **1993**, *12*, 2726. (s) Lumma, W. C., *J. Org. Chem.,* **1981**, *46*, 3668. (t) Kagen, H. and Lillien, I., *J. Org. Chem.,* **1966**, *31*, 3728. (u) Baker, R. H. and Stanonis, D., *J. Am. Chem. Soc.,* **1951**, *73*, 699.
3. (a) Krishna, P. R. and Lopinti, K., *Synlett,* **2007**, 83. (b) Umbreen, S.; Brockhaus, M.; Ehrenberg, H. and Schmidt, B., *Eur. J. Org. Chem.,* **2006**, 4585. (c) El Kaim, L.; Gizolme, M. and Grimaud, L., *Org. Lett.,* **2006**, *8*, 5021. (d) Andrade, C. K. Z.; Takada, S. C. S.; Suarez, P. A. Z. and Alves, M. B., *Synlett*, **2006**, 1539. (e) Krishna, P. R.; Dayaker, G. and Reddy, P. V. N., *Tetrahedron Lett*., **2006**, *47*, 5977. (f) Extance, A. R.; Benzies, D. W. M. and Morrish, J. J., *QSAR & Comb. Sci*., **2006**, *25*, 484. (g) Zhang, X. Y.; Li, Y. Z.; Fan, X. S.; Qu, G. R.; Wang, J. J. and Hu, X. Y., *Chinese Chem. Lett.,* **2006**, *17*, 578. (h) Ngouansavanh, T. and Zhu, J. P., *Angew. Chem. Int. Ed.,* **2006**, *45*, 3495. (i) Fan, X. S.; Li, Y. Z.; Zhang, X. Y.; Qu, G. R. and Wang, J. J., *Can. J. Chem.,* **2006**, *84*, 794. (j) Mironov, M. A.; Ivantsova, M. N.; Tokareva, M. I. and Mokrushin, V. S., *Tetrahedron Lett*., **2005**, *46*, 3957. (k) Banfi, L. and Riva, R., *Org. React.,* **2005**, *65*, 1. (l) Cuny, G.; Gamez-Montano, R. and Zhu, J. P., *Tetrahedron*, **2004**, *60*, 4879. (m) Lengyel, I.; Cesare, V. and Taldone, T., *Tetrahedron*, **2004**, *60*, 1107. (n) Banfi, L.; Basso, A.; Guanti, G. and Riva, R., *Mol. Diversity,* **2003**, *6*, 227. (o) Frey, R.; Galbraith, S. G.; Guelfi, S.; Lamberth, C. and Zeller, M., *Synlett*, **2003**, 1536. (p) Xia, Q. and Ganem, B., *Synthesis*, **2002**, 1969. (q) Jenner, G., *Tetrahedron Lett*., **2002**, *43*, 1235. (r) Owens, T. D.; Araldi, G.-L.; Nutt, R. F. and Semple, J. E., *Tetrahedron Lett.,* **2001**, *42*, 6271. (s) Kim, S. W.; Bauer, S. M. and Armstrong, R. W., *Tetrahedron Lett*., **1998**, *39*, 7031. (t) Bossio, R.; Marcaccini, S. and Pepino, R., *Liebigs Ann. Chem.,* **1991**, 1107. (u) Carofiglio, T.; Floriani, C.; Chiesi-Villa, A. and Rizzoli, C., *Organometallics,* **1991**, *10*, 1659. (v) Rachon, J., *Chimia*, 1983, 37, 299. (w) Falck, J. R. and Manna, S., *Tetrahedron Lett.,* **1981**, *22*, 619. (x) Eckert, H., *Synthesis*, **1977**, 332. (y) Hagedorn, I. and Eholzer, U., *Chem. Ber.,* **1965**, *98*, 936.

(z) Ugi, I. and Meyr, R., *Chem. Ber.,* **1964**, *94*, 2229. (aa) Fetzer, U. and Ugi, I., *Ann.,* **1962**, *659*, 184.

4. Banfi, L.; Guanti, G.; Riva, R.; Basso, A. and Calcagno, E., *Tetrahedron Lett*., **2002**, *43*, 4067.
5. Basso, A.; Banfi, L.; Riva, R.; Piaggio, P. and Guanti, G., *Tetrahedron Lett*., **2003**, *44*, 2367.
6. Oaksmith, J. M.; Peters, U. and Ganem, B., *J. Am. Chem. Soc.,* **2004**, *126*, 13606.
7. de Nooy, A. E. J.; Masci, G. and Crescenzi, V., *Macromolecules,* **1999**, *32*, 1318.
8. Bock, H. and Ugi, I., *J. Prakt. Chem.,* **1997**, *339*, 385.
9. Dömling, A. and Ugi, I., *Angew. Chem. Int. Ed. Engl.,* **2000**, *39*, 3168.
10. (a) Seebach, D.; Adam, G.; Gees, T.; Schiess, M. and Weigand, W., *Ber*., **1988**, *121*, 507. (b) Schiess, M. and Seebach, D., *Helv. Chim. Acta,* **1983**, *66*, 1618.
11. (a) Bayh, O.; Awad, H.; Mongin, F.; Hoarau, C.; Bischoff, L.; Trécourt, F.; Quéguiner, G.; Marsais, F.; Blanco, F.; Abarca, B. and Ballesteros, R., *J. Org. Chem.,* **2005**, *70*, 5190. (b) Beck, B.; Picard, A.; Herdtweck, E. and Dömling, A., *Org. Lett.,* **2004**, *6*, 39. (c) Wright, D. L.; Robotham, C. V. and Aboud, K., *Tetrahedron Lett.,* **2002**, *43*, 943. (d) Beck, K.; Magnin-Lachaux, M.; Herdtweck, E. and Dömling, A., *Org. Lett.,* **2001**, *3*, 2875. (e) Baker, R. H. and Linn, L. E., *J. Am. Chem. Soc.,* **1948**, *70*, 3721. (f) Baker, R. H. and Schlesinger, A. H., *J. Am. Chem. Soc.,* **1945**, *67*, 1499. (g) Passerini, M. and Ragni, G., *Gazz. Chim. Ital.,* **1931**, *61*, 964. (h) Passerini, M., *Gazz. Chim. Ital*., **1924**, *54*, 529.

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Paterno-Büchi Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Paterno and Chieffi in 1909,[1] and subsequently extended by Büchi et al. in 1954.[2] It is a photo-induced [2 + 2] cycloaddition of carbonyl compounds with olefins or other unsaturated substrates to form four-membered cyclic ethers, known as oxetanes,[3] with high regio- and stereoselectivity.[3b,4] Therefore, this reaction is generally known as the Paterno-Büchi reaction.[3,4a,4b,4e,5,6] Occasionally, this reaction is also referred to as the Paterno-Büchi cycloaddition,[7] Paterno-Büchi photocycloaddition,[4b,4c,8] or Paterno-Büchi coupling.[4c,9] All three types of ketones (i.e., dialkyl, diaryl, and aryl alkyl ketones) and aldehydes undergo the Paterno-Büchi reaction, even though some of these carbonyl compounds may undergo other types of photoreactions, including Norrish type I and type II reactions.[10] As a result, the Paterno-Büchi reaction is often sluggish.[4d] However, in the presence of an electron-enriched alkene, such as an enol ether or a polyalkylalkene, the Paterno-Büchi reaction dominates.[4e] In addition, the Paterno-Büchi reaction also competes with the radical polymerization of alkenes.[4d] In this reaction, the carbonyl compound is irradiated to either a singlet[4a,5j,5l,7c] or triplet[4a,4b,5d,5e,5j–5l,7l] excited state; then the electronically excited carbonyl group attacks the alkene at ground state, although such cycloaddition often takes place through a triplet carbonyl group.[5l] When the Paterno-Büchi reaction occurs through a triplet carbonyl, as in the case of the reaction with electron-rich alkenes (e.g., enol ethers), it is nonconcerted,[5j] and a biradical intermediate forms via an electrophilic attack from an n-π^* triplet carbonyl to form a C-O bond,[5l] which then cyclizes to oxetane with a low-energy barrier.[5j] In comparison, the singlet Paterno-Büchi reaction proceeds through conical intersections, via a nonconcerted C-O attack and a concerted C-C attack pathway.[5j] In addition, if electron transfer is exothermic, it is very possible that the Paterno-Büchi reaction occurs through the electron-transfer

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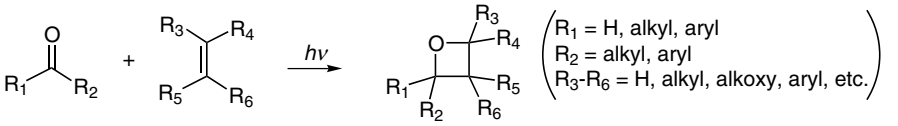
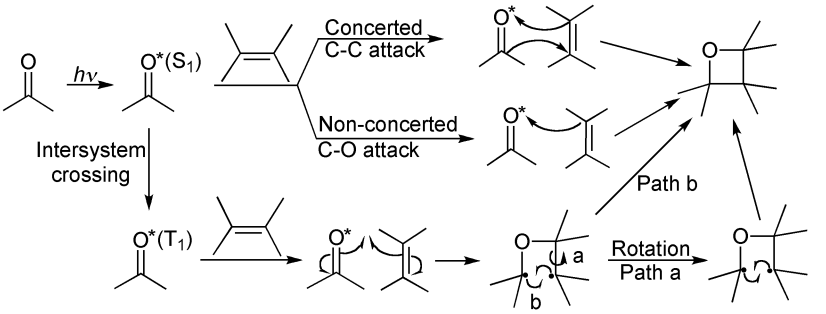
pathway.[4b] Moreover, other reaction intermediates are also found for the Paterno-Büchi reaction, such as exciplexes[11] and ion-radical pairs.[12] On the other hand, the regioselectivity of major oxetane from asymmetric olefins follows the *Markovnikov Rule* through the formation of the most stable biradical intermediates.[51] However, the stereoselectivity is controlled by the nature of reaction pair. It has been found that the spin-orbit coupling-controlled intersystem crossing determines the stereochemical outcome.[3b] In addition, temperature[3a,5d,13] and hydrogen bonding[4a] also affect the stereoselectivity. If the intersystem crossing at low temperature is much faster than bond rotation of biradical, then the resulting oxetane reflects the initial stereochemistry of the corresponding biradical.[13] In contrast, if the biradical is relatively stable, then the stereochemistry does not depend on the geometry of olefin.[13] Paterno-Büchi reaction is important not only because of its wide application in organic synthesis but also because of its major mutation processes for DNA through two adjacent pyrimidine bases.[5c] The cycloreversion of oxetane by photoelectron transfer (i.e., retro Paterno-Büchi reaction) is the tool for enzyme-catalyzed DNA repair.[14]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A general mechanism of the Paterno-Büchi reaction through either a singlet or triplet excitation state of the carbonyl compound is illustrated below, regardless of stereochemistry.



D. MODIFICATION

N/A

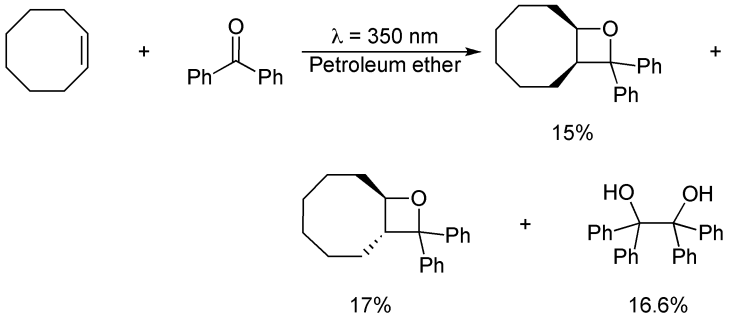
E. APPLICATIONS

This reaction has a wide application in organic synthesis.

F. RELATED REACTIONS

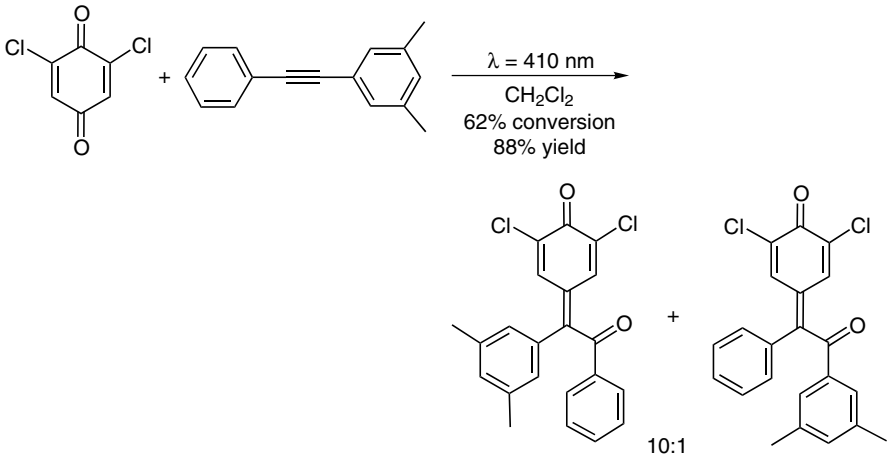
This reaction is related to regular [2 + 2] *Photoreaction* and *de Mayo Reaction.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 5d.

Under a nitrogen atmosphere, a solution of 2.11 g benzophenone (11.6 mmol) and 3.83 g *cis*-cyclooctene (34.8 mmol) in 300 mL petroleum ether at 5°C was irradiated in a Rayonet photoreactor at 350 nm for 24 h. A white precipitate (350 mg) was formed during the irradiation, which was collected by filtration and identified as 1,1,2,2-tetraphenylethanediol (benzpinacol) by ^{1}H- and ^{13}C-NMR spectroscopy. Distillation of the solvent and most of the residual olefin at 50°C (10 mbar) afforded 3.66 g yellow oil, which contained both diastereomeric oxetanes (*cis/trans* ≈ 40:60 by ^{13}C NMR spectroscopy). The crude product mixture (1.83 g) was purified by silica gel column chromatography with Et_2O/petroleum ether (1:10) as the eluent to afford 256 mg *cis*-10,10-diphenyl-9-oxabicyclo[6.2.0]decane as a colorless oil, in a yield of 15%. In addition, 285 mg *trans*-10,10-diphenyl-9-oxabicyclo[6.2.0]decane was obtained as a colorless oil, in a yield of 17%. Further purification of each diastereomers was carried out by bulb-to-bulb distillation (Kugelrohr) at 100°C (0.03 mmHg).



Reference 3d.

To a quartz cuvette fitted with a Teflon stopcock was added 53 mg 2,6-dichlorobenzoquinone and 63 mg phenyl *m*-xylyl acetylene in CH_2Cl_2 in a 0.1 M solution of each substance under argon. The cuvette was then placed in a clear Dewar flask filled with water at 25°C and irradiated with focused light from a medium-pressure mercury lamp (500 W) passed through an aqueous IR filter and an ESCO 410 nm filter. This ensured that the quinone itself was excited and not the diarylacetylene. After 22 h, the solvent was evaporated, and the residue was subjected to flash chromatography. 1-(3,5-Dimethylphenyl)-1-benzoyl-1-methylene-3,5-dichlorocyclohexa-2,5-dien-4-one was obtained as the major product, which was further recrystallized from acetonitrile, m.p., 191–192°C. The minor product was identified only by GC/MS. The total yield of quinone methide was 88% based on 62% of conversion.

Other references related to the Paterno-Büchi reaction are cited in the literature.[15]

H. REFERENCES

1. Paterno, E. and Chieffi, G., *Gazz. Chim. Ital.*, **1909**, *39*, 341.
2. Büchi, G., Inman, C. G. and Lipinski, E. S., *J. Am. Chem. Soc.*, **1954**, *76*, 4327.
3. (a) Adam, W.; Stegmann, V. R. and Weinkötz, S., *J. Am. Chem. Soc.,* **2001**, *123*, 2452. (b) Kutateladze, A. G., *J. Am. Chem. Soc.,* **2001**, *123*, 9279. (c) Adam, W.; Peters, K.; Peters, E. M. and Stegmann, V. R., *J. Am. Chem. Soc.,* **2000**, *122*, 2958. (d) Bosch, E.; Hubig, S. M. and Kochi, J. K., *J. Am. Chem. Soc.,* **1998**, *120*, 386. (e) Turro, N. J. and Farrington, G. L., *J. Am. Chem. Soc.,* **1980**, *102*, 6051.
4. (a) Griesbeck, A. G. and Bondock, S., *J. Am. Chem. Soc.,* **2001**, *123*, 6191. (b) Abe, M.; Fujimoto, K. and Nojima, M., *J. Am. Chem. Soc.,* **2000**, *122*, 4005. (c) Sun, D. L.; Hubig, S. M. and Kochi, J. K., *J. Org. Chem.,* **1999**, *64*, 2250. (d) Bach, T. and Schröder, J., *J. Org. Chem.,* **1999**, *64*, 1265. (e) Hu, S. K. and Neckers, D. C., *J. Org. Chem.,* **1997**, *62*, 564.
5. (a) Okamoto, H.; Yamaji, M.; Satake, K.; Tobita, S. and Kimura, M., *J. Org. Chem.,* **2004**, *69*, 7860. (b) D'Auria, M.; Emanuele, L.; Racioppi, R. and Romaniello, G., *Curr. Org. Chem.,* **2003**, *7*, 1443. (c) Thomas, M.; Guillaume, D.; Fourrey, J.-L. and Clivio, P., *J. Am. Chem. Soc.,* **2002**, *124*, 2400. (d) Adam, W. and Stegmann, V. R., *J. Am. Chem. Soc.,* **2002**, *124*, 3600. (e) Abe, M.; Torii, E. and Nojima, M., *J. Org. Chem.,* **2000**, *65*, 3426. (f) Griesbeck, A. G.; Fiege, M.; Bondock, S. and Gudipati, M. S., *Org. Lett.,* **2000**, *2*, 3623. (g) Dvorak, C. A.; Dufour, C.; Iwasa, S. and Rawal, V. H., *J. Org. Chem.,* **1998**, *63*, 5302. (h) Bach, T.; Jödicke, K.; Kather, K. and Fröhlich, R., *J. Am. Chem. Soc.,* **1997**, *119*, 2437. (i) Hu, S. K. and Neckers, D. C., *J. Org. Chem.,* **1997**, *62*, 6820. (j) Palmer, I. J.; Ragazos, I. N.; Bernardi, F.; Olivucci, M. and Robb, M. A., *J. Am. Chem. Soc.,* **1994**, *116*, 2121. (k) Adam, W.; Kliem, U.; Mosandl, T.; Peters, E.-M.; Peters, K. and von Schnering, H. G., *J. Org. Chem.,* **1988**, *53*, 4986. (l) Dalton, J. C.; Wriede, P. A. and Turro, N. J., *J. Am. Chem. Soc.,* **1970**, *92*, 1318.
6. (a) D'Auria, M.; Emanuele, L.; Pace, V. and Racioppi, R., *Lett. Org. Chem.,* **2006**, *3*, 350. (b) D'Auria, M.; Emanuele, L. and Racioppi, R., *Int. J. Photoenergy,* **2006**, 84645/1. (c) Song, Q.-H.; Wang, H.-B.; Li, X.-B.; Hei, X.-M.; Guo, Q.-X. and Yu, S.-Q., *J. Photochem. Photobio., A: Chem.,* **2006**, *183*, 198. (d) D'Auria, M.; Emanuele, L. and Racioppi, R., *Lett. Org. Chem.,* **2006**, *3*, 244. (e) Hei, X.-M.; Song, Q.-H.; Li, X.-B.; Tang, W.-J.; Wang, H.-B. and Guo, Q.-X., *J. Org. Chem.,* **2005**, *70*, 2522. (f) Pinter, B.; De Proft, F.; Veszpremi, T. and Geerlings, P., *J. Chem. Sci. (Bangalore),* **2005**, *117*, 561. (g) D'Auria, M.; Emanuele, L. and Racioppi, R., *J. Photochem. Photobio., A: Chem.,* **2004**, *163*, 103. (h) D'Auria, M.; Emanuele, L. and Racioppi, R., *Photochem. Photobio. Sci.,* **2004**, *3*, 927. (i) Abe, M.; Kawakami, T.; Ohata, S.; Nozaki, K. and Nojima, M., *J. Am. Chem. Soc.,* **2004**, *126*, 2838. (j) D'Auria, M.; Emanuele, L. and Racioppi,

R., *Photochem. Photobio. Sci.,* **2003**, *2*, 904. (k) D'Auria, M.; Emanuele, L.; Poggi, G.; Racioppi, R. and Romaniello, G., *Tetrahedron*, **2002**, *58*, 5045. (l) Kang, T. and Scheffer, J. R., *Org. Lett.,* **2001**, *3*, 3361. (m) Abe, M.; Tachibana, K.; Fujimoto, K. and Nojima, M., *Synthesis*, **2001**, 1243. (n) Adam, W. and Stegmann, V. R., *Synthesis*, **2001**, 1203. (o) Xue, J.; Zhang, Y.; Wu, T.; Fun, H.-K. and Xu, J.-H., *J. Chem. Soc., Perkin Trans. I,* **2001**, 183. (p) Goez, M. and Frisch, I., *J. Information Recording,* **2000**, *25*, 287. (q) Van Wolven, C.; Dopp, D. and Fischer, M. A., *J. Information Recording,* **2000**, *25*, 209. (r) Bach, T.; Brummerhop, H. and Harms, K., *Chem. Eur. J.,* **2000**, *6*, 3838. (s) D'Auria, M.; Racioppi, R. and Romaniello, G., *Eur. J. Org. Chem.,* **2000**, 3265. (t) Gan, C. Y.; Gable, R. W. and Lambert, J. N., *Aust. J. Chem.,* **1999**, *52*, 629. (u) Bach, T. and Brummerhop, H., *Angew. Chem. Int. Ed.,* **1998**, *37*, 3400. (v) Thopate, S. R.; Kulkarni, M. G. and Puranik, V. G., *Angew. Chem. Int. Ed.,* **1998**, *37*, 1110. (w) Park, S.-K.; Lee, S.-J.; Baek, K. and Yu, C.-M., *Bull. Korean Chem. Soc.,* **1998**, *19*, 35. (x) Bach, T., *Liebigs Ann./Recueil,* **1997**, 1627. (y) Chung, W.-S. and Ho, C.-C., *Chem. Commun.,* **1997**, 317. (z) Buhr, S.; Griesbeck, A. G.; Lex, J.; Mattay, J. and Schroeer, J., *Tetrahedron Lett*., **1996**, *37*, 1195. (aa) Bach, T. and Joedicke, K., *Chem. Ber.,* **1993**, *126*, 2457. (bb) Lange, G. L. and Bosch, M., *Tetrahedron Lett*., **1971**, 315. (cc) Yang, N.-C.; Loeschen, R. L. and Mitchell, D., *J. Am. Chem. Soc.,* **1967**, *89*, 5465.

7. (a) Encinas, S.; Belmadoui, N.; Climent, M. J.; Gil, S. and Miranda, M. A., *Chem. Res. Toxicol.,* **2004**, *17*, 857. (b) Hubig, S. M.; Sun, D. L. and Kochi, J. K., *J. Chem. Soc., Perkin Trans. II,* **1999**, 781. (c) Adam, W. and Hannemann, K., *J. Am. Chem. Soc.,* **1983**, *105*, 714.
8. Fleming, S. A. and Jones, R. W., *J. Heterocycl. Chem.,* **1990**, *27*, 1167.
9. Wang, X. Y.; Yan, B. Z. and Wang, T., *Chinese Chem. Lett.,* **2003**, *14*, 270.
10. See *Norrish Type I Reaction* (P. 2062) and *Norrish Type II Reaction* (P. 2067).
11. (a) Caldwell, R. A.; Hrncir, D. C.; Munoz, T., and Unett, D. J., *J. Am. Chem. Soc*., **1996**, *118*, 8741. (b) Schore, N. E. and Turro, N. J., *J. Am. Chem. Soc*., **1975**, *97*, 2482. (c) Caldwell, R. A.; Sovocool, G. W. and Gajewski, R. P., *J. Am. Chem. Soc.,* **1973**, *95*, 2549.
12. (a) Griesbeck, A. G.; Mauder, H. and Stadtmüller, S., *Acc. Chem. Res*., **1994**, *27*, 70. (b) Eckert, G. and Goez, M., *J. Am. Chem. Soc*., **1994**, *116*, 11999. (c) Gersdorf, J.; Mattay, J. and Görner, H., *J. Am. Chem. Soc.,* **1987**, *109*, 1203. (d) Freilich, S. C. and Peters, K. S., *J. Am. Chem. Soc*., **1985**, *107*, 3819. (e) Freilich, S. C. and Peters, K. S., *J. Am. Chem. Soc*., **1981**, *103*, 6255.
13. Goez, M. and Eckert, G., *J. Am. Chem. Soc.,* **1996**, *118*, 140.
14. Pérez-Ruiz, R.; Izquierdo, M. A. and Miranda, M. A., *J. Org. Chem.,* **2003**, *68*, 10103.
15. (a) Xia, W. J.; Yang, C.; Patrick, B. O.; Scheffer, J. R. and Scott, C., *J. Am. Chem. Soc.,* **2005**, *127*, 2725. (b) Lhiaubet-Vallet, V.; Encinas, S. and Miranda, M. A., *J. Am. Chem. Soc.,* **2005**, *127*, 12774. (c) Suau, R.; García-Segura, R.; Sánchez-Sánchez, C.; Pérez-Inestrosa, E. and Pedraza, A. M., *Tetrahedron,* **2003**, *59*, 2913. (d) Lonchar, M.; Bora, U.; Boruah, R. C. and Sandhu, J. S., *Synth. Commun.,* **2002**, *32*, 3611. (e) Goez, M. and Frisch, I., *J. Phys. Chem. A,* **2002**, *106*, 8079. (f) Reddy, T. J. and Rawal, V. H., *Org. Lett.,* **2000**, *2*, 2711. (g) Bach, T., *Synlett,* **2000**, 1699. (h) Inoue, Y.; Wada, T.; Asaoka, S.; Saot, H. and Pete, J. P., *J. Chem. Soc., Chem. Commun.,* **2000**, 251. (i) D'Auria, M. and Racioppi, R., *ARKIVOC,* **2000**, 1(*ii*), 133. (j) Elliott, M. C., *J. Chem. Soc., Perkin Trans. I,* **1998**, 4175. (k) Griesbeck, A. G.; Buhr, S.; Fiege, M.; Schmickler, H. and Lex, J., *J. Org. Chem.,* **1998**, *63*, 3847. (l) Bach, T.; Kather, K. and Krämer, O., *J. Org. Chem.,* **1998**, *63*, 1910. (m) Fleming, S. A. and Gao, J. J., *Tetrahedron Lett.,* **1997**, *38*, 5407. (n) Nidy, E. G.; Wicnienski, N. A.; Chidester, C. G.; Dobrowolski, P. J.; Mizsak, S. A.; Toy, A.; Runge, T. A.; Qualls, S. J.; Kelly, R. C. and Johnson, R. A., *J. Org. Chem.,* **1997**, *62*, 4900. (o) Rawal, V. H.; Eschbach, A.; Dufour, C. and Iwasa, S., *Pure & Appl. Chem.,* **1996**, *68*, 675. (p) Kirschberg, T. and Mattay, J., *J. Org. Chem.,* **1996**, *61*, 8885. (q) Cantrell, T. S. and Allen, A. C., *J. Org. Chem.,* **1989**, *54*, 135. (r) Cantrell, T. S.; Allen, A. C. and Ziffert, H., *J. Org. Chem.,* **1989**, *54*, 140. (s) Caldwell, R. A.; Majima, T. and Pac, C. J., *J. Am. Chem. Soc.,* **1982**, *104*, 629. (t) Frimer, A. A.; Farkash, T. and Sprecher, M., *J. Org. Chem.,* **1979**, *44*, 989. (u) Saltiel, J.; Coates, R. M. and Dauben, W. G., *J. Am. Chem. Soc.,* **1966**, *88*, 2745.

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Pauson-Khand Reaction

(Pauson-Khand Cyclization, Pauson-Khand Cycloaddition)

A. GENERAL DESCRIPTION OF THE REACTION

The reaction was first reported by Khand and Pauson et al. in 1973.[1] It is the dicobalt octacarbonyl [$Co_2(CO)_8$] mediated or promoted one-step synthesis of α,β-unsaturated cyclopentenone from the [2+2+1] cycloaddition of alkyne, alkene and carbon monoxide, through an intermediate of alkynedicobalt hexacarbonyl complex. Therefore, this reaction is generally known as the Pauson-Khand reaction,[2] Pauson-Khand cyclization,[2u,2z,3] or Pauson-Khand cycloaddition.[4] Occasionally, this reaction is also referred to as the Pauson-Khand annulation,[5] Pauson-Khand multicomponent cycloaddition,[6] Pauson-Khand carbonylative cocyclization,[7] Pauson-Khand bicyclization,[8] Khand annulation,[9] Khand cycloaddition,[9] Khand cyclization[9a] (cyclisation[10]), or Khand reaction.[11] Among these names, the Pauson-Khand reaction is the one used most often.

It is accepted that this reaction involves the formation of the alkynedicobalt hexacarbonyl complex from an alkyne and $Co_2(CO)_8$ by the evolving of two CO ligands,[12] followed by the alkene coordination at one of the two enantiotopic Co atoms with concomitant CO insertion,[13] and final reductive elimination of the metal to an α,β-unsaturated cyclopentenone.[2z] In the traditional protocol, the reaction mixture is heated in toluene at 110°C, or tertiary amine *N*-oxides are added to promote the reaction at ambient temperature.[2v] For the purpose of stereochemical control, many Pauson-Khand reactions are designed as intramolecular reactions[2cc,3f,3n,3p,5b,6,14] or using cyclic alkenes, such as norbornene.[12b,15] It has been found that the reactivity of cyclic alkenes is in the order of cyclohexene < cyclopentene < norbornene.[15a] For the intermolecular Pauson-Khand reaction, alkene is positioned adjacent to the less bulky acetylenic substituent during coordination because of steric hindrance, and a subsequent C–C bond forms between an alkenic

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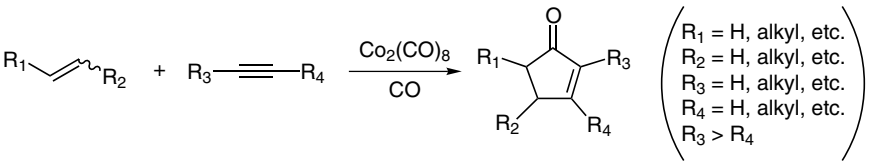
carbon and the closer acetylenic carbon, so that the larger group on alkyne is often found at the α-position of the resulting cyclopentenone.[13] Although the Pauson-Khand reaction is one of the most powerful reactions for forming very complicated structures with stereochemical control, it still has some drawbacks, such as the application of a stoichiometric amount of $Co_2(CO)_8$,[12a,16] high pressure of CO,[17] troublesome purification protocols,[2v] and low yields that depend on alkynes and alkenes.[2v] Therefore, the original protocol of the Pauson-Khand reaction has been extensively modified by the use of different catalysts or reaction conditions.

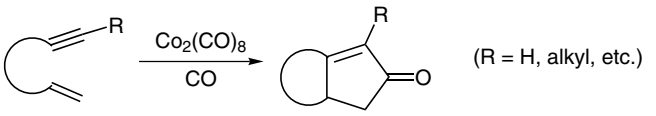
It has been found that besides $Co_2(CO)_8$, many other transition metal complexes are effective for promoting this reaction. For example, some of cobalt-based catalysts are $Co_2(CO)_8$, $Co_2(CO)_8$ in combination with $P(OPh_3)_3$,[18] $Co_2(CO)_8$/tetramethylthiourea (TMTU),[19] (ind)Co(COD),[20] $Co(acac)_2$ (with $NaBH_4$),[21] $Co_4(CO)_{12}$,[22] $Co_3(CO)_9(\mu^3\text{-CH})$,[23] $CoBr_2$/Zn/CO,[24] P,S-cobalt complexes,[25] and *N*-heterocyclic carbene dicobalt complex.[26] Titanium-based catalysts include $Cp_2Ti(PMe_3)_2$,[27] Cp_2TiCl_2/*n*-BuLi,[27] and (*S*,*S*)(EBTHI)Ti(CO)$_2$.[3m,3q] Some of the ruthenium-based catalysts are $Ru_3(CO)_{12}$,[14k,28] $[RuCl_2(CO)_3]_2$,[14k] Cp*RuCl(cod),[14k] and Ru(cod)(cot).[14k] Rhodium-based catalysts are $[RhCl(CO)_2]_2$,[29] *trans*-$[RhCl(CO)(dppp)]_2$[14j] and $[Rh(COD)Cl]_2$,[30] cobalt-rhodium heterobimetallic nanoparticle,[2f] and rhodium bisbenzodioxanPhos complex.[3c] Iridium-based catalysts are (S)-tolBINAP-Ir complex[31] and $[Ir(COD)Cl]_2$,[31] and molybdenum-based catalysts include $Mo(CO)_6$,[2q,14i,32] heterobimetallic (Mo-Co) complexes,[15c] and $Mo(CO)_3(DMF)_3$.[33] Among the molybdenum-based catalysts, $Mo(CO)_3(DMF)_3$ works even in the absence of any promoter. In addition, nickel and palladium are also effective for the Pauson-Khand reaction, such as $Ni(COD)_2$/ligand[27] and $PdCl_2$/TMTU.[34]

The Pauson-Khand reaction has also been carried out under different conditions, such as the use of chiral ligands, including PuPHOS,[2r,2ac,25] CamPHOS,[2r] and camphorsultam;[12b] the use of aldehydes as the carbon monoxide source;[17,30,35] the use of solid-supported cobalt catalyst to enhance purification, such as the dry-state adsorption;[2z] the use of colloidal cobalt nanoparticle;[36] and the use of metallic cobalt supported on mesoporous silica prepared by decomposing $Co_2(CO)_8$ on mesoporous silica supports (SBA-15 and MCM-41) in the refluxing toluene solution.[14h,36b] Other modifications include different promoting methods, such as photo-irradiation,[3d,16b] microwave irradiation,[2v] molecular sieves,[6,37] TEMPO,[38] *N*-oxides,[39] and supercritical fluids.[40] Furthermore, the cycloaddition between allene and carbon monoxide under similar conditions is known as the allenic Pauson-Khand reaction,[2q,14f,27,41] and the reaction among alkyne, carbodiimide, and CO is referred to as the *aza*-Pauson-Khand reaction.[42]

B. GENERAL REACTION SCHEME



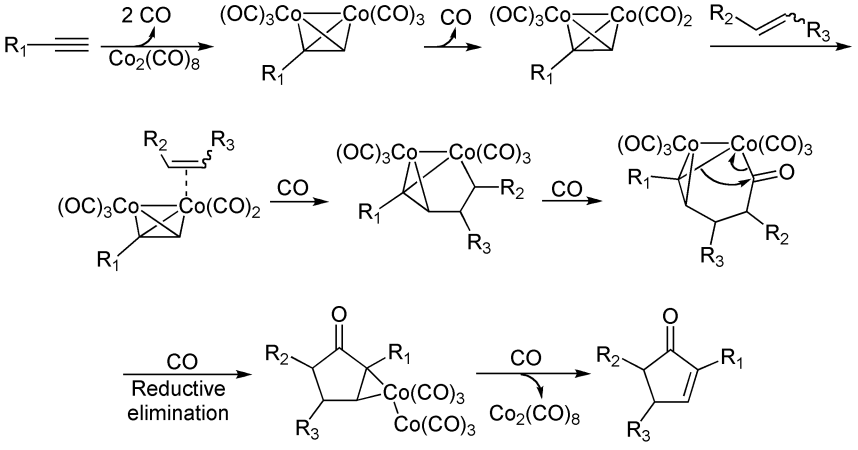
Intermolecular Pauson-Khand reaction



Intramolecular Pauson-Khand reaction

C. PROPOSED MECHANISMS

Displayed here is a general mechanism for the Pauson-Khand reaction, according to several studies.[12c,13,43]



D. MODIFICATION

This reaction has been extensively modified as described in Section A.

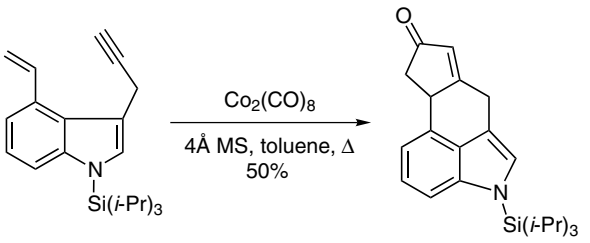
E. APPLICATIONS

This reaction has wide application in organic synthesis.

F. RELATED REACTIONS

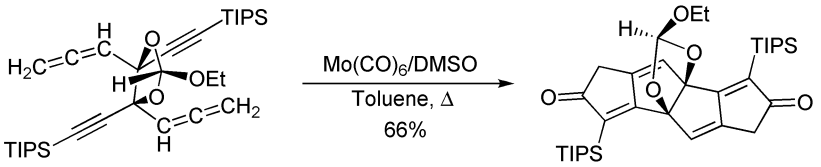
This reaction is related to the *Nicholas Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 44.

To a round-bottomed flask were added 0.33 g *N*-triisopropylsilyl-3-propargyl-4-vinyl indole (1.0 mmol), 2.64 g powered 4Å molecular sieves, and 20 mL dry toluene under argon at room temperature, followed by 0.41 g $Co_2(CO)_8$ (1.2 mmol). The resulting mixture was stirred for 2 h until total complexation of the enyne by TLC. Then the solution was refluxed for 18 h. After filtration and solvent evaporation, the residue was purified by flash chromatography (hexane/EtOAc, 4:1) to afford 0.18 g 4-triisopropylsilyl-4,6,6a,7-tetrahydroindeno[6,5,4-*cd*]-indol-8-one as a pale yellow oil, in a yield of 50%.



Reference 2q.

A mixture of 6.3 g $Mo(CO)_6$ (24 mmol) and 120 mL toluene was heated to 50°C for 2 hours to form a saturated solution. After that, a solution of 1.35 g *ortho*-ester (2.43 mmol) and 2.01 g DMSO (26 mmol) in 20 mL dry toluene was added. The resulting mixture was heated at 53–55°C for 36 h and then was filtered to remove the solids. The precipitate was washed with hexanes (2 × 20 mL). The combined organic layers were concentrated under reduced pressure, and the residue was purified by gradient silica gel column chromatography using hexanes/EtOAc (100:0–95:5) as the eluent, to afford 0.96 g tetraene, in a yield of 66%. This tetraene can be further purified by crystallization from hexanes.

Other references related to the Pauson-Khand reaction are cited in the literature.[45]

H. REFERENCES

1. (a) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E. and Foreman, M. I., *J. Chem. Soc., Perkin Trans. I*, **1973**, 977. (b) Khand, I. U. and Pauson, P. L., *J. Chem. Res. (M)*, **1977**, 168. (c) Pauson, P. L. and Khand, I. U., *Ann. N. Y. Acad. Sci.,* **1977**, *295*, 2.
2. (a) Muller, J.-L.; Klankermayer, J. and Leitner, W., *Chem. Commun.,* **2007**, 1939. (b) Inagaki, F.; Kawamura, T. and Mukai, C., *Tetrahedron*, **2007**, *63*, 5154. (c) Madu, C. E.; Seshadri, H. and Lovely, C. J., *Tetrahedron*, **2007**, *63*, 5019. (d) Banide, E. V.; Mueller-Bunz, H.; Manning, A. R.;

Evans, P. and McGlinchey, M. J., *Angew. Chem. Int. Ed.,* **2007**, *46*, 2907. (e) Saito, T.; Sugizaki, K.; Otani, T. and Suyama, T., *Org. Lett.,* **2007**, *9*, 1239. (f) Park, J. H.; Kim, S. Y.; Kim, S. M.; Lee, S. I. and Chung, Y. K., *Synlett,* **2007**, 453. (g) Muller, J.-L.; Rickers, A. and Leitner, W., *Adv. Synth. Catal.,* **2007**, *349*, 287. (h) Cuevas, F.; Garcia-Granda, C.; Buschmann, H.; Torrens, A.; Yenes, S. and Pericas, M. A., *Synlett,* **2007**, 119. (i) Cabot, R.; Lledo, A.; Reves, M.; Riera, A. and Verdaguer, X., *Organometallics*, **2007**, *26*, 1134. (j) Adrio, J. and Carretero, J. C., *J. Am. Chem. Soc.,* **2007**, *129*, 778. (k) Struebing, D. and Beller, M., *Top. Organomet. Chem.,* **2006**, *18*, 165. (l) Sezer, S.; Oezdemirhan, D.; Sahin, E. and Tanyeli, C., *Tetrahedron: Asymmetry,* **2006**, *17*, 2981. (m) Krafft, M. E.; Kyne, G. M.; Hirosawa, C.; Schmidt, P.; Abboud, K. A. and L'Helias, N., *Tetrahedron*, **2006**, *62*, 11782. (n) Kim, D. H.; Kim, K. and Chung, Y. K., *J. Org. Chem.,* **2006**, *71*, 8264. (o) McNeill, E.; Chen, I. and Ting, A. Y., *Org. Lett.,* **2006**, *8*, 4593. (p) De Bruin, T. J. M.; Michel, C.; Vekey, K.; Greene, A. E.; Gimbert, Y. and Milet, A., *J. Organomet. Chem.,* **2006**, *691*, 4281. (q) Kaasalainen, E.; Tois, J.; Russo, L.; Rissanen, K. and Helaja, J., *Tetrahedron Lett*., **2006**, *47*, 5669. (r) Cao, H.; Ornum, S. G. V.; Deschamps, J.; Flippen-Anderson, J.; Laib, F. and Cook, J. M., *J. Am. Chem. Soc.,* **2005**, *127*, 933. (s) Solà, J.; Riera, A.; Verdaguer, X. and Maestro, M. A., *J. Am. Chem. Soc.,* **2005**, *127*, 13629. (t) Gibson, S. E. and Stevenazzi, A., *Angew. Chem. Int. Ed. Engl.,* **2003**, *42*, 1800. (u) Cao, H.; Flippen-Anderson, J. and Cook, J. M., *J. Am. Chem. Soc.,* **2003**, *125*, 3230. (v) Kubota, H.; Lim, J. W.; Depew, K. M. and Schreiber, S. L., *Chem. & Biology,* **2002**, *9*, 265. (w) Iqbal, M.; Vyse, N.; Dauvergne, J. and Evans, P., *Tetrahedron Lett.,* **2002**, *43*, 7859. (x) Lovely, C. J. and Seshadri, H., *Synth. Commun.,* **2001**, *31*, 2479. (y) Yamanaka, M. and Nakamura, E., *J. Am. Chem. Soc.,* **2001**, *123*, 1703. (z) de Bruin, T. J. M.; Milet, A.; Robert, F.; Gimbert, Y. and Greene, A. E., *J. Am. Chem. Soc.,* **2001**, *123*, 7184. (aa) Mihovilovic, M. D.; Adelwöhrer, C. and Stanetty, P., *ARKIVOC,* **2001**, 28. (bb) Brummond, K. M. and Kent, J. L., *Tetrahedron,* **2000**, *56*, 3263. (cc) Brummond, K. M.; Lu, J. L. and Petersen, J., *J. Am. Chem. Soc.,* **2000**, *122*, 4915. (dd) Verdaguer, X.; Moyano, A.; Pericàs, M. A.; Riera, A.; Maestro, M. A. and Mahía, J., *J. Am. Chem. Soc.,* **2000**, *122*, 10242. (ee) Spitzer, J. L.; Kurth, M. J. and Schore, N. E., *Tetrahedron,* **1997**, *53*, 6791.

3. (a) Pico, A. and Moyano, A., *ARKIVOC,* **2007**, (*iv*), 132. (b) Crawford, J. J.; Kerr, W. J.; McLaughlin, M.; Morrison, A. J.; Pauson, P. L. and Thurston, G. J., *Tetrahedron*, **2006**, *62*, 11360. (c) Kwong, F. Y.; Lee, H. W.; Qiu, L. Q.; Lam, W. H.; Li, Y.-M.; Kwong, H. L. and Chan, A. S. C., *Adv. Synth. Catal.,* **2005**, *347*, 1750. (d) Winkler, J. D.; Lee, E. C. Y. and Nevels, L. I., *Org. Lett.,* **2005**, *7*, 1489. (e) Dragutan, I.; Dragutan, V.; Delaude, L. and Demonceau, A., *ARKIVOC,* **2005**, 206. (f) Moriarty, R. M.; Rani, N.; Enache, L. A.; Rao, M. S.; Batra, H.; Guo, L.; Penmasta, R. A.; Staszewski, J. P.; Tuladhar, S. M.; Prakash, O.; Crich, D.; Hirtopeanu, A. and Gilardi, R., *J. Org. Chem.,* **2004**, *69*, 1890. (g) Smit, W. A.; Tumanov, V. V. and Zatonsky, G. V., *Russ. Chem. Bull.,* **2003**, *52*, 2461. (h) Komoriya, S., *Farumashia*, **2002**, *38*, 244. (i) Lovely, C. J.; Seshadri, H.; Wayland, B. R. and Cordes, A. W., *Org. Lett.,* **2001**, *3*, 2607. (j) Marchueta, I.; Olivella, S.; Solà, L.; Moyano, A.; Pericàs, M. A. and Riera, A., *Org. Lett.,* **2001**, *3*, 3197. (k) Mihovilovic, M. D.; Adelwoehrer, C. and Stanetty, P., *ARKIVOC,* **2001**, *2*(*ii*), 28. (l) Carretero, J. C. and Adrio, J., *Synthesis*, **2001**, 1888. (m) Hicks, F. A. and Buchwald, S. L., *J. Am. Chem. Soc.,* **1999**, *121*, 7026. (n) Bolton, G. L.; Hodges, J. C. and Rubin, J. R., *Tetrahedron,* **1997**, *53*, 6611. (o) Quattropani, A.; Anderson, G.; Bernardinelli, G. and Kündig, E. P., *J. Am. Chem. Soc.,* **1997**, *119*, 4773. (p) Bolton, G. L., *Tetrahedron Lett.,* **1996**, *37*, 3433. (q) Hicks, F. A. and Buchwald, S. L., *J. Am. Chem. Soc.,* **1996**, *118*, 11688. (r) Alcaide, B.; Polanco, C. and Sierra, M. A., *Tetrahedron Lett*., **1996**, *37*, 6901. (s) Bernardes, V.; Kann, N.; Riera, A.; Moyano, A.; Pericas, M. A. and Greene, A. E., *J. Org. Chem.,* **1995**, *60*, 6670. (t) Halterman, R. L.; Ramsey, T. M.; Pailes, N. A. and Khan, M. A., *J. Organomet. Chem.,* **1995**, *497*, 43. (u) Becker, D. P. and Flynn, D. L., *Tetrahedron*, **1993**, *49*, 5047. (v) Jeong, N.; Yoo, S. E.; Lee, S. J.; Lee, S. H. and Chung, Y. K., *Tetrahedron Lett*., **1991**, *32*, 2137. (w) Poch, M.; Valenti, E.; Moyano, A.; Pericas, M. A.; Castro, J.; DeNicola, A. and Greene, A. E., *Tetrahedron Lett*., **1990**, *31*, 7505. (x) Shambayati, S.; Crowe, W. E. and Schreiber, S. L., *Tetrahedron Lett*., **1990**, *31*, 5289. (y) Mulzer, J.; Graske, K. D. and

Kirste, B., *Liebigs Ann. Chem.,* **1988**, 891. (z) Schore, N. E. and Knudsen, M. J., *J. Org. Chem.,* **1987**, *52*, 569.

4. (a) Günter, M. and Gais, H.-J., *J. Org. Chem.,* **2003**, *68*, 8037. (b) Shen, L. C. and Hsung, R. P., *Tetrahedron Lett*., **2003**, *44*, 9353. (c) Areces, P.; Durán, M. A. A.; Plumet, J.; Hursthouse, M. B. and Light, M. E., *J. Org. Chem.,* **2002**, *67*, 3506. (d) Wilson, M. S. and Dake, G. R., *Org. Lett.,* **2001**, *3*, 2041. (e) Brummond, K. M. and Wan, H. H., *Tetrahedron Lett*., **1998**, *39*, 931. (f) Ahmar, M.; Locatelli, C.; Colombier, D. and Cazes, B., *Tetrahedron Lett*., **1997**, *38*, 5281. (g) Kent, J. L.; Wan, H. H. and Brummond, K. M., *Tetrahedron Lett*., **1995**, *36*, 2407. (h) Krafft, M. E.; Scott, I. L.; Romero, R. H.; Feibelmann, S. and van Pelt, C. E., *J. Am. Chem. Soc.,* **1993**, *115*, 7199. (i) Gybin, A. S.; Smit, V. A.; Caple, R.; Veretenov, A. L.; Shashkov, A. S.; Vorontsova, L. G.; Kurella, M. G.; Chertkov, V. S.; Carapetyan, A. A.; Kosnikov, A. Y.; Alexanyan, M. S.; Lindeman, S. V.; Panov, V. N.; Maleev, A. V.; Struchkov, Y. T. and Sharpe, S. M., *J. Am. Chem. Soc.,* **1992**, *114*, 5555. (j) Schore, N. E., *Org. React.,* **1991**, *40*, 1. (k) Schore, N. E. and Rowley, E. G., *J. Am. Chem. Soc.,* **1988**, *110*, 5224. (l) MacWhorter, S. E.; Sampath, V.; Olmstead, M. M. and Schore, N. E., *J. Org. Chem.,* **1988**, *53*, 203.
5. (a) Brown, J. A.; Irvine, S.; Kerr, W. J. and Pearson, C. M., *Org. Biomol. Chem.,* **2005**, *3*, 2396. (b) Evans, P. A. and Robinson, J. E., *J. Am. Chem. Soc.,* **2001**, *123*, 4609.
6. Pérez-Serrano, L.; Blanco-Urgoiti, J.; Casarrubios, L.; Domínguez, G. and Pérez-Castells, J., *J. Org. Chem.,* **2000**, *65*, 3513.
7. Ahmar, M.; Knoke, M.; de Meijere, A. and Cazes, B., *Synthesis*, **2007**, 442.
8. Verdaguer, X.; Moyano, A.; Pericas, M. A.; Riera, A.; Greene, A. E.; Piniella, J. F. and Alvarez-Larena, A., *J. Organomet. Chem.,* **1992**, *433*, 305.
9. (a) Kerr, W. J.; McLaughlin, M.; Morrison, A. J. and Pauson, P. L., *Org. Lett.,* **2001**, *3*, 2945. (b) Kerr, W. J.; McLaghlin, M.; Pauson, P. L. and Robertson, S. M., *Chem. Commun.,* **1999**, 2171.
10. Kerr, W. J.; Lindsay, D. M.; McLaughlin, M. and Pauson, P. L., *Chem. Commun.,* **2000**, 1467.
11. Kerr, W. J.; McLaughlin, M. and Pauson, P. L., *J. Organomet. Chem*., **2001**, *630*, 118.
12. (a) Adrio, J. and Carreter, J. C., *J. Am. Chem. Soc.,* **1999**, *121*, 7411. (b) Fonquerna, S.; Moyano, A. and Pericàs, M. A. and Riera, A., *J. Am. Chem. Soc.,* **1997**, *119*, 10225. (c) Krafft, M. E.; Wilson, A. M.; Dasse, O. A.; Shao, B.; Cheung, Y. Y.; Fu, Z.; Bonaga, L. V. R. and Mollman, M. K., *J. Am. Chem. Soc.,* **1996**, *118*, 6080.
13. Robert, F.; Milet, A.; Gimbert, Y.; Konya, D. and Greene, A. E., *J. Am. Chem. Soc.,* **2001**, *123*, 5396.
14. (a) Inagaki, F. and Mukai, C., *Org. Lett.,* **2006**, *8*, 1217. (b) Seigal, B. A.; An, M. H. and Snapper, M. L., *Angew. Chem. Int. Ed.,* **2005**, *44*, 4929. (c) Brummond, K. M.; Curran, D. P.; Mitasev, B. and Fischer, S., *J. Org. Chem.,* **2005**, *70*, 1745. (d) Yeh, M.-C. P.; Tsao, W.-C.; Ho, J.-S.; Tai, C.-C.; Chiou, D.-Y. and Tu, L.-H., *Organometallics,* **2004**, *23*, 792. (e) Mukai, C.; Nomura, I. and Kitagaki, S., *J. Org. Chem.,* **2003**, *68*, 1376. (f) Brummond, K. M.; Kerekes, A. D. and Wang, H. H., *J. Org. Chem.,* **2002**, *67*, 5156. (g) Mukai, C.; Nomura, I.; Yamanishi, K. and Hanaoka, M., *Org. Lett.,* **2002**,4, 1755. (h) Kim, S.-W.; Son, S. U.; Lee, S. I.; Hyeon, T. W. and Chung, Y. K., *J. Am. Chem. Soc.,* **2000**, *122*, 1550. (i) Shiu, Y.-T.; Madhushaw, R. J.; Li, W.-T.; Lin, Y.-C.; Lee, G.-H.; Peng, S.-M.; Liao, F.-L.; Wang, S.-L. and Liu, R.-S., *J. Am. Chem. Soc.,* **1999**, *121*, 4066.(j) Jeong, N.; Lee, S. H. and Sung, B. K., *Organometallics,* **1998**, *17*, 3642. (k) Kondo, T.; Suzuki, N.; Okada, T. and Mitsudo, T.-A., *J. Am. Chem. Soc.,* **1997**, *119*, 6187.
15. (a) de Bruin, T. J. M.; Milet, A.; Greene, A. E. and Gimbert, Y., *J. Org. Chem.,* **2004**, *69*, 1075. (b) Rivero, M. R.; de la Rosa, J. C. and Carretero, J. C., *J. Am. Chem. Soc.,* **2003**, *125*, 14992. (c) Rios, R.; Pericàs, M. A.; Moyano, A.; Maestro, M. A. and Mahía, J., *Org. Lett.,* **2002**, 4, 1205.
16. (a) Castro, J.; Moyano, A.; Pericàs, M. A.; Riera, A.; Alvarez-Larena, A. and Piniella, J. F., *J. Am. Chem. Soc.,* **2000**, *122*, 7944. (b) Pagenkopf, B. L. and Livinghouse, T., *J. Am. Chem. Soc.,* **1996**, *118*, 2285.

17. Morimoto, T.; Fuji, K.; Tsutsumi, K. and Kakiuchi, K., *J. Am. Chem. Soc.,* **2002**, *124*, 3806.
18. Jeong, N.; Hwang, S. H.; Lee, Y. and Chung, Y. K., *J. Am. Chem. Soc.,* **1994**, *116*, 3159.
19. Tang, Y. F.; Deng, L. J.; Zhang, Y. D.; Dong, G. B.; Chen, J. H. and Yang, Z., *Org. Lett.,* **2005**, *7*, 593.
20. Lee, B. Y.; Chung, Y. K.; Jeong, N.; Lee, Y. and Hwang, S. H., *J. Am. Chem. Soc.,* **1994**, *116*, 8793.
21. Lee, N. Y. and Chung, Y. K., *Tetrahedron Lett.,* **1996**, *37*, 3145.
22. Kim, J. W. and Chung, Y. K., *Synthesis,* **1998**, 142.
23. Sugihara, T. and Yamaguchi, M., *J. Am. Chem. Soc.,* **1998**, *120*, 10782.
24. Rajesh, T. and Periasamy, M. *Tetrahedron Lett.,* **1999**, *40*, 817.
25. Verdaguer, X.; Lledó, López-Mosquera, C.; Maestro, M. A.; Pericàs, M. A. and Riera, A., *J. Org. Chem.,* **2004**, *69*, 8053.
26. Gibson, S. E.; Johnstone, C.; Loch, J. A.; Steed, J. W. and Stevenazzi, A., *Organometallics,* **2003**, *22*, 5374.
27. (a) Berk, S. C.; Grossman, R. B. and Buchwald, S. L. *J. Am. Chem. Soc.,* **1994**, *116*, 8593. (b) Berk, S. C.; Grossman, R. B. and Buchwald, S. L., *J. Am. Chem. Soc.,* **1993**, *115*, 4912.
28. Morimoto, T.; Chatani, N.; Fukumoto, Y. and Murai, S., *J. Org. Chem.,* **1997**, 62, 3762.
29. Koga, Y.; Kobayashi, T. and Narasaka, K. *Chem. Lett.,* **1998**, 249.
30. Shibata, T.; Toshida, N. and Takagi, K., *Org. Lett.,* **2002**, *4*, 1619.
31. Shibata, T. and Takagi, K., *J. Am. Chem. Soc.,* **2000**, *122*, 9852.
32. Brummond, K. M.; Chen, H. F.; Fisher, K. D.; Kerekes, A. D.; Richards, B.; Sill, P. C. and Geib, S. J., *Org. Lett.,* **2002**, *4*, 1931.
33. Adrio, J.; Rivero, M. R. and Carretero, J. C., *Org. Lett.,* **2005**, *7*, 431.
34. Tang, Y. F; Deng, L. J.; Zhang, Y. D.; Dong, G. B.; Chen, J. H. and Yang, Z., *Org. Lett.,* **2005**, *7*, 1657.
35. Shibata, T.; Toshida, N. and Takagi, K., *J. Org. Chem.,* **2002**, *67*, 7446.
36. (a) Son, S. U.; Park, K. H. and Chung, Y. K., *Org. Lett.,* **2002**, *4*, 3983. (b) Son, S. U.; Lee, S. I.; Chung, Y. K.; Kim, S.-W. and Hyeon, T. H., *Org. Lett.,* **2002**, *4*, 277.
37. Pérez-Serrano, L.; Casarrubios, L.; Domínguez, G. and Pérez-Castells, J., *Org. Lett.,* **1999**, *1*, 1187.
38. Lagunas, A.; Payeras, A. M. i.; Jimeno, C. and Pericàs, M. A., *Org. Lett.,* **2005**, *7*, 3033.
39. Shambayati, S.; Crowe, W. E. and Schreiber, S. L., *Tetrahedron Lett*., **1990**, *31*, 5289.
40. Jeong, N.; Hwang, S. H.; Lee, Y. W. and Lim, J. S., *J. Am. Chem. Soc.,* **1997**, *119*, 10549.
41. (a) Pallerla, M. K. and Fox, J. M., *Org. Lett.,* **2005**, *7*, 3593. (b) Brummond, K. M. and Gao, D., *Org. Lett.,* **2003**, *5*, 3491.
42. Mukai, C.; Yoshida, T.; Sorimachi, M. and Odani, A., *Org. Lett.,* **2006**, *8*, 83.
43. (a) Gimbert, Y.; Lesage, D.; Milet, A.; Fournier, F.; Greene, A. E. and Tabet, J.-C., *Org. Lett.,* **2003**, *5*, 4073. (b) Schulte, J. H.; Gleiter, R. and Rominger, F., *Org. Lett.,* **2002**, *4*, 3301.
44. Pérez-Serrano, L.; Domínguez, G. and Pérez-Castells, J., *J. Org. Chem.,* **2004**, *69*, 5413.
45. (a) Hotha, S. and Tripathi, A., *J. Comb. Chem.,* **2005**, *7*, 968. (b) Mukai, C.; Inagaki, F.; Yoshida, T.; Yoshitani, K.; Hara, Y. and Kitagaki, S., *J. Org. Chem.,* **2005**, *70*, 7159. (c) Tang, Y. F.; Zhang, Y. D.; Dai, M. J.; Luo, T. P.; Deng, L. J.; Chen, J. H. and Yang, Z., *Org. Lett.,* **2005**, *7*, 885. (d) Rosillo, M.; Domínguez, G.; Casarrubios, L. and Pérez-Castells, J., *J. Org. Chem.,* **2005**, *70*, 10611. (e) Itami, K.;Mitsudo, K.; Fujita, K.; Ohashi, Y. and Yoshida, J.-i., *J. Am. Chem. Soc.,* **2004**, *126*, 11058. (f) Park, K. H.; Jung, I. G. and Chung, Y. K., *Org. Lett.,* **2004**, *6*, 1183. (g) Blanco-Urgoiti, J.; Añorbe, L.; Pérez-Serrano, L.; Domínguez, G. and Pérez-Castells, J., *Chem. Soc. Rev.,* **2004**, *33*, 32. (h) Urgiotti, U., *Chem. Soc. Rev.,* **2004**, *33*, 32. (i) Park, K. H.;

Song, S. U. and Chung, Y. K., *Tetrahedron Lett.,* **2003**, *44*, 425. (j) Rivero, M. R. and Carretero, J. C., *J. Org. Chem.,* **2003**, *68*, 2975. (k) Koenig, S. G.; Miller, S. M.; Leonard, K. A.; Löwe, R. S.; Chen, B. C. and Austin, D. J., *Org. Lett.,* **2003**, *5*, 2203. (l) Gibson, S. E.; Lewis, S. E.; Loch, J. A.; Steed, J. W. and Tozer, M. J., *Organometallics,* **2003**, *22*, 5382. (m) Krafft, M. E.; Boñaga, L. V. R.; Felts, A. S.; Hirosawa, C. and Kerrigan, S., *J. Org. Chem.,* **2003**, *68*, 6039. (n) Sturla, S. J. and Buchwald, S. L., *J. Org. Chem.,* **2002**, *67*, 3398. (o) Jiang, B. and Xu, M., *Org. Lett.,* **2002**, *4*, 4077. (p) Park, K. H.; Son, S. U. and Chung, Y. K., *Org. Lett.,* **2002**, *4*, 4361. (q) Jeong, N.; Sung, B. K.; Kim, J. S.; Park, S. B., Seo, S. D.; Shin, J. Y.; In, K. Y. and Choi, Y. K., *Pure & Appl. Chem.,* **2002**, *74*, 85. (r) Ishizaki, M.; Niimi, Y. and Hoshino, O., *Chem. Lett.,* **2001**, 546. (s) Pal, A. and Bhattacharjya, A., *J. Org. Chem.,* **2001**, *66*, 9071. (t) Marchueta, I.; Verdaguer, X.; Moyano, A.; Pericàs, M. A. and Riera, A., *Org. Lett.,* **2001**, *3*, 3193. (u) Sugihara, T.; Yamaguchi, M. and Nishizawa, M., *Chem. Eur. J.*, **2001**, *7*, 1589. (v) Jeong, N.; Sung, B. K. and Choi, Y. K., *J. Am. Chem. Soc.,* **2000**, *122*, 6771. (w) Mukai, C.; Sonobe, H.; Kim, J. S. and Hanaoka, M., *J. Org. Chem.,* **2000**, *65*, 6654. (x) Xiong, H.; Hsung, R. P.; Wei, L.-L.; Berry, C. R.; Mulder, J. A. and Stockwell, B., *Org. Lett.,* **2000**, *2*, 2869. (y) Fletcher, A. J. and Christie, S. D. R., *J. Chem. Soc., Perkin Trans. I,* **2000**, 1657. (z) Chung, Y. K., *Coord. Chem. Res.,* **1999**, *188*, 297. (aa) Brummond, K. M. and Lu, J. L.,*J. Am. Chem. Soc.,* **1999**, *121*, 5087. (bb) Sugihara, T.; Yamaguchi, M. and Nishizawa, M., *Rev. Heteroatom Chem.,* **1999**, *21*, 179. (cc) Balsells, J.; Moyano, A.; Riera, A. and Pericàs, M. A., *Org. Lett.,* **1999**, *1*, 1981. (dd) Derdau, V.; Laschat, S.; Dix, I. and Jones, P. G., *Organometallics,* **1999**, *18*, 3859. (ee) Gimbert, Y.; Robert, F.; Durif, A.; Averbuch, M.-T.; Kann, N. and Greene, A. E., *J. Org. Chem.,* **1999**, *64*, 3492. (ff) Arjona, O.; Csáky, A. G.; Murcia, M. C. and Plumet, J., *J. Org. Chem.,* **1999**, *64*, 7338. (gg) Marco-Contelles, J. and Ruiz-Caro, J., *J. Org. Chem.,* **1999**, *64*, 8302. (hh) Kowalczyk, B. A.; Smith, T. C. and Dauben, W. G., *J. Org. Chem.,* **1998**, *63*, 1379. (ii) Belanger, D. B.; O'Mahony, D. J. R. and Livinghouse, T., *Tetrahedron Lett.,* **1998**, *39*, 7637. (jj) Sugihara, T. and Yamaguchi, M., *Synlett,* **1998**, 1384. (kk) Geis, O. and Schmalz, H.-G., *Angew. Chem. Int. Ed. Engl.,* **1998**, *37*, 911. (ll) Ahmar, M.; Chabanis, O.; Cauthier, J. and Cazes, B., *Tetrahedron Lett.,* **1997**, 38, 5277. (mm) Marco-Contelles, J., *J. Org. Chem.,* **1996**, *61*, 7666. (nn) Schore, N. E., *Org. React.,* **1991**, 41, 1. (oo) Pauson, P. L. and Brown, S. W., *J. Chem. Soc., Perkin Trans. I,* **1990**, 1205. (pp) Magnus, P. and Principe, L. M., *Tetrahedron Lett.,* **1985**, *26*, 4851. (qq) Pauson, P. L., *Tetrahedron,* **1985**, *41*, 5855. (rr) Schore, N. E. and Croudace, M. C., *J. Org. Chem.,* **1981**, *46*, 5436.

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Payne Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Kohler et al. in 1931,[1] and its mechanism was proposed as early as 1957 by Angyal and Gilham.[2] It is a base-promoted stereospecific migration of 2,3-epoxy alcohols into isomeric epoxy alcohols with an inversion of configuration at the C-2 carbon of the original epoxide ring as of an S_N2 substitution[3] and was initially known as a β-oxanol rearrangement.[4] However, after Payne's extensive study on this reaction in 1962,[5] it is now generally referred to as the Payne rearrangement[6] or epoxide migration.[2,5,6g,7] Occasionally, this reaction is also called the Payne reaction.[8]

It should be pointed out that this rearrangement is reversible,[6g] and the equilibrium favors the more substituted epoxide isomer. It is a powerful method for the introduction of a different functionality when the migration of epoxide is followed by a ring opening from the nucleophilic attack of another nucleophile.[6g] In this reaction, solvent plays an important role. For example, the epoxy alcohol when treated with sodium hydride in THF would not yield the expected product from rearrangement, but gives the expected product when treated with NaOH in aqueous solution.[9] The delay of Payne rearrangement in THF has made THF a good medium for direct attacking of epoxide with an ylide generated *in situ*.[6d] On the other hand, it is known that the direction of such reversible rearrangement of epoxy alcohol is controlled by kinetics, not by thermodynamics,[10] and the application of a chiral epoxide migration catalyst results in the catalytic kinetic resolution of epoxy alcohols.[11] The rearrangement between 2,3-epoxy amine and aziridine alcohol under similar conditions is generally known as the *aza*-Payne rearrangement;[3,7a,8,12] and the migration between 2,3-epoxy thiol and thiirane alcohol is referred to as the *thia*-Payne rearrangement.[6g] However, different from the normal Payne rearrangement, the *aza*-Payne and *thia*-Payne rearrangements have the potential to form different products; thus the formation of aziridine and thiirane alcohols is referred to as

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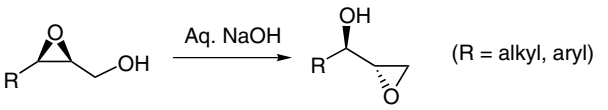
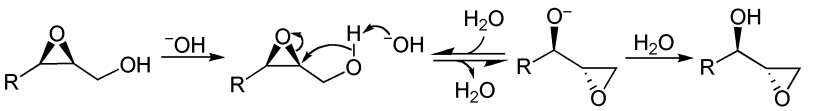
the *forward aza-* and *thia*-Payne rearrangements, respectively; whereas the rearrangement from aziridine alcohol or thiirane alcohol to the corresponding epoxy amine or thiol is known as the *reverse aza-* or *thia*-Payne rearrangement.[6g] The forward *aza-* and *thia*-Payne rearrangements are favored by complexation with Lewis acid, such as BF_3,[13] $AlMe_3$,[14] and TMSOTf.[15] It should be pointed out that the *aza*-Payne rearrangement followed by a ring opening has been used for the preparation of hydroxyethylamine dipeptide isostere (HDI) structures.[16]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is possible that a semiconcerted mechanism is involved in this rearrangement in aqueous solution, whereas in THF, a contact ion pair is probably the real reactive species, which does not attack the epoxide ring. A tentative mechanism is proposed here.



D. MODIFICATION

The *aza-* and *thia*-Payne rearrangement should be considered an extension of the normal Payne rearrangement.

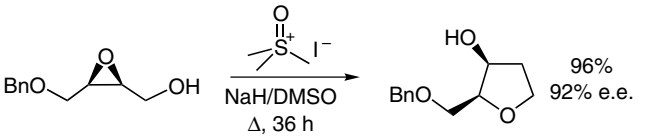
E. APPLICATIONS

This reaction has wide application in organic synthesis, especially in conjunction with the subsequent ring opening of a newly formed epoxide ring with other nucleophiles.

F. RELATED REACTIONS

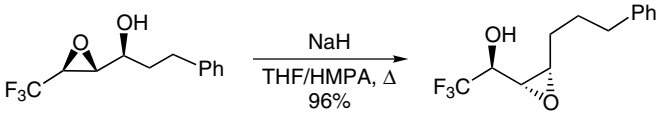
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 6d.

To a flame-dried flask was added NaH (prepared by sodium metal-dried pentane wash from 4.0 g 60% NaH in mineral oil (100 mmol, 10 eq.)) and 100 mL CaH_2-dried DMSO through a syringe. Trimethylsulfoxonium iodide (22.0 g, 100 mmol, 10.0 eq.) was then added in small portions over 20–30 min. After the addition of the trimethylsulfoxonium iodide was complete, the reaction was stirred for an additional 30 min until the bubbling of the milk white suspension ceased. The epoxy alcohol (1.94 g, 10 mmol, 1.0 eq.) dissolved in a small amount of dry DMSO was added dropwise, and the reaction was covered with aluminum foil and heated to 80–85°C for 36 h. The dark brown mixture was cooled and diluted with two times the volume of water and 1 mL saturated NH_4Cl. The mixture was extracted several times with EtOAc; the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was column chromatographed using a hexane/EtOAc gradient to give 2-benzyloxymethylenyl-3-hydroxy-tetrahydrofuran as a thick oil, in a yield of 96% with 92% e.e.



Reference 6e.

To a stirring solution of 0.048 g sodium hydride (1.20 mmol, 60% in paraffin liquid) and 0.86 mL hexamethylphosphoric triamide (HMPA, 4.94 mmol) in 5 mL THF at 0°C was added 0.246 g (*E*)-*syn*-4,5-epoxy-6,6,6-trifluoro-1-phenyl-3-hexanol (1.00 mmol). After being stirred for 3 h at room temperature, the reaction mixture was quenched with 1 mL 3 *N*HCl and extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$. Upon evaporation of the solvent, the residue was purified by silica gel column chromatography to afford 0.237 g (*Z*)-*anti*-3,4-epoxy-1,1,1-trifluoro-6-phenyl-2-hexanol, in a yield of 96%.

Other references related to the Payne rearrangement are cited in the literature.[17]

H. REFERENCES

1. Kohler, E. P.; Richtmyer, N. K. and Hester, W. F., *J. Am. Chem. Soc.,* **1931**, *53*, 205.
2. Angyal, S. J. and Gilham, P. T., *J. Chem. Soc.,* **1957**, 3691.
3. Ibuka, T.; Nakai, K.; Habashita, H.; Hotta, Y.; Otaka, A.; Tamamura, H.; Fujii, N.; Mimura, N.; Miwa, Y.; Taga, T.; Chounan, Y. and Yamamoto, Y., *J. Org. Chem.,* **1995**, *60*, 2044.
4. Kohler, E. P. and Bickel, C. L., *J. Am. Chem. Soc.,* **1935**, *57*, 1099.
5. Payne, G. B., *J. Org. Chem.,* **1962**, *27*, 3819.

6. (a) Oliw, E. H.; Garscha, U.; Nilsson, T. and Cristea, M., *Anal. Biochem.,* **2006**, *354*, 111. (b) Clay, M. D. and Fallis, A. G., *Angew. Chem. Int. Ed*., **2005**, *44*, 4039. (c) D'Hooghe, M.; Rottier, M.; Jolie, R.; de Kimpe, N., *Synlett,* **2005**, 931. (d) Schomaker, J. M.; Pulgam, V. R. and Borhan, B., *J. Am. Chem. Soc.,* **2004**, *126*, 13600. (e) Yamazaki, T.; Ichige, T. and Kitazume, T., *Org. Lett.,* **2004**, *6*, 4073. (f) Rodilla, J. M. L.; Díez, D.; Urones, J. G. and Rocha, P. M., *Molecules,* **2004**, *9*, 300. (g) Hanson, R. M., *Org. React.,* **2002**, *60*, 1. (h) Birman, V. B. and Danishefsky, S. J., *J. Am. Chem. Soc.,* **2002**, *124*, 2080. (i) Jung, M. E. and van den Heuvel, A., *Tetrahedron Lett*., **2002**, *43*, 8169. (j) Mao, X. S.; Volkers, A. A.; Klunder, A. J. H. and Zwanenburg, B., *Chinese Chem. Lett.,* **2001**, *12*, 585. (k) Spencer, T. A.; Li, D. S.; Russel, J. S.; Tomkinson, N. C. O. and Willson, T. M., *J. Org. Chem.,* **2000**, *65*, 1919. (l) Suzuki, Y.; Nishimaki, R.; Ishikawa, M.; Murata, T.; Takao, K.-I and Tadano, K.-i., *J. Org. Chem.,* **2000**, *65*, 8595. (m) Stick, R. V.; Tilbrook, D. M. G. and Williams, S. J., *Aust. J. Chem.*, **1999**, *52*, 885. (n) Dua, S.; Bowie, J. H.; Taylor, M. S. and Buntine, M. A., *Int. J. Mass Spec. Ion. Proc*., **1997**, *165/166*, 139. (o) Dols, P. P. M. A.; Arnouts, E. G.; Rohaan, J.; Klunder, A. J. H. and Zwanenburg, B., *Tetrahedron*, **1994**, *50*, 3473. (p) Konosu, T.; Miyaoka, T.; Tajima, Y. and Oida, S., *Chem. Pharm. Bull.,* **1992**, *40*, 562. (q) Ganem, B., *Chemtracts: Org. Chem*., **1990**, *3*, 381. (r) Page, P. C. Bulman; R., Christopher M. and Sutherland, I. O., *J. Chem. Soc., Perkin Trans. I,* **1990**, 1375. (s) Swindell, C. S. and Patel, B. P., *J. Org. Chem.,* **1990**, *55*, 3. (t) Myers, A. G. and Widdowson, K. L., *Tetrahedron Lett.,* **1988**, *29*, 6389. (u) Sharpless, K. B.; Behrens, C. H.; Katsuki, T.; Lee, A. W. M.; Martin, V. S.; Takatani, M.; Viti, S. M.; Walker, F. J. and Woodard, S. S., *Pure & Appl. Chem.,* **1983**, 55.
7. (a) Bouyacoub, A. and Volatron, F., *Eur. J. Org. Chem.,* **2002**, 4143. (b) Bock, K.; Castilla, I. M.; Lundt, I. and Pedersen, C., *Acta Chem. Scand.,* **1989**, *43*, 264.
8. Bilke, J. L.; Dzuganova, M.; Fröhlick, R. and Würthwein, E.-U., *Org. Lett.,* **2005**, *7*, 3267.
9. Bajwa, J. S. and Sunay, U. B., *J. Labeled Compd. Radiopharm.,* **1997**, *39*, 787.
10. Dua, S.; Taylor, M. S.; Buntine, M. A. and Bowie, J. H., *J. Chem. Soc., Perkin Trans. II,* **1997**, 1991.
11. Wu, M. H.; Hansen, K. B. and Jacobsen, E. N., *Angew. Chem. Int. Ed. Engl.,* **1999**, *38*, 2012.
12. (a) Feng, X. C.; Qiu, G. F.; Liang, S. C.; Teng, H. B.; Wu, L. M. and Hu, X. M., *Tetrahedron: Asymmetry*, **2006**, *17*, 1394. (b) Tamamura, H.; Hori, T.; Otaka, A. and Fujii, N., *J. Chem. Soc., Perkin Trans. I,* **2002**, 998. (c) Tamamura, H.; Hori, T.; Otaka, A. and Fujii, N., *J. Chem. Soc., Perkin Trans. I,* **2002**, 577. (d) Hudlicky, T.; Rinner, U.; Gonzalez, D.; Akgun, H.; Schilling, S.; Siengalewicz, P.; Martinot, T. A. and Pettit, G. R., *J. Org. Chem.,* **2002**, *67*, 8726. (e) Rinner, U.; Siengalewicz, P. and Hudlicky, T., *Org. Lett.,* **2002**, *4*, 115. (f) Ibuka, T., *Chem. Soc. Rev.,* **1998**, *27*, 145. (g) Rayner, C. M., *Synlett,* **1997**, 11. (h) Liu, Q. Y.; Marchington, A. P. and Rayner, C. M., *Tetrahedron,* **1997**, *53*, 15729. (i) Ibuka, T.; Nakai, K.; Akaji, M.; Tamamura, H.; Fujii, N. and Yamamoto, Y., *Tetrahedron*, **1996**, *52*, 11739. (j) Nakai, K.; Ibuka, T.; Otaka, A.; Tamamura, H.; Fujii, N. and Yamamoto, Y., *Tetrahedron Lett*., **1995**, *36*, 6247.
13. Latif, F.; Malik, A. and Völker, W., *Liebigs Ann. Chem.* **1987**, 717.
14. Najime, R.; Pilard, S. and Vaultier, M., *Tetrahedron Lett.,* **1992**, *33*, 5351.
15. Liu, Q. Y.; Marchington, A. P.; Boden, N. and Rayner, C. M., *J. Chem. Soc., Perkin Trans. I,* **1997**, 511.
16. (a) Tamamura, H.; Kato, T.; Otaka, A. and Fujii, N., *Org. Biomol. Chem.,* **2003**, *1*, 2468. (b) Lundt, I and Madsen, R., *Top. Curr. Chem.,* **2001**, *215*, 177.
17. (a) Torssell, S. and Somfai, P., *Org. Biomol. Chem.,* **2004**, *2*, 1643. (b) Zwanenburg, B. and ten Holte, P., *Top. Curr. Chem.,* **2001**, *216*, 93. (c) Inoue, S.; Asami, M.; Honda, K.; Shrestha, K. S.; Takahashi, M. and Yoshino, T., *Synlett,* **1998**, 679. (d) Von dem Bussche-Hünnefeld, C. and Seebach, D., *Ber.,* **1992**, *125*, 1273. (e) Behrens, C. H.; Ko, S. Y.; Sharpless, K. B. and Walker, F. J., *J. Org. Chem.,* **1985**, *50*, 5687. (f) Behrens, C. H. and Sharpless, K. B., *Aldrichimica Acta,* **1983**, *16*, 67. (g) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D. and Walker, F. J., *J. Org. Chem.,* **1982**, *47*, 1373.

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Pearlman's Catalyst

A. GENERAL DESCRIPTION OF THE REACTION

Palladium hydroxide on carbon was first reported by Pearlman in 1967[1] and is now referred to as the Pearlman's catalyst in general.[2] It can be purchased from Aldrich in 20 wt %, which may contain water up to 50%.[3] It is a very active catalyst for the hydrogenation of carbon-carbon double bonds,[4] *hetero*-multiple bonds such as azide,[2g] and debenzylation.[2o] In particular, this reagent is good for hydrogenolysis of benzyl-nitrogen bonds under conditions in which other palladium-on-carbon catalysts fail[3]—for example, the removal of carbamate[2k] and benzylcarbamate functional groups.[2m] In addition, the Pearlman's catalyst has been used for the oxidation of Si-H bonds[2c] and the removal of the mesylate group on a phenyl ring.[2h] Most importantly, the Pearlman's catalyst is effective for the direct arylation of aryl iodides and bromides, with a high arylation-to-hydrodehalogenation ratio (> 30:1), both intermolecularly and intramolecularly;[2a] in addition, this arylation can tolerate an electron-withdrawing group on the aromatic ring and is also effective for high sterically hindered substrates.[2a]

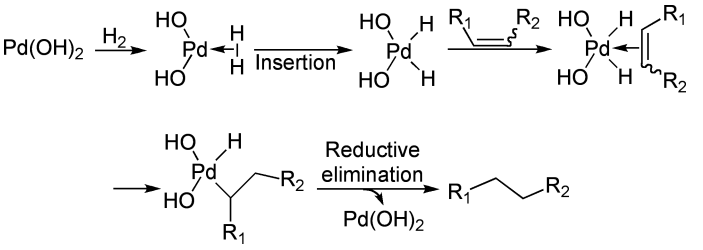
B. GENERAL REACTION SCHEME

$$Pd(OH)_2/C$$

C. PROPOSED MECHANISMS

Displayed below is the mechanism for the catalytic hydrogenation of a carbon-carbon double bond.

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang



D. MODIFICATION

This catalyst has been extended to the arylation of aryl iodides and bromides.[2a]

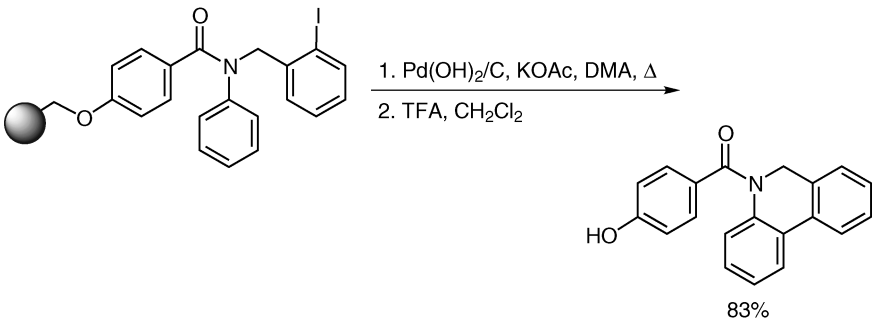
E. APPLICATIONS

This catalyst has wide application in hydrogenation and debenzylation as well as in arylation.

F. RELATED REACTIONS

N/A

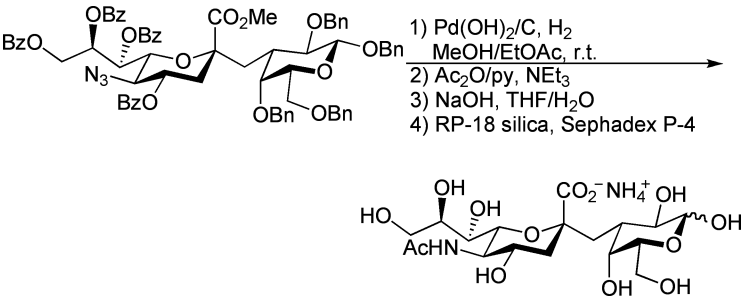
G. CITED EXPERIMENTAL EXAMPLES



Reference 2a.

To a 2- mL screw-cap vial equipped with a magnetic stir bar, were added 2 eq. potassium acetate, 0.1 eq. $Pd(OH)_2/C$, and 1 eq. *N*-phenyl-*N*-(*o*-iodo)benzyl 4-hydroxy-benzoamide loaded on Wang resin and 0.2 mL DMA under nitrogen atmosphere. The reaction mixture was then heated overnight at 145°C under stirring. After the reaction was judged complete by TLC analysis, the heat source was removed, and the reaction mixture was allowed to cool. The crude mixture was then treated with trifluoroacetic acid in THF to cleave the product off the Wang resin. The solution was evaporated, and the residue was

purified via silica gel column chromatography using EtOAc/hexanes as the eluent to afford 83% *N*-(4-hydroxybenzoyl)-(6H)-phenanthridine, m.p., 142–144°C.



Reference 2g.

A mixture of 10 mg benzyl 2,4,6-tri-*O*-benzyl-3-deoxy-3-*C*-[{methyl-(2,6-anhydro-5-azido-4,7,8,9-*tetra*-*O*-benzoyl-3,5-dideoxy-D-*erythro*-D-*manno*-non-2-yl)onate}-methyl]-*β*-D-*galacto*-hexopyranoside (32 μmol) and 18 mg $Pd(OH)_2$/C in 6 mL mixed solvent of MeOH and EtOAc (4:1) was kept under an atmosphere of hydrogen for 24 h. Then, the mixture was filtered through Celite and concentrated; the residue was taken up in a 1:1 mixture of pyridine and Ac_2O. After being stirred for 24 h at room temperature, the mixture was concentrated in vacuo and co-evaporated several times with toluene. Purification of the residue by flash chromatography (toluene/acetone, 6:1) afforded 3.8 mg amino sugar (3.65 μmol), in a yield of 45%. This amino sugar was dissolved in 10 mL THF-H_2O mixture (1:1), and 2 mL 0.1 M NaOH was added. After being stirred for 14 h at room temperature, the reaction mixture was lyophilized and passed through a RP-18 silica gel column (H_2O/EtOH, 9:1) and further purified by gel filtration on a Sephadex P-4 column eluting with a 0.3% NH_4HCO_3 buffer solution (flow rate: 0.7 mL/min, $t_R = 28$ min). After removal of the buffer solution, the residue was lyophilized from water to give 0.9 mg 3-deoxy-3-*C*-[{ammonium-(5-acetamido-2,6-anhydro-3,5-dideoxy-D-*erythro*-L-*manno*-non-2-yl)onate}-methyl]-D-*galacto*-hexopyranose as a white amorphous solid.

Other references related to the Pearlman's catalyst are cited in the literature.[5]

H. REFERENCES

1. Pearlman, W. M., *Tetrahedron Lett.,* **1967**, 1663.
2. (a) Parisien, M.; Valette, D. and Fagnou, K., *J. Org. Chem.,* **2005**, *70*, 7578. (b) Beckmann, J.; Duthie, A.; Reeske, G. and Schürmann, M., *Organometallics,* **2005**, *24*, 3629. (c) Beckmann, J.; Dakternieks, D.; Duthie, A. and Foitzik, R. C., *Silicon Chem.,* **2003**, *2*, 27. (d) Mori, Y. and Seki, M., *J. Org. Chem.,* **2003**, *68*, 1571. (e) Ambrósio, J. C. L.; Santos, R. H. A. and Correia, C. R. D., *J. Braz. Chem. Soc.,* **2003**, *14*, 27. (f) Eguchi, M. and Kahn, M., *Mini Rev. Med. Chem.,* **2002**, *2*, 447. (g) Notz, W.; Hartel, C.; Waldscheck, B. and Schmidt, R. R., *J. Org. Chem.,* **2001**, *66*, 4250. (h) Kozikowski, A. P.; Tückmantel, W. and George, C., *J. Org. Chem.,* **2000**, *65*, 5371. (i) Lee, K.-Y.; Kim, Y.-H.; Oh, C.-Y. and Ham, W.-H., *Org. Lett.,* **2000**, *2*, 4041. (j) Capecchi, T.; de Koning, C. B. and Michael, J. P., *J. Chem. Soc., Perkin Trans. I,* **2000**, 2681. (k) Geall, A. J. and Blagbrough, I. S., *Tetrahedron Lett.,* **1998**, *39*, 443. (l) Capecchi, T.; de Koning, C.

B. and Michael, J. P., *Tetrahedron Lett*., **1998**, *39*, 5429. (m) Blagbrough, I. S. and Geall, A. J., *Tetrahedron Lett.,* **1998**, *39*, 439. (n) Poerwono, H.; Higashiyama, K.; Yamauchi, T.; Kubo, H.; Ohmiya, S. and Takahashi, H., *Tetrahedron,* **1998**, *54*, 13955. (o) Andrés, J. M.; Barrio, R.; Martínez, M. A.; Pedrosa, R. and Pérez-Encabo, A., *J. Org. Chem.,* **1996**, *61*, 4210. (p) Bernotas, R. C. and Cube, R. V., *Synth. Commun.,* **1990**, *20*, 1209. (q) Bittman, R.; Witzke, N. M.; Lee, T.-C.; Blank, M. L. and Snyder, F., *J. Lipid Res.,* **1987**, *28*, 733.

3. Aldrich catalog Milwaukee, WI **2006–2007**.
4. Angle, S. R. and Henry, R. M., *J. Org. Chem.,* **1997**, *62*, 8549.
5. (a) Shi, C.; Huang, Z.; Kilic, S.; Xu, J.; Enick, R. M.; Beckman, E. J.; Carr, A. J.; Melendez, R. E. and Hamilton, A. D., *Science,* **1999**, *286*, 1540. (b) Lautens, M.; Kumanovic, S. and Meyer, C., *Angew. Chem. Int. Ed. Engl.,* **1996**, *35*, 1329. (c) Anslow, A. S.; Cox, G. G. and Harwood, L. M., *Chem. Heterocycl. Compd.,* **1995**, *31*, 1222. (d) Andreotti, A. H. and Kahne, D., *J. Am. Chem. Soc.,* **1993**, *115*, 3352.

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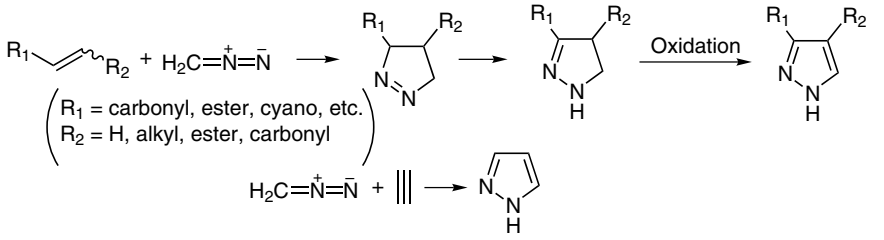
Pechmann Pyrazole Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first developed by Pechmann in 1895.[1] It is the preparation of pyrazole derivatives involving a *1,3-Dipolar Cycloaddition* between a diazomethane (or other diazonium salt) and a molecule with carbon-carbon double bonds to pyrazoline and subsequent oxidation. It has been found that a carbonyl, ester, or cyano group that conjugates to the olefinic double bond, facilitates the formation of pyrazoline; whereas a phenyl group decreases the reactivity,[2] as shown in the cycloadditions of diazomethane with *p*-quinones,[3] 1,4-naphthoquinonedibenzenesulfonimide,[4] methyl crotonate,[5] and citraconic acid.[6] Upon the mixing of diazomethane with α,β-unsaturated esters or acid, a Δ^1-pyrazoline in which the nitrogen atom is always linked to the α-carbon of the carbonyl group is formed, which rearranges in the presence of hydrochloric acid to give Δ^2-pyrazoline containing a carbon-nitrogen double bond in conjugation with the carbonyl group.[7] Upon oxidation, (e.g., with bromine,) pyrazole derivatives are yielded,[5,6] although the dehydrogenation some times occurs without an oxidant present.[8] In addition, a direct preparation of pyrazole from *1,3-Dipolar Cycloaddition* between diazomethane and acetylene was also developed by Pechmann.[9]

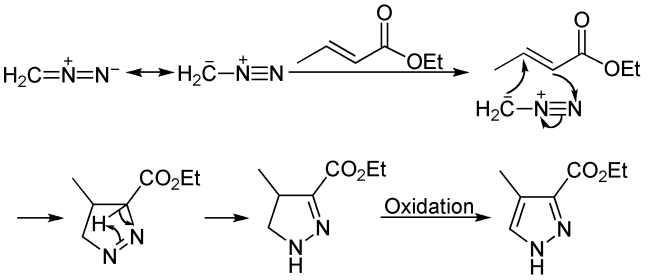
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Displayed below is the mechanism for the reaction between diazomethane and ethyl 2-butenate.



D. MODIFICATION

N/A

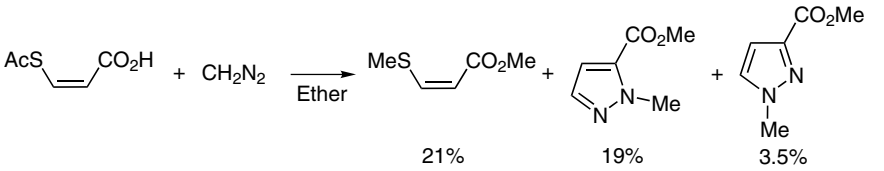
E. APPLICATIONS

This reaction has a general application in the preparation of pyrazole derivatives as well as cyclopropane derivatives upon decomposition of pyrazolines.

F. RELATED REACTIONS

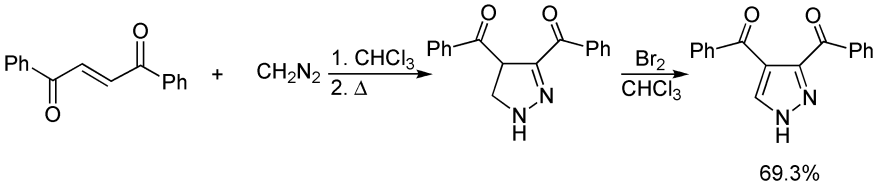
This reaction is related to 1,3-*Dipolar Cycloaddition*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 10.

To an undistilled diazomethane in ether, decanted from KOH pellets was added 1.0 g methyl *cis*-3-thioacetyl-acrylate (6.3 eq.). The temperature was maintained at −5 to 0°C for ∼8 h and then allowed to warm to room temperature. After standing for 3.5 days, the ether was removed under reduced pressure. The residue was chromatographed on silica gel with chloroform to afford 208.4 mg methyl *cis*-3-methylthio-acrylate (21%, b.p., 43–45°C at 0.5 mmHg), 185.6 mg 1-methyl-5-carbomethoxypyrazole (19%, b.p., 49–51°C at 0.5 mmHg), and 34 mg 1-methyl-3-carbomethoxypyrazole (3.5%, b.p. 126–127°C, 1.4 mmHg).



Reference 7.

The solution of diazomethane (2.7 g, 0.065 mol, prepared from 10.3 g nitrosomethylurea in 100 mL ether) was cooled to −10°C and poured into a cold (−10°C) solution of 15.7 g *trans*-dibenzoylethylene (0.065 mol) in 100 mL $CHCl_3$. The reaction was so fast that the product precipitated within 5 min. The mixture was allowed to stand at −10°C for 30 min, and then the solid was removed and dried in a vacuum desiccator to afford 18.0 g Δ^1-3,4-dibenzoylpyrazoline, in a yield of 99.6%, m.p. 108°C. This product was heated for 20 min in an oil bath at 115–120°C and then crystallized twice from 75% aqueous EtOH to afford Δ^2-3,4-dibenzoylpyrazoline, m.p., 129–129.5°C. To 50 mL $CHCl_3$ solution containing 8.34 g Δ^2-3,4-dibenzoylpyrazoline (0.03 mol) at 0°C was added a solution of 4.8 g bromine (0.03 mol) in 15 mL $CHCl_3$ at such a rate that the temperature did not exceed 12°C. An orange precipitate formed during the reaction. After the addition was complete, the solvent was evaporated at room temperature in a current of dry air. Much hydrogen bromide evolved, and the color of the solid changed to yellow. The residue was washed with water, then dissolved in 60 mL EtOH, filtered, and set aside for crystallization; 5.77 g 3,4-dibenzoylpyrazole was obtained after two recrystallizations from MeOH, in a yield of 69.3%, m.p. 169°C.

Other references related to the Pechmann pyrazole synthesis are cited in the literature.[11]

H. REFERENCES

1. Von Pechmann, H., *Ber.,* **1895**, *28*, 855.
2. (a) Smith, L. I., *Chem. Rev.,* **1938**, 23, 193. (b) Oliveri-Mandala, E., *Gazz. Chim. Ital.,* **1911**, *40*, 117.
3. (a) Bergmann, E. and Bergmann, F., *J. Org. Chem.,* **1938**, *3*, 125. (b) Fieser, L. F. and Hartwell, J. L., *J. Am. Chem. Soc.,* **1935**, *57*, 1479. (c) Fieser, L. F. and Peters, M. A., *J. Am. Chem. Soc.,* **1931**, *53*, 4080. (d) von Pechmann, H. and Seel, E., *Ber.,* **1899**, *82*, 2292.
4. Adams, R. and Moje, W., *J. Am. Chem. Soc.,* **1952**, *74*, 5560.
5. Jones, R. G., *J. Am. Chem. Soc.,* **1949**, *71*, 3994.
6. Dains, F. B. and Harger, R. N., *J. Am. Chem. Soc.,* **1918**, *40*, 562.
7. Smith, L. I. and Howard, K. L., *J. Am. Chem. Soc.,* **1943**, *65*, 159.
8. (a) von Auwers, *Ber.,* **1933**, *66*, 1198. (b) von Auwers, *Ann.,* **1929**, *470*, 284. (c) von Pechmann, H., *Ber.,* **1900**, *33*, 3590. (d) von Pechmann, H., *Ber.,* **1900**, *33*, 3594. (e) von Pechmann, H., *Ber.,* **1900**, *33*, 3597.
9. von Pechmann, H., *Ber.,* **1898**, *31*, 2950.
10. Witiak, D. T. and Lu, M. C., *J. Org. Chem.,* **1968**, *33*, 4451.
11. (a) Kottenhahn, A. P., *J. Org. Chem.,* **1963**, *28*, 3433. (b) Rondestvedt, C. S. and Chang, P. K., *J. Am. Chem. Soc.,* **1955**, *77*, 6532. (c) Noyce, D. S.; Ryder, E. and Walker, B. H., *J. Org. Chem.,* **1955**, *20*, 1681. (d) Mustafa, A. and Kamel, M., *J. Am. Chem. Soc.,* **1953**, *75*, 2939. (e) Adams, R. and Blomstrom, D. C., *J. Am. Chem. Soc.,* **1953**, *75*, 3405. (f) Kuhn, R. and Henkel, K., *Ann.,* **1941**, *549*, 279. (g) Huckel, W.; Datow, J. and Simmersbach, E., *Z. Physik. Chem.,* **1940**, *186A*, 129. (h) Smith, L. I. and Pings, W. B., *J. Org. Chem.,* **1937**, *2*, 95. (i) von Pechmann, H., *Ber.,* **1896**, *29*, 2161. (j) von Pechmann, H. and Mank, P., *Ber.,* **1895**, *28*, 2374.

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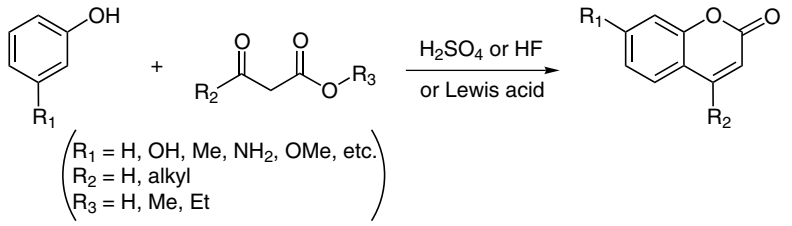
Pechmann Reaction
(Pechmann Condensation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Pechmann and Duisberg in 1883.[1] It is an acid-promoted synthesis of coumarin derivatives from the condensation of phenols and β-ketoesters or β-keto carboxylic acids and is generally known as the Pechmann reaction[2,3] or Pechmann condensation.[2l,4,5] Occasionally, this reaction is also referred to as the Pechmann coumarin synthesis,[2h,6] Pechmann cyclization,[4b,4c,7] Pechmann coumarin condensation,[2m,8] Pechmann cyclocondensation,[9] or the Pechmann synthesis.[2n,10] This reaction, under acidic conditions, involves an esterification or transesterification, followed by a cyclization and dehydration. It has been found that the outcome of this reaction depends on the nature of phenols, β-keto esters, and condensation reagents.[2e,2p] For example, only phenols with electron-donating groups at the *meta*-position of the hydroxy group readily undergo the Pechman condensation,[2p] whereas phenols with electron-withdrawing groups at the *meta*-positions[2p] or with electron-donating groups at other positions[2f] fail for this reaction. On the other hand, the α-substituents and γ-substituents[2p] on β-keto esters retard this reaction. Although this reaction is often carried out with concentrated H_2SO_4[2i] or 70% H_2SO_4,[2g] other acids, including Lewis acids, are also effective in promoting this reaction, such as $POCl_3$,[2p,4a] P_2O_5,[3n] HF,[2k] sulfamic acid,[3h] TFA,[11] triflic acid,[2b] polyphosphoric acid,[3kk,3rr] $KHSO_4$,[5e] dipyridine copper chloride,[5c] $ZnCl_2$,[2f,2g,2p,3l] AgOTf,[3a] $AlCl_3$,[2p,3tt] molecular iodine,[3a] VCl_3,[3b] $BF_3{\cdot}2H_2O$,[3c] BF_3,[3ss] $BiCl_3$,[5d] $ZrCl_4$,[3g] $SiCl_4$,[3nn] and $Yb(OTf)_3^{3j}$. However, the application of the common condensation reagent of P_2O_5 often results in the formation of chromone derivatives.[2p]

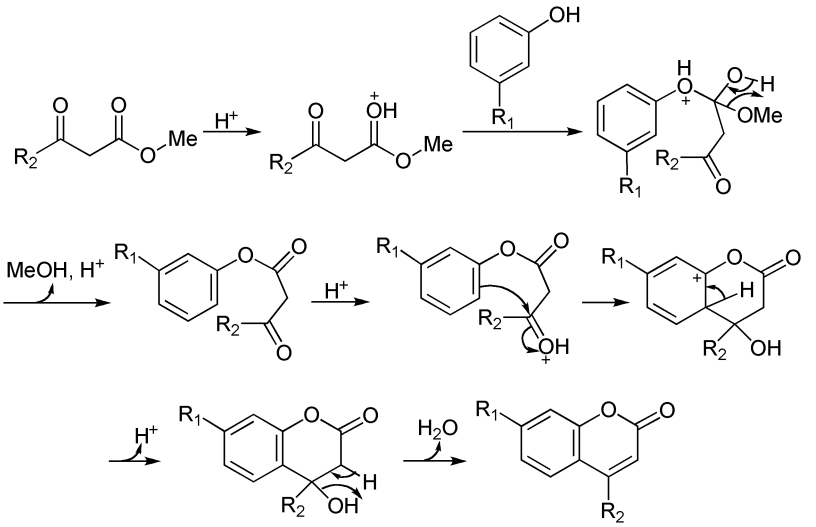
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Displayed below is a general mechanism for the Pechmann reaction between a phenol with a *meta*-electron-donating group and methyl β-keto ester under acidic conditions.



D. MODIFICATION

This reaction has been extensively modified to occur under various conditions, via the promotion by different acidic catalysts, including Lewis, acids, as described in Section A. In addition, cation exchange resin,[3h,3j,3o] Amberlyst ion-exchange resin,[3d] Nafion-H[5m] and Nafion resin/silica nanocomposites,[3k] Montmorillonite clay[3t,5j] and graphite/montmorillonite K10[3q] have been used as the condensation reagents. Moreover, this reaction has been generally accelerated by the use of microwave[3l,3n,3q,3s,5h,6a,10a,12] or ultrasound irradiation;[5d] in addition, this reaction can also be accelerated if carried out in neutral ionic liquid[5f] or acidic ionic liquid (e.g., non-chloroaluminate[3e] or Lewis acidic chloroalminate ionic liquid[5i]).

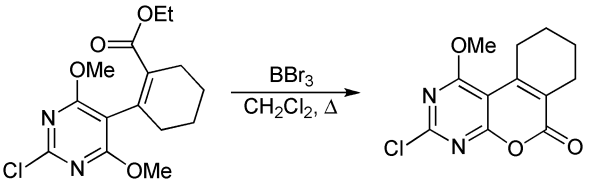
E. APPLICATIONS

This reaction has general application in the preparation of coumarin derivatives.

F. RELATED REACTIONS

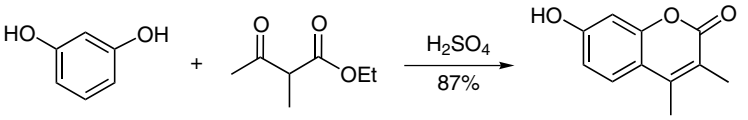
This reaction is related to the *Mentzer Pyrone Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4a.

To a flask were added 60 mL CH_2Cl_2, 2.7 g 2-(2-chloro-4,6-dimethoxy-pyrimidin-5-yl)-cyclohex-1-enecarboxylic acid ethyl ester (8.3 mmol), and 41 mL 1.0 M BBr_3 solution in CH_2Cl_2. The mixture was refluxed for 16 h and then cooled to 0°C; 20 mL MeOH was added. The reaction mixture was mixed with water and finally extracted with CH_2Cl_2. Upon evaporation of solvent, the residue was suspended in hexane then filtrated and washed with hexane to give, after drying ,1.57 g 2-chloro-4-methoxy-5,6,7,8-tetrahydro-10-oxa-1,3-diaza-phenanthren-9-one, in a yield of 71%, m.p., 184–186°C.



Reference 2c.

To a 1:1.5 molar ratio mixture of resorcinol (starting with 8 mmol) and ethyl 2-methylacetoacetate at 0°C was added an excess amount of 98% H_2SO_4 over 1 h. Then the mixture was stirred at room temperature until the reaction was complete as monitored by TLC ($\sim$ 16 h). The mixture was poured into ice water and allowed to stand overnight. The precipitated solid was filtered, washed with water until neutral, and dried in vacuo to afford 87% 3,4-dimethyl-7-hydroxycoumarin, which formed colorless crystals from EtOH, m.p., 220°C dec.

Other references related to the Pechmann reaction are cited in the literature.[13]

H. REFERENCES

1. Pechmann, H. V. and Duisberg, C., *Ber*., **1883**, *16*, 2119.
2. (a) Trenor, S. R.; Shultz, A. R.; Love, B. J. and Long, T. E., *Chem. Rev.,* **2004**, *104*, 3059. (b) Sekino, E.; Kumamoto, T.; Tanaka, T.; Ikeda, T. and Ishikawa, T., *J. Org. Chem.,* **2004**, *69*, 2760. (c) Xie, L.; Takeuchi, Y.; Cosentino, L. M.; McPhail, A. T. and Lee, K.-H., *J. Med. Chem.,* **2001**, *44*, 664. (d) Wulff, H.; Rauer, H.; Düring, T.; Hanselmann, C.; Ruff, K.; Wrisch, A.; Grissmer, S. and Hänsel, W., *J. Med. Chem.,* **1998**, *41*, 4542. (e) Panetta, J. A. and Rapoport, H., *J. Org. Chem.,* **1982**, *47*, 946. (f) Bissell, E. R.; Larson, D. K. and Croudace, M. C., *J. Chem. Eng. Data,* **1981**, *26*, 348. (g) Bissell, E. R.; Mitchell, A. R. and Smith, R. E., *J. Org. Chem.,* **1980**, *45*, 2283. (h) Krajniak, E. R.; Ritchie, E. and Taylor, W. C., *Aust. J. Chem.,* **1973**, *26*, 899. (i) Mital, R. L.; Gupta, R. R. and Jain, S. K., *J. Chem. Eng. Data,* **1972**, *17*, 383. (j) Sato, K. and Amakasu, T., *J. Org. Chem.,* **1968**, *33*, 2446. (k) Cook, C. E.; Corley, R. C. and Wall, M. E., *J. Org. Chem.,* **1965**, *30*, 4114. (l) Finnegan, R. A.; Gilbert, B.; Eisenbraun, E. J. and Djerassi, C., *J. Org. Chem.,* **1960**, *25*, 2169. (m) Boekelheide, V. and Pennington, F. C., *J. Am. Chem. Soc.,* **1952**, *74*, 1558. (n) Laskowski, S. C. and Clinton, R. O., *J. Am. Chem. Soc.,* **1950**, *72*, 3987. (o) Sethna, S. and Phadke, R., *Org. React.,* **1953**, *7*, 1. (p) Sethna, S. M. and Shah, N. M., *Chem. Rev.,* **1945**, *36*, 1.
3. (a) Wu, J.; Diao, T. N.; Sun, W. and Li, Y. Z., *Synth. Commun.,* **2006**, *36*, 2949. (b) Kumar, B. S.; Kumar, P. S.; Srinivasulu, N.; Rajitha, B.; Reddy, Y. T,; Reddy, P. N. and Udupi, R. H., *Chem. Heterocycl. Compd.,* **2006**, *42*, 172. (c) Stoyanov, E. V. and Mezger, J., *Molecules,* **2005**, *10*, 762. (d) Sabou, R.; Hoelderich, W. F.; Ramprasad, D. and Weinand, R., *J. Catal.,* **2005**, *232*, 34. (e) Gu, Y. L.; Zhang, J.; Duan, Z. Y. and Deng, Y. Q., *Adv. Synth. Catal.,* **2005**, *347*, 512. (f) Tyurin, R. V.; Antonov, A. N.; Minyaeva, L. G. and Mezheritskii, V. V., *Russ. J. Org. Chem.,* **2004**, *40*, 1828. (g) Smitha, G. and Reddy, C. S., *Synth. Commun.,* **2004**, *34*, 3997. (h) Singh, P. R.; Singh, D. U. and Samant, S. D., *Synlett,* **2004**, 1909. (i) Kolancilar, H. and Oyman, U., *J. Indian Chem. Soc.,* **2003**, *80*, 853. (j) Wang, L. M.; Xia, J. J.; Tian, H.; Qian, C. T. and Ma, Y., *Indian J. Chem., Sect. B.,* **2003**, *42B*, 2097. (k) Laufer, M. C.; Hausmann, H. and Holderich, W. F., *J. Catal.,* **2003**, *218*, 315. (l) Shockravi, A.; Heravi, M. M. and Valizadeh, H., *Phosphorus, Sulfur and Silicon and the Related Elements,* **2003**, *178*, 143. (m) Luck, R. L. and Mendenhall, G. D., *Acta Cryst., Sect. E: Struct. Reports Online,* **2002**, *E58*, o1387. (n) Shockravi, A.; Valizadeh, H. and Heravi, M. M., *Phosphorus, Sulfur & Silicon & Related Elements,* **2002**, *177*, 2835. (o) Subhas Bose, D.; Rudradas, A. P. and Hari Babu, M., *Tetrahedron Lett*., **2002**, *43*, 9195. (p) Khandekar, A. C. and Khadilkar, B. M., *Synlett,* **2002**, 152. (q) Frere, S.; Thiery, V. and Besson, T., *Tetrahedron Lett*., **2001**, *42*, 2791. (r) Holden, M. S. and Crouch, R. D., *J. Chem. Edu.,* **1998**, *75*, 1631. (s) Singh, V.; Singh, J.; Kaur, K. P. and Kad, G. L., *J. Chem. Res. (S),* **1997**, 58. (t) Biswas, G. K.; Basu, K.; Barua, A. K. and Bhattacharyya, P., *Indian J. Chem., Sect. B,* **1992**, *31B*, 628. (u) Khan, M. A. and Romeiro, G. A., *Quim. Nova*, **1990**, *13*, 3. (v) Hua, D. H.; Saha, S.; Maeng, J. C. and Bensoussan, D., *Synlett*, **1990**, 233. (w) Corrie, J. E. T., *J. Chem. Soc., Perkin Trans. I,* **1990**, 2151. (x) Osborne, A. G., *Tetrahedron*, **1983**, *39*, 1523. (y) Wolfbeis, O. S., *Monatsch. Chem.,* **1982**, *113*, 365. (z) Merchant, J. R.; Koshti, N. M. and Bakre, K. M., *J. Heterocycl. Chem.,* **1981**, *18*, 1655. (aa) Kappe, T. and Mayer, C., *Synthesis*, **1981**, 524. (bb) Osborne, A. G., *Tetrahedron*, **1981**, *37*, 2021. (cc) Bakre, K. M. and Merchant, J. R., *Indian J. Chem., Sect. B,* **1981**, *20B*, 346. (dd) Belletire, J. L.; Donahue, K. and Kellogg, M., *J. Heterocycl. Chem.,* **1979**, *16*, 803. (ee) Merchant, J. R.; Patell, J. R. and Thakkar, S. M., *Indian J. Chem.,* **1974**, *12*, 657. (ff) Kappe, Th.; Baxevanidis, G. and Ziegler, E., *Monatsh. Chem.*, **1971**, *102*, 1392. (gg) Kappe, T. and Ziegler, E., *Org. Prep. Proc.,* **1969**, *1*, 61. (hh) Trivedi, K. N., *J. Indian Chem. Soc.,* **1965**, *42*, 273. (ii) Winkler, and Whetstone, *J. Org. Chem.,* **1961**, *26*, 784. (jj) John, E. V. O. and Israelstam, S. S., *J. Org. Chem.,* **1961**, *26*, 240. (kk) Barris, B. E. and Israelstam, S. S., *J. South African Chem. Inst.,* **1960**, *13*, 125. (ll) Kuwayama, Y., *Yakugaku Zasshi,* **1960**, *80*, 913. (mm) Kapil, R. S. and Joshi, S. S., *J. Indian Chem. Soc.,* **1959**, *36*, 596. (nn) Trivedi, K. N., *Curr. Sci.,* **1959**, *28*, 67.

(oo) Israelstam, S. S. and John, E. V. O., *Chem. Ind. (London)* **1958**, 1262. (pp) Dann, O. and Illing, G., *Ann.*, **1957**, *605*, 158. (qq) Mehta, D. H.; Salimath, R. S. and Shah, N. M., *J. Indian Chem. Soc.*, **1956**, *33*, 135. (rr) Koo, J., *Chem. Ind. (London),* **1955**, 445. (ss) Shah, L. G.; Shah, G. D. and Shah, R. C., *J. Indian Chem. Soc.,* **1955**, *32*, 302. (tt) Dixit, V. M. and Kanakudati, A. M., *J. Indian Chem. Soc.,* **1951**, *28*, 323. (uu) Dixit, V. M. and Mulay, L. N., *Proc. Indian Acad. Sci., Sect. A,* **1948**, *27A*, 14. (vv) Shah, N. M.; Shah, R. C., *Ber.,* **1939**, *72B*, 215. (ww) Shah, N. M. and Shah, R. C., *Ber.,* **1938**, *71B*, 2075.

4. (a) Sellès, P. and Mueller, U., *Org. Lett.,* **2004**, *6*, 277. (b) Trost, B. M.; Toste, F. D. and Greenman, K., *J. Am. Chem. Soc.,* **2003**, *125*, 4518. (c) Sinev, M.; Landsmann, P.; Sineva, E.; Ittah, V. and Haas, E., *Bioconjugate Chem.,* **2000**, *11*, 352. (d) Trost, B. M. and Toste, F. D., *J. Am. Chem. Soc.,* **1996**, *118*, 6305. (e) Molyneux, R. J. and Jurd, L., *Aust. J. Chem.,* **1974**, *27*, 2697. (f) Lele, S. S.; Savant, N. G. and Sethna, S., *J. Org. Chem.,* **1960**, *25*, 1713. (g) Merchant, J. R. and Shah, R. C., *J. Org. Chem.,* **1957**, *22*, 884.
5. (a) Selvakumar, S.; Chidambaram, M. and Singh, A. P., *Catal. Commun.,* **2007**, *8*, 777. (b) Maheswara, M.; Siddaiah, V.; Damu, G. L. V.; Rao, Y. K. and Rao, C. V., *J. Mol. Catal. A: Chem.,* **2006**, *255*, 49. (c) Rajitha, B.; Kumar, V. N.; Someshwar, P.; Madhav, J. V.; Reddy, P. N. and Reddy, Y. T., *ARKIVOC,* **2006**, (*xii*), 23. (d) Patil, S.; Bhat, R.; Raje, V. and Samant, S., *Synth. Commun.,* **2006**, *36*, 525. (e) Qian, J. H. and Suo, J. S., *J. Chem. Res.,* **2005**, 486. (f) Potdar, M. K.; Rasalkar, M. S.; Mohile, W. S. and Salunkhe, M. M., *J. Mol. Catal. A: Chem.,* **2005**, *235*, 249. (g) Das, B.; Venkateswarlu, K.; Mahender, G. and Holla, H., *J. Chem. Res.,* **2004**, 836. (h) Helavi, V. B.; Solabannavar, S. B.; Salunkhe, R. S. and Mane, R. B., *J. Chem. Res. (S),* **2003**, 279. (i) Potdar, M. K.; Mohile, S. S. and Salunkhe, M. M., *Tetrahedron Lett.*, **2001**, *42*, 9285. (j) Li, T.-S.; Zhang, Z.-H.; Yang, F. and Fu, C.-G., *J. Chem. Res. (S),* **1998**, 38. (k) Hua, D. H.; Saha, S.; Roche, D.; Maeng, J. C.; Iguchi, S. and Baldwin, C., *J. Org. Chem.,* **1992**, *57*, 399. (l) Narayanan, V. and Bennet, C., *Indian J. Chem., Sect. B,* **1983**, *22B*, 686. (m) Chaudhari, D. D., *Chem. Ind. (London),* **1983**, 568. (n) Mujumdar, A. S. and Usgaonkar, R. N., *Curr. Sci.,* **1982**, *51*, 94. (o) Kostova, I. N.; Pardeshi, N.; Rangaswami, S. and Lee, Y.-W., *Indian J. Chem., Sect. B,* **1980**, *19B*, 859. (p) Ahluwalia, V. K.; Dhingra, S. and Kapur, K., *Indian J. Chem., Sect. B,* **1979**, *18B*, 79. (q) Wagle, D. R.; Usgaonkar, U. and Usgaonkar, R. N., *Indian J. Chem., Sect. B,* **1978**, *16B*, 378. (r) Mujumdar, A. S. and Usgaonkar, R. N., *Indian J. Chem., Sect. B,* **1977**, *15B*, 520. (s) Hirata, T. and Suga, T., *Bull. Chem. Soc. Jpn.,* **1974**, *47*, 244. (t) Thakor, V. M. and Acharya, A. B., *J. Indian Chem. Soc.,* **1971**, *48*, 499. (u) Kaufman, K. D.; Kelly, R. C. and Eaton, D. C., *J. Org. Chem.,* **1967**, *32*, 504. (v) Usgaonkar, R. N.; Thakor, V. M.; Jadhav, G. V. and Shah, R. C., *J. Indian Chem. Soc.,* **1953**, *30*, 765. (w) Usgaonkar, R. N.; Thakor, V. M.; Jadhav, G. V. and Shah, R. C., *J. Indian Chem. Soc.*, **1953**, *30*, 743. (x) Usgaonkar, R. N.; Thakor, V. M. and Jadhav, G. V., *J. Indian Chem. Soc.*, **1953**, *30*, 535. (y) Mody, C. S. and Shah, R. C., *Proc. Indian Acad. Sci., Sect. A,* **1951**, *34A*, 77. (z) Adams, R. and Mecorney, J. W., *J. Am. Chem. Soc.,* **1944**, *66*, 802. (aa) Kotwani, N. G.; Sethna, S. M. and Advani, G. D., *Proc. Indian Acad. Sci., Sect. A,* **1942**, *15A*, 441. (bb) Kulkarni, D. R.; Alimchandani, R. L. and Shah, N. M., *J. Indian Chem. Soc.*, **1941**, *18*, 113. (cc) Sethna, S. M. and Shah, R. C., *J. Indian Chem. Soc.*, **1940**, *17*, 211. (dd) Sethna, S. M. and Shah, R. C., *J. Indian Chem. Soc.*, **1940**, *17*, 37.
6. (a) Manhas, M. S.; Ganguly, S. N.; Mukherjee, S.; Jain, A. K. and Bose, A. K., *Tetrahedron Lett.,* **2006**, *47*, 2423. (b) Dorlars, A.; Schllhammer, C.-W. and Schroeder, J., *Angew. Chem. Int. Ed. Engl.,* **1975**, *14*, 665.
7. Hamann, L. G., *J. Org. Chem.,* **2000**, *65*, 3233.
8. (a) Rodriguez-Dominguez, J. C. and Kirsch, G., *Synthesis,* **2006**, 1895. (b) Boekelheide, V. and Michels, A. P., *J. Am. Chem. Soc.,* **1952**, *74*, 256.
9. Dutt, S. and Karmakar, T. K. *Synthesis,* **1981**, 826.
10. (a) Rajanarendar, E.; Ramesh, P. and Ramu, K., *Indian J. Chem., Sect. B,* **2004**, *43B*, 2650. (b) Harvey, R. G.; Cortez, C.; Ananthanarayan, T. P. and Schmolka, S., *J. Org. Chem.,* **1988**, *53*,

3936. (c) Kraus, G. A. and Pezzanite, J. O., *J. Org. Chem.,* **1979**, *44*, 2480. (d) Crosby, D. G. and Berthold, R. V., *J. Org. Chem.,* **1962**, *27*, 3083.

11. Woods, L. L. and Sapp, J., *J. Org. Chem.,* **1962**, *27*, 3703.
12. Sugino, T. and Tanaka, K., *Chem. Lett*., **2001**, 110.
13. (a) Fillion, E.; Dumas, A. M.; Kuropatwa, B. A.; Malhotra, N. R. and Sitler, T. C., *J. Org. Chem.,* **2006**, *71*, 409. (b) De, S. K. and Gibbs, R. A., *Synthesis*, **2005**, 1231. (c) Chen, C.-T.; Chiang, C.-L.; Lin, Y.-C.; Chan, L.-H.; Huang, C.-H.; Tsai, Z.-W. and Chen, C.-T., *Org. Lett.,* **2003**, *5*, 1261. (d) Chatterjee, A. K.; Toste, F. D.; Goldberg, S. D. and Grubbs, R. H., *Pure & Appl. Chem.,* **2003**, *75*, 421. (e) Gao, Q.; Wang, L. and Liang, X. T., *Chin. Chem. Lett.,* **2002**, *13*, 714. (f) Gnerre, C.; Catto, M.; Leonetti, F.; Weber, P.; Carrupt, P.-A.; Altomare, C.; Carotti, A. and Testa, B., *J. Med. Chem.,* **2000**, *43*, 4747. ((g) Atkins, R. L. and Bliss, D. E., *J. Org. Chem.,* **1978**, *43*, 1975. ((h) Esse, R. C. and Christensen, B. E., *J. Org. Chem.,* **1960**, *25*, 1565. ((i) Woodruff, E. H., *Org. Synth. Coll. ,* **1955**, *3*, 581.

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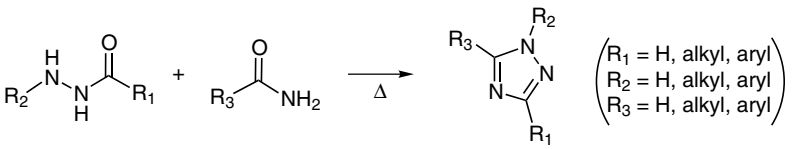
Pellizzari Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Pellizzari in 1894.[1] It is the preparation of 1,2,4-triazole derivatives by baking the mixture of amide and acyl hydrazide. Therefore, it is generally known as the Pellizzari reaction.[2] This reaction is usually carried out at temperatures $> 250^{\circ}C$,[2b] but very reactive substrates can proceed at relatively lower temperatures, such as the coupling between diphenylformamidine and formhydrazide at $150^{\circ}C$.[3] This reaction is very useful for the preparation of monosubstituted-, disubstituted-, and 1,3,5-trisubstituted-1,2,4-1*H*-triazoles.[2b] However, at such a high temperature, transamination may occur between amide and acyl hydrazide, especially for the aliphatic acid hydrazides,[4] resulting in a mixture of triazoles and a lower yield of the expected triazole. It has been found that co-heating the mixture of formamide and hydrazine hydrochloride with two equivalents of pulverized KOH can improve the yield of 1,2,4-triazole to almost 17%.[5]

B. GENERAL REACTION SCHEME



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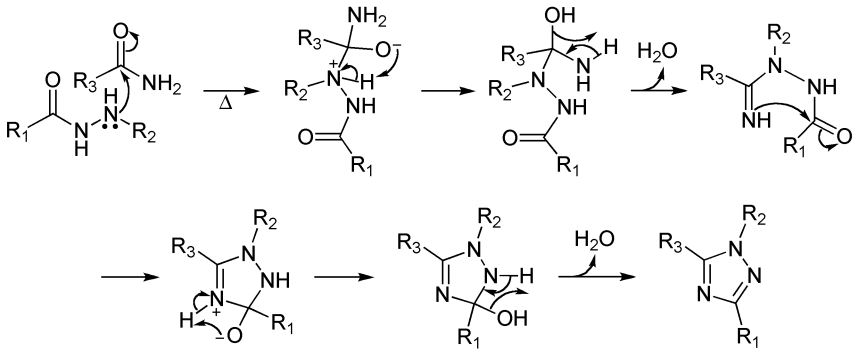
C. PROPOSED MECHANISMS

A general mechanism is outlined below for the Pellizzari reaction.



D. MODIFICATION

N/A

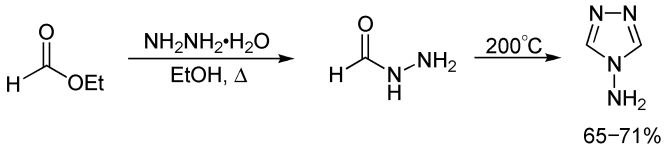
E. APPLICATIONS

This reaction can be used to prepare monosubstituted-, disubstituted-, and trisubstituted 1,2,4-1*H*-triazoles.

F. RELATED REACTIONS

This reaction is related to the *Einhorn-Brunner Reaction*.

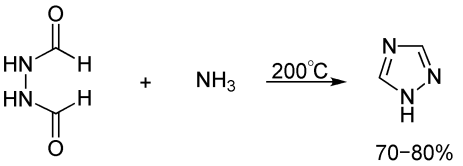
G. CITED EXPERIMENTAL EXAMPLES



Reference 6.

To a 1-L round-bottomed flask equipped with an efficient water condenser were added 148 g ethyl formate (2 mol) and 150 mL 95% EtOH. Then 120 g 85% hydrazine hydrate was added cautiously under stirring within 10 min. After the reaction had subsided, the solution was refluxed on a steam bath for 18 h. Then the bulk of the water and EtOH was removed by evaporation under reduced pressure until the volume in the flask was ~150 mL. The

resulting syrup (i.e., the crude formhydrazide), was heated under atmospheric pressure for 3 h, during which time the temperature of the bath was raised from 150° to 200°C. After cooling to ~100°C, the oil was taken up in 50 mL 95% EtOH, and 5 g Norite was added. The filtered solution was then diluted with 75 mL ether and placed in an ice box to cool. The crystalline product was filtered, washed with 50 mL 1:2 EtOH-ether and dried to give 55–60 g aminotriazole, in a yield of 65–71%, m.p., 77–78°C. Further purification can be undertaken by recrystallization from 95% EtOH by 2 mL EtOH per gram of aminotriazole followed by 2.5 mL ether, giving a melting point of 81–82°C.



Reference 7.

A mixture of 95 g *N*,*N*′-diformylhydrazine (1.08 mol) and 500 mL liquid NH_3 was heated in a steel pressure vessel at 200°C for 24 h. After removal of the ammonia, the residue was extracted with hot EtOAc. The extract was evaporated and the residue was distilled under reduced pressure to afford 70–80% 1,2,4-trazole, b.p. 124°C at 5 mmHg. A sample was recrystallized from EtOAc, m.p., 120°C.

Other references related to the Pellizzari reaction are cited in the literature.[8]

H. REFERENCES

1. (a) Pellizzari, G., *Gazz. Chim. Ital.,* **1894**, *24*, 222. (b) Pellizzari, G., *Ber.,* **1894**, *27B*, 801.
2. (a) Lin, Y.-I.; Lang, S. A.; Lovell, M. F. and Perkinson, N. A., *J. Org. Chem.,* **1979**, *44*, 4160. (b) Potts, K. T., *Chem. Rev.,* **1960**, *60*, 87. (c) Atkinson, M. R. and Polya, J. B., *J. Chem. Soc.,* **1952**, 3418.
3. Otting, W. and Staab, H. A., *Ann.,* **1959**, *622*, 23.
4. Rode, N. V. and Gerchuk, M. P., *J. Gen. Chem. USSR,* **1958**, *28*, 1365.
5. Strain, H. H., *J. Am. Chem. Soc.,* **1927**, *49*, 1995.
6. Allen, C. F. H. and Bell, A., *Org. Synth. Coll.,* **1955**, 3, 96.
7. Ainsworth, C. and Jones, R. G., *J. Am. Chem. Soc.,* **1955**, *77*, 621.
8. (a) Van Koningsbruggen, P. J.; Haasnoot, J. G.; Vreugdenhil, W.; Reedijk, J. and Kahn, O., *Inorg. Chim. Acta,* **1995**, *239*, 5. (b) Miles, R. W.; Samano, V. and Robins, M. J., *J. Org. Chem.,* **1995**, *60*, 7066. (c) Heitke, B. T. and McCarty, C. G., *J. Org. Chem.,* **1974**, *39*, 1522. (d) Ainsworth, C., *Org. Synth. Coll.,* **1973**, *5*, 1070. (e) Browne, E. J., *Aust. J. Chem.,* **1971**, *24*, 393. (f) Creagh, L. T. and Truitt, P., *J. Org. Chem.,* **1968**, *33*, 2956. (g) Ainsworth, C.; Easton, N. R.; Livezey, M.; Morrison, D. E. and Gibson, W. R., *J. Med. Pharm. Chem.,* **1962**, *5*, 383. (h) Steck, E. A.; Brundage, R. P. and Fletcher, L. T., *J. Am. Chem. Soc.,* **1958**, *80*, 3929. (i) Wiley, R. H. and Hart, A. J., *J. Org. Chem.,* **1953**, *18*, 1368. (j) Kaiser, D. W.; Peters, G. A. and Wystrach, V. P., *J. Org. Chem.,* **1953**, *18*, 1610. (k) Pellizzari, G. and Massa, C., *J. Chem. Soc.,* **1901**, *80*, 488.

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Perkin Reaction

(Perkin Condensation, Perkin Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Perkin in 1868.[1] It is the direct preparation of cinnamic acid derivatives from the thermal condensation between aromatic aldehydes and aliphatic carboxylic acid anhydrides or carboxylic derivatives (e.g., amide[2]) in the presence of a basic compound functioning as a catalyst. Therefore, this reaction is generally known as the Perkin reaction,[3,4] Perkin condensation,[2,3j,5] or Perkin synthesis.[5g,6] Occasionally, this reaction is also referred to as the Perkin cinnamic acid synthesis[4j,4o,4q] or Perkin coumarin synthesis.[7] Under the normal conditions, benzaldehyde is condensed with acid anhydride and the alkali salt of the same acid as the catalyst. However, it has been reported that the salt of the fatty acid as a base is not specific,[2] and the carbonates, acetates, phosphates, sulfites, and sulfides of sodium or potassium are all effective for this reaction.[2] In addition, even a strong organic base such as tertiary amine[3j,5d,6f,8] and pyridine[3b,9] are good catalysts for the Perkin reaction. It has been found that the Perkin reaction depends on the basicity of the catalyst, the activation of anhydride, and the nature of aromatic aldehyde. For example, the alkali acetate catalyzed Perkin reaction between *o*-chlorobenzaldehyde and acetic anhydride at 180°C for 8 h gives the following yields: Li^+, 58%; Na^+, 71%; K^+, 78%; Rb^+, 82%, showing the effect of basicity and concentration of the acetate.[8a] In addition, the electron-withdrawing groups on benzaldehydes have been found to facilitate the Perkin reaction, with a ρ value of $+2.25$ in the Hammet equation.[8a] Furthermore, other higher-order aliphatic acid anhydrides, such as butyric anhydride, normally give lower yields of α-alkyl cinnamic acids.[3b] It has been proposed that this reaction involves the enolization of anhydride and

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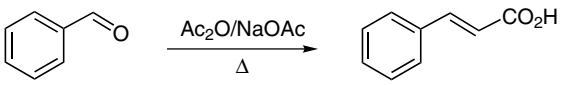
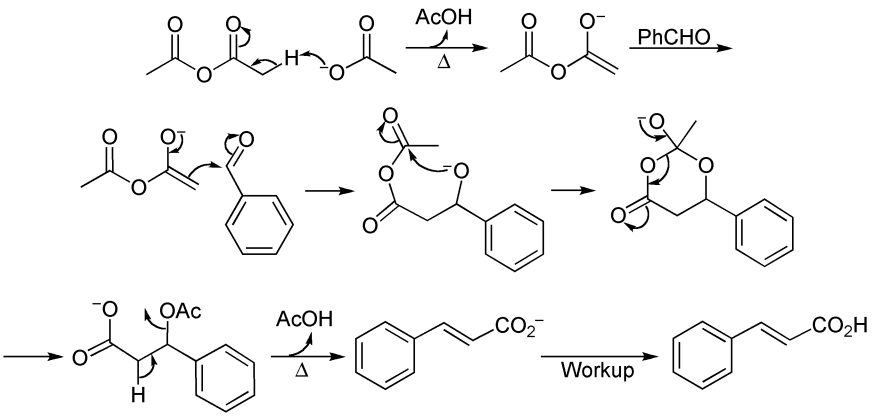
Aldol Condensation with an aromatic aldehyde, followed by the dehydration of aldol product to give the derivative of cinnamic acid.[2,6f,6g]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Displayed below is the mechanism for the sodium acetate catalyzed reaction between benzaldehyde and acetic anhydride.



D. MODIFICATION

The most important modification of the Perkin reaction was developed by Oglialoro using the sodium salt of acetic acid (e.g., phenylacetic acid,[3f,5i] phenoxyacetic acid[5l]) in condensation with acetic anhydride and an aldehyde (e.g., benzaldehyde,[3f,5i,5l,10] paraldehyde[11]). This type of reaction is referred to as the Perkin-Oglialoro reaction,[12] Perkin-Oglialoro condensation,[10,13] or Oglialoro modification.[3d,3g,5i] Other modifications include the use of different bases as the catalysts, (e.g., $NaB(OMe)_4$-LiCl,[3a] CaH_2,[3i] CsOAc,[3b] and CsF[3b]), the use of microwave irradiation and cesium acetate or fluoride in combination with a small amount of pyridine as catalyst[3b] and the continuous distillation of acetic acid to enhance the conversion rate.[8b]

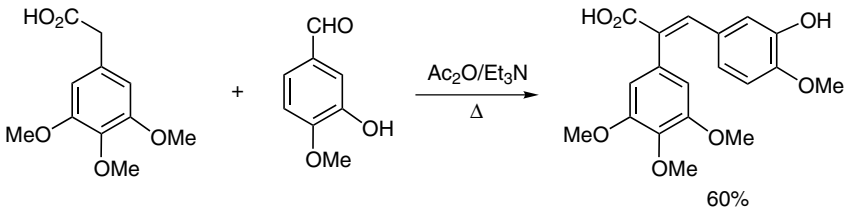
E. APPLICATIONS

This reaction is very useful for the preparation of cinnamic acid derivatives.

F. RELATED REACTIONS

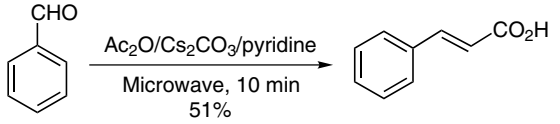
This reaction is related to the *Claisen Condensation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 5d.

A mixture of 0.67 g 3-hydroxy-4-methoxybenzaldehyde (4.4 mmol), 2.0 g 3,4,5-trimethoxyphenylacetic acid (8.84 mmol), 4 mL acetic anhydride, and 2 mL triethylamine was refluxed for 3 h. After acidification with 6 mL conc. HCl, the resulting solid was filtered off and recrystallized from ethanol to give 950 mg *E*-2-(3′,4′,5′-trimethoxyphenyl)-3-(3′-hydroxy-4′-methoxyphenyl)prop-2-enoic acid as fine yellow needles, in a yield of 60%, m.p., 237–239°C.



Reference 3b.

A mixture of 0.05 mol freshly distilled benzaldehyde, 0.1 mol acetic anhydride, and 0.05 mol Cs_2CO_3 with a small amount of pyridine was heated in a 800-W microwave oven for 10 min. The reaction mixture was then poured into 100 mL 5 % $NaHCO_3$, and the unreacted aldehyde was extracted with Et_2O (3 × 50 mL). The aqueous layer was filtered, and the clear filtrate was heated to boil and acidified to pH 2 by the addition of HCl. The crystalline product was filtered, washed with cold water, and dried to give 51% cinnamic acid, m.p. 133–134°C.

Other references related to the Perkin reaction are cited in the literature.[14]

H. REFERENCES

1. (a) Perkin, W. H., *J. Chem. Soc.,* **1868**, *21*, 53. (b) Perkin, W. H., *J. Chem. Soc.,* **1868**, *21*, 181.
2. Dippy, J. F. J. and Evans, R. M., *J. Org. Chem.,* **1949**, *14*, 451.
3. (a) Chiriac, C. I.; Tanasa, F. and Onciu, M., *Revue Roumaine Chim.,* **2005**, *50*, 627. (b) Veverkova, E.; Pacherova, E. and Toma, S., *Chem. Papers,* **1999**, *53*, 257. (c) Galust'yan, G. G. and Kadyrov, C. S., *Chem. Heterocycl. Compd.,* **1969**, *3*, 299. (d) Von Strandtmann, M.; Cohen, M. P.; Puchalski, C. and Shavel, J., *J. Org. Chem.,* **1968**, *33*, 4306. (e) Zimmerman, H. E. and Ahramjian, L., *J. Am. Chem. Soc.,* **1959**, *81*, 2086. (f) Buckles, R. E.; Bellis, M. P. and Coder, W. D., *J. Am. Chem. Soc.,* **1951**, *73*, 4972. (g) Thielcke, G. W. and Becker, E. I., *J. Org. Chem.,* **1950**, *15*, 1241. (h) Angel, H. S. and Day, A. R., *J. Am. Chem. Soc.,* **1950**, *72*, 3874. (i) Zuffanti, S. and Sardella, J. J., *J. Am. Chem. Soc.,* **1950**, *72*, 4322. (j) Schwenk, E. and Papa, D., *J. Am. Chem. Soc.,* **1945**,

67, 1432. (k) Hauser, C. R. and Breslow, D. S., *J. Am. Chem. Soc.,* **1940**, *62*, 593. (l) Hurd, C. D. and Thomas, C. L., *J. Am. Chem. Soc.,* **1933**, *55*, 275.

4. (a) Yu, H. and Ning, Z.-X., *Huanan Ligong Daxue Xuebao, Ziran Kexueban*, **2006**, *34*, 27. (b) Zhang, H. J.; Shi, L. and Chen, J. C., *Jingxi Shiyou Huagong Jinzhan*, **2006**, *7*, 42. (c) Tan, L.-Q.; Huang, M.; Ye, X.-J. and Zeng, D.-H., *Huaxue Yu Shengwu Gongcheng*, **2005**, *22*, 39. (d) Zhang, H.-J.; Shi, L.; Chen, J.-C.; Jing, R.-D. and Jia, X.-P., *Shandong Huagong*, **2004**, *33*, 4. (e) Sevenard, D. V., *Tetrahedron Lett.,* **2003**, *44*, 7119. (f) Solladié, G.; Pasturel-Jacopé, Y. and Maignan, J., *Tetrahedron,* **2003**, *59*, 3315. (g) Wu, S. S., *Huaxue Shijie*, **2002**, *43*, 599. (h) Chen, Z.-T.; Xiao, S.-Y.; Tian, S.-G. and Li, Z.-L., *Chongqing Daxue Xuebao, Ziran Kexueban*, **2002**, *25*, 85. (i) Jiang, X. H.; Qin, B. B.; Liu, Q. Z. and Fan, J. E., *Huaxue Yanjiu Yu Yingyong*, **1999**, *11*, 541. (j) Wang, W.; Meng, F J. and Gao, H. B., *Yingyong Huaxue,* **1989**, *6*, 82. (k) Naraya, R. and Kulkarni, R. A., *Curr. Sci.,* **1979**, *48*, 394. (l) Pohjala, E., *Acta Chem. Scand., Ser. B,* **1976**, *B30*, 198. (m) Pohjala, E., *Heterocycles,* **1975**, *3*, 615. (n) Pohjala, E., *Heterocycles*, **1974**, *2*, 585. (o) Lock, G. and Bayer, E., *Ber.,* **1939**, *72B*, 1064. (p) Brodskii, D. A., *Zh. Obsh. Khim.,* **1938**, *8*, 1534. (q) Bock, F.; Lock, G. and Schmidt, K., *Monatsh. Chem.,* **1934**, *64*, 399. (r) Ogawa, S., *Bull. Chem. Soc. Jpn.,* **1927**, *2*, 20.

5. (a) Cserenyi, S.; Felfoeldi, K.; Forgo, P. and Palinko, I., *J. Fluor. Chem.,* **2006**, *127*, 850. (b) Chandrasekhar, S. and Karri, P., *Tetrahedron Lett*., **2006**, *47*, 2249. (c) Tripathi, S.; Misra, K. and Sanghvi, Y. S., *Synth. Commun.,* **2005**, *35*, 3069. (d) Gaukroger, K.; Hadfield, J. A.; Hepworth, L. A.; Lawrence, N. J. and McGown, A. T., *J. Org. Chem.,* **2001**, *66*, 8135. (e) Palinko, I.; Kukovecz, A.; Torok, B. and Kortvelyesi, T., *Monatsh. Chem.,* **2000**, *131*, 1097. (f) Nesmeyanov, A. N.; Tolstaya, T. P.; Vanchikova, L. N. and Petrakov, A. V., *Russ. Chem. Bull.,* **1980**, *29*, 1789. (g) Buckles, R. E. and Cooper, J. A., *J. Org. Chem.,* **1965**, *30*, 1588. (h) Ketcham, R., *J. Chem. Edu.,* **1964**, *41*, 565. (i) Ketcham, R. and Jambotkar, D., *J. Org. Chem.,* **1963**, *28*, 1034. (j) Buckles, E. and Bremer, K. G., *J. Am. Chem. Soc.,* **1953**, *75*, 1487. (k) Dippy, J. F. J. and Evans, R. M., *J. Org. Chem.,* **1950**, *15*, 451. (l) Papa, D. and Schwenk, E., *J. Am. Chem. Soc.,* **1947**, *69*, 3022.

6. (a) Ren, B. Y.; Chen, G. B. and Gou, X. H., *Huaxue Shijie*, **1996**, *37*, 21. (b) Melikyan, G. S.; Lacova, M.; Kralova, K.; El-Shaaer, H. M.; Henselova, M. and Avetisyan, A. A., *Chem. Papers,* **1993**, *47*, 388. (c) Koepp, E. and Vögtle, F., *Synthesis,* **1987**, 177. (d) Lacova, M. and Hrnciar, P., *Chem. Papers,* **1985**, *39*, 135. (e) Scipioni, A. and Borsetto, V., *Annali Chim. (Italy),* **1952**, *42*, 185. (f) Hauser, C. R. and Breslow, D. S., *J. Am. Chem. Soc.,* **1939**, *61*, 793. (g) Breslow, D. S. and Hauser, C. R., *J. Am. Chem. Soc.,* **1939**, *61*, 786. (h) Kalnins, P., *Ber.,* **1936**, *69B*, 2843.

7. (a) Crawford, I. M. and Shaw, J. A. M., *J. Chem. Soc.,* **1953**, 3435. (b) Spath, E. and Holzen, H., *Ber.,* **1934**, *67B*, 264.

8. (a) Ogata, Y. and Tsuchida, M., *J. Org. Chem.,* **1959**, *24*, 78. (b) Utermohlen, W. P. and Wallace, E. L., *J. Org. Chem.,* **1947**, *12*, 547.

9. Bacharach, G. and Grogan, F., *J. Am. Chem. Soc.,* **1928**, *50*, 3333.

10. Tarbell, D. S.; Smith, R. F. and Boekelheide, V., *J. Am. Chem. Soc.,* **1954**, *76*, 2470.

11. Gilman, H. and Harris, S. A., *J. Am. Chem. Soc.,* **1927**, *49*, 1825.

12. Borges, F.; Roleira, F.; Milhazes, N.; Santana, L. and Uriarte, E., *Curr. Med. Chem.,* **2005**, *12*, 887.

13. (a) Bakunin, M. and Peccerillo, D., *Gazz. Chim. Ital.,* **1935**, *65*, 1145. (b) Kalnin, P., *Helv. Chim. Acta,* **1928**, *11*, 982.

14. (a) Letcher, R. M.; Nhamo, L. R. M. and Gumiro, I. T., *J. Chem. Soc.*, *Perkin Trans. I,* **1972**, 206. (b) Crawford, M. and Little, W. T., *J. Chem. Soc.,* **1959**, 722. (c) MacPeek, D. L.; Starcher, P. S. and Phillips, B., *J. Am. Chem. Soc.,* **1959**, *81*, 680. (d) Johnson, J. R., *Org. React.,* **1942**, *1*, 210. (e) Perkin, W. H., *J. Chem. Soc.,* **1877**, *31*, 388. (f) Paternò, E. and Oglialoro, A., *Ber.,* **1874**, *7*, 80.

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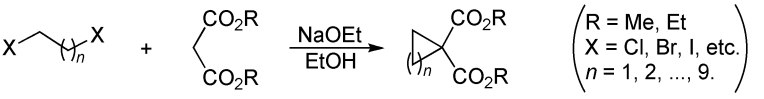
Perkin Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Perkin in 1883.[1] It is the nucleophilic alkylation between malonic ester and α,ω-alkyl dihalide to form cyclic aliphatic 1,1-diester or acid and is known as the Perkin reaction[2] or Perkin synthesis.[2] Although it was once referred to as the Perkin condensation,[3] this name should not be used for this type of reaction. Using this protocol, Perkin successfully prepared cyclopropane-,[4] cyclobutane-,[5] cyclopentane-,[6] cyclohexane-,[7] and cycloheptane-1,1-dicarboxylic acids.[8] However, this reaction is often complicated by the side reaction that forms $\alpha,\alpha,\omega,\omega$-tetracarboxylic ester from the S_N2 reaction between malonic ester and α,ω-alkyl dihalide,[9] this side reaction can be depressed if alcoholic sodium malonic ester is added slowly to the α,ω-alkyl dihalide with vigorous stirring.[9b] It is interesting that the K_2CO_3 promoted a reaction between dimethyl 1,3-acetonedicarboxylate and *trans*-1,4-dibromobutene yields vinyldihydrofuran.[10]

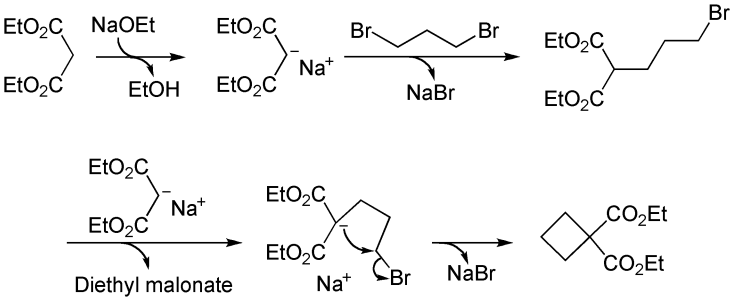
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

Displayed here is a representative reaction between diethyl malonate and 1,3-dibromopropane in absolute EtOH, using NaOEt as the base.



D. MODIFICATION

This reaction has been modified by the addition of alcoholic sodium malonic ester to a solution of α,ω-alkyl dihalide to depress the side reaction.[9b]

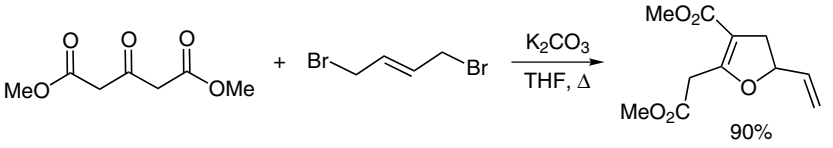
E. APPLICATIONS

This reaction is one of the major organic reactions for the preparation of alicyclic compounds.

F. RELATED REACTIONS

This reaction is related to *Malonic Ester Synthesis*.

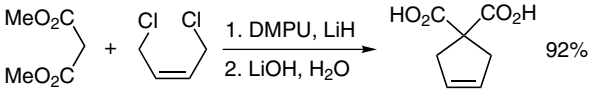
G. CITED EXPERIMENTAL EXAMPLES



Reference 10.

To a 1 mmol solution of dimethyl acetonedicarboxylate in 15 mL dry THF was added 2.5 mmol powdered K_2CO_3. The mixture was stirred under nitrogen for 15 min at room temperature. Then 1 mmol *trans*-1,4-dibromo-2-butene in 10 mL dry THF was added through a syringe, and the resulting reaction mixture was refluxed until the completion of

reaction as monitored by TLC. After cooling to room temperature, the solution was filtered through a short pad of Celite, and the solution was evaporated under reduced pressure. The residue was purified by rapid flash chromatography to afford 90% 4,5-dihydro-2-methoxycarbonylmethyl-3-methylcarboxylate-5-vinylfuran, $R_f = 0.59$ (Et_2O/pentane, 7:3).



Reference 11.

To a 1-L two-necked, round-bottomed flask equipped with a magnetic stirring bar were added 33.0 g dimethyl malonate (0.25 mol), 50 mL dry *N*,*N*-dimethylpropyleneurea (DMPU), and 450 mL dry THF under a current of nitrogen. The mixture was cooled in an ice bath, and 5.0 g LiH powder (0.629 mol) was added in one portion under stirring. The nitrogen flow was discontinued, and the flask was sealed with a rubber septa connecting to a Nujor-filled bubbler by syringe needle. After 15 min, the ice bath was removed and stirring was continued until hydrogen evolution ceased, whereupon 28.4 mL *cis*-1,4-dichloro-2-butene (0.269 mol) was added rapidly by syringe. The mixture was heated at 40–45°C for 24 h and then cooled to 20°C; 50 mL water was added dropwise followed by 31.5 g solid $LiOH{\cdot}H_2O$ (0.750 mol). After the mixture was stirred at 20°C for another 24 h, an additional 350 mL water was added under stirring, and the whole mixture was extracted by EtOAc (5 × 500 mL); each washing was back washed with 30 mL brine. The combined aqueous phase was then acidified with 160 mL 6 N HCl and extracted with EtOAc (3 × 500 mL). The combined organic layers were washed with 3 N HCl (3 × 100 mL) and brine (2 × 50 mL), and dried over Na_2SO_4. Upon removal of the solvent by rotary evaporation and traces of solvent under high vacuum (1 h at 0.1 mmHg), 35.8 g 3-cyclopentene-1,1-dicarboxylic acid was obtained as an off-white solid, in a yield of 92%, m.p. 163–165°C.

Other references related to the Perkin synthesis are cited in the literature.[12]

H. REFERENCES

1. Perkin, W. H., *Ber.,* **1883**, *16*, 1793.
2. van Heyningen, E., *J. Am. Chem. Soc.,* **1954**, *76*, 2241.
3. Dox, A. W. and Yoder, L., *J. Am. Chem. Soc.,* **1921**, *43*, 1366.
4. (a) Perkin, W. H., *Ber.,* **1884**, *17*, 54. (b) Perkin, W. H., *Ber.,* **1885**, *18*, 1734. (c) Perkin, W. H., *J. Chem. Soc.,* **1885**, *47*, 801.
5. (a) Perkin, W. H., *J. Chem. Soc.,* **1887**, *51*, 1. (b) Perkin, W. H., *J. Chem. Soc.,* **1887**, *51*, 849. (c) Colman, and Perkin, W. H., *J. Chem. Soc.,* **1887**, *51*, 228. (d) Blackstock and Perkin, W. H., *Proc. Chem. Soc.,* **1913**, *29*, 76.
6. (a) Colman and Perkin, W. H., *J. Chem. Soc.,* **1888**, *53*, 185. (b) Haworth and Perkin, W. H., *J. Chem. Soc.,* **1894**, *65*, 86.
7. Kipping and Perkin, W. H., *J. Chem. Soc.,* **1890**, *57*, 304.
8. Haworth and Perkin, W. H., *J. Chem. Soc.,* **1894**, *65*, 591.

9. (a) FitzGerald, P. A.; Carr, M. W.; Davey, T. W.; Serelis, A. K.; Such, C. H. and Warr, G. G., *J. Colloid Interface Sci.,* **2004**, *275*, 649. (b) Dox, A. W. and Yoder, L., *J. Am. Chem. Soc.,* **1921**, *43*, 677.
10. Lavoisier-Gallo, T.; Charonnet, E.; Pons, J.-M.; Rajzman, M.; Faure, R. and Rodriguez, J., *Chem. Eur. J.,* **2001**, 1056.
11. Deprés, J.-P. and Greene, A. E., *Org. Synth. Coll.,* **2004**, *10*, 228.
12. (a) Meinwald, J.; Gassman, P. G. and Crandall, J. K., *J. Org. Chem.,* **1962**, *27*, 3366. (b) Cason, J. and Allen, C. F., *J. Am. Chem. Soc.,* **1950**, *72*, 1036. (c) Heisig and Stodola, *Org. Synth.,* **1943**, *23*, 16. (d) Goldsworthy, L. J., *J. Chem. Soc.,* **1934**, 377. (e) Perkin, W. H., *J. Chem. Soc.,* **1929**, 1347. (f) Kerr, C. A., *J. Am. Chem. Soc.,* **1929**, *51*, 614. (g) Freer, P. C. and Perkin, W. H., *J. Chem. Soc.,* **1888**, *53*, 202.

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Perkow Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Perkow in 1952.[1] It is the preparation of vinyl (or enol) phosphates from α-halo carbonyl compounds and trivalent phosphorus reagents and is generally known as the Perkow reaction.[2,3] In addition, this reaction is referred to as the Perkow synthesis,[4] Perkow rearrangement,[5] anomalous Arbuzov reaction,[6] Perkow-Arbuzov reaction,[7] or vinyl ester reaction.[8] Generally speaking, α-halo aldehydes are more reactive than α-halo ketones; whereas α-halo esters are the least reactive species for the Perkow reaction, and α-halo amides do not react at all.[2k] On the other hand, the α-halo carbonyl compounds also show a general reactivity scale of I > Br > Cl.[2k] The more α-halo atoms in the carbonyl compound, the faster the reaction occurs.[2k] For example, chloral and bromal undergo the Perkow reaction most readily, and such a vigorous reaction is usually controlled by either lowering the reaction temperature or carrying it out in an inert solvent;[1,4b,9] the normal Perkow reaction is carried out at 100–150°C.[2k] The trivalent phosphorus reagent should contain at least one alkoxy group, whose alkyl group is capable of evolving as a carbonium ion, and should not have a hydrogen or hydroxy group attaching to a phosphorus atom.[2k] Thus trialkyl phosphites, dialkyl ethylphosphonites, dialkyl phenylphosphonites, and methyl diphenylphosphinite are all possible reagents for this reaction;[2d] but trialkylphosphines, triaryl phosphates, and phosphorotriamidites do not undergo the Perkow reaction.[2k] For trialkyl phosphites with different alkyl groups, the smallest alkyl group is usually eliminated in this reaction; similarly, for phosphites containing one or two phenoxy groups, the alkyl group is always removed as alkyl halide.[2k] Both the electronic character of phosphorus[2b,2c] and the steric effects[2d,2h] are prominent in the Perkow reaction, as indicated by the predominant *trans*-configuration in vinyl phosphates,[2i] resulting from the initial attack of trialkyl phosphite from the less hindered side of halogen

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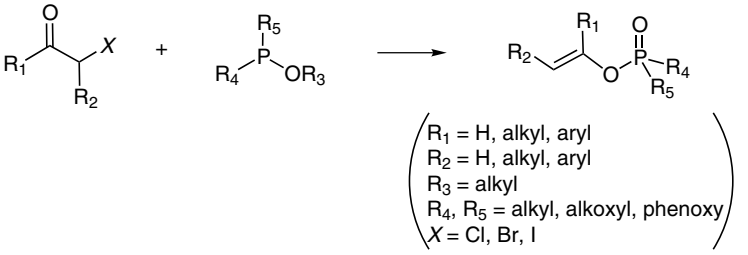
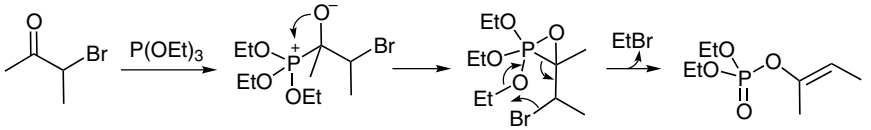
in eclipsed or gauched form of the α-halo ketones. α-Bromoketone gives more *trans*-vinyl phosphate isomer than does chloroketone.[2h] The reaction rate of triisopropyl phosphite is slower than that of triethyl phosphite in the Perkow reaction.[2h] However, this reaction is often complicated by the *Michaelis-Arbuzov Rearrangement*, by which phosphonate is formed instead of phosphate.[2k] It is known that the course of the reaction depends on the nature and position of halogen on the carbonyl compounds as well as the reaction temperature.[2k] In general, more Perkow products are produced from α-iodo ketones, even at low temperature, whereas more Michaelis-Arbuzov products are generated from α-chloroketone at high temperature.[2k] In addition, α-halo ketones with a halogen atom at the primary carbon prefer Michaelis-Arbuzov products, whereas ketones with a halogen atom at the secondary carbon yields more Perkow products. Moreover, the ketones containing more than one α-halogen atom, give exclusively or almost exclusively Perkow products.[2k]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

For this reaction, a variety of mechanisms have been proposed, in favor of the initial attack of the phosphorus atom on the α-halogen,[2f,10] the carbonyl oxygen,[11] the α-carbon bound to the halogen,[9,12] or the carbonyl carbon.[2b,2c,2h,8b,13] However, more and more experimental evidence supports the initial attack of phosphite on the carbonyl group as the rate-limiting step,[2h] followed by the rearrangement of the phosphorus moiety to oxygen to form the enol phosphonium halide.[2f,2h] Evidence in favor of halogen attack includes the formation of only *cis*-vinyl phosphates from α,α-dibromoketones and α-bromo-α-phenyl ketones.[2f] A representative mechanism is outlined here between 2-bromo-2-butanone and triethylphosphite.



D. MODIFICATION

N/A

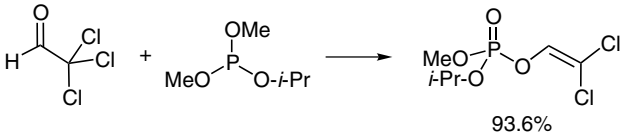
E. APPLICATIONS

This reaction is one of the major reactions for the preparation of vinyl phosphates.

F. RELATED REACTIONS

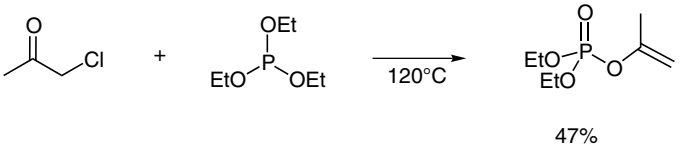
This reaction is related to the *Michaelis-Arbuzov Rearrangement.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 14.

To a solution of 76 g freshly distilled chloral (0.517 mol) in 75 mL CH_2Cl_2, was added dropwise 87 g dimethyl isopropyl phosphite (0.573 mol) within 1.5 h to maintain the moderate reflux. After the addition was completed, the refluxing was extended for an additional 30 min, then both solvent and excess phosphite were removed through rotary evaporation at 60°C (25 mmHg) to give 129 g of a colorless liquid. GLPC analysis showed that this liquid contained 93% 2,2-dichlorovinyl isopropyl methyl phosphate, in a yield of 93.6%. The liquid was distilled, and 109 g product was collected at 79°C (0.04 mmHg) as four fractions, which contained 10%, 6%, 4%, and 4% of dimethyl isopropyl phosphite, respectively, according to GPLC analysis. Then fraction 4 (containing only 4% of phosphite) was further chromatographed on a deactivated silica gel, eluting with 2% ether in CH_2Cl_2 to afford 5.76 g pure phosphate.



Reference 2e.

To 0.20 mol triethyl phosphite heated to 120°C was added 0.20 mol chloroacetone in small portions. After completion of the addition, the mixture was stirred at 120°C for 1 h, then the temperature was raised to 170°C for an additional hour, whereupon 47% of diethyl 2-propenyl phosphate was distilled, b.p. 64°C at 0.9 mmHg.

Other references related to the Perkow reaction are cited in the literature.[15]

H. REFERENCES

1. Perkow, W.; Ullerich, K. and Meyer, F., *Naturwissenschaften,* **1952**, *39*, 353 [*Chem. Abstr.,* **1953**, *47*, 8248].
2. (a) Alexandratos, S. D. and Hussain, L. A., *Macromolecules,* **1998**, *31*, 3235. (b) Sekine, M.; Okimoto, K.; Yamada, K. and Hata, T., *J. Org. Chem.,* **1981**, *46*, 2097. (c) Sekine, M.; Nakajima, M. and Hata, T., *J. Org. Chem.,* **1981**, *46*, 4030. (d) Pilgram, K. and Hass, D. K., *J. Med. Chem.,* **1975**, *18*, 1204. (e) Jung, A. and Engel, R., *J. Org. Chem.,* **1975**, *40*, 3652. (f) Borowitz, I. J.; Yee,

K. C. and Crouch, R. K., *J. Org. Chem.,* **1973**, *38*, 1713. (g) Frampton, R. D.; Tidwell, T. T. and Young, V. A., *J. Am. Chem. Soc.,* **1972**, *94*, 1271. (h) Borowitz, I. J.; Firstenberg, S.; Borowitz, G. B. and Schuessler, D., *J. Am. Chem. Soc.,* **1972**, *94*, 1623. (i) Borowitz, I. J.; Firstenberg, S.; Casper, E. W. R. and Crouch, R. K., *J. Org. Chem.,* **1971**, *36*, 3282. (j) Newallis, P. E.; Lombardo, P.; Gilbert, E. E.; Spencer, E. Y. and Morello, A., *J. Agri. Food Chem.,* **1967**, *15*, 940. (k) Thompson, J. E., *J. Org. Chem.,* **1965**, *30*, 4276. (l) Lichtenthaler, F. W., *Chem. Rev.,* **1961**, *61*, 607.

3. (a) Moriguchi, T.; Okada, K.; Seio, K. and Sekine, M., *Lett. Org. Chem.,* **2004**, *1*, 246. (b) Mironov, V. F.; Burnaeva, L. A.; Bobrov, M. E.; Pashkevich, K. I.; Konovalova, I. V. and Aminova, R. M., *Zh. Obsh. Khim.,* **1994**, *64*, 1362. (c) Mironov, V. F.; Burnaeva, L. M.; Khunutdinova, D. Kh. and Konovalova, I. V., *Zh. Obsh. Khim.,* **1993**, *63*, 2233. (d) Kostka, K. and Modranka, R., *Phosphorus, Sulfur & Silicon & Related Elements*, **1992**, *70*, 29. (e) Mironov, V. F.; Mavleev, R. A.; Konovalova, I. V. and Pudovik, A. N., *Zh. Obsh. Khim.,* **1991**, *61*, 1259. (f) Thiem, J. and Rasch, E., *Nucleosides & Nucleotides*, **1985**, *4*, 487. (g) Koziara, A.; Mlotkowska, B.; Majewski, P.; Sledzinski, B. and Zwierzak, A., *Pol. J. Chem.,* **1981**, *55*, 399. (h) Gazizov, T. Kh.; Sudarev, Yu. I.; Kibardin, A. M.; Belyalov, R. U. and Pudovik, A. N., *Zh. Obsh. Khim.,* **1981**, *51*, 8. (i) Gololobov, Yu. G. and Danchenko, M. N., *Zh. Obsh. Khim.,* **1980**, *50*, 1226. (j) Winkler, T. and Bencze, W. L., *Helv. Chim. Acta,* **1980**, *63*, 402. (k) Galdecki, Z.; Glowka, M. L. and Zwierzak, A., *Phosphorus & Sulfur & Related Elements*, **1979**, *5*, 299. (l) Petnehazy, I.; Szakal, G.; Rusz, K. and Toke, L., *Acta Chim. Acad. Sci. Hungaricae,* **1979**, *98*, 447. (m) Gololobov, Yu. G. and Danchenko, M. N., *Zh. Obsh. Khim.,* **1979**, *49*, 231. (n) Sledzinski, B.; Cieslak, L. and Wasiak-Wisniewska, D., *Organika,* **1977**, 19. (o) Sledzinski, B., *Organika*, **1977**, 11. (p) Mikhailik, S. K.; Dudchenko, T. N. and Gololobov, Yu. G., *Zh. Obsh. Khim.,* **1976**, *46*, 2154. (q) Thiem, J.; Rasch, D. and Paulsen, H., *Chem. Ber.,* **1976**, *109*, 3588. (r) Denney, D. B. and Wagner, F. A., *Phosphorus & Related Group V Elements*, **1973**, *3*, 27. (s) Gaydou, E. M.; Buono, G. and Freze, R., *Bull. Soc. Chim. Fr.,* **1973**, 2284. (t) Honig, M. L. and Sheer, M. L., *J. Org. Chem.,* **1973**, *38*, 3434. (u) Borowitz, I. J. and Crouch, R. K., *Phosphorus & Related Group V Elements*, **1973**, *2*, 209. (v) Konecny, J.; Dousse, R. and Rosales, J., *Helv. Chim. Acta,* **1972**, *55*, 3048. (w) Gaydou, E. M., *Tetrahedron Lett*., **1972**, 4473. (x) Napier, R. P.; Kemp, R. T. and Melton, T. M., *Phosphorus & Related Group V Elements*, **1972**, *2*, 141. (y) Gaydou, E.; Peiffer, G. and Guillemonat, A., *Tetrahedron Lett*., **1971**, 239. (z) Fleming, I. and Owen, C. R., *J. Chem. Soc. D,* **1970**, 1402. (aa) Ayres, J. S. and Osborne, G. O., *Chem. Commun.,* **1968**, 195.
4. (a) De Selms, R. C. and Lin, T.-W. *J. Org. Chem.,* **1967**, *32*, 2023. (b) Barthel, W. F.; Alexander, B. H.; Giang, P. A. and Hall, S. A., *J. Am. Chem. Soc.,* **1955**, *77*, 2424.
5. (a) Abramov, V. S. and Druzhina, Z. S., *Zh. Obsh. Khim.,* **1967**, *37*, 718. (b) Wadsworth, W. S. and Emmons, W. D., *J. Am. Chem. Soc.,* **1962**, *84*, 610. (c) Speziale, A. J. and Freeman, R. C., *J. Am. Chem. Soc.,* **1960**, *82*, 903. (d) Speziale, A. J. and Freeman, R. C., *J. Org. Chem.,* **1958**, *23*, 1883.
6. (a) Pudovik, A. N. and Biktomirova, L. G., *Zh. Obsh. Khim.,* **1957**, *27*, 2104 [*Chem. Abstr.,* **1958**, *52*, 6156]. (b) Pudovik, A. N. and Biktomirova, L. G., *Zh. Obsh. Khim.,* **1957**, *27*, 1708 [*Chem. Abstr.,* **1958**, *52*, 3714]. (c) Pudovik, A. N., *Zh. Obsh. Khim.,* **1955**, *25*, 2173 [*Chem. Abstr.,* **1956**, *50*, 8486].
7. Toke, L.; Petnehazy, I.; Szakal, G.; Hudson, H. R.; Powroznyk, L. and Cooksey, C. J., *ACS Symposium Ser.*, **1981**, *171*, 513.
8. (a) Allen, J. F.; Reed, S. K.; Johnson, O. H. and Brunsvold, N. J., *J. Am. Chem. Soc.,* **1956**, *78*, 3715. (b) Allen, J. F. and Johnson, O. H., *J. Am. Chem. Soc.,* **1955**, *77*, 2871.
9. Perkow, W., *Ber.,* **1954**, *87*, 755.
10. (a) Miller, B., *J. Org. Chem.,* **1963**, *28*, 345. (b) Borowitz, I. J. and Virkhaus, R., *J. Am. Chem. Soc.,* **1963**, *85*, 2183. (c) Hoffmann, H. and Diehr, H. J., *Tetrahedron Lett.,* **1962**, 583. (d) Miller, B., *J. Org. Chem.,* **1961**, *26*, 4781.

11. Trippett, S., *J. Chem. Soc.,* **1962**, 2337.
12. (a) Cramer, F., *Angew. Chem.,* **1960**, *72*, 236. (b) Spencer, E. Y.; Todd, A. R. and Webb, R. F., *J. Chem. Soc.,* **1958**, 2968. (c) Perkow, W.; Krochow, E. W. and Knoevenagel, K., *Chem. Ber.,* **1955**, *88*, 662.
13. (a) Chopard, P. A.; Clark, V. M.; Hudoson, R. F. and Kirby, A. J., *Tetrahedron,* **1965**, *21*, 1961. (b) Kharasch, M. S. and Bengelsdorf, I. S., *J. Org. Chem.,* **1955**, *20*, 1356.
14. Morales, J. G.; Whetstone, R. R.; Stoutamire, D. W. and Hass, D. K., *J. Med. Chem.,* **1972**, *15*, 1225.
15. (a) Onys'ko, P. P.; Kim, T. V.; Kiseleva, E. I. and Sinitsa, A. D., *Russ. J. Gen. Chem.,* **2001**, *71*, 143. (b) Sundaram, A. K. and Woodard, R. W., *J. Org. Chem.,* **2000**, *65*, 5891. (c) Attia, S. Y.; Berry, J. P.; Koshy, K. M.; Leung, Y.-K.; Lyznicki, E. P.; Nowlan, V. J.; Oyama, K. and Tidwell, T. T., *J. Am. Chem. Soc.,* **1977**, *99*, 3401. (d) Marecek, J. F. and Griffith, D. L., *J. Am. Chem. Soc.,* **1970**, *92*, 917. (e) Arbuzow, B. A., *Pure & Appl. Chem.,* **1964**, *9*, 306. (f) Mattson, A. M.; Fay, R. W.; Gaines, T. B. and Pearce, G. W., *J. Agri. Food Chem.,* **1960**, *8*, 196. (g) Levene, P. A., *Org. Synth. Coll.,* **1943**, *2*, 88.

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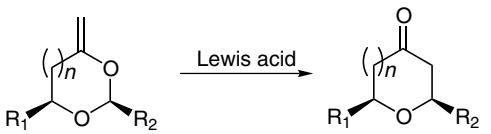
Petasis-Ferrier Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Petasis in 1995.[1] It is a Lewis acid promoted or induced conversion of enol acetals (e.g., 4-alkylidenyl-1,3-dioxanes[2]) into tetrahydropyranones.[3] Because this reaction is very similar to the *Ferrier Rearrangement*, it is normally called the Petasis-Ferrier rearrangement.[2–4] The Lewis acids that can promote this rearrangement include $BF_3{\cdot}Et_2O$, $ZnCl_2$, $TiCl_2(O\text{-}i\text{-}Pr)_2$, $MeAlCl_2$, and Me_2AlCl.[4h] It has been proposed that this reaction occurs via fragmentation, followed by *endo*-cyclization onto an oxocarbenium.[5] This reaction can tolerate a variety of functional groups, including silyl ether,[4h] and can directly produce *cis*-2,6-disubstituted tetrahydropyranone when Me_2AlCl is used as the Lewis acid, without the *Meerwein-Ponndorf-Verley Reduction* per Petasi's original procedure.[2,4h] This reaction has also been extended to the preparation of compounds containing medium-size rings.[4d]

B. GENERAL REACTION SCHEME



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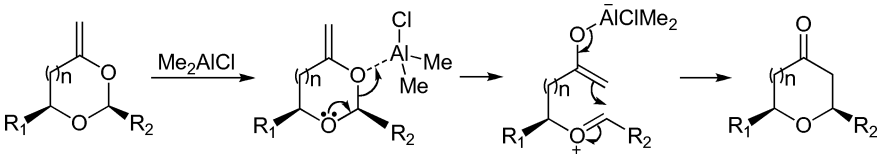
C. PROPOSED MECHANISMS

A modified version of the mechanism described by O'Neil et al.[4d] is illustrated here.



D. MODIFICATION

The original procedure has been modified to use Me_2AlCl as the promoter,[2,4h] and the alkylidenyl in 1,3-dioxane has been extended to a *spiro*-cyclopropanyl group.[4d]

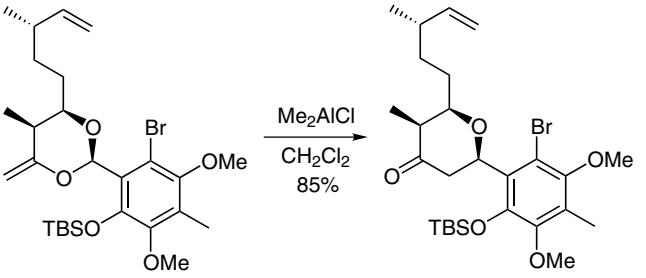
E. APPLICATIONS

This reaction is generally useful for the preparation of tetrahydropyrans, tetrahydropyranones, and medium cyclic compounds.

F. RELATED REACTIONS

This reaction is related to the *Ferrier-II Rearrangement*.

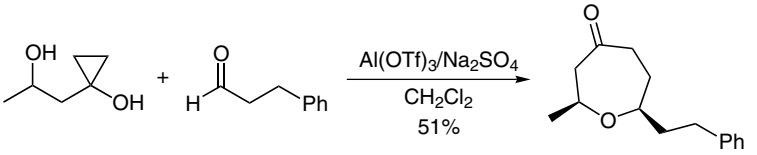
G. CITED EXPERIMENTAL EXAMPLES



Reference 4c.

To a solution of 1.6 g enol-acetal (2.9 mmol) in 36 mL dichloromethane was added 3.6 mL 1 M Me_2AlCl (3.6 mmol) in dichloromethane at $-78^{\circ}C$. The reaction mixture was stirred for 10 min then quenched at $-78^{\circ}C$ with 1.5 mL Et_3N, followed by 20 mL saturated aqueous $NaHCO_3$. The reaction mixture was then diluted with 100 mL dichloromethane, allowed to warm to 0–5°C, and acidified with 1 N HCl to pH 2. The aqueous phase was

extracted with dichloromethane (3 × 100 mL), and the combined organic extracts were dried over Na_2SO_4, and then concentrated in vacuo. Flash chromatography purification with 5% EtOAc in hexanes as the eluent afforded 1.4 g pyranone as a colorless oil, in a yield of 85%.



Reference 4d.

To a −10°C suspension of 1.5 mL CH_2Cl_2 and 430 mg Na_2SO_4 (3.02 mmol) was added 102 μL 3-phenylpropionaldehyde (0.772 mmol) under argon, followed by 73 mg $Al(OTf)_3$ (0.154 mmol). In a separate flask, a solution of 89.7 mg diol (0.772 mmol) in CH_2Cl_2 (1 mL) was prepared and added to the reaction flask via cannula. The resultant solution was stirred for 2 h, then a solution of 772 μL 1.0 M $TiCl_4$ in CH_2Cl_2 (0.772 mmol) was added. The resultant solution was stirred for 0.5 h. The reaction was then diluted with 10 mL CH_2Cl_2 and quenched with 10 mL saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, vacuum filtered, and concentrated in vacuo. Flash chromatography (EtOAc/hexanes,15:85) provided 91.8 mg keto-oxepane as a pale yellow oil, in a yield of 51%.

Other references related to the Petasis-Ferrier rearrangement are cited in the literature.[6]

H. REFERENCES

1. Petasis, N. A. and Lu, S.-P., *J. Am. Chem. Soc*., **1995**, *117*, 6394.
2. Smith, A. B.; Minbiole, K. P.; Verhoest, P. R. and Beauchamp, T. J., *Org. Lett.,* **1999**, *1*, 913.
3. Smith, A. B.; Minbiole, K. P.; Verhoest, P. R. and Schelhaas, M., *J. Am. Chem. Soc.*, **2001**, *123*, 10942.
4. (a) Smith, A. B. and Simov, V., *Org. Lett.*, **2006**, *8*, 3315. (b) Smith, A. B.; Mesaros, E. F. and Meyer, E. A., *J. Am. Chem. Soc.*, **2006**, *128*, 5292. (c) Smith, A. B.; Mesaros, E. F. and Meyer, E. A., *J. Am. Chem. Soc.*, **2005**, *127*, 6948. (d) O'Neil, K. E.; Kingree, S. V. and Minbiole, K. P. C., *Org. Lett.*, **2005**, *7*, 515. (e) Smith, A. B.; Sfouggatakis, C.; Gotchev, D. B.; Shirakami, S.; Bauer, D.; Zhu, W. Y. and Doughty, V. A., *Org. Lett.*, **2004**, *6*, 3637. (f) Smith, A. B.; Safonov, I. G. and Corbett, R. M., *J. Am. Chem. Soc.*, **2002**, *124*, 11102. (g) Smith, A. B.; Minbiole, K. P.; Verhoest, P. R. and Schelhaas, M., *J. Am. Chem. Soc.*, **2001**, *123*, 10942. (h) Smith, A. B.; Berhoest, P. R.; Minbiole, K. P. and Lim, J. J., *Org. Lett.*, **1999**, *1*, 909.
5. Petasis, N. A. and Lu, S.-P., *Tetrahedron Lett*., **1996**, *37*, 141.
6. Ferrier, R. J. and Middleton, S., *Chem. Rev.*, **1993**, *93*, 2779.

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Peterson Olefination

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Peterson in 1968.[1] It is a two-step synthesis of olefin involving the addition of an α-silyl carbanion to a carbonyl compound to form β-silyl alcohol (or β-hydroxy silane) and the elimination of silol. Therefore, this reaction is generally known as the Peterson olefination.[2,3] In addition, this reaction is also referred to as the Peterson reaction[2k,4] and Peterson elimination.[2f,5] Occasionally, the Peterson olefination is also called the Peterson alkenation[6] or Peterson alkenylation.[7]

As a complementary olefination method of *Wittig Reaction*, the Peterson olefination has the following advantages: a higher reactivity of α-silyl carbanions than the corresponding phosphorus reagents toward both ketones and aldehydes,[2k,8] a better *Z*-selectivity than the corresponding stabilized phosphorous components,[8] and a simpler workup and purification procedure without phosphorus side products.[2k] However, the low availability of certain α-silyl carbanions has limited its general use in organic synthesis,[2d,4h] especially for methylene derivatives,[4h] which may be obtained via the application of trimethylsilylmethyl magnesium chloride[2j] or [bis(trimethylsilyl)methyl]-lithium.[2x] Generally, the β-silyl alcohol generated from an α-silyl carbanion with an electron-withdrawing group undergoes elimination instantaneously to give the olefin as an *E*/*Z* mixture but in favor of *E* olefin,[2x] whereas the β-silyl alcohol arising from α-silyl carbanion with an electron-donating group could be isolated and converted into the corresponding olefin with controllable stereochemistry.[2x] Treatment of the isolated β-silyl alcohol with acid results in an *anti*-elimination, whereas the treatment of the same substrate with base leads to a *syn*-elimination.[5b,9] In this reaction, the α-silyl carbanions can be generated from direct lithiation of silane with a strong lithium base,[10] from lithium halogen exchange,[11] or from the addition of a carbanion to vinylsilane,[12] etc. On the other hand, besides the addition of α-silyl

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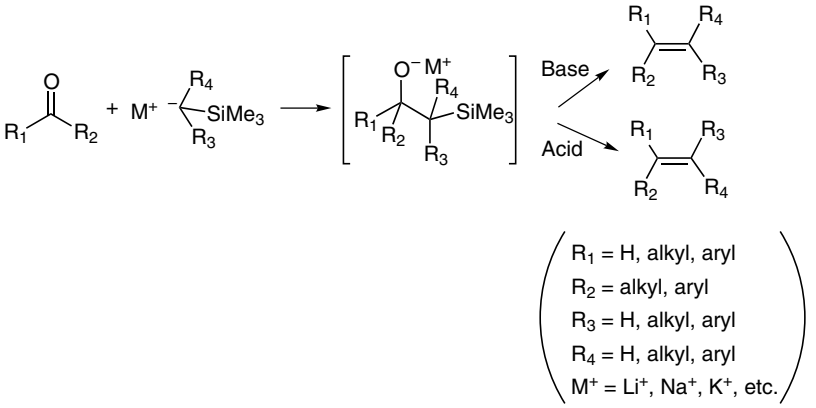
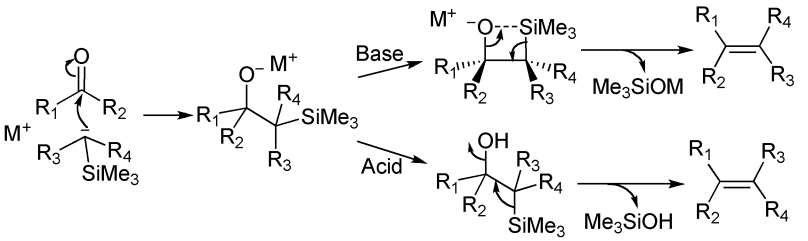
carbanion to carbonyl compounds, other methods are suitable for the generation of α-silyl alcohols, such as the addition of carbanion to α-silyl ketone[9b] or α-silyl epoxide.[9a] Acids such as H_2SO_4,[13] CF_3COOH,[2d] HF·Pyr,[2j] and $SOCl_2$[2m] are effective reagents for the elimination step. In addition, it has been found that fluoride (e.g., CsF)[2s,4u,7] and zinc bromide can be used as catalysts for this reaction.[2s]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A general mechanism is outlined below for the Peterson olefination.



D. MODIFICATION

This reaction has been modified by the use of an α-silyl selenoacetamide to generate *E*-olefins in preference[2g] and the use of an α-silyl thioether[2i] and *N*-cyclohexyl-(2-triethylsilylpropylidene)imine[2d] as α-silyl carbanion precursors. In addition, a germanium-Peterson reaction[4l] and a tin-Peterson reaction[4n] have been developed. Furthermore, an asymmetric version of the Peterson olefination has been developed by the use of an external chiral tridentate amino diether as a chiral ligand.[2k]

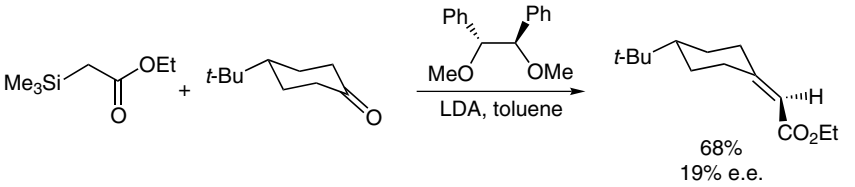
E. APPLICATIONS

This reaction has general application in the preparation of olefins.

F. RELATED REACTIONS

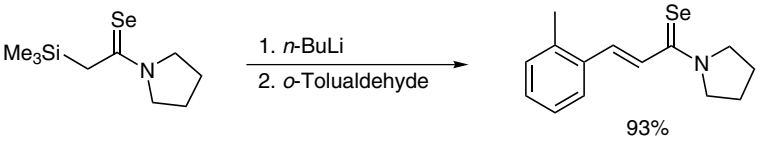
This reaction is related to the *Wittig Reaction* and *Tebbe Olefination*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2k.

A solution of 1.5 mmol ethyl trimethylsilanylacetate and 2.0 mmol chiral pinacol methyl ether in 6.0 mL toluene was added to a solution of LDA (1.6 mmol) in 5.0 mL toluene at −78°C. The mixture was stirred at −20°C for 1 h and cooled to −78°C again. Then a solution of 1.0 mmol 4-*tert*-butyl-cyclohexanone in 4 mL toluene was added dropwise over a period of 3 min, and the resulting mixture was stirred at room temperature for 5 h. Upon removal of the solvent, the residue was purified by silica gel column chromatography to afford 68% of (*S*)-(+)-ethyl (4-*tert*-butylcyclohexylidene)acetate as a colorless oil, with 19% e.e.



Reference 2g.

To 2.5 mL THF solution containing 0.26 g α-trimethylsilyl selenoacetamide (1.05 mmol) was added 0.625 mL 1.6 M *n*-BuLi (1.0 mmol) at 0°C; the mixture was stirred for 15 min. Then 0.12 mL *o*-tolualdehyde (1.0 mmol) was added; the reaction mixture instantly changed to reddish orange. After being stirred at room temperature for an additional hour, the reaction mixture was poured onto water and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography using hexane/dichloromethane as an eluent to give 0.258 g (*E*)-1-(3-(2-methylphenyl)-1-selenoxo-2-propenyl)pyrrolidine as a reddish orange solid, in a yield of 93%, m.p. 137–140°C.

Other references related to the Peterson olefination are cited in the literature.[14]

H. REFERENCES

1. Peterson, D. J., *J. Org. Chem.,* **1968**, *33*, 780.
2. (a) Halton, B. and Cooney, M. J., *Aust. J. Chem.,* **2006**, *59*, 118. (b) Kozytska, M. V. and Dudley, G. B., *Chem. Commun.,* **2005**, 3047. (c) Felpin, F.-X. and Lebreton, J., *Curr. Org. Synth.,* **2004**, *1*, 83. (d) Zeng, X. Z.; Zeng, F. X. and Negishi, E.-i., *Org. Lett.,* **2004**, *6*, 3245. (e) Iabal, M.; Li, Y. F. and Evans, P., *Tetrahedron,* **2004**, *60*, 2531. (f) Michel, S. J.; Sedelmeier, G. H.; Niedere, D.; Schuerch, F.; Seger, M.; Schreiner, K.; Daeffler, R.; Osmani, A.; Bixel, D.; Loiseleur, O.; Cercus, J.; Stettler, H.; Schaer, K. and Gamboni, R., *Org. Proc. Res. Dev.,* **2004**, *8*, 113. (g) Murai, T.; Fujishima, A.; Iwamoto, C. and Kato, S., *J. Org. Chem.,* **2003**, *68*, 7979. (h) Van Staden, L. F.; Gravestock, D. and Ager, D. J., *Chem. Soc. Rev.,* **2002**, *31*, 195. (i) Perales, J. B.; Makino, N. F. and Vranken, D. L. V., *J. Org. Chem.,* **2002**, *67*, 6711. (j) Ling, T. T.; Rivas, F. and Theodorakis, E. A., *Tetrahedron Lett.,* **2002**, *43*, 9019. (k) Iguchi, M. and Tomioka, K., *Org. Lett.,* **2002**, *4*, 4329. (l) Khripach, V. A.; Zhabinskii, V. N.; Konstantinova, O. V.; Khripach, N. B.; Antonchick, A. P. and Schneider, B., *Steroids,* **2002**, *67*, 597. (m) Faust, R., *Eur. J. Org. Chem.,* **2001**, 2797. (n) Clayden, J.; Johnson, P. and Pink, J. H., *J. Chem. Soc*., *Perkin Trans. I*, **2001**, 371. (o) Faust, R. and Mitzel, F., *J. Chem. Soc*., *Perkin Trans. I*, **2000**, 3746. (p) Hayes, B. L.; Adams, T. A.; Pickin, K. A.; Day, C. S. and Welker, M. E., *Organometallics,* **2000**, *19*, 2730. (q) Fürstner, A. and Krause, H., *J. Org. Chem.,* **1999**, *64*, 8281. (r) Wang, K. K.; Liu, B. and Petersen, J. L., *J. Am. Chem. Soc.,* **1996**, *118*, 6860. (s) Bellassoued, M. and Ozanne, N., *J. Org. Chem.,* **1995**, *60*, 6582. (t) Grigorieva, N. Y.; Pinsker, O. A. and Moiseenkov, A. M., *Mendeleev Commun.,* **1994**, 129. (u) Feringa, B. L.; Jager, W. F. and de Lange, B., *Tetrahedron Lett.,* **1992**, *33*, 2887. (v) Barrett, A. G. M. and Flygare, J. A., *J. Org. Chem.,* **1991**, *56*, 638. (w) Snieckus, V., *Pure & Appl. Chem.,* **1990**, *62*, 671. (x) Hudrlik, P. F.; Agwaramgbo, E. L. O. and Hudrlik, A. M., *J. Org. Chem.,* **1989**, *54*, 5613. (y) Scheide, G. M. and Neilson, R. H., *Organometallics,* **1989**, *8*, 1987. (z) Brouwer, A. C.; Hummelen, J. C.; Luider, T. M.; van Bolhuis, F. and Wynberg, H., *Tetrahedron Lett.,* **1988**, *29*, 3137. (aa) Cohen, T.; Sherbine, J. P.; Matz, J. R.; Hutchins, R. R.; McHenry, B. M. and Willey, P. R., *J. Am. Chem. Soc.,* **1984**, *106*, 3245. (bb) Schubert, H. H. and Stang, P. J., *J. Org. Chem.,* **1984**, *49*, 5087. (cc) Carey, F. A. and Frank, W. C., *J. Org. Chem.,* **1982**, *47*, 3548.
3. (a) Fernandez, M. C.; Diaz, A.; Guillin, J. J.; Blanco, O.; Ruiz, M. and Ojea, V., *J. Org. Chem.,* **2006**, *71*, 6958. (b) Pulido, F. J. and Barbero, A., *Nat. Protocols,* **2006**, 2068. (c) Suzuki, H.; Ohta, S. and Kuroda, C., *Synth. Commun.,* **2004**, *34*, 1383. (d) Izod, K.; McFarlane, W. and Tyson, B. V., *Eur. J. Org. Chem.,* **2004**, 1043. (e) Halton, B.; Boese, R. and Dixon, G. M., *Eur. J. Org. Chem.,* **2003**, 4507. (f) Asakura, N.; Usuki, Y. and Iio, H., *J. Fluor. Chem.,* **2003**, *124*, 81. (g) Hazelard, D.; Ollivier, J.; Paugam, R. and Salauen, J., *Synlett*, **2003**, 1155. (h) Adam, W. and Ortega-Schulte, C. M., *Synlett*, **2003**, 414. (i) Barbero, A.; Blanco, Y.; Garcia, C. and Pulido, F. J., *Synthesis,* **2000**, 1223. (j) Welch, J. T.; Gregor, T. and Kornilov, A., *Isr. J. Chem.,* **1999**, *39*, 171. (k) Fassler, J.; Linden, A. and Bienz, S., *Tetrahedron*, **1999**, *55*, 1717. (l) Lin, J. and Welch, J. T., *Tetrahedron Lett*., **1998**, *39*, 9613. (m) van Staden, L. F.; Bartels-Rahm, B.; Field, J. S. and Emslie, N. D., *Tetrahedron,* **1998**, *54*, 3255. (n) Harmata, M. and Jones, D. E., *Tetrahedron Lett*., **1997**, *38*, 3861. (o) van Staden, L. F.; Bartels-Rahm, B. and Emsile, N. D., *Tetrahedron Lett*., **1997**, *38*, 1851. (p) Bratovanov, S. and Bienz, S., *Main Group Metal Chem.,* **1996**, *19*, 769. (q) Guertler, S.; Ruf, S.; Johner, M. and Otto, H. H., *Pharmazie*, **1996**, *51*, 811. (r) Waschbusch, R.; Carran, J. and Savignac, P., *Tetrahedron*, **1996**, *52*, 14199. (s) Grigorieva, N. Ya.; Pinsker, O. A.; Buevich, A. V. and Moiseenkov, A. M., *Izv. Akad. Nauk, Ser. Khim.,* **1995**, 509. (t) Roche, D.; Madesclaire, M.; Chavignon, O. and Teulade, J. C., *Sulfur Lett*., **1993**, *16*, 221. (u) Okamoto, S.; Tani, K.; Sato, F.; Sharpless, K. B. and Zargarian, D., *Tetrahedron Lett*., **1993**, *34*, 2509. (v) Roche, D.; Chavignon, O.; Teulade, J. C. and Madesclaire, M., *Sulfur Lett*., **1992**, *15*, 127. (w) Couture, A.; Cornet, H. and Grandclaudon, P., *J. Organomet. Chem.,* **1992**, *440*, 7. (x) Kishi, N.; Maeda, T.; Mikami, K. and Nakai, T., *Tetrahedron*, **1992**, *48*, 4087. (y) Katritzky, A. R.; Lue, P. and Malhotra, N., *Gazz.*

Chim. Ital., **1991**, *121*, 471. (z) Mladenova, M. and Gaudemar-Bardone, F., *Phosphorus, Sulfur & Silicon & Related Elements*, **1991**, *62*, 257. (aa) Halton, B.; Lu, Q. and Stang, P. J., *Aust. J. Chem.,* **1990**, *43*, 1277. (bb) Palomo, C.; Aizpurua, J. M.; Garcia, J. M.; Picard, J. P. and Dunogues, J., *Tetrahedron Lett*., **1990**, *31*, 1921. (cc) Tanaka, J.; Kanemasa, S.; Ninomiya, Y. and Tsuge, O., *Bull. Chem. Soc. Jpn.,* **1990**, *63*, 466. (dd) Ager, D. J., *Org. React.,* **1990**, *38*, 1. (ee) Cuevas, J. C.; Patil, P. and Snieckus, V., *Tetrahedron Lett*., **1989**, *30*, 5841. (ff) Kanemasa, S.; Kobayashi, H.; Tanaka, J. and Tsuge, O., *Bull. Chem. Soc. Jpn.,* **1988**, *61*, 3957. (gg) Bartoli, G.; Bosco, M.; Dalpozzo, R. and Todesco, P. E., *J. Chem. Soc., Chem. Commun.,* **1988**, 807. (hh) Mikami, K.; Maeda, T. and Nakai, T., *Tetrahedron Lett*., **1986**, *27*, 4189. (ii) Kanemasa, S.; Tanaka, J.; Nagahama, H. and Tsuge, O., *Bull. Chem. Soc. Jpn.,* **1985**, *58*, 3385. (jj) Craig, D.; Ley, S. V.; Simpkins, N. S.; Whitham, G. H. and Prior, M. J., *J. Chem. Soc., Perkin Trans. I,* **1985**, 1949. (kk) Crimmin, M. J.; O'Hanlon, P. J. and Rogers, N. H., *J. Chem. Soc., Perkin Trans. I,* **1985**, 541. (ll) Tsuge, O.; Kanemasa, S. and Ninomiya, Y., *Chem. Lett.,* **1984**, 1993. (mm) Yamamoto, K.; Kimura, T. and Tomo, Y., *Tetrahedron Lett*., **1984**, *25*, 2155. (nn) Ley, S. V. and Simpkins, N. S., *J. Chem. Soc., Chem. Commun.,* **1983**, 1281. (oo) Sato, F.; Tanaka, Y. and Kanbara, H., *J. Chem. Soc., Chem. Commun.,* **1983**, 1024. (pp) Rutschmann, S. B., *Schweiz. Labor.-Zeitsch.,* **1983**, *40*, 270. (qq) Yamamoto, K. and Tomo, Y., *Tetrahedron Lett*., **1983**, *24*, 1997. (rr) Schank, K. and Schroeder, F., *J. Liebigs Ann. Chem.,* **1977**, 1676. (ss) Trindle, C.; Hwang, J.-T. and Carey, F. A., *J. Org. Chem.,* **1973**, *38*, 2664.

4. (a) Kojima, S.; Fukuzaki, T.; Yamakawa, A. and Murai, Y., *Org. Lett*., **2004**, *6*, 3917. (b) Ager, D. J., *Sci. Synth.,* **2002**, *4*, 789. (c) Fuerstner, A.; Brehm, C. and Cancho-Grande, Y., *Org. Lett.,* **2001**, *3*, 3955. (d) Kojima, S.; Inai, H.; Hidaka, T. and Ohkata, K., *Chem. Commun.,* **2000**, 1795. (e) Tonder, J. E.; Begtrup, M.; Hansen, J. B. and Olesen, P. H., *Tetrahedron,* **2000**, *56*, 1139. (f) Naganuma, K.; Kawashima, T. and Okazaki, R., *Chem. Lett.,* **1999**, 1139. (g) Mlynarski, J. and Banaszek, A., *Tetrahedron,* **1999**, *55*, 2785. (h) Katritzky, A. R.; Cheng, D.; Henderson, S. A. and Li, J. Q., *J. Org. Chem.,* **1998**, *63*, 6704. (i) Bassindale, A. R.; Ellis, R. J. and Taylor, P. G., *J. Chem. Res. (S),* **1996**, 34. (j) Li, Z. H. and Zhu, C. F., *Huaxue Shiji,* **1995**, *17*, 91. (k) Krempner, C.; Reinke, H. and Oehme, H., *Chem. Ber.,* **1995**, *128*, 143. (l) Kawashima, T.; Iwama, N.; Tokitoh, N. and Okazaki, R., *J. Org. Chem.,* **1994**, *59*, 491. (m) Vohra, R. and MacLean, D. B., *Tetrahedron Lett*., **1993**, *34*, 7673. (n) Kawashima, T.; Iwama, N. and Okazaki, R., *J. Am. Chem. Soc.,* **1993**, *115*, 2507. (o) Kawashima, T.; Iwama, N. and Okazaki, R., *J. Am. Chem. Soc.,* **1992**, *114*, 7598. (p) Bravo-Zhivotovskii, D.; Braude, V.; Stanger, A.; Kapon, M. and Apeloig, Y., *Organometallics*, **1992**, *11*, 2326. (q) Inoue, S. and Sato, Y., *J. Org. Chem.,* **1991**, *56*, 347. (r) Palomo, C.; Aizpurua, J. M.; Garcia, J. M.; Ganboa, I.; Cossio, F. P.; Lecea, B. and López, C., *J. Org. Chem.,* **1990**, *55*, 2498. (s) Fuerstner, A., *J. Organomet. Chem.,* **1987**, *336*, C33. (t) Takano, S.; Sato, N.; Otaki, S. and Ogasawara, K., *Heterocycles,* **1987**, *25*, 69. (u) Shimizu, S. and Ogata, M., *J. Org. Chem.,* **1987**, *52*, 2314. (v) Johnson, C. R. and Tait, B. D., *J. Org. Chem.,* **1987**, *52*, 281. (w) Sato, T.; Tsunekawa, H.; Kohama, H. and Fujisawa, T., *Chem. Lett.,* **1986**, 1553. (x) Ager, D. J., *J. Chem. Soc., Perkin Trans. I,* **1986**, 183. (y) Bassindale, A. R.; Ellis, R. J.; Lau, J. C. Y. and Taylor, P. G., *J. Chem. Soc., Perkin Trans. II,* **1986**, 593. (z) Ager, D. J.; Cooke, G. E.; East, M. B.; Mole, S. J.; Rampersaud, A. and Webb, V. J., *Organometallics,* **1986**, *5*, 1906. (aa) Boeckman, R. K. and Chinn, R. L., *Tetrahedron Lett*., **1985**, *26*, 5005. (bb) Takano, S.; Otaki, S. and Ogasawara, K., *Heterocycles,* **1985**, *23*, 2811. (cc) Takano, S.; Otaki, S. and Ogasawara, K., *J. Chem. Soc., Chem. Commun.,* **1985**, 485. (dd) Bassindale, A. R.; Ellis, E. J. and Taylor, P. G., *Tetrahedron Lett*., **1984**, *25*, 2705.

5. (a) Trost, B. M.; Ball, Z. T. and Kang, E.-J., *Org. Lett.,* **2005**, *7*, 4911. (b) Heo, J.-N.; Holson, E. B. and Roush, W. R., *Org. Lett.,* **2003**, *5*, 1697. (c) Fleming, I.; Morgan, I. T. and Sarkar, A. K., *J. Chem. Soc., Perkin Trans. I,* **1998**, 2749. (d) Lautens, M.; Ma, S. H.; Belter, R. K.; Chiu, P. and Leschziner, A., *J. Org. Chem.,* **1992**, *57*, 4065. (e) Fleming, I.; Morgan, I. T. and Sarkar, A. K., *J. Chem. Soc., Chem. Commun.,* **1990**, 1575. (f) Murray, C. K.; Warner, B. P.; Dragisich, V.;

Wulff, W. D. and Rogers, R. D., *Organometallics,* **1990**, *9*, 3142. (g) Prior, M. J. and Whitham, G. H., *J. Chem. Soc., Perkin Trans. I,* **1986**, 683.

6. Lasarte, J.; Palomo, C.; Picard, J. P.; Dunogues, J. and Aizpurua, J. M., *J. Chem. Soc., Chem. Commun.,* **1989**, 72.
7. Palomo, C.; Aizpurua, J. M.; Legido, M.; Picard, J. P.; Dunogues, J. and Constantieux, T., *Tetrahedron Lett*., **1992**, *33*, 3903.
8. Gillies, M. B.; Tønder, J. E.; Tanner, D. and Norrby, P.-O., *J. Org. Chem.,* **2002**, *67*, 7378.
9. (a) Hudrlik, P. F.; Hudrlik, A. M.; Misra, R. N.; Peterson, D.; Withers, G. P. and Kulkarni, A. K., *J. Org. Chem.,* **1980**, *45*, 4444. (b) Utimoto, K.; Obayashi, M. and Nozaki, H., *J. Org. Chem.,* **1976**, *41*, 2940.
10. Kaiho, T.; Masamune, S. and Toyoda, T., *J. Org. Chem.,* **1982**, *47*, 1612.
11. (a) Miller, R. B. and Al-Hassan, M. I., *J. Org. Chem.,* **1983**, *48*, 4113. (b) Chan, T. H.; Mychajlowskij, W.; Ong, B. S. and Harpp, D. N., *J. Org. Chem.,* **1978**, *43*, 1526.
12. Chan, T. H. and Chang, E., *J. Org. Chem.,* **1974**, *39*, 3264.
13. Whitmore, F. C.; Sommer, L. H.; Gold, J. and van Strien, R. E., *J. Am. Chem. Soc.,* **1947**, *69*, 1551.
14. (a) Aubele, D. L.; Wan, S. Y. and Floreancig, P. E., *Angew. Chem. Int. Ed.,* **2005**, *44*, 3485. (b) Suzuki, H.; Ohta, S. and Kuroda, C., *Synth. Commun.,* **2004**, *34*, 1383. (c) Iqbal, M. and Evans, P., *Tetrahedron Lett.,* **2003**, *44*, 5741. (d) Lebsack, A. D.; Overman, L. E. and Valentkovitch, R. J., *J. Am. Chem. Soc.,* **2001**, *123*, 4851. (e) Harrington, P. E. and Tius, M. A., *J. Am. Chem. Soc.,* **2001**, *123*, 8509. (f) Chiang, C.-C.; Chen, Y.-H.; Hsieh, Y.-T. and Luh, T.-Y., *J. Org. Chem.,* **2000**, *65*, 4694. (g) Fritzsche, G.; Gleiter, R.; Irngartiner, H. and Oeser, T., *Eur. J. Org. Chem.,* **1999**, 73. (h) Halton, B.; Cooney, M. J.; Boese, R. and Maulitz, A. H., *J. Org. Chem.,* **1998**, *63*, 1583. (i) Halton, B. and Stang, P. J., *Synlett,* **1997**, 145. (j) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Reddy, G. V.; Portonovo, P. S.; Zhang, H. M.; Fanelli, D.; Reddy, R. T.; Zhou, P. and Carroll, P. J., *J. Org. Chem.,* **1997**, *62*, 2555. (k) Orita, A.; Yoshioka, N. and Otera, J., *Chem. Lett.,* **1997**, 1023. (l) Halton, B.; Kay, A. J.; Zhi-mei, Z.; Boese, R. and Haumann, T., *J. Chem. Soc., Perkin Trans. I,* **1996**, 1445. (m) Grigorieva, N. Y.; Pinsker, O. A.; Buevich, A. V. and Moiseenkov, A. M., *Russ. Chem. Bull.,* **1995**, *44*, 492. (n) Halton, B.; Cooney, M. J.; Davey, T. W.; Forman, G. S.; Lu, Q.; Boese, R.; Bläser, D. and Maulitz, A. H., *J. Chem. Soc., Perkin Trans. I,* **1995**, 2819. (o) Bell, D.; Crowe, E. A.; Dixon, N. J.; Geen, G. R.; Mena, I. S. and Shiplon, M. R., *Tetrahedron,* **1994**, *50*, 6643. (p) Barrett, A. G. M.; Hill, J. M.; Wallace, E. M. and Glygare, J. A., *Synlett,* **1991**, 764. (q) Palomo, C.; Aizpurua, J. M. and Aurrekoetxea, N., *Tetrahedron Lett.,* **1990**, *31*, 2209. (r) Overman, L. E. and Thompson, A. S., *J. Am. Chem. Soc.,* **1988**, *110*, 2248. (s) Funk, R. L.; Novak, P. M. and Abelman, M. M., *Tetrahedron Lett.,* **1988**, *29*, 1493. (t) Ager, D. J., *Synthesis,* **1984**, 384. (u) Hudrlik, P. F. and Kulkarni, A. K., *J. Am. Chem. Soc.,* **1981**, *103*, 6251. (v) Kende, A. S. and Blacklock, T. J., *Tetrahedron Lett.,* **1980**, *21*, 3119. (w) Birkofer, L. and Stiehl, O., *Top. Curr. Chem.,* **1980**, *88*, 58. (x) Van der Ley, M.; Porskamp, P. A. T. W.; Lammerink, B. H. M. and Zwanenburg, B., *Tetrahedron Lett.,* **1978**, 811. (y) Chan, T. H., *Acc. Chem. Res.,* **1977**, *10*, 442.

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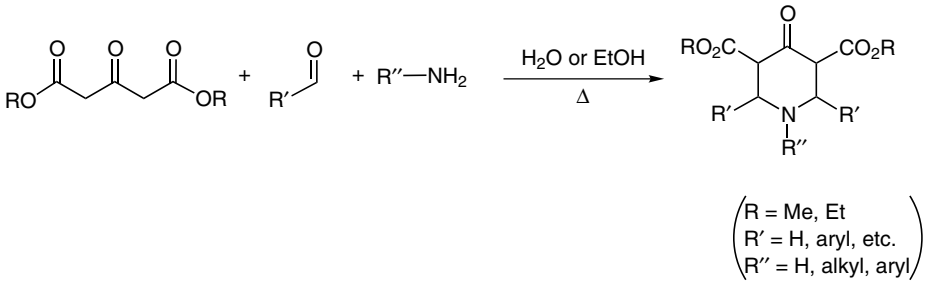
Petrenko-Kritschenko Piperidone Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Petrenko-Kritschenko in 1906.[1] It is the preparation of piperidone via a double *Mannich Reaction* from acetonedicarboxylic ester, two equivalents of aldehyde, and ammonia (or a primary amine), and is known as the Petrenko-Kritschenko piperidone synthesis.[2] In this reaction, the mixture of reaction components is usually refluxed in an aqueous or alcoholic solution, and the resulting product is difficult to purify.[3] It has been found that the addition of acid to the reaction medium is useful for this reaction.[2]

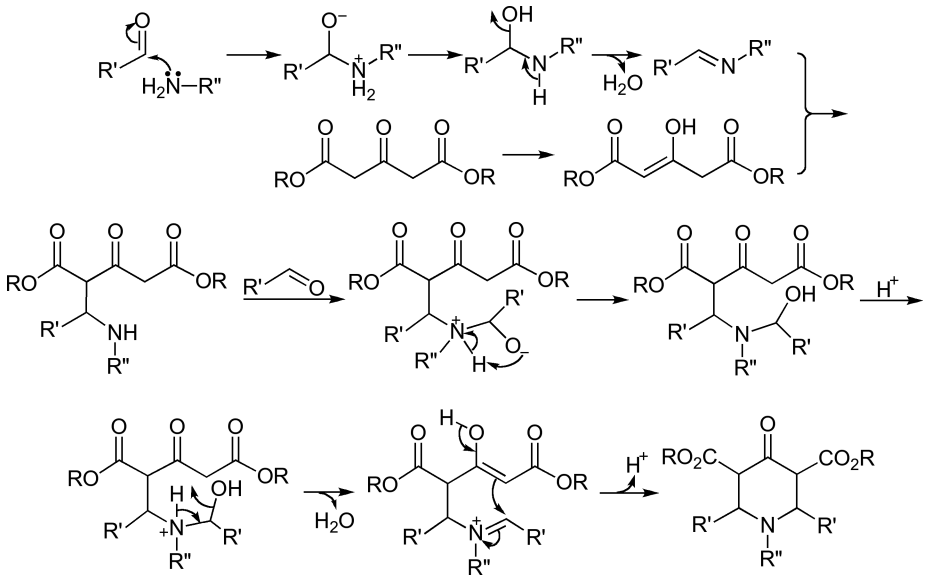
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

Displayed here is the detailed mechanism in the presence of an acid.



D. MODIFICATION

This reaction has been modified by the use of ammonia acetate in acetic acid as the reaction medium and source of ammonia.[2]

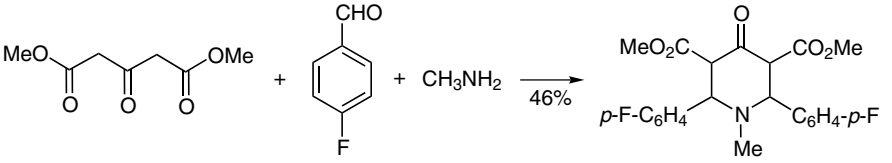
E. APPLICATIONS

This reaction is useful for the preparation of piperidone derivatives.

F. RELATED REACTIONS

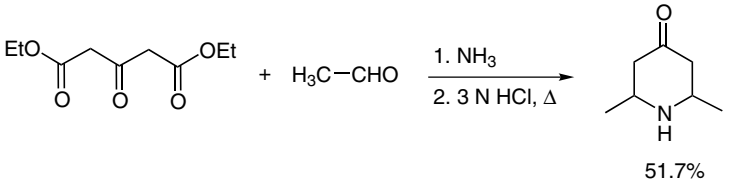
This reaction is related to the *Hantzsch Dihydropyridine Synthesis, Chichibabin Pyridine Synthesis*, and *Mannich Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4.

Exactly 0.04 mol *p*-fluorobenzaldehyde and 1.5 mL 40% aqueous solution of methylamine were dissolved in 20 mL methanol, and the mixture was cooled to 0°C. Over a course of ~1 h, 0.02 mol dimethyl oxoglutarate was added dropwise to the mixture under stirring at 0°C. The solution was allowed to stand overnight at 5°C. The resulting precipitate was filtered and washed by ether to give 3.84 g dimethyl 2,6-di-(4-fluorophenyl)-*N*-methyl-4-piperidone-3,5-dicarboxylate, in a yield of 46%, m.p. 128–130°C. When no precipitate formed, the solvent was removed in vacuo at 40–50°C, and the remaining residue was dissolved in ethanol or treated with Et_2O to obtain the crystal.



Reference 5.

Into a mixture of 101 g diethyl acetonedicarboxylate and 44 g acetaldehyde maintained at -25 ± 5°C was bubbled ammonia until tests showed that the liquid was saturated. The solution was stored at 0°C for 20 h, by which time it was a white sludge. To this mixture was added 250 mL 3 *N*HCl, and the solution was heated on a steam bath. Carbon dioxide soon began to evolve and continued to evolve even after 24 h yet very slowly. The solution was evaporated almost to dryness, and 25 mL water was added to the tan heavy precipitate and evaporated again. To the residue was added a solution of 100 g Na_2CO_3 in 480 mL H_2O and 200 mL $CHCl_3$; the layers were shaken and separated. The aqueous layer was extracted with CH_2Cl_2 (6×200 mL) until ethereal picric acid showed no yellow color. The organic layers were dried over $MgSO_4$ and distilled to give 32.9 g 2,6-dimethyl-piperidone as colorless liquid, in a yield of 51.7%, b.p. 99–105°C (25 mmHg).

Other references related to the Petrenko-Kritschenko piperidone synthesis are cited in the literature.[6]

H. REFERENCES

1. (a) Petrenko-Kritschenko, P. I. and Zoneff, N., *Ber.,* **1906**, *39*, 1358. (b) Petrenko-Kritschenko, P. and Zoneff, N., *Zh. Russkago Fiziko-Khim. Obsh.,* **1906**, *38*, 551.
2. Weiss, M., *J. Am. Chem. Soc.,* **1952**, *74*, 200.
3. Noller, C. R. and Ballah, V., *J. Am. Chem. Soc.,* **1948**, *70*, 3853.
4. Siener, T.; Cambareri, A.; Kuhl, U.; Englberger, W.; Haurand, M.; Kögel, B. and Holzgrabe, U., *J. Med. Chem.,* **2000**, *43*, 3746.
5. Hall, H. K., *J. Am. Chem. Soc.,* **1957**, *79*, 5444.
6. (a) Holzgrabe, U. and Erciyas, E., *Arch. Pharm.,* **1992**, *325*, 657. (b) Lutz, W. B.; Lazarus, S. and Meltzer, R. I., *J. Org. Chem.,* **1962**, *27*, 1695. (c) Brownlee, G.; Copp, F. C.; Duffin, W. M. and Tonkin, I. M., *Biochem. J.,* **1943**, *37*, 572. (d) Mannich, C. and Hieronimus, O., *Ber.,* **1942**, *75*, 49. (e) Robinson, R., *J. Chem. Soc.,* **1917**, *111*, 762. (f) Robinson, R., *J. Chem. Soc.,* **1917**, *111*, 876. (g) Petrenko-Kritchenko, P., *J. Prakt. Chem.,* **1912**, *85*, 1. (h) Petrenko-Kritschenko, P. and Schottle, J., *Ber.,* **1910**, *43*, 203. (i) Petrenko-Kritschenko, P. and Schottle, S., *Ber.,* **1909**, *42*, 2020. (j) Petrenko-Kritschenko, P. and Petrov, W., *Ber.,* **1908**, *41*, 1692.

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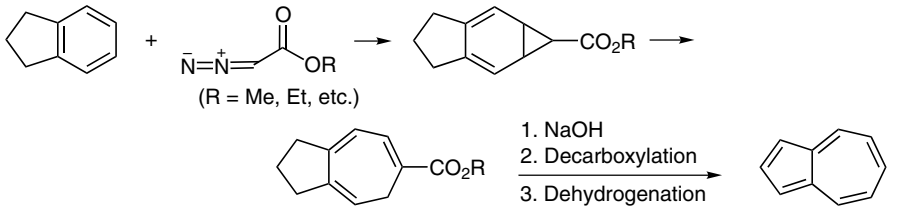
Pfau-Plattner Azulene Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Pfau and Plattner in 1939[1] after their earlier preparation of azulene from cyclopentenocycloheptanone[2] by the application of the ring expansion protocol discovered by Buchner in 1885.[3] It is a multistep preparation of azulene involving decomposition of diazoacetic ester, addition of the resulting carbene to indane, rearrangement of cycloheptatriene, hydrolysis of ester, decarboxylation, and dehydrogenation. Azulene is an isomeric structure of naphthalene[3b] with an intense blue or blue-violet color.[4] The dehydrogenation can be carried out by heating cycloheptatriene with sulfur, selenium, or palladium-charcoal,[4b] and the resulting azulene can be purified by the formation of a complex with trinitrobenzene[5] or use of column chromatography and partition procedures.[3b] This reaction has been improved by the direct addition of carbene to indane followed by dehydrogenation with a much higher yield.[6] In addition, this reaction has been modified by the intramolecular carbene addition of 4-phenyl 1-diazo-2-butanone followed by dehydrogenation.[7]

B. GENERAL REACTION SCHEME



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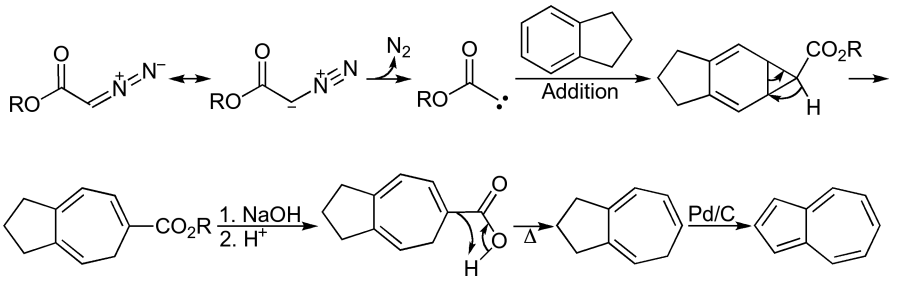
C. PROPOSED MECHANISMS



D. MODIFICATION

This reaction has been modified by the direct addition of carbene, generated from diazomethane, to indane[6] and intramolecular carbene addition to the phenyl ring from 4-phenyl-1-diazo-2-butanone,[7] followed by dehydrogenation.

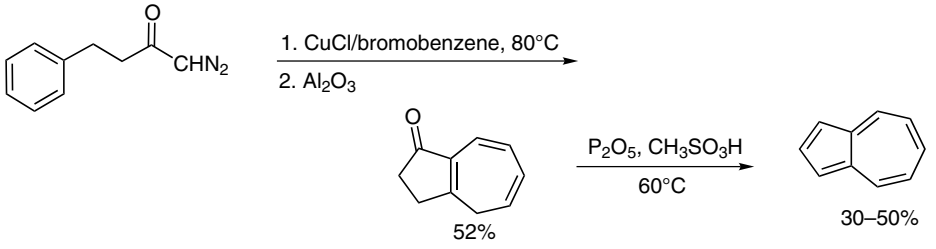
E. APPLICATIONS

This reaction has a limited use in organic synthesis, specifically for the azulene derivatives.

F. RELATED REACTIONS

This reaction is related to the *Büchner Ring Expansion*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4a.

To an oven-dried, 5-L three-necked flask equipped with a mechanical stirrer, a constant addition funnel, and a reflux condenser were added 3 L freshly distilled bromobenzene over CaH_2 and 0.8 g fresh anhydrous CuCl under nitrogen. At 80°C, 1 L dry bromobenzene containing 20.4 g 4-phenyl-1-diazo-2-butanone was added to the vigorously stirred suspension

dropwise for a period of 7 h. Heating and stirring were continued for an additional 1 h, then the pale yellow reaction mixture was cooled and filtered through 30 g alumina to remove CuCl and isomerize the unconjugated trienone to the more stable isomer. The alumina was washed with 500 mL EtOAc, and the combined organic filtrates were concentrated at 40°C (20–0.5 mmHg) to a brown oil. Chromatography on 200 g silica gel using EtOAc/petroleum ether (15:85) as the eluant gave 8.9 g 3,4-dihydro-1(2H)-azulenone as a light brown oil, in a yield of 52%.

To a homogeneous mixture of 5 g P_2O_5 (35 mmol) and 34 mL freshly distilled methanesulfonic acid at 60°C under nitrogen was added 0.48 g 3,4-dihydro-1(2H)-azulenone (3.3 mmol) dropwise under stirring within 7 min. The solution rapidly darkened to orange-brown. Progress of the reaction was followed by removing one-drop aliquots and quenching them in H_2O/hexane. The UV spectra of the hexane layer showed a gradual decrease at 226 nm and an increase at 274 nm. After ~6 h, the absorption at 226 nm was no longer discernible, and the reaction mixture was poured into 500 mL ice-cold water and extracted twice with pentane. The dark blue pentane layers were combined, washed with water until neutral, followed by brine, dried over $MgSO_4$, and concentrated under reduced pressure. The oily blue residue was purified by preparative layer chromatography on silica gel by using pentane as the eluent to give 130–210 mg azulene as beautiful dark blue crystals, in a yield of 30–50%, m.p. 98–98.5°C.

More experimental procedures are available in the literature.[6a,8] Other references related to the Pfau-Plattner azulene synthesis are cited in the literature.[9]

H. REFERENCES

1. Pfau, A. S. and Plattner, P. A., *Helv. Chim. Acta,* **1939**, *22*, 202.
2. Pfau, A. S. and Plattner, P. A., *Helv. Chim. Acta,* **1936**, *19*, 858.
3. (a) Ye, T. and McKervey, M. A., *Chem. Rev.,* **1994**, *94*, 1091. (b) Gordon, M., *Chem. Rev.,* **1952**, *50*, 127. (c) Braren, W. and Buchner, E., *Ber.,* **1901**, *34*, 982. (d) Büchner, E. and Curtius, T., *Ber.,* **1885**, *18*, 2377.
4. (a) Scott, L. T.; Minton, M. A. and Kirms, M. A., *J. Am. Chem. Soc.,* **1980**, *102*, 6311. (b) Horning, E. C., *Chem. Rev.,* **1943**, *33*, 89.
5. (a) Herz, W., *J. Am. Chem. Soc.,* **1951**, *73*, 4923. (b) Haagen-Smit, A. J. and Fong, C. T. O., *J. Am. Chem. Soc.,* **1948**, *70*, 2075.
6. Doering, W. von E.; Mayer, J. R. and DePuy, C. H., *J. Am. Chem. Soc.,* **1953**, *75*, 2386.
7. (a) Scott, L. T.; Grütter, P. and Chamberlain, R. E., *J. Am. Chem. Soc.,* **1984**, *106*, 4852. (b) Scott, L. T.; Minton, M. A. and Kirms, M. A., *J. Am. Chem. Soc.,* **1980**, *102*, 6311.
8. Luhowy, R. and Keehn, P. M., *J. Am. Chem. Soc.,* **1977**, *99*, 3797.
9. (a) Hansen, H. J., *Chimia*, **1997**, *51*, 147. (b) Hansen, H. J., *Chimia,* **1996**, *50*, 489. (c) Hafner, K., *Angew. Chem.,* **1958**, *70*, 419. (d) Reid, D. H., *Chem. Soc. Spec. Publ.,* **1958**, *12*, 69. (e) Herz, W., *J. Am. Chem. Soc.,* **1953**, *75*, 73. (f) Herz, W., *J. Am. Chem. Soc.,* **1952**, *74*, 1350. (g) Anderson, A. G. and Nelson, J. A., *J. Am. Chem. Soc.,* **1951**, *73*, 232. (h) Pommer, H., *Angew. Chem.,* **1950**, *62*, 283. (i) Treibs, W. and Froitzheim, H., *Ann.,* **1949**, *564*, 43. (j) Nunn, J. R. and Rapson, W. S., *J. Chem. Soc.,* **1949**, 825. (k) Plattner, P. A.; Fürst, A. and Keller, W., *Helv. Chim. Acta,* **1949**, *32*, 2464. (l) D'yakonov, I. A., *Zh. Obsh. Khim.,* **1949**, *19*, 1734. (m) Plattner, P. A.; Fürst, A.; Chopin, J. and Winteler, G., *Helv. Chim. Acta,* **1948**, *31*, 501. (n) Plattner, P. A. and Roniger, H., *Helv. Chim. Acta,* **1942**, *25*, 590. (o) Plattner, P. A. and Wyss, J., *Helv. Chim. Acta,* **1941**, *24*, 483. (p) Plattner, P. A. and Wyss, J., *Helv. Chim. Acta,* **1940**, *23*, 907.

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Pfitzinger Reaction

(Pfitzinger Quinoline Synthesis, Pfitzinger Synthesis, Pfitzinger Condensation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Pfitzinger in 1886.[1] It is a base-promoted condensation between an enolizable carbonyl compound and isatinate originating from isatin to form 2- or 2,3-disubstituted quinoline or cinchoninic acid derivative. Therefore, this reaction is generally known as the Pfitzinger reaction,[2,3] Pfitzinger condensation,[2r,2t,2u,2v,2y,4] or Pfitzinger synthesis.[2u,2y,5] Occasionally, it is also referred to as the Pfitzinger quinoline synthesis.[6] The isatins being used for this reaction include 5-sulfamoylisatin,[2b,2f] 5-methylisatin,[2x,7] methyl isatin-4-carboxylate,[5a] 5-bromoisatin,[2r] isatin,[2b,2h,2q,2x,2bb,5c,7] and isatic acid.[2t,2z] The enolizable carbonyl compounds suitable for this reaction include acetone,[2b,8] methyl aryl ketones[2b] (e.g., acetophenone,[9] *p*-fluoroacetophenone[2h]), methyl heteroaryl ketones,[2b] cyclohexanone,[2b] cyclopentanone (for *p*-quinindane),[2l,4c] cyclooctanone,[2r] cyclopentadecanone,[2r] malonates,[2b] keto ester[2c] (e.g., acetoacetic acid esters[2b]), keto ethers[2aa,2bb] (or alkoxy ketones,[2aa,2bb] such as ethoxyacetone,[2bb] ethoxymethyl ethyl ketone,[2bb] toloxypropanones,[7] and thiophenoxyacetone[2x]), anhydride,[6a] chalcones,[3d] 2-undecanone,[2o] phloroglucinol,[2m] 2-acetylphenothiazine,[10] and lactam acetal.[11] From these carbonyl compounds, the unsymmetrical methyl ketones often result in the formation of 2-alkyl quinolines.[2u] However, for alkyl aryl ketones, such as $ArC(O)(CH_2)_nCH_3$, only ketones with $n < 3$ can undergo this reaction, due to the steric hindrance;[2v] similarly, ketones with a general form of $ArC(O)CH_2Ar'$ don't undergo this reaction if Ar′ carries a large *ortho*-substituent, even when Ar′ carries two small methyl groups.[4d]

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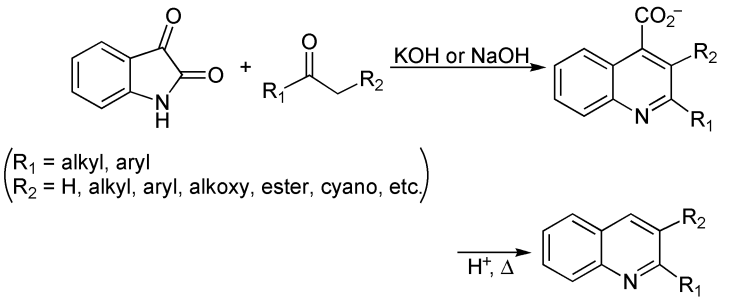
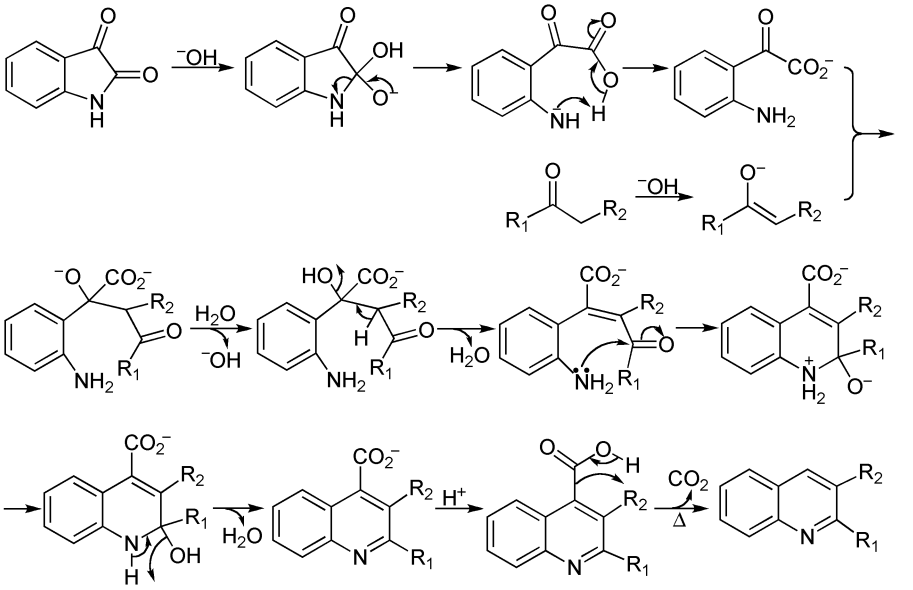
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Displayed below is a general mechanism for this reaction.



D. MODIFICATION

This reaction has been modified to occur under acidic conditions[4b,12] and microwave irradiation.[2e]

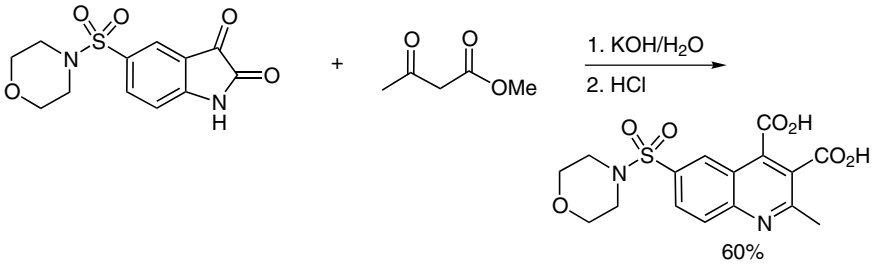
E. APPLICATIONS

This reaction has a broad application in the preparation of quinoline derivatives.

F. RELATED REACTIONS

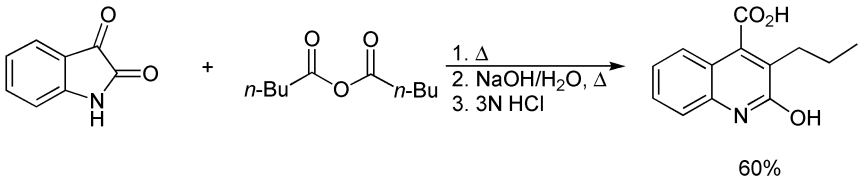
This reaction is related to the *Friedländer Condensation* and *Niementowski Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2c.

To a suspension of 13.33 g 5-(morpholin-4-ylsulfonyl)-1*H*-indole-2,3-dione (45 mmol) in 100 mL H_2O, was added 20 g KOH under a nitrogen atmosphere. Then 14.62 g methyl acetoacetate (126 mmoL) was added, and the reaction mixture was stirred for 12 h. The mixture was cooled to 0°C, then 40 mL conc. HCl was slowly added. The resulting precipitate was filtered off, washed with water, and dried in vacuo at 70°C to give 60% 2-methyl-6-(morpholine-4-sulfonyl)-3,4-quinolinedicarboxylic acid.



Reference 6.

A mixture of 10 g isatin (68 mmol) and 18 mL valeric anhydride was heated under refluxing for 3 h. The resulting solution was then allowed to cool to room temperature, and the solid formed was collected by filtration, washed with small amounts of Et_2O, dried, and suspended in 30 mL H_2O. Sodium hydroxide pellets (4.3 g, 110 mmol) were added, and the resulting mixture was refluxed for 3 h, cooled, and acidified with 3 *N* HCl. The precipitate was collected by filtration, washed with cold water, and then dried under reduced pressure to constant weight, to afford 8.0 g 2-hydroxy-3-propyl-4-quinolinecarboxylic acid as a white solid, in a yield of 60%, m.p. 266–268°C.

Other references related to the Pfitzinger reaction are cited in the literature.[13]

H. REFERENCES

1. Pfitzinger, W., *J. Prakt. Chem.,* **1886**, *33*, 100.
2. (a) Kravchenko, D. V.; Kysil, V. M.; Ilyn, A. P.; Tkachenko, S. E.; Maliarchouk, S.; Okun, I. M. and Ivachtchenko, A. V., *Synth. Commun.,* **2006**, *36*, 911. (b) Ivachtchenko, A. V.; Kobak, V. V.; Ilyn, A. P.; Khvat, A. V.; Kysil, V. M.; Williams, C. T.; Kuzovkova, J. A. and Kravchenko, D. V., *J. Comb. Chem.,* **2005**, *7*, 227. (c) Kravchenko, D. V.; Kuzovkova, Y. A.; Kysil, V. M.; Tkachenko, S. E.; Maliarchouk, S.; Okun, I. M.; Balakin, K. V. and Ivachtchenko, A. V., *J. Med. Chem.,* **2005**, *48*, 3680. (d) Kouznetsov, V. V.; Méndez, L. Y. V. and Gómez, C. M. M., *Curr. Org. Chem.,* **2005**, *9*, 141. (e) Ashry, E. S. H. E.; Ramadan, E. S.; Hamid, H. A. and Hagar, M., *Synth. Commun.,* **2005**, *35*, 2243. (f) Ivachtchenko, A. V.; Kobak, V. V.; Il'yin, A. P.; Trifilenkov, A. S. and Busel, A. A., *J. Comb. Chem.,* **2003**, *5*, 645. (g) Da Silva, J. F. M.; Garden, S. J. and Pinto, A. C., *J. Braz. Chem. Soc.,* **2001**, *12*, 273. (h) Giardina, G. A. M.; Raveglia, L. F.; Grugni, M.; Sarau, H. M.; Farina, C.; Medhurst, A. D.; Graziani, D.; Schmidt, D. B.; Rigolio, R.; Luttmann, M.; Cavagnera, S.; Foley, J. J.; Vecchietti, V. and Hay, D. W. P., *J. Med. Chem.,* **1999**, *42*, 1053. (i) Chiang, L. Y.; Swirczewski, J. W.; Kastrup, R.; Hsu, C. S. and Upasani, R. B., *J. Am. Chem. Soc.,* **1991**, *113*, 6574. (j) Ozawa, F.; Yanagihara, H. and Yamamoto, A., *J. Org. Chem.,* **1986**, *51*, 415. (k) Munson, H. R.; Johnson, R. E.; Sanders, J. M.; Ohnmacht, C. J. and Lutz, R. E., *J. Med. Chem.,* **1975**, *18*, 1232. (l) Eisch, J. J. and Gadek, F. J., *J. Org. Chem.,* **1971**, *36*, 2065. (m) Hlubucek, J.; Ritchie, E. and Taylor, W. C., *Aust. J. Chem.,* **1970**, *23*, 1881. (n) Markgraf, J. H.; Katt, R. J.; Scott, W. L. and Shefrin, R. N., *J. Org. Chem.,* **1969**, *34*, 4131. (o) Gottstein, W. J.; Roberts, H.; Wells, I. C. and Cheney, L. C., *J. Org. Chem.,* **1964**, *29*, 3065. (p) Bruice, T. C., *J. Am. Chem. Soc.,* **1957**, *79*, 702. (q) Cromwell, N. H. and Mercer, G. D., *J. Am. Chem. Soc.,* **1957**, *79*, 3815. (r) Jacquignon, P. and Buu-Hoï, N. P., *J. Org. Chem.,* **1957**, *22*, 72. (s) Buu-Hoï, N. P. and Sy, M., *J. Org. Chem.,* **1956**, *21*, 136. (t) Skinner, C. G. and Henze, H. R., *J. Am. Chem. Soc.,* **1955**, *77*, 3810. (u) Henze, H. R. and Carroll, D. W., *J. Am. Chem. Soc.,* **1954**, *76*, 4580. (v) Buu-Hoï, N. P.; Royer, R.; Xuong, N. D. and Jacquignon, P., *J. Org. Chem.,* **1953**, *18*, 1209. (w) Henze, H. R.; Melton, J. W. and Forman, E. O., *J. Am. Chem. Soc.,* **1948**, *70*, 2622. (x) Knight, J. A.; Porter, H. K. and Calaway, P. K., *J. Am. Chem. Soc.,* **1944**, *66*, 1893. (y) Isbell, A. F. and Henze, H. R., *J. Am. Chem. Soc.,* **1944**, *66*, 2096. (z) Manske, R. H., *Chem. Rev.,* **1942**, *30*, 113. (aa) Lesesne, S. D. and Henze, H. R., *J. Am. Chem. Soc.,* **1942**, *64*, 1897. (bb) Cross, L. B. and Henze, H. R., *J. Am. Chem. Soc.,* **1939**, *61*, 2730. (cc) Calaway, P. K. and Henze, H. R., *J. Am. Chem. Soc.,* **1939**, *61*, 1355.
3. (a) Kravchenko, D. V.; Kysil, V. M.; Tkachenko, S. E.; Maliarchouk, S.; Okun, I. M. and Ivachtchenko, A. V., *Heterocycl. Commun.,* **2006**, *12*, 15. (b) Shvekhgeimer, M.-G. A., *Chem. Heterocycl. Compd.,* **2004**, *40*, 257. (c) Ivachtchenko, A. V.; Khvat, A. V.; Kobak, V. V.; Kysil, V. M. and Williams, C. T., *Tetrahedron Lett*., **2004**, *45*, 5473. (d) Lasikova, A. and Vegh, D., *Chem. Papers,* **1997**, *51*, 408. (e) El-Abbady, A. M.; Omara, M. A. and Kandil, N. G., *Rev. Roumaine Chim*., **1973**, *18*, 899. (f) Andre, J.; Jacquignon, P.; Perin, F. and Buu-Hoi, N. P., *Bull. Soc. Chim. Fr.,* **1970**, *11*, 3908. (g) Kholodov, L. E.; Syrova, G. P.; Yashunskii, V. G. and Sheinker, Yu. N., *Khim. Geterotsiklicheskikh Soedinenii,* **1970**, *78*. (h) Palmer, M. H. and McIntyre, P. S., *J. Chem. Soc. B,* **1969**, 539. (i) Buu-Hoï, N. P.; Jacquignon, P. and Beranger, S., *Bull. Soc. Chim. Fr.,* **1968**, 2476. (j) Al-Tai, F. A.; El-Abbady, A. M. and Al-Tai, A. S., *J. Chem. United Arab Republic,* **1967**, *10*, 339. (k) Al-Tai, F. A.; Sarkis, G. Y. and Al-Janabi, J. M., *Bull. Coll. Sci., (Baghdad),* **1966**, *9*, 55. (l) Takagi, K.; Hubert-Habart, M.; Cheutin, A. and Royer, R., *Bull. Soc. Chim. Fr.,* **1966**, 3136. (m) Al-Tai, F. A. and Sarkis, G. Y., *Bull. Coll. Sci. (Baghdad)*, **1963**, *7*, 11. (n) Kaslow, C. E. and Moe, H., *J. Org. Chem.,* **1960**, *25*, 1512. (o) Buu-Hoï, Ng. Ph. and Jacquignon, P., *Bull. Soc. Chim. Fr.,* **1958**, 1567. (p) Al-Ta'I, F. A., *Proc. Iraqi Sci. Soc.,* **1957**, *1*, 27. (q) Buu-Hoï, Ng. Ph.; Sy, M. and Xuong, Ng. D., *Bull. Soc. Chim. Fr.,* **1956**, 629. (r) Delaby, R.; Tsatsas, G. and Lusinchi, X., *Bull. Soc. Chim. Fr.,* **1955**, 1609. (s) Buu-Hoï, Ng. Ph. and Miquel, J. F., *J. Chem. Soc.,* **1953**, 3768. (t) Buu-Hoï, Ng. Ph.; Hoan, Ng. and Xuong, Ng. D., *J. Chem. Soc.,* **1952**, 279.

(u) Okuda, N., *Yakugaku Zasshi*, **1951**, *71*, 1275. (v) de Clercq, M. and Buu-Hoï., *Compt. Rend.,* **1948**, *227*, 1377. (w) de Clercq, M. and Buu-Hoï., *Compt. Rend.,* **1948**, *227*, 1251. (x) Buu-Hoï and Royer, R., *J. Chem. Soc.,* **1948**, 106. (y) Cagniant, P. and Deluzarche, A., *Compt. Rend.,* **1946**, *223*, 1148. (z) Buu-Hoï, N. P. and Royer, R., *Bull. Soc. Chim. Fr.,* **1946**, 374. (aa) Buu-Hoï, N. P. and Cagniant, P., *Bull. Soc. Chim. Fr.,* **1946**, 134. (bb) Buu-Hoï, N. P. and Cagniant, P., *Bull. Soc. Chim. Fr.,* **1946**, 123. (cc) Buu-Hoï, N. P., *J. Chem. Soc.,* **1946**, 795. (dd) Crippa, G. B. and Scevola, E., *Gazz. Chim. Ital.,* **1937**, *67*, 119. (ee) Robinson, E. A. and Bogert, M. T., *J. Org. Chem.,* **1936**, *1*, 65.

4. (a) Bryson, T. A.; Gibson, J. M.; Stewart, J. J.; Voegtle, H.; Tiwari, A.; Dawson, J. H.; Marley, W. and Harmon, B., *Green Chem.,* **2003**, *5*, 177. (b) Lackey, K. and Sternbach, D. D., *Synthesis*, **1993**, 993. (c) Lutz, R. E. and Sanders, J. M., *J. Med. Chem.,* **1976**, *19*, 407. (d) Mueller, G. P. and Stobaugh, R. E., *J. Am. Chem. Soc.,* **1950**, *72*, 1598.
5. (a) Braña, M. F.; Gradillas, A.; Gómez, A.; Acero, N.; Llinares, F.; Muñoz-Mingarro, D.; Abradelo, C.; Rey-Stolle, F.; Yuste, M.; Campos, J.; Gallo, M. A. and Espinosa, A., *J. Med. Chem.,* **2004**, *47*, 2236. (b) Deady, L. W.; Kaye, A. J.; Finlay, G. J.; Baguley, B. C. and Denny, W. A., *J. Med. Chem.,* **1997**, *40*, 2040. (c) Bergstrom, F. W., *Chem. Rev.,* **1944**, *35*, 77.
6. (a) Cappelli, A.; Gallelli, A.; Manini, M.; Anzini, M.; Mennuni, L.; Makovec, F.; Menziani, M. C.; Alcaro, S.; Ortuso, F. and Vomero, S., *J. Med. Chem.,* **2005**, *48*, 3564. (b) Gainor, J. A. and Weinreb, S. M., *J. Org. Chem.,* **1982**, *47*, 2833.
7. Dowell, A. M.; McCullough, H. S. and Calaway, P. K., *J. Am. Chem. Soc.,* **1948**, *70*, 226.
8. Brasyunas, V. B.; Andreyanova, T. A.; Safonova, T. S.; Solov'eva, N. P.; Turchin, K. F. and Sheinker, Y. N., *Chem. Heterocycl. Compd.,* **1988**, *24*, 670.
9. (a) Bass, Y.; Morgan, R. J.; Donovan, R. J. and Baker, A. D., *Synth. Commun.,* **1997**, *27*, 2165. (b) Atwell, G. J.; Baguley, B. C. and Denny, W. A., *J. Med. Chem.,* **1989**, *32*, 396.
10. Sparatore, F.; Savelli, F. and Cordella, G., *Il Farmaco,* **1980**, *35*, 735.
11. Singh, J.; Sardana, V. and Anand, N., *Indian J. Chem. Sect. B,* **1989**, 28*B*, 1031.
12. Lackey, K.; Besterman, J. M.; Fletcher, W.; Leitner, P.; Morton, B. and Sternbach, D. D., *J. Med. Chem.,* **1995**, 38, 906.
13. (a) Shvekhgeimer, M.-G. A. and Kondrashova, N. N., *Chem. Heterocycl. Compd.,* **2002**, *38*, 253. (b) Beller, M.; Thiel, O. R.; Trauthwein, H. and Hartung, C. G., *Chem. Eur. J.,* **2000**, *6*, 2513. (c) Rice, K. C.; Boone, B. J.; Rubin, A. B. and Rauls, T. J., *J. Med. Chem.,* **1976**, *19*, 887. (d) Cragoe, E. J. and Robb, C. M., *Org. Synth. Coll., V,* **1973**, *5*, 635. (e) Pfitzinger, W., *J. Prakt. Chem.,* **1888**, *38*, 582.

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Pfitzner-Moffatt Oxidation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Pfitzner and Moffatt in 1963.[1] It is the oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones under mild and almost neutral conditions by the combination of dimethyl sulfoxide (DMSO) and dicyclohexylcarbodiimide (DCC) in the presence of a proton source, such as phosphoric acid or pyridinium trifluoroacetate. This method was initially known as the Pfitzner-Moffatt technique,[2] and is now referred in general to as the Pfitzner-Moffatt oxidation.[3] Occasionally, it is called the Moffatt oxidation,[4] and the combination of DMSO and DCC is known as the Pfitzner-Moffatt reagent.[5] This reaction is applicable to primary and secondary hydroxyl groups in a variety of compounds, including alkaloids, steroids, and carbohydrates, in which other functional groups such as olefin, amine, tosylate, and tertiary hydroxyl groups are not affected.[2] However, this reaction also has some drawbacks. For example, the equatorial OHs in steroids are readily oxidized, whereas some axial OHs are inert to the Pfitzner-Moffatt reagent.[6] In addition, the oxidation of nucleotides with free 3′-hydroxyl groups such as thymidine 5′-phosphate and free 3′-hydroxyl containing nucleosides in the presence of anhydrous phosphoric acid, leads to the cleavage of the *N*-glycosidic bond and the release of the nitrogenous bases.[7] In this reaction, the amount of DMSO can be 10–100% of solvent, in combination with another inert molecule, such as benzene, as the co-solvent.[2] Strong mineral acids such as H_2SO_4, HCl, and $HClO_4$ are not good activators for DMSO.[2] It has been proposed that this reaction involves the activation of DMSO by DCC through an acid-catalyzed process, followed by an alcohol attack to form dimethylalkoxysulfonium salt and *N*,*N*′-dicyclohexylurea, and the formation of carbonyl compounds via proton transfers

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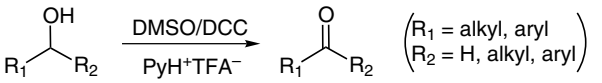
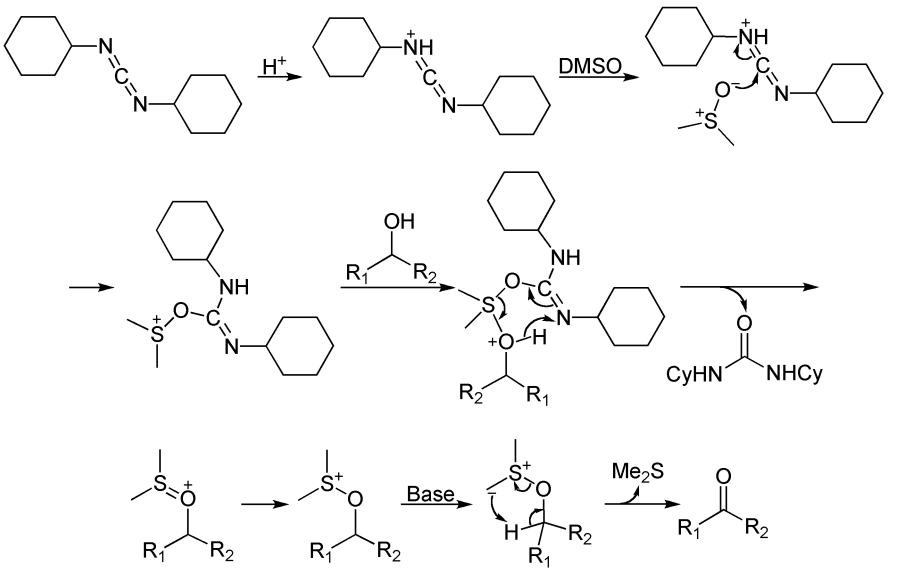
and the evolution of dimethylsulfide.[2,8] Sometimes, this reaction also yields by-products of $R_2CHO\text{-}CH_2SCH_3$ arising from the rearrangement.[2]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Displayed below is the mechanism for Pfitzner-Moffatt oxidation in the presence of both an acid and base.



D. MODIFICATION

N/A

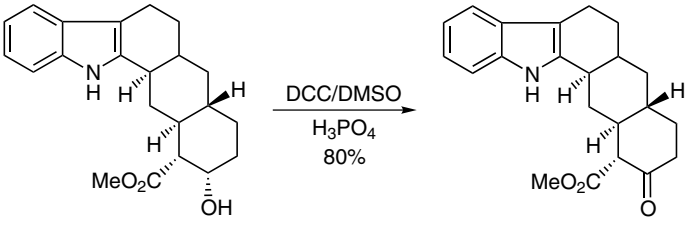
E. APPLICATIONS

This reaction has general application in the oxidation of primary and secondary alcohols to corresponding aldehydes and ketones.

F. RELATED REACTIONS

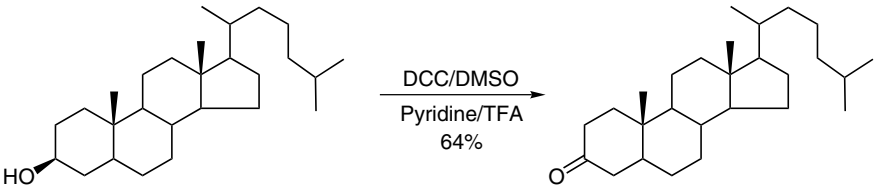
This reaction is related to the *Albright-Goldman Oxidation, Kornblum Oxidation*, and *Parikh-Doering Oxidation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 9.

To a solution of 28.32 g yohimbine (0.080 mol) and 49.04 g DCC (0.24 mol) in dry DMSO (120 mL) was added 12.0 g crystalline orthophosphoric acid (0.12 mol). The mixture was allowed to stand for 17 h at room temperature and was diluted with CH_2Cl_2. The solid was filtered, and the product remained in the filter cake as a phosphate salt and was extracted from the *N*,*N*′-dicyclohexylurea with hot acetic acid water (1:2). Basification of the chilled extract with concentrated NH_4OH, filtration, and trituration of the solid with alcohol afforded 80% yohimbinone, m.p. 250–254°C (dec.).



Reference 10.

A mixture of 1.16 g cholestan-3β-ol (2.99 mmol), 1.85 g DCC (8.98 mmol), 0.24 mL pyridine (3 mmol), 5 mL DMSO (74 mmol), and 0.12 mL trifluoroacetic acid (1.5 mmol) was stirred for 5 h at room temperature. The addition of dry EtOAc to the reaction solution resulted in the precipitation of *N*,*N*′-dicyclohexylurea, which was filtered, washed with dry benzene. The filtrate was washed with water, dried, and concentrated in vacuo. The residue was chromatographed on Woelm neutral alumina to give 32% of cholestan-3β-ol and 64% of cholestan-3-one.

Other references related to the Pfitzner-Moffatt oxidation are cited in the literature.[11]

H. REFERENCES

1. Pfitzner, K. E. and Moffatt, J. G., *J. Am. Chem. Soc.,* **1963**, *85*, 3027. (two communication papers on the same page).
2. Epstein, W. W. and Sweat, F. W., *Chem. Rev.,* **1967**, *67*, 247.
3. (a) Borschberg, H.-J., *Curr. Org. Chem.,* **2005**, *9*, 1465. (b) Ma, Z. K. and Nemoto, P. A., *Curr. Med. Chem. Anti-Infective Agents,* **2002**, *1*, 15. (c) Tatsuta, K., *Curr. Org. Chem.,* **2001**, *5*, 207. (d) Fukuyama, T. and Liu, G., *Pure & Appl. Chem.,* **1997**, *69*, 501. (e) Sauerbrei, B.; Niggemann, J.; Groger, S.; Lee, S. and Floss, H. G., *Carbohydr. Res.,* **1996**, *280*, 223. (f) Samano, V. and Robins, M. J., *J. Org. Chem.,* **1990**, *55*, 5186. (g) Ochiai, M.; Ukita, T.; Iwaki, S.; Nagao, Y. and Fujita, E., *J. Org. Chem.,* **1989**, *54*, 4832. (h) Liu, H. J. and Nyangulu, J. M., *Tetrahedron Lett*., **1988**, *29*, 3167. (i) Roensch, H., *Zeitsch. Chem.,* **1984**, *24*, 153. (j) Balerna, M.; Lombet, A.; Chicheportiche, R.; Romey, G. and Lazdunski, M., *Biochim. Biophys. Acta,* **1981**, *644*, 219. (k) Chicheportiche, R.; Balerna, M.; Lombet, A.; Romey, G. and Lazdunski, M., *Eur. J. Biochem./FEBS,* **1980**, *104*, 617. (l) Montgomery, J. A.; Thomas, H. J.; Kisliuk, R. L. and Gaumont, Y., *J. Med. Chem.,* **1979**, *22*, 109. (m) Yagen, B.; O'Grodnick, J. S.; Caspi, E. and Tamm, C., *J. Chem. Soc., Perkin Trans. I,* **1974**, 1994. (n) Saeki, H. and Ohki, E., *Chem. Pharm. Bull.,* **1970**, *18*, 789.
4. (a) Taber, D. F.; Amedio, J. C. and Jung, K.-Y., *J. Org. Chem.,* **1987**, *52*, 5621. (b) Wigfield, D. C.; Feiner, S. and Phelps, D. J., *Steroids*, **1972**, *20*, 435.
5. (a) Robins, M. J.; Samano, V. and Johnson, M. D., *J. Org. Chem.,* **1990**, *55*, 410. (b) Paquette, L. A.; Balogh, D. W.; Ternansky, R. J.; Begley, W. J. and Banwell, M. G., *J. Org. Chem.,* **1983**, *48*, 3282. (c) Brimacombe, J. S.; Bryan, J. G. H.; Husain, A.; Stacey, M. and Tolley, M. S., *Carbohydr. Res.,* **1967**, *3*, 318.
6. Pfitzner, K. E. and Moffatt, J. G., *J. Am. Chem. Soc.,* **1965**, *87*, 5670.
7. Pfitzner, K. E. and Moffatt, J. G., *J. Am. Chem. Soc.,* **1965**, *87*, 5661.
8. Fenselau, A. H. and Moffatt, J. G., *J. Am. Chem. Soc.,* **1966**, *88*, 1762.
9. Albright, J. D. and Goldman, L., *J. Org. Chem.,* **1965**, *30*, 1107.
10. Sweat, F. W. and Epstein, W. W., *J. Org. Chem.,* **1967**, *32*, 835.
11. (a) Griffon, J.-F.; Montgomery, J. A. and Secrist, J. A., *Nucleosides, Nucleotides & Nucleic Acids,* **2001**, *20*, 649. (b) Gunji, H. and Vasella, A., *Helv. Chim. Acta,* **2000**, *83*, 1331. (c) Lee, T. V., *Comp. Org. Synth.,* **1991**, *7*, 291. (d) Tidwell, T. T., *Org. React.,* **1990**, *39*, 297. (e) Schobert, R., *Synthesis,* **1987**, 741. (f) Binkley, R. W.; Hehemann, D. G. and Binkley, W. W., *J. Org. Chem.,* **1978**, *43*, 2573. (g) Albright, J. D., *J. Org. Chem.,* **1974**, *39*, 1977. (h) Harmon, R. E.; Zenarosa, C. V. and Gupta, S. K., *J. Org. Chem.,* **1970**, *35*, 1936. (i) Burdon, M. G. and Moffatt, J. G., *J. Am. Chem. Soc.,* **1967**, *89*, 4725. (j) Parikh, J. R. and Doering, W. von E., *J. Am. Chem. Soc.,* **1967**, *89*, 5505. (k) Albright, J. D. and Goldman, L., *J. Am. Chem. Soc.,* **1965**, *87*, 4214.

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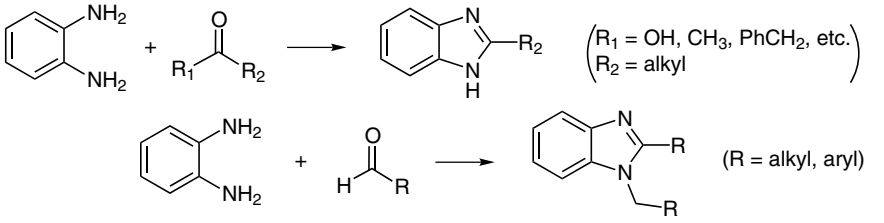
Phillips-Ladenburg Benzimidazole Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

Although the first benzimidazole was prepared by Hobrecker in 1872,[1] it was Ladenburg who extensively explored the preparation of benzimidazole derivatives by the condensation between *ortho*-amino aniline and carbonyl compounds (aldehydes and ketones) in 1875.[2] Subsequently, Phillips further extended Ladenburg's preparation to the condensation between *ortho*-amino aniline and acetic acid[2a] to produce different kinds of carboxylic acids in the presence of dilute mineral acid.[3] Therefore, the preparation of benzimidazole from *ortho*-amino aniline is referred to as the Ladenburg method,[4] Phillips method,[4c] Phillips modification,[5] or the Phillips-Ladenburg reaction.[6] It has been proposed that the condensation between *ortho*-amino aniline and carbonyl compounds involves the formation of a Schiff base intermediate,[4b] whereas the condensation between *ortho*-amino aniline and acid proceeds via the *N*,*N*′-diacyl and monoacyl intermediate.[7] This condensation generally works for aliphatic acids[5] and is feasible for aromatic acids if the condensations are carried out above 180°C in sealed reaction vessels.[8]

B. GENERAL REACTION SCHEME



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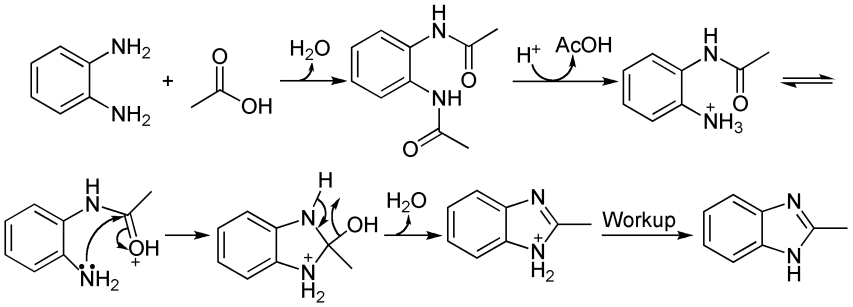
C. PROPOSED MECHANISMS

The mechanism for the conditions of the Phillips modification—that is the condensation between *ortho*-amino aniline and carboxylic acid—is exemplified by the reaction with acetic acid in the presence of mineral acid.



D. MODIFICATION

This reaction has been modified for preparing oxazole, thiazole, and perimidine derivatives from the condensation of the corresponding *o*-aminophenol, *o*-aminobenzenethiol, and 1,8-naphthalenediamine with ketones.[9]

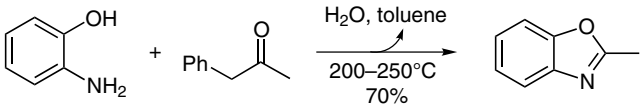
E. APPLICATIONS

This reaction is very useful in the preparation of benzimidazole derivatives.

F. RELATED REACTIONS

N/A

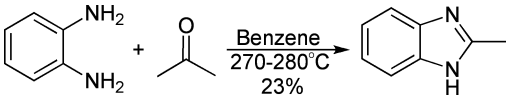
G. CITED EXPERIMENTAL EXAMPLES



Reference 9.

A mixture of 11 g *o*-aminophenol (0.1 mol) and 27 g benzyl methyl ketone (0.2 mol) was heated in a flask equipped with an inside thermometer and a condenser set downward for distillation for 6 h. The heating was maintained so that a temperature of $\approx 200^{\circ}$C was rapidly approached in the first hour and slowly raised to 250°C at the end of 6 h. The slightly yellow distillate (10 g) collected in the ice-cooled receiver consisted of two layers. The lower layer

(1–2 g) was found to be water, which had formed in the course of the reaction. The entire distillate was then taken up in 25 mL ether and dried over anhydrous Na_2SO_4. The filtered ether solution was fractioned, and the fraction boiling at 110–111°C (3 g) was identified as toluene by oxidation to benzoic acid with potassium permanganate. The dark brown viscous residue in the reaction flask was further distilled under reduced pressure, and the fraction coming over at 135–145 °C at 114 mmHg (10 g) was crude 2-methylbenzoxazole in 70% yield.



Reference 4b.

A mixture of 5.4 g fresh *o*-phenylenediamine recrystallized from heptane and water, 29.0 g acetone, and 20 mL dry benzene was heated. The initial gas evolution temperature was 260°C, and heating was carried out at 270–280°C for 2 h, during which time ~ 600 mL gas was evolved. Upon removal of volatile substances, successive recrystallizations from water of the heated residue gave 1.5 g 2-methylbenzimidazole as white leaflets, in a yield of 23%, m.p. 174.5–175.5°C.

Other references related to the Phillips-Ladenburg benzimidazole synthesis are cited in the literature. [10]

H. REFERENCES

1. Hobrecker, F., *Ber.,* **1872**, *5*, 920.
2. (a) Ladenburg, A., *Ber.,* **1875**, *8*, 677. (b) Ladenburg, A., *Ber.,* **1877**, *10*, 1123. (c) Ladenburg, A., *Ber.,* **1878**, *11*, 590. (d) Ladenburg, A., *Ber.,* **1878**, *11*, 1648. (e) Ladenburg, A. and Rügheimer, L., *Ber.,* **1879**, *12*, 951.
3. (a) Phillips, M. A., *J. Chem. Soc.,* **1928**, 172. (b) Phillips, M. A., *J. Chem. Soc.,* **1928**, 2395. (c) Phillips, M. A., *J. Chem. Soc.,* **1928**, 3134. (d) Phillips, M. A., *J. Chem. Soc.,* **1929**, 2820. (e) Phillips, M. A., *J. Chem. Soc.,* **1930**, 1409. (f) Phillips, M. A., *J. Chem. Soc.,* **1930**, 1416. (g) Phillips, M. A., *J. Chem. Soc.,* **1931**, 1143. (h) Phillips, M. A., *J. Chem. Soc.,* **1931**, 1151.
4. (a) Nguyen, T. T. H.; Urban, J.; Klinotova, E.; Sejbal, J.; Protiva, J.; Drasar, P. and Protiva, M., *Coll. Czech. Chem. Commun.,* **1995**, *60*, 257. (b) Elderfield, R. C. and McCarthy, J. R., *J. Am. Chem. Soc.,* **1951**, *73*, 975. (c) Wagner, E. C., *J. Org. Chem.,* **1940**, *5*, 133.
5. Wright, J. B., *Chem. Rev.,* **1951**, *48*, 397.
6. Matevosyan, G. L. and Zavlin, P. M., *Chem. Heterocycl. Compd.,* **1990**, *26*, 599.
7. (a) McCoy, G. and Day, A. R., *J. Am. Chem. Soc.,* **1943**, *65*, 2159. (b) Roeder, C. H. and Day, A. R., *J. Org. Chem.,* **1941**, *6*, 25.
8. Poraï-Koshits, B. A.; Ginzburg, O. F. and Efros, L. S., *J. Gen. Chem. USSR,* **1947**, *17*, 1768. [*Chem. Abstr.,* **1948**, *42*, 5903].
9. Kreysa, F. J.; Maturi, V. F.; Finn, J. J.; McClarnon, J. J. and Lombardo, F., *J. Am. Chem. Soc.,* **1951**, *73*, 1155.
10. Hölljes, E. L. and Wagner, E. C., *J. Org. Chem.,* **1944**, *9*, 31.

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Photo-Fries Rearrangement
(Photo-Fries Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Anderson and Reese in 1960.[1,2] It is the photo-initiated intramolecular[3] rearrangement of phenyl or aryl esters to isomeric acyl phenols or other acyl hydroxyl aromatics via acyl and phenoxy or aryloxy radical pairs. Because it is similar to the Lewis acid-promoted *Fries Rearrangement* discovered by Fries in 1908,[4] the photo-initiated rearrangement of phenyl or aryl esters is generally known as the photo-Fries rearrangement[5,6] or photo-Fries reaction.[5c,5h,7] This reaction is usually carried out in an aprotic solvent,[3a] proceeding directly from the lowest excited singlet state of ester[2,5a,5c] with quantum yields in the range of 0.1–0.3,[5a] and often competes with the de-excitation of the excited singlet state of the resulting phenol, which normally absorbs 10–100 times stronger than its precursor.[2b] This reaction is affected by electronic nature of substrate as well as the reaction environment. Although no apparent isotopic effect has been observed within an experimental error of 2%,[7k] the electron-deficiency of the carboxyl carbon and electron-enrichment of the *ortho*-position of the phenol ring facilitate the homolytic cleavage of C-O bond to form both phenoxy and acyl radicals.[8] For example, phenol *para*-cyano benozate rearranges faster than phenol *para-t*-butylbenzoate.[8] The photo-generated phenoxy and acyl radicals might combine together to form the precursor again or might form *ortho*- or *para*-acyl phenol before these radicals escape from the solvent cage to yield phenol. Thus the *ortho*- or *para*-acyl phenol is known as the *cage product*.[5d,5i] Compared with the normal Fries rearrangement catalyzed by Lewis acid, which gives predominantly *para*-acyl phenol product,[9] the photo-Fries rearrangement produces *ortho*-acyl phenol as the major product,[5f] even though it is known that both the *ortho*- and the *para*- positions of phenol are electron rich[10] because "formation of *para*-acyl phenol requires a greater extent of rotation of radical" than that in *ortho*-product. This regioselectivity is even enhanced when the photo-Fries rearrangement is carried out within a restricted environment, such as in the

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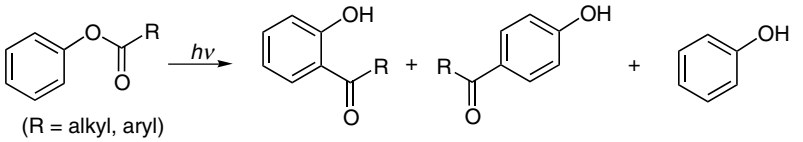
presence of zeolite. For example, less than 10% of *para*-products are formed from both phenyl acetate and phenyl benzoate within Li- and Na*X*, and *Y* zeolites, whereas no *para*-products are produced in K*X* and K*Y* zeolites.[7h] Similarly, only substituted 2-naphthols are observed from 1-naphthyl acetate and 1-naphthyl benzoate in *X* and *Y* zeolites.[5e] Occasionally, the migration of an acyl group to the *meta*-position is also noted.[7p,11] It should be pointed out that certain antibodies are capable of catalyzing the photo-Fries rearrangement.[5c]

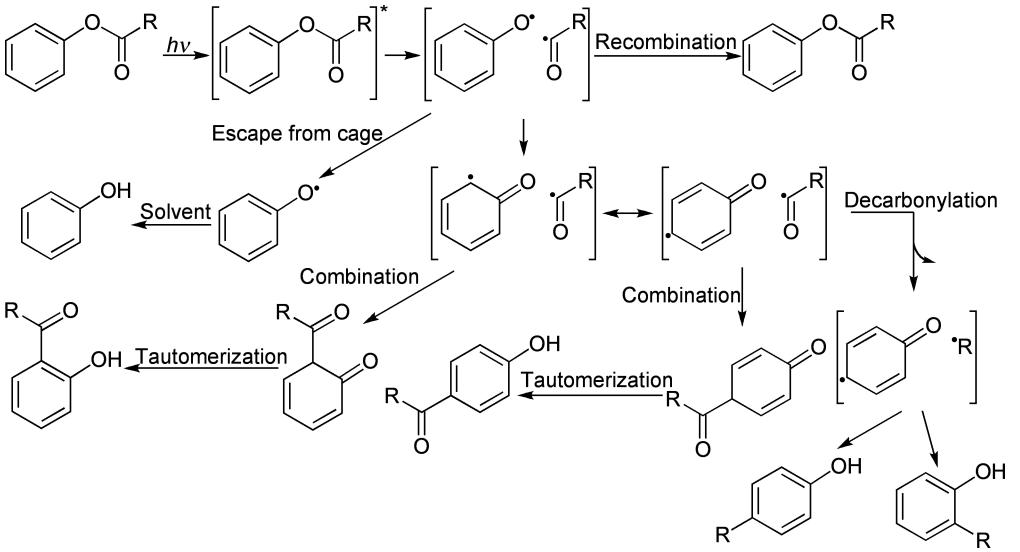
Besides phenyl and aryl esters, other kinds of compounds can also undergo the homolytic cleavage from photo-irradiation, such as amide,[6vv,6uuu] diphenyl ether,[2b,5c] phenyl benzyl ether,[2b] aryl sulfonate,[6zz,12] acetanilide,[6oo,12b,13] sulfonanilide,[6hh,14] *N*-arylsulfonamides,[6h] phenylsulfamates,[15] benzenesulfonanilide,[6hh] *N*-sulfonylcarbazoles,[6ll] aryl *N*-chloroacetylanthranilates,[6x] *N*-phenyl-urethane,[6oo] and phenyl cinnamate.[6sss,6eeee,7m,16] In the case of unsymmetrical phenyl ether, the actual homolytic cleavage pathway (i.e., via aryloxy-phenyl or aryl-phenoxy cleavage), depends on the substituents and correlates with the Hammett σ constants.[5c] The special case of rearrangement for acyl anilide is known as the photoanilide rearrangement.[17] Although the photo-Fries rearrangement is known to occur via the first excited singlet, the rearrangement of phenylsulfamates and cinnamates occur via the upper triplet excitation states.[15,18]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A general mechanism is displayed here including the processes of radical recombination, decarbonylation, and rearrangement.



D. MODIFICATION

This reaction has been modified extensively to proceed under different conditions. For example, it has been performed in liquid crystalline matrixes,[6gg] in zeolite,[7f] in supercritical CO_2,[5g] on a silica gel surface,[6ggg] or in the presence of cyclodextrin.[3a,6o,6v,6z,6hh,6mm,6oo,7b,19] In addition, this reaction has been catalyzed by photoacid.[6ff] Moreover, this reaction has been extended to various substrates other than the regular phenyl (or aryl) esters as described earlier.

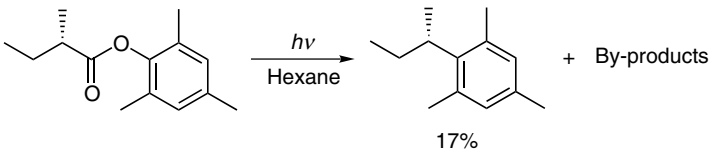
E. APPLICATIONS

This reaction may not be very useful in the actual organic synthesis because of its different by-products.

F. RELATED REACTIONS

This reaction is related to the *Fries Rearrangement*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 5a.

To 150 mL hexane was added 124 mg 2,4,6-trimethylphenyl (*S*)-(-)-2-methylbutyrate (0.56 mmol). The solution was placed in a doughnut-shaped quartz flask that was irradiated from a low-pressure mercury lamp at 25°C for 12 h while argon was bubbled through. Upon removal of solvent, the residue was chromatographed on a silica-gel column with hexane/ether (10:1) as the eluent to afford 17 mg (*S*)-(+)-2-methylpropyl-2,4,6-trimethylbenzene (17% isolated yield and 26% conversion), 43 mg starting material (35% recovery), and 25 mg unidentified products.

Other references related to the photo-Fries rearrangement are cited in the literature.[20]

H. REFERENCES

1. Anderson, J. C. and Reese, C. B., *Proc. Chem. Soc.,* **1960**, 217.
2. (a) Gritsan, N. P.; Tsentalovich, Y. P.; Yurkovskaya, A. V. and Sagdeev, R. Z., *J. Phys. Chem.,* **1996**, *100*, 4448. (b) Kalmus, C. E. and Hercules, D. M., *J. Am. Chem. Soc.,* **1974**, *96*, 449.
3. (a) Veglia, A. V. and de Rossi, R. H., *J. Org. Chem.,* **1993**, *58*, 4941. (b) Anderson, J. C. and Reese, C. B., *Proc. Chem. Soc.,* **1963**, 1781. (c) Kobsa, H., *J. Org. Chem.,* **1962**, *27*, 2293.

4. Fries, K. and Fink, G., *Ber.,* **1908**, *41*, 4271.

5. (a) Mori, T.; Weiss, R. G. and Inoue, Y., *J. Am. Chem. Soc.,* **2004**, *126*, 8961. (b) Lochbrunner, S.; Zissler, M.; Piel, J.; Riedle, E.; Spiegel, A. and Bach, T., *J. Chem. Phys.,* **2004**, *120*, 11634. (c) Dickerson, T. J.; Tremblay, M. R.; Hoffman, T. Z.; Ruiz, D. I. and Janda, K. D., *J. Am. Chem. Soc.,* **2003**, *125*, 15395. (d) Tung, C.-H.; Wu, L.-Z.; Zhang, L.-P.; Li, H.-R.; Yi, X.-Y.; Song, K.; Xu, M.; Yuan, Z.-Y.; Guan, J.-Q.; Wang, H.-W.; Ying, Y.-M. and Xu, X.-H., *Pure & Appl. Chem.,* **2000**, *72*, 2289. (e) Warrier, M.; Turro, N. J. and Ramamurthy, V., *Tetrahedron Lett.,* **2000**, *41*, 7163. (f) Andraos, J.; Barclay, G. G.; Medeiros, D. R.; Baldovi, M. V.; Scaiano, J. C. and Sinta, R., *Chem. Mater.,* **1998**, *10*, 1694. (g) Andrew, D.; des Islet, B. T.; Margaritis, A. and Weedon, A. C., *J. Am. Chem. Soc.,* **1995**, *117*, 6132. (h) García, H.; Primo, J. and Miranda, M. A., *Synthesis*, **1985**, 901. (i) Nakagaki, R.; Hiramatsu, M.; Watanabe, T.; Tanimoto, Y. and Nagakura, S., *J. Phys. Chem.,* **1985**, *89*, 3222. (j) Lo, J.; Lee, S. N. and Pearce, E. M., *J. Appl. Poly. Sci.,* **1984**, *29*, 35. (k) Crouse, D. J.; Hurlbut, S. L. and Wheeler, M. S., *J. Org. Chem.,* **1981**, *46*, 374. (l) Adam, W.; de Sanabia, J. A. and Fischer, H., *J. Org. Chem.,* **1973**, *38*, 2571. (m) Humphrey, J. S.; Shultz, A. R. and Jaquiss, D. B. G., *Macromolecules,* **1973**, *6*, 305. (n) Pappas, S. P.; Alexander, J. E.; Long, G. L. and Zehr, R. D., *J. Org. Chem.,* **1972**, *37*, 1258.

6. (a) Griesser, T.; Hoefler, T.; Temmel, S.; Kern, W. and Trimmel, G., *Chem. Mater.,* **2007**, *19*, 3011. (b) Hoefler, T.; Griesser, T.; Gstrein, X.; Trimmel, G.; Jakopic, G. and Kern, W., *Polymer,* **2007**, *48*, 1930. (c) Ferrini, S.; Ponticelli, F. and Taddei, M., *J. Org. Chem.,* **2006**, *71*, 9217. (d) Siskos, M. G.; Zarkadis, A. K.; Gritzapis, P. S.; Brede, O.; Hermann, R.; Melissas, V. S.; Gurzadyan, G. G.; Triantafyllou, A. S. and Georgakilas, V., *J. Photochem. Photobio., A: Chem.,* **2006**, *182*, 17. (e) Crevatin, L. K.; Bonesi, S. M. and Erra-Balsells, R., *Helv. Chim. Acta,* **2006**, *89*, 1147. (f) Luo, C. P.; Passin, P. and Weiss, R. G., *Photochem. Photobiol.,* **2006**, *82*, 163. (g) Park, K. K.; Kim, S.-H. and Park, J. W., *J. Photochem. Photobio., A: Chem.,* **2004**, *163*, 241. (h) Park, K. K.; Lee, J. J. and Ryu, J., *Tetrahedron*, **2003**, *59*, 7651. (i) Miranda, M. A. and Galindo, F., *Mol. & Supramol. Photochem.,* **2003**, *9*, 43. (j) Park, K. K.; Lee, H. J.; Kim, E. H. and Kang, S. K., *J. Photochem. Photobio., A: Chem.,* **2003**, 159, 17. (k) Gu, W. Q.; Bi, S. G. and Weiss, R. G., *Photochem. & Photobio. Sci.,* **2002**, *1*, 52. (l) Magnus, P. and Lescop, C., *Tetrahedron Lett*., **2001**, *42*, 7193. (m) Lin, M.-S. and Le, C.-T., *Polymer Preprints,* **2001**, *42*, 39. (n) Rusu, E.; Comanita, E. and Onciu, M., *Roumanian Chem. Quart. Rev*., **2000**, *7*, 241. (o) Banu, H. S.; Pitchumani, K. and Srinivasan, C., *Tetrahedron,* **1999**, *55*, 12655. (p) Nowakowska, M.; Storsberg, J.; Zapotoczny, S. and Guillet, J. E., *New J. Chem.,* **1999**, *23*, 617. (q) Bonesi, S. M. and Erra-Balsells, R., *J. Photochem. Photobio., A: Chem.,* **1997**, *110*, 271. (r) Molokov, I. F.; Tsentalovich, Yu. P.; Yurkovskaya, A. V. and Sagdeev, R. Z., *J. Photochem. Photobio., A: Chem.,* **1997**, *110*, 159. (s) Gritsan, N. P.; Tsentalovich, Y. P.; Yurkovskaya, A. V. and Sagdeev, R. Z., *J. Phys. Chem.,* **1996**, *100*, 4448. (t) Jimenez, M. C.; Leal, P.; Miranda, M. A. and Tormos, R., *J. Chem. Soc., Chem. Commun.,* **1995**, 2009. (u) Suau, R.; Torres, G. and Valpuesta, M., *Tetrahedron Lett*., **1995**, *36*, 1311. (v) Pitchumani, K.; Velusamy, P.; Manickam, M. C. D. and Srinivasan, C., *Proc. Indian Acad. Sci., Chem. Sci.,* **1994**, *106*, 49. (w) Arai, T.; Tobita, S. and Shizuka, H., *Chem. Phys. Lett.,* **1994**, *223*, 521. (x) Algarra, F. and Miranda, M. A., *Heterocycles,* **1993**, *36*, 2335. (y) Chauhan, R. P. S.; Singh, M. P.; Dubey, V. K. and Singh, U. B., *Asian J. Chem.,* **1993**, 5, 831. (z) Pitchumani, K.; Manickam, M. C. D. and Srinivasan, C., *Indian J. Chem., Sect. B,* **1993**, *32B*, 1074. (aa) Whitcombe, M. J.; Gilbert, A. and Mitchell, G. R., *Polymer*, **1993**, *34*, 1347. (bb) Sridar, V. and Sundara Rao, V. S., *J. Photochem. Photobio., A: Chem.,* **1992**, *69*, 325. (cc) Xie, R. Q.; Liu, Y. C. and Lei, X. G., *Res. Chem. Intermediates,* **1992**, *18*, 61. (dd) Seto, H.; Kosemura, H. and Fujimoto, Y., *J. Chem. Soc., Chem. Commun.,* **1992**, 908. (ee) Miranda, M. A.; Primo, J. and Tormos, R., *Heterocycles*, **1991**, *32*, 1159. (ff) Loong, W. A. and Su, A. N., *Microelectronic Eng.,* **1991**, *13*, 101. (gg) Stumpe, J.; Selbmann, C. and Dreysig, D., *J. Photochem. Photobio., A: Chem.,* **1991**, *58*, 15. (hh) Pitchumani, K.; Manickam, M. C. D. and Srinivasan, C., *Tetrahedron Lett*., **1991**, *32*, 2975. (ii) Katagi, T., *Nippon Noyaku Gakkaishi*, **1991**, *16*, 57. (jj) Belled, C.; Miranda, M. A. and Simon-Fuentes, A., *Anales Quim.,* **1990**, *86*, 431. (kk) Chan, A. C. and Hilliard, P. R., *Tetrahedron*

Lett., **1989**, *30*, 6483. (ll) Chakrabarti, A.; Biswas, G. K. and Chakraborty, D. P., *Tetrahedron,* **1989**, *45*, 5059. (mm) Syamala, M. S.; Rao, B. N. and Ramamurthy, V., *Tetrahedron*, **1988**, *44*, 7234. (nn) Miranda, M. A.; Primo, J. and Tormos, R., *Heterocycles*, **1988**, *27*, 673. (oo) Nassetta, M.; De Rossi, R. H. and Cosa, J. J., *Can. J. Chem.,* **1988**, *66*, 2794. (pp) Garcia, H.; Miranda, M. A. and Primo, J., *J. Chem. Res. (S),* **1986**, 100. (qq) Sharma, P. K. and Khanna, R. N., *Acta Chim. Hungarica,* **1985**, *120*, 159. (rr) Garcia, H.; Martinez-Utrilla, R. and Miranda, M. A., *Tetrahedron,* **1985**, *41*, 3131. (ss) Garcia, H.; Iborra, S.; Miranda, M. A. and Primo, J., *Heterocycles*, **1985**, *23*, 1983. (tt) Sharma, P. K. and Khanna, R. N., *Monatsh. Chem.,* **1985**, *116*, 353. (uu) Sharma, P. K. and Khanna, R. N., *Indian J. Chem., Sect. B,* **1984**, *23B*, 891. (vv) Abdel-Malik, M. M. and De Mayo, P., *Can. J. Chem.,* **1984**, *62*, 1275. (ww) Tessier, T.; Frechet, J. M. J.; Ito, H. and Willson, C. G., *Polymer Preprints,* **1984**, *25*, 313. (xx) Pathak, V. P.; Saini, T. R. and Khanna, R. N., *Monatsh. Chem.,* **1983**, *114*, 1269. (yy) Li, X. B.; Winnik, M. A. and Guillet, J. E., *J. Poly. Sci., Poly. Chem. Ed.,* **1983**, *21*, 1263. (zz) Olson, D. R., *J. Appl. Poly. Sci.,* **1983**, *28*, 1159. (aaa) Garcia, H.; Miranda, M. A.; Roquet-Jalmar, M. F. and Martinez-Utrilla, R., *Liebigs Ann. Chem.,* **1982**, 2238. (bbb) Farina, F.; Martinez-Utrilla, R. and Paredes, M. C., *Tetrahedron*, **1982**, *38*, 1531. (ccc) Martinez-Utrilla, R. and Miranda, M. A., *Tetrahedron Lett*., **1980**, *21*, 2281. (ddd) Crouse, D. J.; Hurlbut, S. L. and Wheeler, D. M. S., *Synth. Commun.,* **1979**, *9*, 877. (eee) Maki, Y. and Sako, M., *J. Chem. Soc., Perkin Trans. I,* **1979**, 1478. (fff) Erndt, A.; Sepiol, J.; Pyrc, G. and Krajewska, A., *Pol. J. Chem.,* **1979**, *53*, 533. (ggg) Avnir, D.; De Mayo, P. and Ono, I., *J. Chem. Soc., Chem. Commun.,* **1978**, 1109. (hhh) Mehlhorn, A.; Schwenzer, B.; Brueckner, H. J. and Schwetlick, K., *Tetrahedron*, **1978**, 34, 481. (iii) Escobar, C.; Farina, F.; Martinez-Utrilla, R. and Paredes, M. C., *J. Chem. Res. (S),* **1977**, 266. (jjj) Mehlhorn, A.; Schwenzer, B. and Schwetlick, K., *Tetrahedron*, **1977**, *33*, 1489. (kkk) Mehlhorn, A.; Schwenzer, B. and Schwetlick, K., *Tetrahedron*, **1977**, *33*, 1483. (lll) Gaitonde, V. D. and Hosangadi, B. D., *Indian J. Chem., Sect. B,* **1977**, *15*, 83. (mmm) Tsutsumi, K.; Matsui, K. and Shizuka, H., *Mol. Photochem.,* **1976**, *7*, 325. (nnn) Veierov, D.; Bercovici, T.; Fischer, E.; Mazur, Y. and Yogev, A., *Helv. Chim. Acta,* **1975**, *58*, 1240. (ooo) Noack, R. and Schwetlick, K., *Tetrahedron,* **1974**, *30*, 3799. (ppp) Kanaoka, Y. and Hatanaka, Y., *Heterocycles*, **1974**, *2*, 423. (qqq) Adam, W., *J. Chem. Soc., Chem. Commun.,* **1974**, 289. (rrr) Ohto, Y.; Shizuka, H.; Sekiguchi, S. and Matsui, K., *Bull. Chem. Soc. Jpn.,* **1974**, *47*, 1209. (sss) Onodera, J. and Obara, H., *Bull. Chem. Soc. Jpn.,* **1974**, *47*, 240. (ttt) Tamura, Y.; Uraoka, J.; Fukumori, S. and Kita, Y., *Chem. Pharm. Bull.,* **1973**, *21*, 1372. (uuu) Katsuhara, Y.; Maruyama, H.; Shigemitsu, Y. and Odaira, Y., *Tetrahedron Lett*., **1973**, 1323. (vvv) Hobbs, P. L. and Magnus, P. D., *J. Chem. Soc., Perkin Trans. I,* **1973**, 469. (www) Nasielski-Hinkens, R.; Maeck, J. and Tenvoorde, M., *Tetrahedron,* **1972**, *28*, 5025. (xxx) Inoue, T.; Shigemitsu, Y. and Odaira, Y., *J. Chem. Soc., Chem. Commun.,* **1972**, 668. (yyy) Kende, A. S. and Belletire, J. L., *Tetrahedron Lett*., **1972**, 2145. (zzz) Kalmus, C. E. and Hercules, D. M., *Tetrahedron Lett*., **1972**, 1575. (aaaa) Humphrey, J. S. and Roller, R. S., *Mol. Photochem.,* **1971**, *3*, 35. (bbbb) Hageman, H. J., *Tetrahedron*, **1969**, *25*, 6015. (cccc) Snell, B. K., *J. Chem. Soc. C,* **1968**, 2367. (dddd) Bellus, D.; Hrdlovic, P. and Slama, P., *Coll. Czech. Chem. Commun.,* **1968**, *33*, 2646. (eeee) Obara, H. and Takahashi, H., *Bull. Chem. Soc. Jpn.,* **1967**, *40*, 1012. (ffff) Stratenus, J. L. and Havinga, E., *Rec. Trav. Chim. Pays-Bas,* **1966**, *85*, 434. (gggg) Finnegan, R. A. and Hagen, A. W., *Tetrahedron Lett*., **1963**, 365.

7. (a) Kaanumalle, L. S.; Gibb, C. L. D.; Gibb, B. C. and Ramamurthy, V., *Org. Biomol. Chem.,* **2007**, *5*, 236. (b) Koodanjeri, S.; Pradhan, A. R.; Kaanumalle, L. S. and Ramamurthy, V., *Tetrahedron Lett*., **2003**, *44*, 3207. (c) Gu, W. Q.; Warrier, M.; Ramamurthy, V. and Weiss, R. G., *J. Am. Chem. Soc.,* **1999**, *121*, 9467. (d) Tung, C.-H. and Xu, X.-H., *Tetrahedron Lett*., **1999**, *40*, 127. (e) Ko, S. H. and Chae, W. K., *Bull. Korean Chem. Soc.,* **1998**, *19*, 513. (f) Pitchumani, K.; Warrier, M.; Cui, C.; Weiss, R. G. and Ramamurthy, V., *Tetrahedron Lett*., **1996**, *37*, 6251. (g) Baldvins, J. E.; Cui, C. X. and Weiss, R. G., *Photochem. Photobio.,* **1996**, *63*, 726. (h) Pitchumani, K.; Warrier, M. and Ramamurthy, V., *J. Am. Chem. Soc.,* **1996**, *118*, 9428. (i) Wang, Z. Y.; Holden, D. A. and McCourt, F. R. W., *Macromolecules*, **1990**, *23*, 3773. (j) Belled, C.; Miranda, M. A. and Simon-Fuentes, A., *Anales Quim., Ser. C,* **1989**, *85*, 39. (k) Shine, H. J. and Subotkowski,

W., *J. Org. Chem.,* **1987**, *52*, 3815. (l) Jayachandran, T.; Manimaran, T. and Ramakrishnan, V. T., *Proc. Indian Acad. Sci., Chem. Sci.,* **1986**, *97*, 41. (m) Lohse, D.; Kuehler, E. and Schwetlick, K., *Zeitsch. Phys. Chem.,* **1978**, *259*, 762. (n) Stumpe, J.; Mehlhorn, A. and Schwetlick, K., *J. Photochem.,* **1978**, *8*, 1. (o) Li, S. K. L. and Guillet, J. E., *Macromolecules*, **1977**, *10*, 840. (p) Crump, D. R.; Franck, R. W.; Gruska, R.; Ozorio, A. A.; Pagnotta, M.; Siuta, G. J. and White, J. G., *J. Org. Chem.,* **1977**, *42*, 105. (q) Keroulas, H.; Ouannes, C. and Beugelmans, R., *Bull. Soc. Chim. Fr,* **1975**, 793. (r) Le Goff, M. T. and Beugelmans, R., *Bull. Soc. Chim. Fr,* **1974**, 2047. (s) Plank, D. A., *Tetrahedron Lett*., **1969**, *50*, 4365. (t) Sandner, M. R.; Hedaya, E. and Trecker, D. J., *J. Am. Chem. Soc.,* **1968**, *90*, 7249. (u) Plank, D. A., *Tetrahedron Lett*., **1968**, 5423.

8. Coppinger, G. M. and Bell, E. R., *J. Phys. Chem.,* **1966**, *70*, 3479.
9. Jefferson, A. and Wangchareontrakul, S., *Aust. J. Chem.,* **1985**, *38*, 604.
10. Meyer, J. W. and Hammond, G. S., *J. Am. Chem. Soc.,* **1977**, *94*, 2219.
11. (a) Adam, W., *J. Chem. Soc., Chem. Commun.,* **1974**, 289. (b) Finnegan, R. A. and Mattice, J. J., *Tetrahedron,* **1965**, *21*, 1015. (c) Anderson, J. C. and Reese, C. G, *J. Chem. Soc.,* **1963**, 781.
12. (a) Miranda, P. M. and Factor, A., *J. Polym. Sci., Part A,* **1989**, *27*, 4427. (b) Bellus, D., *Adv. Photochem.,* **1971**, *8*, 109.
13. (a) Shizuka, H., *Bull. Chem. Soc. Jpn.,* **1969**, *42*, 52. (b) Shizuka, H. and Tanaka, T., *Bull. Chem. Soc. Jpn.,* **1968**, *41*, 2343. (c) Elad, D., *Tetrahedron Lett.,* **1963**, 873.
14. Nozaki, H.; Okada, R.; Noyori, R. and Kawanisi, M., *Tetrahedron,* **1966**, *22*, 2177.
15. Lally, J. M. and Spillane, W. J., *J. Chem. Soc., Perkin. Trans. II,* **1991**, 803.
16. (a) Subramanian, P.; Greed, D.; Griffin, A. C.; Hoyle, C. E. and Venkataram, K., *J. Photochem. Photobiol. A: Chem.,* **1991**, *61*, 317. (b) Obara, H.; Takahashi, H. and Hirano, H., *Bull. Chem. Soc. Jpn.,* **1969**, *42*, 560.
17. Rao, D. V. and Lamberti, V., *J. Org. Chem.,* **1967**, *32*, 2896.
18. Lally, J. M. and Spillane, W. J., *J. Chem. Soc., Chem. Commun.,* **1987**, 8.
19. Veglia, A. V.; Sanchez, A. M. and de Rossi, R. H., *J. Org. Chem.,* **1990**, *55*, 4083.
20. (a) Arumugam, S.; Vutukuri, D. R.; Thayumanavan, S. and Ramamurthy, V., *J. Am. Chem. Soc.,* **2005**, *127*, 13200. (b) Mori, T.; Takamoto, M.; Saito, H.; Furo, T.; Wada, T. and Inoue, Y., *Chem. Lett.,* **2004**, *33*, 254. (c) Mori, T.; Takamoto, M.; Saito, H.; Furo, T.; Wada, T. and Inoue, Y., *Chem. Lett.,* **2004**, *33*, 256. (d) Mori, T.; Takamoto, M.; Wada, T. and Inoue, Y, *Photochem. Photobiol. Sci.,* **2003**, *2*, 1187. (e) Sakamoto, M.; Yagi, T.; Fujita, S.; Mino, T.; Karatsu, T. and Fujita, T., *J. Org. Chem.,* **2002**, *67*, 1843. (f) Gu, W. Q. and Weiss, R. G., *J. Org. Chem.,* **2001**, *66*, 1775. (g) Yoon, H. J.; Ko, S. H.; Ko, M. K. and Chae, W. K., *Bull. Korean Chem. Soc.,* **2000**, *21*, 901. (h) Sapich, B.; Stumpe, J.; Krawinkel, T. and Kricheldorf, H. R., *Macromolecules,* **1998**, *31*, 1016. (i) Cui, C. X.; Wang, X. C. and Weiss, R. G., *J. Org. Chem.,* **1996**, *61*, 1962. (j) Cui, C. X. and Weiss, R. G., *J. Am. Chem. Soc.,* **1993**, *15*, 9820. (k) Jefferson, A. and Wangchareontrakul, S., *Aust. J. Chem.,* **1985**, *38*, 605. ((l) Lown, J. W. and Sondhi, S. M., *J. Org. Chem.,* **1984**, *49*, 2844.

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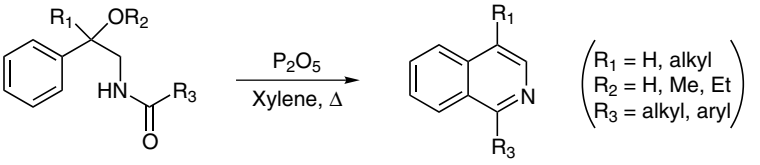
Pictet-Gams Synthesis
(Pictet-Gams Cyclization)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Pictet and Gams in 1910.[1] It is the transformation of *N*-acyl 2-hydroxy (or alkoxy) phenylethylamine into isoquinoline derivatives by the treatment with a dehydration agent such as P_2O_5 in toluene or xylene.[2] This reaction is a modification of the *Bischler-Napieralski Isoquinoline Synthesis*,[3] and is generally known as the Pictet-Gams reaction,[3f,4] Pictet-Gams synthesis,[2,4a–4e,5] or Pictet-Gams isoquinoline synthesis.[4d,4e,6] Occasionally, it is also referred to as the Pictet-Gams cyclization,[5,7] or Pictet-Gams ring closure reaction.[8]

This reaction is a stepwise reaction[3f] involving the loss of the first water (or alcohol) molecule to form the styrylamide intermediate,[2,3f,9] followed by a ring closure and loss of the second water molecule. Although this reaction overcomes the further dehydrogenation in the *Bischler-Napieralski Isoquinoline Synthesis*,[3b] it is trammeled by the availability of its starting material,[5] and the occasional formation of oxazoline by-products,[2,3f,5,9a] as in the case of *N*-acyl 2-trifluoromethyl-2-hydroxy-phenylethylamine.[7] It is recommended that the treatment of carbinol by an alkaline-dehydrating agent, such as the Grignard reagent, would reduce the amount of oxazolines formed.[9b]

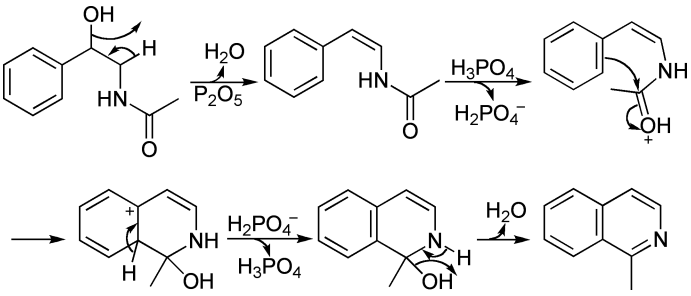
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

A representative mechanism is displayed here for *N*-acetyl 2-hydroxy phenylethylamine.



D. MODIFICATION

$POCl_3$ has been applied as the dehydration reagent.[3b,5]

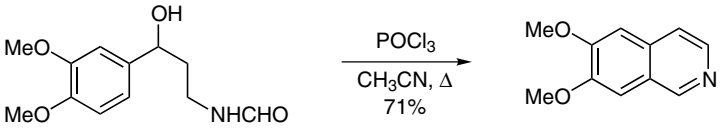
E. APPLICATIONS

This reaction is useful for the preparation of isoquinoline derivatives.

F. RELATED REACTIONS

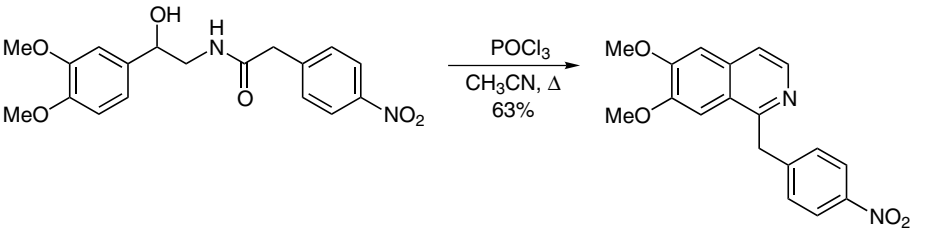
This reaction is related to the *Bischler-Napieralski Isoquinoline Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 5.

To a refluxing solution of 1.0 g *N*-[2-hydroxy-2-(3,4-dimethoxyphenyl)ethyl]formamide in 40 mL CH_3CN was added 2 mL $POCl_3$ mixed with 5 mL CH_3CN dropwise. After 1 hour, the mixture was cooled, the solvent was evaporated, and the residue was transferred to a separation funnel by ice water and washed with ether. The aqueous layer was basified with conc. NH_4OH and extracted with CH_2Cl_2. Upon removal of solvent, the residue was chromatographed to afford 0.628 g 6,7-dimethoxyisoquinoline, in a yield of 71%, m.p. 89–90°C.



Reference 3b.

A mixture of 0.12 mol *N*-[2-hydroxy-2-(3,4-dimethoxyphenyl)ethyl]-4-nitrobenzeneacetamide and 27.5 g $POCl_3$ (0.18 mol) in 500 mL CH_3CN was refluxed for 30 min. After the mixture was cooled, the solvent was removed under reduced pressure. The residue was dissolved in 400 mL 4 N HCl and washed with $CHCl_3$ (2×200 mL); the aqueous layer was basified with 50% NaOH and extracted with $CHCl_3$ (2×100 mL). The combined $CHCl_3$ extracts were dried over $MgSO_4$. Upon removal of solvent, the residue was purified by silica gel column chromatography ($CHCl_3$/MeOH/NH_4OH, 94:5:1). The collected fraction was dried and recrystallized from $CHCl_3/Et_2O$ to afford 63% 6,7-dimethoxy-1-(4-nitrobenzyl)isoquinoline, m.p. 195–196°C.

Other references related to the Pictet-Gams synthesis are cited in the literature.[10]

H. REFERENCES

1. Pictet, A. and Gams, A., *Ber.,* **1910**, *43*, 2384.
2. Bergstrom, F. W.,*Chem. Rev.,* **1944**, *35*, 77.
3. (a) Doi, S.; Shirai, N. and Sato, Y., *J. Chem. Soc., Perkin Trans. I,* **1997**, 2217. (b) Walker, K. A.; Boots, M. R.; Stubbins, J. F.; Rogers, M. E. and Davis, C. W., *J. Med. Chem.,* **1983**, *26*, 174. (c) Szabo, J.; Simon, L. and Vinkler, E., *Acta Pharm. Hungarica,* **1969**, *39*, 106. (d) Fujitani, K.; Matsumoto, N.; Yoshioka, K.; Yoshida, I. and Inubushi, Y., *Yakugaku Zasshi*, **1964**, *84*, 333. (e) Fujitani, I. K. and Kishimoto, T., *Yakugaku Zasshi*, **1964**, *84*, 329. (f) Whaley, W. M. and Hartung, W. H., *J. Org. Chem.,* **1949**, *14*, 650.
4. (a) Kopczynski, T., *Pol. J. Chem.,* **1994**, *68*, 73. (b) Kopczynski, T., *Pol. J. Chem.,* **1985**, *59*, 375. (c) Kopczynski, T. and Goszczynski, S., *Pol. J. Chem.,* **1981**, *55*, 393. (d) Ardabilchi, N. and Fitton, A. O., *J. Chem. Res. (S),* **1979**, 310. (e) Ardabilchi, N.; Fitton, A. O.; Frost, J. R.; Oppong-Boachie, F. K.; Hadi, A. H. A. and Sharif, A. M., *J. Chem. Soc., Perkin Trans. I,* **1979**, 539. (f) Fitton, A. O.; Frost, J. R.; Zakaria, M. M. and Andrew, G., *J. Chem. Soc., Chem. Commun.,* **1973**, 889. (g) Dutta, N. L.; Wadia, M. S. and Bindra, A. P., *J. Indian Chem. Soc.,* **1971**, *48*, 873. (h) Bindra, A. A.; Wadia, M. S. and Dutta, N. L., *Tetrahedron Lett*., **1968**, 2677. (i) Herz, W. and Tsai, L., *J. Am. Chem. Soc.,* **1955**, *77*, 3529.
5. Falck, J. R.; Manna, S. and Mioskowski, C., *J. Org. Chem.,* **1981**, *46*, 3742.
6. (a) Ardabilchi, N.; Fitton, A. O.; Haidi, A. H. A. and Thompson, J. R., *J. Chem. Res. (S),* **1982**, 156. (b) Ardabilchi, N.; Fitton, A. O.; Frost, J. R. and Oppong-Boachie, F., *Tetrahedron Lett*., **1977**, 4107.
7. Poszavacz, L. and Simig, G., *J. Heterocycl. Chem.,* **2000**, *37*, 343.
8. Poszavacz, L. and Simig, G., *Tetrahedron,* **2001**, *57*, 8573.
9. (a) Krabbe, W.; Eisenlohr, W. and Schöne, H. G., *Ber.,* **1940**, *73*, 656. (b) Krabbe, W.; Polzin, E. and Culemeyer, K., *Ber.,* **1940**, *73*, 652. (c) Krabbe, W.; Böhlk, H. H. and Schmidt, K. H.,

Ber., **1938**, *71*, 64. (d) Kozlov, N. S. and Rodman, G., *J. Gen. Chem. USSR,* **1937**, *7*, 836 [*Chem. Abstr.,* **1937**, *31*, 5775]. (e) Kozlov, N. S. and Serko, O., *J. Gen. Chem. USSR,* **1937**, *7*, 832 [*Chem. Abstr.,* **1937**, *31*, 5775]. (f) Krabbe, W., *Ber.,* **1936**, *69*, 1569.

10. (a) Minter, D. E. and Re, M. A., *J. Org. Chem.,* **1988**, *53*, 2653. (b) Bindra, A. A.; Wadia, M. S. and Dutta, N. L., *Tetrahedron Lett.,* **1968**, 2677. (c) Gensler, W. Y., *Heterocycl. Compd.,* **1952**, *4*, 361. (d) Whaley, W. M. and Govindachari, T. R., *Org. React.,* **1951**, *6*, 151. (e) Von Fodor, G., *Ber.,* **1943**, *76*, 1216. (f) Bruckner, V. and von Fodor, G., *Ber.,* **1938**, *71*, 541. (g) Rosenmund, K. W.; Nothnagel, M. and Reisenfeldt, H., *Ber.,* **1927**, *60*, 392. (h) Forsyth, R.; Kelly, C. I. and Pyman, F. L., *J. Chem. Soc.,* **1925**, *127*, 1659. (i) Rosenmund, K. W., *Ber.,* **1913**, *46*, 1034.

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Pictet-Spengler Reaction

(Pictet-Spengler Cyclization, Pictet-Spengler Condensation)

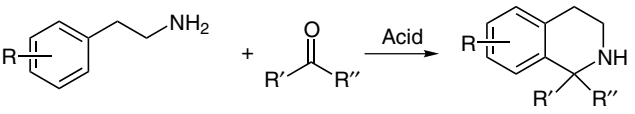
A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Pictet and Spengler in 1911.[1] It is the synthesis of tetrahydroisoquinoline or tetrahydro-β-carboline derivatives by the condensation of an arylethylamine and a carbonyl compound, primarily an aldehyde. Therefore, this reaction is generally known as the Pictet-Spengler reaction.[2,3] In addition, this reaction is also referred to as the Pictet-Spengler cyclization,[2a,2c,2g,3rr,4] Pictet-Spengler condensation,[3cc,5] or the Pictet-Spengler synthesis.[2c,3ss,6] Occasionally, it is called the Pictet-Spengler heterocyclization.[3ab] It is known that this reaction involves the formation of an imine from aldehyde and arylethylamine, which under acidic conditions electrophilically attacks the aromatic ring via the iminium intermediate to give tetrahydroisoquinolines.[2a] A comparable reaction from ketones may involve the formation of an enamine intermediate. Arylethylamine, such as phenylethylamine, phenylalanine, and tyrosine are all feasible amines,[2a] whereas certain aldehydes and ketones are not suitable candidates for this reaction, including acetone[2g] and some benzaldehydes with an *ortho*- electron-donating group.[4w] This reaction is best carried out under acidic conditions,[2a] although examples under basic conditions are also known.[7] The extension of this reaction by the formation of an *N*-acyliminium intermediate from the acylation of imine with acyl halide is now known as the *N*-acyliminium Pictet-Spengler reaction,[2a,3u,3y,3kk,8] *N*-acyliminium Pictet-Spengler condensation,[8e] or acyl Pictet-Spengler reaction,[3v,3hh] and has been adapted to solid-support condition promoted by a Lewis acid.[2a] Likewise, the cyclization of 2-aryl ethanol under similar reaction conditions gives [3,4]-benzo-dihydropyran derivatives and is referred to as the *oxa*-Pictet-Spengler reaction,[3p,3gg,3uu] or *oxa*-Pictet-Spengler cyclization.[4e,4m,4n]

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

It has been found that in aqueous solution HCl and trifluoroacetic acid are superior to CH_3COOH, HCOOH, CSA, and TCA.[8c] Current studies of this reaction focus on the diastereoselective and enantioselective synthesis of tetrahydroisoquinolines via chirality transfer from the auxiliary group of either the arylethylamine or the carbonyl component,[2c,3sss,3uuu,9] or the application of chiral Lewis acid.[3oo,10]

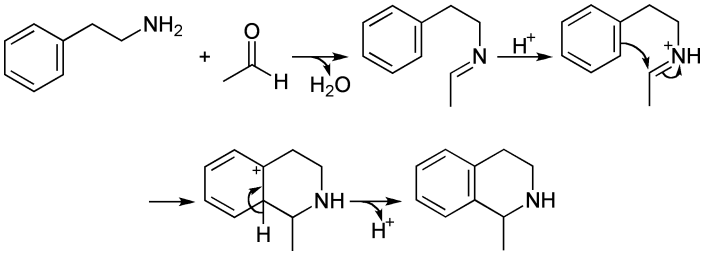
B. GENERAL REACTION SCHEME



R = electron-donating substituent
R′ = alkyl, aryl with electron-withdrawing group
R″ = H (preferred), alkyl

C. PROPOSED MECHANISMS

The mechanism is exemplified by the reaction between phenylethylamine and acetaldehyde in the presence of an acid.



D. MODIFICATION

This reaction has been extensively modified to different variants, such as the solid-support reaction,[3ll,3aaaa] *N*-acyliminium Pictet-Spengler reaction,[2a,3u,3v,3y,3hh,3kk,8] *oxa*-Pictet-Spengler reaction,[3p,3gg,3uu,4e,4m,4n] and stereoselective version of Pictet-Spengler reaction,[2c,3sss,3ooo,3uuu,9,10] In addition, the *N*-sulfonyl[3o] or sulfinyl[3xx] Pictet-Spengler reaction, and the keteniminium Pictet-Spengler cyclization[4o] and vinylogous Pictet-Spengler cyclization[2g] have also been reported. Moreover, this reaction has been promoted by microwave[3bb,3dd] or catalyzed by protic acid,[6c] superacid,[4q] or Lewis acid,[3ooo] such as $AuCl_3$/AgOTf,[8a] $Yb(OTf)_3$-TMSCl,[3ww] and zeolite.[3ff]

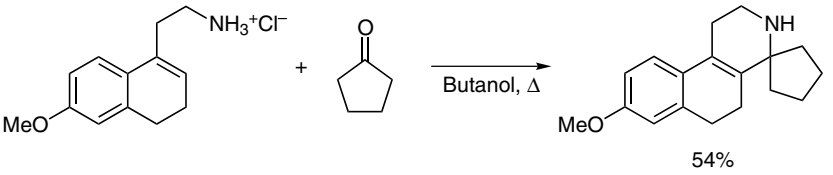
E. APPLICATIONS

This reaction has a wide and important application in alkaloid synthesis.[2g,5l]

F. RELATED REACTIONS

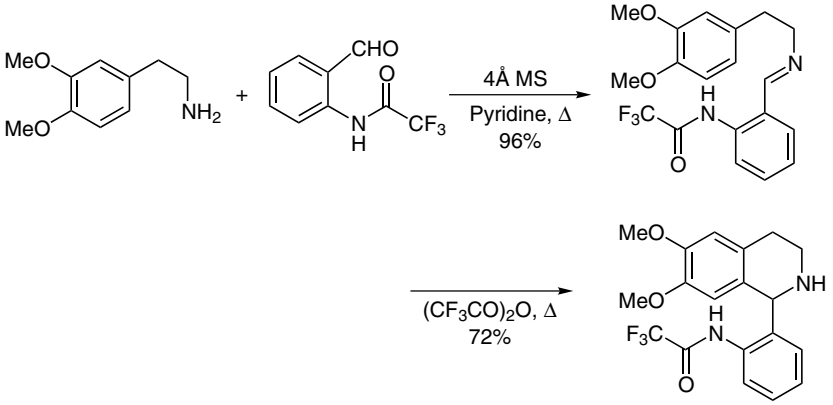
This reaction is related to the *Bischler-Napieralski Isoquinoline Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2g.

To 3 mL butanol were added 100 mg 2-(6-methoxy-3,4-dihydronaphthalen-1-yl)-ethylamine hydrochloride (0.45 mmol) and 53 mg cyclopentanone (0.63 mmol). The solution was then refluxed for 72 h, extracted with EtOAc, and washed with aqueous $NaHCO_3$. Upon removal of the solvent, the residue was purified by column chromatography to afford 60.4 mg 4-spirocyclopenta-8-methoxy-1,2,3,4,5,6-hexahydrobenzo[*f*]isoquinoline as a white solid, in a yield of 54%, $R_f = 0.19$ (MeOH/$CHCl_3$, 1:4).



Reference 4w.

A mixture of 2.17 g 2-(trifluoroacetylamino)benzaldehyde (10.0 mmol), 1.81 g homoveratrylamine (10.0 mmol), 1.0 g 4Å molecular sieves, and 15 mL pyridine was refluxed for 36 h. After filtration, the filtrate was concentrated under reduced pressure, and the resulting residue was purified on silica gel column using EtOAc/hexanes (2:3) as the eluent to afford 3.65 g *N*-[2-(3,4-dimethoxyphenyl)ethyl]-2-(trifluoroacetylamino)benzylidenimine as a yellow solid, in a yield of 96%. Recrystallization from EtOH afforded 3.0 g yellow needles, in a yield of 78%, m.p. 116.5°C. Then 1.0 g of the solid (2.63 mmol) was mixed with 3.0 mL trifluoroacetic anhydride (21.4 mmol), and the resulting mixture was heated at 80°C for 24 h. After removal of the volatiles in vacuo, the residue was purified by flash

chromatography using EtOAc/hexanes (1:2) as the eluent to give 900 mg 6,7-dimethoxy-2-(trifluoroacetyl)-1-[2-(trifluoroacetylamino)phenyl]-1,2,3,4-tetrahydroisoquinoline as a yellow solid, in a yield of 72%, m.p. 74.5°C.

Other references related to the Pictet-Spengler reaction are cited in literature.[11]

H. REFERENCES

1. Pictet, A. and Spengler, T., *Ber.,* **1911**, *44*, 2030.
2. (a) Nielsen, T. E. and Meldal, M., *J. Comb. Chem.,* **2005**, *7*, 599. (b) Konno, T.; Chae, J. H.; Miyabe, T. and Ishihara, T., *J. Org. Chem.,* **2005**, *70*, 10172. (c) Chrzanowska, M. and Rozwadowska, M. D., *Chem. Rev.,* **2004**, *104*, 3341. (d) Zhang, Z. and Schafer, L. L., *Org. Lett.,* **2003**, *5*, 4733. (e) Magnus, P.; Matthews, K. S. and Lynch, V., *Org. Lett.,* **2003**, *5*, 2181. (f) Roesch, K. R.; Zhang, H. M. and Larock, R. C., *J. Org. Chem.,* **2001**, *66*, 8042. (g) Cesati, R. R. and Katzenellenbogen, J. A., *Org. Lett.,* **2000**, *2*, 3635. (h) Kitamura, M.; Hsiao, Y.; Ohta, M.; Tsukamoto, M.; Ohta, T.; Takaya, H. and Noyori, R., *J. Org. Chem.,* **1994**, *59*, 297. (i) Wood, G. W.; Mak, N. and Hogg, A. M., *Anal. Chem.,* **1976**, *48*, 981. (j) Shan, R. J.; Vaghani, D. D. and Merchant, J. R., *J. Org. Chem.,* **1961**, *26*, 3533.
3. (a) El Kaim, L.; Gageat, M.; Gaultier, L. and Grimaud, L., *Synlett*, **2007**, 500. (b) Diness, F.; Beyer, J. and Meldal, M., *Chem. Eur. J.,* **2007**, *13*, 2169. (c) Saha, B.; Sharma, S.; Sawant, D. and Kundu, B., *Tetrahedron Lett*., **2007**, *48*, 1379. (d) Saito, A.; Numaguchi, J. and Hanzawa, Y., *Tetrahedron Lett*., **2007**, *48*, 835. (e) Han, D. M.; Foersterling, F. H.; Deschamps, J. R.; Parrish, D.; Liu, X. X.; Yin, W. Y.; Huang, S. M. and Cook, J. M., *J. Nat. Prod.,* **2007**, *70*, 75. (f) Zheng, X. F.; Wang, X. L.; Chang, J. B. and Zhao, K., *Synlett,* **2006**, 3277. (g) Lee, S.-G.; Hong, S.-P.; Kim, D. Y.; Song, J. J.; Ro, H.-S. and Sung, M.-H., *FEBS J.,* **2006**, *273*, 5564. (h) Sharma, S. D.; Bhaduri, S. and Kaur, G., *Indian J. Chem., Sect. B,* **2006**, *45B*, 2710. (i) Youn, S. W., *Org. Prep. Proc. Int.,* **2006**, *38*, 505. (j) Diness, F.; Beyer, J. and Meldal, M., *Chem. Eur. J.,* **2006**, *12*, 8056. (k) David, E.; Rangheard, C.; Pellet-Rostaing, S. and Lemaire, M., *Synlett,* **2006**, 2016. (l) De la Figuera, N.; Fiol, S.; Fernandez, J.-C.; Forns, P.; Fernandez-Forner, D. and Albericio, F., *Synlett*, **2006**, 1903. (m) Wang, H.-M.; Hou, R.-S.; Huang, H.-Y. and Chen, L.-C., *Heterocycles*, **2006**, *68*, 1651. (n) Cheng, P. and Chen, J. J., *Huaxue Tongbao*, **2006**, *69*, w065/1. (o) Liu, J.; Jian, T. Y.; Sebhat, I. and Nargund, R., *Tetrahedron Lett*., **2006**, *47*, 5115. (p) Hegedues, A. and Hell, Z., *Org. Biomol. Chem.,* **2006**, *4*, 1220. (q) Duggineni, S.; Sawant, D.; Saha, B. and Kundu, B., *Tetrahedron*, **2006**, *62*, 3228. (r) Aubry, S.; Pellet-Rostaing, S.; Faure, R. and Lemaire, M., *J. Heterocycl. Chem.,* **2006**, *43*, 139. (s) Seayad, J.; Seayad, A. M. and List, B., *J. Am. Chem. Soc.,* **2006**, *128*, 1086. (t) Larghi, E. L.; Amongero, M.; Bracca, A. B. J. and Kaufman, T. S., *ARKIVOC,* **2005**, (*xii)*, 98. (u) Nielsen, T. E.; Le Quement, S. and Meldal, M., *Tetrahedron Lett*., **2005**, *46*, 7959. (v) Belyk, K., *Chemtracts,* **2005**, *18*, 57. (w) Manabe, K.; Nobutou, D. and Kobayashi, S., *Bioorg. Med. Chem.,* **2005**, *13*, 5154. (x) Numa, M. M. D.; Lee, L. V.; Hsu, C.-C.; Bower, K. E. and Wong, C.-H., *ChemBioChem*, **2005**, *6*, 1002. (y) Nielsen, T. E. and Meldal, M., *Org. Lett.,* **2005**, *7*, 2695. (z) Li, D. H.; Zhang, Y. B.; Guo, W. and Xia, C. Z., *Heterocycles*, **2005**, *65*, 1063. (aa) Kundu, B.; Sawant, D.; Partani, P. and Kesarwani, A. P., *J. Org. Chem.,* **2005**, *70*, 4889. (bb) Mesangeau, C.; Yous, S.; Peres, B.; Lesieur, D. and Besson, T., *Tetrahedron Lett*., **2005**, *46*, 2465. (cc) Kundu, B.; Sawant, D. and Chhabra, R., *J. Comb. Chem.,* **2005**, *7*, 317. (dd) Kuo, F.-M.; Tseng, M.-C.; Yen, Y.-H. and Chu, Y.-H., *Tetrahedron,* **2004**, *60*, 12075. (ee) Campiglia, P.; Gomez-Monterrey, I.; Lama, T.; Novellino, E. and Grieco, P., *Mol. Diversity,* **2004**, *8*, 427. (ff) Hegedues, A. and Hell, Z., *Tetrahedron Lett*., **2004**, *45*, 8553. (gg) Zhao, B.-X.; Sha, L.; Tan, W.; Zuo, H. and Wang, D.-W., *Youji Huaxue,* **2004**, *24*, 1300. (hh) Taylor, M. S. and Jacobsen, E. N., *J. Am. Chem. Soc.,* **2004**, *126*, 10558. (ii) Wang, Y.; Liu, Z. Z.; Chen, S. Z. and Liang, X. T., *Chinese Chem. Lett.,* **2004**, *15*, 505. (jj) Kane, T. R.; Ly, C. Q.; Kelly, D. E. and Dener, J. M.,

J. Comb. Chem., **2004**, *6*, 564. (kk) Alberch, L.; Bailey, P. D.; Clingan, P. D.; Mills, T. J.; Price, R. A. and Pritchard, R. G., *Eur. J. Org. Chem.,* **2004**, 1887. (ll) Nielsen, T. E.; Diness, F. and Meldal, M., *Curr. Opinion Drug. Discovery & Dev.,* **2003**, *6*, 801. (mm) Horiguchi, Y.; Nakamura, M.; Saitoh, T. and Sano, T., *Chem. Pharm. Bull.,* **2003**, *51*, 1368. (nn) Venkov, A. P. and Angelov, P. A., *Synth. Commun.,* **2003**, *33*, 3025. (oo) Horiguchi, Y.; Nakamura, M.; Kida, A.; Kodama, H.; Saitoh, T. and Sano, T., *Heterocycles,* **2003**, *59*, 691. (pp) Srinivasan, N. and Ganesan, A., *Chem. Commun.,* **2003**, 916. (qq) Tsuji, R.; Nakagawa, M. and Nishida, A., *Tetrahedron: Asymmetry*, **2003**, *14*, 177. (rr) Silveira, C. C.; Bernardi, C. R.; Braga, A. L. and Kaufman, T. S., *Tetrahedron Lett*., **2003**, *44*, 6137. (ss) Fasfous, I. I.; El-Abadelah, M. M. and Sabri, S. S., *J. Heterocycl. Chem.,* **2002**, *39*, 225. (tt) Pezzella, A. and Prota, G., *Tetrahedron Lett*., **2002**, *43*, 6719. (uu) Miles, W. H.; Heinsohn, S. K.; Brennan, M. K.; Swarr, D. T.; Eidam, P. M. and Gelato, K. A., *Synthesis,* **2002**, 1541. (vv) Horiguchi, Y.; Kodama, H.; Nakamura, M.; Yoshimura, T.; Hanezi, K.; Hamada, H.; Saitoh, T. and Sano, T., *Chem. Pharm. Bull.,* **2002**, *50*, 253. (ww) Tsuji, R.; Yamanaka, M.; Nishida, A. and Nakagawa, M., *Chem. Lett.,* **2002**, 428. (xx) Gremmen, C.; Wanner, M. J. and Koomen, G.-J., *Tetrahedron Lett*., **2001**, *42*, 8885. (yy) Somei, M.; Teranishi, S.; Yamada, K. and Yamada, F., *Chem. Pharm. Bull.,* **2001**, *49*, 1159. (zz) Singh, K.; Deb, P. K. and Venugopalan, P., *Tetrahedron*, **2001**, *57*, 7939. (aaa) Spengler, J.; Schedel, H.; Sieler, J.; Quaedflieg, P. J. L. M.; Broxterman, Q. B.; Duchateau, A. L. L. and Burger, K., *Synthesis,* **2001**, 1513. (bbb) Manini, P.; d'Ischia, M. and Prota, G., *Bioorg. Med. Chem.,* **2001**, *9*, 923. (ccc) Bagutsky, V. V. and Kulinkovich, O. G., *Chem. Heterocycl. Compd.,* **2000**, *36*, 537. (ddd) Koike, T.; Shinohara, Y.; Tobinaga, S. and Takeuchi, N., *Chem. Pharm. Bull.,* **2000**, *48*, 1898. (eee) Yu, S.; Berner, O. M. and Cook, J. M., *J. Am. Chem. Soc.,* **2000**, *122*, 7827. (fff) Singh, K. and Deb, P. K., *Tetrahedron Lett.,* **2000**, *41*, 4977. (ggg) Dondas, H. A.; Duraisingham, J.; Grigg, R.; MacLachlan, W. S.; MacPherson, D. T.; Thornton-Pett, M.; Sridharan, V. and Suganthan, S., *Tetrahedron,* **2000**, *56*, 4063. (hhh) Li, X. F.; Zhang, L. S.; Hall, S. E. and Tam, J. P., *Tetrahedron Lett*., **2000**, *41*, 4069. (iii) Ducrot, P.; Rabhi, C. and Thal, C., *Tetrahedron*, **2000**, *56*, 2683. (jjj) Yu, P.; Wang, T.; Li, J. and Cook, J. M., *J. Org. Chem.,* **2000**, *65*, 3173. (kkk) Li, J.; Wang, T.; Yu, P.; Peterson, A.; Weber, R.; Soerens, D.; Grubisha, D.; Bennett, D. and Cook, J. M., *J. Am. Chem. Soc.,* **1999**, *121*, 6998. (lll) Albaneze-Walker, J.; Rossen, K.; Reamer, R. A.; Volante, R. P. and Reider, P. J., *Tetrahedron Lett*., **1999**, *40*, 4917. (mmm) Yokoyama, A.; Ohwada, T. and Shudo, K., *J. Org. Chem.,* **1999**, *64*, 611. (nnn) Hino, T. and Nakagawa, M., *Heterocycles,* **1998**, *49*, 499. (ooo) Yamada, H.; Kawate, T.; Matsumizu, M.; Nishida, A.; Yamaguchi, K. and Nakagawa, M., *J. Org. Chem.,* **1998**, *63*, 6348. (ppp) Li, J. and Cook, J. M., *J. Org. Chem.,* **1998**, *63*, 4166. (qqq) Rousseau, J.-F. and Dodd, R. H., *J. Org. Chem.,* **1998**, *63*, 2731. (rrr) Watson, T. J. N., *J. Org. Chem.,* **1998**, *63*, 406. (sss) Comins, D. L.; Thakker, P. M.; Baevsky, M. F. and Badawi, M. M., *Tetrahedron*, **1997**, *53*, 16327. (ttt) Cox, E. D.; Hamaker, L. K.; Li, J.; Yu, P.; Czerwinski, K. M.; Deng, L.; Bennett, D. W.; Cook, J. M.; Watson, W. H. and Krawiec, M., *J. Org. Chem.,* **1997**, *62*, 44. (uuu) Schmidt, G.; Waldmann, H.; Henke, H. and Burkard, M., *Chem. Eur. J.,* **1996**, *2*, 1566. (vvv) Dai, W.-M.; Zhu, H. J. and Hao, X.-J., *Tetrahedron Lett*., **1996**, *37*, 5971. (www) Legseir, B.; Aichaoui, H. and Ladjama, D., *J. Soc. Algerieene Chim.,* **1996**, *6*, 17. (xxx) Mayer, J. P.; Bankaitis-Davis, D.; Zhang, J. W.; Beaton, G.; Bjergarde, K.; Andersen, C. M.; Goodman, B. A. and Herrera, C. J., *Tetrahedron Lett*., **1996**, *37*, 5633. (yyy) Stokker, G. E., *Tetrahedron Lett*., **1996**, *37*, 5453. (zzz) Gan, T. and Cook, J. M., *Tetrahedron Lett*., **1996**, *37*, 5033. (aaaa) Yang, L. H. and Guo, L. Q., *Tetrahedron Lett*., **1996**, *37*, 5041.

4. (a) Vincent, G.; Lane, J. W. and Williams, R. M., *Tetrahedron Lett*., **2007**, *48*, 3719. (b) Wang, X. L.; Zheng, X. F.; Liu, R. H.; Reiner, J. and Chang, J. B., *Tetrahedron*, **2007**, *63*, 3389. (c) Xiang, J. B.; Zheng, L. Y.; Chen, F.; Dang, Q. and Bai, X., *Org. Lett.,* **2007**, *9*, 765. (d) Yang, M.-L.; Kuo, P.-C.; Damu, A. G.; Chang, R.-J.; Chiou, W.-F. and Wu, T.-S., *Tetrahedron*, **2006**, *62*, 10900. (e) Larghi, E. L. and Kaufman, T. S., *Synthesis,* **2006**, 187. (f) Lee, S.-C.; Choi, S. Y.; Chung, Y. K. and Park, S. B., *Tetrahedron Lett*., **2006**, *47*, 6843. (g) Muthukrishnan, M.; More, S. V.; Garud, D. R.; Ramana, C. V.; Joshi, R. R. and Joshi, R. A., *J. Heterocycl. Chem.,* **2006**, *43*, 767. (h) Che, X.; Zheng, L. Y.; Dang, Q. and Bai, X., *Tetrahedron,* **2006**, *62*, 2563. (i) Silveira, C. C.;

Vieira, A. S. and Kaufman, T. S., *Tetrahedron Lett*., **2006**, *47*, 7545. (j) Duncton, M. A. J.; Smith, L. M.; Burdzovic-Wizeman, S.; Burns, A.; Liu, H.; Mao, Y. Y.; Wong, W. C. and Kiselyov, A. S., *J. Org. Chem.,* **2005**, *70*, 9629. (k) Silveira, C. C.; Felix, L. A.; Braga, A. L. and Kaufman, T. S., *Org. Lett.,* **2005**, *7*, 3701. (l) Subramaniyan, G.; Jayashankaran, J.; Manian, R. D. R. S. and Raghunathan, R., *Synlett,* **2005**, 1167. (m) Fernandes, R. A. and Brueckner, R., *Synlett,* **2005**, 1281. (n) Zhang, X. Q.; Li, X. J.; Lanter, J. C. and Sui, Z. H., *Org. Lett.,* **2005**, *7*, 2043. (o) Zhang, Y. S.; Hsung, R. P.; Zhang, X. J.; Huang, J.; Slafer, B. W. and Davis, A., *Org. Lett.,* **2005**, *7*, 1047. (p) Luo, S. J.; Zhao, J. R. and Zhai, H. B., *J. Org. Chem.,* **2004**, *69*, 4548. (q) Nakamura, S.; Tanaka, M.; Taniguchi, T.; Uchiyama, M. and Ohwada, T., *Org. Lett.,* **2003**, *5*, 2087. (r) Padwa, A.; Danca, M. D.; Hardcastle, K. I. and McClure, M. S., *J. Org. Chem.,* **2003**, *68*, 929. (s) Dickner, T. and Laschat, S.,*Helv. Chim. Acta,* **2001**, *84*, 2064. (t) Cho, S.-D.; Song, S.-Y.; Hur, E.-J.; Chen, M.; Joo, W.-H.; Falck, J. R.; Yoon, Y.-J. and Shin, D.-S., *Tetrahedron Lett*., **2001**, *42*, 6251. (u) Silveira, C. C.; Bernardi, C. R.; Braga, A. L. and Kaufman, T. S., *Tetrahedron Lett*., **2001**, *42*, 8947. (v) Herberich, B.; Kinugawa, M.; Vazquez, A. and Williams, R. M., *Tetrahedron Lett*., **2001**, *42*, 543. (w) Von Nussbaum, F.; Miller, B.; Wild, S.; Hilger, C. S.; Schumann, S.; Zorbas, H.; Beck, W. and Steglich, W., *J. Med. Chem.,* **1999**, *42*, 3478. (x) Munchhof, M. J. and Meyers, A. I., *J. Org. Chem.,* **1996**, *61*, 4607.

5. (a) Choo, Y.-M. and Hamann, M. T., *Heterocycles*, **2007**, *71*, 245. (b) Ohya, T., *J. Agri. Food Chem.,* **2006**, *54*, 6909. (c) Manini, P.; Napolitano, A. and d'Ischia, M., *Carbohydr. Res.,* **2005**, *340*, 2719. (d) Larghi, E. L.; Amongero, M.; Bracca, A. B. J. and Kaufman, T. S., *ARKIVOC,* **2005**, (*xii*), 98. (e) Kaufman, T. S., *New Methods Asymm. Synth. Nitrogen Heterocycl.*, **2005**, 99. (f) Ohya, T. and Niitsu, M., *Life Sci.,* **2005**, *76*, 1199. (g) Wang, H.-M.; Su, C.-H.; Kang, I.-J. and Chen, L.-C., *J. Chinese Chem. Soc.,* **2002**, *49*, 375. (h) Kang, I.-J.; Wang, H.-M.; Su, C.-H. and Chen, L.-C., *Heterocycles,* **2002**, *57*, 1. (i) Manini, P.; d'Ischia, M. and Prota, G., *J. Org. Chem.,* **2001**, *66*, 5048. (j) Manini, P.; d'Ischia, M. and Prota, G., *J. Org. Chem.,* **2000**, *65*, 4269. (k) Silveira, C. C.; Bernardi, C. R.; Braga, A. L. and Kaufman, T. S., *Tetrahedron Lett*., **1999**, *40*, 4969. (l) Napolitano, A.; Pezzella, A. and Prota, G., *Chem. Res. Toxicol.,* **1999**, *12*, 1090. (m) van Maarseveen, J. H.; Mulders, S. J. E.; Aben, R. W. M.; Kruse, C. G. and Scheeren, H. W., *Tetrahedron*, **1995**, *51*, 4841. (n) Geraghty, C. A. and Cashaw, J. L., *J. Chromatography,* **1989**, *489*, 399. (o) Clezy, P. S.; Duncan, M. W. and Smythe, G. A., *Aust. J. Chem.,* **1988**, *41*, 483. (p) Czarnocki, Z.; MacLean, D. B. and Szarek, W. A., *J. Chem. Soc., Chem. Commun.,* **1985**, 1318. (q) Vercauteren, J.; Lavaud, C.; Lévy, J. and Massiot, G., *J. Org. Chem.,* **1984**, *49*, 2278. (r) Sandler, M.; Glover, V.; Armando, I. and Clow, A., *Prog. Clin. Biol. Res.,* **1982**, *90*, 215. (s) King, G. S.; Goodwin, B. L. and Sandler, M., *J. Pharm. Pharmacol.,* **1974**, *26*, 476.

6. (a) Dabaien, S. A.; El-Abadelah, M. M.; Haddad, S. F. and Duddeck, H., *Heterocycles,* **2007**, *71*, 835. (b) Connors, R. V.; Zhang, A. J. and Shuttleworth, S. J., *Tetrahedron Lett*., **2002**, *43*, 6661. (c) Cheung, G. K.; Earle, M. J.; Fairhurst, R. A.; Heaney, H.; Shuhaibar, K. F.; Eyley, S. C. and Ince, F., *Synlett,* **1991**, 721. (d) Comins, D. L. and Badawi, M. M., *Tetrahedron Lett*., **1991**, *32*, 2995. (e) Grigg, R.; Gunaratne, H. Q. N. and McNaghten, E., *J. Chem. Soc., Perkin Trans. I,* **1983**, 185. (f) Whaley, W. M. and Govindachari, T. R. *Org. React.,* **1951**, *6*, 151.

7. (a) Sun, Q. and Kyle, D. J., *Comb. Chem. High Throughput Screening,* **2002**, *5*, 75. (b) Hutchins, S. M. and Chapman, K. T., *Tetrahedron Lett.,* **1996**, *37*, 4865.

8. (a) Youn, S. W., *J. Org. Chem.,* **2006**, *71*, 2521. (b) Revell, J. D.; Srinivasan, N. and Ganesan, A., *Synlett,* **2004**, *8*, 1428. (c) Nielsen, T. E. and Meldal, M., *J. Org. Chem.,* **2004**, *69*, 3765. (d) Bonnet, D. and Ganesan, A., *J. Comb. Chem.,* **2002**, *4*, 546. (e) Wang, H. and Ganesan, A., *Org. Lett.,* **1999**, *1*, 1647.

9. (a) Gremmen, C.; Willemse, B.; Wanner, M. J. and Koomen, G.-J., *Org. Lett.,* **2000**, *2*, 1955. (b) Czarnocke, A. and Arazby, Z., *Heterocycles,* **1999**, *44*, 2871. (c) Soe, T.; Kawate, T.; Fukui, N.; Hino, T. and Nakagawa, M., *Heterocycles,* **1996**, *50*, 1033. (d) Cox, E. D. and Cook, J. M., *Chem. Rev.,* **1995**, *95*, 1797. (e) Rozwadowska, M. D., *Heterocycles,* **1994**, *39*, 903. (f) Waldmann, H. and Schmidt, G., *Tetrahedron,* **1994**, *50*, 11865.

10. Seayad, J.; Seayad, A. M. and List, B., *J. Am. Chem. Soc.,* **2006**, *128*, 1086.
11. (a) Kinderman, S. S.; Wekking, M. M. T.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H. and Rutjes, F.P. J. T., *J. Org. Chem.,* **2005**, *70*, 5519. (b) Nielsen, T. E.; Diness, F. and Meldal, M., *Curr. Opinion Drug Discovery Dev.,* **2003**, *6*. 801. (c) Flippin, L. A. and Muchowski, J. M., *J. Org. Chem.,* **1993**, *58*, 2631. (d) Dominguez, E.; Lete, E.; Badia, M. D.; Villa, M. J.; Castedo, L. and Dominguez, D.,*Tetrahedron*, **1987**, *43*, 1943. (e) Menachery, M. D.; Lavanier, G. L.; Wetherly, M. L.; Guinaudeau, H. and Shamma, M., *J. Nat. Prod.,* **1986**, *49*, 745. (f) Bailey, P. D.; Hollinshead, S. P. and Dauter, Z., *J. Chem. Soc., Chem. Commun.,* **1985**, 1507. (g) Kametani, T. and Fukumoto, K., Isoquinolines in *The Chemistry of Heterocyclic Compounds,* ed. Grethe, G., Wiley, New York, **1981**, *38*, pt.1, pp 139–274. (h) Ernst, H.,; Hauser, B. and Winterfeldt, E.*, Ber.,* **1981**, *114*, 1894. (i) Soerens, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, G. S.; Yamanaka, E.; Hutchins, L.; DiPierro, M. and Cook, J. M.*, J. Org. Chem.,* **1979**, *44*, 535. (j) Stuart, K. and Woo-Ming, R., *Heterocycles,* **1975**, *3*, 223. (k) Abramovitch, R. A. and Spenser, I. D., *Adv. Heterocycl. Chem.,* **1964**, *3*, 79. (l) Bailey, C. F. and McElvain, S. M., *J. Am. Chem. Soc.,* **1930**, *52*, 4013.

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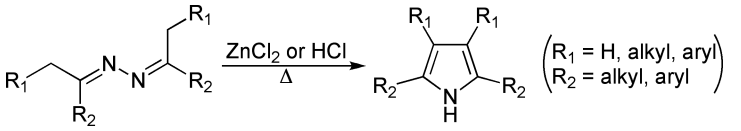
Piloty-Robinson Pyrrole Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Piloty in 1910.[1] It is the thermal transformation of enolizable ketazines into pyrrole derivatives in the presence of a catalytic amount of Lewis acid (e.g., $ZnCl_2$) or Brønsted acid (e.g., HCl)[2] and is known as the Piloty pyrrole synthesis,[2,3] Piloty reaction,[3,4] Piloty cyclization,[4b] or Piloty synthesis.[4b,5] In 1918, Robinson extensively studied this reaction again, especially for the mechanism,[6] since then the Piloty pyrrole synthesis has also been referred to as the Piloty-Robinson pyrrole synthesis[7] or simply the Piloty-Robinson synthesis[7b,8] or Piloty-Robinson reaction.[8a] It should be pointed out that for the thermal transformation of aliphatic ketazines, a competitive route also occurs to give pyrazoline as a by-product.[6,9]

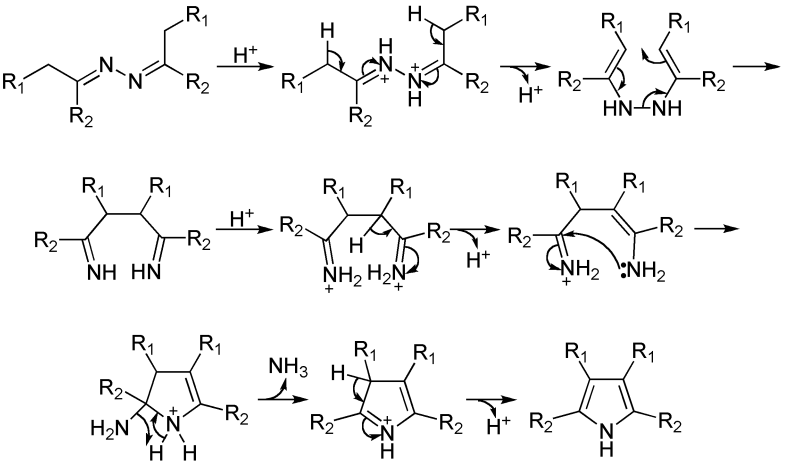
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

It has been proposed that this reaction involves a series of processes, including the tautomerization of ketazine into bisvinylhydrazine, [3,3] rearrangement, ring formation, and the subsequent elimination of ammonia, as shown below.[7b,8c,9]



D. MODIFICATION

This reaction has been modified to occur under solid-supported condition[5a] or under microwave irradiation.[8a] In addition, the base-promoted transformation from ketazine into pyrrole has also been established by the treatment of alkyl aryl ketazine with two equivalents of strong base, such as LDA.[2] However, such reaction can lead to the formation of pyrrole, tetrahydropyridazine, or pyrazole, depending on the nature of ketazine. In general, the ketazine dianions with an electron-donating group at their carbon termini form pyrroles, whereas ketazine dianions without a substituent at the terminal carbon or with an electron-withdrawing group at the terminal carbon yield tetrahydropyridazines and pyrazoles.[2]

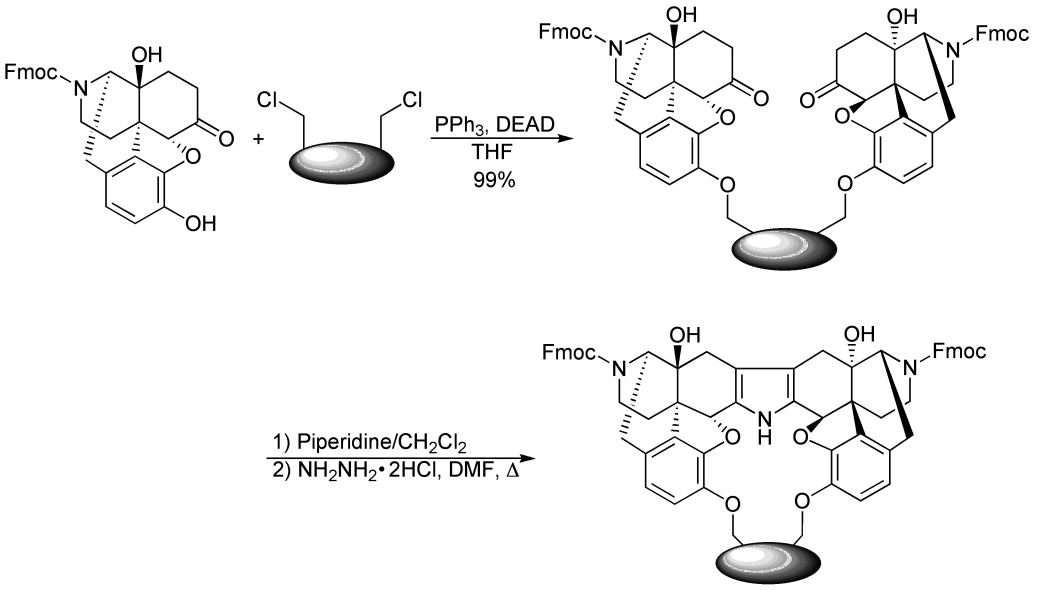
E. APPLICATIONS

This reaction is generally useful for the preparation of pyrrole derivatives.

F. RELATED REACTIONS

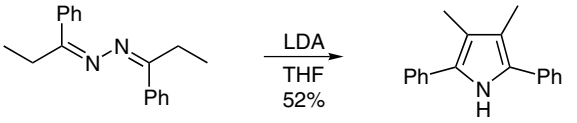
This reaction is related to the *Fischer Indole Synthesis, Hantzsch Pyrrole Synthesis, Knorr Pyrrole Synthesis* and *Paal-Knorr Pyrrole Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 5a.

To a mixture of 4.58 g morphinan (9.0 mmol), 3.0 g Wang resin (0.52 mmol/g, 1.56 mmol), and 1.33 g PPh_3 (5.1 mmol) in 30 mL anhydrous THF was added 2.04 mL 40% toluene solution of diethylazodicarboxylate (DEAD, 4.5 mmol) dropwise for 15 min at room temperature. The mixture was shaken at the same temperature for 16 h then the reaction solvent was removed by filtration. The remaining resin was washed three times, each with 30 mL DMF, MeOH, THF, and CH_2Cl_2, respectively, and dried in vacuo to afford 4.41 g resin, in a yield of 99%. This resin was then suspended in 35.2 mL CH_2Cl_2, and 8.8 mL piperidine was added dropwise at room temperature. The mixture was shaken at this temperature for 16 h and the solvent was removed by filtration. The remaining resin was washed three times, each with 40 mL DMF, MeOH, THF, and CH_2Cl_2, respectively, and dried in vacuo to afford 4.26 g of a new resin. This resin was again suspended in 42 mL DMF, and 865 mg hydrazine dihydrochloride (8.4 mmol) was added directly at room temperature. The mixture was heated at 50°C for 24 h and then allowed to cool to room temperature. The solvent was removed by filtration. The resulting resin was washed three times, each with 40 mL DMF, MeOH, THF, and CH_2Cl_2, respectively, and dried in vacuo to afford 4.04 g the resin bound pyrrole derivative.



Reference 2.

Under argon, a solution of 3.3 mmol diisopropylamine in 10 mL dry THF was treated with 3.3 mmol *n*-BuLi (15% hexane solution) at 0°C. After 10 min, 1.5 mmol propiophenone azine in 5 mL THF was added to the LDA solution at room temperature. Immediately, the yellow color of the starting ketazine turned to deep reddish brown and gradually to deep green within a few minutes. After being stirred for 24 h at room temperature, the reaction mixture was quenched with degassed water and extracted with ether. After drying over Na_2SO_4 and evaporation of the solvent, 52% 3,4-dimethyl-2,5-diphenylpyrrole was isolated through silica gel column chromatography using benzene as an eluent, m.p. 138–139°C.

Other references related to the Piloty-Robinson pyrrole synthesis are cited in the literature.[10]

H. REFERENCES

1. Piloty, von O., *Ber.,* **1910**, *43*, 489.
2. Tamaru, Y.; Harada, T. and Yoshida, Z.-I., *J. Org. Chem.,* **1978**, *43*, 3370.
3. (a) Robinson, B., *The Fischer Indole Synthesis,* John Wiley & Sons, New York, **1982**. (b) Posvic, H.; Dombro, R.; Ito, H. and Telinski, T., *J. Org. Chem.,* **1974**, *39*, 2575. (c) Robinson, B., *Chem. Rev.,* **1969**, *69*, 227.
4. (a) Kukushkin, Y. N.; Krylov, V. K.; Kaplan, S. F.; Calligaris, M.; Zangrando, E.; Pombeiro, A. J. L. and Kukushkin, V. Yu., *Inorg. Chim. Acta,* **1999**, *285*, 116. (b) Robinson, B., *Tetrahedron,* **1964**, *20*, 515. (c) Paolini, D., *Gazz. Chim. Ital.,* **1931**, *61*, 551.
5. (a) Tanaka, H.; Moriwaki, M. and Takahashi, T., *Org. Lett.,* **2003**, *5*, 3807. (b) Schmitz, E. and Fechner-Simon, H., *Org. Prep. & Proc.,* **1969**, *1*, 253.
6. Robinson, G. M. and Robinson, R., *J. Chem. Soc.,* **1918**, *43*, 639.
7. (a) Jones, R. A. Y. and Bunnett, J. F., *Pure & Appl. Chem.,* **1989**, *61*, 725. (b) Hollins, C., *J. Am. Chem. Soc.,* **1922**, *44*, 1598.
8. (a) Milgram, B. C.; Eskildsen, K.; Richter, S. M.; Scheidt, W. R. and Scheidt, K. A., *J. Org. Chem.,* **2007**, *72*, 3941. (b) Portoghese, P. S.; Lipkowski, A. W. and Takemori, A. E., *J. Med. Chem.,* **1987**, *30*, 239. (c) Lutz, R. P., *Chem. Rev.,* **1984**, *84*, 205.
9. Robinson, B., *Chem. Rev.,* **1963**, *63*, 373.
10. (a) Heimgartner, H.; Hansen, H.-J. and Schmid, H., *3,3-Rearrangements of Iminium Salts* in *Iminium Salts in Organic Chemistry*, ed. Böhme, H. and Viehe, H., Wiley-Interscience, New York, **1979**, 2, pp. 655–731. (b) Lancaster, R. E. and VanderWerf, C. A., *J. Org. Chem.,* **1958**, *23*, 1208. (c) Allen, C. F. H. and Wilson, C. V., *J. Am. Chem. Soc.,* **1943**, *65*, 611. (d) Piloty, von O. and Hirsch, P., *Ann.,* **1913**, *395*, 63.

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Pinacol Coupling Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Fittig in 1859.[1] It is a synthesis of vicinal diols from carbonyl compounds via reductive coupling. Because vicinal diol (or 1,2-diol) is generally known as pinacol, the reductive coupling of carbonyl compounds to give vicinal diols is known simply as the pinacol coupling[2] or pinacol coupling reaction.[2a,2j,2m,2s,2u,2w,3,4] Specifically, the coupling between two different carbonyl groups is referred to as pinacol cross-coupling[5] or cross-pinacol coupling,[6] whereas the dimerization of a carbonyl group itself to give a symmetrically substituted 1,2-diol is called homo-pinacol coupling.[6] It is known that this reaction involves the initial single electron transfer (SET) from a low-valent metal to the carbonyl group to form a ketal radical, which then couples to form pinacol.[2q,2r,3e,7] Therefore, the molecules, which can be reduced to radicals or radical anions, undergo similar radical coupling reaction. Some of these molecules are aldehydes,[2h,2l,2u,3c,8] ketones,[2l,2r,3k,5b,9] α-ketoamides,[2j] α,β-unsaturated amides,[3f] alkyl dinitrone,[2c] benzaldimines (i.e., Schiff bases),[10] ferrocenylideneamine,[6] and aldehyde complexes.[2s]

On the other hand, the large number of low-valent metals and their salts or complexes that can function as single-electron donors all are able to promote this reaction, thus different reaction systems have been established. These electron donors fall into different categories: single metals, metal salts, metallic redox pairs, metal cation complexes, hydrides, multi-component systems, and others. Among these electron donors, single low-valent metals that have been applied for the pinacol coupling include Al,[2l] Ce,[2q] Fe,[2q] In,[2l] Mg[2l] (or Rieke Mg[11]), Mn,[2l] Nb,[2t] Sn,[2t] U,[2g] Al,[12] and In;[2l] in addition, Mg[2l] and Mn[2l] have even been used for the aqueous pinacol coupling reactions, such as the Mg mediated pinacol coupling in 0.1 M NH_4Cl solution[2m] under ultrasound irradiation.[8] The metal salts that are suitable for this reaction are Ce(O-*t*-Bu)$_3$,[2h] SmI_2,[2j,3f] Sm(OTf)$_3$,[3a] $TiCl_3$,[2k,2l,2m] and $TiCl_4$/EtCN.[3e]

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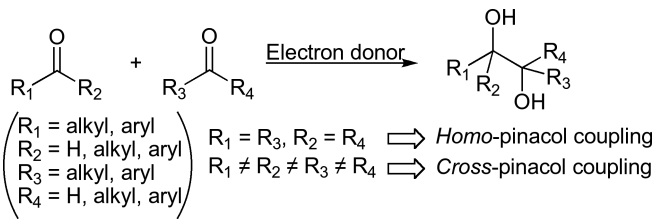
It is interesting that SmI_2 can promote the coupling of α,β-unsaturated amides to give 1,6-diamides,[3f] whereas $TiCl_4$/EtCN initiates the coupling of α,β-unsaturated aldehyde selectively to give *dl*-diol;[3e] $Sm(OTf)_3$ produces (*R*,*R*)-diol.[3a] The metallic redox pairs include Al-Hg,[2a] Mg-Hg/$TiCl_4$,[9] Et_2AlI/Sm,[2l] SmI_2/Mg,[2r] $SmCl_3$/Sm,[2d] $SmCl_3$/Mg,[2d] $TiCl_3(DME)_{1.5}$/Zn-Cu,[13] VCl_3/Al,[2a] and $ZnCl_2$/Zn.[2l] Among these metallic redox pairs, $SmCl_3$/Mg,[2d] $SmCl_3$/Sm,[2d] VCl_3/Al[2a] and $ZnCl_2$/Zn[2l] have also been used to promote the pinacol coupling in aqueous solution. It has been suggested that for the system of SmI_2/Mg, the concentration of metals should be higher than that of ketone to lower the possibility of side reactions, such as *Benzoin Condensation* and *Tishchenko Reaction*.[2r] The metal cation complexes that are feasible for pinacol coupling are the complexes of chromium (II),[2l] titanium (e.g., $[Cp_2TiCl]_2$,[2k,2l,2t,14] Cp_2TiPh,[2f] Ti(III)-salen,[3d] and titanium-Schiff base complexes[2g,2l]), vanadium (e.g., $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$,[2w,3j,5a,15] $Cp_2VCl_2/Me_3SiCl/Zn$,[3h,3i] and Cp_2VCl_2/$PhMe_2SiCl$/Al/imidazole[10]), and zirconium (e.g., anionic zirconaoxirane[5b]). Among these metal cation complexes, $[Cp_2TiCl]_2$ can be used for both anhydrous and deoxygenated aqueous solutions,[2k] which gives very high diastereoselectivity. Similarly, Cp_2TiPh shows a high *threo*-selectivity,[2f] and $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ selectively induces the formation of *syn,syn*-diols.[15] As for the hydrides that have been used for the pinacol coupling, Bu_3SnH,[2m,2n,2u] Ph_3SnH,[2q] Bu_3GeH,[2q] and $(TMS)_3SiH$[2q] have all been proven to be good electron carriers. Besides the systems mentioned for the pinacol coupling, there are many complicated systems that consist of at least three components, such as TBOxCr(III)Cl/Mn/Et_3SiCl,[3c] Mg/TMSCl/HMPA,[2r] SmI_2/HMPA/*t*-BuOH,[2j] Sm/I_2/Ti(O-*i*-Pr)$_4$,[2l] SmI_2/Mg/TMSCl/HMPA,[2b] Ti(III)/Zn/TMSCl,[2l] and tricarbonyl(benzaldehyde)chromium/SmI_2[2s]. It should be pointed out that the multicomponent system of tricarbonyl(benzaldehyde)chromium/SmI_2 gives only high *threo*-selectivity, whereas Sm/I_2/Ti(O-*i*-Pr)$_4$ mediated pinacol coupling must be carried out in anhydrous alcohol.[2l] Other reaction conditions use Al/KOH in dry MeOH,[2l] SmI_2/TMSCl,[2l] and $TiCl_4$/tetrabutylammonium iodide (or $MePh_3PI$ or $MeEt_3NI$);[16] the last system works only for aromatic aldehydes affording high *dl*-selectivity.

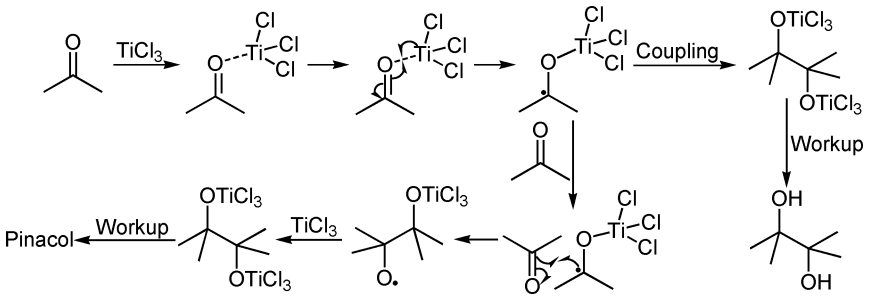
It should be pointed out that the homogeneous reaction conditions often give higher diastereoselectivies than the heterogeneous ones;[3g] in addition, trialkylchlorosilanes appearing in a few of these reaction systems are believed to cleave the metal-oxygen bond to recycle the catalysts,[17] by which triethylsilylchloride may offer better stereoselectivity than trimethylsilylchloride.[3c] On the other hand, certain pinacol couplings are reversible because of the newly formed carbon-carbon bonds are unusually weak, such as those in tetraarylpinacol.[3k] In addition, some ketones because of the steric hindrance will not undergo the pinacol coupling, such as 2,2,6,6-tetramethylcyclohexanone.[3k]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

An illustrative mechanism is displayed here for the coupling of acetone in the presence of $TiCl_3$, in which the carbonyl oxygen may coordinate to $TiCl_3$ and a single electron transfer occurs to give a ketal radical. The ketal radicals may couple together to give a pinacol dianion or attack a second carbonyl group to give alkoxy radical that is then reduced by $TiCl_3$ to a pinacol dianion. Final workup yields the pinacol.



D. MODIFICATION

This reaction has been extensively modified by the use of different single electron transfer systems as described in Section A, in either anhydrous or aqueous solution.

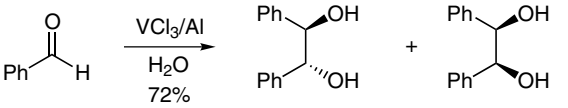
E. APPLICATIONS

This reaction has general application in the preparation of vicinal diols.

F. RELATED REACTIONS

This reaction is related to the *McMurry Coupling*.

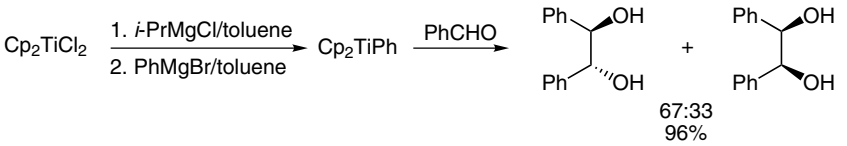
G. CITED EXPERIMENTAL EXAMPLES



Reference 2a.

A suspension of 81 mg activated aluminum powder (3 mmol) and 52 mg VCl_3 (0.33 mmol) in 1–2 mL water was stirred for ~5 min at room temperature. Then 0.106 gram of benzaldehyde (1 mmol) was added to the mixture, which was stirred vigorously for

3 days. The reaction was quenched with 1 N HCl, and extracted with ether (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography using hexanes/EtOAc (3:1) as the eluent to afford 72% pinacol product with a *dl*/*meso* ratio of 56:44.



Reference 2f.

To a suspension of 747 mg Cp_2TiCl_2 (3.0 mmol) in 10 mL dry degassed toluene was added a solution of freshly prepared *i*-PrMgCl from 259 mg *i*-PrCl (3.3 mmol) and 160 mg Mg (6.6 mmol) in 5 mL dry degassed ether under an argon atmosphere at room temperature. The reaction mixture was stirred for 30 min. To the resultant green solution was added a solution of freshly prepared PhMgBr from 471 mg phenyl bromide (3.0 mmol) and 146 mg magnesium (6.0 mmol) in 5 mL dry degassed ether at room temperature; the reaction mixture was stirred for further 30 min. To this dark green Cp_2TiPh solution, 212 mg benzaldehyde (2 mmol) was added at room temperature, and the reaction mixture was stirred for 1 h. The reaction was quenched by 10 mL 1 N HCl, and the mixture was stirred for 30 min. The organic layer was separated and washed with 20 mL brine. The aqueous layer was extracted with EtOAc (20 mL × 3). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel flash column chromatography using hexanes/EtOAc (2:1) as the eluent to give 206 mg hydrobenzoin as white solids, in a yield of 96%.

Other references related to pinacol coupling reaction are cited in the literature.[18]

H. REFERENCES

1. Fittig, R., *Ann.,* **1859**, *110*, 17.
2. (a) Xu, X. L. and Hirao, T., *J. Org. Chem.,* **2005**, *70*, 8594. (b) Ueda, T.; Kanomata, N. and Machida, H., *Org. Lett.,* **2005**, *7*, 2365. (c) Ebran, J.-P.; Hazell, R. G. and Skrydstrup, T., *Chem. Commun.,* **2005**, 5402. (d) Matsukawa, S. and Hinakubo, Y., *Org. Lett.,* **2003**, *5*, 1221. (e) Lake, K.; Dorrell, M.; Blackman, N.; Khan, M. A. and Nicholas, K. M., *Organometallics,* **2003**, *22*, 4260. (f) Yamamoto, Y.; Hattori, R.; Miwa, T.; Nakagai, Y.-i.; Kubota, T.; Yamamoto, C.; Okamoto, Y. and Itoh, K., *J. Org. Chem.,* **2001**, *66*, 3865. (g) Bensari, A.; Renaud, J.-L. and Riant, O., *Org. Lett.,* **2001**, *3*, 3863. (h) Groth, U. and Jeske, M., *Synlett,* **2001**, 129. (i) Halterman, R. L.; Zhu, C. J.; Chen, Z. L.; Dunlap, M. S.; Khan, M. A. and Nicholas, K. M., *Organometallics,* **2000**, *19*, 3824. (j) Kim, Y. H.; Kim, S. M.; Park, D. H. and Youn, S. W., *Pure & Appl. Chem.,* **2000**, *72*, 1691. (k) Spencer, R. P. and Schwartz, J., *Tetrahedron,* **2000**, *56*, 2103. (l) Bhar, S. and Panja, C., *Green Chem.,* **1999**, 253. (m) Zhang, W.-C. and Li, C.-J., *J. Org. Chem.,* **1999**, *64*, 3230. (n) Hays, D. S. and Fu, G. C., *J. Org. Chem.,* **1998**, *63*, 6375. (o) Kornienko, A.; Marnera, G. and d'Alarcao, M., *Carbohydr. Res.,* **1998**, *310*, 141. (p) Li, C.-J.; Meng, Y.; Yi, X.-H.; Ma, J. H. and Chan, T.-H., *J. Org. Chem.,* **1998**, *63*, 7498. (q) Rieke, R. D. and Kim, S.-H., *J. Org. Chem.,* **1998**, *63*, 5235. (r) Nomura, R.; Matsuno, T. and Endo, T., *J. Am. Chem. Soc.,* **1996**, *118*, 11666. (s) Taniguchi,

N.; Kaneta, N. and Uemura, M., *J. Org. Chem.,* **1996**, *61*, 6088. (t) Barden, M. C. and Schwartz, J., *J. Am. Chem. Soc.,* **1996**, *118*, 5484. (u) Hays, D. S. and Fu, G. C., *J. Am. Chem. Soc.,* **1995**, *117*, 7283. (v) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F. and Giaroni, P., *J. Org. Chem.,* **1992**, *57*, 782. (w) Raw, A. S. and Pedersen, S. F., *J. Org. Chem.,* **1991**, *56*, 830.

3. (a) Fukuzawa, S.-i.; Yahara, Y.; Kamiyama, A.; Hara, M. and Kikuchi, S., *Org. Lett.,* **2005**, *7*, 5809. (b) Mukaiyama, T.; Ogawa, Y.; Kuroda, K. and Matsuo, J.-I., *Chem. Lett.,* **2004**, *33*, 1412. (c) Takenaka, N.; Xia, G. Y. and Yamamoto, H., *J. Am. Chem. Soc.,* **2004**, *126*, 13198. (d) Chatterjee, A.; Bennur, T. H. and Joshi, N. N., *J. Org. Chem.,* **2003**, *68*, 5668. (e) Shimizu, M.; Goto, H. and Hayakawa, R., *Org. Lett.,* **2002**, *4*, 4097. (f) Kim, Y. H.; Kim, S. M. and Youn, S. W., *Pure & Appl. Chem.,* **2001**, *73*, 283. (g) Hashimoto, Y.; Mizuno, U.; Matsuok, H.; Miyahara, T.; Takakura, M.; Yoshimoto, M.; Oshima, K.; Utimoto, K. and Matsubara, S., *J. Am. Chem. Soc.,* **2001**, *123*, 1503. (h) Hirao, T.; Asahara, M.; Muguruma, Y. and Ogawa, A., *J. Org. Chem.,* **1998**, *63*, 2812. (i) Hatano, B.; Ogawa, A. and Hirao, T., *J. Org. Chem.,* **1998**, *63*, 9421. (j) Kraynack, E. A. and Pedersen, S. F., *J. Org. Chem.,* **1993**, *58*, 6114. (k) McMurry, J. E. and Choy, W., *J. Org. Chem.,* 1**9**78, *43*, 1800.
4. (a) Li, Y.-G. and Chi, X.-B., *Youji Huaxue,* **2007**, *27*, 431. (b) Chatterjee, A. and Joshi, N. N., *Tetrahedron,* **2006**, *62*, 12137. (c) Wen, J. W.; Tan, Q. T. and You, T. P., *J. Mol. Catal. A: Chem.,* **2006**, *258*, 159. (d) Wen, J. W.; Zhao, J.; Wang, X.; Dong, J. Y. and You, T. P., *J. Mol. Catal. A: Chem.,* **2006**, *245*, 242. (e) Wang, S.-X.; Wang, K. and Li, J.-T., *Synth. Commun.,* **2005**, *35*, 2387. (f) Schmidt, D. R., *Chemtracts*, **2005**, *18*, 52. (g) Yang, J.-H.; Li, J.-T.; Zhao, J.-L. and Li, T.-S., *Synth. Commun.,* **2004**, *34*, 993. (h) Arai, S.; Sudo, Y. and Nishida, A., *Chem. Pharm. Bull.,* **2004**, *52*, 287. (i) Shimizu, M.; Suzuki, I. and Makino, H., *Synlett*, **2003**, 1635. (j) Shimizu, M.; Iwata, A. and Makino, H., *Synlett*, **2002**, 1538. (k) Hashimoto, Y.; Mizuno, U.; Matsuoka, H.; Miyahara, T.; Takakura, M.; Yoshimoto, M.; Oshima, K.; Utimoto, K. and Matsubara, S., *J. Am. Chem. Soc.,* **2001**, *123*, 4869. (l) Mukaiyama, T.; Yoshimura, N. and Igarashi, K., *Chem. Lett.,* **2000**, 838.
5. (a) Konradi, A. W.; Kemp, S. J. and Pedersen, S. F., *J. Am. Chem. Soc.,* **1994**, *116*, 1316. (b) Askham, F. R. and Carroll, K. M., *J. Org. Chem.,* **1993**, *58*, 7328. (c) Konradi, A. W. and Pedersen, S. F., *J. Org. Chem.,* **1990**, *55*, 4506. (d) Park, J. H. and Pedersen, S. F., *J. Org. Chem.,* **1990**, *55*, 5924. (e) Freudenberger, J. H.; Konradi, A. W. and Pedersen, S. F., *J. Am. Chem. Soc.,* **1989**, *111*, 8014.
6. Taniguchi, N. and Uemura, M., *J. Am. Chem. Soc.,* **2000**, *122*, 8301.
7. Talukdar, S. and Banerji, A., *J. Org. Chem.,* **1998**, *63*, 3468.
8. Li, J.-T.; Bian, Y.-J.; Zang, H.-J. and Li, T.-S., *Synth. Commun.,* **2002**, *32*, 547.
9. Mundy, B. P.; Srinivasa, R.; Kim, Y. S.; Dolph, T. and Warnet, R. J., *J. Org. Chem.,* **1982**, *47*, 1657.
10. Hirao, T.; Hatano, B.; Imamoto, Y. and Ogawa, A., *J. Org. Chem.,* **1999**, *64*, 7665.
11. Furstner, A.; Csuk, R.; Rohrer, C. and Weidmann, H., *J. Chem. Soc., Perkin Trans. I,* **1988**, 1729.
12. Li, L.-H. and Chan, T. H., *Org. Lett.,* **2000**, *2*, 1129.
13. McMurry, J. E. and Dushin, R. G., *J. Am. Chem. Soc.,* **1989**, *111*, 8928.
14. Barden, M. C. and Schwartz, J., *J. Org. Chem.,* **1997**, *62*, 7520.
15. Yasui, Y., *Aust. J. Chem.,* **2002**, *55*, 685.
16. Tsuritani, T.; Ito, S.; Shinokubo, H. and Oshima, K., *J. Org. Chem.,* **2000**, *65*, 5066.
17. (a) Fürstner, A. and Shi, N., *J. Am. Chem. Soc.,* **1996**, *118*, 2533. (b) Fürstner, A. and Shi, N., *J. Am. Chem. Soc.,* **1996**, *118*, 12349. (c) Fürstner, A. and Hupperts, A., *J. Am. Chem. Soc.,* **1995**, *117*, 4468.
18. (a) Aspinall, H. C.; Greeves, N. and Valla, C., *Org. Lett.*, **2005**, *7*, 1919. (b) Shi, L.; Fan, C.-A.; Tu, Y.-Q.; Wang, M. and Zhang, F.-M., *Tetrahedron,* **2004**, *60*, 2851. (c) Agustsson, S. O.; Hu, C. H.; Englert, U.; Marx, T.; Wesemann, L. and Ganter, C., *Organometallics,* **2002**, *21*, 2993.

(d) Kim, S. M.; Byun, I. S. and Kim, Y. H., *Angew. Chem. Int. Ed.*, **2000**, *39*, 728. (e) De Gracia, I. S.; Dietrich, H.; Bobo, S. and Chiara, J. L., *J. Org. Chem.,* **1998**, *63*, 5883. (f) Gansäuer, A. and Bauer, D., *J. Org. Chem.,* **1998**, *63*, 2070. (g) Li, C.-J.; Meng, Y.; Yi, X.-H.; Ma, J. H. and Chan, T.-H., *J. Org. Chem.,* **1997**, *62*, 8632. (h) Swindell, C. S. and Fan, W. M., *J. Org. Chem.,* **1996**, *61*, 1109. (i) Swindell, C. S.; Chander, M. C.; Heerding, J. M.; Klimko, P. G.; Rahman, L. T.; Raman, J. V. and Venkataraman, H., *J. Org. Chem.,* **1996**, *61*, 1101. (j) Namy, J. L.; Souppe, J. and Kagan, H. B., *Tetrahedron Lett*., **1983**, *24*, 765. (k) Souppe, J.; Danon, L.; Namy, J. L. and Kagan, H. B., *J. Organomet*. *Chem*., **1983**, *250*, 227. (l) McMurry, J. E. and Krepski, L. R., *J. Org. Chem.,* **1976**, *41*, 3929.

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Pinacol Rearrangement

(Pinacol-Pinacolone Rearrangement)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Fittig in 1860.[1] It is an acid-promoted 1,2-rearrangement of vicinal diols to corresponding aldehydes or ketones. Because the vicinal diols are commonly called the pinaocls, this transformation is generally known as the pinacol rearrangement[2,3] or pinacol-pinacolone rearrangement.[2e,2g,4,5] Although this reaction is often carried out in H_2SO_4,[2m,2o,2r,2s,2v,2z,2aa,2bb,4c,6] many other acidic conditions have also been successfully used for this reaction, including the application of Brønsted and Lewis acids. Examples of Brønsted acids are HCO_2H,[2v] $HClO_4$,[2p,7] AcOH with a catalytic amount of H_2SO_4,[2x] AcOH with iodine,[8] and silica gel impregnated with H_3PO_4;[6d] representative Lewis acids include BF_3 in acetic acid,[2cc] $ZnCl_2$ in acetic anhydride,[2cc] $MgBr_2$,[9] and $AlCl_3$ in the absence of solvent.[2b] Some of these conditions produce higher yields than the corresponding rearrangements performed in H_2SO_4. For example, when pinacol is passed over a silica gel impregnated with H_3PO_4, it is converted into pinacolone in 94% yield, whereas the same reaction in H_2SO_4 yields only 65–72% product.[6d] It is agreed that this reaction is a stepwise rearrangement involving the formation of a carbocation intermediate by the dehydration of the protonated diol,[2e,2g,2k,2m,4b,10] the rate-limiting step,[2k] and the skeletal rearrangement by the migration of a neighboring substituent to the carbocation site.[10] However, both the computational[2g] study and the experimental results for the reaction in gas-phase or aprotic solvents[6b,11] indicate that a concerted mechanism dominates over the stepwise mechanism, because the dehydration of protonated diols is facilitated through the stabilization of resulting carbocation, and the activation energy for the 1,2-rearrangement of the stabilized carbocation is higher than a concerted pinacol rearrangement.[2g]

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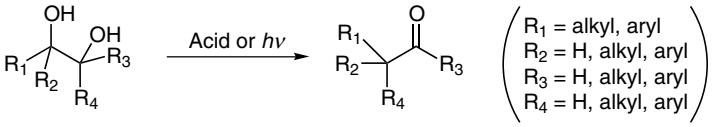
On the other hand, to make this rearrangement a practical tool for organic synthesis, it is very important to know which hydroxyl group will be dehydrated and which group will migrate in both symmetric and asymmetric pinacols. The regioselectivity for this rearrangement is determined by the formation of the primarily formed carbocations,[10] the acid used,[2z,2ac,12] and the migratory aptitudes of the substituents on the vicinal diols.[2e] It is possible that in an asymmetric pinacol, the decrease of the basicity of one hydroxyl group caused by its neighboring substituents might facilitate the protonation on the other hydroxyl group.[2m] In addition, it has been reported that for certain pinacol rearrangements, the treatment by Brønsted and Lewis acids leads to different pinacolones.[2z,2ac,12] The migratory aptitudes of substituents on diols are generally determined by their electron density and steric hindrance. The groups with high electron density are easier to migrate than are the groups with electron deficiency, because such migration groups will rearrange to the new-formed carbocation.[12,13] Thus cyclopropyl,[2g] vinyl,[2g] 2-thienyl,[13] 2,5-dimethyl-3-thienyl,[2y] and 2-furyl[13] groups are all good migratory groups, whereas 2- and 3-pyridyl groups have smaller migratory aptitudes than a phenyl group.[2y] In addition, a good migratory group might not move in the pinacol rearrangement unless it can reach the adjacent carbon atom by a single movement from the opposite face of the leaving hydroxyl group,[2f] involving the so-called *Walden Inversion*.[2ee,2gg] Thus the electron-donating group, such as methoxy, enhances the migratory aptitude of the phenyl group at the *para*-position but depresses the aptitude when it sits at the *ortho*-position.[2x,4h] Similarly, the migratory aptitude of groups may be reversed between symmetric and asymmetric pinacols.[2o,4g] In addition, it has been established that the migration is stereospecific, with retention of the configuration of the migrating group.[2d,6a,14] It should be pointed out that both solvent[2bb] and temperature[2p] will affect the outcome of the pinacol rearrangemet. For example, the pinacol rearrangement can occur regularly in primary or secondary alcohols but not in tertiary alcohols because tertiary alcohols will be protonated and hydrated as well.[2x,2bb]

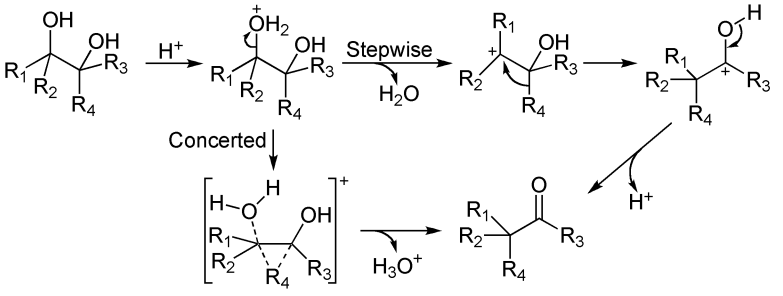
Beside pinacols, some other molecules can undertake a similar reaction through the formation of a carbocation and migration of a group to the carbocation, such as α-halohydrins,[2dd] α-hydroxy epoxides,[12,15] and aziridines.[15a] The rearrangement of aziridines under similar conditions is known as the *aza*-pinacol rearrangement,[15a] whereas α-hydroxy epoxides undergo semi-pinacol rearrangements to give aldols.[15b] Moreover, a similar rearrangement involving a double bond is referred to as the vinylogous pinacol rearrangement.[16] Furthermore, the pinacol rearrangement, promoted by photo-irradiation,[2j,10,17] thermolysis,[16] or in supercritical CO_2[18] can also occur in the absence of an acid; the photo-irradiation activated pinacol rearrangement is generally called photochemical pinacol rearrangement.[2j,10,17]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A simple pinacol rearrangement promoted by a protic acid is displayed here, including both stepwise and concerted pathways, though the stepwise route is the primary pathway.



D. MODIFICATION

This reaction has been extensively modified by the application of different initiation systems, including a variety of Brønsted and Lewis acids, photochemical irradiation, and supercritical CO_2. In addition, this rearrangement has been successfully extended to α-halohydrin, aziridines, and α-hydroxy epoxides, as noted in Section A.

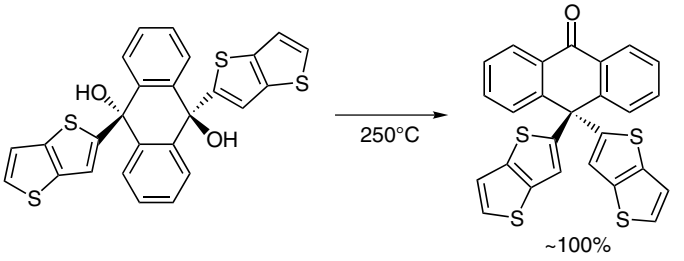
E. APPLICATIONS

This reaction has very broad application in organic synthesis.

F. RELATED REACTIONS

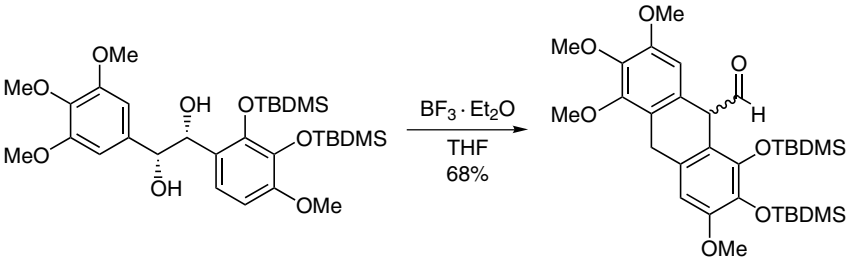
This reaction is related to the *Nametkin Rearrangement, Retropinacol Rearrangement*, *Tiffeneau Reaction*, and *Wagner-Meerwein Rearrangement*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 16.

Trans-9,10-bis(thieno[3,2-*b*]thienyl)-9,10-dihydroxy-9,10-dihydroanthracene (3.1 g, 6.3 mmol) was heated to 250°C on a hot plate equipped with a thermometer under a stereomicroscope to yield 2.92 g 10,10-bis(thieno[3,2-*b*]thienyl)-9,10-dihydroanthracene-9-one (6.2 mmol) in almost quantitative yield. An analytically pure sample was obtained by recrystallization from CH_2Cl_2/hexane, m.p. > 330°C.



Reference 2d.

$BF_3{\cdot}Et_2O$ (0.82 mL, 6.7 mmol, 2 eq.) was added dropwise to a stirred solution of 2.1 g (1*R*,1*R*)-1-[2′,3′-di[(*tert*-butyldimethylsilyl)oxy]-4′-methoxyphenyl]-2-(3,4,5-trimethoxyphenyl) ethane-1,2-diol (3.3 mmol) in 20 mL anhydrous THF under argon at room temperature. After 1 h, saturated aqueous $NaHCO_3$ was added to the mixture before extraction with EtOAc (4 × 15 mL) and drying of the combined organics. Evaporation of the solvent in vacuo afforded a light brown oil, which was subjected to flash column chromatography using hexanes/EtOAc (15:1) as the eluent to afford 1.3 g (±)-2-(2′,3′-di[(*tert*-butyldimethylsilyl)oxy]-4′-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)acetaldehyde as a clear oil that crystallized from MeOH as a colorless solid, in a yield of 68%.

Other references related to the pinacol rearrangement are cited in the literature.[19]

H. REFERENCES

1. (a) Fittig, R., *Ann.,* **1860**, *114*, 54. (b) Berson, J. A., *Angew. Chem. Int. Ed.,* **2002**, *41*, 4655.
2. (a) Sawada, T.; Nishiyama, Y.; Tabuchi, W.; Ishikawa, M.; Tsutsumi, E.; Kuwahara, Y. and Shosenji, H., *Org. Lett.,* **2006**, *8*, 1995. (b) Rashidi-Ranjbar, P. and Kianmehr, E., *Molecules,* **2001**, *6*, 442. (c) Kim, D. J.; Shim, P. J.; Lee, J. K.; Park, C. W.; Hong, S. W. and Kim, S. H., *J. Org. Chem.,* **2000**, *65*, 4864. (d) Pettit, G. R.; Lippert, J. W. and Herald, D. L., *J. Org. Chem.,* **2000**, *65*, 7438. (e) Pandey, R. K.; Isaac, M.; MacDonald, I.; Medforth, C. J.; Senge, M. O.; Dougherty, T. J. and Smith, K. M., *J. Org. Chem.,* **1997**, *62*, 1463. (f) Patra, D. and Ghosh, S., *J. Org. Chem.,* **1995**, *60*, 2526. (g) Nakamurat, K. and Osamura, Y., *J. Am. Chem. Soc.,* **1993**, *115*, 9112. (h) Martinelli, M. J.; Khau, V. V. and Horcher, L. M., *J. Org. Chem.,* **1993**, *58*, 5546. (i) de Petries, G.; Giacomello, P.; Pizzabiocca, A.; Renzi, G. and Speranza, M., *J. Am. Chem. Soc.,* **1988**, *110*, 1098. (j) Zimmerman, H. E. and Nuss, J. M., *J. Org. Chem.,* **1986**, *51*, 4604. (k) De Petries, G.; Giacomello, P.; Picotti, T.; Pizzabiocca, A.; Renzi, G. and Speranza, M., *J. Am. Chem. Soc.,* **1986**, *108*, 7491. (l) Kametani, T.; Nemoto, H.; Suzuki, K. and Fukumoto, K., *J. Org. Chem.,* **1976**, *41*, 2988. (m) Botteron, D. G. and Wood, G., *J. Org. Chem.,* **1965**, *28*, 3871. (n) Murphy, H. W., *J. Pharm. Sci.,* **1964**, *53*, 298. (o) Huffman, J. W. and Browder, L. E., *J. Org. Chem.,* **1962**, *27*, 3208. (p) Smith, W. B.; Kmet, T. J. and Rao, P. S., *J. Am. Chem. Soc.,* **1961**, *83*, 2190. (q) Collins, C. J.; Ralney, W. T.; Smith, W. B. and Kaye, I. A., *J. Am. Chem. Soc.,* **1959**, *81*, 460. (r) Collins, C. J. and Bowman, N. S., *J. Am. Chem. Soc.,* **1959**,

81, 3614. (s) Raaen, V. F. and Collins, C. J., *J. Am. Chem. Soc.,* **1958**, *80*, 1409. (t) Deno, N. C. and Perizzolo, C., *J. Org. Chem.,* **1957**, *22*, 836. (u) Zelinski, R. P. and Jursich, M., *J. Am. Chem. Soc.,* **1956**, *78*, 1015. (v) Benjamin, B. M. and Collins, C. J., *J. Am. Chem. Soc.,* **1956**, *78*, 4329. (w) Collins, C. J., *J. Am. Chem. Soc.,* **1955**, *77*, 5517. (x) Brown, R. F., *J. Am. Chem. Soc.,* **1954**, *76*, 1279. (y) Kegelman, M. R. and Brown, E. V., *J. Am. Chem. Soc.,* **1954**, *76*, 2711. (z) Lyle, G. G.; Covey, R. A. and Lyle, R. E., *J. Am. Chem. Soc.,* **1954**, *76*, 2713. (aa) Davis, R. B. and Erman, W. F., *J. Am. Chem. Soc.,* **1954**, *76*, 3477. (bb) Brown, R. F.; Nordmann, J. B. and Madoff, M., *J. Am. Chem. Soc.,* **1952**, *74*, 432. (cc) Lyle, R. E. and Lyle, G. G., *J. Am. Chem. Soc.,* **1952**, *74*, 4059. (dd) Lane, J. F. and Walters, D. R., *J. Am. Chem. Soc.,* **1951**, *73*, 4234. (ee) Bartlett, P. D. and Brown, R. F., *J. Am. Chem. Soc.,* **1940**, *62*, 2927. (ff) Bartlett, P. D. and Bavley, A., *J. Am. Chem. Soc.,* **1938**, *60*, 2416. (gg) Bartlett, P. D. and Pockel, I., *J. Am. Chem. Soc.,* **1937**, *59*, 820.

3. (a) Suzuki, K.; Takikawa, H.; Hachisu, Y. and Bode, J. W., *Angew. Chem. Int. Ed.,* **2007**, *46*, 3252. (b) Kirsch, S. F.; Binder, J. T.; Crone, B.; Duschek, A.; Haug, T. T.; Litbert, C. and Menz, H., *Angew. Chem. Int. Ed.,* **2007**, *46*, 2310. (c) Nagaraju, N. and Shamshuddin, S. Z. M., *Indian J. Chem. Tech.,* **2007**, *14*, 47. (d) Snape, T. J., *Org. Biomol. Chem.,* **2006**, *4*, 4144. (e) Yahyaee, M.; Kianmehr, E.; Foroutan-nejad, C. and Beheshti, S., *Bull. Korean Chem. Soc.,* **2006**, *27*, 1246. (f) Zhou, W.-J.; Gao, J.-B.; Xue, Q.-S.; Gao, G.-H. and He, M.-Y., *Fenzi Cuihua*, **2006**, *20*, 119. (g) Gao, F. and Lu, X. Y., *Huagong Xuebao (Chinese Edition)*, **2006**, *57*, 60. (h) Birsa, M. L.; Jones, P. G. and Hopf, H., *Eur. J. Org. Chem.,* **2005**, 3263. (i) Marson, C. M.; Oare, C. A.; McGregor, J.; Walsgrove, T.; Grinter, T. J. and Adams, H., *Tetrahedron Lett*., **2002**, *44*, 141. (j) De Lezaeta, M.; Sattar, W.; Svoronos, P.; Karimi, S. and Subramaniam, G., *Tetrahedron Lett*., **2002**, *43*, 9307. (k) Otsuka, H.; Onozuka, I.; Shioya, T. and Endo, T., *Macromol. Chem. Phys.,* **2002**, *203*, 1824. (l) Shinohara, T. and Suzuki, K., *Tetrahedron Lett*., **2002**, *43*, 6937.

4. (a) Shinde, A. B.; Shrigadi, N. B.; Bhat, R. P. and Samant, S. D., *Synth. Commun.,* **2004**, *34*, 309. (b) Chen, Y. H.; Medforth, C. J.; Smith, K. M.; Alderfer, J.; Dougherty, T. J. and Pandey, R. K., *J. Org. Chem.,* **2001**, *66*, 3930. (c) Reeve, W. and Karickhoff, M., *J. Am. Chem. Soc.,* **1956**, *78*, 6053. (d) Ayers, G. W., *J. Am. Chem. Soc.,* **1938**, *60*, 2957. (e) Bachmann, W. E. and Chu, E. J.-H., *J. Am. Chem. Soc.,* **1936**, *58*, 1118. (f) Bachmann, W. E. and Chu, E. J.-H., *J. Am. Chem. Soc.,* **1935**, *57*, 1095. (g) Bachmann, W. E. and Sternberger, H. R., *J. Am. Chem. Soc.,* **1934**, *56*, 170. (h) Bachmann, W. E. and Ferguson, J. W., *J. Am. Chem. Soc.,* **1934**, *56*, 2081. (i) Bachmann, W. E. and Sternberger, H. R., *J. Am. Chem. Soc.,* **1933**, *55*, 3819.

5. (a) Shamshuddin, S. Z. M.; Kuriakose, G. and Nagaraju, N., *Indian J. Chem. Tech.,* **2005**, *12*, 447. (b) Ortin, Y.; Grealis, J.; Scully, C.; Mueller-Bunz, H.; Manning, A. R. and McGlinchey, M. J., *J. Organomet. Chem.,* **2004**, *689*, 4683. (c) Pachuau, Z. and Lyngdoh, R. H. D., *J. Chem. Sci. (Bangalore),* **2004**, *116*, 83. (d) Loeser, E.; Chen, G.-P.; He, T.; Prasad, K. and Repic, O., *Tetrahedron Lett*., **2002**, *43*, 2161. (e) Lopez, L.; Mele, G. and Mazzeo, C., *J. Chem. Soc., Perkin Trans. I,* **1994**, 779. (f) Arce de Sanabia, J. and Carrion, A. E., *Tetrahedron Lett*., **1993**, *34*, 7837. (g) Nishikawa, T.; Ino, A.; Isobe, M. and Goto, T., *Chem. Lett.,* **1991**, 1271. (h) Kakimoto, M.; Seri, T. and Imai, Y., *Bull. Chem. Soc. Jpn.,* **1988**, *61*, 2643. (i) Tadros, W.; Sakla, A. B.; Awad, S. B. and Helmy, Abdul A. A., *Helv. Chim. Acta,* **1972**, *55*, 2808. (j) Das, K. G.; Chinchwadkar, C. A. and Kulkarni, P. S., *Chimia,* **1968**, *22*, 88. (k) Raaen, V. F. and Collins, C. J., *J. Am. Chem. Soc.,* **1958**, *80*, 4432. (l) Bunton, C. A.; Hadwick, T.; Llewellyn, D. R. and Pocker, Y., *J. Chem. Soc.,* **1958**, 403. (m) Duncan, J. F. and Lynn, K. R., *Aust. J. Chem.,* **1957**, *10*, 160. (n) Duncan, J. F. and Lynn, K. R., *Aust. J. Chem.,* **1957**, 10, 7. (o) Duncan, J. F. and Lynn, K. R., *Aust. J. Chem.,* **1957**, *10*, 1. (p) Duncan, J. F. and Lynn, K. R., *J. Chem. Soc.,* **1956**, 3674. (q) Duncan, J. F. and Lynn, K. R., *J. Chem. Soc.,* **1956**, 3519. (r) Duncan, J. F. and Lynn, K. R., *J. Chem. Soc.,* **1956**, 3512. (s) Bunton, C. A.; Hadwick, T.; Llewellyn, D. R. and Pocker, Y., *Chem. Ind.(London),* **1956**, 547. (t) Hatt, H. H.; Pilgrim, A. and Stephenson, E. F. M., *J. Chem. Soc.,* **1941**, 478. (u) Bachmann, W. E. and Chu, E. J.-H., *J. Am. Chem. Soc.,* **1936**, *58*, 1118. (v) Bachmann, W. E., *J. Am. Chem. Soc.,* **1932**, *54*, 2112.

6. (a) Mundy, B. P. and Ottenberger, R. D., *J. Org. Chem.,* **1973**, *38*, 2109. (b) Stiles, M. and Mayer, R. P., *J. Am. Chem. Soc.,* **1959**, *81*, 1497. (c) Brown, R. F., *J. Am. Chem. Soc.,* **1952**, *74*, 428. (d) Emerson, W. S., *J. Am. Chem. Soc.,* **1947**, *69*, 1212.
7. (a) Smith, W. B.; Bowman, R. E. and Kmet, T. J., *J. Am. Chem. Soc.,* **1959**, *81*, 997. (b) Gebhart, H. J. and Adams, K. H., *J. Am. Chem. Soc.,* **1954**, *76*, 3925.
8. Beale, C. H. and Hatt, H. H., *J. Am. Chem. Soc.,* **1932**, *54*, 2405.
9. Hirata, T. and Suga, T., *J. Org. Chem.,* **1971**, *36*, 412.
10. Mladenova, G.; Singh, G.; Acton, A.; Chen, L.; Rinco, O.; Johnston, L. J. and Lee-Ruff, E., *J. Org. Chem.,* **2004**, *69*, 2017.
11. (a) Berti, G.; Macchia, B.; Macchia, F. and Monti, L., *J. Chem. Soc. C,* **1971**, 3371. (b) Barili, P. L.; Berti, G.; Macchia, B.; Macchia, F. and Monti, L., *J. Chem. Soc. C,* **1971**, 1168.
12. Alexander, E. R. and Dittmer, D. C., *J. Am. Chem. Soc.,* **1951**, *73*, 1665.
13. Kegelman, M. R. and Brown, E. V., *J. Am. Chem. Soc.,* **1953**, *75*, 5961.
14. (a) Crowley, H. C. and Culvenor, C. C. J., *Aust. J. Chem.,* **1960**, 14, 269. (b) Mislow, K. and Siegel, M., *J. Am. Chem. Soc.,* **1952**, *74*, 1060.
15. (a) Sugihara, Y.; Iimura, S. and Nakayama, J., *Chem. Commun.,* **2002**, 134. (b) Bickley, J. F.; Hauer, B.; Pena, P. C. A.; Roberts, S. M. and Skidmore, J., *J. Chem. Soc*., *Perkin Trans. I*, **2001**, 1253.
16. Sekiya, R.; Kiyo-oka, K.; Imakubo, T. and Kobayashi, K., *J. Am. Chem. Soc.,* **2000**, *122*, 10282.
17. Hoang, M.; Gadosy, T.; Ghazi, H.; Hou, D.-F.; Hopkinson, A. C.; Johnston, L. J. and Lee-Ruff, E., *J. Org. Chem.,* **1998**, *63*, 7168.
18. Ikushima, Y.; Hatakeda, K.; Sato, O.; Yokoyama, T. and Arai, M., *J. Am. Chem. Soc.,* **2000**, *122*, 1908.
19. (a) Bach, T. and Eilers, F., *J. Org. Chem.,* **1999**, *64*, 8041. (b) Dua, S. K.; Whait, R. B.; Alexander, M. J.; Hayes, R. N.; Lebedev, A. T.; Eichinger, P. C. H. and Bowie, J. H., *J. Am. Chem. Soc.,* **1993**, *115*, 5709. (c) Hirst, G. C.; Howard, P. N. and Overman, L. E., *J. Am. Chem. Soc.,* **1989**, *111*, 1514. (d) Toda, F. and Shigemasa, T., *J. Chem. Soc., Perkin Trans. 1*, **1989**, 209. (e) Nakamura, E. and Kuwajima, I., *J. Am. Chem. Soc.,* **1977**, *99*, 961. (f) Sheehan, J. C. and Zoller, U., *J. Org. Chem.,* **1974**, *39*, 3415. (g) Bose, A. K. and Steinberg, N. G., *J. Org. Chem.,* **1971**, *36*, 2400. (h) Weiss, B. and Stiller, R. L., *J. Org. Chem.,* **1966**, *31*, 2023. (i) Kleinfelter, D. C. and Dye, T. E., *J. Am. Chem. Soc.,* **1966**, *88*, 3174. (j) Collins, C. J.; Cheema, Z. K.; Werth, R. G. and Benjamin, B. M., *J. Am. Chem. Soc.,* **1964**, *86*, 4913. (k) Sands, R. D. and Botteron, D. G., *J. Org. Chem.,* **1963**, *28*, 2690. (l) Collins, C. J., *Quart. Rev.,* **1960**, *14*, 357. (m) Bencze, W. L. and Allen, M. J., *J. Am. Chem. Soc.,* **1959**, *81*, 4015. (n) Winstein, S. and Ingraham, L. L., *J. Am. Chem. Soc.,* **1955**, *77*, 1738. (o) Kegelman, M. R. and Brown, E. V., *J. Am. Chem. Soc.,* **1953**, *75*, 4649. (p) Allen, M. J., *J. Am. Chem. Soc.,* **1951**, *73*, 1841. (q) Lane, J. F. and Walters, D. R., *J. Am. Chem. Soc.,* **1951**, *73*, 4238. (r) Lane, J. F. and Spialter, L., *J. Am. Chem. Soc.,* **1951**, *73*, 4408. (s) Bachmann, W. E. and Moser, F. H., *J. Am. Chem. Soc.,* 1932, 54, 1124.

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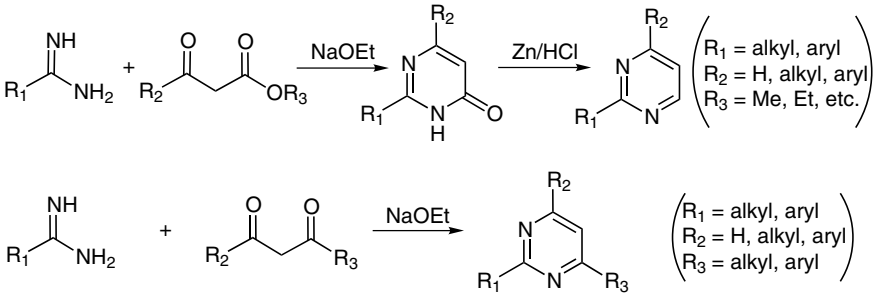
Pinner Condensation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Pinner in 1884.[1] It is a strong base-promoted condensation between a non-*N*-substituted amidine and a β-keto ester[2] or β-diketone[2b,3] to form a type of nitrogenous heterocycle known as pyrimidine, suggested initially by Pinner.[4] Thus it is referred to as the Pinner condensation[2a,5] or Pinner synthesis.[6] However, the preparation of pyrimidine hydrocarbon depends on the successful reduction of the carbonyl group at the 6-position and dehydration,[4] which in some cases is extremely difficult with reducing reagents such as zinc in either NaOH or HCl solution,[2d] although zinc reduction is the most commonly used method.[4] It has been found that using an excess amount of sodium ethylate at high temperature can result in pyrimidine in higher yield,[6] even though extending the reaction time has no obvious effect on the yield.[7]

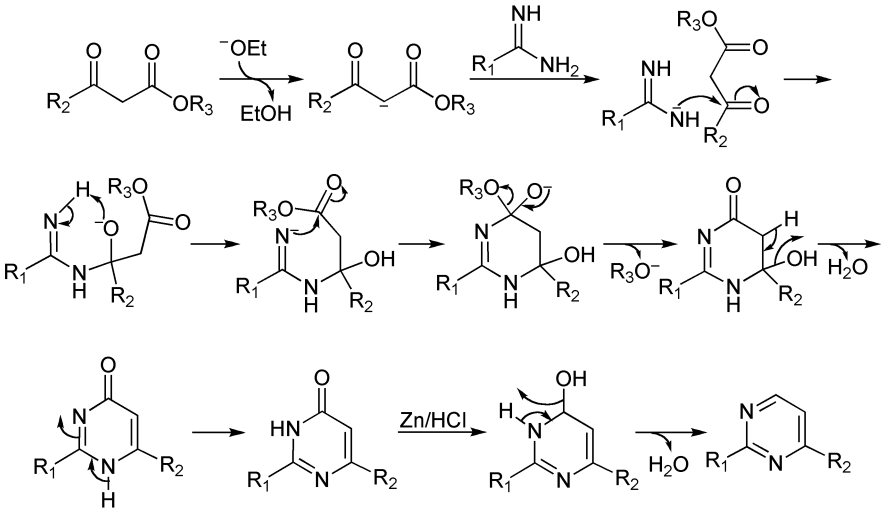
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

Only the mechanism of the reaction between amidine and β-keto ester is provided here because the reaction between amidine and β-diketone undergoes a similar reaction pathway.



D. MODIFICATION

This reaction has been extended to the condensation between amidine and β-cyano ester,[8] amidine and β-hydroxyacetylene,[9] amidine and malonate,[10] *N*-vinyl amidine and acetal,[11] and a three-component reaction of amidine with aldehyde and acetylene.[12]

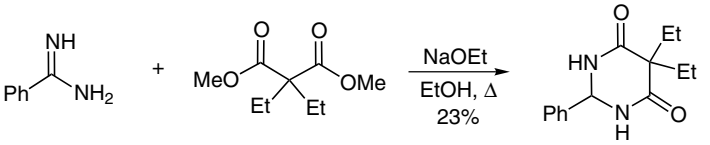
E. APPLICATIONS

This reaction is one of the most common methods for the preparation of pyrimidine derivatives.

F. RELATED REACTIONS

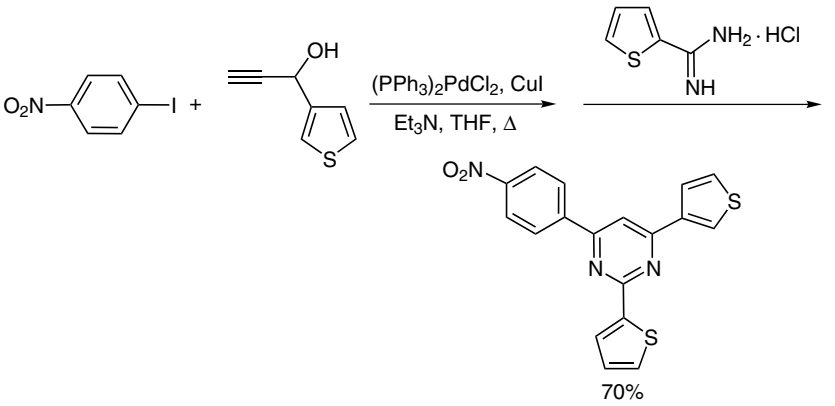
This reaction is related to the *Pinner Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

To a 75 mL solution of NaOEt in absolute ethanol prepared by addition of 4.5 g sodium in absolute ethanol were added 9.0 g benzamidine hydrochloride and 10 g carefully purified methyl α,α-diethylmalonate. The mixture was heated for 5 h at 70°C. The alcohol was partially removed by a current of dry air, and the residue was acidified with a slight excess of conc. HCl. After removal of the precipitated NaCl, the solution was further concentrated on the steam bath. The addition of water caused 5,5-diethyl-2-phenyl-4,6-diketo-tetrahydro-pyrimidine to separate in white needles, in an amount of 3.0 g. The product was further purified by recrystallization from dilute acetic acid.



Reference 9.

To a magnetically stirred solution of 0.25 g 4-iodo nitrobenzene (1.0 mmol), 22 mg $Pd(PPh_3)_2Cl_2$ (0.02 mmol), and 2 mg CuI (0.01 mmol) in a degassed mixture of 10 mL THF and 5 mL triethylamine under nitrogen was added a solution of 145 mg 1-(3-thienyl)-propyn-1-ol (1.05 mmol) in 10 mL THF dropwise at room temperature over a period of 30 min. The mixture was refluxed for 16 h and was allowed to cool to room temperature. Then 165 mg 2-thienyl amidinium chloride (1.0 mmol) was added, and the reaction mixture was refluxed again for 48 h. After cooling, the solvents were removed in vacuo, and the residue was dissolved in CH_2Cl_2 and filtered through a short pad of silica gel. The solvents were evaporated in vacuo, and the residue was recrystallized from CH_2Cl_2/pentane to give 255 mg analytically pure 2-(2-thienyl)-4-(3-thienyl)-6-(4-nitrophenyl) pyrimidine as a beige powder, in a yield of 70%.

Other references related to the Pinner condensation are cited in the literature.[13]

H. REFERENCES

1. Pinner, A., *Ber.,* **1884**, *17*, 2519.
2. (a) Jeong, J. U.; Chen, X. H.; Rahman, A.; Yamashita, D. S. and Luengo, J. I., *Org. Lett.,* **2004**, *6*, 1013. (b) Hale, W. J. and Brill, H. C., *J. Am. Chem. Soc.,* **1912**, *34*, 82. (c) Pinner, A., *Ber.,* **1895**, *28*, 480. (d) Pinner, A., *Ber.,* **1885**, *18*, 2845.
3. Pinner, A., *Ber.,* **1893**, *26*, 2125.
4. Johnson, T. B. and Hahn, D. A., *Chem. Rev.,* **1933**, *13*, 193.

5. Ghosh, U. and Katzenellenbogen, J. A., *J. Heterocycl. Chem.,* **2002**, *39*, 1101.
6. Snyder, H. R. and Foster, H. M., *J. Am. Chem. Soc.,* **1954**, *76*, 118.
7. Dox, A. W. and Yoder, L., *J. Am. Chem. Soc.,* **1922**, *44*, 361.
8. West, R. A. and Beauchamp, L., *J. Org. Chem.,* **1961**, *26*, 3809.
9. Müller, T. J. J.; Braun, R. and Ansorge, M., *Org. Lett.,* **2000**, *2*, 1967.
10. Gershon, H.; Braun, R.; Scala, A. and Rodin, R., *J. Med. Chem.,* **1964**, *7*, 808.
11. Sakai, N.; Aoki, Y.; Sasada, T. and Konakahara, T., *Org. Lett.,* **2005**, *7*, 4705.
12. Guzmán, A.; Romero, M.; Talamás, F. X.; Villena, R.; Greenhouse, R. and Muchowski, J. M., *J. Org. Chem.,* **1996**, *61*, 2470.
13. (a) Schomaker, J. M. and Delia, T. J., *J. Org. Chem.,* **2001**, *66*, 7125. (b) Wang, T. S. and Cloudsdale, I. S., *Synth. Commun.,* **1997**, *27*, 2521. (c) Yamanaka, H.; Takekawa, T.; Morita, K.; Ishihara, T. and Gupton, J. T., *Tetrahedron Lett.,* **1996**, *37*, 1829. (d) Papet, A.-L. and Marsura, A., *Synthesis,* **1993**, 478. (e) Stolle, W. A. W.; Frissen, A. E.; Marcelis, A. T. M. and van der Plas, H. C., *J. Org. Chem.,* **1992**, *57*, 3000. (f) Medwid, J. B.; Paul, R.; Baker, J. S.; Brockman, J. A.; Du, M. T.; Hallett, W. A.; Hanifin, J. W.; Hardy, R. A.; Tarrant, M. E.; Torley, L. W. and Wrenn, S., *J. Med. Chem.,* **1990**, *33*, 1230. (g) Schenone, P.; Sansebastiano, L. and Mosti, L., *J. Heterocycl. Chem.,* **1990**, *27*, 295. (h) Kvita, V., *Synthesis,* **1986**, 786. (i) Potts, K. T.; Cipullo, M. J.; Ralli, P. and Theodoridis, G., *J. Org. Chem.,* **1983**, *48*, 4841. (j) Kreutzberger, A. and Tesch, U. H.,*Chem. Ber.,* **1976**, *109*, 3255. (k) Chauhan, S. M. S. and Junjappa, H., *Synthesis,* **1974**, 880. (l) Bredereck, H.; Effenberger, F.; Botsch, H. and Rehn, H.,*Ber.,* **1965**, *98*, 1081. (m) Inoue, S.; Saggiomo, A. J.; Nodiff, E. A., *J. Org. Chem.,* **1961**, *26*, 4504. (n) Taylor, E. C.; Knoff, R. J.; Meyer, R. F.; Holmes, A. and Hoefle, M. L., *J. Am. Chem. Soc.,* **1960**, *82*, 5711. (o) Dodson, R. M. and Seyler, J. K., *J. Org. Chem*., **1952**, *16*, 461. (p) Clarke, R. A. and Christensen, B. E., *J. Am. Chem. Soc.,* **1948**, *70*, 1818. (q) Johnson, T. B., *J. Ind. Eng. Chem.,* **1918**, *10*, 306. (r) Wheeler, H. L. and Liddle, L. M., *J. Am. Chem. Soc.,* **1908**, *30*, 1156. (s) Gabriel, S. and Colman, J., *Ber.,* **1899**, *32*, 1529. (t) Pinner, A., *Ber.,* **1893**, *26*, 2122. (u) Pinner, A., *Chem. Ber.,* **1889**, *22*, 1612. (v) Pinner, A., *Ber.,* **1887**, *20*, 2361. (w) Pinner, A., *Ber.,* **1885**, *18*, 759.

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Pinner Reaction

A. GENERAL DESCRIPTION OF THE REACTION

Although this reaction was first reported by Beckurts and Otto in 1876,[1] the extensive studies on this reaction appeared in Pinner's work in 1877.[2] It is the transformation of nitriles into imidines or their salts by the treatment of nitriles with an excess of strong acid and one equivalent of alcohol followed by an excess of ammonia or amines. Therefore, it is generally known as the Pinner synthesis,[3a−3c] or Pinner reaction.[3d−3g] This reaction is generally carried out at 0°C[3c,4] with anhydrous ethanol and an excess amount of hydrochloric acid in a dry solvent, such as $CHCl_3$,[5] nitrobenzene,[5] dioxane,[6] benzene,[3b,5,7] or ether,[7b,8] affording five types of imidines, depending on the applied nitrogenous components. According to the substitution and distribution patterns of groups on nitrogen, imidines can be divided into unsubstituted (**I**), monosubstituted (**II**), symmetrically disubstituted (**III**), asymmetrically disubstituted (**IV**), and trisubstituted imidines (**V**), as shown in Figure 1.[9] The extremely reactive trichloroacetonitrile can react with alcohol in the absence of acid.[10] Besides ethanol and methanol, other alcohols are suitable for this reaction, including propanol,[11] isopropanol,[12] butanol,[11] isobutanol,[2a] octanol,[13] decanol,[13] benzyl alcohol,[14] phenol,[15] and thiophenol.[11,16] In addition, almost all the aromatic and aliphatic nitriles can undergo this reaction,[9] with only a few exceptions, such as the acyl cyanides (e.g., acetyl and benzoyl cyanides),[9] certain *ortho*-substituted aromatic nitirles (e.g., *o*-tolunitrile, 2-nitro-4-methylbenzonitrile, 2-amino-4-methylbenzonitrile, α-naphthonitrile),[9] and 9,9′-bifluoryl-1,1′-dinitrile.[17] It should be emphasized that this reaction must be carried out under anhydrous conditions, because imidine is not stable enough in the presence of moisture and can decompose to a nitrile or ester.[9] Especially, in the presence of a hydrogen ion, the formation of ester is accelerated.[9] In addition, in the presence of an excess amount of alcohol, the *ortho* ester may be generated from the imido ester intermediate.[3c]

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B. GENERAL REACTION SCHEME

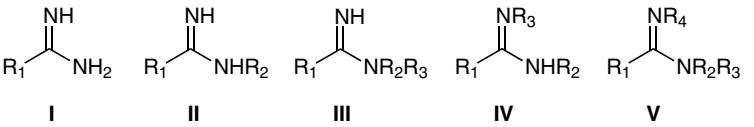
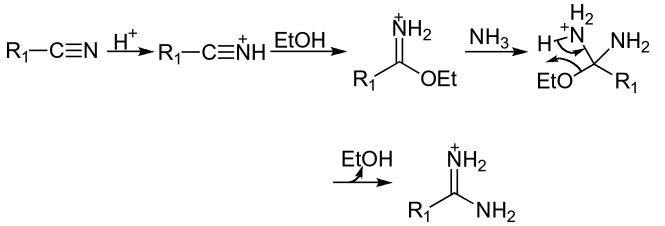


FIGURE 1. *Five types of imidines.*

C. PROPOSED MECHANISMS

A general mechanism is illustrated here for the reaction of nitrile with ethanol and ammonia.



D. MODIFICATION

N/A

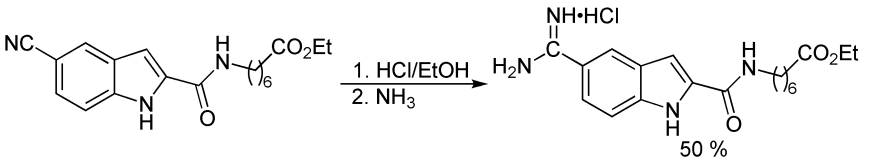
E. APPLICATIONS

This reaction is still the general method for the preparation of imidines. In addition, the thioimidate salts from thioglycolic acid has been used to the characterization of nitriles.[18]

F. RELATED REACTIONS

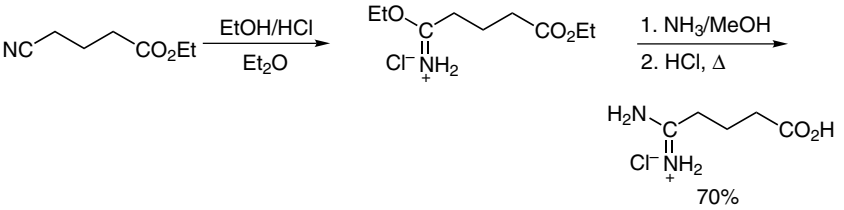
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 19.

A solution of 1.50 g heptanoic acid 7-[[(5-cyano-1*H*-indol-2-yl)carbonyl]-amino] ethyl ester (4.18 mmol) in 250 mL EtOH was treated with a stream of HCl gas for 30 min. The reaction vessel was sealed, and the solution was stirred for 48 h until ^{1}H NMR indicated the completion of conversion to the imino ether. The reaction was concentrated in vacuo, reconstituted in EtOH, and evaporated in vacuo again. The residue was taken up in 250 mL EtOH, and the mixture was treated with a stream of NH_3 gas for 30 min. The vessel was sealed, and the contents were stirred for 24 h for the consumption of imino ether. The reaction mixture was concentrated in vacuo to afford 820 mg of the corresponding amidino ester hydrochloride as a white solid, in a yield of 50%.



Reference 8a.

A solution of 9.84 g ethyl 4-cyanobutyrate (69.3 mmol) and 8.5 mL absolute ethanol (145 mmol) in 100 mL dry ether was cooled in an ice bath before gently saturating with HCl gas. The solution was then allowed to come to room temperature before capping the flask tightly and stirring at room temperature for 18 h. The solution was concentrated in vacuo to a viscous oil that rapidly solidified on standing. To the residue was added 40 mL 2.0 M ammonia in methanol (80 mmol) with ice bath cooling. The mixture was stirred vigorously for 5 min before the ice bath was removed. Stirring was continued for 1 h. The solvent was evaporated in vacuo, leaving a yellow oil and a solid. Then 100 mL absolute ethanol was added, and the mixture was stirred until all of the oil had dissolved. The mixture was chilled overnight at -20°C and filtered. Concentration of the filtrate in vacuo left an oil that still contained some solid. The mixture was then taken up in 100 mL $CHCl_3$ and filtered again. Concentration of the filtrate left $\sim$ 15 g crude amidine ester as a viscous yellow oil, which was dissolved in 150 mL conc. HCl and stirred at 95°C (bath temperature) for 1 h. The solution was concentrated in vacuo (aspirator first, then 0.5 mmHg), leaving 10.8 g pale yellow crystalline solid, of which 9.84 g solid was purified by recrystallization from 130 mL absolute ethanol and 0.5 mL pyridine to give 7.34 g 5-amino-5-iminopentanoic acid as white flakes, in a yield of 70%, m.p., 175–176°C.

Other references related to the Pinner reaction are cited in the literature.[20]

H. REFERENCES

1. Beckurts, H. and Otto, R., *Ber.,* **1876**, *9*, 1590.
2. (a) Pinner, A. and Klein, F., *Ber.,* **1877**, *10*, 1889. (b) Pinner, A. and Klein, F., *Ber.,* **1878**, *11*, 1475. (c) Pinner, A., *Ber.,* **1883**, *16*, 352. (d) Pinner, A., *Ber.,* **1883**, *16*, 1643. (e) Pinner, A., *Ber.,* **1883**, *16*, 1655. (f) Pinner, A., *Ber.,* **1890**, *23*, 161. (g) Pinner, A. and Dietz, R., *Ber.,* **1890**, *23*, 2942. (h) Pinner, A., *Ber.,* **1895**, *28*, 473.

3. (a) Michelin, R. A.; Bertani, R.; Mosson, M.; Bombieri, G.; Benetollo, F. and Angelici, R. J., *Organometallics,* **1991**, *10*, 1751. (b) Schaefer, F. C. and Peters, G. A., *J. Org. Chem.,* **1961**, *26*, 2778. (c) Roger, R. and Neilson, D. G., *Chem. Rev.,* **1960**, *60*, 179. (d) Herr, R. J.; Vogt, P. F.; Meckler, H.; Trova, M. P.; Schow, S. R. and Petter, R. C., *J. Org. Chem.,* **2002**, *67*, 188. (e) Muller, T. J.; Braun, R. and Ansorge, M., *Org. Lett.,* **2000**, *2*, 1967. (f) Medwid, J. B.; Paul, R.; Baker, J. S.; Brockman, J. A.; Du, M. T.; Hallett, W. A.; Hanifin, J. W.; Hardy, R. A.; Tarrant, M. E.; Torley, L. W. and Wrenn, S., *J. Med. Chem.,* **1990**, *33*, 1230. (g) Poupaert, J.; Bruylants, A. and Crooy, P., *Synthesis*, **1972**, 622.
4. Harmon, R. E.; Stanley, F.; Gupta, S. K. and Johnson, J., *J. Org. Chem.,* **1970**, *35*, 3444.
5. Ashley, J. N.; Barber, H. J.; Ewins, a. J.; Newbery, G. and Self, A. D. H., *J. Chem. Soc.,* **1942**, 103.
6. (a) Bose, A. K.; Greer, F.; Gots, J. S. and Price, C. C., *J. Org. Chem.,* **1959**, *24*, 1309. (b) King, H. and Wright, E. V., *J. Chem. Soc.,* **1939**, 253.
7. (a) Allen, R. E.; Schumann, E. L.; Day, W. C. and van Campen, M. G., *J. Am. Chem. Soc.,* **1958**, *80*, 591. (b) Pinner, A., "*Die Imidöather und ihre Derivate*" Oppenheim, Berlin, **1 892**.
8. (a) Larsen, S. D.; Connell, M. A.; Cudahy, M. M.; Evans, B. R.; May, P. D.; Meglasson, M. D.; O'Sullivan, T. J.; Schostarez, H. J.; Sih, J. C.; Stevens, F. C.; Tanis, S. P.; Tegley, C. M.; Tucker, J. A.; Vaillancourt, V. A.; Vidmar, T. J.; Watt, W. and Yu, J. H., *J. Med. Chem.,* **2001**, *44*, 1217. (b) Mengelberg, M., *Ber.,* **1956**, *89*, 1185. (c) Rising, M. M. and Zee, T.-W., *J. Am. Chem. Soc.,* **1928**, *50*, 1208.
9. Shriner, R. L. and Neumann, F. W., *Chem. Rev.,* **1944**, *35*, 351.
10. Steinkopf, W., *J. Prakt. Chem.,* **1910**, *81*, 97.
11. Hartigan, R. H. and Cloke, J. B., *J. Am. Chem. Soc.,* **1945**, *67*, 709.
12. Cornforth, J. W. and Cornforth, R. H., *J. Chem. Soc.,* **1947**, 96.
13. Pearl, I. A. and Beyer, D. L., *J. Am. Chem. Soc.,* **1952**, *74*, 3189.
14. Houben, J. and Pfankuch, E., *Ber.,* **1926**, *59*, 2392.
15. (a) McElvain, S. M. and Fajardo-Pinzon, B., *J. Am. Chem. Soc.,* **1945**, *67*, 690. (b) Houben, J., *Ber.,* **1926**, *59*, 2878.
16. Autenrieth, W. and Brüning, A., *Ber.,* **1903**, *36*, 3464.
17. Ray, F. E.; Weisburger, E. K. and Weisburger, J. H., *J. Org. Chem.,* **1948**, *13*, 655.
18. Condo, F. E.; Hinkel, E. T.; Fassero, A. and Shriner, R. L., *J. Am. Chem. Soc.,* **1937**, *59*, 230.
19. Sall, D. J.; Arfsten, A. E.; Bastian, J. A.; Denney, M. L.; Harms, C. S.; McCowan, J. R.; Morin, J. M.; Rose, J. W.; Scarborough, R. M.; Smyth, M. S.; Um, S. L.; Utterback, B. G.; Vasileff, R. T.; Wikel, J. H.; Wyss, V. L. and Jakubowski, J. A., *J. Med. Chem.,* **1997**, *40*, 2843.
20. (a) Decroix, B.; Morel, J. and Pastour, P.*, J. Chem. Res.,* **1978**, 134. (b) Compagnon, P. L. and Moeque, M., *Ann. Chim. (Paris),* **1970**, *5*, 23. (c) Huffman, K. R. and Schaefer, F. C., *J. Org. Chem.,* **1963**, *28*, 1812. (d) Zil'berman, E. N., *Russ. Chem. Rev.,* **1962**, *31*, 615. (e) Taylor, E. C. and Ehrhart, W. A., *J. Am. Chem. Soc.,* **1960**, *82*, 3138. (f) McElvain, S. M. and Schroeder, J. P., *J. Am. Chem. Soc.,* **1949**, *71*, 40. (g) Dox, A. W., *Org. Synth. Coll.,* **1941**, 1, 5.

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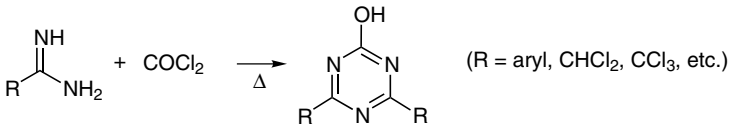
Pinner S-Triazine Synthesis
(Pinner Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Pinner in 1890.[1] It is the synthesis of 2-hydroxy-4,6-diaryl-*sym*-triazines (or *sym*-triazines) from the condensation of aryl amidines and phosgene via the intermediate of bisimidylurea[2] and is known as the Pinner synthesis.[2,3] It has been found that a large amount of bisimidylurea intermediate can be isolated when the reaction is carried out in an ice-salt cooled bath, whereas the yield of *sym*-triazine is enhanced when the reaction temperature is increased.[2] However, this reaction might not be suitable for aliphatic amidines, including propionamidine,[1] caproamidine[1] and acetamidine,[2] except for the alkylamidines with strong electron-withdrawing groups, such as α,α,α-trichloroacetamidine, which trimerizes to form *sym*-triazine at room temperature.[4] Alternatively, other types of *sym*-triazines can be prepared from the thermal trimerization of amidine, such as by heating benzamidine to 115°C,[5] or treating simple *sym*-triazine with amidine.[6] It should be pointed out that Pinner also reported an alternative method for the preparation of *sym*-triazine from the direct trimerization of benzonitrile with fuming sulfuric acid as early as 1878.[7]

B. GENERAL REACTION SCHEME



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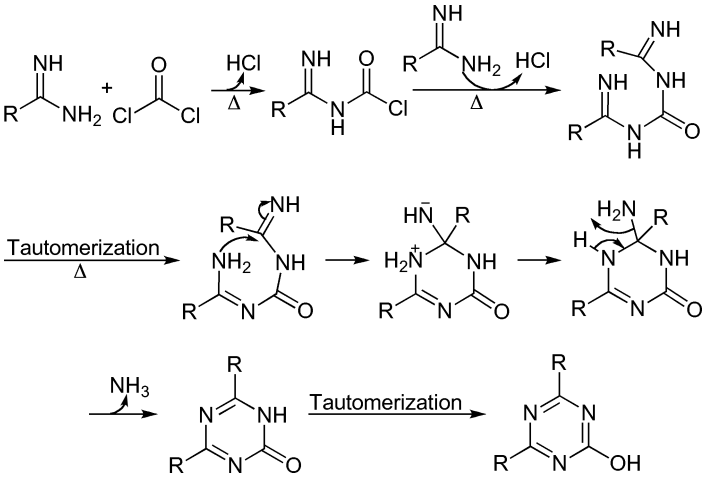
C. PROPOSED MECHANISMS

Displayed below is a tentative mechanism for this reaction.



D. MODIFICATION

This reaction has been extended to the trimerization of imidates,[8] and the reaction between amidine salt and imidate.[9] In addition, the reaction between amidrazone and α,β-dicarbonyl compounds has been used for the preparation of *as*-triazines or 1,2,4-triazines.[10]

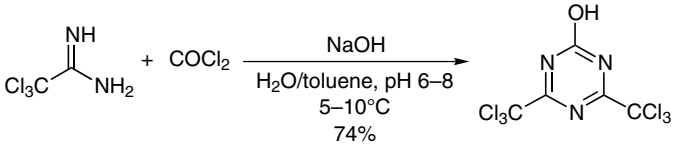
E. APPLICATIONS

This reaction is useful for the preparation of *sym*-triazines.

F. RELATED REACTIONS

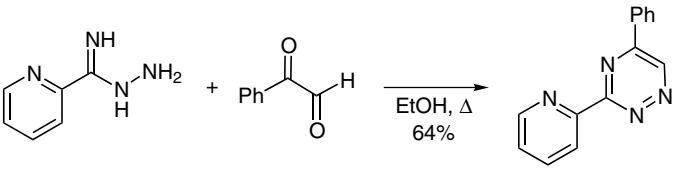
This reaction is related to the *Pinner Reaction* and *Pinner Condensation.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 2.

To 400 mL H_2O at 25°C was added 54.0 g trichloroacetamidine (0.33 mol) under stirring. The amidine dissolved completely upon the addition of approximately one quarter of a solution of 20 g NaOH in 50 mL H_2O. The solution was cooled to and maintained at 5–10°C throughout the course of the reaction. A solution of 25 g $COCl_2$ (0.25 mol) in 120 mL toluene was added dropwise with efficient stirring until the pH reached 6. By alternate addition of phosgene and more of the NaOH solution, the pH was maintained at 8–9. Finally, the pH was brought to 6, and the solid was filtered by suction and dried in vacuo over P_2O_5 to afford 41.0 g 6-hydroxy-2,4-bis-(trichloromethyl)-*s*-triazine, in a yield of 74%, m.p. 218–224°C. A small amount of product was further purified by first dissolving it in EtOH and subsequently adding cold water, m.p. 222–224°C.



Reference 10a.

An ethanolic solution of 1.52 g phenylglyoxal (10 mmol) was depolymerized by refluxing for 4 h and then cooled in acetone and dry ice. To this solution was added 1.36 g 2-pyridylamidrazone (10 mmol), and the mixture was refluxed for 2 h. The cooled solution was diluted with water, and the resultant precipitate was filtered to give 1.5 g 5-phenyl-3-(2-pyridyl)-*as*-triazine, in a yield of 64%, m.p. 142.5–145°C.

Other references related to the Pinner *s*-triazine synthesis are cited in literature.[11]

H. REFERENCES

1. Pinner, A., *Ber.,* **1890**, *23*, 2919.
2. Schroeder, H. and Grundmann, C., *J. Am. Chem. Soc.,* **1956**, *78*, 2447.
3. Schroeder, H., *J. Am. Chem. Soc.,* **1959**, *81*, 5658.
4. Schaefer, F. C.; Hechenbleikner, I.; Peters, G. A. and Wystrach, V. P., *J. Am. Chem. Soc.,* **1959**, *81*, 1466.
5. Pinner, A., *Die Imidoäther und ihre Derivate,* Robert Oppenheim (Gustav Schmidt), Berlin, Germany, **1892**, p. 155.
6. Schaefer, F. C. and Peters, G. A., *J. Am. Chem. Soc.,* **1959**, *81*, 1470.
7. Pinner, A. and Klein, F., *Ber.,* **1878**, *11*, 764.
8. Schaefer, F. C. and Peters, G. A., *J. Org. Chem.,* **1961**, *26*, 2778.
9. (a) Bader, H., *J. Org. Chem.,* **1965**, *30*, 930. (b) Schaefer, F. C., *J. Org. Chem.,* **1962**, *27*, 3608. (c) Schaefer, F. C. and Peters, G. A., *J. Org. Chem.,* **1961**, *26*, 2784.
10. (a) O'rourke, M.; Lang, S. A. and Cohen, E., *J. Med. Chem.,* **1977**, *20*, 723. (b) Case, F. H., *J. Org. Chem.,* **1965**, *30*, 931.
11. (a) Lawrence, S. A., *Amines: Synthesis, Properties and Applications,* Cambridge University Press Cambridge, **2004**. (b) Swamer, F. W.; Reynolds, G. A. and Hauser, C. R., *J. Org. Chem.,* **1951**, *16*, 43. (c) Rappaport, T., *Ber.,* **1901**, *34*, 1990. (d) Flatow, P., *Ber.,* **1897**, *30*, 2006. (e) Pinner, A., *Ber.,* **1895**, *28*, 483. (f) Ephraim, J., *Ber.,* **1893**, *26*, 2226. (g) Pinner, A., *Ber.,* **1892**, *25*, 1414.

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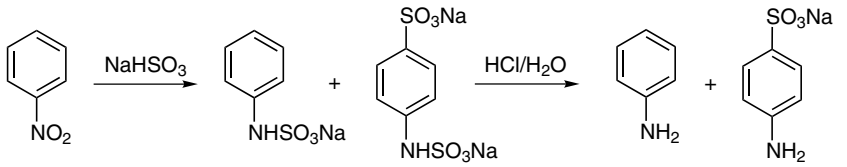
Piria Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Piria in 1851.[1] It is a two-step preparation of aromatic amines and amino sulfonic acids by the reduction of aromatic nitro compounds with bisulfite followed by hydrolysis in mineral acid.[2] Therefore, this reaction is generally known as the Piria reaction.[2,3] It has been proposed that the nitro group is initially reduced to a nitroso group, and aromatic ring sulfonation occurs at or beyond the stage of the nitroso formation,[2a] with the sulfonic group at either the *ortho*- or the *para*-position toward the nitro group.[2a] However, in the case of 4-nitrophenol, the sulfonic group enters the *meta*-position of the nitro group, possibly through 1,4-addition of $NaHSO_3$ to the -N=C-C=C- system present in the quinone-oxime form of the intermediate.[2a] In addition, the aromatic nitroso intermediate is further reduced to sulfaminic acid salt (e.g., $RNHSO_3Na$),[3h] as supported by the isolation of such molecule during reduction without successive acidic hydrolysis or by independent hydrolysis of sulfaminic acid into amine and sulfuric acid.[3h] In addition, it has been found that sodium sulfite reduces the nitro compound faster than sodium bisulfite, and the partially neutralized $NaHSO_3$ is even more effective in this reaction.[2b] Furthermore, it has been found that the reduction is faster when it is carried out in a dilute solution, indicating an ionic reduction.[2b] For the case of α-nitronaphthalene, amino-naphthalene disulfonic acid was isolated in a yield of 66%; the other two products normally found in a regular Piria reaction are obtained in a yield of only 32%.[2b]

B. GENERAL REACTION SCHEME



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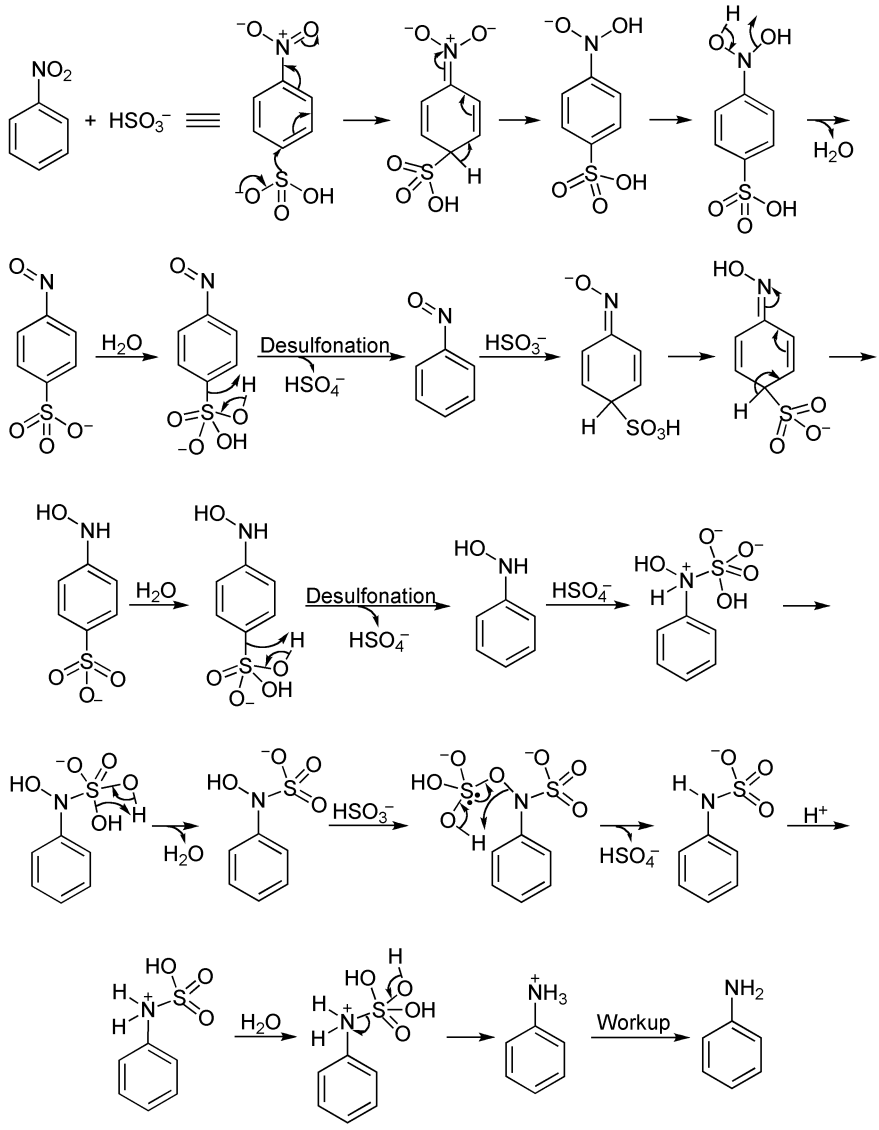
C. PROPOSED MECHANISMS

Although some mechanistic studies have been published about this reaction, a general route for the formation of an aromatic amine or aromatic aminosulfonic acid has been proposed.[3f] However, mechanistic details are not available from the literature. Displayed here is a tentative mechanism for the production of aniline from nitrobenzene. The formation of 2- and 4-aminobenzenesulfonic acid should proceed along a similar pathway.



D. MODIFICATION

N/A

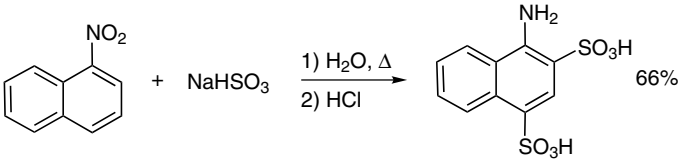
E. APPLICATIONS

This reaction has general application in the preparation of aromatic amines.

F. RELATED REACTIONS

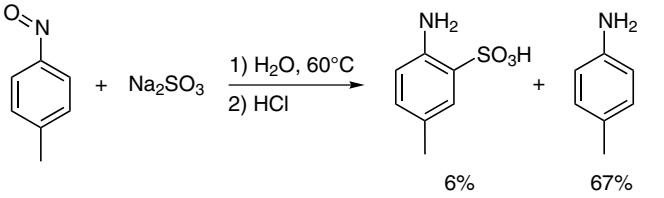
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 2b.

A mixture of 35.0 g α-nitronaphthalene (0.2 mol), 200 mL 5.2 *N* $NaHSO_3$ (75% excess), and 250 mL H_2O was heated under a return condenser until the mixture was completely homogeneous. The contents of the flask were evaporated to 300 mL and treated with 50 mL 12 *N* HCl to give a heavy white precipitate, which was filtered from the cooled solution. This mixture was warmed with 300 mL water, which dissolved the salts present, leaving the naphthionic acid (solubility of 0.024 g in 100 mL water); 13.5 g aminosulfonic acid was thus obtained, in a yield of 29%. The combined filtrates were saturated with NaCl, and the precipitate produced was filtered off. It was nearly free from inorganic salts. When dry, it weighed 31 g, which, on the basis of a monosodium salt of a naphthylamine disulfonic acid is equivalent to a yield of 66%.



Reference 2a.

To 200 mL aqueous solution of 16.6 g Na_2SO_3 at 60°C was added 4.0 g *p*-nitrosotoluene. The mixture was shaken until the green color had disappeared (~5 min). Then 15 mL conc. HCl was added, and the solution was evaporated to 50 mL. On cooling, a solid formed that was filtered off, triturated with water, refiltered, dried, and weighed as 0.45 g, which is equivalent to a 6% yield of *p*-toluidine sulfonic acid. The filtrates were made alkaline with NaOH and extracted with ether. The extracts were combined and dried, and the ether was evaporated to afford 2.4 g *p*-toluidine, in a yield of 67%.

Other references related to the Piria reaction are cited in the literature.[4]

H. REFERENCES

1. Piria, R., *Ann.,* **1851**, *78*, 31.
2. (a) Lauer, W. M.; Sprung, M. M. and Langkammerer, C. M., *J. Am. Chem. Soc.,* **1936**, *58*, 225. (b) Hunter, W. H. and Sprung, M. M., *J. Am. Chem. Soc.,* **1931**, *53*, 1432.
3. (a) Spillane, W. J.; Ryder, C. A.; Concagh, D. G. and Kelly, L. M., *J. Chem. Soc*., *Perkin Trans. II*, **2001**, 103. (b) Vrba, Z. and Allan, Z. J., *Coll. Czech. Chem. Commun.,* **1968**, *33*, 4426. (c) Vrba, Z. and Allan, Z. J., *J. Phys. Chem.,* **1968**, *33*, 431. (d) Mastagli, P.; Lambert, P.; Hirigoyen, C. and Pourriere, J., *Compt. Rend.*, **1960**, *250*, 1507. (e) Giua, M. and Rostagno, W., *Annali Chim. (Italy),* **1953**, *43*, 766. (f) Goldblum, K. B. and Montonna, R. E., *J. Org. Chem.,* **1948**, *13*, 179. (g) Bogdanov, S. V. and Kheifets, S. A., *Zh. Obsh. Khim.,* **1937**, *7*, 911. (h) Hunter, W. H. and Sprung, M. M., *J. Am. Chem. Soc.,* **1931**, *53*, 1443.
4. (a) Budziarek, R., *Chem. & Ind. (London),* **1978**, 583. (b) Vbra, Z. and Allan, Z. J., *Collect. Czech. Chem. Commun.*, **1968**, *33*, 431. (c) Giua, M. and Rostagno, W., *Ann. Chim. (Rome),* **1953**, *43*, 766. (d) Bunnett, J. F. and Zahler, R. E., *Chem. Rev.,* **1951**, *49*, 398. (e) Bucherer, H. T. and Borsch, H., *J. Prakt. Chem.,* **1925**, *111*, 313. (f) Weil, H. and Wassermann, P., *Ber.,* **1922**, 55B, 2533. (g) Weil, H. and Moser, E., *Ber.,* **1922**, *55*, 732. (h) Nietzki, R. and Helbach, C., *Ber.,* **1896**, *29*, 2448. (i) Willgerodt, C., *J. Prakt. Chem.,* **1885**, *32*, 117. (j) Smit, J. A. R., *Ber.,* **1875**, *8*, 1442. (k) Carius, *Z. Chem. Pharm.,* **1861**, 632. (l) Hilkenkamp, L., *Ann. Pharm.,* **1855**, *95*, 86.

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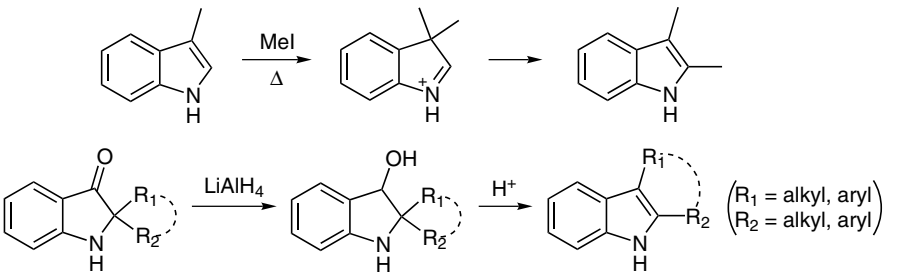
Plancher Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Plancher in 1896.[1] It is the migration of an alkyl or aryl group from position 2 to position 3 of indolenines, or vice versa,[2] to form compounds originating from a more stable carbocation intermediate. Therefore, this reaction is generally known as the Plancher rearrangement.[2,3] The overall rearrangement is controlled not only by the migratory aptitude of the migrating group but also by the thermodynamic stability of the rearranged product.[2] However, such rearrangement normally does not occur at room temperature.[2b]

B. GENERAL REACTION SCHEME



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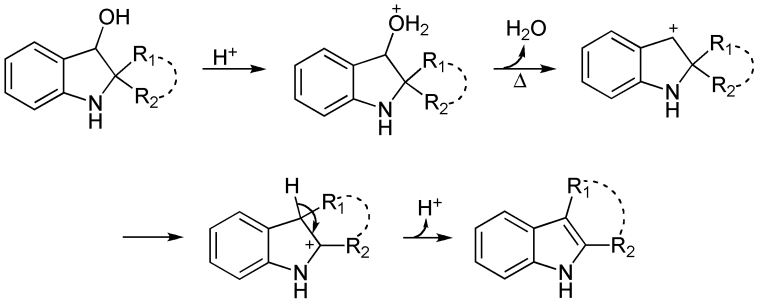
C. PROPOSED MECHANISMS



D. MODIFICATION

N/A

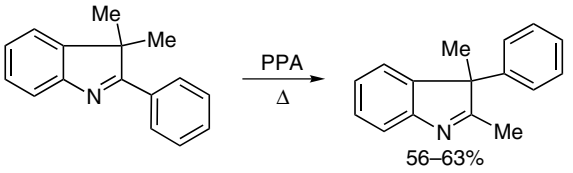
E. APPLICATIONS

This reaction has a limited application in the preparation of indole derivatives.

F. RELATED REACTIONS

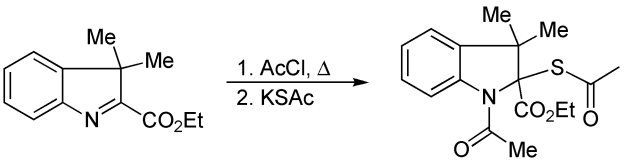
This reaction is related to the *Wagner-Meerwein Rearrangement.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 3h.

To 25 g stirred polyphosphoric acid was poured slowly 8.15 g 3,3-dimethyl-2-phenyl-3H-indole. The mixture was stirred until a uniform consistency was attained, and no attempt was made to moderate the exothermic reaction that took place. After the initial reaction subsided, the flask was placed in a hot air bath, and the bath temperature was raised to 150°C. The reaction mixture was heated at this temperature for 3–5 h, and without being cooled the reaction mixture was poured into 250 mL cold water. The solution was neutralized with solid K_2CO_3, and the tar-like material that separated was taken up in ether. The ether solution was washed with water, dried over anhydrous potassium carbonate, and concentrated by distillation. All volatile solvents were removed from the residue by heating under reduced pressure, and 89–90% 3H-indoles were obtained. The composition analysis indicated 70% 2,3-dimethyl-3-phenyl-3H-indole and 30% starting material.



Reference 3d.

A solution of 434 mg ethyl 3,3-dimethyl-3H-2-indolecarboxylate (2 mmol) in 4 mL freshly distilled acetyl chloride was kept at 40°C for 15 h, during which time the reaction was monitored by TLC (4% EtOH in benzene). After the addition of 5 mL benzene, solvent and excess reagent were removed under vacuum, and exclusion of moisture gave a light brown oil, of which TLC indicated two spots with R_f values smaller than the starting material. To this light brown oil was added an alcoholic solution of 570 mg potassium thioacetate (5 mmol) after which KCl separated. Stirring was continued for 2 h; the alcohol was removed and the residue was extracted with ether. The ether layer was washed with 5% $NaHCO_3$ and water until neutral and dried over Na_2SO_4. Upon removal of solvent, 545 mg of a yellow oil was obtained, which was purified by silica gel column chromatography (4% EtOH in benzene) to afford ethyl 1-acetyl-2-thioacetyl-3,3-dimethylindoline-2-carboxylate and its isomer, besides the recovery of 30 mg starting material.

Other references related to the Plancher rearrangement are cited in the literature.[4]

H. REFERENCES

1. Ciamician, G. and Plancher, G., *Ber.,* **1896**, *29*, 2475.
2. Witkop, B. and Patrick, J. B., *J. Am. Chem. Soc.,* **1951**, *73*, 1558.
3. (a) Hallett, D. J.; Gerhard, U.; Goodacre, S. C.; Hitzel, L.; Sparey, T. J.; Thomas, S.; Rowley, M. and Ball, R. G., *J. Org. Chem.,* **2000**, *65*, 4984. (b) Banerji, J.; Saha, M.; Kanrar, S. and Mukherjee, P., *Indian J. Chem., Sect. B,* **1995**, *34B*, 1095. (c) Tolmachev, A. A.; Babichenko, L. N. and Sheinkman, A. K., *Khim. Geterotsiklicheskikh Soedinenii*, **1992**, 1481. (d) Ottenheym, H. C. J.; Spande, T. F. and Witkop, B., *J. Am. Chem. Soc.,* **1973**, *95*, 1989. (e) Golubev, V. E. and Suvorov, N. N., *Chem. Heterocycl. Compd.,* **1970**, *6*, 701. (f) Kanaoka, Y.; Miyashita, K. and Yonemitsu, O., *J. Chem. Soc. D,* **1969**, 1365. (g) Nicoletti, R.; Forcellese, M. L. and Germani, C., *Gazz. Chim. Ital.,* **1967**, *97*, 685. (h) Evans, F. J.; Lyle, G. G.; Watkins, J. and Lyle, R. E., *J. Org. Chem.,* **1962**, *27*, 1553. (i) Noland, W. E. and Baude, F. J., *J. Org. Chem.,* **1966**, *31*, 3321. (j) Nakazaki, M.; Yamamoto, K. and Yamagami, K., *Bull. Chem. Soc. Jpn.,* **1960**, *33*, 466. (k) Boyd-Barret, H. S., *J. Chem. Soc.,* **1932**, 321.
4. (a) Motorina, I. A. and Sviridova, L. A., *Chem. Heterocycl. Compd.,* **1992**, *28*, 689. (b) Jackson, A. H. and Smith, P., *Tetrahedron,* **1968**, *24*, 2227. (c) Evans, F. J. and Lyle, R. E., *Chem. Ind. (London),* **1963**, 986. (d) Nakazaki, M., *Bull. Chem. Soc. Jpn.,* **1960**, *33*, 472. (e) Witkop, B. and Patrick, J. B., *J. Am. Chem. Soc.,* **1953**, *75*, 2572. (f) Witkop, B. and Patrick, J. B., *J. Am. Chem. Soc.,* **1951**, *73*, 713. (g) Witkop, B. and Patrick, J. B., *J. Am. Chem. Soc.,* **1951**, *73*, 2188. (h) Garry, *Ann. Chim.,* **1942**, *17*, 5. (i) Robinson, R. and Suginome, H., *J. Chem. Soc.,* **1932**, 298. (j) Plancher, G. and Bonaviva, *Gazz. Chim. Ital.,* **1902**, *32*, 414. (k) Plancher, G., *Atti. R. Accad. Lincei,* **1900**, *9*, 115. (l) Plancher, G. and Bettinelli, D., *Gazz. Chim. Ital.,* **1899**, *29*, 106. (m) Plancher, G., *Gazz. Chim. Ital.,* **1898**, *28*, 374. (n) Plancher, G. and Bonaviva, *Gazz. Chim. Ital.,* **1898**, *28*, 333. (o) Plancher, G. and Bonaviva, *Gazz. Chim. Ital.,* **1898**, *28*, 405.

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Polonovski Reaction
(Polonovski-Potier Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Polonovski in 1927.[1] It is the transformation of a tertiary amine oxide into a *N*,*N*-disubstituted acetamide and an aldehyde by treatment of the tertiary amine oxide with acetic anhydride or acetyl chloride. Therefore, this reaction is generally known as the Polonovski reaction.[2] Because the resulting acetylated tertiary amine oxide can undergo different reaction pathways, including the elimination of an α-hydrogen and the cleavage of one alkyl group (e.g., methyl) on the nitrogen atom to form different iminium intermediates,[2oo] this reaction is also referred to as the Polonovski transformation,[3] Polonovski demethylation,[4] Polonovski rearrangement,[5] or Polonovski elimination.[3] In addition, the replacement of acetic anhydride or acetyl chloride by trifluoroacetic anhydride, as introduced by Potier in 1968,[6] has made the Polonovski reaction a very useful transformation in alkaloid chemistry, because the Polonovski reaction under the modified condition can stop at the iminium stage, which can be trapped by the addition of cyanide to form an amino nitrile.[7] Therefore, this modification is generally known as the Polonovski-Potier reaction.[7a,7b,8] Occasionally, this reaction is also referred to as the Potier modification,[9] Potier-Polonovski rearrangement,[10] and Potier-Polonovski fragmentation.[11] It has been found that the elimination occurs via an E2 type mechanism,[7h] by which one of the carbon-nitrogen bonds to be broken must be both activated toward the cleavage by an adjacent electron-donating group and oriented *anti*-periplanar to the N-O bond.[2g] However, *cis*-elimination has also been observed for nupharidine-type alkaloids.[3] It has been reported that a similar transformation can also be promoted by an enzyme such as iron cytochrome P-450.[12]

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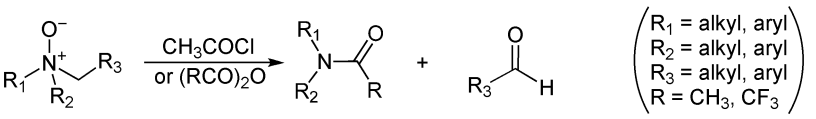
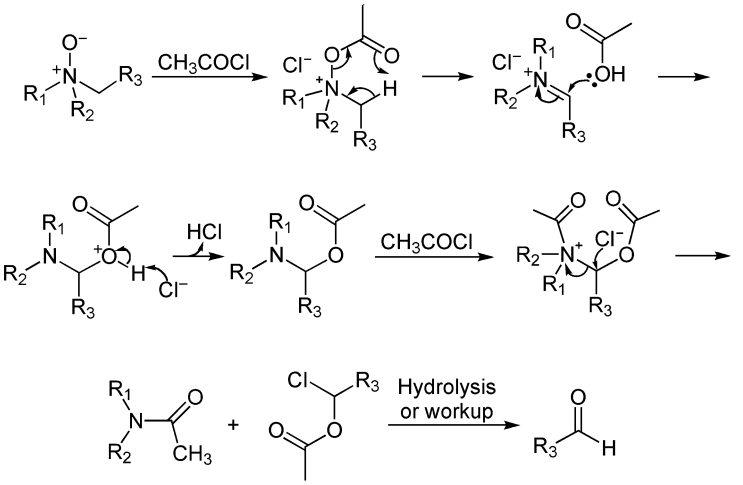
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

As mechanistic information is not available in detail, a tentative mechanism is proposed below by the treatment of acetyl chloride.



D. MODIFICATION

This reaction has been modified by the replacement of acetic anhydride or acetyl chloride with trifluoroacetic anhydride to obtain an iminium intermediate,[2ao,6] followed by the addition of cyanide to give amino nitriles.[7]

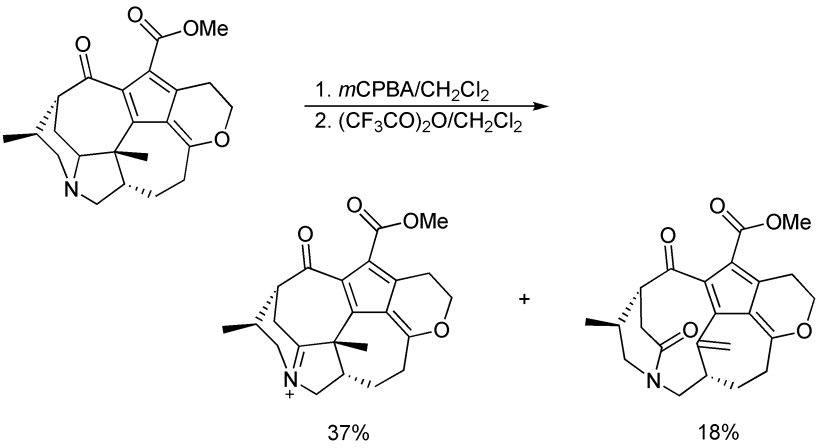
E. APPLICATIONS

This reaction has wide application in the transformation of alkaloids.

F. RELATED REACTIONS

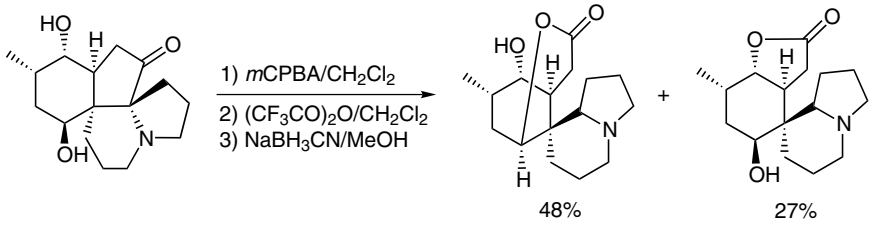
This reaction is related to *Hofmann Elimination*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2f.

m-Chloroperbenzoic acid (6 mg, 0.035 mmol) in 0.1 mL CH_2Cl_2 was added to a stirred solution of 10 mg daphnicyclidin D (0.026 mmol) in 0.1 mL CH_2Cl_2 at 0°C, and the mixture was stirred for 1 h. After the reaction mixture was concentrated, 10 μL trifluoroacetic anhydride (0.072 mmol) was added to the stirred solution of the residue in 0.2 mL dry CH_2Cl_2 under nitrogen at −20°C for 1 h. After the solvent was evaporated, the residue was subjected to C_{18} HPLC (25% CH_3CN in MeOH with 0.1% TFA) to afford 3.7 mg daphnicyclidins E and 1.8 mg daphnicyclidins J, respectively.



Reference 2g.

m-Chloroperbenzoic acid (8 mg, 0.047 mmol) in 0.1 mL CH_2Cl_2 was added at 0°C to a stirred solution of 10 mg serratinine (0.036 mmol) in 0.1 mL CH_2Cl_2. After 1 h, the reaction mixture was concentrated, and then 0.02 mL trifluoroacetic anhydride (0.14 mmol) was added to a stirred solution of the residue in 0.2 mL dry CH_2Cl_2 under nitrogen at −20°C. After 1 h, excess solvent and trifluoroacetic anhydride were immediately distilled off in vacuo at 0°C. The residue was dissolved in 0.1 mL MeOH, and an excess amount of $NaBH_3CN$ was added at 0°C. After 15 min the reaction mixture was poured into 10 mL H_2O and extracted with $CHCl_3$. Upon removal of solvent, the residue was purified on C_{18} HPLC (15% CH_3CN in MeOH with 0.1% TFA) to afford 4.8 mg Serratezomine A (48%) and 2.7 mg of its isomer (27%).

Other references related to the Polonovski reaction are cited in the literature.[13]

H. REFERENCES

1. Polonovski, M. and Polonovski, M., *Bull. Soc. Chim.,* **1927**, *41*, 1190.
2. (a) Lee, H. W.; Ahn, J. B.; Lee, J. H.; Kang, S. K.; Ahn, S. K. and Ha, D.-C., *Heterocycles*, **2006**, *68*, 915. (b) Thavaneswaran, S. and Scammells, P. J., *Bioorg. Med. Chem. Lett.,* **2006**, *16*, 2868. (c) Yun, H. D., *Synlett*, **2004**, 1321. (d) McCamley, K.; Ripper, J. A.; Singer, R. D. and Scammells, P. J., *J. Org. Chem.,* **2003**, *68*, 9847. (e) Moldovai, I., *Magyar Kemiai Folyoirat*, **2002**, *108*, 291. (f) Morita, H.; Yoshida, N. and Kobayashi, J., *J. Org. Chem.,* **2002**, *67*, 2278. (g) Morita, H. and Kobayahsi, J., *J. Org. Chem.,* **2002**, *67*, 5378. (h) Mary, A.; Renko, D. Z.; Guillou, C. and Thal, C., *Tetrahedron Lett*., **1997**, *38*, 5151. (i) Lounasmaa, M.; Jokela, R.; Halonen, M. and Miettinen, J., *Heterocycles*, **1993**, *36*, 2523. (j) Lounasmaa, M. and Karvinen, E., *Tetrahedron*, **1991**, *47*, 6371. (k) Grierson, D., *Org. React.,* **1990**, *39*, 85. (l) Magnus, P.; Stamford, S. A. and Ladlow, M., *J. Am. Chem. Soc.,* **1990**, *112*, 8210. (m) Tamminen, T.; Jokela, R.; Tirkkonen, B. and Lounasmaa, M., *Tetrahedron*, **1989**, *45*, 2683. (n) Bartsch, H.; Erker, T. and Schwarz, O., *Liebigs Ann. Chem*., **1988**, 491. (o) Lounasmaa, M.; Karvinen, E.; Koskinen, A. and Jokela, R., *Tetrahedron*, **1987**, *43*, 2135. (p) Okazaki, R. and Itoh, Y., *Chem. Lett.,* **1987**, 1575. (q) Danishefsky, S. and Feigelson, G. B., *Heterocycles,* **1987**, *25*, 301. (r) Miki, Y.; Tomii, O.; Utsunomiya, M.; Takemura, S. and Ikeda, M., *Chem. Pharm. Bull.,* **1986**, *34*, 3588. (s) Moldvai, I.; Vedres, A.; Toth, G.; Szantay, C. and Szantay, C., *Tetrahedron Lett*., **1986**, *27*, 2775. (t) Rajaraman, R.; Rajalakshmi, S. and Chinnasamy, P., *Indian J. Chem., Sect. B,* **1986**, *25B*, 517. (u) Fujimori, K.; Takata, T.; Fujiwara, S.; Kikuchi, O. and Oae, S., *Tetrahedron Lett*., **1986**, *27*, 1617. (v) Jokela, R.; Schuller, S. and Lounasmaa, M., *Heterocycles*, **1985**, *23*, 1751. (w) Lounasmaa, M.; Jokela, R. and Tamminen, T., *Tetrahedron Lett*., **1985**, *26*, 801. (x) Lounasmaa, M. and Koskinen, A., *Heterocycles*, **1984**, *22*, 1591. (y) Koskinen, A. and Lounasmaa, M., *Tetrahedron Lett*., **1983**, *24*, 1951. (z) Koskinen, A. and Lounasmaa, M., *Tetrahedron*, **1983**, *39*, 1627. (aa) Langenskioeld, T. and Lounasmaa, M., *Heterocycles*, **1983**, *20*, 671. (bb) Bartsch, H. and Schwarz, O., *J. Heterocycl. Chem.,* **1982**, *19*, 1189. (cc) Lounasmaa, M. and Koskinen, A., *Heterocycles*, **1982**, *19*, 2115. (dd) Lounasmaa, M. and Koskinen, A., *Tetrahedron Lett*., **1982**, *23*, 349. (ee) M'Pati, J.; Mangeney, P. and Langlois, Y., *Tetrahedron Lett*., **1981**, *22*, 4405. (ff) Potier, P., *Proc. Phytochem. Soc. Eur.,* **1980**, *17*, 159. (gg) Ikeda, M. and Tamura, Y., *Yuki Gosei Kagaku Kyokaishi*, **1980**, *38*, 10. (hh) Schecker, H. G. and Zinner, G., *Chemiker-Zeit.,* **1979**, *103*, 317. (ii) Schecker, H. G. and Zinner, G., *Pharm. Zeit.,* **1979**, *124*, 1767. (jj) Mangeney, P., *Tetrahedron,* **1978**, *34*, 1359. (kk) Potier, P., *Revista Latinoamer. Quim.*, **1978**, *9*, 47. (ll) Honma, Y. and Ban, Y., *Heterocycles,* **1977**, *6*, 291. (mm) Nakagawa, A.; Suzuki, K.; Iwasaki, K.; Kaji, K.; Omura, S.; Jakubowski, A. and Tishler, M., *Chem. Pharm. Bull.,* **1976**, *24*, 1749. (nn) Jessop, R. A. and Lindsay Smith, J. R., *J. Chem. Soc., Perkin Trans. I,* **1976**, 1801. (oo) Langlois, N.; Guykritte, F.; Langlois, Y. and Potier, P., *J. Am. Chem. Soc.,* **1976**, *98*, 7017. (pp) Cervinka, O.; Fabryova, A. and Zikmund, J., *Coll. Czech. Chem. Commun.,* **1976**, *41*, 1372. (qq) Hayashi, Y.; Nagano, Y.; Hongyo, S. and Teramura, K., *Tetrahedron Lett*., **1974**, 1299. (rr) Stuetz, P. and Stadler, P. A., *Tetrahedron Lett*., **1973**, 5095. (ss) Volz, H. and Ruchti, L., *Justus Liebigs Ann. Chem.,* **1972**, *763*, 184. (tt) Husson, H. P.; Chevolot, L.; Langlois, Y.; Thal, C. and Potier, P., *J. Chem. Soc., Chem. Commun.,* **1972**, 930. (uu) Ferles, M. and Jankovsky, M., *Coll. Czech. Chem. Commun.,* **1971**, *36*, 4103. (vv) Ahond, A.; Cave, A.; Kan-Fan, C. and Potier, P., *Bull. Soc. Chim. Fr.,* **1970**, 2707. (ww) Michelot, R., *Bull. Soc. Chim. Fr.,* **1969**, 4377. (xx) Russell, G. A. and Mikol, G. J., *Mechanisms Mol. Migration,* **1968**, *1*, 157. (yy) Renaud, R. N. and Leitch, L. C., *Can. J. Chem.,* **1968**, *46*, 385. (zz) Cave, A. and Michelot, R., *Compt. Rend.,* **1967**, *265*, 669. (aaa) Kolsaker, P. and Meth-Cohn, O., *Chem. Commun. (London),* **1965**, 423. (bbb) Michelot, R. and Tchoubar, B., *Bull. Soc. Chim. Fr.,* **1965**, 1896. (ccc) Oae, S.; Kitao, T. and Kawamura, S., *Tetrahedron*, **1963**, *19*, 1783. (ddd) Huisgen, R.; Bayerlein, F. and Heydkamp, W., *Chem. Ber.,* **1959**, *92*, 3223.
3. LaLonde, R. T.; Auer, E.; Wong, C. F. and Muralidharan, V. P., *J. Am. Chem. Soc.,* **1971**, *93*, 2501.

4. (a) Manninen, K. and Hakala, E., *Acta Chem. Scand., Ser. B,* **1986**, *B40*, 598. (b) Krouwer, J. S. and Richmond, J. P., *J. Org. Chem.,* **1978**, *43*, 2464.
5. (a) Blechert, S., *Liebigs Ann. Chem.,* **1985**, 2073. (b) Sunjic, V.; Kajfez, F.; Kolbah, D.; Hofman, H. and Stromar, M., *Tetrahedron Lett.,* **1973**, 3209.
6. Cavé, A., Kan-Fan, C., Potier, P. and Le Men, J., *Tetrahedron,* **1967**, *23*, 4681.
7. (a) Thomas, O. P.; Zaparucka, A. and Husson, H. P., *Tetrahedron Lett.,* **2001**, *42*, 3291. (b) Suau, R.; Najera, F. and Rico, R., *Tetrahedron,* **2000**, *56*, 9713. (c) Henriques, A.; Kan, C.; Chiaroni, A.; Riche, C.; Husson, H. P.; Kan, S. K. and Lounasmaa, M., *J. Org. Chem.,* **1982**, *47*, 803.
8. (a) Putkonen, T., *Preparation of Indole Alkaloids via 1,4-Dihydropyridine Stage or Cyano-masked Iminium Intermediates*. Helsinki University of Technology, Organic Chemistry Report, **2003**, *4*. (b) Gomez, J.-M.; Gil, L.; Ferroud, C.; Gateau-Olesker, A.; Martin, M.-T. and Marazano, C., *J. Org. Chem.,* **2001**, *66*, 4898. (c) Renko, D.; Mary, A.; Guillou, C.; Potier, P. and Thal, C., *Tetrahedron Lett*., **1998**, *39*, 4251. (d) Lewin, G.; Schaeffer, C.; Morgant, G. and Nguyen-Huy, D., *J. Org. Chem.,* **1996**, *61*, 9614. (e) Lounasmaa, M.; Belle, D. D. and Tolvanen, A., *Liebigs Ann*., **1995**, 1385. (f) Kan-Fan, C.; Quirion, J.-C. and Husson, H.-P., *Nat. Prod. Lett.,* **1993**, *3*, 291. (g) Photiou, A.; Sheikh, M. N.; Bafaloukos, D. and Retsas, S., *J. Cancer Res. Clinical Oncology,* **1992**, *118*, 249. (h) Compernolle, F.; Saleh, M. A.; van den Branden, S.; Toppet, S. and Hoornaert, G., *J. Org. Chem.,* **1991**, *56*, 2386. (i) Lewin, G.; Poisson, J.; Schaeffer, C. and Volland, J. P., *Tetrahedron*, **1990**, *46*, 7775. (j) Bosch, J.; Delgado, A.; Boncompte, F.; Soriano, C. and Bonjoch, J., *Anales Quim., Ser. C,* **1988**, *84*, 60.
9. Atta-ur-Rahman and Choudhary, M. I., *Pure & Appl. Chem.,* **1994**, *66*, 1967.
10. (a) Kende, A. S., *Pure & Appl. Chem.,* **1997**, *69*, 407. (b) Kende, A. S.; Liu, K. and Brands, K. M. J., *J. Am. Chem. Soc.,* **1995**, *117*, 10597.
11. Sundberg, R. J.; Hunt, P. J.; Desos, P. and Gadamasetti, K. G., *J. Org. Chem.,* **1991**, *56*, 1689.
12. Thal, C.; Dufour, M.; Potier, P.; Jaouen, M. and Mansuy, D., *J. Am. Chem. Soc.,* **1981**, *103*, 4956.
13. (a) Bentley, K. W., *Nat. Prod. Reports,* **2002**, *19*, 332. (b) Cocquet, G.; Ferroud, C.; Simon, P. and Taberna, P.-L., *J. Chem. Soc., Perkin Trans. II,* **2000**, 1147. (c) Sundberg, R. J.; Gadamasetti, K. G. and Hunt, P. J., *Tetrahedron,* **1992**, *48*, 277. (d) Ishizuka, T. and Kunieda, T., *Tetrahedron Lett.,* **1987**, *28*, 4185. (e) Chapman, R. F.; Phillips, N. I. J. and Ward, R. S., *Heterocycles,* **1986**, *24*, 3115. (f) Lounasmaa, M. and Koskinen, A., *Heterocycles,* **1984**, *22*, 1591. (g) Murahashi, S.-I. and Yano, T., *J. Am. Chem. Soc.,* **1980**, *102*, 2456. (h) Potier, P., *J. Nat. Prod.,* **1980**, *43*, 72. (i) Mangeney, P.; Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y. and Potier, P., *J. Am. Chem. Soc.,* **1979**, *101*, 2243. (j) Scott, A. I.; Yeh, C. L. and Greenslade, D., *J. Chem. Soc.*, *Chem. Commun.,* **1978**, 947. (k) Potier, P.; Langlois, N.; Langlois, Y. and Gueritte, F., *J. Chem. Soc., Chem. Commun.,* **1975**, 670. (l) Wenkert, E.; Chauncy, B. and Wentland, S. H., *Synth. Commun.,* **1973**, *3*, 73. (m) Ahond, A., Cavé, A., Kan-Fan, C., Langlois, Y. and Potier, P., *J. Chem. Soc., Chem. Commun.,* **1972**, 517. (n) Katritzky, A. R. and Lagowski, J. N., *Chemistry of Heterocyclic N-Oxides*, Academic Press: New York, **1971**, p. 279. (o) Ahond, A.; Cavé, A.; Kan-Fan, C.; Husson, H.-P.; de Rostolan, J. and Potier, P., *J. Am. Chem. Soc.,* **1968**, *90*, 5622.

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Pomeranz-Fritsch Reaction

(Pomeranz-Fritsch Synthesis, Pomeranz-Fritsch Isoquinoline Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first and concurrently reported by Pomeranz[1] and Fritsch[2] in 1893. It is the synthesis of isoquinolines via an acid-promoted electrophilic cyclization of benzalaminoacetals prepared from aromatic aldehydes and aminoacetals. Therefore, this reaction is known as the Pomeranz-Fritsch cyclization,[3] Pomeranz-Fritsch isoquinoline synthesis,[3,4] Pomeranz-Fritsch reaction,[4a,5,6] Pomeranz-Fritsch ring closure,[7] Pomeranz-Fritsch ring synthesis,[8] or Pomeranz-Fritsch synthesis.[3a,4a,9]

This reaction can directly give isoquinoline derivatives[10] and is generally favored by electron-donating substituents on the benzalaminoacetal;[4a,10] in addition, the cyclization normally occurs at the *para*-position of the electron-donating group, even though both *para*- and *ortho*-positions are available.[4a] In the presence of an electron-withdrawing group such as a nitro group, oxazoles instead of isoquinolines are formed.[5h] In this reaction, the feasible acid promoters include hydrochloric acid,[11] the combination of hydrochloric acid and acetic acid,[4a] methanesulfonic acid,[4a] orthophosphoric acid,[3b] perchloric acid,[12] polyphosphoric acid,[3b,5k,6a] sulfuric acid,[13] the combination of sulfuric acid and phosphorus pentoxide,[5h,7b] triflic acid,[4a] trifluoroacetic acids,[4a] and BF_3 in trifluoroacetic anhydride.[6c] However, as the traditional Pomeranz-Fritsch reaction gives low yields of isoquinolines,[4a] probably because of the steric and electronic effect[10] and the partial deactivation of the phenyl ring by the formation of a protonated imino group,[4a] this reaction has been extensively modified, such as the Bobbitt modification,[3a,4b,9e,14] Fischer modification,[9e,9f]

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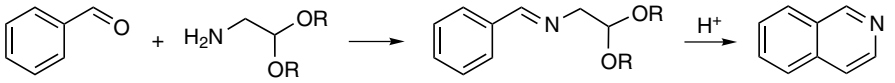
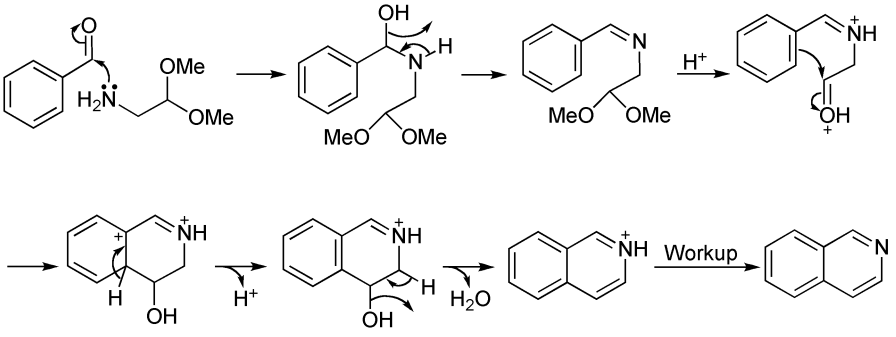
Jackson modification[4a,4c] and Schlittler-Müller modification.[4e,7c] The Fischer modification involves the treatment of benzalaminoacetal with fuming sulfuric acid,[9e] whereas Bobbitt modification produces tetrahydroisoquinoline derivative through the hydrogenation of an imine intermediate *in situ* to an aminoacetal, which in turn is converted into product by the acid-promoted cyclization and hydrogenation.[3a] This modification for tetrahydroisoquinoline is also known as the Pomeranz-Fritsch-Bobbitt cyclization.[3a] The Schlittler-Müller modification involves the preparation of benzalaminoacetal from benzyl amines and glyoxal semiacetal.[4e,7c] In addition, this reaction has been extended to prepare other types of aromatic heterocycles, such as thieno[2,3-c] and thieno[3,2-c]pyridines by intromolecular cyclization to thiophene ring.[5k]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Illustrated below is the mechanism of the reaction between benzaldehyde and dimethyl α-amino acetaldehyde.



D. MODIFICATION

This reaction has been modified to different variants, such as the Bobbitt modification, Fischer modification, and the Schlittler-Müller modification. In addition, different acids have been used as the promoters for this reaction.

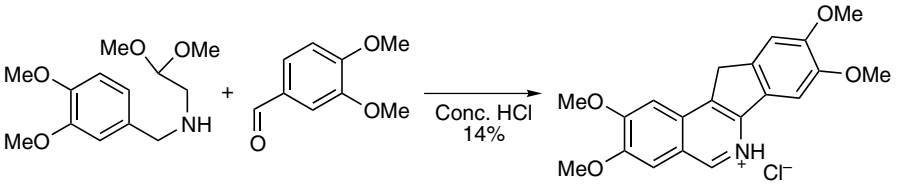
E. APPLICATIONS

This reaction has general application in the preparation of isoquinoline derivatives.

F. RELATED REACTIONS

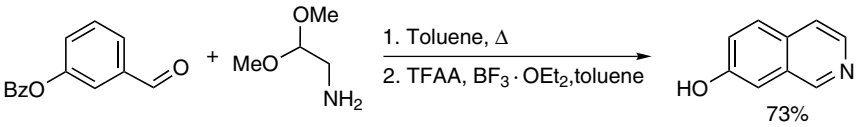
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 4a.

A mixture of 2.93 g (3,4-dimethoxybenzyl)-(2,2-dimethoxyethyl)amine (11.5 mmol), 4.11 g veratraldehyde (24.7 mmol) and conc. HCl was stirred at 100°C for 3 h. The reaction mixture was cooled and washed with ether (50 mL × 3), then basified with NH_4OH. The mixture was extracted with $CHCl_3$ (4 × 50 mL), the combined organic layers were washed with 100 mL H_2O, dried over Na_2SO_4, and concentrated. The residue was dissolved in 200 mL $CHCl_3$, the resulting solution was filtered, and 40 mL 2 M HCl in ether was added to the filtrate. The precipitate that formed was recrystallyzed from 300 mL MeOH to provide 0.594 g 2,3,8,9-tetramethoxy-11*H*-indeno[1,2-*c*]isoquinoline hydrochloride as a bright yellow hygroscopic solid, in a yield of 14%, m.p. 254–255°C.



Reference 15.

To a solution of 106 g 3-(benzyloxy)benzaldehyde (0.5 mol) in 1100 mL toluene was added 79 g aminoacetaldehyde dimethyl acetal (0.75 mol). The mixture was refluxed for 6 h using a Dean-Stark trap. After the mixture was cooled to 5°C, 212 mL trifluoracetic acid anhydride (1.5 mol) and 185 mL $BF_3{\cdot}Et_2O$ (1.5 mol) were added under nitrogen in succession at such a rate that the internal temperature was kept below 10°C. After 5 days of stirring at room temperature, the precipitated material was separated by filtration, washed with diethyl ether several times, and dissolved in 750 mL H_2O. The pH was adjusted to 9 by adding concentrated aqueous ammonia, and the precipitated product was separated by filtration, followed by washing with Et_2O and drying in vacuo to afford 53.2 g isoquinolin-7-ol as light yellow solid, in a yield of 73%, m.p, 228–230°C.

Other references related to the Pomeranz-Fritsch reaction are cited in the literature.[16]

H. REFERENCES

1. Pomeranz, C., *Monatsh.,* **1893**, *14*, 116.
2. Fritsch, P., *Ber.,* **1893**, *26*, 419.

3. (a) Chrzanowska, M. and Rozwadowska, M. D., *Chem. Rev.,* **2004**, *104*, 3341. (b) Dalton, L. K.; Demerac, S.; Elmes, B. C.; Loder, J. W.; Swan, J. M. and Teitei, T., *Aust. J. Chem.,* **1967**, *20*, 2715.
4. (a) Ioanoviciu, A.; Antony, S.; Pommier, Y.; Staker, B. L.; Stewart, L. and Cushman, M., *J. Med. Chem.,* **2005**, *48*, 4803. (b) Shirasaka, T.; Takuma, Y.; Shimpuku, T. and Imaki, N., *J. Org. Chem.,* **1990**, *55*, 3767. (c) Birch, A. J.; Jackson, A. H. and Shannon, P. V. R., *J. Chem. Soc., Perkin Trans. I,* **1974**, 2185. (d) Inubushi, Y. and Fujitani, K., *Yakugaku Zasshi,* **1958**, *78*, 486. (e) Schlittler, E. and Muller, J., *Helv. Chim. Acta,* **1948**, *31*, 914.
5. (a) Rodrigues, J. A. R.; Abramovitch, R. A.; de Sousa, J. D. F. and Leiva, G. C., *J. Org. Chem.,* **2004**, *69*, 2920. (b) Dai, G. X. and Larock, R. C., *J. Org. Chem.,* **2003**, *68*, 920. (c) Roesch, K. R.; Zhang, H. M. and Larock, R. C., *J. Org. Chem.,* **2001**, *66*, 8042. (d) Dai, G. X. and Larock, R. C., *Org. Lett.,* **2001**, *3*, 4035. (e) Orito, K.; Miyazawa, M.; Kanbayashi, R.; Tokuda, M. and Suginome, H., *J. Org. Chem.,* **1999**, *64*, 6583. (f) Kanojia, R. M.; Lever, O. W.; Press, J. B.; Williams, L.; Werblood, H. M.; Giardino, E. C.; Falotico, R. and Tobia, A. J., *J. Med. Chem.,* **1989**, *32*, 990. (g) Grunewald, G. L.; Dahanukar, V. H.; Caldwell, T. M. and Criscione, K. R., *J. Med. Chem.,* **1997**, *40*, 3997. (h) Brown, E. V., *J. Org. Chem.,* **1977**, *42*, 3208. (i) Bobbitt, J. M. and Dutta, C. P., *J. Org. Chem.,* **1969**, *34*, 2001. (j) Herz, W. and Tsai, L., *J. Am. Chem. Soc.,* **1955**, *77*, 3520. (k) Herz, W. and Tsai, L., *J. Am. Chem. Soc.,* **1953**, *75*, 5122.
6. (a) Bevis, M. J.; Forbes, E. J. and Uff, B. C., *Tetrahedron,* **2001**, *25*, 1585. (b) Katritzky, A. R.; Yang, Z. J. and Cundy, D. J., *Heteroatom Chem*., **1994**, *5*, 103. (c) Bevis, M. J.; Forbes, E. J.; Naik, N. N. and Uff, B. C., *Tetrahedron,* **1971**, *27*, 1253. (d) Kametani, T.; Ohkubo, K. and Takano, S., *Yakugaku Zasshi,* **1969**, *89*, 1048. (e) Herz, W. and Tocker, S., *J. Am. Chem. Soc.,* **1955**, *77*, 6355. (f) Guthrie, D. A.; Frank, A. W. and Purves, C. B., *Can. J. Chem.,* **1955**, *33*, 729. (g) Gensler, W. J., *Org. React.,* **1951**, *6*, 191.
7. (a) Solomons, W. E. and Mathison, I. W., *J. Heterocycl. Chem.,* **1980**, *17*, 1569. (b) Mathison, I. W., *J. Med. Chem.,* **1968**, *11*, 181. (c) Schlittler, E. and Muller, J., *Helv. Chim. Acta,* **1948**, *31*, 1119.
8. Armengol, M.; Helliwell, M. and Joule, J. A., *ARKIVOC,* **2000**, *1*, 832.
9. (a) Hirsenkorn, R., *Tetrahedron Lett.,* **1991**, *32*, 1775. (b) Hendrickson, J. B. and Rodriguez, C., *J. Org. Chem.,* **1983**, *48*, 3344. (c) Miller, R. B. and Frincke, J. M., *J. Org. Chem.,* **1980**, *45*, 5312. (d) Gensler, W. J.; Shamasundar, K. T. and Marburg, S., *J. Org. Chem.,* **1968**, *33*, 2861. (e) Bobbitt, J. M.; Kiely, J. M.; Khanna, K. L. and Ebermann, R., *J. Org. Chem.,* **1965**, *30*, 2247. (f) Bobbitt, J. M.; Winter, D. P. and Kiely, J. M., *J. Org. Chem.,* **1965**, *30*, 2459.
10. Flippin, L. A. and Muchowski, J. M., *J. Org. Chem.,* **1993**, *58*, 2631.
11. Bobbitt, J. M., *Adv. Heterocycl. Chem*., **1973**, *15*, 99.
12. Gee, K. R.; Barmettler, P.; Rhodes, M. R.; McBurney, R. N.; Reddy, N. L.; Hu, L. Y.; Cotter, R. E.; Hamilton, P. N.; Weber, E. and Keana, J. F., *J. Med. Chem.,* **1993**, *36*, 1938.
13. Kakefuda, A.; Watanabe, T.; Takahashi, T.; Sakamoto, S. and Tsukamoto, S. I., *Synth. Commun.,* **2001**, *31*, 401.
14. (a) Bobbitt, J. M. and Sih, J. C., *J. Org. Chem.,* **1968**, *33*, 856. (b) Bobbitt, J. M.; Roy, D. N.; Marchand, A. and Allen, C. W., *J. Org. Chem.,* **1967**, *32*, 2225.
15. Kucznierz, R.; Grams, F.; Leinert, H.; Marzenell, K.; Engh, R. A. and von der Saal, W., *J. Med. Chem.,* **1998**, *41*, 4983.
16. (a) Korivi, R. P. and Cheng, C.-H., *Org. Lett.,* **2005**, *7*, 5179. (b) Kanojia, R. M.; Press, J. B.; Lever, O. W.; Williams, L.; McNally, J. J.; Tobia, A. J.; Falotico, R. and Moore, J. B., *J. Med. Chem.,* **1988**, *31*, 1363. (c) Bobbitt, J. M. and Bourque, A. J., *Heterocycles,* **1987**, *25*, 601. (d) Pomeranz, C., *Monatsh.,* **1897**, *18*, 1. (e) Pomeranz, C., *Monatsh.,* **1894**, *15*, 299.

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Ponzio Reaction

A. GENERAL DESCRIPTION OF THE REACTION

Although this reaction was first reported by Scholl in 1888[1] and extended by Born in 1896,[2] it was Ponzio who initially extended this reaction to aromatic compounds in 1897.[3] It is the transformation of ketoximes into *gem*-dinitro compounds via a pseudonitrole intermediate by means of oxidation with dinitrogen tetraoxide[4] and is generally known as the Ponzio reaction.[4,5] Besides the formation of *gem*-dinitro compounds, some other byproducts are also formed during this oxidation. For example, the oxidation of benzaldoxime yields 16% benzaldoxime peroxide, 16% diphenylglyoxime peroxide, 12% benzaldehyde, and 50% dinitrophenylmethane.[6] This reaction particularly works for aromatic oximes, such as *p*-tolylaldoxime, and anisaldoxime.[7] It should be pointed out that *meta*-nitro dinitrophenylmethane from *meta*-nitro benzaldehyde oxime is a more powerful explosive than TNT.[8] According to Ponzio, the oximes of benzaldehyde, hydroxymethyl phenyl ketone, and methyl phenyl 1,2-diketone all give the corresponding dinitromethanes accordingly, whereas the ketoximes of benzoylformic acid, acetophenone and benzophenone give negative results.[7] However, the oximes of a few aliphatic ketones can also be converted into corresponding *gem*-dinitro compounds, such as the oximes of acetone,[1] ethyl methyl ketone,[1] diethyl ketone,[1] methyl propyl ketone,[2] methyl isopropyl ketone,[2] and di-*n*-propyl ketone.[2] It has been reported that the oxidation of glyoximes such as dimethyl, methyl, and phenyl glyoximes yields glyoxime peroxides as the predominant products,[7] while the oxidation of mono-oxime of 1,2-diketone by dinitrogen tetraoxide leads to the formation of 1,2-diketone as well as carboxylic acid and *gem*-dinitro compounds from the carbon-carbon bond cleavage.[7,9]

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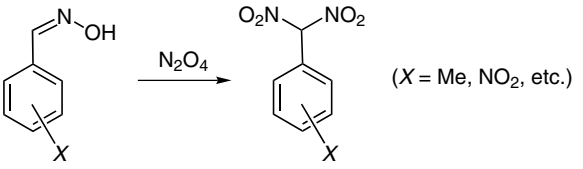
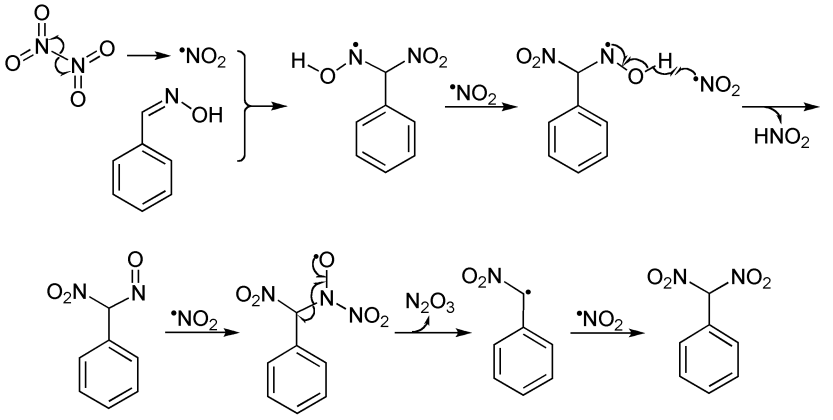
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Because mechanistic information for this reaction is not available, a tentative mechanism is proposed here. It is assumed that dinitrogen tetraoxide may decompose homolytically to give a nitrogen dioxide radical, which adds to the carbon-nitrogen double bond to introduce the first nitro group.



D. MODIFICATION

N/A

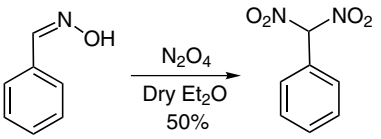
E. APPLICATIONS

This reaction is useful for the preparation of α,α-dinitrotoluene derivatives.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 10.

To 200 mL boiling anhydrous ether containing 5.0 g benzaldoxime (0.042 mol) was added 2.1 g dinitrogen tetraoxide (0.022 mol) in 10 mL anhydrous ether dropwise with stirring at a rate that maintained a gentle reflux (∼3 min). Stirring was continued for an additional 3 min, then 50 g ice was added. The ether layer was separated, washed once with water, and extracted with ice-cold 4% NH_4OH solution until the extracts were no longer colored. The red alkaline solution was washed with 100 mL ether, placed in a beaker, and covered with 50 mL ether. Upon careful neutralization at 0°C with aqueous oxalic acid, the red color disappeared. The aqueous solution then was extracted with 50 mL ether; the combined ether extracts were washed once with ice-cold water and dried for 10 min with anhydrous $MgSO_4$. Ether was removed in vacuo, to afford 3.5 g phenylnitrolic acid as pale yellow needles, in a yield of 50%, m.p. 56–57°C (dec.). The product was stable at −20°C for several weeks, but decomposed within a few hours at room temperature.

Other references related to the Ponzio reaction are cited in the literature.[11]

H. REFERENCES

1. Scholl, R., *Ber.,* **1888**, *21*, 506.
2. Born, G., *Ber.,* **1896**, *29*, 90.
3. Ponzio, G., *Gazz. Chim. Ital.,* **1897**, *27*, 171. *Chem. Zentr.,* **1897**, 857.
4. Bedford, C. D. and Nielsen, A. T., *J. Org. Chem.,* **1978**, *43*, 2460.
5. (a) Honey, P. J.; Millar, R. W. and Coombes, R. G., *ACS Symposium Ser.,* **1996,** *623*, 134. (b) Baum, K. and Nguyen, N. V., *J. Org. Chem.,* **1992**, *57*, 3026. (c) Suzuki, H.; Takaoka, H.; Yamamoto, H. and Ogawa, T., *Bull. Chem. Soc. Jpn.,* **1988**, *61*, 2927. (d) Fruttero, R.; Ferrarotti, B. and Gasco, A., *J. Org. Chem.,* **1987**, *52*, 3442. (e) Fieser, L. F. and Doering, W. von E., *J. Am. Chem. Soc.,* **1968**, *90*, 2252.
6. Ponzio, G., *Atti Accad. Lincei Roma,* **1906**, *15*, 118. *Chem. Zentr.,* **1906**, 1003.
7. Riebsomer, J. L., *Chem. Rev.,* **1945**, *36*, 157.
8. Milone, M. and Massa, A., *Gazz. Chim. Ital.,* **1940**, *70*, 196.
9. (a) Ponzio, G., *Gazz. Chim. Ital.,* **1901**, *31*, 262. *Chem. Zentr.,* **1901**, 1319. (b) Ponzio, G., *Gazz. Chim. Ital.,* **1901**, *31*, 133. *Chem. Zentr.,* **1901**, 1007. (c) Ponzio, G., *J. Prakt. Chem.,* **1900**, *62*, 543. (d) Ponzio, G. and de Gaspari, A., *Gazz. Chim. Ital.,* **1898**, *28*, 269. *Chem. Zentr.,* **1898**, 965.
10. Boyer, J. H. and Alul, H., *J. Am. Chem. Soc.,* **1959**, *81*, 4237.
11. (a) Suzuki, H.; takaoka, H.; Yamamoto, H. and Ogawa, T., *Bull. Chem. Soc. Jpn.,* **1988**, *61*, 2927. (b) Bull, J. R.; Jones, E. R. H. and Meakins, G. D., *J. Chem. Soc.,* **1965**, 2601. (c) Ponzio, G., *Gazz. Chim. Ital.,* **1909**, *39*, 326. (d) Ponzio, G., *Gazz. Chim. Ital.,* **1908**, *38*, 509. (e) Ponzio, G., *J. Prakt. Chem.,* **1906**, *73*, 494. (f) Ponzio, G., *Gazz. Chim. Ital.,* **1906**, *36*, 288.

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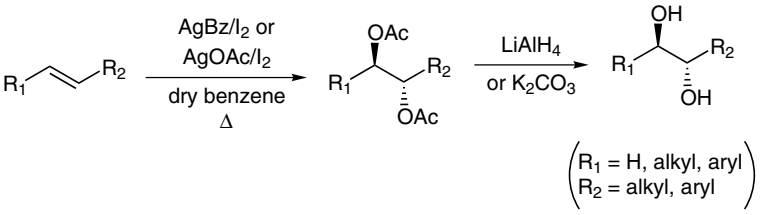
Prévost Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Prévost in 1933.[1] It is the one-pot transformation of alkenes into *trans* 1,2-diols through the joint oxidation with silver(I) carboxylate and iodine in an anhydrous solvent followed by the reduction or hydrolysis of 1,2-dicarboxylate intermediates.[2] Therefore, this reaction is generally known as the Prévost reaction.[2c,3] Occasionally, it is also referred to as the Prévost *trans*-dihydroxylation.[4] In addition, because this reaction is the complement of the *Woodward cis-Hydroxylation*,[5] for the conversion of the alkenes into vicinal diols, the Prévost reaction is also called the Woodward-Prévost reaction[2a,2c,5] or Prévost-Woodward reaction.[3a,6] In this reaction, silver(I) carboxylate can be silver(I) acetate[2a,3a] or silver(I) benzoate.[3a,3b,4] It has been reported that this reaction may involve the formation of an α-halocarboxylate, which can be easily transformed into the corresponding *trans*-1,2-dicarboxylate[2a] through a (cyclic) dioxolanyl cation intermediate in the presence of metal carboxylate[2c] from stereoselective nucleophilic displacement of the α-halo group.[2a] However, this reaction also has some drawbacks, such as poor facial selectivity of *epi*-iodination in cyclic substrates,[7] low reactivity of some haloacetates due to steric hindrance,[6c] rearrangement during the oxidation,[3i,6a] and low yields.[8]

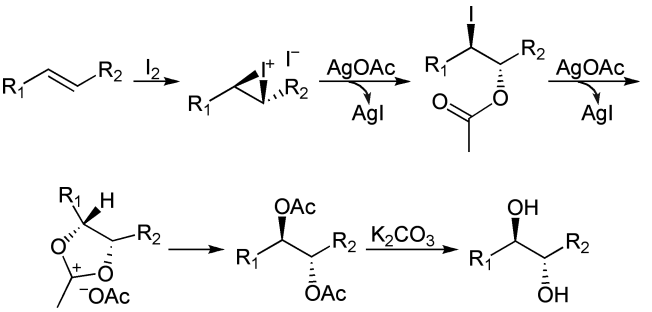
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

Because detailed mechanistic information is not available, a tentative mechanism is proposed here. It is assumed that iodine first adds to the double bond to form an iodonium cation in a process similar to the bromination of alkene, then nucleophilic attack from acetate leads to the formation of the *trans*-α-iodoacetate. In the presence of silver acetate, α-iodo leaves to give a dioxoanyl carbocation, which is attacked by the second acetate anion to give *trans*-1,2-diacetate. Upon hydrolysis or $LiAlH_4$ reduction, diacetate is transformed into *trans*-1,2-diol. The displayed mechanism is similar to the one proposed by Sudalai.[3a]



D. MODIFICATION

This reaction has been modified by the use of Hg(II),[9] Cu(II),[6a,10] Th(I),[11] and Pb(IV)[12] salts in the related reactions. In addition, $Bi(OAc)_3$ is also used for this reaction because of its low toxicity, reasonable cost, and tolerance to moisture.[2c] Furthermore, similar reaction has been catalyzed by LiBr in the presence of either $NaIO_4$ or $PhI(OAc)_2$.[3a]

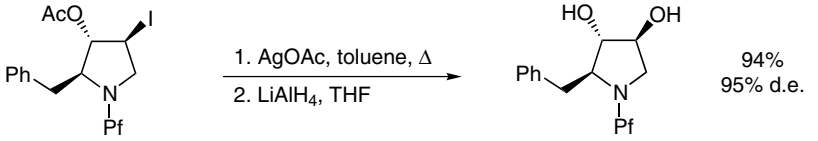
E. APPLICATIONS

This reaction is very useful for the conversion of alkenes into adjacent *trans*-diols.

F. RELATED REACTIONS

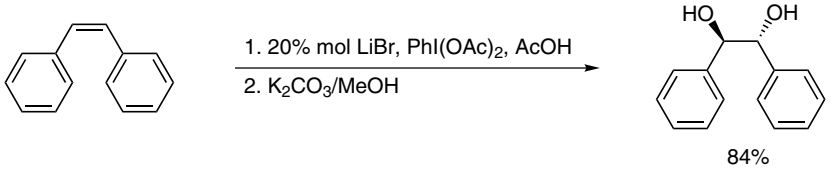
This reaction is related to the *Woodward cis-Hydroxylation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2a.

A mixture of 0.4 mmol 2-benzyl-3-acetyl-4-iodo-*N*-(9-phenylfluoren-9-yl) pyrrolidine and 0.133 g AgOAc (0.8 mmol) was refluxed in 4 mL anhydrous toluene for 3 h. Then the reaction mixture was filtered, and toluene was evaporated. The residue was reduced by 0.030 g $LiAlH_4$ (0.8 mmol) in 4 mL THF at 0°C. The mixture was filtered, and THF was removed in vacuo. The residue was purified by column chromatography using hexanes/EtOAc as the eluent to afford 94% (2*S*, 3*S*, 4*S*)-2-benzyl-3,4-dihydroxy-*N*-(9-phenylfluoren-9-yl) pyrrolidine with 95% d.e.



Reference 3a.

To a 25-mL round-bottomed flask were added 3 mmol *cis*-stilbene, 0.6 mmol LiBr, 3 mmol $PhI(OA(c)_2$, and 5 mL acetic acid. The mixture was heated at 95°C for 18 h then cooled to room temperature and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with saturated sodium thiosulfate solution, water, aqueous $NaHCO_3$, and dried over Na_2SO_4. Upon removal of solvent, 4.5 mmol K_2CO_3 and 20 mL MeOH were added to the flask containing the residue, and the mixture was stirred at room temperature for 24 h. When MeOH was removed by rotatory evaporation, the residue was taken up by EtOAc (3 × 30 mL). The combined organic phases were washed with water and brine and dried over Na_2SO_4. Upon removal of solvent, the residue was purified by column chromatography using petroleum ether/EtOAc (7:3) as the eluent to afford 84% of *trans*-diol.

Other references related to the Prévost reaction are cited in the literature.[13]

H. REFERENCES

1. (a) Prévost, C., *Compt. Rend.,* **1933**, *196*, 1129. (b) Prévost, C., *Compt. Rend.,* **1933**, *197*, 1661. (c) Prévost, C. and Lutz, B., *Compt. Rend.,* **1933**, *198*, 2264.
2. (a) Kim, J. H.; Long, M. J. C.; Kim, J. Y. and Park, K. H., *Org. Lett.,* **2004**, *6*, 2273. (b) Bergstad, K.; Piet, J. J. N. and Bäckvall, J.-E., *J. Org. Chem.,* **1999**, *64*, 2545. (c) Trainor, R. W.; Deacon, G. B.; Jackson, W. R. and Giunta, N., *Aust. J. Chem.,* **1992**, *45*, 1265.
3. (a) Emmanuvel, L.; Shaikh, T. M. A. and Sudalai, A., *Org. Lett.,* **2005**, *7*, 5071. (b) Zajc, B., *J. Org. Chem.,* **1999**, *64*, 1902. (c) Ciganek, E. and Calabrese, J. C., *J. Org. Chem.,* **1995**, *60*, 4439. (d) Prasad, K. J. R. and Subramaniam, M., *Indian J. Chem., Sect. B,* **1994**, *33B*, 696. (e) Campi, E. M.; Deacon, G. B.; Edwards, G. L.; Fitzroy, M. D.; Giunta, N.; Jackson, W. R. and Trainor, R., *J. Chem. Soc., Chem. Commun.,* **1989**, 407. (f) Cambie, R. C.; Hayward, R. C.; Jurlina, J. L.; Rutledge, P. S. and Woodgate, P. D., *Aust. J. Chem.,* **1981**, *34*, 1349. (g) Grewal, G. S., *J. Res. (Punjab Agricultural Univ.*), **1977**, *14*, 468. (h) Cambie, R. C.; Potter, G. J.; Rutledge, P. S. and Woodgate, P. D., *J. Chem. Soc., Perkin Trans. I,* **1977**, 530. (i) Kamano, Y. and Tozawa, M., *Yuki Gosei Kagaku Kyokaishi*, **1976**, *34*, 118. (j) Atta-ur-Rehman; Waheed, N. and Ghazala, M., *Z. Naturforsch., Teil B,* **1976**, *31B*, 264. (k) Parrilli, M.; Dovinola, V. and Mangoni, L., *Gazz. Chim. Ital.,* **1974**, 104, 829. (l) Tozawa, M., *Jikeikai Med. J.*, **1973**, *20*, 95. (m) Tozawa, M., *Jikeikai Med. J.*, **1973**, *20*, 67. (n) Tozawa, M., *Jikeikai Med. J.*, **1973**, *20*, 79. (o) Tozawa, M., *Jikeikai Med. J.*, **1973**, *20*, 87. (p) Suehiro, T.; Hirai, M. and Niitsu, M., *Bull. Chem. Soc. Jpn.,* **1970**, *43*,

3301. (q) Smissman, E. E. and Robinson, R. A., *J. Org. Chem.,* **1970**, *35*, 3532. (r) Smadja, W., *Compt. Rend.,* **1969**, *268*, 271. (s) Mangoni, L. and Dovinola, V., *Gazz. Chim. Ital.,* **1969**, *99*, 176. (t) Dovinola, V. and Mangoni, L., *Gazz. Chim. Ital.,* **1969**, *99*, 195. (u) Norman, R. O. C. and Thomas, C. B., *J. Chem. Soc. B,* **1967**, 604. (v) Ferretti, A. and Tesi, G., *J. Chem. Soc.,* **1965**, 520. (w) Ferretti, A. and Tesi, G., *Tetrahedron Lett*., **1964**, 2975. (x) Lemieux, R. U. and Levine, S., *Can. J. Chem.,* **1962**, *40*, 1926. (y) Briggs, L. H.; Cain, B. F.; Cambie, R. C.; Davis, B. R. and Rutledge, P. S., *J. Chem. Soc.,* **1962**, 1850. (z) Briggs, L. H.; Cain, B. F. and Davis, B. R., *Tetrahedron Lett*., **1960**, 9. (aa) Wiberg, K. B. and Saegebarth, K. A., *J. Am. Chem. Soc.,* **1957**, *79*, 6256. (bb) McCasland, G. E. and Horswill, E. C., *J. Am. Chem. Soc.,* **1954**, *76*, 1654.

4. Li, W.-D. Z. and Peng, Y., *Org. Lett.,* **2005**, *7*, 3069.
5. (a) Myint, Y. Y. and Pasha, M. A., *Indian J. Chem., Sect. B,* **2004**, *43B*, 590. (b) Donohoe, T. J.; Headley, C. E.; Cousins, R. P. C. and Cowley, A., *Org. Lett.,* **2003**, *5*, 999. (c) Hamm, S.; Hennig, L.; Findeisen, M.; Muller, D. and Welzel, P., *Tetrahedron,* **2000**, *56*, 1345. (d) Katoch, R.; Baig, M. H. A. and Trivedi, G. K., *J. Chem. Res. (S),* **1998**, 524. (e) Cambie, R. C.; Craw, P. A.; Hughes, R. J.; Rutledge, P. S. and Woodgate, P. D., *Aust. J. Chem.,* **1982**, *35*, 2111.
6. (a) Uyeo, S.; Koshiro, A.; Irie, H. and Yamamoto, K., *Chem. Pharm. Bull.,* **1967**, *15*, 582. (b) Iwai, I.; Koshiro, A.; Kurabayashi, M.; Mishima, H.; Uyeo, S. and Yamamoto, K., *Chem. Commun.,* **1965**, 118.
7. (a) Brimble, M. A. and Nairn, M. R., *J. Org. Chem.,* **1996**, *61*, 4801. (b) Whitesell, J. K. and Minton, M. A., *J. Am. Chem. Soc.,* **1987**, *109*, 6403.
8. Kamano, P. Y.; Pettit, G. R.; Tozawa, M.; Komeichi, Y. and Inoue, M., *J. Org. Chem.,* **1975**, *40*, 2136.
9. Georgoulis, C. and Valery, J., *Bull. Soc. Chim. Fr.,* **1975**, 1431.
10. (a) Horiuchi, C. A. and Satoh, J. Y., *Bull. Chem. Soc. Jpn.,* **1987**, *60*, 426. (b) Georgoulis, C. and Valery, J., *Synthesis,* **1978**, 402.
11. Cambie, R. C. and Rutledge, P. S., *Org. Synth. Coll.*, **1988**, *6*, 348.
12. Gutsulyak, R. B. and Serguchev, Y. A., *J. Org. Chem. USSR,* **1990**, *26*, 1383.
13. (a) Myint, Y. Y. and Pasha, M. A., *J. Chem. Res.,* **2004**, 333. (b) Campell, M. M.; Sainsburg, M. and Yavarzadeh, R., *Tetrahedron,* **1984**, *40*, 5063. (c) Mangoni, L. and Dovinola, V., *Gazz. Chim. Ital.,* **1970**, *100*, 467. (d) Wilson, C. V., *Org. React.,* **1957**, *9*, 332. (e) Prévost, C. and Wiemann, J., *Compt. Rend.,* **1937**, *204*, 700. (f) Prévost, C., *Compt. Rend.,* **1935**, *200*, 942.

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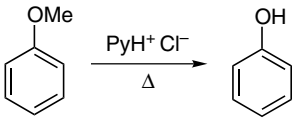
Prey Ether Cleavage

A. GENERAL DESCRIPTION OF THE REACTION

Although this reaction was first reported by Klemenc in 1916,[1] it was Prey who modified the original protocol in 1941 and made it a simple and convenient method to cleave the aliphatic-aromatic ethers by heating the mixture of appropriate ether and pyridine hydrochloride.[2] Therefore, this transformation is called the Prey ether cleavage herein. To date, this reaction has been used to remove the methyl groups in anisole,[2a] phenetole,[3] *o*-methoxphenol,[3] *o*-dimethoxybenzene,[3] anisaldehyde,[3] methoxy-illudinine,[4] and 3,5-dichloro-2-methoxy-6-methylacetophenone.[5] In addition, by removal of a methyl group, a series of phenol derivatives have been prepared, such as *p*-pentadecylphenol,[6] desoxymorphine,[7] and β-dihydrothebainol.[8] It should be pointed out that phenyl ethyl ether can also be cleaved by this reaction but at a relatively lower speed.[3] It has been found that a few percent of pyridine hydrochloride is adequate for this reaction if dry hydrogen chloride is passed into the reaction system,[3] although dry hydrogen chloride itself does not cleave the listed ethers under similar conditions.[2b]

B. GENERAL REACTION SCHEME



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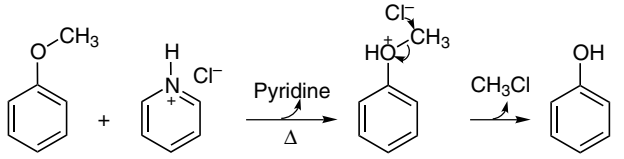
C. PROPOSED MECHANISMS

It is believed that methyl aromatic ether is protonated from the thermally stable pyridine hydrochloride to form an oxonium ion, which undergoes nucleophilic substitution with chloride to evolve methyl chloride and yield phenol derivatives, as exemplified here by the reaction of anisole.



D. MODIFICATION

This reaction has been modified by passing dry hydrogen chloride into the reaction system with a small amount of pyridinium chloride present.

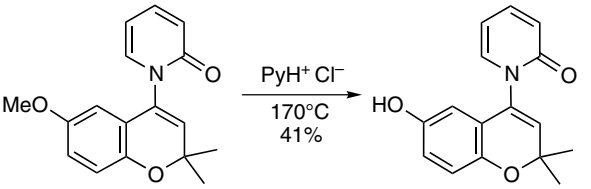
E. APPLICATIONS

This reaction has been used to cleave methyl aromatic ethers and phenoxy esters.[9] In addition, this reaction has been successfully used for determining methoxyl groups to an accuracy of 1% by conversion of pyridine hydrochloride into *N*-methylpyridinium chloride.[2c]

F. RELATED REACTIONS

N/A

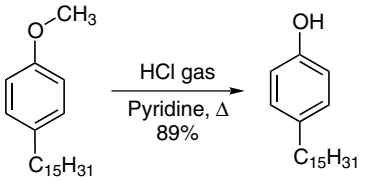
G. CITED EXPERIMENTAL EXAMPLES



Reference 10.

A mixture of 5.67 g 4-(1,2-dihydro-2-oxo-1-pyridyl)-6-methoxy-2,2-dimethyl-2*H*-1-benzopyran (20 mmol) and 6.93 g pyridine hydrochloride (60 mmol) was heated to melt at 170°C for 2 h. The hot solution was poured into 150 mL 2% H_2SO_4, and the product was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated. The

residue was purified by crystallization from MeOH to afford 2.21 g 4-(1,2-dihydro-2-oxo-1-pyridyl)-6-hydroxy-2,2-dimethyl-2*H*-1-benzopyran, in a yield of 41%.



Reference 6.

A solution of 8.92 g *p*-pentadecylanisole (0.028 mol) in 50 mL dry pyridine was refluxed, and a strong steam of HCl gas was passed into the stirred mixture. Refluxing ceased after minutes, and the mixture was heated again for 4.5 h then allowed to cool. Water (50 mL) and 100 mL Et_2O were added to the flask, and the phases were separated. The aqueous layer was extracted with Et_2O (2 × 100 mL), and the combined ether layers were washed with H_2O, dried over $MgSO_4$, and evaporated under reduced pressure to give an off-white solid, which was recrystallized from hexane to give 7.7 g *p*-pentadecylphenol, in a yield of 89%, m.p. 71.4–73°C.

Other references related to the Prey ether cleavage are cited in the literature.[11]

H. REFERENCES

1. Klemenc, A., *Ber.,* **1916**, *49*, 1371.
2. (a) Prey, V., *Ber.,* **1941**, *74*, 1219. (b) Prey, B., *Ber.,* **1942**, *75*, 350. (c) Prey, B., *Ber.,* **1942**, *75*, 445. (d) Prey, B., *Ber.,* **1942**, *75*, 537. (e) Prey, B. *Ber.,* **1943**, *76*, 156.
3. Burwell, R. L., *Chem. Rev.,* **1954**, *54*, 615.
4. Nair, M. S. R.; Takeshita, H.; McMorris, T. C. and Anchel, M., *J. Org. Chem.,* **1969**, *34*, 240.
5. Cremer, S. E. and Tarbell, D. S., *J. Org. Chem.,* **1961**, *26*, 3653.
6. Milbert, A. N. and Wiley, R. A., *J. Med. Chem.,* **1978**, *21*, 245.
7. Rapoport, H. and Bonner, R. M., *J. Am. Chem. Soc.,* **1951**, *73*, 2872.
8. Gates, M. and Tschudi, G., *J. Am. Chem. Soc.,* **1956**, *78*, 1380.
9. Marquardt, R. P. and Luce, E. N., *J. Agri. Food Chem.,* **1961**, *9*, 266.
10. Mannhold, R.; Cruciani, G.; Weber, H.; Lemoine, H.; Derix, A.; Weichel, C. and Clementi, M., *J. Med. Chem.,* **1999**, *42*, 981.
11. (a) Cava, M. P. and Bhattacharyya, N. K., *J. Org. Chem.,* **1958**, *23*, 1287. (b) Hochstein, F. A.; Stephens, C. R.; Conover, L. H.; Regna, P. P.; Pasternack, R.; Gordon, P. N.; Pilgrim, F. J.; Brunings, K. J. and Woodward, R. B., *J. Am. Chem. Soc.,* **1953**, *75*, 5455. (c) Rapoport, H.; King, T. P. and Lavigne, J. B., *J. Am. Chem. Soc.,* **1951**, *73*, 2718. (d) Rapoport, H. and Bonner, R. M., *J. Am. Chem. Soc.,* **1951**, *73*, 5485. (e) Wilds, A. L. and McCormack, W. B., *J. Am. Chem. Soc.,* **1948**, *70*, 4127.

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Prilezhaev Reaction

(Prilezhaev Epoxidation, Prileschajew Epoxidation, Prilezhaev Oxidation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Prilezhaev (also known as Prileschajew) in 1909.[1,2] It is the convenient transformation of alkenes with isolated olefinic double bond into epoxides[2b,2e] (i.e., oxirane[3]) or glycols[4] by means of oxidation with organic peracid in a neutral[4b] organic medium. Therefore, this reaction is generally known as the Prilezhaev reaction.[5] In addition, it is also referred to as the Prileschajew reaction,[6] Prilezhaev epoxidation[5a,7] or Prilezhaev oxidation;[8] while the organic peracid is known as the Prileschajew reagent.[9] This reaction can be carried out in many common organic solvents such as acetone, chloroform, diethyl ether, and dioxane,[3] using perbenzoic acid (also known as benzoyl hydrogen peroxide[10] or benzoylhydroperoxide[4b]) as the oxidant. This reaction is especially useful for the epoxidation of nonvolatile, water-insoluble olefins.[3] Although this reaction usually gives good to quantitative yields,[3,10] the actual yields and reaction time depend on both the peracid used and the number and nature of groups attaching to the olefinic double bond. For example, furoic peracid has been found to be more reactive than perbenzoic acid and camphoric acid peracid, whereas phthalic acid peracid is almost inactive for this reaction.[11] In addition, the introduction of an electron-withdrawing group to a phenyl ring increases the electrophilicity and reactivity of perbenzoic acid, thus the application of *m*-chloro-perbenzoic acid (*m*CPBA, or 3-chloroperbenzoic acid) in epoxidation of olefins is specifically known as *m*CPBA epoxidation.[12] In addition, the Prilezhaev epoxidation is tolerable for many functional groups, including aromatic ring, ester, and ether,[5c] and has shown excellent face selectivity for certain kinds of olefins. Such face selectivity may

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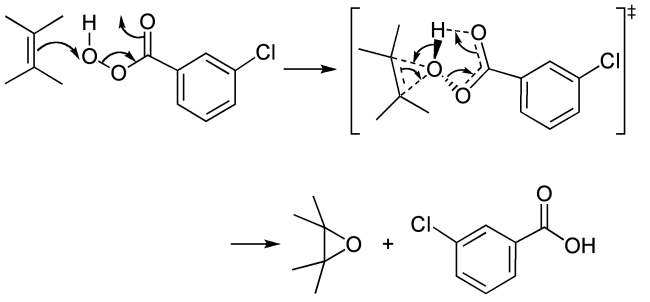
arise from steric hindrance, hydrogen bonding, and aromatic π-π stacking.[12d] The steric hindrance is clearly shown in the epoxidation of sterically hindered alkenes (e.g., steroidal olefins).[13] The effect of hydrogen bonding on face selectivity is observable during the epoxidation of cyclic alkenones[14] and olefins with hydrogen-bonding acceptors (e.g., allyl alcohols,[15] allylamides,[16] allyl carbamates,[17] allyl ethers,[18] α-diones,[19] and unsaturated carboxylic acids[20]). The face selectivity arising from hydrogen bonding is especially shown in the epoxidation of 3-hydroxycyclohexene to *syn*-epoxide, whereas the epoxidation of 3-methoxycyclohexene gives predominantly *anti*-product.[21] Such high diastereoselectivity is attributed to the hydroxy-group directivity.[2b,22]

B. GENERAL REACTION SCHEME

C. PROPOSED MECHANISMS

Many mechanisms have been proposed for this reaction, such as the epoxidation via initial attack of a hydroxyl cation,[23] *1,3-Dipolar Cycloaddition* of a hydroxycarbonyl oxide to an olefinic double bond,[24] and the commonly accepted planar "butterfly" transition state,[2a,2b,24a,25] by which the π HOMO orbital of the olefin approaches the terminal oxygen of perbenzoic acid and interacts with the σ^* LUMO of the O-O bond at 180°.[25c] The planar butterfly transition state is further extended by Sharpless to a *spiro*-transition state,[26] which has been consolidated by many other investigators.[2c,25b,27] An illustrative mechanism from *m*CPBA epoxidation is provided here.



D. MODIFICATION

The reaction has been modified to avoid the application of perbenzoic acid by treating the solutions of olefins with air or oxygen in the presence of benzaldehyde so that perbenzoic

acid is generated *in situ* and consumed as it is formed.[28] In addition, such epoxidation has been catalyzed by organometallic complex such as Mn(salen).[5a]

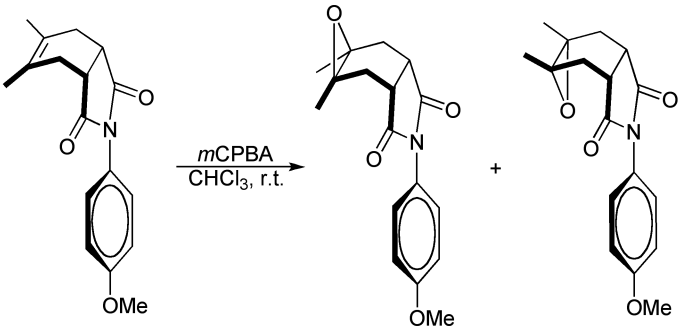
E. APPLICATIONS

This reaction has a very broad application in organic synthesis.

F. RELATED REACTIONS

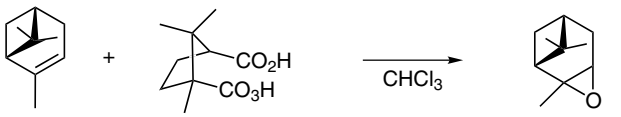
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 12d.

To a 100-mL round-bottomed flask equipped with a dropping funnel capped with a $CaCl_2$ drying tube were added 0.392 mmol 2-(4-methoxyphenyl)-5,6-dimethyl-3a,4,7,7a-tetrahydroisoindole-1,3-dione and 10 mL $CHCl_3$. Then 0.588 mmol *m*CPBA in 5 mL $CHCl_3$ was added to the flask dropwise via the dropping funnel over 20 min. The solution was stirred at room temperature for 3 h, washed successively with 100 mL 20% aq. $NaHSO_3$, 100 mL saturated aq. $NaHCO_3$, and 50 mL H_2O and dried over anhydrous $MgSO_4$. Upon the removal of solvent, the residue was separated by silica gel column chromatography with hexanes/EtOAc (1:1) as the eluent to afford 29% 9-(4-methoxyphenyl)-3,5-dimethyl-4-oxa-9-azatricyclo-[5.3.0.$0^{3,5}$]decane-8,10-dione (colorless crystals, m.p. 144–145°C) and 40% of its isomer (colorless crystals, m.p. 179–181°C).



Reference 11.

A total of 5 g d-pinene was mixed with a large excess of camphoric acid peracid in $CHCl_3$, and the mixture was allowed to stand at 0°C for 3 days. It was then shaken with a 10% NaOH to remove the unused peracid and camphoric acid and was finally washed with H_2O and dried over anhydrous Na_2SO_4 for 24 h. Upon removal of $CHCl_3$, the remaining liquid was purified by fractional distillation, b.p. 102–103°C at 50 mmHg.

Other references related to the Prilezhaev reaction are cited in the literature.[29]

H. REFERENCES

1. Prileschajew, N., *Ber.,* **1909**, *42*, 4811.
2. (a) Cui, M.; Adam, W.; Shen, J. H.; Luo, X. M.; Tan, X. J.; Chen, K. X.; Ji, R. Y. and Jiang, H. L., *J. Org. Chem.,* **2002**, *67*, 1427. (b) Adam, W.; Bach, R. D.; Dmitrenko, O. and Saha-Möller, C. R., *J. Org. Chem.,* **2000**, *65*, 6715. (c) Bach, R. D.; Estévez, C. M.; Winter, J. E. and Glukhovtsev, M. N., *J. Am. Chem. Soc.,* **1998**, *120*, 680. (d) Kuo, M.-C. and Chou, T.-C., *Ind. Eng. Chem. Res.,* **1987**, *26*, 277. (e) Saffer, A. and Johnson, B. L., *Ind. Eng. Chem.,* **1948**, *40*, 538.
3. Swern, D., *Chem. Rev.,* **1949**, *45*, 1.
4. (a) Adam, W.; Bosio, S. G.; Turro, N. J. and Wolff, B. T., *J. Org. Chem.,* **2004**, *69*, 1704. (b) Hibbert, H. and Burt, C. P., *J. Am. Chem. Soc.,* **1925**, *47*, 2240.
5. (a) Khavrutskii, I. V.; Musaev, D. G. and Morokuma, K., *Proc. Natl. Acad. Sci., USA,* **2004**, *101*, 5743. (b) Lederer, M. O.; Schuler, A. and Ohmenhäuser, M., *J. Agri. Food Chem.,* **1999**, *47*, 4611. (c) Boyd, T. J. and Schrock, R. R., *Macromolecules,* **1999**, *32*, 6608. (d) De Cock, C. J. C.; De Keyser, J. L.; Poupaert, J. H. and Dumont, P., *Bull. Soc. Chim. Belg.,* **1987**, *96*, 783. (e) Schnurpfeil, D., *Zeitsch. Chem.,* **1980**, *20*, 445. (f) Makitra, R. G. and Pirig, Y. N., *Zh. Fizicheskoi Khimii,* **1978**, *52*, 785. (g) Sytilin, M. S., *Ukr. Khim. Zh.,* **1977**, *43*, 634. (h) Sapunov, V. N. and Lebedev, N. N., *Izv. Vysshikh Uchebnykh Zavedenii, Khim. Khim. Tekh.,* **1965**, *8*, 771.
6. Harry-O'Kuru, R. E. and Carriere, C. J., *J. Agrc. Food Chem.,* **2002**, *50*, 3214.
7. (a) Kulinkovich, O. G., *Russ. Chem. Bull.,* **2004**, *53*, 1065. (b) Moiseev, I. I., *Kinetics and Catalysis,* **2001**, *42*, 1. (c) Eisch, J. J.; Liu, Z.-R. and Singh, M., *J. Org. Chem.,* **1992**, *57*, 1618.
8. Eisch, J. J.; Liu, Z.-R.; Ma, X. and Zheng, G.-X., *J. Org. Chem.,* **1992**, *57*, 5140.
9. Namyslo, J. C. and Kaufmann, D. E., *Chem. Rev.,* **2003**, *103*, 1485.
10. Brooks, B. T. and Brooks, W. B., *J. Am. Chem. Soc.,* **1933**, *55*, 4309.
11. Milas, N. A. and Cliff, I. S., *J. Am. Chem. Soc.,* **1933**, *55*, 352.
12. (a) Feldman, A. K.; Colasson, B.; Sharpless, K. B. and Fokin, V. V., *J. Am. Chem. Soc.,* **2005**, *127*, 13444. (b) Matsuo, G.; Kawamura, K.; Hori, N.; Matsukura, H. and Nakata, T., *J. Am. Chem. Soc.,* **2004**, *126*, 14374. (c) Bach, R. D.; Dmitrenko, O.; Adam, W. and Schambony, S., *J. Am. Chem. Soc.,* **2003**, *125*, 924. (d) Kishikawa, K.; Naruse, M.; Kohmoto, S.; Yamamoto, M. and Yamaguchi, K., *J. Chem. Soc., Perkin Trans. I*, **2001**, 462. (e) Adam, W.; Peters, K.; Peters, E.-M. and Schambony, S. B., *J. Am. Chem. Soc.,* **2001**, *123*, 7228. (f) Frimer, A. A.; Afri, M.; Baumel, S. D.; Gilinsky-Sharon, P.; Rosenthal, Z. and Gottlieb, H. E., *J. Org. Chem.,* **2000**, *65*, 1807. (g) Kim, C.; Traylor, T. G. and Perrin, C. L., *J. Am. Chem. Soc.,* **1998**, *120*, 9513. (h) Shea, K. J. and Kim, J. S., *J. Am. Chem. Soc.,* **1992**, *114*, 3044.
13. (a) Kehrli, A.; Taylor, D. A. and Niven, M., *J. Chem. Soc., Perkin Trans. I*, **1990**, 2057. (b) Cambie, R. C.; Read, C. M.; Rutledge, P. S.; Walker, G. J.; Woodgate, P. D. and Hanson, J. R., *J. Chem. Soc., Perkin Trans. I*, **1980**, 2581. (c) Trost, B. M. and Matsumura, Y., *J. Org. Chem.*, **1977**, *42*, 2036.

14. (a) Armstrong, A.; Barsanti, P. A.; Clark, P. A. and Wood, A., *J. Chem. Soc.*, *Perkin Trans. I*, **1996**, 1373. (b) Armstrong, A.; Barsanti, P. A.; Clark, P. A. and Wood, A., *Tetrahedron Lett.*, **1994**, *35*, 6155.
15. (a) Ekhato, I. V.; Silverton, J. V. and Robinson, C. H., *J. Org. Chem.,* **1988**, *53*, 2180. (b) Sharpless, K. B.; Behrens, C. H.; Katsuki, T.; Lee, A. W. M.; Martin, V. S.; Takatani, M.; Viti, S. M.; Walker, F. J. and Woodard, S. S., *Pure & Appl. Chem.,* **1983**, *55*, 589.
16. Roush, W. R.; Straub, J. A. and Brown, R. J., *J. Org. Chem.*, **1987**, *52*, 5127.
17. Kocovsky, P., *Tetrahedron Lett.,* **1988**, *29*, 2475.
18. Bowles, S. A.; Campbell, M. M.; Sainsbury, M. and Davies, G. M., *Tetrahedron,* **1990**, *46*, 3981.
19. Liao, C. C.; Lin, H. S.; hseu, T. H.; Tang, C.-P. and Wang, J. L., *J. Am. Chem. Soc.,* **1982**, *104*, 292.
20. Furber, M. and Mander, L. N., *J. Am. Chem. Soc.,* **1987**, *109*, 6389.
21. (a) Henbest, H. B., *Proc. Chem. Soc.,* **1963**, 159. (b) Henbest, H. B. and Wilson, R. A. L., *J. Chem. Soc.,* **1957**, 1958.
22. Adam, W. and Wirth, T., *Acc. Chem. Res.,* **1999**, *32*, 703.
23. Waters, W. A., *Mechanism of Oxidation of Organic Compounds,* John Wiely & Sons, New York, **1965**.
24. (a) Plesnicar, B.; Tasevski, M. and Azman, A., *J. Am. Chem. Soc.,* **1978**, *100*, 743. (b) Kwart, H.; Starcher, P. S. and Tinsley, S. W., *J. Chem. Soc., Chem. Commun.,* **1967**, 335.
25. (a) Angelis, Y. S. and Orfanopoulos, M., *J. Org. Chem.*, **1997**, *62*, 6083. (b) Houk, K. N.; Liu, J.; DeMello, N. C. and Condroski, K. R., *J. Am. Chem. Soc.*, **1997**, *119*, 10147. (c) Woods, K. W. and Beak, P., *J. Am. Chem. Soc.,* **1991**, *113*, 6281. (d) Bach, R. D.; Owensby, A. L.; Gonzalez, C.; Schlegel, H. B. and McDouall, J. J. W., *J. Am. Chem. Soc.*, **1991**, *113*, 2338. (e) Rebek, J.; Marshall, L. and McManis, J. W. R., *J. Org. Chem.*, **1986**, *51*, 1649. (f) Bartlett, P. D., *Rec. Chem. Prog.,* **1950**, *11*, 47.
26. Sharpless, K. B. and Verhoeven, T. R., *Aldrichim. Acta,* **1979**, *12*, 63.
27. (a) Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M. and Rastelli, A., *J. Org. Chem*., **2000**, *65*, 2030. (b) Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M. and Rastelli, A., *J. Org. Chem*., **1999**, *64*, 3853. (c) Bach, R. D.; Glukhovtsev, M. N. and Gonzalez, C., *J. Am. Chem. Soc.,* **1998**, *120*, 9902. (d) Singleton, D. A.; Merrigan, S. R.; Liu, J. and Houk, N. K., *J. Am. Chem. Soc.,* **1997**, *119*, 3385. (e) Bach, R. D.; Ayala, P. Y. and Schlegel, H. B., *J. Am. Chem. Soc.,* **1996**, *118*, 12758. (f) Bach, R. D.; Winter, J. E. and McDouall, J., *J. Am. Chem. Soc.,* **1995**, *117*, 8586.
28. (a) Swern, D.; Findley, T. W. and Scantan, J. T., *J. Am. Chem. Soc.,* **1944**, *66*, 1925. (b) Pigulevskii, G. V., *J. Gen. Chem. USSR,* **1934**, *4*, 616. (c) Raymond, E., *J. Chim. Phys.,* **1931**, *28*, 480.
29. (a) Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M. and Rastelli, A., *J. Org. Chem*., **2005**, *70*, 9573. (b) Adam, W.; Bosio, S. G. and Wolff, B. T., *Org. Lett.*, **2003**, *5*, 819. (c) Koerner, T.; Slebocka-Tilk, H. and Brown, R. S., *J. Org. Chem.*, **1999**, *64*, 196. (d) Eckrich, R.; Neumann, B.; Stammler, H.-G. and Kuck, D., *J. Org. Chem*., **1996**, *61*, 3839. (e) Filler, R.; Camara, B. R. and Naqvi, S. M., *J. Am. Chem. Soc.,* **1959**, *81*, 658. (f) Swern, D.; Billen, G. N. and Scanlan, J. T., *J. Am. Chem. Soc.,* **1946**, *68*, 1504. (g) Muskat, I. E. and Herrman, M., *J. Am. Chem. Soc.,* **1932**, *54*, 2001. (h) Braun, G., *J. Am. Chem. Soc.,* **1929**, *51*, 228. (i) Prileschajew, N., *Bull. Soc. Chim.,* **1927**, *41*, 687. (j) Prileschajew, N., *Ber.,* **1926**, *59*, 194. (k) Prileschajew, N., *J. Russ. Phys. Chem. Soc.,* **1912**, *44*, 613. (l) Prileschajew, N., *J. Russ. Phys. Chem. Soc.,* **1911**, *43*, 609. (m) Prileschajew, N., *J. Russ. Phys. Chem. Soc.,* **1910**, *42*, 1387.

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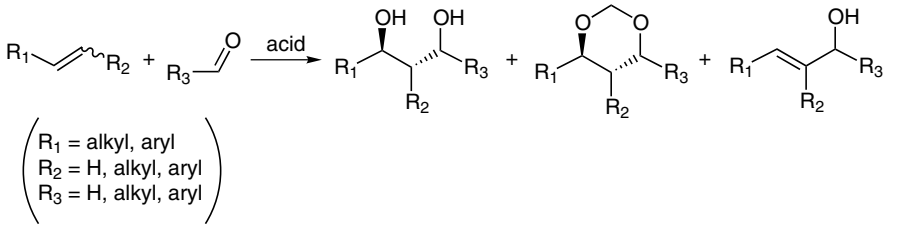
Prins Reaction
(Prins Cyclization)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Kriewitz in 1899[1] and studied extensively by Prins since 1917.[2] It is an acid-catalyzed condensation between aldehydes and olefins to form a variety of compounds such as 1,3-dioxanes, 1,3-diols, allyl alcohols, or 1,3-diesters, depending on the nature of alkenes and the reaction conditions. Therefore, this reaction is generally known as the Prins reaction[3] or Prins cyclization.[4] In addition, this reaction is also referred to as aldol-Prins reaction[4aa] or Prins-pinacol reaction.[4y,5] This reaction can be carried out in an aqueous or an anhydrous medium,[3ee] and the aldehydes can be aliphatic, aromatic, α,β-unsaturated aldehydes or even cyclic acetals.[4aa] The acid can be either a Brønsted acid or a Lewis acid, by which the commonly used Brønsted acid is 10–65% sulfuric acid,[3u,3y,3cc,3gg] and the Lewis acid can be $AlCl_3$,[3gg] $ZnCl_2$,[3gg] BF_3,[6] $InCl_3$,[7] etc. In this reaction, the commonly used aldehyde is formaldehyde.[3m,3n,3r,3s,3u,3v,3y,3bb,3dd–3gg] It has been found that in aqueous solution with sulfuric acid as the catalyst, both 1,3-dioxanes and 1,3-diols can be obtained from olefins;[8] in addition, 1,3-dienes may be formed from the reaction between formaldehyde and trisubstituted olefins because of the dehydration.[9] When an excess amount of formaldehyde is used—for example, more than 10-fold—1,3-dioxane is predominantly formed.[3r] However, in the presence of an anhydrous organic acid and when sulfuric acid is used as the catalyst, diesters of 1,3-glycols are produced.[3gg] For the reaction between styrene and formaldehyde, telomer may be formed at a low ratio of formaldehyde over styrene.[3u] On the other hand, the Prins reaction has been found to be highly stereoselective with *trans*-addition for both alicyclic and acylic olefins,[3t,3v,3bb,3dd] especially the *anti*/*syn* ratio of formed diols increases when the size of aldehydes increase.[3m] It should be pointed out that if the formed carbonium ion is highly stabilized, the Prins reaction may be controlled by thermodynamics.[3v]

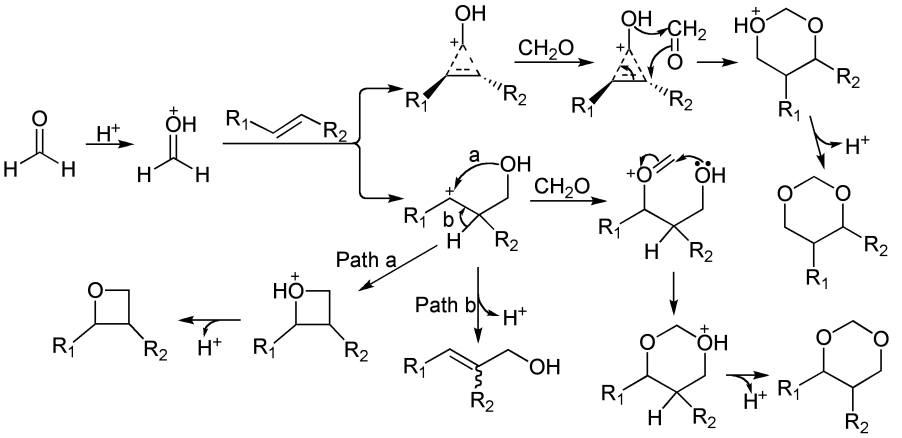
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is proposed that this reaction involves an acid-activated formaldehyde intermediate[3ee] (i.e., in the form of hydroxymethyl carbonium ion[3ff]) that electrophilically attacks the olefinic double bond to form an oxetane oxonium ion[3v,3z,10] or a three-member bridged carbocation,[3t] which upon solvolysis yields 1,3-glycol or 1,3-dioxane. An illustrative mechanism is given here.



D. MODIFICATION

This reaction has been extended to the reaction between aldehydes and alkenyl complexes of boranes, silanes, and stannes to give allylic alcohols,[3m] where the reaction with alkenyl complexes of silanes is known as the silyl-Prins reaction.[7] In addition, several Lewis acids-mediated or -promoted Prins reactions have recently been developed, including the application of TMSI,[4w] hafnium (IV) bis(perfluorooctanesulfonyl)amides (in fluorous biphase system),[3d] iron (III) species,[4m] and 2,6-di-*tert*-butylphenoxy(difluoro)borane.[3j]

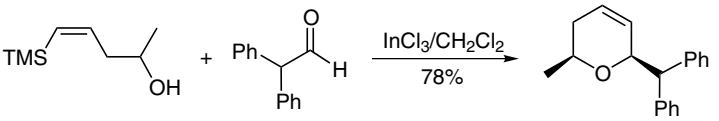
E. APPLICATIONS

This reaction has had wide application in organic synthesis, especially in the 1930s to 1940s for the production of dienes in large quantities for synthetic rubber manufacturing.

F. RELATED REACTIONS

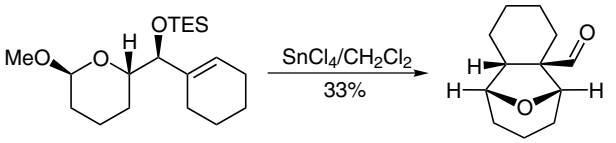
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

To a solution of 20 mL CH_2Cl_2 containing 0.39 g diphenylacetaldehyde (2 mmol) was added 0.44 g $InCl_3$ (2 mmol) under an atmosphere of nitrogen, and the resulting solution was stirred for 1 h. After this time, 0.32 g (*Z*)-5-trimethylsilylpent-4-en-2-ol (2 mmol) was added, and the reaction mixture was stirred at room temperature for an additional 16 h. The reaction mixture was then quenched with 10 mL distilled water, and the water layer was extracted with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$. Upon removal of solvent, the residue was purified by column chromatography using hexane/Et_2O (10:1) as the eluent to afford 0.41 g (±)-*cis*-2-benzhydryl-6-methyl-5,6-dihydro-2H-pyran as a colorless solid, in a yield of 78%, R_f = 0.43 (petroleum ether/Et_2O = 10 : 1), m.p. 75–77°C (from petroleum ether).



Reference 4y.

Tin (IV) chloride ($SnCl_4$, 42 μL, 0.23 mmol) was added dropwise to a solution of 0.16 g *rel*-(2*R*,6*R*)-[(6-methoxytetrahydropyran-2-yl)cyclohex-1-enyl]-*rel-(R)*-methoxytriethylsilane (0.46 mmol) in 9.5 mL CH_2Cl_2 at 0°C. After maintaining the reaction at 0°C for 30 min, the reaction mixture was poured into 5 mL saturated aqueous $NaHCO_3$, and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with 10 mL brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography using hexanes/EtOAc (49:1) to afford 30 mg 12-oxatricyclo[6.3.1.$0^{2,7}$]dodecane aldehyde as a clear pale yellow oil, in a yield of 33%.

Other references related to the Prins reaction are cited in the literature.[11]

H. REFERENCES

1. (a) Kriewitz, O., *Ber.,* **1899**, *32*, 57. (b) Kriewitz, O., *J. Chem. Soc.,* **1899**, *76*, 298.
2. (a) Prins, H. J., *Chem. Weekblad,* **1917**, 14, 627. (b) Prins, H. J., *Chem. Weekblad,* **1917**, *14*, 932.

3. (a) Shimizu, M.; Baba, T.; Toudou, S. and Hachiya, I., *Chem. Lett.,* **2007**, *36*, 12. (b) Rybina, A. V.; Shepelevich, I. S.; Talipov, R. F.; Galin, F. Z. and Spirikhin, L. V., *Chem. Nat. Compd.,* **2006**, *42*, 740. (c) Rybina, A. V.; Shepelevich, I. S.; Talipov, R. F. and Galin, F. Z., *Chem. Nat. Compd.,* **2006**, *42*, 620. (d) Hao, X. H. and Hoshi, N., *Chem. Lett.,* **2006**, *35*, 1102. (e) Konshin, P. S.; Vershinin, S. S.; Kotlov, V. M.; Miftakhova, Z. R. and Zorin, V. V., *Bashkirskii Khim. Zh.,* **2006**, *13*, 78. (f) Liu, Y. H. and Magomedov, N. A., *Synlett*, **2005**, 3075. (g) Sreedhar, B.; Swapna, V.; Sridhar, C.; Saileela, D. and Sunitha, A., *Synth. Commun.,* **2005**, *35*, 1177. (h) Braddock, D. C. and Matsuno, A., *Synlett*, **2004**, 2521. (i) Drudis-Sole, G.; Ujaque, G.; Maseras, F. and Lledos, A., *Compt. Rend. Chim.,* **2004**, *7*, 885. (j) Bach, T. and Lobel, J., *Synthesis,* **2002**, 2521. (k) Wolfling, J.; Frank, E.; Mernyak, E.; Bunkoczi, G.; Cvesta S., Jose A. and Schneider, G., *Tetrahedron,* **2002**, *58*, 6851. (l) Braddock, D. C.; Badine, D. M. and Gottschalk, T., *Synlett*, **2001**, 1909. (m) Lin, Y.-L.; Cheng, M.-H.; Chen, W.-C.; Peng, S.-M.; Wang, S.-L.; Kuo, H. Y. and Liu, R.-S., *J. Org. Chem.,* **2001**, *66*, 1781. (n) Alexandratos, S. D. and Miller, D. H. J., *Macromolecules,* **2000**, *33*, 2011. (o) Tietze, L. F., *Chem. Rev.,* **1996**, *96*, 115. (p) Mehta, G., *Pure & Appl. Chem.,* **1990**, *62*, 1263. (q) Safarov, M. G.; Nigmatullin, N. G. and Komissarov, V. D., *Russ. Chem. Bull.,* **1976**, *25*, 1123. (r) Casy, A. F.; Simmonds, A. B. and Staniforth, D., *J. Org. Chem.,* **1972**, *37*, 3189. (s) Schowen, K. B.; Smissman, E. E. and Schowen, R. L., *J. Org. Chem.,* **1968**, *33*, 1873. (t) Dolby, L. J.; Meneghini, F. A. and Koizumi, T., *J. Org. Chem.,* **1968**, *33*, 3060. (u) Dolby, L. J.; Wilkins, C. L. and Rodia, R. M., *J. Org. Chem.,* **1968**, *33*, 4155. (v) Smissman, E. E.; Schnettler, R. A. and Protoghese, P. S., *J. Org. Chem.,* **1965**, *30*, 797. (w) Sauers, R. R. and Sonnet, P. E., *J. Org. Chem.,* **1964**, *29*, 754. (x) Ramaswami, S.; Ramaswami, S. K. and Bhattacharyya, S. C., *J. Org. Chem.,* **1964**, *29*, 2245. (y) Dolby, L. J.; Lieske, C. N.; Rosencrantz, D. R. and Schwarz, M. J., *J. Am. Chem. Soc.,* **1963**, *85*, 47. (z) Lebel, N. A., Liesemer, R. N. and Mehemedbasich, E., *J. Org. Chem.,* **1963**, *28*, 615. (aa) Dolby, L. J. and Schwarz, M. J., *J. Org. Chem.,* **1963**, *28*, 1456. (bb) Portoghese, P. S. and Smissman, E. E., *J. Org. Chem.,* **1962**, *27*, 719. (cc) Dolby, L. J., *J. Org. Chem.,* **1962**, *27*, 2971. (dd) Smissman, E. E. and Witiak, D. T., *J. Org. Chem.,* **1960**, *25*, 471. (ee) Yang, N. C.; Yang, D.-D. H. and Ross, C. B., *J. Am. Chem. Soc.,* **1959**, *81*, 133. (ff) Smissman, E. E. and Mode, R. A., *J. Am. Chem. Soc.,* **1957**, *79*, 3447. (gg) Arundale, E. and Mikeska, L. A., *Chem. Rev.,* **1952**, *51*, 505.

4. (a) Liu, F. and Loh, T.-P., *Org. Lett.,* **2007**, *9*, 2063. (b) Yadav, J. S.; Reddy, B. V. S.; Kumar, G. G. K. S. N. and Reddy, G. M., *Chem. Lett.,* **2007**, *36*, 426. (c) Yadav, J. S.; Reddy, B. V. S.; Kumar, G. G. K. S. N. and Swamy, T., *Tetrahedron Lett*., **2007**, *48*, 2205. (d) Elliot, M. C.; El Sayed, N. N. E. and Paine, J. S., *Eur. J. Org. Chem.,* **2007**, 792. (e) Chan, K.-P.; Ling, Y. H. and Loh, T.-P., *Chem. Commun.,* **2007**, 939. (f) Yadav, J. S.; Rao, P. P.; Reddy, M. S.; Rao, N. V. and Prasad, A. R., *Tetrahedron Lett*., **2007**, *48*, 1469. (g) Miranda, P. O.; Carballo, R. M.; Ramirez, M. A.; Martin, V. S. and Padron, J. I., *ARKIVOC,* **2007**, (iv), 331. (h) Chan, K.-P.; Seow, A.-H. and Loh, T.-P., *Tetrahedron Lett*., **2007**, *48*, 37. (i) Bennett, C. E.; Figueroa, R.; Hart, D. J. and Yang, D. X., *Heterocycles,* **2006**, *70*, 119. (j) Jasti, R. and Rychnovsky, S. D., *J. Am. Chem. Soc.,* **2006**, *128*, 13640. (k) Jimenez-Nunez, E.; Claverie, C. K.; Nieto-Oberhuber, C. and Echavarren, A. M., *Angew. Chem. Int. Ed.,* **2006**, *45*, 5452. (l) Vasconcellos, M. L. A. A. and Miranda, L. S. M., *Quim. Nova,* **2006**, *29*, 834. (m) Carballo, R. M.; Ramirez, M. A.; Rodriguez, M. L.; Martin, V. S. and Padron, J. I., *Org. Lett.,* **2006**, *8*, 3837. (n) Yadav, J. S.; Reddy, M. S. and Prasad, A. R., *Tetrahedron Lett*., **2006**, *47*, 4995. (o) Yadav, J. S.; Reddy, M. S. and Prasad, A. R., *Tetrahedron Lett*., **2006**, *47*, 4937. (p) Bahnck, K. B. and Rychnovsky, S. D., *Chem. Commun.,* **2006**, 2388. (q) Jasti, R. and Rychnovsky, S. D., *Org. Lett.,* **2006**, *8*, 2175. (r) Miranda, P. O.; Ramirez, M. A.; Martin, V. S. and Padron, J. I., *Org. Lett.,* **2006**, *8*, 1633. (s) Kataoka, K.; Ode, Y.; Matsumoto, M. and Nokami, J., *Tetrahedron*, **2006**, *62*, 2471. (t) Mullen, C. A. and Gagne, M. R., *Org. Lett.,* **2006**, *8*, 665. (u) Cariou, C. A. M. and Snaith, J. S., *Org. Biomol. Chem.,* **2006**, *4*, 5. (v) Miles, R. B.; Davis, C. E. and Coates, R. M., *J. Org. Chem.,* **2006**, *71*, 1493. (w) Sabitha, G.; Reddy, K. B.; Reddy, G. S. K. K.; Fatima, N. and Yadav, J. S., *Synlett,* **2005**, 2347. (x) Yang, X.-F.; Wang, M. W.; Zhang, Y. H. and Li, C.-J., *Synlett*, **2005**, 1912. (y) Overman, L. E. and Velthuisen, E. J., *Org. Lett.,* **2004**, *6*, 3853. (z) Aubele, D. L.; Lee,, C. A. and Floreancig, P. E., *Org. Lett.,*

2003, *5*, 4521. (aa) Kopecky, D. J. and Rychnovsky, S. D., *J. Am. Chem. Soc.,* **2001**, *123*, 8420. (bb) Rychnovsky, S. D.; Marumoto, S. and Jaber, J. J., *Org. Lett.,* **2001**, *3*, 3815.

5. (a) Overman, L. E. and Velthuisen, E. J., *J. Org. Chem.,* **2006**, *71*, 1581. (b) Armstrong, A. and Shanahan, S. E., *Org. Lett.,* **2005**, *7*, 1335.
6. (a) Loder, D. J., *U.S. Pat*., July 14, **1943**, 2,289,548 [*Chem. Abstr.,* **1943**, *37*, 388]. (b) Loder, D. J., *U.S. Pat*., May 9, **1939**, 2,158,031 [*Chem. Abstr.,* **1939**, *33*, 6343].
7. Dobbs, A. P., Guesné, S. J. J.; Martinovic, S.; Coles, S. J. and Hursthouse, M. B., *J. Org. Chem.,* **2003**, *68*, 7880.
8. (a) Prins, H. J., *J. Chem. Soc.,* **1920**, *118*, 42. (b) Prins, H. J., *Pro. Acad. Sci. Amsterdam,* **1919**, *22*, 51.
9. (a) Arundale, E. and Mikeska, L. A., *U.S. Pat*., June 6, **1944**, 2,350,485 [*Chem. Abstr.,* **1944**, *38*, 4957]. (b) Rosen, R. and Arundale, E., *U.S. Pat*., Jan. 30, **1945**, 2,368, 494. [*Chem. Abstr.,* **1945**, *39*, 4529].
10. (a) Bernardi, L. and Leone, A., *Tetrahedron Lett.,* **1964**, 499. (b) Blomquist, A. T. and wolinsky, J., *J. Am. Chem. Soc.,* **1957**, *79*, 6025.
11. (a) Fletcher, M. D.; Jones, A. and Turner, J. J., *Ann. Reports Sect. B, (Org. Chem.),* **2005**, *101*, 49. (b) Oikawa, H. and Tokiwano, T., *Nat. Prod. Rep.,* **2004**, *21*, 321. (c) Langer, P.; Freifeld, I. and Shojaei, H., *Chem. Commun.,* **2003**, 3044. (d) Kocovsky, P.; Ahmed, G.; Syrogl, J.; Malkov, A. V. and Steele, J., *J. Org. Chem.,* **1999**, *64*, 2765. (e) Andersen, N. H.; Hadley, S. W.; Kelly, J. D. and Bacon, E. R., *J. Org. Chem.,* **1985**, *50*, 4144. (f) Snider, B. B. and Jackson, A. C., *J. Org. Chem.,* **1983**, *48*, 1471. (g) Adams, D. R. and Bhatnagar, S. P., *Synthesis,* **1977**, 661. (h) Dolby, L. J.; Wilkins, C. and Frey, T. G., *J. Org. Chem.,* **1966**, *31*, 1110. (i) Shriner, R. L. and Ruby, P. R., *Org. Synth. Coll.,* **1963**, *4*, 786.

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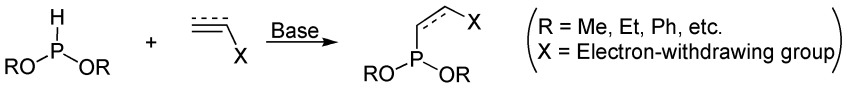
Pudovik Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Pudovik in 1950.[1] It is a base-promoted nucleophilic addition[2] of organophosphorus anion to alkenes or alkynes[3] and is generally known as the Pudovik reaction.[4,5] Occasionally, it is also referred to as the Pudovik addition.[4b] In addition, since Abramov discovered a similar addition reaction of phosphorus compounds to carbonyl compounds at the same time,[6] the addition of organophosphorus compounds to activated unsaturated systems (e.g., alkenes,[2,3] alkynes,[2,3] ketones,[4h,7] aldehydes,[4h,7] and imines[1b,1d,8]) is generally called the Pudovik-Abramov reaction.[7a] This type of reaction has been reported to occur via an ionic or radical mechanisms.[3] The outcome of this reaction depends on the structure of unsaturated substrates, the phosphorus reagents, and the experimental conditions.[3] For example, in the addition of dialkylphosphite to aldehyde, the labile proton on the phosphorus atom (P-H) can be easily removed by a catalytic amount of di-*n*-butylamine,[4c] whereas solid-supported base such as Al_2O_3/KOH has been used for deprotonation of a series of secondary phosphines and phosphites.[4e]

B. GENERAL REACTION SCHEME



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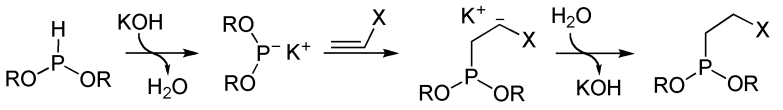
C. PROPOSED MECHANISMS

Illustrated here is the reaction mechanism between dialkylphosphite and an activated alkene in the presence of KOH.



D. MODIFICATION

This reaction has been extended to the addition of organophosphorus compounds on imines.[1b,1d,8]

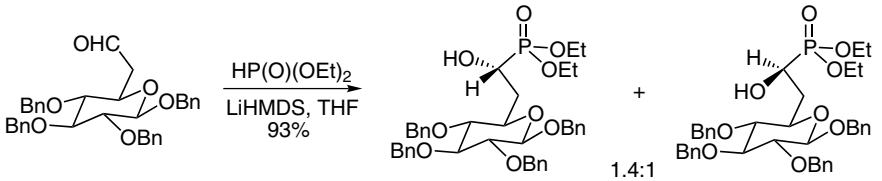
E. APPLICATIONS

This reaction has very broad application in the preparation of an array of organophosphorus compounds.

F. RELATED REACTIONS

This reaction is related to the *Atherton-Todd Reaction* and *Kabachnik-Fields Reaction.*

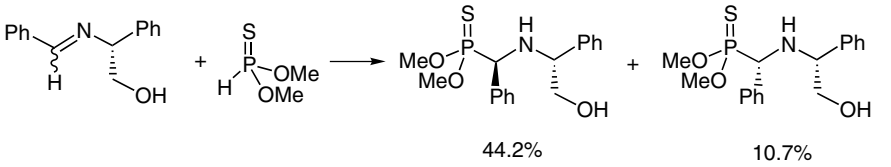
G. CITED EXPERIMENTAL EXAMPLES



Reference 4g.

To a solution of 0.16 mL diethyl phosphite (1.23 mmol) in 0.7 mL THF at −78°C was added 1.23 mL 1 M LiHMDS solution in THF (1.23 mmol). The resulting solution was stirred for 5 min at −78°C, followed by the addition, via cannula, of a solution of 618 mg benzyl 6-deoxy-6-formyl-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (1.12 mmol) in 5 mL THF at −78°C. After 10 min, the reaction was quenched with aqueous NH_4Cl and Et_2O. The aqueous layer was further extracted with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and evaporated. Upon removal of solvent, 650 mg benzyl 6-deoxy-6-[diethylphosphono(1′-hydroxy)-methyl]-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside was obtained as a mixture of diastereomers (1.4:1 ratio), which are

separable by silica gel flash column chromatography using hexanes/EtOAc (1:1) as the eluent. On a smaller scale of starting material, the same procedure gave 108 mg diastereomeric mixture, in a yield of 93%, the major diastereomer (first eluting) has melting point of 122–123°C.



44.2% 10.7%

Reference 8.

To a solution of 0.51 g (*R*)-(+)-2-phenylglycinol (3.72 mmol) in 10 mL dry toluene containing 0.5 g 3Å molecular sieves was added 0.38 mL benzaldehyde (3.74 mmol), and the resulting solution was stirred at room temperature for 2 h until an aliquot showed completion by the presence of the imino proton at δ 8.51. The reaction was filtered through Celite, and 0.31 mL dimethyl thiophosphite (3.69 mmol) was added. The reaction mixture was stirred at 0°C for 12 h, concentrated to an oil and subjected to column chromatography using hexanes/Et_2O as the eluent. A major diastereomer of *O*,*O*-dimethyl (*RS*)-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}(phenyl)methyl-phosphonothioate, in the amount of 0.578 g was obtained, in a yield of 44.2%, and 0.14 g minor diastereomer (10.7%) and 0.27 g diasteromeric mixture (20.6%) were obtained as well.

Other references related to the Pudovik reaction are cited in the literature.[9]

H. REFERENCES

1. Pudovik, A. N., *Doklady Akad. Nauk. SSSR,* **1950**, *73*, 499 [*Chem. Abstr.,* **1951**, *45*, 2856].
2. Georgiev, E. M.; Kaneti, J.; Troev, K. and Roundhill, D. M., *J. Am. Chem. Soc.,* **1993**, *115*, 10964.
3. Semenzin, D.; Etemad-Moghadam, G.; Albouy, D.; Diallo, O. and Koenig, M., *J. Org. Chem.,* **1997**, *62*, 2414.
4. (a) Dembitsky, V. M.; Al Quntar, A. A. A.; Haj-Yehia, A. and Srebnik, M., *Mini-Rev. Org. Chem.,* **2005**, *2*, 91. (b) Déjugnat, C.; Etemad-Moghadam, G. and Rico-Lattes, I., *Chem. Commun.,* **2003**, 1858. (c) Xie, Y. L.; Zhu, Q.; Qin, X. R. and Xie, Y. Y., *Chin. Chem. Lett.,* **2003**, *14*, 25. (d) Dimukhametov, M. N.; Bayandina, E. V.; Davydova, E. Y.; Gubaidullin, A. T.; Litvinov, I. A. and Alfonsov, V. A., *Mendeleev Commun.,* **2003**, 1. (e) Tedeschi, L. and Enders, D., *Org. Lett.,* **2001**, *3*, 3515. (f) Vercruysse, K.; Déjugnat, C.; Munoz, A. and Etemad-Moghadam, G., *Eur. J. Org. Chem.,* **2000**, 281. (g) Berkowitz, D. B.; Bose, M.; Pfannenstiel, T. J. and Doukov, T., *J. Org. Chem.,* **2000**, *65*, 4498. (h) Galkin, V. I.; Khabibullina, A. B.; Bakhtiyarova, I. V.; Cherkasov, R. A. and Pudovik, A. N., *Zh. Obsh. Khim. (Russ. J. Gen. Chem.),* **1990**, *60*, 92. (i) Galkin, V. I. and Cherkasov, R. A., *Chem. Organophsoph. Compds.,* **1989**, 43. (j) Galkin, V. I.; Khabibullina, A. B.; Bakhtiyarova, I. V.; Cherkasov, R. A. and Pudovik, A. N., *Zh. Obsh. Khim., (Russ. J. Gen. Chem.),* **1988**, *58*, 1002.
5. (a) Sobanov, A. A.; Zolotukhin, A. V.; Galkina, I. V.; Galkin, V. I. and Cherkasov, R. A., *Russ. J. Gen. Chem.,* **2006**, *76*, 421. (b) Sobanov, A. A.; Zolotukhin, A. V.; Galkin, V. I.; Mostovaya, O. A.; Cherkasov, R. A. and Pudovik, A. N., *Russ. J. Gen. Chem.,* **2003**, *73*, 871. (c) Sobanov, A. A.; Zolotukhin, A. V.; Galkin, V. I.; Cherkasov, R. A. and Pudovik, A. N., *Russ. J. Gen.*

Chem., **2002**, *72*, 1067. (d) Albouy, D.; Lasperas, M.; Etemad-Moghadam, G. and Koenig, M., *Tetrahedron Lett*., **1999**, *40*, 2311. (e) Qian, C. T. and Huang, T. S., *Fenzi Cuihua*, **1997**, *11*, 455. (f) Yokomatsu, T.; Yamagishi, T. and Shibuya, S., *J. Chem. Soc., Perkin Trans. I,* **1997**, 1527. (g) Groeger, H.; Wilken, J. and Martens, J., *Zeitsch. Naturforsch., B: Chem. Sci.,* **1996**, *51*, 1305. (h) Ovchinnikov, V. V., *Zh. Obsh. Khim.,* **1996**, *66*, 463. (i) Groeger, H. and Martens, J., *Synth. Commun.,* **1996**, *26*, 1903. (j) Safina, Yu. G.; Malkova, G. Sh. and Cherkasov, R. A., *Zh. Obsh. Khim.,* **1991**, *61*, 620. (k) Galkin, V. I.; Galkina, I. V.; Khabibullina, A. B.; Al Kurdi, Halil; Cherkasov, R. A. and Pudovik, A. N., *Dokl. Akad. Nauk SSSR,* **1990**, *314*, 1408. (l) Nesterov, L. V.; Krepysheva, N. E. and Aleksandrova, N. A., *Zh. Obsh. Khim.,* **1984**, *54*, 54. (m) Malenko, D. M. and Gololobov, Yu. G., *Zh. Obsh. Khim.,* **1978**, *48*, 2793.

6. Abramov, V. S., *Doklady Akad. Nauk. SSSR,* **1950**, *73*, 487. *Chem. Abstr.,* **1951**, *45*, 2855.
7. (a) Chen, S. J. and Coward, J. K., *J. Org. Chem.,* **1998**, *63*, 502. (b) Gawron, O.; Grelecki, C.; Reilly, W. and Sands, J., *J. Am. Chem. Soc.,* **1953**, *75*, 3591.
8. Tongcharoensirikul, P.; Suarez, A. I.; Voelker, T. and Thompson, C. M., *J. Org. Chem.,* **2004**, *69*, 2322.
9. (a) Kaïm, L. E.; Gaultier, L.; Grimaud, L. and Santos, A. D., *Synlett,* **2005**, 2335. (b) Cai, J. X.; Zhou, Z. H.; Zhao, G. F. and Tang, C. C., *Heteroatom Chem.,* **2003**, *14*, 312. (c) Jeanmaire, T.; hervaud, Y. and Boutevin, B., *Phosphorus, Sulfur & Silicon & Related Elements,* **2002**, *177*, 1137. (d) Otmar, M.; Polakova, L.; Masojidkova, M. and Holy, A., *Coll. Czech. Chem. Commun.,* **2001**, *66*, 507. (e) Ding, Y. X. and Huang, X. G., *Heteroatom Chem.,* **1999**, *10*, 55. (f) Kumaraswamy, S.; Selvi, R. S. and Swamy, K. C. K., *Synthesis,* **1997**, 207. (g) Cherkasov, R. A.; Galkin, V. I.; Khabibullina, A. B. and Kurdy, K. A., *Phorphorus, Sulfur & Silicon & Related Elements,* **1990**, *49/50*, 614. (h) Galkin, V. I.; Bakhtiyarova, I. V.; Cherkasov, R. A. and Pudovik, A. N., *Doklady Akad. Nauk. SSSR.,* **1989**, *308*, 1135. (i) Sekine, M.; Nakajima, M. and Hata, T., *J. Org. Chem.,* **1981**, *46*, 4030. (j) Sekine, M.; Okimoto, K.; Yamada, K. and Hata, T., *J. Org. Chem.,* **1981**, *46*, 2097. (k) Evans, D. A.; Hurst, K. M. and Takacs, J. M., *J. Am. Chem. Soc.,* **1978**, *100*, 3467. (l) Schroeder, J. P.; Tew, L. B. and Peters, V. M., *J. Org. Chem.,* **1970**, *35*, 3181. (m) Berlin, K. D. and Taylor, H. A., *J. Am. Chem. Soc.,* **1964**, *86*, 3862.

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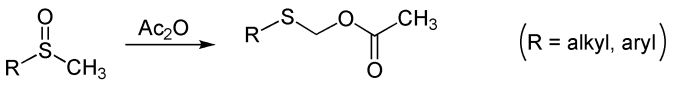
Pummerer Rearrangement
(Pummerer Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Pummerer in 1909.[1] It is an acid (e.g., HCl) or an anhydride (e.g., Ac_2O or TFAA) promoted transformation of sulfoxide bearing an α-proton to α-substituted sulfide through a sulfenium (or thionium) intermediate;[2] more generally, it is the reduction of sulfonium sulfur with concomitant oxidation or substitution at the α-carbon of sulfonium.[3] Therefore, this reaction is generally known as the Pummerer rearrangement[4,5] or Pummerer reaction.[2a,3,4a,4k,4o,4s,4t,6] Occasionally, the Pummerer cyclization is used to stand for the formation of heterocycles via the addition of an intramolecular nucleophile to the sulfenium intermediate.[4h,6o,6p,7] Besides HCl and acyclic anhydrides, some other Brønsted acids or Lewis acids are also used to activate this reaction, such as *p*-toluenesulfonic acid,[4y] ZnI_2,[4h] TMSOTf,[4m,6o] DAST(diethylaminosulfur trifluoride),[8]and Me_3SiX.[9] In addition, the Pummerer rearrangement can also occur under thermal conditions without promoters,[4u,4y] although it may be suppressed by the application of zeolite.[10] In this reaction, the formed sulfenium (or sulfonium) intermediate is very electrophilic, which can even react with some weak nucleophiles such as xylene and anisole.[4y]

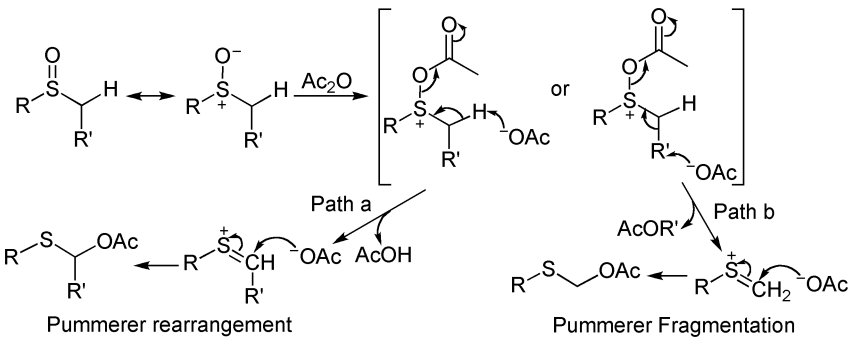
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

Many mechanisms have been proposed for this reaction, that include: (*a*) the rearrangement via a carbonium intermediate involving either a concerted cyclic elimination of acetic acid, elimination of HOAc with an external base or elimination to form a sulfonium ylide, (*b*) internal transfer of the acetoxy group through either cyclic rearrangement, 1,2-shift of ylide, homolytic dissociation and recombination, or nucleophilic displacement of ylide.[3] Nevertheless, all these mechanisms involve the intermediate of a sulfur-stabilized carbonium ion, and if there isn't a conjugate electron-withdrawing group (e.g., carbonyl group) at the β-position of sulfoxide group,[11] the acetoxyl group always migrates to the least substituted α-carbon of sulfoxide.[3] Overall, the general accepted mechanism involves the activation of the sulfoxide through the conversion of the sulfoxide oxygen into a good leaving group either by acylation or protonation, followed by the formation of a sulfenium (thionium) ion,[2b,4h] a rate- and product-determining step,[3] and subsequent nucleophilic addition from different nuclophiles. It should be pointed out that after the activation of the sulfoxide oxygen atom, the migration of hydrogen to form a sulfenium ion affords the normal Pummerer rearrangement product, whereas the cleavage of α-alkyl group to generate a new sulfenium ion leads to the formation of new sulfide, and this process is known as the Pummerer fragmentation.[5b] An illustrative mechanism is provided here.



D. MODIFICATION

Because of its versatility, this reaction has been extended to different variants. For example, the thermal conversion of linear α-silyl sulfoxides into siloxymethyl sulfide for the preparation of carbonyl compounds,[12] vinyl sulfides,[4j] etc. is now known as sila-Pummerer rearrangement;[4e,5a,7e,12,13] in addition, the base treatment of α-chlorosulfoxide in the presence of trimethylsilyl chloride to form thioester is known as the silicon Pummerer rearrangement.[4x] Likewise, the reaction of vinylic sulfoxides[4e,9] or *o*-alkylphenyl sulfoxides[5c] via an electrophilic thionium ion from γ-proton loss is known as the vinylogous Pummerer reaction. Moreover, if a nucleophile adds to the vinylic bond, then this variant is also known as additive Pummerer reaction;[4j,6i,14] whereas the treatment of sulfoxide with DAST[8] or n-$Bu_4NH_2F_3$[5s] to produce α-fluorosulfide is referred to as the fluoro-Pummerer rearrangement, and the rearrangement involving the cleavage of an α-stannyl or an allylic stannyl group is called the tin-Pummerer rearrangement[5m] or

vinylogous tin-Pummerer rearrangement,[4e] respectively. The comparable rearrangement of selenium compounds is known as seleno Pummerer reaction or additive seleno Pummerer rearrangement.[4j]

On the other hand, sulfoxides bearing an α-proton may undergo a similar reaction to form thioether when they are treated with a Grignard reagent,[15] and α-thiomethyl ester might eliminate α-proton to form thionium for nucleophilic addition when it is treated with phenyliodine(III) bis-trifluoroacetate.[16]

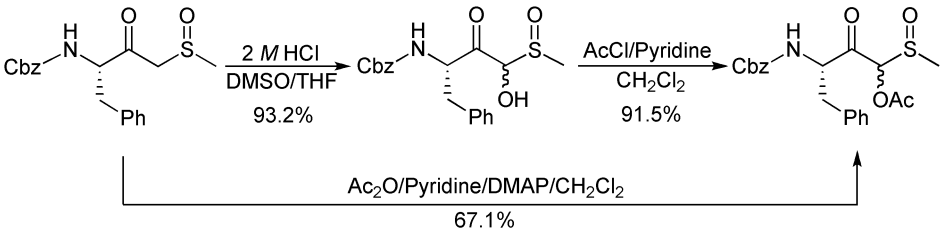
E. APPLICATIONS

This reaction has very broad application in organic synthesis, such as the formation of an aldehyde by hydrolysis of α-acyloxysulfide,[17] the generation of vinyl sulfide by elimination of α-acyloxy group,[18] and the synthesis of glyoxal from β-ketosulfoxide.[4z] In addition, the formed vinyl sulfide has been used as an intermediate for many other reactions, such as *Diels-Alder Cycloaddition*[4s] and *Michael Addition*.[4j]

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES

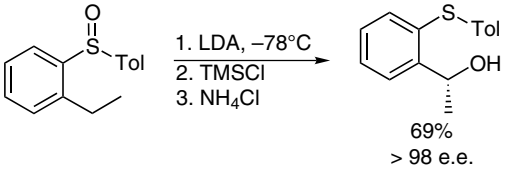


Reference 11.

(3*S*)-3-(*N*-Benzyloxycarbonyl)amino-1-methylsulfinyl-2-oxo-4-phenylbutane (166.2 mg, 0.462 mmol) was added to a mixture of 4.6 mL CH_2Cl_2, 0.5 mL pyridine, and 0.5 mL acetic anhydride, followed by 3 mg 4-dimethylamino pyridine. The resulting mixture was stirred at ambient temperature for 17.5 h, then 10 mL 1 M HCl and 15 mL EtOAc were added. The organic layer was separated and washed with 10 mL saturated $NaHCO_3$ aqueous solution and 10 mL brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified through preparative silica gel thin-layer chromatography to afford 124.5 mg (3*S*)-1-acetoxy-3-(*N*-benzyloxy-carbonyl)amino-1-methylthio-2-oxo-4-phenylbutane as a colorless solid, in a yield of 67.1%.

Alternatively, 708.6 mg (3*S*)-3-(*N*-benzyloxycarbonyl)amino-1-methylsulfinyl-2-oxo-4-phenylbutane (1.97 mmol) was dissolved in a mixture of 15 mL DMSO and 6 mL THF. Then 7.5 mL 2 M HCl was added. After the mixture was stirred for 18 h at ambient temperature, it was cooled in an ice bath and neutralized with 15 mL saturated $NaHCO_3$

aqueous solution (15 mL). Water (50 mL) and 50 mL EtOAc were added to the mixture. After the organic layer was separated, the resulting aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with 50 mL water and 30 milliliter brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was crystallized in *n*-hexane/EtOAc to give 659.7 mg crude (3*S*)-3-(*N*-benzyloxycarbonyl)amino-1-hydroxy-1-methylthio-2-oxo-4-phenylbutane as a colorless crystal, in yield of 93.2%. This intermediate was then acetylated in CH_2Cl_2 with pyridine and acetyl chloride to afford 91.5% (3*S*)-1-acetoxy-3-(*N*-benzyloxycarbonyl)amino-1-methylthio-2-oxo-4-phenylbutane.



Reference 9.

To 3.0 mL THF solution containing 0.89 mmol *i*-Pr_2NH was added 0.6 mmol 2.3 M *n*-BuLi in hexane at 0°C. After being stirred for 30 min, the mixture was cooled to −78°C. Then a solution of 0.5 mmol (*S*)-1-ethyl-2-(*p*-tolylsulfinyl)benzene in 2 mL THF was added. After the mixture was stirred for 1 h, 1.5 mmol freshly distilled TMSCl was added at −78°C. When the reaction was completed (< 1 min), the mixture was hydrolyzed with a mixture of 1 mL saturated NH_4Cl and 1 mL CH_3CN at −78°C, then the solution was warmed to room temperature for overnight. The mixture was extracted with Et_2O (3 × 10 mL), washed twice with 10 mL saturated NH_4Cl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography using hexane/EtOAc (2:1) as the eluent to afford 69% (1*R*)-1-2-(*p*-tolylsulfanyl)phenylethan-1-ol as a colorless oil, with 98% e.e.

Other references related to the Pummerer rearrangement are cited in the literature.[19]

H. REFERENCES

1. Pummerer, R., *Ber.,* **1909**, *42*, 2282.
2. (a) Padwa, A., *Pure & Appl. Chem.,* **2003**, *75*, 47. (b) Bates, D. K.; Winters, R. T. and Picard, J. A., *J. Org. Chem.,* **1992**, *57*, 3094.
3. Johnson, C. R. and Phillips, W. G., *J. Am. Chem. Soc.,* **1969**, *91*, 682.
4. (a) Veerapen, N.; Taylor, S. A.; Walsby, C. J. and Pinto, B. M., *J. Am. Chem. Soc.,* **2006**, *128*, 227. (b) Keum, G. C.; Hwang, C. H.; Kang, S. B.; Kim, Y. S. and Lee, E., *J. Am. Chem. Soc.,* **2005**, *127*, 10396. (c) Tai, C.-H.; Wu, H.-C. and Li, W.-R., *Org. Lett.,* **2004**, *6*, 2905. (d) Keum, G. C.; Kang, S. B.; Kim, Y. S. and Lee, E., *Org. Lett.,* **2004**, *6*, 1895. (e) Ruano, J. L. G.; Aleman, J. and Padwa, A., *Org. Lett.,* **2004**, *6*, 1757. (f) Paquette, L. A.; Fabris, F.; Gallou, F. and Dong, S. Z., *J. Org. Chem.,* **2003**, *68*, 8625. (g) Zhang, X. G. and Qing, F.-L., *J. Org. Chem.,* **2002**, *67*, 1016. (h) Padwa, A.; Danca, D. M.; Ginn, J. D. and Lynch, S. M., *J. Braz. Chem. Soc.,* **2001**, *12*, 571. (i) Fustero, S.; Navarro, A.; Pina, B.; Soler, J. G.; Bartolomé, A.; Asensio, A.; Simón, A.; Bravo, P.; Fronza, G.; Volonterio, A. and Zanda, M., *Org. Lett.,* **2001**, *3*, 2621. (j) Hagiwara, H.; Kafuku, K.; Sakai, H.; Kirita, M.; Hoshi, T.; Suzuki, T. and Ando, M., *J. Chem. Soc., Perkin*

Trans. I, **2000**, 2577. (k) Iwama, T.; Kataoka, T.; Muraoka, O. and Tanabe, G., *J. Org. Chem.,* **1998**, *63*, 8355. (l) Ueng, S.-N.; Blumenstein, M. and Grohmann, K. G., *J. Org. Chem.,* **1997**, *62*, 2432. (m) Yoshimura, Y.; Watanabe, M.; Satoh, H.; Ashida, N.; Ijichi, K.; Sakata, S.; Machida, H. and Matsuda, A., *J. Med. Chem.,* **1997**, *40*, 2177. (n) Yoshimura, Y.; Kitano, K.; Yamada, K.; Satoh, H.; Watanabe, M.; Miura, S.; Sakata, S.; Sasaki, T. and Matsuda, A., *J. Org. Chem.,* **1997**, *62*, 3140. (o) Volonterio, A.; Zanda, M.; Bravo, P.; Fronza, G.; Cavicchio, G. and Crucianelli, M., *J. Org. Chem.,* **1997**,*62*, 8031. (p) Callis, D. J.; Thomas, N. F.; Pearson, D. P. J. and Potter, B. V. L., *J. Org. Chem.,* **1996**, *61*, 4634. (q) McElhinney, R. S.; McCormick, J. E.; Bibby, M. C.; Double, J. A.; Radacic, M. and Djumont, P., *J. Med. Chem.,* **1996**, *39*, 1403. (r) Arnone, A.; Bravo, P.; Capelli, S.; Fronza, G.; Meille, S. V.; Zanda, M.; Cavicchio, G. and Crucianelli, M., *J. Org. Chem.,* **1996**, *61*, 3375. (s) Padwa, A.; Cochran, J. E. and Kappe, C. O., *J. Org. Chem.,* **1996**, *61*, 3706. (t) Bonjoch, J.; Catena, J. and Valls, N., *J. Org. Chem.,* **1996**, *61*, 7106. (u) Wladislaw, B.; Marzorati, L. and Biaggio, F. C., *J. Org. Chem.,* **1993**, *58*, 6132. (v) Kim, C. U.; Misco, P. F. and McGregor, D. N., *J. Org. Chem.,* **1982**, *47*, 170. (w) Mikolajczyk, M.; Zatorski, A.; Grzejszczak, S.; Costisella, B. and Midura, W., *J. Org. Chem.,* **1978**, *43*, 2518. (x) More, K. M. and Wemple, J., *J. Org. Chem.,* **1978**, *43*, 2713. (y) Bates, D. K., *J. Org. Chem.,* **1977**, *42*, 3452. (z) Becker, H.-D.; Mikol, G. J. and Russell, G. A., *J. Am. Chem. Soc.,* **1963**, *85*, 3410.

5. (a) Suslova, E. N.; Ushakov, I. A. and Shainyan, B. A., *Russ. J. Gen. Chem.,* **2007**, *77*, 253. (b) Laleu, B.; Machado, M. S. and Lacour, J., *Chem. Commun.,* **2006**, 2786. (c) Garcia Ruano, J.; Aleman, J.; Aranda, M.; Arevalo, M. and Padwa, A., *Phosphorus, Sulfur & Silicon & Related Elements,* **2005**, *180*, 1497. (d) Fujita, J.; Matsuda, H.; Yamamoto, K.; Morii, Y.; Hashimoto, M.; Okuno, T. and Hashimoto, K., *Tetrahedron*, **2004**, *60*, 6829. (e) Tai, C.-H.; Wu, H.-C. and Li, W.-R., *Org. Lett.,* **2004**, *6*, 2905. (f) Matsuda, H.; Fujita, J.; Morii, Y.; Hashimoto, M.; Okuno, T. and Hashimoto, K., *Tetrahedron Lett*., **2003**, *44*, 4089. (g) Crescenza, A.; Botta, M.; Corelli, F. and Tafi, A., *Heterocycles*, **1999**, *51*, 1639. (h) Hu, Y. H.; Ou, L. G. and Bai, D. L., *Tetrahedron Lett*., **1999**, *40*, 545. (i) Kirpichenko, S. V.; Suslova, E. N.; Albanov, A. I. and Shainyan, B. A., *Tetrahedron Lett*., **1999**, *40*, 185. (j) Kobayashi, K.; Takahashi, O.; Namatame, K.; Kikuchi, O. and Furukawa, N., *Chem. Lett.,* **1998**, 515. (k) Yoshimura, Y.; Kitano, K.; Yamada, K.; Sakata, S.; Miura, S.; Ashida, N.; Machida, H. and Matsuda, A., *Nucleic Acids Symp. Ser*., **1997**, *37*, 43. (l) Naka, H.; Sato, S.; Horn, E. and Furukawa, N., *Heterocycles*, **1997**, *46*, 177. (m) Hatlelid, J.; Bennech, T. and Undheim, K., *Acta Chem. Scand.,* **1997**, *51*, 1092. (n) Cassel, S.; Chaimbault, P.; Lafosse, M.; Lorin, C. and Rollin, P., *Sulfur Lett.,* **1996**, *20*, 63. (o) Harwood, L. M. and Lilley, I. A., *Synlett*, **1996**, 1010. (p) Kita, Y.; Takeda, Y.; Iio, K.; Yokogawa, K.; Takahashi, K. and Akai, S., *Tetrahedron Lett*., **1996**, *37*, 7545. (q) Dwyer, O., *Synlett*, **1995**, 1163. (r) Arnone, A.; Bravo, P.; Bruche, L.; Crucianelli, M.; Vichi, L. and Zanda, M., *Tetrahedron Lett*., **1995**, *36*, 7301. (s) Furuta, S.; Kuroboshi, M. and Hiyama, T., *Tetrahedron Lett*., **1995**, *36*, 8243. (t) Stamos, I. K. and Kotzamani, H. K., *J. Heterocycl. Chem.,* **1995**, *32*, 947.

6. (a) Akai, S. and Kita, Y., *Top. Curr. Chem.,* **2007**, *274*, 35. (b) Miller, M.; Tsang, W.; Merritt, A. and Procter, D. J., *Chem. Commun.,* **2007**, 498. (c) Feldman, K. S. and Karatjas, A. G., *Org. Lett.,* **2006**, *8*, 4137. (d) Nagao, Y.; Miyamoto, S.; Miyamoto, M.; Takeshige, H.; Hayashi, K.; Sano, S.; Shiro, M.; Yamaguchi, K. and Sei, Y., *J. Am. Chem. Soc.,* **2006**, *128*, 9722. (e) Hou, R.-S.; Wang, H.-M.; Chang, Y.-W. and Chen, L.-C., *J. Chinese Chem. Soc.,* **2006**, *53*, 431. (f) Akai, S.; Kawashita, N.; Wada, Y.; Satoh, H.; Alinejad, A. H.; Kakiguchi, K.; Kuriwaki, I. and Kita, Y., *Tetrahedron Lett*., **2006**, *47*, 1881. (g) Feldman, K. S.; Vidulova, D. B. and Karatjas, A. G., *J. Org. Chem.,* **2005**, *70*, 6429. (h) Feldman, K. S. and Skoumbourdis, A. P., *Org. Lett.,* **2005**, *7*, 929. (i) Padwa, A.; Nara, S. and Wang, Q., *J. Org. Chem.,* **2005**, *70*, 8538. (j) Jaoued, N. G.; Oueslati, R. and Hedhli, A.,*Synth. Commun.,* **2005**, *35*, 543. (k) Hahn, H.-G.; Nam, K. D. and Mah, H., *J. Korean Chem. Soc.,* **2004**, *48*, 443. (l) Feldman, K. S. and Vidulova, D. B., *Org. Lett.,* **2004**, *6*, 1869. (m) Bur, S. K. and Padwa, A., *Chem. Rev.,* **2004**, *104*, 2401. (n) Nakayama, J.; Lida, S.; Sugihara, Y. and Ishii, A., *J. Sulfur Chem.,* **2004**, *25*, 13. (o) Montaño, R. G. and Zhu, J. P., *Chem. Commun.,* **2002**, 2448. (p) Amat, M.; Hadida, S.; Pshenichnyi, G. and Bosch, J., *J. Org.*

Chem., **1997**, *62*, 3158. (q) Nishizono, N.; Koike, N.; Yamagata, Y.; Fujii, S. and Matsuda, A., *Tetrahedron Lett.,* **1996**, *42*, 7569. (r) Trofimov, B. A.; Chernysheva, N. A.; Khilko, M. Y. and Gusarova, N. K., *Russ. Chem. Bull.,* **1991**, *40*, 1919. (s) Fedorov, N. V.; Anisimov, A. V. and Viktorova, E. A., *Chem. Heterocycl. Compd.,* **1989**, *25*, 1083. (t) King, R. R., *J. Org. Chem.,* **1978**, *43*, 3784.

7. (a) Horiguchi, Y.; Ogawa, K.; Saitoh, T. and Sano, T., *Chem. Pharm. Bull.,* **2004**, *52*, 214. (b) Saitoh, T.; Shikiya, K.; Horiguchi, Y. and Sano, T., *Chem. Pharm. Bull.,* **2003**, *51*, 667. (c) Padwa, A.; Heidelbaugh, T. M. and Kuethe, J. T., *J. Org. Chem.,* **2000**, *65*, 2368. (d) Padwa, A.; Heidelbaugh, T. M. and Kuethe, J. T., *J. Org. Chem.,* **1999**, *64*, 2038. (e) Still, I. W. J. and Toste, F. D., *Heteroatom Chem.,* **1994**, *5*, 251. (f) Amat, M. and Bosch, J., *J. Org. Chem.,* **1992**, *57*, 5792. (g) Vishwakarma, L. C. and Martin, A. R., *J. Heterocycl. Chem.,* **1982**, *19*, 103.
8. Zhou, H. and van der Donk, W. A., *Org. Lett.,* **2001**, *3*, 593.
9. Ruano, J. L. G.; Alemán, J.; Aranda, M. T.; Arévalo, M. J. and Padwa, A., *Org. Lett.,* **2005**, *7*, 19.
10. Clennan, E. L.; Zhou, W. H. and Chan, J., *J. Org. Chem.,* **2002**, *67*, 9368.
11. Suzuki, T.; Honda, Y.; Izawa, K. and Williams, R. M., *J. Org. Chem.,* **2005**, *70*, 7317.
12. Shainyan, B. A.; Kirpichenko, S. V. and Freeman, F., *J. Am. Chem. Soc.,* **2004**, *126*, 11456.
13. (a) Perales, J. B.; Makino, N. F. and Van Vranken, D. L., *J. Org. Chem.,* **2002**, *67*, 6711. (b) Reich, H. J. and Shah, S. K., *J. Org. Chem.,* **1977**, *42*, 1773.
14. Craig, D. and Daniels, K., *Tetrahedron,* **1993**, *49*, 11263.
15. Cheng, W.-L. and Luh, T.-Y., *J. Org. Chem.,* **1992**, *57*, 3516.
16. Pohnert, G., *J. Prakt. Chem.,* **2000**, *342*, 731.
17. Sugihara, H.; Tanikaga, R. and Kaji, A., *Synthesis,* **1978**, 881.
18. Hagiwara, H.; Nakayama, K. and Uda, H., *Bull. Chem. Soc. Jpn.,* **1975**, *48*, 3769.
19. (a) Choo, H.; Chen, X.; Yadav, V.; Wang, J. N.; Schinazi, R. F. and Chu, C. K., *J. Med. Chem.,* **2006**, *49*, 1635. (b) Boudou, M. and Enders, D., *J. Org. Chem.,* **2005**, *70*, 9486. (c) Padwa, A., *Pure & Appl. Chem.,* **2004**, *76*, 1933. (d) Notz, W.; Hartel, C.; Waldscheck, B. and Schmidt, R. R., *J. Org. Chem.,* **2001**, *66*, 4250. (e) Bell, R. P. L.; Sobolev, A.; Wijnberg, J. B. P. A. and de Groot, A., *J. Org. Chem.,* **1998**, *63*, 122. (f) Kita, Y.; Shibata, N.; Kawano, N.; Fujui, S. and Fujimori, C., *Tetrahedron Lett.,* **1994**, *35*, 3575. (g) Majumdar, G. and Mal, D., *Indian J. Chem.,* **1994**, *33B*, 700. (h) Jug, M. E.; Kim, C. and von dem Busschez, L., *J. Org. Chem.,* **1994**, *59*, 3248. (i) Su, H.; Hiwatari, Y.; Soenosawa, M.; Sasuga, K.; Shirai, K. and Kumamoto, T., *Bull. Chem. Soc. Jpn.,* **1993**, *66*, 2603. (j) De Lucchi, O.; Miotti, U. and Modena, G., *Org. React.,* **1991**, *40*, 157. (k) Kita, Y.; Tamura, O.; Miki, T. and Tamura, Y., *Tetrahedron Lett.,* **1987**, *28*, 6479. (l) Kita, Y.; Yasuda, H.; Tamura, O.; Itoh, F. and Tamura, Y., *Tetrahedron Lett.,* **1984**, *25*, 4681. (m) Pummerer, R., *Ber.,* **1910**, *43*, 1401.

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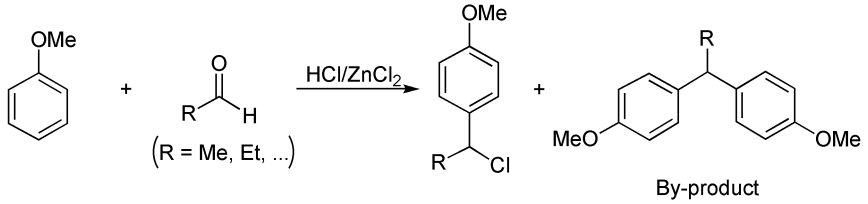
Quelet Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Quelet in 1932,[1] a natural extension of the *Blanc Chloromethylation*. It is the preparation of *para*-α-chloroalkyl aromatic derivatives by passing dry hydrochloric acid through the solution of a phenolic ether and an aliphatic aldehyde in the presence or absence of a Lewis acid reagent (e.g., $ZnCl_2$), and is known as the Quelet reaction[2] or the Blanc-Quelet reaction.[3] Although this reaction often occurs at the *para*-position of phenolic ether, it also takes place at the *ortho*-position if the *para*-position is blocked. Compared to the *Blanc Chloromethylation*, the Quelet reaction is much more sensitive to the substituent on the phenolic ether and is more limited in scope.[4] For example, a single halogen atom on the aromatic ring may cause the deactivation, such as the chloroethylation of *o*-, *m*- and *p*-chloroanisole, *m*- and *p*-bromoanisole from acetaaldehyde.[4] In addition, this reaction is also contaminated by further alkylation of the aromatic nucleus from the α-chloroalkyl aromatic to give bis-aryl-alkane.[4,5]

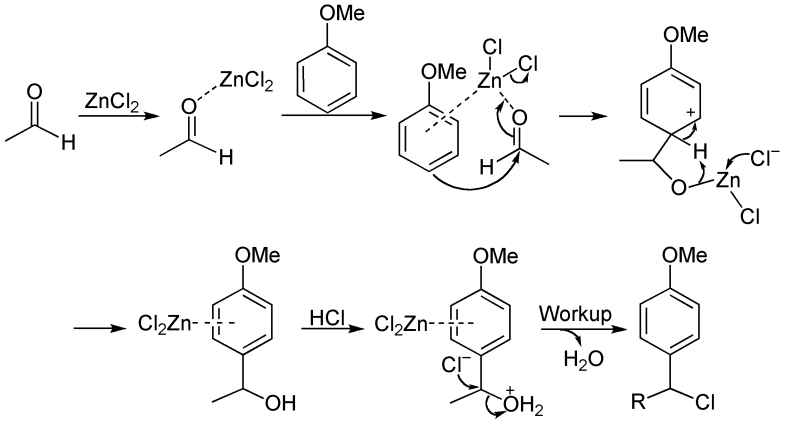
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

Displayed here is an illustration of the reaction mechanism between anisole and acetaldehyde in the presence of $ZnCl_2$.



D. MODIFICATION

N/A

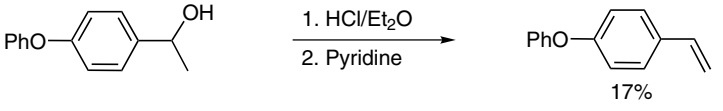
E. APPLICATIONS

This reaction has been used for the preparation of different styrene derivatives.[4,5a]

F. RELATED REACTIONS

This reaction is closely related to the *Blanc Chloromethylation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4.

To a 1-L, three-necked, round-bottomed flask equipped with a condenser and gas absorption trap, a stirrer and an inlet tube were added 300 mL Et_2O and 50 g a mixture of 1-(4-phenoxyphenyl)-ethanol and its ether prepared from the Quelet chloroalkylation (the inlet tube should be under the surface of the solution). Then dry gaseous hydrogen chloride was passed into the stirred solution for 4 h, and heat was evolved at first. The mixture

became dark brown as the reaction proceeded. Most of the ether was then removed by distillation, and 175 mL pyridine was added. The resulting mixture was heated at 115°C for 6 h, after which the mixture was poured into 750 g ice and 250 mL conc. HCl. This mixture was extracted with $CHCl_3$ (200 mL, then 2 × 100 mL), and the combined organic layers were washed with water (3 × 100 mL) and dried over $MgSO_4$. Upon removal of solvent, the residue was fractionally distilled through a 6-in., Fenske-type column to give 8.2 g 4-phenoxystyrene, in a yield of 17%, b.p. 111–113°C.

Other references related to the Quelet reaction are cited in the literature.[6]

H. REFERENCES

1. Quelet, R., *Compt. Rend.,* **1932**, *195*, 155.
2. (a) Ueda, U. and Oda, R., *Kogyo Kagaku Zasshi,* **1945**, *48*, 58. (b) Ueda, U. and Oda, R., *Kogyo Kagaku Zasshi*, **1944**, *47*, 844. (c) Ueda, U. and Oda, R., *Kogyo Kagaku Zasshi*, **1944**, *47*, 565.
3. (a) Ichikawa, N. and Togashi, E.-i., *Nippon Kagaku Kaishi*, **1950**, *71*, 598. (b) Ichikawa, N., *Nippon Kagaku Kaishi,* **1950**, *71*, 303.
4. Frank, R. L.; Adams, C. E.; Allen, R. E.; Gander, R. and Smith, P. V., *J. Am. Chem. Soc.,* **1946**, *68*, 1365.
5. (a) Emerson, W. S., *Chem. Rev.,* **1949**, *45*, 347. (b) Quelet, R., *Bull. Soc. Chim.,* **1934**, *51*, 1026.
6. (a) Jodra, L. Q.; Salvador, A. R. and Andrés, V. M., *Ind. Eng. Chem. Prod. Res. Dev.,* **1982**, *21*, 87. (b) Olah, G. A.; Beal, D. A. and Olah, J. A., *J. Org. Chem.,* **1976**, *41*, 1627. (c) Minoura, Y. and Tsukasa, M., *J. Appl. Poly. Sci.,* **1968**, *12*, 2509. (d) Profft, E. and Drux, R., *J. Prakt. Chem.,* **1956**, *3*, 274. (e) Neda, U. and Oda, R., *J. Soc. Chem. Ind. Jpn.,* **1944**, *47*, 565. (f) Quelet, R., *Bull. Soc. Chim. Fr.,* **1940**, *7*, 205. (g) Quelet, R., *Bull. Soc. Chim. Fr.,* **1940**, *7*, 196. (h) Fuson, R. C. and McKeever, C. H., *J. Am. Chem. Soc.,* **1940**, *62*, 784. (i) Quelet, R. and Ducasse, J., *Compt. Rend.,* **1939**, *208*, 1317. (j) Quelet, R. and Allard, J., *Compt. Rend.,* **1937**, *205*, 238. (k) Quelet, R. and Anglade, M., *Bull. Soc. Chim. Fr.,* **1936**, *3*, 2200. (l) Quelet, R., *Compt. Rend.,* **1936**, *202*, 956. (m) Quelet, R., *Compt. Rend.,* **1934**, *199*, 150. (n) Quelet, R., *Compt. Rend.,* **1934**, *198*, 102. (o) Quelet, R., *Compt. Rend.,* **1933**, *196*, 1411. (p) Quelet, R. and Germain, Y., *Compt. Rend.,* **1936**, *202*, 1442.

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Radziszewski Reaction

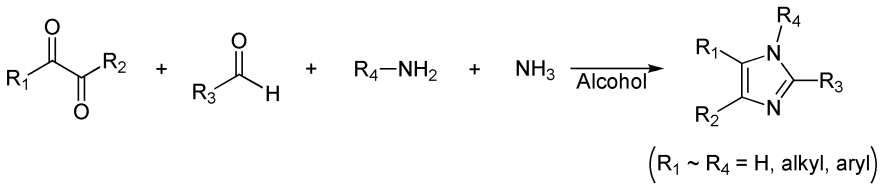
A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Debus in 1858,[1] fully developed by Radziszewski beginning in 1882,[2] and further modified by Weidenhagen in 1935.[3] It is the synthesis of an imidazole derivative by the condensation of an α-dicarbonyl compound (e.g., glyoxal), an aldehyde and two equivalents of dry ammonia in alcohol. Therefore, this reaction is generally known as the Radziszewski reaction.[4] Occasionally, it is also called the Radziszewski synthesis,[5] *Weidenhagen Synthesis*,[5] or Debus-Radziszewski imidazole synthesis.[6] As a result, imidazole is also referred to as glyoxaline because of this reaction.[7] Other names that have been designated for imidazoles include iminazole[7] and 1,3-diazole,[7] which have been rarely used in recent literature; whereas the term *imidazole* was originally chosen as the name for such molecules by Hantzsch[8] and was given official recognition.[9]

In this reaction, a variety of α-dicarbonyl compounds—including glyoxal,[4b] pyruvaldehyde,[5b] porphyrin-2,3-diones,[10] and benzil[2a]—have been successfully used to the synthesis of corresponding imidazole derivatives. It is interesting that the replacement of one equivalent ammonia with a primary amine results in the formation of 1-substituted imidazoles.[11] Although this reaction in general gives poor yields of imidazoles[5b,12] and suffers from some side reactions (e.g., the reverse *Aldol Condensation* and oxazole formation)[12a] the condensation of benzil with benzaldehyde and ammonia in alcohol gives nearly a quantitative yield of 2,3,5-triphenylimidazole (lophine).[2a,13] This reaction is useful for the preparation of imidazoles with a substituent at position 2 from adjacent di-carbonyl compounds.[5a] In fact, this reaction is the only reaction of industrial importance for the production of imidazole derivatives.

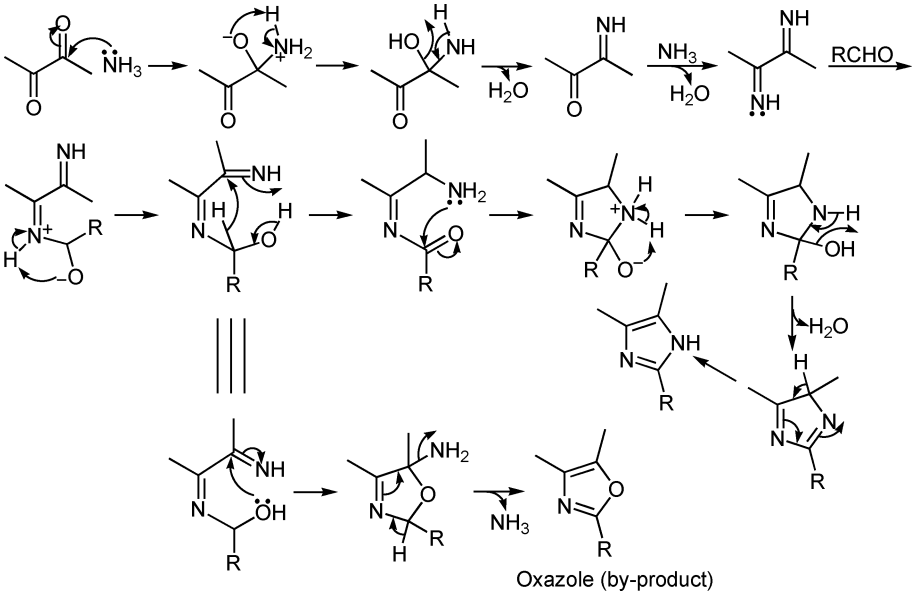
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Although there is no general mechanism for this reaction in the cited literature, it is plausible that ammonia (or primary amine) reacts with an α-dicarbonyl compound to form α-diimine, which then condenses with an aldehyde, as displayed here. In the meantime, it is also possible to form an oxazole by-product from this multicomponent condensation.



D. MODIFICATION

This reaction has been extended by Weidenhagen through the condensation of α-acetoacetone, cupric acetate, and aqueous ammonia to afford imidazoles in yields up to 60%.[3,14] This method is thus known as the Weidenhagen modification[4b,15] or *Weidenhagen Synthesis*.[5a] In addition, the Radziszewski reaction has been further modified to proceed in acetic acid by the use of ammonium acetate or ammonium carbonate as the source of ammonia to give imidazoles of markedly improved yields,[16] and this protocol has been recently carried out under microwave irradiation.[12a] Furthermore, it has been reported that the reaction of an amidine with an α-halo ketone also readily yields imidazoles.[12b]

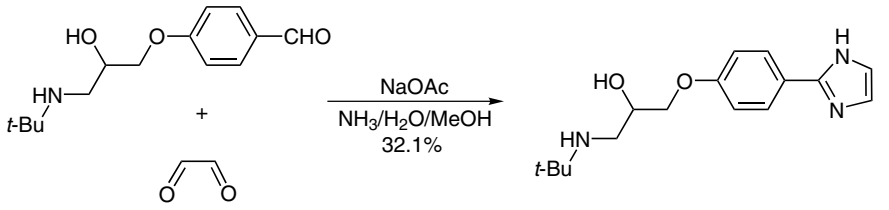
E. APPLICATIONS

This reaction is very useful for the preparation of imidazole derivatives.

F. RELATED REACTIONS

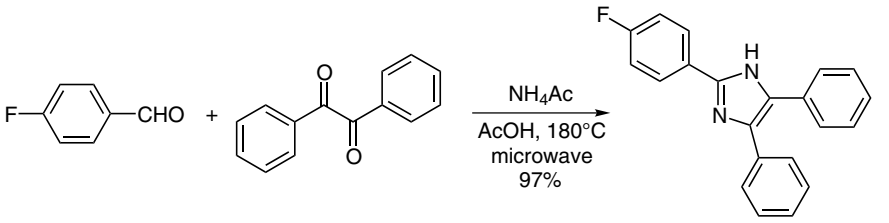
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 4b.

A mixture of 10 g 4-[3-(*tert*-butylamino)-2-hydroxypropoxy]-benzaldehyde (0.04 mol), 31 g 40% glyoxal (0.22 mol), 26 g $NaOAc{\cdot}3H_2O$ (0.19 mol), 100 mL concentrated ammonium hydroxide (NH_4OH), and 250 mL MeOH was stirred overnight at room temperature. After removal of MeOH under reduced pressure, the aqueous layer was treated with 100 mL saturated Na_2CO_3 solution and extracted with $CHCl_3$ (3×200 mL). The combined organic layers were dried, filtered, and concentrated. The residue was chromatographed on silica gel using 30% MeOH-$CHCl_3$ as the eluent, and 3.7 g 2-[4-[3-(*tert*-butylamino)-2-hydroxypropoxy]-phenyl]imidazole was obtained after final crystallization from CH_3CN, in a yield of 32.1%.



Reference 12a.

To a 2-mL Smithsynthesizer™ reaction vial containing a magnetic stir bar were added 1.0 mL acetic acid, 42 mg benzil (0.2 mmol), 25 mg 4-fluorobenzaldehyde (0.2 mmol), and 154 mg ammonium acetate (2.0 mmol). The reaction vessel was heated in the Smithsynthesizer reactor cavity for 5 min at 180°C, after which the vessel was rapidly cooled to 40°C by the unit. The reaction mixture was added dropwise to a concentrated NH_4OH solution cooled to 0°C and immediately formed a white precipitate, which was collected by filtration and washed with H_2O. The solid was dried in a vacuum oven for 18 h at 50°C to

afford 61 mg 2-(4-fluorophenyl)-4,5-diphenylimidazole as a bright white solid, in a yield of 97%.

Other references related to the Radziszewski reaction are cited in the literature.[17]

H. REFERENCES

1. Debus, H., *Ann.,* **1858**, *107*, 204.
2. (a) Radziszewski, B., *Ber.,* **1882**, *15*, 1493. (b) Radziszewski, B., *Ber.,* **1882**, *15*, 2706. (c) Radziszewski, B., *Ber.,* **1883**, *16*, 487. (d) Radziszewski, B., *Ber.,* **1883**, *16*, 747.
3. (a) Weidenhagen, E., *Ber.*, **1935**, *68*, 1953. (b) Weidenhagen, E., *Ber.*, **1937**, *70*, 570.
4. (a) Breslin, H. J.; Miskowski, T. A.; Rafferty, B. M.; Coutinho, S. V.; Palmer, J. M.; Wallace, N. H.; Schneider, C. R.; Kimball, E. S.; Zhang, S.-P.; Li, J.; Colburn, R. W.; Stone, D. J.; Martinez, R. P. and He, W., *J. Med. Chem.,* **2004**, *47*, 5009. (b) Baldwin, J. J.; Engelhardt, E. L.; Hirschmann, R.; Lundell, G. F.; Ponticello, G. S.; Ludden, C. T.; Sweet, C. S.; Scriabine, A.; Share, N. N. and Hall, R., *J. Med. Chem.,* **1979**, *22*, 687. (c) James, D. S. and Fanta, P. E., *J. Org. Chem.,* **1962**, *28*, 390.
5. (a) Curtis, N. J. and Brown, R. S., *J. Org. Chem.,* **1980**, *45*, 4038. (b) Oliver, J. E. and Sonnet, P. E., *J. Org. Chem.,* **1973**, *38*, 1437.
6. Tymoshenko, D. O., *ARKIVOC,* **2005**, (*viii)*, 1.
7. (a) Townsend, L. B., *Chem. Rev.,* **1967**, *67*, 533. (b) Fox, S. W., *Chem. Rev.,* **1943**, *32*, 47.
8. Hantzsch, A., *Ann.,* **1888**, *249*, 2.
9. Patterson, A. M. and Capell, L. T., *The Ring Index,* Reinhold Publishing, New York, **1940**, p. 42.
10. Crossley, M. J. and McDonald, J. A., *J. Chem. Soc*., *Perkin Trans. I*, **1999**, 2429.
11. Hofmann, K., *Imidazole and Its Derivatives*, Part I, Interscience Publishers, New York, **1953**.
12. (a) Wolkenberg, S. E.; Wisnoski, D. D.; Leister, W. H.; Wang, Y.; Zhao, Z. J. and Lindsley, C. W., *Org. Lett.,* **2004**, *6*, 1453. (b) Baldwin, J. J.; Christy, M. E.; Denny, G. H.; Habecker, C. N.; Freedman, M. B.; Lyle, P. A.; Ponticello, G. S.; Varga, S. L.; Gross, D. M. and Sweet, C. S., *J. Med. Chem.,* **1986**, *29*, 1065.
13. Wiley, R. H., *Chem. Rev.,* **1945**, *37*, 401.
14. (a) Weidenhagen, R. and Rienacker, H., *Ber.,* **1939**, *72*, 57. (b) Weidenhagen, R. and Wegner, H., *Ber.,* **1938**, *71*, 2124. (c) Weidenhagen, R. and Weeden, U., *Ber.,* **1938**, *71*, 2347. (d) Weidenhagen, R. and Wegner, H., *Ber.,* **1937**, *70*, 2309. (e) Weidenhagen, R., *Ber.,* **1936**, *69*, 2263. (f) Weidenhagen, R. and Herrmann, R., *Ber.,* **1935**, *68*, 2205. (g) Weidenhagen, R. and Herrmann, R., *Angew. Chem.,* **1935**, *48*, 596.
15. Baldwin, J. J.; Lumma, P. K.; Novello, F. C.; Ponticello, G. S.; Sprague, J. M. and Duggan, D. E., *J. Med. Chem.,* **1977**, *20*, 1189.
16. (a) Steck, E. A. and Day, A. R., *J. Am. Chem. Soc.,* **1943**, *65*, 452. (b) Davidson, D.; Weiss, M. and Jelling, M., *J. Org. Chem.,* **1937**, *2*, 319.
17. (a) Acke, D. R. J.; Orru, R. V. A. and Stevens, C. V., *QSAR & Combinatorial Sci.,* **2006**, 25, 474. (b) Wróblewska, A.; Huta, O. M.; Midyanyj, S. V.; Patsay, I. O.; Rak, J. and Blazejowski, J., *J. Org. Chem.,* **2004**, *69*, 1607. (c) McKenna, J. M.; Halley, F.; Souness, J. E.; Mclay, I. M.; Pickett, S. D.; Collis, A. J.; Page, K. and Ahmed, I., *J. Med. Chem.,* **2002**, *45*, 2173. (d) Zhou, Y. H.; Baker, W. E.; Kazmaier, P. M. and Buncel, E., *Can. J. Chem.,* **1998**, *76*, 884. (e) Ross, M. G., *Imidazole and Benzimidazole Synthesis*, Academic Press: San Diego, CA, **1997**. (f) Ling, Y.-z.; Li, J.-S.; Liu, Y.; Kato, K.; Klus, G. T. and Brodie, A., *J. Med. Chem.,* **1997**, *40*, 3297. (g) Sarchar, S.; Siev, D. and Mjalli, A. M. M., *Tetrahedron Lett.,* **1996**, *37*, 835. (h) Baldwin, J. J.;

Denny, G. H.; Hirschmann, R.; Freedman, M. B.; Ponticello, G. S.; Gross, D. M. and Sweet, C. S., *J. Med. Chem.,* **1983**, *26*, 950. (i) Tsuda, T.; Yoshimoto, K. and Nishikawa, T., *Chem. Pharm. Bull.,* **1981**, *29*, 3593. (j) Shibamoto, T. and Bernhard, R. A., *J. Agri. Food Chem.,* **1978**, *26*, 183. (k) Wolff, J. and Covelli, I., *Eur. J. Biochem.,* **1969**, *9*, 371. (l) Pozharskii, A. F.; Garnovskii, A. D. and Simonov, A. M., *Russ. Chem. Rev.,* **1966**, *35*, 122. (m) White, E. H. and Harding, M. J. C., *J. Am. Chem. Soc.,* **1964**, *86*, 5686. (n) Kyrides, L. P.; Zienty, F. B.; Steahly, G. W. and Morrill, H. L., *J. Org. Chem.,* **1947**, *12*, 577.

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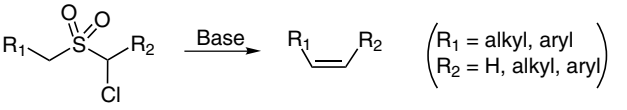
Ramberg-Bäcklund Reaction
(Ramberg-Bäcklund rearrangement)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Ramberg and Bäcklund in 1940.[1] It is a base-promoted transformation of α-halosulfones into olefins with extrusion of SO_2 via an episulfone intermediate and is generally known as the Ramberg-Bäcklund reaction[2,3] or Ramberg-Bäcklund rearrangement.[2a,2c,2e,2f,2k,4] In addition, this reaction is occasionally referred to as the Ramberg-Bäcklund elimination,[2f] Ramberg-Bäcklund olefination,[5] Ramberg-Bäcklund synthesis,[5c] or Ramberg-Bäcklund olefin synthesis.[6] This reaction is applicable for nearly all α-halosulfones having at least one α'-hydrogen and occurs at very mild conditions. For example, it requires only a dilute base and moderate temperatures (room temperature to 100°C)[4e] and usually gives the *cis*-elimination product.[2i,4d] It is assumed that this reaction involves the deprotonation of α'-hydrogen to generate a sulfonyl carbanion, which undergoes an intramolecular nucleophilic displacement of α-halogen (a S_N2 reaction) to form an episulfone intermediate that is converted directly to a corresponding olefin.[4m] This mechanism is supported by the deuterium exchange experiment[7] as well as the actual isolation of 2,3-diphenylvinylenesulfone.[8] It has been reported that the α-halosulfones in general are very prone to 1,3-elimination to form episulfone when exposed to a base, regardless of the number of α-halogens;[4l] in addition, the formed episulfones being sufficiently stable may undergo a base-promoted process to evolve SO_2.[2p] However, the base treatment of trichloromethyl sulfones leads to the formation of sulfonic acid.[4l] More information about this reaction is provided in a few reviews.[3d,9]

B. GENERAL REACTION SCHEME



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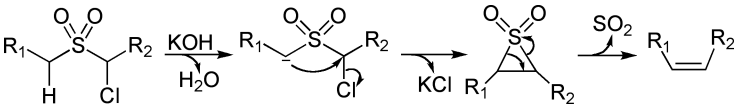
C. PROPOSED MECHANISMS

Displayed below is a general mechanism for the reaction between an α-chlorosulfone and KOH.



D. MODIFICATION

This reaction has been modified by the *in situ* chlorination of sulfone using CCl_4 as a chlorination reagent.[2d] In addition, the sulfones have been mixed with powdered KOH and Al_2O_3 to improve the extrusion of SO_2.[2o] The reaction is also extended to a solid-phase supported condition (e.g., resin).[2a]

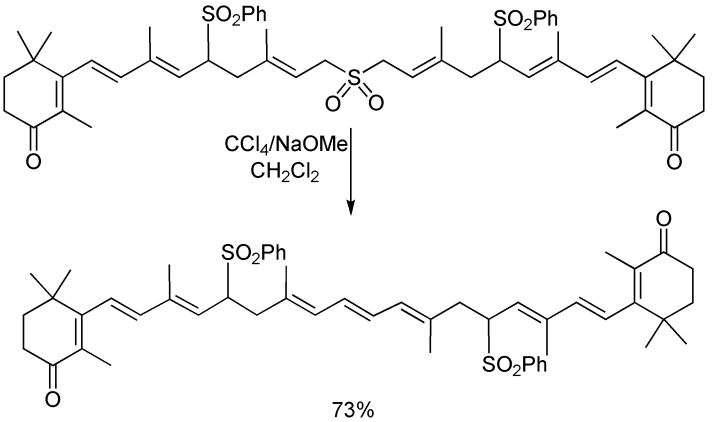
E. APPLICATIONS

This reaction has very broad application in organic synthesis, especially for the preparation of natural products[2i,10] and C-glycosides.[2k,2l,11]

F. RELATED REACTIONS

Mechanistically, this reaction is similar to the *Favorskii Rearrangement*.

G. CITED EXPERIMENTAL EXAMPLES

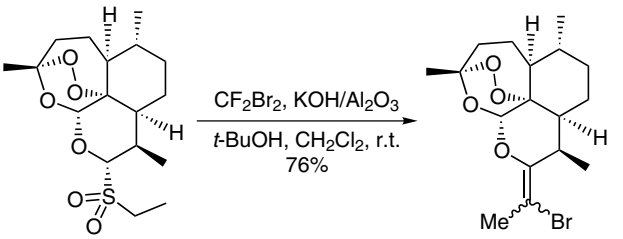


73%

Reference 2d.

To a stirred solution of 350 mg bis(5-benzenesulfonyl-3,7-dimethyl-9-(3-oxo-2,6,6-trimethyl-1-cyclohexenyl)-2,6,8-nonatrienyl) sulfone (0.38 mmol) in 10 mL CH_2Cl_2 was added 5 mL CCl_4 and 0.17 g NaOMe (3.14 mmol). The mixture was stirred at room temperature for 4.5 h, then 5 mL H_2O was added. The reaction mixture was extracted with CH_2Cl_2, washed with a saturated aqueous $NaHCO_3$ solution and H_2O, dried over anhydrous Na_2SO_4,

filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography to afford 236 mg 1,18-bis(3-oxo-2,6,6-trimethyl-1-cyclohexenyl)-5,14-dibenzenesulfonyl-3,7,12,16-tetramethyl-1,3,7,9,11,15,17-eicosaheptaene, in a yield of 73%.



Reference 4a.

10*R*-Ethanesulfonyldihydroartemisinin (220 mg, 0.61 mmol) was added to a stirred suspension of 3.80 g alumina-supported potassium hydroxide (KOH/Al_2O_3) in 45 mL CH_2Cl_2 and 9 mL *tert*-butyl alcohol at 5°C under nitrogen atmosphere. Then 0.73 mL dibromodifluoromethane (7.7 mmol) was added dropwise through a syringe for 5 min with additional stirring for 1 h at room temperature. After the reaction was complete, the excess solid reagent (KOH/Al_2O_3) was removed by suction filtration through a pad of Celite. The filter residue was washed thoroughly with CH_2Cl_2, and the combined filtrates were concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 76% 10-(1-bromoethylidene)-deoxoartemisinin. *E*-10-(1-bromoethylidene)-deoxoartemisinin, white crystals, m.p., 104–105°C; *Z*-10-(1-bromoethylidene)-deoxoartemisinin, white crystals, m.p., 120–121°C.

Other references related to the Ramberg-Bäcklund reaction are cited in the literature.[12]

H. REFERENCES

1. Ramberg, L. and Bäcklund, B., *Arkiv Kemi Mineral Geol.,* **1940**, *13A*, 50 [*Chem. Abstr.,* **1940**, *34*, 4725].
2. (a) Cerè, V.; Minzoni, M.; Pollicino, S.; Ricci, A.; Gasparrini, F.; Giogli, A. and D'Acquarica, I., *J. Comb. Chem.,* **2006**, *8*, 74. (b) Taylor, R. J.; McAllister, G. D. and Franck, R. W., *Carbohydr. Res.,* **2006**, *341*, 1298. (c) Paquette, L. A.; Liu, Z. S. and Efremov, I., *J. Org. Chem.,* **2005**, *70*, 514. (d) Choi, S. Y. and Koo, S. H., *J. Org. Chem.,* **2005**, *70*, 3328. (e) Chow, H.-F.; Ng, M.-K.; Leung, C.-W. and Wang, G.-X., *J. Am. Chem. Soc.,* **2004**, *126*, 12907. (f) Block, E.; Jeon, H. R.; Zhang, S.-Z. and Dikarev, E. V., *Org. Lett.,* **2004**, *6*, 437. (g) Pasetto, P. and Franck, R. W., *J. Org. Chem.,* **2003**, *68*, 8042. (h) Wei, C. M.; Mo, K.-F. and Chan, T.-L., *J. Org. Chem.,* **2003**, *68*, 2948. (i) Foot, J. S.; Giblin, G. M. P. and Taylor, R. J. K., *Org. Lett.,* **2003**, *5*, 4441. (j) Yao, Q. W., *Org. Lett.,* **2002**, *4*, 427. (k) Yang, G. L.; Franck, R. W.; Byun, H.-S.; Bittman, R.; Samadder, P. and Arthur, G., *Org. Lett.,* **1999**, *1*, 2149. (l) Belica, P. S. and Franck, R. W., *Tetrahedron Lett.,* **1998**, *39*, 8225. (m) Lawrence, N. J. and Muhammad, F., *Tetrahedron,* **1998**, *54*, 15361. (n) Evans, P. and Taylor, R. J. K., *Tetrahedron Lett.,* **1997**, *38*, 3055. (o) Yang, F.-M. and Lin, S.-T., *J. Org. Chem.,* **1997**, *62*, 2727. (p) King, J. F.; Gill, M. S. and Klassen, D. F., *Pure & Appl. Chem.,* **1996**, *68*, 825. (q) Grumann, A.; Marley, H. and Taylor, R. J. K., *Tetrahedron Lett.,* **1995**,

36, 7767. (r) Becker, K. B. and Labhart, M. P., *Helv. Chim. Acta,* **1983**, *66*, 1090. (s) Nakayama, J.; Ohshima, E.; Ishii, A. and Hoshino, M., *J. Org. Chem.,* **1983**, *48*, 60. (t) Bordwell, F. G. and Williams, J. M., *J. Am. Chem. Soc.,* **1968**, *90*, 435.

3. (a) Robinson, J. E. and Taylor, R. J. K., *Chem. Commun.,* **2007**, 1617. (b) Foot, J. S.; Giblin, G. M. P.; Whitwood, A. C. and Taylor, R. J. K., *Org. Biomol. Chem.,* **2005**, *3*, 756. (c) Wada, A., *Bitamin*, **2005**, *79*, 172. (d) Taylor, R. J. K. and Casy, G., *Org. React.,* **2003**, *62*, 357. (e) Wang, X.-L.; Cao, X.-P. and Zhou, Z.-L., *Youji Huaxue*, **2003**, *23*, 120. (f) Cao, X. P.; Yang, Y. Y. and Wang, X. L., *J. Chem. Soc., Perkin Trans. I,* **2002**, 2485. (g) Cao, X.-P., *Tetrahedron*, **2002**, *58*, 1301. (h) Cao, X.-P., *Huaxue Xuebao*, **2000**, *58*, 112. (i) Vasin, V. A.; Romanova, E. V.; Kostryukov, S. G. and Razin, V. V., *Mendeleev Commun*., **1998**, 122.
4. (a) Oh, S. T.; Jeong, I. H. and Lee, S. J., *J. Org. Chem.,* **2004**, *69*, 984. (b) Bernard, A. M.; Frongia, A. and Piras, P. P., *Synth. Commun.,* **2003**, *33*, 801. (c) Yang, G. L.; Franck, R. W.; Bittman, R.; Samadder, P. and Arthur, G., *Org. Lett.,* **2001**, *3*, 197. (d) Paul Raj, C.; Pichnit, T. and Braverman, S., *Tetrahedron Lett.,* **2000**, *41*, 1501. (e) MaGee, D. I. and Beck, E. J., *J. Org. Chem.,* **2000**, *65*, 8367. (f) MaGee, D. I. and Beck, E. J., *Can. J. Chem.,* **2000**, *78*, 1060. (g) Rigby, J. H.; Warshakoon, N. C. and Payen, A. J., *J. Am. Chem. Soc.,* **1999**, *121*, 8237. (h) Braverman, S. and Zafrani, Y., *Tetrahedron*, **1998**, *54*, 1901. (i) Evans, P. and Taylor, R. J. K., *Synlett*, **1997**, 1043. (j) Rigby, J. H. and Warshakoon, N. C., *J. Org. Chem.,* **1996**, *61*, 7644. (k) Wladislaw, B.; Marzorati, L.; Torres Russo, V. F.; Zaim, M. H. and Vitta, C. D., *Tetrahedron Lett.,* **1995**, *36*, 8367. (l) Paquette, L. A. and Wittenbrook, L. S., *J. Am. Chem. Soc.,* **1968**, *90*, 6790. (m) Paquette, L. A., *J. Am. Chem. Soc.,* **1964**, *86*, 4089.
5. (a) Alvarez, E.; Delgado, M.; Diaz, M. T.; Liu, H. X.; Perez, R. and Martin, J. D., *Tetrahedron Lett*., **1996**, *37*, 2865. (b) Trost, B. M. and Shi, Z., *J. Am. Chem. Soc.,* **1994**, *116*, 7459. (c) Ranasinghe, M. G. and Fuchs, P. L., *J. Am. Chem. Soc.,* **1989**, *111*, 779.
6. Chen, T. B. R. A.; Burger, J. J. and De Waard, E. R., *Tetrahedron Lett*., **1977**, 4527.
7. (a) Neureiter, N. P., *J. Am. Chem. Soc.,* **1966**, *88*, 558. (b) Neureiter, N. P. and Bordwell, F. G., *J. Am. Chem. Soc.,* **1963**, *85*, 1209.
8. Carpino, L. A. and McAdams, L. V., *J. Am. Chem. Soc.,* **1965**, *87*, 5804.
9. (a) Grumann, A.; Marley, H. and Taylor, R. J. K., *Tetrahedron Lett.,* **1995**, *36*, 7767. (b) Doomes, E. and McKnight, A. A., *J. Heterocycl. Chem.,* **1995**, *32*, 1467. (c) Hartman, G. D. and Hartman, R. D., *Synthesis,* **1982**, 504. (d) Paquette, L. A., *Org. React.,* **1977**, *25*, 1. (e) Bordwell, F. G., *Acc. Chem. Res.,* **1970**, *3*, 28. (f) Paquette, L. A., *Acc. Chem. Res.,* **1968**, *1*, 209.
10. (a) McAllister, G. D. and Taylor, R. J. K., *Tetrahedron Lett.,* **2001**, *42*, 1197. (b) Cerè , V.; Mantovani, G.; Peri, F.; Pollicino, S. and Ricci, A*., Tetrahedron,* **2000**, *56*, 1225. (c) Cerè, V.; Peri, F. and Pollicino, S*., Tetrahedron Lett.,* **1997**, *38*, 7797. (d) Schmittberger, T. and Ungen, D*., Tetrahedron Lett.,* **1997**, *38*, 2837. (e) Boeckman, R. K.; Yoon, S. K. and Heckendorn, D. K., *J. Am. Chem. Soc.,* **1991**, *113*, 9682.
11. (a) Griffin, F. K.; Paterson, D. E.; Murphy, P. V. and Taylor, R. J. K., *Eur. J. Org. Chem.,* **2002**, 1305. (b) Paterson, D. E.; Griffin, F. K.; Alcaraz, M.-L. and Taylor, R. J. K., *Eur. J. Org. Chem.,* **2002**, 1323. (c) Ohnishi, Y. and Ichikawa, Y., *Bioorg. Med. Chem. Lett.,* **2002**, *12*, 997. (d) Griffin, F. K.; Murphy, P. V.; Paterson, D. E. and Taylor, R. J. K., *Tetrahedron Lett.,* **1998**, *39*, 8179. (e) Alcaraz, M.-L.; Griffin, F. K.; Paterson, D. E. and Taylor R. J. K., *Tetrahedron Lett.,* **1998**, *39*, 8183.
12. (a) Franck, R. W. and Tsuji, M., *Acc. Chem. Res.,* **2006**, *39*, 692. (b) Bouchez, L. C. and Vogel, P., *Chem. Eur. J.,* **2005**, *11*, 4609. (c) Sarkar, T. K., *Sci. Synth.,* **2002**, *4*, 837. (d) Paquette, L. A., *Synlett,* **2001**, 1. (e) Taylor, R. J. K., *Chem. Commun.,* **1999**, 217. (f) Matsuyama, H.; Miyazawa, Y.; Takei, Y. and Kobayashi, M., *J. Org. Chem.,* **1987**, *52*, 1703. (g) Meyers, C. Y.; Malte, A. M. and Matthews, W. S., *J. Am. Chem. Soc.,* **1969**, *91*, 7510. (h) Paquette, L. A., *J. Am. Chem. Soc.,* **1964**, *86*, 4085.

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Raney Nickel

A. GENERAL DESCRIPTION OF THE REACTION

This reagent was first reported by Raney in 1925.[1] It is a porous nickel suspension primarily prepared from alkali soaking of 50% nickel-aluminum alloy[2] but can also be prepared by acid soaking (e.g., HCl). According to the temperature and alkali concentration,[3] different types of Raney nickel can be prepared, such as W-2,[4] W-6,[2a,3] and T-1.[3] It has been found that Raney nickels retain about one half to one hydrogen per atom of nickel, with the hydrogen attached in a metastable state.[5] This catalyst has surface area of 50–120 m^2/g, with 20% of that being metal and 80% non metal, with an average pore diameter of 84 Å, and with a high resistance to sintering.[6] It has been found that the activity of this catalyst is proportional to its hydrogen content, and the surface area decreases linearly with loss of hydrogen until ~70% of hydrogen is removed.[5] In addition, the activity of Raney nickel decreases along with the storing time.[7]

Generally speaking, Raney nickel has many applications in organic synthesis, such as reduction, oxidation, *N*-alkylation, desulfurization, dehydration and cleavage of chemical bonds. When employing a gaseous hydrogen source, many functional groups can be reduced, and even toluene can be hydrogenated.[8] However, without gaseous hydrogen, carbon-carbon double bonds, carbonyls, nitro groups, hydrazo, and azoxy groups are reduced.[9] In addition, other reagents have also been used as reducing reagents or hydrogen donors in the presence of Raney nickel, such as hydrazinium monoformate for the reduction of nitrile and nitro moieties,[10] hydrazine hydrate with an excess of alcohol for selective reduction of nitro groups in the presence of carbonyls,[11] and isopropanol for the reduction of aromatic rings (benzene) to cyclohexane and for the dehalogenation of halogenated aromatics.[12] Alternatively, the combination of Raney nickel and platinum has been used for the reduction of nitriles to primary amines,[13] and the combination of $Ti(O\text{-}i\text{-}Pr)_4$ and Raney nickel can

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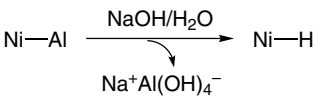
transform aliphatic ketones into enantiomeric amines through reductive amination in the presence of (*R*)- or (*S*)-α-methylbenzylamine.[14]

Other general applications of Raney nickel include desulfurization[15] and deselenization. It has been found that the desulfurization of sulfides[16] and sulfoxides[17] occurs through a radical process with complete racemization of chirality at the carbon atom adjacent to the sulfur atom, whereas the desulfurization of sulfones affords 90% retention of optical activity with apparent inversion of configuration at the carbon atom adjacent to sulfur.[18] However, the combination of Raney nickel and sodium hypophosphite leads to the retention of stereochemistry during desulfurization of optically active secondary alcohol.[19] It should be pointed out that the carbon-carbon bond may be cleaved under the condition of desulfurization, as shown in the hydrogenolysis of ethylenedithiol and its ether.[20] In deselenization, diselenides and phenyl selenobenzoate are transformed into selenides by Raney nickel.[21] Furthermore, Raney nickel has been used for the oxidation of secondary alcohols into ketones in refluxing benzene without hydrogen acceptor added,[22] and converting 1,4-diol into lactone.[23] On the other hand, alcohols can be used as alkylating agents in the presence of a Raney nickel catalyst, such as the alkylation of butylamine, *N*,*N*-dibutylamine with ethanol and propanol,[24] and the alkylation of piperazine.[25] In addition to these applications, Raney nickel has been widely used for the cleavage of chemical bonds; which include (*a*) the carbon-carbon bond during desulfurization (e.g., the cleavage of ethylenedithiol and its ether);[20] (*b*) *N*-*N* bond in conversion of carboxylic acid hydrazides into amides and ammonia;[26] (*c*) *O*-*O* bond in conversion of ozonide into aldehyde and ketone;[27] (*d*) *C*-*O* bond in decarboxylation of alkyl formates to alcohols and potential ketones,[28] and *C*-*O* bond during dehydration of alcohols, such as benzyl alcohol to toluene,[9] glycerol to 1,2-propanediol,[29] 2-propanolpyridine to 2-ethylpyridine and 2-methyl-6-ethylpyridine,[30] mandelamide to racemic phenylacetamide,[31] and tertiary alcohol to alkanes;[32] and (*e*) *N*-*B* bond in decomposition of borane-amine complex (except for Et_3N and pyridine) in the presence of methanol.[33] Interestingly, it has been found that the activity of Raney nickel can be enhanced by addition of cobalt,[34] amyl chloride,[35] platinum chloride ($PtCl_4$),[36] or platinum chloride in combination with Et_3N.[37] However, Raney nickel can also be poisoned by sulfur compounds[38] and HCl and organic halides.[35] It has been found that organic chlorides and bromides are moderately toxic to Raney nickel, and iodides are highly toxic. In addition, propyl chloride and halides with more than one halogen atom on the same carbon are also highly toxic.[35]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

The aluminum in nickel-aluminum alloy would be soaked out and displaced by hydrogen, thus no further mechanism is needed.

D. MODIFICATION

Raney nickel has been prepared from nickel-magnesium alloy.[4] In addition, Raney cobalt in ethanol or dioxane shows a reactivity similar to Raney nickel.[39]

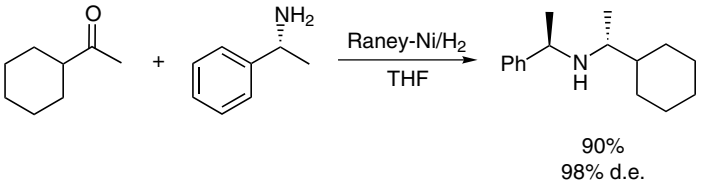
E. APPLICATIONS

This catalyst has very broad applications in organic synthesis.

F. RELATED REACTIONS

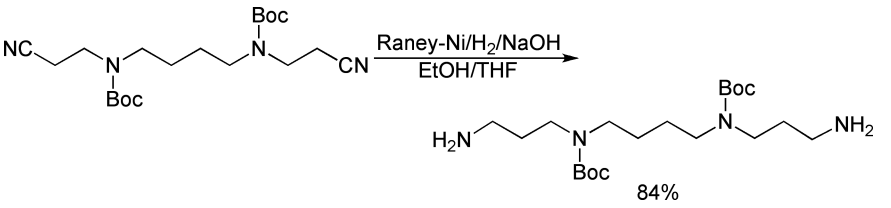
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 14.

In an anhydrous solvent (any one from THF, MTBE, DME, hexane, toluene, CH_2Cl_2, 1,2-dichloroethane, EtOAc, and EtOH) were added 2.50 mmol methyl cyclohexyl ketone, 3.12 mmol titanium tetraisopropoxide, and 2.62–2.75 mmol (*R*)-α-methylbenzylamine. The solution was stirred at room temperature for 30 min. Raney-Ni (70–100 wt %) triturated with EtOH (twice) and the reaction solvent (twice) was added to the reaction solution, and the reaction vessel was pressurized to 120 psi (8.3 bar) with hydrogen. When the reaction completed, the mixture was stirred with 10 mL 1.0 M NaOH for 1 h. The heterogeneous mixture was then filtered through a bed of Celite and washed with EtOAc. The filtrate was evaporated to remove the low boiling organics, and the remaining aqueous solution was then extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and then concentrated. The residue was purified by flash column chromatography to afford 90% (1*R*)-*N*-((*R*)-1-cyclohexylethyl)-1-phenylethanamine in 98% d.e.



Reference 13.

N_1,N_4-Di(*tert*-butyloxycarbonyl)-N_1,N_4-di(2′-cyano-ethyl)-1,4-butanediamine (1.70 g, 4.31 mmol) was dissolved in a mixture of 80 mL absolute ethanol and 20 mL THF. Raney-nickel (2.1 g, 17.8 mmol) as a 50% suspension in water was added together with 10 mL 2 N NaOH, and the reaction mixture was shaken under 45 psi hydrogen pressure at room temperature for 8 h. After the catalyst was filtered off and the solvents were removed in vacuo, a mixture of 100 mL water and 30 mL CH_2Cl_2 was added, and the organic phase was separated. The aqueous phase was further extracted with CH_2Cl_2 (3 × 30 mL), the combined organic layers were dried with Na_2SO_4. Upon removal of solvent in vacuo, 1.45 g N_1,N_4-di(*tert*-butyloxycarbonyl)-N_1,N_4-di(3-aminopropyl)-1,4-butanediamine was obtained as a yellow, highly viscous oil, in a yield of 84%. This product could be further purified by silica gel column chromatography using Et_3N/MeOH (1:10) as the eluent, R_f = 0.36 (35% aq. NH_3/MeOH, 1:10).

Other references related to Raney nickel are cited in the literature.[40]

H. REFERENCES

1. Raney, M., *U.S. Pat.,* Dec. 1, **1925**, 1,563,587. [*Chem. Abstr.,* **1926**, *20*, 515.]
2. (a) Smith, H. A.; Bedoit, W. C. and Fuzek, J. F., *J. Am. Chem. Soc.,* **1949**, *71*, 3769. (b) Adkins, H. and Billica, H. R., *J. Am. Chem. Soc.,* **1948**, *70*, 695. (c) Pavlic, A. A. and Adkins, H., *J. Am. Chem. Soc.,* **1946**, *68*, 1471. (d) Covert, L. W. and Adkins, H., *J. Am. Chem. Soc.,* **1932**, *54*, 4116.
3. Dominguez, X. A.; Lopez, I. C. and Franco, R., *J. Org. Chem.,* **1961**, *26*, 1625.
4. Pattison, J. N. and Degering, E. F., *J. Am. Chem. Soc.,* **1950**, *72*, 5756.
5. Smith, H. A.; Chadwell, A. J. and Kirslis, S. S., *J. Phys. Chem.,* **1955**, *59*, 820.
6. Kokes, R. J. and Emmett, P. H., *J. Am. Chem. Soc.,* **1961**, *83*, 29.
7. Pattison, J. N. and Degering, E. F., *J. Am. Chem. Soc.,* **1951**, *73*, 486.
8. Littman, H. and Bliss, H., *Ind. Eng. Chem.,* **1959**, *51*, 659.
9. Mozingo, R.; Spencer, C. and Folkers, K., *J. Am. Chem. Soc.,* **1944**, *66*, 1859.
10. Gowda, S. and Gowda, D. C., *Tetrahedron,* **2002**, *58*, 2211.
11. Balcom, D. and Furst, A., *J. Am. Chem. Soc.,* **1953**, *75*, 4334.
12. Srivastava, S.; Minore, J.; Cheung, C. K. and le Noble, W. J., *J. Org. Chem.,* **1985**, *50*, 394.
13. Klenke, B. and Gilbert, I. H., *J. Org. Chem.,* **2001**, *66*, 2480.
14. Nugent, T. C.; Wakchaure, V. N.; Ghosh, A. K. and Mohanty, R. R., *Org. Lett.,* **2005**, *7*, 4967.
15. Hauptmann, H. and Walter, W. F., *Chem. Rev.,* **1961**, *61*, 347.
16. Cope, A. C. and Engelhart, J. E., *J. Org. Chem.,* **1969**, *34*, 3199.
17. Bonner, W. A., *J. Am. Chem. Soc.,* **1952**, *74*, 5089.
18. (a) Bonner, W. A., *J. Am. Chem. Soc.,* **1952**, *74*, 1033. (b) Bonner, W. A., *J. Am. Chem. Soc.,* **1952**, *74*, 1034.
19. Node, M.; Nishide, K.; Shigeta, Y.; Obata, K.; Shiraki, H. and Kunishige, H., *Tetrahedron,* **1997**, *53*, 12883.
20. Synder, H. R. and Cannon, G. W., *J. Am. Chem. Soc.,* **1944**, *66*, 155.
21. Hauptmann, H. and Walter, W. F., *J. Am. Chem. Soc.,* **1955**, *77*, 4929.
22. Krafft, M. E. and Zorc, B., *J. Org. Chem.,* **1986**, *51*, 5482.
23. Berson, J. A. and Jones, W. M., *J. Org. Chem.,* **1956**, *21*, 1325.
24. Rice, R. G.; Kohn, E. J. and Daasch, L. W., *J. Org. Chem.,* **1958**, *23*, 1352.

25. Plante, L. T. and Clapp, L. B., *J. Org. Chem.,* **1956**, *21*, 86.
26. Ainsworth, C., *J. Am. Chem. Soc.,* **1954**, *76*, 5774.
27. Cook, N. C. and Whitmore, F. C., *J. Am. Chem. Soc.,* **1941**, *63*, 3540.
28. Sandner, M. R. and Trecker, D. J., *J. Org. Chem.,* **1973**, *38*, 3954.
29. Perosa, A. and Tundo, P., *Ind. Eng. Chem. Res.,* **2005**, *44*, 8535.
30. Reinecke, M. G. and Kray, L. R., *J. Am. Chem. Soc.,* **1964**, *86*, 5355.
31. Bonner, W. A., *J. Am. Chem. Soc.,* **1954**, *76*, 6350.
32. Krafft, M. E. and Crooks, W. J., *J. Org. Chem.,* **1988**, *53*, 432.
33. Couturier, M.; Tucker, J. L.; Andersen, B. M.; Dubé, P. and Negri, J. T., *Org. Lett.,* **2001**, *3*, 465.
34. Lee, H.-K.; Jung, E.-E. and Lee, J.-S., *Mater. Chem. Phys.,* **1998**, *55*, 89.
35. Pattison, J. N. and Degering, E. F., *J. Am. Chem. Soc.,* **1951**, *73*, 611.
36. Scholnik, S. S.; Reasenberg, J. R.; Lieber, E. and Smith, G. B. L., *J. Am. Chem. Soc.,* **1941**, *63*, 1192.
37. Levering, D. R. and Lieber, E., *J. Am. Chem. Soc.,* **1949**, *71*, 1515.
38. Maxted, E. B. and Titt, R. A., *J. Soc. Chem. Ind., London,* **1938**, *57*, 197.
39. Reeve, W. and Christian, J., *J. Am. Chem. Soc.,* **1956**, *78*, 860.
40. (a) Hendsbee, J. A.; Thring, R. W. and Dick, D. G., *J. Can. Petroleum Tech.,* **2006**, *45*, 47. (b) Osawa, T.; Yoshino, K.; Takimoto, K.; Takayasu, O. and Harada, T., *Catal. Lett.,* **2006**, *112*, 167. (c) Toom, L.; Grennberg, H. and Gogoll, A., *Synthesis*, **2006**, 2064. (d) Morgenstern, D. A. and Fornango, J. P., *Energy & Fuels*, **2005**, *19*, 1708. (e) Birry, L. and Lasia, A., *J. Appl. Electrochem.,* **2004**, *34*, 735. (f) Nemtseva, M. P.; Lefedova, O. V.; Gostikin, V. P. and Zuenko, M. A., *Zh. Fizicheskoi Khimii*, **2003**, *77*, 1023. (g) Gowda, D. C.; Gowda, S. and Abiraj, K., *Indian J. Chem., Sect. B,* **2003**, *42B*, 1774. (h) Ilikti, H.; Rekik, N. and Thomalla, M., *J. Appl. Electrochem.,* **2002**, *32*, 603. (i) Nakagawa, S.; Tai, A.; Okuyama, T. and Sugimura, T., *Top. Catal.,* **2000**, *13*, 187. (j) Petro, J.; Bota, A.; Laszlo, K.; Beyer, H.; Kalman, E. and Dodony, I., *Appl. Catal., A: General,* **2000**, *190*, 73. (k) Mukhopadhyay, S.; Chandnani, K. H. and Chandalia, S. B., *Org. Proc. Res. Dev.,* **2000**, *4*, 254. (l) Zeifert, B. H.; Salmones, J.; Hernandez, J. A.; Reynoso, R.; Nava, N.; Cabanas-Moreno, J. G. and Aguilar-Rios, G., *Catal. Lett.,* **1999**, *63*, 161. (m) Zupancic, S.; Svete, J. and Stanovnik, B., *J. Heterocycl. Chem.,* **1999**, *36*, 607. (n) Nakabayashi, I.; Moriga, T.; Matsui, H.; Tomida, T. and Ashida, T., *Curr. Top. Catal.,* **1997**, *1*, 1. (o) Jung, E.-E.; Lee, H.-K.; Lee, K.-J.; Yang, Y.-S.; Park, S.-G. and Lee, J.-S., *J. Ind. Eng. Chem., (Seoul),* **1997**, *3*, 24. (p) Regla, I.; Reyes, A.; Korber, C.; Demare, P.; Estrada, O. and Juaristi, E., *Synth. Commun.,* **1997**, *27*, 817. (q) Borucinsky, T.; Rausch, S. and Wendt, H., *J. Appl. Electrochem.,* **1997**, *27*, 762. (r) Larghi, E. L. and Kaufman, T. S., *Tetrahedron Lett.,* **1997**, *38*, 3159. (s) Jiang, Y.-L.; Hu, Y.-Q.; Feng, S.-Q.; Wu, J.-S.; Wu, Z.-W. and Yuan, Y.-C., *Synth. Commun.,* **1996**, *26*, 161. (t) Vidal, S.; Masson, J.; Court, J. and Cividino, P., *J. Chim. Phys. Phys.-Chim. Biol.,* **1995**, *92*, 2060. (u) Choquette, Y.; Brossard, L. and Ménard, H., *J. Appl. Electrochem.,* **1990**, *20*, 855. (v) Noller, H. and Lin, W. M., *React. Kinetics Catal. Lett.,* **1982**, *21*, 479. (w) Watt, G. W. and Parker, S. G., *J. Am. Chem. Soc.,* **1952**, *74*, 1103. (x) Hauptmann, H. and Wladislaw, B., *J. Am. Chem. Soc.,* **1950**, *72*, 707. (y) Hauptmann, H. and Wladislaw, B., *J. Am. Chem. Soc.,* **1950**, *72*, 710. (z) Kleiderer, E. C. and Kornfeld, E. C., *J. Org. Chem.,* **1948**, *13*, 455. (aa) Grillot, G. F., *J. Am. Chem. Soc.,* **1944**, *66*, 2124. (bb) Hoehn, W. M. and Ungnade, H. E., *J. Am. Chem. Soc.,* **1943**, *65*, 124.

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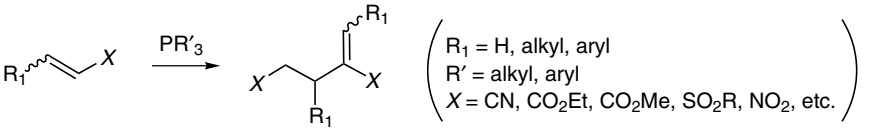
Rauhut-Currier Reaction
(Rauhut-Currier Dimerization)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Rauhut and Currier in 1963.[1] It is a phosphine-catalyzed dimerization of electron-deficient alkenes[2] and is generally known as the Rauhut-Currier reaction[2,3] or Rauhut-Currier dimerization.[2a] Although this reaction is reported to have relatively low selectivity and low yield,[4] the dimerization of methyl acrylate at temperatures between 50° and 110°C always gives head-to-tail dimer,[5] and the intramolecular dimerization of unsymmetrical bis(enones) with sufficient steric or electronic bias gives single products.[2b] In addition, the reaction between ethyl acrylate and acrynitrile in *t*-butanol at 100°C in the presence of tributylphosphine gives 48% of only one type cross-condensation product as well as the self-dimerization products.[5a] The reaction of acrynitrile is very fast under the Rauhut-Currier reaction conditions at refluxing temperatures, which leads to the vigorous polymerization of acrynitrile.[5b] However, the dimer and trimer of acrynitrile can still be obtained if such reaction were carried out in acetonitrile by addition of an extra proton donor such as water or *t*-butanol, and separation of tributylphosphine before isolation of the product.[5b]

B. GENERAL REACTION SCHEME



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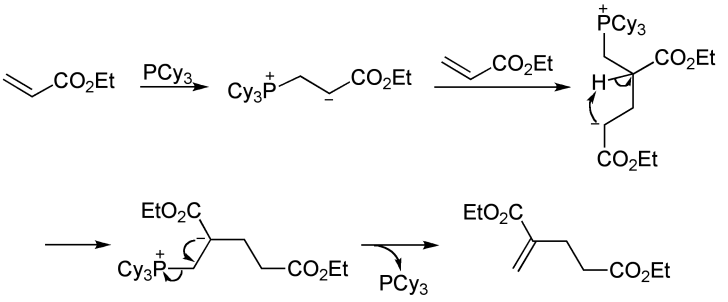
C. PROPOSED MECHANISMS

It is proposed that this reaction involves a reversible conjugate addition of phosphine to electron-deficient alkenes, followed by a *Michael Addition* of the resulting carbanion to the second alkene, and subsequent proton migration and elimination of phosphine,[2a] as illustrated here by the tricyclohexylphosphine catalyzed reaction of ethyl acrylate.



D. MODIFICATION

This reaction has been modified by the use of proazaphosphatranes[3] and tricyclohexylphsophine in combination with CS_2[6] as catalysts. In addition, the organometallic complexes of phosphine such as $Cp^*Ru(PCy_3)H_3$,[7] have been used as catalysts as well. It has been found that the activity of this type catalyst varies along with the phosphine ligands in the order of $P(OR)_3 < PAr_3 < PR_3$, with an optimal ratio of 1.5:1 for ligand to Ru.[8] Moreover, this reaction has been extended to the addition of activated alkenes to aldehydes, and it has been found that intramolecular addition of *cis*-alkene to aldehyde is faster than that of *trans*-alkene.[3]

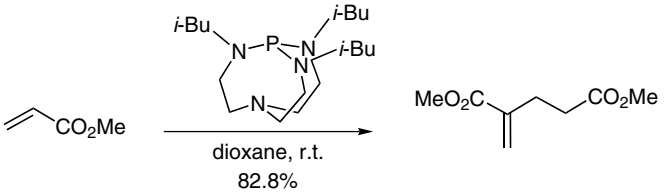
E. APPLICATIONS

This reaction should have general application in organic synthesis but has not yet been extensively explored.

F. RELATED REACTIONS

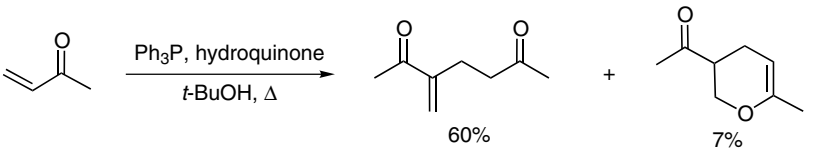
This reaction is very closely related to the *Baylis-Hillman Reaction*, and is also related to *Stetter Reaction* and *Benzoin Condensation* in mechanism.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4.

To a solution of 431 mg methyl acrylate (5 mmol) in 2 mL dioxane was added 0.5 mmol tri-isobutyl proazaphosphatranes in the same solvent by syringe. The mixture was stirred at room temperature for 3 h, then the solvent was removed under vacuum. The residue was purified by column chromatography using EtOAc/hexanes (1:4) as eluent to afford 82.8% 2-methylene-pentanedioic acid dimethyl ester.



Reference 5a.

To a 350-mL glass-lined reactor were added 20 g methyl vinyl ketone (285 mmol), 0.2 g hydroquinone, 1.85 g Ph_3P (7.1 mmol), and 100 g *t*-butanol under nitrogen. Then the reaction was sealed under nitrogen and heated at 118°C for 8 h. *t*-Butanol and unreacted methyl vinyl ketone were removed by vacuum distillation, and the residue was distilled through a small Vigreux column to afford 8.6 g fraction with a boiling point in the range of 55–75°C at 1.2 mmHg, along with 4.5 g residue. Gas-liquid chromatography analysis on the DC-710 column at 180–200°C showed the presence of 7.2 g 3-methylene-2,6-heptanedione (60% yield), 0.8 g 5-acetyl-5,6-dihydro-2-methylpyran (7% yield), and 0.4 g of an unknown compound. The expected 3-methylene-2,6-heptanedione was isolated by further fractional distillation through a 2-ft spinning-band column at 91–92°C (5 mmHg), with m.p. 5–7°C. Recrystallization of earlier distillation residue from ethanol yielded 1.4 gram triphenylphosphine, with a recovery of 75%. (*Note:* The original paper claimed 0.8 g 6-acetyl-5,6-dihydro-2-methylpyran, but is corrected here.)

Other references related to the Rauhut-Currier reaction are cited in the literature.[9]

H. REFERENCES

1. Rauhut, M. and Currier, H., (American Cyanamide Co.), *U.S. Pat.*, Jan. 22, **1963**, 3,074,999.
2. (a) Lee, K. Y.; Gowrisankar, S. and Kim, J. N., *Bull. Korean Chem. Soc.,* **2005**, *26*, 1481. (b) Wang, L.-C.; Luis, A. L.; Agapiou, K.; Jang, H.-Y. and Krische, M. J., *J. Am. Chem. Soc.,* **2002**, *124*, 2402.
3. Teng, W.-D.; Huang, R.; Kwong, C. K.-W.; Shi, M. and Toy, P. H., *J. Org. Chem.,* **2006**, *71*, 368.
4. Su, W. P.; McLeod, D. and Verkade, J. G., *J. Org. Chem.,* **2003**, *68*, 9499.
5. (a) McClure, J. D., *J. Org. Chem.,* **1970**, *35*, 3045. (b) Baizer, M. M. and Anderson, J. D., *J. Org. Chem.,* **1965**, *30*, 1357.
6. Cookson, R. C. and Smith, S. A., *J. Chem. Soc., Perkin. Trans. I,* **1979**, 2447.
7. Yi, C. S. and Liu, N., *J. Organomet. Chem.,* **1998**, *553*, 157.
8. McKinney, R. J. and Colton, M. C., *Organometallics,* **1986**, *5*, 1080.
9. (a) Methot, J. L. and Roush, W. R., *Adv. Synth. Catal.*, **2004**, *346*, 1035. (b) Luis, A. L. and Krische, M. J., *Synthesis,* **2004**, 2579. (c) Basavaiah, D.; Rao, A. J. and Satyanarayana, T., *Chem. Rev.,* **2003**, *103*, 811. (d) Methot, J. L. and Roush, W. R., *Org. Lett.,* **2003**, *5*, 4223. (e) Mergott, D.

J.; Frank, S. A. and Roush, W. R., *Org. Lett*., **2002**, *4*, 3157. (f) Jenner, G., *Tetrahedron Lett.,* **2000**, *41*, 3091. (g) Tembe, G. L.; Bandyopadhyay, A. R.; Ganeshpure, P. A. and Satish, S., *Catal. Rev. Sci. Eng.,* **1996**, *38*, 299. (h) Basavaiah, D.; Gowriswari, V. V. L. and Bharathi, T. K., *Tetrahedron Lett.,* **1987**, *28*, 4591. (i) Drewes, S. E.; Emslie, N. D. and Karodia, N., *Synth. Commun.,* **1990**, *20*, 1915. (j) White, D. A., *Synth. React. Inorg. Met. Org. Chem.,* **1977**, *7*, 433. (k) McClure, J. D., *U.S. Pat.*, Dec. 21, **1965**, 3,225,083.

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Reed Reaction

(Reed Process, Reed Sulfochlorination)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Reed in 1936.[1] It is a photochemical transformation of hydrocarbon into aliphatic sulfonyl chlorides in the presence of sulfuryl chloride or sulfur dioxide and chlorine under actinic light illumination[2] and is known as the Reed reaction[2,3] or Reed process.[2b] This reaction is a primary industrial process for production of aliphatic sulfonyl chlorides with long hydrocarbon chains, which have wide applications in synthetic detergents[3a] and wetting agents.[2b,3b] This reaction is assumed to occur via a free-radical mechanism,[3a,4] and usually gives the mixtures of both sulfochlorination and chlorination products, including monosulfonyl chlorides, chloroalkyl monosulfonyl chlorides, polysulfonyl chlorides, chloroalkyl polysulfonyl chlorides, and alkyl chlorides and alkyl polychlorides.[2b] It has been found that under certain carefully controlled conditions, monosulfonyl chlorides can be produced predominantly[5] because the ratio of chlorination to sulfochlorination decreases along with the increase in the ratio of SO_2/Cl_2 supplied and both light intensity and frequency; in addition, lower reaction temperatures and smaller bubble size are also favorable for the production of sulfonyl chlorides with high purity.[2a] Although this reaction has been extensively used for the preparation of sulfonyl chlorides of long hydrocarbon chains, the corresponding sulfonyl chlorides from propane,[6] butane,[7] and isobutene[8] have also been successfully prepared from this reaction.

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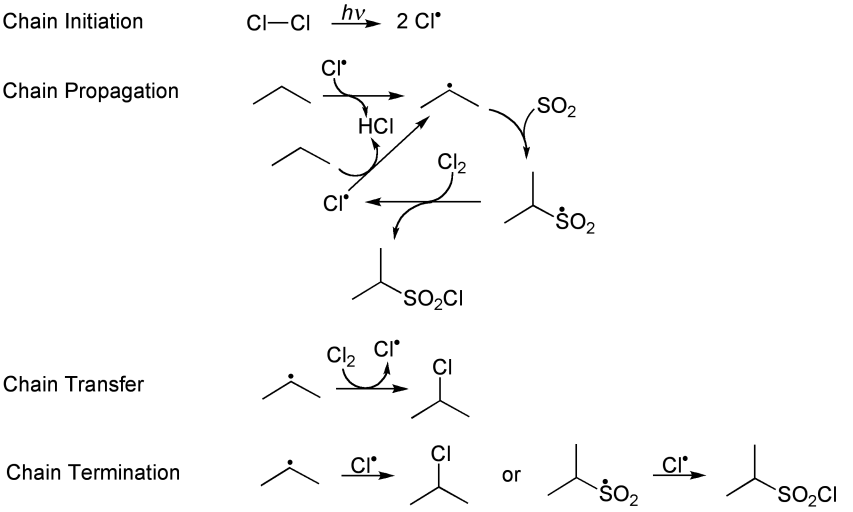
B. GENERAL REACTION SCHEME

C. PROPOSED MECHANISMS

It is believed that chlorine cleaves homolytically under UV light to generate the initial chlorine radical, which abstracts a proton from the hydrocarbon to form an alkyl radical that combines with sulfur dioxide, as illustrated here by the representative chain reactions of propane. It should be pointed out that proton abstraction by the chlorine radical occurs predominantly at tertiary or secondary carbons rather than at the primary carbons (i.e., terminal CH_3).



D. MODIFICATION

This reaction has been modified by the use of gamma-ray illumination; gamma-rays hold much higher energy than UV light. In this modification, the cleavage of a carbon-hydrogen bond is assumed to be the initiation step, which is rate-limiting step under the dose rate (intensity of gamma-ray) below 40 rad/min. However, the reaction rate depends on the supply of SO_2 and Cl_2 when the intensity is 400 rad/min.[2a] In addition, this reaction has been modified to initiate from free-radical initiators such as peroxides[9] and tetraethyl-lead.[2a]

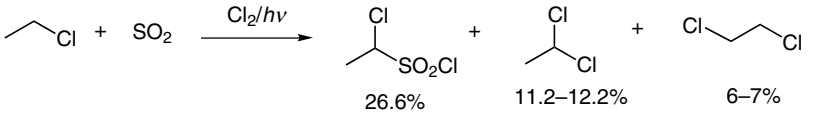
E. APPLICATIONS

This reaction has wide industrial application in the production of synthetic detergents[3a] and wetting agents[2b,3b] as well as for the modification of polyethylene.[3a]

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3a.

To a round-bottomed flask equipped with a gas inlet tube and a dry ice cooled condenser, was added 1.0 mol ethyl chloride and 2.34 mol sulfur dioxide. Then 1.31 mol chlorine was slowly passed into the ethyl chloride and sulfur dioxide mixture through the gas inlet within 3.5 h while illuminated by one or two Westinghouse RS 275-watt sunlamps at a distance of about 6 in. The reaction mixture was first separated by atmosphere pressure distillation from a water bath, and the low-boiling fraction was added to 20% NaOH solution frozen at −70°C and warmed slowly to 0°C to remove HCl, SO_2, and SO_2Cl_2. Then the aqueous solution was neutralized with HCl, and the dichloroethanes were separated by steam distillation to give 6–7% 1,2-dichloroethane (b.p. 83°C) and 11.2–12.2% 1,1-dichloroethane (b.p. 57°C). The residue from initial distillation was further subjected to vacuum distillation to give 26.6% 2-chloroethanesulfonyl chloride as a water white lachrymatory liquid, b.p. 84°C at 12 mmHg. (*Note:* The author has no idea about the status of 20% NaOH solution frozen at −70°C, i.e., whether it is a solid, semi-solid or a solution).

Other references related to the Reed reaction are cited in the literature.[9]

H. REFERENCES

1. Reed, C. F., *U.S. Pat.*, June 30, **1936**, 2,046,090.
2. (a) Schneider, A. and Chu, J. C., *I&EC Proc. Design & Develop.,* **1964**, *3*, 164. (b) Lisk, G. F., *Ind. Eng. Chem.,* **1948**, *40*, 1671.
3. (a) Walling, C. and Pease, W. F., *J. Org. Chem.,* **1958**, *23*, 478. (b) Lisk, G. F., *Ind. Eng. Chem.,* **1949**, *41*, 1923.
4. (a) Stauff, J., *Z. Electrochem.,* **1942**, *48*, 550. (b) Kharasch, M. S.; Chao, T. H. and Brown, H. C., *J. Am. Chem. Soc.,* **1940**, *62*, 2394.
5. (a) Asinger, F., *Ger. Pat.,* Jan. 6, **1942**, 715,747. (b) I. G. Farbenindustrie A. G., *Ger. Pat.,* Feb. 19, **1942**, 717,680.
6. Asinger, F.; Schmidt, W. and Ebeneder, F., *Ber.,* **1942**, *75*, 34.
7. Asinger, F.; Ebeneder, F. and Böck, E., *Ber.,* **1942**, *75*, 42.
8. Asinger, F. and Ebeneder, F., *Ber.,* **1942**, *75*, 344.
9. Grubb, H. M. and Tucker, E. G., *U.S. Pat.,* Sep. 17, **1945**, 2,412,679.
10. (a) Boynton, H. G.; Lewis, E. W. and Watson, A. T., *Ind. Eng. Chem.,* **1959**, *51*, 267. (b) Gilbert, E. E. and Jones, E. P., *Ind. Eng. Chem.,* **1953**, *45*, 2041. (c) Brooks, R. E.; Strain, D. E. and McAlevy, A., *India Rubber World*, **1953**, *127*, 791. (d) Nottes, G. and Mapstone, G. E., *J. Inst. Petroleum,* **1952**, *38*, 178. (e) Kroepelin, H.; Eberstein, A. F.; Freiss, W.; Kabisch, G. and Opitz, W., *Angew. Chem.,* **1952**, *64*, 273. (f) Helberger, J. H.; Manecke, G. and Fischer, H. M., *Ann.,* **1949**, *562*, 23. (g) Reed, C. F. and Horn, C. L., *U.S. Pat.,* Nov. 18, **1941**, 2,263,312. (h) Reed, C. F., *U.S. Pat.,* Sep. 26, **1939**, 2,174,492. (i) Kharasch, M. S. and Read, A. T., *J. Am. Chem. Soc.,* **1939**, *61*, 3089.

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Reformatsky Reaction

(Reformatskii Reaction, Reformatsky Condensation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Reformatsky (also spelled as Reformatskii) in 1887.[1] It is a zinc-mediated formation of β-hydroxy esters from the condensation between α-bromoester and an aldehyde or ketone, or more generally the reaction between an activated alkyl halide with a carbonyl compound in the presence of zinc to form a hydroxy compound.[2] Therefore, this reaction is generally known as the Reformatsky reaction,[3,4] or Reformatskii reaction.[5,6] Occasionally, it is also referred to as the Reformatsky (Reformatskii) condensation,[3f,3n,7] or Reformatsky addition.[8] The inserted complex between zinc and α-bromoester is generally referred to as the Reformatsky reagent.[9] Since its discovery, this reaction has been extensively explored because of its high functional group tolerance.[9c] However, the traditional Reformatsky protocol is also known to have several drawbacks, including a problem in its initiation and regulation because of the heterogeneity;[9f] the requirement for fresh preparation of zinc reagent;[9c,10] low reproducibility and access only to the thermodynamic products;[11] low yields because of the enolization of the Reformtasky reagent and many associated side reactions under the reaction condition, including the self-condensation of carbonyl compounds and α-bromoester;[12] elimination of α-bromoester;[12] and *retro*-Reformatsky fragmentation.[13] According to what now known, the use of an excess amount of zinc and α-bromoester can improve the yields,[3l] and the resulting addition products are better decomposed by use of dry hydrogen chloride[14] or 50% H_2SO_4.[15] Suitable solvents include 1,4-dioxane,[7c] THF,[12] Et_2O,[16] and benzene;[3j,12,14,17] but generally, benzene, especially the mixed solvent of benzene (e.g., benzene-ether), is the solvent of choice.[18] In addition, the small variation in the alcoholic moiety of α-bromoester remarkably

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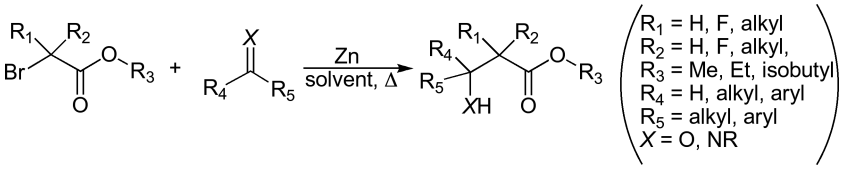
affects the reactivity of the α-bromoester.[19] For example, the methyl and ethyl α-bromoesters react regularly, whereas isopropyl, *t*-butyl and neopentyl esters are inert. It is interesting that the isobutyl ester reacts comparably with ethyl ester, which would be a choice when ethyl ester is involved in many side reactions.[19]

So far, this reaction has been used for the addition of Reformatsky reagent to aldehydes, ketones, thienyl aldehyde,[2,3g] isatins[3p] to prepare hydroxy compounds; to anils for β-amino esters;[20] to aroyl chloride[21] and 3-acyloxazolidin-2-ones[22] for β-keto esters; and to phenyl esters to form β-keto esters when neither the phenyl ester nor the α-bromoester bears α-hydrogen.[3m] In addition, many variants of α-bromoesters have been developed or used successfully for this reaction, such as α-bromolactone,[23] γ-bromocrotonate,[3g,3j,5l] bromofluoroacetate,[3f,24] iododifluoroacetate,[25] α-chloroesters,[9f,17b] α-methylene-β-bromoester,[9d] *N*,*N*-dialkyl-α-haloamides,[3k] and α,α-disubstituted α-bromoester[26] (e.g., methyl or ethyl α-bromoisobutyrate[3a,3b,3m,21,27]). Among these variants, iododifluoroacetate leads to the formation of α,α-difluoro-β-hydroxyester,[25] while bromofluoroacetate yields α-fluoro-β-hydroxyester in comparable yield with simple α-bromoester, though it does so more sluggishly.[3f] However, α,α-disubstituted α-bromoesters would produce the tetrasubstituted β-lactones rather than regular β-hydroxy esters when they react with ketones in DMF.[26] It is interesting that for the case of ethyl α-bromoisobutyrate, though β-lactones are formed predominantly under different conditions—such as using zinc or indium powder or at a sacrificial zinc or indium anode—the normal β-hydroxy esters will form at a sacrificial zinc anode if a catalytic amount of $NiBr_2$ is added.[27a] Similarly, the reaction of α-methylene-β-bromoester reacting with cyclic ketone will give spiro-α-methylene-γ-lactone.[9d] In contrast, the reaction of γ-halocrotonate, the so-called vinylogous Reformatsky reaction,[3j,28] is substrate- and solvent-dependent. For example, the reaction between methyl γ-bromocrotonate with cyclohexanone, 4-methylcyclohexanone, β-tetralone, and 3,4,5-trimethoxybenzaldehyde in boiling benzene yields normal vinylogous Reformatsky products,[3j] i.e., products resulting from γ-addition, whereas the same reaction in boiling ether yields α-substituted vinylacetate, probably because of charge migration in the organic zinc reagent.[3g] Likewise, the reaction between methyl γ-bromocrotonate with 2-methyl cyclohexanone and α-tetralone produces the vinylogous product through the γ-position addition.[3j] This reaction has been extensively reviewed.[29]

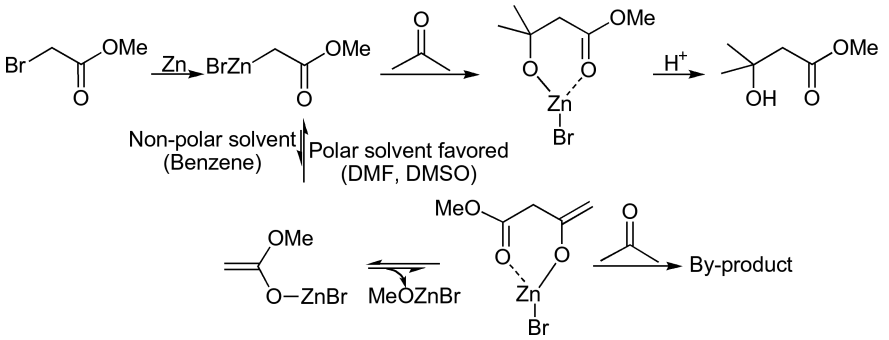
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Mechanistically, the insertion complex between zinc and α-bromoester generated *in situ* exists at least in two forms, such as the *C*-metalated and *O*-metalated species,[9g] and the

C-metalated species is normally referred to as the Reformatsky reagent.[9e,9f] These two species may further aggregate to form dimer by elimination of alkoxyzinc bromide,[9i] though the *C*-metalated species is the active one in this reaction. This assertion is supported first by the partial recovery of ketone during the complete consumption of zinc when an equivalent zinc and ketone are used;[3o] and second, by the titration experiment on ethyl α-bromoisobutyrate, in which 70% active reagent and 30% dimeric substance were identified.[9i] According to these experimental results, an illustrative mechanism is proposed here using acetone and methyl α-bromoacetate as an example.



D. MODIFICATION

This reaction has been extensively modified, and these modifications in general can be grouped into five categories: (a) different forms of active zinc, (b) other metallic reagents rather than zinc, (c) combination of zinc and other chemicals, (d) different catalysts, and (e) different reaction environment. So far, because of slow initiation of zinc in the traditional Reformatsky reaction, several types of activated zincs have been used, such as acid-washed zinc,[15] sand-paper polished zinc foil,[14] finely divided metallic zinc reduced from zinc halide by alkali metal (K),[30] granular zinc in a continuous flow system,[12] sacrificial zinc anode,[9f] Et_2Zn,[9b,9c] Zn/Ag,[31] and Zn/Cu.[17b,32] In addition, other metals or their salts have been successfully used for the substitution of the zinc reagent, including cadmium,[18,33] germanium (reduced from GeX_4 or GeX_2 by K),[34] lithium,[35] magnesium,[36] $CrCl_2$,[11] and SmI_2.[37] The combinations of zinc and other chemicals include Zn/Et_3Al,[38] $Zn/CeCl_3$,[24] $Zn/B(OMe)_3$ (in THF),[17a,39] Zn/TMSCl (5–10 mol %),[16] and $Et_2Zn/RhCl(PPh_3)_3$.[10b] In addition, $NiBr_2$(bipy),[9f] $Co(PPh_3)_4$,[40] Cp_2TiX,[8] and ate-type tin complexes of $Li^+[Bu_2SnI_3]^-$/HMPA[41] have been used to mediate this reaction. Finally, this reaction has been carried out under nontraditional conditions, such as in concentrated aqueous solution without co-solvent,[42] in an agate mortar and pestle without solvent,[43] on supported solid phase,[44] in ionic liquid,[45] and by sonic[39] or high intensity ultrasound acceleration.[46] In addition, different ligands, such as cinchona alkaloids[47] and (-)-*N*,*N*-dimethylaminoisoborneol ((-)-DAIB),[9a] have been used to enhance the enantioselectivity.

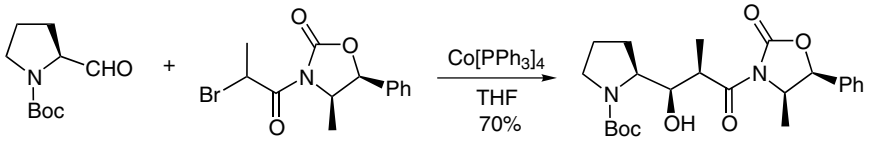
E. APPLICATIONS

This reaction has very broad applications in organic synthesis.

F. RELATED REACTIONS

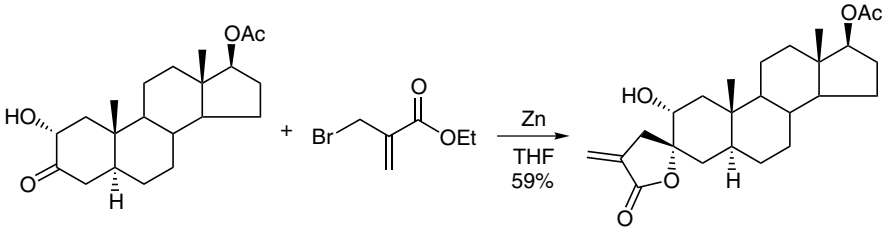
This reaction is related to the *Aldol Condensation*, *Blaise Condensation*, and *Luche Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 40.

To a solution of 0.31 g 3-(2-bromopropionyl)-4*R*-methyl-5*S*-phenyloxazolidin-2-one (1 mmol) in 5 mL anhydrous THF cooled to 0°C, was added 1 mmol $Co[PPh_3]_4$ solution dropwise over 30 min. Then 0.20 g *N*-Boc-L-prolinal (1 mmol) was added to the dark brown solution. After being stirred for 2 h, the reaction mixture was poured into cold 0.1 *N* HCl and extracted with EtOAc. Upon removal of solvent under reduced pressure, the residue was purified by flash column chromatography using hexane/EtOAc (4:1) as the eluent to afford 0.30 g (4*R*,5*S*,2′*R*,3′*R*,2″*S*)-3-[3′-(*N*-*tert*-butoxycarbonyl-2″-pyrrolidinyl)-3′-hydroxy-2′-methylpropanoyl)-4-methyl-5-phenyl-2-oxazolidinone as a colorless foam, in a yield of 70%.



Reference 9d.

To a solution of 1 mmol of *keto* steroid in 8 mL anhydrous THF under argon was added 1.2 mmol freshly activated zinc dust, and the mixture was stirred at 37°C for 15 min. Then 1.2 mmol ethyl 2-(bromomethyl)acrylate in 4 mL anhydrous THF was added, and the reaction was monitored intermittently by TLC. After being stirred at 37°C for 15 h, the reaction mixture was cooled to room temperature, and 2 mL 10% (w/v) HCl was added. After being kept at room temperature for 0.5 h, the solution was filtered and extracted with EtOAc, washed with water and brine, and dried over anhydrous Na_2SO_4. Upon removal of solvent, the residue was purified by column chromatography to afford 59% spiro-α-methylene-γ-butyrolactone, m.p. 256°C.

Other references related to the Reformatsky reaction are cited in the literature.[48]

H. REFERENCES

1. Reformatskii, S., *Ber.,* **1887**, *20*, 1210.
2. Schuetz, R. D. and Houff, W. H., *J. Am. Chem. Soc.,* **1955**, *77*, 1836.

3. (a) Shchepin, V. V.; Fotin, D. V. and Vakhrin, M. I., *Russ. J. Org. Chem.,* **2004**, *40*, 834. (b) Shchepin, V. V.; Fotin, D. V. and Shurov, S. N., *Russ. J. Org. Chem.,* **2003**, *39*, 1231. (c) Lee, P. H.; Bang, K. C.; Lee, K. Y.; Sung, S.-Y. and Chang, S. B., *Synth. Commun.,* **2001**, *31*, 3781. (d) McKinney, A. R. and Ridley, D. D., *Aust. J. Chem.,* **2001**, *54*, 757. (e) Ruggeri, R. B. and Heathcock, C. H., *Pure & Appl. Chem.,* **1989**, *61*, 289. (f) McBee, E. T.; Pierce, O. R. and Christman, D. L., *J. Am. Chem. Soc.,* **1955**, *77*, 1581. (g) Schuetz, R. D. and Houff, W. H., *J. Am. Chem. Soc.,* **1955**, *77*, 1839. (h) Dreiding, A. S. and Tomasewski, A. J., *J. Am. Chem. Soc.,* **1954**, *76*, 6388. (i) Hauser, C. R. and Puterbaugh, W. H., *J. Am. Chem. Soc.,* **1953**, *75*, 1068. (j) Dreiding, A. S. and Pratt, R. J., *J. Am. Chem. Soc.,* **1953**, *75*, 3717. (k) Drake, N. L.; Eaker, C. M. and Shenk, W., *J. Am. Chem. Soc.,* **1948**, *70*, 677. (l) Hussey, A. S. and Newman, M. S., *J. Am. Chem. Soc.,* **1948**, *70*, 3024. (m) Bloom, M. S. and Hauser, C. R., *J. Am. Chem. Soc.,* **1944**, *66*, 152. (n) Fuson, R. C. and Southwick, P. L., *J. Am. Chem. Soc.,* **1944**, *66*, 679. (o) Newman, M. S., *J. Am. Chem. Soc.,* **1942**, *64*, 2131. (p) Myers, F. J. and Lindwall, H. G., *J. Am. Chem. Soc.,* **1938**, *60*, 644. (q) Fuson, R. C. and Farlow, M. W., *J. Am. Chem. Soc.,* **1934**, *56*, 1593.

4. (a) Yu, L.-T.; Ho, M.-T.; Chang, C.-Y. and Yang, T.-K., *Tetrahedron: Asymmetry*, **2007**, *18*, 949. (b) Cozzi, P. G., *Angew. Chem. Int. Ed.,* **2007**, *46*, 2568. (c) Lombardo, M.; Gualandi, A.; Pasi, F. and Trombini, C., *Adv. Synth. Catal.,* **2007**, *349*, 465. (d) Shchepin, V. V.; Stepanyan, Y. G.; Silaichev, P. S.; Russkikh, N. U.; Shnurov, S. N. and Rakitin, A. R., *Russ. J. Gen. Chem.,* **2006**, *76*, 1804. (e) Shchepin, V. V.; Kirillov, N. F. and Melekhin, V. S., *Russ. J. Org. Chem.,* **2006**, *42*, 1486. (f) Cozzi, P. G., *Adv. Synth. Catal.,* **2006**, *348*, 2075. (g) Shchepin, V. V.; Kirillov, N. F.; Melekhin, V. S. and Vakhrin, M. I., *Russ. J. Gen. Chem.,* **2006**, *76*, 1421. (h) Shchepin, V. V.; Kirillov, N. F.; Vakhrin, M. I.; Bayanova, O. B.; Shurov, S. N. and Silaichev, P. S., *Russ. J. Gen. Chem.,* **2006**, *76*, 1146. (i) Babu, S. A.; Yasuda, M.; Okabe, Y.; Shibata, I. and Baba, A., *Org. Lett.,* **2006**, *8*, 3029. (j) Cozzi, P. G. and Rivalta, E., *Pure & Appl. Chem.,* **2006**, *78*, 287. (k) Ribeiro, C. M. R. and Cordeiro de Farias, F. M., *Mini-Rev. Org. Chem.,* **2006**, *3*, 1. (l) Schepin, V. V. and Silaychev, P. S., *Chem. Heterocycl. Compd.,* **2005**, *41*, 1545. (m) Dondoni, A.; Massi, A. and Sabbatini, S., *Chem. Eur. J.,* **2005**, *11*, 7110. (n) Cozzi, P. G. and Rivalta, E., *Angew. Chem. Int. Ed.,* **2005**, *44*, 3600. (o) Cao, Y.-Y.; Yang, R.-S.; Bai, D.-H.; He, S.-L.; Zhao, Y.; Yang, E.-C. and Hao, J.-K., *Huaxue Shiji,* **2005**, *27*, 79. (p) Orsini, F. and Lucci, E. M., *Tetrahedron Lett*., **2005**, *46*, 1909. (q) Shchepin, V. V.; Korzun, A. E. and Sazhneva, Y. K., *Russ. J. Org. Chem.,* **2004**, *40*, 1500. (r) Shchepin, V. V.; Fotin, D. V.; Fotin, V. V. and Vakhrin, M. I., *Russ. J. Org. Chem.,* **2004**, *40*, 892. (s) Gurjar, M. K.; Reddy, D. S.; Bhadbhade, M. M. and Gonnade, R. G., *Tetrahedron*, **2004**, *60*, 10269. (t) Chavan, S. P.; Shivasankar, K. and Sivappa, R., *J. Chem. Res.,* **2004**, 406. (u) Inagaki, H.; Sugita, K.; Miyauchi, R. N.; Miyauchi, S.; Takeda, T.; Itoh, M.; Takahashi, H. and Takemura, M., *ARKIVOC,* **2003**, (*viii*), 112.

5. (a) Schwarz, K. H.; Kleiner, K.; Ludwig, R. and Schick, H., *J. Org. Chem.,* **1992**, *57*, 4013. (b) Molander, G. A.; Etter, J. B.; Harring, L. S. and Thorel, P. J., *J. Am. Chem. Soc.,* **1991**, *113*, 8036. (c) Datta, A.; Ila, H. and Junjappa, H., *J. Org. Chem.,* **1990**, *55*, 6231. (d) Datta, A.; Ila, H. and Junjappa, H., *J. Org. Chem.,* **1990**, *55*, 5589. (e) Fukuzawa, S.; Sumimoto, N.; Fujinami, T. and Sakai, S., *J. Org. Chem.,* **1990**, *55*, 1628. (f) Palomo, C.; Cossio, F. P.; Arrieta, A.; Odriozola, J. M.; Oiarbide, M. and Ontoria, J. M., *J. Org. Chem.,* **1989**, *54*, 5736. (g) Ruggeri, R. B. and Heathcock, C. H., *J. Org. Chem.,* **1987**, *52*, 5745. (h) Dewar, M. J. S. and Merz, K. M., *J. Am. Chem. Soc.,* **1987**, *109*, 76553. (i) Molander, G. A. and Etter, J. B., *J. Am. Chem. Soc.,* **1987**, *109*, 6556. (j) Oshino, H.; Nakamura, E. and Kuwajima, I., *J. Org. Chem.,* **1985**, *50*, 2802. (k) Rice, L. E.; Boston, M. C.; Finklea, H. O.; Suder, B. J.; Frazier, J. O. and Hudlicky, T., *J. Org. Chem.,* **1984**, *49*, 1845. (l) Plattner, J. J.; Gawronska, E. and Rinehart, K. L., *J. Org. Chem.,* **1982**, *47*, 3440. (m) Kamernitskii, A. V.; Krivoruchko, V. A.; Litvinovskaya, R. P. and Reshetova, I. G., *Russ. Chem. Bull.,* **1975**, *24*, 1954. (n) Klimova, L. I.; Malanina, G. G. and Suvorov, N. N., *Chem. Heterocycl. Compd.,* **1971**, *7*, 998.

6. (a) Cozzi, P. G., *Angew. Chem. Int. Ed.,* **2006**, *45*, 2951. (b) Shchepin, V. V.; Silaychev, P. S. and Stepanyan, Y. G., *Chem. Heterocycl. Compd.,* **2005**, *41*, 794. (c) Shchepin, V. V. and Fotin, D. V.,

Russ. J. Org. Chem., **2005**, *41*, 1011. (d) Shchepin, V. V.; Fotin, D. V.; Vakhrin, M. I. and Shurov, S. N., *Russ. J. Gen. Chem.,* **2004**, *74*, 1406. (e) Sorochinsky, A.; Voloshin, N.; Markovsky, A.; Belik, M.; Yasuda, N.; Uekusa, H.; Ono, T.; Berbasov, D. O. and Soloshonok, V. A., *J. Org. Chem.,* **2003**, *68*, 7448. (f) Fujiwara, Y.; Katagiri, T. and Uneyama, K., *Tetrahedron Lett*., **2003**, *44*, 6161. (g) Shchepin, V. V. and Fotin, D. V., *Chem. Heterocycl. Compd.,* **2002**, *38*, 1430. (h) Medebielle, M.; Onomura, O.; Keirouz, R.; Okada, E.; Yano, H. and Terauchi, T., *Synthesis*, **2002**, 2601. (i) Kanai, K.; Wakabayashi, H. and Honda, T., *Heterocycles*, **2002**, *58*, 47. (j) Bang, K.; Lee, K.; Park, Y. K. and Lee, P. H., *Bull. Korean Chem. Soc.,* **2002**, *23*, 1272. (k) Chung, W. J.; Higashiya, S. and Welch, J. T., *J. Fluor. Chem.,* **2001**, *112*, 343. (l) Michael, J. P.; de Koning, C. B.; Hosken, G. D. and Stanbury, T. V., *Tetrahedron*, **2001**, *57*, 9635. (m) Chattopadhyay, A. and Salaskar, A., *Synthesis*, **2000**, 561. (n) Kagoshima, H.; Hashimoto, Y. and Saigo, K., *Tetrahedron Lett*., **1998**, *39*, 8465. (o) Coe, P. L.; Lohr, M. and Rochin, C., *J. Chem. Soc., Perkin Trans. I,* **1998**, 2803. (p) Mi, A.-Q.; Wang, Z.-Y.; Zhang, X.-M.; Fu, F.-M. and Jiang, Y.-Z., *Huaxue Xuebao*, **1998**, *56*, 719. (q) Inoue, S.; Iwabuchi, Y.; Irie, H. and Hatakeyama, S., *Synlett,* **1998**, 735. (r) Wessjohann, L. and Wild, H., *Synlett*, **1997**, 731. (s) Gabriel, T. and Wessjohann, L., *Tetrahedron Lett*., **1997**, *38*, 4387. (t) Wessjohann, L. and Wild, H., *Synthesis*, **1997**, 512. (u) Mi, A. Q.; Zhang, X. M. and Wang, Z. Y., *Hecheng Huaxue*, **1996**, *4*, 317. (v) Andres, J. M.; Martinez, M. A.; Pedrosa, R. and Perez-Encabo, A., *Synthesis*, **1996**, 1070. (w) Shankar, B. B.; Kirkup, M. P.; McCombie, S. W.; Clader, J. W. and Ganguly, A. K., *Tetrahedron Lett*., **1996**, *37*, 4095. (x) Mastantuono, A.; Pini, D.; Rolfini, C. and Salvadori, P., *Chirality*, **1995**, *7*, 499.

7. (a) Baldoli, C.; Del Buttero, P.; Licandro, E.; Papagni, A. and Pilati, T., *Tetrahedron*, **1996**, *52*, 4849. (b) Buechi, G. and Wuest, H., *J. Am. Chem. Soc.,* **1965**, *87*, 1589. (c) Lasslo, A. and Webster, G. L., *J. Am. Chem. Soc.,* **1953**, *75*, 5980. (d) Lipkin, D. and Stewart, T. D., *J. Am. Chem. Soc.,* **1939**, *61*, 3295. (e) Fuson, R. C.; Arnold, R. T. and Cooke, H. G., *J. Am. Chem. Soc.,* **1938**, *60*, 2272.
8. Parrish, J. D.; Shelton, D. R. and Little, R. D., *Org. Lett.,* **2003**, *5*, 3615.
9. (a) Kloetzing, R. J.; Thaler, T. and Knochel, P., *Org. Lett.,* **2006**, *8*, 1125. (b) Laroche, M.-F.; Belotti, D. and Cossy, J., *Org. Lett.,* **2005**, *7*, 171. (c) Adrian, J. C. and Snapper, M. L., *J. Org. Chem.,* **2003**, *68*, 2143. (d) Sawant, M. S.; Katoch, R.; Trivedi, G. K. and Desai, U. R., *J. Chem. Soc., Perkin Trans. I,* **1998**, 843. (e) Katritzaky, A. R.; Hong, Q. M. and Yang, Z. J., *J. Org. Chem.*, **1995**, *60*, 3405. (f) Conan, A.; Sibille, S.; Périchon, J., *J. Org. Chem.,* **1991**, *56*, 2018. (g) Dekker, J.; Budzelaar, P. H. M.; Boersma, J.; van der Kerk, G. J. M. and Spek, A. L., *Organometallics,* **1984**, *3*, 1403. (h) Vaughan, W. R. and Knoess, H. P., *J. Org. Chem.,* **1970**, *35*, 2394. (i) Vaughan, W. R.; Bernstein, S. C. and Lorber, M. E., *J. Org. Chem.,* **1965**, *30*, 1790.
10. (a) Babu, S. A.; Yasuda, M.; Shibata, I. and Baba, A., *J. Org. Chem.,* **2005**, *70*, 10408. (b) Kanai, K.; Wakabayashi, H. and Honda, T., *Org. Lett.,* **2000**, *2*, 2549.
11. Wessjohann, L. and Gabriel, T., *J. Org. Chem.,* **1997**, *62*, 3772.
12. Ruppert, J. F. and White, J. D., *J. Org. Chem.,* **1974**, *39*, 269.
13. Zhao, M.-X.; Wang, M.-X.; Yu, C.-Y.; Huang, Z.-T. and Fleet, G. W. J., *J. Org. Chem.,* **2004**, *69*, 997.
14. Natelson, S. and Gottfried, S. P., *J. Am. Chem. Soc.,* **1939**, *61*, 970.
15. Frankenfeld, J. W. and Werner, J. J., *J. Org. Chem.,* **1969**, *34*, 3689.
16. Picotin, G. and Miginiac, P., *J. Org. Chem.,* **1987**, *52*, 4796.
17. (a) Rathke, M. W. and Lindert, A., *J. Org. Chem.,* **1970**, *35*, 3966. (b) Nieuwland, J. A. and Daly, S. F., *J. Am. Chem. Soc.,* **1931**, *53*, 1842.
18. Cason, J. and Fessenden, R. J., *J. Org. Chem.,* **1957**, *22*, 1326.
19. Newman, M. S. and Evans, F. J., *J. Am. Chem. Soc.,* **1955**, *77*, 946.
20. Gilman, H. and Speeter, M., *J. Am. Chem. Soc.,* **1943**, *65*, 2255.
21. Bayless, P. L. and Hauser, C. R., *J. Am. Chem. Soc.,* **1954**, *76*, 2306.

22. Kashima, C.; Huang, X. C.; Harada, Y. and Hosomi, A., *J. Org. Chem.,* **1993**, *58*, 793.
23. Torabi, H.; Evans, R. L. and Stavely, H. E., *J. Org. Chem.,* **1969**, *34*, 3792.
24. Ocampo, R.; Dolbier, W. R.; Abboud, K. A. and Zuluaga, F., *J. Org. Chem.,* **2002**, *67*, 72.
25. Curran, T. T., *J. Org. Chem.,* **1993**, *58*, 6360.
26. Wedler, C.; Ludwig, R. and Schick, H., *Pure & Appl. Chem.,* **1997**, *69*, 605.
27. (a) Schick, H.; Ludwig, R.; Schwarz, K.-H.; Kleiner, K. and Kunath, A., *J. Org. Chem.,* **1994**, *59*, 3161. (b) Johnson, P. Y. and Zitsman, J., *J. Org. Chem.,* **1973**, *38*, 2346.
28. (a) Fan, R. L. and Hudlicky, T., *Tetrahedron Lett.,* **1989**, *30*, 5533. (b) Hudlicky, T.; Radesca, L. and Rigby, H. L., *J. Org. Chem.,* **1987**, *52*, 4397. (c) Hudlicky, T.; Natchus, M. G.; Kwart, L. D. and Colwell, B. L., *J. Org. Chem.,* **1985**, *50*, 4300.
29. (a) Ocampo, R. and Dolbier, W. J., *Tetrahedron,* **2004**, *60*, 9325. (b) Orsini, F. and Sello, G., *Curr. Org. Synth*., **2004**, *1*, 111. (c) Rathke, M. W. and Weipert, P., *Comp. Org. Synth.,* **1991**, *2*, 277. (d) Fürstner, A., *Synthesis,* **1989**, 571. (e) Rathke, M. W., *Org. React.,* **1975**, *22*, 423. (f) Gaudemar, M., *Organometal. Chem. Rev. A,* **1972**, *8*, 183. (g) Diaper, D. G. M. and Kukis, A., *Chem. Rev.,* **1959**, *59*, 89. (h) Shriner, R. L., *Org. React.,* **1942**, *1*, 1.
30. (a) Rieke, R. D.; Li, P. T.; Burns, T. P. and Uhm, S. J., *J. Org. Chem.,* **1981**, *46*, 4323. (b) Chao, L. C. and Rieke, R. D., *J. Org. Chem.,* **1975**, *40*, 2253. (c) Rieke, R. D. and Uhm, S. J., *Synthesis,* **1975**, 452. (d) Rieke, R. D.; Uhm, S. J. and Hudnall, P. M., *J. Chem. Soc., Chem. Commun.,* **1973**, 269.
31. Bortolussi, M. and Seyden-Penne, J., *Synth. Commun.,* **1989**, *19*, 2355.
32. (a) Mylari, B. L. and Zembrowski, W. J., *J. Org. Chem.,* **1991**, *56*, 2587. (b) Santaniello, E. and Manzocchi, A., *Synthesis,* **1977**, 698.
33. Burkhardt, E. R. and Rieke, R. D., *J. Org. Chem.,* **1985**, *50*, 416.
34. Kagoshima, H.; Hashimoto, Y.; Oguro, D. and Saigo, K., *J. Org. Chem.,* **1998**, *63*, 691.
35. Villieras, J.; Perriot, P.; Bourgain, M. and Normant, J. F., *J. Organomet. Chem*., **1975**, *102*, 129.
36. (a) Borno, A. and Bigley, D. B., *J. Chem. Soc., Perkin Trans. II,* **1983**, 1311. (b) Moriwake, T., *J. Org. Chem.,* **1966**, *31*, 983.
37. (a) Obringer, M.; Colobert, F.; Neugnot, B. and Solladié, G., *Org. Lett.,* **2003**, *5*, 629. (b) Reddy, P. P.; Yen, K.-F. and Uang, B.-J., *J. Org. Chem.,* **2002**, *67*, 1034. (c) Fukuzawa, S.-i.; Matsuzawa, H. and Yoshimitsu, S.-I., *J. Org. Chem.,* **2000**, *65*, 1702. (d) Ichikawa, S.; Shuto, S.; Minakawa, N. and Matsuda, A., *J. Org. Chem.,* **1997**, *62*, 1368.
38. Shimada, T.; Yoshioka, M.; Konno, T. and Ishihara, T., *Org. Lett.,* **2006**, *8*, 1129.
39. Han, B.-H. and Boudjouk, P., *J. Org. Chem.,* **1982**, *47*, 5030.
40. Pettit, G. R. and Grealish, M. P., *J. Org. Chem.,* **2001**, *66*, 8640.
41. Shibata, I.; Suwa, T.; Sakakibara, H. and Baba, A., *Org. Lett.,* **2002**, *4*, 301.
42. Bieber, L. W.; Malvestiti, I. and Storch, E. C., *J. Org. Chem.,* **1997**, *62*, 9061.
43. Tanaka, K.; Kishigami, S. and Toda, F., *J. Org. Chem.,* **1991**, *56*, 4333.
44. Vidal, A.; Nefzi, A. and Houghten, R. A., *J. Org. Chem.,* **2001**, *66*, 8268.
45. Zhao, D. B.; Wu, M.; Kou, Y. and Min, E. Z., *Catalysis Today,* **2002**, *74*, 157.
46. Ross, N. A. and Bartsch, R. A., *J. Org. Chem.,* **2003**, *68*, 360.
47. Ojida, A.; Yamano, T.; Taya, N. and Tasaka, A., *Org. Lett.,* **2002**, *4*, 3051.
48. (a) Moumne, R.; Lavielle, S. and Karoyan, P., *J. Org. Chem.*, **2006**, *71*, 3332. (b) Huguenot, F. and Brigaud, T., *J. Org. Chem.,* **2006**, *71*, 2159. (c) Pan, Y. J.; Homles, C. P. and Tumelty, D., *J. Org. Chem.,* **2005**, *70*, 4897. (d) Scherkenbeck, T. and Siegel, K., *Org. Proc. Res. Dev.,* **2005**, *9*, 216. (e) Emmerson, D. P. G.; Hems, W. P. and Davis, B. G., *Tetrahedron: Asymmetry,* **2005**, *16*, 213. (f) Babu, S. A.; Yasuda, M.; Shibata, I. and Baba, A., *Org. Lett.,* **2004**, *6*, 4475. (g) Clark, J. D.; Weisenburger, G. A.; Anderson, D. K.; Colson, P.-J.; Edney, A. D.; Gallagher, D. J.; Kleine, H. P.; Knable, C. M.; Lantz, M. K.; Moore, C. M. V.; Murphy, J. B.; Rogers, T. E.; Ruminski, P. G.; Shah,

A. S.; Storer, N. and Wise, B. E., *Org. Proc. Res. Dev.,* **2004**, *8*, 51. (h) Molander, G. A.; Brown, G. A. and de Gracia, I. S., *J. Org. Chem.,* **2002**, *67*, 3459. (i) Kovács, L., *Molecules,* **2000**, *5*, 127. (j) Vedejs, E. and Duncan, S. M., *J. Org. Chem.,* **2000**, *65*, 6073. (k) Sawant, M. S.; Nadkarni, P. J.; Desai, U. R.; Katoch, R.; Korde, S. S. and Trivedi, G. K., *J. Chem. Soc*., *Perkin Trans. I*, **1999**, 2537. (l) Marcotte, S.; Pannecoucke, X.; Feasson, C. and Quirion, J.-C., *J. Org. Chem.,* **1999**, *64*, 8461. (m) Andrés, J. M.; Martín, Y.; Pedrosa, R. and Pérez-Encabo, A. *Tetrahedron,* **1997**, *53*, 3787. (n) Mi, A.; Wang, Z.; Zhang, J. and Jiang, Y., *Synth. Commun.,* **1997**, *27*, 1469. (o) Dutta, L. N.; Bhattacharyya, M. and Sarkar, A. K., *Can. J. Chem.,* **1995**, *73*, 1556. (p) Hansen, M. M.; Bartlett, P. A. and Heathcock, C. H., *Organometallics*, **1987**, *6*, 2069. (q) Liu, W.-S. and Glover, G. I., *J. Org. Chem.,* **1978**, *43*, 754. (r) Gedye, R. N.; Arora, P. and Khalil, A. H., *Can. J. Chem.,* **1975**, *53*, 1943. (s) Ziegler, F. E. and Condon, M. E., *J. Org. Chem.,* **1971**, *36*, 3707. (t) Torabi, H.; Evans, R. L. and Stavely, H. E., *J. Org. Chem.,* **1969**, *34*, 3796. (u) Piper, J. R. and Stevens, F. J., *J. Org. Chem.,* **1962**, *27*, 3134. (v) Klemm, L. H. and Bower, G. M., *J. Org. Chem.,* **1958**, *23*, 344. (w) Zimmerman, H. E. and Traxler, M. D., *J. Am. Chem. Soc.,* **1957**, *79*, 1920. (x) Pretka, J. E. and Lindwall, H. G., *J. Org. Chem.,* **1954**, *19*, 1080. (y) Fuson, R. C. and Thomas, N., *J. Org. Chem.,* **1953**, *16*, 1762. (z) Dauben, W. G. and Teranishi, R., *J. Org. Chem.,* **1951**, *16*, 550. (aa) Miller, R. E. and Nord, F. F., *J. Org. Chem.,* **1951**, *16*, 728. (bb) Miller, R. E. and Nord, F. F., *J. Org. Chem.,* **1950**, *15*, 89. (cc) Oroshnik, W. and Spoerri, P. E., *J. Am. Chem. Soc.,* **1945**, *67*, 721. (dd) Johnson, T. B., *J. Am. Chem. Soc.,* **1913**, *35*, 582. (ee) Reformatsky, S., *J. Prakt. Chem.,* **1896**, *54*, 469. (ff) Reformatsky, S., *J. Chem. Soc.,* **1896**, *70*, 126. (gg) Reformatskii, S., *J. Russ. Phys. Chem. Soc.,* **1890**, *22*, 44.

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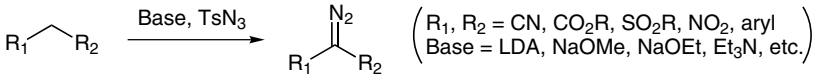
Regitz Diazo Transfer

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Regitz in 1967.[1] It is a base-promoted transfer of a diazo group from an azide to an active methyl or methylene moiety of a substrate with one or more electron-withdrawing groups. Therefore, it is known as the Regitz diazo transfer.[2] The azides developed for this reaction include the most commonly used toluenesulfonyl azide (tosyl azide, TsN_3),[1,2b,3] and others such as *p*-acetamidobenzenesulfonyl azide,[4] 2,4,6-triisopropylbenzenesulfonyl azide (trisyl azide),[3a,5] 4-nitrobenzenesulfonyl azide (PNBSA),[6] methanesulfonyl azide (mesyl azide),[7] *p*-carboxybenzenesulfonyl azide,[8] trifluoromethanesulfonyl azide,[9] 2-azido-3-ethylbenzenethiazolium tetrafluoroborate,[10] 1-ethyl-2-azidopyridinium tetrafluoroborate,[10] (azidochloromethylene)-dimethylammonium chloride,[11] naphthalene-2-sulfonyl azide,[12] *p*-(*n*-dodecyl)benzenesulfonyl azide,[12] diphenyl phosphorazindaze,[13] *p*-nitrophenyl azide,[14] and polystyrene benzenesulfonyl azide.[15] The active methyl or methylene group adjacent to a single electron-withdrawing group is often activated by acylation before the diazotization, followed by deacylation.[6,16] It is worth noting that this reaction has some intrinsic drawbacks such as the azo coupling of the diazo compound with the starting material,[15] the unpredictable transfer of the azido group,[3a] and the difficulty in separation of the excess reagent and *p*-toluenesulfonamide.[7] For example, trisyl azide is superior to TsN_3 during the diazotization of cyclic ketone but predominantly transfers an azido group to the acyclic imide and ester enolate.[17]

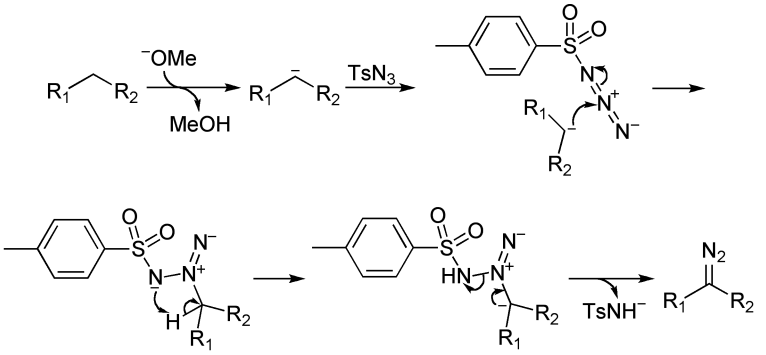
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME

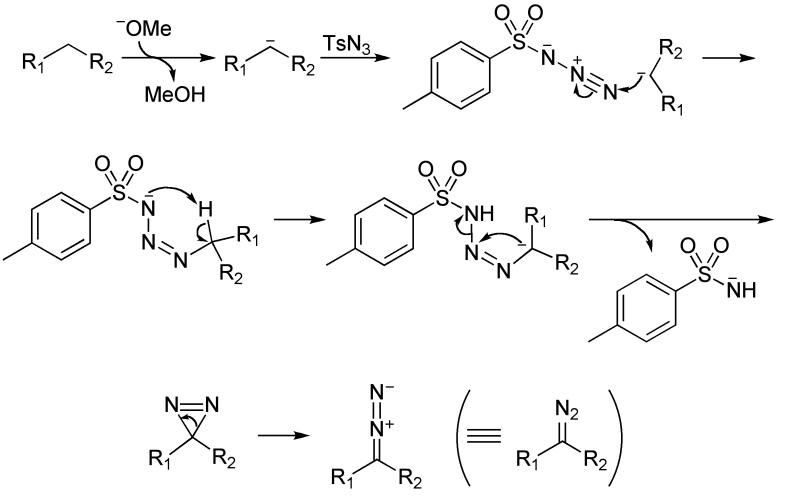


C. PROPOSED MECHANISMS

Two tentative mechanisms are proposed here for the reaction of TsN_3, where the attack of the generated carbanion at the middle nitrogen of TsN_3 is displayed in Scheme 1, and the attack of the carbanion at the terminal nitrogen of TsN_3 is shown in Scheme 2.



SCHEME 1. *Carbanion attack at the middle nitrogen.*



SCHEME 2. *Carbanion attack at the terminal nitrogen.*

D. MODIFICATION

This reaction has been extensively modified using different diazo sources.

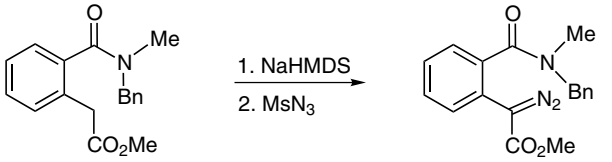
E. APPLICATIONS

This reaction has general applications in organic synthesis, especially for the *1,3-Dipolar Cycloaddition* of diazo compounds.

F. RELATED REACTIONS

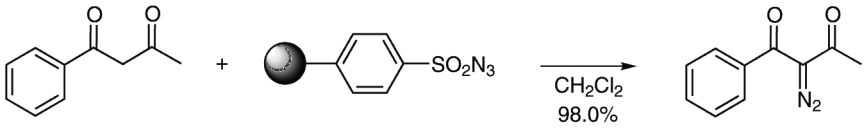
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 18.

To a stirred solution of 0.5 g methyl 2-benzylmethylcarbamoyl phenylacetate (1.6 mmol) in 15 mL THF at −78°C, was added 1.9 mL 1.0 M sodium bis(trimethylsilyl)amide in THF dropwise over a 20 min period. The mixture was stirred at −78°C for 1 h, and 0.2 mL mesyl azide in 1 mL THF was added in one portion. The resulting solution was stirred at −78°C for 2 h, warmed to room temperature, and stirred for an additional 2 h. The mixture was quenched with 30 mL phosphate buffer (pH = 7.0) and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. Upon removal of solvent, the residue was purified by flash chromatography to afford 0.3 g methyl [2-(benzylmethylcarbamoyl)-phenyl]diazoacetate as a pale yellow oil, in a yield of 63%.



Reference 15.

To a 5.0-mL disposable polypropylene/polyethylene syringe was added 500 mg polystyrene benzenesulfonyl azide (0.75 mmol) that was swollen with CH_2Cl_2. A mixture of 81.0 mg 1-benzoylacetone (0.5 mmol) and 0.21 mL Et_3N (1.5 mmol) in 2.0 mL CH_2Cl_2 was drawn into the syringe. Then the syringe was fixed on a LabQuake shaker and rotated at room temperature. The reaction was monitored by TLC (1:1, Et_2O/heptane). After 4 h, the supernatant was collected, and the resin was washed with CH_2Cl_2 (3 × 5 mL). The washes were combined with the supernatant and concentrated to give a pale yellow solid, which was purified by short silica gel column chromatography using heptane/Et_2O as the eluent to afford 92.0 mg 2-diazo-1-phenyl-butane-1,3-dione, in a yield of 98%, m.p. 60–61°C.

Other references related to the Regitz diazo transfer are cited in the literature.[19]

H. REFERENCES

1. Regitz, M., *Angew. Chem. Int. Ed. Engl.,* **1967**, *6*, 733.
2. (a) Bocknack, B. M., *Electrophilic Trapping of Enolates in Tandem Reaction Processes and (1,3-Diketonato)metal Templates for Asymmetric Catalysis*, Ph.D. dissertation, University of Texas at Austin, **2004**. (b) Happer, D. A. R.; Hayman, C. M.; Storer, M. K. and Lever, M., *Aust. J. Chem.,* **2004**, *57*, 467.
3. (a) Benati, L.; Nanni, D. and Spagnolo, P., *J. Org. Chem.,* **1999**, *64*, 5132. (b) Benati, L.; Calestani, G.; Montevecchi, P. C. and Spagnolo, P., *J. Chem. Soc., Perkin Trans. I,* **1995**, 1381. (c) Benati, L.; Calestani, G.; Montevecchi, P. C. and Spagnolo, P., *J. Chem. Soc., Perkin Trans. I,* **1994**, 2637. (d) Benati, L.; Montevecchi, P. C.; Spagnolo, P. and Foresti, E., *J. Chem. Soc., Perkin Trans. I,* **1992**, 2845.
4. Baum, J. S.; Shook, D. A.; Davies, H. M. L. and Smith, H. D., *Synth. Commun*., **1987**, *17*, 1709.
5. Lombardo, L. and Mander, L. N., *Synthesis,* **1980**, 368.
6. Benati, L.; Calestani, G.; Nanni, D. and Spagnolo, P., *J. Org. Chem*., **1998**, *63*, 4679.
7. Taber, D. F.; Ruckle, R. E. and Hennessy, M. J., *J. Org. Chem.,* **1986**, *51*, 4077.
8. Doyle, M. P.; Dorow, R. L.; Terpstra, J. W. and Rodenhouse, R. A., *J. Org. Chem.,* **1985**, *50*, 1663.
9. Cavender, C. J. and Shiner, V. J., *J. Org. Chem.,* **1972**, *37*, 3567.
10. Balli, H.; Low, R.; Muller, V.; Rempfler, H. and Sezen-Gezgin, G., *Helv. Chim. Acta,* **1978**, *61*, 97.
11. Kikel, B. and Viehe, H. G., *Angew. Chem.,* **1980**, *92*, 754.
12. Hazen, G. G.; Weinstock, L. M.; Connell, R. and Bollinger, F. W., *Synth. Commun.,* **1981**, *11*, 947.
13. Diphen: Mori, S.; Sakai, I.; Aoyama, T. and Shioini, T., *Chem. Pharm. Bull.,* **1982**, *30*, 3380.
14. Nitro: Herbranson, D. E. and Hawley, M. D., *J. Electroanal. Chem.,* **1983**, *144*, 423.
15. Green, G. M.; Peet, N. P. and Metz, W. A., *J. Org. Chem.,* **2001**, *66*, 2509.
16. (a) Doyle, M. P.; McKervey, M. A. and Ye, T., *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley-Interscience, New York, **1998**, chap. 1. (b) Ye, T. and McKervey, M. A., C*hem. Rev*., **1994**, *94*, 1091. (c) Regitz, M. and Maas, G., *Diazo Compounds*: *Properties and Synthesis*, Academic Press, New York, **1986**, chap. 13.
17. Evans, D. A.; Britton, T. C.; Ellman, J. A. and Dorow, R. L., *J. Am. Chem. Soc*., **1990**, *112*, 4011.
18. Padwa, A.; Beall, L. S.; Eidell, C. K. and Worsencroft, K. J., *J. Org. Chem.,* **2001**, *66*, 2414.
19. (a) Padwa, A.; Sheehan, S. M. and Straub, C. S., *J. Org. Chem.,* **1999**, *64*, 8648. (b) Williams, W.; Sun, X. and Jebaratnam, D., *J. Org. Chem.,* **1997**, *62*, 4364. (c) Benati, L.; Nanni, D. and Spagnolo, P., *J. Chem. Soc., Perkin Trans. I,* **1997**, 457. (d) Danheiser, R. L.; Miller, R. F. and Brisbois, R. G., *Org. Synth*., **1996**, *73*, 134. (e) Taber, D. F.; Gleeve, D. M.; Herr, R. J.; Moody, K. and Hennessy, M. J., *J. Org. Chem.,* **1995**, *60*, 2283. (f) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G. and Park, S. Z., *J. Org. Chem.,* **1990**, *55*, 1959. (g) Scriven, E. F. V. and Turnbull, K., *Chem. Rev.,* **1988**, *88*, 297. (h) Taber, D. F. and Schuchardt, J. L., *J. Am. Chem. Soc.,* **1985**, *107*, 5289. (i) Hudlicky, T.; Govindan, S. V. and Frazier, J. O., *J. Org. Chem.,* **1985**, *50*, 4166. (j) Chen, E. Y., *J. Org. Chem.,* **1984**, *49*, 3245. (k) Adams, J. L. and Metcalf, B. W., *Tetrahedron Lett.,* **1984**, *25*, 919. (l) Cecconi, F.; Ghilardi, C. A.; Midollini, S. and Orlandini, A., *Angew. Chem. Int. Ed. Engl.,* **1983**, *22*, 554. (m) Crow, W. D.; Gosney, I. and Ormiston, R. A., *J. Chem. Soc., Chem. Commun.,* **1983**, 643. (n) Cohen, H. and Benezra, C., *Can. J. Chem.,* **1974**, *52*, 66. (o) Regitz, M.; Hocker, J. and Liedhegener, A., *Org. Synth. Coll.,* **1973**, *5*, 179. (p) Sherer, H.; Hartmann, A.; Regitz, M.; Tunggal, B. D. and Tunther, H., *Ber.,* **1972**, *105*, 3357. (q) Regitz, M., *Org. Synth.,* **1971**, *51*, 86. (r) Hendrickson, J. B. and Wolff, W. A., *J. Org. Chem.,* **1968**, *33*, 3610. (s) Regitz, M. and Menz, F., *Ber.,* **1968**, *101*, 2622. (t) Regitz, M.; Anschütz, W. and Liedhegener, A., *Ber.,* **1968**, *101*, 3734.

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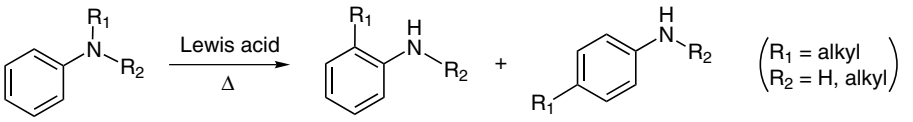
Reilly-Rickinbottom Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Reilly and Hickinbottom in 1920.[1] It is a Lewis acid-promoted thermal rearrangement of an *N*-alkyl aniline into an aryl-substituted aniline through the migration of an alkyl group from the nitrogen atom to the aromatic nucleus and is known as the Reilly-Hickinbottom rearrangement.[2] This reaction has been shown to be intermolecular, not intramolecular.[2b] It is the natural extension of the *Hofmann-Martius Rearrangement*,[2c] and usually yields predominantly *para*-alkylated aromatic amine derivatives without formation of alkyl halides.[2c] In addition, it often gives a higher yield of alkylated product when $ZnCl_2$ is used as catalyst.[2c] The only known exception is the $CoCl_2$-catalyzed rearrangement of *N*-benzylaniline, which gives an appreciable amount of the *ortho* isomer.[3] Sometimes, the multi-alkylated products are also formed in this rearrangement.[4]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A mechanism catalyzed by $ZnCl_2$ involving a carbocation is outlined here. It is possible that the *p*-alkylated aromatic amines are at least partially generated from further migration

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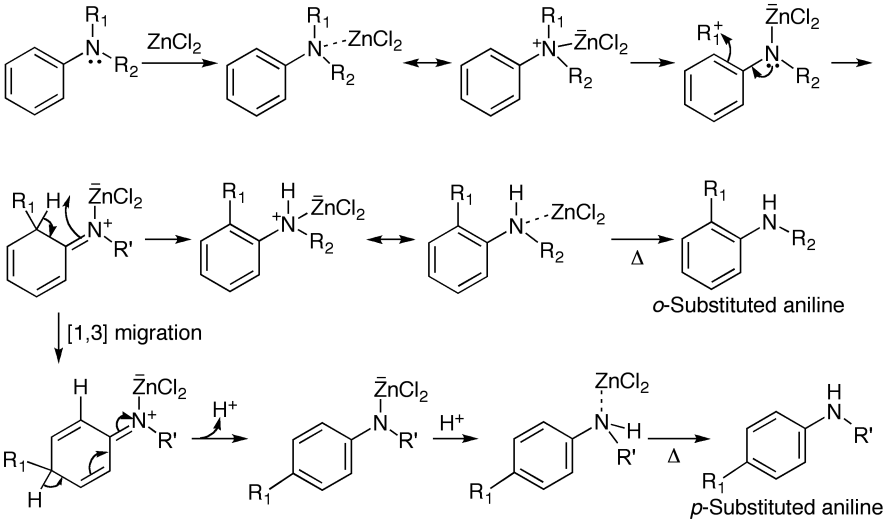
of the alkyl group of *o*-alkylated aromatic amines in the presence of a Lewis acid, resulting in both higher yield and higher ratio of *p*- to *o*-alkylated aromatic amines.



D. MODIFICATION

N/A

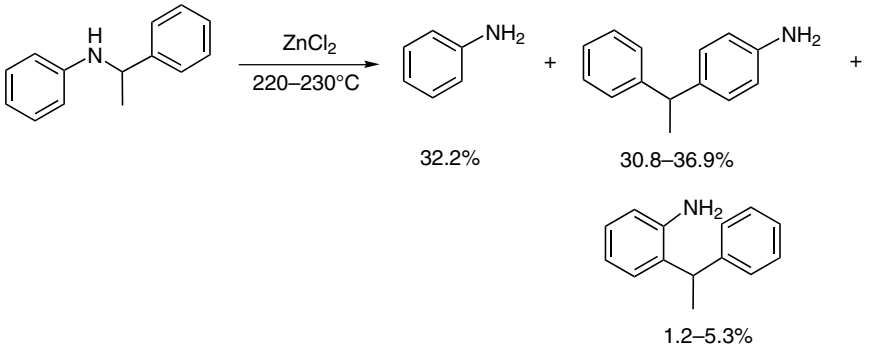
E. APPLICATIONS

This reaction has general application in the preparation of alkyl substituted aryl amines.

F. RELATED REACTIONS

This reaction is related to the *Hofmann-Martius Rearrangement.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 2c.

A mixture of 19.7 g *N*-α-phenylethyl aniline (0.1 mol) and 13.6 g anhydrous $ZnCl_2$ (0.1 mol) was heated in a sealed Pyrex tube at 220–230°C for 6 h. The cooled contents of the tube were digested on the steam bath with 100 mL 10% NaOH, and the resulting mixture was extracted with Et_2O (3 × 100 mL). Then the combined Et_2O layer was extracted with 6 *N* HCl (4 × 100 mL), and the combined aqueous solution was neutralized with 5% NaOH. After that, the aqueous solution was extracted with benzene, dried over K_2CO_3, concentrated, and distilled to afford 3.6 g aniline, 6.8 g (41%) of a mixture of *p*-α-phenylethyl aniline (in a ratio of 75–90%) and *o*-α-phenylethyl aniline (in a ratio of 3–13%), and 2.0 g of a higher boiling product. The acid-insoluble fraction gave 2.0 g polymer.

Other references related to the Reilly-Hickinbottom rearrangement are cited in the literature.[5]

H. REFERENCES

1. Reilly, J. and Hickinbottom, W. J., *J. Chem. Soc.,* **1920**, *117*, 103.
2. (a) Rhee, E. S. and Shine, H. J., *J. Am. Chem. Soc.,* **1986**, *108*, 1000. (b) Wright, G. E., *J. Org. Chem.,* **1980**, *45*, 3128. (c) Hart, H. and Kosak, J. R., *J. Org. Chem.,* **1962**, *27*, 116.
3. Hickinbottom, W. J., *J. Chem. Soc.,* **1937**, 1119.
4. Hill, A. G. and Hill, A. J., *Ind. Eng. Chem.,* **1951**, *43*, 1583.
5. (a) Truce, W. E.; Ray, W. J.; Norman, O. L. and Eickemeyer, D. B., *J. Am. Chem. Soc.,* **1958**, *80*, 3625. (b) Hughes, E. D. and Ingold, C. K., *Quart. Rev., Chem. Soc.,* **1952**, *6*, 34. (c) Drumm, P. J.; O'Connor, W. F. and Reilly, J., *J. Am. Chem. Soc.,* **1940**, *62*, 1241. (d) Hickinbottom, W. J., *J. Chem. Soc.,* **1937**, 404. (e) Hickinbottom, W. J., *J. Chem. Soc.,* **1935**, 1279. (f) Hickinbottom, W. J., *J. Chem. Soc.,* **1934**, 1981. (g) Hickinbottom, W. J., *J. Chem. Soc.,* **1934**, 1700. (h) Hickinbottom, W. J., *J. Chem. Soc.,* **1934**, 319. (i) Hickinbottom, W. J., *J. Chem. Soc.,* **1932**, 2646. (j) Hickinbottom, W. J., *J. Chem. Soc.,* **1932**, 2396. (k) Hickinbottom, W. J., *J. Chem. Soc.,* **1932**, 946. (l) Hickinbottom, W. J. and Ryder, S. E. A., *J. Chem. Soc.,* **1931**, 1281. (m) Hickinbottom, W. J. and Preston, G. H., *J. Chem. Soc.,* **1930**, 1566. (n) Hickinbottom, W. J. and Wayne, A. C., *J. Chem. Soc.,* **1930**, 1558. (o) Hickinbottom, W. J., *J. Chem. Soc.,* **1927**, *124*, 64.

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Reimer-Tiemann Reaction
(Reimer-Tiemann Formylation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Reimer[1] and subsequently extended by Reimer and Tieman in 1876.[2] It is the transformation of a formyl group onto the *ortho*- or *para*-position of an activating group in an electron-rich aromatic compound by warming with chloroform and aqueous alkali; therefore, it is generally known as the Reimer-Tiemann reaction.[3,4] Occasionally, this reaction is also referred to as the Reimer-Tiemann formylation,[5] Reimer-Tiemann aldehyde synthesis,[5g,6] or Reimer-Tiemann process.[7] In this reaction, the electron-rich aromatic compounds include phenols, naphthols,[4k] pyrroles,[8] indoles,[9] quinoxalines,[4i] thiazoles,[4i] tropolone,[10] and even pyrimidines with at least one hydroxy and two methyl groups.[4h] However, this reaction generally gives low yields of aromatic aldehydes[4b,5d,11] along with the recovery of starting material[4b,11] and some by-products, such as orthoformic ester,[12] hydroxy acids[13] and triphenylmethane resin.[11,15] Although the use of an excess amount of base and chloroform can reduce the amount of phenol recovered, the amount of triphenylmethane resin is increased too.[11] Other drawbacks of this reaction are associated with the biphasic nature of the reaction system, such as the inefficiency of mass transfer between the layers.[5a,5d] In addition, the presence of an alcohol may alter the nature of the biphasic system, but in most cases the addition of alcohol resulted in even lower yields.[15] It has been found that this reaction generally favors the *ortho*-formylated product because of the electrostatic effect,[4j] however, the *ortho*/*para* ratio varies along with the solvent,[16] substituents on the aromatic substrate,[4g] the haloform,[14] and alkali base[15b,17] used. For example, the methyl group increases the rate of *ortho*-formylation in *p*-cresol and decreases the *para*-formylation because of steric effect, whereas the formyl group decreases the *ortho*-formylation on *p*-hydroxybenzaldehyde.[4g] The larger the size of the cation in the alkali base, the more *para*-formylated product produced;[4i] likewise, the higher the concentration of phenoxide, the more *o*-substituted product formed.[4j] This is because the phenoxide and

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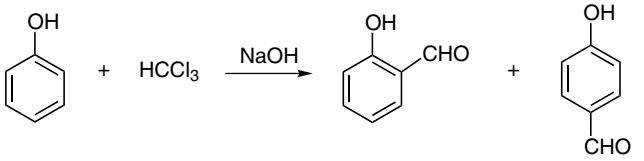
alkali cation form contacted ion pairs in high concentration, favoring the *o*-substitution. In a dilute solution, or with large cation size, such as Cs^+ or K^+, more loose ion pairs form.

It should be pointed out that certain five-, six- and seven-membered ring systems also undergo the ring expansion reaction, such as the formation of 3-chloropyridine from pyrrole (*Ciamician-Dennstedt Reaction*),[8a,18] chloroquinolines from indole,[9a,9d,19] and chloronaphthalenes and chloroazulenes from indenes.[20] On the other hand, the *ortho*- or *para*-substituted phenols, naphthols, and tetralols also produce 2,2- or 4,4-disubstituted cyclohexadienones, along with the normal Reimer-Tiemann products;[4i] in some cases, cyclohexadienones are the only products under Reimer-Tiemann reaction conditions, as exemplified by the formation of 1-methyl-1-dichloromethyl-2-keto-1,2-dihydronaphthalene from 1-methyl-2-naphthol, 1-allyl-1-dichloromethyl-2-keto-1,2-dihydronaphthalene from 1-allyl-2-naphthol, and 1-(3-chloro-2-butenyl)-1-dichloromethyl-2-keto-1,2-dihydronaphthalene from 1-(3-chloro-2-butenyl)-2-naphthol, respectively.[4k]

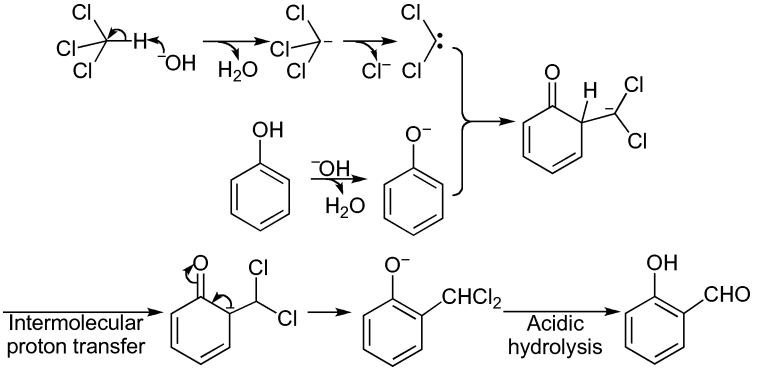
Nevertheless, compared to other formylation reactions, such as the *Duff Formylation, Gattermann Aldehyde Synthesis*, and *Gattermann-Koch Formylation*, the Reimer-Tiemann reaction is the only one that occurs under basic conditions, and in certain cases, it is the only feasible method for the direct formylation,[4i] e.g., the formylation of oestrogens.[5d]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is well known that under basic conditions, phenol is converted into phenoxide and chloroform is transformed into dichlorocarbene, a highly electron-deficient species, thus the Reimer-Tiemann reaction involves the electrophilic attack of dichlorocarbene on phenoxide, followed by intermolecular proton transfer, as indicated by the deuterium and tritium isotope labeling experiment.[21] An illustrative mechanism is thus provided for the formation of salicylaldehyde.



D. MODIFICATION

This reaction has been improved by use of a slightly "hydrated solid-liquid medium."[4b] In addition, photochemical Reimer-Tiemann reactions[3g,3i,3dd,3ff,22] have been developed that may involve an irreversible charge transfer.[22]

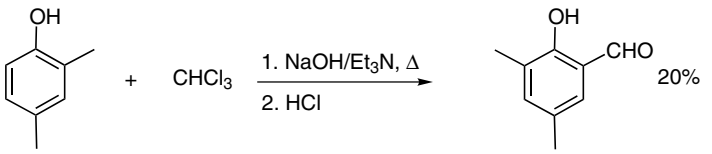
E. APPLICATIONS

This reaction has general application in the formylation of electron-rich aromatic compounds.

F. RELATED REACTIONS

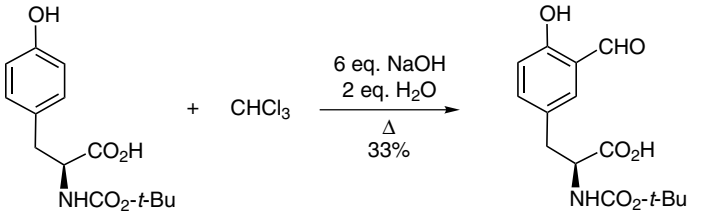
This reaction is related to the *Ciamician-Dennstedt Reaction*, *Duff Reaction*, *Gatterman Aldehyde Synthesis*, and *Gattermann-Koch Formylation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4c.

A mixture of 83 mL 2,4-dimethylphenol and 4.2 mL triethylamine in 350 mL chloroform was added dropwise to 800 mL 50% NaOH in water at 75°C with vigorous stirring under refluxing. Then the reaction mixture was acidified with 110 mL concentrated HCl. After the addition of sufficient water to dissolve the salt, the dark oil layer was collected, and the product was extracted with CH_2Cl_2. After evaporation of the solvent, the product was purified by steam distillation, silica gel chromatography, and bisulfite reaction to give ~20% 2-hydroxy-3,5-dimethylbenzaldehyde. (*Note:* Vigorous stirring under reflux should stand for the refluxing of chloroform).



Reference 4b.

To a suspension of 2.0 g *N*-Boc-L-tyrosine (7.12 mmol) and 0.256 mL water in 30 mL $CHCl_3$ was added 1.71 g powdered NaOH (42.72 mmol). After the mixture was refluxed for 4 h, an additional 0.42 g NaOH (10.68 mmol) was added over 1.5 h. The reaction was then diluted with water and EtOAc, and the aqueous layer was acidified to pH 1 with 1 *N* HCl and back extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Flash column chromatography using $CHCl_3$/MeOH (12:1) with 1% acetic acid as the eluent afforded 0.72 g *N*-[(1,1-dimethylethoxy)-carbonyl]-3-(3-formyl-4-hydroxyphenyl)-L-alanine (33%) and 0.62 g *N*-Boc-L-tyrosine (31% recovery).

Other references related to the Reimer-Tiemann reaction are cited in the literature.[23]

H. REFERENCES

1. Reimer, K., *Ber.,* **1876**, *9*, 423.
2. (a) Reimer, K. and Tiemann, F., *Ber.,* **1876**, *9*, 824. (b) Reimer, K. and Tiemann, F., *Ber.,* **1876**, *9*, 1268. (c) Reimer, K. and Tiemann, F., *Ber.,* **1876**, *9*, 1285.
3. (a) Vibhute, Y. B.; Lonkar, S. M.; Sayyed, M. A. and Baseer, M. A., *Mendeleev Commun*., **2007**, *17*, 51. (b) Iles, A.; Fortt, R. and de Mello, A. J., *Lab on a Chip*, **2005**, *5*, 540. (c) Zeng, Z.; Jin, L. M.; Jiao, X. Y. and Guo, C. C., *Jingxi Huagong Zhongjianti*, **2004**, *34*, 17. (d) Xu, H.; Zhao, X.-S.; Cao, L.-H. and Yu, W.-M., *Huaxue Yu Nianhe,* **2003**, 264. (e) Castillo, R.; Moliner, V. and Andres, J., *Chem. Phys. Lett.,* **2000**, *318*, 270. (f) Castillo, R.; Moliner, V.; Andres, J.; Oliva, M.; Safont, V. S. and Bohm, S., *J. Phys. Org. Chem.,* **1998**, *11*, 670. (g) Ravichandran, R., *J. Mol. Catal. A: Chem.,* **1998**, *130*, L205. (h) Zeng, H. W.; Zhang, T.; Liu, L. and Lai, W. M., *Huanan Ligong Daxue Xuebao, Ziran Kexueban,* **1997**, *25*, 70. (i) Jimenez, M. C.; Miranda, M. A. and Tormos, R., *Tetrahedron*, **1995**, *51*, 5825. (j) Wu, L. C.; Zheng, Q. P. and Xiao, S. Z., *Huaxue Shijie,* **1994**, *35*, 454. (k) He, M. and Yuan, L. B., *Liaoning Shifan Daxue Xuebao, Ziran Kexueban,* **1994**, *17*, 131. (l) Hu, S. W.; Liang, B. X.; Qian, F. and Li, Z. L., *Huaxue Shiji*, **1993**, *15*, 184. (m) Chen, J. J.; Du, Z. M.; Shi, Y. Z.; Song, T. and Hu, H. W., *Gaodeng Xuexiao Huaxue Xuebao*, **1992**, *13*, 1415. (n) Divakar, S.; Maheswaran, M. M. and Narayan, M. S., *Indian J. Chem., Sect. B,* **1992**, *31B*, 543. (o) Liu, Y.; Gao, Y. L. and Deng, J. H., *Huaxue Shijie*, **1991**, *32*, 265. (p) Gaonkar, A. V. and Kirtany, J. K., *Indian J. Chem., Sect. B,* **1991**, *30B*, 800. (q) Li, Z. Z. and Zhou, Y., *Huaxue Shijie*, **1991**, *32*, 18. (r) Langlois, B. R., *Tetrahedron Lett*., **1991**, *32*, 3691. (s) Kang, R. H.; Zhang, X. L.; Li, G. P. and Zhang, L. P., *Gaodeng Xuexiao Huaxue Xuebao*, **1990**, *11*, 420. (t) Cochran, J. C. and Melville, M. G., *Synth. Commun.,* **1990**, *20*, 609. (u) Yang, Y. and Pi, Z. L., *Hunan Shifan Daxue Ziran Kexue Xuebao*, **1989**, *12*, 318. (v) Thoer, A.; Denis, G.; Delmas, M. and Gaset, A., *Synth. Commun.,* **1988**, *18*, 2095. (w) Yang, Y. J. and Pi, Z. L., *Hunan Shifan Daxue Ziran Kexue Xuebao*, **1988**, *11*, 133. (x) Ding, X. T.; Zhang, L. and Ge, Y., *Huaxue Xuebao*, **1988**, *46*, 155. (y) Ding, X. T.; Zhang, L. and Ge, Y., *Kexue Tongbao*, **1987**, *32*, 860. (z) Foxley, G. H., *School Sci. Rev.*, **1987**, *68*, 711. (aa) Neumann, R. and Sasson, Y., *Synthesis*, **1986**, 569. (bb) Bird, C. W.; Brown, A. L. and Chan, C. C., *Tetrahedron*, **1985**, *41*, 4685. (cc) Bird, C. W. and Brown, A. L., *Chem. & Ind. (London),* **1983**, 827. (dd) Fahmy, A. M.; Mahgoub, S. A.; Aly, M. M. and Badr, M. Z. A., *Bull. Faculty Sci., Assiut Univ.*, **1982**, *11*, 17. (ee) Thakar, K. A. and Bhawal, B. M., *Indian J. Chem., Sect. B,* **1977**, *15B*, 1056. (ff) Hirao, K.; Ikegame, M. and Yonemitsu, O., *Tetrahedron*, **1974**, *30*, 2301. (gg) Krajniak, E. R.; Ritchie, E. and Taylor, W. C., *Aust. J. Chem.,* **1973**, *26*, 1337. (hh) Thakar, K. A. and Goswami, D. D., *J. Indian Chem. Soc.,* **1972**, *49*, 707. (ii) Ravina, E. and Montanes, J. M., *Anal. Quim.,* **1969**, *65*, 709. (jj) Montanes del Olmo, J. M. and Ravina, E., *Anal. Quim.,* **1969**, *65*, 613. (kk) Kobayashi, S.; Azekawa, M. and Taoka, M., *Chem. Pharm. Bull.,* **1969**, *17*, 1279. (ll) Kobayashi, S.; Azekawa, M. and Morita,

H., *Chem. Pharm. Bull.,* **1969**, *17*, 89. (mm) Kobayashi, S.; Tagawa, S. and Nakajima, S., *Chem. Pharm. Bull.,* **1963**, *11*, 123. (nn) Cohen, S.; Thom, E. and Bendich, A., *J. Org. Chem.,* **1963**, *28*, 1379. (oo) Gibson, M. S., *J. Chem. Soc.,* **1961**, 2251. (pp) Robinson, E. A., *J. Chem. Soc.,* **1961**, 1663. (qq) Wynberg, H., *J. Am. Chem. Soc.,* **1954**, *76*, 4998. (rr) Heath, H.; Lawson, A. and Rimington, C., *J. Chem. Soc.,* **1951**, 2223. (ss) Rapson, W. S.; Saunder, D. H. and Stewart, E. T., *J. Chem. Soc.,* **1944**, 74. (tt) Arnold, R. T.; Zaugg, H. E. and Sprung, J., *J. Am. Chem. Soc.,* **1941**, *63*, 1314. (uu) Hodgson, H. H. and Nixon, J., *J. Chem. Soc.,* **1929**, 1632. (vv) Hodgson, H. H. and Jenkinson, T. A., *J. Chem. Soc.,* **1929**, 1639. (ww) Hodgson, H. H. and Jenkinson, T. A., *J. Chem. Soc.,* **1929**, 469. (xx) Hodgson, H. H. and Jenkinson, T. A., *J. Chem. Soc.,* **1927**, 3041.

4. (a) Nogueda-Torres, B.; Rodríguez-Páez, L.; Ramírez, I. B. and Ramírez, C. W., *Revista Latinoamer. Micribiol.,* **2001**, *43*, 1. (b) Jung, M. E. and Lazarova, T. I., *J. Org. Chem.,* **1997**, *62*, 1553. (c) Whittaker, M. M.; Duncan, W. R. and Whittaker, J. W., *Inorg. Chem.,* **1996**, *35*, 382. (d) Wynberg, H. and Meijer, E. W., *Org. React.,* **1982**, *28*, 1. (e) Fee, W. W.; Pulsford, J. D. and Vowles, P. D., *Aust. J. Chem.,* **1973**, *26*, 675. (f) Kobayashi, S.; Tagawa, S. and Nakajima, S., *Chem. Pharm. Bull.,* **1963**, *11*, 123. (g) Hine, J. and van der Veen, J. M., *J. Org. Chem.,* **1961**, *26*, 1406. (h) Wiley, R. H. and Yamamoto, Y., *J. Org. Chem.,* **1960**, *25*, 1906. (i) Wynberg, H., *Chem. Rev.,* **1960**, *60*, 169. (j) Hine, J. and van der Veen, J. M., *J. Am. Chem. Soc.,* **1959**, *81*, 6446. (k) Dodson, R. M. and Webb, W. P., *J. Am. Chem. Soc.,* **1951**, *73*, 2767. (l) Gilman, H.; Arntzen, C. E. and Webb, F. J., *J. Org. Chem.,* **1945**, *10*, 374.
5. (a) Fortt, R.; Iles, A. and de Mello, A., Paper Given at 7th International Conference on Miniaturized Chemical and Biochemical Aanlysis Systems, Squaw Valley, Calif., Oct. 5–9, **2003**. (b) Morera, E. and Ortar, G., *Synth. Commun.,* **2001**, *31*, 2115. (c) Jendralla, H.; Granzer, E.; Von Kerekjarto, B.; Krause, R.; Schacht, U.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Kesseler, K.; Wess, G.; Chen, L.-J.; Granata, S.; Herchen, J.; Kleine, H.; Schussler, H. and Wagner, K., *J. Med. Chem.,* **1991**, *34*, 2962. (d) Pert, D. J. and Ridley, D. D., *Aust. J. Chem.,* **1989**, *42*, 405. (e) Smith, K. M.; Bobe, F. W.; Minnetian, O. M.; Hope, H. and Yanuck, M. D., *J. Org. Chem.,* **1985**, 50, 790. (f) Ohara, M. and Fukuda, J., *Pharmazie*, **1978**, *33*, 467. (g) Fuson, R. C. and Miller, T. G., *J. Org. Chem.,* **1952**, *17*, 316.
6. Verzele, M. and Sion, H., *Bull. Soc. Chim. Belg.,* **1956**, *65*, 627.
7. Wang, Y. C., *Xiandai Huagong*, **1986**, *36*, 23.
8. (a) Fischer, H.; Beller, H. and Stern, A., *Ber.,* **1928**, *61*, 1078. (b) Hodgson, H. H. and Jenkinson, T. A., *J. Chem. Soc.,* **1927**, 1740. (c) Auwers, K. and Keil, G., *Ber.,* **1903**, *36*, 1861.
9. (a) Marchant, R. H. and Harvey, D. G., *J. Chem. Soc.,* **1951**, 1808. (b) Blume, R. G. and Lindwall, H. G., *J. Org. Chem.,* **1945**, *10*, 255. (c) Boyd, W. J. and Robson, W., *Biochem. J.,* **1933**, *29*, 555. (d) Ellinger, A., *Ber.,* **1906**, *39*, 2515.
10. Cook, J. W.; Raphael, R. A. and Scott, A. I., *J. Chem. Soc.,* **1952**, 4416.
11. Wynberg, H., *J. Am. Chem. Soc.,* **1954**, *76*, 4996.
12. (a) Wynberg, H. and Johnson, W. S., *J. Org. Chem.,* **1959**, *24*, 1421. (b) Driver, J. E., *J. Am. Chem. Soc.,* **1924**, *46*, 2090. (c) Tiemann, F., *Ber.,* **1882**, *15*, 2685. (d) Weddige, A., *J. Prakt. Chem.,* **1882**, *26*, 444.
13. Berlingozzi, S. and Badolato, P., *Atti Accad. Nazl. Lincei,* **1924**, *33*, 290.
14. Armstrong, D. E. and Richardson, D. H., *J. Chem. Soc.,* **1933**, 496.
15. (a) Russell, A. and Lockhart, L. B., *Org. Synth.,* **1942**, *22*, 63. (b) Bobranski, B., *Ber.,* **1936**, *69*, 1113. (c) Kochanska, L. and Bobranski, B., *Ber.,* **1936**, *69*, 1807.
16. Sen, R. N. and Ray, S. K., *J. Indian Chem. Soc.,* **1932**, *9*, 173.
17. Brady, O. L. and Jakobovits, J., *J. Chem. Soc.,* **1950**, 767.
18. Bamberger, E. and Djierdjian, G., *Ber.,* **1900**, *33*, 536.
19. Magnanini, G., *Ber.,* **1887**, *20*, 2608.
20. Parham, W. E. and Reiff, H. E., *J. Am. Chem. Soc.,* **1955**, *77*, 1177.

21. Kemp, D. S., *J. Org. Chem.,* **1971**, *36*, 202.

22. Shade, J. E.; Pearson, W. H.; Brown, J. E. and Bitterwolf, T. E., *Organometallics,* **1995**, *14*, 157.

23. (a) Aronson, C. L.; Beloskur, D.; Frampton, I. S.; McKie, J. and Montbriand, P., *Poly. Bull.,* **2004**, *52*, 409. (b) Fomine, S.; Delgado, C.; Fomina, L.; Gaviño, R. and Ogawa, T., *Macromol. Chem. Phys.,* **1997**, *198*, 3065. (c) Fritz, G. L.; Mills, G. D.; Warthen, J. D. and Waters, R. M., *J. Chem. Ecology,* **1989**, *15*, 2607. (d) Rocke, A. J. and Ihde, A. J., *J. Chem. Edu.,* **1986**, *63*, 309. (e) Sasson, Y. and Yonovich, M., *Tetrahedron Lett.,* **1979**, *39*, 3753. (f) Wynberg, H. and Johnson, W. S., *J. Org. Chem.,* **1959**, *24*, 1424. (g) Russell, A. and Lockhart, L. B., *Org. Synth. Coll.,* **1955**, *3*, 463. (h) Ferguson, L. N., *Chem. Rev.,* **1946**, *38*, 229.

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Reissert Compound
(Reissert Reaction)

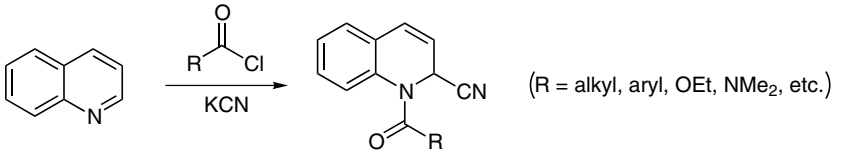
A. GENERAL DESCRIPTION OF THE REACTION

The compound 1-benzoyl-2-cyano-1,2-dihydroquinoline was first reported by Reissert in 1905 from the reaction between quinoline, benzoyl chloride, and aqueous potassium cyanide.[1] Subsequently, Grosheintz and Fischer extended this reaction to prepare acyl cyanodihydroquinoline from aliphatic acyl chloride with hydrogen cyanide and two equivalents of quinoline in dry benzene.[2] Later on, other types of heterocycles—such as isoquinoline,[3] benzimidazole,[4] 1,6-naphthyridines,[5] phenanthridine,[6] pyrimidine,[7] indazole,[8] purine,[9] quinazoline,[10] quinoxaline,[11] phthalazine,[12] pyridazine,[13] phenanthroline,[14] pyrazine,[15] oxazole,[16] and especially, pyridines[17]—were found to give compounds with structures similar to Reissert's dihydroquinoline. Thus all of these compounds, prepared similarly, are generally referred to as Reissert compounds,[18,19] and the method to prepare these types of compounds is known as the Reissert reaction[20] or Reissert-type reaction.[20d,20e] Among them, 2-cyano-1-benzoyldihydroquinoline is known as quinoline Reissert compound,[21] and 1-cyano-2-benzoyldihydroisoquinoline prepared from isoquinoline is known as isoquinoline Reissert compound,[18e,22] the corresponding 1,2,3,4-tetrahydro derivatives are referred to as dihydro-Reissert compounds.[22] Besides the regular benzoyl and acetyl[23] Reissert compounds, molecules with benzoyl substituted by sulfonyl,[24] alkoxycarbonyl,[25] carbamoyl,[26] and phosphate[27] have also been prepared. However, the preparation from aroyl and cinnamoyl chloride is unsuccessful in benzonitrile, ether, dioxane, acetone, or chloroform.[28] Reissert compounds can be easily converted into their conjugated bases through deprotonation, a process that has been widely used in organic synthesis. Generally speaking, because of the unsaturation of dihydroquinoline or dihydroisoquinoline moieties, Reissert compounds can undergo many reactions that normal alkenes undergo, such as polymerization[18c] and cyclopropanation.[29] More importantly, Reissert compounds can undergo a few reactions of particular interest. For example, upon acidic hydrolysis,

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

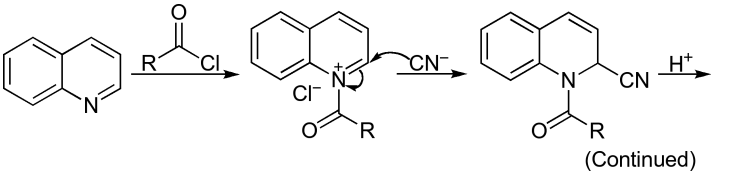
Reissert compounds decompose to aldehyde (from the acyl moiety) and quinaldic acid;[2,30] while when treated with PCl_5 in chloroform, Reissert compounds decompose to 2-cyano quinoline and benzoyl chloride.[31] In addition, Reissert compounds rearrange to *C*-acyl quinolines or isoquinolines when heated in strong base.[22] Similarly, the conjugate base of a Reissert compound can undergo alkylation with alkylating reagents, and the alkylated Reissert compound decomposes to alkyl-substituted quinolines or isoquinolines when treated with base.[21] In addition, these conjugate bases also condense with aldehydes to form secondary alcohols or their esters, of which the acyl groups migrate from nitrogen to oxygen in alkaline solution.[22] Furthermore, the condensation of Reissert compounds with Grignard reagents results in the formation of carbinols, which rearrange to 2-acyl quinolines when treated with NaH.[32] Moreover, cyclic urethanes can be prepared from the conjugate bases of alkoxycarbonyl Reissert compounds with aromatic aldehydes.[22,33] It should be emphasized that among these reactions, the one that decomposes to aldehyde under acidic conditions provides a route to convert acyl chloride into aldehyde.[2,30]

B. GENERAL REACTION SCHEME

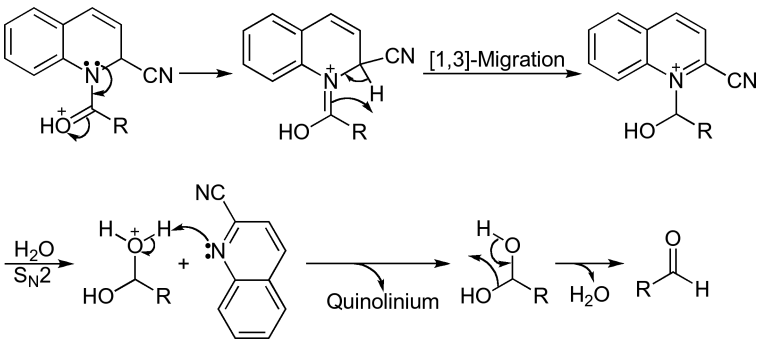


C. PROPOSED MECHANISMS

Although it has been proposed that the formation of Reissert compounds involves the addition of hydrogen cyanide to the carbon-nitrogen double bond followed by the acylation of the resultant secondary amine,[33] the actual reaction may involve the acylation before the addition.[20d] Because quinoline, isoquinoline and pyridine are basic, they can form salt with acyl chloride to further polarize the carbon-nitrogen double and facilitate the addition of cyanide, although pyridine and quinoline are inert toward the addition of cyanide without activation. On the other hand, the decomposition of the Reissert compounds to aldehyde under acidic conditions is believed to involve the protonation of the amido oxygen to form a conjugate acid and the cleavage of 2-proton and dissociation to aldehyde and quinaldonitrile;[30c] or it may involve protonation and cleavage to form a transient acyl anion, which abstracts a proton to form aldehyde.[30d,34] Displayed here is the formation of a Reissert compound and its acidic conversion into aldehyde.



(Continued)



D. MODIFICATION

Generally, the use of other heterocycles[3–17] besides quinoline would be considered modifications of the original Reissert protocol. This reaction has been extended to convert an acyl chloride into an aldehyde through a one-pot process by adding the acyl chloride to a solution of quinoline and hydrocyanic acid, and subsequent steam distillation of the entire mixture with sulfuric acid.[2] In addition, the formation of the Reissert compound has been modified to occur enantioselectively using TMSCN as the nucleophilic species in the presence of a Lewis acid–Lewis base bifunctional catalyst.[20d,35] Moreover, tri-*n*-butyltin cyanide[19s] and acetone cyanohydrin[20k] are also used for the preparation of the Reissert compounds.

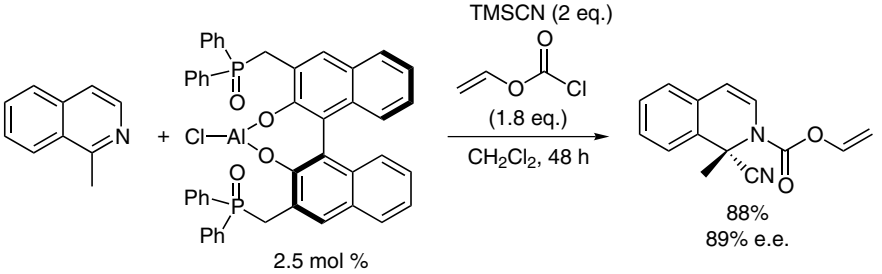
E. APPLICATIONS

Reissert compounds have very wide application in organic synthesis.

F. RELATED REACTIONS

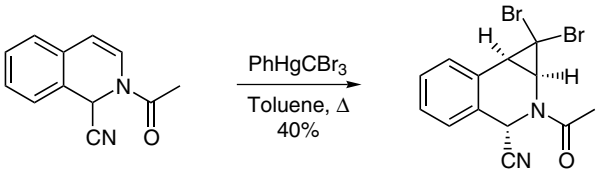
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 35b.

To a solution of 0.015 mmol aluminum catalyst with (*R*)-6,6′-dibromo-3,3′-bis (diphenylphosphinoylmethyl)-2,2′-dihydroxy-1,1′-binaphthyl as ligand in CH_2Cl_2 was added 0.6 mmol 1-methyl-isoquinoline in 2.25 mL CH_2Cl_2, followed by 160 μL TMSCN (1.2 mmol) and 91.8 μL vinyl chloroformate (1.08 mmol) at −60°C. After 48 h, the reaction was quenched by 5% NH_3 aqueous solution, and extracted with EtOAc. Upon removal of solvent under reduced pressure, the reside was purified by column chromatography using hexane/EtOAc as the eluent to afford 91% (+)-1-cyano-1-methyl-1,2-dihydroisoquinoline-2-carboxylic acid vinyl ester as a colorless oil, with 84% e.e. as determined by chiral HPLC analysis.



Reference 29.

A mixture of 2.64 g phenyltribromomethyl mercury (5 mmol) and 0.99 g 1-cyano-2-acetyl-1,2-dihydroisoquinoline (5 mmol, prepared from KCN and acetyl chloride) in 50 mL toluene was heated at 80°C for 2.5 h. The precipitated phenylmercuric chloride was removed by filtration, and the solvent was removed in vacuo. The residue was crystallized from ether-hexane to yield 745 mg 2-acetyl-1,1-dibromo-1a,2,3,7b-tetrahydro-1H-cycloprop[c]-isoquinaldonitrile, in a yield of 40%, m.p., 174–175°C.

Other references related to the Reissert compounds are cited in the literature.[36]

H. REFERENCES

1. Reissert, A., *Ber*., **1905**, *38*, 1603.
2. Grosheintz, J. M. and Fischer, H. O. L., *J. Am. Chem. Soc.,* **1941**, *63*, 2021.
3. (a) Uff, B. C.; Kershaw, J. R. and Neumeyer, J. L., *Org. Synth. Coll.,* **1988**, *4*, 115. (b) Ezquerra, J. and Alvarez-Builla, J., *J. Chem. Soc., Chem. Commun.,* **1984**, 54. (c) Weinstock, J. and Boekelheide, V., *Org. Synth. Coll. Vol.,* **1963**, *4*, 641.
4. (a) Jois, Y. H. R. and Gibson, H. W., *J. Org. Chem.,* **1991**, *56*, 865. (b) Uff, B. C.; Ho, Y. P.; Burford, D. L. W. and Popp, F. D., *J. Heterocycl. Chem.,* **1987**, *24*, 1349.
5. (a) Hamada, Y. and Shigemura, K., *Yakugaku Zasshi*, **1979**, *99*, 982. (b) Hamada, Y.; Takeuchi, I. and Matsuoka, H., *Chem. Pharm. Bull.,* **1970**, *18*, 1026.
6. Kant, J. and Popp, F. D., *J. Heterocycl. Chem.,* **1984**, *21*, 425.
7. (a) Higashino, T.; Sato, S.; Miyashita, A. and Katori, T., *Chem. Pharm. Bull.,* **1987**, *35*, 4078. (b) Higashino, T.; Sato, S.; Miyashita, A. and Katori, T., *Chem. Pharm. Bull.,* **1986**, *34*, 4569.
8. Uff, B. C.; Ho, Y. P. and Popp, F. D., *Synth. Commun.,* **1989**, *19*, 1239.
9. Tanji, K.; Sato, S.; Miyashita, A.; Oishi, E. and Higashino, T., *Chem. Pharm. Bull.,* **1989**, *37*, 187.
10. (a) Uff, B. C.; Joshi, B. L. and Popp, F. D., *J. Chem. Soc., Perkin Trans. I,* **1986**, 2295. (b) Kant, J.; Popp, F. D. and Uff, B. C., *J. Heterocycl. Chem.,* **1985**, *22*, 1313. (c) Kant, J.; Popp, F. D.; Joshi, B. L. and Uff, B. C., *Chem. & Ind. (London),* **1984**, 415.

11. Veeraraghavan, S. and Popp, F. D., *J. Heterocycl. Chem.,* **1981**, *18*, 775.
12. Bhattacharjee, D. and Popp, F. D., *J. Heterocycl. Chem.,* **1980**, *17*, 1035.
13. Dostal, W. and Heinisch, G., *J. Heterocycl. Chem.,* **1985**, *22*, 1543.
14. (a) Hamada, Y.; Morishita, K. and Hirota, M., *Chem. Pharm. Bull.,* **1978**, *26*, 350. (b) Kloc, K. and Mlochowski, J., *Roczniki Chem.,* **1975**, *49*, 1621.
15. Abushanab, E.; Lee, D. Y. and Goodman, L., *J. Org. Chem.,* **1975**, *40*, 3376.
16. Goto, Y. and Yamazaki, M., *Chem. Pharm. Bull.,* **1970**, *18*, 756.
17. (a) Baxter, P. N. W.; Connor, J. A.; Schweizer, W. B. and Wallis, J. D., *J. Chem. Soc., Dalton Trans.,* **1992**, 3015. (b) Popp, F. D.; Takeuchi, I.; Kant, J. and Hamada, Y., *J. Chem. Soc., Chem. Commun.,* **1987**, 1765. (c) Bass, R. J.; Popp, F. D. and Kant, J., *J. Heterocycl. Chem.,* **1984**, *21*, 1119. (d) Ochiai, E. and Nakayama, I., *Yakugaku Zasshi,* **1945**, *65*, 7.
18. (a) Sieck, O.; Schaller, S.; Grimme, S. and Liebscher, J., *Synlett,* **2003**, 337. (b) Perrin, S.; Monnier, K.; Laude, B.; Kubicki, M. and Blacque, O., *Eur. J. Org. Chem.,* **1999**, 297. (c) Pandya, A. and Gibson, H. W., *Polymer Bull.,* **1991**, *25*, 17. (d) Hung, T. V.; Mooney, B. A.; Prager, R. H. and Ward, A. D., *Aust. J. Chem.,* **1981**, *34*, 151. (e) Gibson, H. W. and Bailey, F. C., *J. Poly. Sci.: Poly. Chem. Ed.,* **1976**, *14*, 1661. (f) Walters, L. R.; Iyer, N. T. and McEwen, W. E., *J. Am. Chem. Soc.,* **1958**, *80*, 1177.
19. (a) Evain, M.; Pauvert, M.; Collet, S. and Guingant, A., *Acta Cryst., Sect. E: Struct. Reports Online*, **2002**, *E58*, o1121. (b) Perrin, S.; Monnier, K.; Laude, B.; Kubicki, M. M. and Blacque, O., *Tetrahedron Lett*., **1998**, *39*, 1753. (c) Perrin, S.; Monnier, K. and Laude, B., *Bull. Soc. Chim. Belg.,* **1996**, *105*, 777. (d) Duarte, F. F. and Popp, F. D., *J. Heterocycl. Chem.,* **1994**, *31*, 819. (e) Duarte, F. F.; Popp, F. D. and Holder, A. J., *J. Heterocycl. Chem.,* **1993**, *30*, 893. (f) Hahn, J. T.; Kant, J.; Popp, F. D.; Chhabra, S. R. and Uff, B. C., *J. Heterocycl. Chem.,* **1992**, *29*, 1165. (g) Duarte, F. F. and Popp, F. D., *J. Heterocycl. Chem.,* **1991**, *28*, 1801. (h) Jois, Y. H. R.; Berg, M. A. G.; Merola, J. S. and Gibson, H. W., *Tetrahedron Lett*., **1991**, *32*, 2997. (i) Duarte, F. F. and Popp, F. D., *Heterocycles*, **1991**, *32*, 723. (j) Pandya, A. and Gibson, H. W., *Polymer Commun.,* **1991**, *32*, 134. (k) Gibson, H. W.; Guilani, B. and Rasco, M. R., *Macromolecules*, **1991**, *24*, 3700. (l) Miyashita, A.; Sato, S.; Taido, N.; Tanji, K.; Oishi, E. and Higashino, T., *Chem. Pharm. Bull.,* **1990**, *38*, 230. (m) Uff, B. C.; Burford, D. L. W. and Ho, Y. P., *J. Chem. Res. (S),* **1989**, 386. (n) Uff, B. C.; Ho, Y. P.; Brown, D. S.; Fisher, I.; Popp, F. D. and Kant, J., *J. Chem. Res. (S),* **1989**, 346. (o) Popp, F. D. and Duarte, F. F., *Org. Prep. Proc. Int.,* **1989**, *21*, 366. (p) Hahn, J. T. and Popp, F. D., *J. Heterocycl. Chem.,* **1989**, *26*, 1357. (q) Popp, F. D.; Duarte, F. F. and Uff, B. C., *J. Heterocycl. Chem.,* **1987**, *24*, 1353. (r) Cooney, J. V.; Beaver, B. D. and McEwen, W. E., *J. Heterocycl. Chem.,* **1985**, *22*, 635. (s) Popp, F. D. and Kant, J., *Heterocycles*, **1985**, *23*, 2193.
20. (a) Pauvert, M.; Collet, S. C.; Bertrand, M.-J.; Guingant, A. Y. and Evain, M., *Tetrahedron Lett*., **2005**, *46*, 2983. (b) Ichikawa, E.; Suzuki, M.; Yabu, K.; Albert, M.; Kanai, M. and Shibasaki, M., *J. Am. Chem. Soc.,* **2004**, *126*, 11808. (c) Taylor, M. S. and Jacobsen, E. N., *J. Am. Chem. Soc.,* **2004**, *126*, 10558. (d) Takamura, M.; Funabashi, K.; Kanai, M. and Shibasaki, M., *J. Am. Chem. Soc.,* **2001**, *123*, 6801. (e) Takamura, M.; Funabashi, K.; Kanai, M. and Shibasaki, M., *J. Am. Chem. Soc.,* **2000**, *122*, 6327. (f) Clark, R. D.; Langston, J. and Langston, J. A., *Can. J. Chem.,* **1994**, *72*, 23. (g) Takeuchi, I.; Hamada, Y.; Hatano, K.; Kurono, Y. and Yashiro, T., *Chem. Pharm. Bull.,* **1990**, *38*, 1504. (h) Nasielski, J.; Heilporn, S.; Nasielski-Hinkens, R.; Tinant, B. and Declercq, J. P., *Tetrahedron*, **1989**, *45*, 7795. (i) Shibata, Y.; Takeuchi, I. and Hamada, Y., *Yakugaku Zasshi*, **1987**, *107*, 945. (j) Higashino, T.; Kokubo, H.; Goto, A.; Takemoto, M. and Hayashi, E., *Chem. Pharm. Bull.,* **1984**, *32*, 3690. (k) Sergovskaya, N. L.; Tsizin, Y. S. and Chernyak, S. A., *Khim. Geterotsiklicheskikh Soedinenii,* **1984**, 803. (l) Uff, B. C. and Budhram, R. S., *Heterocycles*, **1977**, *6*, 1789. (m) Yamanaka, H., *Chem. Pharm. Bull.,* **1959**, *7*, 297. (n) Kaneko, C., *Chem. Pharm. Bull.,* **1960**, *8*, 286. (o) Collins, R. F. and Henshall, T., *J. Chem. Soc.,* **1956**, 1881. (p) Ueda, K., *Yakugaku Zasshi*, **1937**, *57*, 825.

21. Boekelheide, V. and Weinstock, J., *J. Am. Chem. Soc.,* **1952**, *74*, 660.
22. Rozwadowska, M. D., *Can. J. Chem.,* **1977**, *55*, 164.
23. (a) Böhme, H. and Schweitzer, R., *Arch. Pharm.,* **1970**, *303*, 225. (b) Popp, F. D., *Adv. Heterocycl. Chem.,* **1968**, *9*, 1.
24. Wefer, J. M.; Catala, A. and Popp, F. D., *J. Org. Chem.,* **1965**, *30*, 3075.
25. (a) Popp, F. D.; Katz, L. E.; Klinowski, C. W. and Wefer, J. M., *J. Org. Chem.,* **1968**, *33*, 4447. (b) Hull, R., *J. Chem. Soc.,* **1968**, 1777.
26. Popp, F. D.; Wefer, J. M. and Catala, A., *J. Heterocycl. Chem.,* **1965**, *2*, 317.
27. Spatz, d. M. and Popp, F. D., *J. Heterocycl. Chem.,* **1968**, *5*, 497.
28. Woodward, R. B., *J. Am. Chem. Soc.,* **1940**, *62*, 1626.
29. Lantos, I. and Katerinopoulos, H. E., *Can. J. Chem.,* **1991**, *69*, 1033.
30. (a) Popp, F. D. and McEwen, W. E., *J. Am. Chem. Soc.,* **1957**, *79*, 3773. (b) Cobb, R. L. and McEwen, W. E., *J. Am. Chem. Soc.,* **1955**, *77*, 5042. (c) McEwen, W. E. and Hazlett, R. N., *J. Am. Chem. Soc.,* **1949**, *71*, 1949.
31. Kaufmann, A. and Dandliker, P., *Ber.,* **1913**, *46*, 2924.
32. Wolf, A. P.; McEwen, W. E. and Glazier, R. H., *J. Am. Chem. Soc.,* **1956**, *78*, 861.
33. Mowry, D. T., *Chem. Rev.,* **1948**, *42*, 189.
34. Colonna, M., *Gazz. Chim. Ital.,* **1952**, *82*, 503.
35. (a) Gröger, H., *Chem. Eur. J.,* **2001**, *7*, 5246. (b) Funabashi, K.; Ratni, H.; Kanai, M. and Shibasaki, M., *J. Am. Chem. Soc.,* **2001**, *123*, 10784.
36. (a) Tron, G. C. and Zhu, J. P., *Synlett,* **2005**, 532. (b) Venkov, A. P.; Statkova-Abeghe, S. M. and Donova, A. K., *Centr. Eur. J. Chem.,* **2004**, *2*, 234. (c) Bushby, N.; Moody, C. J.; Riddick, D. A. and Waldron, I. R., *J. Chem. Soc*., *Perkin Trans. I*, **2001**, 2183. (d) Leblanc, J. P.; Rorrer, K. and Gibson, H. W., *J. Org. Chem.,* **1994**, *59*, 674. (e) Leblanc, J.-P. and Gibson, H. W., *J. Org. Chem.,* **1994**, *59*, 1072. (f) Pandya, A. and Gibson, H. W., *J. Org. Chem.,* **1993**, *58*, 2851. (g) Gibson, H. W. and Guilani, B., *J. Org. Chem.,* **1990**, *55*, 4226. (h) Popp, F. D., *Bull. Soc. Chim. Belg.,* **1981**, *90*, 609. (i) Bhattacharjee, D. and Popp, F. D., *J. Pharm. Sci.,* **1980**, *69*, 120. (j) McEwen, W. E.; Grossi, A. V.; MacDonald, R. J. and Stamegna, A. P., *J. Org. Chem.,* **1980**, *45*, 1301. (k) Popp, F. D., *Adv. Heterocycl. Chem.,* **1979**, *24*, 187. (l) Ruchirawat, S.; Phadungkul, N.; Chuankamnerdkarn, M. and Thebtaranonth, C., *Heterocycles,* **1977**, *6*, 43. (m) Cook, M. J.; Katritzky, A. R. and Page, A. D., *J. Am. Chem. Soc.,* **1977**, *99*, 165. (n) Gibson, H. W. and Bailey, F. C., *Macromolecules,* **1976**, *9*, 221. (o) George, T.; Mehta, D. V. and Dabholker, D. A., *J. Org. Chem.,* **1974**, *39*, 1965. (p) Popp, F. D., *Heterocycles,* **1973**, *1*, 165. (q) Baranov, S. N.; Dumbai, M. A. and Krivun, S. V., *Chem. Heterocycl. Compd.,* **1972**, *8*, 1185. (r) Popp, F. D. and Purcell, D. H., *Synthesis,* **1970**, 591. (s) Wefer, J. M. and Popp, F. D., *J. Org. Chem.,* **1967**, *32*, 1999. (t) Popp, F. D.; Gibson, H. W. and Noble, A. C., *J. Org. Chem.,* **1966**, *31*, 2296. (u) Evanguelidou, E. K. and McEwen, W. E., *J. Org. Chem.,* **1966**, *31*, 4110. (v) Popp, F. D. and McEwen, W. E., *J. Am. Chem. Soc.,* **1958**, *80*, 1181. (w) McEwen, W. E. and Cobb, R. L., *Chem. Rev.,* **1955**, *55*, 511. (x) Collins, R. F., *J. Am. Chem. Soc.,* **1955**, *77*, 4921. (y) Mosettig, E., *Org. React.,* **1954**, *8*, 220. (z) Boekelheide, V. and Godfrey, J. C., *J. Am. Chem. Soc.,* **1953**, *75*, 3679. (aa) McEwen, W. E.; Kindall, J. V.; Hazlett, R. N. and Glazier, R. H., *J. Am. Chem. Soc.,* **1951**, *73*, 4591. (bb) Padbury, J. J. and Lindwall, H. G., *J. Am. Chem. Soc.,* **1945**, *67*, 1268.

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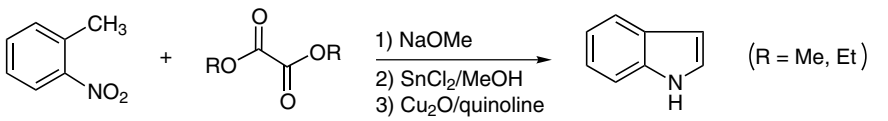
Reissert Indole Synthesis
(Reissert Condensation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Reissert in 1896.[1] It is a multistep synthesis of indole derivatives from *ortho*-nitrotoluene involving the basic condensation of *o*-nitrotoluene with oxalic ester to *o*-nitrophenylpyruvic ester, reduction of the nitro group to an amino group, cyclization to indole-2-carboxylic acid and final decarboxylation. Therefore, it is generally known as the Reissert indole synthesis.[2] In addition, it is also referred to as the Reissert condensation[2h,2m] or Reissert synthesis.[3] In this reaction, *o*-nitrotoluene can be deprotonated with sodium ethoxide or potassium ethoxide, in which potassium ethoxide offers better results than sodium ethoxide.[4] The resulting *o*-nitrophenylpyruvic ester can be reduced by zinc in acetic acid, stannous chloride in MeOH,[5] or alkaline ferrous hydroxide,[6] or it can be hydrogenated by Pd/C in EtOH or PtO_2 in either EtOH or acetic acid.[2e] It has been found that the hydrogenation of 2-nitrophenylpyruvate ester with 5% Pd/C in EtOH is the best reduction condition for Reissert indole synthesis, although it is accompanied with up to 10% of 1,2,3,4-tetrahydro-2-quinolone as byproduct.[2e] If two *ortho*-nitro groups exist in phenylpyruvate ester, then the nitro group with the least steric hindrance undergoes reduction and cyclization before the reduction of the other one.[5] The 2-carboxyl group in the resulting indole derivative can be removed by heating with copper chromite in quinoline.[6]

B. GENERAL REACTION SCHEME



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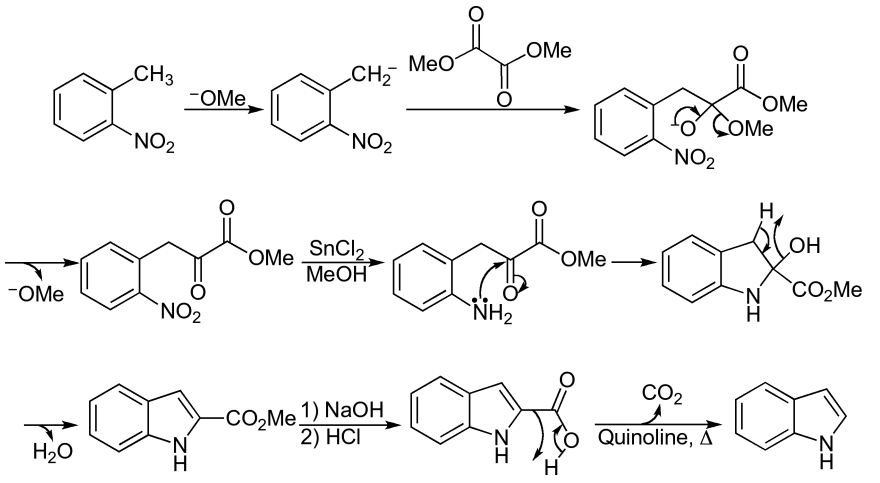
C. PROPOSED MECHANISMS

Displayed below is the reaction route for the Reissert indole synthesis from *o*-nitrotoluene and dimethyl oxalate, where the hydrolysis of methyl indole-2-carboxylate could be omitted, depending on the reaction conditions.



D. MODIFICATION

This reaction has been modified by reduction of *o*-nitrophenylpyruvic ester with stannous chloride dihydrate in DME at ambient temperature followed by the addition of aqueous titanium trichloride to improve both the purity and yield.[2d]

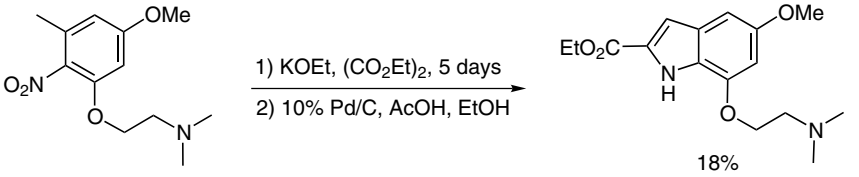
E. APPLICATIONS

This reaction has general application in the preparation of indole derivatives, and in some aspects, this reaction is even more useful than *Fischer Indole Synthesis*.[2m]

F. RELATED REACTIONS

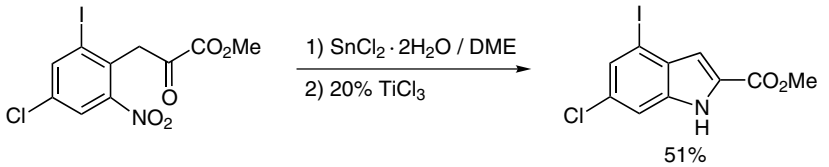
This reaction is related to the *Batcho-Leimgruber Indole Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 3b.

Powdered potassium, prepared from 0.308 g potassium (7.87 mmol) in 6 mL xylene heated at 100°C and stirred rapidly while cooling, was washed with anhydrous Et_2O and covered with 10 mL Et_2O. Then 1.3 mL absolute EtOH (22.0 mmol) was added, and the mixture was stirred and refluxed until the potassium dissolved (~ 3 h). The cooled mixture was treated with 1.07 mL diethyl oxalate (7.87 mmol) and then with a solution of 2.0 g 2-(5-methoxy-3-methyl-2-nitrophenyloxy)-*N,N*-dimethylethanamine (7.87 mmol) in 5 mL dry Et_2O. After 115 h, the dark red precipitate was removed by filtration and washed with Et_2O. The red solid (1.189 g) was dissolved in 45 mL absolute EtOH, acidified with 0.78 mL acetic acid, and hydrogenated over 0.44 g 10% Pd/C at 1 atm of hydrogen for 8 h. The mixture was filtered through Celite, concentrated, diluted with 100 mL 0.2 M aqueous Na_2CO_3, and extracted with EtOAc. The combined extracts were washed with water and brine, dried over Na_2SO_4, evaporated, and purified by flash chromatography using 2% Et_3N in EtOAc as the eluent to give 0.44 g ethyl 7-[2-(dimethylamino)ethoxy]-5-methoxy-1*H*-indole-2-carboxylate as an oil, in a yield of 18%. (*Note*: 1.3 mL absolute EtOH was labeled 2.2 mmol in the original procedure but was corrected here.)



Reference 2d.

To a solution of 1.16 kg $SnCl_2{\cdot}2H_2O$ (5.15 mol) in 1.65 L dimethoxyethane at room temperature was added 880 g crude methyl (2-iodo-4-chloro-6-nitrophenyl)pyruvate, while the temperature was maintained < 30°C. After the mixture was stirred for an additional hour at room temperature, 20% aqueous $TiCl_3$ solution prepared from 2.65 kg $TiCl_3$ (3.43 mol) was then added dropwise to the mixture under cooling with an ice bath to keep the temperature < 10°C. The resulting mixture was stirred at 0–10°C for an additional hour, and 5.6 L 6 *N* HCl and 9.6 L 2:1 EtOAc/toluene mixture were added. The organic layer was separated, washed with 5.6 L 1 *N* HCl, and concentrated to give 632 g crude product. This product was suspended in 6.3 L acetonitrile, which dissolved after refluxing for 30 min, and the solution was allowed to cool to room temperature. The precipitate was filtered, washed with ice-cooled CH_3CN (2 × 600 mL), and dried in vacuo to give 295 g methyl 4-iodo-6-chloroindole-2-carboxylate as a white solid, in a yield of 51% with 93 wt % purity, m.p. 216–218°C.

Other references related to the Reissert indole synthesis are cited in the literature.[7]

H. REFERENCES

1. Reissert, A., *Ber.,* **1896**, *29*, 639.
2. (a) Humphrey, G. R. and Kuethe, J. T., *Chem. Rev.,* **2006**, 106, 2875. (b) Islam, M. S.; Brennan, C.; Wang, Q. W. and Hossain, M. M., *J. Org. Chem.,* **2006**, *71*, 4675. (c) Murakami, Y., *Yakagaku Zasshi (Pharm. Soc. Jpn.),* **2002**, *122*, 869. (d) Katayama, S.; Ae, N. and Nagata, R., *J. Org. Chem.,* **2001**, *66*, 3474. (e) Suzuki, H., Gyoutoku, H.; Yokoo, H.; Shinba, M.; Sato, Y.; Yamada,

H. and Murakami, Y., *Synlett,* **2000**, 1196. (f) Moskal, J. and van Leusen, A. M., *J. Org. Chem.,* **1986**, *51*, 4131. (g) Cannon, J. G.; Lee, T.; Ilhan, M.; Koons, J. and Long, J. P., *J. Med. Chem.,* **1984**, *27*, 386. (h) Kozikowski, A. P.; Greco, M. N. and Springer, J. P., *J. Am. Chem. Soc.,* **1982**, *104*, 7622. (i) Cannon, J. G.; Demopoulos, B. J.; Long, J. P.; Flynn, J. R. and Sharabi, F. M., *J. Med. Chem.,* **1981**, *24*, 238. (j) Kozikowski, A. P. and Greco, M. N., *J. Am. Chem. Soc.,* **1980**, *102*, 1165. (k) Badger, G. M. and Rao, R. P., *Aust. J. Chem.,* **1964**, *17*, 1399. (l) Robinson, B., *Chem. Rev.,* **1962**, *62*, 373. (m) Lindwall, H. G. and Mantell, G. J., *J. Org. Chem.,* **1953**, 18, *345*.

3. (a) Kamijo, S. and Yamamoto, Y., *J. Org. Chem.,* **2003**, *68*, 4764. (b) Milbank, J. B. J.; Tercel, M.; Atwell, G. J.; Wilson, W. R.; Hogg, A. and Denny, W. A., *J. Med. Chem.,* **1999**, *42*, 649. (c) Blasko, G.; Kerekes, P. and Makleit, S., *Alkaloids*, **1987**, *31*, 1. (d) Gannon, W. F.; Benigni, J. D.; Dickson, D. E. and Minnis, R. L., *J. Org. Chem.,* **1969**, *34*, 3002.
4. Johnson, J. R.; Hasbrouck, R. B.; Dutcher, J. D. and Bruce, W. F., *J. Am. Chem. Soc.,* **1945**, *67*, 423.
5. (a) Dong, W. T. and Jimenez, L. S., *J. Org. Chem.,* **1999**, *64*, 2520. (b) Wang, Z. and Jimenez, L. S., *J. Org. Chem.,* **1996**, *61*, 816.
6. Hydorn, A. E., *J. Org. Chem.,* **1967**, *32*, 4100.
7. (a) Gallou, F.; Yee, N.; Qiu, F.; Senanayake, C.; Linz, G.; Schnaubelt, J. and Soyka, R., *Synlett,* **2004**, 883. (b) Butin, A. V.; Stroganova, T. A.; Lodina, I. V. and Krapivin, G. D., *Tetrahedron Lett.,* **2001**, *42*, 2031. (c) Bergman, J. and Sand, P., *Org. Synth. Coll.*, **1993**, *3*, 493. (d) Gallagher, G.; Lavanchy, P. G.; Webster, C. A.; Wilson, J. W.; Hieble, J. P. and DeMarinis, R. M., *J. Med. Chem.,* **1985**, *28*, 1533. (e) Cannon, J. G.; Lukszo, J. and Max, G. A., *J. Heterocycl. Chem.,* **1983**, *20*, 149. (f) Gainor, J. A. and Weinreb, S. M., *J. Org. Chem.,* **1982**, *47*, 2833. (g) Gainor, J. A. and Weinreb, S. M., *J. Org. Chem.,* **1981**, *46*, 4317. (h) Leadbetter, G.; Fost, D. L.; Ekwuribe, N. N. and Remers, W. A., *J. Org. Chem.,* **1974**, *39*, 3580. (i) Noland, W. E. and Baude, F. J., *Org. Synth. Coll.*, **1973**, *5*, 567. (j) Crohare, R.; Merkuza, M.; Gonzalez, H. A. and Ruveda, E. A., *Heterocyclic Chem.*, **1970**, *7*, 729. (k) Hirata, T.; Yamada, Y. and Matsui, M., *Tetrahedron Lett.*, **1969**, 19. (l) Mosettig, E., *Org. React.,* **1954**, *8*, 220. (m) Blaike, K. G. and Perkin, W. H., *J. Chem. Soc.,* **1924**, *125*, 29. (n) Gabriel, S.; Gerhard, W. and Wolter, R., *Ber.,* **1923**, *56*, 1024. (o) Kermack, W. O.; Perkin, W. H. and Robinson, R., *J. Chem. Soc.,* **1921**, 1602. (p) Reissert, A. and Heller, H., *Ber.,* **1904**, *37*, 4364. (q) Reissert, A., *Ber.,* **1897**, *30*, 1030.

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Reppe Alkyne Cyclotrimerization

A. GENERAL DESCRIPTION OF THE REACTION

Although the thermal trimerization of acetylene to benzene was first reported by Berthelot in 1866 at temperatures $> 400^{\circ}C$,[1] it was Reppe who initially reported in 1949 the Ni(II) complex catalyzed [2 + 2 + 2] cyclotrimerization of alkynes,[2] a highly convergent and atom-economic approach to benzene derivatives.[3] This reaction is generally known as the alkyne cyclotrimerization.[3,4] Occasionally, it is also referred to as the alkyne trimerization.[5] When acetylene is used as the alkyne source, the corresponding reaction is more specifically called the metal-catalyzed acetylene trimerization[6] or acetylene cyclotrimerization.[3,7] This symmetry-allowed reaction is a highly exothermic transformation because three π-bonds are converted into three carbon-carbon σ-bonds in a one-step process,[6a] liberating as much as 142 Kcal/mol of energy.[8] However, in the absence of catalyst, this transformation encounters an unbelievably high activation energy, in the range of 60–80 Kcal/mol,[9] thus the pure trimerization of alkyne is almost useless for organic synthesis. By means of catalysis from a transition metal complex, the cyclotrimerization of alkynes is remarkably easy and is tolerable for a wide variety of functional groups, such as vinyl, aryl, ether, hydroxyl, ester, carboxyl, amino and silyl.[6b] In addition, the conjugated alkynes are found to be more reactive than the unconjugated ones.[10] Among the transition metals, the complexes from group VIII elements such as Co, Rh, Ni and Pd have the highest activities,[4j] and cobalt complexes are almost always the first choice (e.g., CpCo(L)CO, L = CO, PR_3, olefin).[10] Although Ni complexes are less reactive than their cobalt analogs, as indicated by the fruitless reaction between diyne-Ni complex and most disubstituted alkynes,[11] the nickel complex is

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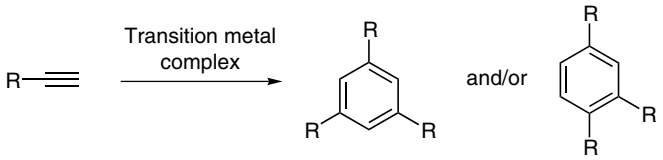
the only one successfully used in asymmetric reactions.[11,12] It has been found that Pd is the most active element among Ni, Pd, and Pt;[7j] and while the Rh-related Grubbs catalyst is almost as effective as cobalt catalyst, the corresponding reaction takes place via a completely different mechanism.[10] In addition, this reaction has been successfully catalyzed by other metal complexes such as Copper complex,[13] Iridium complex,[4f] tantalum-η^2-alkyne complexes,[4g] titanium complexes,[4h,4s] chromium (VI) complex,[4ab] dirhodaborane,[4l] Grubbs catalyst or Wilkinson's catalyst,[4p] as well as metal cluster[14] (e.g., $Os_3(\mu\text{-}SbPh_2)(\mu\text{-}H)(\mu^3,\eta^2\text{-}C_6H_4)(CO)_9$[4n]) and metal porphyrin complexes.[15] Moreover, enamine-directed[4q] and microwave promoted non-metal catalyzed alkyne cyclotrimerization[4c] have also been developed.

It is worth noting that when this reaction involves three different asymmetric alkynes, the regioselectivity is unpredictable, generating as many as 38 different isomers.[7e] For example, monosubstituted alkynes form 1,2,4- and 1,3,5-trialkylbenzenes, with the ratio varying along with the reaction conditions, including the kinetic vs. thermodynamic control and the electronic and spatial requirements of the catalyst.[6b] Recent developments have improved the regioselectivity by use of a partial or total intramolecular version[10] of cyclotrimerization using a silyl[16] or borate tether.[4i] Also of special interest, the cyclotrimerization through titanium metalation, known as metalative Reppe reaction,[7e,17] converts three different asymmetric alkynes into single aromatic compounds.[17]

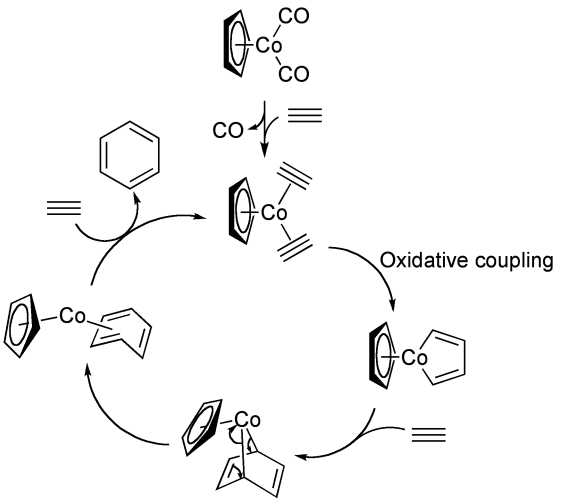
B. GENERAL REACTION SCHEME



(R = H, OH, NH_2, CO_2R', CO_2H, OR′, vinyl, aryl, alkyl, SR'_3, etc.)

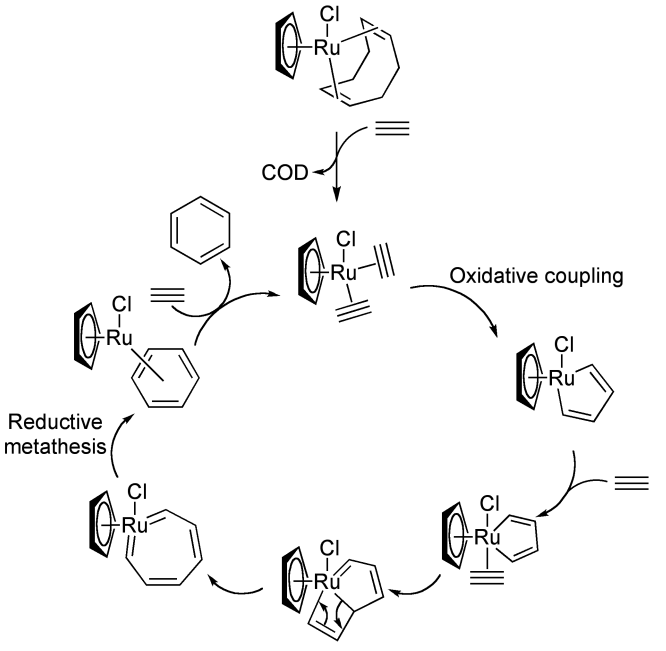
C. PROPOSED MECHANISMS

Although it is known that transition metal complexes can form three-membered metallocycles with alkenes and alkynes,[18] the cobalt-catalyzed reaction (using $CpCo(CO)_2$, for example) involves the formation of a cobalt-dialkyne complex, which transforms into metallocyclopentadiene through oxidative coupling,[6,18] and the insertion or addition of the third alkyne on metallocyclopentadiene leads to the metallocycle, which produces a benzene derivative by reductive elimination of the metal complex.[10] However, a theoretical study shows that this reaction may involve the direct addition of cobalt cyclopentadiene with the third alkyne in a fashion of *Diels-Alder Cycloaddition* to form the cyclopentadiene-cobalt-η^4-cyclohexatriene intermediate, which decomposes to yield the benzene derivative, instead of via reductive elimination.[6a] Thus a revised mechanism is displayed in Scheme 1. Alternatively, the metallocyclopentadiene may dimerize to give a cyclooctatetraene intermediate that decomposes into a benzene derivative and an alkyne, which is also an energetically feasible process.[7j,19]



SCHEME 1. *Mechanism of cobalt complex–catalyzed alkyne cyclotrimerization.*

In contrast, the cyclotrimerization catalyzed by the Grubbs catalyst involves consecutive intramolecular ring metathesis through carbene complexes[10] or formation of a ruthenabicyclo[3.2.0]heptatriene intermediate[3] similar to that formed in the cobalt complex-catalyzed reaction. This mechanism is illustrated in Scheme 2 using acetylene as the alkyne source and CpRuCl[COD] as catalyst.



SCHEME 2. *Mechanism of ruthenium complex–catalyzed alkyne cyclotrimerization.*

D. MODIFICATION

This reaction has been successfully extended to the reaction between alkynes and nitriles[3,6b,10,20] (which function as "heteroalkynes"), especially the electron-deficient nitriles,[4j] for preparing heterocycles, such as pyridines, by which the cobalt complex is the only choice of the catalyst.[10] In addition, the reaction has been extended to other reaction partners, such as olefins,[21] isocyanate (to form pyridone),[3] isothiocyanate (to form thiopyranimines),[3] and carbon disulfide (to give dithiopyrone).[3] Furthermore, the metalative Reppe reaction[7e,17] and the reaction using Grubbs catalyst[3,10] or the addition of Lewis acid (e.g., aluminum phenoxide)[22] have been developed to give cycloadducts regioselectively. It is worth mentioning that several non-metallic complexes catalyzed cyclotrimerizations of alkynes have also been developed: the diethylamine-catalyzed reaction of aroylethyne to 1,3,5-triaroyl benzene,[23] the disilane (Si_2Cl_6)-catalyzed cyclotrimerization of alkyne involving a free-radical mechanism[4w] and enamine-directed[4q] and microwave-promoted alkyne cyclotrimerization.[4c]

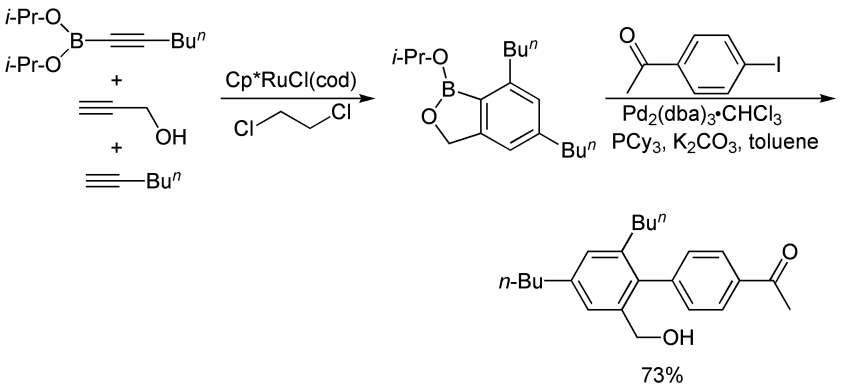
E. APPLICATIONS

This reaction has very wide applications in organic synthesis.

F. RELATED REACTIONS

N/A

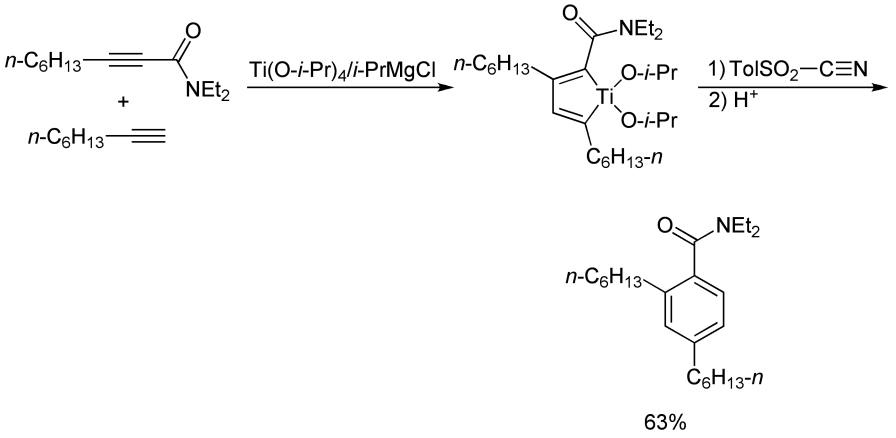
G. CITED EXPERIMENTAL EXAMPLES



Reference 4i.

To 1 mL degassed dry 1,2-dichloroethane containing 9.5 mg Cp*RuCl(cod) (0.025 mmol), 105.1 mg 1-hexynyl-boronate (0.50 mmol) and 104.3 mg 1-hexyne (2.0 mmol) was added 30.8 mg propargyl alcohol (0.55 mmol) in 3 mL degassed dry 1,2-dichloroethane over 15 min at room temperature under an argon atmosphere. The resulting mixture was stirred at room temperature under an argon atmosphere for 5 h,

and then the solvent was removed under reduced pressure. To the residue were added 13.0 mg $Pd_2(dba)_3{\cdot}CHCl_3$ (0.0125 mmol), 15.9 mg PCy_3 (0.055 mmol), 184.5 mg *p*-iodoacetophenone (0.75 mmol), 3.5 mL toluene, and 1.5 mL 2 M K_2CO_3 solution. The reaction mixture was degassed at –78°C under reduced pressure and refilled with argon. After heating at 70°C for 3 h, the resultant solution was extracted with EtOAc (3 mL × 3), and the combined organic layers were dried over $MgSO_4$. Upon removal of solvent under reduced pressure, the residue was purified by silica gel flash column chromatography using hexane/EtOAc (6:1) as the eluent to afford 123.4 mg biphenyl as a pale yellow oil, in a yield of 73%, $R_f = 0.2$ (hexane/EtOAc, 3:1).



Reference 20.

To a stirred solution of 30 mg *N,N*-diethyl-2-nonynamide (0.143 mmol) and 0.053 mL $Ti(O\text{-}i\text{-}Pr)_4$ (0.179 mmol) in 2 mL Et_2O was added 0.295 mL 1.36 M *i*-PrMgCl in Et_2O (0.401 mmol) at −78°C under argon to give a yellow homogeneous solution. The solution was warmed to −50°C over 30 min, during which time its color turned red. After the solution was stirred at −50°C for an additional 5 h, 0.017 mL 1-octyne (0.115 mmol) was introduced at −50°C, and the solution was stirred for another 3 h. Then 31 mg pulverized *p*-toluenesulfonylnitrile (0.172 mmol) was added, and the reaction mixture was stirred for 3 h at −50°C. The reaction was terminated by the addition of 0.05 mL water and quickly warmed up to room temperature. The resulting heterogeneous mixture was dried over anhydrous Na_2SO_4 and filtered through a short pad of Celite. The filtrate was concentrated in vacuo to give a crude oil, which was purified by silica gel column chromatography to afford 25 mg *N,N*-diethyl-3,5-dihexyl-2-picolinamide as a colorless oil, in a yield of 63%.

Other references related to the Reppe alkyne cyclotrimerization are cited in the literature.[24]

H. REFERENCES

1. (a) Bertholet, M., *Compt. Rend. Hebd. Seances Acad. Sci.,* **1866**, *62*, 905. (b) Nieuwland, J. A. and Vogt, R. R., *The Chemistry of Acetylene,* Reinhold, New York, **1945**.

2. (a) Reppe, W.; Schlichting, O.; Klager, K. and Toepel, T., *Ann.,* **1948**, *560*, 1. (b) Reppe, W. and Schweckendiek, W., *Ann.,* **1948**, *560*, 104.
3. Yamamoto, Y.; Kinpara, K.; Saigoku, T.; Takagishi, H.; Okuda, S.; Nishiyama, H. and Itoh, K., *J. Am. Chem. Soc.,* **2005**, *127*, 605.
4. (a) Tanaka, K.; Sagae, H.; Toyoda, K.; Noguchi, K. and Hirano, M., *J. Am. Chem. Soc.,* **2007**, *129*, 1522. (b) Tanaka, K.; Sagae, H.; Toyoda, K. and Noguchi, K., *Eur. J. Org. Chem.,* **2006**, 3575. (c) Saaby, S.; Baxendale, I. R. and Ley, S. V., *Org. Biomol. Chem.,* **2005**, *3*, 3365. (d) Yamamoto, Y., *Curr. Org. Chem.,* **2005**, *9*, 503. (e) Tanaka, K.; Nishida, G.; Wada, A. and Noguchi, K., *Angew. Chem. Int. Ed.,* **2004**, *43*, 6510. (f) Fabbian, M.; Marsich, N. and Farnetti, E., *Inorg. Chim. Acta,* **2004**, *357*, 2881. (g) Oshiki, T.; Nomoto, H.; Tanaka, K. and Takai, K., *Bull. Chem. Soc. Jpn.,* **2004**, *77*, 1009. (h) Ladipo, F. T.; Sarveswaran, V.; Kingston, J. V.; Huyck, R. A.; Bylikin, S. Y.; Carr, S. D.; Watts, R. and Parkin, S., *J. Organomet. Chem.,* **2004**, *689*, 502. (i) Yamamoto, Y.; Ishii, J.-I.; Nishiyama, H. and Itoh, K., *J. Am. Chem. Soc.,* **2004**, *126*, 3712. (j) Yamamoto, Y.; Arakawa, T.; Ogawa, R. and Itoh, K., *J. Am. Chem. Soc.,* **2003**, *125*, 12143. (k) Yong, L. and Butenschoen, H., *Chem. Commun.,* **2002**, 2852. (l) Yan, H.; Beatty, A. M. and Fehlner, T. P., *Organometallics,* **2002**, *21*, 5029. (m) Witulski, B. and Alayrac, C., *Angew. Chem. Int. Ed.,* **2002**, *41*, 3281. (n) Deng, M. L. and Leong, W. K., *Organometallics,* **2002**, *21*, 1221. (o) McDonald, F. E. and Smolentsev, V., *Org. Lett.,* **2002**, *4*, 745. (p) Witulski, B.; Stengel, T. and Fernandez-Hernandez, J. M., *Chem. Commun.,* **2000**, 1965. (q) Pigge, F. C. and Ghasedi, F., *Tetrahedron Lett.,* **2000**, *41*, 6545. (r) Sherrill, A. B.; Lusvardi, V. S. and Barteau, M. A., *Langmuir,* **1999**, *15*, 7615. (s) Ozerov, O. V.; Ladipo, F. T. and Patrick, B. O., *J. Am. Chem. Soc.,* **1999**, *121*, 7941. (t) Das, S. K. and Roy, R., *Tetrahedron Lett*., **1999**, *40*, 4015. (u) Hecht, S. and Frechet, J. M. J., *J. Am. Chem. Soc.,* **1999**, *121*, 4084. (v) Baxter, R. J.; Knox, G. R.; Pauson, P. L. and Spicer, M. D., *Organometallics,* **1999**, *18*, 197. (w) Yang, J. C. and Verkade, J. G., *J. Am. Chem. Soc.,* **1998**, *120*, 6834. (x) Pertici, P.; Verrazzani, A.; Vitulli, G.; Baldwin, R. and Bennett, M. A., *J. Organomet. Chem.,* **1998**, *551*, 37. (y) McKee, C., *Appl. Catal., A: General,* **1995**, *132*, N2. (z) McDonald, F. E.; Zhu, H. Y. H. and Holmquist, C. R., *J. Am. Chem. Soc.,* **1995**, *117*, 6605. (aa) Taber, D. F. and Rahimizadeh, M., *Tetrahedron Lett*., **1994**, *35*, 9139. (bb) Ferrieri, R. A. and Wolf, A. P., *J. Phys. Chem.,* **1984**, *88*, 2256.
5. Pigge, F. C. and Zheng, Z. M., *Tetrahedron Lett*., **2001**, *42*, 8259.
6. (a) Hardesty, J. H.; Koerner, J. B.; Albright, T. A. and Lee, G.-Y., *J. Am. Chem. Soc.,* **1999**, *121*, 6055. (b) Vollhardt, K. P. C., *Acc. Chem. Res.,* **1977**, *10*, 1.
7. (a) Martinez, M.; Michelini, M. del C.; Rivalta, I.; Russo, N. and Sicilia, E., *Inorg. Chem.,* **2005**, *44*, 9807. (b) Boudjahem, A.-G.; Monteverdi, S.; Mercy, M. and Bettahar, M. M., *Appl. Catal., A: General,* **2003**, *250*, 49. (c) Lee, A. F.; Ormerod, R. M.; Wilson, K.; Lambert, R. M.; Goldoni, A. and Baraldi, A., *Surface Sci.,* **2002**, *501*, L165. (d) Ferrari, A. M.; Giordano, L.; Pacchioni, G.; Abbet, S. and Heiz, U., *J. Phys. Chem. B,* **2002**, *106*, 3173. (e) Suzuji, D.; Urabe, H. and Sato, F., *J. Am. Chem. Soc.,* **2001**, *123*, 7925. (f) Abbet, S.; Sanchez, A.; Heiz, U.; Schneider, W.-D.; Ferrari, A. M.; Pacchioni, G. and Rosch, N., *Surface Sci.,* **2000**, *454–456*, 984. (g) Abbet, S.; Sanchez, A.; Heiz, U.; Schneider, W.-D.; Ferrari, A. M.; Pacchioni, G. and Roesch, N., *J. Am. Chem. Soc.,* **2000**, *122*, 3453. (h) Tysoe, W. T., *Isr. J. Chem.,* **1998**, *38*, 313. (i) Holmblad, P. M. and Goodman, D. W., *J. Phys. Chem. B,* **1997**, *101*, 8883. (j) Szanyi, J. and Paffett, M. T., *J. Am. Chem. Soc.,* **1995**, *107*, 1034. (k) Bianchini, C.; Caulton, K. G.; Chardon, C.; Doublet, M.-L.; Eisenstein, O.; Jackson, S. A.; Johnson, T. J.; Meli, A.; Peruzzini, M.; Streib, W. E.; Vacca, A. and Vizza, F., *Organometallics*, **1994**, *13*, 2010. (l) Lepetit, C.; Kermarec, M.; Che, M. and Thomas, J. M., *Colloids & Surface, A: Physiochem. Eng. Aspects,* **1993**, *72*, 265. (m) Lambregts, M. J.; Munson, E. J.; Kheir, A. A. and Haw, J. F., *J. Am. Chem. Soc.,* **1992**, *114*, 6875. (n) Bianchini, C.; Caulton, K. G.; Chardon, C.; Eisenstein, O.; Folting, K.; Johnson, T. J.; Meli, A.; Peruzzini, M.; Rauscher, D. J.; Streib, W. E. and Vizza, F., *J. Am. Chem. Soc.,* **1991**, *113*, 5127. (o) Kazanskii, V. B.; Elev, I. V. and Shelimov, B. N., *J. Mol. Catal.,* **1983**, *21*, 265. (p) Moseley, K. and Maitlis, P. M., *J. Chem. Soc. D,* **1971**, 1604.

8. Benson, S. W., *Thermochemical Kinetics*, John Wiley & Sons, New York, **1968**.
9. (a) Bach, R. D.; Wolber, G. J. and Schlegel, H. B., *J. Am. Chem. Soc.,* **1985**, *107*, 2837. (b) Houk, K. N.; Gandour, R. W.; Strozier, R. W.; Rondan, N. G.; Paquette, L. A., *J. Am. Chem. Soc.,* **1979**, *101*, 6797.
10. Saito, S. and Yamamoto, Y., *Chem. Rev.,* **2000**, *100*, 2901.
11. (a) Sato, Y.; Nishimata, T. and Mori, M., *Heterocycles,* **1997**, *44*, 443. (b) Sato, Y.; Nishimata, T. and Mori, M., *J. Org. Chem.,* **1994**, *59*, 6133.
12. Stará, I. G.; Stary, I.; Kollárovic, A.; Teply, F.; Vyskocil, S and Sÿaman, D., *Tetrahedron Lett.,* **1999**, *40*, 1993.
13. Avery, N. J., *J. Am. Chem. Soc.,* **1985**, *107*, 6711.
14. Abbet, S.; Sanchez, A.; Heiz, U.; Schneider, W.-D.; Ferrari, A. M.; Pacchioni, G. and Rösch, N., *J. Am. Chem. Soc.,* **2000**, *122*, 3453.
15. Fletcher, J. T. and Therien, M. J., *J. Am. Chem. Soc.,* **2000**, *122*, 12393.
16. Chouraqui, G.; Petit, M.; Aubert, C. and Malacria, M., *Org. Lett.,* **2004**, *6*, 1519.
17. Tanaka, R.; Nakano, Y.; Suzuki, D.; Urabe, H. and Sato, F., *J. Am. Chem. Soc.,* **2002**, *124*, 9682.
18. Negishi, E.-I., *Acc. Chem. Res.,* **1987**, *20*, 65.
19. Pacchioni, G. and Lambert, R. M., *Surface Sci.,* **1994**, *304*, 208.
20. Suzuki, D.; Tanaka, R.; Urabe, H. and Sato, F., *J. Am. Chem. Soc.,* **2002**, *124*, 3518.
21. (a) Yamamoto, Y.; Kitahara. H.; Ogawa, R.; Kawaguchi, H.; Tatsumi, K. and Itoh, K., *J. Am. Chem. Soc.,* **2000**, *122*, 4310. (b) Yamamoto, Y.; Kitahara. H.; Hattori, R. and Itoh, K., *Organometallics,* **1998**, *17*, 1910.
22. Mori, N.; Ikeda, S.-I. and Sato, Y., *J. Am. Chem. Soc.,* **1999**, *121*, 2722.
23. Balasubramanian, K.; Selvaraj, P.; and Venkataramani, S., *Synthesis,* **1980**, 29.
24. (a) Sato, Y.; Tamura, T. and Mori, M.*, Angew. Chem. Int. Ed.,* **2004**, *43*, 2436. (b) Sorensen, E. J., *Angew. Chem. Int. Ed*., **2004**, *43*, 1998. (c) Tanaka, K.; Nishida, G.; Wada, A. and Noguchi, K., *Angew. Chem. Int. Ed*., **2004**, *43*, 6510. (d) Paneque, M.; Poveda, M. L.; Rendón, N. and Mereiter, K., *J. Am. Chem. Soc.,* **2004**, *126*, 1610. (e) Teply, F.; Stará, I. G.; Stary, I.; Kollárovic, A.; Sÿaman, D.; Vyskocil, S. and Fiedler, P., *J. Org. Chem.,* **2003**, *68*, 5193. (f) Kirchner, K.; Calhorda, M. J.; Schmid, R. and Veiros, L. F., *J. Am. Chem. Soc.,* **2003**, *125*, 11721. (g) Yamamoto, Y.; Takagishi, H. and Itoh, K., *J. Am. Chem. Soc.,* **2002**, *124*, 28. (h) Witulski, B.; Zimmermann, A. and Gowans, N. D.*, Chem. Commun*., **2002**, 2984. (i) Eichberg, M. J.; Dorta, R. L.; Grotjahn, D. B.; Lamottke, K.; Schmidt, M. and Vollhardt, K. P. C., *J. Am. Chem. Soc.,* **2001**, *123*, 9324. (j) Eichberg, M. J.; Dorta, R. L.; Lamottke, K. and Vollhardt, K. P. C.*, Org. Lett.* **2000**, *2*, 2479. (k) Herberhold, M.; Yan, H.; Milius, W. and Wrackmeyer, B., *Organometallics,* **2000**, *19*, 4289. (l) Lautens, M.; Klute, W. and Tam, W., *Chem. Rev*., **1996**, *96*, 49. (m) Nickel, T.; Goddard, R.; Krüger, C.; Pörschke, K.-R., *Angew. Chem. Int. Ed. Engl.,* **1994**, *33*, 879. (n) Pope, R. M.; VanOrden, S. L.; Cooper, B. T. and Buckner, S. W., *Organometallics*, **1992**, *11*, 2001. (o) Imamura, H.; Miura, H. and Konishi, T., *Chem. Lett.,* **1990**, 1495. (p) Trost, B. M., *Science,* **1991**, *254*, 1471. (q) Neeson, S. J. and Stevenson, P. J.*, Tetrahedron,* **1989**, *45*, 6239. (r) Schore, N. E., *Chem. Rev*., **1988**, *88*, 1081. (s) Halterman, R. L. and Vollhardt, K. P. C.*, Organometallics* **1988**, *7*, 886. (t) Lecker, S. H.; Nguyen, N. H. and Vollhardt, K. P. C., *J. Am. Chem. Soc.,* **1986**, *108*, 856. (u) Parnell, C. A. and Vollhardt, K. P. C., *Tetrahedron,* **1985**, *41*, 5791. (v) Vollhardt, K. P. C., *Angew. Chem. Int. Ed. Engl*., **1984**, *23*, 539. (w) Earl, R. A. and Vollhardt, K. P. C., *J. Org. Chem.,* **1984**, *49*, 4786. (x) Earl, R. A. and Vollhardt, K. P. C., *J. Am. Chem. Soc.,* **1983**, *105*, 6991. (y) Funk, R. L. and Vollhardt, K. P. C., *J. Am. Chem. Soc.,* **1980**, *102*, 5253.

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Reppe Carbonylation

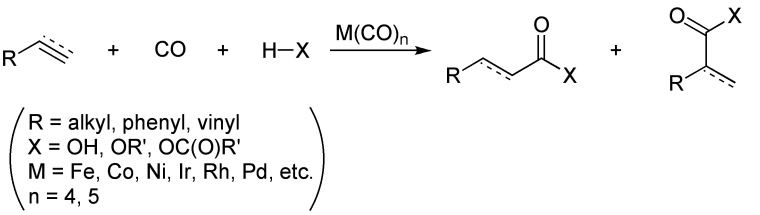
A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Reppe in 1953.[1] It is a three-component reaction to transform unsaturated hydrocarbons (e.g., alkene, alkyne, conjugated dienes, styrene, etc.) and carbon monoxide (CO) into a variety of saturated or unsaturated acids, esters, or anhydrides using a CO complex of group VIII transition metals as a catalyst with water, alcohol, or acid as a nucleophile, respectively.[2] This reaction, as a part of the Reppe chemistry,[3] is generally known as the Reppe carbonylation[2,4] or the Reppe process.[5] Occasionally, it is also referred to as the Reppe reaction.[6] However, when water is applied as the nucleophile, the corresponding Reppe carbonylation is also referred to as hydrocarboxylation;[2] when alcohol is chosen as a nucleophile for the production of ester, the reaction is known as hydroesterification, hydroalkoxycarbonylation or hydrocarbalkoxylation.[2] In this reaction, although carbon monoxide complexes of all group VIII transition metals are active catalysts, the cobalt and palladium complexes are the most active ones.[2] In addition, this reaction is very versatile and tolerable for a wide variety of functional groups.[2] Theoretical calculations have indicated that this reaction is a thermodynamically favored and kinetically easy process.[4b] For the carbonylation of alkenes, it has been found that the reaction rate generally follows the order of aliphatic alcohols $\approx$ acids $>$ water $>$ phenols,[7] whereas among the alcoholic nucleophiles, the reactivity order is primary $>$ secondary $>$ tertiary alcohols,[7,8] although aliphatic alcohols with a carbon chain length between one and six have no apparent effect on the reaction rate.[7,9] However, in the presence of hydrogen, the effect of steric bulkiness vanishes.[10] For the carbonylation of alkynes, it has been found that water increases the reaction rate and especially the rate for the formation of linear acids.[2]

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

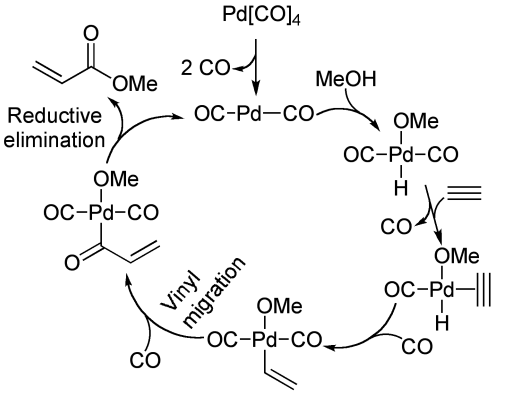
In alkaline solution of an iron-carbon monoxide complex, the alkenes are converted into aldehydes and finally alcohols of one more carbon atom.[6a] Under these conditions, the iron complex of carbon monoxide was found to be binuclear,[11] whereas the mononuclear complex is labile at temperatures above 140°C.[12] In addition, it has been found that aldehyde is an initial product that is reduced to alcohol in the second stage of the reaction, and the nature of the base plays an important role in controlling the reaction path, either to produce aldehyde (e.g., KOH) or alcohol (e.g., alkyl amines).[6a] The formation of aldehyde is known as Reppe hydroformylation or the Reppe reaction.[6a]

B. GENERAL REACTION SCHEME

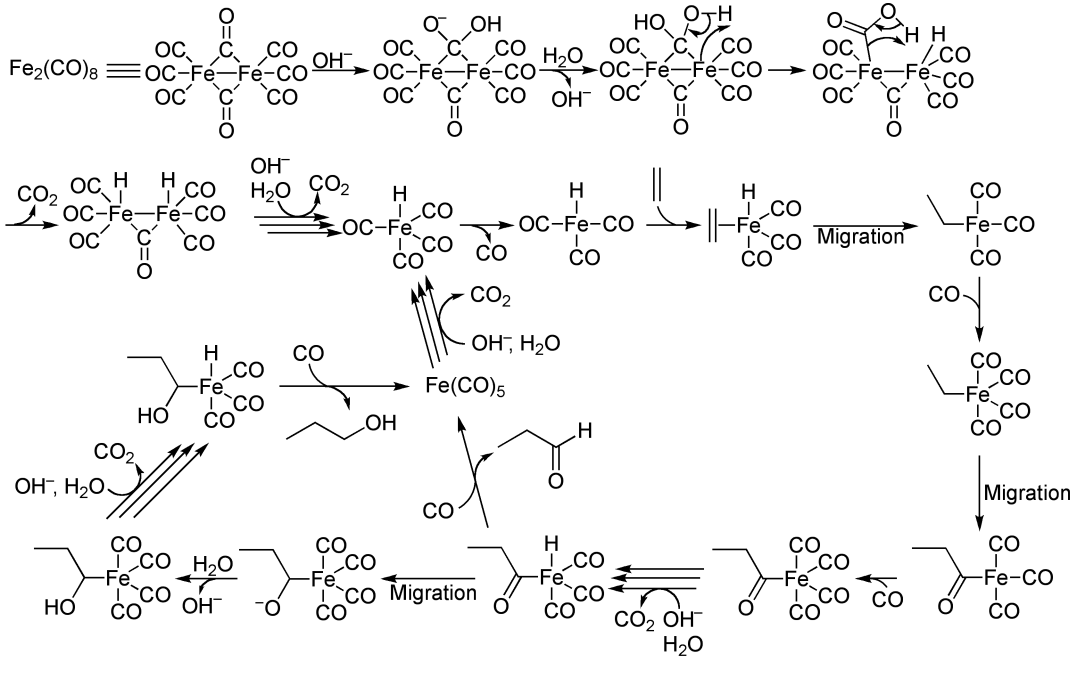


C. PROPOSED MECHANISMS

For the Reppe carbonylation, it is proposed that the reaction involves the initial oxidative addition of a nucleophile to the transition metal complex, followed by the complexation of an unsaturated hydrocarbon to the metal and insertion into a metal-H bond. Subsequently, migration of hydrocarbon species to CO followed by a reductive elimination afford the corresponding product.[4a] Scheme 1 illustrates the formation of ester from acetylene, CO, and methanol in the presence of a catalytic amount of $Pd[CO]_4$. In addition, a mechanism analogous to that of *Hydroformylation*[13] is proposed and displayed in Scheme 2 for the Reppe formylation.



SCHEME 1. *Preparation of ester from acetylene, CO, and alcohol by the Reppe carbonylation.*



SCHEME 2. *Formation of alcohol and aldehyde from ethylene and CO in the presence of* $Fe_2(CO)_8$.

D. MODIFICATION

N/A

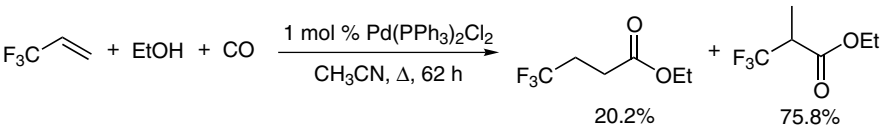
E. APPLICATIONS

This reaction has important application in industrial manipulation.[3b]

F. RELATED REACTIONS

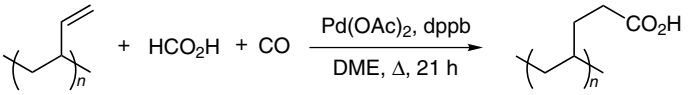
This reaction is related to the *Hydroformylation.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 13.

To a 50-mL stainless-steel autoclave fitted with a magnetic stirring bar were added 0.1 mmol $Pd(PPh_3)_2Cl_2$, 3 mL degassed ethanol, and 10 mL degassed acetonitrile. The autoclave was cooled with dry ice/acetone and evacuated, then 0.96 g gaseous trifluoropropene (10 mmol) was introduced and the autoclave was pressurized with CO up to 110 atm (at room temperature). The autoclave was heated to 100°C under stirring for 62 h. After that, the autoclave was rapidly cooled with ice water, and CO was carefully purged out to afford 75.8% ethyl 2-methyl-3,3,3-trifluoropropionate and 20.2% ethyl γ,γ,γ-trifluorobutyrate.



Reference 14.

To a 45-mL autoclave equipped with a glass liner containing a stirring bar were added 4 mL DME, 4.5 mg palladium acetate (0.02 mmol), and 17 mg dppb (0.04 mmol). To this mixture was added a solution of 270 mg 1,2-polybutadiene in 1 mL DME (equivalent to 5 mmol of vinyl groups) and then 460 mg formic acid (10 mmol). The autoclave was purged with CO and pressurized to 100 psi, and heated at 150°C for 21 h. Then the autoclave was cooled to room temperature, CO was vented, and the reaction mixture was filtered and evaporated to near dryness. Ether (30 mL) was used to rinse all the mass out of autoclave, and the polymer product precipitated instantly. After extracting with 30 mL 2 M NaOH, the ether layer was dried over $MgSO_4$ and evaporated to give a solid residue that did not contain any traces of starting polymer. The aqueous solution was acidified by 30 mL 6 M HCl,

and the precipitated polyacid was collected by filtration and dried in vacuo. A small amount of polyacid adhering to the glass wall was further recovered by small amount of acetone.

Other references related to the Reppe carbonylation are cited in the literature.[15]

H. REFERENCES

1. (a) Reppe, W., *Ann.,* **1953**, *582*, 1. (b) Reppe, W. and Kroper, H., *Ann.,* **1953**, *582*, 38. (c) Reppe, W.; Kroper, H.; Kutepow, N. and Pistor, H., *Ann.,* **1953**, *582*, 72. (d) Reppe, W.; Kroper, H.; Pistor, H. and Weissbarth, O., *Ann.,* **1953**, *582*, 87. (e) Reppe, W. and Vetter, H., *Ann.,* **1953**, *582*, 133.
2. Kiss, G., *Chem. Rev.,* **2001**, *101*, 3435.
3. (a) Hempstead, C. and Worthington, W., ed., *Encyclopedia of 20th-Century Technology*, Routledge Reference, New York **2007**. (b) Abelshauser, W.; von Hippel, W.; Johnson, J. A. and Stokes, R. G., *German Industry and Global Enterprise, BASF: The History of a Company*, Cambridge University Press, Cambridge, **2004**. (c) Ministry of Economic Affairs of The Netherlands, *Technology Roadmap Catalysis: Catalysis, Key to sustainability*, Ministry of Economic Affairs of the Netherlands, Amsterdam, **2001**.
4. (a) Bodis, J., *Revista Chim. (Bucharest)*, **2005**, *56*, 1062. (b) De Angelis, F.; Sgamellotti, A. and Re, N., *Organometallics,* **2000**, *19*, 4104. (c) De Angelis, F.; Re, N.; Sgamellotti, A.; Selloni, A.; Weber, J. and Floriani, C., *Chem. Phys. Lett.,* **1998**, *291*, 57. (d) Laurer, P., *Ind. Chim. Belg.,* **1967**, *32*, 646.
5. (a) Barborak, J. C. and Cann, K., *Organometallics,* **1982**, 1,1726. (b) Kindler, H. and Eisfeld, K., *Ind. Chim. Belg.,* **1967**, *32*, 650. (c) Suzuki, S.; Ito, H.; Tatemichi, H. and Kimata, S., *Kogyo Kagaku Zasshi*, **1951**, *54*, 511. (d) Ohashi, K.; Suzuki, S. and Ito, H., *Kogyo Kagaku Zasshi*, **1951**, *54*, 454.
6. (a) Massoudi, R.; Kim, J. H.; King, R. B. and King, A. D., *J. Am. Chem. Soc.,* **1987**, *109*, 7428. (b) Mullen, A., *Reactivity & Struct.: Concepts in Org. Chem.,* **1980**, *11*, 243. (c) Bogoradovskaya, N. M.; Imyanitov, N. S. and Rudkovskii, D. M., *Zh. Prikladnoi Khim. (Sankt-Peterburg)*, **1973**, *46*, 616.
7. (a) Knifton, J. F., *J. Am. Oil Chem. Soc.,* **1978**, *55*, 496. (b) Knifton, J. F., *J. Org. Chem.,* **1976**, *41*, 2885.
8. Cavinato, G. and Toniolo, L., *J. Mol. Catal.,* **1990**, *58*, 251.
9. Cavinato, G. and Toniolo, L., *J. Mol. Catal. A: Chem.,* **1996**, *104*, 221.
10. Lin, I. J. B.; Liao, J. C. and Chuang, C. C., *J. Chin. Chem. Soc.,* **1991**, *38*, 483.
11. Sternberg, H. W.; Friedel, R. A.; Markby, R. and Wender, I., *J. Am. Chem. Soc.,* **1956**, *78*, 3621.
12. Funaioli, T.; Cavazza, C.; Marchetti, F. and Fachinetti, G., *Inorg. Chem.,* **1999**, 38,3361.
13. Fuchikami, T.; Ohishi, K. and Ojima, I., *J. Org. Chem.,* **1983**, *48*, 3803.
14. Ajjou, A. N. and Alper, H., *Macromolecules,* **1996**, *29*, 1784.
15. (a) Nozaki, K., *Chem. Record,* **2005**, *5*, 376. (b) Tsuji, J., *Palladium Reagents and Catalysts,* John Wiley & Sons, New York, **1999**. (c) Indris, O. and Stahl, W., *J. Phys. Chem. A,* **1999**, *103*, 11310. (d) Bertoux, F.; Monflier, E.; Castanet, Y. and Mortreux, A., *J. Mol. Catal. A: Chem.,* **1999**, *143*, 11. (e) Wender, I. and Pino, P., *Organic Synthesis via Metal Carbonyls,* Wiley-Interscience, New York, **1997**, 2. (f) Keijsper, J.; Arnoldy, P.; Doyle, M. J. and Drent, E., *Recl. Trav. Chim. Pays-Bas,* **1996**, *115*, 248. (g) Beller, M.; Cornils, B.; Frohning, C. D. and Kohlpaintner, C. W., *J. Mol. Catal. A: Chem.,* **1995**, *104*, 17. (h) Drent, E.; Arnoldy, P. and Budzelaar, P. H. M., *J. Organomet. Chem.,* **1994**, *475*, 57. (i) Cavell, K. J., *Aust. J. Chem.,* **1994**, *47*, 769. (j) Narayanan, P.; Kaye, B. and

Cole-Hamilton, D. J., *J. Mater. Chem.,* **1993**, *3*, 19. (k) Chiusoli, G. P., *Transition Met. Chem.,* **1991**, *16*, 553. (l) Papp, H. and Baerns, M., in *New Trends in CO Activation,* ed., Guczi, L., Elsevier Science Publishers, **1991**. (m) Roper, M., *Stud. Surf. Sci. Catal.,* **1991**, *64*, 381. (n) Milstein, D., *Acc. Chem. Res.,* **1988**, *21*, 428. (o) Ojima, I., *Chem. Rev.,* **1988**, *88*, 1011. (p) Hellmold, P. and Schnurpfeil, D., *Acetylenchemie*, VEB Deutscher Verlag für Grundstoffindustrie, Leipzig, **1986**. (q) Escaffre, P.; Thorez, A. and Kalck, P., *J. Mol. Catal.,* **1985**, *33*, 87. (r) Mullen, A., in *New Syntheses with Carbon Monoxide*, Springer-Verlag, New York, **1980**, p. 243. (s) Cassar, L.; Chiusoli, G. P. and Guerrieri, F., *Synthesis,* **1973**, 509. (t) Tsuji, J., *Acc. Chem. Res.,* **1969**, *2*, 144. (u) Bird, C. W., *Chem. Rev.,* **1962**, *62*, 283.

531

Reppe Cyclization

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Reppe in 1948.[1] It is a nickel complex-catalyzed [2+ 2+ 2+ 2] cyclotetramerization of acetylene to cyclooctatetraene (COT), and is generally known as the Reppe cyclization.[2] Occasionally, it is also referred to as the Reppe reaction,[3] Reppe synthesis,[4] or Reppe cyclooctatetraene synthesis.[5] The nickel catalysts used for this reaction include $Ni(acac)_2$,[6] $Ni_2(COT)_2$,[7] 1,2-diaza diene nickel complex ($Ni(dad)_2$)[8] and even vapor-deposited nickel.[9] This reaction is the showcase of efficiency for organometallic complex-catalyzed reactions. For example, cyclooctatetraene was synthesized from pseudopelletierine by a 13-step manipulation in 1901 in very low yield,[10] whereas up to 90% yield of cyclooctatetraene can be obtained by pressurizing acetylene into a warm suspension of $Ni(CN)_2$ and CaC_2 in THF,[1a,11] or $NiBr_2/CaC_2$.[6a] In addition, it is known that the turnover number can be as high as up to 10^6 in neat propargylic alcohol, regardless of the catalyst.[12] Although it has been reported that nickel catalyst does not work for disubstituted alkynes,[13] in a few cases, disubstituted alkynes form octa-substituted cyclooctatetraenes, as evidenced in the reaction of 1-methyl-2-phenyl-acetylene on nickel prepared by vapor deposition[9] and cobalt complex-catalyzed cyclization of acetylenedicarboxylic acid ester.[14] In general, this reaction does not hold regioselectivity,[13c] and 1,2,4,7-tetrasubstituted cyclooctatetraene and 1,2,4,6- and 1,3,5,7-tetrasubstituted cyclooctatetraenes are often produced from monosubstituted acetylenes.[13c] Other types of substituted cyclooctatetraenes can be produced by application of monosubstituted or disubstituted acetylene with 3 equivalents of acetylene.[15] Often, this reaction is accompanied with side reactions yielding benzene derivatives.[15d,16]

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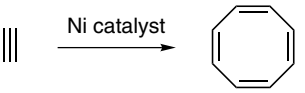
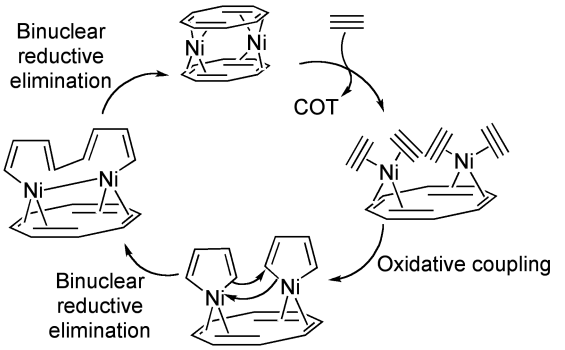
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

This reaction is believed to involve a number of complex processes,[17] by which four alkynes coordinate to a metal center to undergo either a stepwise coupling or a concerted "zipper-type" cyclization.[2d,13c] However, the $Ni_2(COT)_2$-catalyzed reaction involves the formation of a bis(cyclopentadienylnickel) complex,[7] a homobimetallic center,[2c] as supported by the actual determination of the structure from X-ray crystallography;[7] by the fast initiation of the reaction without an induction period when used directly for alkynes compared to other types of catalysts,[18] and by kinetic studies and labeling experiments.[2d,3,5] An illustrative mechanism catalyzed by $Ni_2(COT)_2$ is given here.



D. MODIFICATION

This reaction has been modified by use of the sterically hindered 1,2-diaza diene nickel complex, $Ni(dad)_2$ as catalyst to improve the regioselectivity. Under these conditions, primary propargylic alcohol is converted to 1,3,5,7-tetrasubstittued COT,[8] whereas secondary propargylic alcohol and propargylic esters are transformed into 1,3,6,8-tetrasubstituted COTs,[19] and propargylic ether is converted into 1,4,5,8-tetrasubstituted COT.[20] In addition, the ruthenium catalyst $[(Ph_3P)_3Ru(CO)H_2]$ has also been used successfully to convert diphenylbutadiyne into cyclooctatetraene.[21] It should be mentioned that a combination of Lewis acid and base (e.g., $AlBr_3$ and Et_3N) has also been developed to transform terminal acetylenes into 1,3,5,7- and 1,2,5,6-tetrasubstituted *syn*-tricyclo[4.2.0.$0^{2,5}$]octadienes which rearrange into 1,3,5,7- and 1,2,5,6-tetrasubstituted cyclooctatetraene through thermal or photochemical ring opening.[6b]

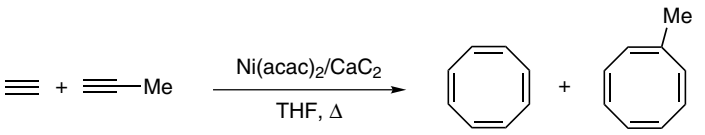
E. APPLICATIONS

This reaction has general application in the preparation of cyclooctatetraene derivatives.

F. RELATED REACTIONS

This reaction is closely related to the *Reppe Alkyne Cyclotrimerization*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 15d.

To a 1-L stainless-steel autoclave cooled with dry ice and trichloroethylene were added 10 g nickel acetylacetonate, 20 g powdered calcium carbide, and 30 g propyne dissolved in 250 mL THF also cooled with dry ice and trichloroethylene. The system was sealed, and the air was evacuated and replaced by acetylene to a pressure of 150–300 psi. The mixture was stirred and heated at 70–90°C for 7–12 hours while the acetylene was maintained at same pressure by represurizing acetylene at frequent intervals. After that, the mixture was steam distilled until 2 L of distillate was collected to separate volatile material (e.g., THF, benzene, substituted benzene, and cyclooctatetraene) from a water-insoluble residue (largely cuprene from polymerization of alkyne). The water-insoluble portion of the residue was separated by filtration, and extracted in a Soxhlet apparatus for 24 h with benzene containing a small amount of hydroquinone as a polymerization inhibitor. The benzene extract was concentrated and distilled, and the crude distillate was combined with the residue obtained by fractionation of the organic portion of the steam distillate (after the benzene, and cyclooctatetraene present had been removed as low-boiling fractions). This process yielded 40 g cyclooctatetraene and 14.1 g methylcyclooctatetraene (16%). Methylcyclooctatetraene was further purified by conversion into the crystalline silver nitrate complex and regeneration by shaking with a 100% excess of concentrated NH_4OH, extraction with pentane and redistillation, b.p. 84.5°C at 67 mmHg.

Other references related to the Reppe cyclization are cited in the literature.[22]

H. REFERENCES

1. (a) Reppe, W.; Schlichting, O.; Klager, K. and Toepel, T., *Ann*., **1948**, *560*, 1. (b) Reppe, W. and Schweckendiek, W., *Ann*., **1948**, *560*, 104.
2. (a) Duncan, M. A., *Int. Rev. Phys. Chem*., **2003**, *22*, 407. (b) Walters, R. S.; Jaeger, T. D. and Duncan, M. A., *J. Phys. Chem. A*, **2002**, *106*, 10482. (c) Arif, A. M.; Chandler, D. J. and Jones, R. A., *Organometallics*, **1987**, *6*, 506. (d) Colborn, R. E. and Vollhardt, K. P. C., *J. Am. Chem. Soc*., **1986**, *108*, 5470.
3. Lawrle, C. J.; Gable, K. P. and Carpenter, B. K., *Organometallics*, **1989**, *8*, 2274.
4. Schrauzer, G. N. and Eichler, S., *Chem. Ber.,* **1962**, *95*, 550.
5. Colborn, R. E. and Vollhardt, K. P. C., *J. Am. Chem. Soc.,* **1981**, *103*, 6259.

6. (a) Lautens, M.; Klute, W. and Tam, W., *Chem. Rev*., **1996**, *96*, 49. (b) Boussie, T. R. and Streitwieser, A., *J. Org. Chem*., **1993**, *58*, 2377.
7. Wilke, G., *Pure & Appl. Chem*., **1978**, *50*, 677.
8. Tom Dieck, H.; Svoboda, M. and Kopf, J., *Z. Naturforsch*., **1978**, *33B*, 1381.
9. Simons, L. H. and Lagowski, J. J., *Fund. Res. Homogeneous Catal*., **1978**, *2*, 73.
10. (a) Cope, A. C. and Bailey, W. J., *J. Am. Chem. Soc*., **1948**, *70*, 2305. (b) Willstaätter, R. and Heidelberger, M., *Ber*., **1913**, *46*, 517. (c) Willstätter, R. and Waser, E., *Ber*., **1911**, *44*, 3423.
11. Cornforth, J. W., *Aust. J. Chem*., **1993**, *46*, 157.
12. Walther, D.; Braun, D.; Schulz, W. and Rosenthal, U., *Z. Anorg. Allg. Chem*., **1989**, *577*, 270.
13. (a) Sato, Y.; Nishimata, T. and Mori, M., *Heterocycles*, **1997**, *44*, 443. (b) Sato, Y.; Nishimata, T. and Mori, M., *J. Org. Chem*., **1994**, *59*, 6133. (c) Schore, N. E., *Chem. Rev.*, **1988**, *88*, 1081.
14. Mao, F.; Schut, D. M. and Tyler, D. R., *Organometallics*, **1996**, *15*, 4770.
15. (a) Cope, A. C. and Pike, R. M., *J. Am. Chem. Soc*., **1953**, *75*, 3220. (b) Cope, A. C. and Rugan, D. F., *J. Am. Chem. Soc*., **1953**, *75*, 3215. (c) Cope, A. C. and Smith, D. S., *J. Am. Chem. Soc*., **1952**, *74*, 5136. (d) Cope, A. C. and Campbell, H. C., *J. Am. Chem. Soc*., **1952**, *74*, 179. (e) Cope, A. C. and Campbell, H. C., *J. Am. Chem. Soc*., **1951**, *73*, 3536.
16. See *Reppe Alkyne Cyclotrimerization* herein (P. 2345).
17. Maitlis, P. M., *Acc. Chem. Res*., **1976**, *9*, 93.
18. Wilke, G., *Angew. Chem. Int. Ed. Engl*., **1988**, *27*, 185.
19. Diercks, R. and tom Dieck, H., *Ber*., **1985**, *118*, 428.
20. Diercks, R.; Stamp, L. and tom Dieck, H., *Ber*., **1984**, *117*, 1913.
21. Lu, P.; Hong, H. P.; Cai, G. P.; Djurovich, P.; Weber, W. P. and Thompson, M. E., *J. Am. Chem. Soc*., **2000**, *122*, 7480.
22. (a) Straub, B. F. and Gollub, C., *Chem. Eur. J.*, **2004**, *10*, 3081. (b) Mathur, P.; Bhunia, A. K.; Mobin, S. M.; Singh, V. K. and Srinivasu, C., *Organometallics*, **2004**, *23*, 3694. (c) Roesky, P. W., *Eur. J. Inorg. Chem*., **2001**, 1653. (d) Green, M.; Norman, N. C. and Orpen, A. G., *J. Am. Chem. Soc*., **1981**, *103*, 1269. (e) Jolly, P. W. and Wilke, G., *"The Organic Chemistry of Nickel"*, John Wiley & Sons, New York, **1974**. (f) Heimbach, P., *Angew. Chem. Int. Ed. Engl*., **1973**, *12*, 975. (g) Reinsch, E.-A., *Theoretica Chem. Acta*, **1968**, *11*, 296. (h) Cope, A. C. and Meili, J. E., *J. Am. Chem. Soc*., **1967**, *89*, 1883. (i) Schröder, G., "*Cyclooctatetraen*", Verlag Chemie: Weinheim/Bergstr., Germany, **1965**. (j) Fredericks, R. J.; Lynch, D. G. and Daniels, W. E., *J. Poly. Sci. Part B: Poly. Lett*., **1964**, *2*, 803. (k) Leto, J. R. and Leto, M. F., *J. Am. Chem. Soc.*, **1961**, *83*, 2944. (l) Cairns, T. L.; Engelhardt, V. A.; Jackson, H. L.; Kalb, G. H. and Sauer, J. C., *J. Am. Chem. Soc*., **1952**, *74*, 5636.

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Reppe Vinylation
(Reppe Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Reppe in 1931.[1] It is a strong-base catalyzed addition of acetylene to form a variety of vinylic compounds and is known as the Reppe vinylation or Reppe synthesis.[2] In this reaction, vinyl ethers, vinyl sulfides, vinyl phenyl ethers, vinyl esters, and vinyl amines have been prepared by the addition of acetylene with alcohols, thiols or disulfides, phenols, carboxylic acids, and amines, respectively, at temperatures from 160° to 200°C and acetylene pressure from 100 to 300 psi.[3] It is known that acetylene is an explosive substance; however, acetylene can be handled safely under these reaction conditions by either diluting acetylene with inert material (e.g., N_2,[2,3] CO_2[3]), by using special apparatus, in which the amount of free space in the reaction system is minimized by packing material (e.g., steel or porcelain Raschig ring), or by using bunches of small reaction tubes.[3] The option of dilution with inert nitrogen is good for an autoclave operation, whereas the condition with minimized free space is good for continuous operation, especially with solid contact catalyst.[3] For the preparation of vinyl ethers from alcohols, the best catalysts are KOH and potassium alkoxide,[3] and the reactivity is in the order of primary alcohols > secondary alcohols > tertiary alcohols,[3,4] where the carbon chain in primary alcohols can be from C_1 to C_{18}, and the short-chain alcohols are best carried out in continuous fashion.[3] In addition, polyhydroxyl alcohols, such as ethylene glycol, glycerol, sorbitol,[3] pentaerythritol,[5] and sugar derivatives (e.g., mannitol[6]) can also be vinylated under these conditions to produce divinyl, trivinyl, or multivinyl ethers or cyclic acetals.[3] However, there is the potential that the potassium alkoxide catalyst may gradually diminish because of the transformation of the fatty acids into corresponding potassium carboxylates and hydrogen at such high temperature.[3] For the reaction between amines and acetylene, zinc or cadmium acetates are used as catalyst; however, alkylidenimines are formed instead of vinyl amines from primary aliphatic amines.[7] In addition, the β- or γ-hydroxy primary

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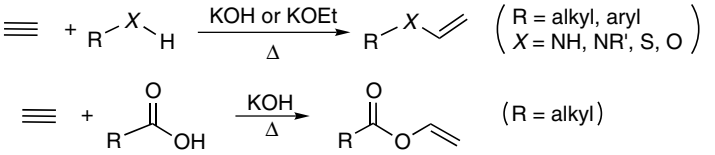
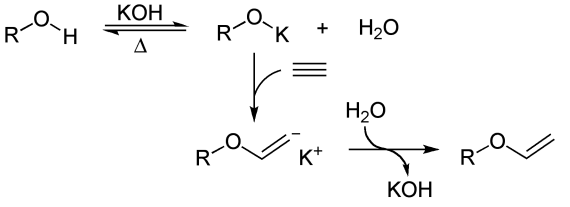
or secondary amines are converted into 2-methyloxazolidines or 2-methyltetrahydro-1,3-oxazines in reaction with acetylene with or without catalyst present, and nitrogen is the atom involved in the addition rather than oxygen.[8] For example, *N*-phenylethanolamine is converted into *N*-phenyloxazolidine with acetylene when zinc or cadmium acetate is used as catalyst.[9] Other less basic nitrogen-containing compounds, such as carbazoles, cyclic amides, pyrrolidones,[3] and *N*-monoalkyl sulfonamides,[10] have been vinylated under similar conditions with acetylene, even though *N*-monoaryl sulfonamide, *p*-toluenesulfonanilide, butanesulfonamide, and unsubstituted sulfonamides failed for this reaction.[10] Similarly, fatty acids such as lauric acid, stearic acid, and oleic acid have been successfully converted into corresponding vinyl esters;[11] and many phenols, especially monoalkylated phenols can be vinylated at 160°C using zinc naphthenate as catalyst.[3]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is believed that a strong base such as KOH or potassium alkoxide will deprotonate the active hydrogen from the reactants, such as alcohols, thiols, amines, carboxylic acids, and phenols, to generate the nucleophiles that add to acetylene, as illustrated by the formation of vinyl ether from alcohol and acetylene. This can qualitatively explain the reactivity order among primary, secondary, and tertiary alcohols, without considering the steric hindrance. It is known that tertiary alcohol is less acidic than secondary and primary alcohol, therefore, less potassium *t*-butoxide will be formed than primary potassium alkoxide from KOH.[4]



D. MODIFICATION

The preparation of vinyl sulfides (or thioethers) has been extended by X-ray[12] or UV[13] irradiated addition of thiols to acetylene, and $Pd(OAc)_2$ or $Pd(PPh_3)_4$[14] catalyzed addition of thiol or disulfide to alkynes. In addition, alkyl halides (e.g., ethyl bromide, *n*-butyl bromide, *sec*-butyl bromide, benzyl chloride, etc.) have been successfully converted into corresponding vinyl sulfide through a one-pot process addition of acetylene mediated by thiourea.[15]

Furthermore, $[Pd(Triphos)](CF_3SO_3)_2$ has been used as an effective catalyst for the addition of amine to alkyne,[16] and the vinyl carbamate derivatives can be prepared in one step from acetylene, CO_2, and one of the following amines: dialkylamine, morpholine, piperidine, and pyrrolidine, using $RuCl_3 \cdot 3H_2O$ or $[RuCl_2(norbornadiene)]_n$ as the catalyst.[17] In addition, the preparation of vinyl phenyl ethers has been modified using tributyl(vinyl)tin[18] or 2,4,6-trivinylcyclotriboroxane-pyridine complex[19] as the vinyl source.

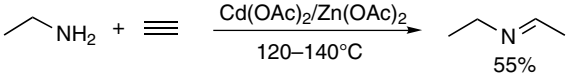
E. APPLICATIONS

This reaction has very important industrial applications for the production of vinylic monomers for polymerization.

F. RELATED REACTIONS

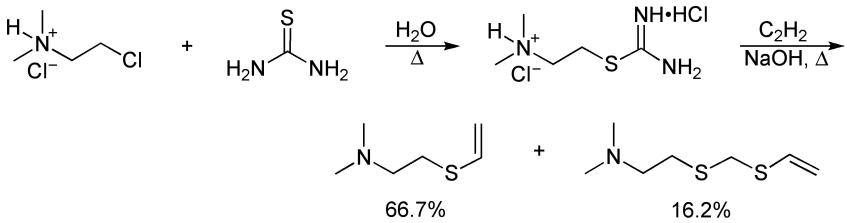
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 7.

An autoclave containing a catalyst prepared from 2.5 g cadmium acetate dihydrate and 2.5 g zinc acetate dihydrate was evacuated, chilled in dry ice acetone and charged with 188.5 g ethylamine (4.18 mol) and acetylene to a pressure of 200 psi. The sealed autoclave was then heated at 120°C for 17 h and at 140°C for 12 h. More acetylene was added after cooling at 20°C before a final heating period of 6 h at 140°C. The maximum pressure was recorded as 785 psi. When the autoclave was cooled down to room temperature, the gases were vented slowly through traps at dry ice temperature. Than 50 g of a colorless liquid, assumed to be mostly ethylamine, was trapped. The minimum amount of acetylene absorbed was calculated to be 78 g (3 mol). The product was distilled in a 24-in. column of 23 mm diameter, which was packed with Podbielniak, stainless steel. Approximately 100 g ethylamine was recovered, and 77 g *N*-ethylethylidenimine was obtained, in a yield of 55% based on the ethylamine consumed, b.p. 38–47°C.



Reference 15a.

A solution of 477 g dimethylaminoethyl isothiouronium chloride hydrochloride was prepared by refluxing 144 g dimethylaminoethyl chloride hydrochloride (1 mol) and 83 g thiourea (1.1 mol) in 250 mL water for 6 h. Then 415 mL of this solution was charged to a 1-L autoclave with 160 mL 50% aqueous NaOH (3 mol). The autoclave was rushed with acetylene and heated to 120°C in 16 min and maintained at 120–132°C for 1 h at a maximum acetylene pressure of 480 psi. The total acetylene absorption was 1.73 mol. The reactor was cooled to room temperature, and the products were removed under nitrogen pressure. The crude products (744 g) were in two layers. The upper oil layer (173 g) was separated and flash distilled to give 145 g distillate (including 15 g water) and 25 g dry salt-like residue. The dry distillate (123 g) was fractionated through a 12 in. Vigreux column to give 85 g dimethylaminoethyl vinyl sulfide (66.7 %) and 15 g dimethylaminoethylthioethyl vinyl sulfide (16.2%).

Other references related to Reppe vinylation are cited in the literature.[20]

H. REFERENCES

1. (a) Reppe, W., *Fr. Pat.*, May 6, **1931**, 724,955. (b) Reppe, W., *Brt. Pat.*, March 24, **1932**, 369,297. (c) Reppe, W., *Ger. Pat.*, Sept. 25, **1932**, 584,840. (d) Reppe, W., *U.S. Pat.*, May 22, **1934**, 1,959,927.
2. (a) Kaupp, G.; Luebben, D. and Sauerland, O., *Phosphorus, Sulfur & Silicon & Related Elements*, **1990**, *53*, 109. (b) Schildknecht, C. E.; Zoss, A. O. and McKinley, C., *Ind. Eng. Chem.,* **1947**, *39*, 180.
3. Hanford, W. E. and Fuller, D. L., *Ind. Eng. Chem.,* **1948**, *40*, 1171.
4. Holly, E. D., *J. Org. Chem.,* **1959**, *24*, 1752.
5. Shachat, N. and Bagnell, J. J., *J. Org. Chem.,* **1962**, *27*, 471.
6. Shtishevskii, V. V. and Obolonskaya, N. A., *J. Gen. Chem. USSR,* **1950**, *20*, 671 [*Chem. Abstr.,* **1950**, *44*, 7766].
7. Kruse, C. W. and Kleinschmidt, R. F., *J. Am. Chem. Soc.,* **1961**, *83*, 213.
8. Watanabe, W. H. and Conlon, L. E., *J. Am. Chem. Soc.,* **1957**, *79*, 2825.
9. Copenhaver, J. W. and Gigelow, M. H., *Acetylene and Carbon Monoxide Chemistry,* Reinhold Publishing New York, **1949**, p. 36.
10. Cairns, T. L. and Sauer, J. C., *J. Org. Chem.,* **1955**, *20*, 627.
11. Reppe, W., *U.S. Pat.*, Dec. 29, **1936**, 2,066,075.
12. Stacey, F. W. and Harris, J. F., *J. Am. Chem. Soc.,* **1963**, *85*, 963.
13. Strausz, O. P.; Hikida, T. and Gunning, H. E., *Can. J. Chem.,* **1965**, *43*, 717.
14. Ogawa, A.; Kawakami, J.-i.; Mihara, M.; Ikeda, T.; Sonoda, N. and Hirao, T., *J. Am. Chem. Soc.,* **1997**, *119*, 12380.
15. (a) Schneider, H. J.; Bagnell, J. J. and Murdoch, G. C., *J. Org. Chem.,* **1961**, *26*, 1982. (b) Schneider, H. J.; Bagnell, J. J. and Murdoch, G. C., *J. Org. Chem.,* **1961**, *26*, 1980.
16. Müller, T. E.; Berger, M.; Grosche, M.; Herdtweck, E. and Schmidtchen, F. P., *Organometallics,* **2001**, *20*, 4384.
17. Mahé, R.; Sasaki, Y.; Bruneau, C. and Dixneuf, P. H., *J. Org. Chem.,* **1989**, *54*, 1518.
18. Blouin, M. and Frenette, R., *J. Org. Chem.,* **2001**, *66*, 9043.
19. McKinley, N. F. and O'Shea, D. F., *J. Org. Chem.,* **2004**, *69*, 5087.
20. (a) Volkov, A. N.; Volkova, K. A.; Levanova, E. P. and Trofimov, B. A., *Russ. Chem. Bull.,* **1983**, *32*, 186. (b) Hudrlik, P. F. and Hudrlik, A. M., *J. Org. Chem.,* **1973**, *38*, 4254. (c) Gusarova, N.

K.; Trofimov, B. A. and Amosova, S. V., *Russ. Chem. Bull.,* **1972**, *21*, 1047. (d) Chiellini, E., *Macromolecules,* **1970**, *3*, 527. (e) Perrine, T. D.; glaudemans, C. P. J.; Ness, R. K.; Kyle, J. and Fletcher, H. G., *J. Org. Chem.,* **1967**, *32*, 664. (f) Zimmerman, R. L.; Jones, G. D. and Nummy, W. R., *I&EC Prod. Res. Dev.,* **1963**, *2*, 296. (g) Sims, V. A. and Vitcha, J. F., *I&EC Prod. Res. Dev.,* **1963**, *2*, 293. (h) Berry, J. W.; Tucker, H. and Deutschman, A. J., *I&EC Prod. Res. Dev.,* **1963**, *2*, 318. (i) Schneider, H. J.; Bagnell, J. J. and Murdoch, G. C., *J. Org. Chem.,* **1961**, *26*, 1987. (j) Lewis, J. B. and Hedrick, G. W., *J. Org. Chem.,* **1960**, *25*, 623. (k) Mikhant'ev, B. I. and Lapenko, V. L., *J. Gen. Chem. USSR.,* **1957**, *27*, 2972 [*Chem. Abstr.,* **1958**, *52*, 8055]. (l) Reppe, W., *Ann.,* **1956**, *601*, 128. (m) Reppe, W., *Ann.,* **1956**, *601*, 100. (n) Miller, S. I. and Shkapenko, G., *J. Am. Chem. Soc.,* **1955**, *77*, 5038. (o) Reppe, W., *Ann.,* **1953**, *582*, 1. (p) Adelman, R. L., *J. Am. Chem. Soc.,* **1953**, *75*, 2678. (q) Rowlands, D. C.; Greenlee, K. W.; Derfer, J. M. and Boord, C. E., *J. Org. Chem.,* **1952**, *17*, 807. (r) Adelman, R. L., *J. Org. Chem.,* **1949**, *14*, 1047. (s) Kline, G. M., *Modern Plastics,* **1945**, *23*, 157.

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Retro-Diels-Alder Reaction

(*Retro*-Diels-Alder Cleavage, *Retro*-Diels-Alder Fragmentation)

A. GENERAL DESCRIPTION OF THE REACTION

The first useful *retro*-Diels-Alder reaction was reported by Diels and Thiele as early as 1938.[1] It is a thermally allowed [$_{\pi}4_{s}+_{\pi}2_{s}$] cycloreversion[2] of an organic compound with a double bond in a six-membered ring, leading to the formation of a diene and a dienophile, i.e., the reversed process of the *Diels-Alder Cycloaddition*. Thus this reaction is generally known as the *retro*-Diels-Alder fragmentation,[3] or *retro*-Diels-Alder reaction.[2,3a,3y,5] Occasionally, it is also referred to as the *retro*-Diels-Alder cleavage.[6] Even though the *Diels-Alder Cycloaddition* is thermodynamically reversible, the *Diels-Alder Cycloaddition* products (i.e., the Diels-Alder cycloadducts) are fairly stable, and the *retro*-Diels-Alder reaction does not occur regularly, as demonstrated by the ample examples of the resistance of norbornenes and norbornadienes toward thermolysis.[4x] This is because two stronger σ-bonds must break for the formation of two π-bonds. However, as the unimolecular *retro*-Diels-Alder reaction is dominated by enthalpy of activation with small contribution from entropy of activation,[2,7] most *retro*-Diels-Alder reactions take place at very high temperature,[4i] if the resulting dienes and dienophiles are more stable.[4t] This is demonstrated by the thermal cracking of dicyclopentadiene at 180°C, a usual process for producing fresh cyclopentadiene in the laboratory. For the thermal *retro*-Diels-Alder reaction, it is possible to observe the lengthening of two breaking C–C σ bonds at the ground state,[8] and the ring strain may further weaken the breaking σ bonds. For example, the two breakable σ bonds in bicyclo[2.2.2]octene are found to be about 0.009 Å longer than corresponding σ bonds in bicyclo[2.2.2]octane; whereas the two σ bonds in bicyclo[2.2.1]heptene are ~0.02 Å longer than those of the saturated analogue.[9] Besides the normal thermolysis of Diels-Alder cycloadducts, a few conditions have also been reported to facilitate

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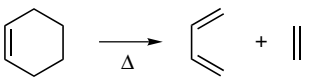
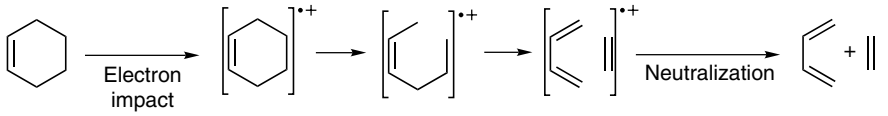
the *retro*-Diels-Alder reaction, such as the use of a catalytic antibody[4b,10] (e.g., antibody 9D9[11]), photo-initiation[4s,4u] (either by powerful irradiation or low power with longer illumination time[12]), electron impact,[3y,3aa] laser induction in the presence of SiF_4,[4w] flash vacuum pyrolysis,[4k,13] and the combination of Lewis acid and diene scavenger (e.g., $MeAlCl_2$ + maleic anhydride).[14] Among these conditions, the laser-induced *retro*-Diels-Alder reactions of norbornadiene, cyclohexene, 4-vinylcyclohexene, and 2,3-dihydropyran take place at ambient temperature;[4w] the antibody-catalyzed *retro*-Diels-Alder reaction to give nitroxyl and anthracene is found to be independent of a buffer, co-solvent effect, as well as pH when pH is regulated between 4 and 10;[4b] and electron impact-induced fragmentation is popularly used for structure determination in mass spectroscopy which may proceed through a stepwise or concerted process.[3aa] In addition, some special structural components may facilitate the *retro*-Diels-Alder reaction too, such as the anionic oxygen in *endo*-bicyclo[2.2.1]hepta-5-en-2-ol generated by treatment with phenyl magnesium bromide,[6d] the carbanion intermediate as in 7-phenylnorbornenyl,[4x] cycloadduct of 5-cyanocyclopentadiene,[4t] the trimethylsilyl group[4o] and the siloxy group,[4m] where the acceleration of the *retro*-Diels-Alder reaction from the carbanion intermediate is attributed to the "formation of resonance stabilized and weakly basic anions" from more strongly anionic cycloadducts,[4t] and the effect of the siloxy group can be seen even three bonds away from the reaction center.[4m] It should be mentioned that the thermal *retro*-Diels-Alder reaction of anthracene cycloadducts is accelerated by electron-donating groups[4m,4n] in the order of NH_2 > OH > OPh > OMe > Me > H,[4n] whereas it is less affected by electron-withdrawing groups and steric effects.[4m,4n] It is interesting that the reaction of anthracenedione is observed to be faster in aqueous solution than that in organic solvent and can be accelerated by addition of glucose and retarded by addition of organic solvent to the aqueous solution.[4h]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Mechanistically, the *retro*-Diels-Alder reaction is comparable to the *Diels-Alder Reaction*[4h] in that it may take place through a concerted or a stepwise path. Because this reaction is dominated by the enthalpy of activation rather than the entropy of activation, it is generally accelerated by the electron-withdrawing groups on the resulting dienophiles and the electron-donating groups on the forming dienes.[4h] The theoretical computation on the *retro*-Diels-Alder reaction of norbornene has indicated that the concerted mechanism is favored over the diradical in a stepwise route by 12.4 Kcal/mol,[4d] but the reaction of cyclohexene to form ethylene and butadiene does occur through an asymmetric stepwise mechanism from MINDO/3 calculation[4v] as well as by electron impact fragmentation study.[3aa] Under the conditions of high-energy photo-irradiation, the excited π^* singlet may be rapidly converted to diradicals directly.[3a] An illustrative mechanism is provided here for the reaction of cyclohexene to ethylene and butadiene under the electron impact condition.



D. MODIFICATION

This reaction has been extensively modified by the use of different reaction conditions as described in earlier sections.

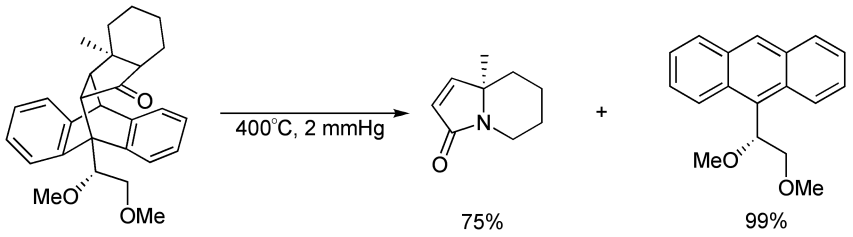
E. APPLICATIONS

This reaction has very wide application in organic synthesis, such as the formation of quinones,[4o] benzoquinones,[4h] heterocycles (e.g., oxazoles,[15] imidazoles,[15] pyridazine,[4c] pyrrole,[4c] furan[4c]) and olefins with stereospecificity[4z,14,16] as well as the protection of double bonds.[4r]

F. RELATED REACTIONS

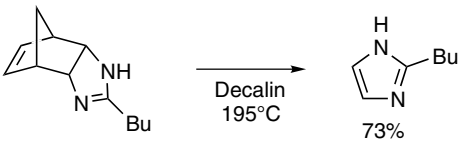
This reaction is closely related to the *Diels-Alder Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 13.

The starting material (20.8 mg, 0.049 mmol) was placed in a small porcelain crucible, which was then inserted into one end of a fused silica tube with ball joints sealed by a glass cap held on by a clamp. The tube was then placed in a tube furnace with the other end connected to a high vacuum through a trap at -78°C. The tube was heated to 400°C for 4 min under high vacuum (< 2 mmHg). The cycloreversion products condensed on the glass tube as soon as they exited the tube furnace and were not detected in the traps. After cooling, the products were collected from the tube by washing with $CHCl_3$. After removal of solvent, the residue was purified by flash chromatography with EtOAc to afford 5.6 mg (+)-(*R*)–6,7,8,8a–tetrahydro–8a-methyl-5*H*-indolizin-3-one as a colorless oil (75% yield, $R_f = 0.13$, hexane/EtOAc, 1:1) and 13.9 mg (-)-(*R*)-9-(1,2-dimethoxyethyl)anthracene, in 99% recovery.



Reference 15.

(3aα,4a,7a,7aα)-2-Butyl-3a,4,7,7a-tetrahydro-4,7-methano-1H-benzimidazole (210 mg, 1.11 mmol) in 5 mL decalin was heated at 195°C for 2 h. The cooled reaction mixture was then applied to a silica gel column chromatography using 10% MeOH in $CHCl_3$ as the eluent to afford 100 mg 2-butylimidazole as an off-white solid, in a yield of 73%. The sample was further purified by vacuum sublimation at 70°C at 0.15 mmHg to give a white solid, m.p. 53–54°C.

Other references related to *retro*-Diels-Alder reaction are cited in the literature.[17]

H. REFERENCES

1. Diels, O. and Thiele, W. E., *Ber.,* **1938**, *71*, 1173.
2. Jenner, G.; Papadopoulos, M. and Rimmelin, J., *J. Org. Chem.,* **1983**, *48*, 748.
3. (a) Lewis, D. K.; Glenar, D. A.; Hughes, S.; Kalra, B. L.; Schlier, J.; Shukla, R. and Baldwin, J. E., *J. Am. Chem. Soc.,* **2001**, *123*, 996. (b) Lemaire, D.; Serani, L.; Laprevote, O.; Ovcharenko, V.; Pihlaja, K. and Stajer, G., *Eur. Mass Spect.,* **1999**, *5*, 253. (c) Morlender-Vais, N. and Mandelbaum, A., *J. Mass Spect.,* **1998**, *33*, 229. (d) Denekamp, C.; Weisz, A. and Mandelbaum, A., *J. Mass Spect.,* **1996**, *31*, 1028. (e) Mandelbaum, A., *Appl. Mass Spect. Org. Stereochem.*, **1994**, 299. (f) Brown, R. F. C.; Choi, N. and Eastwood, F. W., *Tetrahedron Lett*., **1992**, *33*, 3787. (g) Etinger, A. and Mandelbaum, A., *Org. Mass Spect.,* **1992**, *27*, 761. (h) Hanawa, F.; Tahara, S. and Mizutani, J., *Heterocycles*, **1991**, *32*, 1563. (i) Weisz, A. and Mandelbaum, A., *Org. Mass Spect.,* **1989**, *24*, 37. (j) Vincenti, M.; Horning, S. R. and Cooks, R. G., *Org. Mass Spect.,* **1988**, *23*, 585. (k) Lees, M.; Boussoufi, A.; Bakasse, M.; Nourrisson, G. and Duguay, G., *Sulfur Lett*., **1988**, *8*, 147. (l) Lin, S. T.; Kuo, Y. H. and Lee, M. S., *J. Chin. Chem. Soc. (Taipei),* **1988**, *35*, 359. (m) Weisz, A.; Iberkleid, E.; Mandelbaum, A.; Blum, W. and Richter, W. J., *Org. Mass Spect.,* **1987**, *22*, 3. (n) Tomas-Lorente, F. and Tomas-Barberan, F. A., *Revista Agroquim. Tecnologia Alimentos,* **1986**, *26*, 203. (o) Evans, J. M. and Gower, J. L., *Org. Mass Spect.,* **1985**, *20*, 440. (p) Turecek, F.; Pancir, J.; Stahl, D. and Gaumann, T., *Org. Mass Spect.,* **1985**, *20*, 360. (q) Mandelbaum, A.; Weisz, A. and Karpati, A., *Int. J. Mass Spect. & Ion Phys.,* **1983**, *47*, 415. (r) Morizur, J. P.; Mercier, J. and Sarraf, M., *Org. Mass Spect.,* **1982**, *17*, 327. (s) Bel, P. and Mandelbaum, A., *Org. Mass Spect.,* **1981**, *16*, 513. (t) Eguchi, S., *Org. Mass Spect.,* **1979**, *14*, 345. (u) Mintas, M.; Klepo, Z.; Jakopcic, K. and Klasinc, L., *Org. Mass Spect.,* **1979**, *14*, 254. (v) Eguchi, S., *Org. Mass Spect.,* **1978**, *13*, 653. (w) Zitrin, S.; Yinon, J. and Mandelbaum, A., *Tetrahedron*, **1978**, *34*, 1199. (x) Koch, T. H.; Higgins, R. H. and Schuster, H. F., *Tetrahedron Lett*., **1977**, 431. (y) Dixon, J. S.; Midgley, I. and Djerassi, C., *J. Am. Chem. Soc.,* **1977**, *99*, 3432. (z) Mandelbaum, A. and Bel, P., *Adv. Mass Spect.,* **1974**, *6*, 25. (aa) Karpati, A.; Rave, A.; Deutsch, J. and Mandelbaum, A., *J. Am. Chem. Soc.,* **1973**, *95*, 4244. (bb) Lesman, T. and Deutsch, J., *Org. Mass Spect.,* **1973**, *7*, 1321. (cc) Budzikiewicz, H.; Brauman, J. I. and Djerassi, C., *Tetrahedron*, **1965**, *21*, 1855.
4. (a) Suzuki, K.; Inomata, K. and Endo, Y., *Org. Lett.,* **2004**, *6*, 409. (b) Reymond, J.-L., *J. Immuno. Methods,* **2002**, *269*, 125. (c) Warrener, R. N. and Harrison, P. A., *Molecules,* **2001**, *6*, 353. (d) Beno, B. R.; Wilsey, S. and Houk, K. N., *J. Am. Chem. Soc.,* **1999**, *121*, 4816. (e) Teplyakov, A. V.; Lal, P.; Noah, Y. A. and Bent, S. F., *J. Am. Chem. Soc.,* **1998**, *120*, 7377. (f) Tian, J.; Houk,

K. N. and Klärner, F. G., *J. Phys. Chem. A,* **1998**, *102*, 7662. (g) Horn, B. A.; Herek, J. L. and Zewail, A. H., *J. Am. Chem. Soc.,* **1996**, *118*, 8755. (h) Wijnen, J. W. and Engberts, J. B. F. N., *J. Org. Chem.,* **1997**, *62*, 2039. (i) Lee, B. Y.; Moon, H. J.; Chung, Y. K. and Jeong, N., *J. Am. Chem. Soc.,* **1994**, *116*, 2163. (j) Rogers, C. and Keay, B. A., *Can. J. Chem.,* **1993**, *71*, 611. (k) Gajewski, J. J. and Paul, G. C., *J. Org. Chem.,* **1990**, *55*, 4575. (l) Whitney, S. E.; Winters, M. and Richborn, B., *J. Org. Chem.,* **1990**, *55*, 929. (m) Chung, Y. S.; Duerr, B. F.; McKelvey, T. A.; Nanjappan, P. and Czarnik, A. W., *J. Org. Chem.,* **1989**, *54*, 1018. (n) Chung, Y.-S.; Duerr, B. F.; Nanjappan, P. and Czarnik, A. W., *J. Org. Chem.,* **1988**, *53*, 1334. (o) Magnus, P.; Cairns, P. M. and Moursounidis, J., *J. Am. Chem. Soc.,* **1987**, *109*, 2469. (p) Magnus, P. and Cairns, P. M., *J. Am. Chem. Soc.,* **1986**, *108*, 217. (q) Nanjappan, P. and Czarnik, A. W., *J. Org. Chem.,* **1986**, *51*, 2851. (r) Anderson, W. K. and Milowsky, A. S., *J. Org. Chem.,* **1985**, *50*, 5423. (s) Schultz, A. G.; Dittami, J. P.; Myong, S. O. and Sha, C.-K., *J. Am. Chem. Soc.,* **1983**, *105*, 3273. (t) RajanBabu, T. V.; Eaton, D. F. and Fukunaga, T., *J. Org. Chem.,* **1983**, *48*, 652. (u) Schultz, A. G. and Myong, S. O., *J. Org. Chem.,* **1983**, *48*, 2432. (v) Dewar, M. J. S.; Olivella, S. and Rzepa, H. S., *J. Am. Chem. Soc.,* **1978**, *100*, 5650. (w) Garcia, D. and Keehn, P. M., *J. Am. Chem. Soc.,* **1978**, *100*, 6111. (x) Bowman, E. S.; Hughes, G. B. and Grutzner, J. B., *J. Am. Chem. Soc.,* **1976**, *98*, 8273. (y) Nelsen, S. F., *J. Am. Chem. Soc.,* **1974**, *96*, 5669. (z) Hammerum, S. and Djerassi, C., *J. Am. Chem. Soc.,* **1973**, *95*, 5806. (aa) Herndon, W. C.; Cooper, W. B. and Chambers, M. J., *J. Phys. Chem.,* **1964**, *68*, 2016.

5. (a) Miklos, F.; Stajer, G. and Fulop, F., *Lett. Org. Chem.,* **2006**, *3*, 915. (b) Kotha, S.; Banerjee, S.; Patil, M. P. and Sunoj, R. B., *Org. Biomol. Chem.,* **2006**, *4*, 1854. (c) Branowska, D., *Molecules*, **2005**, *10*, 274. (d) Gomez, M. V.; Cantin, A.; Corma, A. and De la Hoz, A., *J. Mol. Catal. A: Chem.,* **2005**, *240*, 16. (e) Wang, G.-W.; Chen, Z.-X.; Murata, Y. and Komatsu, K., *Tetrahedron*, **2005**, *61*, 4851. (f) Segi, M.; Zhou, A. and Honda, M., *Phosphorus, Sulfur & Silicon & Related Elements*, **2005**, *180*, 1045. (g) Stajer, G.; Miklos, F.; Kanizsai, I.; Csende, F.; Sillanpaa, R. and Sohar, P., *Eur. J. Org. Chem.,* **2004**, 3701. (h) Stajer, G.; Csende, F. and Fueloep, F., *Curr. Org. Chem.,* **2003**, *7*, 1423. (i) Goiti, E.; Huglin, M. B. and Rego, J. M., *Macromol. Rapid Commun.,* **2003**, *24*, 692. (j) Zhou, A.; Segi, M. and Nakajima, T., *Tetrahedron Lett*., **2003**, *44*, 1179. (k) Atherton, J. C. C. and Jones, S., *Tetrahedron Lett*., **2002**, *43*, 9097. (l) Banwell, M. G.; Clark, G. R.; Hockless, D. C. R. and Pallich, S., *Aust. J. Chem.,* **2001**, *54*, 691. (m) Stajer, G.; Miklos, F.; Sohar, P. and Sillanpaa, R., *Eur. J. Org. Chem.,* **2001**, 4153. (n) Allen, D. M.; Batsanov, A. S.; Brooke, G. M. and Lockett, S. J., *J. Fluor. Chem.,* **2001**, *108*, 57. (o) Sohar, P.; Miklos, F.; Csampai, A. and Stajer, G., *J. Chem. Soc., Perkin Trans. I,* **2001**, 558. (p) Leung, P.-H.; Lang, H.; Zhang, X.; Selvaratnam, S. and Vittal, J. J., *Tetrahedron: Asymmetry*, **2000**, *11*, 2661. (q) Xu, Y. P.; Alavanja, M.-M.; Johnson, V. L.; Yasaki, G. and King, S. B., *Tetrahedron Lett*., **2000**, *41*, 4265. (r) Wang, Q. and Posner, G. H., *Chemtracts,* **1998**, *11*, 1025. (s) Rickborn, B., *Org. React.,* **1998**, *52*, 1. (t) Bortolussi, M.; Bloch, R. and Loupy, A., *J. Chem. Res. (S),* **1998**, 34.
6. (a) Takayama, M.; Nomura, T. and Nojima, K., *Rapid Commun. Mass Spect.*, **1995**, *9*, 383. (b) Kirby, G. W. and McGregor, W. M., *J. Chem. Soc., Perkin Trans. I,* **1990**, 3175. (c) Chernyshev, E. A.; Bashkirova, S. A.; Komalenkova, N. G.; Kel'man, M. Ya. and Bochkarev, V. N., *Dokl. Akad. Nauk SSSR,* **1984**, *276*, 1151. (d) Vara Prasad, J. V. N.; Iyer, P. and Pillai, C. N., *J. Org. Chem.,* **1982**, *47*, 1380. (e) Turecek, F. and Hanus, V., *Org. Mass Spect.,* **1980**, *15*, 4. (f) Gringore, O.; Haslouin, J. and Rouessac, F., *Bull. Soc. Chim. Fr.,* **1976**, 1523.
7. (a) Desimoni, G.; Faita, G.; Pasini, D. and Righetti, P. P., *Tetrahedron,* **1992**, *48*, 1667. (b) Sauer, J. and Sustmann, R., *Angew. Chem. Int. Ed. Engl.,* **1980**, *19*, 779.
8. Pool, B. R. and White, J. M., *Org. Lett.,* **2000**, *2*, 3505.
9. Birney, D.; Lim, T. K.; Koh, J. H. P.; Pool, B. R. and White, J. M., *J. Am. Chem. Soc.,* **2002**, *124*, 5091.
10. Bahr, N.; Güller, R.; Reymond, J.-L. and Lerner, R. A., *J. Am. Chem. Soc.,* **1996**, *118*, 3550.
11. Bensel, N.; Bahr, N.; Reymond, M. T.; Schenkels, C. and Reymound, J.-L., *Helv. Chim. Acta,* **1999**, *82*, 44.

12. Safaei-Ghomi, J.; Tajbahksh, M. and Kazemi-Kani, Z., *Acta Chim. Slov.,* **2004**, *51*, 545.
13. Burgess, K. L.; Lajkiewicz, N. J.; Sanyal, A.; Yan, W. L. and Snyder, J. K., *Org. Lett.,* **2005**, *7*, 31.
14. Grieco, P. A. and Abood, N., *J. Org. Chem.,* **1989**, *54*, 6008.
15. Eissenstat, M. A. and Weaver, J. D., *J. Org. Chem.,* **1993**, *58*, 3387.
16. Manka, J. T.; douglass, A. G.; Kaszynski, P. and Friedli, A. C., *J. Org. Chem.,* **2000**, *65*, 5202.
17. (a) Nakayama, J.; Aoki, S.; Takayama, J.; Sakamoto, A.; Sugihara, Y. and Ishii, A., *J. Am. Chem. Soc.,* **2004**, *126*, 9085. (b) Leach, A. G.; Houk, K. N. and Reymond, J.-L., *J. Org. Chem.,* **2004**, *69*, 3683. (c) Brocksom, T. J.; Nakamura, J.; Ferreira, M. L. and Brocksom, U., *J. Braz. Chem. Soc.,* **2001**, *12*, 597. (d) Choi, C.-K.; Tomita, I. and Endo, T., *Macromolecules,* **2000**, *33*, 1487. (e) Klunder, A. J. H.; Zhu, J. and Zwanenburg, B., *Chem. Rev.,* **1999**, *99*, 1163. (f) Houk, K. N.; Wilsey, S. L.; Beno, B. R.; Kless, A.; Nendel, M. and Tian, J., *Pure & Appl. Chem.,* **1998**, *70*, 1947. (g) Goussé, C.; Gandini, A. and Hodge, P., *Macromolecules,* **1998**, *31*, 314. (h) Szántay, C.; Moldvai, I.; Tárkányi, G. and Szántay, C., *J. Org. Chem.,* **1996**, *61*, 2946. (i) Mahajna, M.; Quistad, G. B. and Casida, J. E., *Chem. Res. Toxicol.,* **1996**, *9*, 241. (j) Eisenberg, S. W. E.; Kurth, M. J. and Fink, W. H., *J. Org. Chem.,* **1995**, *60*, 3736. (k) Vallée, Y.; Khalid, M.; Ripoll, J. L. and Hakiki, A., *Synth. Commun.,* **1993**, *23*, 1267. (l) Tobia, D.; Harrison, R.; Phillips, B.; White, T. L.; DiMare, M. and Rickborn, B., *J. Org. Chem.,* **1993**, *58*, 6701. (m) Brown, R. F. C., *Pure & Appl. Chem.,* **1990**, *62*, 1981. (n) Lehd, M. and Jensen, F., *J. Org. Chem.,* **1990**, *55*, 1034. (o) Ichihara, A., *Synthesis,* **1987**, 207. (p) Lasne, M.-C. and Ripoll, J.-L., *Synthesis,* **1985**, 121. (q) Jurczak, J.; Kawczynski, A. L. and Kozluk, T., *J. Org. Chem.,* **1985**, *50*, 1106. (r) Gokou, C. T.; Pradere, J.-P. and Quiniou, H., *J. Org. Chem.,* **1985**, *50*, 1545. (s) Turecek, F. and Hanus, V., *Mass Spectr. Rev.,* **1984**, *3*, 85. (t) Sellers, S. F.; Dolbier, W. R.; Koroniak, H. and Al-Fekri, D. M., *J. Org. Chem.,* **1984**, *49*, 1033. (u) Bly, R. S.; Bly, R. K. and Shibata, T., *J. Org. Chem.,* **1983**, *48*, 101. (v) Hunt, D. F.; Giordani, A. B.; Shabanowitz, J. and Rhodes, G., *J. Org. Chem.,* **1982**, *47*, 738. (w) Papies, O. and Grimme, W., *Tetrahedron Lett.,* **1980**, *21*, 2799. (x) Adam, W. and de Lucchi, O., *J. Org. Chem.,* **1980**, *45*, 4167. (y) Lee, M. W. and Herndon, W. C., *J. Org. Chem.,* **1978**, *43*, 518. (z) Gilbert, A. and Walsh, R., *J. Am. Chem. Soc.,* **1976**, *98*, 1606. (aa) Hudrlik, P. F.; Hudrlik, A. M. and Wan, C.-N., *J. Org. Chem.,* **1975**, *40*, 1116. (bb) Kwart, H. and King, K., *Chem. Rev.,* **1968**, *68*, 415. (cc) Herndon, W. C. and Manion, J. M., *J. Org. Chem.,* **1968**, *33*, 4504. (dd) Herndon, W. C.; Grayson, C. R. and Manion, J. M., *J. Org. Chem.,* **1967**, *32*, 526.

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Retro-Ene Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was probably reported initially by Perkins and Cruz in 1927 during the preparation of undecylenic acid from ricinoleic acid, the major component of castor oil.[1] It is an intramolecular thermolysis of organic compounds with an unsaturated functional group involving the transfer of a γ-hydrogen to the unsaturated center via a six-membered transition state to yield both ene and enophile.[2] This reaction is thus generally known as the *retro*-ene reaction.[3,4] In addition, it is also referred to as *retro*-ene fragmentation,[2b,5] *retro*-ene decomposition[6] or *retro*-ene elimination.[7] Theoretically, this reaction belongs to a group of reactions known as pericyclic reactions,[8] but involves a [1,5]-H sigmatropic migration.[4a] In this reaction, the unsaturated functional groups include alkenyl,[9] alkynyl,[4c] allenyl,[4d,10] cyclopropyl,[11] carbonyl,[12] diazo,[13] and iminyl,[2a] occurring in the molecules of olefins, 1,6-dienes,[9] allyltrimethylsilanes,[14] acetylenic ethers,[4g,15] allylic and propargylic diazenes,[16] allylic sulfinic acid,[17] β-hydroxyethyl pyrazine,[4h] cyclic α-hydroxynitrosamines,[18] metastable immonium salts,[2a] allenic esters, allenic amides,[4d] etc. In most cases, this reaction involves a concerted mechanism,[2,4g,9,15,17,19] and gives a product with the stereochemical integrity preserved.[15] While olefins prefer an envelope-like transition state geometry,[20] only the *retro*-ene reaction through a planar transition state geometry is feasible for acetylene.[20b,21] Consequently, the *retro*-ene reaction does not take place among cyclic alkenes smaller than a seven-membered ring[22] or fused rings, of which one or more atoms involved in the reaction are part of the fused ring, except for a cyclopropyl ring.[12a,23] For the case of immonium salt, the alkyl group at γ-carbon facilitates the *retro*-ene reaction by distributing a substantial fraction of positive charge at the transition state.[2a] In addition, olefins with an acetylene group at β-position will undergo a competing *Cope Rearrangement* rather than the *retro*-ene reaction.[20b]

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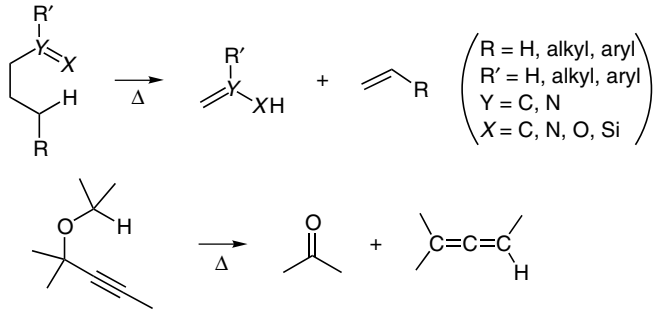
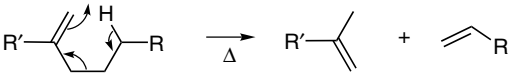
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is known that this reaction involves a concerted six-member transition state, as illustrated below.



D. MODIFICATION

This reaction has been extended to a variety of compounds with unsaturated functional groups, as described in Section A.

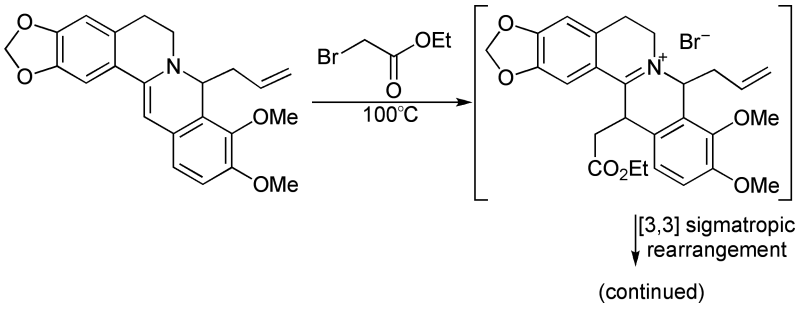
E. APPLICATIONS

This reaction has broad applications in organic synthesis.

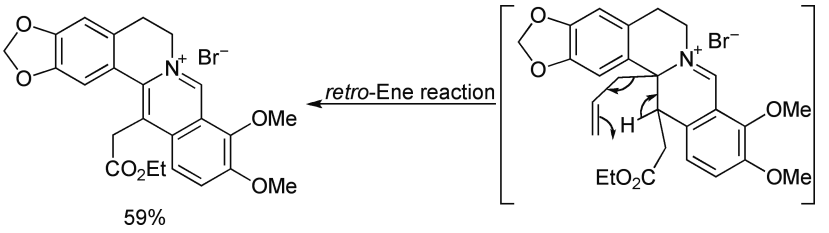
F. RELATED REACTIONS

This reaction is related to the *Alder Ene Reaction.*

G. CITED EXPERIMENTAL EXAMPLES

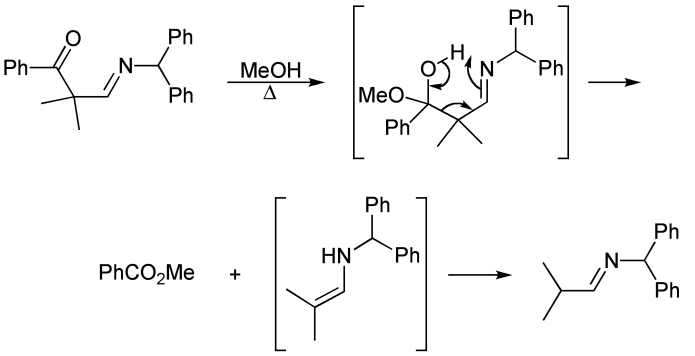


(continued)



Reference 24.

To a flask containing 50.5 mg 8-allyldihydroberberine (0.13 mmol) at 0°C was added 2 mL dry ethyl bromoacetate (18.03 mmol) during stirring under a nitrogen atmosphere. The solution was then heated to 100°C for 2.5 h to give a suspension. Then dry toluene was added, the mixture was filtered, and the filtrate was evaporated to afford 57.3 mg 13-(2-ethoxy-2-oxoethyl)-9,10-dimethoxy-5,6-dihydrobenzo[g]-1,3-benzodioxolo[5,6-a]quinolizinium bromide as an orange-yellow solid, which was further purified by recrystallization from dichloromethane containing 1% MeOH, and diethyl ether to give 39.3 mg pure product, as yellow needles, in a yield of 59%, m.p., 202–204°C.



Reference 4i.

A solution of 1.0 g *N*-(diphenylmethyl)-4-aza-2,2-dimethyl-l-phenyl-3-butenone (3 mmol) in 60 mL MeOH was refluxed for 8 h. The solvent was evaporated, and the residual oil was distilled under reduced pressure at 100°C (80 mmHg) to remove methyl benzoate, and the residue was purified to give *N*-(diphenylmethyl)-2-methylpropanimine. No yield was given in this experiment.

Other references related to the *retro*-ene reaction are cited in the literature.[25]

H. REFERENCES

1. Perkins, G. A. and Cruz, A. O., *J. Am. Chem. Soc.,* **1927**, *49*, 1070.
2. (a) Sølling, T. I. and Hammerum, S., *J. Chem. Soc*., *Perkin Trans., II*, **2001**, 2324. (b) Paderes, G. D. and Jorgensen, W. L., *J. Org. Chem.,* **1992**, *57*, 1904.

3. (a) Izadyar, M.; Jahangir, A. H. and Gholami, M. R., *J. Chem. Res.,* **2004**, 585. (b) Izadyar, M.; Gholami, M. R. and Haghgu, M., *THEOCHEM*, **2004**, *686*, 37. (c) Giner, J.-L. and Arigoni, D., *Chem. Commun.,* **2002**, 1388. (d) Chung, H.-A.; Kang, Y.-J.; Kweon, D.-H. and Yoon, Y.-J., *J. Heterocycl. Chem.,* **1999**, *36*, 413. (e) Chung, H.-A.; Kang, Y.-J.; Chung, J.-W.; Cho, S.-D. and Yoon, Y.-J., *J. Heterocycl. Chem.,* **1999**, *36*, 277. (f) Briard, E.; Dat, Y.; Levillain, J. and Ripoll, J.-L., *Tetrahedron Lett*., **1997**, *38*, 8707. (g) Systermans, A.; Lefevre, V.; Ripoll, J.-L.; Pieplu, T.; Hoggan, P. E.; Joanteguy, S.; Chrostowska-Senio, A. and Pfister-Guillouzo, G., *New J. Chem.,* **1997**, *21*, 383. (h) Bodajla, M.; Jones, G. R. and Ramsden, C. A., *Tetrahedron Lett*., **1997**, *38*, 2573. (i) Murray, W. V.; Turchi, I. J. and Bussolari, J. C., *J. Chem. Soc., Perkin Trans. II,* **1996**, 2715. (j) Lefevre, V.; Dat, Y. and Ripoll, J.-L., *Tetrahedron Lett*., **1996**, *37*, 7017. (k) Kim, S.-K.; Cho, S.-D.; Kweon, D.-H.; Lee, S.-G.; Chung, J.-W.; Shin, S. C. and Yoon, Y.-J., *J. Heterocycl. Chem.,* **1996**, *33*, 245. (l) Srikrishna, A.; Krishnan, K.; Venkateswarlu, S. and Kumar, P. P., *J. Chem. Soc., Perkin Trans. I,* **1995**, 2033. (m) Srikrishna, A.; Venkateswarlu, S.; Nagaraju, S. and Krishnan, K., *Tetrahedron*, **1994**, *50*, 8765. (n) Kim, S. K.; Moon, J. G.; Lee, S. G.; Choi, S. Y.; Cho, S. D.; Choi, W. Y. and Jin Yoon, Y., *J. Heterocycl. Chem.,* **1993**, *30*, 353. (o) Ripoll, J. L. and Vallee, Y., *Synthesis*, **1993**, 659. (p) Gaul, M. D.; Fowler, K. W. and Grieco, P. A., *Tetrahedron Lett*., **1993**, *34*, 3099. (q) Ito, K. and Miyajima, S., *J. Heterocycl. Chem.,* **1992**, *29*, 1037. (r) Yokozawa, T.; Tanaka, M. and Endo, T., *J. Poly. Sci., Part C: Poly. Lett.,* **1989**, *27*, 197. (s) Armesto, D.; Ramos, A. and Perez-Ossorio, R., *Tetrahedron Lett*., **1982**, *23*, 5195. (t) Rajappa, S.; Rajagopalan, T. G.; Sreenivasan, R. and Kanal, S., *J. Chem. Soc., Perkin Trans. I,* **1979**, 2001.
4. (a) Yu, Z.-X. and Houk, K. N ., *J. Am. Chem. Soc.,* **2003**, *125*, 13825. (b) Jung, M. E. and Davidov, P., *Org. Lett.,* **2001**, *3*, 3025. (c) Romo, D.; Harrison, P. H. M.; Jenkins, S. I.; Riddoch, R. W.; Park, K. J.; Yang, H. W.; Zhoa, C. X. and Wright, G. D., *Bioorg. Med. Chem.,* **1998**, *6*, 1255. (d) Bibas, H.; Koch, R. and Wentrup, C., *J. Org. Chem.,* **1998**, *63,* 2619. (e) MaGee, D. I.; Ramaseshan, M. and Leach, J. D., *Can. J. Chem.,* **1995**, *73*, 2111. (f) Myers, A. G. and Finney, N. S., *J. Am. Chem. Soc.,* **1990**, *112*, 9641. (g) Dubac, J. and Laporterie, A., *Chem. Rev.,* **1987**, *87*, 319. (h) Houminer, Y.; Fenner, R. A.; Secor, H. V. and Seeman, J. I., *J. Org. Chem.,* **1987**, *52*, 3971. (i) Armesto, D.; Horspool, W. H.; Pérez-Ossorio, R. and Ramos, A., *J. Org. Chem.,* **1987**, *52*, 3378. (j) Houminer, Y., *J. Org. Chem.,* **1980**, *45*, 999. (k) Marvell, E. N. and Rusay, R., *J. Org. Chem.,* **1977**, *42*, 3336.
5. (a) Saczewski, J.; Brzozowski, Z. and Gdaniec, M., *Tetrahedron,* **2005**, *61*, 5303. (b) Sotelo, E. and Ravina, E., *Synlett*, **2003**, 1113. (c) Sotelo, E.; Coelho, A. and Ravina, E., *Tetrahedron Lett*., **2003**, *44*, 4459. (d) Kim, S.-K.; Cho, S.-D. and Yoon, Y.-J., *J. Heterocycl. Chem.,* **1997**, *3*4, 1135. (e) Kim, S.-K.; Cho, S.-D.; Moon, J.-K. and Yoon, Y.-J., *J. Heterocycl. Chem.,* **1996**, *33*, 615. (f) De Croutte, H.; Janousek, Z.; Pongo, L.; Merenyi, R. and Viehe, H. G., *Bull. Soc. Chim. Fr.,* **1990**, 745. (g) Tolstikov, G. A.; Ismailov, S. A. and Miftakhov, M. S., *Zh. Org. Khim.,* **1990**, *26*, 1806. (h) Tolstikov, G. A.; Ismailov, S. A.; Vel'der, Ya. L. and Miftakhov, M. S., *Zh. Org. Khim.,* **1990**, *26*, 672. (i) Earl, R. A. and Vollhardt, K. P. C., *Heterocycles*, **1982**, *19*, 265. (j) Virk, P. S., *Fuel*, **1979**, *58*, 149.
6. (a) King, K. D., *Int. J. Chem. Kinetics,* **1981**, *13*, 245. (b) King, K. D., *Int. J. Chem. Kinetics,* **1979**, *11*, 1071.
7. (a) Rodriguez, L. J.; Vidal, A. B.; Izquierdo, R. E.; Fermin, J. R. and Anez, R., *THEOCHEM,* **2006**, *769*, 211. (b) Rodriguez, L. J.; Fermin, J.; Anez, R. and Ocando-Mavarez, E., *J. Phys. Org. Chem.,* **2002**, *15*, 826. (c) Rodriguez, L. J.; Anez, R. and Ocando-Mavarez, E., *THEOCHEM*, **2001**, *536*, 53. (d) Rodriguez, L.; Munoz, W.; Martin, G. and Ocando-Mavarez, E., *Heteroatom Chem*., **1997**, *8*, 85.
8. Bly, R. S.; Raja, M. and Bly, R. K., *Organometallics,* **1992**, *11*, 1220.
9. Egger, K. W. and Vitins, P., *J. Am. Chem. Soc.,* **1974**, *96*, 2714.
10. Price, J. D. and Johnson, R. P., *Tetrahedron Lett.,* **1985**, *26*, 2499.
11. Hanafusa, T.; Beiladeanu, L. and Winstein, S., *J. Am. Chem. Soc.,* **1965**, *87*, 3510.

12. (a) Creary, X.; Hudock, F.; Keller, M.; Kerwin, J. F. and Dinnocenzo, J. P., *J. Org. Chem.,* **1977**, *42*, 409. (b) Monti, S. A. and McAninch, T. W., *Tetrahedron Lett.,* **1974**, 3239.
13. Tezuka, T. and Otsuka, T., *Chem. Lett.,* **1989**, 1051.
14. (a) Barton, T. J.; Burns, S. A.; Davidson, I. M. T.; Ijadi-Maghsoodi, S. and Wood, I. T., *J. Am. Chem. Soc.,* **1984**, *106*, 6367. (b) Davidson, I. M. T. and Wood, I. T., *J. Organomet. Chem.,* **1980**, *202*, C65.
15. Viola, A.; Dudding, G. F. and Proverb, R. J., *J. Am. Chem. Soc.,* **1977**, *99*, 7390.
16. (a) Myers, A. G. and Kukkola, P. J., *J. Am. Chem. Soc.,* **1990**, *112*, 8208. (b) Myers, A. G.; Finney, N. S. and Kuo, E. Y., *Tetrahedron Lett.,* **1989**, *30*, 5747. (c) Corey, E. J.; Cane, D. E. and Libit, L., *J. Am. Chem. Soc.,* **1971**, *93*, 7016. (d) Sato, T.; Homma, I. and Nakamura, S., *Tetrahedron Lett.,* **1969**, 871.
17. Hiscock, S. D.; Isaacs, N. S.; King, M. D.; Sue, R. E.; White, R. H. and Young, D. J., *J. Org. Chem.,* **1995**, *60*, 7166.
18. Wu, H.; Loeppky, R. N. and Glaser, R., *J. Org. Chem.,* **2005**, *70*, 6790.
19. Várnai, P. and Keserü, G. M., *J. Org. Chem.,* **1996**, *61,* 5831.
20. (a) Loncharich, R. J. and Houk, K. N., *J. Am. Chem. Soc.,* **1987**, *109*, 6947. (b) Viola, A.; McMillan, J. H.; Proverg, R. J. and Yates, B. L., *J. Am. Chem. Soc.,* **1971**, *93*, 6967.
21. (a) Viola, A.; Proverb, R. J.; Yates, B. L. and Larrahendo, J., *Tetrahedron Lett.,* **1971**, 4981. (b) Arnold, R. T. and Smolinsky, G., *J. Am. Chem. Soc.,* **1960**, *82*, 4918.
22. Arnold, R. T. and Smolinsky, G., *J. Am. Chem. Soc.,* **1959**, *81*, 6443.
23. Marvell, E. N. and Cheng, J. C. P., *J. Org. Chem.,* **1980**, *45*, 4511.
24. Bremner, J. B. and Samosorn, S., *Aust. J. Chem.,* **2003**, *56*, 871.
25. (a) Craita, C.; Bouchez, L.; Turks, M.; Huang, X.; Fonquerne, F.; Murcia, M. C. and Vogel, P., *Phosphorus, Sulfur & Silicon & Related Elements,* **2005**, *180*, 1223. (b) Schobert, R. and Gordon, G. J., *Curr. Org. Chem.,* **2002**, *6*, 1181. (c) Morrow, G. R. and Rae, I. D., *Aust. J. Chem.,* **1987**, *40*, 1477. (d) Oppolzer, W.; Battig, K. and Hudlicky, T., *Tetrahedron,* **1981**, *37*, 4359. (e) Brady, W. T. and Saidi, K., *J. Org. Chem.,* **1979**, *44*, 733. (f) Kurosawa, H., *Inorg. Chem.,* **1975**, *14*, 2148. (g) Ruden, R. A., *J. Org. Chem.,* **1974**, *39*, 3607. (h) Baldwin, J. E.; Pinschmidt, R. K. and Andrist, A. H., *J. Am. Chem. Soc.,* **1970**, *92*, 5249. (i) Bigley, D. B. and May, R. W., *J. Chem. Soc. B,* **1967**, 557. (j) Smith, G. G. and Yates, B. L., *J. Chem. Soc.,* **1965**, 7242.

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Retropinacol Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Zelinsky and Zelikow in 1901.[1] It is the conversion of alcohols with a tertiary β-carbon into olefin along with the migration of an alkyl group from the tertiary β-carbon in the presence of an acid. Therefore, this reaction is generally known as the retropinacol rearrangement.[2] It is known that alcohol is protonated to form an oxonium in the presence of an acid, which dehydrates to give the carbonium ion; the generated carbonium ion does not rearrange by itself, whereas the migration is facilitated by the base (conjugate base) attack at the β-position.[2q] Thus the extent of the rearrangement is determined by the strength of the base and the accessibility of the β-position to the base, so that shielding the β-carbon by either a bulky group or an electron-rich group can prevent the retropinacol rearrangement.[2q] Strictly speaking, the retropinacol rearrangement is the reverse of normal *Pinacol Rearrangement*, as demonstrated from the reaction between pinacolone and liquid sulfur trioxide to yield cyclic sulfate.[3]

B. GENERAL REACTION SCHEME

(R_1, R_2, R_3, R_4 = alkyl
R_1 or R_2 could migrate also)

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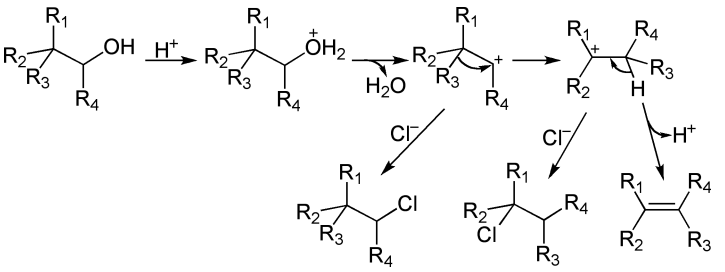
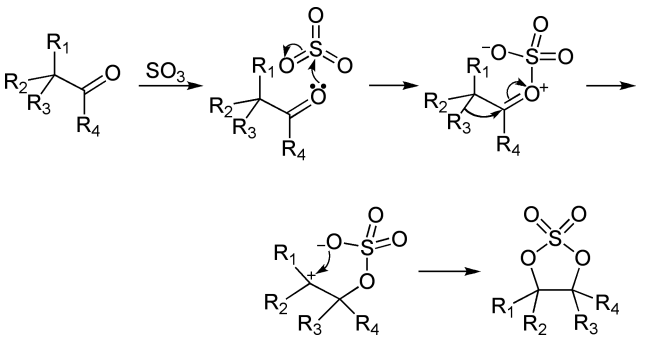
C. PROPOSED MECHANISMS

The rearrangement of alcohol with a tertiary β-carbon in the presence of an acid is illustrated in Scheme 1, along with its competing reactions to form corresponding alkyl chlorides. In addition, the mechanism for the formation of a cyclic sulfate from pinacolone and liquid sulfur trioxide is provided in Scheme 2.



SCHEME 1. *Mechanism of retropinacol rearrangement.*



SCHEME 2. *Reaction between sulfur trioxide and pinacolone to form a cyclic sulfate.*

D. MODIFICATION

A base triggered retropinacol rearrangement has been developed, by the use of 2-chloro-1,1,2-trifluoroethyldiethylamine.[2k]

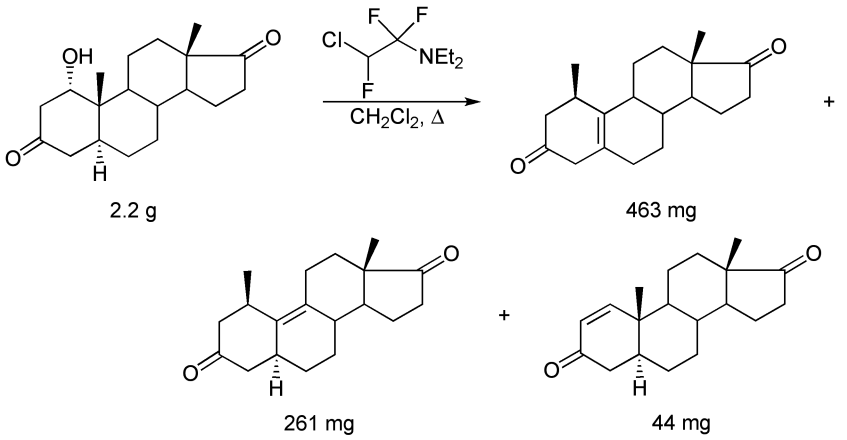
E. APPLICATIONS

This reaction has certain applications in organic synthesis.

F. RELATED REACTIONS

This reaction is related to the *Pinacol Rearrangement* and *Wagner-Meerwein Rearrangement*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2k.

A mixture of 2.2 g 1α-hydroxy-5α-androstane-3,17-dione and 2.2 mL 2-chloro-1,1,2-trifluoroethyldiethylamine in 25 mL CH_2Cl_2 was refluxed for 15 min, after which time the TLC indicated the completion of the reaction. This solution was washed with water, aqueous $NaHCO_3$ and water again, then dried over Na_2SO_4 and evaporated under vacuum to an oil. The residue was chromatographed on 200 g silica gel using EtOAc/benzene (1:19) as the eluent to afford 463 mg 1β-methylestr-5(10)-ene-3,17-dione, m.p. 136°C. This product was further purified by recrystallization from benzene/hexane to yield 257 mg pure 1β-methylestr-5(10)-ene-3,17-dione, m.p. 139–140°C. From the benzene mother liquors from which crude 1α-hydroxy-5α-androstane-3,17-dione was crystallized, 261 mg 1β-methylestr-9-ene-3,17-dione was recovered. Continued elution of the column (from which the two compounds and their mixture were obtained) with 5% EtOAc in benzene afforded 44 mg impure 10β-methylestr-1(2)-ene-3,17-dione, m.p. 99–107°C.

Other references relatd to the retropinacol rearrangement are cited in the literature.[4]

H. REFERENCES

1. Zelinsky, N. and Zelikow, J., *Ber.,* **1901**, *34*, 3249.
2. (a) Zhichareva, G. P.; Yakhontov, L. N.; Marshalkin, M. F.; Turchin, K. F.; Kuleshova, E. F. and Sheinker, Y. N., *Pharm. Chem. J.,* **1991**, *25*, 22. (b) Harrison, L. M. and Fennessey, P. V., *J. Steroid Biochem.,* **1990**, *36*, 407. (c) Zhdanov, Yu. A.; Luk'yanov, S. M.; Borodaev, S. V. and Borodaeva, S. V., *Zh. Org. Khim.,* **1986**, *22*, 1173. (d) Luk'yanov, S. M.; Borodaev, S. V. and Borodaeva, S. V., *Zh. Org. Khim.,* **1983**, *19*, 2153. (e) Luk'yanov, S. M. and Borodaev, S. V., *Zh. Org. Khim.,* **1983**, *19*, 458. (f) Saidkhodzhaev, A. I., *Chem. Nat. Compd.,* **1980**, *15*, 379. (g) Tyun'kina, N. I.; Preobrazhenskii, A. V.; Bragin, O. V. and Liberman, A. L., *Russ. Chem. Bull.,* **1977**, *26*, 1424. (h) Shakhnazaryan, G. M., *Armyanskii Khim. Zh*., **1974**, *27*, 677. (i) Rigaudy, J. and Baranne-Lafont, J., *Tetrahedron Lett*., **1965**, 1375. (j) Hueckel, W. and Gupte, S. K., *Ann.,* **1965**, *685*, 105. (k) Smith, L. L.; Foell, T. J. and Teller, D. M., *J. Org. Chem.,* **1965**, *30*, 3781. (l) Johns, W. F. and Mueller, G. P., *J. Org. Chem.,* **1963**, *28*, 1854. (m) Artsybasheva, Yu. P. and Favorskaya, I. A.,

Zh. Obsh. Khim., **1963**, *33*, 1047. (n) Johns, W. F., *J. Org. Chem.,* **1961**, *26*, 4583. (o) Felkin, H. and Le Ny, G., *Bull. Soc. Chim. Fr.,* **1957**, 1169. (p) Mousseron, M.; Jacquier, R. and Christol, H., *Compt. Rend.*, **1956**, *243*, 1532. (q) Scott, R. B. and Gayle, J. B., *J. Org. Chem.,* **1953**, *16*, 740.

3. Sheehan, J. C. and Zoller, U., *J. Org. Chem.,* **1974**, *39*, 3415.
4. (a) Suzuki, T.; Ichioka, K.; Higuchi, H.; Kawai, H.; Fujiwara, K.; Ohkita, M.; Tsuji, T. and Takahashi, Y., *J. Org. Chem.,* **2005**, *70*, 5592. (b) Zhang, W.; Yang, L.; Wu, L.-M.; Liu, Y.-C. and Liu, Z.-L., *J. Chem. Soc., Perkin Trans. II,* **1998**, 1189. (c) Kimura, T.; Minabe, M. and Suzuki, K., *J. Org. Chem.,* **1978**, *43*, 1247. (d) Dostrovsky, I. and Hughes, E. D., *J. Chem. Soc.,* **1946**, 166. (e) Whitmore, F. C.; Wittle, E. L. and Popkin, A. H., *J. Am. Chem. Soc.,* **1939**, *61*, 1586. (f) Whitmore, F. C. and Rothrock, H. S., *J. Am. Chem. Soc.,* **1932**, *54*, 3431. (g) Batemall, D. E. and Marvel, C. S., *J. Am. Chem. Soc.,* **1927**, *49*, 2914.

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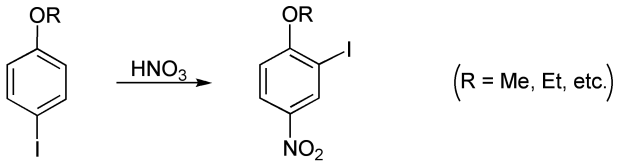
Reverdin Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Reverdin in 1896.[1] It is the preparation of 2-iodo-4-nitro-anisole from the nitration of 4-iodo-anisole, involving the migration of iodine from the 4-position to the 2-position during the nitration and is generally known as the Reverdin rearrangement.[2] Occasionally, it is also referred to as the Reverdin reaction.[3] It should be pointed out that bromine can migrate in a fashion similar to iodine and only a catalytic amount of nitro source is needed if a nitro group already exists on the aromatic ring.[3]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

This reaction is assumed to take place via an initial *ipso* attack of nitro at the iodo position and the subsequent liberation of iodine,[4] which then halogenates at the intermediate to form 2-iodo-4-nitro-anisole and 2,4-diiodoanisole, the latter is then slowly nitrosodeiodinated.[2b]

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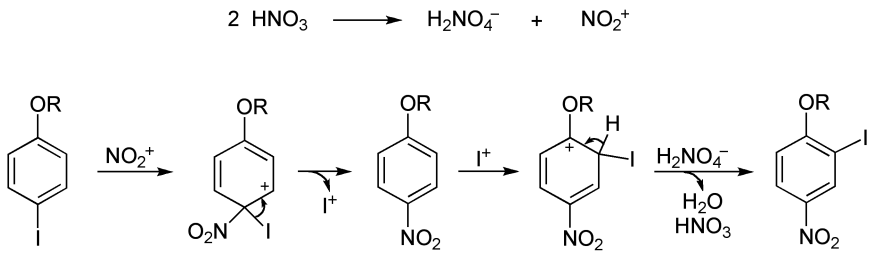


D. MODIFICATION

N/A

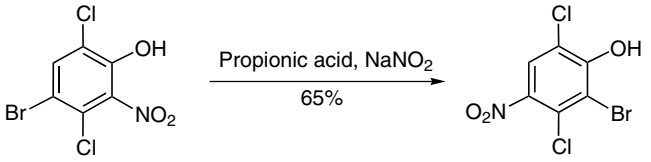
E. APPLICATIONS

This reaction has certain applications in organic synthesis.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3.

A 20-mL scintillation vial equipped with a magnetic stir bar was charged with 1.33 g 4-bromo-3,6-dichloro-2-nitrophenol (4.64 mmol), 10 mL propionic acid, and 0.022 g sodium nitrite (0.32 mmol) and capped. The hazy red-orange solution was stirred at room temperature for 2 h and then poured into 10 mL brine. The mixture was extracted with ethyl ether (2 × 10 mL), and the combined ether layers were dried over anhydrous Na_2SO_4. Upon evaporation of solvent, 1.27 g of an orange solid was obtained, which was recrystallized three times from cyclohexane to afford 0.86 g 2-bromo-3,6-dichloro-4-nitrophenol, in a yield of 65%, m.p., 129–130°C (dec.).

Other references related to the Reverdin rearrangement are cited in the literature.[5]

H. REFERENCES

1. (a) Reverdin, F., *Ber.,* **1896**, *29*, 997. (b) Reverdin, F., *Ber.,* **1896**, *29*, 1000. (c) Reverdin, F., *Ber.,* **1896**, *29*, 2595.
2. (a) Muramoto, Y.; Asakura, H. and Suzuki, H., *Nippon Kagaku Kaishi*, **1978**, 259. (b) Moodie, R. B. and Schofield, K., *Acc. Chem. Res.,* **1976**, *9*, 287. (c) Olah, G. A. and Melby, E. G., *J. Am. Chem. Soc.,* **1973**, *95*, 4971. (d) Gershon, H. and McNeil, M. W., *J. Heterocycl. Chem.,* **1971**, *8*, 821. (e) Banthorpe, D. V., *Chem. Rev.,* **1970**, *70*, 295.
3. Conlon, D. A.; Lynch, J. E.; Hartner, F. W.; Reamer, R. A. and Volante, R. P., *J. Org. Chem.,* **1996**, *61*, 6425.
4. Perrin, C. L. and Skinner, G. A., *J. Am. Chem. Soc.,* **1971**, *93*, 3389.
5. (a) Taylor, E. C.; Altland, H. W. and McKillop, A., *J. Org. Chem.,* **1975**, *40*, 3441. (b) Butler, A. R. and Sanderson, A. P., *J. Chem. Soc., Perkin Trans. II,* **1974**, 1784. (c) Butler, A. R. and Sanderson, A. P., *J. Chem. Soc., Perkin Trans. II,* **1972**, 989. (d) Page, D. F. and Clinton, R. O., *J. Org. Chem.,* **1962**, *27*, 218. (e) Meltzer, R. I.; Lustgarten, D. M. and Fischman, A., *J. Org. Chem.,* **1957**, *22*, 1577. (f) Nightingale, D. V., *Chem. Rev.,* **1947**, *40*, 117. (g) Jacobs, T. L.; Winstein, S.; Linden, G. B. and Seymour, D., *J. Org. Chem.,* **1946**, *11*, 223. (h) Gilman, H. and Shirley, D. A., *J. Am. Chem. Soc.,* **1944**, *66*, 888. (i) Dains, F. B.; Magers, A. W. and Steiner, W. L., *J. Am. Chem. Soc.,* **1930**, *52*, 1570. (j) Holleman, A. F., *Chem. Rev.,* **1924**, *1*, 187. (k) Misslin, E. and Bau, A., *Helv. Chim. Acta,* **1919**, *2*, 285. (l) Robinson, G. M., *J. Chem. Soc.,* **1916**, *109*, 1078. (m) Meldola, R. and Hollely, W. F., *J. Chem. Soc., Trans.,* **1915**, *107*, 610. (n) Reverdin, F., *Bull. Soc. Chim. Fr.,* **1907**, 618. (o) Reverdin, F. and Düring, F., *Ber.,* **1899**, *32*, 152. (p) Reverdin, F. and Eckhard, F., *Ber.,* **1899**, *32*, 2622. (q) Reverdin, F., *Ber.,* **1897**, *30*, 3000.

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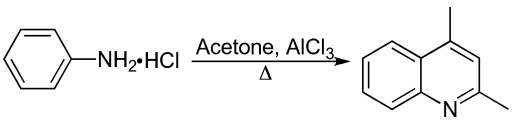
Riehm Quinoline Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Engler and Riehm in 1885.[1] It is a synthesis of 2,4-dimethylquinoline from the thermal condensation of aniline hydrochloride and acetone[2] or mesityl oxide along with the evolution of water and methane,[3] and is known as the Riehm quinoline synthesis.[4] This reaction can occur under the conditions with or without any condensation reagents[2] and may evolve other hydrocarbons as well.[2,3b]

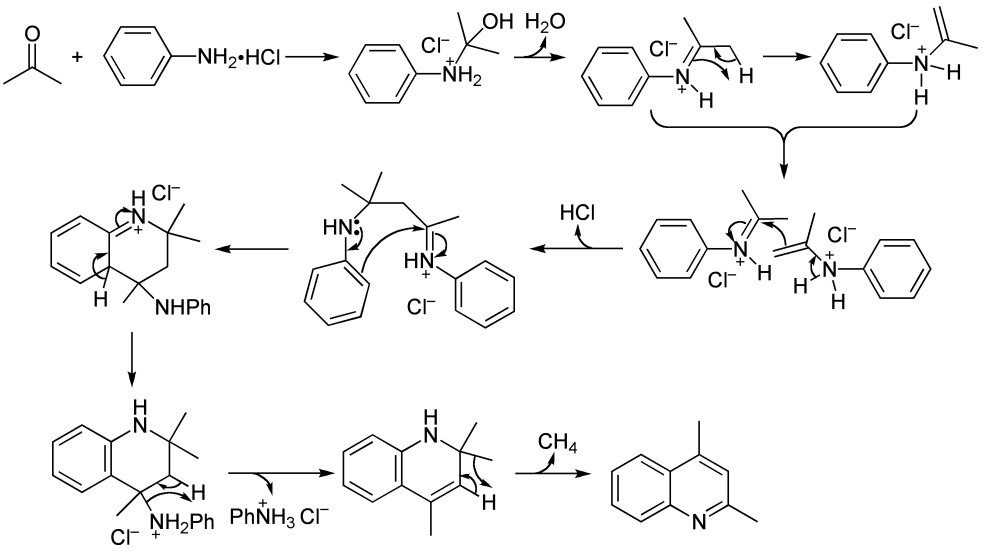
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

This reaction is assumed to involve the formation of ketylidene or alkylidene anils,[5] which dimerizes and cyclizes to give 1,2-dihydroquinoline.[3a,4] This intermediate then aromatizes by evolving the methyl or other hydrocarbon moiety in the presence of an acidic or a basic catalyst.[4] An illustrative mechanism is given here for the reaction between acetone and aniline hydrochloride.

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang



D. MODIFICATION

This reaction was modified by addition of iodine to the mixture of aniline and ketone to initiate the reaction.[4]

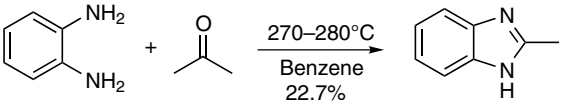
E. APPLICATIONS

This reaction is useful for the preparations of 2,4-disubstituted quinolines.

F. RELATED REACTIONS

This reaction is related to *Doebner Reaction* and *Doebner-von Miller Quinoline Synthesis*.

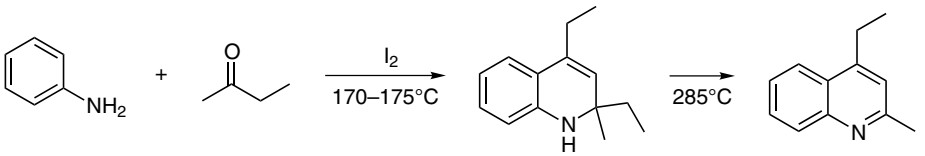
G. CITED EXPERIMENTAL EXAMPLES



Reference 3a.

A 100-mL flask was equippd with a Claisen adapter that was sealed with a graduated tube for measuring the amount of water from azeotropic distillation. In addition, the center arm of the adapter was closed with a stopper, and the side arm was connected with a refluxing condenser, of which the top led to a solid dry ice trap and then to a 1500-mL eudiometer. The capillary tube with stopcock at the top of the eudiometer was sealed for the removal of

gas sample. To the 100-mL flask of this reaction system, were added 5.4 g freshly prepared *o*-phenylenediamine (recrystallized from heptane then water), 29.0 g freshly distilled acetone, and 20 mL dry benzene; the flask was heated with a heating mantle packed with glass wool for 2 h at 270–280°C. Gas evolution initially occurred at 260°C. After the reaction, the volatile solvent was removed by evaporation, and the residue was purified by crystallization from water to afford 1.5 g 2-methylbenzimidazole as white leaflets, in a yield of 22.7%, m.p. 174.0–175.5°C.



Reference 4.

2-Butanone (835 g) was passed into the reaction mixture of 279 g aniline and 9.0 g iodine maintained at 170–175°C. After the reaction, the residual 2-butanone and aniline was separated by preliminary distillation, and the residue was fractionated on a 4-ft. glass helix column, and the fraction that boiled at 170–174°C at 28 mmHg was collected to afford 95 g 2,4-diethyl-2-methyl-1,2-dihydroquinoline. Then the hydrochloride salt of dihydroquinoline was heated at 285°C for 5 min, and the residue was fractionated again to give 2-methyl-4-ethylquinoline.

Other references related to the Riehm quinoline synthesis are cited in the literature.[6]

H. REFERENCES

1. Engler, C. and Riehm, P., *Ber.,* **1885**, *18*, 2245.
2. Manske, R. H. F., *Chem. Rev.,* **1942**, *30*, 113.
3. (a) Elderfield, R. C. and McCarthy, J. R., *J. Am. Chem. Soc.,* **1951**, *73*, 975. (b) Cromwell, N. H., *Chem. Rev.,* **1946**, 83.
4. Zobian, E. J.; Kelley, W. S. and Dunathan, H. C., *J. Org. Chem.,* **1964**, *29*, 584.
5. Barr, W. L., *J. Am. Chem. Soc.,* **1930**, *52*, 2422.
6. (a) Andraos, J., *Org. Proc. Res. Dev.,* **2005**, *9*, 404. (b) Vaughan, W. E., *Org. Synth. Coll.* **1955**, *3*, 329. (c) Craig, D., *J. Am. Chem. Soc.,* **1938**, *60*, 1458. (d) Reddelien, G. and Thurm, A., *Ber.,* **1932**, *65*, 1511. (e) Riehm, P., *Ann.,* **1887**, *238*, 9. (f) Levin, J. and Riehm, P., *Ber.,* **1886**, *19*, 1394.

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Rieke Metal

A. GENERAL DESCRIPTION OF THE REACTION

This reagent was initially prepared by Rieke and Hudnall in 1972.[1] It is a general method of preparing superfine (e.g., nanometer size[2]) and highly active[3] and dispersed[4] metal particles of low valence from the heterogeneous reduction of corresponding anhydrous metal salts[5] by highly reductive metal (e.g., K, Na, Li)[6,7] or hydride (e.g., $NaBEt_3H$, $LiBEt_3H$)[2] in ethereal (e.g., THF,[3,8] DME,[3] glyme[9]) or hydrocarbon solvent (e.g., toluene[2]), in the presence of an electron-carrier such as naphthalene.[9a] The resultant low-valent metal (LVT)[10] is known as Rieke metal,[11] for example, Rieke Mg,[8] Rieke Zn,[12] and Rieke Ni.[11] So far, low-valent Cr, Mo, W, Mg, Mn, Ni, Zn, etc. have been prepared by this method. It has been found that the choice of solvent affects the outcome of this reduction, as indicated by the formation of metal colloid of Cr, Mo, and W in high yield from the reduction of $CrCl_3$, $MoCl_3$ and $MoCl_4$ with $NaBEt_3H$ in toluene at room temperature, whereas metal carbides (M_2C) are obtained from the reduction by $NaBEt_3H$ or $LiBEt_3H$ in THF of the same metal salts.[2] However, this preparation method for Rieke metal has a few limitations, such as the chemical incompatibility with certain functional groups (e.g., NO_2, CN, etc.),[9a] long reaction time,[11] necessary removal of a large amount of naphthalene before or after the reaction induced by these active metals,[11] and the intrinsic tendency toward deactivation and the need for further activation.[10]

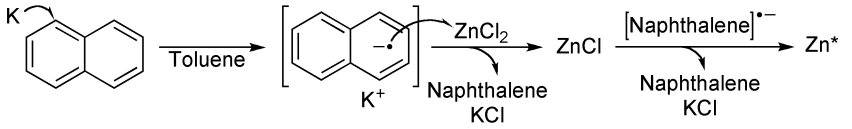
B. GENERAL REACTION SCHEME

$$MX_n \xrightarrow[\text{Ether or toluene}]{\text{K, Naphthalene}} M^* \quad \begin{pmatrix} M = \text{Cr, Mg, Mn, Mo, Ni, W, Zn, etc.} \\ X = \text{Cl} \\ n = 1, 2, 3, \text{etc.} \end{pmatrix}$$

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

The highly active low valent metal is assumed to form via an electron-transfer reaction mediated by naphthalene[9] or biphenylene,[5] as illustrated below for the reduction of zinc chloride by potassium in toluene.



D. MODIFICATION

This preparation has been modified by electronic reduction in DMF solution containing 0.3 M $Bu_4N^+BF_4^-$ as electrolyte in an undivided cell with a platinum cathode and the anode prepared from the expected metal as cation source.[11]

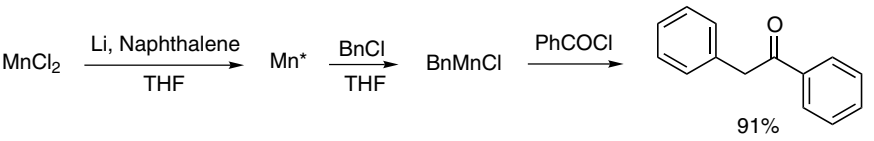
E. APPLICATIONS

Rieke metal has broad application in organic synthesis that requires an active metal of low valence, such as the *McMurry Coupling* (Cr) and the *Reformatsky Reaction* (Zn).

F. RELATED REACTIONS

N/A

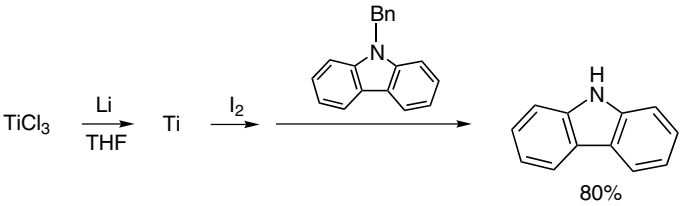
G. CITED EXPERIMENTAL EXAMPLES



Reference 13.

To a mixture of 0.139 g lithium (20 mmol), 0.256 g naphthalene (2 mmol), and 3.087 g manganese iodide (10 mmol) was added 15 mL freshly distilled THF via syringe at room temperature. The resulting mixture was then stirred at room temperature for 30 min to give a black slurry. To this highly active manganese slurry being stirred at room temperature was then added 1.13 g benzyl chloride (9 mmol) via syringe, and the resulting mixture was stirred at room temperature for 20 min. The reaction was monitored by gas chromatography. After the completion of the oxidative addition, the mixture was cooled to 0°C, and 1,2-dibromoethane was added to the mixture at the same temperature to scavenge the excess amount of active manganese for 5 min. The resulting mixture was transferred via cannula to the benzoyl chloride solution in THF at room temperature. After being stirred for 30 min, the

mixture was quenched with 3 M HCl solution and extracted with diethyl ether. The combined organic layers were washed with $NaHCO_3$, $Na_2S_2O_3$, and brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by flash column chromatography using EtOAc/hexanes as the eluent to afford 1.786 g benzyl phenyl ketone as a white solid, in a yield of 91%, m.p. 55–56°C.



Reference 10.

To a mixture of 1.55 g $TiCl_3$ (10 mmol) and 0.231 g Li (33 mmol) was added 50 mL dry THF, the resulting mixture was refluxed for 3 h under argon. After cooling, 0.635 g crystalline iodine (2.5 mmol) was added in portion and the mixture was stirred for 5 min. On addition of iodine, the black suspension of low valent titanium gradually turned brown. To this activated LVT-I_2 reagent, was added 0.643 g *N*-benzyl carbazole (2.5 mmol) in 5 mL THF. The resulting solution was then stirred at room temperature for 16 h, then diluted with hexane and passed through a short pad of Celite. Upon removal of THF, the residue was mixed with an EtOAc/hexanes (20:80) mixture, washed with brine, and dried over Na_2SO_4. After evaporation, the residue was purified by preparative TLC (SiO_2, hexane) to afford 0.335 g carbazole, in a yield of 80%.

Other references related to the Rieke metal are cited in the literature.[14]

H. REFERENCES

1. Rieke, R. D. and Hudnall, P. M., *J. Am. Chem. Soc.,* **1972**, *94*, 7178.
2. Zeng, D. and Hampden-Smith, M. J., *Chem. Mater.,* **1993**, *5*, 681.
3. McMurry, J. E.; Fleming, M. P.; Kees, K. L. and Krepski, L. R., *J. Org. Chem.,* **1978**, *43*, 3255.
4. Corrias, A.; Ennas, G.; Licheri, G.; Marongiu, G. and Paschina, G., *Chem. Mater.,* **1990**, *2*, 363.
5. Yanagisawa, A.; Habaue, S.; Yasue, K. and Yamamoto, H., *J. Am. Chem. Soc.,* **1994**, *116*, 6130.
6. (a) Rieke, R. D. and Bales, S. E., *J. Am. Chem. Soc.,* **1974**, *96*, 1775. (b) Rieke, R. D. and Mea, S. E., *J. Chem. Soc., Chem. Commun.,* **1973**, 789. (c) Rieke, R. D.; Hudnall, P. M. and Uhm, S., *J. Chem. Soc., Chem. Commun.,* **1973**, 269.
7. (a) Fürstner, A., *Active Metals-Preparation, Characterization, Applications*, VCH, Weinheim, **1996**. (b) Cintas, P., *Activated Metals in Organic Synthesis*, CRC Press, Boca Raton, Fla., **1993**.
8. Russell, J. M.; Sabat, M. and Grimes, R. N., *Organometallics,* **2002**, *21,* 5613.
9. (a) Inaba, S.-I.; Matsumoto, H. and Rieke, R. D., *J. Org. Chem.,* **1984**, *49*, 2093. (b) Rieke, R. D.; Li, P. T.-J.; Burns, T. P. and Uhm, S. T., *J. Org. Chem.,* **1981**, *46*, 4323.
10. Talukdar, S.; Nayak, S. K. and Banerji, A., *J. Org. Chem.,* **1998**, *63,* 4925.
11. Yasuhara, A.; Kasano, A. and Sakamoto, T., *Organometallics,* **1998**, *17,* 4754.
12. Hyldtoft, L. and Madsen, R., *J. Am. Chem. Soc.,* **2000**, *122,* 8444.

13. Kim, S.-H. and Rieke, R. D., *J. Org. Chem.,* **2000**, *65,* 2322.

14. (a) O'Brien, R. A. and Rieke, R. D., *J. Org. Chem.,* **1990**, *55*, 188. (b) Rieke, R. D., *Science,* **1989**, *246*, 1260. (c) Rochfort, G. L. and Rieke, R. D., *Inorg. Chem.,* **1986**, *25*, 348. (d) Inaba, S.; Matsumoto, H. and Rieke, R. D., *Tetrahedron Lett.,* **1982**, *23*, 4215. (e) Evans, W. J.; Wayda, A. L.; Chang, C.-W. and Cwirla, W. M., *J. Am. Chem. Soc.,* **1978**, *100*, 333. (f) Rieke, R. D., *Acc. Chem. Res.,* **1977**, *10*, 301. (g) Rieke, R. D., *Top. Curr. Chem.,* **1975**, *59*, 1. (h) Rieke, R. D. and Uhm, S. J., *Synthesis,* **1975**, 452. (i) Rieke, R. D.; Ofele, K. and Fischer, E. O., *J. Organomet. Chem.,* **1974**, *76*, C19.

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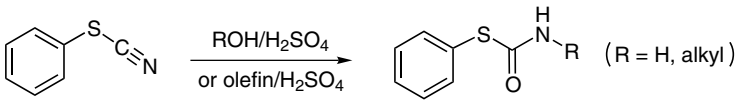
Riemenschneider Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Riemschneider in 1949.[1] It is an acidic transformation of alkyl or aryl thiocyanates into thiocarbamates and is known as the Riemschneider reaction.[2] In this reaction, when thiocyanates are treated with concentrated sulfuric acid, the corresponding thiocarbamates are obtained.[3] In parallel, when thiocyanates are treated with concentrated sulfuric acid in the presence of alcohol or olefin, the corresponding *N*-substituted carbamates are yielded.[4] The alcohols or olefins that are stable in the presence of sulfuric acid, including isopropyl alcohol, *sec*-butyl alcohol, *t*-butyl alcohol, cyclohexanol, isobutylene, and camphene all are suitable for this reaction, whereas low-order alcohols such as methanol and ethanol do not react with thiocyanate to give the corresponding *N*-substituted thiocarbamates.[4] In addition, the benzyl thiocyante[4] and some *ortho*-substituted phenyl thiocyanates cannot be transformed into the corresponding thiocarbamates under these conditions because they are sensitive to sulfuric acid.[3,4] Some unsuitable thiocyanates are *o*-carboxyl, *o*-methoxy, *o*-nitrophenyl thiocyanates,[3] and *o*-methyl-4-amino phenyl thiocyanate.[4]

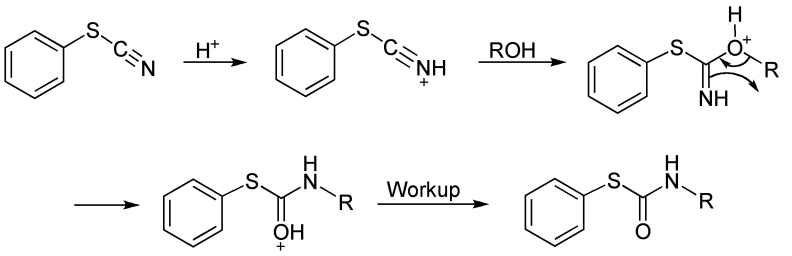
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

Illustrated below is the mechanism for the reaction between phenyl thiocyanate and a general alcohol.



D. MODIFICATION

N/A

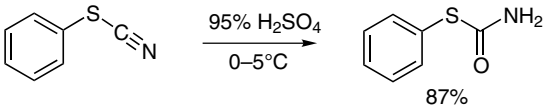
E. APPLICATIONS

This reaction has general application in organic synthesis as well as in analytical chemistry.

F. RELATED REACTIONS

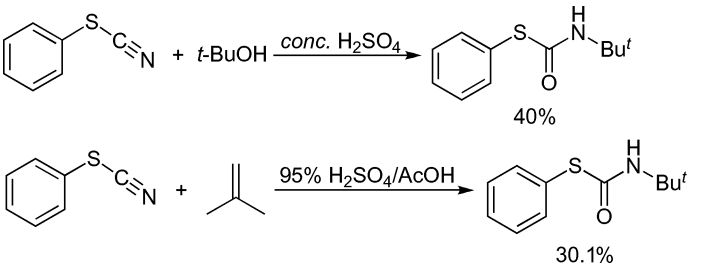
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3.

A benzene solution of 2 g phenyl thiocyanate was treated slowly under shaking and ice cooling with 10 mL 95% H_2SO_4. The mixture was kept at 0–5°C for 15 h and then poured on ice. The precipitate was collected, washed with water, and dried in air. The phenylthiocarbamate was a needle crystal, m.p. 98°C; the yield was 87%.



Reference 4.

From *t*-Butyl Alcohol

To a mixture of concentrated sulfuric acid and 1.85 g *t*-butyl alcohol (25 mmol), was added 3.4 g phenyl thiocyanate (25 mmol) dropwise under stirring. After all the phenyl thiocyanate was added to the solution, the stirring was continued for 5 h with cooling on an ice bath. Then the reaction mixture was stirred into 250 mL ice water to yield yellow crystals, which were further purified by recrystallization several times from hexane following treatment with activated charcoal, m.p. 115°C. The yield was 40%.

From Isobutylene

To a mixture of 30 mL glacial acetic acid and 5 mL 95% sulfuric acid, was added 7.0 g phenyl thiocyanate (51 mmol) dropwise. At the same time, a slow stream of isobutylene was passed through the reaction mixture at a temperature of 10°C; within 40 min, the reaction mixture absorbed 6.0 g isobutylene (107 mmol). After being maintained at 10°C for 24 h, the contents of the reaction vessel were poured into 250 mL ice water, and extracted with ether. The combined ethereal solution was dried and evaporated. The residue was fractionated to give 5.5 g phenyl thiocyanate (71–73°C at 1.5 mmHg), the residue remained after the distillation was recrystallized from hexane to afford 0.7 g *N*-*t*-butyl phenylcarbamate, in a yield of 30.1% based on 21.4% conversion.

Other references related to the Riemschneider reaction are cited in the literature.[5]

H. REFERENCES

1. Riemschneider, R. and Wojahn, F., *Pharmazie,* **1949**, *4*, 460.
2. Schmidt, K. and Kollek-Bös, P., *J. Am. Chem. Soc.,* **1953**, *75*, 6067.
3. Riemschneider, R.; Wojahn, F. and Orlick, G., *J. Am. Chem. Soc.,* **1951**, *73*, 5905.
4. Riemschneider, R., *J. Am. Chem. Soc.,* **1956**, *78*, 844.
5. (a) Klásek, A.; Mrkvicka, V.; Pevec, A. and Kosmrlj, J., *J. Org. Chem.,* **2004**, *69*, 5646. (b) Wynne, J. H.; Jensen, S. D. and Snow, A. W., *J. Org. Chem.,* **2003**, *68*, 3733. (c) Sápi, A.; Fetter, J.; Lempert, K.; Kajtár-Peredy, M. and Czira, G., *Tetrahedron,* **1997**, *53*, 12729. (d) LeMaréchal, A. M.; Robert, A. and Leban, I., *J. Chem. Soc., Perkin Trans. I,* **1993**, 351. (e) Zil'berman, E. N. and Lazaris, A. Y., *J. Gen. Chem. USSR,* **1963**, *33*, 1012. (f) Riemschneider, R. and Orlick, G., *Monatsh. Chem.,* **1953**, *84*, 316. (g) Riemschneider, R., *Monatsh. Chem.,* **1953**, *84*, 1228. (h) Riemschneider, R. and Orlick, G., *Angew. Chem.,* **1952**, *64*, 420. (i) Riemschneider, R., *Chim. Ind. (Milan),* **1952**, *34*, 353. (j) Riemschneider, R., *Z. Naturforsch.,* **1952**, *7b*, 277. (k) Riemschneider, R., *Chim. Ind. (Milan),* **1951**, *33*, 483. (l) Riemschneider, R., *Chim. Ind. (Paris),* **1950**, *64*, 99.

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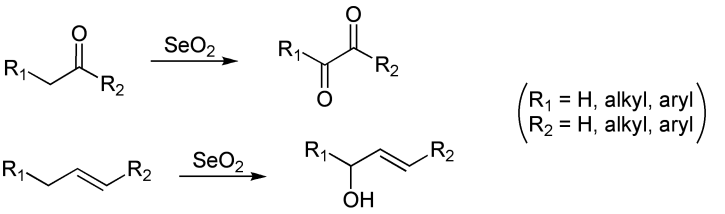
Riley Oxidation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Riley in 1930.[1] It is the oxidation of a methyl or methylene group activated by an adjacent double bond, carbonyl, aromatic, etc. into a carbonyl or alkoxyl group using selenium dioxide as the mild oxidant. Therefore, it is generally known as the Riley oxidation.[2] In this reaction, the methylene group is activated by a carbonyl group, and converted into an adjacent carbonyl group again;[3] whereas a hydroxy group is often introduced onto the allylic methylene group,[4] and the position of the double bond often remains untouched under the condition of allylic oxidation.[4c] In addition, the methylene group in an allylic moiety can be trapped at the alcohol stage by carrying out the reaction in acetic anhydride or acetic acid.[5] At low temperature, saturated hydrocarbons, alcohols, ethers, acids, esters, and most halides will not be oxidized by SeO_2;[5b] but at high temperature, even the double bond can be oxidized, as indicated by the high yield of glyoxal (80%) from ethylene,[6] and 19% of methylglyoxal from propylene at 220–240°C.[6c] The recovered selenium can be oxidized and used again.[5b] This reaction can also be carried out at room temperature under sunlight or UV.[5b]

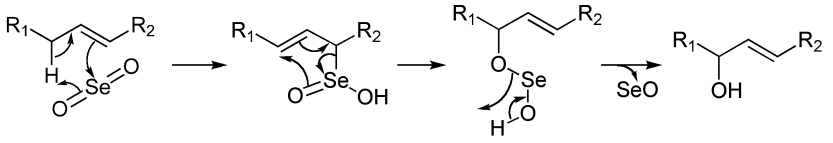
B. GENERAL REACTION SCHEME



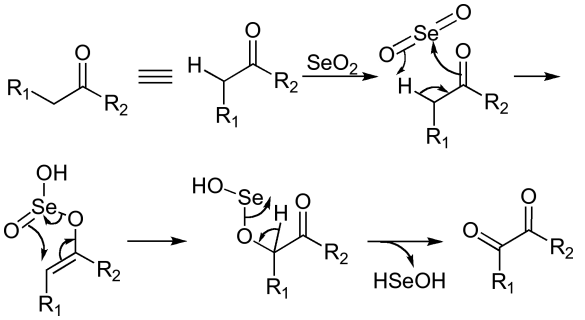
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

The allylic oxidation is assumed to occur through an initial ene reaction followed by a [2,3]-sigmatropic rearrangement,[4b,4f] as illustrated in Scheme 1. Although not many mechanistic studies are available for the oxidation of a ketone or aldehyde to an adjacent dicarbonyl compound, it is plausible that such oxidation by SeO_2 undergoes a similar reaction pathway, as shown in the tentative mechanism outlined in Scheme 2.



SCHEME 1. *Mechanism of allyl alcohol formation by SeO_2 oxidation.*



SCHEME 2. *Tentative mechanism for the oxidation of ketone (or aldehyde) from SeO_2.*

D. MODIFICATION

N/A

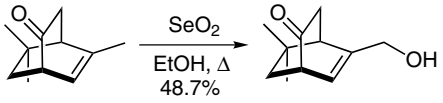
E. APPLICATIONS

This reaction has wide application in organic synthesis, especially for the preparation of allyl alcohol with retention of stereochemistry,[4d,4f,4g] and 1,2-diketones.[3]

F. RELATED REACTIONS

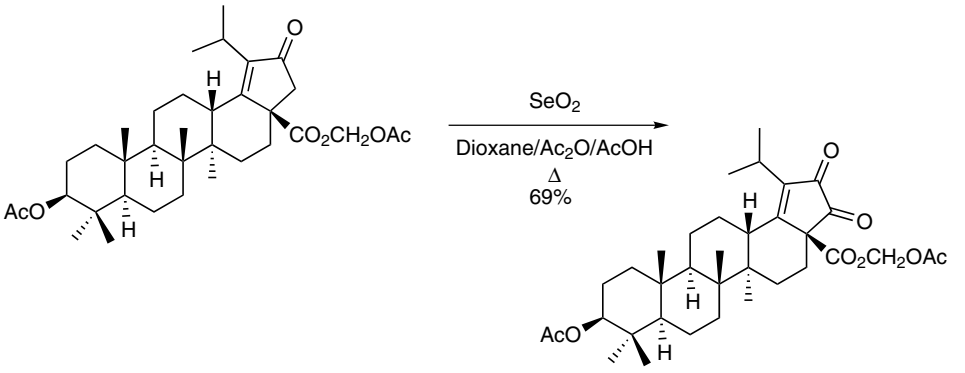
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 8.

A 2-mL magnetically stirred 95% ethanol solution containing 348 mg 2,7,7-trimethylbicyclo[2.2.2]oct-2-en-5-one (2.12 mmol) was treated dropwise with 2 mL 95% ethanol solution containing 250 mg SeO_2 (2.26 mmol). The reaction mixture was stirred and refluxed for 48 h, then diluted with ether and washed with brine. The ethereal phase was dried and concentrated to leave a residue that was purified by silica gel chromatography using 5% ether in petroleum ether as an eluent to afford 186 mg 2-hydroxymethyl-7,7-dimethylbicyclo[2.2.2]-oct-2-en-5-one as a colorless liquid (48.7%), and 52 mg of starting material (15% recovery).



Reference 3b.

A mixture of 5 mL dioxane solution containing 250 mg acetoxymethyl 3β-acetoxy-21-oxolup-18-en-28-oate (0.43 mmol), 200 mg SeO_2 (1.8 mmol), 2.5 mL AcOH, and 0.25 mL Ac_2O was refluxed until the oxidation was completed as monitored by TLC (PhMe/Et_2O, 10:1). After cooling, precipitated selenium was removed by filtration, and the filtrate was poured slowly into an excess of vigorously stirred water. The red-orange precipitate was filtered under reduced pressure, washed carefully with H_2O, and air dried. The crude product was dissolved in $CHCl_3$, and the solution was filtered through a column of alumina. The column was eluted with $CHCl_3$, and the filtrate was evaporated under reduced pressure. The residue was crystallized from butanone to afford 176 mg acetoxymethyl 3β-acetoxy-21,22-dioxolup-18-ene-28-oate as pale-orange needles, in a yield of 69%, m.p. 227–228°C.

Other references related to the Riley oxidation are cited in the literature.[7]

H. REFERENCES

1. Riley, H. L., *Brit. Pat.,* **1931**, Aug. 17, 354,798.
2. (a) Dalavoy, V. S.; Deodhar, V. B. and Nayak, U. R., *Indian J. Chem., Sect. B,* **1987**, *26B*, 1. (b) Goudgaon, N. M. and Nayak, U. R., *Indian J. Chem., Sect. B,* **1985**, *24B*, 589.
3. (a) Muccioli, G. G.; Wouters, J.; Charlier, C.; Scriba, G. K. E.; Pizza, T.; di Pace, P.; de Martino, P.; Poppitz, W.; Poupaert, J. H. and Lambert, D. M., *J. Med. Chem.,* **2006**, *49*, 872. (b) Sÿarek, J.; Klinot, J.; Dzubák, P.; Klinotová, E.; Nosková, V.; Krecek, V.; Korinková, G.; Thomson, J. O.; Janost'áková, A.; Wang, S. D.; Parsons, S.; Fischer, P. M.; Zhelev, N. Z. and Hajdúch, M., *J. Med. Chem.,* **2003**, *46*, 5402. (c) Kokke, W. C. M. C., *J. Org. Chem.,* **1973**, *38*, 2989. (d) Jerussi, R. A. and Speyer, D., *J. Org. Chem.,* **1966**, *31*, 3199. (e) Singh, G., *J. Am. Chem. Soc.,* **1956**, *78*, 5109.

(f) Rabjohn, N., *Org. React.,* **1949**, *5*, 331. (g) Riley, H. A. and Gray, A. R., *Org. Synth. Coll.*, **1943**, *2*, 509. (h) Dane, E. and Schmitt, J., *Ann.,* **1939**, *537*, 246.

4. (a) Nickel, A.; Maruyama, T.; Tang, H. F.; Murphy, P. D.; Greene, B.; Yusuff, N. and Wood, J. L., *J. Am. Chem. Soc.,* **2004**, *126*, 16300. (b) Bélanger, G.; Hong, F.-T.; Overman, L. E.; Rogers, B. N.; Tellew, J. E. and Trenkle, W. C., *J. Org. Chem.,* **2002**, *67*, 7880. (c) Singleton, D. A. and Hang, C., *J. Org. Chem.,* **2000**, *65*, 7554. (d) Paquette, L. A.; Maleczka, R. E. and Qiu, F.-Y., *J. Org. Chem.,* **1991**, *56*, 2455. (e) Williams, D. R.; Bremmer, M. L.; Brown, D. L. and D'Antuono, J., *J. Org. Chem.,* **1985**, *50*, 2807. (f) Stephenson, L. M. and Speth, D. R., *J. Org. Chem.,* **1979**, *44*, 4683. (g) Trachtenberg, E. N. and Carver, J. R., *J. Org. Chem.,* **1970**, *35*, 1646.
5. (a) DeWolfe, R. H. and Young, W. G., *Chem. Rev.,* **1956**, *56*, 753. (b) Waitkins, G. R. and Clark, C. W., *Chem. Rev.,* **1945**, *36*, 235.
6. (a) Lu Valle, J. E. and Schomaker, V., *J. Am. Chem. Soc.,* **1939**, *61*, 3521. (b) Riley, H. L., *Brit. Pat.,* July 8, **1932**, 376,306. (c) Riley, H. L. and Friend, N. A. C., *J. Chem. Soc.,* **1932**, 2342.
7. (a) Kvasnica, M.; Tislerova, I.; Sarek, J.; Sejbal, J. and Cisarova, I., *Coll. Czech. Chem. Commun.,* **2005**, *70*, 1447. (b) Arnó, M.; Betancur-Galvis, L.; Bueno-Sanchez, J. G.; González, M. A. and Zaragonzá, R. J., *Tetrahedron,* **2003**, *59*, 6455. (c) Bazhina, G. N. and Manukov, É, N., *Chem. Nat. Compd.,* **1995**, *31*, 423. (d) Camps, F.; Coll, J. and Parente, A., *Synthesis,* **1978**, 215. (e) Hori, T. and Sharpless, K. B., *J. Org. Chem.,* **1978**, *43*, 1689. (f) Umbreit, M. A. and Sharpless, K. B., *J. Am. Chem. Soc.,* **1977**, *99*, 5526. (g) Knuppen, R.; Haupt, O. and Breuer, H., *Biochem. J.,* **1967**, *105*, 971. (h) Fieser, L. F. and Goto, T., *J. Am. Chem. Soc.,* **1960**, *82*, 1693. (i) Colonge, J. and Reymermier, M., *Compt. Rend.,* **1953**, *237*, 226. (j) Fieser, L. F. and Ourisson, G., *J. Am. Chem. Soc.,* **1953**, *75*, 4404. (k) Butz, L. W.; Davis, B. L. and Gaddis, A. M., *J. Org. Chem.,* **1947**, *14*, 122. (l) Riley, H. L., Morley, J. F. and Friend, N. A. C., *J. Chem. Soc.,* **1932**, 1875.

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Ritter Reaction

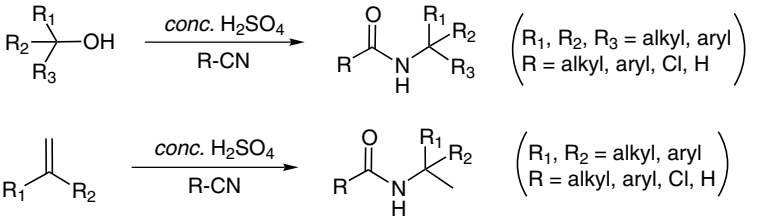
A. GENERAL DESCRIPTION OF THE REACTION

This reaction can be traced back as early as in 1922, when Kohler et al. investigated the reaction between methyl cyanoacetate and benzal-acetophenone or benzal-*p*-chloro-acetophenone in the presence of hydrogen chloride or hydrogen bromide to form lactams.[1] Subsequently, Bus reported the reaction of *N*-hydroxymethyl phthalimide with nitriles in the presence of sulfuric acid.[2] It was Ritter who extensively studied and extended the reaction of nitriles;[3] therefore, a strong acid-promoted amidation of alcohol or olefin with nitrile is generally known as the Ritter reaction.[4,5] Under strong acidic conditions, both alcohol and olefin are protonated to generate a carbocation with an empty *p*-orbital that can be filled by the lone pair electrons on the nitrogen atom of nitriles to form the nitrilium ion, which is converted to an amide upon hydrolysis.[4g,4n,4q,4w] Besides alcohols and olefins, some other types of molecules can also undergo this reaction under similar conditions by formation of carbocations such as trioxane,[4s] *N*-tosylazetidine,[6] aziridine,[4c] oxirane,[5uu] and epoxide.[4b,5e] It has been found that the outcome of this reaction depends on the reactivity of nitriles and the stability of carbocations,[4r] thus the reactions from tertiary alcohols normally give much higher yields than those from primary and secondary alcohols.[4r] In addition, temperature may affect the reaction, as demonstrated from the reaction between nitrile and chalcone, which takes place at temperatures $> 55^{\circ}C$ even when sulfuric acid is replaced by the much milder phosphoric acid and diluted with acetic acid; whereas the same reaction occurs more slowly below $55^{\circ}C$.[4z] Furthermore, it has been found that stereochemistry is completely retained in this reaction when a bromo group is present at the neighboring position, through the bromo bridge intermediate, as indicated from the exclusive formation of *threo*-2-acetamido-3-bromobutane and *threo*-2-benzamido-3-bromobutane from *threo*-3-bromo-2-butanol with acetonitrile and benzonitrile, respectively.[4u] However, given the

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

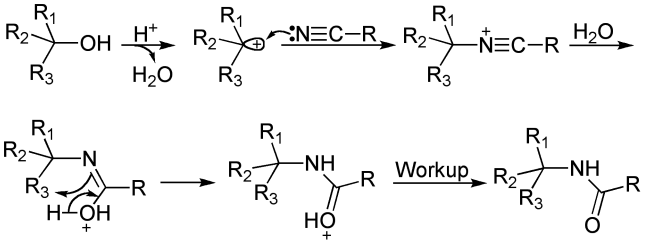
nature of this reaction, the Ritter reaction is also in competition with other side reactions involving carbocations, such as the ring-enlargement of cyclic carbocations[4w] and the rearrangement of carbocations.[4t]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

This reaction involves the initial formation of a carbocation from olefin or alcohol when treated with a strong acid such as sulfuric acid that is subsequently attacked by the lone pair electrons of the nitrogen atom of a nitrile to give a nitrilium ion, which, on addition of water during workup, hydrolyzes to form an amide,[4g,4n,4q,4w] as illustrated below using a general tertiary alcohol as an example.



D. MODIFICATION

The original reaction protocol has been extensively modified, including the activation of a primary alcohol with trifluoromethanesulfonic anhydride,[7] stabilization of primary carbocations with transition-metal complex (e.g., $Co(CO)_3$),[4r] replacement of sulfuric acid by Pd^{2+},[4p] liquid hydrogen fluoride,[4v] P_2O_5/SiO_2,[5b] bismuth salt (III),[5d,5e] heteropolyacids,[5g,5h] or a Lewis acid-assisted Brønsted acid, which is prepared from a 1:2 molar mixture of $B(OH)_3$ and 4,5,6,7-tetrachlorocatechol.[4a] In addition, the Ritter reaction has been extended to the reaction of nitrile with either aldose[5a] or ketose.[5ee] Further modifications include the sulfur mediated Ritter reaction;[5z] the application of acetic acid as co-solvent;[4o] and the reactions between olefin and cyanogen chloride,[8] haloolefin and nitrile,[9] camphene and hydrogen cyanide,[10] and especially metal cation and nitriles.[11]

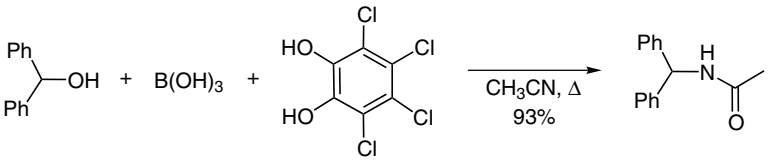
E. APPLICATIONS

This reaction has very wide applications in organic synthesis, not only for the general preparation of amides[5a] but also for a variety of monocyclic and fused heterocyclic compounds,[4m] bridged heterocycles,[4m] and polyamides.[4s,4x]

F. RELATED REACTIONS

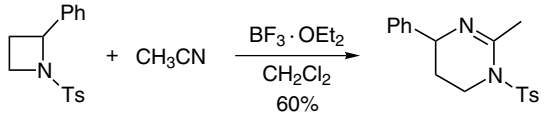
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 4a.

A dry, 10-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a reflux condenser was charged with 6.2 mg $B(OH)_3$ (0.10 mmol), 50 mg tetrachlorocatechol (0.20 mmol), and 368 mg diphenylmethanol (2.0 mmol) in 5 mL acetonitrile. The mixture was refluxed for 11 h and then cooled to ambient temperature and mixed with saturated aqueous $NaHCO_3$. The product was extracted with EtOAc, and the combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography to afford 93% *N*-α,α-diphenylmethyl acetamide, m.p. 151°C.



Reference 6.

To a 10-mL round-bottomed flask were added 211 mg 2-phenyl-*N*-tosyl azetidine (1 mmol) and 3 mL anhydrous CH_2Cl_2 under argon at room temperature, followed by 1 mmol acetonitrile and a slow addition of 0.2 mmol freshly distilled $BF_3{\cdot}Et_2O$. After 2 h, 2 mL saturated aqueous $NaHCO_3$ solution was added. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2×5 mL). The combined organic layers were washed with water, brine, and dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography using 30% EtOAc in petroleum ether as the eluent to afford 60% 2-methyl-4-phenyl-1-(toluene-4-sulphonyl)-1,4,5,6-tetrahydropyrimidine as a colorless paste, $R_f = 0.42$ (EtOAc/petroleum ether, 2:3).

Other references related to the Ritter reaction are cited in the literature.[12]

H. REFERENCES

1. Kohler, E. P.; Graustein, A. and Merrill, D. R., *J. Am. Chem. Soc.,* **1922**, *44*, 2536.
2. Bus, S. R., *J. Am. Chem. Soc*., **1947**, *69*, 254.
3. (a) Ritter, J. J. and Minieri, P. P., *J. Am. Chem. Soc*., **1948**, *70*, 4045. (b) Ritter, J. J. and Kalish, J., *J. Am. Chem. Soc*., **1948**, *70*, 4048. (c) Hartzel, L. W. and Ritter, J. J., *J. Am. Chem. Soc*., **1949**, *71*, 4130. (d) Ritter, J. J. and Murphy, F. X., *J. Am. Chem. Soc.,* **1952**, *74*, 763.
4. (a) Maki, T.; Ishihara, K. and Yamamoto, H., *Org. Lett.,* **2006**, *8*, 1431. (b) Concellón, J. M.; Suárez, J. R. and del Solar, V., *J. Org. Chem.,* **2005**, *70*, 7447. (c) Concellón, J. M.; Riego, E.; Suárez, J. R.; García-Granda, S. and Díaz, M. R., *Org. Lett.,* **2004**, *6*, 4499. (d) Koval'skaya, S. S.; Kozlov, N. G. and Dikusar, E. A., *Russ. J. Gen. Chem.,* **2004**, *74*, 897. (e) Ho, T.-L. and Chein, R.-J., *J. Org. Chem.,* **2004**, *69*, 591. (f) Gerasimova, N. P.; Nozhnin, N. A.; Ermolaeva, V. V.; Ovchinnikova, A. V.; Moskvichev, Y. A.; Alov, E. M. and Danilova, A. S., *Mendeleev Commun.,* **2003**, *13*, 82. (g) Rosenberg, M. G.; Haslinger, U. and Brinker, U. H., *J. Org. Chem.,* **2002**, *67,* 450. (h) Kouznetsov, V.; Palma, A. and Ewert, C., *Curr. Org. Chem.,* **2001**, *5*, 519. (i) Kozhevnikov, D. N.; Nikitina, T. V.; Rusinov, V. L. and Chupakhin, O. N., *Mendeleev Commun.,* **2000**, *10*, 117. (j) Emelen, K. V.; Wit, T. D.; Hoornaert, G. J. and Compernolle, F., *Org. Lett.,* **2000**, *2*, 3083. (k) Sedlak, M. and Tauer, K., *Molecules,* **2000**, *5*, 730. (l) Chang, S.-J., *Org. Proc. Res. Dev.,* **1999**, *3*, 232. (m) Pich, K. C.; Bishop, R.; Craig, D. C. and Scudder, M. L., *Aust. J. Chem.,* **1994**, *47*, 837. (n) Amini, Bishop, A.; Burgess, G.; Craig, D. C.; Dance, I. G. and Scudder, M. L., *Aust. J. Chem.,* **1989**, *42*, 1919. (o) Bishop, R.; Hawkins, S. C. and Ibana, I. C., *J. Org. Chem.,* **1988**, *53*, 427. (p) Hegedus, L. S.; Mulhern, T. A. and Asada, H., *J. Am. Chem. Soc.,* **1986**, *108*, 6224. (q) Cacace, F.; Ciranni, G. and Giacomello, P., *J. Am. Chem. Soc.,* **1982**, *104*, 2258. (r) Top, S. and Jaouen, G., *J. Org. Chem.,* **1981**, *46*, 78. (s) Ogata, N. and Saito, K., *J. Poly. Sci., Poly. Chem. Ed.,* **1975**, *13*, 2763. (t) Edwards, S. and Marquardt, F.-H., *J. Org. Chem.,* **1974**, *39*, 1963. (u) Wohl, R. A., *J. Org. Chem.,* **1973**, *38*, 3099. (v) Norell, J. R., *J. Org. Chem.,* **1970**, *35*, 1611. (w) Sasaki, T.; Eguchi, S. and Ishii, T., *J. Org. Chem.,* **1970**, *35*, 2257. (x) Ramp, F. L., *J. Poly. Sci., Part A: General Papers,* **1965**, *3*, 1877. (y) Kaluszyner, A.; Blum, S. and Bergmann, E. D., *J. Org. Chem.,* **1963**, *28*, 3588. (z) Scheuer, P. J.; Botelho, H. C. and Pauling, C., *J. Org. Chem.,* **1957**, *22*, 674.
5. (a) Wang, Z. R. D.; Sheikh, S. O.; Cox, S.; Zhang, Y. L. and Massey, K., *Eur. J. Org. Chem.,* **2007**, 2243. (b) Tamaddon, F.; Khoobi, M. and Keshavarz, E., *Tetrahedron Lett*., **2007**, *48*, 3643. (c) Garcia Martinez, A.; Teso Vilar, E.; Moreno-Jimenez, F. and Alvarez Garcia, A. M., *Tetrahedron: Asymmetry*, **2006**, *17*, 2970. (d) Callens, E.; Burton, A. J. and Barrett, A. G. M., *Tetrahedron Lett*., **2006**, *47*, 8699. (e) Pinto, R. M. A.; Salvador, J. A. R. and Le Roux, C., *Synlett,* **2006**, 2047. (f) Liu, J.; Ni, C. F.; Li, Y.; Zhang, L. J.; Wang, G. Y. and Hu, J. B., *Tetrahedron Lett*., **2006**, *47*, 6753. (g) Kartashov, V. R.; Malkova, K. V.; Arkhipova, A. V. and Sokolova, T. N., *Russ. J. Org. Chem.,* **2006**, *42*, 966. (h) Kartashov, V. R.; Arkhipova, A. V.; Malkova, K. V. and Sokolova, T. N., *Russ. Chem. Bull.,* **2006**, *55*, 387. (i) Rao, K. S.; Reddy, D. S.; Pal, M.; Mukkanti, K. and Iqbal, J., *Tetrahedron Lett*., **2006**, *47*, 4385. (j) Vatsouro, I. M.; Shokova, E. A.; Shestakova, A. K.; Chertkov, V. A. and Kovalev, V. V., *Eur. J. Org. Chem.,* **2006**, 522. (k) Shklyaev, Y. V.; Glushkov, V. A.; El'tzov, M. A.; Gatilov, Y. V.; Bagryanskaya, I. Yu. and Tolstikov, A. G., *Mendeleev Commun*., **2005**, 125. (l) Yarovaya, O. I.; Korchagina, D. V.; Rybalova, T. V.; Gatilov, Yu. V.; Polovinka, M. P. and Barkhash, V. A., *Russ. J. Org. Chem.,* **2004**, *40*, 1593. (m) Penner, M.; Taylor, D.; Desautels, D.; Marat, K. and Schweizer, F., *Synlett,* **2005**, 212. (n) Averina, N. V.; Zefirova, O. N.; Zefirov, N. S.; Chekhlov, A. N.; Shilov, G. V. and Aldoshin, S. M., *Russ. J. Org. Chem.,* **2004**, *40*, 1437. (o) Maertens, F.; Van den Bogaert, A.; Compernolle, F. and Hoornaert, G. J., *Eur. J. Org. Chem.,* **2004**, 4648. (p) Shklyaev, Yu. V.; Ismagilov, R. R.; Rozhkova, Yu. S.; Fatykhov, A. A.; Abdrakhmanov, I. B. and Tolstikov, A. G., *Russ. Chem. Bull.,* **2004**, *53*, 906. (q) Averina, N. V.; Borisova, G. S.; Zefirova, O. N.; Selyunina, E. V.; Zyk, N. V. and Zefirov, N. S., *Russ. J. Org. Chem.,* **2004**, *40*, 497. (r) Janin, Y. L.; Decaudin, D.; Monneret, C. and

Poupon, M.-F., *Tetrahedron*, **2004**, *60*, 5481. (s) Koval'skaya, S. S. and Kozlov, N. G., *Russ. J. Gen. Chem.,* **2003**, *73*, 1421. (t) Justribo, V.; Colombo, M. I. and Ruveda, E. A., *J. Undergrad. Chem. Res.,* **2003**, *2*, 117. (u) Justribo, V. and Colombo, M. I., *Tetrahedron Lett*., **2003**, *44*, 8023. (v) Koval'skaya, S. S. and Kozlov, N. G., *Russ. J. Org. Chem.,* **2003**, *39*, 183. (w) Gerasimova, N. P.; Nozhnin, N. A.; Ermolaeva, V. V.; Ovchinnikova, A. V.; Moskvichev, Y. A.; Alov, E. M. and Danilova, A. S., *Mendeleev Commun*., **2003**, 82. (x) Gullickson, G. C. and Lewis, D. E., *Synthesis*, **2003**, 681. (y) Reddy, K. L., *Tetrahedron Lett*., **2003**, *44*, 1453. (z) Eastgate, M. D.; Fox, D. J.; Morley, T. J. and Warren, S., *Synthesis,* **2002**, 2124. (aa) Van Emelen, K.; De Wit, T.; Hoornaert, G. J. and Compernolle, F., *Tetrahedron*, **2002**, *58*, 4225. (bb) Colombo, M. I.; Bohn, M. L. and Ruveda, E. A., *J. Chem. Edu.,* **2002**, *79*, 484. (cc) Koval'skaya, S. S.; Dikusar, E. A.; Kozlov, N. G. and Popova, L. A., *Russ. J. Org. Chem.,* **2001**, *37*, 1225. (dd) Glushkov, V. A.; Shurov, S. N.; Maiorova, O. A.; Postanogova, G. A.; Feshina, E. V. and Shklyaev, Yu. V., *Chem. Heterocycl. Compd.,* **2001**, *37*, 444. (ee) Schweizer, F.; Lohse, A.; Otter, A. and Hindsgaul, O., *Synlett*, **2001**, 1434. (ff) Le Goanvic, D.; Lallemand, M.-C.; Tillequin, F. and Martens, T., *Tetrahedron Lett*., **2001**, *42*, 5175. (gg) Nakano, S.; Igarashi, Y. and Nohira, H., *Tetrahedron: Asymmetry*, **2001**, *12*, 59. (hh) Welniak, M., *Pol. J. Chem.,* **2001**, *75*, 55. (ii) Jirgensons, A.; Kauss, V.; Kalvinsh, I. and Gold, M. R., *Synthesis*, **2000**, 1709. (jj) Koval'skaya, S. S.; Kozlov, N. G. and Dikusar, E. A., *Russ. J. Org. Chem.,* **2000**, *36*, 379. (kk) Kozhevnikov, D. N.; Nikitina, T. N.; Rusinov, V. L. and Chupakhin, O. N., *Mendeleev Commun*., **2000**, 117. (ll) Nikitin, K. V. and Andryukhova, N. P., *Mendeleev Commun*., **2000**, 31. (mm) Hessley, R. K., *J. Chem. Edu.,* **2000**, *77*, 202. (nn) Jirgensons, A.; Kauss, V.; Mishnev, A. F. and Kalvinsh, I., *J. Chem. Soc., Perkin Trans. I,* **1999**, 3527. (oo) Glushkov, V. A.; Shklyaev, Y. V.; Sokol, V. I.; Sergienko, V. S. and Davidov, V. V., *Mendeleev Commun*., **1999**, 170. (pp) Koval'skaya, S. S. and Kozlov, N. G., *Russ. J. Org. Chem.,* **1998**, 34, 1449. (qq) Koval'skaya, S. S. and Kozlov, N. G., *Russ. J. Org. Chem.,* **1998**, *34*, 1131. (rr) Glushkov, V. A.; Shklyaev, Y. V.; Sokol, V. I.; Sergienko, V. S. and Davidov, V. V., *Mendeleev Commun*., **1998**, 227. (ss) Weniak, M., *Pol. J. Chem.,* **1998**, *72*, 1021. (tt) Ishii, H.; Hirano, T.; Maki, S.; Niwa, H. and Ohashi, M., *Tetrahedron Lett*., **1998**, *39*, 2791. (uu) Glushkov, V. A. and Shklyaev, Y. V., *Mendeleev Commun*., **1998**, 17. (vv) Sokolova, T. D.; Cherkaev, G. V.; Boiko, I. P. and Moskovkin, A. S., *Chem. Heterocycl. Compd.,* **1997**, *33*, 676. (ww) Lin, Q. H.; Ball, G. E. and Bishop, R., *Tetrahedron*, **1997**, *53*, 10899. (xx) Tongco, E. C.; Prakash, G. K. S. and Olah, G. A., *Synlett*, **1997**, 1193. (yy) Oki, M.; Hirose, T.; Aki, M.; Morita, N.; Nose, E.; Kataoka, Y.; Ono, M. and Toyota, S., *Bull. Chem. Soc. Jpn.,* **1996**, *69*, 3345. (zz) Thibault-Starzyk, F.; Payen, R. and Lavalley, J.-C., *Chem. Commun.,* **1996**, 2667. (aaa) Luzgin, M. V. and Stepanov, A. G., *Mendeleev Commun*., **1996**, 238. (bbb) Chen, H. G.; Goel, O. P. and Knobelsdorf, J., *Tetrahedron Lett.,* **1996**, *37*, 8129. (ccc) Djaidi, D.; Bishop, R.; Craig, D. C. and Scudder, M. L., *J. Chem. Soc., Perkin Trans. I,* **1996**, 1859. (ddd) Welniak, M., *Pol. J. Chem.,* **1996**, *70*, 752. (eee) Taylor, G. M.; Baker, S. J.; Gedney, A.; Pearson, D. J. and Sibley, G. E. M., *Tetrahedron Lett*., **1996**, *37*, 1297. (fff) Bobyleva, A. A.; Lukovskaya, E. V.; Pehk, T. I.; Karoza, G. A. and Belikova, N. A., *Zh. Org. Khim.,* **1994**, *30*, 1632. (ggg) Crouch, R. D., *J. Chem. Edu.,* **1994**, *71*, A200. (hhh) Firouzabadi, H.; Sardarian, A. R. and Badparva, H., *Synth. Commun.,* **1994**, *24*, 601. (iii) Narayanan, C. R. and Landge, A. B., *Indian J. Chem., Sect. B,* **1993**, *32B*, 299. (jjj) Koval'skaya, S. S.; Kozlov, N. G. and Zyryanov, V. A., *Zh. Obsh. Khim.,* **1992**, *62*, 878. (kkk) Olah, G. A. and Wang, Q., *Synthesis*, **1992**, 1090. (lll) Popova, L. A.; Kozlov, N. G.; Shavyrin, S. V.; Biba, V. I. and Knizhnikov, V. A., *Zh. Org. Khim.,* **1992**, *28*, 737. (mmm) Ismail, A. E. H.; Hamed, A.; Zeid, I. and Jochims, J. C., *Tetrahedron,* **1992**, *48*, 8271.

6. Prasad, B. A. B.; Bisai, A. and Singh, V. K., *Org. Lett.,* **2004**, *6*, 4829.
7. Martinez, A. G.; Alvarez, R. M.; Vilar, E. T.; Fraile, A. G.; Hanack, M. and Subramanian, L. R., *Tetrahedron Lett*., **1989**, *30*, 581.
8. (a) Cowen, F. M., *J. Org. Chem.,* **1955**, *20*, 287. (b) Smolin, E. M., *J. Org. Chem.,* **1955**, *20*, 295.
9. (a) Malen, C. and Boissier, J. R., *Bull. Soc. Chim. Fr.,* **1956**, 923. (b) Maugé, R.; Malen, C. and Boissier, J. R., *Bull. Soc. Chim. Fr.,* **1956**, 926.

10. Stein, G. A.; Sletzinger, M.; Arnold, H.; Reinhold, D.; Gaines, W. and Pfister, K., *J. Am. Chem. Soc.,* **1956**, *78*, 1514.

11. Tellers, D. M.; Ritter, J. C. M. and Bergman, R. G., *Inorg. Chem*., **1999**, *38*, 4810.

12. (a) Saibabu Kotti, S. R. S.; Timmons, C. and Li, G. G., *Chem. Biol. & Drug Design,* **2006**, *67*, 101. (b) Nenajdenko, V. G.; Shevchenko, N. E.; Balenkova, E. S. and Alabugin, I. V., *Chem. Rev.,* **2003**, *103,* 229. (c) Booker-Milburn, K. I.; Guly, D. J.; Cox, B. and Procopiou, P. A., *Org. Lett.,* **2003**, *5*, 3313. (d) Glushkov, V. A.; Ausheva, O. G. and Shklyaev, Y. V., *Russ. Chem. Bull.,* **2002**, *51*, 709. (e) Zwanenburg, B., *Pure & Appl. Chem.,* **1999**, *71*, 423. (f) Johansen, S. K.; Kornø, H. T. and Lundt, I., *Synthesis,* **1999**, 171. (g) de Lijser, H. J. P. and Arnold, D. R., *J. Phys. Chem. A,* **1998**,*102,* 5592. (h) Johnson, F. and Madronero, R., *Adv. Heterocycl. Chem.,* **1996**, *6*, 95. (i) Samaniego, W. N.; Baldessari, A.; Ponce, M. A.; Rodriguez, J. B.; Gros, E. G.; Caram, J. A. and Marschoff, C. M., *Tetrahedron Lett*., **1994**, *35,* 6967. (j) Fink, D. M. and Effland, R. C., *Synth. Commun.,* **1994**, *24*, 2793. (k) Toshimitsu, A.; Hirosawa, C. and Tamao, K., *Tetrahedron,* **1994**, *50*, 8997. (l) Narayanan, C. R.; Kulkarni, A. K.; Landgi, A. B. and Wadia, M. S., *Synthesis,* **1977**, 35. (m) Ryan, R. J. and Julia, S., *Tetrahedron,* **1973**, *29*, 3649. (n) Bourgery, G.; Frankel, J. J.; Julia, S. and Ryan, R., *Tetrahedron,* **1972**, *28*, 1377. (o) Beeby, P. J. and Sternhell, S., *Aust. J. Chem.,* **1971**, *24*, 809. (p) Krimen, L. I.; Cota, D. J., *Org. React.,* **1969**, *17*, 213. (q) Sanguigni, J. A. and Levine, R., *J. Med. Chem.,* **1964**, *7*, 573. (r) Hohenlohe-Oehringen, K. and Bretschneider, H., *Monatsh.,* **1962**, *98*, 645. (s) Cronyn, M. W. and Riesser, G. H., *J. Am. Chem. Soc.,* **1953**, *75*, 1664. (t) Plaut, H. and Ritter, J. J., *J. Am. Chem. Soc.,* **1951**, *73*, 4076. (u) Lusskin, R. M. and Ritter, J. J., *J. Am. Chem. Soc.,* **1950**, *72*, 5577. (v) Gates, M.; Woodward, R. B.; Newhall, W. F. and Kuenzl, R., *J. Am. Chem. Soc.,* **1950**, *72*, 1141. (w) Benson, F. R. and Ritter, J. J., *J. Am. Chem. Soc.,* **1949**, *71*, 4128.

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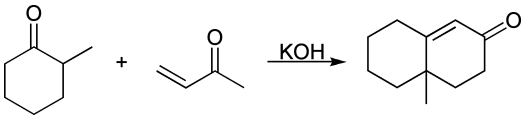
Robinson Annulation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Rapson and Robinson in 1935.[1] It is the synthesis of α,β-unsaturated cyclohexanone resulting from the attachment of four carbon units to a ketone's carbonyl and α-carbon atom, respectively.[2] This reaction involves the following steps: the generation of an enolate from the ketone, *Michael Addition* of the enolate to the α,β-unsaturated ketone, *Aldol Condensation*, and dehydration. Therefore, this reaction is generally known as the Robinson annulation,[2–4] or Robinson annelation.[5] Occasionally, it is also referred to as the Robinson cyclization[6] or Robinson transposition reaction.[7] In addition, the corresponding reaction involving a nitrogen atom is similarly called the *aza*-Robinson annulation.[8] This reaction has been widely used in organic synthesis,[3,4] especially in the preparation of steroids.[2,5g,9]

B. GENERAL REACTION SCHEME



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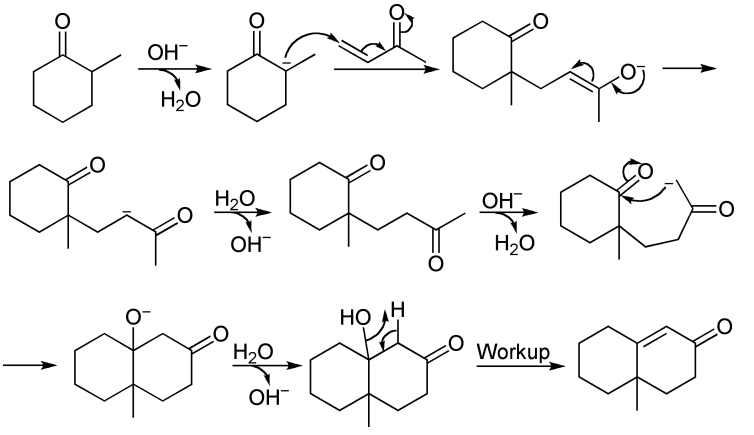
C. PROPOSED MECHANISMS

Displayed here is the mechanism of the Robinson annulation between cyclohexanone and vinyl methyl ketone in the presence of KOH.



D. MODIFICATION

This reaction has been extended to the *Michael Addition* on α,β-unsaturated nitrile by temporarily chelating the Grignard reagent to γ-hydroxy unsaturated nitrile.[3d] An alternative route involving a free-radical β-alkylation of nonactivated carbon atoms and subsequent anionic cyclization has been developed as a complementary route of the Robinson annulation.[3g] In addition, this reaction has been modified to occur under antibody catalysis[4r] or with the combination of a lithium enolate with aluminum tris(2,6-diphenylphenoxide).[4s] Further modifications include the Robinson annulation in supercritical CO_2,[5a] the reaction promoted by K_2CO_3 under ultrasound,[4c] and the solid-supported reaction under microwave irradiation.[4h]

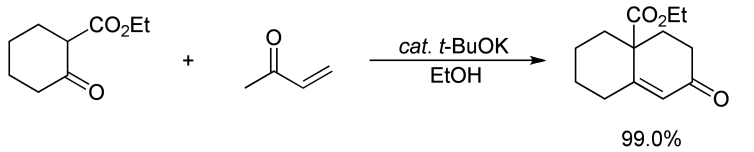
E. APPLICATIONS

This reaction has wide application in organic synthesis.

F. RELATED REACTIONS

This reaction is related to the *Aldol Condensation, Michael Addition*, and *Wichterle Reaction*.

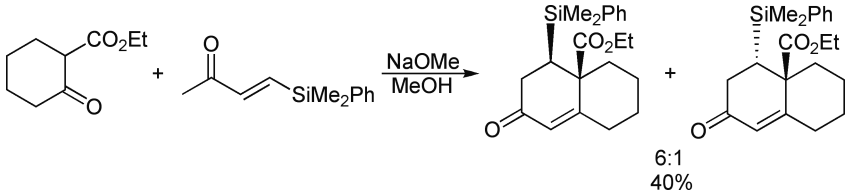
G. CITED EXPERIMENTAL EXAMPLES



99.0%

Reference 3c.

Potassium *t*-butoxide (296 mg, 2.65 mmol) was dissolved in 25 mL ethanol at 0°C under argon and stirred for 20 min. Then 8 mL ethyl 2-oxocyclohexanecarboxylate (50 mmol) was added slowly at the same temperature. After 15 min at 0°C, 4.15 mL methyl vinyl ketone (50 mmol) was added over 5 h via syringe pump. Then the resulting deep orange solution was refluxed for 6 h. The reaction mixture was cooled to ambient temperature. After being stirred for 18 h, the mixture was poured into a separatory funnel containing 30 mL saturated NH_4Cl and extracted with Et_2O (3 × 200 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to give 11.0 g crude product as an orange oil, in a yield of 99.0%.



Reference 3b.

Sodium metal was dissolved in 4 mL methanol at ambient temperature. After complete dissolution, 2.1 mL ethyl 2-oxocyclohexanecarboxylate (14.7 mmol) was added slowly via syringe. After 15 min, 1.63 g β-phenyldimethylsilylvinyl methyl ketone (7.99 mmol) dissolved in 0.5 mL MeOH was added over 7 h via syringe pump. At the end of addition, the deep orange solution was stirred at ambient temperature for 18 h. Then the mixture was refluxed in a preheated bath at 80–85°C for 24 h before being cooled to ambient temperature. The reaction mixture was then poured into a separatory funnel containing 50 mL saturated NH_4Cl, and extracted with Et_2O. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under vacuum to give a crude orange oil, which was purified by flash column chromatography using hexanes/EtOAc (5:1) as the eluent to afford 1.03 g (±)-(4*R*,4a*R*) methyl 4-(dimethylphenylsilyl)-2-oxo-2,3,4,4a,5,6,7,8-octahydronaphthalene-4a-carboxylate and (±)-(4*S*,4a*R*) methyl 4-(dimethylphenylsilyl)-2-oxo-2,3,4,4a,5,6,7,8-octahydronaphthalene-4a-carboxylate as a 6:1 mixture of diastereomers, in a yield of 40%. These diastereomeric mixtures were further separated by a second column chromatography using hexane/EtOAc (8:1) to yield each diastereomer with analytical purity.

Other references related to the Robinson annulation are cited in the literature.[10]

H. REFERENCES

1. Rapson, W. S. and Robinson, R., *J. Chem. Soc.,* **1935**, 1285.
2. Meyer, W. L.; Brannon, M. J.; Burgos, C. da G.; Goodwin, T. E. and Howard, R. W., *J. Org. Chem.,* **1985**, *50*, 438.
3. (a) Ghosh, S.; Rivas, F.; Fischer, D.; González, M. A. and Theodorakis, E. A., *Org. Lett.,* **2004**, *6*, 941. (b) Jung, M. E. and Piizzi, G., *J. Org. Chem.,* **2003**, *68*, 2572. (c) Jung, M. E. and Piizzi, G., *Org. Lett.,* **2003**, *5*, 137. (d) Fleming, F. F.; Zhang, Z. Y.; Wang, Q. Z. and Steward, O. W., *J. Org. Chem.,* **2003**, *68*, 7646. (e) Tochtrop, G. P.; DeKoster, G. T.; Cistola, D. P. and Covey, D. F., *J. Org. Chem.,* **2002**, *67*, 6764. (f) Holt, D. J.; Barker, W. D.; Jenkins, P. R.; Panda, J. and Ghosh, S., *J. Org. Chem.,* **2000**, *65,* 482. (g) Petrovic, G. and Cekovic, Z.,

Org. Lett., **2000**, *2*, 3769. (h) Meulemans, T. M.; Stork, G. A.; Macaev, F. Z.; Jansen, B. J. M. and de Groot, A., *J. Org. Chem.,* **1999**, *64,* 9178. (i) Paquette, L. A.; Lassalle, G. Y. and Lovely, C. J., *J. Org. Chem.,* **1993**, *58*, 4254.

4. (a) He, L., *Hecheng Huaxue*, **2007**, *15*, 231. (b) Zewge, D.; Malak, M. H.; Thompson, H. W.; Lalancette, R. A. and Brunskill, A. P. J., *Acta Cryst., Sect. E: Struct. Reports Online*, **2007**, *E63*, o479. (c) Safaei-Ghomi, J. and Alishahi, Z., *Org. Prep. Proc. Int.,* **2006**, *38*, 417. (d) Delaude, L.; Grandjean, J. and Noels, A. F., *J. Chem. Edu.,* **2006**, *83*, 1225. (e) Payette, J. N.; Honda, T.; Yoshizawa, H.; Favaloro, F. G. and Gribble, G. W., *J. Org. Chem.,* **2006**, *71*, 416. (f) Jung, M. E. and Maderna, A., *Tetrahedron Lett*., **2005**, *46*, 5057. (g) Singletary, J. A.; Lam, H. and Dudley, G. B., *J. Org. Chem.,* **2005**, *70*, 739. (h) Takatori, K.; Nakayama, M.; Futaishi, N.; Yamada, S.; Hirayama, S. and Kajiwara, M., *Chem. Pharm. Bull.,* **2003**, *51*, 455. (i) Liu, H.-J.; Ly, T. W.; Tai, C.-L.; Wu, J.-D.; Liang, J.-W.; Guo, J.-C.; Tseng, N.-W. and Shia, K.-S., *Tetrahedron*, **2003**, *59*, 1209. (j) Rajagopal, D.; Narayanan, R. and Swaminathan, S., *Proc. Indian Acad. Sci., Chem. Sci.,* **2001**, *113*, 197. (k) Morrison, D. W.; Forbes, D. C. and Davis, J. H., *Tetrahedron Lett*., **2001**, *42*, 6053. (l) Rajagopal, D.; Narayanan, R. and Swaminathan, S., *Tetrahedron Lett*., **2001**, *42*, 4887. (m) Tai, C.-L.; Ly, T. W.; Wu, J.-D.; Shia, K.-S. and Liu, H.-J., *Synlett*, **2001**, 214. (n) Bui, T. and Barbas, C. F., *Tetrahedron Lett*., **2000**, *41*, 6951. (o) Jansen, B. J. M.; Hendrikx, C. C. J.; Masalov, N.; Stork, G. A.; Meulemans, T. M.; Macaev, F. Z. and De Groot, A., *Tetrahedron,* **2000**, *56*, 2075. (p) Watanabe, H.; Onoda, T. and Kitahara, T., *Tetrahedron Lett*., **1999**, *40*, 2545. (q) Feng, X. Q. and Edstrom, E. D., *Tetrahedron: Asymmetry*, **1999**, *10*, 99. (r) Zhong, G. F.; Hoffmann, T.; Lerner, R. A.; Danishefsky, S. and Barbas, F. F., *J. Am. Chem. Soc.,* **1997**, *119*, 8131. (s) Saito, S.; Shimada, I.; Takamori, Y.; Tanaka, M.; Maruoka, K. and Yamamoto, H., *Bull. Chem. Soc. Jpn.,* **1997**, *70*, 1671. (t) Kim, S. and Fuchs, P. L., *J. Am. Chem. Soc.,* **1993**, *115*, 5934. (u) Banwell, M. G.; Bonadio, A.; Turner, K. A.; Ireland, N. K. and Mackay, M. F., *Aust. J. Chem.,* **1993**, *46*, 325. (v) Kim, S.; Emeric, G. and Fuchs, P. L., *J. Org. Chem.,* **1992**, *57*, 7362. (w) Hebda, C.; Szykula, J. and Zabza, A., *Pol. J. Chem.,* **1991**, *65*, 313. (x) Bonnert, R. V.; Howarth, J.; Jenkins, P. R. and Lawrence, N. J., *J. Chem. Soc., Perkin Trans. I,* **1991**, 1225. (y) Martens, J. and Luebben, S., *Arch. Pharm.,* **1991**, *324*, 59. (z) Akhrem, A. A.; Lakhvich, F. A.; Khripach, V. A. and Pyrko, A. N., *Zh. Org. Khim.,* **1990**, *26*, 1932. (aa) Nussbaumer, C., *Helv. Chim. Acta,* **1990**, *73*, 1621. (bb) Sato, T.; Wakahara, Y.; Otera, J. and Nozaki, H., *Tetrahedron Lett*., **1990**, *31*, 1581. (cc) Taber, D. F.; Mack, J. F.; Rheingold, A. L. and Geib, S. J., *J. Org. Chem.,* **1989**, *54*, 3831. (dd) Soriano, D. S.; Lombardi, A. M.; Persichini, P. J. and Nalewajek, D., *J. Chem. Edu.,* **1988**, *65*, 637. (ee) Bonnert, R. V. and Jenkins, P. R., *J. Chem. Soc., Chem. Commun.,* **1987**, 6. (ff) Kuo, F. and Fuchs, P. L., *Synth. Commun.,* **1986**, *16*, 1745. (gg) Olsen, R. S.; Fataftah, Z. A. and Rathke, M. W., *Synth. Commun.,* **1986**, *16*, 1133. (hh) Bhattacharya, A.; Dolling, U. H.; Grabowski, E.; Karady, S.; Ryan, K. M. and Weinstock, L. M., *Angew. Chem.,* **1986**, *98*, 442. (ii) Hackett, S. and Livinghouse, T., *J. Org. Chem.,* **1986**, *51*, 1629. (jj) Schultz, A. G. and Shannon, P. J., *J. Org. Chem.,* **1985**, *50*, 4421. (kk) Huffman, J. W.; Potnis, S. M. and Satish, A. V., *J. Org. Chem.,* **1985**, *50*, 4266. (ll) Kaenel, H. R. and Brossi, M., *Schweizerische Lab.-Zeit.*, **1984**, *41*, 236. (mm) Carter, B.; Laing, M. and Sommerville, P., *South Afri. J. Chem.,* **1984**, *37*, 53. (nn) Dauben, W. G. and Bunce, R. A., *J. Org. Chem.,* **1983**, *48*, 4642. (oo) Banerjee, A. K.; Rizo, M. S.; Alonso, M. E.; Rojas, A.; Haack, J. L.; House, H. O. and VanDerveer, D., *J. Org. Chem.,* **1981**, *46*, 1755. (pp) Kamat, P. L. and Shaligram, A. M., *Indian J. Chem., Sect. B,* **1980**, *19B*, 904. (qq) Corey, E. J.; Johnson, A. P. and Long, A. K., *J. Org. Chem.,* **1980**, *45*, 2051. (rr) Snitman, D. L.; Tsai, M.-Y. and Watt, D. S., *Synth. Commun.,* **1978**, *8*, 195. (ss) Dave, V. and Whitehurst, J. S., *Tetrahedron,* **1974**, *30*, 745. (tt) Dave, V. and Whitehurst, J. S., *J. Chem. Soc., Perkin Trans. I,* **1973**, 393. (uu) Scanio, C. J. V. and Starrett, R. M., *J. Am. Chem. Soc.,* **1971**, *93*, 1539.

5. (a) Kawanami, H.; Matsushima, K. and Ikushima, Y., *Ind. Eng. Chem. Res.,* **2005**, *44*, 9561. (b) Kalluraya, B. and Rai, G., *Synth. Commun.,* **2003**, *33*, 3589. (c) Snider, B. B. and Shi, B.,

Tetrahedron Lett., **2001**, *42*, 9123. (d) Haynes, R. K.; Vonwiller, S. C. and Hambley, T. W., *J. Org. Chem.,* **1989**, *54*, 5162. (e) Ziegler, F. E. and Hwang, K. J., *J. Org. Chem.,* **1983**, *48*, 3349. (f) Kikuchi, M. and Yoshikoshi, A., *Bull. Chem. Soc. Jpn.,* **1981**, *54*, 3420. (g) Gawley, R. E., *Synthesis,* **1976**, 777. (h) Zoretic, P. A.; Bendiksen, B. and Branchaud, B., *J. Org. Chem.,* **1976**, *41*, 3767. (i) Marshall, J. A. and Warne, T. M., *J. Org. Chem.,* **1971**, *36*, 178.

6. (a) Kondo, K.; Yamano, T. and Takemoto, K., *Makromol. Chem.,* **1985**, *186*, 1781. (b) Agami, C.; Meynier, F.; Puchot, C.; Guilhem, J. and Pascard, C., *Tetrahedron,* **1984**, *40*, 1031.
7. (a) Pariza, R. J. and Fuchs, P. L., *J. Org. Chem.,* **1985**, *50*, 4252. (b) Pariza, R. J. and Fuchs, P. L., *J. Org. Chem.,* **1983**, *48*, 2304.
8. (a) Guarna, A.; Lombardi, E.; Machetti, F.; Occhiato, E. G. and Scarpi, D., *J. Org. Chem.,* **2000**, *65*, 8093. (b) Fang, F. G.; Prato, M.; Kim, G. and Danishefsky, S. J., *Tetrahedron Lett.,* **1989**, *30*, 3625.
9. Jung, M. E., *Tetrahedron,* **1976**, *32*, 3.
10. (a) Christoffers, J.; Zhang, Y. W.; Frey, W. and Fischer, P., *Synlett,* **2006**, 624. (b) Buchschacher, P.; Fürst, A. and Gutzwiller, J., *Org. Synth.,* **1990**, *7*, 368. (c) McMurry, J. E., *Org. Synth. Coll.,* **1988**, *6*, 781. (d) Heathcock, C. H.; Mahaim, C.; Schlecht, M. F. and Utawanit, T., *J. Org. Chem.,* **1984**, *49*, 3264. (e) Still, W. C. and VanMiddlesworth, F. L., *J. Org. Chem.,* **1977**, *42*, 1258. (f) Kobayashi, M. and Matsumoto, T., *Chem. Lett.,* **1973**, 957. (g) Heathcock, C. H.; Ellis, J. E.; McMurry, J. E. and Coppolino, A., *Tetrahedron Lett.,* **1971**, *12*, 4995. (h) Bergman, E. D.; Gingberg, D. and Pappo, R., *Org. React.,* **1959**, *10*, 179. (i) Wichterle, O.; Prochazka, J. and Hofman, J., *Coll. Czech. Chem. Commun.,* **1948**, *13*, 300.

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Robinson-Gabriel Oxazole Synthesis

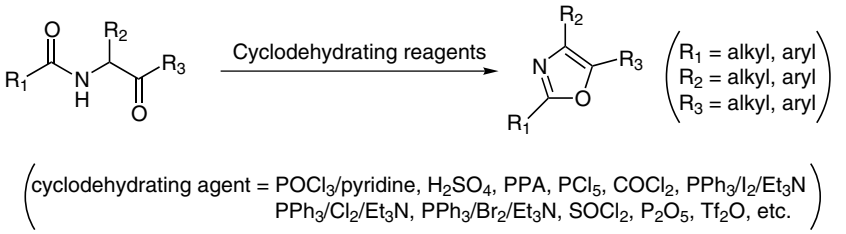
(Robinson-Gabriel Cyclodehydration, Robinson-Gabriel Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Gabriel in 1907[1] and subsequently by Robinson in 1909.[2] It is the synthesis of 2,5- and 2,4,5-substituted oxazole derivatives by the intramolecular condensation and dehydration of *N*-acyl α-aminoketones in the presence of a dehydration reagent such as PCl_5 or sulfuric acid. This reaction is thus known as the Robinson-Gabriel cyclization,[3] Robinson-Gabriel cyclodehydration,[4] Robinson-Gabriel dehydration,[4d,4e] Robinson-Gabriel oxazole synthesis,[4g,5] Robinson-Gabriel reaction,[4g,4h,6] or Robinson-Gabriel synthesis.[4a,5d,6b,7] Other cyclodehydrating reagents include the Burgess reagent ([(methoxycarbonyl-sulfamoyl) triethylammoniumhydroxide inner salt], i.e., $Et_3N^+SO_2N^-CO_2Me$),[4b,4f,8] phosphorus oxychloride ($POCl_3$),[4a,6b,7e] polyphosphoric acid (PPA),[5d,6b] phosgene ($COCl_2$),[6b] hexachloroethane/triphenylphosphine,[4b] triphenylphosphine/iodine/triethylamine,[3c,4c,6b,9] $SOCl_2$,[5a] trifluoroacetic anhydride,[4a,6b] triflic anhydride,[4a] P_2O_5,[7d] and anhydrous hydrogen fluoride.[6b] However, polyphosphoric acid is found to be superior to most of the above dehydrating reagents.[5d] As the nature of this reaction requires the application of harsh conditions, this reaction is not applicable to molecules with acid-labile functional groups.[5a]

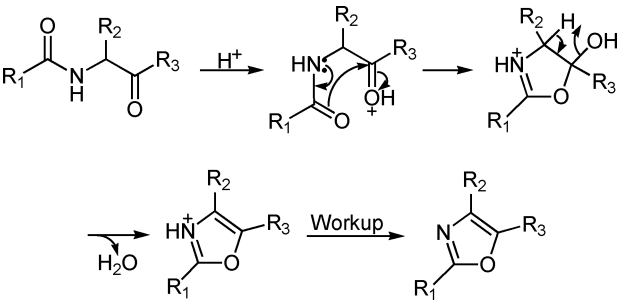
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

This reaction, through the isotopic labeling experiment,[5d,7g] is proved to involve the protonation of the ketone carbonyl, followed by nucleophilic attack by the amido oxygen to form dihydrooxazolol, which dehydrates to form oxazole,[4a] as illustrated below by an example using sulfuric acid as the dehydrating reagents.



D. MODIFICATION

The initial protocol has been extensively modified by the application of different dehydrating reagents as listed earlier, in which $POCl_3$/pyridine is a recently added reagent,[4b,4e–4g] and the application of $PPh_3/Cl_2/Et_3N$,[10] $PPh_3/Br_2/Et_3N$,[8] or Burgess reagent[8] has allowed the synthesis of oxazole derivatives in solid phase under milder conditions. Alternatively, the oxazoles and bis-oxazoles can be prepared from side chain oxidation of α-hydroxy amides followed by cyclodehydration with $PPh_3/I_2/Et_3N$,[3c] or cyclization of activated α-hydroxy amides to oxazolines followed by dehydrogenation,[4j] or the one-pot condensation between α-amino ketone and triethyl orthoester.[7f]

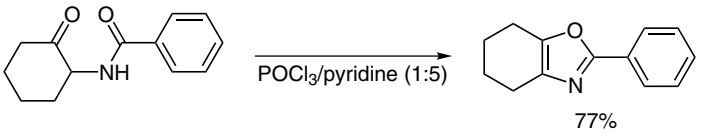
E. APPLICATIONS

This reaction has general application in the syntheses of 2,5-disubstituted and 2,4,5-trisubstituted oxazole derivatives, especially for the syntheses of 2,5-diaryloxazoles.[5d]

F. RELATED REACTIONS

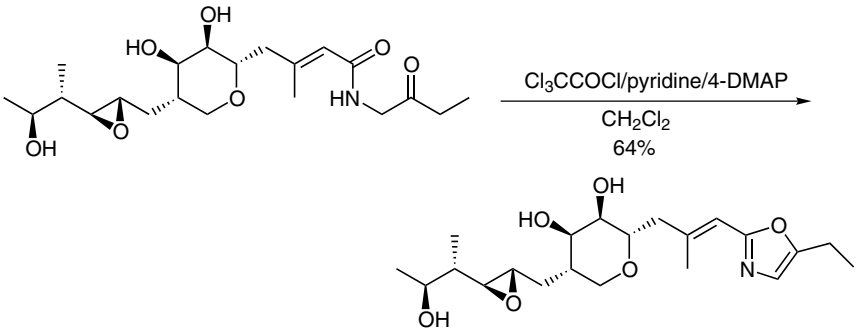
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 4g.

To 2.5 mL dry pyridine solution containing 217 mg *N*-benzoyl-2-amino cyclohexanone (1.0 mmol) at 25°C was added 0.5 mL $POCl_3$. The resultant solution was then stirred for 3 hours. Upon completion, the reaction mixture was diluted with 10 mL EtOAc, transferred into 25 mL saturated aqueous $NaHCO_3$ cooled at 0°C, and extracted with EtOAc (3 × 15 mL). The combined organic layers were then washed with 25 mL water and brine each, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography to afford 77% 2-phenyl-5,5,6,6,7,7,8,8-tetrahydrobenzooxazole as a white solid, $R_f = 0.64$ (EtOAc/hexanes, 1:1).



Reference 7c.

To an ice bath-cooled 23 mL CH_2Cl_2 solution containing 960 mg *N*-(2-oxobutyl)-monamide (2.32 mmol), 46.4 mmol pyridine (20 eq.), and a few crystals of 4-(dimethylamino)-pyridine was added 20.9 mmol trichloroacetyl chloride (9 eq.). After being stirred for 30 min, the solution was washed with saturated aqueous $NaHCO_3$ solution, and then evaporated under reduced pressure. The residue was dissolved in 12 mL methanol, and the solution was cooled to 0°C before the addition of 7 mmol K_2CO_3 (3 eq.). After 15 min at 0°C, brine and EtOAc were added, and the organic layer was separated. The aqueous layer was further extracted with EtOAc, and the combined extracts were washed with brine, dried over $MgSO_4$, and then evaporated under reduced pressure. The residue was chromatographed on silica using 0–10% methanol in CH_2Cl_2 as the eluent to give 5-ethyl-2-(1-normon-2-yl)oxazole (589 mg), in a yield of 64%.

Other references related to the Robinson-Gabriel oxazole synthesis are cited in the literature.[11]

H. REFERENCES

1. Gabriel, S., *Ber.,* **1907**, *40*, 2647.
2. Robinson, R., *J. Chem. Soc.,* **1909**, 2167.
3. (a) Biron, E.; Chatterjee, J. and Kessler, H., *Org. Lett.,* **2006**, *8*, 2417. (b) Panchishin, S. Ya.; Smolii, O. B.; Chernega, A. N.; Rusanov, E. B. and Drach, B. S., *Russ. J. Gen. Chem.,* **2005**, *75*, 518. (c) Wipf, P. and Miller, C. P., *J. Org. Chem.,* **1993**, *58*, 3604.
4. (a) Keni, M. and Tepe, J. J., *J. Org. Chem.,* **2005**, *70*, 4211. (b) Davies, J. R.; Kane, P. D.; Moody, C. J. and Slawin, A. M. Z., *J. Org. Chem.,* **2005**, *70*, 5840. (c) Davies, J. R.; Kane, P. D. and Moody, C. J., *J. Org. Chem.,* **2005**, *70*, 7305. (d) Nicolaou, K. C.; Snyder, S. A.; Huang, X. H.; Simonsen, K. B.; Koumbis, A. E. and Bigot, A., *J. Am. Chem. Soc.,* **2004**, *126*, 10162. (e) Nicolaou, K. C.; Snyder, S. A.; Giuseppone, N.; Huang, X. H.; Bella, M.; Reddy, M. V.; Rao, P. B.; Koubmis, A. E., Giannakakou, P. and O'Brate, A., *J. Am. Chem. Soc.,* **2004**, *126*, 10174. (f) Nicolaou, K. C.; Chen, D. Y.-K.; Huang, X. H.; Ling, T. T.; Bella, M. and Snyder, S. A., *J. Am. Chem. Soc.,* **2004**, *126*, 12888. (g) Nicolaou, K. C.; Hao, J. L.; Reddy, M. V.; Rao, P. B.; Rassias, G.; Snyder, S. A.; Huang, X. H.; Chen, D. Y.-K.; Brenzovich, W. E.; Giuseppone, N.; Giannakakou, P. and O'Brate, A., *J. Am. Chem. Soc.,* **2004**, *126*, 12897. (h) Godfrey, A. G.; Brooks, D. A.; Hay, L. A.; Peters, M.; McCarthy, J. R. and Mitchell, D., *J. Org. Chem.,* **2003**, *68*, 2623. (i) Parsons, R. L. and Heathcock, C. H., *J. Org. Chem.,* **1994**, *59*, 4733. (j) Evans, D. A.; Gage, J. R. and Leighton, J. L., *J. Am. Chem. Soc.,* **1992**, *114*, 9434.
5. (a) Wipf, P.; Aoyama, Y. and Benedum, T. E., *Org. Lett.,* **2004**, *6*, 3593. (b) Brain, C. T. and Paul, J. M., *Synlett,* **1999**, 1642. (c) Wipf, P. and Venkatraman, S., *J. Org. Chem.,* **1996**, *61,* 6517. (d) Turchi, I. J. and Dewar, M. J. S., *Chem. Rev.,* **1975**, *75*, 389.
6. (a) Yang, Y.-H. and Shi, M., *Tetrahedron Lett*., **2005**, *46*, 6285. (b) Pulici, M.; Quartieri, F. and Felder, E. R., *J. Comb. Chem.,* **2005**, *7,* 463. (c) Akaji, K. and Kiso, Y., *Tetrahedron,* **1999**, *55*, 10685.
7. (a) Morwick, T.; Hrapchak, M.; DeTuri, M. and Campbell, S., *Org. Lett.,* **2002**, *4*, 2665. (b) Wipf, P. and Venkatraman, S., *J. Org. Chem.,* **1996**, *61,* 8004. (c) Brown, P.; Davies, D. T.; O'Hanlon, P. J. and Wilson, J. M., *J. Med. Chem.,* **1996**, *39,* 446. (d) Hassner, A. and Fischer, B., *J. Org. Chem.,* **1991**, *56*, 3419. (e) White, R. L.; Wessels, F. L.; Schwan, T. J. and Ellis, K. O., *J. Med. Chem.,* **1987**, *30*, 263. (f) LaMattina, J. L., *J. Org. Chem.,* **1980**, *45*, 2261. (g) Wasserman, H. H. and Vinick, F. J., *J. Org. Chem.,* **1973**, *38*, 2407. (h) Iwakura, Y.; Toda, F.; Kusakawa, N. and Suzuki, H., *J. Poly. Sci., Poly. Lett. Ed.,* **1968**, *6*, 5.
8. Spanka, C.; Clapham, B. and Janda, K. D., *J. Org. Chem.,* **2002**, *67*, 3045.
9. Mann, E. and Kessler, H., *Org. Lett.,* **2003**, *5*, 4567.
10. Clapham, B.; Spanka, C. and Janda, K. D., *Org. Lett.,* **2001**, *3*, 2173.
11. (a) Lakhan, R. and Ternai, B., *Adv. Heterocycl. Chem.,* **1974**, *17*, 99. (b) Lister, J. and Robinson, R., *J. Chem. Soc.,* **1912**, 1297. (c) Gabriel, S., *Ber.,* **1910**, *43*, 1283.

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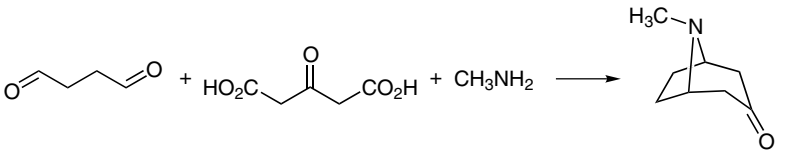
Robinson-Schöpf Condensation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Robinson in 1917[1] and subsequently improved by Schöpf in 1935.[2] It is an ingenious one-pot multicomponent synthesis of tropinone from succindialdehyde, acetonedicarboxylic acid and methylamine in aqueous solution involving a double *Mannich Reaction*.[3] This reaction is thus known as the Robinson tropinone synthesis,[4] Robinson synthesis,[3a,4a,5] Robinson-Schöpf reaction,[3c,6] Robinson-Schöpf condensation,[7] or Robinson condensation.[4c] It has been reported that the Robinson tropinone synthesis can take place without any racemization at the stereogenic center adjacent to the aldehyde group, as demonstrated by the formation of *L-allo*-teloidinone from *D*-tartaraldehyde, and *D-allo*-teloidinone from *L*-tartaraldehyde respectively.[4a]

B. GENERAL REACTION SCHEME



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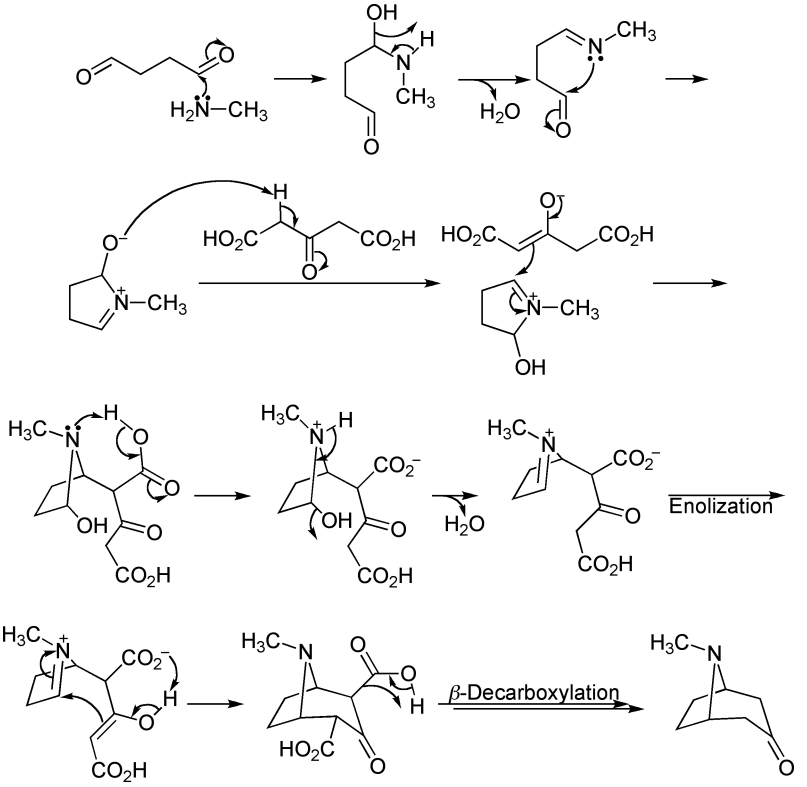
C. PROPOSED MECHANISMS

The condensation of *cis*-cyclopentane-1,3-dialdehyde with high stereospecificity indicates that the reaction involves a stepwise process in which the cyclization step is affected by the nonbonded interactions.[3c] An illustrative mechanism is provided below for the reaction among succindialdehyde, acetonedicarboxylic acid, and methylamine.



D. MODIFICATION

This reaction has been extended to *cis*-cyclopentane-1,3-dialdehyde, methylamine, and acetonedicarboxylic acid to give a tricyclic amino ketone with high stereospecificity, of which the *N*-methyl group is primarily in the axial configuration with respect to the piperidone ring, and nitrogen and carbon bridges are *anti* to each other.[3c] Further modification can be found in the reaction using dialdehyde dioxime or 2,5-dimethoxytetrahydrofuran[3a] or *bis*-dimethyl acetal[7b] as the precursor of unstable dialdehyde.

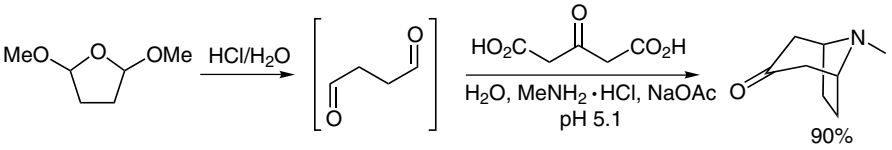
E. APPLICATIONS

This reaction has been used to the preparation of several alkaloids including cocaine, and atropine.[8]

F. RELATED REACTIONS

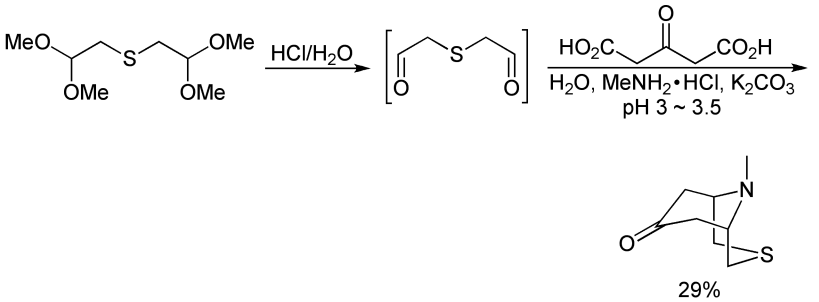
This reaction is related to the *Petrenko-Kritschenko Piperidone Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 3a.

To a 50 mL aqueous solution of 20.4 g 2,5-dimethoxytetrahydrofuran (0.154 mol) was added 2 mL conc. HCl (25 mmol), and the mixture was heated at 70–75°C for 30 min and then cooled to ambient temperature. A 500-mL, four-necked flask equipped with a thermometer, pH probe, mechanical stirrer, and nitrogen inlet was charged with 150 mL water, 50.0 g NaOAc (0.61 mol), 15 mL 40% $MeNH_2$ aqueous solution (0.17 mol), 14.2 mL conc. HCl (0.18 mol), and 24.8 g acetonedicarboxylic acid (0.17 mol). The solution (pH 5.1) was cooled to 10°C, and the dialdehyde solution was added to this flask over 10 min (final pH at end of addition was 5.1). The mixture was warmed to 40°C over 10 min, stirred at 40°C for 50 min, and then cooled to 20°C. Then the solution was alkalinized with 12.5 mL 50% NaOH solution to pH 10, and 40 g NaCl was added. After the NaCl was completely dissolved, the aqueous solution was extracted with CH_2Cl_2 (3 × 85 mL). The combined CH_2Cl_2 layers were concentrated to give 18.7 g tropinone as an off-white solid, in a yield of 90%, m.p. 40–42°C.



Reference 7b.

Thiodiacetaldehyde bis(dimethylaceta1) (265 g, 1.26 mol) was hydrolyzed in 700 mL hot water containing 12 mL conc. HCl. After completion of hydrolysis, the solution was cooled to 25°C, and 94 g methylamine hydrochloride (1.39 mol) and 220 g acetonedicarboxylic acid (1.51 mol) were added. The mixture was stirred, and solid K_2CO_3 was added slowly until the pH of the solution was 3.0. The clear solution was allowed to stand at room temperature in the dark, and the pH was held between 3.0 and 3.5 by the addition of hydrochloric acid after 2 h and after 7 h. After 24 h, the dark brown solution was acidified to pH 2 with

6 *N* HCl and extracted with four portions of ether. The aqueous solution was then made strongly alkaline, saturated with K_2CO_3, and extracted with 17 portions of CH_2Cl_2. The combined extracts were dried over Na_2SO_4, concentrated to 200 mL, and thoroughly mixed with alumina (20 mesh) to give, after the evaporation of the solvent, a brown powder that was placed in a Soxhlet thimble and extracted with ether. From the ether extracts, a dark crystalline solid was obtained, which on sublimation in vacuo afforded 62 g 9-methyl-3-thiagranatanin-7-one, in a yield of 29%, m.p. 124–128°C. The product could be further purified via recrystallization from benzene-ligroin, m.p. 126–128°C. No improvement in yield was seen in smaller scale experiments carried out in buffered solution at pH 3, in dilute solution, or in solution containing an excess amount of acetonedicarboxylic acid.

Other references related to the Robinson-Schöpf condensation are cited in the literature.[9]

H. REFERENCES

1. (a) Robinson, R., *J. Chem. Soc.,* **1917**, *111*, 762. (b) Robinson, R., *J. Chem. Soc.,* **1917**, *111*, 876.
2. (a) Schöpf, C. and Lehman, G., *Ann.,* **1935**, *518*, 1. (b) Schöpf, C., *Angew. Chem.,* **1937**, *50*, 779. (c) Schöpf, C., *Angew. Chem.,* **1937**, *50*, 797.
3. (a) Burks, J. E.; Espinosa, L.; LaBell, E. S.; McGill, J. M.; Ritter, A. R.; Speakman, J. L.; Williams, M. A.; Bradley, D. A.; Haehl, M. G. and Schmid, C. R., *Org. Proc. Res. Dev.,* **1997**, *1*, 198. (b) Hemscheidt, T. and Spenser, I. D., *J. Am. Chem. Soc.,* **1996**, *118,* 1799. (c) Paquette, L. A. and Heimaster, J. W., *J. Am. Chem. Soc.,* **1966**, *88*, 763.
4. (a) Pollini, G. P.; Benetti, S.; de Risi, C. and Zanirato, V., *Chem. Rev.,* **2006**, *106*, 2434. (b) Bienaymé, H.; Hulme, C.; Oddon, G. and Schmitt, P., *Chem. Eur. J.,* **2000**, *6*, 3321. (c) Agocs, P.; Koczka, K.; Weisz, I. and Kovacs, K., *Monatsh. Chem.,* **1971**, *102*, 591.
5. (a) Bora, U.; Saikia, A. and Boruah, R. C., *Org. Lett.,* **2003**, *5*, 435. (b) Mondal, N.; Mandal, S. C.; Das, G. K. and Mukherjee, S., *J. Chem. Res. (S),* **2003**, 580. (c) Baliah, V.; Jeyaraman, R. and Chandrasekaran, L., *Chem. Rev.,* **1983**, *83*, 379. (d) Findlay, S. P., *J. Org. Chem.,* **1957**, *22*, 1385.
6. Schloss, J. D.; Leit, S. M. and Paquette, L. A., *J. Org. Chem.,* **2000**, *65,* 7119.
7. (a) Guthrie, R. D. and McCarthy, J. F., *J. Chem. Soc. C,* **1967**, 62. (b) Zirkle, C. L.; Gerns, F. R.; Pavloff, A. M. and Burger, A., *J. Org. Chem.,* **1961**, *26*, 395. (c) Stern, R. and Wasserman, H. H., *J. Org. Chem.,* **1959**, *24*, 1689. (d) Alder, K.; Wirtz, H. and Koppelberg, H., *Ann.,* **1956**, *601*, 138.
8. Tietze, L. F., *Chem. Rev.*, **1996**, *96*, 115.
9. (a) Córdova, A., *Acc. Chem. Res.,* **2004**, *37*, 102. (b) Singh, S., *Chem. Rev.,* **2000**, *100,* 925. (c) Jarevang, T.; Anke, H.; Anke, T.; Erkel, G. and Sterner, O.*, Acta Chem. Scand.,* **1998**, *52*, 1350. (d) Langlois, M.; Yang, D.; Soulier, J. L. and Florac, C.*, Synth. Commun.,* **1992**, *22*, 3115. (e) Stevens, R. V. and Lee, A. W. M., *J. Am. Chem. Soc.,* **1979**, *101*, 7032. (f) Hajos, Z. G. and Parrish, D. R., *J. Org. Chem.,* **1973**, *38*, 3244. (g) Bottini, A. T. and Gal, J., *J. Org. Chem.,* **1971**, *36*, 1718. (h) Alder, K.; Wirtz, H. and Koppelberg, H.*, Ann.,* **1956**, *601*, 147. (i) Findlay, S. P., *J. Org. Chem.,* **1956**, *21*, 644. (j) Meinwald, J.; Emerman, S. L.; Yang, N. C. and Büchi, G., *J. Am. Chem. Soc.,* **1955**, *77*, 4401. (k) Cope, A. C.; Dryden, H. L.; Overberger, C. G. and D'Addieco, A. A., *J. Am. Chem. Soc.,* **1951**, *73*, 3416. (l) Blount, B. K. and Robinson, R., *J. Chem. Soc.,* **1932**, 2485.

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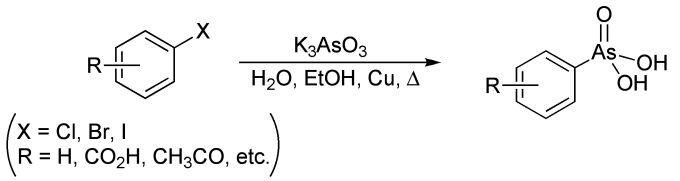
Rosenmund Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Rosenmund in 1921.[1] It is the synthesis of an arylarsonic acid by refluxing the mixture of an aryl halide and aqueous tripotassium arsenite in the presence of alkali, alcohol, and copper powder,[2] and is known as the Rosenmund reaction[3] or Rosenmund synthesis.[4]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

As no mechanistic information is available, it is assumed that this reaction follows a nucleophilic substitution pattern, as illustrated below.

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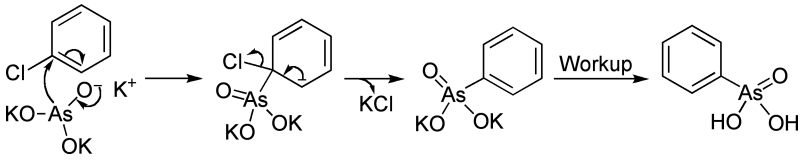


D. MODIFICATION

This reaction was extended by Albert and Schulenberg for the preparation of *p*-acetophenone-arsonic acid.[5]

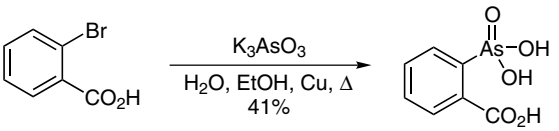
E. APPLICATIONS

This reaction is useful for the preparation of arylarsonic acid.

F. RELATED REACTIONS

This reaction is related to the *Bart Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4.

Under stirring, a mixture of 20 g *o*-bromobenzoic acid (0.1 mol), 63 mL 10% KOH solution, 20 mL EtOH, 40 mL 50% K_3AsO_3 solution, and a little freshly reduced copper was refluxed at 90–95°C for 12 h. The reaction mixture was filtered while hot to remove the copper; the filtrate was acidified with 20 mL conc. HCl and was evaporated to dryness on a steam cone. The residue was extracted with absolute methanol, and the methanol extract was evaporated to dryness. The residue was washed with ether to remove salicylic acid and unreacted *o*-bromobenzoic acid. The ether washed residue was recrystallized twice from hot water after decolorization with bone black to afford 10.1 g *o*-carboxyphenylarsonic acid, in a yield of 41%.

Other references related to the Rosenmund reaction are cited in the literature.[6]

H. REFERENCES

1. Rosenmund, K. W., *Ber.,* **1921**, *54B*, 438.
2. Lewis, W. L., *Ind. Eng. Chem.,* **1923**, *15*, 17.
3. Cullen, W. R. and Reimer, K. J., *Chem. Rev.,* **1989**, *89*, 713.
4. Hamilton, C. S. and Ludeman, C. G., *J. Am. Chem. Soc.,* **1930**, *52*, 3284.
5. Albert, A. and Schulenberg, W., *German Patent*, Nov. 15, **1928**, *468*, 403.
6. (a) Beck, W. W. and Hamilton, C. S., *J. Am. Chem. Soc.,* **1938**, *60*, 620. (b) Parmelee, H. M. and Hamilton, C. S., *J. Am. Chem. Soc.,* **1933**, *55*, 1463.

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Rosenmund Reduction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Rosenmund in 1918.[1] It is the transformation of an acyl chloride into corresponding aldehyde by the hydrogenation in a toluene solution over barium sulfate-supported palladium. Therefore, it is generally known as the Rosenmund reduction.[2] Occasionally, it is also referred to as the Rosenmund-Zetzsche reduction,[3] Rosenmund hydrogenation,[4] or Rosenmund hydrogenolysis.[5] This reaction is normally carried out by bubbling hydrogen gas through a rigorously dry solvent with 5–10% palladium catalyst in suspension, and the yield of aldehyde critically depends on the resistance of the aldehyde toward further reduction.[2u,6] Thus a variety of molecules are added as catalyst "poisons," "modifiers," or "regulators."[2d,6] These molecules include sodium acetate,[7] nitrogenous bases, such as quinoline with sulfur,[2v] *N*,*N*-dimethylaniline,[8] ethyldiisopropylamine,[9] 2,6-dimethylpyridine,[10] and sulfur-containing molecules, such as thiourea,[4a] thiophene,[4a] and dibenzothiophene,[4a] though the regulator is not always necessary for the reduction.[6,11] The presence of poisons or regulators is believed to block sites with the most catalytic activity and prevent undesired reactions;[2d] however, recent studies indicate that these poisonous molecules do not actually block the active sites but alter the surface of the catalyst,[2d,6] such as the formation of thin palladium particles.[6] During the Rosenmund reduction, it has been found that the reducible groups such as nitro and chloro in aromatic compounds are reduced;[2u] in addition, aliphatic aldehydes can be obtained in high yield (e.g., 80–90%) when aliphatic acyl chlorides are reduced in anhydrous acetone or EtOAc over palladium hydroxide-$BaSO_4$ in the presence of dimethylaniline.[2u] Reduction of unsaturated acyl chlorides in some cases result in the overreduction of double bonds and the extensive rearrangement of the double bond as well,[2aa] although in many cases the corresponding unsaturated aldehydes are obtained.[12] However, because palladium

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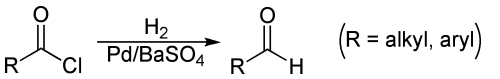
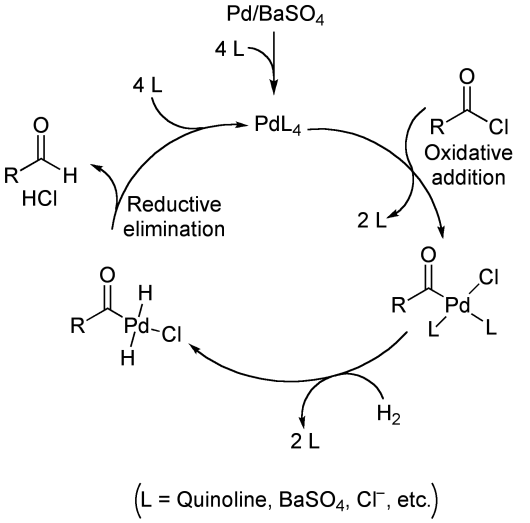
catalyst is labile under these reaction conditions and the particle size and surface structure change quickly,[6] the Rosenmund reduction is an unreliable and irreproducible method for organic synthesis,[6] and it is often in competition with other side reactions. For example, alcohols are often the by-products of the Rosenmund reduction.[2u] In addition, hydrocarbons with one less carbon atom formed by removal of an entire –COCl group are also obtained from the Rosenmund reduction;[2u] especially during the reduction of aromatic acyl chloride, as demonstrated by the formation of tetraphenylethane from diphenylacetyl chloride.[2w] Furthermore, some acyl chlorides do not undergo the Rosenmund reduction. For example, the reduction of trichloroacetyl chloride affords 50–60% of dichloroacetyl chloride instead of the expected chloral,[2t] the reduction of succinyl chloride leads to the formation of butyrolactone, and the reduction of adipyl chloride yields the corresponding aldehyde and cyclopentanecarboxylic acid as well.[13] Because of its intrinsic problems of reproducibility, the Rosenmund reduction has been widely replaced by the more reliable *Brown Hydroboration*,[2d] using lithium tributoxyborohydride as the reducing reagent.[2r]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Because the reduction mechanism is not as clear as that of *Lindlar Hydrogenation*,[2q] a tentative mechanism in the presence of quinoline containing sulfur is provided below.



D. MODIFICATION

This reaction has been modified by employing THF as solvent at 0°C for the production of aliphatic aldehydes.[10] In addition, $Ru(PCy_3)_2(H)Cl_2$ has been used as a catalyst for the Rosenmund reduction.[2b]

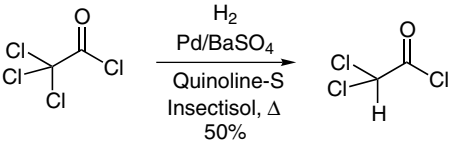
E. APPLICATIONS

This reaction had wide application in the preparation of aldehydes before the development of better methods in modern organic synthesis.

F. RELATED REACTIONS

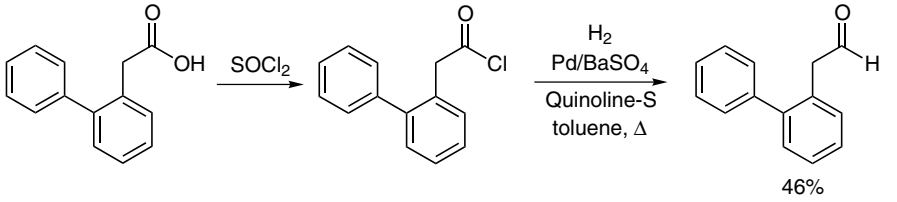
This reaction is related to the *Lindlar Hydrogenation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2t.

The mixture of 40 g trichloroacetyl chloride (0.22 mol), 4.0 g 2% $Pd/BaSO_4$ catalyst, 0.4 mL quinoline-S regulator, and 190 mL freshly refined petroleum fraction (i.e., Insectisol, refluxed over sodium and distilled fraction, b.p.190–220°C) was heated to 140°C. Hydrogen was passed through the stirred mixture at such a rate that a millimole of HCl per minute was collected in the aqueous exit gas scrubber. After 0.22 mol HCl had been titrated ($\sim$ 5 h), the mixture was cooled, filtered, and distilled. The fraction at 104–106°C (729 mmHg) was collected to afford 15.5 g dichloroacetyl chloride, in a yield of 50%.



Reference 2s.

The 2-biphenylylacetyl chloride was prepared by refluxing 25.5 g 2-biphenylylacetic acid with 18 mL thionyl chloride. An excess amount of thionyl chloride was removed under vacuum (water pump) at the temperature of a steam bath, and last traces of thionyl chloride were entrained by means of dry toluene. Then 0.5 g quinoline-sulfur regulator and 5.0 g $Pd/BaSO_4$ catalyst were added. Hydrogen was passed through the stirred solution until no more HCl evolved, then the catalyst was filtered off, and the filtrate was diluted with 100 mL ether. The resulting solution was stirred with a saturated aqueous Na_2SO_3 solution for 24 h. The addition product was collected, washed with ether, and decomposed by stirring with 250 mL 10% Na_2CO_3 solution for 3 h. The aldehyde was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated. The residue was distilled to afford 10.9 g 2-biphenylylacetaldehyde as a colorless oil, in a yield of 46%, b.p. 130–133°C at 2 mmHg.

Other references related to the Rosenmund reduction are cited in the literature.[14]

H. REFERENCES

1. (a) Rosenmund, K. W., *Ber.,* **1918**, *51*, 585. (b) Rosenmund, K. W. and Zetzsche, F., *Ber.,* **1921**, *54*, 425.
2. (a) Chandnani, K. H. and Chandalia, S. B., *Org. Proc. Res. Dev.,* **1999**, *3*, 416. (b) Grushin, V. V. and Alper, H., *J. Org. Chem.,* **1991**, *56*, 5159. (c) Jones, R. A. Y. and Bunnett, J. F., *Pure & Appl. Chem.,* **1989**, *61*, 725. (d) McEwen, A. B.; Guttieri, M. J.; Maier, W. F.; Laine, R. M. and Shvo, Y., *J. Org. Chem.,* **1983**, *48*, 4436. (e) Black, D. S. C. and Rothnie, N. E., *Aust. J. Chem.,* **1983**, *36*, 2395. (f) Jethani, K. R.; Mehta, P. H. and Chandalia, S. B., *Indian J. Technol.,* **1981**, *19*, 349. (g) Peters, J. A. and Van Bekkum, H., *Rec. Trav. Chim. Pays-Bas,* **1981**, *100*, 21. (h) Wojtanis, J.; Sila, B. and Lesiak, T., *Khim. Geterotsiklicheskikh Soedinenii*, **1977**, 744. (i) Brutcher, F. V.; Vanderwerff, W. D. and Dreikorn, B., *J. Org. Chem.,* **1972**, *37*, 297. (j) Wenkert, E.; Dave, K. G.; Dainis, I. and Reynolds, G. D., *Aust. J. Chem.,* **1970**, *23*, 73. (k) Wagner, D. P.; Gurien, H. and Rachlin, A. I., *Ann. N. Y. Acad. Sci.,* **1970**, *172*, 186. (l) Fitch, R. M. and Chow, C. D., *J. Poly. Sci., Part A: Poly. Chem.,* **1967**, *5*, 381. (m) White, H. B.; Sulya, L. L. and Cain, C. E., *J. Lipid Res.,* **1967**, *8*, 158. (n) Newman, M. S. and Gill, N., *J. Org. Chem.,* **1966**, *31*, 3860. (o) Tsuji, J.; Ono, K. and Kajimoto, T., *Tetrahedron Lett*., **1965**, 4565. (p) Chiusoli, G. and Agnes, G., *Chim. Ind. (Italy),* **1964**, *46*, 548. (q) Mitsui, S. and Takeuchi, Y., *Nippon Kagaku Zasshi*, **1961**, *82*, 499. (r) Brown, H. C. and McFarlin, R. F., *J. Am. Chem. Soc.,* **1956**, *78*, 252. (s) Bradsher, C. K. and Jackson, W. J., *J. Am. Chem. Soc.,* **1954**, *76*, 734. (t) Sellers, J. W. and Bissinger, W. E., *J. Am. Chem. Soc.,* **1954**, *76*, 4486. (u) Sonntag, N. O. V., *Chem. Rev.,* **1953**, *52*, 237. (v) Burger, A. and Hornbaker, E. D., *J. Org. Chem.,* **1953**, *18*, 192. (w) Burr, J. G., *J. Am. Chem. Soc.,* **1951**, *73*, 3502. (x) Detweiler, W. K. and Amstutz, E. D., *J. Am. Chem. Soc.,* **1950**, *72*, 2882. (y) Lee, S. H. and Simmons, C. C., *Proc. Oklahoma Acad. Sci.,* **1950**, *31*, 125. (z) Eliel, E. L. and Burgstahler, A. W., *J. Am. Chem. Soc.,* **1949**, *71*, 2251. (aa) English, J. and Velick, S. F., *J. Am. Chem. Soc.,* **1945**, *67*, 1413.
3. Balenovic, K.; Bregant, N.; Cerar, D.; Fles, D. and Jambresic, I., *J. Org. Chem.,* **1953**, *18*, 297.
4. (a) Affrosman, S. and Thomson, S. J., *J. Chem. Soc.,* **1962**, 2024. (b) Gensler, W. J., *Chem. Rev.,* **1957**, *57*, 191.
5. (a) Yadav, V. G. and Chandalia, S. B., *Org. Proc. Res. Dev.,* **1997**, *1*, 226. (b) Bold, G.; Steiner, H.; Moesch, L. and Walliser, B., *Helv. Chim. Acta,* **1990**, *73*, 405.
6. Maier, W. F.; Chettle, S. J.; Rai, R. S. and Thomas, G., *J. Am. Chem. Soc.,* **1986**, *108*, 2608.
7. Rachlin, A. I.; Gurien, H. and Wagner, D. P., *Org. Synth.,* **1971**, *51*, 8.
8. Sakurai, Y. and Tanabe, Y., *J. Pharm. Soc. Jpn.,* **1944**, *64*, 25.
9. Peters, J. A. and Bekkum, H. V., *Rec. Trav. Chim. Pays-Bas,* **1971**, *90*, 1323.
10. Burgstahler, A. W.; Weigel, L. O. and Shaefer, C. G., *Synthesis,* **1976**, 767.
11. Mosettig, E. and Mozingo, R., *Org. React.,* **1948**, *4*, 362.
12. Rosenmund, K. W. and Zetsche, F., *Ber.,* **1932**, *65*, 1481.
13. Froschl, N.; Maier, A. and Heuberger, A., *Monatsh.,* **1932**, *59*, 256.
14. (a) Witczak, M. and Kwiecień, H., *Synth. Commun.,* **2005**, *35*, 2223. (b) Meffre, P. R., *Amino Acids,* **1999**, *16*, 251. (c) Chen, C.-Y.; Senanayake, C. H.; Bill, T. J.; Larsen, R. D.; Verhoeven, T. R. and Reider, P. J., *J. Org. Chem.,* **1994**, *59*, 3738. (d) *Org. Synth. Coll., VI* **1988**, *6*, 1007. (e) Doolittle, R. E.; Tumlinson, J. H.; Proveaux, A. T. *and* Heath, R. R., *J. Chem. Ecology,* **1980**, *6*, 473. (f) Vojtanis, E.; Sila, B. and Lesyak, T., *Chem. Heterocycl. Compd.,* **1977**, *13*, 601. (g) Quéguiner, G. and Pastour, P., *Bull. Soc. Chim. Fr.,* **1968**, 4117. (h) Rylander, P. N., *Catalytic Hydrogenation over Platinum Metals*, Academic Press, New York, **1967**, pp. 398–404. (i) Von Hahn, H. and Grün, F., *Helv. Chim. Acta,* **1955**, *38*, 1803. (j) Cason, J.; Allinger, N. L. and Sumrell, G., *J. Org. Chem.,* **1953**, *18*, 850. (k) Cook, E. W. and Major, R. T., *J. Am. Chem. Soc.,* **1936**, *58*, 2410.

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Rosenmund-von Braun Reaction

(Rosenmund-von Braun Nitrile Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Rosenmund et al. in 1919[1] and subsequently modified by von Braun et al. in 1931.[2] It is the synthesis of an aryl nitrile from an aryl halide and cuprous cyanide in a high boiling solvent. Therefore, it is generally known as the Rosenmund-von Braun reaction[3] or Rosenmund-von Braun cyanation.[3c,4] Occasionally, it is also referred to as the Rosenmund-von Braun aromatic nitrile synthesis,[3x] Rosenmund-von Braun cyanodehalogenation,[3c] Rosenmund-von Braun nitrile synthesis,[5] or Rosenmund-von Braun synthesis.[3x,6] This is a biphasic reaction in temperatures ranging from 150°C to 280°C,[3d,5a] using high boiling point solvents such as nitrobenzene,[3e] NMP[3c,7] and DMF.[3c] In addition, this reaction is an auto-catalyzed reaction,[5] as demonstrated by the reaction between *p*-bromotoluene and CuCN, which at 250°C completes only 15% within the first 60 min, while 60% more product is formed in the subsequent 30 min of reaction.[5a] Moreover, the presence of a small amount of nitrile effectively reduces the induction period.[3x] Some nitrogenous bases such as tertiary amine[8] and pyridine[5a]also promote this reaction. It has been found that $CuSO_4$ has a catalytic effect for this reaction, whereas hydroquinone retards the formation of aromatic nitrile, indicating that this reaction involves the divalent copper ion.[3x,5a] However, this reaction also has a few associated problems: the requirement for extreme reaction conditions (150–280°C);[3d] a harsh work-up process by heating with HCl and $FeCl_3$;[3c] a stoichiometric amount of cuprous cyanide which leads to the formation of equivalent amount of copper halide which may complicate the product separation and cause the problem of waste disposal as well.[3d]

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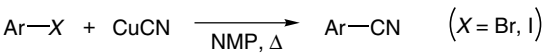
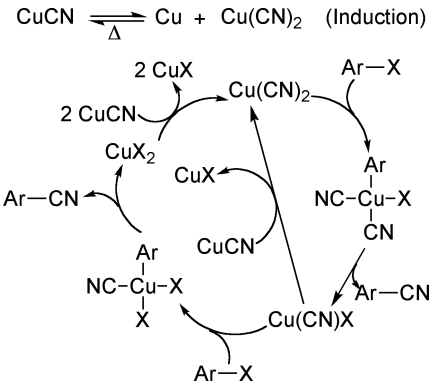
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

Although it has been reported that divalent copper is involved in this reaction, and a mechanism has been proposed to rationalize the reaction,[3x,5a] it is doubtful that the reaction involves the free aryl cation, Cu^{+} and Cu^{2+} ions. Thus an alternative mechanism is proposed below.



D. MODIFICATION

This reaction was modified by the replacement of CuCN with cheaper NaCN in the presence of palladium[9] or nickel catalyst,[10] as exemplified by the 5% $Pd(PPh_3)_4$/10% CuI catalyzed reaction[11] and the $Ni(CN)_2$ or $NaCN/NiBr_2$ based reaction under microwave irradiation[3f] for aryl bromide.[3b,3e] The latter condition is also used for the cyanation of aryl chloride with NaCN and $NiBr_2$.[3e] In addition, this reaction has also been extended to the preparation of some α,β-unsaturated nitriles.[3x] Further modifications include the copper-catalyzed domino halogen exchange-cyanation[3d] and the application of ionic liquid as reaction media.[3e,3h]

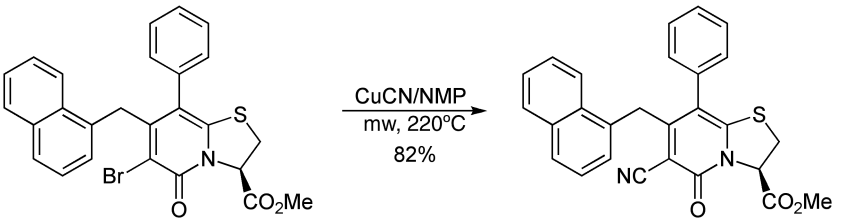
E. APPLICATIONS

This reaction has general application in the preparation of aromatic nitriles.

F. RELATED REACTIONS

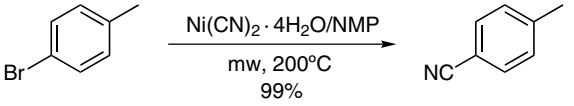
This reaction is related to the *Sandmeyer Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 3c.

At room temperature, 120 mg CuCN (1.3 mmol) was added to a stirred solution of 150 mg (3*R*)-6-bromo-7-naphthalen-1-ylmethyl-5-oxo-8-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-α]pyridine-3-carboxylic acid methyl ester (0.30 mmol) in 1.0 mL NMP. The mixture was heated at 220°C for 20 min under microwave irradiation, and the solvent was then removed by lyophilization from deionized water. The residue was thoroughly extracted with CH_2Cl_2, dried, and concentrated. Silica gel column chromatography using heptane/EtOAc (1:1) as the eluent afforded 110 mg (3*R*)-6-cyano-7-naphthalen-1-ylmethyl-5-oxo-8-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-α]pyridine-3-carboxylic acid methyl ester as a white foam, in a yield of 82%.



Reference 3e.

In a 10-mL glass tube were placed 0.171 g 4-bromotoluene (1.0 mmol), 110 mg $Ni(CN)_2{\cdot}4H_2O$ (0.6 mmol), 1.0 mL NMP, and a magnetic stir bar. The vessel was sealed with a septum and placed into the microwave cavity, and irradiated at 200°C for 10 min. After allowing the mixture to cool to room temperature, the reaction mixture was transferred to a separating funnel, and the tube was washed with water and then with ether. All washings were added to the separating funnel then another 20 mL water and Et_2O each were added, and the organic layer was separated. The aqueous layer was further extracted with Et_2O, and the combined organic layers were washed with water (3×40 mL) to remove remaining NMP. The organic layer was dried over $MgSO_4$ and concentrated to afford 99% of 4-methyl benzonitrile.

Other references related to the Rosenmund-von Braun reaction are cited in the literature.[12]

H. REFERENCES

1. Rosenmund, K. W. and Struck, E., *Ber.,* **1919**, *52*, 1749.
2. von Braun, J. and Manz, G., *Ann.,* **1931**, *488*, 111.
3. (a) Hatsuda, M. and Seki, M., *Tetrahedron,* **2005**, *61*, 9908. (b) Cai, L. Z.; Liu, X.; Tao, X. C. and Shen, D., *Synth. Commun.,* **2004**, *34*, 1215. (c) Pemberton, N.; Åberg, V.; Almstedt,

H.; Westermark, A. and Almqvist, F., *J. Org. Chem.,* **2004**, *69*, 7830. (d) Zanon, J.; Klapars, A. and Buchwald, S. L., *J. Am. Chem. Soc.,* **2003**, *125*, 2890. (e) Arvela, R. K. and Leadbeater, N. E., *J. Org. Chem.,* **2003**, *68*, 9122. (f) Ghaffarzadeh, M.; Bolourtchian, M.; Halvagar, M. R. and Hosseini, M., *J. Chem. Res. (S),* **2003**, 814. (g) Makhseed, S. and McKeown, N. B., *J. Porphyrins & Phthalocyanines,* **2003**, *7*, 125. (h) Wu, J. X.; Beck, B. and Ren, R. X., *Tetrahedron Lett.,* **2002**, *43*, 387. (i) Drechsler, U. and Hanack, M., *Synlett,* **1998**, 1207. (j) Ponchant, M.; Hinnen, F.; Demphel, S. and Crouzel, C., *Appl. Radiation & Isotopes,* **1997**, *48*, 755. (k) Osburn, E. J.; Schmidt, A.; Chau, L. K.; Chen, S. Y.; Smolenyak, P.; Armstrong, N. R. and O'Brian, D. F., *Adv. Mater. (Germany),* **1996**, *8*, 926. (l) Gordon, J. L. M.; Hartshorn, M. P.; Robinson, W. T.; Sies, C. W.; Wells, B. A.; Wikaira, J. L. and Wright, G. J., *Aust. J. Chem.,* **1990**, *43*, 579. (m) Fisher, T. H.; Dershem, S. M. and Prewitt, M. L., *J. Org. Chem.,* **1990**, *55*, 1040. (n) Iwatsuki, S.; Itoh, T.; Shimizu, Y. and Enomoto, T., *Macromolecules,* **1989**, *22*, 38. (o) Tanabe, T., *Gunma Daigaku Kyoyobu Kiyo*, **1985**, *19*, 119. (p) Oehlke, J.; Schroetter, E.; Dove, S.; Schick, H. and Niedrich, H., *Pharmazie,* **1983**, *38*, 591. (q) Kovshev, E. I.; Solov'eva, L. I.; Mikhalenko, S. A. and Luk'yanets, E. A., *Zh. Vsesoyuznogo Khim. Obsh. Mendeleeva,* **1976**, *21*, 465. (r) Ito, T. and Watanabe, K., *Bull. Chem. Soc. Jpn.,* **1968**, *41*, 419. (s) Bell, M. R.; Oesterlin, R.; Beyler, A. L.; Harding, H. R. and Potts, G. O., *J. Med. Chem.,* **1967**, *10*, 264. (t) Lele, S. S.; Patel, M. G. and Sethna, S., *J. Org. Chem.,* **1962**, *27*, 637. (u) Shah, M. V. and Sethna, S., *J. Chem. Soc.,* **1961**, 2663. (v) Akanuma, K.; Amamiya, H.; Hayashi, T.; Watanabe, K. and Hata, K., *Nippon Kagaku Zasshi*, **1960**, *81*, 333. (w) Lawton, E. A. and McRitchie, D. D., *J. Org. Chem.,* **1959**, *24*, 26. (x) Mowry, D. T., *Chem. Rev.,* **1948**, *42*, 189.

4. (a) Cristau, H.-J.; Ouali, A.; Spindler, J.-F. and Taillefer, M., *Chem. Eur. J.,* **2005**, *11*, 2483. (b) Carr, R. M.; Cable, K. M.; Wells, G. N. and Sutherland, D. R., *J. Labelled Compd. & Radiopharm.,* **1994**, *34*, 887. (c) Bouyssou, P.; Le Goff, C. and Chenault, J., *J. Heterocycl. Chem.,* **1992**, *29*, 895. (d) Ellis, G. P. and Hudson, H. V., *J. Chem. Res. (S),* **1985**, 372. (e) Lyukmanov, N. F. and Kovshev, E. I., *Khim. Geterotsiklicheskikh Soedinenii,* **1983**, 994. (f) Gaekwad, Y. G. and Sethna, S., *J. Indian Chem. Soc.,* **1978**, *55*, 794.
5. (a) Koelsch, C. F. and Whitney, A. G., *J. Org. Chem.,* **1941**, *6*, 795. (b) Kielsch, C. F., *J. Am. Chem. Soc.,* **1936**, *58*, 1328.
6. Schweikart, K.-H.; Hanack, M.; Luer, L. and Oelkrug, D., *Eur. J. Org. Chem.,* **2001**, 293.
7. Martinelli, M. J.; Leanna, M. R.; Varie, D. L.; Peterson, B. C.; Kress, T. J.; Wepsiec, J. P. and Khau, V. V., *Tetrahedron Lett.,* **1990**, *31*, 7579.
8. Hochwalt, C. A., *U.S. Pat.,* Apr. 30, **1946**, 2,399,349.
9. (a) Sundermeier, M.; Zapf, A.; Beller, M. and Sans, J., *Tetrahedron Lett.,* **2001**, *42*, 6707. (b) Tschaen, D. M.; Desmond, R.; King, A. O.; Fortin, M. C.; Pipik, B.; King, S. and Verhoeven, T. R., *Synth. Commun.,* **1994**, *24*, 887.
10. (a) Percec, V.; Bae, J.-Y. and Hill, D. H., *J. Org. Chem.* **1995**, *60*, 6895. (b) Sakakibara, Y.; Ido, Y.; Sasaki, K.; Sakai, M. and Uchino, N., *Bull. Chem. Soc. Jpn.,* **1993**, *66*, 2776. (c) Cassar, L., *J. Organomet. Chem.,* **1973**, *54*, C57.
11. Anderson, B. A.; Bell, E. C.; Ginah, F. O.; Harn, N. K.; Pagh, L. M. and Wepsiec, J. P., *J. Org. Chem.,* **1998**, *63*, 8224.
12. (a) Anderson, B. A.; Becke, L. M.; Booher, R. N.; Flaugh, M. E.; Harn, N. K.; Kress, T. J.; Varie, D. L. and Wepsiec, J. P., *J. Org. Chem.,* **1997**, *62,* 8634. (b) Connor, J. A.; Leeming, S. W. and Price, R., *J. Chem. Soc., Perkin Trans. I,* **1990**, 1127. (c) Ellis, G. P. and Romney-Alexander, T. M., *Chem. Rev.,* **1987**, *87*, 779. (d) Takagi, K.; Okamoto, T.; Sakakibara, Y.; Ohno, A.; Oka, S. and Hayama, N., *Bull. Chem. Soc. Jpn.,* **1975**, *48*, 3298. (e) Rieger, P. H.; Bernal, I.; Reinmuth, W. H. and Fraenkel, G. K., *J. Am. Chem. Soc.,* **1963**, *85*, 683. (f) Newman M. S. and Boden H., *J. Org. Chem.*, **1961**, *26*, 2525. (g) Newton, A., *J. Am. Chem. Soc.,* **1943**, *65*, 2441. (h) Pongratz, A., *Monatsh. Chem.,* **1927**, *48*, 585. (i) Rosenmund, K. W. and Harms, H., *Ber.,* **1920**, *53*, 2226. (j) Rosenmund, K. W. and Struck, E., *Ger. Pat.,* **1920**, Oct. 4, 327,049.

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Rothemund Reaction
(Rothemund Condensation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Rothemund in 1935.[1] It is a one-pot synthesis of porphine or isoporphine by the thermal condensation of aldehydes with pyrroles and is generally known as the Rothemund condensation,[2] Rothemund synthesis,[2e,2g,3] or Rothemund reaction.[2e,4] Occasionally, it is also referred to as the Rothemund-Lindsey reaction.[4b,5] Nowadays, this reaction has become the mainstay for the synthesis of porphyrins,[4g] especially for 5,10,15,20-,[2g] (or $\alpha,\beta,\gamma,\delta$-)[6] tetrasubstituted hindered *meso*-porphyrins. Initial studies have indicated that the condensation between pyrrole and aldehyde can occur under various conditions, such as in gaseous acetaldehyde (or formaldehyde) when reacted with pure acetaldehyde or formaldehyde, in methanol at room temperature or at refluxing temperature, or in methanol at 85–90°C in a sealed tube.[1] It has also been found that the same reaction in a sealed tube at 150–155°C yields different products,[6b] and the addition of pyridine,[1] $CaCO_3/MgO$,[1] or $PbCrO_4$[1] results in higher yields of porphyrins. Thus many current preparations of porphyrin derivatives have been carried out in heterocyclic base, such as 2,4,6-collidine.[2g] Furthermore, the addition of a metal ion species, such as Cu(I)[7] and Co(II)[8] can increase the yield of expected porphyrins, as demonstrated by the duplication of the yield of porphyrin by use of zinc acetate.[9] Such enhancement of the yield is attributed to the acidifying effect of the added metal ion rather than to the template effect.[4i] Furthermore, it is known that the reaction involving an electron-deficient aldehyde normally leads to a higher yield of porphyrin than the electron-rich one,[2b] and the substituent on aldehyde will control the course of this reaction,[2b] in which a number of porphyrin analogues might form, such as chlorin,[4k] sapphyrin,[4c] isosmaragdyrin,[10] ozaphyrin,[11] hexaphyrin,[12] and corrole.[2e] It is the complication of this reaction by formation of other analogues and the difficulty in isolation of porphyrin out of these contaminants that results in the low yield of porphyrin.[2b] Among those porphyrin analogues, there might be "inverted"[2c,4g] or

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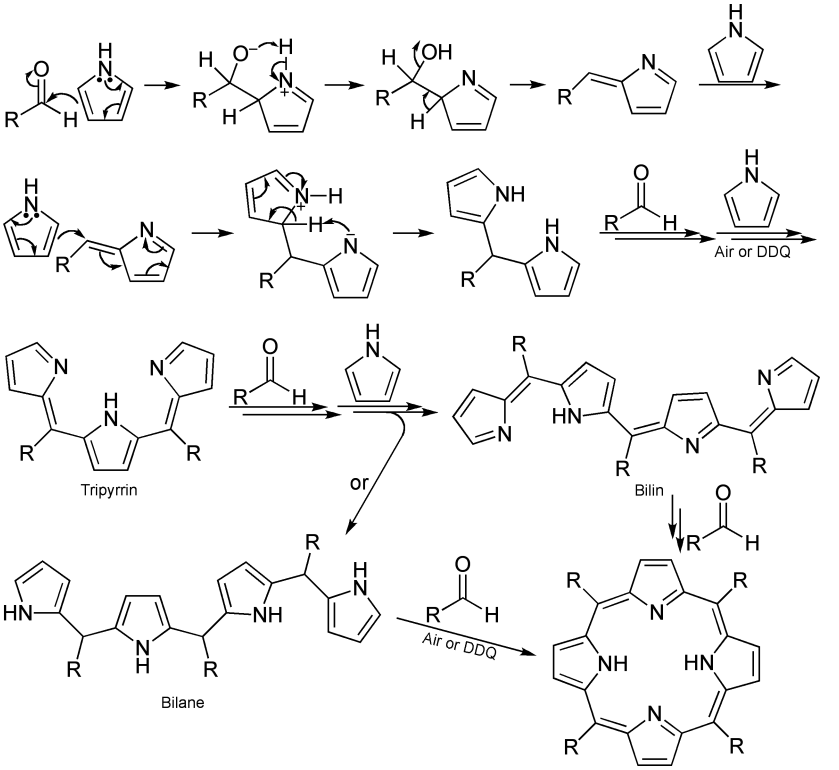
"*N*-confused"[4a,4c,4e,4f] (or mutant,[4d] carba[4d]) porphyrin, of which the position of nitrogen and carbon atoms are interchanged in one of the pyrrole rings.

B. GENERAL REACTION SCHEME

C. PROPOSED MECHANISMS

This one-pot synthesis of porphyrin may involve a series of condensation and dehydration steps[4k] to form bipyrrin, tripyrrin, and bilane or bilin. The bilane or bilin then condenses with one more aldehyde molecule and cyclizes to give porphyrin and its analogues. Displayed here is an illustrative reaction route for the formation of porphyrin.



D. MODIFICATION

This reaction has been modified by Alder and Longo by heating the mixture of pyrrole and aldehyde in propionic acid at 141°C while open to air to give unhindered porphyrin derivatives.[13] However, such modification often causes problems such as the formation of a high level of tar material that complicates the purification process, the incompatibility with certain functional groups on aldehydes, and the low batch-to-batch reproducibility.[4i] On the other hand, Lindsey has carried out the reaction in the presence of a catalytic amount of BF_3 or TFA under equilibrium conditions, followed by oxidation with an electron-deficient quinone,[4i,14] such as DDQ.[2b,4a,4i] In addition, this reaction has been extended to the preparation of corrole by the application of an excess amount of pyrrole.[2e]

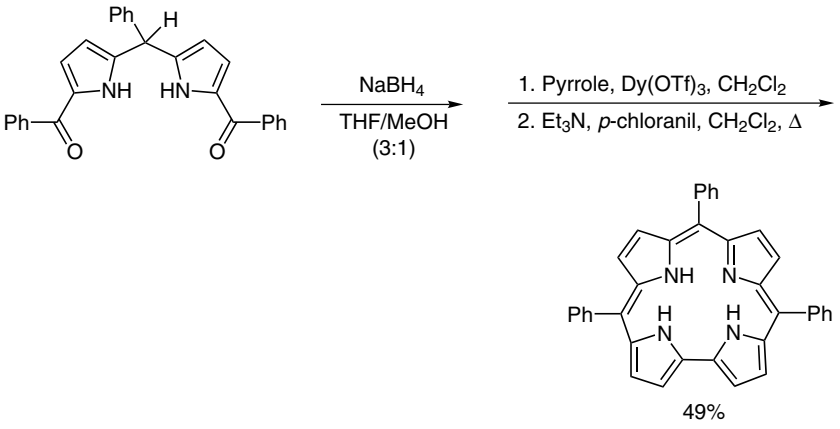
E. APPLICATIONS

This reaction is the primary method for the preparation of porphyrin derivatives and their analogues.

F. RELATED REACTIONS

This reaction is related to the *Bakelite Process*.

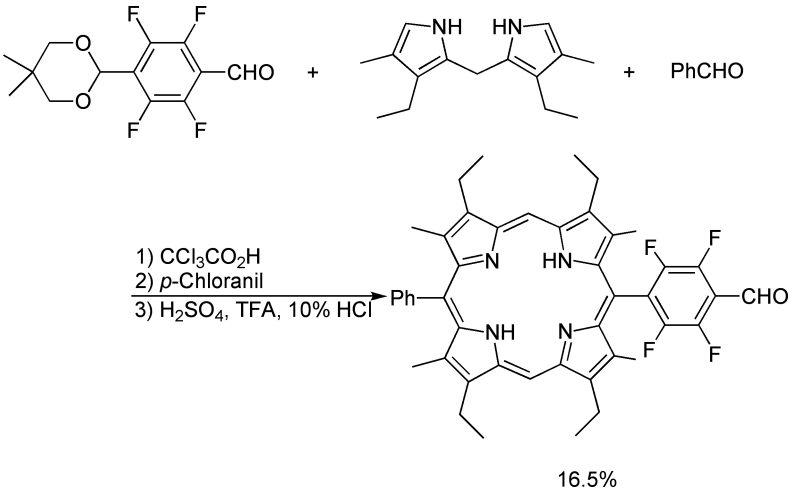
G. CITED EXPERIMENTAL EXAMPLES



Reference 15.

Phenyl-bis(2-(5-benzoyl)pyrrolyl) methane (215 mg, 0.5 mmol) in 40 mL THF/MeOH (3:1) was reduced by 946 mg $NaBH_4$ (25.0 mmol) to afford the corresponding carbinol, which upon being dried under vacuum for 30 min was immediately subjected to condense with 3.47 mL pyrrole (50 mmol) in the presence of 122 mg $Dy(OTf)_3$ (0.2 mmol) in 200 mL CH_2Cl_2 for 1.3 h at room temperature. After the addition of 0.139 mL triethylamine

(1.0 mmol) and 246 mg *p*-chloranil (1.00 mmol), the mixture was refluxed for 45 min. Then the entire reaction mixture was filtered through a pad of silica gel, and eluted with CH_2Cl_2. The filtrate was concentrated to dryness. The residue was then dissolved in 75 mL CH_2Cl_2, adsorbed onto 15 g silica gel, concentrated, and purified by silica gel column chromatography using CH_2Cl_2/hexanes (1:1) as the eluent to afford 128 mg 5,10,15-triphenylcorrole, in a yield of 49%.



16.5%

Reference 5.

Benzaldehyde (0.110 mL, 1.09 mmol) and 317 mg 2,3,5,6-tetrafluoro-4-(5,5-dimethyl-1,3-dioxan-2-yl)benzaldehyde (1.09 mmol) were dissolved in 15 mL dry acetonitrile. Then 2 mL dry acetonitrile containing 21.0 mg dry trichloroacetic acid (0.129 mmol) was added, and the resulting mixture was stirred under argon in the dark. After that, a solution of 500 mg bis(3-ethyl-4-methyl-2-pyrrolyl)methane (2.17 mmol) in 3 mL dry acetonitrile was added to the mixture, and the resulting mixture was stirred for 5.5 h. Then a suspension of 790 mg *p*-chloranil (3.21 mmol) in 15 mL dry THF was added, and the mixture was stirred overnight. The reaction mixture was passed through a short alumina column and washed by acetonitrile. Upon evaporation of the solvent, the residue was separated by silica gel column chromatography with CH_2Cl_2 as an eluent and was further separated by gel permeation chromatography (GPC) using THF as an eluent. The second fraction was collected and further purified by silica gel column chromatography using EtOAc/hexane (1:1) as the eluent to afford 146 mg 5-(4-(5,5-dimethyl-1,3-dioxan-2-yl)-2,3,5,6-tetrafluorophenyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethyl-15-phenylporphyrin, in a yield of 16.5%.

The acetal porphyrin (100 mg) was dissolved in a mixture of TFA (5 mL), 5 mL 10% HCl, and 1 drop concentrated H_2SO_4. The resulting mixture was moderately refluxed for 3 h. After being cooled to room temperature, the reaction mixture was neutralized with saturated $NaHCO_3$ aqueous solution. Then the aqueous solution was extracted with EtOAc, washed with brine, and dried over Na_2SO_4. Upon removal of the solvent, 5-(4-formyl-2,3,5,6-tetrafluorophenyl)-2,8,12,18-tetraethyl-3,7,13, 17-tetramethyl-15-phenylporphyrin was obtained, in a yield of 100%. (*Note:* The description of the original protocol is not clear; a few steps were omitted.)

Other references related to the Rothemund reaction are cited in literature.[16]

H. REFERENCES

1. Rothemund, P., *J. Am. Chem. Soc.,* **1935**, *57*, 2010.
2. (a) Shen, Z.; Uno, H.; Shimizu, Y. and Ono, N., *Org. Biomol. Chem.,* **2004**, *2*, 3442. (b) Krivokapic, A.; Cowley, A. R. and Anderson, H. L., *J. Org. Chem.,* **2003**, *68*, 1089. (c) Schmidt, I.; Chmielewski, P. J. and Ciunik, Z., *J. Org. Chem.,* **2002**, *67*, 8917. (d) Colby, D. A. and Lash, T. D., *Chem. Eur. J.,* **2002**, *8*, 5397. (e) Paolesse, R.; Nardis, S.; Sagone, F. Khoury, R. G., *J. Org. Chem.,* **2001**, *66,* 550. (f) Ohkubo, K.; Sagawa, T. and Ishida, H., *Inorg. Chem.,* **1992**, *31*, 2682. (g) Williamson, M. M.; Prosser-McCartha, C. M.; Mukundan, S. and Hill, C. L., *Inorg. Chem.,* **1988**, *27*, 1061. (h) Hill, C. L. and Williamson, M. M., *J. Chem. Soc., Chem. Commun.,* **1985**, 1228. (i) Haushalter, R. C.; Butler, W. M. and Rudolph, R. W., *J. Am. Chem. Soc.,* **1981**, *103*, 2620.
3. (a) Schmidt, I. and Chmielewski, P. J., *Tetrahedron Lett*., **2001**, *42*, 1151. (b) Crossley, M. J.; Thordarson, P.; Bannerman, J. P. and Maynard, P. J., *J. Porphyrins & Phthalocyanines,* **1998**, *2*, 511. (c) Chmielewski, P. J.; Latos-Grazynski, L. and Rachlewicz, K., *Chem. Eur. J.*, **1995**, *1*, 68. (d) Marchon, J. C.; Ramasseul, R. and Ulrich, J., *J. Heterocycl. Chem.,* **1987**, *24*, 1037.
4. (a) Srinivasan, A. and Furuta, H., *Acc. Chem. Res.,* **2005**, *38*, 10. (b) Lash, T. D.; Colby, D. A. and Ferrence, G. M., *Eur. J. Org. Chem.,* **2003**, 4533. (c) Pushpan, S. K. and Chandrashekar, T. K., *Pure & Appl. Chem.,* **2002**, *74*, 2045. (d) Pushpan, S. K.; Venkatraman, S.; Anand, V. G.; Sankar, J.; Rath, H. and Chandrashekar, T. K., *Proc. Indian Acad. Sci. (Chem. Sci.),* **2002**, *114*, 311. (e) Pushpan, S. K.; Srinivasan, A.; Anand, V. G.; Venkatraman, S.; Chandrashekar, T. K.; Joshi, B. S.; Roy, R. and Furuta, H., *J. Am. Chem. Soc.,* **2001**, *123,* 5138. (f) Pushpan, S. K.; Srinivasan, A.; Anand, V. R. G.; Chandrashekar, T. K.; Subramanian, A.; Roy, R.; Sugiura, K.-i. and Sakata, Y., *J. Org. Chem.,* **2001**, *66,* 153. (g) Lash, T. D.; Richter, D. T. and Shiner, C. M., *J. Org. Chem.,* **1999**, *64,* 7973. (h) Paolesse, R.; Mini, S.; Sagone, F.; Boschi, T.; Jaquinod, L.; Nurco, D. J. and Smith, K. M., *Chem. Commun.,* **1999**, 1307. (i) Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C. and Marguerettaz, A. M., *J. Org. Chem.,* **1987**, *52*, 827. (j) Little, R. G., *J. Heterocycl. Chem.,* **1981**, *18*, 833. (k) Badger, G. M.; Jones, R. A. and Laslett, R. L., *Aust. J. Chem.,* **1964**, *17*, 1028.
5. Inokuma, Y. and Osuka, A., *Org. Lett.,* **2004**, *6*, 3663.
6. (a) Rothemund, P., *J. Am. Chem. Soc.*, **1939**, *61*, 2912. (b) Rothemund, P., *J. Am. Chem. Soc.,* **1936**, *58*, 625.
7. Corwin, A. H. and Sydow, V. L., *J. Am. Chem. Soc.,* **1953**, *75*, 4484.
8. Johnson, A. W.; Kay, I. T.; Markham, E.; Price, R. and Shaw, K. B., *J. Chem. Soc.,* **1959**, 3416.
9. Rothemund, P. and Menotti, A. R., *J. Am. Chem. Soc.,* **1941**, *63*, 267.
10. (a) Srinivasan, A.; Pushpan, S. K.; Kumar, M. R.; Chandrashekar, T. K. and Roy, R., *Tetrahedron,* **1999**, *55*, 6671. (b) Srinivasan, A.; Reddy, V. M.; Narayanan, S. J.; Sridevi, B.; Pushpan, S. K.; Kumar, M. R.; Chandrashekar, T. K., *Angew. Chem. Int. Ed. Engl.,* **1997**, *36*, 2598.
11. (a) Miller, D. C.; Johnson, M. R. and Ibers, J. A., *J. Org. Chem.,* **1994**, *59*, 2877. (b) Miller, D. C.; Johnson, M. R.; Becker, J. J. and Ibers, J. A., *J. Heterocycl. Chem.,* **1993**, *30*, 1485.
12. (a) Neves, M. G. P. M. S.; Martins, R. M.; Tomé, A. C.; Silverstre, A. J. D.; Silva, A. M. S.; Félix, V.; Drew, M. G. B. and Cavaleiro, J. A. S., *Chem. Commun.,* **1999**, 385. (b) Rachlewicz, K.; Sprutta, N.; Chmielewski, P. J. and Latos-Grazynski, L., *J. Chem. Soc., Perkin Trans. II,* **1998**, 969.
13. (a) Kim, J. B.; Adler, A. D. and Longo, F. R., *Synthesis of Porphyrins from Monopyrroles* in *Porphyrins*, ed. Dolphin, D. Academic, New York, **1978**, *1,* pp. 85–100. (b) Adler, A. D.; Longo, F. R.; Finarelli, J. D.; Goldmacher, J.; Assour, J. and Korsakoff, L., *J. Org. Chem.,* **1967**, *32*, 476.
14. (a) Lindsey, J. S.; MarCrum, K. A.; Tyhonas, J. S. and Chuang, Y.-Y., *J. Org. Chem.,* **1994**, *59*, 579. (b) Lindsey, J. S. and Wagner, R. W., *J. Org. Chem.,* **1989**, *54*, 828.

15. Geier, G. R.; Chick, J. F. B.; Callinan, J. B.; Reid, C. G. and Auguscinski, W. P., *J. Org. Chem.,* **2004**, *69*, 4159.

16. (a) Rucareanu, S.; Schuwey, A. and Gossauer, A., *J. Am. Chem. Soc.,* **2006**, *128*, 3396. (b) Chandraskekar, T. K.; Venkatraman, S.; Prabhuraja, V.; Misra, R. and Baskar, V., *Phosphorus, Sulfur & Silicon & Related Elements,* **2005**, *180*, 845. (c) Richter, D. T. and Lash, T. D., *J. Org. Chem.,* **2004**, *69*, 8842. (d) Lash, T. D.; Colby, D. A.; Graham, S. R. and Chaney, S. T., *J. Org. Chem.,* **2004**, *69*, 8851. (e) Ghosh, A., *Angew. Chem. Int. Ed.,* **2004**, *43*, 1918. (f) Sessler, J. L. and Seidel, D., *Angew. Chem. Int. Ed.,* **2003**, *42*, 5134. (g) Pawlicki, M.; Latos-Grazynski, L. and Szterenberg, L., *J. Org. Chem.,* **2002**, *67*, 5644. (h) Narayanan, S. J.; Sridevi, B.; Chandrashekar, T. K.; Vij, A. and Roy, R., *Angew. Chem. Int. Ed.,* **1998**, *37*, 3394. (i) Simoneit, B. R. T., *Origins of Life & Evolution Biospheres,* **1995**, *25*, 119. (j) Morozov, V. V.; Semeikin, A. S.; Gnedin, B. G. and Berezin, B. D., *Chem. Heterocycl. Compd.,* **1988**, *24*, 628. (k) Thomas, D. W. and Martell, A. E., *J. Am. Chem. Soc.,* **1959**, *81*, 5111. (l) Thomas, D. W. and Martell, A. E., *J. Am. Chem. Soc.,* **1956**, *78*, 1335. (m) Ueno, K. and Martell, A. E., *J. Phys. Chem.,* **1956**, *60*, 934. (n) Priestoff, J. H. and Banks, C. V., *J. Am. Chem. Soc.,* **1954**, *76*, 937. (o) Rothemund, P. and Menotti, A. R., *J. Am. Chem. Soc.,* **1948**, *70*, 1808. (p) Ball, R. H.; Dorough, G. D. and Calvin, M., *J. Am. Chem. Soc.,* **1946**, *68*, 2278. (q) Aronoff, S. and Calvin, M., *J. Org. Chem.,* **1943**, *8*, 205. (r) Rothemund, P. and Menotti, A. R., *J. Am. Chem. Soc.,* **1941**, *63*, 217.

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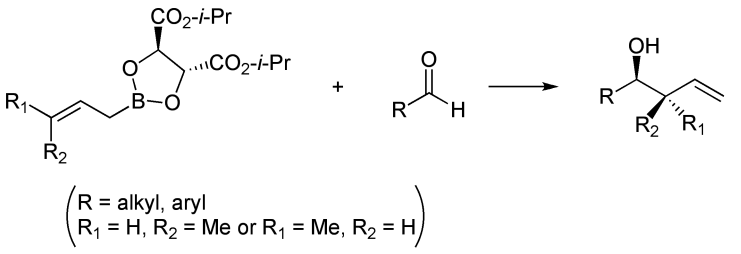
Roush Crotylboration

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Roush in 1985.[1] It is an enantioselective synthesis of a chiral alcohol by the condensation between a crotylboronate derived from diisopropyl-(*R*,*R*)-tartrate and an achiral aldehyde. Therefore, it is known as the Roush crotylboration,[2] Roush asymmetric crotylboration,[3] or Roush crotylboronate chemistry.[4] The (*Z*)- or (*E*)-crotylboronate derived from diisopropyl-(*R*,*R*)-tartrate can be readily prepared from *cis*-2-butene or *trans*-2-butene by a series of treatments on 2-butene with *n*-BuLi/KO-*t*-Bu, B(*i*-Pr)$_3$, acid and diisopropyl tartrate, respectively. The initial configuration of 2-butene is preserved during the preparation, and the resulting crotylboronates are referred to as the Roush crotylboranes[5] or Roush crotyl boronate reagents,[3] which are very convenient to use and can be stored in the freezer in toluene solution.[3] In addition, no extra oxidation step is necessary during the workup stage after the addition of the Roush crotylborane to aldehyde.[3] It has been found that the (*Z*)-crotylboronate results in a *syn*-homoallylic alcohol in preference,[6] whereas (*E*)-crotylboronate yields the corresponding *anti* allylic alcohol in favored amounts.[6b] However, these crotylboronates can yield only good to moderate enantioselectivity for the addition to most achiral aldehydes with a typical e.e. between 60% and $\sim$ 87%,[7] except for the reaction with metal carbonyl-complexed unsaturated aldehydes, which gives e.e. in the range of 83–98%.[8] Guided by the reaction mechanism, Roush's group has developed a second generation of crotylboronates with a chiral auxiliary of (*R*,*R*)-*N*,*N*′-bis-(2,2,2-trifluoroethyl)-*N*,*N*′-ethylenetartramide, which rank among the most highly enantioselective reagents. It should be pointed out that the auxiliary group can be easily recycled after the reaction.[9]

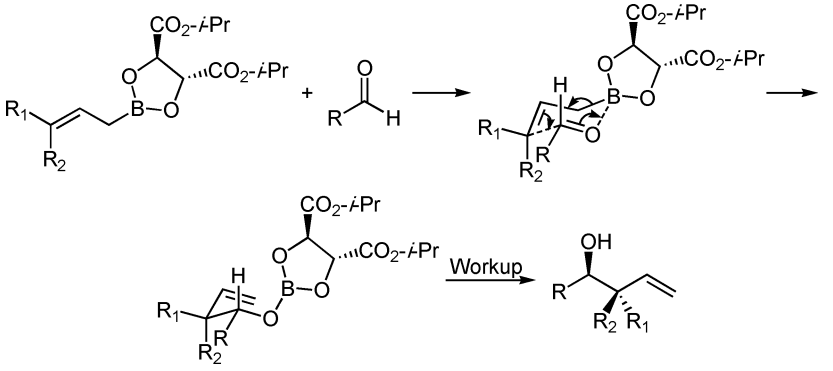
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

An illustrative mechanism is provided here for the addition of crotylboronate to aldehyde with control of stereochemistry.



D. MODIFICATION

This reaction has been modified by the application of (*R*,*R*)-*N*,*N*′-bis-(2,2,2-trifluoroethyl)-*N*,*N*′-ethylenetartramide as a chiral auxiliary to obtain the highest enantioselectivity.[9]

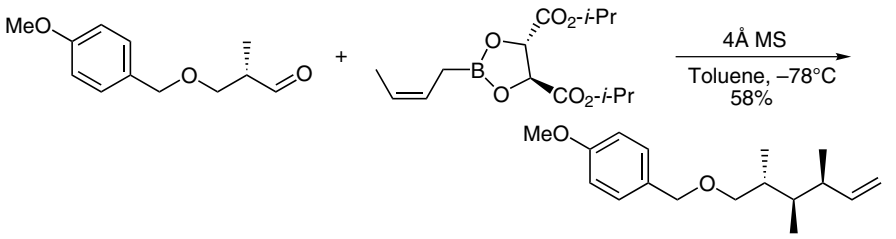
E. APPLICATIONS

This reaction has wide application in asymmetric synthesis.

F. RELATED REACTIONS

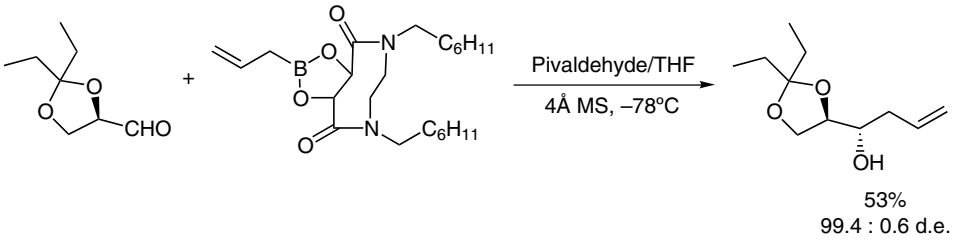
This reaction is related to the *Evans Aldol Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 6a.

A mixture of 32.2 g (4*S*,5*S*)-2-[(2*Z*)-2-butenyl]-1,3,2-dioxaborolane-4,5-dicarboxylic acid bis(1-methylethyl) ester (108.0 mmol), 450 mL anhydrous toluene, and 3.22 g 4Å molecular sieves was stirred at room temperature for 30 min under nitrogen and cooled to −78°C. Then 15.0 g (2*S*)-3-[(4-methoxyphenyl)methoxy]-2-methyl-propanal (72.0 mmol) in 50 mL anhydrous toluene was slowly added, while maintaining the temperature at −78°C. The resulting mixture was maintained at −78°C for 18 h, then carefully quenched with a suspension of 1 g $NaBH_4$ in 100 mL absolute ethanol. The mixture was warmed to 0°C, diluted with 500 mL 1 *N* NaOH, and stirred vigorously for 2 h. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 100 mL). The organic layers were combined, dried over K_2CO_3, and concentrated. The residue was purified by flash chromatography over SiO_2 using EtOAc/hexanes (1:9) to afford 11.0 g (2*S*,3*R*,4*S*)-1-[(4-methoxyphenyl)methoxy]-2,4-dimethyl-5-hexen-3-ol as a clear oil, in a yield of 58%.



Reference 9.

A mixture of 0.66 mmol allylboronate with (*R*,*R*)-*N*,*N*′-bis(cyclohexylmethyl)-*N*,*N*′-ethylenetartramide as chiral auxiliary, 1.0 mL THF, and 600 mg 4Å powdered molecular sieves was stirred at room temperature for 30 min and was cooled again to −78°C. A solution of 5.2 μL pivaldehyde (0.044 mmol) in 200 μL dry THF was added dropwise. After the addition was complete, the solution was warmed to room temperature and stirred for 30 min. The mixture was cooled to −78°C again and then a solution of 0.069 g D-glyceraldehyde pentylidene ketal (0.44 mmol) in 0.2 mL dry THF was added dropwise down the side of the flask. After the addition was complete, the solution was maintained at −78°C for 36 h. Excess acetaldehyde was then added dropwise via syringe, the cooling bath was removed, and the solution was warmed to room temperature. The mixture was filtered

through a plug of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography using hexane/Et_2O (9:1) to afford 0.047 g *erythro*-1,2-*O*-pentylidenehex-5-en-1,2,3-triol with 99.4:0.6 diastereoselectivity, as determined by capillary GC analysis, in a yield of 53%.

Other references related to the Roush crotylboration are cited in the literature[10].

H. REFERENCES

1. Roush, W. R.; Walts, A. E. and Hoong, L. K., *J. Am. Chem. Soc.,* **1985**, *107*, 8186.
2. (a) Suenaga, K.; Kimura, T.; Kuroda, T.; Matsui, K.; Miya, S.; Kuribayashi, S.; Sakakura, A. and Kigoshi, H., *Tetrahedron,* **2006**, *62*, 8278. (b) Yeung, K.-S. and Paterson, I., *Chem. Rev.,* **2005**, *105*, 4237. (c) Smith, A. B.; Friestad, G. K.; Barbosa, J.; Bertounesque, E.; Hull, K. G.; Iwashima, M.; Qiu, Y. P.; Salvatore, B. A.; Spoors, P. G. and Duan, J. J.-W., *J. Am. Chem. Soc.,* **1999**, *121,* 10468.
3. Oikawa, M.; Ueno, T.; Oikawa, H. and Ichihara, A., *J. Org. Chem.,* **1996**, *60*, 5048.
4. Zheng, W. J.; DeMattei, J. A.; Wu, J.-P.; Duan, J. J.-W.; Cook, L. R.; Oinuma, H. and Kishi, Y., *J. Am. Chem. Soc.,* **1996**, *118,* 7946.
5. Faul, M. M. and Huff, B. E., *Chem. Rev.,* **2000**, *100,* 2407.
6. (a) Francavilla, C.; Chen, W. C. and Kinder, F. R., *Org. Lett.,* **2003**, *5*, 1233. (b) White, J. D.; Hanselmann, R.; Jackson, R. W.; Porter, W. J.; Ohba, Y.; Tiller, T. and Wang, S., *J. Org. Chem.,* **2001**, *66,* 5217. (c) Brown, H. C. and Narla, G., *J. Org. Chem.,* **1995**, *60*, 4686.
7. (a) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D. and Halterman, R. L., *J. Am. Chem. Soc.,* **1990**, *112*, 6339. (b) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J. and Park, J. C., *J. Org. Chem.,* **1990**, *55*, 4109.
8. (a) Roush, W. R. and Park, J. C., *J. Org. Chem.,* **1990**, *55*, 1143. (b) Roush, W. R. and Park, J. C., *Tetrahedron Lett.,* **1990**, *31*, 4707.
9. Roush, W. R. and Grover, P. T., *J. Org. Chem.,* **1995**, *60*, 3806.
10. (a) Flamme, E. M. and Roush, W. R., *J. Am. Chem. Soc.,* **2002**, *124*, 13644. (b) Knapp, S. and Dong, Y., *Tetrahedron Lett.,* **1997***, 38*, 3813. (c) Roush, W. R. and Wada, C. K., *J. Am. Chem. Soc.,* **1994**, *116*, 2151. (d) White, J. D. and Johnson, A. T., *J. Org. Chem.,* **1994**, *59*, 3347. (e) White, J. D.; Porter, W. J. and Tiller, T., *Synlett,* **1993**, 535. (f) Roush, W. R. and Marron, T. G., *Tetrahedron Lett.,* **1993**, *34*, 5421. (g) Roush, W. R. and Brown, B. B., *J. Am. Chem. Soc.,* **1993**, *115*, 2268. (h) Roush, W. R.; Roush, W. R. and Grover, P. T., *Tetrahedron,* **1992**, *48*, 1981. (i) Chen, S.-H.; Horvath, R. F.; Joglar, J.; Fisher, M. J. and Danishefsky, S. J., *J. Org. Chem.,* **1991**, *56*, 5834. (j) Hoong, L. K.; Palmer, M. A. J.; Straub, J. A. and Palkowitz, A. D., *J. Org. Chem.,* **1990**, *55*, 4117. (k) Roush, W. R.; Palkowitz, A. D. and Ando, K., *J. Am. Chem. Soc.,* **1990**, *112*, 6348. (l) White, J. D. and Johnson, A. T., *J. Org. Chem.,* **1990**, *55*, 5938. (m) Roush, W. R. and Palkowitz, A. D., *J. Org. Chem.,* **1989**, *54*, 3009. (n) Hoffmann, R. W.; Dresely, S. and Hildebrandt, B., *Ber.,* **1988**, *121*, 2225.

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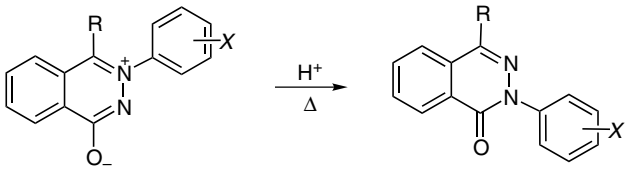
Rowe Rearrangement

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was reportd by Rowe et al. in 1926.[1] It is an acid-promoted thermal transformation of *pseudo*-phthalazones into phthalazones[2] and is commonly known as the Rowe rearrangement.[2,3] This reaction is generally carried out in a 1.2 *N* HCl solution at 180°C in a sealed tube for a few hours,[2,3] and the migratory attendance of the aryl group depends on its substituents and the nature of the substituent at the 4-position of the *pseudo*-phthalazone.[2] For example, an electron-withdrawing group at the 2- or 4-position of the aryl, such as nitro, facilitates the rearrangement of the aryl moiety, whereas an electron-donating group, such as methyl, at the 2- or 4-position retards such migration.[2] During this intramolecular rearrangement, the aryl group remains attached to the same nitrogen atom,[2] indicating the nitrogen atoms in diazonium ions are not equivalent.[3]

B. GENERAL REACTION SCHEME

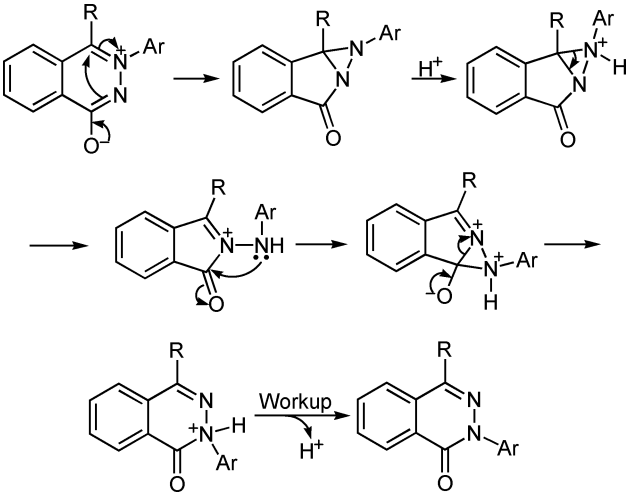


(*X* = 2- or 4-Me, Cl, NO_2, etc.)

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

Although the reaction mechanism has been studied via an isotopic labeling experiment, the proposed mechanism is still not clear. Thus a revised and tentative mechanism is displayed here. In this mechanism, the initial addition of an amido nitrogen to the iminium ion eliminates the charge, but the protonation of nitrogen increases the ring strain, and the three-membered ring opens.



D. MODIFICATION

N/A

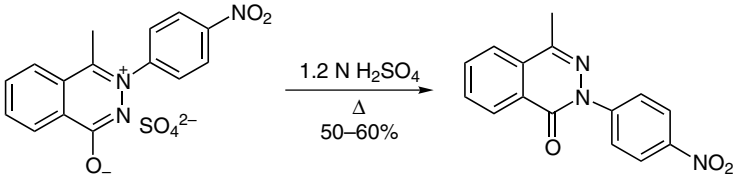
E. APPLICATIONS

This reaction has limited application in organic synthesis but is useful for mechanistic study.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3.

A mixture of 2.5 g ψ-phthalazone sulfate and 36 mL 1.2 *N* H_2SO_4 was sealed in a glass tube, and heated at 180°C for 9 h to give 50–60% of 2-(4-nitrophenyl)-4-methylphthalazone, m.p. 215.5–216.5°C after recrystallization from acetic acid/water. Considering the actual content of free base in the sulfate mixture (65%), the yield was adjusted to 86–91%.

Other references related to the Rowe rearrangement are cited in the literature[4].

H. REFERENCES

1. Rowe, F. M.; Levin, E.; Burns, A. C.; Davies, J. S. H. and Tepper, W., *J. Chem. Soc.,* **1926**, 690.
2. Vaughan, W. R., *Chem. Rev.,* **1948**, *43*, 447.
3. Vaughan, W. R.; McCane, D. I. and Sloan, G. J., *J. Am. Chem. Soc.,* **1951**, *73*, 2298.
4. (a) Rowe, F. M.; Adams, D. A. W.; Peters, A. T. and Gillam, A. E., *J. Chem. Soc.,* **1948**, 487. (b) Rowe, F. M.; Adams, D. A. W.; Peters, A. T. and Gillam, A. E., *J. Chem. Soc.,* **1937**, 90. (c) Rowe, F. M.; Dovey, W. C.; Garforth, B.; Levin, E.; Pask, J. D. and Peters, A. T., *J. Chem. Soc.,* **1935**, 1796. (d) Rowe, F. M.; Jambuserwala, G. B. and Partridge, H. W., *J. Chem. Soc.,* **1935**, 1134. (e) Rowe, F. M. and Dunbar, C., *J. Chem. Soc.,* **1932**, 11.

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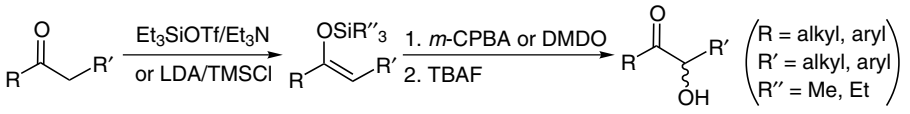
Rubottom Oxidation
(Rubottom Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Rubottom[1] and Brook et al.[2] concurrently in 1974. It is the transformation of a ketone into the corresponding α-hydroxyketone by means of the epoxidation or dihydroxylation of a silyl enolate of the ketone with *m*-chloroperbenzoic acid (*m*-CPBA) or dimethyldioxirane (DMDO). Therefore, this reaction is generally known as the Rubottom reaction[3] or Rubottom oxidation.[3a,4] Under certain conditions, the Rubottom oxidation can establish a hydroxyl group enantioselectively, such as in the introduction of *cis*-hydroxyl group with respect to the isopropyl group in 8α,11β-dimethyl-13β-hydroxy-12β-isopropyl-5β,15-isopropylidenedioxy-14-keto-($\Delta^{1,2}$,$\Delta^{3,4}$)-tricycle.[4] The silyl group can be cleaved by means of tetra-*N*-butylammonium fluoride (TBAF).[4a]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is assumed that the epoxidation of the silyl enolate yields an anomeric effect-stabilized silyloxy carbocation, which transforms into α-silyloxy ketone via 1,4-silyl migration. Hydrolysis of such α-silyloxy ketone gives the α-hydroxy ketone. A general illustration of this reaction is provided here.

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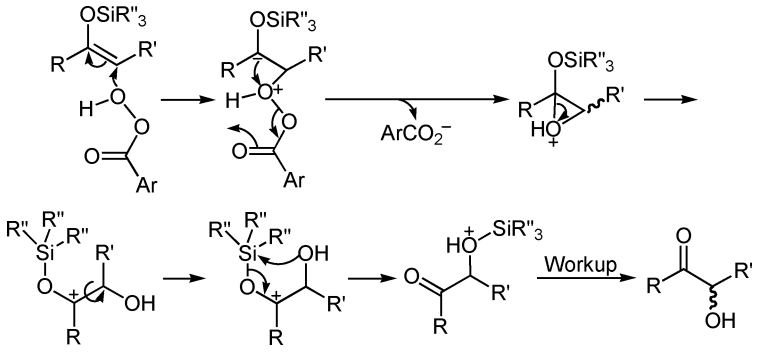


D. MODIFICATION

The oxidation of the silyl enolate has been extended by the application of DMDO rather than *m*-CPBA.

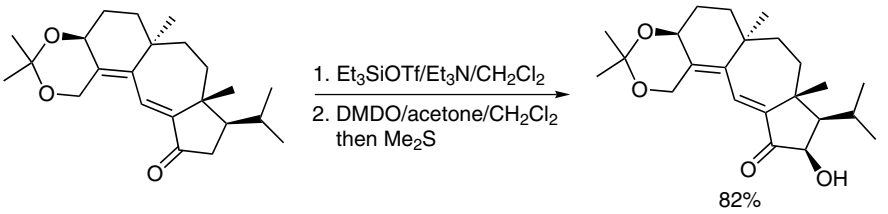
E. APPLICATIONS

This reaction has general application in the transformation of ketones into α-hydroxyl ketones.

F. RELATED REACTIONS

N/A

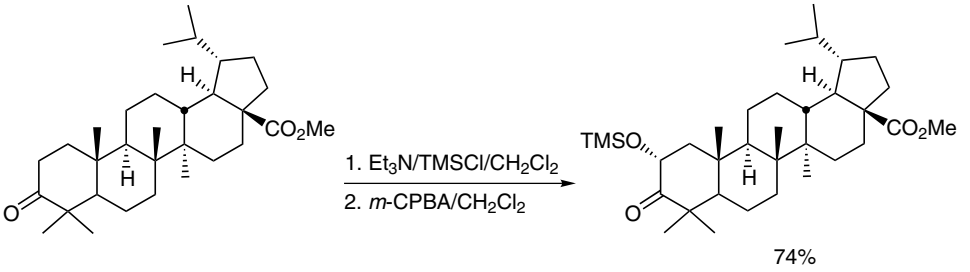
G. CITED EXPERIMENTAL EXAMPLES



Reference 4a.

To a 10-mL pear-shaped flask were added 8.5 mg 8α,11β-dimethyl-12β-isopropyl-5β,15-isopropylidenedioxy-14-keto-($\Delta^{1,2}$,$\Delta^{3,4}$)-tricycle (0.024 mmol, 1.0 eq.) and 1 mL CH_2Cl_2 under argon, followed by 33 μL Et_3N (0.24 mmol, 10.0 eq.) and 27 μL Et_3SiOTf (0.12 mmol, 5.0 eq.). The mixture was stirred for 10 min and then diluted with 5 mL EtOAc, washed with 1 mL saturated $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. This oil was azeotropically dried with toluene,

then dissolved in 2.4 mL CH_2Cl_2 in a 10-mL pear-shaped flask, and cooled to −78°C under argon. A solution of 0.52 μL DMDO (0.036 mmol, 1.5 eq.) in CH_2Cl_2 was added dropwise down the side of the flask. The resulting solution was stirred for 15 min at −78°C, and 27 μL Me_2S (0.37 mmol, 15 eq.) was added to quench the excess amount of DMDO. The quenched reaction solution was stirred for 5 min at −78°C, allowed to warm to room temperature, and then concentrated under reduced pressure. The residue was purified by flash column chromatography using EtOAc/hexanes (1:19 to 1:4) to afford 7.3 mg 8α,11β-dimethyl-13β-hydroxy-12β-isopropyl-5β,15-isopropylidenedioxy-14-keto-($\Delta^{1,2}$,$\Delta^{3,4}$)-tricycle as a colorless oil, in a yield of 82%. This compound can be further purified by recrystallization via vapor diffusion between EtOAc and hexanes to provide white needles, m.p. 184.6–186.4°C, $R_f = 0.28$ (hexane/EtOAc, 4:1).



Reference 5.

To a solution of 183 mg methyl 3-oxo-28-lupanoate (0.389 mmol) in 8 mL CH_2Cl_2 at –78°C under argon was added with stirring 0.54 mL triethylamine (3.87 mmol) followed by 0.352 mL trimethylsilyl trifluoromethanesulfonate (TMSOTf, 1.95 mmol). After 1 h at –78°C, the reaction was quenched by 3 mL saturated aqueous $NaHCO_3$ solution, and extracted with hexanes (3 × 3 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude silyl enol ether was dissolved in 8 mL CH_2Cl_2 at 0°C, and 10 mL precooled CH_2Cl_2 solution containing 107 mg *m*-CPBA (0.434 mmol) was added. The mixture was stirred for 2 h and quenched by 5 mL saturated aqueous $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 (3 × 5 mL), washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel using hexanes/EtOAc (97:3) as the eluent afforded 156 mg methyl 2-*O*-trimethylsilyl-3-oxo-28-lupanoate as a colorless oil, in a yield of 74%, $R_f = 0.52$ (hexanes/EtOAc, 9:1).

Other references related to the Rubottom oxidation are cited in the literature.[6]

H. REFERENCES

1. Rubottom, G. M.; Vazquez, M. A. and Pelegrin. D. R., *Tetrahedron Lett.,* **1974**, 4319.
2. Brook, A. G. and Macrae, D. M., *J. Organomet. Chem.,* **1974**, *77*, C19.
3. (a) Frontier, A. J.; Raghavan, S. and Danishefsky, S. J., *J. Am. Chem. Soc.,* **2000**, *122,* 6151. (b) Gleiter, R.; Staib, M. and Ackermann, U., *Liebigs Ann.*, **1995**, 1655. (c) Johnson, C. R.; Golebiowski, A. and Steensma, D. H., *J. Am. Chem. Soc.,* **1992**, *114*, 9414. (d) Gleiter, R. Kraemer, R.; Irngartinger, H. and Bissinger, C., *J. Org. Chem.,* **1992**, *57*, 252.

4. (a) Mandal, M.; Yun, H. D.; Dudley, G. B.; Lin, S. N.; Tan, D. S. and Danishefsky, S. J., *J. Org. Chem.,* **2005**, *70*, 10619. (b) Jauch, J., *Tetrahedron,* **1994**, *50*, 1203.

5. Deng, Y. H. and Snyder, J. K., *J. Org. Chem.,* **2002**, *67,* 2864.

6. (a) Yamaguchi, J.; Toyoshima, M.; Shoji, M.; Kakeya, H.; Osada, H. and Hayashi, Y., *Angew. Chem. Int. Ed.,* **2006**, *45*, 789. (b) Hiersemann, M. and Helmboldt, H., *Top. Curr. Chem.,* **2005**, *243*, 73. (c) Hartung, I. V. and Hoffmann, H. M. R., *Angew. Chem. Int. Ed.,* **2004**, *43*, 1934. (d) Christoffers, J.; Werner, T.; Unger, S. and Frey, W., *Eur. J. Org. Chem.,* **2003**, 425. (e) Sakaguchi, S.; Yamamoto, Y.; Sugimoto, T.; Yamamoto, H. and Ishii, Y., *J. Org. Chem.,* **1999**, *64,* 5954. (f) Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A. and DiGrandi, M. J., *J. Am. Chem. Soc.,* **1996**, *118*, 2843. (g) VanderRoest, J. M. and Grieco, P. A., *J. Org. Chem.,* **1996**, *61*, 5316. (h) Crimmins, M. T.; Jung, D. K. and Gray, J. L., *J. Am. Chem. Soc.,* **1993**, *115*, 3146. (i) Sakata, Y. and Ishii, Y., *J. Org. Chem.,* **1991**, *56*, 6233. (j) Rubottom, G. M.; Gruber, J. M.; Juve, H. D. and Charleson, D. A., *Org. Synth.,* **1986**, *64*, 118. (k) Rubottom, G. M. and Gruber, J. M., *J. Org. Chem.,* **1978**, *43*, 1599. (l) Rubottom, G. M.; Gruber, J. M.; Boeckman, R. K.; Ramaiah, M. and Medwid, J. B., *Tetrahedron Lett.,* **1978**, 4603. (m) Hassner, A.; Reuss, R. H. and Pinnick, H. W., *J. Org. Chem.,* **1975**, *40*, 3427.

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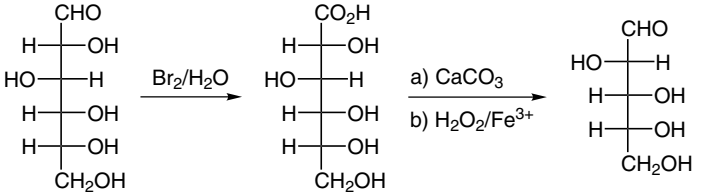
Ruff Degradation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Ruff in 1892.[1] It is a transformation of an aldose to its analog of one less carbon atom by oxidation of the original aldose into aldonic acid followed by the decarboxylation of the corresponding calcium salt of aldonic acid with hydrogen peroxide in the presence of ferric acetate [$Fe(OAc)_3$]. Therefore, this reaction is generally known as the Ruff degradation.[2] Occasionally, it is also referred to as the Ruff oxidative degradation[3] or Ruff reaction.[2w] For example, D-arabinose is easily prepared from calcium D-gluconate,[2u,4] and D-lyxose is degraded from calcium D-galactonate.[2u] In addition, this reaction can be used for the general conversion of α-hydroxy acids into aldehydes.[2s] Although the Ruff degradation has been widely used for the structural determination and the preparation of new sugars, it suffers from difficulty in separating the sugar from the gross quantities of organic and inorganic materials presenting in the reaction mixture.[2u] It has been reported that this reaction can be catalyzed by titanium-containing zeolites.[3c]

B. GENERAL REACTION SCHEME



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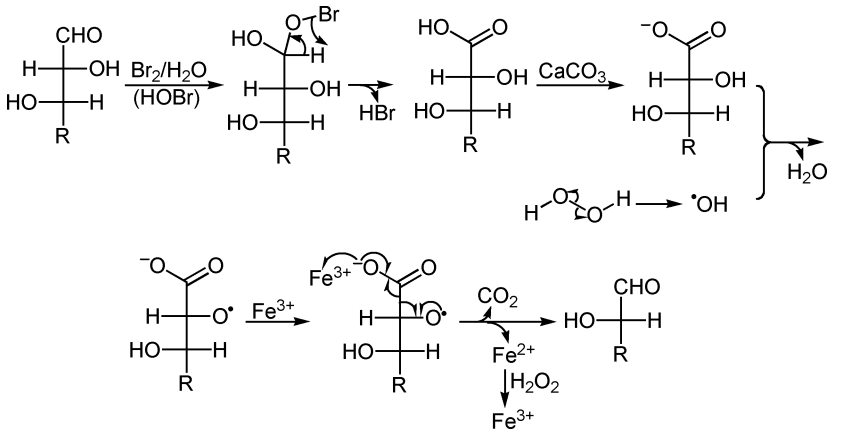
C. PROPOSED MECHANISMS

Displayed here is an illustration of the Ruff degradation.



D. MODIFICATION

This reaction has been optimized by the application of an active and reliable catalyst prepared by double decomposition of ferric sulfate with barium acetate.[5]

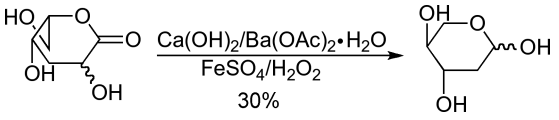
E. APPLICATIONS

This reaction has general application in the structural determination of carbohydrate.

F. RELATED REACTIONS

This reaction is related to the *Weerman Reaction*, *Wohl Degradation*, and *Fenton Reaction*.

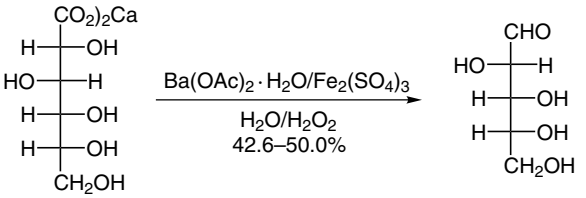
G. CITED EXPERIMENTAL EXAMPLES



Reference 2h.

To a stirred mixture of 1.716 g 3-deoxy-L-hexonolactone, 34 mL water, 442 mg calcium hydroxide, 272 mg barium acetate monohydrate, and 170 mg hydrous ferrous sulfate was added 2 mL 30% H_2O_2, and an additional 2 mL 30% H_2O_2 was added after 45 min of

stirring. Then the solution was kept at room temperature for 2 h with occasional stirring, and then treated with decolorizing carbon and filtered. The filtrate was passed successively through columns of Amberlite IR-120 (H^+) (40 mL) and Amberlite IR-4 (OH^-) (40 mL). Concentration in vacuo gave 430 mg of a yellow syrup, in a yield of 30%.



Reference 5.

A solution of 20.86 g barium acetate monohydrate (0.076 mol) in 60 mL water and a solution of 10.2 g ferric sulfate (0.0255 mol) in 60 mL water (equimolecular quantities) are poured into 2 L distilled water in a 4-L glass beaker. Calcium gluconate dihydrate (200 g, 0.43 mol) was then added, and the solution was heated to boil with stirring. The solution was then removed from the flame, allowed to settle, and filtered on a Buchner funnel precoated with filtercel. To the clear amber-colored filtrate, 1 L water was added, and the solution was cooled to 35°C, then 120 mL 30% H_2O_2 was added. Within a few minutes, an evolution of gas began, and the temperature rose spontaneously to ~ 55°C. The reaction was complete in about 30 min, as indicated by the sudden appearance of a dark purple color. After the mixture cooled to 40°C, an additional 120 mL 30% H_2O_2 was added, whereupon a new reaction took place very similarly. The dark turbid solution was then filtered through carbon on a Buchner funnel and concentrated to 250 mL under vacuum. To this solution was added 1500 mL methanol with shaking, and the granular precipitate was filtered on a Buchner funnel precoated with carbon and washed with 300 mL methanol. To the clear filtrate was added 900 mL ether with shaking. After 5 min of settling, the new granular precipitate was filtered on a carbon-coated Buchner funnel. The filtrate was concentrated to a syrup under vacuum. When it had become so stiff as barely to flow, it was taken up in ~100 mL warm methanol and poured out into an Erlenmeyer flask; another 25 mL methanol was used for rinsing. Crystallization took place readily without seeding. After a few hours in the refrigerator, the sugar was filtered, washed with MeOH and dried. The yield was 55–65 g or ~ 42.6–50% of the theoretical amount. It was recrystallized by being dissolved in two thirds its weight of water and filter with carbon rapidly while hot; five volumes of methanol was added. Sharp prisms of D-arabinose separated in a yield of 80% of the crude substance used. The product was dried at 60°C under vacuum for 2 h, m.p. 155.5–156.5°C.

Other references related to the Ruff degradation are cited in the literature.[6]

H. REFERENCES

1. (a) Ruff, O., *Ber.,* **1898**, *31*, 1573. (b) Ruff, O. and Meusser, A., *Ber.,* **1899**, *32*, 3672. (c) Ruff, O., *Ber.,* **1899**, *32*, 2273. (d) Fischer, E. and Ruff, O., *Ber.,* **1900**, *33*, 2142. (e) Ruff, O. and Ollendorff, G., *Ber.,* **1900**, *33*, 1798. (f) Ruff, O.; Meusser, A. and Kohn, H., *Ber.,* **1901**, *34*, 1362. (g) Ruff, O.; Kohn, H.; Meusser, A. and Franz, A., *Ber.,* **1902**, *35*, 2360.

2. (a) Stapley, J. A. and BeMiller, J. N., *Carbohydr. Res.,* **2007**, *342*, 407. (b) Lukac, L.; Krihova, A.; Matulova, M. and Petrus, L., *Chem. Papers,* **1993**, *47*, 124. (c) Schmidt, M. A. and Jann, K., *Eur. J. Biochem.,* **1983**, *131*, 509. (d) Weckesser, J.; Drews, G.; Indira, R. and Mayer, H., *J. Bacteriology,* **1977**, *130*, 629. (e) Buchanan, K. J.; Goosen, A. and Lovelock, J. D., *South Afri. J. Chem.,* **1977**, *30*, 191. (f) Weckesser, J.; Mayer, H.; Drews, G. and Fromme, I., *J. Bacteriology,* **1975**, *123*, 449. (g) Dröge, W.; Lehmann, V.; Lüderitz, O. and Westphal, O., *Eur. J. Biochem.,* **1970**, *14*, 175. (h) Kuzuhara, H. and Fletcher, H. G., *J. Org. Chem.,* **1968**, *33*, 1816. (i) Feather, M. S. and Harris, J. F., *J. Am. Chem. Soc.,* **1967**, *89*, 5661. (j) Whistler, R. L. and BeMiller, J. N., *Methods Carbohydr. Chem.,* **1962**, *1*, 79. (k) White, E. V., *Methods Carbohydr. Chem.,* **1962**, *1*, 77. (l) Wood, H. B. and Fletcher, H. G., *J. Org. Chem.,* **1961**, *26*, 1969. (m) Sowden, J. C. and Strobach, D. R., *J. Am. Chem. Soc.,* **1960**, *82*, 3707. (n) Wolfrom, M. L.; Webber, J. M. and Shafizadeh, F., *J. Am. Chem. Soc.,* **1959**, *81*, 1217. (o) Schaffer, R., *J. Am. Chem. Soc.,* **1959**, *81*, 5452. (p) Pazur, J. H., *J. Am. Chem. Soc.,* **1955**, *77*, 1015. (q) Sowden, J. C., *J. Am. Chem. Soc.,* **1954**, *76*, 3541. (r) Sowden, J. C. and Spriggs, A. S., *J. Am. Chem. Soc.,* **1954**, *76*, 3539. (s) MacGee, J. and Doudoroff, M., *J. Biol. Chem.,* **1954**, *210*, 617. (t) Sowden, J. C. and Kuenne, D. J., *J. Am. Chem. Soc.,* **1953**, *75*, 2788. (u) Fletcher, H. G.; Diehl, H. W. and Hudson, C. S., *J. Am. Chem. Soc.,* **1950**, *72*, 4546. (v) Hockett, R. C., *J. Am. Chem. Soc.,* **1935**, *57*, 2265. (w) Swan, D. R. and Evans, W. L., *J. Am. Chem. Soc.,* **1935**, *57*, 200. (x) Hockett, R. C., *J. Am. Chem. Soc.,* **1935**, *57*, 2260.

3. (a) Hourdin, G.; Germain, A.; Moreau, C. and Fajula, F., *J. Catal.,* **2002**, *209*, 217. (b) Hourdin, G.; Germain, A.; Moreau, C. and Fajula, F., *Special Pub.-Royal Soc. Chem.,* **2001**, *266*, 176. (c) Hourdin G.; Germain A.; Moreau C. and Fajula F., *Catal. Lett.,* **2000**, *69*, 241.

4. Stanek, J.; Cerny, M.; Kocourek, J. and Pacak, J., *The Monosaccharides*, Academic Press, New York, **1963**, p. 114.

5. Hockett, R. C. and Hudson, C. S., *J. Am. Chem. Soc.,* **1934**, *56*, 1632.

6. (a) Marcq, O.; Barbe, J.-M.; Trichet, A. and Guilard, R., *Carbohydr. Res.,* **2001**, *333*, 233. (b) Aspinall, G. O.; Krishnamurthy, T. N.; Furda, I. and Khan, R., *Can. J. Chem.* **1975**, *53*, 2171. (c) de Wilt, H. G. J. and van der Baan, H. S., *Ind. Eng. Chem. Prod. Res. Dev.,* **1972**, *11*, 374. (d) Bagdian, G.; Dröge, W.; Kotelko, K.; Lüderitz, O. and Westphal, O., *Biochem. Z.,* **1966**, *344*, 197. (e) Murray, D. H. and Prokop, J., *J. Pharm. Sci.,* **1965**, *54*, 1637. (f) Isbell, H. S.; Holt, N. B. and Frush, H. L., *J. Res. Nat. Bureau Standards,* **1956**, *57*, 95. (g) Neish, A. C., *Can. J. Chem.,* **1954**, *32*, 334.

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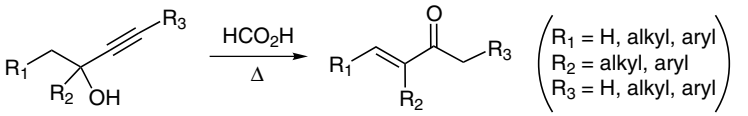
Rupe Rearrangement
(Rupe Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Rupe and Kambli in 1926.[1] It is a formic acid-promoted thermal transformation[2] of tertiary α-acetylenic alcohols into α,β-unsaturated ketones, and is generally known as the Rupe reaction[2c,3] or Rupe rearrangement.[2,3c,3e,4] Besides formic acid, other acids[2c] and even the salt of silver carbonate[4b] can trigger this reaction as well. In many cases, this reaction is competed by the *Meyer-Schuster Rearrangement*, which also leads to the formation of α,β-unsaturated ketones or aldehydes.[2a,3e,4d,5] However, there is a distinct difference between these two reactions. For example, the Rupe rearrangement involves dehydration to form a vinyl acetylene intermediate, and the hydration of this intermediate gives the α,β-unsaturated ketone;[2a,2c,3a,3d,3e,5] while the *Meyer-Schuster Rearrangement* is a 1,3- or allylic shift to form an allenic carbonium intermediate, and the hydration of this intermediate leads to a different α,β-unsaturated ketone,[2c] and an aldehyde from the rearrangement of a terminal acetylene.[2a] In certain cases, only the Rupe rearrangement takes place, as in the case of phenylethynylcarbinol with a methoxy group at the *para*-position of the phenyl group.[3e]

B. GENERAL REACTION SCHEME



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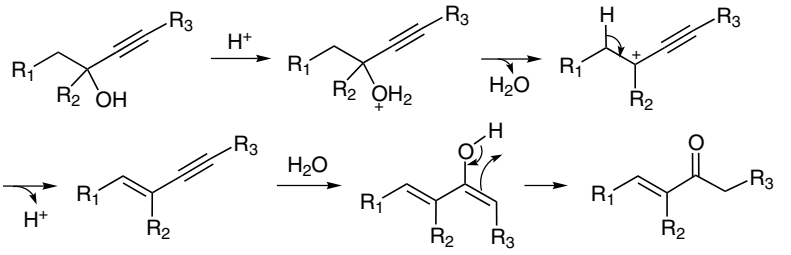
C. PROPOSED MECHANISMS

This reaction involves the protonation of a tertiary alcohol and dehydration to form a tertiary carbonium ion that expels the α-proton to form an enyne intermediate. Hydration of the acetylene moiety yields the α,β-unsaturated ketone.[2a] A general illustration of this reaction is provided below, as well as the possible competition to yield the *Meyer-Schuster Rearrangement* product.



D. MODIFICATION

This reaction has been initiated by the application of silver carbonate.[4b]

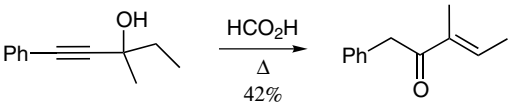
E. APPLICATIONS

This reaction has general application in the preparation of α,β-unsaturated ketones.

F. RELATED REACTIONS

This reaction is related to the *Meyer-Schuster Rearrangement.*

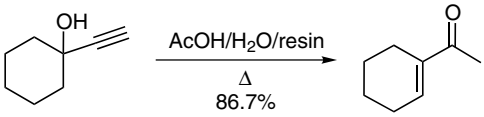
G. CITED EXPERIMENTAL EXAMPLES



Reference 3e.

The mixture of 38 g methylethyl-(phenylethynyl)carbinol (0.218 mol) and 300 mL 88% formic acid was refluxed vigorously for 3 h. The reaction mixture became cloudy and a clear red oil rose to the surface. After cooling, the mixture was transferred to a beaker and neutralized with solid $NaHCO_3$. The resulting neutral mixture was transferred into a separation funnel, and extracted with benzene (4×50 mL). The combined organic layers

were washed with brine and dried, and the benzene was removed by distillation. The residue was fractionated under reduced pressure using a modified Claisen flask to afford 16.1 g 1-phenyl-3-methyl-pent-3-ene-2-one as a pale yellow viscous liquid, in a yield of 42%, b.p., 154–157°C at 24 mmHg.



Reference 6.

A stirred mixture of 39.0 g 1-ethynylcyclohexanol, 100 mL acetic acid, 10 mL H_2O, and 20 g resin was refluxed for 45 min. As soon as the reflux temperature had been reached, the resin began to darken, and in a few min had changed from the original brown to almost black. After cooling, the resin was filtered off and washed with ether. The filtrate and washings were diluted with water and made slightly alkaline by the cautious addition of 40% NaOH solution. This mixture was extracted with ether, and the combined ether layers were washed with brine and filtered through anhydrous $MgSO_4$. Upon removal of ether, the residue was distilled to afford 33.8 g 1-acetyl cyclohexene, in a yield of 86.7%, b.p. 96–98°C at 22 mmHg.

Other references related to the Rupe rearrangement are cited in the literature.[7]

H. REFERENCES

1. Rupe, H. and Kambli, E., *Helv. Chim. Acta,* **1926**, *9,* 672.
2. (a) Swaminathan, S. and Narayanan, K. V., *Chem. Rev.,* **1971**, *71*, 429. (b) Gibson, H. W., *Chem. Rev.,* **1969**, *69*, 673. (c) Hennion, G. F.; Davis, R. B. and Maloney, D. E., *J. Am. Chem. Soc.,* **1949**, *71*, 2813.
3. (a) Dabdoub, M. J.; Justino, A.; Guerrero, P. G. and Zukerman-Schpector, J., *Organometallics,* **1998**, *17,* 1901. (b) Gomez, L.; Calas, P. and Commeyras, A., *J. Chem. Soc., Chem. Commun.,* **1985**, 1493. (c) Hasbrouck, R. W. and Kiessling, A. D. A., *J. Org. Chem.,* **1973**, *38*, 2103. (d) Huffman, J. W. and Arapakos, P. G., *J. Org. Chem.,* **1965**, *30*, 1604. (e) Smissman, E. E.; Johnsen, R. H.; Carlson, A. W. and Aycock, B. F., *J. Am. Chem. Soc.,* **1956**, *78*, 3395.
4. (a) Weinmann, H.; Harre, M.; Neh, H.; Nickisch, K.; Skoetsch, C. and Tilstam, U., *Org. Proc. Res. Dev.,* **2002**, *6*, 216. (b) Wang, X. H.; Ni, Z. J.; Lu, X. J.; Hollis, A.; Banks, H.; Rodriguez, A. and Padwa, A., *J. Org. Chem.,* **1993**, *58*, 5377. (c) Olah, G. A. and Fung, A. P., *Synthesis,* **1981**, 473. (d) Edens, M.; Boerner, D.; Chase, C. R.; Nass, D. and Schiavelli, M. D., *J. Org. Chem.,* **1977**, *42*, 3403. (e) Merkel, D., *Zeitsch. Chem.,* **1969**, *9*, 63. (f) Sharefkin, J. G. and Goghosian, E. M., *Anal. Chem.,* **1961**, *33*, 640. (g) Parham, W. E.; Wheeler, E. L.; Dodson, R. M. and Fenton, S. W., *J. Am. Chem. Soc.,* **1954**, *76*, 5380. (h) Heilmann, R. and Glenat, R., *Bull. Soc. Chim. Fr.,* **1954**, 59. (i) Sobotka, H. and Bloch, E., *Chem. Rev.,* **1943**, *34*, 435.
5. Jadot, J. and Doyen, N., *Bull. Soc. Roy. Sci. Liege,* **1955**, *24*, 2.
6. Newman, M. S., *J. Am. Chem. Soc.,* **1953**, *75*, 4740.
7. (a) Koval'skaya, S. S.; Kozlov, N. G. and Dikusar, E. A., *Russ. J. Org. Chem.,* **2005**, *41*, 832. (b) Koval'skaya, S. S.; Kozlov, N. G. and Dikusar, E. A., *Russ. J. Org. Chem.,* **2004**, *40*, 668. (c) Amato, C. and Calas, P., *Synthesis*, **2003**, 2709. (d) Buser, D.; Pauling, H.; Thum, A. and Bonrath, W., *Molecules,* **2002**, *7*, 341. (e) Stark, H.; Sadek, B.; Krause, M.; Hüls, A.; Ligneau,

X.; Ganellin, C. R.; Arrang, J.-M.; Schwartz, J.-C. and Schunack, W., *J. Med. Chem.* **2000,** *43*, 3987. (f) Lukyanov, S. M.; Koblik, A. V. and Muradyan, L. A., *Russ. Chem. Rev.,* **1998**, *67*, 817. (g) Freeman, J. P., *J. Org. Chem.,* **1957**, *22*, 1608. (h) Ansell, M. F.; Hancock, J. W. and Hickinbottom, W. J., *J. Chem. Soc.,* **1956**, 911. (i) Heilman, R. and Glenet, R., *Compt. Rend.,* **1952**, *234*, 1557. (j) Price, C. C. and Meisel, S. L., *J. Am. Chem. Soc.,* **1947**, *71*, 1497. (k) Hurd, C. D. and Christ, R. E., *J. Am. Chem. Soc.,* **1937**, *59*, 118. (l) Rupe, H.; Messner, W. and Kambli, E., *Helv. Chim. Acta,* **1928**, *11*, 449. (m) Rupe, H. and Giesler, L., *Helv. Chim. Acta,* **1928**, *11*, 656. (n) Rupe, H.; Wirz, A. and Lotter, P., *Helv. Chim. Acta,* **1928**, *11*, 965.

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Sabatier-Senderens Reduction

A. GENERAL DESCRIPTION OF THE REACTION

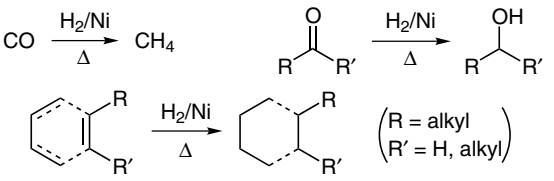
This reaction can be traced back to Debus's transformation of hydrocyanic acid into methylamine over platinum in 1863, De Wilde's hydrogenation of acetylene into ethylene and ethane in 1874,[1] and Mond's extensive work from 1890 to 1895.[2] However, it was in 1899 that Sabatier and Senderens established nickel-based hydrogenation[3] and converted the unsaturated organic molecules (e.g., ketones, aldehydes, alkenes and aromatics) into corresponding saturated compounds (i.e., alcohols, hydrocarbons) by passing the vapor of organic molecules and hydrogen over hot, finely divided nickel. This nickel-based vapor phase hydrogenation became one of the most practically useful reactions and won Sabatier the Nobel Prize in 1912.[1] It is generally known as the Sabatier-Senderens reduction.[4]

This reaction is different from reductions using nascent hydrogen as the reducing agent, such as amalgam of sodium in alcohol (alkaline condition) and or zinc or tin with hydrochloric acid (acidic medium). In this reaction, the purity of nickel and reaction temperature are found to be critical for successful hydrogenation.[1] For example, trace amounts of sulfur, bromine, or iodine will deactivate the nickel catalyst; in addition, it has been found that each hydrogenation process takes place only within a well-defined temperature range,[1] as evidenced by the hydrogenation of benzene to cyclohexane at temperatures ranging from 70° to 190°C, with an optimal temperature between 170° and 190°C, and the further reduction of benzene to methane accompanied by the deposited carbon on nickel at temperatures > 300°C.[5] Under the correct hydrogenation conditions, Sabatier et al. successfully converted oleic acid into stearic acid, acetone to isopropanol, carbon monoxide into methane or a gaseous mixture rich in methane, phenol and *p*-cresol into cyclohexanol and *p*-methylcyclohexanol, benzene to cyclohexane, and naphthalene to tetralin, etc.[1] All these reductions afford the expected products, except for the hydrogenation of naphthalene; other

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

reducing methods may lead to the unexpected products, as demonstrated by the reduction of benzene with hydroiodic acid at 250°C to afford methyl cyclopentane,[1] and the hydrogenation of only one phenyl group of triphenylcarbinol over the Adam's platinum oxide catalyst.[6] At the same time, Sabatier et al. also found that the reduced cobalt, iron, copper, and powdered platinum have catalytic activities similar to nickel. Copper in particular is known to be superior to nickel during the hydrogenation of nitrobenzene to aniline, due to its insensitivity to accidental impurities.[1] It is interesting that Sabatier was able to reduce naphthalene into only tetralin,[7,8] other researchers have successfully converted naphthalene into decalin over nickel.[9]

B. GENERAL REACTION SCHEME

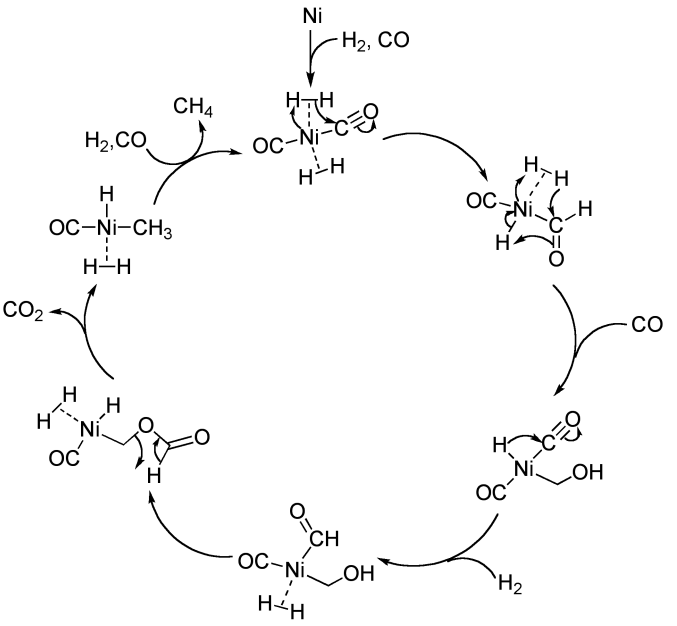


C. PROPOSED MECHANISMS

Although Sabatier proposed that the hydrogenation occurs via nickel perhydride (NiH_2) from the well-prepared and pure nickel, via a poorer hydride from nickel with impurities, or at a very high temperature,[1] it is clear that nickel can absorb a great deal of hydrogen, as indicated by the current use of the nickel hydrogen (Ni/H_2) battery cell.[10] On the other hand, the hydrogenation of carbon monoxide into methane is assumed to involve the formation of an intermediate complex, CHxO, on the nickel surface[11] or an active carbon intermediate from the dissociation of carbon monoxide,[11] which is hydrogenated into methane. In addition, it has been proposed that hydrogen or non-hydrogen gas assists the dissociation of carbon monoxide.[11a] Alternatively, the Sabatier-Senderens reduction may proceed in another route, in which nickel inserts into hydrogen via oxidative addition, and the resulting intermediate forms a coordination complex with carbon monoxide; then a series of transformations, including acyl transfer and reductive elimination, take place until the formation of methane. In addition, the deposited carbon on nickel might be caused by dehydrogenation occurring at an elevated temperature. Displayed here is a tentative mechanism (next page) to illustrate the formation of methane from carbon monoxide.

D. MODIFICATION

In terms of hydrogenation, the Sabatier-Senderens reduction has been extensively modified, as shown by the *Fischer-Tropsch Synthesis* (or process), the *Adkins Catalyst*, and *Raney-Nickel Catalyst*. In addition, the silica black-supported nickel catalyst,[12] and nickel-based complex reducing agents (Nic, e.g. NaH-RONa-$Ni(OAc)_2$),[13] have also been developed, the latter is a heterogeneous hydrogenation catalyst that works at atmospheric pressure.



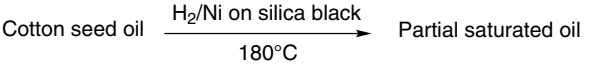
E. APPLICATIONS

This reaction has an important application in organic synthesis, especially in the transformation of carbon monoxide or carbon dioxide into organic compounds.

F. RELATED REACTIONS

This reaction is related to the *Fischer-Tropsch Synthesis* and *Raney-Nickel*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 12.

To a reaction flask were added 50 mL cotton seed oil and 2.5 g silica black-supported nickel catalyst, and the mixture was agitated until complete suspension was attained. Then the mixture was stirred with a mechanical stirrer for 10 min, and the flask was placed in a furnace and connected with a hydrogen tube that reached to the bottom of the flask. The flask was maintained at 180°C for different time intervals, while hydrogen was bubbled through at the rate of 400–450 bubbles/min at ordinary atmospheric pressure. At the end of hydrogenation period, the experiment was stopped, and the product was filtered through asbestos at 140°C. The degree of unsaturation for the oil was verified by iodine numbers.

Other references related to the Sabatier-Senderens reduction are cited in the literature.[14]

H. REFERENCES

1. Sabatier, P., in *Nobel Lectures, Chemistry 1901–1921*, Elsevier Publishing, Amsterdam, **1966**.
2. (a) Mond, L.; Langer, C. and Quincke, F., *J. Chem. Soc.,* **1890**, *57*, 749. (b) Mond, L.; Langer, C. and Quincke, F., *Chem. News,* **1890**, *62*, 97. (c) Mond, L. and Langer, C., *J. Soc. Chem., Trans.,* **1891**, *59*, 1090. (d) Mond, L. and Quincke, F., *J. Chem. Soc., Trans.,* **1891**, *59*, 604. (e) Mond, L., *J. Soc. Chem. Ind.,* **1895**, *14*, 945.
3. Sabatier, P. and Senderens, J. B., *Compt. Rend.,* **1899**, *128*, 1173.
4. Sabatier, P. and Mailhe, A., *Ann. Chim. Phys.,* **1908**, *10*, 527.
5. Bancroft, W. D. and George, A. B., *J. Phys. Chem.,* **1931**, *35*, 2219.
6. Levene, P. A. and Stevens, P. G., *J. Biol. Chem.,* **1930**, *89*, 471.
7. Sabatier, P. and Senderens, J. B., *Compt. Rend.,* **1901**, *132*, 1254.
8. (a) Lush, E. I., *Brit. Pat.,* Jan. 24, **1929**, 304,403. (b) Lush, E. I., *J. Soc. Chem. Ind.,* **1927**, *46*, 454.
9. (a) Cerveny, W. J. and Corson, B. B., *J. Am. Chem. Soc.,* **1944**, *66*, 2123. (b) Smith, H. M.; Rall, H. T. and Grandone, P., *U. S. Bureau of Mines. Tech. Paper,* **1938**, **587** (c) Leroux, H., *Compt. Rend.,* **1904**, *139*, 672.
10. (a) Button, R.; Pease, G.; Birchenough, A. and Petrik, J., *Ni/H Cell Short Circuit Test*, Electrical Systems Division, NASA LeRC, Preliminary Test Report 14, Apr. 20, **1992**. (b) Sobornitskii, V. I. and Krapivnyi, N. G., *Material Science,* **1992**, *27*, 239. (c) Visscher, W. and Barendrecht, E., *J. Appl. Electrochem.,* **1980**, *10*, 269.
11. (a) Sehested, J.; Dahl, S.; Jacobsen, J. and Rostrup-Nielsen, J. R., *J. Phys. Chem. B,* **2005**, *109*, 2432. (b) Lee, P.-I. and Schwarz, J. A., *Ind. Eng. Chem. Proc. Des. Dev.,* **1986**, *25*, 76.
12. Williams, L. R. and Jacobson, C. A., *Ind. Eng. Chem.,* **1934**, *26*, 800.
13. Brunet, J.-J.; Gallois, P. and Caubere, P., *J. Org. Chem.,* **1980**, *45*, 1937.
14. (a) Samuel, P., *Bull. Catal. Soc. India,* **2003**, *2*, 82. (b) Grabke, H. J., *Mater. Corr.,* **1998**, *49*, 317. (c) Alstrup, I., *J. Catal.,* **1995**, *151*, 216. (d) Coenen, J. W. E.; van Nisselroy, P. F. M. T.; de Croon, M. H. J. M.; van Dooren, P. F. H. A. and van Meerten, R. Z. C., *Appl. Catal.,* **1986**, *25*, 1. (e) McNaughton, N. J.; Abell, P. I.; Wright, I. P.; Fallick, A. E. and Pillinger, C. T., *J. Phys. E.: Sci. Instrum.,* **1983**, *16*, 505. (f) Spencer, N. D. and Somorjai, G. A., *Rep. Prog. Phys.,* **1983**, *46*, 1. (g) Harms, A.; Höhlein, B.; Jørn, E. and Skov, A., *Oil Gas J.,* **1980**, *78*, 120. (h) Goodmann, D. W.; Kelley, R. D.; Madey, T. E. and White, J. M., *J. Catal.,* **1980**, *64*, 479. (i) Rostrup-Nielsen, J. R. and Pedersen, K., *J. Catal.,* **1979**, *59*, 395. (j) Bresler, S. A. and Ireland, J. D., *Chem. Eng.,* **1972**, *1*, 94. (k) Gueron, J. and Magat, M., *Ann. Rev. Phys. Chem.,* **1971**, *22*, 1. (l) Shuikin, N. I. and Erivanskaya, L. A., *Russ. Chem. Rev.,* **1960**, *29*, 309. (m) Bailey, A. E., *Ind. Eng. Chem.,* **1952**, *44*, 990. (n) Litkenhous, E. E., *Ind. Eng. Chem.,* **1939**, *31*, 1059. (o) Litkenhous, E. E. and Mann, C. A., *Ind. Eng. Chem.,* **1937**, *29*, 934. (p) Adkins, H.; Cramer, H. I. and Connor, R., *J. Am. Chem. Soc.,* **1931**, *53*, 1402. (q) Adkins, H. and Cramer, H. I., *J. Am. Chem. Soc.,* **1930**, *52*, 4349. (r) Adkins, H.; Connor, R. and Cramer, H., *J. Am. Chem. Soc.,* **1930**, *52*, 5192. (s) Sabatier, P., *Ind. Eng. Chem.,* **1926**, 1005. (t) Gauger, A. W., *J. Am. Chem. Soc.,* **1924**, *46*, 674. (u) Sabatier, P. and Senderens, J. B., *Bull. Soc. Chim.,* **1907**, *[4] 1*, 107. (v) Sabatier, P. and Senderens, J. B., *Ann. Chim. Phys.,* **1905**, *[8] 4*, 368. (w) Sabatier, P. and Mailhe, A., *Compt. Rend.,* **1904**, *139*, 345. (x) Sabatier, P. and Senderens, J. B., *Compt. Rend.,* **1902**, *134*, 514. (y) Sabatier, P. and Senderens, J. B., *Compt. Rend.,* **1901**, *132*, 1255. (z) Sabatier, P. and Senderens, J. B., *Compt. Rend.,* **1901**, *132*, 210.

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Saegusa Cyclization
(Saegusa Indole Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Saegusa, et al. in 1977.[1] It is the synthesis of indole and 2- or 3-substituted indole derivatives by means of the lithiation of *ortho*-alkyl phenyl isocyanide and subsequently intramolecular cyclization. Therefore, it is known as the Saegusa cyclization.[2] In this reaction, the treatment of *ortho*-alkyl phenyl isocyanide with two equivalents of base such as LDA or LiTMP in diglyme at low temperature followed by intramolecular cyclization leads to the formation of simple indole, while the reaction between *o*-lithomethylphenyl isocyanide and an electrophile (e.g., alkyl halide, epoxide, etc.) followed by lithiation and ring closure produces 3-substituted indoles.[1] This reaction is solvent dependent and can give indoles in quantitative yields.[1] For example, the lithiation of *o*-tolyl isocyanide by LDA in ether or THF results in the low yield of indole, along with the formation of a substantial amount of *N*,*N*-diisopropyl-*N*′-(*o*-tolyl)-formamidine.[1] This is probably attributed to the strong coordination from the two oxygen atoms in diglyme to the lithium cation, whereas only one oxygen atom exists in ether, THF, or monoglyme. Furthermore, *o*-(acylmethyl)phenyl isocyanides prepared from the acylation of *o*-lithomethylphenyl isocyanide with allyl carboxylates can yield 3-acyl indoles or 2-alkyl indoles by the treatment with cuprous oxide or acid.[3]

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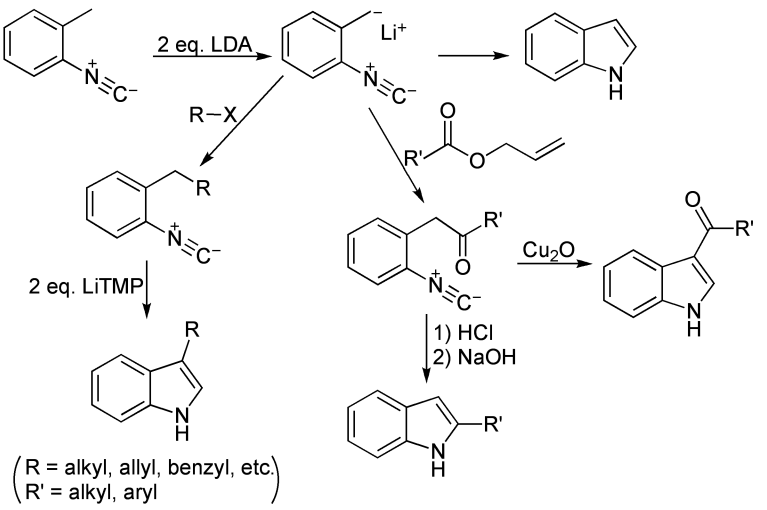
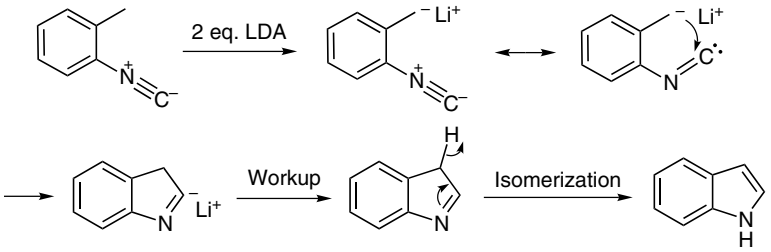
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

A simple mechanism is provided below for the preparation of indole.



D. MODIFICATION

This reaction has been modified by the activation of the *ortho*-benzylic proton with ruthenium complexing to tetramethyl ethylene diphosphine.[4] In addition, the *o*-alkynyl phenylisocyanide has been converted into indolene or indole derivatives via radical initiated cyclization.[5]

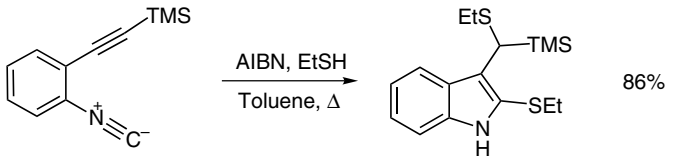
E. APPLICATIONS

This reaction has certain application in the preparation of indole derivatives.

F. RELATED REACTIONS

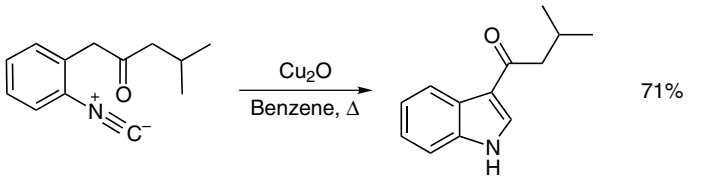
This reaction is related to the *Madelung Indole Synthesis*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 5.

A mixture of 1.13 g *ortho*-isonitrile phenyl trimethylsilyl acetylene (5.68 mmol), 2.10 ethanethiol (28.4 mmol), 0.14 g AIBN (0.85 mmol), and 142.0 mL toluene was refluxed for 15 min and then concentrated in vacuo. The residue was purified by alumina column chromatography using hexanes/EtOAc (10:1) as the eluent to afford 1.57 g 2-ethylthio-3-(1-trimethylsilyl-1′-ethylthio)methyl indole as a pale yellow solid, in a yield of 86%, m.p. 94–96°C.



Reference 3.

A mixture of 302 mg *o*-[(3-methylbutyroyl)methyl]phenyl isocyanide (1.5 mmol) and 29 mg Cu_2O (0.2 mmol) in 5 mL benzene was refluxed under nitrogen for 2 h and monitored by IR for the characteristic IR peak of the isonitrile group. The reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by silica gel column chromatography using $CHCl_3$/EtOAc (1:1) to afford 71% 3-(isobutyroyl)indole, m.p. 135.5–137.0°C, $R_f = 0.76$ ($CHCl_3$/EtOAc, 1:1).

Other references related to the Saegusa indole synthesis are cited in the literature.[6]

H. REFERENCES

1. Ito, Y.; Kobayashi, K. and Saegusa, T., *J. Am. Chem. Soc.,* **1977**, *99*, 3532.
2. Haeflinger, W. and Knecht, H., *Tetrahedron Lett.,* **1984**, *25*, 289.
3. Ito, Y.; Kobayashi, K. and Saegusa, T., *J. Org. Chem.,* **1979**, *44*, 2030.
4. Jones, W. D. and Kosar, W. P., *J. Am. Chem. Soc.,* **1986**, *108*, 5640.
5. Rainier, J. D. and Kennedy, A. R., *J. Org. Chem.,* **2000**, *65,* 6213.

6. (a) Kamijo, S. and Yamamoto, Y., *J. Org. Chem.,* **2003**, *68*, 4764. (b) Chauder, B.; Green, L. and Snieckus, V., *Pure & Appl. Chem.,* **1999**, *71*, 1521. (c) Hsu, G. C.; Kosar, W. P. and Jones, W. D., *Organometallics,* **1994**, *13*, 385. (d) Michelin, R. A.; Facchin, G.; Braga, D. and Sabatino, P., *Organometallics,* **1986**, *5*, 2265. (e) Ito, Y.; Kobayashi, K.; Seko, N. and Saegusa, T., *Bull. Chem. Soc. Jpn.,* **1984**, *57*, 73. (f) Ito, Y.; Inubushi, Y.; Sugaya, T.; Kobayashi, K. and Saegusa, T., *Bull. Chem. Soc. Jpn.,* **1978**, *54*, 1186.

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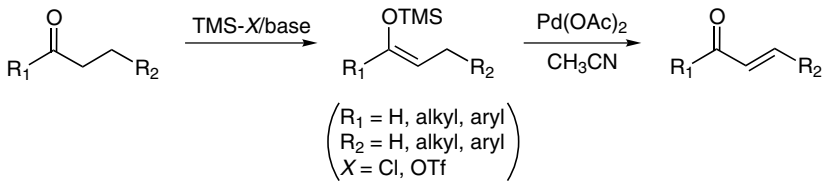
Saegusa Oxidation
(Saegusa-Ito Oxidation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Saegusa et al. in 1978.[1] It is a two-step process for the regioselective conversion of a ketone into an α,β-unsaturated ketone, involving the transformation of the ketone into a silyl enol ether and palladium (II) acetate (i.e., $Pd(OAc)_2$) mediated dehydrosilylation in acetonitrile. Therefore, this reaction is generally known as the Saegusa oxidation.[2] Occasionally, it is also referred to as the Saegusa-Ito oxidation[3] or Saegusa-Ito reaction.[4] Currently, a variety of protocols have been developed for the preparation of silyl enol ethers, including TMSCl/LHMDS,[5] TMSCl/LDA,[6] TMSCl/LDA/Et_3N,[2h] TMSCl/LiTMP,[4] TMSOTf/Et_3N,[7] TMSOTf/2,6-lutidine,[2d] and TMSOTf/EtN(i-Pr)$_2$.[3b] Although this reaction normally requires a stoichiometric amount of palladium (II) acetate,[1,8] it also takes place when less than an equivalent[1,9] of or even a catalytic amount of $Pd(OAc)_2$[2e,2h,4,8–10] is present, if an oxidating reagent exists in the reaction system. These oxidants include oxygen,[2e,8a] diallyl carbonate,[4] benzoquinone,[2h] iodoxybenzoic acid (IBX),[11] t-BuOOH,[10] and $Cu(OAc)_2$.[9] Even though this reaction has become one of the most convenient reactions for the preparation of α,β-unsaturated ketones,[8b] sometimes it still fails.[2a,3a,9,12] However, the modification of the standard protocol by the addition of water[9] or base[2g,3a] often works properly.

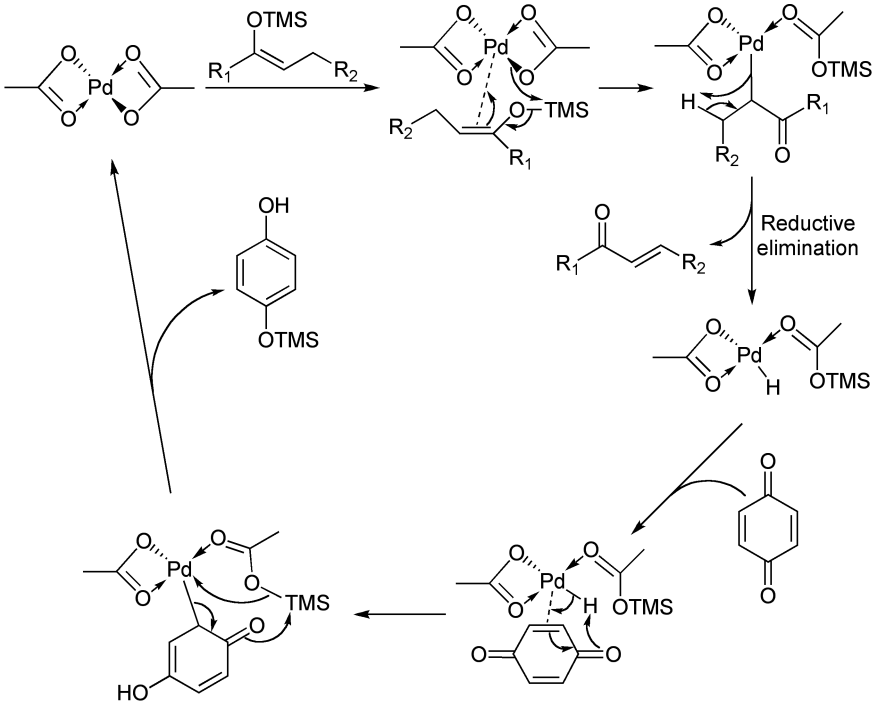
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

In $Pd(OAc)_2$, Pd(II) has 8 out-shell electrons in total, and requires 10 more electrons to satisfy the 18-e rule. Because acetate is a bidenate ligand, $Pd(OAc)_2$ itself can in fact bind to only one more ligand, which possibly is the double bond of the silyl enol ether. The migration of the silyl group leads to the addition of palladium to the double bond, and reductive elimination of palladium results in the α,β-unsaturated ketone. If an oxidant exists in the reaction system, the palladium species from the reductive elimination is oxidized to Pd(II), which enters the catalytic cycle again. An illustrative mechanism focusing on the dehydroxysilylation in CH_3CN is displayed below, using quinone as the oxidant.



D. MODIFICATION

This reaction has been extensively modified to a catalytic version by the use of different oxidants.[2e,2h,4,8–10] Especially, different α,β-unsaturated ketones can be obtained from the same silyl enol ether by the use of different bases, such as Na_2HPO_4 and $CsCO_3$.[10]

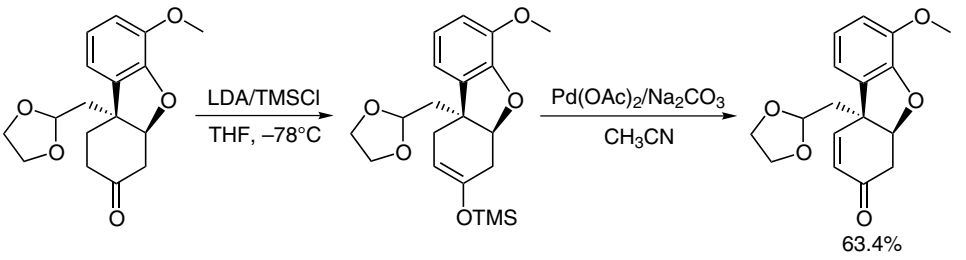
E. APPLICATIONS

This reaction has been widely used for the preparation of α,β-unsaturated ketones, and the cleavage of tertiary cyclobutanols.[8a]

F. RELATED REACTIONS

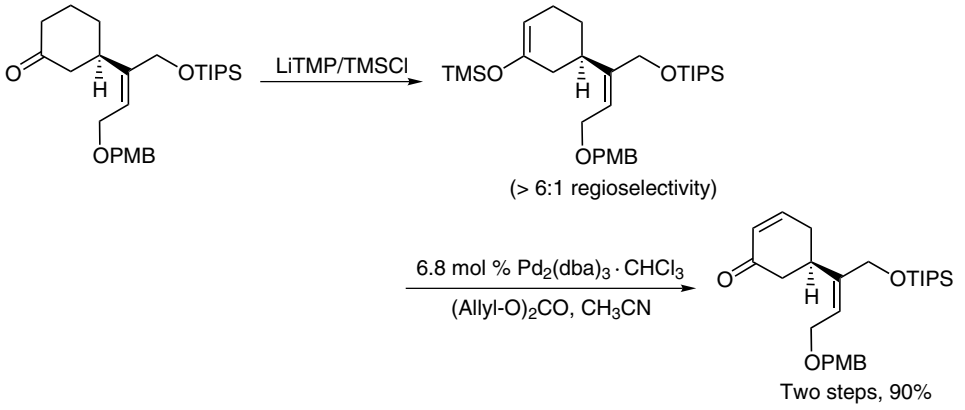
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3a.

To a solution of LDA freshly prepared from 1.70 mL diisopropylamine (12 mmol) and 4 mL 1.5 M *n*-BuLi in hexane (6 mmol) in 10 mL THF at –78°C under argon was added dropwise a solution of 600 mg ketone (2 mmol) in 4 mL THF. After 15 min, 5 mL chlorotrimethylsilane (4 mmol) was added, and the reaction was allowed to warm to 0°C. The mixture was quenched with 8 mL H_2O, extracted with Et_2O (4 × 10 mL), dried over $MgSO_4$, and concentrated in vacuo. The resulting silyl enol ether was taken up by 30 mL acetonitrile; 275.6 mg anhydrous Na_2CO_3 (2.6 mmol) and 583.5 mg palladium acetate (2.6 mmol) were added in turn. The reaction mixture was stirred for 12 h under a nitrogen atmosphere. Then the mixture was filtered with a short gel column and washed by EtOAc. Upon removal of solvent, the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (8:1) as the eluent to afford 378 mg enone (63.4%) along with 104 mg starting ketone (17.0% recovery).



Reference 4.

To a solution of 0.22 mL 2,2,6,6-tetramethylpiperidine (1.31 mmol, 1.5 eq.) in 6.0 mL THF was added 0.79 mL 1.48 M BuLi in hexane (1.22 mmol, 1.4 eq.) at 4°C (ice water bath). After being stirred for 1 h at the same temperature, the reaction mixture was cooled

to –78°C. TMSCl (0.17 mL, 1.22 mmol,1.4 eq.) was then added, followed by 402 mg starting material (0.873 mmol) in 6.0 mL THF via cannula. After being stirred for 2 h at –78°C, the reaction mixture was allowed to warm up, quenched by saturated $NaHCO_3$ aqueous solution, extracted with Et_2O, dried over Na_2SO_4, and concentrated. The residue was dissolved in 4.7 mL CH_3CN, then 0.17 mL diallyl carbonate (1.2 mmol, 1.4 eq.) and 61.0 mg $Pd_2(dba)_3{\cdot}CHCl_3$ (59 μmol, 6.8 mol %) were added at room temperature. After being stirred for 12 h at room temperature, the reaction mixture was quenched by saturated $NaHCO_3$ aqueous solution, extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography using 15%–20% EtOAc in hexane as the eluent to afford 361.3 mg (*R*)-5-[(*E*)-3-(4-methoxybenzyloxy)-1-triisopropylsilyloxymethyl-1-propenyl]cyclohex-2-enone and its regioisomer (> 6:1) as a colorless oil (90% for two steps, $R_f = 0.43$ (hexane/EtOAc, 3:1)), and 35 mg starting material (9% recovery).

Other references related to the Saegusa oxidation are cited in the literature.[13]

H. REFERENCES

1. Ito, Y.; Hirao, T. and Saegusa, T., *J. Org. Chem*., **1978**, *43*, 1011.
2. (a) Greshock, T. J. and Funk, R. L., *Org. Lett.,* **2006**, *8*, 2643. (b) Lee, H.-Y.; Tae, H. S.; Kim, B. G. and Choi, H.-M., *Tetrahedron Lett.,* **2003**, *44*, 5803. (c) Lecornue, F. and Ollivier J., *Org. Biomol. Chem.,* **2003**, *1*, 3600. (d) Barrett, A. G. M.; Blaney, F.; Campbell, A. D.; Hamprecht, D.; Meyer, T.; White, A. J. P.; Witty, D. and Williams, D. J., *J. Org. Chem.,* **2002**, *67*, 2735. (e) Thompson, C. F.; Jamison, T. F. and Jacobsen, E. N., *J. Am. Chem. Soc.,* **2001**, *123,* 9974. (f) Flower, K. R., *Organometallic Chemistry,* Royal Society of Chemistry, London **2001**, *29*, 384. (g) Williams, D. R. and Turske, R. A., *Org. Lett.,* **2000**, *2*, 3217. (h) Limanto, J. and Snapper, M. L., *J. Am. Chem. Soc.,* **2000**, *122,* 8071. (i) Porth, S.; Bats, J. W.; Trauner, D.; giester, G. and Mulzer, J., *Angew. Chem. Int. Ed.,* **1999**, *38*, 2015. (j) Wood, J. L. and Smith, A. B., *J. Am. Chem. Soc.,* **1992**, *114*, 10075. (k) Kim, M. S.; Applegate, L. A.; Park, O. S.; Vasudevan, S. and Watt, D. S., *Synth. Commun.,* **1990**, *20*, 989.
3. (a) Hu, X.-D.; Tu, Y. Q.; Zhang, E.; Gao, S. H.; Wang, S. H.; Wang, A. X.; Fan, C.-A. and Wang, M., *Org. Lett.,* **2006**, *8*, 1823. (b) Rigby, J. H.; Cavezza, A. and Heeg, M. J., *J. Am. Chem. Soc.,* **1998**, *120,* 3664.
4. Ohshima, T.; Xu, Y. J.; Takita, R.; Shimizu, S.; Zhong, D. F. and Shibasaki, M., *J. Am. Chem. Soc.,* **2002**, *124*, 14546.
5. Herzon, S. B. and Myers, A. G., *J. Am. Chem. Soc.,* **2005**, *127*, 5342.
6. Paquette, L. A.; Lanter, J. C. and Wang, H.-L., *J. Org. Chem.,* **1996**, *61,* 1119.
7. Sha, C.-K.; Huang, S.-J. and Zhan, Z.-P., *J. Org. Chem.,* **2002**, *67,* 831.
8. (a) Stahl, S. S., *Angew. Chem. Int. Ed.,* **2004**, *43*, 3400. (b) Högenauer, K. and Mulzer, J., *Org. Lett.,* **2001**, *3*, 1495.
9. Takayama, H.; Koike, T.; Aimi, N. and Sakai, S.-*I*., *J. Org. Chem.,* **1992**, *57*, 2173.
10. Yu, J.-Q.; Wu, H.-C. and Corey, E. J., *Org. Lett.,* **2005**, *7*, 1415.
11. Nicolaou, K. C.; Gray, D. L. F.; Montagnon, T. and Harrison, S. T., *Angew. Chem. Int. Ed*., **2002**, *41*, 996.
12. Han, G. H.; LaPorte, M. G.; Folmer, J. J.; Werner, K. M. and Weinreb, S. M., *J. Org. Chem.,* **2000**, *65*, 6293.
13. (a) Cramer, N.; Buchweitz, M.; Laschat, S.; Frey, W.; Baro, A.; Mathieu, D.; Richter, C. and Schwalbe, H., *Chem. Eur. J.,* **2006**, *12*, 2488. (b) Basler, B.; Brandes, S.; Spiegel, A. and Bach,

T., *Top. Curr. Chem.,* **2005**, *243*, 1. (c) Ohmori, N., *J. Chem. Soc., Perkin Trans. 1*, **2002**, 755. (d) Porth, S.; Bats, J. W.; Trauner, D.; Giester, G. and Mulzer, J., *Angew. Chem.,* **1999**, *111*, 2159. (e) Bonjoch, J.; Solé, D.; García-Rubio, S. and Bosch, J., *J. Am. Chem. Soc.,* **1997**, *119,* 7230. (f) Smith, A. B.; Nolen, E. G.; Shirai, R.; Blase, F. R., Ohta, M.; Chida, N.; Hartz, R. A.; Fitch, D. M.; Clark, W. M. and Sprengeler, P. A., *J. Org. Chem.,* **1995**, *60*, 7837. (g) Larock, R. C.; Hightower, T. R.; Kraus, G. A.; Hahn, P. and Zheng, D., *Tetrahedron Lett.,* **1995**, *36*, 2423. (h) Kirschning, A., *J. Org. Chem.,* **1995**, *60*, 1228. (i) Minami, I.; Takahashi, K.; Shimizu, I.; Kimura, T. and Tsuji, J., *Tetrahedron,* **1986**, *42*, 2971. (j) Koskinen, A. M. P. and Rapoport, H., *J. Med. Chem.,* **1985**, *28*, 1301. (k) Rubottom, G. M. and Juve, H. D., *J. Org. Chem.,* **1983**, *48*, 422. (l) Overman, L. E. and Freerks, R. L., *J. Org. Chem.,* **1981**, *46*, 2833.

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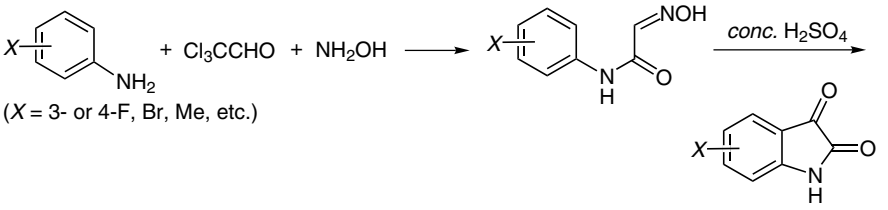
Sandmeyer Isatin Synthesis
(Sandmeyer Synthesis)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Sandmeyer in 1919.[1] It is a synthesis of isatin derivative involving the condensation of chloral (i.e., trichloroacetaldehyde), hydroxylamine, and a primary aryl amine to an α-isonitrosoacetanilide and subsequent electrophilic cyclization of the latter in the presence of a strong acid such as concentrated sulfuric acid.[2] Therefore, this reaction is generally known as the Sandmeyer isatin synthesis[2a,3] or the Sandmeyer synthesis.[4] During this reaction, the oximino intermediate can be isolated by extraction with warm 2 *N* NaOH followed by the precipitation with a 2 *N* HCl solution and purified by recrystallization in ethanol.[5] The isatin derivatives from this reaction have been used as the starting material for quinolines, acridines, and indophenazines.[3c] It is possible that the oximino intermediate from the *meta*-substituted aryl amine may form two stereoisomers during electrophilic cyclization (i.e., the 4- and 6-substituted isatins), which cannot be separated completely by fractional crystallization.[6] It is interesting that these two stereoisomers could be completely and rapidly isolated by precipitation of 4-isomer (usually red needles) with acetic acid followed by the precipitation of 6-isomer (usually yellow plates) by concentrated HCl.[6] However, this reaction fails to convert the oximino intermediates arising from nitroanilines,[7] 2-fluoroanilines, and 2,4-difluoroanilines[3c] into the corresponding isatin derivatives.

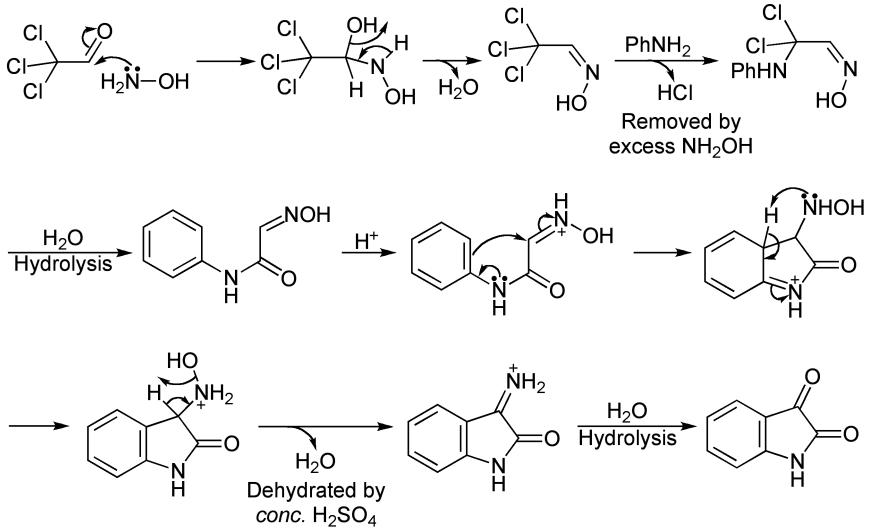
Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is assumed that hydroxylamine condenses with chloral to give oxime, which then undergoes the nucleophilic substitution with aniline, and hydrolyzes to give oximino intermediate under basic conditions. In the presence of a strong acid, such as concentrated sulfuric acid, the oximino compound cyclizes via nucleophilic addition of aromatic ring to C=N double bond. An illustrative mechanism is provided below.



D. MODIFICATION

The oximino intermediate has been cyclized with PPA as the dehydrating reagent.[3a]

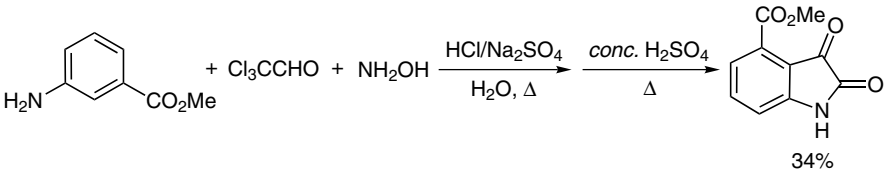
E. APPLICATIONS

This reaction has a general application in the synthesis of isatin derivatives, which could be used as the starting materials for quinolines, acridines and indophenazines etc.

F. RELATED REACTIONS

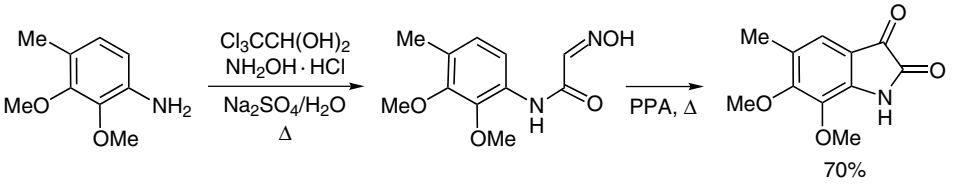
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 4a.

A mixture of 13.6 g methyl 3-aminobenzoate (0.09 mol), 16.1 g chloral hydrate (0.09 mol), 234.4 g Na_2SO_4, 19.8 g hydroxylamine hydrochloride (0.29 mol), 145 mL water, and 8 mL concentrated HCl was refluxed for 2 h and then kept at room temperature overnight. The cream color isonitroso intermediate was filtered off, washed with water, and dried to give 16.0 g intermediate, in a yield of 80%. This compound in a total of 16.0 g (0.07 mol), was added in portions to 70 mL *conc*. H_2SO_4 maintained at 70–75°C over a period of 30 min under stirring. The resulting mixture was then heated at 80°C until the reaction was complete, as monitored by TLC ($CHCl_3$/EtOH, 8:2). After being cooled to room temperature, the mixture was slowly poured onto ice. The aqueous phase was extracted with EtOAc; the combined organic layers were dried over $MgSO_4$, filtered, and evaporated. The resulting orange solid was purified by gradient flash column chromatography on silica gel, eluting with $CHCl_3$/EtOH (8:2) to give 5.0 g methyl 4-isatincarboxylate, in a yield of 34%, m.p. 215–217°C.



Reference 3a.

After a mixture of 1.68 g chloral hydrate (10.2 mmol), 2.03 g hydroxylamine hydrochloride (29.2 mmol), 13.4 g anhydrous Na_2SO_4, and 45 mL water was stirred at 45–50°C for 15 min, a 7.0 mL solution prepared from 1.517 g aniline, 0.75 mL *conc*. HCl, and water was added. The resulting mixture was heated for 1 h each at 45–50°C, 55–60°C and 65–70°C. An additional 0.45 g chloral hydrate and 4.1 g hydroxylamine hydrochloride were added, and the reaction mixture was heated at 75–80°C for another hour. When the mixture was cooled in ice water, a light brown precipitate formed, which was filtered to afford 1.58 g *N*-(2,3-dimethoxy-4-methylphenyl)-2-(hydroxyimino)-acetamide of sufficient purity, in a yield of 73%. To 20 mL polyphosphoric acid at 100°C was added 2.0 g *N*-(2,3-dimethoxy-4-methylphenyl)-2-(hydroxyimino)-acetamide (8.39 mmol) over a period of 5 min. After 20 min, the reaction mixture was cooled, and 40 mL water was carefully added to yield an orange precipitate, which was filtered to give 1.30 g 6,7-dimethoxy-5-methyl-1H-indole-2,3-dione, in a yield of 70%. This compound could be further purified by recrystallization in methanol, m.p. 180.5–181.5°C.

Other references related to the Sandmeyer isatin synthesis are cited in the literature.[8]

H. REFERENCES

1. Sandmeyer, T., *Helv. Chim. Acta,* **1919**, *2*, 234.
2. (a) Gribble, G. W., *J. Chem. Soc*., *Perkin Trans. I*, **2000**, 1045. (b) Gassman, P. G.; Cue, B. W. and Luh, T.-Y., *J. Org. Chem.,* **1977**, *42*, 1344. (c) Sumpter, W. C., *Chem. Rev.,* **1944**, *34,* 393.
3. (a) Gainor, J. A. and Weinreb, S. M., *J. Org. Chem.,* **1982**, *47*, 2833. (b) Ermili, A. and Giuliano, R., *Gazz. Chim. Ital.,* **1959**, *89*, 517. (c) Yen, V. Q.; Buu-Hoï, N. P. and Xuong, N. D., *J. Org. Chem.,* **1958**, *23*, 1858. (d) Piozzi, F., *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat*., **1957**, *22*, 629. (e) Sheibley, F. E. and McNulty, J. S., *J. Org. Chem.,* **1956**, *21*, 171. (f) Favini, G. and Piozzi, F., *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat*., **1955**, *19*, 44. (g) Piozzi, F. and Favini, G., *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat*., **1955**, *18*, 647.
4. (a) Braña, M. F.; Gradillas, A.; Gómez, A.; Acero, N.; Llinares, F.; Muñoz-Mingarro, D.; Abradelo, C.; Rey-Stolle, F.; Yuste, M.; Campos, J.; Gallo, M. A. and Espinosa, A., *J. Med. Chem.,* **2004**, *47,* 2236. (b) Senear, A. E.; Sargent, H.; Mead, J. F. and Koepfli, J. B., *J. Am. Chem. Soc.,* **1946**, *68*, 2695.
5. Sadler, P. W. and Warren, R. L., *J. Am. Chem. Soc.,* **1956**, *78*, 1251.
6. Sadler, P. W., *J. Org. Chem.,* **1956**, *21*, 169.
7. (a) Rupe, H. and Kersten, L., *Helv. Chim. Acta,* **1926**, *9*, 578. (b) Borsche, W.; Weussmann, H. and Fritzsche, A., *Ber.,* **1924**, *57*, 1149.
8. (a) Pirrung, M. C.; Pansare, S. V.; Sarma, K. D.; Keith, K. A. and Kern, E. R., *J. Med. Chem.,* **2005**, *48,* 3045. (b) Da Silva, F.; Garden, S. and Pinto, A., *J. Braz. Chem. Soc.,* **2001**, *12*, 273. (c) Garden, S. J., Torres, J. C.; Ferreira, A. A.; Silva, R. B. and Pinto, A. C., *Tetrahedron Lett.,* **1997**, *38*, 1501. (d) Taylor, A., *J. Chem. Res. Miniprint,* **1980**, *10*, 4154. (e) Popp, F. D., *Adv. Heterocycl. Chem.,* **1975**, *18*, 1. (f) Yoda, N. and Kurihara, M., *J. Poly. Sci.: Marcomol. Rev.,* **1971**, *5*, 109. (g) Bartlett, M. F.; Dickel, D. F. and Taylor, W. I., *J. Am. Chem. Soc.,* **1958**, *80*, 126. (h) Astill, B. D. and Boekelheide, V., *J. Am. Chem. Soc.,* **1955**, *77*, 4079. (i) Baker, B. R.; Schaub, R. E.; Joseph, J. P.; McEvoy, F. J. and Williams, J. H., *J. Org. Chem.,* **1952**, *17*, 164. (j) Marvel, C. S. and Hiers, G. S., *Org. Synth. Coll.,* **1943**, *1*, 327. (k) Martinet, J. and Cousset, P., *Compt. Rend.,* **1921**, *172*, 1234.

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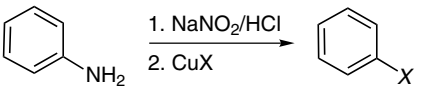
Sandmeyer Reaction
(Sandmeyer Transformation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Sandmeyer in 1884 during the preparation of phenylacetylene from benzenediazonium chloride and cuprous acetylide.[1] It is a two-step synthesis of aryl halides or cyanides from primary aryl amines involving the formation of diazonium salts of the corresponding amines with nitrous acid and the transformation of diazo intermediates into aryl halides or cyanides with cuprous halides or cyanide. This reaction is therefore generally referred to as the Sandmeyer reaction.[2,3] Occasionally, it is also known as the Sandmeyer transformation.[4] In addition, the preparation of aryl nitrile from this reaction is specifically known as the Sandmeyer nitrile synthesis.[2v] Likewise, the combination of the alkali halide and cuprous halide is known as the Sandmeyer reagent.[2v,5] It is clear that the halo group introduced into the aromatic ring originates from cuprous halide instead of the diazonium halide, as supported by the formation of *p*-dichlorobenzene from *p*-chlorobenzenediazonium bromide and cuprous chloride as well as the production of *p*-chloro-bromobenzene from *p*-chlorobenzenediazonium chloride and cuprous bromide.[6] In addition, the halogen exchange has also been observed in the Sandmeyer reaction.[3a,3n] Although cupric or ferrous chloride does not promote this reaction,[1a] it has been found that a saturated solution of $CaCl_2$, $ZnCl_2$, and zinc ammonia chloride [$Zn(NH_3)_2Cl_2$], with maximal concentration of chloride ions, reacts equally well with aryl diazonium salt to give aryl chloride.[1a] In contrast, the yield of aryl nitrile can be improved by a reaction of diazonium salt with nickel cyanide (i.e., $Ni(CN)_2$), rather than CuCN,[1a] whereas other salts of cyanide such as that with Fe, Cr, and Zn are not effective.[7] It should be pointed out that the iodonation of the aromatic diazonium salt does not need the presence of cuprous iodide.[1a,2e] Overall, this reaction usually gives less than a quantitative yield of aryl halide due to the formation of some side products, including biaryl, azobenzene, and phenol.[1a,2b,8]

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

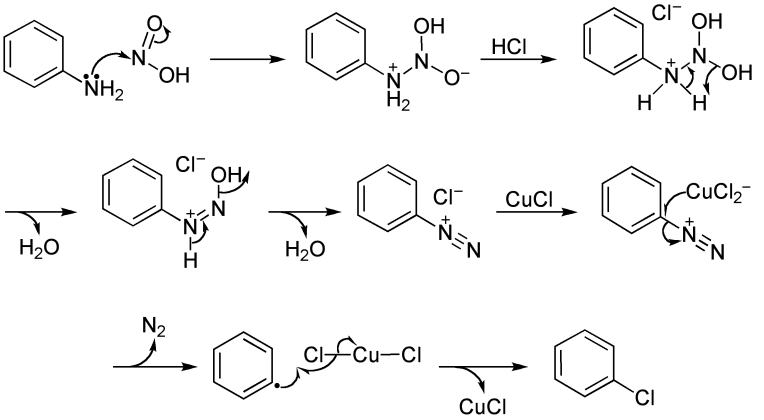
B. GENERAL REACTION SCHEME



(*X* = Cl, Br, I, CN, SCN, SeCN, etc.)

C. PROPOSED MECHANISMS

Although different mechanisms have been proposed for this reaction, including the addition of cuprous chloride to the N=N double bond, the formation of cupric salt from oxidation-reduction, the formation of copper complex $[CuCl_4]^{2-}$,[1a] and the isolation of $C_6H_5N_2Cu_2Br_3$ crystal as the reaction intermediate,[3l] more recent experimental evidence supports the concept that this reaction involves an aryl radical,[1a,2x,3f,3p] as illustrated below.



D. MODIFICATION

A standard condition has been optimized for this reaction, in which the aryl amine is diazotized in 10 times its amount of acetic acid, followed by the addition of one equivalent of cuprous halide in hydrohalic acid. Under these conditions, the acetate salt of aryl amine is relatively soluble, and less froth and tarry material are formed during diazo transformation.[9] In addition, chlorination, bromination, and iodonation of *p*-haloaniline to dihalobenzenes under such standard conditions give almost comparable average yields. Other modifications of this reaction include the formation of phenyl selenocyanate by the reaction with potassium selenocyanate,[2c] and aryl nitrile by the reaction with nickel cyanide.[1a] Moreover, this reaction has been extended to the preparation of phenyl thiocyanate, phenyl isothiocyanate[3h] and aromatic sulfonyl chloride.[3o]

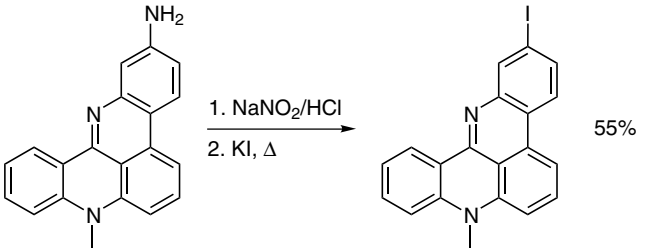
E. APPLICATIONS

This reaction has very general application in the preparation of aryl halides and nitriles.

F. RELATED REACTIONS

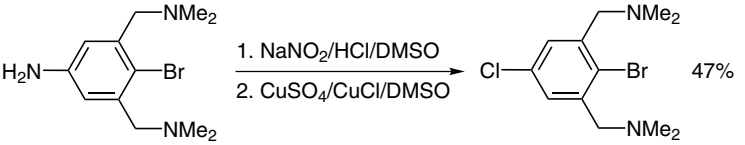
This reaction is related to the *Gattermann Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 2e.

A solution of 87 mg $NaNO_2$ (1.26 mmol) in 2 mL water was added dropwise to a solution of 250 mg 2-amino-8-methyl-8*H*-quino[4,3,2-*kl*]acridine (0.84 mmol) in 50 mL 2 M HCl at 0°C. After the mixture was stirred at 0°C for 15 min, a solution of 0.24 g KI (1.47 mmol) in 10 mL water was added dropwise, and the resulting mixture was heated for 0.5 h at 80°C. After cooling, the reaction mixture was alkalinized to pH 12 with 10% NaOH, and the product was extracted with $CHCl_3$ (4 × 50 mL). Upon removal of solvent, the residue was purified by column chromatography using 0.25% MeOH in $CHCl_3$ as the eluent, to afford 190 mg 2-iodo-8-methyl-8*H*-quino[4,3,2-*kl*]acridine, as a yellow solid, in a yield of 55%, m.p. 265–268°C.



Reference 2q.

To a stirred solution of 9.0 g 5-amino-2-bromo-1,3-bis-[(dimethylamino)methyl] benzene (31.4 mmol) in 75 mL DMSO was added 15 mL concentrated HCl dropwise. The reaction mixture was cooled to 0°C, and subsequently, a mixture of 15 mL *conc*. HCl and 6.1 g $NaNO_2$ in 50 mL DMSO was added, while the temperature of the reaction mixture was maintained at 10°C. After this addition, 7.86 g $CuSO_4$ (31.4 mmol) and 1.55 g CuCl (15.7 mmol) were added. There was immediate gas evolution, and the greenish mixture was then stirred for an additional 16 h, while the temperature was slowly raised to room temperature. The reaction mixture was poured into 400 mL 2 M NaOH, whereupon the solution turned blue and then brown. To this heterogeneous mixture was added 200 mL CH_2Cl_2, and the whole mixture was filtered through a G4 glass frit with a layer of infusorial earth. The organic layer of the orange filtrate was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to afford a yellow oil. Fractional distillation under reduced pressure at 0.05 mmHg produced 4.56 g 2-bromo-5-chloro-1,3-bis[(dimethylamino)methyl]benzene, in a yield of 47%.

Other references related to the Sandmeyer reaction are cited in the literature.[10]

H. REFERENCES

1. (a) Hodgson, H. H., *Chem. Rev.,* **1947**, *40*, 251. (b) Sandmeyer, T., *Ber.,* **1884**, *17*, 1633.
2. (a) Ghosh, S.; Kinney, W. A.; Gauthier, D. A.; Lawson, E. C.; Hudlicky, T. and Maryanoff, B. E., *Can. J. Chem.,* **2006**, *84*, 555. (b) Chiang, C.-L.; Shu, C.-F. and Chen, C.-T., *Org. Lett.,* **2005**, *7*, 3717. (c) Kan, J. T. W. and Toy, P. H., *J. Sulfur Chem.,* **2005**, *26*, 509. (d) Lee, J. K.; Na, J. H.; Kim, T. H.; Kim, Y.-S.; Park, W. H. and Lee, T. S., *Mat. Sci. Eng.,* **2004**, *C24*, 261. (e) Hutchinson, I.; McCarroll, A. J.; Heald, R. A. and Stevens, M. F. G., *Org. Biomol. Chem.,* **2004**, *2*, 220. (f) Marino, S. T.; Stachurska-Buczek, D.; Huggins, D. A.; Krywult, B. M.; Sheehan, C. S.; Nguyen, T.; Choi, N.; Parsons, J. G.; Griffiths, P. G.; James, I. W.; Bray, A. M.; White, J. M. and Boyce, R. S., *Molecules,* **2004**, *9*, 405. (g) Jeschke, P.; Uneme, H.; Benet-Buchholz, J.; Stölting, J.; Sirges, W.; Beck, M. E. and Etzel, W., *Pflanzenschutz-Nachrichten Bayer,* **2003**, *56*, 5. (h) Hlavac, J.; Buchtik, R.; Slouka, J.; Hradil, P. and Wiedermannova, I., *ARKIVOC,* **2003**, 22. (i) Learmonth, D. A., *Bioconjugate Chem.,* **2003**, *14,* 262. (j) Niedan, V. W.; Keppler, F.; Ahlsdorf, B. and Schöler, H. F., *Biogeochemistry,* **2003**, *62*, 277. (k) Manimaran, M.; Snider, G. L.; Lent, C. S.; Sarveswaran, V.; Lieberman, M.; Li, Z. H. and Fehlner, T. P., *Ultramicroscopy*, **2003**, *97*, 55. (l) Reed, N. N.; Delgado, M.; Hereford, K.; Clapham, B. and Janda, K. D., *Bioorg. Med. Chem. Lett.,* **2002**, *12*, 2047. (m) Zhang, P. L.; Zuckett, J. M. F.; Woolfrey, J.; Tran, K.; Huang, B.; Wong, P.; Sinha, U.; Park, G.; Reed, A.; Malinowski, J.; Hollenbach, S.; Scarborough, R. M. and Zhu, B.-Y., *Bioorg. Med. Chem. Lett.,* **2002**, *12*, 1657. (n) Bakulev, V. A.; Morzerin, Y. Y.; Shafran, Y. Y. and Mokrushin, V. S., *ARKIVOC,* **2002**, 166. (o) Paasivirta, J., "The Handbook of Environmental Chemistry," in *New Types of Persistent Halogenated Compounds,* Vol. 3, Pt. K., ed. Paasivirta, J., Springer-Verlag, Berlin, **2000**, Ch.1. (p) Wang, J. B.; Chen, B. and Bao, J., *J. Org. Chem.,* **1998**, *63,* 1853. (q) Van de Kuil, L. A.; Luitjes, H.; Grove, D. M.; Zwikker, J. W.; van der Linden, J. G. M.; Roelofsen, A. M.; Jenneskens, L. W.; Drenth, W. and van Koten, G., *Organometallics,* **1994**, *13*, 468. (r) Nau, W. M.; Harrer, H. M. and Adam, W., *J. Am. Chem. Soc.,* **1994**, *116*, 10972. (s) Clive, D. L. J., *Pure & Appl. Chem.,* **1988**, *60*, 1645. (t) Glennon, R. A.; Young, R.; Benington, F. and Morint, R. D., *J. Med. Chem.,* **1982**, *25*, 1163. (u) Ellis, J.; Gellert, E. and Robson, J., *Aust. J. Chem.,* **1973**, *26*, 907. (v) Wall, L. A.; Pummer, W. J.; Fearn, J. E. and Antonucci, J. M., *J. Res. Nat. Bureau Standards Phys. Chem.,* **1963**, *67A*, 481. (w) Cadogan, J. I. G.; Roy, D. A. and Smith, D. M., *J. Chem. Soc., C.,* **1962**, 1249. (x) Dickerman, S. C.; Weiss, K. and Ingberman, A. K., *J. Am. Chem. Soc.,* **1958**, *80*, 1904. (y) Kochi, J. K., *J. Am. Chem. Soc.,* **1957**, *79*, 2942. (z) Hodgson, H. H.; Birtwell, S. and Walker, J., *J. Chem. Soc.,* **1942**, 376.
3. (a) Krapcho, A. P. and Haydar, S. N., *Heterocycl. Commun.,* **1998**, *4*, 291. (b) Hanson, P.; Jones, J. R.; Gilbert, B. C. and Timms, A. W., *J. Chem. Soc., Perkin Trans. II,* **1991**, 1009. (c) Kulic, J. and Adamek, M., *Chem. Prumysl*, **1989**, *39*, 354. (d) Dai, W. Z., *Huaxue Tongbao*, **1989**, 43. (e) Galli, C., *J. Chem. Soc., Perkin Trans. II,* **1984**, 897. (f) Galli, C., *J. Chem. Soc., Perkin Trans. II,* **1982**, 1139. (g) Chikamoto, T. and Nagata, S., *Chem. Lett.,* **1980**, 737. (h) Takino, Y.; Sawanishi, N. and Iritani, N., *Yakugaku Zasshi,* **1975**, *95*, 949. (i) Nakatani, Y., *Tetrahedron Lett*., **1970**, 4455. (j) Kobayashi, M.; Yamada, E.; Matsui, M. and Kobori, N., *Org. Prep. Proc.,* **1969**, *1*, 221. (k) Minisci, F.; Cecere, M. and Galli, R., *Chem. Ind. (Italy),* **1968**, *50*, 225. (l) Roemming, C. and Eaerstad, K., *Chem. Commun. (London),* **1965**, 299. (m) Minisci, F., *Gazz. Chim. Ital.,* **1960**, *90*, 1307. (n) Lamm, B., *Acta Chem. Scand.,* **1959**, 13, 1254. (o) Veres, K., *Chemie (Prague),* **1958**, *10*, 47. (p) Nonhebel, D. C. and Waters, W. A., *Adv. Catal.,* **1957**, *9*, 353. (q) Bergmann, E. D. and Bentov, M., *J. Org. Chem.,* **1955**, *20*, 1654. (r) Marek, J., *Chem. Listy Vedu Prumysl*, **1955**, *49*, 1034. (s) Liberman, A. L.; Sterligov, O. D.; Lapshina, T. V. and Kazanskii, B. A., *Dokl. Akad. Nauk SSSR,* **1953**, *91*, 845. (t) Cowdrey, W. A. and Davies, D. S., *J. Chem. Soc.,* 1949, S48. (u) Mozgova, K. K., *Zh. Obsh. Khim.,* **1949**, *19*, 755. (v) Pfeil, E. and Velten, O., *Ann.,* **1949**, *565*, 183. (w) Bruker, A. B. and Maklyaev, F. L., *Dokl. Akad. Nauk SSSR,* **1948**, *63*, 271. (x) Hodgson, H. H., *J. Chem. Soc.,* **1946**, 745. (y) Hodgson, H. H. and Sibbald, D. D. R., *J. Chem. Soc.,* **1945**, 545. (z) Hodgson, H. H. and Sibbald, D. D. R., *J. Chem. Soc.,* **1944**, 393. (aa) Waters, W. A.,

J. Chem. Soc., **1942**, 266. (bb) Hodgson, H. H. and Walker, J., *J. Chem. Soc.,* **1933**, 1620. (cc) Keme, I. F., *Chem.-Zeitung,* **1922**, *40*, 1042. (dd) Heller, G. and Tischner, W., *Ber.,* **1911**, *44*, 250. (ee) Heller, G., *Angew. Chem.,* **1910**, *23*, 389. (ff) Walter, J., *J. Prakt. Chem.,* **1896**, *53*, 427.

4. Evans, D. A.; Wood, M. R.; Trotter, B. W.; Richardson, T. I.; Barrow, J. C. and Katz, J. L., *Angew. Chem. Int. Ed.,* **1998**, *37*, 2700.
5. Hodgson, H. H. and Mahadevan, A. P., *J. Chem. Soc.,* **1947**, 173.
6. Hantzsch, A. and Blagden, G. W., *Ber.,* **1900**, *33*, 2544.
7. Korczynski, A. and Fandrich, B., *Compt. Rend.,* **1926**, *183*, 421.
8. (a) Sandmeyer, T., *Ber.,* **1890**, *23*, 1881. (b) Tobias, G., *Ber.,* **1890**, *23*, 1628.
9. Fry, H. S. and Grote, I. W., *J. Am. Chem. Soc.,* **1926**, *48*, 710.
10. (a) Hanson, P.; Rowell, S. C.; Walton, P. H. and Timms, A. W., *Org. Biomol. Chem.,* **2004**, *2*, 1838. (b) Takekawa, M.; Fujimaki, Y.; Ohshima, S. and Fujisawa, S., *Polycycl. Aromatic Compd.,* **2002**, *22*, 259. (c) Jeschke, P.; Moriya, K.; Lantzsch, R.; Seifert, H.; Lindner, W.; Jelich, K.; Göhrt, A.; Beck, M. E. and Etzel, W., *Pflanzenschutz-Nachrichten Bayer,* **2001**, *54*, 147. (d) Boger, D. L.; Kim, S. H.; Miyazaki, S.; Strittmatter, H.; Weng, J.-H.; Mori, Y.; Rogel, O.; Castle, S. L. and McAtee, J., *J. Am. Chem. Soc.*, **2000**, *122*, 7416. (e) Suzuki, N.; Azuma, T.; Kaneko, Y.; Izawa, Y.; Tomioka, H. and Nomoto, T., *J. Chem. Soc., Perkin Trans. I,* **1987**, 645. (f) Corral, C.; Lasso, A.; Lissavetzky, J.; Sanchez Alvarez-Insua, A. and Valdeolmillos, A. M., *Heterocycles,* **1985**, *23*, 1431. (g) Doyle, M. P., *J. Org. Chem.,* **1977**, *42*, 2426. (h) Kazharkin, L. I. and Kalinin, V. N., *Russ. Chem. Bull.,* **1968**, *17*, 671. (i) Coudrey, W. A. and Davies, D. S., *Quart. Rev.,* **1952**, *6*, 358. (j) Bachman, G. B. and Picha, G. M., *J. Am. Chem. Soc.,* **1946**, *68*, 1599. (k) Sandmeyer, T., *Ber.,* **1884**, *17*, 2650.

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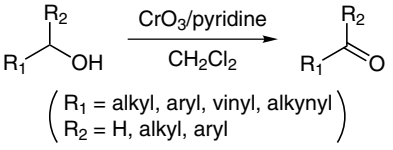
Sarett Oxidation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Sarett et al. in 1953[1] after the initial preparation of a relevant oxidation reagent in 1948.[2] It is a mild oxidation of primary or secondary alcohols into corresponding aldehydes or ketones using chromium trioxide and pyridine complex as the oxidant and is generally referred to as the Sarett oxidation.[3] Likewise, the complex from anhydrous chromium trioxide and pyridine is commonly termed the Sarett's reagent.[4] The advantage of using Sarett's reagent is its relatively high solubility in the chlorinated hydrocarbons,[5] in which the allylic oxidation[6] and α-oxidation of alkyne[4b] can be effectively performed. For example, methylene chloride, the most commonly used solvent for the Sarett oxidation, has a solubility of 12.5 g per 100 mL for the chromium trioxide-pyridine complex.[7] In addition, Sarett's reagent can be prepared directly in methylene chloride,[7] which is superior to pyridinium chlorochromate (PCC) in the α-oxidation of alkyne because of the rapid formation of product.[4b]

B. GENERAL REACTION SCHEME



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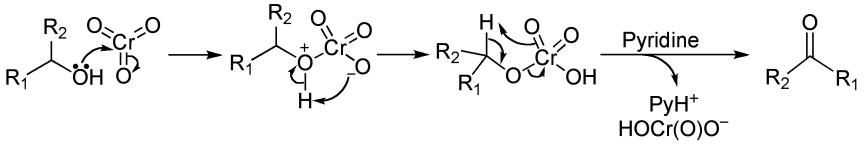
C. PROPOSED MECHANISMS

An illustrative mechanism is provided below for the Sarett oxidation.



D. MODIFICATION

This reaction has been modified by using methylene chloride as the reaction solvent.[5,7]

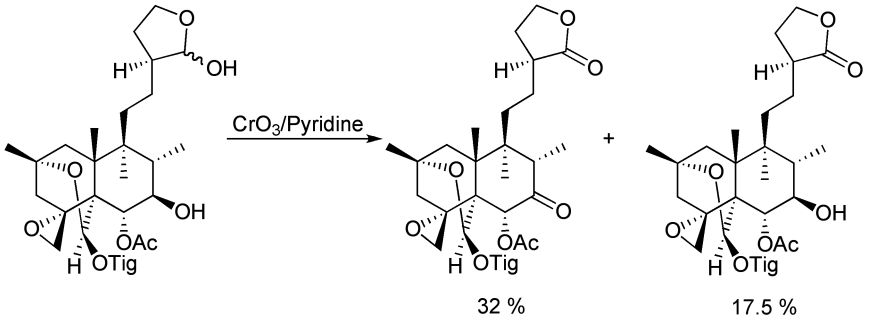
E. APPLICATIONS

This reaction has broad application in organic synthesis.

F. RELATED REACTIONS

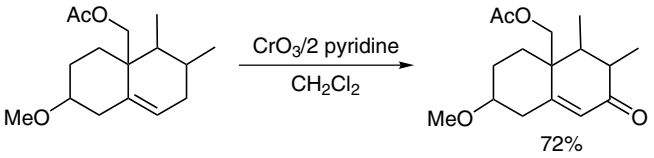
This reaction is related to *Corey-Schmidt Oxidation* and *Corey-Suggs Oxidation*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 3a.

To a solution of 320 mg scutegalin B (0.63 mmol) in 17 mL pyridine was added a mixture of 1.7 g CrO_3 and 17 mL pyridine, and the mixture was left at room temperature for 24 hours. Then the mixture was poured into 100 mL water and extracted with Et_2O (5 × 25 mL). The combined organic layers were dried over Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (1:1) as the eluent, to afford 102 mg [(13*S*,19*R*)-6α-acetoxy-4α,18-epoxy-7-oxoneoclerodan-16,15-olide 19,2α-(19-*O*-tigloyl) hemiacetal] (an amorphous white solid, 32%, m.p. 115–120°C) and 56 mg of [(13*S*,19*R*)-6α-acetoxy-4α,18-epoxy-7β-hydroxyneoclerodan-16,15-olide 19,2α-(19-*O*-tigloyl) hemiacetal] as colorless needles, in a yield of 17.5%, m.p. 223–226°C (from EtOAc).



Reference 8.

To a rapidly stirred mixture of 7.75 g dry pyridine and 220 mL CH_2Cl_2, was added 4.9 g chromium trioxide, and the resulting mixture was stirred at room temperature for additional 20 min. Then, to this solution was added 2.5 g chloest-5-ene-3b-19-diol 3-methyl ether 19-acetate in 10 mL CH_2Cl_2 in one portion, and the mixture was stirred for 17 h. At the end of this period, an additional portion of $CrO_3 \cdot 2$pyridine complex, prepared from 1.52 g chromium trioxide and 2.4 g pyridine in 100 mL CH_2Cl_2, was added, and the mixture was stirred for another 7 h. The solution was diluted with 600 mL ether and washed with saturated $NaHCO_3$ solution (3 × 75 mL), 3% HCl (2 × 75 mL), saturated $NaHCO_3$ solution (1 × 100 mL) and brine (1 × 100 mL). The organic layer was dried over $MgSO_4$, and evaporated in vacuo. The resulting brown oil was purified by silica gel column chromatography using hexanes/EtOAc (3:1) as the eluent to afford 1.78 g 7-oxochloest-5-ene-3b,19-diol 3-methyl ether 19-acetate, in a yield of 72%, m.p. 95–96.5°C.

Other references related to the Sarett oxidation are cited in the literature.[9]

H. REFERENCES

1. Poos, G. I.; Arth, G. E.; Beyler, R. E. and Sarett, L. H., *J. Am. Chem. Soc.,* **1953**, *75*, 422.
2. Sisler, H. H.; Bush, J. D. and Accountius, O. E., *J. Am. Chem. Soc.,* **1948**, *70*, 3827.
3. (a) Rodríguez, B.; Rodríguez, B.; de la Torre, M.; Simmonds, M. S. J. and Blaney, W. M., *J. Nat. Prod.,* **1999**, *62,* 594. (b) Enzell, C., *Pure & Appl. Chem.,* **1985**, *57*, 693. (c) Friedman, O. M.; Wodinsky, I. and Myles, A., *Cancer Treat. Reports,* **1976**, *60*, 337. (d) Meyer, W. L.; Clemans, G. B. and Manning, R. A., *J. Org. Chem.,* **1975**, *40*, 3686. (e) Talapatra, B.; Dutta, S.; Maiti, B. C.; Pradhan, D. K. and Talapatra, S. K., *Aust. J. Chem.,* **1974**, *27*, 2711. (f) Marshall, J. L. and Walter, S. R., *J. Am. Chem. Soc.,* **1974**, *96*, 6358. (g) Gassman, P. G. and Pape, P. G., *J. Org. Chem.,* **1964**, *29*, 160. (h) Stenberg, V. I. and Perkins, R. J., *N. Dakota Acad. Sci.*, **1962**, *16*, 10. (i) Buchi, G. and White, D. M., *J. Am. Chem. Soc.,* **1957**, *79*, 750.
4. (a) Johnson, C. R. and Penning, T. D., *J. Am. Chem. Soc.,* **1988**, *110*, 4726. (b) Sheats, W. B.; Olli, L. K.; Stout, R.; Lundeen, J. T.; Justus, R. and Nigh, W. G., *J. Org. Chem.,* **1979**, *44*, 4075. (c) Andrieux, J.; Bodo, B.; Cunha, H.; Deschamps-Vallet, C.; Meyer-Dayan, M. and Molho, D., *Bull. Soc. Chim. Fr.,* **1976**, 1975. (d) Brown, H. C.; Garg, C. P. and Liu, K.-T., *J. Org. Chem.,* **1971**, *36*, 387. (e) Newman, M. S. and Din, Z. U., *J. Org. Chem.,* **1971**, *36*, 966. (f) Hoffman, J. M. and Schlessinger, R. H., *J. Am. Chem. Soc.,* **1969**, *91*, 3953. (g) Witaker, K. E.; Galbraith, B. E. and Snyder, H. R., *J. Org. Chem.,* **1969**, *34*, 1411.
5. Collins, J. C.; Hess, W. W. and Frank, F. J., *Tetrahedron Lett.,* **1968**, 3363.
6. Dauben, W. G.; Lorber, M. and Fullerton, D. S., *J. Org. Chem.,* **1969**, *34*, 3587.
7. Ratcliffe, R. and Rodehorst, R., *J. Org. Chem.,* **1970**, *35*, 4000.
8. Moriarty, R. M. and Paaren, H. E., *J. Org. Chem.,* **1981**, *46*, 970.
9. (a) Ottow, E.; Cleve, A.; Neef, G. and Schwede, W., *J. Prakt. Chem.,* **1997**, *339*, 365. (b) Quijano, L.; Calderón, J. S. and Ríos, T., *Cell. Mol. Life Sci.,* **1981**, *37*, 542. (c) Saidkhodzhaev, A. I.,

Chem. Nat. Compd., **1980**, *15*, 379. (d) Murray, R. K.; Goff, D. L. and Ford, T. M., *J. Org. Chem.,* **1977**, *42*, 3870. (e) Ratcliffe, R. W., *Org. Synth.,* **1976**, *55*, 84. (f) Hasan, F. and Rocek, J., *J. Am. Chem. Soc.,* **1975**, *97*, 1444. (g) Hasan, F. and Rocek, J., *J. Am. Chem. Soc.,* **1975**, *97*, 3762. (h) Mori, K., *Tetrahedron Lett.,* **1973**, 2635. (i) Collins, J. C. and Hess, W. W., *Org. Synth.,* **1972**, *52*, 5. (j) House, H. O., *Modern Synthetic Reactions,* Benjamin, Menlo Park, Calif., **1972**, pp. 264–273. (k) Chinn, L. J., *J. Org. Chem.,* **1967**, *32*, 687. (l) Stenberg, V. I. and Perkins, R. J., *J. Org. Chem.,* **1963**, *28*, 323. (m) Holum, J. R., *J. Org. Chem.,* **1961**, *26*, 4814. (n) Kris, E. J., *Chem. & Ind. (London),* **1961**, 1834. (o) Walker, B. H., *J. Org. Chem.,* **1960**, *25*, 1047. (p) Wall, M. E.; Serota, S. and Eddy, C. R., *J. Am. Chem. Soc.,* **1955**, *77*, 1230. (q) André, A. F. St.; MacPhillamy, H. B.; Nelson, J. A.; Shabica, A. C. and Scholz, C. R., *J. Am. Chem. Soc.,* **1952**, *74*, 5506.

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Saytzeff Rule
(Zaitsev Rule)

A. GENERAL DESCRIPTION OF THE REACTION

This rule was first formulated by Saytzeff (Zaitsev) in 1875.[1] It is a rule for predicting the regio-selectivity of olefin formation by the elimination of secondary or tertiary alkyl halides, in which the proton is eliminated preferentially from the carbon bearing the smallest number of protons; therefore, it is generally known as the Saytzeff rule[2] or Zaitsev rule.[3] Nowadays, it is more generally accepted that the elimination of aliphatic halides, alcohols, esters, etc. forms thermodynamically stable products,[4] and this elimination is termed as the Zaitsev elimination.[5] The regioselectivity to give a more stable olefin is referred to as the Saytzeff regiospecificity,[6] and the corresponding olefin is known as the Saytzeff product,[7] or Zaitsev product.[8] The Saytzeff rule does not apply to the pyrolysis of esters in the gas phase (e.g., $> 400^{o}C$)[9] and the elimination of onium salts,[2n] such as the quaternary ammonium salts and substituted sulfonium salts, of which the *Hofmann Rule* works and the least-substituted olefins predominate in the products.[2d,4b,10] The unimolecular elimination such as the *Chugaev Reaction*[11] and the pyrolysis of esters in the liquid phase (e.g., $< 200^{o}C$)[9] also follows the Saytzeff rule. Furthermore, the steric effect during the elimination may also lead to the product obeying the *Hofmann Rule*,[12] as indicated by the increased ratio of 1-/2-olefin from the elimination of a series compounds of $RCH_2CBr(CH_3)_2$, in which R varies from Me, Et, *i*-Pr to *t*-Bu.[13] Similarly, the size of the base applied in the elimination also affects the regioselectivity between the Saytzeff and Hofmann rules.[12a,14] It is interesting that the steric effect may also result in the Saytzeff product from the elimination of an ammonium salt.[2d]

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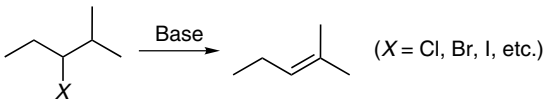
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is well known that in the absence of a significantly steric interaction, the formation of a more stable olefin during elimination is attributed to electronic stabilization (e.g., hyperconjugative factors) of the double bond in the transition state.[2f,10,12a,14] It is not necessary to illustrate the mechanism here.

D. MODIFICATION

The complexes of Group IVB (d0) metal with benzamidinate have been used for the transformation of olefins into the most stable isomers.[15]

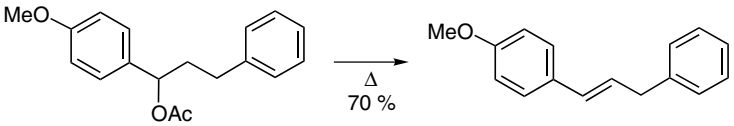
E. APPLICATIONS

This rule is very useful in predicting the regioselectivity of elimination.

F. RELATED REACTIONS

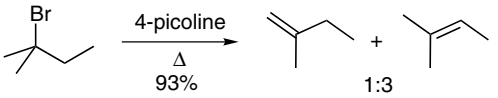
This rule is related to the *Hofmann Rule.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 10a.

To a small flask equipped with a short refractional column was added 10.0 g 1-(*p*-anisyl)-3-phenylpropyl acetate. The flask was heated with a soft Bunsen flame until acetic acid began to distil. Heating was continued at such a rate that the acetic acid distilled rapidly, until the calculated amount had been collected in a graduated centrifuge tube. The residue was then cooled, taken up in CH_2Cl_2, and washed free of any excess acid. Upon removal of the solvent, the residue was distilled under reduced pressure to afford 5.5 g 1-(*p*-anisyl)-3-phenylpropene, in a yield of 70%, b.p. 160°C at 1 mmHg.



Reference 14.

To a 200-mL round-bottomed flask equipped with a Todd microcolumn was placed 100 ml of 4-picoline and 15.10 g *t*-amyl bromide (0.1 mol). The mixture was rapidly heated to reflux. Olefin was removed at the top of the column as rapidly as it appeared there. The collected sample was washed with water and separated to give 6.46 g methyl butene, in a yield of 93%. The refractive index of 1.3850 indicated a composition of 25% 2-methyl-1-butene and 75% 2-methyl-2-butene.

Other references related to the Saytzeff rule are cited in the literature.[16]

H. REFERENCES

1. Saytzeff, A., *Ann.,* **1875**, *179*, 296.
2. (a) Reinecke, M. G. and Smith, W. B., *J. Chem. Edu.,* **1995**, *72*, 541. (b) Chuchanl, G. and Martín, I., *J. Phys. Chem.,* **1980**, *84*, 3188. (c) Skinner, A. C. and Davis, J., *J. Chem. Edu.,* **1971**, *48*, 653. (d) Feit, I. N. and Saunders, W. H., *J. Am. Chem. Soc.,* **1970**, *92*, 5615. (e) Taber, R. L. and Champion, W. C., *J. Chem. Edu.,* **1967**, *44*, 620. (f) Brown, H. C. and Klimisch, R. L., *J. Am. Chem. Soc.,* **1966**, *88*, 1425. (g) Saunders, W. H.; Fahrenholtz, S. R.; Caress, E. A.; Lowe, J. P. and Schreiber, M., *J. Am. Chem. Soc.,* **1965**, *87*, 3401. (h) Smith, W. B. and Watson, W. H., *J. Am. Chem. Soc.*, **1962**, *84*, 3174. (i) DePuy, C. H. and King, R. W., *Chem. Rev.,* **1960**, *60*, 431. (j) Banthorpe, D. V. and Hughes, E. D., *Bull. Soc. Chim. Fr,* **1960**, 1373. (k) Hughes, E. D. and Wilby, J., *J. Chem. Soc.,* **1960**, 4094. (l) Praill, P. F. G., *Chem. Ind. (London),* **1959**, 1123. (m) Shoppee, C. W.; Evans, D. E. and Summers, G. H. R., *J. Chem. Soc.,* **1957**, 97. (n) Brown, H. C. and Moritani, I., *J. Am. Chem. Soc.,* **1953**, *75*, 4112. (o) Brown, H. C. and Berneis, H. L., *J. Am. Chem. Soc.,* **1953**, *75*, 10. (p) Shiner, V. J., *J. Am. Chem. Soc.,* **1952**, *74*, 5285. (q) Cardwell, H. M. E. and Kilner, A. E. H., *J. Chem. Soc.,* **1951**, 2430.
3. (a) Greve, B. and Imming, P., *J. Org. Chem.,* **1997**, *62,* 8058. (b) Gallagher, T. F. and Adams, J. L., *J. Org. Chem.,* **1992**, *57*, 3347. (c) Renneke, R. F.; Kadkhodayan, M.; Pasquali, M. and Hill, C. L., *J. Am. Chem. Soc.,* **1991**, *113*, 8357. (d) Renneke, R. F.; Pasquali, M. and Hill, C. L., *J. Am. Chem. Soc.,* **1990**, *112*, 6585. (e) Roche, V. F.; Roche, E. B. and Nagel, D. L., *J. Org. Chem.,* **1982**, *47*, 1368. (f) Freidlina, R. Kh.; Kost, V. N. and Nesmeyanov, A. N., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1955**, 233. (g) Meshcheryakov, A. P. and Petrova, L. V., *Izv. Akad. Nauk SSSR, Ser. Khim.,* **1952**, 152. (h) Egloff, G. and Hulla, G., *Chem. Rev.,* **1945**, *36,* 63.
4. (a) Dabbagh, H. A. and Salehi, J. M., *J. Org. Chem.,* **1998**, *63,* 7619. (b) Bailey, W. J. and King, C., *J. Am. Chem. Soc.,* **1955**, *77*, 75.
5. (a) Sung, K. S. and Wang, Y. Y., *J. Org. Chem.,* **2003**, *68*, 2771. (b) Bloodworth, A. J.; Bowyer, K. J. and Mitchell, J. C., *J. Org. Chem.,* **1986**, *51*, 1790. (c) Maccioni, A. and Secci, M., *Annali Chim. (Italy),* **1964**, *54*, 266.
6. Hassner, A., *J. Org. Chem.,* **1968**, *33*, 2684.
7. (a) Mohan, T.; Arumugam, S.; Wang, T.; Jacobsen, R. A. and Verkade, J. G., *Heteroatom Chem.,* **1996**, *7*, 455. (b) Gurudutt, K. N. and Shaw, A. K., *Indian J. Chem., Sect. B,* **1989**, *28B*, 422. (c) Wolkoff, P., *J. Org. Chem.,* **1982**, *47*, 1944. (d) Snyder, C. H. and Soto, A. R., *Tetrahedron Lett*., **1965**, 3261. (e) Brower, K. R. and Chen, J. S., *J. Am. Chem. Soc.,* **1965**, *87*, 3396. (f) Holm, T.,

Acta Chem. Scand., **1964**, *18*, 1577. (g) Botteron, D. G. and Shulman, G. P., *J. Org. Chem.,* **1962**, *27*, 2007. (h) DePuy, C. H. and Froemsdorf, D. H., *J. Am. Chem. Soc.,* **1960**, *82*, 634. (i) Baumgarten, H. E.; Bower, F. A.; Setterquist, R. A. and Allen, R. E., *J. Am. Chem. Soc.,* **1958**, *80*, 4588.

8. (a) Guan, H.-P.; Ksebati, M. B.; Kern, E. R. and Zemlicka, J., *J. Org. Chem.,* **2000**, *65,* 5177. (b) Kates, S. A.; Dombroski, M. A. and Snider, B. B., *J. Org. Chem.,* **1990**, *55*, 2427.
9. Bailey, W. J. and Hale, W. F., *J. Am. Chem. Soc.,* **1959**, *81*, 647.
10. (a) DePuy, C. H. and Leary, R. E., *J. Am. Chem. Soc.,* **1957**, *79*, 3705. (b) Saunders, W. H. and Williams, R. A., *J. Am. Chem. Soc.,* **1957**, *79*, 3712.
11. (a) Benkeser, R. A. and Hazdra, J. J., *J. Am. Chem. Soc.,* **1959**, *81*, 228.
12. (a) Brown, H. C.; Moritani, I. and Okamoto, Y., *J. Am. Chem. Soc.,* **1956**, *78*, 2193. (b) Brown, H. C. and Moritani, I., *J. Am. Chem. Soc.,* **1955**, *77*, 3607.
13. Brown, H. C.; Moritani, I. and Nakagawa, M., *J. Am. Chem. Soc.,* **1956**, *78*, 2190.
14. Brown, H. C. and Nakagawa, M., *J. Am. Chem. Soc.,* **1956**, *78*, 2197.
15. Averbuj, C. and Eisen, M. S., *J. Am. Chem. Soc.,* **1999**, *121,* 8755.
16. (a) Bunnett, J. F. and Baciocchi, E., *J. Org. Chem.,* **1970**, *35*, 76. (b) Froemsdorf, D. H.; Collins, C. H.; Hammond, G. S. and DePuy, C. H., *J. Am. Chem. Soc.,* **1959**, *81*, 643. (c) Benkeser, R. A.; Hazdra, J. J. and Burrous, M. L., *J. Am. Chem. Soc.,* **1959**, *81*, 5374. (d) Shiner, V. J. and Smith, M. L., *J. Am. Chem. Soc.,* **1958**, *80*, 4095. (e) DePuy, C. H. and Froemsdorf, D. H., *J. Am. Chem. Soc.,* **1957**, *79*, 3710. (f) Krug, R. C. and Yen, T. F., *J. Org. Chem.,* **1956**, *21*, 1441. (g) Brown, H. C. and Moritani, I., *J. Am. Chem. Soc.,* **1955**, *77*, 3623. (h) Shiner, V. J.; Boskin, M. J. and Smith, M. L., *J. Am. Chem. Soc.,* **1955**, *77*, 5525. (i) Cristol, S. J., *J. Am. Chem. Soc.,* **1947**, *69*, 338.

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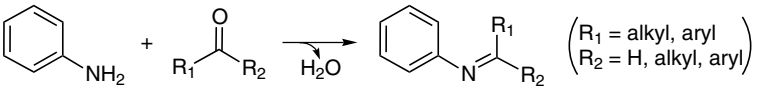
Schiff Base

A. GENERAL DESCRIPTION OF THE REACTION

The first Schiff base was reported by Schiff in 1864.[1] It is a special type of imine derivative formed by the condensation between a primary aromatic amine and an aldehyde or ketone, but sometimes the condensation products from aliphatic amine and ketone[2] or aldehyde[3] are also referred to as the Schiff bases.[4] It has been reported that under certain conditions, the formation of a Schiff base linkage proceeds reversibly without any additives.[5] In addition, imine formation is observed to take place faster in a slightly acidic conditions,[5] but the formed imine is subject to hydrolysis in a more acidic medium.[6] The prepared Schiff bases have found wide uses, such as to tune the metal-center electronic factors,[4b,7] the model compounds for the study of active sites of metalloenzymes,[8] and the chelators in coordination chemistry.[4d–4p,7,9,10] It should be pointed out that the salens (e.g., oxomanganese salen [*N*,*N*′-ethylene-bis(salicylideneaminato)] complex) are widely used in the *Jacobsen-Katsuki Epoxidation*,[10,11] and the chromium(III) complexes with chiral tridentate Schiff base is successfully used to catalyze the highly enantioselective and diastereoselective *hetero-Diels-Alder Cycloaddition*,[2a] etc. In addition, some Schiff bases have shown different biological activities, including antituberculous activity[12] and obstruction of the growth of animal tumors.[2d]

B. GENERAL REACTION SCHEME



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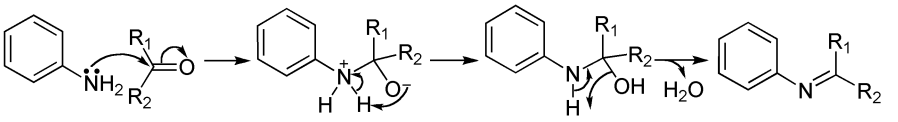
C. PROPOSED MECHANISMS

An illustrative mechanism for the formation of a Schiff base is given here.



D. MODIFICATION

N/A

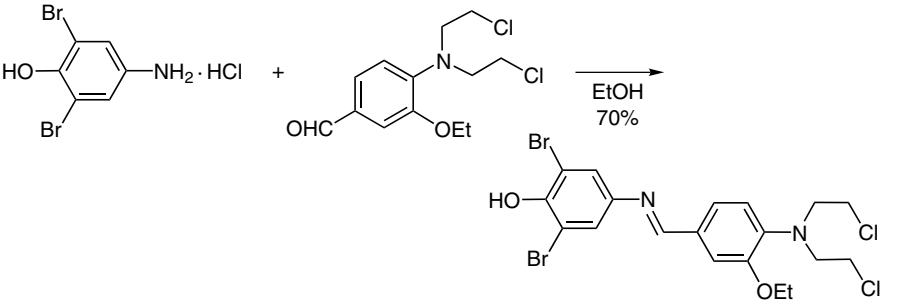
E. APPLICATIONS

The Schiff base has wide application in coordination chemistry as well as in organic synthesis.

F. RELATED REACTIONS

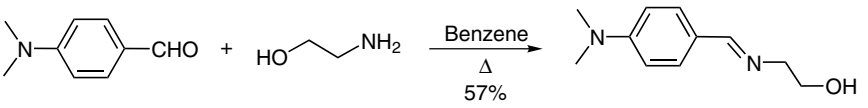
The Schiff base is related to the formation of imine.

G. CITED EXPERIMENTAL EXAMPLES



Reference 13.

To a solution of 3.0 g 2,6-dibromo-4-aminophenol hydrochloride (10 mmol) in dry warm ethanol was added a *conc*. ethanol solution of 2.9 g 4-[*N*,*N*-bis(2-chloroethyl)amino]-3-ethoxybenzaldehyde (10 mmol). The resulting dark red solution was stirred for a few hours and then cooled in ice to deposit the crystal solid. The crystal was filtered and washed with absolute ethanol and diethyl ether, and dried to afford 3.4 g 4-({4-[*N*,*N*-bis(2-chloroethyl)amino]-3-ethoxybenzylidene}-amino)-2,6-dibromophenol hydrochloride, in a yield of 70%.



Reference 2e.

A mixture of 14.92 g *p-N,N*-dimethylaminobenzaldehyde (0.1 mol), 4.45 g ethanolamine, and 50 mL dry benzene in a Dean-Stark moisture determination apparatus was refluxed in an oil bath until the volume of water collected in the trap remained constant (2–3 h). The benzene was removed by distillation under reduced pressure, and the residual oil was poured onto an ice-water mixture. The solid crystalline mass was triturated with cold water, collected on a suction filter, and washed on the filter with several portions of cold water. After drying the crystals on the filter by use of a rubber dam followed by air drying, the crude material was dissolved in boiling petroleum ether (b.p. 30–60°C), treated with Norite A for 15 min, and filtered. The filtrate was cooled in an ice-water bath to induce crystallization. The crystals were collected on a suction filter and washed with several small portions of cold petroleum ether, in a yield of 57%, m.p. 103–104°C.

Other references related to the Schiff base are cited in the literature.[14]

H. REFERENCES

1. Schiff, H., *Ann.,* **1864**, *3*, 343.
2. (a) Ruck, R. T. and Jacobsen, E. N., *J. Am. Chem. Soc.,* **2002**, *124*, 2882. (b) Li, Z.; Fernández, M. and Jacobsen, E. N., *Org. Lett.,* **1999**, *1*, 1611. (c) Sigman, M. S. and Jacobsen, E. N., *J. Am. Chem. Soc.,* **1998**, *120*, 4901. (d) Hodnett, E. M. and Dunn, W. J., *J. Med. Chem.,* **1972**, *15*, 339. (e) Nakamichi, M. and Webster, G. L., *J. Org. Chem.,* **1957**, *22*, 159. (f) Emerson, W. S.; Hess, S. M. and Uhlb, F. C., *J. Am. Chem. Soc.,* **1941**, *63*, 872.
3. Takeuchi, T.; Böttcher, A.; Quezada, C. M.; Simon, M. I.; Meade, T. J. and Gray, H. B., *J. Am. Chem. Soc.,* **1998**, *120*, 8555.
4. (a) Huang, S.-Y.; Lian, M.-N.; Tian, H. and Wang, G.-P., *Zhongguo Xiandai Yingyong Yaoxue*, **2007**, *24*, 92. (b) Liu, X.; Yu, T.-Z.; Ding, X.-S. and Qian, L., *Fenzi Kexue Xuebao,* **2007**, *23*, 135. (c) Zhang, G.-X. and Yang, R.-H., *Shandong Huagong*, **2007**, *36*, 1. (d) Rosu, T.; Gulea, A.; Pahontu, E. and Cotovaia, A., *Revista Chim. (Romania),* **2007**, *58*, 475. (e) Liu, B.; Fang, C.; Dong, Z.-B. and Li, J.-S., *Lett. Org. Chem.,* **2007**, *4*, 172. (f) Singh, Y., *Phosphorus, Sulfur & Silicon & Related Elements*, **2007**, *182*, 1805. (g) Leovac, V. M.; Joksovic, M. D.; Divjakovic, V.; Jovanovic, L. S.; Saranovic, Z. and Pevec, A., *J. Inorg. Biochem.,* **2007**, *101*, 1094. (h) Boghaei, D. M. and Gharagozlou, M., *J. Coord. Chem.,* **2007**, *60*, 339. (i) Zeng, W. F.; Chen, Y. H.; Chiang, M. Y. and Cheng, C. P., *Polyhedron,* **2007**, *26*, 1303. (j) Ravoof, T. B. S. A.; Crouse, K. A.; Tahir, M. I. M.; Cowley, A. R. and Akbar Ali, M., *Polyhedron,* **2007**, *26*, 1159. (k) Gaballa, A. S.; Asker, M. S.; Barakat, A. S. and Teleb, S. M., *Spectrochimica Acta, Part A: Mol. Biomol. Spect.,* **2007**, *67A*, 114. (l) Bansod, A. and Aswar, A., *Chinese J. Chem.,* **2007**, *25*, 154. (m) Langer, V.; Popkov, A.; Nadvornik, M. and Lycka, A., *Polyhedron,* **2007**, *26*, 911. (n) Selvakumar, P. M.; Suresh, E. and Subramanian, P. S., *Polyhedron,* **2007**, 26, 749. (o) Yu, T. Z.; Su, W. M.; Li, W. L.; Hong, Z. R.; Hua, R. N. and Li, B., *Thin Solid Films*, **2007**, *515*, 4080. (p) Rai, B. K. and Sharma, K., *Orient. J. Chem.,* **2006**, *22*, 645.
5. Dohno, C.; Okamoto, A. and Saito, I., *J. Am. Chem. Soc.,* **2005**, *127*, 16681.
6. Sumerford, W. T.; Hartung, W. H. and Jenkins, G. L., *J. Am. Chem. Soc.,* **1940**, *62*, 2082.

7. Schuetz, S. A.; Day, V. W.; Sommer, R. D.; Rheingold, A. L. and Belot, J. A., *Inorg. Chem.,* **2001**, *40*, 5292. [*Note*: In this article, enamine is claimed to be a Schiff base.]
8. (a) Feichtinger, D. and Plattner, D. A., *Angew. Chem. Int. Ed. Engl.,* **1997**, *36*, 1718. (b) Lu, Z. and Crabtree, R. H., *J. Am. Chem. Soc*., **1995**, *117*, 3994. (c) Berkassel, A., *Bioorg. Chem.,* **1991**, *19*, 101. (d) Dolphin, D., *Vitamin B12*, John Wiley & Sons, New York, **1984**.
9. (a) Sessler, J. L.; Tomat, E.; Mody, T. D.; Lynch, V. M.; Veauthier, J. M.; Mirsaidov, U. and Markert, J. T., *Inorg. Chem.,* **2005**, *44*, 2125. (b) Nimitsiriwat, N.; Marshall, E. L.; Gibson, V. C.; Elsegood, M. R. and Dale, S. H., *J. Am. Chem. Soc.,* **2004**, *126*, 13598.
10. See *Jacobsen-Katsuki Epoxidation* herein (P. 1534).
11. (a) Chen, C.; Hong, L.; Xu, Z.-Q.; Liu, L. and Wang, R., *Org. Lett.,* **2006**, *8*, 2277. (b) Won, D.-H.; Yoon, D.-W.; Hong, S.-J.; Ha, K. S.; Sessler, J. L. and Lee, C.-H., *Bull. Korean Chem. Soc.,* **2006**, *27*, 925. (c) Arnold, P. L.; Blake, A. J.; Wilson, C. and Love, J. B., *Inorg. Chem.,* **2004**, *43*, 8206. (d) Mandlik, P. R. and Aswar, A. S., *Pol. J. Chem.,* **2003**, *77*, 129. (e) Cindric, M.; Strukan, N.; Vrdoljak, V.; Kajfez, T. and Kamenar, B., *Croat. Chem. Acta,* **2003**, *76*, 257. (f) Oshima, S.; Hirayama, N.; Kubono, K.; Kokusen, H. and Honjo, T., *Anal. Sci.(Supplement),* **2001**, *17*, 1287. (g) Khalil, S. M. E., *Chem. Papers,* **2000**, *54*, 12. (h) Ruiz-Molina, D.; Veciana, J.; Wurst, K.; Hendrickson, D. N. and Rovira, C., *Inorg. Chem.,* **2000**, *39*, 617. (i) Cameron, P. A.; Gibson, V. C.; Redshaw, C.; Segal, J. A.; Bruce, M. D.; White, A. J. P. and Williams, D. J., *Chem. Commun.,* **1999**, 1883. (j) Marinovich, A. F.; O'Mahony, R. S.; Waters, J. M. and Waters, T. N. M., *Croat. Chem. Acta,* **1999**, *72*, 685. (k) Vance, A. L.; Alcock, N. W.; Busch, D. H. and Heppert, J. A., *Inorg. Chem.,* **1997**, *36*, 5132.
12. Merchant, J. R. and Chothia, D. S., *J. Med. Chem.,* **1970**, *13*, 335.
13. Shekawat, D. R.; Sabnis, S. S. and Deliwala, C. V., *J. Med. Chem.,* **1972**, *15*, 1196.
14. (a) Sessler, J. L.; Tomat, E. and Lynch, V. M., *J. Am. Chem. Soc.,* **2006**, *128*, 4184. (b) Viswanathamurthi, P. V.; Karvembu, R.; Tharaneeswaran, V. and Natarajan, K., *J. Chem. Sci.,* **2005**, *117*, 235. (c) Sessler, J. L.; Roznyatovskiy, V.; Pantos, G. D.; Borisova, N. E.; Reshetova, M. D.; Lynch, V. M.; Khrustalev, V. N. and Ustynyuk, Y. A., *Org. Lett.,* **2005**, *7*, 5277. (d) Iwakura, I.; Ikeno, T. and Yamada, T., *Org. Lett.,* **2004**, *6*, 949. (e) Kolandaivel, P. and Kanakaraju, R., *Int. J. Mol. Sci.,* **2004**, *5*, 1. (f) Tsvelikhovsky, D.; Gelman, D.; Molander, G. A. and Blum, J., *Org. Lett.,* **2004**, *6*, 1995. (g) Kuwata, O.; Yuan, C.; Misra, S.; Govindjee, R. and Ebrey, T. G., *Biochemistry (Moscow),* **2001**, *66*, 1283. (h) Okino, T. and Takemoto, Y., *Org. Lett.,* **2001**, *3*, 1515. (i) Tajkhorshid, E.; Paizs, B. and Suhai, S., *J. Phys. Chem. B,* **1997**, *101*, 8021. (j) Hu, J. G. G.; Griffin, R. G. and Herzfeld, J., *J. Am. Chem. Soc.,* **1997**, *119*, 9495. (k) Hodnett, E. M. and Mooney, P. D., *J. Med. Chem.,* **1970**, *13*, 786. (l) Goldman, I. M.; Larson, J. K.; Tretter, J. R. and Andrews, E. G., *J. Am. Chem. Soc.,* **1969**, *91*, 4941. (m) Bahner, C. T.; Brotherton, D. and Brotherton, M. K., *J. Med. Chem.,* **1968**, *11*, 405. (n) Murahashi, S., *J. Am. Chem. Soc.,* **1955**, *77*, 6403. (o) Ferguson, L. N. and Robinson, J. K., *J. Am. Chem. Soc.,* **1949**, *71*, 742. (p) Sprung, M. M., *Chem. Rev.,* **1940**, *26*, 297. (q) Scudi, J. V.; Ratish, H. D. and Bullowa, J. G. M., *J. Am. Chem. Soc.,* **1939**, *61*, 2554. (r) Schiff, H., *Ber.,* **1892**, *25*, 1936. (s) Schiff, H., *Ann.,* **1881**, *210*, 114. (t) Schiff, H., *Ann.,* **1880**, *201*, 355. (u) Schiff, H., *Ann.,* **1868**, *148*, 330. (v) Schiff, H., *Ann.,* **1867**, *140*, 93.

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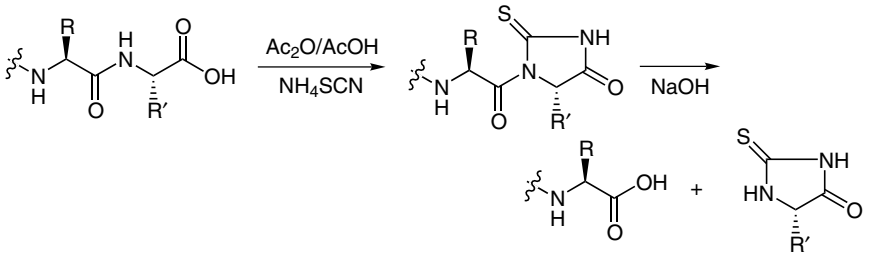
Schlack-Kumpf Reaction
(Johnson Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Johnson in 1911,[1] and subsequently used by Schlack and Kumpf in 1926[2] to sequence peptides and proteins from the C-terminal. It is the synthesis of 2-thiohydantoins from α-amino acids with thiocyanate and acetic anhydride; therefore, it is simply called the Johnson reaction;[3] however, because it has an important use for peptide and protein sequencing, this reaction is mostly known as the Schlack-Kumpf reaction.[4] In this reaction, the terminal carboxyl group is activated by the formation of a mixed anhydride with acetic anhydride,[5] which then reacts with ammonium thiocyanate to give a peptidyl 2-thiohydantoin, the 2-thiohydantoin is then cleaved from the peptide chain to expose the second carboxyl group as the new terminal carboxyl group by the treatment with a base. However, this reaction does have a few disadvantages: the severity of the conditions for the complete conversion of terminal carboxyl group into peptidyl 2-thiohydantoin and its cleavage.[6] In addition, the C-terminal aspartate, proline[3b,6,7]—as well as other amino acids such as lysine, glutamine, glutamate, and arginine[8]—all have difficulty forming the corresponding 2-thiohydantoin derivatives.

B. GENERAL REACTION SCHEME



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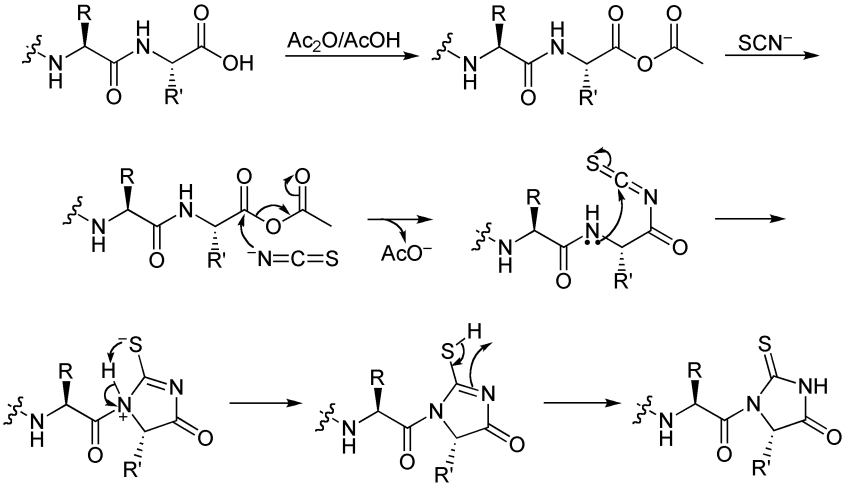
C. PROPOSED MECHANISMS

Only the mechanism for the formation of peptidyl 2-thiohydantoin is illustrated here.



D. MODIFICATION

This reaction has been extended to the reaction of terminal amino acids with thiocyanic acid[7b,9] (also developed initially by Johnson[10]) and trimethylsilyl isothiocyanate[11] for the formation of thiohydantoin. In addition, 12 *N* HCl[11] and acetohydroxamate[8] have been used to cleave the 2-thiohydantoin from the peptide chain.

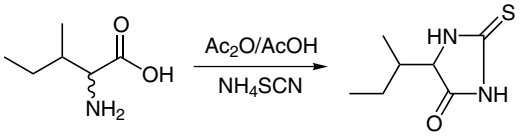
E. APPLICATIONS

This reaction has a general application in the preparation of 2-thiohydantoins from pure amino acids but mostly is used for the sequencing of peptide and protein starting from the C-terminal.

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



DL-Isoleucine

Reference 8c.

A mixture of 10 mmol amino acid, 0.9 g ammonium thiocyanate, 10 mL acetic anhydride, and 1.3 mL acetic acid was heated at 100°C for 30 min. Then the mixture was poured into 50 mL water, and an oil separated from the water, which subsequently crystallized. Further purification was accomplished by recrystallization of the crude 2-thiohydantoin from ethanol. The 5-*sec*-butyl-2-thiohydantoin from racemic DL-isoleucine has melting point of 163°C. (no yield was given for this preparation).

Other references related to the Schlack-Kumpf reaction are cited in the literature.[12]

H. REFERENCES

1. (a) Johnson, T. B. and Nicolet, B. H., *J. Am. Chem. Soc.*, **1911**, *33*, 1973. (b) Johnson, T. B. and Scott, W. M., *J. Am. Chem. Soc.*, **1913**, *35*, 1136.
2. Schlach, P. and Kumpf, W., *Z. Physiol. Chem.*, **1926**, *154*, 125.
3. (a) Bardos, T. J.; Gordon, H. L. and Heenan, E. F., *J. Am. Chem. Soc.*, **1955**, *77*, 3115. (b) Fox, S. W.; Hurst, T. L.; Griffith, J. F. and Underwood, O., *J. Am. Chem. Soc.*, **1955**, *77*, 3119.
4. (a) Duggan, B. M.; Laslett, R. L. and Wilshire, J. F. K., *Aust. J. Chem.*, **1996**, *49*, 541. (b) Casagranda, F.; Duggan, B. M.; Kirkpatrick, A.; Laslett, R. L. and Wilshire, J. F. K., *Aust. J. Chem.*, **1996**, *49*, 551.
5. Meuth, J. L.; Harris, D. E.; Dwulet, F. E.; Crowl-Powers, M. L. and Gurd, F. R. N., *Biochemistry*, **1982**, *21*, 3750.
6. Bailey, J. M. and Shively, J. E., *Biochemistry*, **1990**, *29*, 3145.
7. (a) Suzuki, T.; Song, K.-D.; Itagaki, Y. and Tuzimura, K., *Org. Mass Spect.*, **1976**, *11*, 557. (b) Stark, G. R., *Biochemistry*, **1968**, *7*, 1796. (c) Turner, R. A. and Schmerzler, G., *Biochim. Biophys. Acta*, **1954**, *13*, 553.
8. (a) Miller, C. G.; Kong, C.-T. and Shively, J. E., *Techniques in Protein Chemistry,* ed. Hugli, T. E. Academic Press, New York, **1989**, pp. 67–78. (b) Baptist, V. H. and Bull, H. B., *J. Am. Chem. Soc.*, **1953**, *75*, 1727. (c) Kuck, J. F. R.; Herda, J. J.; Kovac, W. E. and Karabinos, J. V., *J. Am. Chem. Soc.*, **1951**, *73*, 5470.
9. Dwulet, F. E. and Gurd, F. R. N., *Int. J. Peptide Protein Res.*, **1979**, *13*, 122.
10. (a) Johnson, T. B. and Bengis, R., *J. Am. Chem. Soc.*, **1913**, *35*, 1605. (b) Johnson, T. B. and Scott, W. M., *J. Am. Chem. Soc.*, **1913**, *35*, 1130. (c) Johnson, T. B. and Nicolet, B. H., *J. Am. Chem. Soc.*, **1912**, *34*, 1973.
11. Hawke, D. H.; Lahm, H.-W.; Shively, J. E. and Todd, C. W., *Anal. Biochem.*, **1987**, *166*, 298.
12. (a) Samyn, B.; Hardeman, K.; van der Eychen, J. and van Beeumen, J., *Anal. Chem.*, **2000**, *72*, 1389. (b) Shepherd, R. G.; Willson, S. D.; Howard, K. S.; Bell, P. H.; Davies, D. S.; Davis, S. B.; Eigner, E. A. and Shakespeare, N. E., *J. Am. Chem. Soc.*, **1956**, *78*, 5067. (c) Ramachandran, L. K.; Epp, A. and McConnell, W. B., *Anal. Chem.*, **1955**, *27*, 1734. (d) Turner, R. A. and Schmerzler, G., *J. Am. Chem. Soc.*, **1954**, *76*, 949. (e) Synge, R. L. M., *Chem. Rev.*, **1943**, *32*, 135.

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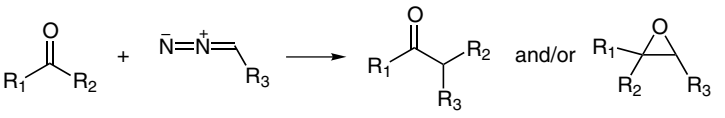
Schlotterbeck Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Meyer in 1905,[1] and was closely investigated by Schlotterbeck beginning in 1907.[2] It is the reaction between a carbonyl compound (aldehyde and ketone) and a diazoalkane to form a new ketone or oxirane (i.e., epoxide) and is generally referred to as the Schlotterbeck reaction.[3] This reaction is not always clean-cut, forming either a ketone or an epoxide.[4] For example, *m*- and *p*-nitrobenzaldehydes react with diazomethane to give corresponding acetophenones, whereas *o*-nitrobenzaldehyde affords *o*-nitrostyrene oxide.[3d] For another example, piperonal reacts with two equivalents of diazomethane to afford safrole oxide.[5] As a result, this reaction is currently of no general use in organic synthesis,[3d] and alternative methods have been used for the preparation of ketones. However, this reaction is useful for the preparation of β-keto ester from ethyl diazoacetate.[2b]

B. GENERAL REACTION SCHEME

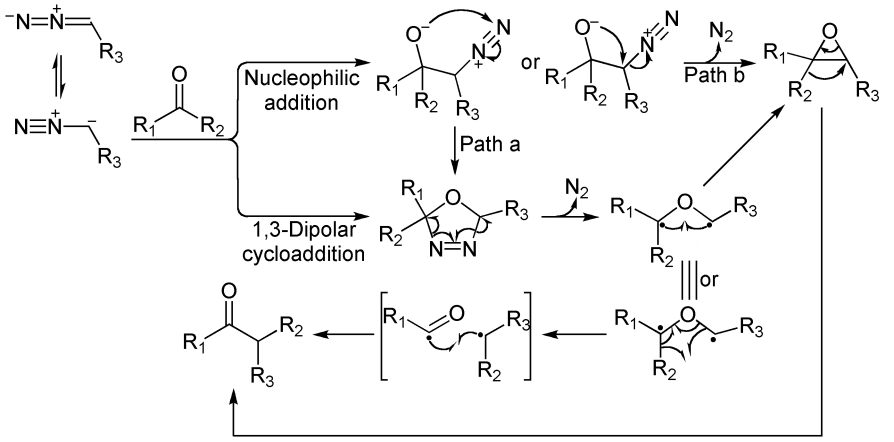


(R_1 = alkyl, aryl; R_2 = H, alkyl, aryl; R_3 = H, alkyl, CO_2Et, etc.)

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

Although a free radical mechanism has been proposed for this reaction,[6] it is much more plausible that the Schlotterbeck reaction involves a nucleophilic attack of the diazoalkane[7] on the carbonyl group to form a diazonium betaine or neutral Δ^2-1,2,3-oxadiazoline intermediate, which then decomposes to give either a ketone or an epoxide[8] as illustrated here.



D. MODIFICATION

This reaction has been extended to directly convert aldehydes into β-keto esters by reacting with ethyl diazoacetate in the presence of a catalytic amount of $SnCl_2$.[9] In addition, the reaction between diazoalkanes and acyl halides to form α-halomethyl ketones, known as the *Nierenstein Reaction*, should be considered as another extension of the Schlotterbeck reaction.

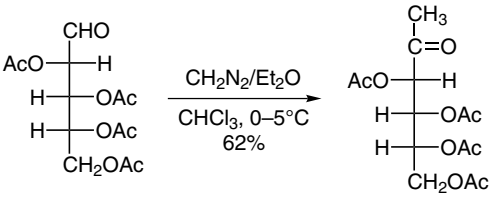
E. APPLICATIONS

This reaction is currently of limited application in organic synthesis.

F. RELATED REACTIONS

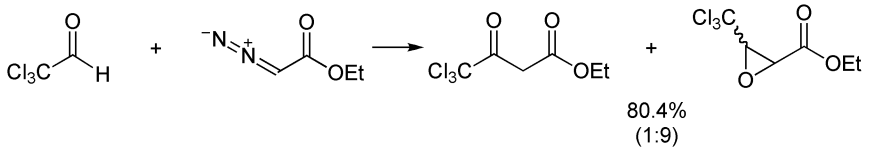
This reaction is closely related to the *Nierenstein Reaction*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 10.

The diazomethane generated by the decomposition of 20 mL urethane was distilled in an ether stream directly into an absolute chloroform solution of 24 g *aldehydo*-D-arabinose tetraacetate cooled to 0–5°C. There was a steady, vigorous evolution of nitrogen as the reaction proceeded. The yellow color of the diazomethane was discharged very quickly until about three fourths of the total quantity had been added. The solution then acquired a permanent yellow tinge, indicating an excess of diazomethane. After the solution stood overnight at room temperature, the color vanished. The amorphous precipitate of polymethylenes was removed by filtration, and the solvent was removed by evaporation. The syrup was taken up in 50 mL absolute ethanol, and the solution made opalescent by the addition of petroleum ether. The product of 1-*deoxy*-keto-D-fructose tetraacetate on standing in an ice box (two crops) crystallized slowly to give 15.4 g beautiful cubic crystals, in a yield of 62%, m.p. 75–77°C. Pure product was obtained after four recrystallizations from 95% ethanol, m.p. 77–78°C.



Reference 3a.

Redistilled chloral (59.0 g, 0.4 mol) and 45.6 g ethyl diazoacetate (0.4 mol) were mixed according to Schlotterbeck's procedure. The yellow liquid obtained was fractionally distilled under reduced pressure to yield 75.0 g of a mixture of ethyl trichloroacetoacetate and ethyl 3-(trichloromethyl)glycidate in a ratio of 1:9, in a yield of 80.4%, b.p. 80°C at 1 mmHg. The product gave a positive ferric chloride test. This yellow liquid was then dissolved in ether and washed three times with ice-cooled 10% ammonium hydroxide solution and then with water until the water layer was neutral when tested with litmus paper. The ether layer was dried over anhydrous $MgSO_4$, and the ether was removed by distillation. The remaining yellow oil was fractionally distilled in vacuo to give 45 g ethyl 3-(trichloromethyl) glycidate, with a yield of 48.2% based on the original starting material, b.p. 85°C at 1.5 mmHg.

Other references related to the Schlotterbeck reaction are cited in the literature.[11]

H. REFERENCES

1. Meyer, H., *Monatsh.*, **1905**, *26*, 1295.
2. (a) Schlotterbeck, F., *Ber.*, **1907**, *40B*, 479. (b) Schlotterbeck, F., *Ber.*, **1907**, *40B*, 3000. (c) Schlotterbeck, F., *Ber.*, **1909**, *42B*, 2559.
3. (a) Wald, D. K. and Joullié, M. M., *J. Org. Chem.*, **1966**, *31*, 3369. (b) Fried, J. and Elderfield, R. C., *J. Org. Chem.*, **1941**, *6*, 577. (c) Hey, D. H. and Waters, W. A., *Chem. Rev.*, **1937**, *21*, 169. (d) Smith, L. I., *Chem. Rev.*, **1938**, *23*, 193. (e) Malkin, T. and Nierenstein, M., *J. Am. Chem. Soc.*, **1930**, *52*, 1504. (f) Lewis, H. H.; Nierenstein, M. and Rich, E. M., *J. Am. Chem. Soc.*, **1925**, *47*, 1728.
4. (a) Arndt, F.; Eistert, B. and Ender, W., *Ber.*, **1929**, *62B*, 44. (b) Arndt, F.; Eistert, B. and Partale, W., *Ber.*, **1928**, *61B*, 1107. (c) Arndt, F.; Eistert, B. and Amende, J., *Ber.*, **1928**, *61B*, 1949. (d) Arndt, F. and Partale, W., *Ber.*, **1927**, *60B*, 446.
5. (a) Mosettig, E., *Ber.*, **1929**, *62B*, 1271. (b) Mosettig, E., *Ber.*, **1928**, *61B*, 1391.
6. Mosettig, E. and Burger, A., *J. Am. Chem. Soc.*, **1930**, *52*, 3456.
7. Robinson, R. and Smith, L. H., *J. Chem. Soc.*, **1937**, 371.
8. Shimizu, N. and Bartlett, P. D., *J. Am. Chem. Soc.*, **1978**, *100*, 4260.
9. Holmquist, C. R. and Roskamp, E. J., *J. Org. Chem.*, **1989**, *54*, 3258.
10. Wolfrom, M. L.; Weisblat, D. I.; Zophy, W. H. and Waisbrot, S. W., *J. Am. Chem. Soc.*, **1941**, *63*, 201.
11. (a) Alonso, M. E.; Garcia, M. del C. and Chitty, A. W., *J. Org. Chem.*, **1985**, *50*, 3445. (b) Russell, P. B., *J. Am. Chem. Soc.*, **1953**, *75*, 5315. (c) Smith, L. I. and Pings, W. B., *J. Org. Chem.*, **1937**, *2*, 95. (d) Meyer, H., *Ber.*, **1907**, *40B*, 847.

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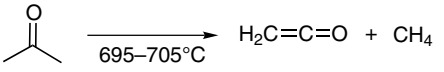
Schmidlin Ketene Synthesis

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Schmidlin and Bergman in 1910.[1] It is a gaseous synthesis of ketene by thermal decomposition[2] or pyrogenic decomposition[3] of acetone through a combustion tube filled with pieces of clay,[2b,4] in a temperature range of 500–750°C. The optimal temperature is the maximum temperature that is compatible with the decomposition of ketene itself by heat,[4] and is found in the range of 695–705°C.[3b] At this temperature, acetone decomposes into ketene and methane.[4,5] In general, three major factors that will affect the yield of ketene in this reaction are the choice of the combustion tube, the reaction temperature, and the fraction of acetone decomposed. For example, this reaction cannot be conducted through a metal tube, either a copper tube[4] or an iron pipe[3b] because carbon may form via dehydrogenation in the presence of some metal oxides.[3b] Although the quartz static system is a suitable reaction environment for ketene synthesis,[6] the yield of ketenes is essentially similar to that conducted in the glass tube.[7] In addition, it has been observed that acetone decomposes into methane, carbon monoxide, and acetylene at 1000°C in a 1-m long copper tube,[4] whereas it yields mesityl oxide between 410° and 420°C over a thoria catalyst[8] as well as over alumina or zirconia.[4] At the optimal temperature in a glass tube, it has been found that the best yield of ketene obtainable is ∼ 35% when less than 40% of acetone is decomposed,[3b] indicating that a comparatively rapid flow of the acetone vapor is needed to carry the ketene out of the reaction chamber once it is generated.[4]

B. GENERAL REACTION SCHEME



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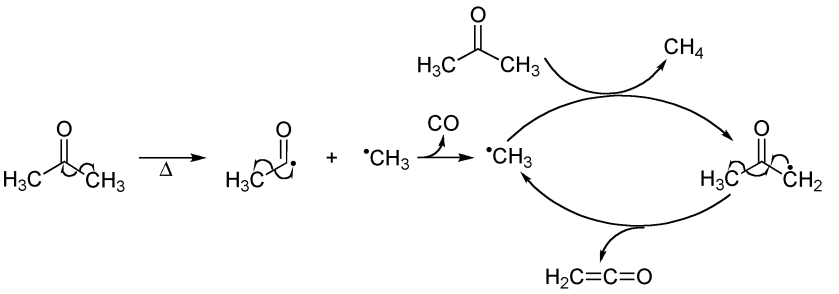
C. PROPOSED MECHANISMS

It is assumed that acetone at such high temperatures decomposes into methyl and acetyl radicals, and the latter further degrades into methyl radical and carbon monoxide. Then methyl radical abstracts one hydrogen atom from acetone to give methane and an acetylmethyl radical that decomposes into ketene and another methyl radical.[2b] Displayed here is the reaction mechanism for the Schmidlin ketene synthesis.



D. MODIFICATION

N/A

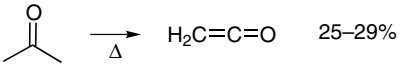
E. APPLICATIONS

This reaction is very useful for the production of ketene and is cheaper than the analogous thermal decomposition of acetic anhydride[9] and acetyl chloride.[4]

F. RELATED REACTIONS

N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3a.

A 500-mL two-necked round-bottomed flask was equipped with a dropping funnel and an adaptor to a glass combustion tube filled with broken porcelain. The other end of the combustion tube was connected with a refluxing condenser through a three-way stopcock, one to a flask to collect the condensed acetone and the other for connecting with the condenser. The evolved gas from the condenser is led to another reactor to trap the ketene via a tube. To this reaction setup, 126 mL acetone (1.7 mol) was added to the dropping funnel, and the flask was heated by boiling water. The combustion tube was heated by 14 burners,

and tiles are placed over the burners and adjusted to yield a maximum temperature. When the combustion tube was fully heated, acetone was dropped into the flask at a rate of 3–4 mL/min, and about half the acetone was recovered from the condenser. The ketene was produced in 25–29%.

Other references related to the Schmidlin ketene synthesis are cited in the literature.[10]

H. REFERENCES

1. Schmidlin, J. and Bergman, M., *Ber.*, **1910**, *43*, 2821.
2. (a) Gattermann, L., *Laboratory Methods of Organic Chemistry*, MacMillan, New York, **1937**. (b) Rice, F. O.; Greenberg, J.; Waters, C. E. and Vollrath, R. E., *J. Am. Chem. Soc.*, **1934**, *56*, 1760.
3. (a) Hurd, C. D., *Org. Synth. Coll.*, **1941**, *1*, 330. (b) Hurd, C. D. and Tallyn, W. H., *J. Am. Chem. Soc.*, **1925**, *47*, 1427.
4. Hurd, C. D. and Cochran, P. B., *J. Am. Chem. Soc.*, **1923**, *45*, 515.
5. Freudenheim, M. E., *J. Phys. Chem.*, **1918**, *22*, 184.
6. Hinshelwood, C. N. and Hutchinson, W. K., *Proc. Roy. Soc. (London)*, **1926**, *111A*, 245.
7. Rice, F. O. and Vollrath, R. E., *Proc. Nat. Acad. Sci. USA*, **1929**, *15*, 702.
8. Maihle, A. and de Godon, F., *Bull. Soc. Chim.*, **1917**, *21*, 61.
9. (a) Deakin, S. and Wilsmore, N. T. M., *J. Chem. Soc.*, **1910**, *97*, 1968. (b) Wilsmore, N. T. M., *J. Chem. Soc.*, **1907**, *91*, 1938.
10. (a) Quadbeck, G., *Angew. Chem.*, **1956**, *68*, 361. (b) Hanford, W. E. and Sauer, J. C., *Org. React.*, **1946**, *3*, 109. (c) Williams, J. W. and Hurd, C. D., *J. Org. Chem.*, **1940**, *5*, 122. (d) Dashkevich, B. N., *Zh. Obsh. Khim.*, **1938**, *8*, 779. (e) Al, J., *Angew. Chem.*, **1932**, *45*, 545. (f) Berl, and Kullmann, *Ber.*, **1932**, *65*, 1114. (g) Ott, E.; Schröter, R. and Packendorff, K., *J. Prakt. Chem.*, **1931**, *130*, 177. (h) Ploeg, W., *Rec. Trav. Chim. Pays-Bas Belg.*, **1926**, *45*, 342. (i) Staudinger, H. and Hauser, E., *Helv. Chim. Acta*, **1921**, *4*, 887.

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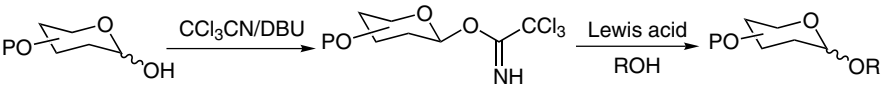
Schmidt Glycosylation
(Schmidt Glycosidation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction, originating from Sinaÿ's glycosyl imidate donor reported in 1976,[1] has been extensively explored by Schmidt and co-workers since 1980.[2] It is a Lewis acid-catalyzed glycosylation using glycosyl trichloroacetimidate as the donor. Therefore, this reaction is generally known as the Schmidt glycosylation.[3] Occasionally, it is also referred to as the Schmidt glycosidation,[4] Schmidt coupling,[3h,5] or Schmidt trichloroacetimidate method.[6] Nowadays, it is one of the most popular methods for glycosylation, second only to the glycosylation with a thioglycoside donor.[7] In this reaction, the glycosyl trichloroacetimidate can be simply prepared by the treatment of a carbohydrate precursor with trichloroacetonitrile in the presence of a base, such as DBU, K_2CO_3, Cs_2CO_3, or NaH. When K_2CO_3[8] or DBU[9] is used as the base, β-glycosyl trichloroacetimidate predominates, even though the formation of α- and β-anomeric mixtures is also possible by the treatment of DBU.[10] In contrast, α-glycosyl trichloroacetimidate is formed in preference when Cs_2CO_3[11] or NaH[12] is used. The popularity of this reaction in carbohydrate transformations may be attributed to the mildly acidic coupling conditions and the opportunities to alter α/β selectivity via different glycosyl trichloroacetimidate donors and/or the coupling reagents.[3h] The mild acids compatible with this glycosylation include TMSOTf,[4b,10a,11,13] $BF_3{\cdot}Et_2O$,[10b,14] TBDMSOTf,[10a] TBSOTf,[7] and perchloric acid.[7] Among these promoters, TMSOTf,[10a,11,13d] TBDMSOTf,[10a] and AgOTf[11] often lead to the formation of a β-glycosidic linkage, especially when α-glycosyl trichloroacetimidate is used as the glycosyl donor;[11] in addition, the general 1,2-*trans* selectivity of glycosylation also applies to this reaction, as evidenced in the formation of β-glucoside and α-mannoside.[13e] However, in the presence of $BF_3{\cdot}Et_2O$ promoter, α-glycoside is favored,[10b] and such preference is even observed for the preparation of α-C-glycosides.[15]

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

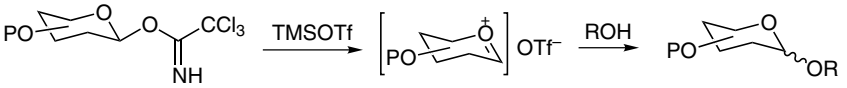
B. GENERAL REACTION SCHEME



(P = protecting group
R = alkyl, carbohydrate, etc.
Lewis acid = TMSOTf, $BF_3 \cdot Et_2O$, etc.)

C. PROPOSED MECHANISMS

Similar to the glycosylation from other types of glycol donors, it is assumed that glycosyl trichloroacetimidate is converted into glycosyl cation, which then couples with a glycosyl acceptor. However, the direct attack of glycosyl trichloroacetimidate by an acceptor (a S_N2 reaction) may also be involved in this reaction, where a higher amount of α-glycosides can be obtained from a β-glycosyl trichloroacetimidate.[13a] A general illustration of the glycosylation is displayed here.



D. MODIFICATION

Glycosyl trifluoroacetimidate has recently been developed as the glycosyl donor,[3f,16] which holds a particularly good reactivity for the glycosylation of sialic acid.[7] In addition, the Schmidt glycosylation has been extended to occur on a solid phase[12a,17] or column,[3] as well as in an ionic liquid (e.g., [emim][OTf] and [bmim][PF_6]).[13a] Especially, in ionic liquids, it has been found that under certain conditions, the Schmidt glycosylation takes place without a Lewis acid catalyst and yields preferentially the β-glycosides from trichloroacetimidate bearing a nonparticipating group at C-2 in [emim][OTf].[13a] Moreover, this reaction has been carried out under sonication, a condition with shortened reaction time, enhanced reactivity, and stereoselectivity.[18]

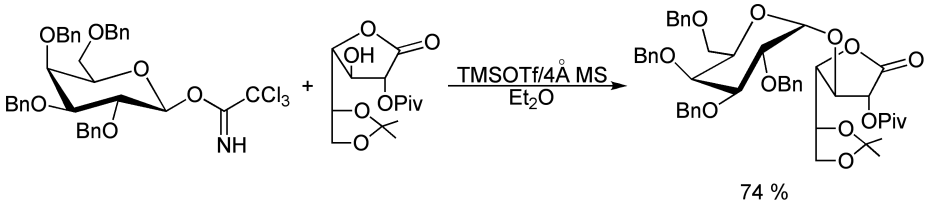
E. APPLICATIONS

This reaction has a very broad application in the carbohydrate transformation.

F. RELATED REACTIONS

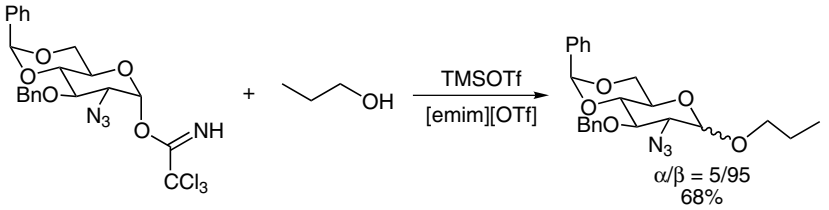
This reaction is related to the *Helferich Glycosylation*. In addition, many other glycol donors have also been developed, which include glycosyl fluorides,[19] 1,2-anhydrosugars,[20] glycosyl phosphates,[21] glycosyl sulfoxide,[22] *n*-pentenyl glycosides,[23] thioglycosides,[24] and thioimidates.[25]

G. CITED EXPERIMENTAL EXAMPLES



Reference 13c.

A mixture of 300 mg *O*-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl)-trichloroacetimidate (0.44 mmol), 141 mg 5,6-*O*-isopropylidene-2-*O*-pivaloyl-D-galactono-1,4-lactone (0.47 mmol), and 500 mg powdered 4Å molecular sieves in dry ether was vigorously stirred at 0°C under an argon atmosphere. After 20 min, 25 μL TMSOTf (0.14 mmol) was slowly added, and the stirring was continued for 2 h. The suspension was neutralized by the addition of *N*,*N*-diisopropyl-*N*-ethylamine, filtered through Celite, and concentrated under reduced pressure. The residue was purified by column chromatography using toluene/EtOAc (20:1) as the eluent to afford 269 mg 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl-(1$\rightarrow$3)-5,6-*O*-isopropylidene-2-*O*-pivaloyl-D-galactono-1,4-lactone as a colorless syrup, in a yield of 74%, R_f = 0.71 (toluene/EtOAc, 5:1).



Reference 13a.

A mixture of 100 mg 2-deoxy-2-azido-3-*O*-benzyl-4,6-*O*-benziliden-α-D-glucopyranoside (0.23 mmol), and 275 mg 2-propanol (4.58 mmol, 20 eq.) was dissolved in 0.5 mL [emim][OTf]. Then 2.3 μmol TMSOTf (0.01 eq.) was added. The reaction was stirred at room temperature for 1 h, and water was added to quench the reaction. The resulting mixture was extracted with $CHCl_3$. Upon removal of the solvent, the residue was purified by flash column chromatography using hexane/EtOAc (9:1) as the eluent to afford 68% of *O*-isopropyl-2-deoxy-2-azido-3-*O*-benzyl-4,6-*O*-benziliden-β-D-glucopyranoside and its α-anomer in a 95:5 ratio.

Other references related to the Schmidt glycosylation are cited in the literature.[26]

H. REFERENCES

1. Pougny, J.-R. and Sinaÿ, P., *Tetrahedron Lett.*, **1976**, 4073.
2. (a) Schmidt, R. R. and Michel, J., *Angew. Chem. Int. Ed. Engl.*, **1980**, *19*, 731. (b) Schmidt, R. R., *Angew. Chem. Int. Ed. Engl.*, **1986**, *25*, 212. (c) Schmidt, R. R. and Kinzy, W., *Adv. Carbohydr.*

Chem. Biochem., **1994**, *50*, 21. (d) Schmidt, R. R. and Jung, K.-H., *Oligosaccharide Synthesis with Trichloroacetimidates* in *Preparative Carbohydrate Chemistry*, ed. Hanessian, S, Dekker, New York, **1997**, pp. 283–312.

3. (a) Sanceau, J.-Y.; Larouche, D.; Caron, B.; Belanger, P.; Coquet, A.; Belanger, A.; Labrie, F. and Gauthier, S., *J. Labelled Compd. Radiopharm.*, **2007**, *50*, 197. (b) Chakraborty, T. K.; Reddy, V. R. and Chattopadhyay, A. K., *Tetrahedron Lett.*, **2006**, *47*, 7435. (c) Pletcher, J. M. and McDonald, F. E., *Org. Lett.*, **2005**, *7*, 4749. (d) Zhang, G. H.; Fu, M. K. and Ning, J., *Carbohydr. Res.*, **2005**, *340*, 155. (e) Paterson, I.; Davies, R. D. M.; Heimann, A. C.; Marquez, R. and Meyer, A., *Org. Lett.*, **2003**, *5*, 4477. (f) Cai, S. T. and Yu, B., *Org. Lett.*, **2003**, *5*, 3827. (g) Wang, H. R.; Zhang, G. H. and Ning, J., *Carbohydr. Res.*, **2003**, *338*, 1033. (h) Myers, A. G.; Glatthar, R.; Hammond, M.; Harrington, P. M.; Kuo, E. Y.; Liang, J.; Schaus, S. E.; Wu, Y. S. and Xiang, J.-N., *J. Am. Chem. Soc.*, **2002**, *124*, 5380. (i) Pozsgay, V., *Angew. Chem. Int. Ed.*, **1998**, *37*, 138. (j) Liu, M. Z.; Yu, B.; Guo, Z. W.; Li, C. and Hui, Y. Z., *Carbohydr. Lett.*, **1997**, *2*, 423. (k) Gurjar, M. K. and Saha, U. K., *Bioorg. Med. Chem. Lett.*, **1993**, *3*, 697.
4. (a) Rele, S. M.; Cui, W. X.; Wang, L. C.; Hou, S. J.; Barr-Zarse, G.; Tatton, D.; Gnanou, Y.; Esko, J. D. and Chaikof, E. L., *J. Am. Chem. Soc.*, **2005**, *127*, 10132. (b) Trost, B. M.; Gunzner, J. L.; Dirat, O. and Rhee, Y. H., *J. Am. Chem. Soc.*, **2002**, *124*, 10396. (c) Trost, B. M.; Dirat, O. and Gunzner, J. L., *Angew. Chem. Int. Ed.*, **2002**, *41*, 841.
5. (a) Garner, P. and Sesenoglu, O., *Org. Lett.*, **2004**, *6*, 1217. (b) Myers, A. G.; Liang, J.; Hammond, M.; Harrington, P. M.; Wu, Y. S. and Kuo, E. Y., *J. Am. Chem. Soc.*, **1998**, *120*, 5319.
6. (a) Harding, J. R.; King, C. D.; Perrie, J. A.; Sinnott, D. and Stachulski, A. V., *Org. Biomol. Chem.*, **2005**, *3*, 1501. (b) Sato, R.; Toma, K.; Nomura, K.; Takagi, M.; Yoshida, T.; Azefu, Y. and Tamiaki, H., *J. Carbohydr. Chem.*, **2004**, *23*, 375. (c) Urban, F. J.; Moore, B. S. and Breitenbach, R., *Tetrahedron Lett.*, **1990**, *31*, 4421.
7. Mukhopadhyay, B.; Maurer, S. V.; Rudolph, M.; van Well, R. M.; Russell, D. A. and Field, R. A., *J. Org. Chem.*, **2005**, *70*, 9059.
8. Katano, K.; An, H. Y.; Aoyagi, Y.; Overhand, M.; Sucheck, S. J. Stevens, W. C.; Hess, C. D.; Zhou, X. and Hecht, S. M., *J. Am. Chem. Soc.*, **1998**, *120*, 11285.
9. Gandolfi-Donadío, L.; Gallo-Rodriguez, C. and de Lederkremer, R. M., *J. Org. Chem.*, **2003**, *68*, 6928.
10. (a) Chong, P. Y. and Roush, W. R., *Org. Lett.*, **2002**, *4*, 4523. (b) Izumi, M.; Tsuruta, O.; Harayama, S. and Hashimoto, H., *J. Org. Chem.*, **1997**, *62*, 992.
11. Larson, D. P. and Heathcock, C. H., *J. Org. Chem.*, **1997**, *62*, 8406.
12. (a) Roussel, F.; Knerr, L.; Grathwohl, M. and Schmidt, R. R., *Org. Lett.*, **2000**, *2*, 3043. (b) Roush, W. R.; Gung, B. W. and Bennett, C. E., *Org. Lett.*, **1999**, *1*, 891.
13. (a) Rencurosi, A.; Lay, L.; Russo, G.; Caneva, E. and Poletti, L., *J. Org. Chem.*, **2005**, *70*, 7765. (b) Fürstner, A.; Ruiz-Caro, J.; Prinz, H. and Waldmann, H., *J. Org. Chem.*, **2004**, *69*, 459. (c) Gandolfi-Donadio, L.; Gallo-Rodriguez, C. and de Lederkremer, R. M., *J. Org. Chem.*, **2002**, *67*, 4430. (d) Yeung, B. K. S.; Hill, D. C.; Janicka, M. and Petillo, P. A., *Org. Lett.*, **2000**, *2*, 1279. (e) Marino-Albernas, J. R.; Bittman, R.; Peters, A. and Mayhew, E., *J. Med. Chem.*, **1996**, *39*, 3241.
14. Lassaletta, J. M.; Carlsson, K.; Garegg, P. J. and Schmidt, R. R., *J. Org. Chem.*, **1996**, *61*, 6873.
15. Dondoni, A.; Marra, A. and Massi, A., *J. Org. Chem.*, **1999**, *64*, 933.
16. (a) Zhang, Z. J. and Yu, B., *J. Org. Chem.*, **2003**, *68*, 6309. (b) Yu, B. and Tao, H. C., *J. Org. Chem.*, **2002**, *67*, 9099. (c) Yu, B. and Tao, H., *Tetrahedron Lett.*, **2001**, 2405.
17. Rademann, J. and Schmidt, R. R., *J. Org. Chem.*, **1997**, *62*, 3650.
18. Deng, S. L.; Gangadharmath, U. and Chang, C.-W. T., *J. Org. Chem.*, **2006**, *71*, 5179.
19. Ito, Y. and Ogawa, T., *J. Am. Chem. Soc.*, **1997**, *119*, 5562.
20. Danishefsky, S. J.; McClure, K. F.; Randolph, J. T. and Ruggeri, R. B., *Science*, **1993**, *260*, 1307.

21. Hewitt, M. C. and Seeberger, P. H., *J. Org. Chem.*, **2001**, *66*, 4233.
22. Liang, R.; Yan, L.; Loebach, J.; Ge, M.; Uozumi, Y.; Sekanina, K.; Horan, N.; Gildersleeve, J.; Smith, A.; Biswas, K. and Kahne, D. E., *Science*, **1996**, *274*, 1520.
23. Rodebaugh, R.; Joshi, S.; Fraser-Reid, B. and Geysen, M. H., *J. Org. Chem.*, **1997**, *62*, 5660.
24. (a) Zhu, T. and Boons, G.-J., *Chem. Eur. J.*, **2001**, *7*, 2382. (b) Nicolaou, K. C.; Watanabe, N.; Li, J.; Pastor, J. and Winssinger, N., *Angew. Chem. Int. Ed. Engl.*, **1998**, *37*, 1559.
25. (a) Demchenko, A. V.; Pornsuriyasak, P.; de Meo, C. and Malysheva, N. N., *Angew. Chem. Int. Ed.*, **2004**, *43*, 3069. (b) Demchenko, A. V., *Curr. Org. Chem.*, **2003**, *7*, 35.
26. (a) Wu, X. Y. and Bundle, D. R., *J. Org. Chem.*, **2005**, *70*, 7381. (b) Yao, N.-H.; He, W.-Y.; Lam, K. S. and Liu, G., *J. Comb. Chem.*, **2004**, *6*, 214. (c) Wu, X. Y. and Schmidt, R. R., *J. Org. Chem.*, **2004**, *69*, 1853. (d) Lee, S. W. and Rosazza, J. P. N., *Org. Lett.*, **2004**, *6*, 365. (e) Bélot, F.; Wright, K.; Costachel, C.; Phalipon, A. and Mulard, L. A., *J. Org. Chem.*, **2004**, *69*, 1060. (f) Du, Y. G.; Wei, G. H. and Linhardt, R. J., *J. Org. Chem.*, **2004**, *69*, 2206. (g) Rele, S. M.; Iyer, S. S.; Baskaran, S. and Chaikof, E. L., *J. Org. Chem.*, **2004**, *69*, 9159. (h) Pekari, K. and Schmidt, R. R., *J. Org. Chem.*, **2003**, *68*, 1295. (i) Zhao, M. M.; McNamara, J. M.; Ho, G.-J.; Emerson, K. M.; Song, Z. G. J.; Tschaen, D. M.; Brands, K. M. J.; Dolling, U.-H.; Grabowski, E. J. J.; Reider, P. J.; Cottrell, I. F.; Ashwood, M. S. and Bishop, B. C., *J. Org. Chem.*, **2002**, *67*, 6743. (j) Roussel, F.; Takhi, M. and Schmidt, R. R., *J. Org. Chem.*, **2001**, *66*, 8540. (k) Wu, X. Y.; Grathwohl, M. and Schmidt, R. R., *Org. Lett.*, **2001**, *3*, 747. (l) Kochetkov, N. K., *Russ. Chem. Rev.*, **2000**, *69*, 795. (m) Wilstermann, M. and Magnusson, G., *J. Org. Chem.*, **1997**, *62*, 7961. (n) Zhang, Z. Y. and Magnusson, G., *J. Org. Chem.*, **1996**, *61*, 2383. (o) Nicolaou, K. C., *Angew. Chem. Int. Ed. Engl.*, **1993**, *32*, 1377. (p) Nicolaou, K. C. and Dai, W.-M., *Angew. Chem. Int. Ed. Engl.*, **1991**, *30*, 1387. (q) Hashimoto, S.-I.; Honda, T. and Ikegami, S., *J. Chem. Soc., Chem. Commun.*, **1989**, 685.

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Schmidt Reaction
(Schmidt Rearrangement)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Schmidt in 1923.[1] It is a reaction between a hydroazoic acid (i.e., azoimide) and a carboxylic acid or a carbonyl compound via an 1,2-migration to form a nitrogen-containing molecule such as primary amine or amide. Therefore, this reaction is generally known as the Schmidt reaction.[2] In particular, the reaction between a hydroazoic acid and a carboxylic acid to yield a primary amine with one less carbon atom by decarboxylation is referred to as the Schmidt rearrangement,[3] Schmidt degradation,[4] or Schmidt decarboxylation.[5] In comparison, the reaction between a hydroazoic acid and a carbonyl compound, generally yielding two possible amides from a ketone or formamide from an aldehyde, is known as the Schmidt rearrangement[6] or Schmidt transformation.[7] Today, the scope of the Schmidt reaction has been extended to include reactions between hydroazoic acid or alkyl azide and other molecules that can form carbocation intermediates under acidic conditions, such as olefins,[4o,8] tertiary alcohols,[9] and some secondary alcohols (e.g., benzhydrols).[3k] As a result, the Schmidt reaction is very versatile and has the advantages of simplicity, readily available reactants, mild reaction conditions, and a certain level of functional group tolerance.[2h] For example, this reaction is often carried out in sulfuric acid,[10] and hydroazoic acid can be generated *in situ* from sodium azide.[2h,4n,10a,10d]

For the degradation of carboxylic acid, factors that may affect the reaction outcome are the ratio of sulfuric acid/carboxylic acid, the reaction temperature and the dilution extent of sulfuric acid.[4o] Even though some of the Schmidt degradations of carboxylic

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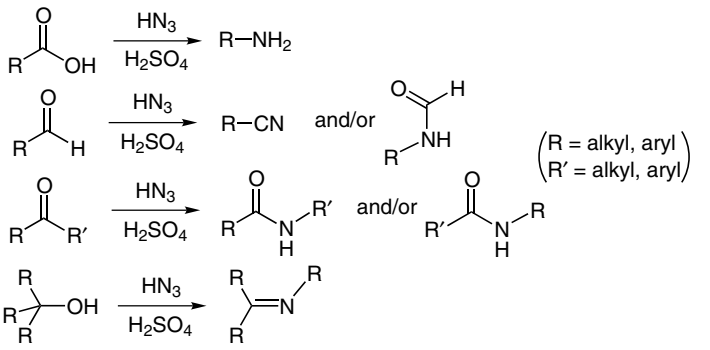
acids are known to be quantitative,[4n] the decarboxylation of carboxylic acids with chain branching at the α-position often gives amines in yields less than the theoretical values, along with the formation of some by-products, such as carbon monoxide, ketones, alcohols, and ammonia.[4o] However, it is intriguing that the reaction between sodium azide and 2-phenyl-2-methylhexanoic acid in sulfuric acid gives 55% aniline.[10a]

The Schmidt reaction between hydroazoic acid and aldehyde often gives formamide.[10d] However, the reaction with benzaldehyde produces both benzonitrile and formanilide, with the yields varying from 70% and 13% to 5% and 50%, respectively, when the ratio of sulfuric acid/benzaldehyde changes from 0.72 to 5.4.[11]

It should be pointed out that the reaction between hydroazoic acid and ketone is much more complicated, yielding two possible amides by the migration of different alkyl or aryl groups, and the ratio of two amides depends on the strength of acid and the migratory aptitude of the two groups. Generally speaking, the aryl group is preferred over the alkyl group for the migration from aminodiazonium ion,[12] and the migrating tendency correlates well with the Hammett substituent constant, in which an electron-donating group on aryl facilitates the migration while an electron-withdrawing group decreases the migrating ability.[13] For example, the migratory aptitude in diarylethylene is found in the order of *p*-anisyl > *p*-tolyl > *p*-biphenyl > phenyl > *p*-chlorophenyl > methyl.[8c] However, such a trend does not always apply to the Schmidt reaction of ketones, where the electronic effect might not be as apparent as that in diarylethylenes.[14] For example, both *p*-chloro-*p*′-methoxybenzophenone and *p*-nitro-*p*′-methoxybenzophenone give two amides in 1:1 ratio.[8b] In addition, the strength of acid also affects the constitution of products. For example, the Schmidt reaction of adamantan-2-one in methanesulfonic acid yields 88% 4(e)-methanesulfonoxyadamantan-2-one and 11% 4-azatricyclo[4.3.1.1^{1,8}]undecan-5-one whereas the same reaction in methanesulfonic acid-acetic acid, water, trichloroacetic acid or trifluoroacetic acid gives 40–61% of bicyclo[3.3.1]non-6-one-3-carbonitrile and 27–60% of 4-azatricyclo[4.3.1.1^{1,8}]undecan-5-one, and also produces 4-acetoxy-adamantan-2-one, 4-hydroxyadamantan-2-one, and 4-azatricyclo[4.3.1.1^{1,8}]-undecan-5-one in sulfuric acid–acetic acid.[15] Moreover, the particular reaction of benzyl azide may give a normal Schmidt reaction product and the unexpected *Mannich Reaction* product, and the ratio of these two products varies, depending on the acid applied.[16] For example, when $TiCl_4$ is used, the Schmidt product is favored, whereas in the presence of TfOH, the Mannich product predominates.[16b] Furthermore, solvent also affects the reaction outcome, even though most reactions are carried out in chloroform. For example, the reactions in ether or benzene in the presence of a 76% sulfuric acid take place in two different pathways, in which the reaction in benzene/76% sulfuric acid is fast and all the substrates remain in the sulfuric acid phase, whereas the reaction in ether is much slower and the reactants stay in the ether phase.[6e]

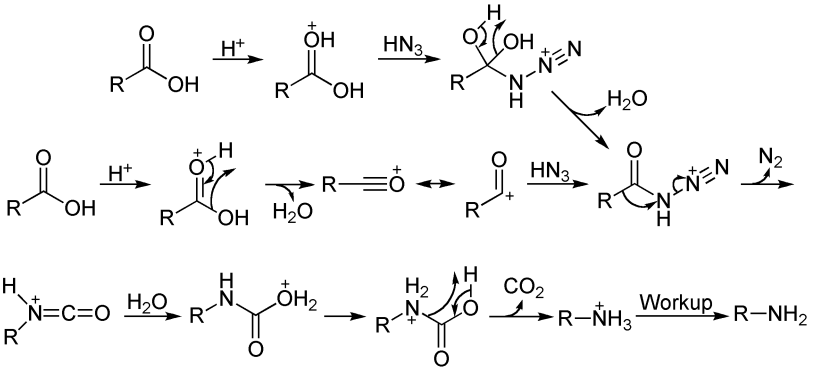
The Schmidt reaction of a simple cyclic ketone yields lactams with the ring expanded,[2g,2h] while the intramolecular Schmidt reaction of cyclic ketone with an azido group at the side chain leads to the formation of bicyclic lactams with nitrogen at the position of fusion.[2h,17] It is interesting that the reaction between a cyclic ketone and 2-azido ethanol can form either a lactam or a lactone by means of the treatment with a different base, in which the lactam is formed when the reaction system is treated with KOH, whereas lactone is generated when $NaHCO_3$ is used as the base.[18] Especially, the reaction between 4-*tert*-butylcyclohexanone and 3-azido-2-methyl-2-phenylpropanol gives lactam in 19:1 stereoselectivity.[19]

B. GENERAL REACTION SCHEME

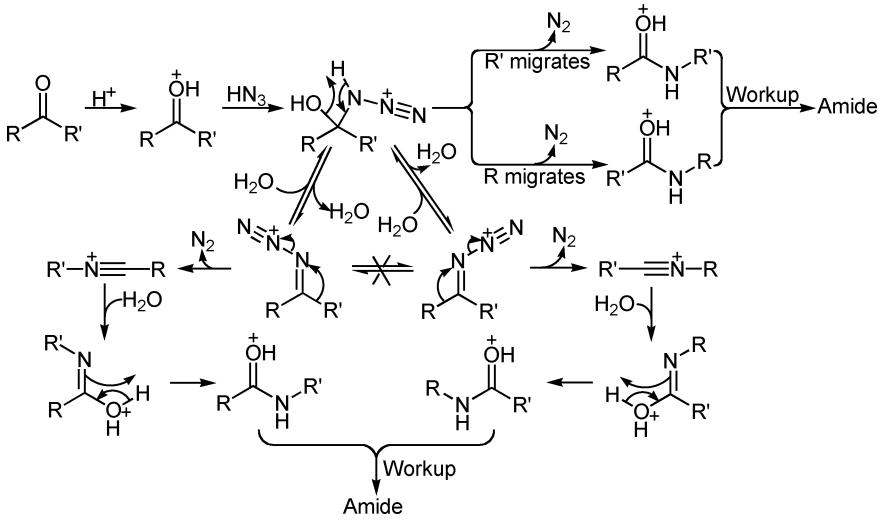


C. PROPOSED MECHANISMS

For the degradation of carboxylic acid, it is known that the reaction involves an acyl azide intermediate, in a manner similar to the *Curtius Rearrangement*,[2g] as shown in Scheme 1. Similar to the acid-catalyzed esterification of alcohol, it is assumed that the carbonyl oxygen is protonated rather than the hydroxyl oxygen. However, for the Schmidt reaction of ketones, it is well accepted that the reaction undergoes in two different routes, both involve the α-hydroxyhydrazidium ion arising from the nucleophilic addition of hydroazoic acid to the protonated carbonyl group.[2m,20] The resulting α-hydroxyhydrazidium ion may rearrange to amides along with the evolution of nitrogen, and the ratio of amides produced depends on the inherent migratory aptitudes of both groups and the abilities of the group acting as the stationary group to stabilize the positive charge. Alternatively, the α-hydroxyhydrazidium ion undergoes dehydration to form iminodiazonium ion,[6d] and the stereospecific migration of the group *antiperiplanar* to the azido group produces an acylium ion, which upon hydration forms the corresponding amide,[2m] as shown in Scheme 2. In this mechanism, the ratio of amides depends on the population of *syn*- and *anti*-iminodiazonium ions arising from different steric repulsions in the transition state of dehydration, which cannot isomerize but may interchange into each other only through the hydration and dehydration process. If the hydration and dehydration process is fast enough, then two iminodiazonium ions can quickly reach an equilibrium, this situation is controlled by the migratory tendency of substituents in the hydroxyhydrazinium ion.[2m,14,20,21]



SCHEME 1. *Schmidt degradation of a carboxylic acid.*



SCHEME 2. *Schmidt reaction with a general ketone.*

D. MODIFICATION

This reaction has been extensively modified. First, the Schmidt reaction is often carried out in a halogenated solvent, such as chloroform, so there exists a potential to form explosive multi-azides. For this matter, DME is suggested as the solvent,[22] or polyphosphoric acid is applied as both acid and reaction medium.[6e,7,23] Second, alkyl azide, retaining the important dipolar character of the azido group, has been widely used for the Schmidt reaction,[6c,16b,17,24] even though it is much less nucleophilic than hydroazoic acid.[2g] In addition, it has been suggested that a higher yield could be obtained for the degradation of succinic acid if it were converted into succinic anhydride before the degradation.[25] Other modifications include the photoinduced Schmidt reaction,[26] the P_2O_5/SiO_2 catalyzed one-pot reaction,[2e] the ionic exchange resin[2j] or silica sulfuric acid[2f] catalyzed Schmidt reaction, the trimethylsilyl azide[3h] or azidotrimethylsilane[2b,3g] mediated Schimdt reaction, and the transition metal activated Schmidt reaction. For example, the reaction between alkyl azide and gold (I) activated alkynes has been used in the preparation of multisubstituted pyrroles;[24a] likewise, mercury salt has been used to promote the Schmidt reaction,[8a] which has the following advantages: the wide applicability, e.g., to even 1,2-disubstituted olefins rather than to only tertiary, allylic, benzylic, or propargylic alcohol to form a stable carbocation intermediate under strong acid conditions as required by the normal Schmidt reaction; tolerance to acid-labile functionalities; and no carbocation rearrangement before the cyclization/rearrangement, which usually occurs in the acid-promoted Schmidt reactions.[2l,8a]

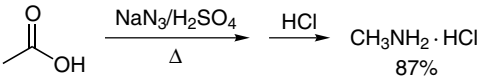
E. APPLICATIONS

The degradation of carboxylic acid has been used for the preparation of amines,[2l,4o,10a,27] amino acids,[28] and structural elucidation, especially via ^{14}C labeling.[4n] The reaction with carbonyl compounds has an even wider application in organic synthesis.

F. RELATED REACTIONS

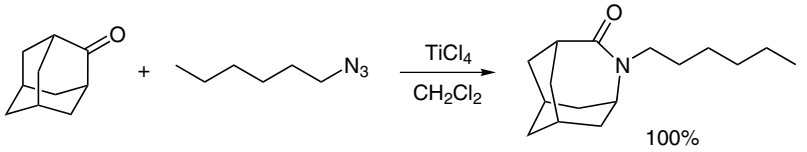
This reaction is related to the *Curtius Rearrangement*, *Hofmann Rearrangement*, *Lossen Rearrangement*, and *Stieglitz Rearrangement*.

G. CITED EXPERIMENTAL EXAMPLES



Reference 4o.

A mixture of 20.0 g 99.5% pure acetic acid (0.33 mol), 232 g concentrated sulfuric acid in chemical purity (2.37 mol), and 27.9 g NaN_3 (0.43 mol) was stirred at 60°C. The methylamine was collected in concentrated HCl, which was evaporated to afford 21.5 g crude methylamine hydrochloride, m.p. 186–220°C. The crude product was recrystallized from absolute ethanol to give 19.5 g beautiful plates without improvement for melting point, in a yield of 87%, in good agreement with the 89% yield of carbon dioxide obtained. In addition, sodium azide was found to decompose ~ 26%.



Reference 16b.

To a mixture of 119 mg 2-adamantanone (0.79 mmol), 200 mg 1-azidohexane (1.58 mmol), and 2.5 mL methylene chloride in an ice bath was added 380 mg $TiCl_4$ (2.0 mmol) dropwise. The reaction was allowed to warm to room temperature, with immediate gas evolution noted. A precipitate formed after 15 min, but the suspension was stirred for a total of 16 h, at which time it was diluted with 20 mL EtOAc and partitioned between 200 mL EtOAc and 30 mL saturated $NaHCO_3$ solution. The organic layer was washed with 30 mL brine and dried over anhydrous Na_2SO_4. Upon evaporation of the EtOAc, the residue was purified by flash column chromatography with EtOAc/hexane (1:4) as the eluent to give 197 mg 4-hexyl-4-azahomoadamantane, as a clear oil, in a yield of 100%.

Other references related to the Schmidt reaction are cited in the literature.[29]

H. REFERENCES

1. Schmidt, K. F., *Angew. Chem.*, **1923**, *36*, 511.
2. (a) Yao, L. and Aube, J., *J. Am. Chem. Soc.*, **2007**, *129*, 2766. (b) Pozgan, F.; Krejan, M.; Polanc, S. and Kocevar, M., *Heterocycles*, **2006**, *69*, 123. (c) Gu, P. M.; Zhao, Y.-M.; Tu, Y. Q.; Ma, Y. F. and Zhang, F. M., *Org. Lett.*, **2006**, *8*, 5271. (d) Nyfeler, E. and Renaud, P., *Chimia*, **2006**, *60*, 276. (e) Hassankhani, A., *Synth. Commun.*, **2006**, *36*, 2211. (f) Eshghi, H.; Hassankhani, A.

and Mosaddegh, E., *J. Chem. Res.*, **2006**, 218. (g) Lang, S. and Murphy, J. A., *Chem. Soc. Rev.*, **2006**, *35*, 146. (h) Casey, M.; Donnelly, J. A.; Ryan, J. C. and Ushioda, S., *ARKIVOC*, **2003**, *(vii)*, 310. (i) Chandrasekhar, S. and Gopalaiah, K., *Tetrahedron Lett*., **2003**, *44*, 7437. (j) Ammar, H.; Fakhfakh, M.; Le Bigot, Y. and El Gharbi, R., *Synth. Commun.*, **2003**, *33*, 1821. (k) Pozgan, F.; Polanc, S. and Kocevar, M., *Heterocycles*, **2002**, *56*, 379. (l) Pearson, W. H. and Fang, W.-k., *J. Org. Chem.*, **1995**, *60*, 4960. (m) Bach, R. D. and Wolber, G. J., *J. Org. Chem.*, **1982**, *47*, 239.

3. (a) Tapia, R. A. and Centella, C., *Synth. Commun.*, **2004**, *34*, 2757. (b) Mphahlele, M. J., *J. Chem. Soc., Perkin Trans. I*, **1999**, 3477. (c) Krow, G. R.; Szczepanski, S. W.; Kim, J. Y.; Liu, N.; Sheikh, A.; Xiao, Y. S. and Yuan, J., *J. Org. Chem.*, **1999**, *64*, 1254. (d) Mphahlele, M. J. and Kaye, P. T., *Magnet. Reson. Chem.*, **1998**, *36*, 69. (e) Daich, A. and Decroix, B., *J. Heterocycl. Chem.*, **1996**, *33*, 873. (f) Norris, P.; Horton, D. and Levine, B. R., *Tetrahedron Lett*., **1995**, *36*, 7811. (g) Kaye, P. T.; Mphahlele, M. J. and Brown, M. E., *J. Chem. Soc., Perkin Trans. II*, **1995**, 835. (h) Kaye, P. T. and Mphahlele, M. J., *Synth. Commun.*, **1995**, *25*, 1495. (i) Mérour, J. Y.; Cossais, F.; Piroelle, S. and Mazeas, D., *J. Heterocycl. Chem.*, **1994**, *31*, 87. (j) Merour, J. Y.; Piroelle, S. and Faure, R., *J. Heterocycl. Chem.*, **1994**, *31*, 141. (k) Tietz, R. F. and McEwen, W. E., *J. Am. Chem. Soc.*, **1955**, *77*, 4007.
4. (a) Kolattukudy, P. E. and Buckner, J. S., *Biochem. Biophys. Res. Commun.*, **1972**, *46*, 801. (b) Tokoroyama, T. and Kubota, T., *J. Chem. Soc. C*, **1971**, 2703. (c) Dahn, H. and Murchu, C. O., *Helv. Chim. Acta*, **1970**, *53*, 1379. (d) Fleshood, H. L. and Pitot, H. C., *J. Biol. Chem.*, **1970**, *245*, 4414. (e) Reinhold, K. and Renz, P., *Ann.*, **1969**, *729*, 231. (f) Berger, H.; Paul, H. and Hilgetag, G., *Chem. Ber.*, **1968**, *101*, 1525. (g) Kaplan, B. H. and Stadtman, E. R., *J. Biol. Chem.*, **1968**, *243*, 1794. (h) Alexander, N. M.; Scheig, R. and Klatskin, G., *J. Lipid Res.*, **1966**, *7*, 197. (i) Whereat, A. F., *J. Lipid Res.*, **1966**, *7*, 671. (j) Gatenbeck, S. and Bentley, R., *Biochem. J.*, **1965**, *94*, 478. (k) Brenner-Holzach, O. and Leuthard, F., *Helv. Chim. Acta*, **1965**, *48*, 1804. (l) Smith, G. N. and Bu'Lock, J. D., *Biochem. Biophys. Res. Commun.*, **1964**, *17*, 433. (m) Birch, A. J.; Hussain, S. F. and Rickards, R. W., *J. Chem. Soc.*, **1964**, 3494. (n) Rabinowitz, J. L. and Pritzker, B., *Anal. Chem.*, **1964**, *36*, 403. (o) Schuerch, C. and Huntress, E. H., *J. Am. Chem. Soc.*, **1949**, *71*, 2233.
5. (a) Monson, K. D. and Hayes, J. M., *Geochim. Cosmochim. Acta*, **1982**, *46*, 139. (b) Akhila, A.; Banthorpe, D. V. and Rowan, M. G., *Phytochemistry*, **1980**, *19*, 1433. (c) Vogler, E. A. and Hayes, J. M., *J. Org. Chem.*, **1979**, *44*, 3682. (d) Law, S. W. T. and Burton, D. N., *Can. J. Chem.*, **1973**, *51*, 241. (e) Hawke, J. C. and Stumpf, P. K., *J. Biol. Chem.*, **1965**, *240*, 4746.
6. (a) Krow, G. R.; Cheung, O. H.; Hu, Z. L. and Lee, Y. B., *J. Org. Chem.*, **1996**, *61*, 5574. (b) Makhova, N. N.; Blinnikov, A. N.; Khmel'nitskii, L. I., *Mendeleev Commun.*, **1995**, 56. (c) Sprecher, M. and Kost, D., *J. Am. Chem. Soc.*, **1994**, *116*, 1016. (d) Richard, J. P.; Amyes, T. L.; Lee, Y.-G. and Jagannadham, V., *J. Am. Chem. Soc.*, **1994**, *116*, 10833. (e) Prager, R. H.; Tippett, J. M. and Ward, A. D., *Aust. J. Chem.*, **1978**, *31*, 1989. (f) Doorenbos, N. J. and Wu, M. T., *J. Org. Chem.*, **1961**, *26*, 2548.
7. Conley, R. T., *J. Org. Chem.*, **1958**, *23*, 1330.
8. (a) Pearson, W. H.; Hutta, D. A. and Fang, W.-K., *J. Org. Chem.*, **2000**, *65*, 8326. (b) Westland, R. D. and McEwen, W. E., *J. Am. Chem. Soc.*, **1952**, *74*, 6141. (c) McEwen, W. E.; Gilliland, M. and Sparr, B. I., *J. Am. Chem. Soc.*, **1950**, *72*, 3212.
9. Mehta, G. and Kotha, S., *Tetrahedron,* **2001**, *57*, 625.
10. (a) Palmere, R. M. and Conley, R. T., *J. Org. Chem.*, **1970**, *35*, 2703. (b) Khuthier, A.-B. and Robertson, J. C., *J. Org. Chem.*, **1970**, *35*, 3760. (c) Carter, K. N., *J. Org. Chem.*, **1966**, *31*, 4257. (d) McEwen, W. E.; Conrad, W. E. and VanderWerf, C. A., *J. Am. Chem. Soc.*, **1952**, *74*, 1168. (e) Smith, P. A. S. and Ashby, B., *J. Am. Chem. Soc.*, **1950**, *72*, 2503. (f) Dice, J. R. and Smith, P. A. S., *J. Org. Chem.*, **1949**, *14*, 179.
11. Schmidt, K. F., *Ger. Pat.,* Apr. 20, **1926**, 427,828.
12. Pearson, W. H. and Fang, W.-K., *J. Org. Chem.*, **2000**, *65*, 7158.
13. McEwen, W. E. and Mehta, N. B., *J. Am. Chem. Soc.*, **1952**, *74*, 526.

14. Smith, P. A. S., *J. Am. Chem. Soc.*, **1954**, *76*, 431.
15. Sasaki, T.; Eguchi, S. and Toru, T., *J. Org. Chem.*, **1970**, *35*, 4109.
16. (a) Wrobleski, A. and Aubé, J., *J. Org. Chem.*, **2001**, *66*, 886. (b) Desai, P.; Schildknegt, K.; Agrios, K. A.; Mossman, C.; Milligan, G. L. and Aubé, J., *J. Am. Chem. Soc.*, **2000**, *122*, 7226.
17. Aubé, J. and Milligan, G. L., *J. Am. Chem. Soc.*, **1991**, *113*, 8965.
18. Aubé, J. and Forsee, J. E., *J. Org. Chem.*, **1999**, *64*, 4381.
19. Katz, C. E. and Aubé, J., *J. Am. Chem. Soc.*, **2003**, *125*, 13948.
20. Fikes, L. E. and Shechter, H., *J. Org. Chem.*, **1979**, *44*, 741.
21. Amyes, T. L. and Richard, J. P., *J. Am. Chem. Soc.*, **1991**, *113*, 1867.
22. Gálvez, N.; Moreno-Mañas, M.; Sebastián, R. M. and Vallribera, A., *Tetrahedron*, **1996**, *52*, 1609.
23. (a) Conley, R. T. and Nowak, B. E., *J. Org. Chem.*, **1961**, *26*, 692. (b) Conley, R. T., *Chem. & Ind.*, **1958**, 438. (c) Conley, R. T., and Nowak, B. E., *Chem. & Ind.*, **1956**, 1161. (d) Snyder, H. R., and Elstron, C. T., *J. Am. Chem. Soc.*, **1954**, *76*, 3039. (e) Snyder, H. R., Elston, C. T., and Kellom, D. B., *J. Am. Chem. Soc.*, **1953**, *75*, 2014.
24. (a) Gorin, D. J.; Davis, N. R. and Toste, F. D., *J. Am. Chem. Soc.*, **2005**, *127*, 11260. (b) Milligan, G. L.; Mossman, C. J. and Aubé, J., *J. Am. Chem. Soc.*, **1995**, *117*, 10449.
25. Phares, E. F. and Long, M. V., *J. Am. Chem. Soc.*, **1955**, *77*, 2556.
26. Evans, P. A. and Modi, D. P., *J. Org. Chem.*, **1995**, *60*, 6662.
27. Datta, S. K.; Grundmann, C. and Bhattacharyya, N. K., *J. Chem. Soc, C*, **1970**, 2058.
28. Rothchild, S. and Fields, M., *J. Org. Chem.*, **1951**, *16*, 1080.
29. (a) Iyengar, R.; Schildknegt, K.; Morton, M. and Aubé, J., *J. Org. Chem.*, **2005**, *70*, 10645. (b) Clive, D. L. J.; Yu, M. L. and Li, Z. Y., *Chem. Commun.*, **2005**, 906. (c) Zeng, Y. B.; Reddy, D. S.; Hirt, E. and Aubé, J., *Org. Lett.*, **2004**, *6*, 4993. (d) Wrobleski, A.; Sahasrabudhe, K. and Aubé, J., *J. Am. Chem. Soc.*, **2004**, *126*, 5475. (e) Sahasrabudhe, K.; Gracias, V.; Furness, K.; Smith, B. T.; Katz, C. E.; Reddy, D. S. and Aubé, J., *J. Am. Chem. Soc.*, **2003**, *125*, 7914. (f) Fürmeier, S. and Metzger, J. O., *Eur. J. Org. Chem.*, **2003**, 885. (g) Pellicciari, R.; Camaioni, E.; Costantino, G.; Marinozzi, M.; Macchiarulo, A.; Moroni, F. and Natalini, B., *Farmaco*, **2003**, *58*, 851. (h) Moroni, F.; Meli, E.; Peruginelli, F.; Chiarugi, A.; Cozzi, A.; Picca, R.; Romagnoli, P.; Pellicciari, R. and Pellegrini-Giampietro, D. E., *Cell Death & Diff.*, **2001**, *8*, 921. (i) Iyengar, R.; Schildknegt, K. and Aubé, J., *Org. Lett.*, **2000**, *2*, 1625. (j) Woodroofe, C. C.; Zhong, B. Y.; Lu, X. L. and Silverman, R. B., *J. Chem. Soc., Perkin Trans. II*, **2000**, 55. (k) Gracias, V.; Milligan, G. L. and Aubé, J., *J. Am. Chem. Soc.*, **1995**, *117*, 8047. (l) Pearson, W. H.; Walavalkar, R.; Schkeryantz, J. M.; Fang, W.-k. and Blickensdorf, J. D., *J. Am. Chem. Soc.*, **1993**, *115*, 10183. (m) Lévai, A.; Timar, T.; Frank, L. and Hosztafi, S., *Heterocycles,* **1992**, *34*, 1523. (n) Yeh, M.-Y.; Tien, H.-J. and Nonaka, T., *J. Org. Chem.*, **1983**, *48*, 1382. (o) Narayanan, R. and Balaram, P., *FEBS Letters*, **1978**, *93*, 38. (p) Koldobskii, G. I.; Ostrovskii, V. A. and Gidaspov, B. Z., *Chem. Heterocycl. Compd.*, **1975**, *11*, 626. (q) Palmere, R. M.; Conley, R. T. and Rabinowitz, J. L., *J. Org. Chem.*, **1972**, *37*, 4095. (r) Moriconi, E. J. and Stemniski, M. A., *J. Org. Chem.*, **1972**, *37*, 2035. (s) Sasaki, T.; Eguchi, S. and Toru, T., *J. Org. Chem.*, **1971**, *36*, 2454. (t) Koldobskii, G. I.; Tereshchenko, G. F.; Gerasimova, E. S. and Bagal, L. I., *Russ. Chem. Rev.*, **1971**, *40*, 835. (u) Fishel, D. L.; Kletecka, G. and Muralidhara, R., *Ohio J. Sci.*, **1970**, *70*, 371. (v) Hassner, A.; Ferdinandi, E. S. and Isbister, R. J., *J. Am. Chem. Soc.*, **1970**, *92*, 1672. (w) Zbarskii, V. L.; Shutov, G. M.; Zhilin, V. F. and Orlova, E. Yu., *Chem. Heterocycl. Compd.*, **1967**, *3*, 124. (x) Moore, H. W. and Shelden, H. R., *J. Org. Chem.*, **1967**, *32*, 3603. (y) Andrews, P.; Hough, L. and Picken, J. M., *Biochem. J.*, **1965**, *97*, 27. (z) Stockel, R. F. and Hall, D. M., *Nature*, **1963**, *197*, 787. (aa) Lansbury, P. T. and Colson, J. G., *J. Am. Chem. Soc.*, **1962**, *84*, 4167. (bb) Boyer, J. H. and Sanders, M., *J. Org. Chem.*, **1961**, *26*, 1644. (cc) Arcus, C. L. and Barrett, G. C., *J. Chem. Soc.*, **1961**, 1408. (dd) Zook, H. D. and Paviak, S. C., *J. Am. Chem. Soc.*, **1955**, *77*, 2501. (ee) Kohlbrenner, P. J. and Schuerch, C., *J. Am. Chem. Soc.*, **1955**, *77*, 6066. (ff) Dickerman, S. C. and Moriconi, E. J., *J. Org. Chem.*, **1955**,

20, 206. (gg) Dickerman, S. C. and Besozzi, A. J., *J. Org. Chem.*, **1954**, *19*, 1855. (hh) Ropp, G. A.; Bonner, W. A.; Clark, M. T. and Raaen, V. F., *J. Am. Chem. Soc.*, **1954**, *76*, 1710. (ii) Bunce, S. C. and Cloke, J. B., *J. Am. Chem. Soc.*, **1954**, *76*, 2244. (jj) Nielsen, D. R. and McEwen, W. E., *J. Am. Chem. Soc.*, **1954**, *76*, 4042. (kk) Lieber, E.; Henry, R. A. and Finnegan, W. G., *J. Am. Chem. Soc.*, **1953**, *75*, 2023. (ll) Smith, P. A. S. and Horwitz, J. P., *J. Am. Chem. Soc.*, **1950**, *72*, 3718. (mm) Szmant, H. H. and McIntosh, J. J., *J. Am. Chem. Soc.*, **1950**, *72*, 4835. (nn) Kuhn, L. P. and DiDomenico, J., *J. Am. Chem. Soc.,* **1950**, *72*, 5777. (oo) Benson, F. R.; Hartzel, L. W. and Savell, W. L., *J. Am. Chem. Soc.*, **1949**, *71*, 1111. (pp) Schuerch, C. and Huntress, E. H., *J. Am. Chem. Soc.*, **1949**, *71*, 2238. (qq) Newman, M. S. and Gildenhorn, H. L., *J. Am. Chem. Soc.*, **1948**, *70*, 317. (rr) Smith, P. A. S., *J. Am. Chem. Soc.*, **1948**, *70*, 320. (ss) Wolff, H., *Org. React.,* **1946**, *3*, 307. (tt) Schmidt, K. F., *Ber.*, **1924**, *57*, 704.

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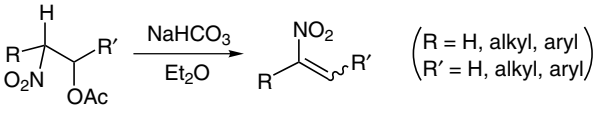
Schmidt-Rutz Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Schmidt and Rutz in 1928.[1] It is the synthesis of nitro-olefins by means of the treatment of acetates of α-nitro-alcohols with sodium bicarbonate and is generally known as the Schmidt-Rutz reaction.[2] Occasionally, it is also referred to as the Schmidt-Rutz degradation.[3] This reaction is suitable for the α-nitro esters with one proton at the α-carbon bonding to the nitro group;[4] however, such restriction is not strictly followed as shown in the formation of 1-nitro-olefins.[5] In addition, the Schmidt-Rutz reaction is applicable to the substrates without any other base-labile functional groups and usually gives nitro-olefins in good yields.[4b,4c,6,7] It has been reported that the best yields can be achieved from the esters of nitro-alcohols with nine or more than nine carbon atoms.[7b] Besides sodium bicarbonate, other mild bases such as potassium bicarbonate, sodium carbonate, and even sodium acetate can be used in this reaction.[2f,4c] The resulting nitro-olefins can be reduced to amines, so that the Schmidt-Rutz reaction has become one of the powerful methods for amines with a definite structure free of isomers.[4b] Moreover, this reaction has been widely used in carbohydrate chemistry, due to a good crystalline capability of nitro carbohydrate acetates, which easily crystallize even in the presence of a large amount of other carbohydrate acetates.[7a]

B. GENERAL REACTION SCHEME



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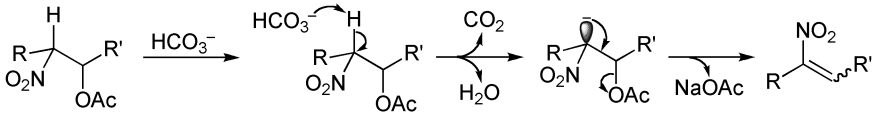
C. PROPOSED MECHANISMS

Due to the presence of a nitro group, the α-proton in α-nitro-alcohol acetate is activated and can easily be deprotonated, so that subsequent elimination occurs once the carbanion is generated, as shown here.



D. MODIFICATION

This reaction has been extended to the sulfonate of α-nitro-alcohol, which undergoes the reaction in the presence of pyridine.[4a]

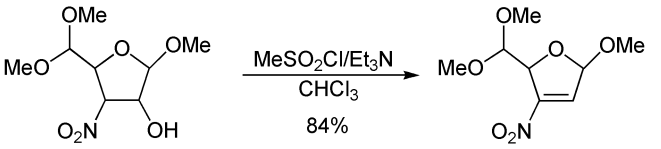
E. APPLICATIONS

This reaction has a general application in the preparation of nitro-olefins.

F. RELATED REACTIONS

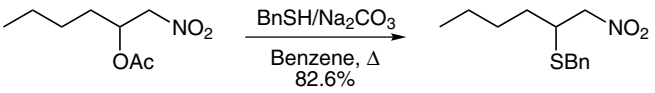
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 8.

To a mixture of 0.508 g methyl 3-deoxy-3-nitro-β-D-ribofuranoside-1,4-dialdose 5,5-dimethyl acetal, 1.0 g triethylamine, and 7.0 mL $CHCl_3$, was gradually added 0.95 g methanesulfonyl chloride. After being stirred at 20°C for 1 h, 15 mL water was added, and the stirring was continued for 0.5 h. The $CHCl_3$ layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with 1% HCl, saturated $NaHCO_3$ solution, and brine and then dried over $MgSO_4$. Vacuum evaporation of the solution afforded 430 mg methyl 2,3-dideoxy-2-ene-3-nitro-β-D-ribofuranoside-1,4-dialdose 5,5-dimethyl acetal as a brown gum, in a yield of 84%.



Reference 9.

A mixture of 18.9 g 2-acetoxy-1-nitrohexane (0.1 mol), 12.4 g benzyl mercaptan (0.1 mol), 5.3 g sodium carbonate (0.05 mol), and 25 mL benzene was refluxed for 3 h. The sodium acetate was filtered from the benzene and dissolved in water, and the aqueous solution was extracted with benzene. The combined benzene solution was dried over $MgSO_4$. Upon removal of benzene, 26.2 g 2-benzylthio-1-nitrohexane was obtained, which was further purified by vacuum distillation to give 20.9 g product, in a yield 82.6%, b.p. 140°C at 0.1 mmHg.

Other references related to the Schmidt-Rutz reaction are cited in the literature.[10]

H. REFERENCES

1. (a) Schmidt, E.; Rutz, G. and Trénel, M., *Ber.*, **1928**, *61*, 472. (b) Schmidt, E. and Rutz, G., *Ber.*, **1928**, *61*, 2142.
2. (a) Seyedi, S. M. and Ghabel, H., *Asian J. Chem.*, **2004**, *16*, 74. (b) Matsuda, A. and Watanabe, K. A., *Nucleosides & Nucleotides*, **1996**, *15*, 205. (c) Rosenthal, A.; Ong, K.-S. and Baker, D. A., *Carbohydr. Res.*, **1970**, *13*, 113. (d) Baer, H. H. and Neilson, T., *Can. J. Chem.*, **1965**, *43*, 840. (e) Baer, H. H.; Kienzle, F. and Neilson, T., *Can. J. Chem.*, **1965**, *43*, 1829. (f) Feuer, H. and Miller, R., *J. Org. Chem.*, **1961**, *26*, 1348.
3. Rosenthal, A. and Schöllnhammer, G., *Can. J. Chem.*, **1972**, *50*, 1780.
4. (a) Riebsomer, J. L., *J. Org. Chem.*, **1946**, *11*, 182. (b) Hass, H. B., *Ind. Eng. Chem.*, **1943**, *35*, 1146. (c) Hass, H. B. and Riley, E. F., *Chem. Rev.*, **1943**, *32*, 373.
5. Brower, F. and Burkett, H., *J. Am. Chem. Soc.*, **1953**, *75*, 1082.
6. Klager, K., *J. Org. Chem.*, **1955**, *20*, 650.
7. (a) Sowden, J. C. and Fischer, H. O. L., *J. Am. Chem. Soc.*, **1947**, *69*, 1048. (b) Nightingale, D. and Janes, J. R., *J. Am. Chem. Soc.*, **1944**, *66*, 352.
8. Weber, J. F.; Talhouk, J. W.; Nachman, R. J.; You, T.-P.; Halaska, R. C.; Williams, T. M. and Mosher, H. S., *J. Org. Chem.*, **1986**, *51*, 2702.
9. Carroll, F. I.; White, J. D. and Wall, M. E., *J. Org. Chem.*, **1963**, *28*, 1236.
10. (a) Baumberger, F.; Beer, D.; Christen, M.; Prewo, R. and Vasella, A., *Helv. Chim. Acta*, **1986**, *69*, 1191. (b) Bailey, W. J. and Hewitt, J. J., *J. Org. Chem.*, **1956**, *21*, 543. (c) Hass, H. B. and Shechter, H., *J. Am. Chem. Soc.,* **1953**, *75*, 1382. (d) Hass, H. B.; Susie, A. G. and Heider, R. L., *J. Org. Chem.*, **1950**, *15*, 8.

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Schmittel Cyclization

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Schmittel et al.[1a] and Gillmann et al.[1b] concurrently in 1995. It is an intramolecular C^2-C^6 cyclization of hepta-1,2,4-triene-6-yne (i.e., enyne-allene) to form a five-membered cyclic structure via a methyl fulvene biradical intermediate and is generally known as the Schmittel cyclization.[2] Occasionally, this reaction is also referred to as the Schmittel reaction[2i,2l,2m,2q,3] or Schmittel ring closure reaction.[2q]

Before the discovery of the Schmittel cyclization, the enyne-allenes were generally considered to undergo C^2-C^7 cyclization to give aromatic compounds, i.e., the *Myers-Saito Cyclization*.[4] Theoretical studies indicate that the Schmittel cyclization is disfavored by 25 Kcal/mol with respect to the *Myers-Saito Cyclization*,[2q] because aromaticity is attained in the *Myers-Saito Cyclization*,[2c] whereas the Schmittel cyclization proceeds via a not completely delocalized π-radical intermediate with a slightly alternating single and double bond.[2r] As a result, the Schmittel cyclization is endothermic at $\sim$10 Kcal/mol, with an activation barrier of 35 Kcal/mol.[2n,2p,2s,4] However, enyne-allenes with an aryl group at the alkynyl terminus can easily undergo the Schmittel cyclization,[1] due to the stabilization of biradical intermediate from the benzylic group.[5] Likewise, the Schmittel cyclization is also facilitated by benzannulation with enyne-allenes.[2q,6] In addition, enyne-allenes with a sterically bulky group (e.g., *t*-butyl, trimethylsilyl) at the alkynyl terminus[6b,7] or eight or nine-membered cyclic enyne-allenes[2s] also undergo the Schmittel cyclization because the steric hindrance burdens the occurrence of the *Myers-Saito Cyclization*. For example, benzannulation lowers the reaction barrier from 30 to 25.2 Kcal/mol for the Schmittel cyclization, whereas it lowers the activation energy only $\sim$ 1.2 Kcal/mol for the corresponding *Myers-Saito Cyclization*, although the endothermicity is lowered by only 1.0 Kcal/mol.[2l] To an extreme extent, the benzannulated enyne-allene with an aryl group

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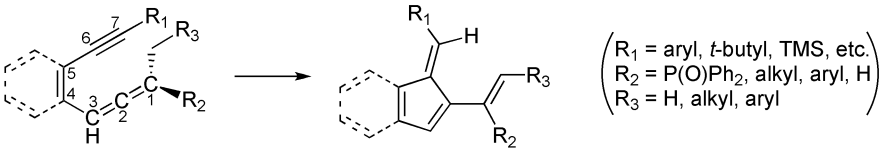
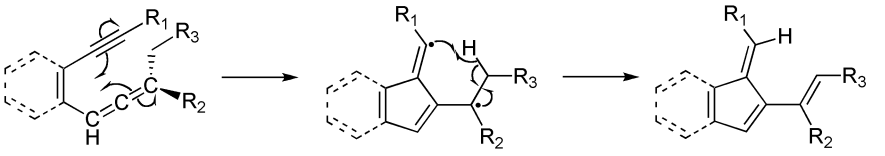
at the alkynyl terminus proceeds via the Schmittel cyclization in mild thermal condition.[6,8] The occurrence of the Schmittel cyclization is attributed to the formation of a strong sp^2-$sp^2\sigma$ bond from sp-hybridized carbons.[2c] Moreover, oxyanion substitute of enyne-allene also switches the preferences of product formation from a biradical to a polar closed-shell singlet, and this effect is more apparent for the Schmittel cyclization.[2p]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

This reaction, similar to the competing reaction of the *Myers-Saito Cyclization*, proceeds via a biradical intermediate,[2d,2j–2l,2n,2o,2q,3] as supported by the trapping of a biradical intermediate with 1,4-cyclohexadiene[10] and the experimental fact that the change of the polarity of solvent has no effect on the reaction rate and the ratio of products formed, indicating the absence of a zwitterionic intermediate.[2c] The proton abstraction by the vinyl radical leads to the formation of fulvene derivatives. An illustration of this reaction is provided here.



D. MODIFICATION

The benzannulation and oxyanion of enyne-allenes to facilitate the Schmittel cyclization can be considered as modifications of this reaction.

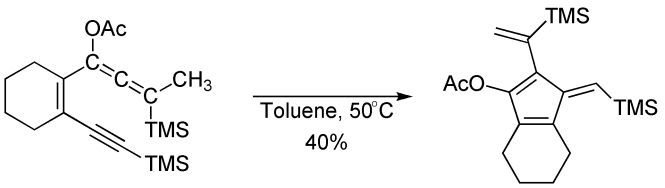
E. APPLICATIONS

This reaction has important application in organic synthesis[2c] as well as in double-stranded DNA cleavage.[2c,3]

F. RELATED REACTIONS

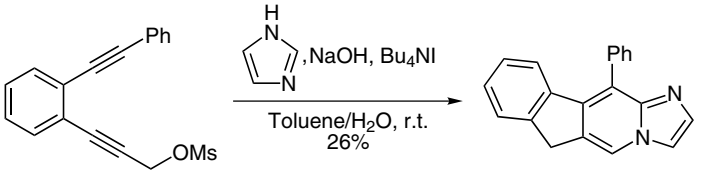
This reaction is related to the *Bergman Cyclization, Moore Cyclization,* and *Myers-Saito Cyclization.*

G. CITED EXPERIMENTAL EXAMPLES



Reference 2b.

A solution of 45 mg 1-(1′-acetoxy-3′-methyl-3′-trimethylsilyl)-2-(2″-trimethylsilyl)-acetyenyl cyclohexene (0.13 mmol) in 0.42 mL toluene was heated to 50°C for 3 h. Then solvent was removed in vacuo, and the residue was purified by flash chromatography with 10% Et_2O/pentane to give 18 mg 4,5,6,7-tetrahydro-2-(1-trimethylsilylvinyl)-1-(trimethylsilylmethylidene) indenyl acetate, in a yield of 40%.



Reference 2d.

To a stirred mixture of 10 mg imidazole (0.15 mmol), 27 mg tetrabutylammonium iodide (0.073 mmol), and 0.52 mL 50% aqueous NaOH in 0.41 mL toluene was added 47 mg 3-(*o*-(2′-phenyl)acetyenyl) phenyl propargyl methanesulfonate (0.15 mmol). After the mixture was stirred at room temperature for 15 min, 0.5 mL toluene and 0.5 mL water were added. The organic layer was separated, washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography using Et_2O/MeOH (100:3) as the eluent to afford 11 mg 11-phenyl-6*H*-indeno[1,2-*d*]imidazo[1,2-*a*]pyridine as a pale yellow solid, in a yield of 26%.

Other references related to the Schmittel cyclization are cited in the literature.[10]

H. REFERENCES

1. (a) Schmittel, M.; Strittmatter, M. and Kiau, S., *Tetrahedron Lett.*, **1995**, *36*, 4975. (b) Gillmann, T.; Hülsen, T.; Massa, W. and Wocadlo, S., *Synlett*, **1995**, 1257.
2. (a) Schmittel, M.; Strittmatter, M.; Mahajan, A. A.; Vavilala, C.; Cinar, M. E. and Maywald, M., *ARKIVOC*, **2007**, (*viii)*, 66. (b) Waddell, M. K.; Bekele, T. and Lipton, M. A., *J. Org. Chem.*, **2006**, *71*, 8372. (c) Bekele, T.; Christian, C. F.; Lipton, M. A. and Singleton, D. A., *J. Am. Chem. Soc.*, **2005**, *127*, 9216. (d) Dai, W. X.; Petersen, J. L. and Wang, K. K., *J. Org. Chem.*, **2005**, *70*, 6647. (e) Lu, Y.-X.; Zou, J.-W.; Wang, H.-Q. and Yu, Q.-S., *J. Mol. Struct. Theochem*, **2005**, *732*, 233. (f) Datta, S. and Liu, R.-S., *Tetrahedron Lett*., **2005**, *46*, 7985. (g) Wang, K. K., *Modern Allene Chem*., **2004**, *2*, 1091. (h) Wu, H.-J.; Lin, C.-F.; Lee, J.-L.; Lu, W.-D.; Lee, C.-Y.; Chen, C.-C. and Wu, M.-J., *Tetrahedron*, **2004**, *60*, 3927. (i) Wenk, H. H.; Winkler, M. and Sander, W.,

Angew. Chem. Int. Ed., **2003**, *42*, 502. (j) Yang, Y. H.; Petersen, J. L. and Wang, K. K., *J. Org. Chem.*, **2003**, *68*, 8545. (k) Yang, Y. H.; Petersen, J. L. and Wang, K. K., *J. Org. Chem.*, **2003**, *68*, 5832. (l) Stahl, F.; Moran, D.; Schleyer, P. von R.; Prall, M. and Schreiner, P. R., *J. Org. Chem.*, **2002**, *67*, 1453. (m) Musch, P. W.; Remenyi, C.; Helten, H. and Engels, B., *J. Am. Chem. Soc.*, **2002**, *124*, 1823. (n) De Visser, S. P.; Filatov, M. and Shaik, S., *Phys. Chem. Chem. Phys.*, **2001**, *3*, 1242. (o) Li, H. B.; Zhang, H.-R.; Petersen, J. L. and Wang, K. K., *J. Org. Chem.*, **2001**, *66*, 6662. (p) Cramer, C. J.; Kormos, B. L.; Seierstad, M.; Sherer, E. C. and Winget, P., *Org. Lett.*, **2001**, *3*, 1881. (q) Prall, M.; Wittkopp, A. and Schreiner, P. R., *J. Phys. Chem. A*, **2001**, *105*, 9265. (r) Wenthold, P. G. and Lipton, M. A., *J. Am. Chem. Soc.*, **2000**, *122*, 9265. (s) Schreiner, P. R. and Prall, M., *J. Am. Chem. Soc.*, **1999**, *121*, 8615. (t) Ferri, F.; Bruückner, R. and Herges, R., *New J. Chem.*, **1998**, *22*, 531.

3. Bui, B. H. and Schreiner, P. R., *Org. Lett.*, **2003**, *5*, 4871.
4. Engels, B. and Hanrath, M., *J. Am. Chem. Soc.*, **1998**, *120*, 6356.
5. (a) Schmittel, M.; Strittmatter, M.; Vollmann, K. and Kiau, S., *Tetrahedron Lett.*, **1996**, *37*, 999. (b) Schmittel, M.; Kiau, S.; Siebert, T. and Strittmatter, M., *Tetrahedron Lett.*, **1996**, *37*, 7691.
6. Musch, P. W. and Engels, B., *J. Am. Chem. Soc*., **2001**, *123*, 5557.
7. (a) Gillmann, T.; Hülsen, T.; Massa, W. and Wocadlo, S., *Synlett*, **1995**, 1257. (b) Rodriguez, A.; Garcia, J. G.; Ramos, B. and Pratt, L. M., *Tetrahedron Lett.*, **1995**, *36*, 7391.
8. (a) Schmittel, M.; Keller, M.; Kiau, S. and Strittmatter, M., *Chem. Eur. J.*, **1997**, *3*, 807. (b) Schmittel, M.; Strittmatter, M. and Kiau, S., *Angew. Chem. Int. Ed. Engl.*, **1996**, *35*, 1843.
9. (a) Engels, B.; Lennartz, C.; Hanrath, M.; Schmittel, M. and Strittmatter, M., *Angew. Chem. Int. Ed. Engl.*, **1998**, *37*, 1960. (b) Engels, B.; Lennartz, C.; Hanrath, M.; Schmittel, M. and Strittmatter, M., *Angew. Chem.*, **1998**, *110*, 2067.
10. (a) Tantillo, D. J., *Ann. Rep. Prog. Chem., Sect. B: Org. Chem.*, **2006**, *102*, 269. (b) Datta, S. and Liu, R.-S., *Tetrahedron Lett.*, **2005**, *46*, 8985. (c) Marco-Contelles, J. and Molina, M. T., *Curr. Org. Chem.*, **2003**, *7*, 1433. (d) Schmittel, M.; Steffen, J.-P.; Maywald, M.; Engels, B.; Helten, H. and Musch, P., *J. Chem. Soc.*, *Perkin Trans. II*, **2001**, 1331. (e) Schmittel, M. and Maywald, M., *Chem. Commun.*, **2001**, 155. (f) Brunette, S. R. and Lipton, M. A., *J. Org. Chem.*, **2000**, *65*, 5114. (g) Schmittel, M.; Rodríguez, D. and Steffen, J.-P., *Angew. Chem. Int. Ed. Engl.*, **2000**, *39*, 2152. (h) Wang, K. K.; Zhang, H.-R. and Petersen, J. L., *J. Org. Chem.*, **1999**, *64*, 1650. (i) Schmittel, M. and Strittmatter, M., *Tetrahedron*, **1998**, *54*, 13751. (j) Schmittel, M. and Kiau, S., *Liebigs Ann./Recl*., **1997**, 733. (k) Schmittel, M.; Steffen, J.-P.; Auer, D. and Maywald, M., *Tetrahedron Lett.*, **1997**, *38*, 6177. (l) Schmittel, M.; Strittmatter, M. and Kiau, S., *Angew. Chem.*, **1996**, *108*, 1952. (m) Schmittel, M.; Maywald, M. and Strittmatter, M., *Synlett*, **1997**, 165.

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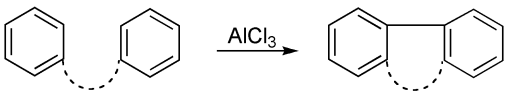
Scholl Reaction
(Scholl Condensation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Scholl in 1910.[1] It is a Lewis acid-catalyzed coupling of aromatic compounds while eliminating two of the aryl-bound hydrogens.[2] Therefore, it is generally known as the Scholl reaction,[2,3] or Scholl condensation.[2a,4] Occasionally, this reaction is also referred to as the Scholl oxidation.[2a,3b] The commonly used Lewis acid is $AlCl_3$,[3c,3v,3x,3cc,3ii] because some other Lewis acids may lead to the formation of by-products. For example, the use of molten $SbCl_3$ results in the formation of a Scholl condensation product as well as some hydro-aromatics arising from hydrogen redistribution.[4g] In addition, the alumina pillars in the clay are also found to catalyze this reaction.[3k] Although this reaction does not take place in the presence of the most protic acids (e.g., 40% HF, benzenesulfonic acid, trifluoroacetic acid, FSO_3H, 98% sulfuric acid, liquid hydrochloric acid),[2b] it does occur in anhydrous HF.[5] Moreover, this reaction is facilitated by the addition of NaCl[2b,3c] or trace amounts of HCl or water.[6] Generally, the yield of this reaction is relatively low,[2b] except for some intramolecular reactions, as indicated by the 66% conversion of 1-phenylbenz[a]anthracene to dibenzo[a,1]pyrene.[7] Presumably, the most exciting result by the Scholl reaction is to form as many as 126 new aryl-aryl bonds in a single step from dendritic oligophenylenes.[8]

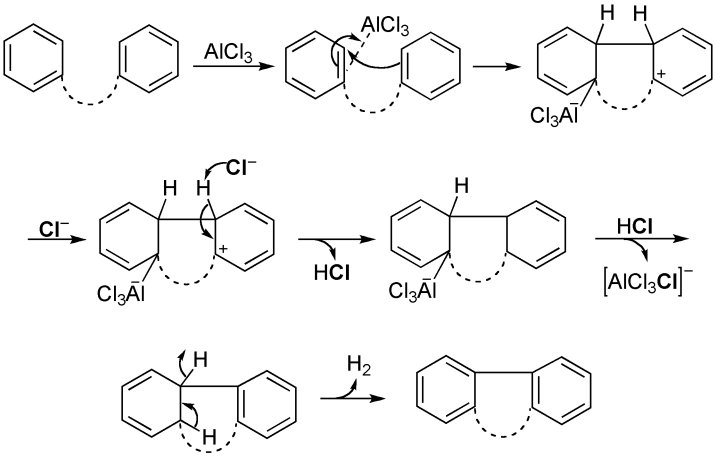
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

Although a mechanism involving a radical cation has been proposed for the Scholl reaction, as indicated by the paramagnetic properties of many polycyclic aromatic hydrocarbons (PAHs) when they are treated with Lewis acids or concentrated sulfuric acid,[3l] it is assumed that the Scholl reaction occurs in a manner similar to the *Friedel-Crafts Alkylation*,[9] involving an arenium cation instead of a radical cation.[3c,6] In detail, the Scholl reaction of hexaphenylbenzene involves the complexation between a Lewis acid and aromatic nucleus, electrophilic addition, and deprotonation,[2a] as illustrated here. In the presence of NaCl or HCl, chloride is beneficial for the elimination of aryl hydrogen by the formation of hydrogen chloride, as indicated by the bold chloride.



D. MODIFICATION

This reaction has been modified by the use of alumina pillars in the clay[3k] or anhydrous HF[5] as the promoter.

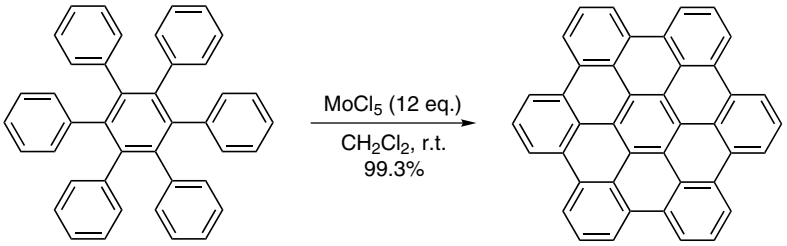
E. APPLICATIONS

This reaction has an important application in the production of polycyclic aromatic hydrocarbons[8] and carbon nanotube segments.[9]

F. RELATED REACTIONS

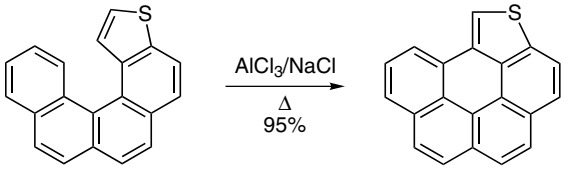
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 2a.

To 10 mL dichloromethane containing 0.1022 g 1,2,3,4,5,6-hexaphenylbenzene (0.187 mmol) was added 0.613 g $MoCl_5$ (2.24 mmol, 12 eq.). The resulting mixture was stirred under nitrogen at ambient temperature for 12 h. Methanol (10 mL) was added to the solution, and the stirring was continued for an additional hour. The reaction mixture then was further diluted with dichloromethane and methanol. The resulting hexa-*peri*-benzocoronene was filtered through a high density sintered glass filter, and washed thoroughly with methanol, dichloromethane, methanol, distilled water, methanol, dichloromethane, tetrahydrofuran, benzene, and again dichloromethane. The crude hexabenzocoronene was dried in the air for 24 h and weighed. In addition, the filtrate was diluted with distilled water and extracted with dichloromethane. The organic layer was washed with distilled water, dried over $MgSO_4$, and evaporated to dryness. The combined weight of hexa-*peri*-benzocoronene was 0.0992 g, in a yield of 99.3%.



Reference 2b.

A mixture of 100 mg aromatic starting material (0.35 mmol), 300 mg NaCl (5.1 mmol), and 1.50 g $AlCl_3$ (11.2 mmol) was heated at 140°C (and the reaction might be monitored by TLC). When the reaction was complete, water was added slowly to the molten mixture under stirring to yield a yellow-orange precipitate, which was taken up by 200 mL benzene, The organic layer was washed with water and saturated $NaHCO_3$ solution, and dried over $MgSO_4$. Upon filtration and evaporation, the residue was purified by column chromatography on alumina using benzene as the eluent. The collected fraction was dried, and the residue was recrystallized twice from methylcyclohexane to afford 95 mg pyreno[5,4,3-cde]benzo[b]thiophene as long orange yellow needles, in a yield of 95%, m.p. 298–299°C.

Other references related to the Scholl reaction are cited in the literature.[10]

H. REFERENCES

1. (a) Scholl, R. and Mansfeld, J., *Ber.*, **1910**, *43*, 1734. (b) Scholl, R.; Seer, C. and Weitzenböck, R., *Ber.*, **1910**, *43*, 2202.
2. (a) Rempala, P.; Kroulík, J. and King, B. T., *J. Am. Chem. Soc.*, **2004**, *126*, 15002. (b) Dopper, J. H.; Oudman, D. and Wynberg, H., *J. Org. Chem.*, **1975**, *40*, 3398.
3. (a) Dou, X.; Yang, X. Y.; Bodwell, G. J.; Wagner, M.; Enkelmann, V. and Muellen, K., *Org. Lett.*, **2007**, 9, 2485. (b) King, B. T.; Kroulik, J.; Robertson, C. R.; Rempala, P.; Hilton, C. L.; Korinek, J. D. and Gortari, L. M., *J. Org. Chem.*, **2007**, 72, 2279. (c) Rempala, P.; Kroulík, J. and King, B. T., *J. Org. Chem.*, **2006**, *71*, 5067. (d) Cataldo, F. and Keheyan, Y., *Int. J. Astrobiology*, **2003**, *2*, 41. (e) Wang, H. Q.; Zeng, F. D.; Zheng, Z. Q. and Huang, D. X., *Gaofenzi Xuebao*, **1999**, 359. (f) Tanaka, M.; Nakashima, H.; Fujiwara, M.; Ando, H. and Souma, Y., *J. Org. Chem.*, **1996**, *61*, 788. (g) Zander, M. and Friedrichsen, W., *Zeitsch. Naturforsch., B: Chem. Sci.*, **1992**, *47*, 1314. (h) Percec, V. and Wang, J. H., *Makromol. Chem., Macromol. Symp.,* **1992**, *54/55*, 337. (i) Percec, V.; Wang, J. H. and Oishi, Y., *J. Poly. Sci., Part A*, **1992**, *30*, 439. (j) Percec, V.; Wang, J. H. and Okita, S., *J. Poly. Sci., Part A*, **1992**, *30*, 429. (k) Percec, V.; Okita, S. and Wang, J. H., *Macromolecules*, **1992**, *25*, 64. (l) Percec, V.; Wang, J. H. and Yu, L. S., *Polymer Bull.*, **1992**, *27*, 503. (m) Percec, V. and Wang, J. H., *Polymer Bull.*, **1991**, *25*, 9. (n) Percec, V. and Wang, J. H., *J. Mater. Chem.*, **1991**, *1*, 1051. (o) Percec, V.; Wang, J. H. and Okita, S., *J. Poly. Sci., Part A*, **1991**, *29*, 1789. (p) Percec, V.; Wang, J. H. and Oishi, Y., *J. Poly. Sci., Part A*, **1991**, *29*, 949. (q) Percec, V.; Wang, J. H.; Oishi, Y. and Feiring, A. E., *J. Poly. Sci. Part A: Poly. Chem.*, **1991**, *29*, 965. (r) Colon, I. and Kwiatkowski, G. T., *J. Poly. Sci. Part A: Poly. Chem.*, **1990**, *28*, 367. (s) Percec, V. and Nava, H., *J. Poly. Sci. Part A: Poly. Chem.,* **1988**, *26*, 783. (t) Hirakawa, K.; Ogiue, E.; Motoyoshiya, J. and Kakurai, T., *Bull. Chem. Soc. Jpn.*, **1987**, *60*, 2292. (u) Percec, V. and Nava, H., *Polymer Preprints*, **1987**, *28*, 254. (v) Bunte, R.; Gundermann, K. D.; Leitich, J.; Polansky, O. E. and Zander, M., *Chem. Ber.*, **1987**, *120*, 247. (w) Nystuen, N. J. and Jones, J. B., *J. Poly. Sci., Poly. Chem. Ed.*, **1985**, *23*, 1433. (x) Zingg, S. P.; Dworkin, A. S.; Sorlie, M.; Chapman, D. M.; Buchanan, A. C. and Smith, G. P., *J. Electrochem. Soc.*, **1984**, *131*, 1602. (y) Staab, H. A.; Diederich, F. and Caplar, V., *Liebigs Ann. Chem*., **1983**, 2262. (z) Berg, J. E.; Erdtman, H.; Hoegberg, H. E.; Karlsson, B.; Pilotti, A. M. and Soederholm, A. C., *Tetrahedron Lett*., **1977**, 1831. (aa) Boger, E.; O'Malley, R. F. and Sardella, D. J., *J. Fluor. Chem.*, **1976**, *8*, 513. (bb) Buchan, R. and Musgrave, O. C., *J. Chem. Soc., Perkin Trans. I*, **1975**, 568. (cc) Wick, A. K., *Helv. Chim. Acta*, **1971**, *54*, 769. (dd) Seshadri, S., *Proc. Symp. Contrib. Chem. Syn. Dyes Mech. Dyeing*, **1968**, 9. (ee) Clowes, G. A., *J. Chem. Soc. C*, **1968**, 2519. (ff) Koptyug, V. A.; Mokrousov, B. I. and Shubin, V. G., *Zh. Org. Khim.*, **1965**, *1*, 975. (gg) Vollmann, H., *Ann.*, **1963**, *669*, 22. (hh) Nenitzescu, C. D. and Balaban, A., *Chem. Ber.*, **1958**, *91*, 2109. (ii) Baddeley, G., *J. Chem. Soc.*, **1943**, 527. (jj) Lukin, A. M., *Promy. Org. Khim.*, **1939**, *6*, 370. (kk) Brass, K.; Willig, E. and Hansen, R., *Ber.,* **1930**, *63B*, 2613.
4. (a) Simoneit, B. R. and Fetzer, J. C., *Org. Geochem.*, **1996**, *24*, 1065. (b) Fetzer, J. C., *Polycycl. Aromat. Compd.*, **1994**, *4*, 19. (c) Lehnig, M.; Reiche, T. and Reiss, S., *Tetrahedron Lett*., **1992**, *33*, 4149. (d) Bakker, M. G.; Claridge, R. F. C. and Kirk, C. M., *J. Chem. Soc., Perkin Trans. II*, **1986**, 1735. (e) Salim, S. S. and Bell, A. T., *Fuel*, **1984**, *63*, 469. (f) Salim, S. S. and Bell, A. T., *Fuel*, **1982**, *61*, 745. (g) Buchanan, A. C.; Dworkin, A. S. and Smith, G. P., *J. Am. Chem. Soc.*, **1980**, *102*, 5262. (h) Poutsma, M. L.; Dworkin, A. S.; Brynestad, J.; Brown, L. L.; Benjamin, B. M. and Smith, G. P., *Tetrahedron Lett*., **1978**, 873. (i) Olah, G. A.; Schilling, P. and Gross, I. M., *J. Am. Chem. Soc.*, **1974**, *96*, 876. (j) Tilak, B. D., *Ind. Chim. Belg.*, **1967**, 32, 50. (k) Tilak, B. D., *Chimia*, **1966**, *20*, 272.
5. Simons, J. H. and McArthur, R. E., *Ind. Eng. Chem.*, **1947**, *39*, 364.
6. (a) Baddeley, G., *J. Chem. Soc.*, **1950**, 994. (b) Baddeley, G. and Kenner, J., *J. Chem. Soc.*, **1935**, 303.

7. Vingiello, F. A.; Yanez, J. and Campbell, J. A., *J. Org. Chem.*, **1971**, *36*, 2053.
8. (a) Simpson, C. D.; Mattersteig, C.; Martin, K.; Gherghel, L.; Bauer, R. E.; Räder, H. J. and Müllen, K., *J. Am. Chem. Soc.*, **2004**, *126*, 3139. (b) Simpson, C. D.; Brand, J. D.; Berresheim, A. J.; Przybilla, L.; Räder, H. J. and Müllen, K., *Chem. Eur. J.*, **2002**, *8*, 1424. (c) Watson, M. D.; Fechtenkötter, A. and Müllen, K., *Chem. Rev.*, **2001**, *101*, 1267. (d) Iyer, V. S; Wehmeier, M.; Brand, J. D.; Keegstra, M. A. and Müllen, K., *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, 1604.
9. Deichmann, M.; Näther, C. and Herges, R., *Org. Lett.*, **2003**, *5*, 1269.
10. (a) Grigoras, M. and Catanescu, C. O., *J. Macromol. Sci., Part C: Polymer Rev.*, **2004**, *44*, 131. (b) Rozas, M. F.; Piro, O. E.; Castellano, E. E.; Mirífico, M. V. and Vasini, E. J., *Synthesis*, **2002**, 2399. (c) Abd-El-Aziz, A. S.; de Denus, C. R.; Zaworotko, M. J. and MacGillivray, L. R., *J. Chem. Soc., Dalton Trans.*, **1995**, 3375. (d) Balaban, A. T., *Pure & Appl. Chem.*, **1993**, *65*, 1. (e) Nenitzescu, C. D. and Balaban, A. T., Aliphatic acylation in *Friedel-Crafts and Related Reactions*, ed., Olah, G., John Wiley & Sons, New York, **1964**, *2*, p. 2, pp. 979–1045. (f) Scholl, R. and Seer, C., *Ann.*, **1912**, *394*, 111.

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Schöllkopf Bis-Lactim Ether Method

(Schöllkopf Bis-Lactim Method)

A. GENERAL DESCRIPTION OF THE REACTION

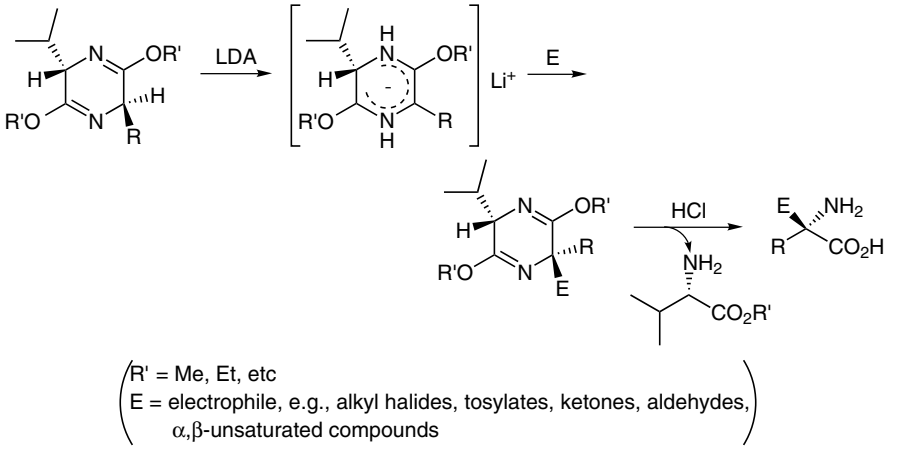
This reaction was first reported by Schöllkopf in 1979.[1] It is a synthesis of an unnatural nonproteinogenic amino acid from the lithiated enolate equivalent of a simple amino acid (e.g., glycine, alanine and valine), which involves the diastereoselective alkylation of the lithiated bis-lactim ether of an amino acid with an electrophile[2] or an *Aldol Reaction* or *Michael Addition* to an α,β-unsaturated molecule[3] and subsequent acidic hydrolysis. Therefore, the intermediate of the bis-lactim ether prepared from corresponding amino acids is generally referred to as the Schöllkopf bis-lactim ether,[3a,3b,4] Schöllkopf chiral auxiliary,[2,5] Schöllkopf reagent,[3a,3b,6] or Schöllkopf bis-lactim ether chiral auxiliary.[2a,7] Likewise, the Schöllkopf bis-lactim ether mediated synthesis of chiral nonproteinogenic amino acid is known as the Schöllkopf bis-lactim ether method,[2b,6b] Schöllkopf bis-lactim method,[6b] or Schöllkopf methodology.[6a] In addition, the reaction between a lithiated Schöllkopf bis-lactim ether and an electrophile is termed as the Schöllkopf alkylation,[8] while the addition of such lithiated intermediate to an α,β-unsaturated compound is referred to as the Schöllkopf-type addition.[8]

To smoothly prepare the Schöllkopf bis-lactim ether from an amino acid, it is important to add 2,6-di-*tert*-butylpyridine to the reaction system.[9] It has been reported that the alkylation of the lithiated Schöllkopf bis-lactim ether in diethyl ether contains high levels of π-facial discrimination,[3a,4m] where the tosylate or halide electrophile is introduced into the opposite side of the bulky group on the bis-lactim ether ring.[8] Such stereochemical outcome for the Schöllkopf alkylation is known as the Schöllkopf's rule or Schöllkopf's observation.[8] However, this rule is not always obeyed, and the reaction is probably controlled by both

Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

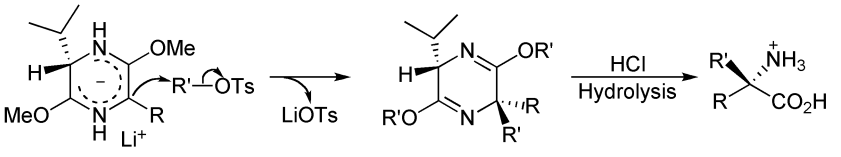
reagent and substrate.[3b] For example, the reaction between the Schöllkopf bis-lactim ether with a benzyl group at the 3-position and methyl iodide or deuterium chloride all give products in favor of *trans* isomers, with a *trans*/*cis* ratio of 4:1; whereas the alkylation with a triflate leads to the formation of a racemic mixture.[8] In addition, due to the low solubility of the lithiated Schöllkopf bis-lactim ether in diethyl ether, a small amount of THF is necessary to ensure a homogenous reaction condition.[4m] For comparison, the conjugated addition of the lithiated Schöllkopf bis-lactim ether to the α,β-unsaturated compounds may yield products with high levels of stereochemical control at both the α- and β-positions.[3b] Furthermore, the lithiated Schöllkopf bis-lactim ether can add to aldehydes or ketones to yield *threo* diastereomers.[4i] It should be emphasized that to ensure a complete hydrolysis of the Schöllkopf bis-lactim ether, it is better to use a higher concentration of HCl,[4d] rather than a mild acidic condition.[10]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is assumed that the alkylation can be considered as a simple nucleophilic substitution, probably via a S_N2 mechanism. For the case of alkylation, due to the steric effect of isopropyl group on the bis-lactim ether ring, the electrophile enters from the opposite side. However, for the alkylation with an alkyl triflate, the reaction could be too fast to display the facial discrimination. For comparison, a "compact" and "relaxed" transition state has been proposed to rationalize the stereochemical outcome for the conjugated addition of the lithiated Schöllkopf bis-lactim ether to an α,β-unsaturated compound, such as α,β-unsaturated phosphonate.[2c] An illustrative diagram is provided here for the alkylation with a general alkyl tosylate.



D. MODIFICATION

This reaction has been modified by exchanging the lithium ion of the Schöllkopf bis-lactim ether intermediate with Sn(II),[11] Cu(I),[12] or Ti(IV)[13] to enhance the diastereoselectivity in *Aldol Condensation* and the *Michael Addition*.

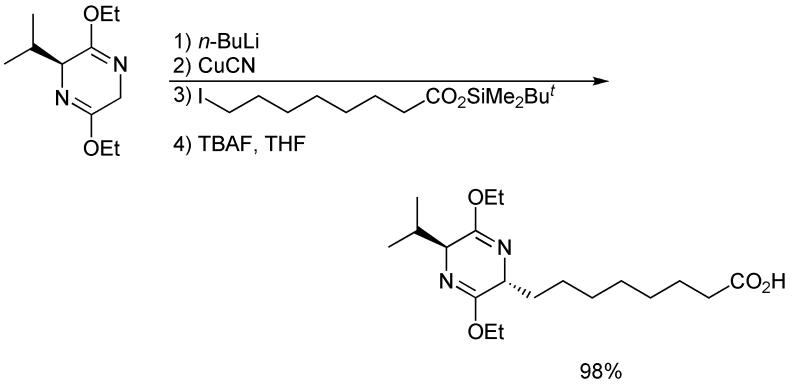
E. APPLICATIONS

This reaction is very useful for the preparation of unnatural, nonproteinogenic amino acids that are used for the synthesis of immunostimulants, hormones, synthetic enzymes, and peptide drugs with special biological properties.[4k]

F. RELATED REACTIONS

N/A

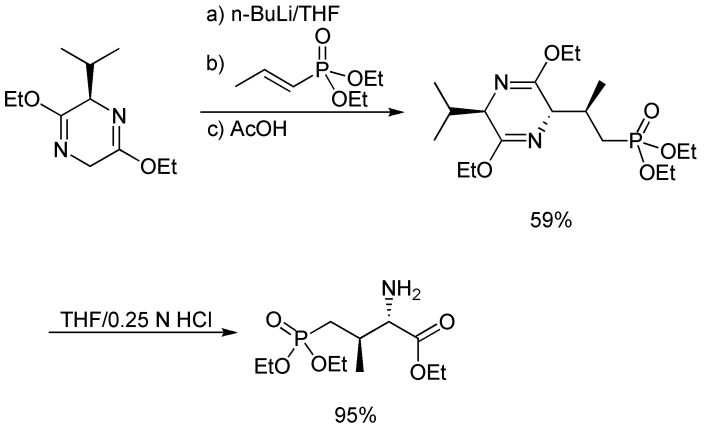
G. CITED EXPERIMENTAL EXAMPLES



Reference 4d.

To 20 mL THF solution containing 2.50 g 6(*S*)-isopropyl-2,5-diethoxy-3,6-dihydropyrazine (11.8 mmol) at −78°C, was added under argon 7.05 mL 1.67 M *n*-BuLi in hexane (1 eq.) dropwise over 10 min. After being stirred for an additional 20 min, the reaction mixture was transferred via a Teflon cannula to 20 mL THF solution of 0.527 g CuCN (5.89 mmol, 0.5 eq.) over 30 min, so that all of CuCN dissolved over this period. Then the solution was cooled to −78°C again, and 20 mL THF solution of 3.39 g *tert*-butyldimethylsilyl 8-iodooctanoate (8.83 mmol, 1.5 eq. with respect to CuCN) precooled to −78°C was transferred via a Teflon cannula. The reaction mixture was then warmed to −23°C and was stirred at this temperature for a further 5 h, after which time the reaction was stored at −23°C for 18 h. The reaction was then quenched with 30 mL concentrated NH_3/saturated NH_4Cl solution (1:9); the resulting mixture was extracted with 750 mL Et_2O in portions, and the combined organic layers were washed with concentrated

NH_3/saturated NH_4Cl solution (1:9, 3 × 300 mL) and dried over Na_2SO_4. Upon removal of solvent in vacuo, 1.44 g crude yellow oil was yielded. To this crude 8-(*R*)-(4(*S*)-isopropyl-3,6-diethoxy-2,5-dihydropyrazin-2-yl)-*tert*-butyldimethylsilyl octanoate (assumed to be 5.89 mmol based on CuCN) under argon was added 17.7 mL 1.0 M tetra-*n*-butylammonium fluoride (TBAF) THF solution, and the mixture was stirred at room temperature for 75 min and then quenched with 35 mL saturated NH_4Cl solution. The reaction mixture was extracted with Et_2O (2 × 125 mL), and the combined organic layers were dried over Na_2SO_4. Upon removal of solvent in vacuo, the 4.77 g white solid was purified by column chromatography using Et_2O/hexane (1:1) containing 0.1% formic acid as the eluent ($R_f = 0.4$) to afford 2.06 g 8-(*R*)-(5(*S*)-isopropyl-3,6-diethoxy-2,5-dihydropyrazin-2-yl)octanoic acid, in a yield of 98% (based on CuCN). The chiral purity was checked by chiral HPLC as single product. After hydrolysis of this product with 1.0 M HCl, the expected amino acid could be obtained. (*Note:* There is an inconsistency of weight in this experimental procedure: from 1.44 g 8-(*R*)-(4(*S*)-isopropyl-3,6-diethoxy-2,5-dihydropyrazin-2-yl)-*tert*-butyldimethylsilyl octanoate, it is impossible to produce 2.06 g 8-(*R*)-(5(*S*)-isopropyl-3,6-diethoxy-2,5-dihydropyrazin-2-yl)octanoic acid by removal of the dimethyl-*tert*-butylsilyl group.)



Reference 3b.

To 1050 mL THF solution containing 22.4 g 3(*R*)-isopropyl-2,5-diethoxy-3,6-dihydropyrazine (105.5 mmol) at −78°C, was added 42.2 mL 2.5 M *n*-BuLi in hexane, and the resulting solution was stirred for 1 h. Then 116 mL THF solution of 10.35 g propenylphosphonate (58.1 mmol) was added dropwise. After being stirred at −78°C until the completion of the reaction, the reaction mixture was quenched with AcOH and warmed to room temperature. Upon removal of the solvent in vacuo, the resulting material was diluted with water and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and evaporated, and the residue was purified by flash column chromatography (silica gel, EtOAc/hexane, 2:1–4:1) to yield 13.4 g (2*S*,5*R*,1′*R*)-3,6-diethoxy-2-[2-(diethoxyphosphoryl)-1-(methyl)ethyl]-2,5-dihydro-5-isopropylpyrazine as a colorless oil, in a yield of 59%, $R_f = 0.46$ (EtOAc).

A mixture of 9.37 g (2*S*,5*R*,1′*R*)-3,6-diethoxy-2-[2-(diethoxyphosphoryl)-1-(methyl)-ethyl]-2,5-dihydro-5-isopropyl-pyrazine (24.0 mmol), 200 mL THF, and 240 mL 0.25 *N* HCl was stirred at room temperature for 24 h. Then the solvent was evaporated to half of its initial volume (< 40°C), and the aqueous solution was made basic (pH = 10) by the

addition of $NaHCO_3$ followed by concentrated ammonia. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by silica gel flash column chromatography (EtOAc to EtOAc/MeOH (8:1)) to afford 6.4 g ethyl (2*S*,3*R*)-2-amino-4-diethoxyphosphoryl-3-methylbutanoate as a colorless oil, in a yield of 95%, $R_f = 0.36$ (EtOAc/MeOH, 10:1).

Other references related to the Schöllkopf bis-lactim ether method are cited in the literature.[14]

H. REFERENCES

1. Schöllkopf, U.; Hartwig, W. and Groth, U., *Angew. Chem. Int. Ed. Engl*., **1979**, *18*, 863.
2. (a) Krikstolaityte, S.; Sackus, A. and Undheim, K., *Chemija*, **2001**, *12*, 76. (b) Ma, C. R.; He, X. H.; Liu, X. X.; Yu, S.; Zhao, S. and Cook, J. M., *Tetrahedron Lett*., **1999**, *40*, 2917.
3. (a) Ruiz, M.; Fernández, M. C.; Díaz, A.; Quintela, J. M. and Ojea, V., *J. Org. Chem*., **2003**, *68*, 7634. (b) Ojea, V.; Ruiz, M.; Shapiro, G. and Pombo-Villar, E., *J. Org. Chem.*, **2000**, *65*, 1984. (c) Ruiz, M.; Ojea, V.; Fernandez, M. C.; Conde, S.; Diaz, A. and Quintela, J. M., *Synlett*, **1999**, 1903. (d) Ojea, V.; Conde, S.; Ruiz, M.; Fernandez, M. C. and Quintela, J. M., *Tetrahedron Lett*., **1997**, *38*, 4311. (e) Williams, R. M., *Synthesis of Optically Active α-Amino Acids,* Pergamon, Oxford, **1989**. (f) Schöllkopf, U.; Pettig, D.; Schulze, E.; Klinge, M.; Egert, E.; Benecke, B. and Noltemeyer, M., *Angew. Chem. Int. Ed. Engl.*, **1988**, *27*, 1194. (g) Pettig, D. and Schöllkopf, U., *Synthesis*, **1988**, 173. (h) Schöllkopf, U. and Schröder, J., *Liebigs Ann. Chem.*, **1988**, 87. (i) Schöllkopf, U.; Kühnle, W.; Egert, E. and Dyrbusch, M., *Angew. Chem. Int. Ed. Engl.*, **1987**, *26*, 480. (j) Hartwig, W. and Born, L., *J. Org. Chem.*, **1987**, *52*, 4352. (k) Schöllkopf, U.; Pettig, D.; Busse, U.; Egert, E. and Dyrbusch, M., *Synthesis*, **1986**, 737.
4. (a) Smith, N. D.; Wohlrab, A. M. and Goodman, M., *Org. Lett*., **2005**, *7*, 255. (b) Bartley, D. M. and Coward, J. K., *J. Org. Chem.*, **2005**, *70*, 6757. (c) Andrews, P. C.; Maguire, M.; Pombo-Villar, E., *Helv. Chim. Acta*, **2002**, *85*, 3516. (d) McNamara, L. M. A.; Andrews, M. J. I.; Mitzel, F.; Siligardi, G. and Tabor, A. B., *J. Org. Chem*., **2001**, *66*, 4585. (e) Dondoni, A. and Marra, A., *Chem. Rev*., **2000**,*100*, 4395. (f) Dittmar, C., *Ber. Forsch. J.*, **2000**, *i-vi*, 1. (g) Davis, F. A.; Srirajan, V. and Titus, D. D., *J. Org. Chem*., **1999**, *64*, 6931. (h) Gao, Y.; Lane-Bell, P. and Vederas, J. C., *J. Org. Chem*., **1998**, *63*, 2133. (i) Blaskovich, M. A.; Evindar, G.; Rose, N. G. W.; Wilkinson, S.; Luo, Y. and Lajoie, G. A., *J. Org. Chem*., **1998**, *63*, 3631. (j) Bois-Choussy, M.; Neuville, L.; Beugelmans, R. and Zhu, J. P., *J. Org. Chem.*, **1996**, *61*, 9309. (k) Hegedus, L. S., *Acc. Chem. Res*., **1995**, *28*, 299. (l) Berkowitz, D. B. and Smith, M. K., *J. Org. Chem*., **1995**, *60*, 1233. (m) Shapiro, G.; Buechler, D.; Marzi, M.; Schmidt, K. and Gomez-Lor, B., *J. Org. Chem*., **1995**, *60*, 4978. (n) Hunig, S.; Klaunzer, N. and Wenner, H., *Chem. Ber.*, **1994**, *127*, 165.
5. (a) Zhou, H.; Liao, X. B.; Yin, W. Y.; Ma, J. and Cook, J. M., *J. Org. Chem.*, **2006**, *71*, 251. (b) Neelamkavil, S.; Mowery, B. P.; Thornton, E. R.; Smith, A. B. and Hirschmann, R., *J. Peptide Res.*, **2005**, *65*, 139. (c) Yu, J. M.; Wearing, X. Y. Z. and Cook, J. M., *J. Org. Chem.*, **2005**, *70*, 3963. (d) Zhou, H.; Liao, X. B. and Cook, J. M., *Org. Lett.*, **2004**, 6, 249. (e) Ma, C. R.; Yu, S.; He, X. H.; Liu, X. X. and Cook, J. M., *Tetrahedron Lett.*, **2000**, *41*, 2781.
6. (a) Kim, D.; Wang, L. P.; Beconi, M.; Eiermann, G. J.; Fisher, M. H.; He, H. B.; Hickey, G. J.; Kowalchick, J. E.; Leiting, B.; Lyons, K.; Marsilio, F.; McCann, M. E.; Patel, R. A.; Petrov, A.; Scapin, G.; Patel, S. B.; Roy, R. S.; Wu, J. K.; Wyvratt, M. J.; Zhang, B. B.; Zhu, L.; Thornberry, N. A. and Weber, A. E., *J. Med. Chem.*, **2005**, *48*, 141. (b) Vivet, B.; Cavelier, F. and Martinez, J., *Eur. J. Org. Chem.*, **2000**, 807.
7. Bull, S. D.; Davies, S. G. and Moss, W. O., *Tetrahedron: Asymmetry*, **1998**, *9*, 321.

8. Subramanian, P. K. and Woodard, R. W., *J. Org. Chem*., **1987**, *52*, 15.
9. Sasaki, Y.; Niida, A.; Tsuji, T.; Shigenaga, A.; Fujii, N. and Otaka, A., *J. Org. Chem*., **2006**, *71*, 4969.
10. (a) Schöllkopf, U.; Busse, U.; Lonsky, R. and Hinrichs, R., *Ann*., **1986**, 2150. (b) Schöllkopf, U., *Enantioselective Synthesis of Nonproteinogenic Amino Acids* in *Topics in Current Chemistry,* ed. Boschke, F. I., Springer, Berlin, **1983**, *109*, pp. 65–84. (c) Schöllkopf, U.; Groth, U. and Deng, C., *Angew. Chem. Int. Ed. Engl.*, **1981**, *20*, 798.
11. (a) Ruiz, M.; Ojea, V. and Quintela, J. M., *Synlett*, **1999**, 204. (b) Ruiz, M.; Ruanova, T. M.; Ojea, V. and Quintela, J. M., *Tetrahedron Lett*., **1999**, *40*, 2021. (c) Kobayashi, S.; Furuta, T.; Hayashi, T.; Nishijima, M. and Hanada, K., *J. Am. Chem. Soc*., **1998**, *120*, 908.
12. Schöllkopf, U. and Schröder, J., *Ann*., **1988**, 87.
13. (a) Schöllkopf, U. and Bardenhagen, J., *Ann*., **1987**, 393. (b) Grauert, M. and Schöllkopf, U., *Ann*., **1985**, 1817.
14. (a) Zhang, F. and Fox, J. M., *Org. Lett*., **2006**, *8*, 2965. (b) Lindsay, K. B. and Skrydstrup, T., *J. Org. Chem*., **2006**, *71*, 4766. (c) Oku, N.; Krishnamoorthy, R.; Benson, A. G.; Ferguson, R. L.; Lipton, M. A.; Phillips, L. R.; Gustafson, K. R. and McMahon, J. B., *J. Org. Chem*., **2005**, *70*, 6842. (d) Li, X. Y.; Yin, W. Y.; Sarma, P. V. V. S.; Zhou, H.; Ma, J. and Cook, J. M., *Tetrahedron Lett*., **2004**, *45*, 8569. (e) Zhao, S.; Liao, X. B.; Wang, T.; Flippen-Anderson, J. and Cook, J. M., *J. Org. Chem.*, **2003**, *68*, 6279. (f) Croce, P. D.; La Rosa, C. and Pizzatti, E. *Tetrahedron: Asymmetry*, **2000**, *11*, 2635. (g) Adamczyk, M.; Fishpaugh, J. R. and Thiruvazhi, M., *Tetrahedron: Asymmetry*, **1999**, *10*, 4151. (h) Kotha, S.; Sreenivasachary, N. and Ilalder, S., *Bioorg. Med. Chem. Lett.*, **1999**, *9*, 2565. (i) Micheli, F.; Di Fabio, R. and Marchioro, C., *Farmaco*, **1999**, *54*, 461. (j) Wirth, T., *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, 225. (k) Jane, D. E.; Chalmers, D. J.; Howard, J. A. K.; Kilpatrick, I. C.; Sunter, D. C.; Thompson, G. A.; Udvarhelyi, P. M.; Wilson, C. and Watkins, J. C., *J. Med. Chem*., **1996**, *39*, 4738. (l) Kotha, S. and Kuki, A., *Chem. Commun*., **1992**, 404. (m) Allen, M. S.; Hamaker, L. K.; La Loggia, H. J. and Cook, J. M., *Synth. Commun*., **1992**, *22*, 2077. (n) Thomas, N. R. and Gani, D., *Tetrahedron*, **1991**, *47*, 497. (o) Subramanian, P.; Kalvin, D. M.; Ramalingam, K. and Woodard, R. W., *J. Org. Chem.*, **1989**, *54*, 270. (p) Sinclair, P. J.; Zhai, D. G.; Reibenspies, J. and Williams, R. M., *J. Am. Chem. Soc*., **1986**, *108*, 1103. (q) Schöllkopf, U., *Pure & Appl. Chem*., **1983**, *55*, 1799. (r) Schöllkopf, U., *Tetrahedron*, **1983**, *39*, 2085. (s) Schöllkopf, U.; Groth, U. and Deng, C. Z., *Angew. Chem. Int. Ed. Engl*., **1981**, *20*, 798.

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Schöllkopf Oxazole Synthesis

(Schöllkopf Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Schöllkopf and Schröder in 1971.[1] It is the formation of a 2-unsubstituted oxazole derivative by the condensation of an α-metalated isocyanide with an acylating reagent. Therefore, this reaction is known as the Schöllkopf oxazole synthesis[2] or Schöllkopf reaction.[3]

In this reaction, the α-alkali metalated isocyanide, generated by the treatment of an isocyanide with an α-hydrogen by a regular base such as butyllithium, potassium *tert*-butoxide, sodium hydride, DBU, and even triethylamine, functions as both nucleophile and electrophile,[4] and reacts with a suitable acylating reagent, including acyl halide, amide,[1] ester,[4] anhydride,[5] and acyl imidzole.[6] During this reaction, the intermediate of α-isocyanoketone is not isolable, and cyclizes to give oxazole at the workup stage.[4] Among the formed oxazole derivatives, the substituent at the 4-position comes from the group on the methylene carbon of the isonitriles, while the substituent at the 5-position has the origin from the acylating reagent.[6] One important utility of the Schöllkopf oxazole synthesis is to prepare amino esters and amino ketones in high yields.[7]

Besides the formation of oxazole derivatives, Schöllkopf and the others have successfully extended the α-alkali metalated isocyanides to the formation of the chain-extended primary amines,[8] 2-oxazolines,[9] 2-thiazoline-4-carboxylic esters,[4] 2-imidazolines,[10] 2-pyrrolines and pyrroles,[11] thiazoles,[12] 2-imidazolin-5-ones,[4] 2-imidazolinones,[4] etc. For example, a simple reaction between lithiomethyl isocyanide with two equivalents of piperonal followed by acetylation of the intermediate with acetic anhydride affords the corresponding oxazoline.[13]

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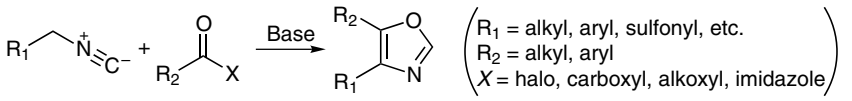
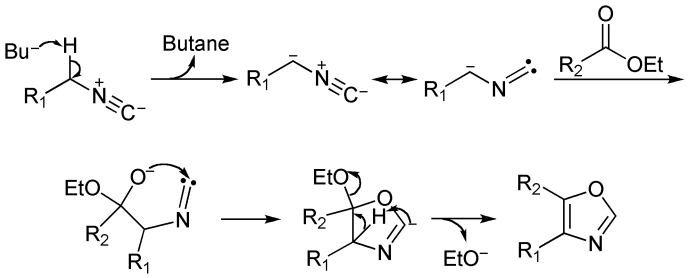
B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

It is assumed that this reaction involves the deprotonation of an α-hydrogen to form an isocyano group stabilized carbanion that adds to the carbonyl group of the acylating agent followed by the cyclization via the attack of alkoxyl anion on the isocyano group, as illustrated here.



D. MODIFICATION

Kozikowski has extended this reaction by using selenol esters as the acylating reagent instead of the acyl chlorides, in which the activated isonitriles in the presence of a soft metal ion have shown a strong affinity for selenium.[2b] This modification is thus referred to as the Kozikowski modification.[2a]

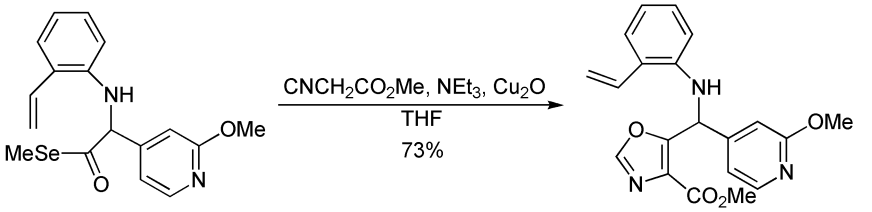
E. APPLICATIONS

This reaction has general application in the preparation of oxazole derivatives.

F. RELATED REACTIONS

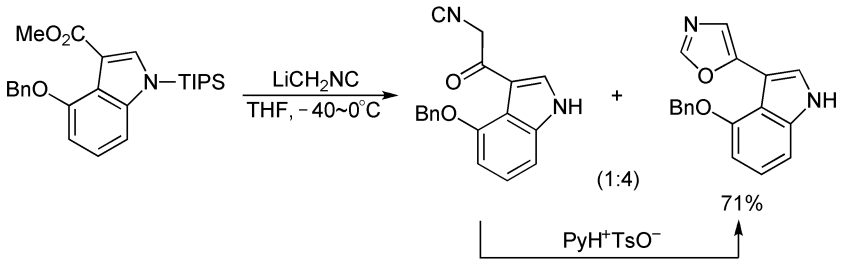
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 2a.

To a mixture of 0.15 g selenol ester (0.41 mmol), 63 mg triethylamine (0.62 mmol), and 0.12 g methyl isocyanoacetate (1.21 mmol) in 5 mL anhydrous THF was added 92 mg anhydrous cuprous oxide (0.62 mmol). After being stirred at room temperature for 1 h, the reaction mixture was filtered through a pad of silica gel, which was eluted with EtOAc. The combined filtrate was concentrated in vacuo and the residue was purified by flash chromatography using EtOAc/hexane (1:3) as the eluent to afford 0.11 g oxazole ester as a colorless oil, in a yield of 73%.



Reference 3a.

To a solution of 0.827 mL methyl isocyanide (15.1 mmol) in 20 mL THF at −78°C was added 5.0 mL 1.5 M *n*-BuLi in hexanes (7.55 mmol). The mixture was stirred for 10 min and warmed to −45°C. To this solution was added 0.661 g 4-benzyloxy-3-methoxycarbonyl-1-(triisopropylsilyl)indole (1.51 mmol) in 5 mL THF dropwise. The resulting solution was stirred at −45°C for 30 min and warmed to 0°C for an additional 30 min. Then the mixture was poured into 50 mL saturated $NaHCO_3$ solution and extracted with EtOAc (3 × 30 mL). The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography using ether/hexanes (2:1–3:1) to afford a 4:1 mixture of oxazole to keto isocyanide products (1:2 ratio in the original article, but 4:1 in the corresponding experimental section). The mixture of products was dissolved in 15 mL CH_2Cl_2 and treated with 0.076 g pyridinium *p*-toluenesulfonate (PPTS) (0.302 mmol) for 2 h. The mixture was concentrated and filtered through a plug of silica gel with ether as the eluent to afford 0.310 g 4-benzyloxy-3-(5-oxazolyl)indole as a white solid, in a yield of 71%, $R_f = 0.29$ (ether/hexane, 3:1). Pure material was obtained by crystallization from CH_2Cl_2, mp 167–168°C.

Other references related to the Schöllkopf oxazole synthesis are cited in the literature.[14]

H. REFERENCES

1. Schöllkopf, U. and Schröder, R., *Angew. Chem. Int. Ed. Engl.*, **1971**, *10*, 333.
2. (a) Subramanyam, C.; Noguchi, M. and Weinreb, S. M., *J. Org. Chem.*, **1989**, *54*, 5580. (b) Kozikowski, A. P. and Ames, A., *J. Am. Chem. Soc.*, **1980**, *102*, 860.
3. (a) Vedejs, E. and Barda, D. A., *Org. Lett.*, **2000**, *2*, 1033. (b) Jacobi, P. A. and Walker, D. G., *J. Am. Chem. Soc.*, **1981**, *103*, 4611.
4. Schöllkopf, U., *Pure & Appl. Chem.*, **1979**, *51*, 1347.
5. Suzuki, M.; Iwasaki, I.; Miyoshi, M.; Okumura, K. and Matsumoto, K., *J. Org. Chem.*, **1973**, *38*, 3571.
6. Turchi, I. J., *Ind. Eng. Chem. Prod. Res. Dev.*, **1981**, *20*, 32.

7. Turchi, I. J. and Dewar, M. J. S., *Chem. Rev.*, **1975**, *75*, 389.
8. Schöllkopf, U.; Hoppe, D. and Jentsch, R., *Angew. Chem. Int. Ed. Engl.*, **1971**, *10*, 331.
9. Schöllkopf, U.; Gerhart, F.; Hoppe, I.; Harms, R.; Hantke, K.; Scheunemann, K.-H.; Eilers, E. and Blume, E., *Liebigs Ann. Chem.*, **1976**, 183.
10. Meyer, R.; Schöllkopf, U. and Böhme, P., *Liebigs Ann. Chem.*, **1977**, 1183.
11. (a) Schöllkopf, U. and Hantke, K., *Liebigs Ann. Chem.*, **1973**, 1571. (b) van Leusen, A. M.; Siderius, H.; Hoogenboom, B. E. and van Leusen, D., *Tetrahedron Lett.*, **1972**, 5337.
12. Hartman, G. D. and Weinstock, L. M., *Synthesis*, **1976**, 681.
13. Kozikowski, A. P. and Ames, A., *J. Org. Chem.*, **1980**, *45*, 2548.
14. (a) Hamada, Y. and Shiori, T., *Tetrahedron Lett.*, **1982**, 235. (b) Schöllkopf, U. and Hoppe, I., *Liebigs Ann. Chem.*, **1980**, 819. (c) Henneke, K.-W.; Schöllkopf, U. and Neudecker, T., *Liebigs Ann. Chem.*, **1979**, 1370. (d) Kozikowski, A. P. and Ames, A., *J. Org. Chem.*, **1978**, *43*, 2735. (e) Schröder, R.; Schöllkopf, U.; Blume, E. and Hoppe, I., *Liebigs Ann. Chem.*, **1975**, 533. (f) Schöllkopf, U. and Schröder, R., *Synthesis*, **1972**, 148.

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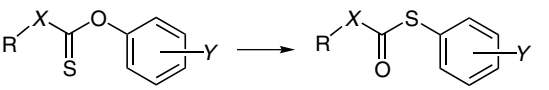
Schönberg Rearrangement
(Schönberg Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Freudenberg on the rearrangement of the methyl xanthate of diacetonehexose in 1927[1] and was subsequently studied by Schönberg on the thermal transformation of thioncarbonates (*O*-aryl) into thiolcarbonates (*S*-aryl) in 1930.[2] Therefore, it is generally known as the Schönberg rearrangement[3] or Schönberg reaction.[3a,4] This reaction has been well documented for aryl thioncarbonates (or xanthates) that lack a β-hydrogen atom,[3a,3i] whereas the thioncarbonates or xanthates with a β-hydrogen atom can also undergo the competing pyrolysis (e.g., *Chugaev Reaction*[5]) to afford olefins.[3a] It is assumed that the Schönberg rearrangement is driven by the higher nucleophilic character of the sulfur atom and the electron-donating capability of the aryl (or alkyl) group;[3i] as a result, the rearrangement is facilitated by electron-withdrawing groups at the *ortho*- and *para*-positions of the *O*-aryl moiety, which sulfur migrates to.[3h] This reaction has an important use in the conversion of phenols to thiophenols,[3i] especially for some substituted thiophenols that are difficult to attain when prepared by other methods.[3e]

B. GENERAL REACTION SCHEME



R = alkyl, aryl
X = O, S
When *Y* = ortho- or para-electron-withdrawing group, reaction is favored

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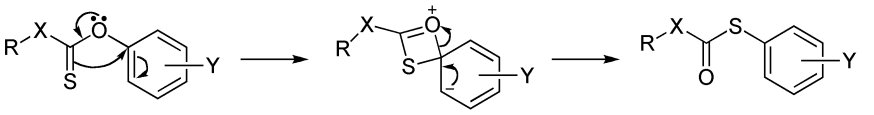
C. PROPOSED MECHANISMS

This reaction has been found to be strictly first order in kinetics.[3h] In addition, experimental evidence has indicated that this reaction is an intramolecular reaction involving the attack of sulfur atom on the *O*-aryl ring via a four-membered cyclic transition state.[3d,3e,3g,3h] An illustrative mechanism is displayed here.



D. MODIFICATION

The yield of this reaction can be considerably improved by conducting a vapor phase pyrolysis.[3e]

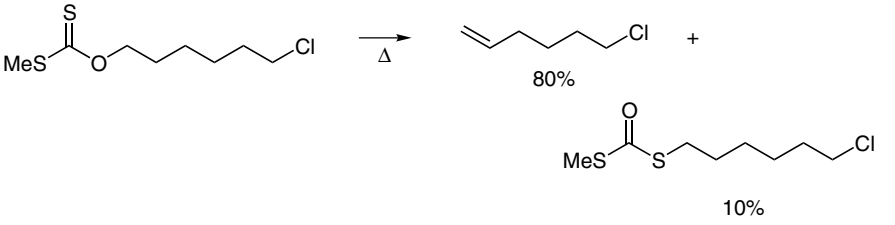
E. APPLICATIONS

This reaction has an important application in the synthesis of substituted thiophenols.

F. RELATED REACTIONS

This reaction is related to the *Chapman Rearrangement* and *Newman-Kwart Rearrangement*.

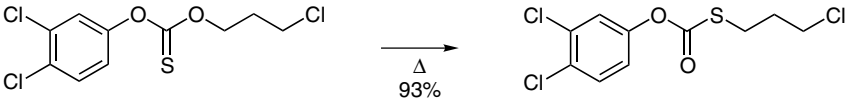
G. CITED EXPERIMENTAL EXAMPLES



Reference 3a.

The yellow methyl 6-chloro-hexyl xanthate (60.0 g, 0.265 mol) was vacuum distilled at 525°C for 3.5 h in a quartz tube, which was, in advance, coupled with two traps cooled by liquid nitrogen. Still under vacuum, the first trap was warmed to room temperature, and the volatile fragments including carbonoxy sulfide and methylmercaptan were automatically transferred to the second trap, which was placed in the hood to allow the contents to

evaporate to avoid the odour. The crude pyrolysate (45 g) in the first trap was fractionated to give 25.3 g 6-chloro-1-hexene (0.21 mol, 81%), and 5.9 g S-(6-chloro-1-hexyl)-S′-methyl dithiocarbonate as a yellow liquid, in a yield of 10%, b.p. 175–176°C at 20 mmHg.



Reference 3g.

A solution of 4.83 g 3,4-dichlorophenyl chlorothionoformate (0.02 mol) in 15 mL $CHCl_3$ was added dropwise to a stirred solution of 2.83 g 3-chloro-1-propanol (0.03 mol) and 1.7 milliliters of pyridine in 15 mL $CHCl_3$ at 0–5°C. After the reaction completed, the solution was washed with 1 *N* NaOH and water, dried, and evaporated. The residue was heated at 170°C for 1 h, and the mixture was distilled at 171°C (0.6 mmHg) to yield 5.6 g 3,4-dichlorophenyl 3-chloropropanethiol carbonate, in a yield of 93%.

Other references related to the Schönberg rearrangement are cited in the literature.[5]

H. REFERENCES

1. Freudenberg, K. and Wolf, A., *Ber.*, **1927**, *60*, 232.
2. (a) Schönberg, A. and Vargha, L., *Ber.*, **1930**, *63*, 178. (b) Schönberg, A.; Vargha, L. and Paul, W., *Ann.*, **1930**, *483*, 107.
3. (a) Jenneskens, L. W.; Hoefs, C. A. M. and Wiersum, U. E., *J. Org. Chem.*, **1989**, *54*, 5811. (b) Tou, J. C., *J. Phys. Chem.*, **1971**, *75*, 1903. (c) Relles, H. M. and Pizzolato, G., *J. Org. Chem.*, **1968**, *33*, 2249. (d) Thomson, J. B.; Brown, P. and Djerassi, C., *J. Am. Chem. Soc.*, **1966**, *88*, 4049. (e) Kwart, H. and Evans, E. R., *J. Org. Chem.*, **1966**, *31*, 410. (f) Kwart, H. and Evans, E. R., *J. Org. Chem.*, **1966**, *31*, 413. (g) Garmaise, D. L. and Paris, G. Y., *J. Org. Chem.*, **1966**, *31*, 2003. (h) Powers, D. H. and Tarbell, D. S., *J. Am. Chem. Soc.*, **1956**, *78*, 70. (i) Al-Kazimi, H. R.; Tarbell, D. S. and Plant, D., *J. Am. Chem. Soc.*, **1955**, *77*, 2479.
4. (a) Huisgen, R.; Kalvinsch, I.; Li, X. Y. and Mloston, G., *Eur. J. Org. Chem.*, **2000**, 1685. (b) Schenck, G. O., *Strahlentherapie*, **1961**, *115*, 497. (c) Bostrom, H., *Farmaco, Edizione Sci.*, **1961**, *16*, 356.
5. (a) Taylor, R., *J. Chem. Soc., Perkin Trans. II*, **1988**, 183. (b) Ohno, A.; Koizumi, T.; Ohnishi, Y. and Tsuchihashi, G., *Org. Mass Spectr.*, **1970**, *3*, 261. (c) Wemple, J., *J. Am. Chem. Soc.*, **1970**, *92*, 6694. (d) Araki, Y. and Aritsune, K., *Bull. Chem. Soc. Jpn.*, **1970**, *43*, 3214. (e) Teague, H. J. and Tucker, W. P., *J. Org. Chem.*, **1967**, *32*, 3140. (f) Griffin, G. W. and O'Connell, E. J., *J. Am. Chem. Soc.*, **1962**, *84*, 4148. (g) Schönberg, A. and Mustafa, A., *Chem. Rev.*, **1947**, *40*, 181. (h) Bachmann, W. E. and Sternberger, H. R., *J. Am. Chem. Soc.*, **1934**, *56*, 170.

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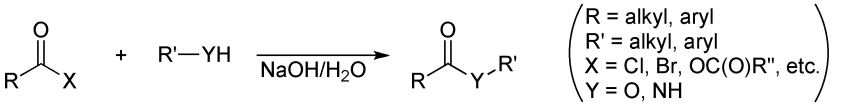
Schotten-Baumann Reaction
(Schotten-Baumann Acylation)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Schotten in 1884[1] and subsequently extended by Baumann in 1886.[2] It is the acylation of alcohols and amines from acyl halide or anhydride in an aqueous alkaline solution (e.g., 1 *M* NaOH),[3] and is generally known as the Schotten-Baumann reaction[4] or Schotten-Baumann acylation.[4s,4u,5] Occasionally, it is also referred to as the Schotten-Baumann method,[4l,4o] or Schotten-Baumann esterification.[4h,4q] Likewise, the formation of benzoyl ester under these conditions is called the Schotten-Baumann benzoylation.[4i] It is assumed that the reaction would perform well if carried out in a biphasic system of water and an immiscible organic solvent (e.g., CH_2Cl_2), which has an important application in the acylation of amino acids.[4t,4x] For example, *p*-nitrohippuric acid and dibenzoylornithine (ornithuric acid) all can be prepared under these conditions.[4t] It is interesting that when tyrosine is acylated with benzoyl chloride under this condition, it forms a dibenzoyl derivative that cannot react with the diazotized sulfanilic acid; whereas histidine yields only a monobenzoyl derivative that can further react with diazonium acid.[4t] However, it has been found that when pyridine is added to scavenge the generated HCl, the reaction yield might be reduced.[4b]

B. GENERAL REACTION SCHEME



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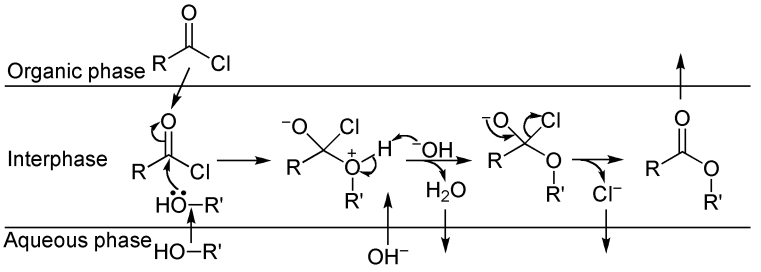
C. PROPOSED MECHANISMS

This reaction should occur in a manner similar to a regular acylation reaction. However, in the presence of a base, the hydrogen chloride is rapidly removed by the base, although the base may also react with acyl chloride or hydrolyze the new-formed ester. A general mechanism of the ester formation is illustrated here.



D. MODIFICATION

This reaction has been made feasible in an ionic liquid such as [bmim][BF_4]$_6$ in the presence of $KHCO_3$.[4a]

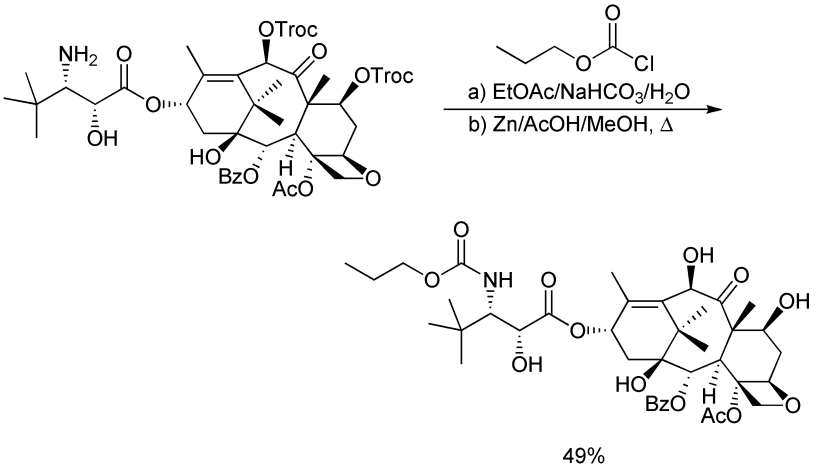
E. APPLICATIONS

This reaction has a certain application in the preparation of esters and amides.

F. RELATED REACTIONS

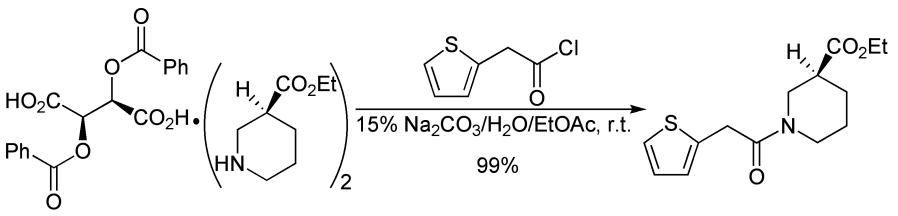
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 5d.

To a mixture of 7 mL EtOAc, 10 mL saturated aqueous $NaHCO_3$ and 10 mL H_2O containing 0.10 g butitaxel starting material (0.096 mmol) was added dropwise a solution of 0.015 g propyl chloroformate (0.13 mmol, 1.3 eq.) in 1 mL EtOAc. The mixture was stirred at 24°C for 30 min and extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with water and brine and dried over Na_2SO_4. Upon removal of solvent under reduced pressure, the residue was purified by silica gel flash column chromatography using EtOAc/hexane (1:3) as the eluent to afford 0.08 g carbamate. This carbamate was then mixed with 0.1 g zinc dust, 3 mL MeOH, and 3 mL acetic acid, and the mixture was heated at 60°C for 2 h. The reaction mixture was cooled to room temperature and filtered. The solvents were removed under reduced pressure, and the residue was dissolved in 15 mL EtOAc, washed with 10 mL saturated aqueous $NaHCO_3$ solution, 10 mL brine, and dried over Na_2SO_4. Upon removal of the solvent, the residue was purified by silica gel flash column chromatography using CH_2Cl_2/MeOH (20:1) as the eluent to afford 0.04 g *N*-debenzoyl-*N*-(propoxycarbonyl)butitaxel as a white solid, in a total yield of 49%, m.p. 155–157°C, $R_f = 0.49$ (EtOAc).



Reference 6.

A 5-L three-necked flask equipped with a mechanical stirrer and a dropping funnel was charged with 182 g ethyl nipecotate·dibenzoyl tartarate salt (271 mmol) followed by 590 mL EtOAc. To the rapidly stirring slurry was added 715 mL water followed by 482 mL 15% Na_2CO_3 (~2.5 eq.) over 15 min via a dropping funnel. After the mixture was stirred briefly, 91.3 g (2-thiophenyl)acetyl chloride (568 mmol) in 111 mL EtOAc was added over 10 min via a dropping funnel, during which time mild gas evolution was observed. Upon completion of the addition, the mixture was allowed to stir for 30 min., at which time the layers were separated, and the aqueous layer was extracted with EtOAc (2 × 350 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The yellow residue was purified by silica gel flash column chromatography using hexane/EtOAc (1:1–1:3) to afford 150 g (*S*)-ethyl-1-(2-thiopheneacetyl)-3-piperidinecarboxylate as a faintly off-white oil, in a yield of 99%.

Other references related to the Schotten-Baumann reaction are cited in the literature.[7]

H. REFERENCES

1. Schotten, C., *Ber.*, **1884**, *17*, 2544.
2. Baumann, E., *Ber.*, **1886**, *19*, 3218.
3. King, J. F.; Gill, M. S. and Klassen, D. F., *Pure & Appl. Chem.*, **1996**, *68*, 825.
4. (a) Rodriquez, M.; Sega, A. and Taddei, M., *Org. Lett.*, **2003**, *5*, 4029. (b) Wu, L. F.; Tuo, X. L.; Cheng, H.; Chen, C. and Wang, X. G., *Macromolecules*, **2001**, *34*, 8005. (c) Geall, A. J.

and Blagbrough, I. S., *Tetrahedron Lett.*, **1998**, *39*, 443. (d) Low, C. M. R.; Broughton, H. B.; Kalindjian, S. B. and McDonald, I. M., *Bioorg. Med. Chem. Lett.*, **1992**, *2*, 325. (e) Yoshimura, T., *Setchaku*, **1984**, *28*, 318. (f) Blanke, S. R. and Blanke, R. V., *J. Anal. Toxicol.*, **1984**, *8*, 231. (g) Hsiang, S.-F. L. and Wu, C.-P., *Huaxue*, **1973**, 94. (h) Tsuda, M.; Tanaka, H.; Tagami, H. and Hori, F., *Makromol. Chem.*, **1973**, *167*, 183. (i) Gutteridge, N. J. A. and Dales, J. R. M., *J. Chem. Soc. C*, **1971**, 122. (j) Tsuchiya, M.; Yoshida, H.; Ogata, T. and Inokawa, S., *Bull. Chem. Soc. Jpn.*, **1969**, *42*, 1756. (k) Babad, E. and Ben-Ishai, D., *J. Heterocycl. Chem.*, **1969**, *6*, 235. (l) Jansson, I.; Leimu, R. and Kauma, K., *Suomen Kemistilehti B*, **1969**, *42*, 6. (m) Ben-Ishai, D.; Babad, E. and Bernstein, Z., *Isr. J. Chem.*, **1968**, *6*, 551. (n) Altman, J. and Ben-Ishai, D., *J. Heterocycl. Chem.*, **1968**, *5*, 679. (o) Jansson, I.; Leimu, R. and Lammi, R., *Suomen Kemistilehti B*, **1968**, *41*, 281. (p) Oshiro, K.; Ogata, T.; Yoshida, H. and Inokawa, S., *Nippon Kagaku Zasshi*, **1968**, *89*, 211. (q) Tsuda, M., *Makromol. Chem.*, **1964**, *72*, 174. (r) Mistryukov, E. A. and Kucherov, V. F., *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1961**, 134. (s) Yamashita, K. and Yashiro, M., *Nippon Nogei Kagaku Kaishi*, **1954**, *28*, 674. (t) Friedler, L. and Smith, J. N., *Biochem. J.*, **1954**, *57*, 396. (u) Wein, J. and Benke, G., *Magyar Kemiai Folyoirat*, **1951**, *57*, 49. (v) Trautner, E. M. and Polya, J. B., *Aust. Chem. Inst. J. & Proc.*, **1948**, *15*, 52. (w) Menalda, F. A., *Recl. Trav. Chim. Pays-Bas Belg.*, **1930**, *49*, 967. (x) Totani, G., *Biochem. J.*, **1916**, *10*, 382.

5. (a) Yen, Y.-H. and Chu, Y.-H., *Tetrahedron Lett.*, **2004**, *45*, 8137. (b) Jain, S. and Mishra, P., *Indian J. Heterocycl. Chem.*, **2004**, *13*, 307. (c) Wego, A.; Jansen, K.; Buschmann, H.; Schollmeyer, E. and Doepp, D., *J. Inclusion Phenomena & Macrocycl. Chem.*, **2002**, *43*, 201. (d) Ali, S. M.; Hoemann, M. Z.; Aubé, J.; Georg, G. I.; Mitscher, L. A. and Jayasinghe, L. R., *J. Med. Chem.*, **1997**, 40,236. (e) Georg, G. I.; Harriman, G. C. B.; Hepperle, M.; Clowers, J. S.; Velde, D. G. V. and Himes, R. H., *J. Org. Chem.*, **1996**, 61,2664. (f) Georg, G. I.; Boge, T. C.; Cheruvallath, Z. S.; Harriman, G. C. B.; Hepperle, M.; Park, H. and Himes, R. H., *Bioorg. Med. Chem. Lett.*, **1994**, *4*, 335. (g) Begg, C. G.; Grimmett, M. R. and Lee, Y.-M., *Aust. J. Chem.*, **1973**, *26*, 415.
6. Moher, E. D.; Tripp, A. E.; Creemer, L. C. and Vicenzi, J. T., *Org. Proc. Res. Dev.*, **2004**, *8*, 593.
7. (a) Gao, S. M.; Wilson, D. M.; Edinboro, L. E.; McGuire, G. M.; Williams, S. G. P. and Karnes, H. T., *J. Liquid Chromat. Related Technol.*, **2003**, *26*, 3413. (b) Frantz, D. E.; Weaver, D. G.; Carey, J. P.; Kress, M. H. and Dolling, U. H., *Org. Lett.*, **2002**, *4*, 4717. (c) Jursic, B. S. and Neumann, D., *Synth. Commun.*, **2001**, *31*, 555. (d) Sano, T.; Sugaya, T.; Inoue, K.; Mizutaki, S.-i.; Ono, Y. and Kasai, M., *Org. Proc. Res. Dev.*, **2000**, *4*, 147. (e) Lele, B. S.; Kulkarni, M. G. and Mashelkar, R. A., *Reactive & Functional Polymers*, **1999**, *40*, 215. (f) Sheradsky, T. and Silcoff, E. R., *Molecules*, **1998**, *3*, 80. (g) Tolstikov, G. A.; Borisova, E. Ya.; Cherkashin, M. I.; Komarov, V. M. and Arzamastsev, E. V., *Russ. Chem. Rev.*, **1991**, *60*, 420. (h) Gupta, R. N.; Eng, F. and Gupta, M. L., *Clin. Chem.*, **1982**, *28*, 32. (i) Teplan, I.; Mezö, I.; Vegh, G. and Silaev, A. B., *Chem. Nat. Compd.*, **1973**, *7*, 460. (j) Kametani, T.; Seino, C.; Yamaki, K.; Shibuya, S.; Fukumoto, K.; Kigasawa, K.; Satoh, F.; Hiiragi, M. and Hayasaka, T., *J. Chem. Soc. C*, **1971**, 1043. (k) Kost, A. N.; Yudin, L. G. and Budylin, V. A., *Chem. Heterocycl. Compd.*, **1966**, *2*, 29. (l) Tsuda, M., *Makromol. Chem.*, **1964**, *72*, 183. (m) Sonntag, N. O. V., *Chem. Rev.*, **1953**, *52*, 272. (n) Abe, Y. and Ihara, T., *Nippon Suisan Gakkaishi*, **1953**, *19*, 737. (o) Abe, Y. and Ihara, T., *Nippon Suisan Gakkaishi*, **1952**, *18*, 47.

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Schwartz Reagent
(Schwartz's Reagent)

A. GENERAL DESCRIPTION OF THE REACTION

The organometallic compound, known as bis(cyclopentadienyl)zirconium(IV) chloride hydride,[1] [zirconium, chlorobis(η^5-2,4-cyclopentadien-1-yl)hydro],[2] or simply zirconocene hydrochloride (Cp_2ZrHCl)[3] was first introduced by Schwartz into organic synthesis in 1974,[4] and is thus referred to as the Schwartz's reagent[5] or Schwartz reagent.[1,3,5a,6] Although the Schwartz reagent is poorly soluble in commonly used solvents (e.g., toluene, THF, CH_2Cl_2)[5a,7] and is also difficult to purify because of its disproportionation,[7] it is still widely used in organic synthesis because of its easy preparation by the reduction of zirconocene dichloride with $LiAlH_4$,[2] compatibility with several functionalities,[6e] and special reactivity. Similar to other hydride reagents, the Schwartz reagent also undergoes reduction in which the carbonyl compounds including aldehydes, ketones, carboxylic acids, and esters are usually reduced to alcohols because of the strong hydridic character of the reagent;[1] in comparison, imines are reduced to amines,[1] dichlorophosphine and dicyano-phosphine are reduced to phosphines (or diketoimines);[8] and nitriles and tertiary amides are converted into corresponding aldehydes.[5a] In addition, the Schwartz reagent usually does not lead to the formation of a mixture as observed in the DIBAL reduction, due to the lack of a strong base.[5a] On the other hand, although the hydrozirconation of unsymmetrical alkynes is observed to proceed with complete stereoselectivity and high regioselectivity to give vinylic zirconium complexes,[3b] the regioselectivity actually depends on the reaction stoichiometry, temperature, solvent, and reaction duration.[3b] For example, the hydrozirconation of (4*S*,5*S*)-4-methyl-5-methoxy-5-benzyl-2-pentyne yields a mixture of vinylic zirconium complex with one equivalent of Schwartz reagent, whereas a thermodynamic vinylic zirconium complex is favored with an excess amount of Schwartz reagent; in addition, a longer reaction period and electron-donating solvent (e.g. THF) favor the thermodynamic product.[3b] Similar to tributyltin hydride, the Schwartz reagent is also known to be an

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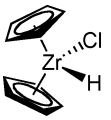
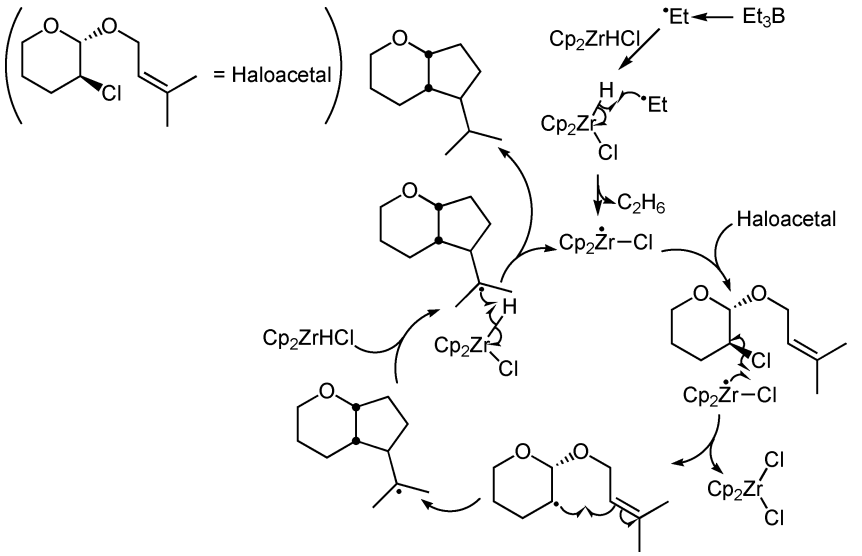
efficient radical chain carrier that can mediate a radical reduction process of alkyl halides,[1,6d] the cyclization of unsaturated haloacetals,[6c] etc. It should be pointed out that the radical cyclization can be performed in the presence of a catalytic amount of Schwartz reagent and sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al).[6d] In addition, triethylborane (Et_3B) can be applied to depress the competitive hydrozirconation during the radical cyclization of terminal olefins, where the cyclization of internal olefins proceed smoothly.[6c]

B. GENERAL REACTION SCHEME



C. PROPOSED MECHANISMS

This reagent can participate in a variety of reactions, involving different reaction mechanisms. For the Schwartz reagent-mediated radical cyclization, it is proposed that the key step is the homolytic cleavage of the zirconium-hydrogen bond,[1] as illustrated here.



D. MODIFICATION

The Schwartz reagent has been replaced by bis(cyclopentadienyl)zirconium(IV) hydride triflate [$Cp_2Zr(H)OTf$], which displays the advantages over the Schwartz reagent, such as less tendency for aggregation and the higher reactivity of hydride due to the weak coordination ability of triflate anion.[7]

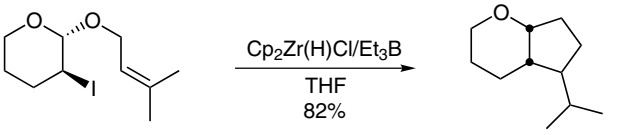
E. APPLICATIONS

This reagent is very useful in organic synthesis.

F. RELATED REACTIONS

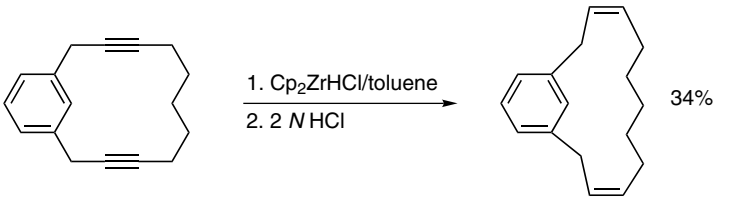
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 1.

To a 50-mL reaction flask were added 387 mg $Cp_2Zr(H)Cl$ (1.5 mmol) and 3.0 mL THF under argon. Then 148 mg (2*R*,3*S*)-3-iodo-2-(3-methyl-2-butenoxy)-tetrahydropyran (0.50 mmol) in 2.0 mL THF and 0.5 mL 1.0 M triethylborane in hexane (0.50 mmol) were added. The resulting heterogeneous mixture turned to a clear yellow solution after being stirred for 1 h at 25°C. After being stirred for an additional 2 h, the mixture was poured into a 30 mL 1 *N* HCl solution and stirred for 15 min. The mixture was extracted with hexane/EtOAc (10:1) (30 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography using hexane/EtOAc (20:1) as the eluent to afford 70 mg product, in a yield of 82%.



Reference 5g.

To a solution of 222 mg [11]metacyclophane-2,9-diyne (1.0 mmol) in 25 mL dry toluene was added 1.30 g Schwartz's reagent (5.0 mmol) at once. The reaction was monitored by TLC. After 4 days, the solution was cooled to 0°C, and 3.0 mL 2.0 *N* HCl (6.0 mmol) was added at once, and the mixture was stirred for additional 10 min. The suspension was filtered, and the residue was washed several times with CH_2Cl_2. The combined filtrate was dried over Na_2SO_4, and the solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether) and further by Kugelrohr distillation to afford 76 mg (*Z*,*Z*)-[11]metacyclophane-2,9-diene as a colorless oil, in a yield of 34%, b.p. 115°C at 0.02 mbar.

Other references related to the Schwartz reagent are cited in the literature. [9]

H. REFERENCES

1. Fujita, K.; Nakamura, T.; Yorimitsu, H. and Oshima, K., *J. Am. Chem. Soc.*, **2001**, *123*, 3137.
2. Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B.; Watson, B. T. and King, S. M., *Org. Synth. Coll*, **1998**, *9*, 162.
3. (a) Fernández-Megía, E., *Synlett*, **1999**, 1179. (b) Panek, J. S. and Hu, T., *J. Org. Chem.*, **1997**, *62*, 4912.
4. Hart, D. W. and Schwartz, J., *J. Am. Chem. Soc.*, **1974**, *96*, 8115.
5. (a) Sorensen, J. L.; Sleeman, M. C. and Schofield, C. J., *Chem. Commun.*, **2005**, 1. (b) Yun, H. D., *Aust. J. Chem.*, **2004**, *57*, 383. (c) Schlörer, N. E. and Berger, S., *Organometallics*, **2001**, *20*, 1703. (d) Gu, X. H. S. and Sponsler, M. B., *Organometallics*, **1998**, *17*, 5920. (e) Curtis, M. A.; Finn, M. G. and Grimes, R. N., *J. Organomet. Chem.*, **1998**, *550*, 469. (f) Zhou, X. B., Stobart, S. R. and Gossage, R. A., *Inorg. Chem.*, **1997**, *36*, 3745. (g) Ramming, M. and Gleiter, R., *J. Org. Chem.*, **1997**, *62*, 5821. (h) Bieger, K.; Bouhadir, G.; Réau, R.; Dahan, F. and Bertrand, G., *J. Am. Chem. Soc.*, **1996**, *118*, 1038. (i) Kalesse, M., *Acros Org. Acta*, **1995**, *1*, 29. (j) Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B.; Watson, B. T. and King, S. M., *Org. Synth.*, **1993**, *71*, 77. (k) Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B.; Watson, B. T. and King, S. M., *Tetrahedron Lett*., **1987**, *28*, 3895. (l) Cesarotti, E.; Chiesa, A.; Maffi, S. and Ugo, R., *Inorg. Chim. Acta*, **1982**, *64*, L207.
6. (a)Van Summeren, R. P.; Feringa, B. L. and Minnaard, A. J., *Org. Biomol. Chem.*, **2005**, *3*, 2524. (b) Horn, A.; Møllendal, H.; Demaison, J.; Petitprez, D.; Moreno, J. R. A.; Benidar, A. and Guillemin, J.-C., *J. Phys. Chem. A,* **2005**, *109*, 3822. (c) Salom-Roig, X. J.; Dénès, F. and Renaud, P., *Synthesis*, **2004**, 1903. (d) Fujita, K.; Yorimitsu, H. and Oshima, K., *Bull. Chem. Soc. Jpn.*, **2004**, *77*, 1727. (e) Gandon, V. and Szymoniak, J., *Chem. Commun.*, **2002**, 1308. (f) Kang, S.-K. and Yoon, S.-K., *J. Chem. Soc*., *Perkin Trans. I*, **2002**, 459. (g) Orain, D. and Guillemin, J.-C., *J. Org. Chem.*, **1999**, *64*, 3563. (h) Maraval, A.; Donnadieu, B.; Igau, A. and Majoral, J.-P., *Organometallics*, **1999**, *18*, 3138. (i) Wipf, P.; Xu, W. J.; Takahashi, H.; Jahn, H. and Coish, P. D. G., *Pure & Appl. Chem.*, **1997**, *69*, 639. (j) Zippi, E. M.; Andres, H.; Morimoto, H. and Williams, P. G., *Synth. Commun.*, **1994**, *24*, 1037. (k) Buerglen, B. and Uhlig, E., *Zeitsch. Anorg. Allgem. Chem.*, **1990**, *581*, 7.
7. Luinstra, G. A.; Rief, U. and Prosenc, M. H., *Organometallics*, **1995**, *14*, 1551.
8. Maraval, A.; Igau, A.; Lepetit, C.; Chrostowska, A.; Sotiropoulos, J.-M.; Pfister-Guillouzo, G.; Donnadieu, B. and Majoral, J. P., *Organometallics*, **2001**, *20*, 25.
9. (a) Wuest, F. R. and berndt, M., *J. Labelled Compd. Radiopharm.*, **2006**, *49*, 91. (b) Hirano, K.; Fujita, K.; Shinokubo, H. and Oshima, K., *Org. Lett.*, **2004**, *6*, 593. (c) Fujita, K.; Shinokubo, H. and Oshima, K., *Angew. Chem. Int. Ed*., **2003**, *42*, 2550. (d) Marek, I., ed., *Titanium and Zirconium in Organic Synthesis,* Wiley-VCH, Weinheim, **2002**. (e) Fujita, K.; Yorimitsu, H. and Oshima, K., *Synlett*, **2002**, 337. (f) Maraval, A.; Arquier, D.; Igau, A.; Coppel, Y.; Donnadieu, B. and Majoral, J.-P., *Organometallics*, **2001**, *20*, 1716. (g) Fujita, K.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S. and Oshima, K., *J. Am. Chem. Soc*., **2001**, *123*, 12115. (h) Kunkely, H. and Vogler, A., *Transition Metal Chem.*, **1998**, *23*, 527. (i) Sun, R. C.; Okabe, M.; Coffen, D. L. and Schwartz, J., *Org. Synth. Coll.* **1998**, *9*, 640. (j) Barden, M. C. and Schwartz, J., *J. Org. Chem.*, **1997**, *62*, 7520. (k) Wipf, P. and Jahn, H., *Tetrahedron*, **1996**, *52*, 12853. (l) Piers, W. E., *J. Chem. Soc., Chem. Commun.*, **1994**, 309. (m) Swanson, D. R.; Nguyen, T.; Noda, Y. and Negishi, E.-I., *Org. Chem.*, **1991**, *56*, 2590. (n) Gibson, T., *Organometallics*, **1987**, *6*, 918. (o) Negishi, E. and Takahashi, T., *Aldrichimica Acta*, **1985**, *18*, 31. (p) William, G. M. and Schwartz, J., *J. Am. Chem. Soc.*, **1982**, *104*, 1122. (q) Laycock, D. E. and Alper, H., *J. Org. Chem.*, **1981**, *46*, 289. (r) William, G. M.; Gell, K. I. and Schwartz, J., *J. Am. Chem. Soc.*, **1980**, *102*, 3660. (s) Temple, J. S. and Schwartz, J., *J. Am. Chem. Soc.*, **1980**, *102*, 7381. (t) Carr, D. B. and Schwartz, J., *J. Am. Chem. Soc.*, **1979**, *101*, 3521. (u) Schwartz, J. and Labinger, J. A., *Angew. Chem. Int. Ed. Engl.*, **1978**, *15*, 33. (v) Sorell, T. N., *Tetrahedron Lett.*, **1978**, 4983. (w) Schwartz, J. and Labinger, J. A., *Angew. Chem. Int. Ed. Engl.*, **1976**, *15*, 333. (x) Bertelo, C. A. and Schwartz, J., *J. Am. Chem. Soc.*, **1976**, *98*, 262. (y) Hart, D. W.; Blackburn, T. F. and Schwartz, J., *J. Am. Chem. Soc.*, **1975**, *97*, 679.

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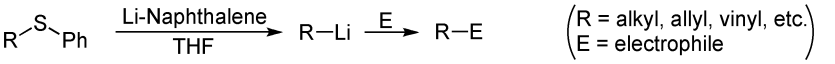
Screttas Lithiation

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Screttas in 1978.[1] It is one of the most common methods for preparing an organic lithium reagent by reductive lithiation of an alkyl or aryl thioether[2] with an aromatic radical anion (e.g., lithium naphthalene) in THF, which is feasible for the preparation of primary, secondary, tertiary,[2a,2c,2d] and even vinyl lithium species.[2a] It has been found that the less stable the organic lithium is, the greater the ease of generating the organic lithium by reductive lithiation.[2a] The resulting lithium reagent can react with a variety of electrophiles, such as epoxides, aldehydes, ketones, α,β-unsaturated compounds, alkyl halides, etc. It has been found that in the presence of titanium isopropoxide or cerium chloride, the addition of allyl lithium to aldehydes or ketones shows high stereoselectivity.[3] In addition, the generated lithium species undergoes an intramolecular cyclization to form four- to six-membered ring structures,[2a,2c] with the reactivity order of secondary > tertiary > primary. In particular, the secondary lithium reagent leads to the formation of cyclobutane or cyclopentane derivatives with extremely high stereoselectivity; however, such cyclization is inhibited by a terminal olefinic methyl group.[2a] In most of the cases, the Screttas lithiation is carried out in THF,[2a,2c,2d,4] with only an exception of dimethyl ether.[2c]

B. GENERAL REACTION SCHEME



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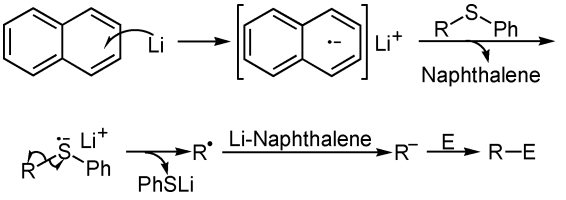
C. PROPOSED MECHANISMS

It is assumed that this reaction involves a radical reductive process. Displayed below is the lithiation of an alkyl phenyl thioether with lithium naphthalene.



D. MODIFICATION

The lithium naphthalene has been replaced by an even more reactive lithium 4,4′-di-*tert*-butylbiphenylyl (LDTBB) or lithium dimethylaminonaphthalene (LDMAN). LDTBB "not only is a more powerful reducing reagent but is less susceptible to radical attack";[2c] in addition, it can be applied in a catalytic amount (5 mol %) by suspension of an excess amount of lithium powder in THF.[2c] For comparison, the use of LDMAN has the advantage of easy removal of DMAN by a dilute acid wash, although LDMAN may decompose when the reaction temperature is above –45°C.[2d]

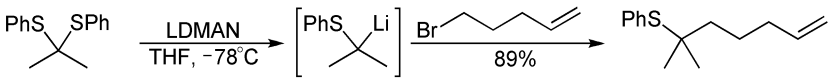
E. APPLICATIONS

This reaction has a very important application in carbanion chemistry and is one of the rare and general methods to prepare organolithium species.[2c]

F. RELATED REACTIONS

N/A

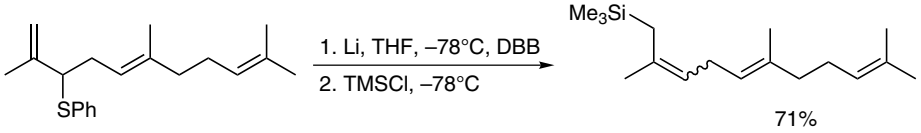
G. CITED EXPERIMENTAL EXAMPLES



Reference 2a.

A LDMAN solution (45 mL, 0.51 M) in THF prepared from 3.8 mL DMAN (23.0 mmol) and 161 mg lithium (23.0 mmol), was cooled to –78°C; then a mixture of 2.90 g 2,2-bis(phenylthio)propane (11.2 mmol) and 10 mL THF was added. The dark green color of the solution turned into dark red. After 10 min of stirring, 1.39 mL 1-bromo-4-pentene (11.2 mmol) was added. The resulting mixture was stirred at –78°C for 2 h, and the

temperature was then raised to –20°C. After the solution had been stirred at –20°C for 30 min, 30 mL saturated aqueous $NaHCO_3$ was added. The reaction mixture was extracted with ether (50 mL × 3). The combined organic layers were washed with 30 mL 5% HCl (to remove DMAN) and 30 mL brine and then dried over anhydrous $MgSO_4$ and filtered through cotton. Upon removal of the solvent in vacuo, the residue was purified by flash chromatography using hexane as the eluent to give 2.19 g 6-methyl-6-phenylthio-1-heptene as a yellow oil, in a yield of 89%.



Reference 2b.

To a two-necked round-bottomed flask equipped with an argon inlet, were added 1.4 mL THF and 22 mg di-*tert*-butylbiphenyl (0.08 mmol). Small lithium pieces in a total amount of 288 mg (41.5 mmol)—prepared by scrapping the dark oxide coating off the surface while immersed in mineral oil and cut into small but shiny pieces and dipped in hexane—was quickly added to the solution of DBB while the flask was rapidly purged with argon. The mixture was sonicated for 5 min at room temperature, then cooled to –78°C. A solution of 200 mg allylthioether (0.83 mmol) in 1 mL THF was added to the preformed solution of LiDBB under argon, and the mixture was stirred until the originally dark green color reappeared; then 180 mg TMSCl (1.66 mmol) was added. The reaction was maintained at –78°C for an additional 5 min and the resulting solution was filtered to remove the excess lithium. The mixture was extracted three times with Et_2O. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated to dryness. The residue was purified by column chromatography (hexane) to afford 184 mg *Z*-(trimethyl-(4-phenyl-3-(phenylthio)but-2-enyl)silane as a colorless oil, in a yield of 71%, $R_f = 0.26$ (hexane).

Other references related to the Screttas lithiation are cited in the literature[5].

H. REFERENCES

1. Screttas, C. G. and Micha-Screttas, M., *J. Org. Chem.*, **1978**, *43*, 1064.
2. (a) Deng, K.; Bensari-Bouguerra, A.; Whetstone, J. and Cohen, T., *J. Org. Chem.*, **2006**, *71*, 2360. (b) Streiff, S.; Ribeiro, N. and Désaubry, L., *J. Org. Chem.*, **2004**, *69*, 7592. (c) Cohen, T.; Kreethadumrongdat, T.; Liu, X. J. and Kulkarni, V., *J. Am. Chem. Soc.*, **2001**, *123*, 3478. (d) Cohen, T. and Bhupathy, M., *Acc. Chem. Res.*, **1989**, *22*, 152.
3. (a) Abraham, W. D. and Cohen, T., *J. Am. Chem. Soc.*, **1991**, *113*, 2313. (b) McCullough, D. W.; Bhupathy, M.; Piccolino, E. and Cohen, T., *Tetrahedron*, **1991**, *47*, 9727. (c) Guo, B. S.; Doubleday, W. and Cohen, T., *J. Am. Chem. Soc*., **1987**, *109*, 4710.
4. Ramón, D. J. and Yus, M., *J. Org. Chem.*, **1991**, *56*, 3825.
5. (a) Foubelo, F.; Abou, A. and Yus, M., *Eur. J. Org. Chem.*, **2005**, 5089. (b) Screttas, C. G.; Heropoulos, G. A.; Micha-Screttas, M. and Steele, B. R., *Tetrahedron Lett.*, **2005**, *46*, 4357. (c) Tang, T.; Ruan, Y. P.; Ye, J. L. and Huang, P. Q., *Synlett*, **2005**, 231. (d) de Vicente, J.; Betzemeier, B. and Rychnovsky, S. D., *Org. Lett.*, **2005**, *7*, 1853. (e) Wang, L. and Floreancig,

P. E., *Org. Lett.*, **2004**, *6*, 569. (f) Cooksey, J.; Gunn, A.; Kocienski, P. J.; Kuhl, A.; Uppal, S.; Christopher, J. A. and Bell, R., *Org. Biomol. Chem.*, **2004**, *2*, 1719. (g) Alonso, F.; Meléndez, J. and Yus, M., *Russ. Chem. Bull.*, **2003**, *52*, 2628. (h) Yus, M.; Martínez, P. and Guijarro, D., *Synth. Commun.*, **2003**, *33*, 2365. (i) Ramón, D. J. and Yus, M., *Eur. J. Org. Chem.*, **2000**, 225. (j) Foubelo, F.; Saleh, S. A. and Yus, M., *J. Org. Chem.*, **2000**, *65*, 3478. (k) Kostas, I. D. and Screttas, C. G., *J. Org. Chem.*, **1997**, *62*, 5575. (l) Almena, J.; Foubelo, F. and Yus, M., *J. Org. Chem.*, **1996**, *61*, 1859. (m) Cherkauskas, J. P. and Cohen, T., *J. Org. Chem.*, **1992**, *57*, 6. (n) Ganem, B., *Chemtracts: Org. Chem*., **1989**, *2*, 148. (o) Screttas, C. G. and Micha-Screttas, *J. Org. Chem.*, **1979**, *44*, 713.

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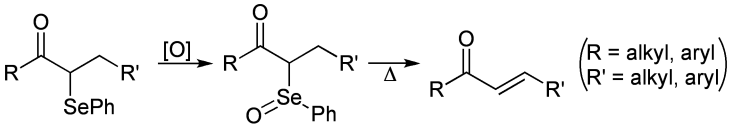
Selenoxide Elimination
(Selenoxide Pyrolysis)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Jones et al. in 1970.[1] It is the synthesis of an olefin via the pyrolysis of an alkyl selenoxide and is generally known as selenoxide elimination[2] or selenoxide pyrolysis.[3] Occasionally, it is also referred to as the selenoxide *syn* elimination[2cc,4] or hydrolytic selenoxide elimination.[5] This reaction often takes place under very mild conditions, with few exceptions at a temperature $> 100^{\circ}C$.[2cc] Because the selenoxide is reluctant to undergo further oxidation, the preparation of selenoxide can be achieved by different oxidants,[2cc] including ozone,[3b,6] *m*CPBA,[2cc] H_2O_2,[7] and $NaIO_4$.[8] It has been found that an electron-withdrawing group accelerates the elimination process and lowers the reaction temperature.[9] For example, α-carbonyl selenoxides can decompose into α,β-unsaturated ketones around or even below room temperature.[2cc,9] In addition, the selenoxide elimination has shown good regioselectivity for the asymmetrical ketones.[2d] It should be pointed out that the selenoxides are extremely polar molecules and are highly hygroscopic.[2aa] Overall, this reaction is suitable for the preparation of allyl alcohols (from epoxide),[10] acetylenes, or allenes (from α-selenoxide alkyene),[2z] dienes,[11] α,β-unsaturated ketones,[2cc] esters,[12] and nitriles.[13]

B. GENERAL REACTION SCHEME



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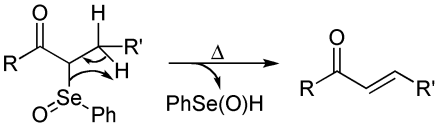
C. PROPOSED MECHANISMS

A simple mechanism is illustrated here for the *syn*-elimination.



D. MODIFICATION

This reaction has been modified by the use of different oxidants to generate the selenoxides. In addition, an antibody-catalyzed selenoxide elimination has been developed.[2g] Moreover, this reaction has been performed under basic conditions.[14]

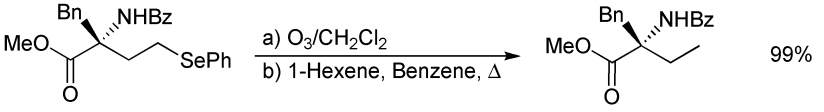
E. APPLICATIONS

This reaction has a very general application in organic synthesis to form olefinic derivatives.

F. RELATED REACTIONS

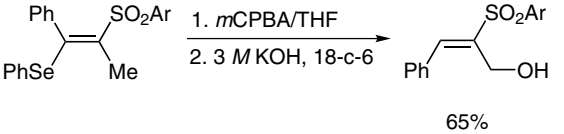
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 3b.

A solution of 6.84 g methyl *N*-benzoyl-2-[2′-(phenylseleno)ethyl]phenylalaninate (14.7 mmol) in 150 mL CH_2Cl_2 at −78°C was bubbled through ozone until the blue color persisted. Then 31.7 mL 1-hexene (255 mmol) was added, and this cold mixture was added dropwise to 500 mL boiling benzene, and the refluxing was continued for 30 min. Upon evaporation of all the solvent, the residue was purified by flash column chromatography using EtOAc/hexane (0:1–1:9) to afford 4.48 g methyl *N*-benzoyl-2-vinylphenylalaninate as a white solid, in a yield of 99%, m.p. 116–117°C.



Reference 14.

A mixture of 298 mg selenide (0.70 mmol), 144 mg *m*CPBA (0.84 mmol), and 10 mL THF was stirred for 5 min. Then 5 mL 3 *M* KOH solution and a catalytic amount of 18-crown-6 were added, and the resulting mixture was stirred vigorously for 18 h at room temperature. The reaction mixture was then extracted with ether, and the combined organic layers were washed with water (2 × 10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by preparative TLC using hexane/EtOAc (4:1) as the eluent to afford 130 mg 3-phenyl-2-(*p*-tolylsulfonyl)-2-propen-1-ol, which was further purified by crystallization from ether/hexane, in a yield of 65%, m.p. 95.5–96.5°C.

Other references related to the selenoxide elimination are cited in the literature.[15]

H. REFERENCES

1. Jones, D. N.; Mundy, D. and Whitehouse, R. D., *J. Chem. Soc., Chem. Commun.*, **1970**, 86.
2. (a) Bayse, C. A. and Allison, B. D., *J. Mol. Modeling*, **2007**, *13*, 47. (b) Clark, J. S.; Winfield, L. J.; Wilson, C. and Blake, A. J., *Synlett*, **2006**, 2191. (c) Nishibayashi, Y. and Uemura, S., *Top. Curr. Chem.*, **2000**, *208*, 201. (d) Back, T. G., *Organoselenium Chem.*, **1999**, 7. (e) Taguchi, T.; Kurishita, M. and Shibuya, A., *J. Fluor. Chem.*, **1999**, *97*, 157. (f) Health, C. E.; Gillam, M. C.; Callis, C. S.; Patto, R. R. and Abelt, C. J., *Carbohydr. Res.*, **1998**, *307*, 371. (g) Zhou, Z. H. S.; Jiang, N. and Hilvert, D., *J. Am. Chem. Soc.*, **1997**, *119*, 3623. (h) Nishibayashi, Y.; Singh, J. D.; Fukuzawa, S.-I. and Uemura, S., *J. Org. Chem.*, **1995**, *60*, 8326. (i) Nishibayashi, Y.; Singh, J. D.; Fukuzawa, S.-I. and Uemura, S., *J. Org. Chem.*, **1995**, *60*, 4114. (j) Kondo, N.; Fueno, H.; Fujimoto, H.; Makino, M.; Nakaoka, H.; Aoki, I. and Uemura, S., *J. Org. Chem.*, **1994**, *59*, 5254. (k) Reich, H. J. and Wollowitz, S., *Org. React.*, **1993**, *44*, 1. (l) Komatsu, N.; Matsunaga, S.; Sugita, T. and Uemura, S., *J. Am. Chem. Soc.*, **1993**, *115*, 5847. (m) Komatsu, N.; Murakami, T.; Nishibayashi, Y.; Sugita, T. and Uemura, S., *J. Org. Chem.*, **1993**, *58*, 3697. (n) Komatsu, N.; Nishibayashi, Y.; Sugita, T. and Uemura, S., *J. Chem. Soc., Chem. Commun.*, **1992**, 46. (o) Haraguchi, K.; Tanaka, H.; Maeda, H.; Itoh, Y.; Saito, S. and Miyasaka, T., *J. Org. Chem.*, **1991**, *56*, 5401. (p) Jephcote, V. J. and Thomas, E. J., *J. Chem. Soc., Perkin Trans. I*, **1991**, 429. (q) Mitchell, R. H.; Weerawarna, K. S. and Bushnell, G. W., *Tetrahedron Lett.*, **1987**, *28*, 5119. (r) Engman, L., *Chem. Scripta*, **1987**, *27*, 515. (s) Mortlock, S. V.; Stacey, N. A.; Thomas, E. J., *J. Chem. Soc., Chem. Commun.*, **1987**, 880. (t) Engman, L., *J. Org. Chem.*, **1987**, *52*, 4086. (u) Engman, L., *Tetrahedron Lett.*, **1985**, *26*, 6385. (v) Jephcote, V. J. and Thomas, E. J., *Tetrahedron Lett.*, **1985**, *26*, 5327. (w) Baldwin, J. E.; Reed, N. V. and Thomas, E. J., *Tetrahedron, Suppl.*, **1981**, 263. (x) Mitchell, R. H., *Can. J. Chem.*, **1980**, *58*, 1398. (y) Renga, J. M. and Reich, H. J., *Org. Synth.*, **1980**, *59*, 58. (z) Reich, H. J. and Willis, W. W., *J. Am. Chem. Soc.*, **1980**, *102*, 5967. (aa) Reich, H. J.; Shah, S. K. and Chow, F., *J. Am. Chem. Soc.*, **1979**, *101*, 6648. (bb) Reich, H. J. and Trend, J. E., *J. Org. Chem.*, **1976**, *41*, 2503. (cc) Reich, H. J.; Renga, J. M. and Reich, I. L., *J. Am. Chem. Soc.*, **1975**, *97*, 5434.
3. (a) de March, P.; Figueredo, M.; Font, J. and Monsalvatje, M., *Synth. Commun.*, **1995**, *25*, 331. (b) Pedersen, M. L. and Berkowitz, D. B., *J. Org. Chem.*, **1993**, *58*, 6966. (c) Hoffmann, H. M. R. and Wulferding, A., *Synlett*, **1993**, 415.
4. Sayama, S. and Onami, T., *Tetrahedron Lett.*, **2000**, *41*, 5557.
5. Engman, L., *Tetrahedron Lett.*, **1987**, *28*, 1463.
6. Ayrey, G.; Barnard, D. and Woodbridge, D. T., *J. Chem. Soc.*, **1962**, 2089.
7. Gould, E. S. and McCullough, J. D., *J. Am. Chem. Soc.*, **1951**, *73*, 3196.
8. Cinquini, M.; Colonna, S. and Giovini, R., *Chem. Ind. (London)*, **1969**, 1737.

9. Sharpless, K. B. and Young, M. W., *J. Org. Chem.*, **1975**, *40*, 947.
10. (a) Sharpless, K. B. and Lauer, R. F., *J. Org. Chem.*, **1974**, *39*, 429. (b) Sharpless, K. B. and Lauer, R. F., *J. Am. Chem. Soc.*, **1973**, *95*, 2697.
11. Reich, H. J. and Shah, S. K., *J. Am. Chem. Soc.*, **1975**, *97*, 3250.
12. (a) Trost, B. M.; Conway, W. P.; Strege, P. E. and Dietsche, T. J., *J. Am. Chem. Soc.*, **1974**, *96*, 7165. (b) Sharpless, K. B.; Lauer, R. F. and Teranishi, A. Y., *J. Am. Chem. Soc.*, **1973**, *95*, 6137.
13. Brattesani, D. N. and Heathcock, C. H., *Tetrahedron Lett.*, **1974**, 2279.
14. Back, T. G.; Collins, S.; Gokhale, U. and Law, K.-W., *J. Org. Chem.*, **1983**, *48*, 4776.
15. Reich, H. J.; Reich, I. L. and Wollowitz, S., *J. Am. Chem. Soc.*, **1978**, *100*, 5981.

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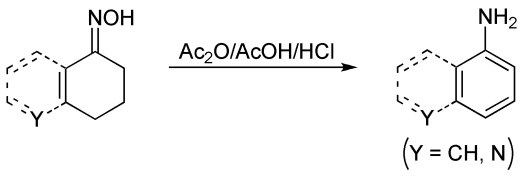
Semmler-Wolff Aromatization

(Semmler-Wolff Rearrangement, Semmler-Wolff Reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Semmler in 1892[1] and subsequently studied by Wolff in 1902[2] and Schroeter in 1911.[3] It is the rearrangement of an oxime of an α,β-unsaturated cyclohexenone (or known as the α,β-unsaturated cyclohexenyl ketoxime) to an aromatic amine in a mixture of acetic anhydride and acetic acid saturated with HCl or HBr.[4] Therefore, this reaction is generally known as the Semmler-Wolff aromatization,[4b,5] Semmler-Wolff rearrangement,[5e,6] or Semmler-Wolff reaction.[7] Occasionally, it is also referred to as the Semmler-Wolff-Schroeter reaction.[8] It should be pointed out that the *Beckmann Rearrangement*,[4b,5d,5e,9] and the fragmentation to nitriles[5d] often compete with the Semmler-Wolff aromatization. In addition, the Semmler-Wolff aromatization is obstructed by the substituents close to the reaction center.[5e]

B. GENERAL REACTION SCHEME



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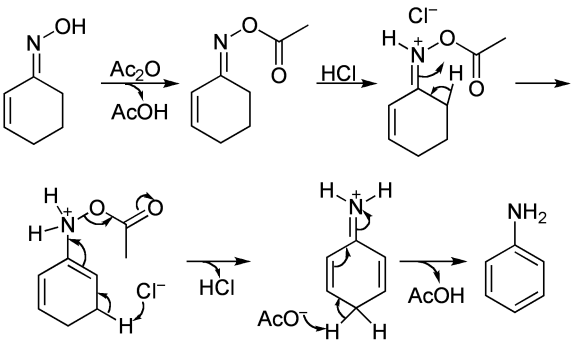
C. PROPOSED MECHANISMS

Illustrated here is the mechanism for the aromatization of an α,β-unsaturated cyclohexenyl ketoxime.



D. MODIFICATION

This reaction has been modified by heating the oximes in acetic anhydride and anhydrous phosphoric acid at 80°C[4a] or heating the mixture of ketoxime and one equivalent of acetyl chloride in toluene in a sealed tube at 80°C[10] to improve the reaction yield.

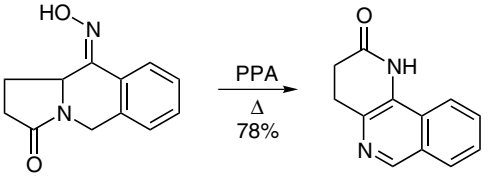
E. APPLICATIONS

This reaction has certain application in the preparation of aromatic amines.

F. RELATED REACTIONS

This reaction is related to the *Beckmann Rearrangement*.

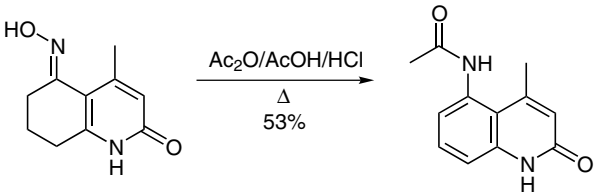
G. CITED EXPERIMENTAL EXAMPLES



Reference 5d.

Finely powdered (±)-(*Z*)-1,10a-dihydropyrrolo[1,2-b]isoquinoline-3,10-(2H,5H)-dione-10-oxime (30 g, 0.14 mol) was added quickly to 600 g hot polyphosphoric acid

(100°C) under stirring. The resulting mixture was vigorously stirred for 10 min during which period the internal temperature increased to 128°C. The hot mixture was decanted over 2.5 L crushed ice and diluted with water to give a solution, that was basified to pH 8–9 with 50% NaOH. Further dilution with water to keep the inorganic salts in solution was necessary. The yellow precipitate was collected by vacuum filtration, and the filter cake was washed thoroughly with water and dried in vacuo at 40°C over NaOH pellets to give 21.6 g crude 1,4-dihydrobenzo[c]-1,5-naphthyridin-2(3H)-one, in a yield of 78%. The product was further purified by preparative HPLC and recrystallization from 95% ethanol to afford yellow crystals, m.p. 227–228°C.



Reference 5e.

To a mixture of 4 mL acetic acid and 1.5 mL acetic anhydride was added 0.5 g 4-methyl-5,6,7,8-tetrahydro-5-(hydroxyimino)-2-hydroxyquinoline (3.0 mmol). The solution was saturated with anhydrous HCl gas and then held at reflux for 18 h. At the end of the reaction period, the solution had become dark, whereupon it was cooled, diluted with water, and allowed to stand for several hours. The white precipitate that formed was washed with water and crystallized from alcohol to provide 0.30 g 4-methyl-5-acetamido-2-quinolone, in a yield of 53%, m.p. 355°C.

Other references related to the Semmler-Wolff aromatization are cited in the literature.[11]

H. REFERENCES

1. Semmler, W., *Ber.*, **1892**, *25*, 3352.
2. Wolff, L., *Ann.*, **1902**, *322*, 351.
3. Schroeter, G., *Ber.*, **1911**, *44*, 1201.
4. (a) Newman, M. S. and Hung, W. M., *J. Org. Chem.*, **1973**, *38*, 4073. (b) Bauer, L. and Hewitson, R. E., *J. Org. Chem.*, **1962**, *27*, 3982.
5. (a) Vijn, R. J.; Arts, H. J.; Maas, P. J. and Castelijns, A. M., *J. Org. Chem.*, **1993**, *58*, 887. (b) Koevar, M.; Stanovnik, B. and Tiler, M., *Monatsh. Chem.*, **1988**, *119*, 597. (c) Trudell, M. L.; Fukada, N. and Cook, J. M., *J. Org. Chem.*, **1987**, *52*, 4293. (d) Martin, L. L.; Scott, S. J.; Agnew, M. N. and Setescak, L. L., *J. Org. Chem.*, **1986**, *51*, 3697. (e) El-Sheikh, M. I. and Cook, J. M., *J. Org. Chem.*, **1980**, *45*, 2585. (f) Tamura, Y.; Yoshimoto, Y.; Sakai, K.; Haruta, J. and Kita, Y., *Synthesis*, **1980**, 887. (g) Tamura, Y.; Yoshimoto, Y.; Sakai, K. and Kita, Y., *Synthesis*, **1980**, 483. (h) Kim, J. K.; Lee, Y. T. and Pak, H. W., *Hwahak Kwa Kongop Ui Chinbo*, **1979**, *19*, 150. (i) Tamura, Y.; Nishikawa, O.; Shimizu, T.; Akita, M. and Kita, Y., *Chem. Ind. (London)*, **1975**, 922. (j) Nunn, A. J. and Rowell, F. J., *J. Chem. Soc., Perkin Trans. I*, **1973**, 2697. (k) Mannering, G. C. and Keene, B. R. T., *Chem. Ind. (London)*, **1973**, 1069. (l) Watthey, J. W. H.; Doebel, K. J.; Vernay, H. F. and Lopano, A. L., *J. Org. Chem.*, **1973**, *38*, 4170. (m) Tamura, Y.; Kita, Y. and Uraoka, J., *Chem. Pharm. Bull.*, **1972**, *20*, 876. (n) Dannenberg, H. and Gross, H. J., *Ber.*

Bunsen-Gesellschaft, **1965**, *69*, 513. (o) Nizamuddin, S. and Chaudhury, D. N., *J. Indian Chem. Soc.*, **1963**, *40*, 960.

6. (a) Smith, W. B. and Sant, M. P., *Org. Prep. Proc. Int.*, **1990**, *22*, 501. (b) Tikk, I.; Deak, G. and Tamas, J., *Acta Chim. Hungarica*, **1988**, *125*, 289. (c) Wentland, M. P.; Albertson, N. F. and Pierson, A. K., *J. Med. Chem.*, **1980**, *23*, 71. (d) Bardakos, V. and Sucrow, W., *Chem. Ber.*, **1976**, *109*, 1898. (e) Yost, Y. and Gutmann, H. R., *J. Chem. Soc. C*, **1969**, 345. (f) Hajos, Z. G.; Parrish, D. R. and Goldberg, M. W., *J. Org. Chem.*, **1968**, *33*, 882. (g) Davey, J. and Keene, B. R. T., *Chem. Ind. (London)*, **1965**, 849.
7. (a) Scopton, A. and Kelly, T. R., *J. Org. Chem.*, **2005**, *70*, 10004. (b) Tian, Q. P.; Pletnev, A. A. and Larock, R. C., *J. Org. Chem.*, **2003**, *68*, 339. (c) Janin, Y. L. and Bisagni, E., *Synthesis*, **1993**, 57. (d) Tikk, I.; Deak, G.; Sohar, P. and Tamas, J., *J. Chem. Res. (S)*, **1987**, 95. (e) Sivasubramanian, S.; Muthusubramanian, S.; Ramasamy, S. and Arumugam, N., *Indian J. Chem., Sect. B*, **1981**, *20B*, 552. (f) Hayashi, E. and Suzuki, S., *Yakugaku Zasshi*, **1975**, *95*, 1439.
8. Moulay, S., *Chem. Edu.: Research & Practice in Europe*, **2002**, *3*, 33.
9. Beringer, F. M. and Ugelow, I. *J. Am. Chem. Soc.*, **1953**, *75*, 2635.
10. Davidson, J. P. and Corey, E. J., *J. Am. Chem. Soc.*, **2003**, *125*, 13486.
11. (a) Beringer, F. M.; Chang, L. L.; Fenster, A. N. and Rosai, R. R., *Tetrahedron*, **1969**, *25*, 4339. (b) Dvolaitzky, M. and Dreiding, A. S., *Helv. Chim. Acta*, **1965**, *48*, 1988. (c) Conley, R. T. and Lange, R. J., *J. Org. Chem.*, **1963**, *28*, 210. (d) Conley, R. T. and Nowak, B. E., *J. Org. Chem.*, **1962**, *27*, 1965. (e) Conley, R. T. and Nowak, B. E., *J. Org. Chem.*, **1962**, *27*, 3196. (f) Collicut, A. R. and Jones, G., *J. Chem. Soc.*, **1960**, 4101. (g) Hill, R. K. and Conley, R. T., *J. Am. Chem. Soc.*, **1960**, *82*, 645. (h) Bhatt, M. V., *Experientia*, **1957**, *13*, 70. (i) Brown, R. F.; van Gulick, N. M. and Schmid, G. H., *J. Am. Chem. Soc.*, **1955**, *77*, 1094. (j) Cooke, R. G. and Dowd, H., *Aust. J. Sci. Res.*, **1953**, *6*, 53. (k) Horning, E. C.; Stromberg, V. I. and Lloyd, H. A., *J. Am. Chem. Soc.*, **1952**, *74*, 5153. (l) Langenbeck, W. and Weissenborn, K., *Ber.*, **1939**, *72*, 724. (m) Blatt, A. H., *Chem. Rev.*, **1933**, *12*, 215. (n) Matsumura, K. and Sone, C., *J. Am. Chem. Soc.*, **1931**, *53*, 1493. (o) Stieglitz, J. and Leech, P. N., *J. Am. Chem. Soc.*, **1914**, *36*, 272.

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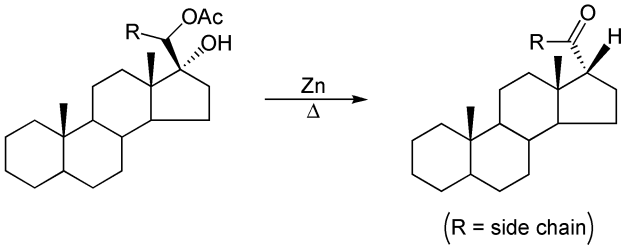
Serini Reaction

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Serini in 1939.[1] It is a zinc-promoted rearrangement of 17-hydroxy-20-acetoxy-steroids into 20-oxo-steroid derivatives with the complete inversion of stereochemistry at C-17 and is generally known as the Serini reaction.[2] Occasionally, it is also referred to as the Logemann-Serini reaction[3] or Serini-Logemann reaction.[4] It has been found that the treatment of steroid derivatives with anhydrous zinc acetate yields the results similar to that when refluxed with zinc, indicating that the function of zinc in the Serini reaction is to generate a Lewis acid.[2f] This reaction has been extended to other cyclic and open-chain 1,2-diol monoacetates as well as corresponding benzoates and *p*-nitrobenzoates.[2f] Under normal conditions, the 1,2-diol monobenzoates or *p*-nitrobenzoates offer better results than the corresponding monoacetates.[2f] If an aromatic ring is attached to the secondary carbon, the corresponding aldehyde might form because of the 1,2-aryl migration.[2f]

B. GENERAL REACTION SCHEME



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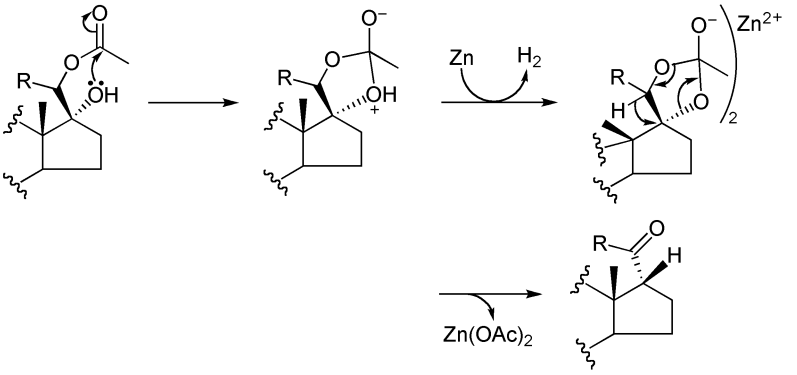
C. PROPOSED MECHANISMS

The mechanism of this reaction has been studied to a certain extent.[2f,2l,4] It has been proposed that zinc is actually converted into a complexing Lewis acid. In addition, the C-O bond, as a part of the monoacetate at C-20, of these steroids never breaks and is transformed into the carbonyl group in the final product while the hydrogen at C-20 migrates to the C-17 position, accompanying with the inversion of stereochemistry at C-17, as illustrated here.[2f,2l]



D. MODIFICATION

This reaction has been extended to other cyclic and open-chain 1,2-diol monoesters.[2f]

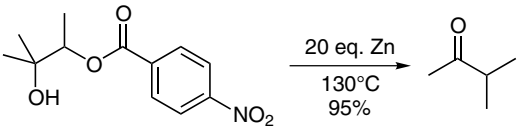
E. APPLICATIONS

This reaction has certain application in steroid chemistry.

F. RELATED REACTIONS

N/A

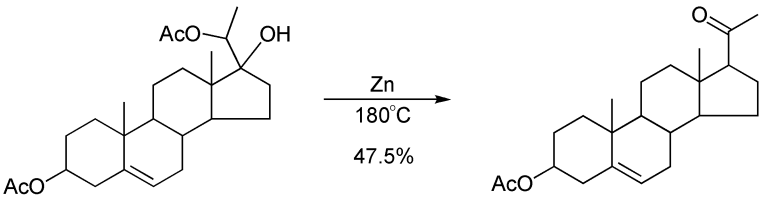
G. CITED EXPERIMENTAL EXAMPLES



Reference 2f.

To a special reaction vessel equipped with a nitrogen inlet and removal trap, was added powdered (3′-methyl-3′-hydroxyl)-2-butyl *p*-nitrobenzoate and 20 eq. of freshly activated zinc dust through a funnel. The reaction vessel was immersed into an oil bath at 130°C for 2.5 h and a steady nitrogen flow (60 bubbles/min) carried the volatile products or by-products

toward the trap, which was cooled with dry ice/acetone. At the end of the reaction, the volatile product (i.e., methyl isopropyl ketone) was collected in the trap, in a yield of 95%.



Reference 2q.

A mixture of 200 mg Δ^5-pregnene-3β,17α,20β-triol-3,20-diacetate and 4.0 g zinc dust was finely ground and heated slowly in an air bath to 180°C at 0.03 mmHg. The material that sublimed was extracted with $CHCl_3$, and the product so collected on crystallization from dilute acetone gave 78 mg 17-iso-Δ^5-pregnene-3β-ol-20-one-3-acetate, in a yield of 47.5%; on further crystallization from alcohol, the substance obtained melted at 159–164°C and 167–168°C. (*Note:* Two different melting points were given in the original work.)

Other references related to the Serini reaction are cited in literature 5.

H. REFERENCES

1. Serini, A., Logemann, W. and Hildebrand, W., *Ber.*, **1939**, *72*, 391.
2. (a) Lee, D.-U., *Bull. Korean Chem. Soc.*, **2002**, *23*, 9. (b) Byon, C.-Y. and Gut, M., *J. Org. Chem.*, **1980**, *45*, 4404. (c) Goto, G.; Yoshioka, K. and Hiraga, K., *Tetrahedron*, **1974**, *30*, 2107. (d) Nambara, T. and Goto, J., *Chem. Pharm. Bull.*, **1971**, *19*, 1937. (e) Balmain, A.; Connolly, J. D.; Ferrari, M.; Ghisalberti, E. L.; Pagnoni, U. M. and Pelizzoni, F., *J. Chem. Soc. D*, **1970**, 1244. (f) Ghere, E., *J. Org. Chem.*, **1970**, *35*, 660. (g) Ghera, E., *Chem. Commun. (London)*, **1968**, 1639. (h) Ghera, E., *Tetrahedron Lett.*, **1967**, 17. (i) Mitsuhashi, H.; Sato, T.; Nomura, T. and Takemori, I., *Chem. Pharm. Bull.*, **1964**, *12*, 981. (j) Goto, T., *Nippon Kagaku Zasshi*, **1962**, *83*, 1137. (k) Goto, T. and Kishi, Y., *Nippon Kagaku Zasshi*, **1962**, *83*, 1236. (l) Goto, T. and Fieser, L. F., *J. Am. Chem. Soc.*, **1961**, *83*, 251. (m) Nazarov, I. N.; Akhrem, A. A. and Kamernitskii, A. V., *Zh. Obsh. Khim.*, **1958**, *28*, 1805. (n) Nazarov, I. N. and Akhrem, A. A., *Zh. Obsh. Khim.*, **1958**, *28*, 1791. (o) Sandoval, A.; Miramontes, L.; Rosenkranz, G.; Djerassi, C. and Sondheimer, F., *J. Am. Chem. Soc.*, **1953**, *75*, 4117. (p) Shoppee, C. W., *J. Chem. Soc.*, **1949**, 1671. (q) Fieser, L. F. and Huang, M. L., *J. Am. Chem. Soc.*, **1949**, *71*, 1840. (r) Shoppee, C. W., *Experientia*, **1948**, *4*, 418.
3. Canonica, L.; Ferrari, M.; Jommi, G.; Pagnoni, U. M. and Pelizzoni, F., *Annali Chim. (Italy)*, **1967**, *57*, 744.
4. Wendler, N. L., *Proc. Chem. Soc.*, **1960**, 422.
5. (a) Gryko, D.; Chako, J. and Jurczak, J., *Chirality*, **2003**, *15*, 514. (b) Cambie, R. C.; Hayward, R. C.; Roberts, J. L. and Rutledge, P. S., *J. Chem. Soc., Perkin Trans. I*, **1974**, 1858. (c) Jaeggi, K. A.; Weiss, E. and Reichstein, T., *Helv. Chim. Acta*, **1963**, *46*, 694. (d) Fieser, L. F. and Fieser, M., *Steroids,* Reinhold Publishing, New York, **1959**, p. 628. (e) Sandoval, A.; Thomas, G. H.; Djerassi, C.; Rosenkranz, G. and Sondheimer, F., *J. Am. Chem. Soc.*, **1955**, *77*, 148. (f) Fieser, L. F. and Fieser, M., *Experientia*, **1948**, *4*, 285.

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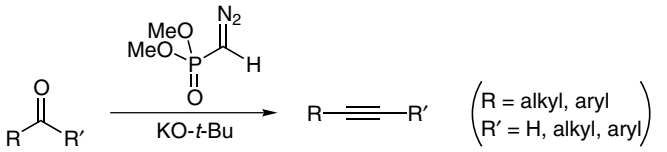
Seyferth-Gilbert Homologation

(Seyferth-Gilbert reaction)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was first reported by Seyferth in 1970[1] and was subsequently extended by Gilbert et al. in 1979.[2] It is the transformation of aldehydes or ketones into alkynes with one more carbon atom by means of the reaction with dimethyl (diazomethyl)phosphonate in the presence of potassium *t*-butoxide. Therefore, it is known as the Seyferth-Gilbert reaction,[3] Seyferth-Gilbert homologation,[4] Gilbert-Seyferth homologation,[5] or Gilbert-Seyferth reaction.[6] Similarly, dimethyl (diazomethyl)phosphonate is referred to as the Seyferth reagent,[7] Seyferth-Gilbert reagent,[8] Seyferth-Gilbert diazophosphonate reagent, Gilbert-Seyferth diazo phosphonic reagent,[9] or simply the Gilbert-Seyferth reagent.[10]

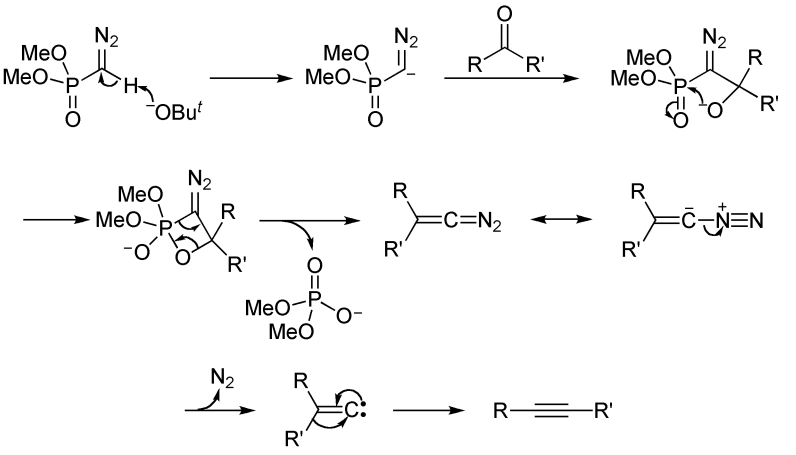
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

It is proposed that this reaction occurs via a mechanism similar to the *Wittig Reaction*.[11] In detail, deprotonation of the Seyferth-Gilbert reagent by potassium *t*-butoxide generates a carbanion, which adds to the carbonyl group to yield an oxaphosphatane; then subsequent elimination of dimethylphosphate leads to the formation of a vinyl diazo intermediate from which the vinyl carbene forms by evolution of nitrogen gas; final 1,2-migration of the substituent on vinyl carbene yields the alkyne. An illustrative mechanism is displayed here.



D. MODIFICATION

This reaction has been modified by Ohira[12] and Bestmann[13] via the generation of dimethyl(diazomethyl)phosphonate *in situ* by the treatment of dimethyl-1-diazo-2-oxopropylphosphonate with methanol and K_2CO_3. This method, often gives a very high yield of terminal alkynes from aldehydes and is also known as the Bestmann modification.[3a,6] Dimethyl-1-diazo-2-oxopropylphosphonate is referred to as Ohira's reagent.[8]

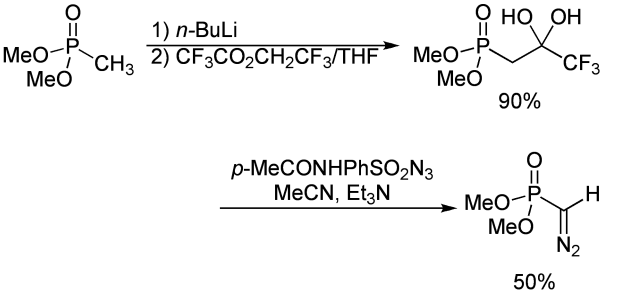
E. APPLICATIONS

This reaction should have a very wide application in organic synthesis, in terms of the preparation of alkynes.

F. RELATED REACTIONS

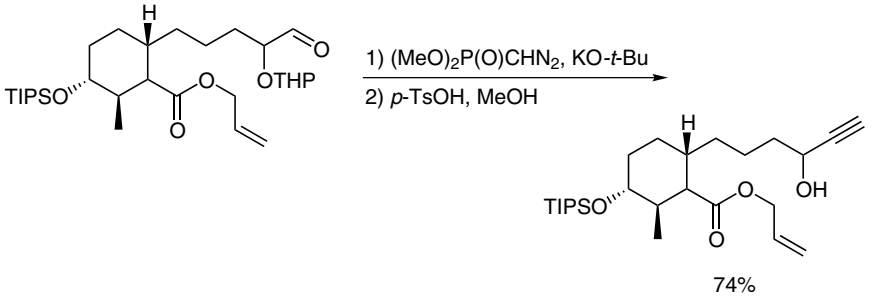
N/A

G. CITED EXPERIMENTAL EXAMPLES



Reference 11.

To a 250-mL, flame-dried, round-bottomed flask, were added 40 mL dry THF and 2.29 g dimethyl methylphosphonate (18.4 mmol), and the mixture was cooled to −78°C. Then 7.66 mL 2.4 M *n*-butyllithium in hexanes (18.4 mmol) was added over 5 min; after the solution was stirred at −78°C for 15–30 min, 5.41 g 2,2,2-trifluoroethyl trifluoroacetate (3.73 mL, 27.6 mmol) was added rapidly (1–2 s), and the resulting mixture was stirred at −78°C for 15 min and was then warmed to room temperature. The crude reaction mixture was partitioned between 250 mL Et_2O and 10 mL 3% HCl solution, the combined organic layers were washed with 10 mL saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to give 90% dimethyl (3,3,3-trifluoro-2,2-dihydroxypropyl)phosphonate, which upon purification from column chromatography had melting point of 57–61°C. This intermediate was immediately dissolved in 40 mL dry CH_3CN, then 3.97 g 4-acetamidobenzenesulfonyl azide (16.5 mmol) was added, and the solution was cooled to 0°C. Triethylamine (1.66 g, 2.29 mL, 16.5 mmol) was slowly added within 5 min. The mixture was allowed to warm to room temperature and was stirred overnight. Solvent was removed by rotary evaporation from the resulting slurry, which contained the precipitated 4-acetamidobenzenesulfonamide. The residual orange oily solid was suspended in $CHCl_3$ and filtered through a coarse glass frit to remove 4-acetamidobenzenesulfonamide, which was washed with a small portion of additional $CHCl_3$. Upon concentration of the filtrate, the residue was purified by column chromatography using EtOAc as the eluent and iodine for visualization to afford 1.23 g dimethyl (diazomethyl)phosphonate, in a yield of 50%.



Reference 4.

A solution of 63 mg dimethyl (diazomethyl)phosphonate (0.42 mmol) in 5 mL THF was treated with 0.42 mL 1 M KO-*t*-Bu at −78°C and stirred for 20 min at this temperature.

Then aldehyde in 5 mL THF was added slowly. The resulting mixture was allowed to slowly warm to 0°C and stirred at 0°C for an additional 8 h, then quenched with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc (2 × 20 mL), the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. This crude acetylene was then dissolved in 10 mL MeOH, and a catalytic amount of *p*-toluenesulfonic acid was added. The mixture was stirred at room temperature for 5 h, and diluted with 20 mL EtOAc, washed sequentially with aqueous saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography using hexane/EtOAc (4:1) as the eluent to afford 117 mg propargyl alcohol as a colorless oil, in a yield of 74%.

Other references related to the Seyferth-Gilbert homologation are cited in the literature.[14]

H. REFERENCES

1. Seyferth, D. and Marmor, R., *Tetrahedron Lett.*, **1970**, 2493.
2. Gilbert, J. C. and Weerasooriya, U., *J. Org. Chem.*, **1979**, *44*, 4997.
3. (a) Wender, P. A.; Hegde, S. G.; Hubbard, R. D. and Zhang, L., *J. Am. Chem. Soc.*, **2002**, *124*, 4956. (b) Comins, D. L.; LaMunyon, D. H. and Chen, X. H., *J. Org. Chem.*, **1997**, *62*, 8182.
4. Ha, J. D.; Lee, D. H. and Cha, J. K., *J. Org. Chem.*, **1997**, *62*, 4550.
5. Powell, N. A. and Roush, W. R., *Org. Lett.*, **2001**, *3*, 453.
6. Mulzer, J. and Öhler, E., *Chem. Rev.*, **2003**, *103*, 3753.
7. (a) Waizumi, N.; Stankovic, A. R. and Rawal, V. H., *J. Am. Chem. Soc.*, **2003**,*125*, 13022. (b) Norcrosst, R. D. and Paterson, I., *Chem. Rev.*, **1995**, *95*, 2041. (c) Buszek, K. R.; Sato, N. and Jeong, Y. M., *J. Am. Chem. Soc.*, **1994**, *116*, 5511.
8. Marshall, J. A. and Adams, N. D., *J. Org. Chem.*, **2002**, *67*, 733.
9. Marshall, J. A. and Bourbeau, M. P., *J. Org. Chem.*, **2002**, *67*, 2751.
10. Evans, M. A. and Morken, J. P., *Org. Lett.*, **2005**, *7*, 3371.
11. Brown, D. G.; Velthuisen, E. J.; Commerford, J. R.; Brisbois, R. G. and Hoye, T. R., *J. Org. Chem.*, **1996**, *61*, 2540.
12. Ohira, S., *Synth. Commun.*, **1989**, *19*, 561.
13. Muller, S.; Liepold, B.; Roth, G. J. and Bestmann, H. J., *Synlett*, **1996**, 521.
14. (a) Swamy, K. C. K. and Kumar, N. S., *Acc. Chem. Res.*, **2006**, *39*, 324. (b) Wang, X.; Bowman, E. J.; Bowman, B. J. and Porco, J. A., *Angew. Chem. Int. Ed.*, **2004**, *43*, 3601. (c) Marshall, J. A. and Johns, B. A., *J. Org. Chem.*, **2000**, *65*, 1501. (d) Scheidt, K. A.; Tasaka, A.; Bannistger, T. D.; Wendt, M. D. and Roush, W. R., *Angew. Chem.*, **1999**, *111*, 1760. (e) Mapp, A. K. and Heathcock, C. H., *J. Org. Chem.*, **1999**, *64*, 23. (f) Rao, M. N.; McGuigan, M. A.; Zhang, X. H.; shaked, Z.; Kinney, W. A.; Bulliard, M.; Laboue, B. and Lee, N. E., *J. Org. Chem.*, **1997**, *62*, 4541. (g) McDermott, T. S.; Mortlock, A. A. and Heathcock, C. H., *J. Org. Chem.*, **1996**, *61*, 700. (h) Brown, D. G.; Velthuisen, E. J.; Commerford, J. R.; Brisbois, R. G. and Hoye, T. R., *J. Org. Chem.*, **1996**, *61*, 2540. (i) Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E. and Schreiber, S. L., *J. Am. Chem. Soc.*, **1990**, *112*, 5583. (j) Gilbert, J. C. and Weerasooriya, U., *J. Org. Chem.*, **1982**, *47*, 1837. (k) Gilbert, J. C. and Weerasooriya, U., *J. Org. Chem.*, **1982**, *47*, 1837. (l) Hauske, J. R.; Guadliana, M. and Desai, K., *J. Org. Chem.*, **1982**, *47*, 5019. (m) Colvin, E. W. and Hamill, B. J., *J. Chem. Soc., Perkin Trans. I*, **1977**, 869. (n) Ratcliffe, R. and Christensen, B., *Tetrahedron Lett.*, **1973**, 4645. (o) Colvin, E. W. and Hamill, B. J., *J. Chem. Soc., Chem. Commun.*, **1973**, 151. (p) Seyferth, D.; Marmor, R. S. and Hilbert, P., *J. Org. Chem.*, **1971**, *36*, 1379.

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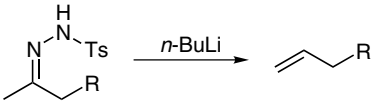
Shapiro Reaction
(Shapiro Elimination)

A. GENERAL DESCRIPTION OF THE REACTION

This reaction was initially reported by Shapiro in 1967.[1] It is a synthesis of olefins by means of a base-promoted decomposition of *p*-toluenesulfonylhydrazones of the corresponding ketones or aldehydes.[2] Therefore, it is generally known as the Shapiro reaction,[2b,3] or Shapiro elimination.[4] Occasionally, it is also referred to as the Shapiro olefination,[5] Shapiro lithiation reaction,[6] Shapiro fragmentation,[3d] or Shapiro degradation.[4d]

Normally, at least two equivalents of a strong base (typically an alkyllithium or lithium dialkylamide) are required to react with the hydrazones, and subsequent aqueous workup will give the expected alkenes.[3j] However, the Shapiro reaction has recently been reported to occur catalytically.[3k] This reaction is commonly carried out under very mild conditions compared to the *Bamford-Stevens Olefination*. In addition, due to the *syn*-dilithio effect,[7] the Shapiro reaction normally affords high yields of alkenes without rearrangement or other side reactions.[2c] Moreover, when the Grignard reagent is used as a base, substituted nitrile can be generated.[3d] The alkenes formed are kinetically controlled products—that is, less substituted alkenes.[2b] It should be pointed out that the Shapiro reaction does not work well with substrates containing only tertiary R-carbon atoms,[8] because the formation of the dianionic intermediate is problematic in this case and substitution at the imino carbon atom competes effectively with the elimination.[8a]

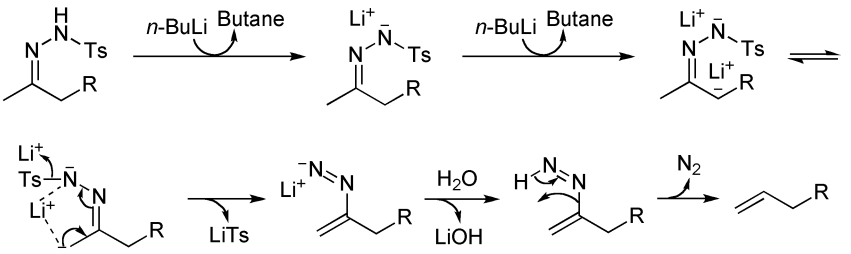
B. GENERAL REACTION SCHEME



Comprehensive Organic Name Reactions and Reagents, by Zerong Wang

C. PROPOSED MECHANISMS

It is assumed that the Shapiro reaction involves the deprotonation of the hydrazone NH and subsequently of an α-CH group, the resultant dianion eliminates *p*-toluenesulfinate followed by the evolution of nitrogen, as illustrated here.[2b]



D. MODIFICATION

This reaction has been modified to occur with only a catalytic amount of lithium amide.[3k]

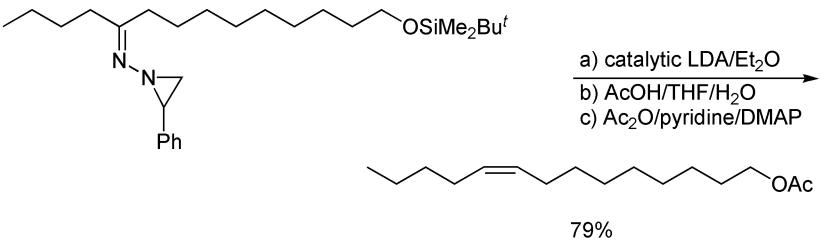
E. APPLICATIONS

This reaction has wide application in the preparation of alkenes or other derivatives.[2]

F. RELATED REACTIONS

This reaction is closely related to the *Bamford-Stevens Reaction*.

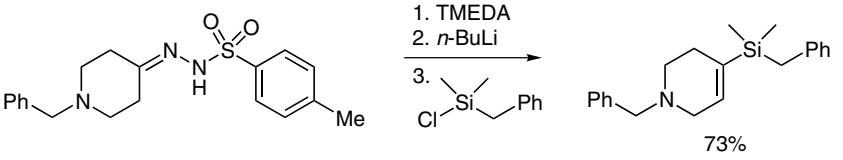
G. CITED EXPERIMENTAL EXAMPLES



Reference 4.

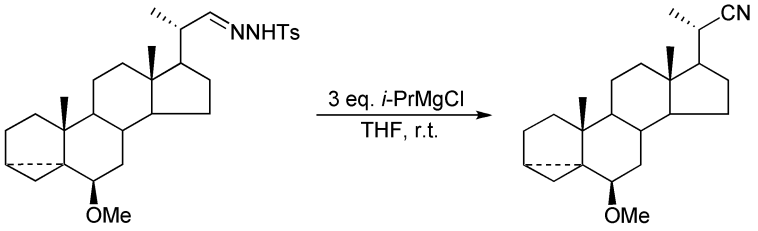
To a solution of 446 mg phenylaziriine (*Z*)-hydrazone of 14-(*tert*-butyldimethylsiloxy)-5-tetradecanone (1.0 mmol) in 1.0 mL dry ether at 0°C under argon atmosphere was added a solution of 0.2 mL 0.5 M LDA in ether/hexane. The mixture was stirred at 0°C for 1 h

and then poured into a mixture of AcOH/THF/H_2O (2:1:1, 40 mL). The mixture was stirred vigorously at room temperature for 3 h. Ether (50 mL) was added, and the organic layer was washed with saturated aqueous $NaHCO_3$ followed by brine, dried over Na_2SO_4, and concentrated. The crude (*Z*)-9-tetradecenol was treated with 142 μL Ac_2O (1.5 mmol) and 121 μL pyridine (1.5 mmol) in 3.0 mL dichloromethane, in the presence of a catalytic amount of DMAP at 25°C for 1 h. A standard workup and purification by column chromatography on silica gel (ether/hexane, 1:8) afforded 201 mg (*Z*)-9-tetradecenyl acetate, in a yield of 79%.



Reference 3b.

To a 1-L round-bottomed flask equipped with an addition funnel and an internal thermometer were added 18.6 g *N*-(1-benzyl-piperidin-4-ylidene)-*N*′-tosyl-hydrazine (52 mmol) and 260 mL hexanes. Under a nitrogen atmosphere, 40 mL TMEDA (267 mmol) was added and the mixture was cooled by dry ice/acetone bath and stirred for 25 min to resolve a white suspension. Then 160 mL 1.6 M *n*-butyllithium in hexanes (256 mmol) was added through the addition funnel dropwise over a period of 20 min, during which the reaction mixture turned into a yellow-orange suspension and the internal temperature rose by ~10°C. After the addition of *n*-BuLi completed, the solution was stirred at −78°C for 15 min and then was allowed to warm to room temperature (~18°C) within 1.5 h while being stirred. Over this time period, bubbling was observed, and the reaction slowly became reddish orange and then reddish brown. Then the solution was cooled by an ice bath for 10 min; after that, 14 mL benzyldimethylsilyl chloride (neat) (77 mmol) was added through a syringe over about 1 min. The reaction mixture quickly turned more reddish in color, and the internal temperature rose by ~15°C. After being stirred overnight, the reaction mixture was placed in an ice bath and quenched by 400 mL water, portionwise at first. The mixture turned from reddish brown to bright yellow, and the internal temperature rose by ~20°C. After separation of the organic phase, the aqueous layer was extracted with hexanes (2 × 150 mL). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (automated column, 330 g SiO_2, 0%–20% EtOAc in hexanes gradient) to afford 12.19 g 1-benzyl-4-(benzyldimethylsilanyl)-1,2,3,6-tetrahydro-pyridine as an orange oil, in a yield of 73%.



Reference 3d.

To a solution of 205 mg (*E*)-tosylhydrazone of 3α,5-cyclo-23,24-dinor-6β-methoxy-5α-cholane-24-al (0.4 mmol) in 1.4 mL THF was added 0.6 mL 2 M *i*-PrMgCl in THF (1.2 mmol). The mixture was stirred at room temperature for 24 h. The excess Grignard reagent was quenched with aqueous NH_4Cl, and the product was extracted with Et_2O and purified via column chromatography, to give 143 mg starting material (70% recovery yield) and 19 milligrams of 20(S)-6β-methoxy-3,5-cyclo-5α-pregnane-20-carbonitrile, in a yield of 14%.

Other references related to the Shapiro reaction are cited in the literature.[9]

H. REFERENCES

1. Shapiro, R. H. and Heath, M. J., *J. Am. Chem. Soc.*, **1967**, *89*, 5734.
2. (a) Chamberlin, A. R.; Bloom, S. H., *Org. React*., **1990**, *39*, 1. (b) Adlington, R. M. and Barrett, A. G. M., *Acc. Chem. Res.*, **1983**, *16*, 55. (c) Shapiro, R. H., *Org. React*., **1976**, *23*, 405.
3. (a) Wolfe, J. P., *Name Reactions for Functional Group Transformations*, **2007**, 405. (b) Morrill, C. and Mani, N. S., *Org. Lett.*, **2007**, *9*, 1505. (c) Tormakangas, O. P.; Toivola, R. J.; Karvinen, E. K. and Koskinen, A. M. P., *Tetrahedron*, **2002**, *58*, 2175. (d) Kurek-Tyrlik, A.; Marczak, S.; Michalak, K.; Wicha, J. and Zarecki, A., *J. Org. Chem.*, **2001**, *66*, 6994. (e) Addie, M. S. and Taylor, R. J. K., *ARKIVOC*, **2000**, *1(v)*, 660. (f) Chang, M.-Y. and Chang, N.-C., *J. Chinese Chem. Soc.*, **1999**, *46*, 41. (g) Corey, E. J.; Lee, J. M. and Roberts, B. E., *Tetrahedron Lett*., **1997**, *38*, 8915. (h) Corey, E. J. and Roberts, B. E., *Tetrahedron Lett*., **1997**, *38*, 8919. (i) Corey, E. J.; Lee, J. M. and Roberts, B. E., *Tetrahedron Lett*., **1997**, *38*, 8915. (j) Siemeling, U.; Neumann, B. and Stammler, H.-G., *J. Org. Chem.*, **1997**, *62*, 3407. (k) Maruoka, K.; Oishi, M. and Yamamoto, H., *J. Am. Chem. Soc.*, **1996**, *118*, 2289. (l) Zvonok, A. M. and Okaev, E. B., *Khim. Geterotsiklicheskikh Soedinenii*, **1996**, 361. (m) Saljoughian, M.; Morimoto, H.; Than, C. and Williams, P. G., *Tetrahedron Lett*., **1996**, *37*, 2923. (n) Wang, Z.-Q.; Zhou, W.-S.; Jiang, Z.-L.; Zhu, Z.-Y. and Wu, Y.-H., *Youji Huaxue*, **1994**, *14*, 541. (o) Kang, J.; Kim, J. H. and Jang, G. S., *Bull. Korean Chem. Soc.*, **1992**, *13*, 192. (p) Shi, G. Q. and Xu, Y. Y., *J. Fluor. Chem.*, **1989**, *44*, 161. (q) Caille, J. C.; Farnier, M. and Guilard, R., *Can. J. Chem.*, **1986**, *64*, 824. (r) Buetikofer, P. A. and Eugster, C. H., *Helv. Chim. Acta*, **1983**, *66*, 1148.
4. (a) Zhou, G.; Gao, X. L.; Guan, Y. K.; Li, W. D. and Li, Y. L., *Chinese Chem. Lett.*, **2001**, *12*, 407. (b) Halterman, R. L.; Ramsey, T. M.; Pailes, N. A. and Khan, M. A., *J. Organomet. Chem.*, **1995**, *497*, 43. (c) Leone, C. L. and Chamberlin, A. R., *Tetrahedron Lett*., **1991**, *32*, 1691. (d) Paquette, L. A.; Liang, S. W.; Waykole, L.; DeLucca, G.; Jendralla, H.; Rogers, R. D.; Kratz, D. and Gleiter, R., *J. Org. Chem*., **1990**, *55*, 1598. (e) Gill, J. C.; Marples, B. A. and Traynor, J. R., *Synth. Commun.*, **1989**, *19*, 155. (f) Nemoto, H.; Hashimoto, M.; Fukumoto, K. and Kametani, T., *J. Chem. Soc., Chem. Commun.*, **1982**, 699. (g) Roberts, W. P. and Shoham, G., *Tetrahedron Lett*., **1981**, *22*, 4895.
5. (a) Coltart, D. M. and Danishefsky, S. J., *Org. Lett.*, **2003**, *5*, 1289. (b) Muneyuki, R.; Yoshimura, Y.; Tori, K.; Terui, Y. and Shoolery, J. N., *J. Org. Chem.*, **1988**, *53*, 358. (c) Mori, K. and Igarashi, Y., *Liebigs Annalen Chem*., **1988**, 93.
6. Rupert, K. C.; Liu, C. C.; Nguyen, T. T.; Whitener, M. A. and Sowa, J. R., *Organometallics*, **2002**, *21*, 144.
7. (a) Adlington, R. M. and Barrett, A. G. M., J. *Chem. Soc., Perkin Trans. I*, **1981**, 2848. (b) Adlington, R. M. and Barrett, A. G. M., *J. Chem. Soc*., *Chem. Commun.*, **1979**, *1122*.
8. (a) Shapiro, R. H.; Lipton, M. F.; Kolonko, K. J.; Buswell, R. L. and Capuano, L. A., *Tetrahedron Lett*., **1975**, 1811. (b) Mori, K.; Matsui, M., *Tetrahedron*, **1970**, *26*, 2801.

9. (a) Faul, M. M.; Ratz, A. M.; Sullivan, K. A.; Trankle, W. G. and Winneroski, L. L., *J. Org. Chem.* **2001**, *66*, 5772. (b) Hamon, D. P. G. and Tuck, K. L., *J. Org. Chem.*, **2000**, *65*, 7839. (c) Keay, B. A.; Maddaford, S. P.; Cristofoli, W. A.; Andersen, N. G.; Passafaro, M. S.; Wilson, N. S. and Nieman, J. A. *Can. J. Chem.* **1997**, *75*, 1163. (d) Paquette, L. A.; Bzowej, E. I. and Kreuzholz, R., *Organometallics*, **1996**, *15*, 4857. (e) Chamberlin, A. R.; Liotta, E. L. and Bond, F. T., *Org. Syn. Coll.*, **1990**, *7*, 77. (f) Trost, B. M. and Nanninga, T. N., *J. Am. Chem. Soc.* **1985**, *107*, 1293. (g) Evans, D. A. and Nelson, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 774. (h) Chamberlin, A. R. and Bond, F. T. *Synthesis* **1979**, 44. (i) Chamberlin, A. R.; Stemke, J. F. and Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147. (j) Stemke, J. E.; Chamberlin, A. R. and Bond, F. T. *Tetrahedron Lett.* **1976**, *34*, 2947. (k) Traas, P. C.; Boelens, H. and Takken, H. J. *Tetrahedron Lett.* **1976**, *26*, 2287.