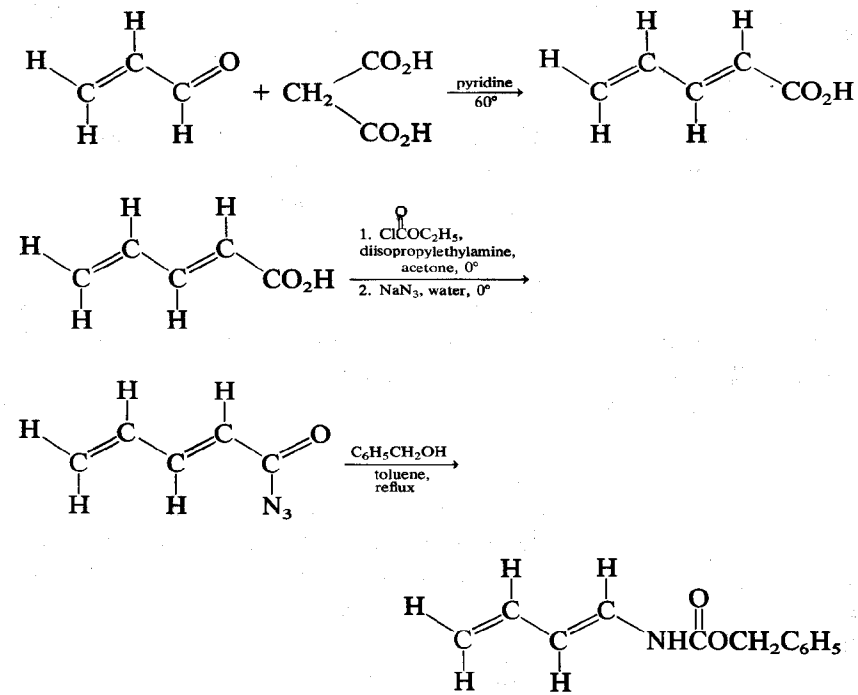
1-*N*-ACYLAMINO-1,3-DIENES FROM 2,4-PENTADIENOIC ACIDS BY THE CURTIUS REARRANGEMENT: BENZYL *trans*-1,3-BUTADIENE-1-CARBAMATE

(Carbamic acid, 1,3-butadienyl-, phenylmethyl ester)



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Checked by PAUL H. LIANG and G. BÜCHI

1. Procedure

A. trans-2,4-*Pentadienoic acid.* A 1-l., three-necked, round-bottomed flask is equipped with a mechanical stirrer, a condenser cooled with ice-cold water (Note 1) and bearing a calcium chloride drying tube, and a powder funnel. The flask is charged with 206 g. (210 ml., 2.6 moles) of pyridine (Note 2), vigorous stirring is

begun, and 208 g. (2.0 moles) of powdered malonic acid (Note 3) is added in portions. The powder funnel is replaced by a 250-ml. pressure-equalizing dropping funnel containing 126 g. (150 ml., 2.25 moles) of acrolein (Note 4). The contents of the flask are stirred vigorously as the acrolein is added over a 30-minute period. The exothermic reaction begins immediately with brisk evolution of carbon dioxide, and the gently refluxing mixture becomes homogeneous. After 1 hour carbon dioxide evolution nearly ceases. The solution is then poured into 1 l. of ice in a 3-l. Erlenmeyer flask, and is carefully acidified with 130 ml. of concentrated sulfuric acid. The aqueous layer is extracted with four 250-ml. portions of dichloromethane, and the organic extracts are dried over magnesium sulfate for *ca.* 10 minutes. The dichloromethane solution is concentrated to *ca.* 300 ml. on a rotary evaporator with the water bath at 20–30°, and allowed to crystallize in a freezer at −10° for several hours. A first crop of 40–50 g. of product, m.p. 72–73°, is collected. Three additional crops are taken following successive concentration of the mother liquor to 150, 70, and 30 ml. After being dried under reduced pressure in the presence of phosphorous pentoxide, the four crops of off-white crystals amount to 82–90 g. (42–46%), m.p. 69–71° (Note 5).

B. *Benzyl* trans-1,3-*butadiene*-1-*carbamate. Caution! The following reaction should be carried out in a fume hood to avoid accidental exposure to toxic hydrazoic acid.* A dry 1-l., three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a thermometer, and a 250-ml. pressure-equalizing dropping funnel bearing a nitrogen inlet. The flask is flushed with nitrogen and charged with 49 g. (0.50 mole) of *trans*-2,4-pentadienoic acid, 80 g. (0.62 mole) of *N,N*-diisopropylethylamine, and 300 ml. of acetone (Note 6). The resulting solution is stirred and cooled to 0° in an ice–salt bath. A solution of 55 g. (0.51 mole) of ethyl chloroformate in 150 ml. of acetone is then added over 30 minutes while the temperature is maintained below 0° (Note 7). Stirring is continued for an additional 30 minutes at 0° after which a chilled solution of 65 g. (1.0 mole) of sodium azide (Note 8) in 170 ml. of water is added over a 20-minute interval, while the temperature is kept below 0°. The contents of the flask are stirred for an additional 10–15 minutes at 0° (Note 9) and poured into 500 ml. of ice-water contained in a 2-l. separatory funnel. The acyl azide is

isolated by extraction with six 250-ml. portions of toluene. The combined toluene extracts are dried over anhydrous magnesium sulfate for 20 minutes and concentrated to a volume of *ca.* 300 ml. on a rotary evaporator with the water bath at 40–50° (Note 10). *Caution! The acyl azide is potentially explosive. The solution should not be evaporated to dryness.* While the toluene solution is being concentrated, a dry 2-l., three-necked, round-bottomed flask is equipped with a mechanical stirrer, a 500-ml. pressure-equalizing dropping funnel, a simple distillation head, and a heating mantle. In this flask are placed 43 g. (0.40 mole) of benzyl alcohol, 250 mg. of 4-*tert*-butylcatechol (Note 11), and 200 ml. of toluene. About 30 ml. of toluene is distilled from the flask to remove trace amounts of water, and the distillation head is then replaced with a condenser fitted with a nitrogen inlet. The toluene solution is stirred and heated at a rapid reflux under a nitrogen atmosphere as the above solution of the acyl azide is added over 30 minutes. The disappearance of the acyl azide and isocyanate is followed by infrared analysis (Note 12). The conversion to the carbamate is complete in 10–30 minutes, after which the solution is cooled rapidly to room temperature by immersing the flask in an ice bath. The toluene is rapidly removed on a rotary evaporator with the water bath at 40–50° to afford a yellow solid residue (Note 13). The crude product is dissolved in 50 ml. of 95% ethanol and allowed to crystallize in a freezer at −25° for several hours. Two crops of pale yellow crystals, m.p. 69–72°, are taken which total 39–46 g. after drying under reduced pressure. Concentration of the mother liquor affords an oily residue that is placed on a 6 × 80-cm. column packed with 500 g. of silica gel (Note 14) and is eluted with 1:9 (v/v) ethyl acetate–hexane. An additional 11–12 g. of crystalline product is obtained from the chromatography, which raises the total yield to 50–58 g. (49–57%) of nearly pure benzyl *trans*-1,3-butadiene-1-carbamate, a pale yellow solid, m.p. 70–73° (Note 15).

2. Notes

1. A water pump purchased from Little Giant Pump Company, Oklahoma City, Oklahoma, was used by the submitters to circulate ice-water through the condenser. The checkers used a dry ice condenser.

2. Reagent-grade pyridine was stored over Linde type 4A molecular sieves for at least 24 hours before use.

3. Malonic acid was purchased from Aldrich Chemical Company, Inc. Most, but not all, of the malonic acid dissolves after 30 minutes. If pyridine is added to the malonic acid, a hard cake results.

4. Acrolein contaminated by 3% water was obtained by the submitters from Aldrich Chemical Company, Inc., and was purified by distillation from anhydrous calcium sulfate, b.p. 53°. The checkers used acrolein purchased from MC and B Manufacturing Chemists.

5. This material is of satisfactory purity for use in Part B. A thin-layer chromatogram on silica gel developed with 1:1 (v/v) ethyl acetate–hexane containing 1% acetic acid and visualized with 10% phosphomolybdic acid in ethanol as spray reagent showed a major spot at $Rf = 0.4$ and a faint spot at $Rf = 0.2$. The crystalline acid may be stored for several months without significant decomposition. A melting point of 72° is reported[2] for *trans*-2,4-pentadienoic acid. The spectral properties of the product are as follows: infrared (chloroform) cm.$^{-1}$: 3200–2700 (OH), 1696 (C=O), 1640, 1600, 1280, 1010; proton magnetic resonance (chloroform-*d*) δ (multiplicity, number of protons, assignment, coupling constant J in Hz.): 5.1–5.8 (multiplet, 2, two *H* at C-5), 5.92 (doublet, 1, *H* at C-2, $J = 15$), 6.2–6.8 (multiplet, 1, *H* at C-4), 7.37 (doublet of doublets, 1, *H* at C-3, $J_{2,3} = 15$, $J_{3,4} = 11$), 12.0 (singlet, 1, $-CO_2H$).

6. *N,N*-Diisopropylethylamine was supplied by Aldrich Chemical Company, Inc., and purified by distillation from sodium hydride, b.p. 127°. Reagent-grade acetone was stored over Linde type 4A molecular sieves for at least 24 hours before use.

7. Ethyl chloroformate obtained from Aldrich Chemical Company, Inc., was distilled, b.p. 93°. The progress of the reaction may be followed by proton magnetic resonance spectroscopy. Aliquots are partitioned between dichloromethane and water, the organic layer is concentrated, and the spectrum is recorded. A quartet from the ethoxy group of the mixed anhydride appears at δ 4.2. Ethyl chloroformate, which exhibits a quartet at δ 4.3, is removed in the concentration step.

8. Analytical reagent–grade sodium azide purchased from Alfa Division, Ventron Corporation, or J. T. Baker Chemical Company was used as supplied.

9. The formation of the acyl azide may be followed by the growth of the 2130-cm.$^{-1}$ (—N=N=N) infrared absorption of concentrated dichloromethane extracts of aliquots removed from the reaction.

10. The solution is concentrated for the purpose of removing residual ethanol. If this step is omitted, ethyl *trans*-1,3-butadiene-1-carbamate will be formed, contaminating the final product.

11. Reagent-grade benzyl alcohol was purified by distillation, b.p. 205°. 4-*tert*-Butylcatechol purchased from Aldrich Chemical Company was sublimed at 50° (0.1 mm.) and recrystallized from hexane.

12. The acyl azide infrared absorption occurs at 2130 cm.$^{-1}$ and the isocyanate at 2270 cm.$^{-1}$.

13. Impure samples of the product are particularly prone to decomposition. The purification steps should be carried out immediately.

14. Grade 60, activity III silica gel, purchased from W. R. Grace and Company, was used.

15. Material of this purity is suitable for most applications and may be stored in a freezer for several months with only slight decomposition. A thin-layer chromatogram on silica gel developed with 1:3 (v/v) ethyl acetate–hexane and visulized by ultraviolet fluorescence showed a single spot. Benzyl *trans*-1,3-butadiene-1-carbamate, like all *N*-acylamino-1,3-dienes, is quite acid sensitive and, for example, can be decomposed by traces of deuterium chloride in chloroform-*d*. A pure sample may be obtained by recrystallization from 1:20 (v/v) ethyl acetate–hexane, m.p. 74–75°. The product has the following spectral properties: infrared (nujol) cm.$^{-1}$: 3300, 1692, 1625, 1515, 1230, 690; proton magnetic resonance (chloroform-*d*) δ (multiplicity, number of protons, assignment, coupling constant J in Hz): 4.8–5.0 (multiplet, 2, two *H* at C-4), 5.15 (singlet, 2, $CH_2C_6H_5$), 5.4–5.8 (multiplet, 2, *H* at *C*-2 and N*H*), 6.26 (apparent doublet of triplets, 1, *H* at C-3, $J = 10$ and 17), 6.71 (broadened doublet, 1, *H* at C-1, $J = 9$), 7.33 (singlet, 5, C_6H_5); carbon magnetic resonance (chloroform-*d*) δ (assign-

ment): 67.5 ($CH_2C_6H_5$), 112.5 (*C*-2), 113.5 (*C*-4), 127.2 (*C*-1), 128.3 (*para*-C_6H_5), 128.4 (*meta*-C_6H_5), 128.7 (*ortho*-C_6H_5), 134.6 (*C*-3), 136.0 (*peri*-C_6H_5), 153.7 (*C*=O).

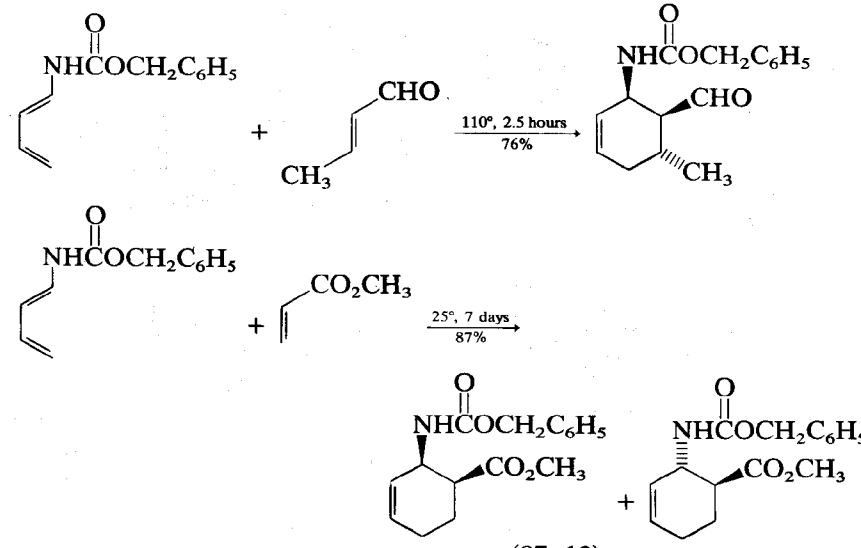
3. Discussion

This procedure illustrates a general method[3] for the preparation of *trans*-1-*N*-acylamino-1,3-butadienes from 2,4-pentadienoic acids. A number of 1,3-butadienyl and 1,3-pentadienyl carbamates, thiocarbamates, and ureas have been prepared by this procedure (Table I).[3] These dienamides are reasonably stable crystalline solids which, when pure, may be stored in a freezer for several months with little decomposition. Since a variety of conjugated dienoic acids are readily accessible from Knoevenagel, Wittig, and related reactions,[4] 1-*N*-acylamino-1,3-butadienes with a diversity of carbon skeletons and heteroatom acyl substituents are potentially available by this method. Although this procedure describes the only known preparation of benzyl *trans*-1,3-butadiene-1-carbamate, a number of similar 1-*N*-acylamino-1,3-butadiene derivatives have been prepared by Curtius rearrangement of 2,4-hexadienoyl azide,[5] by Hofmann rearrangement of 2,4-hexadienamide,[6] by *N*-acylation of 1-*N*-alkylamino-1,3-butadiene anions generated from crotonaldehyde imines,[7] and by thermal rearrangement of trichloroacetimidic esters of acetylenic alcohols.[8]

The Curtius rearrangement procedure described here is a modification of one reported by Winestock.[9] The submitters have found this procedure to be considerably more reproducible when *N*,*N*-diisopropylethylamine is substituted for triethylamine. The procedure described for the preparation of *trans*-2,4-pentadienoic acid is a modification of an earlier one by Doebner.[10] The submitters have found this method to give reproducibly higher yields, and to be more convenient, than other commonly used procedures for preparing this material.[2,11] The use of dichloromethane as the extracting and crystallizing solvent greatly simplifies the isolation of polymer-free samples of the crystalline acid.

trans-1-*N*-Acylamino-1,3-butadienes are useful dienes in Diels-Alder reactions. They are the most convenient synthetic equivalents currently available for the parent 1-amino-1,3-butadienes.

These electron-rich dienamides undergo Diels-Alder cycloaddition with remarkable ease and with high regio- and stereoselectivity.[12,13] As illustrated below, they react readily with even relatively unreactive dienophiles such as methyl acrylate and *trans*-crotonaldehyde. A recent quantitative study[12] has confirmed the expectation of an increase in reactivity with increasing electron-donating ability of the acyl substituent of an acylaminobutadiene, although the effects observed are not large.

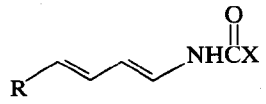


(87 : 13)

The choice of the acyl substituent X for Diels-Alder reactions of 1-*N*-acylamino-1,3-butadienes depends on the particular synthetic problem. The acyl substituent has a moderate effect on the cycloaddition reactivity of these dienes,[12] and also determines what amine unmasking procedures are required. As a result of their stability[12,13] and the variety of amine deprotection procedures available,[14] the diene carbamates are the components of choice in most cases. A particularly attractive aspect of the diene synthesis detailed here is the ability to "tailor" the amino-protecting group

(C—X) for the application at hand. Benzyl *trans*-1,3-butadiene-1-carbamate has the amino group protected with the benzyloxycarbonyl group. The ability to remove this functionality by catalytic

TABLE I
PREPARATION OF *trans*-1-*N*-ACYLAMINO-1,3-BUTADIENES[3]



R	X	Procedure[a]	M.p. (°)	Yield (%)
H	$OCH_2C_6H_5$	A	74–75	53[b]
H	$OC(CH_3)_3$	A	67–68	59
CH_3	OCH_2CH_3	A	91–92	80
H	OCH_2CH_3	A	44–45	71[b]
CH_3	OC_6H_8	A	118–120	72
H	OC_6H_5	B[c]	118–119	66
		A		45
CH_3	$N(CH_2)_4$	B	164–165	77
		A		(10)[d]
H	$N(CH_2)_4$	B	163–164	44
CH_3	SC_6H_5	B	116–118	78
H	SC_6H_5	B	92–93	47

[a] Isocyanate trapped as formed at 100° (Procedure A) or isocyanate preformed at 110° and trapped at 25° (Procedure B).
[b] Mean yield of four runs. All other entries are non-optimized yields from one run.
[c] A few drops of triethylamine were added.
[d] Estimated from the proton magnetic resonance spectrum.

hydrogenation was an important design feature in a recent alkaloid synthesis[13] that utilized this diene.

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

trans-2,4-Pentadienoic acid: 2,4-Pentadienoic acid (8, 9); (626-99-3); (*E*)—(21651-12-7); (*Z*)—(29739-67-1)

Malonic acid (8); Propanedioic acid (9); (141-82-2)

Acrolein (8); 2-Propenal (9); (107-02-8)

Benzyl *trans*-1,3-butadiene-1-carbamate: 1,3-Butadienecarbamic acid, benzyl ester (8); Carbamic acid, 1,3-butadienyl-, phenylmethyl ester (9); (−)

N,*N*-Diisopropylethylamine: Triethylamine, 1,1′-dimethyl- (8); 2-Propanamine, *N*-ethyl-*N*-(1-methylethyl)- (9); (7087-68-5)

Ethyl chloroformate: Formic acid, chloro-, ethyl ester (8); Carbonochloridic acid, ethyl ester (9); (541-41-3)

Benzyl alcohol (8); Benzenemethanol (9); (100-51-6)

4-*tert*-Butylcatechol: Pyrocatechol, 4-*tert*-butyl- (8); 1,2-Benzenediol, 4-(1,1-dimethylethyl)- (9); (98-29-3)

Toluene (8); Benzene, methyl- (9); (108-88-3)

Ethyl *trans*-1,3-butadiene-1-carbamate: 1,3-Butadienecarbamic acid, ethyl ester, (*E*)—(8); Carbamic acid, 1,3-butadienyl-, ethyl ester, (*E*)—(9); (61759-61-3)

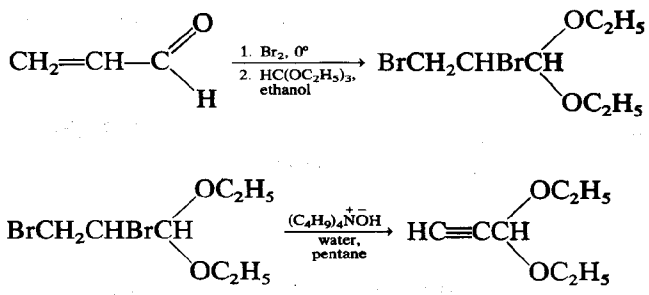
Triethylamine (8); Ethanamine, *N*,*N*-diethyl- (9); (121-44-8)

Methyl acrylate: Acrylic acid, methyl ester (8); 2-Propenoic acid, methyl ester (9); (96-33-3)

trans-Crotonaldehyde: Crotonaldehyde (8); 2-Butenal (9); (4170-30-3); (*E*)—(123-73-9); (*Z*)—(15798-64-8)

ALKYNES VIA PHASE TRANSFER-CATALYZED DEHYDROHALOGENATION: PROPIOLALDEHYDE DIETHYL ACETAL

(1-Propyne, 3,3-diethoxy-)



Submitted by A. Le Coq and A. Gorgues[1]
Checked by G. Saucy and P. S. Manchand

1. Procedure

A. 2,3-*Dibromopropionaldehyde diethyl acetal.* A 500-ml., three-necked, round-bottomed flask is equipped with a mechanical stirrer, a pressure-equalizing dropping funnel fitted with a calcium chloride drying tube, and a thermometer. The flask and dropping funnel are charged with 28.0 g. (0.5 mole) of freshly distilled acrolein and 80.0 g. (0.5 mole) of bromine, respectively. The acrolein is stirred rapidly and cooled to 0° in an ice–salt bath, then bromine is added at a rate such that the temperature is kept at 0–5°, until a permanent red color indicates a slight excess of bromine in the flask. A total of 78–79 g. of bromine is added over a 1-hour period. The crude 2,3-dibromopropionaldehyde is stirred while a solution of 80 g. (0.54 mole) of freshly distilled triethyl orthoformate in 65 ml. of absolute ethanol (Note 1) is added over 15 minutes. The solution warms to 45° and is stirred for 3 hours, after which ethyl formate, ethanol, and triethyl orthoformate are removed on a rotary evaporator. Distillation of the residual liquid through a 15-cm. Vigreux column affords 107–112 g. (74–77%) of 2,3-dibromopropionaldehyde diethyl acetal, b.p. 113–115° (11 mm.), as a pale-yellow liquid (Note 2).

B. *Propiolaldehyde diethyl acetal.* In a 500-ml., three-necked, round-bottomed flask equipped with a mechanical stirrer (Note 3), a double-walled condenser, and a pressure-equalizing dropping funnel are placed 100 g. (0.3 mole) (Note 4) of tetrabutylammonium hydrogen sulfate (Note 5) and 20 ml. of water. The mixture is stirred to form a thick paste to which a solution of 29 g. (0.1 mole) of 2,3-dibromopropionaldehyde diethyl acetal in 75 ml. of pentane is added. The resulting mixture is stirred rapidly and cooled to 10–15° as a cold (10–15°) solution of 60 g. (1.5 moles) of sodium hydroxide in 60 ml. of water is added over 10 minutes. About 5 minutes later the pentane begins to boil and continues to reflux for another 10–20 minutes. The mixture is stirred for 2 hours at room temperature, cooled to 5°, and made slightly acidic (Note 6) by adding *ca.* 120 ml. of cold (*ca.* 5°) 25% (v/v) sulfuric acid in water. Stirring is stopped, the layers are allowed to separate for 30 minutes, and the upper organic layer is carefully decanted (Note 7). The lower, aqueous layer is filtered to remove sodium sulfate, extracted with three 50-ml. portions of pentane, and, if desired, processed to recover the tetrabutylammonium salt (Note 8). The pentane solutions are combined, dried over anhydrous sodium sulfate, and evaporated. The colorless concentrate is distilled to give 7.8–8.6 g. (61–67%) of propiolaldehyde diethyl acetal as a colorless liquid, b.p. 138–139° (760 mm.), 95–96° (170 mm.) (Note 9).

2. Notes

1. Absolute ethanol from a commercial supplier was used without further treatment.

2. The submitters report a yield of 113–122 g. (78–84%), b.p. 113–115° (11 mm.). The literature[2] boiling point is 108–110° (10 mm.). The product obtained by the checkers was analyzed. Analysis calculated for $C_7H_{14}Br_2O_2$: C, 28.99; H, 4.87; Br, 55.11. Found: C, 28.81; H, 4.88; Br, 55.37. The proton magnetic resonance spectrum of the product in chloroform-*d* exhibits the following absorptions: δ (multiplicity, number of protons, assignment, coupling constant J in Hz.): 1.27 (triplet, 6, two OCH_2CH_3, $J = 7$), 3.6–3.9 (multiplet, 6, two OCH_2CH_3 and CH_2Br), 4.22 (apparent doublet of triplets, 1, $CHBr$, $J = 4$ and 7), 4.72 (doublet, 1, $CH(OC_2H_5)_2$, $J = 4$).

3. The submitters used a 1-l. Erlenmeyer flask and a magnetic stirrer. The Erlenmeyer flask was recommended to minimize splattering of the pasty mixture into the condenser. The checkers preferred to use a 500-ml., round-bottomed flask equipped as described above.

4. The submitters found that the yield of product was reduced to *ca.* 50% when only 1 equivalent (0.2 mole) of tetrabutylammonium hydrogen sulfate was used.

5. The submitters purchased tetrabutylammonium hydrogen sulfate with a purity of 97% from Fluka AG, Buchs, Switzerland. This reagent was obtained by the checkers from Aldrich Chemical Company, Inc.

6. Care must be exercised during the acidification, since excess sulfuric acid lowers the yield, presumably through hydrolysis of the acetal.

7. The checkers often obtained a thick emulsion which separated into three layers after standing for *ca.* 2 hours. When this occurred, the mixture was poured into 500 ml. of water, and the product was extracted with three 150-ml. portions of pentane.

8. The following unchecked procedure has been provided by the submitters for the purpose of recovering the tetrabutylammonium salt. The aqueous layer, which contains 12 g. of sodium bromide, is extracted with two 100-ml. portions of dichloromethane. The solution is dried and evaporated giving 91–93 g. (96–98%) of crude tetrabutylammonium bromide which can be recrystallized from ethyl acetate or employed directly for regenerating the hydrogen sulfate salt. The submitters recommend that the bromide be accumulated from several runs and then converted to the hydrogen sulfate by the procedure of Brandström.[3] A two-necked, round-bottomed flask fitted with a short distillation column and a dropping funnel is charged with 196 g. (0.6 mole) of recovered tetrabutylammonium bromide and 300 ml. of chlorobenzene. The contents of the flask are heated, and 92 g. (0.73 mole) of dimethyl sulfate is then added dropwise to the hot solution. The methyl bromide formed distills from the flask and is collected in a trap cooled with a dry ice–acetone mixture. As the rate of production of methyl bromide decreases, the heating is increased until the temperature at the top of the distillation column starts to rise rapidly. A solution of 1.5 ml. of concentrated sulfuric acid in 600 ml. of water is then cautiously added. The mixture is heated at reflux for 48 hours and evaporated to dryness under reduced pressure. After the residue has been dissolved in 500 ml. of dichloromethane, the resulting solution is washed with two 50-ml. portions of water and dried with anhydrous sodium sulfate. Evaporation of the solvent provides 202.5 g. of almost pure tetrabutylammonium hydrogen sulfate which can be recrystallized from isobutyl methyl ketone.

9. The submitters report a yield of 8.6–9.5 g. (67–74%), b.p. 95–96° (170 mm.). A boiling point of 138–139.5° (760 mm.) is given in the literature.[2] The submitters recommend that the product be distilled under reduced pressure. The spectral characteristics of the product are as follows: infrared (liquid film) $cm.^{-1}$: 3260 (≡CH), 2125 (C≡C); proton magnetic resonance (chloroform-*d*) δ (multiplicity, number of protons, assignment, coupling constant *J* in Hz): 1.24 (triplet, 6, two CH_3, $J=7$), 2.58 (doublet, 1, ≡C*H*, $J=2$), 3.71 (apparent quartet of doublets, 4, two $CH_AH_BCH_3$), 5.21 (doublet, 1, $CH(OC_2H_5)_2$ $J=2$).

3. Discussion

The preparation of 2,3-dibromopropionaldehyde diethyl acetal described here is based on the procedure of Grard.[2,4] The dehydrobromination of the dibromide to propiolaldehyde diethyl acetal has previously been carried out with potassium hydroxide in ethanol[2,4] and with sodium amide in liquid ammonia.[5] In the present procedure the elimination is effected with aqueous sodium hydroxide in the presence of the phase-transfer agent, tetrabutylammonium hydrogen sulfate.[6,7] The principal advantage of the phase-transfer procedure is its operational simplicity. The method has been used to prepare diphenyl acetylene (75%), phenylacetylene (87%), *p*-tolylacetylene (77%), and 3-chloropropiolaldehyde diethyl acetal (70%).[8] The halide reactants were the corresponding 1,2-dibromides in the first two examples and vinyl chlorides in the second two cases. The yields obtained with this method are better than those from traditional procedures, and the conditions are generally milder. In addition, the extent of substitution and dehalogenation, side reactions that frequently complicate the synthesis of acetylenes by elimination with alkoxide or amide bases, is diminished.[9] The ability to recover efficiently the

tetrabutylammonium salt enhances the practicality of this procedure.[3]

Propiolaldehyde diethyl acetal has found numerous synthetic applications in the literature which may be briefly summarized. The compound has been utilized in the synthesis of unsaturated and polyunsaturated acetals and aldehydes by alkylation of metallated derivatives,[5,10–13] by Cadiot-Chodkiewicz coupling with halo acetylenes,[13–14] and by reaction with organocuprates.[15] Syntheses of heterocyclic compounds including pyrazoles,[16] isoxazoles,[16] triazoles,[2] and pyrimidines[7,18] have employed this three-carbon building block. Propiolaldehyde diethyl acetal has also been put to use in the synthesis of such natural products as polyacetylenes[19–23] and steroids.[24]

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Propiolaldehyde, diethyl acetal (8); 1-Propyne, 3,3-diethoxy- (9); (10160-87-9)

2,3-Dibromopropionaldehyde diethyl acetal: Propionaldehyde, 2,3-dibromo-, diethyl acetal (8); Propane, 2,3-dibromo-1,1-diethoxy- (9); (10160-86-8)

Acrolein (8); 2-Propenal (9); (107-02-8)

Propionaldehyde, 2,3-dibromo- (8); Propanal, 2,3-dibromo- (9); (5221-17-0)

Triethyl orthoformate: Orthoformic acid, triethyl ester (8); Ethane, 1,1′,1″-[methylidynetris(oxy)]tris- (9); (122-51-0)

Ethyl formate: Formic acid, ethyl ester (8, 9); (109-94-4)

Tetrabutylammonium hydrogen sulfate: Ammonium, tetrabutyl-, sulfate (1:1) (8); 1-Butanaminium, *N,N,N*-tributyl-, sulfate (1:1) (9); (32503-27-8)

Ammonium, tetrabutyl-, bromide (8); 1-Butanaminium, *N,N,N*-tributyl-, bromide (9); (1643-19-2)

Dimethyl sulfate: Sulfuric acid, dimethyl ester (8, 9); (77-78-1)

Isobutyl methyl ketone: 2-Pentanone, 4-methyl- (8, 9); (108-10-1)

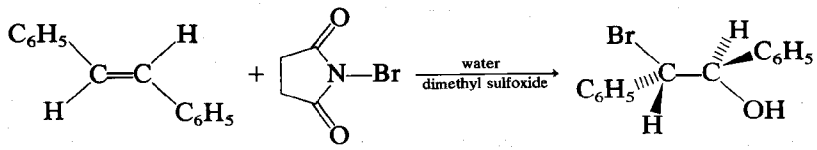
Acetylene, diphenyl- (8); Benzene, 1,1′-(1,2-ethynediyl)bis- (9); (501-65-5)

Phenylacetylene: Benzene, ethynyl- (8, 9); (536-74-3)

p-Tolylacetylene: Toluene, *p*-ethynyl- (8); Benzene, 1-ethynyl-4-methyl- (9); (766-97-2)

Propiolaldehyde, 3-chloro-, diethyl acetal (8); 1-Propyne, 1-chloro-3,3-diethoxy- (9); (62761-29-9)

BROMOHYDRINS FROM ALKENES AND *N*-BROMOSUCCINIMIDE IN DIMETHYL SULFOXIDE: *erythro*-2-BROMO-1,2-DIPHENYLETHANOL



Submitted by A. W. LANGMAN and D. R. DALTON[1]
Checked by I. DAVID REINGOLD and S. MASAMUNE

1. Procedure

A 500-ml., round-bottomed flask equipped with a magnetic stirring bar and a thermometer is charged with 18.0 g. (0.1 mole) of (*E*)-stilbene (Note 1), 5.0 ml. (0.28 mole) of water, and 300 ml. (4.23 moles) of dimethyl sulfoxide (Note 2). The resulting suspension is stirred for 5 minutes at room temperature (20–25°) (Note 3). Stirring is continued as 35.6 g. (0.2 mole) of *N*-bromosuccinimide (Note 4) is added in small portions over *ca.* 10 minutes. A yellow color appears when the first portion of *N*-bromosuccinimide is added, and by the time the addition is complete, the solution is bright orange. During the addition the temperature of the mixture rises to 50–55°, and all the (*E*)-stilbene dissolves. The contents of the flask are stirred for another 15 minutes and then are poured into 1 l. of ice water. The product separates immediately as a white solid (Note 5). The aqueous slurry is transferred to a separatory funnel with the aid of 50-ml. portions of water and ether and is extracted with four 200-ml. portions of ether. The combined ethereal extracts are washed with 250 ml. of water and 250 ml. of sodium chloride solution, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure with a rotary evaporator. During the removal of the solvent, the temperature of the water bath is maintained at *ca.* 30°. The pale yellow crystalline residue is dissolved, to the extent possible, in 600 ml. of hot hexane, and the resulting suspension is filtered while hot to separate a small amount of an insoluble

impurity. Cooling the filtrate provides colorless fibers of analytically pure *erythro*-2-bromo-1,2-diphenylethanol, m.p. 83–84° (Note 6). A second crop of crystals is obtained by concentrating the mother liquor to 200 ml. (Note 7). The combined yield amounts to 22.0–24.9 g. (80–90%) (Note 8).

2. Notes

1. (*E*)-Stilbene, m.p. 123–126°, was purchased from Aldrich Chemical Company, Inc., and was used as received. It is also available from J. T. Baker Chemical Company and from Eastman Organic Chemicals.

2. Reagent-grade dimethyl sulfoxide was used without purification. The amount of dimethyl sulfoxide can be varied. A large excess is employed in this case to facilitate dissolution of the stilbene.

3. The suspension may be warmed to dissolve the alkene more rapidly. (*E*)-Stilbene dissolves completely at *ca.* 65°. If the suspension is warmed, it *must* be cooled below 30° before proceeding further to prevent a vigorous reaction when the *N*-bromosuccinimide is added. The submitters recommend that the warm suspension be cooled under an atmosphere of nitrogen. If a volatile alkene is used, the mixture should be cooled prior to and during the addition of *N*-bromosuccinimide to prevent losses by evaporation.

4. *N*-Bromosuccinimide purchased from Arapahoe Chemical Company was used without purification. If the purity of the *N*-bromosuccinimide is in doubt, it should be titrated before use by the standard iodide–thiosulfate method and purified, if necessary, by recrystallization from 10 times its weight of water.[2] Solutions of *N*-bromosuccinimide in dimethyl sulfoxide cannot be stored, since the solvent is oxidized by the brominating reagent.

5. The product does not appear to deteriorate if allowed to stand at this point.

6. The submitters recrystallized the product from 600 ml. of petroleum ether (b.p. 30–60°) and reported a melting point of 84–84.5°. Melting points recorded in the literature are 84.5–85.5°[3] and 86°.[4]

7. The submitters found that the residue (2.8 g.) obtained upon

evaporation of the mother liquor was largely *erythro*-2-bromo-1,2-diphenylethanol contaminated with a small amount of succinimide. Absorptions for the *threo* isomer could not be detected in the infrared and proton magnetic resonance spectra of this material.

8. The product obtained by the checkers was analyzed. Analysis calculated for $C_{14}H_{13}BrO$: C, 60.67; H, 4.73. Found: C, 60.74; H, 4.77. The spectral properties of the product are as follows: infrared (carbon tetrachloride) $cm.^{-1}$: 3610, 1500, 1460, 700; proton magnetic resonance (chloroform-*d*) δ (multiplicity, number of protons, assignment, coupling constant J in Hz.): 5.06 and 5.16 (AB doublet, 2, C*H*BrC*H*OH, $J = 6.5$), 7.35 (multiplet, 10, aryl *H*).

3. Discussion

The present procedure affords a simple and general method for preparing bromohydrins from alkenes which avoids the heterogeneous solvent systems often used in such reactions. Labeling experiments have demonstrated that the oxygen from the dimethyl sulfoxide appears in the hydroxyl group of the bromohydrin.[5] Therefore the role of the water is to hydrolyze the intermediate β-bromodimethylsulfoxonium ion.

Many alkenes have been converted into their respective bromohydrins by this procedure, usually with high regio- and stereoselectivity (Table I).[5,6] Although the regioselectivity of the addition generally follows Markovnikov's rule, the opposite orientation is observed with alkenes bearing the bulky *tert*-butyl substituent (entries 7–9). The reaction of conjugated dienes with *N*-bromosuccinimide in aqueous dimethyl sulfoxide also occurs in a regio- and stereoselective manner, leading exclusively to vicinal bromohydrins in high yield.[7]

When electron-withdrawing groups are attached to the double bond, the reaction is strongly inhibited and may fail completely. In such cases, the bromide anion, produced by the reaction of dimethyl sulfoxide with *N*-bromosuccinimide, competes with the dimethyl sulfoxide for the bromonium (or bromo carbonium) ion, an intermediate of the reaction. Thus, dibromide may accompany recovered alkene or any bromohydrin formed. Similarly, exogenous anions often compete with dimethyl sulfoxide for the cation.[6]

erythro-2-Bromo-1,2-diphenylethanol has been prepared by reaction of (*E*)-stilbene with *N*-bromoacetamide in buffered aqueous acetone,[3] by addition of hydrogen bromide to (*E*)-stilbene oxide,[4] and by reaction of (*E*)-stilbene with bromotrinitromethane in dimethyl sulfoxide followed by hydrolysis.[8]

TABLE I
BROMOHYDRINS FROM ALKENES WITH *N*-BROMOSUCCINIMIDE IN AQUEOUS DIMETHYL SULFOXIDE

Entry	Alkene	Bromohydrin	Yield (%)[a]
1	(*Z*)-$C_6H_5CH{=}CHC_6H_5$	*threo*-$C_6H_5CH(OH)CH(Br)C_6H_5$	82
2	(*E*)-$C_6H_5CH{=}CHCH_3$	*erythro*-$C_6H_5CH(OH)CH(Br)CH_3$	92
3	(*Z*)-$C_6H_5CH{=}CHCH_3$	*threo*-$C_6H_5CH(OH)CH(Br)CH_3$	95
4	$C_6H_5CH{=}CH_2$	$C_6H_5CH(OH)CH_2Br$	76
5	$C_6H_5{-}C(CH_3){=}CH_2$	$C_6H_5C(CH_3)(OH)CH_2Br$	89
6	$C_6H_5CH_2CH{=}CH_2$	$C_6H_5CH_2CH(OH)CH_2Br$	83
7	(*E*)-$(CH_3)_3CCH{=}CHCH_3$	*erythro*-$(CH_3)_3CCH(Br)CH(OH)CH_3$	90
8	(*Z*)-$(CH_3)_3CCH{=}CHCH_3$	*threo*-$(CH_3)_3CCH(Br)CH(OH)CH_3$	90
9	$(CH_3)_3CCH{=}CH_2$	$(CH_3)_3CCH(Br)CH_2OH$	89
10	$(CH_3)_3CC(CH_3){=}CH_2$	$(CH_3)_3CC(CH_3)(OH)CH_2Br$	60[b]

[a] Average yield from two or more runs.
[b] Accompanied by 24% dibromide.

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(*E*)-Stilbene (8); Benzene, 1,1'-(1,2-ethenediyl)bis-, (*E*)- (9); (103-30-0)

Dimethyl sulfoxide: Methyl sulfoxide (8); Methane, sulfinylbis- (9); (67-68-5)

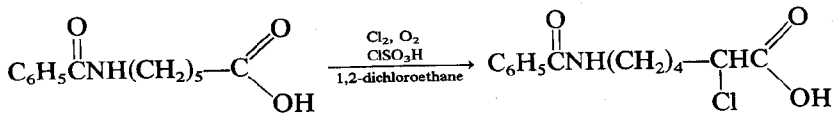
Succinimide, *N*-bromo- (8); 2,5-Pyrrolidinedione, 1-bromo- (9); (128-08-5)

Ethanol, 2-bromo-1,2-diphenyl-, *erythro*- (8, 9); (10368-43-1)

Succinimide (8); 2,5-Pyrrolidinedione (9); (123-56-8)

α-CHLORINATION OF CARBOXYLIC ACIDS MEDIATED BY CHLOROSULFONIC ACID: ε-BENZOYLAMINO-α-CHLOROCAPROIC ACID

(Hexanoic acid, 6-benzoylamino-2-chloro-)



Submitted by YOSHIRO OGATA, TOSHIYUKI SUGIMOTO, and MORIO INAISHI[1]
Checked by ANGELA HOPPMANN and GEORGE BÜCHI

1. Procedure

Caution! Since chlorine is poisonous, this procedure should be conducted in an efficient hood. Chlorosulfonic acid is a strong skin irritant and should be handled with gloves and a protective face shield.

A 500-ml., four-necked, round-bottomed flask is equipped with an air-tight mechanical stirrer (Note 1), a gas dispersion tube with a porous glass frit, a Dimroth reflux condenser (Note 2), and a thermometer. The top of the condenser is connected to a series of three traps with a piece of polyvinyl chloride tubing (Figure 1). The first trap is empty, and the other two contain aqueous 10*N* sodium hydroxide. The gas dispersion tube extends to near the bottom of the flask, just above the stirrer blade, and is connected to a gas-mixing chamber having two inlet tubes, one for oxygen and the other for chlorine. The flask is charged with 47.1 g. (0.2 mole) of ε-benzoylaminocaproic acid (Note 3) and 200 ml. of 1,2-dichloroethane, and the joints are lubricated with silicone grease. The solution is stirred and heated to 60–70°, and then 25.5 g.

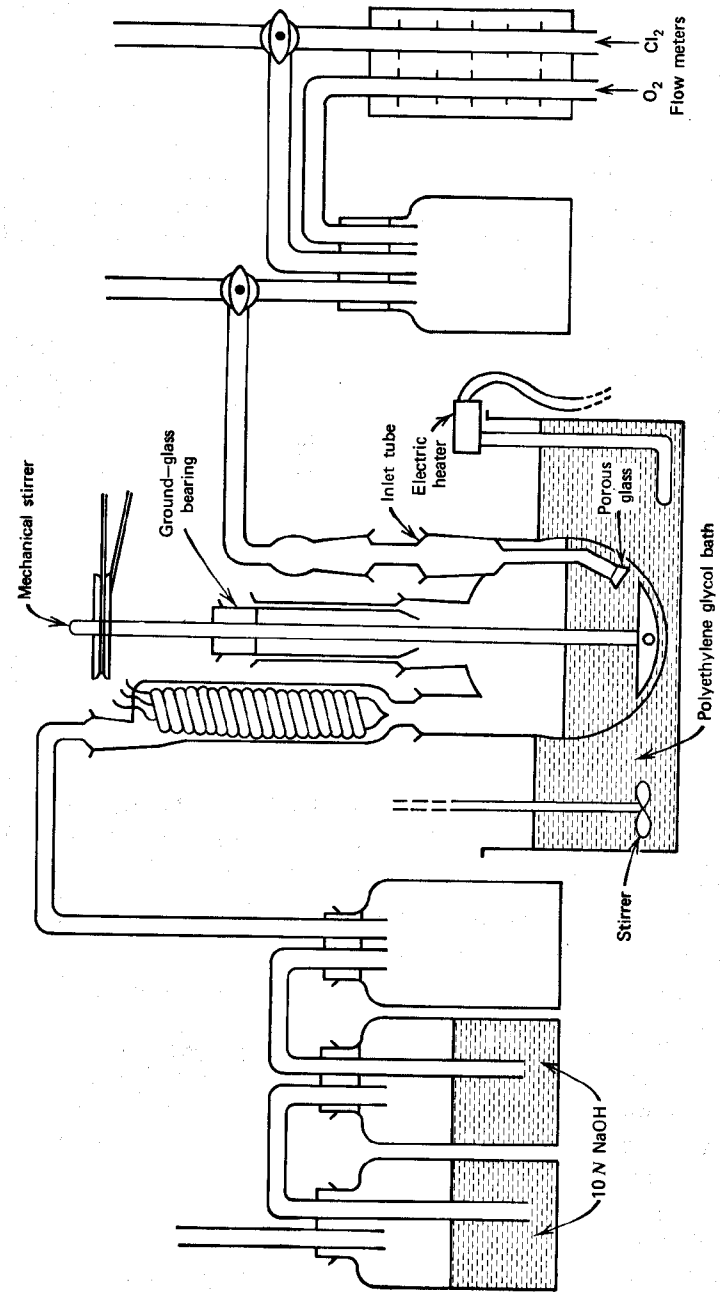


Figure 1.

(0.22 mole) of chlorosulfonic acid (Note 4) is added gradually. A 2:1 (v/v) mixture of gaseous chlorine and oxygen (Note 5) is bubbled into the flask for 3 hours while the contents are stirred and heated at reflux. The chlorine-oxygen gas flow is discontinued, and nitrogen is passed through the reaction mixture for 1 hour at 60–70° to remove chlorine remaining in solution. The flask is stoppered, allowed to stand for 1 hour at room temperature, and stored in a refrigerator for 12 hours. The supernatant liquid is removed, and *ca.* 800 ml. of aqueous 1*N* sodium hydroxide is added to the solid remaining in the flask with ice cooling. Nitrogen is bubbled through the alkaline solution for 30 minutes to expel 1,2-dichloroethane. The solution is decolorized with 5 g. of activated carbon, mixed with *ca.* 400 g. of ice, and acidified to a pH of *ca.* 6 with 6*N* hydrochloric acid. If available, a few seed crystals of ε-benzoylamino-α-chlorocaproic acid are added to the solution to facilitate crystallization. After 1 hour, more 6*N* hydrochloric acid (Note 6) is added gradually until the pH is lowered to 1. An hour later the precipitate is filtered and washed thoroughly with 300 ml. of cold water until sulfate ion in the aqueous wash is no longer detectable with a test solution of barium chloride.

After drying under reduced pressure, the crude, crystalline ε-benzoylamino-α-chlorocaproic acid weighs 39.1–43.1 g. (72–80%) and melts at 138–140°. The product is dissolved in 320 ml. of hot 95% ethanol, 480 ml. of boiling water is added, and the resulting solution is allowed to cool slowly. The crystals are collected, washed with cold water, and dried, affording 26.1–28.2 g. (48–52%) of pure ε-benzoylamino-α-chlorocaproic acid, m.p. 143–144° (Note 7).

2. Notes

1. Vigorous stirring action is necessary to disperse the heavy, viscous mixture. The use of a magnetic stirrer is not advisable since the mixture may separate into two layers. A mechanical stirrer with ground-glass shaft and bearing lubricated with 1,2-dichloroethane is recommended.

2. A Dimroth condenser has an internal, spiral cooling tube with the inlet and outlet both connected at the top. Spiral condensers of this type are available from Ace Glass Incorporated, Vineland, New Jersey 08360. A Dimroth condenser is recommended for use with refluxing liquids that boil up to 160°.[2] Since the points of sealing are situated above the zone with a high temperature gradient, the risk of cracking from thermal stress is minimized. The α-chlorination of aliphatic acids by this procedure is usually carried out at 110–140° (see Table I). The submitters circulated ice-cold water through the condenser.

3. ε-Benzoylaminocaproic acid was prepared by the reaction of benzoyl chloride with ε-aminocaproic acid, as described by Eck and Marvel.[3]

4. Chlorosulfonic acid was purified by distillation before use, b.p. 86–88° (33 mm.).

5. The flow rates of the two gases are regulated by flow meters inserted in parallel between the gas-mixing chamber and the chlorine and oxygen tanks. Appropriate flow rates for chlorine and oxygen are 80–100 and 40–50 ml. per minute, respectively. The checkers purchased gas flow meters from Arthur H. Thomas Company, Philadelphia, Pennsylvania.

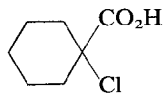
6. If the warm alkaline solution is acidified rapidly with 6*N* hydrochloric acid, the product is likely to separate as an oil.

7. A melting point of 145–147° has been reported.[4] The submitters performed a high-pressure liquid chromatographic analysis on a 25 × 0.2 cm. column packed with porous, dichlorodimethylsilane-treated silica gel (Yanapak DMS). With 40:60 (v/v) methanol–water as carrier liquid and a flow rate of 80–100 ml. per hour, the product appeared as a single peak. The spectral properties of the product are as follows: infrared (potassium bromide) cm.$^{-1}$: 3360, 3040, 2920, 1700, 1600, 1550, 820, 770, 720, 690; proton magnetic resonance (dimethyl sulfoxide-d_6) δ (multiplicity, number of protons, assignment, coupling constant *J* in Hz.): 1.2–2.2 (multiplet, 6, $CH_2CH_2CH_2$), 3.0–3.4 (multiplet, 2, CH_2N), 4.40 (triplet, 1, $CHCl$, $J = 7$), 7.2–7.9 (multiplet, 5, C_6H_5), 8.40 (broad triplet, 1, NH, $J = 6$).

3. Discussion

The present procedure, a modification of one reported earlier by the submitters,[5] has been applied to the α-chlorination of a series of aliphatic carboxylic acids (Table I).[6] In these reactions

TABLE I
α-CHLORO CARBOXYLIC ACIDS PREPARED BY CHLORINATION IN THE PRESENCE OF CHLOROSULFONIC ACID AND OXYGEN[a]

Entry	α-Chloro Acid	Scale (mole)	Temperature (°)	Yield[b] (%)
1	$(CH_3)_2CClCO_2H$	0.45	120	75
2	$CH_3CH_2CHClCO_2H$	0.45	120	82[c]
3	$(CH_3)_2CHCHClCO_2H$	0.60	140	73
4	$CH_3(CH_2)_2C(CH_3)ClCO_2H$	0.35	120	81
5	$CH_3CH_2CH(CH_3)CHClCO_2H$	0.18	120	78
6	$(CH_3)_2CHCH_2CHClCO_2H$	0.16	120	79[d]
7		0.23	110	73

[a] A 4:1:0.04 molar ratio of carboxylic acid, chlorosulfonic acid, and chloranil was used. A 2:1 mixture of chlorine and oxygen was passed into the reaction for 3 hours.
[b] The yields were determined by gas chromatographic analysis after esterification of aliquots with sulfuric acid and methanol in 1,2-dichloroethane.
[c] β-Chloro acid was also formed in 1.6% yield.
[d] β-Chloro acid was also formed in 6.4% yield.

solvent (1,2-dichloroethane) was unnecessary, 0.25 molar equivalents of chlorosulfonic acid was sufficient, and higher temperatures in the range of 110–140° were employed. The α-chloro acids were converted efficiently to the corresponding methyl esters for characterization by reaction with methanol and a catalytic amount of concentrated sulfuric acid in 1,2-dichloroethane at reflux for

10 hours.[7] The methyl esters of the α-chloro acids shown in entries 3–6 have not been previously prepared.

Chlorosulfonic acid is particularly effective at mediating the α-chlorination of carboxylic acids, evidently owing to both its high acidity and its ability to render the reaction mixture more nearly homogeneous than other acidic catalysts. The function of oxygen is to scavenge free radicals, thereby suppressing the free radical chlorination at other positions of the carboxylic acid.[8] The chlorination of isovaleric acid (entry 3) in the absence of oxygen gives an appreciable amount of β-chloro acid. In the presence of oxygen only trace amounts (0–6.4%) of the β-chloro, or other isomers, were formed in the chlorinations shown in the table despite the tertiary hydrogens present in entries 3, 5, and 6.

ε-Benzoylamino-α-chlorocaproic acid has been previously prepared by chlorination of ε-benzoylaminocaproic acid with sulfuryl chloride in the presence of iodine.[4] The corresponding bromo analog has been obtained by reaction with bromine and red phosphorous and subsequent hydrolysis.[9,10] ε-Benzoylamino-α-halocaproic acid is an intermediate in the synthesis of *d,l*-lysine dihydrochloride.[4,11]

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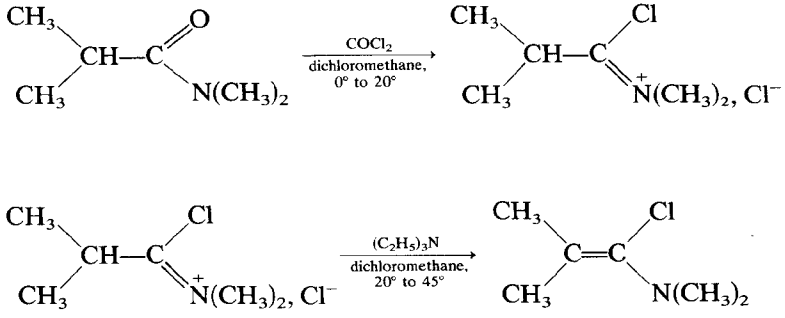
Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

ε-Benzoylamino-α-chlorocaproic acid: Hexanoic acid, 6-benzamido-2-chloro- (8); Hexanoic acid, 6-benzoylamino-2-chloro- (9); (5107-15-3)

Chlorosulfonic acid: Sulfuric acid, chloro- (8, 9); (7790-94-5)
ε-Benzoylaminocaproic acid: Hexanoic acid, 6-benzamido- (8); Hexanoic acid, 6-benzoylamino- (9); (956-09-2)
Ethane, 1,2-dichloro- (8, 9); (107-06-2)
Benzoyl chloride (8, 9); (98-88-4)
ε-Aminocaproic acid: Hexanoic acid, 6-amino- (8, 9); (60-32-2)
Isovaleric acid (8); Butanoic acid, 3-methyl- (9); (503-74-2)
ε-Benzoylamino-α-bromocaproic acid: Hexanoic acid, 6-benzamido-2-bromo- (8); Hexanoic acid, 6-benzoylamino-2-bromo- (9); (—)
Lysine (8, 9); (70-54-2)

α-CHLORO ENAMINES, REACTIVE INTERMEDIATES FOR SYNTHESIS: 1-CHLORO-*N,N*,2-TRIMETHYLPROPENYLAMINE



Submitted by B. HAVEAUX, A. DEKOKER, M. RENS, A. R. SIDANI, J. TOYE, and L. GHOSEZ[1]
Checked by MASAYUKI MURAKAMI, MITSURU YOSHIOKA, and WATARU NAGATA

1. Procedure

Caution! Phosgene is highly toxic. This preparation should be carried out in a well-ventilated hood.

A. 1-*Chloro*-N,N,2-*trimethylpropylideniminium chloride.* A 1-l., three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a pressure-equalizing dropping funnel, an inlet tube

connected to a graduated trap through a flexible polyethylene tube, and a dry-ice condenser connected to a series of three traps. The first and last traps in the series contain sulfuric acid and 10% potassium hydroxide, respectively, and the middle trap is left empty, as shown in Figure 1. Phosgene (85–100 ml., 1.2–1.4 moles) (Note 1) is condensed in the graduated trap which is cooled in a dry ice–acetone bath. The flask is charged with 200 ml. of anhydrous dichloromethane (Note 2) and cooled in an ice–salt bath. The liquid phosgene is slowly poured into the flask (Note 3), the inlet tube is replaced by a thermometer, and 115 g. (1 mole) of freshly distilled *N,N*-dimethylisobutyramide (Note 4) in 150 ml. of anhydrous dichloromethane is added dropwise from the dropping funnel into the flask over 20 minutes. The temperature is maintained at 0° during this time and then is gradually raised to room temperature within *ca.* 1 hour. The gas evolution becomes vigorous, and the phosgene begins to boil. The reaction mixture containing a white precipitate is left overnight at room temperature. The flask is prepared for distillation and connected to a water pump (Note 5) to maintain a slightly reduced pressure in the system. The excess phosgene and most of the solvent are removed by warming the flask in a water bath at *ca.* 50°, and collected in an ice-cold receiver (Note 6). The white or pale-yellow solid remaining in the flask is 1-chloro-*N,N*,2-trimethylpropylideniminium chloride, which is used directly in Part B.

B. 1-*Chloro*-N,N,2-*trimethylpropenylamine.* The flask is equipped with a dropping funnel, a mechanical stirrer, and a reflux condenser that is protected from moisture by connecting it to a sulfuric acid trap. The iminium chloride salt is suspended in 200 ml. of anhydrous dichloromethane, and then 140 g. (1.4 moles) of triethylamine (Note 7) is slowly added to the mixture from the dropping funnel with vigorous stirring over 1 hour (Note 8). The temperature rises to 45°, and the solvent begins to reflux. The resulting suspension is stirred at room temperature for an additional 2 hours, after which 150 ml. of dry, low-boiling petroleum ether (Note 9) is added to complete the precipitation of triethylamine hydrochloride (Note 10). The mixture is quickly filtered under nitrogen (Note 11) into a 1-l. round-bottomed flask through an Iena sintered-glass filter. A 300-ml. portion of petroleum ether is used to wash the flask and the triethylamine

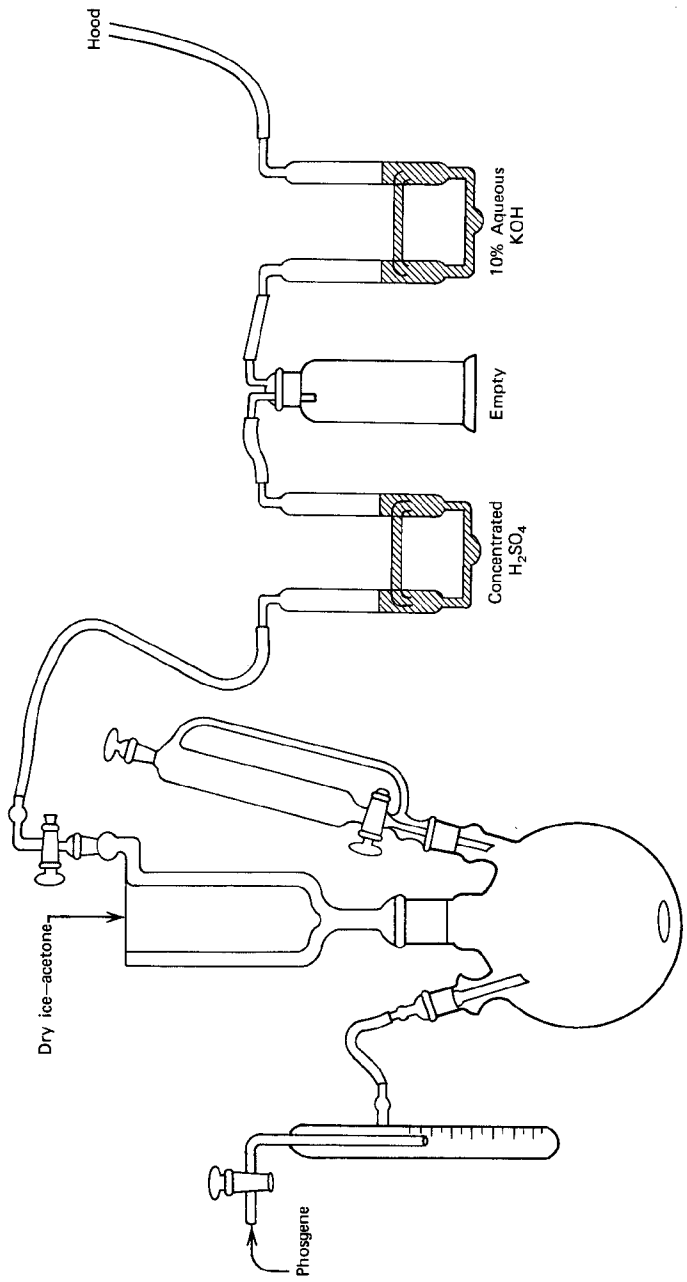


Figure 1.

hydrochloride on the filter. The solvent is removed by distillation under nitrogen. Further distillation through a Vigreux column under nitrogen gives 93–103 g. (69–77%) of 1-chloro-*N*,*N*,2-trimethylpropenylamine, b.p. 125–130° (760 mm.) (Notes 12 and 13). The compound is very sensitive to humidity and should be immediately stored in ampoules (Note 14).

2. Notes

1. The submitters used technical-grade phosgene purchased from Gardner Cryogenics Europe N. V., 1800 Vilvoorde, Belgium.

2. Technical-grade dichloromethane was dried by refluxing over phosphorus pentoxide for 24 hours and distilled.

3. Alternatively phosgene may be allowed to distill into the flask cooled in a dry ice–acetone bath. For this operation the inlet tube should extend to the bottom of the flask.

4. Following a procedure reported in the literature,[2] the checkers prepared *N*,*N*-dimethylisobutyramide, b.p. 67–68° (15 mm.), in 85% yield by treating reagent-grade isobutyryl chloride with 2 molar equivalents of reagent-grade dimethylamine in anhydrous ethyl ether at 0°. The reported boiling point for *N*,*N*-dimethylisobutyramide is 175–176° (744 mm.)[2]. Isobutyrl chloride and dimethylamine were both purchased from Tokyo Kasei Kogyo Company Ltd., Tokyo, Japan. These two reagents are also available from Aldrich Chemical Company, Inc., and the Specialty Gas Division, J. T. Baker Chemical Company, respectively.

5. A phosphorus pentoxide tube is placed between the water pump and the distillation apparatus.

6. The submitters found that filling the flask with argon helped to reduce exposure to moisture in the air.

7. The submitters used Baker-grade triethylamine purchased from J. T. Baker Chemicals N.V., P.O. Box 1, Deventer, Holland, after distillation from potassium hydroxide.

8. The reaction is exothermic. The checkers found that the yield of the final product was raised from 57% in the first run to 71% in the second and third runs when the triethylamine was added at 30–34° with slight cooling. Another procedural change made by the checkers in Part A in these last two runs was that the dry ice condenser was kept in place for more than 8 hours after the

addition of *N,N*-dimethylisobutyramide was completed. In the first run the condenser was removed after 20 minutes.

9. The submitters used technical petroleum ether, b.p. $<70°$, which was distilled from sodium wire.

10. Leaving the reaction mixture overnight before filtration did not affect the yield.

11. A slow stream of dry nitrogen was passed through an inverted funnel that was placed over the filtration apparatus.

12. The checkers collected several fractions during the distillation. Early fractions boiling at 100–125° (760 mm.) were shown to be a mixture of the product and triethylamine. The product from two runs carried out at one-half scale was collected in two main fractions amounting to 2.2–5.8 g., b.p. 125–130° (760 mm.), and 41.7–45.4 g., 130–134° (760 mm.). The total yield was 47.5–47.6 g. (71%), b.p. 125–134°. The submitters obtained 105–110 g. (78–82%), b.p. 129–130° (760 mm.).

13. The checkers obtained an analysis on the distilled product. Analysis calculated for $C_6H_{12}NCl$: C, 53.93; H, 9.05; N, 10.48; Cl, 26.54. Found: C, 54.51; H, 9.21; N, 10.69; Cl, 26.49. The spectral properties of the product are as follows: infrared (carbon tetrachloride) cm.$^{-1}$: 1653, 1470, 1451, 1295, 1124, 1013; proton magnetic resonance (*ca.* 15% w/v in carbon tetrachloride) δ (multiplicity, number of protons, assignment): 1.73 (singlet, 3, allylic CH_3), 1.79 (singlet, 3, allylic CH_3), 2.37 (singlet, 6, two N—CH_3); proton magnetic resonance (about 15% w/v in chloroform-*d*) δ (multiplicity, number of protons, assignment): 1.77 (singlet, 6, two allylic CH_3) and 2.38 (singlet, 6, two N—CH_3); mass spectrum (225°, 70 e.v.) *m/e* (relative intensity): 135 ($M+2$, 24), 133 (M, 77), 98 (100), 83 (56), 82 (23), 72 (31), 44 (36), 42 (60).

14. The tubes should be sealed immediately to avoid hydrolysis. In spite of this precaution, a light precipitate is always formed.

3. Discussion

1-Chloro-*N,N*,2-trimethylpropenylamine has been prepared by reaction of 2-methylpropenylidenebis(dimethylamine) with phosphorous trichloride or dichlorophenylphosphine.[3] The present method[4] is far more convenient and general. The reagents are

inexpensive, the amide reactants are readily available, and the procedure is applicable to the synthesis of various α-chloro enamines on a large scale with only minor modifications (Table I).[5]

The reaction of the more basic amides with phosgene is exothermic (*Caution!*); consequently the reaction mixture must be cooled in an ice bath. With the less reactive amides (e.g., entries 2, 4, 5, and 8–10), however, the reaction often requires several days. It can be accelerated by the addition of catalytic amounts of *N,N*-dimethylformamide. With the monosubstituted acetamides or acetanilides, the solution must be saturated with gaseous hydrogen chloride before adding phosgene to avoid the formation of β-chlorocarbonyl α-chloro enamines resulting from elimination of hydrogen chloride and acylation of the α-chloro enamine with phosgene. The subsequent elimination reaction must be conducted with an excess of triethylamine in ethyl ether, carbon tetrachloride, or petroleum ether. Dichloromethane and chloroform are not suitable since these solvents promote the formation of condensation products to a considerable extent. With the exceptions of entries 7–10, α-chloroenamines derived from monosubstituted acetamides are unstable and should be kept in solution at concentrations below 1 *M*.

Most α-chloro enamines can be readily converted into the corresponding α-fluoro enamines by reaction with potassium or cesium fluoride or to the iodo enamines by reaction with potassium iodide.[6] All α-halo enamines are highly hygroscopic and must be stored in sealed tubes.

α-Halo enamines are useful organic reagents that show versatile chemical behavior and have great synthetic potential.[5] As enamines derived from carboxylic acid halides, they react with a variety of electrophilic reagents on C-2 to give, after hydrolysis, a carboxamide substituted at the α-position. Moreover, spontaneous or catalyzed ionization leads to keteniminium ions that are strongly electrophilic and add various nucleophilic reagents at C-1.[5,7-9] Keteniminium ions are also capable of undergoing [2+2]-cycloaddition reactions with olefins,[10] acetylenes,[11] and imines[12] extremely readily. 1-Chloro-*N,N*.2-trimethylpropenylamine is also a highly effective reagent for the replacement of hydroxyl groups by chlorine, a reaction that occurs at temperatures as low as −40°

TABLE I

SYNTHESIS OF α-CHLORO ENAMINES FROM AMIDES

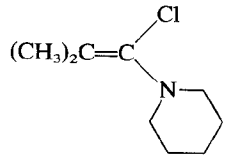
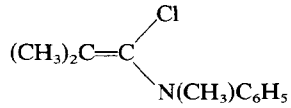
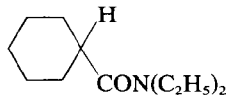
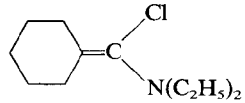
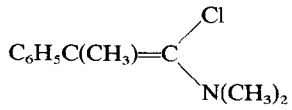
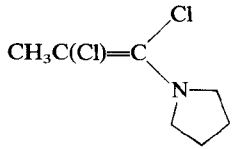
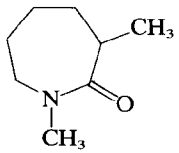
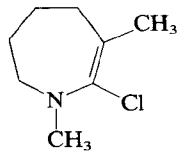
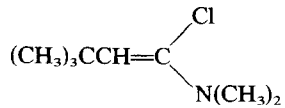
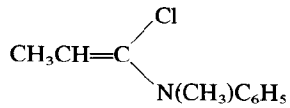
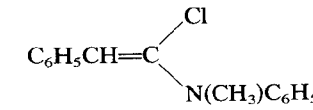
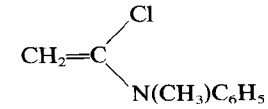
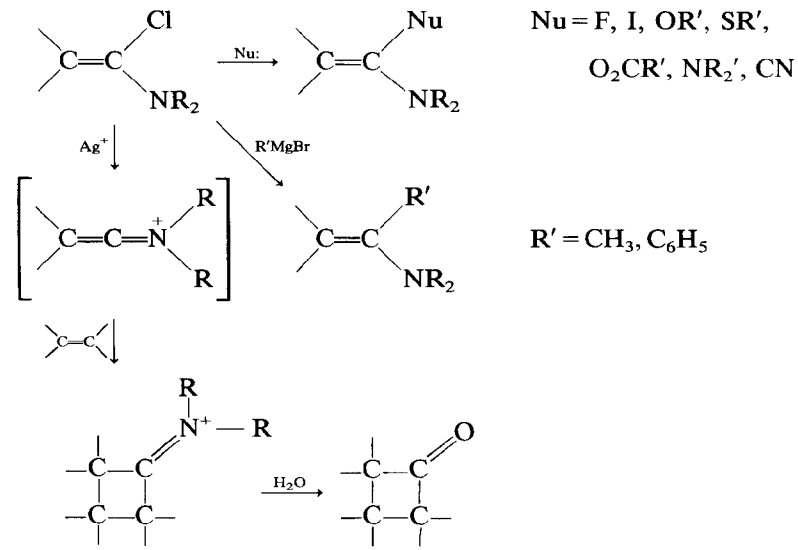
Entry	Amide	α-Chloro Enamine	Yield (%)
1			85
2	$(CH_3)_2CHCON(CH_3)C_6H_5$		55–79
3			40
4	$C_6H_5CH(CH_3)CON(CH_3)_2$		76[a]
5	$CH_3CH(Cl)CON$ 		60–70[a]
6			75
7	$(CH_3)_3CCH_2CON(CH_3)_2$		65[a]
8	$CH_3CH_2CON(CH_3)C_6H_5$		45–62[a]

TABLE I (*Contd.*)

Entry	Amide	α-Chloro Enamine	Yield (%)
9	$C_6H_5CH_2CON(CH_3)C_6H_5$		45
10	$CH_3CON(CH_3)C_6H_5$		42

[a] The product is a mixture of *cis* and *trans* isomers.

and under neutral conditions.[5] A summary of some of the reactions of α-chloro enamines follows.



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3. H. Weingarten, *J. Org. Chem.*, **35,** 3970 (1970).
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5. For a review see L. Ghosez and J. Marchand-Brynaert, "α-Halo Enamines and Keteniminium Salts" in H. Böhme and H. G. Viehe, Eds., "Iminium Salts in Organic Chemistry," Part 1 Vol. 9 in the series "Advances in Organic Chemistry," E. C. Taylor, Ed., John Wiley & Sons, Wiley-Interscience, New York, 1976, p. 421.
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11. C. Hoornaert, A. M. Hesbain-Frisque, and L. Ghosez, *Angew. Chem. Int. Ed. Engl.*, **14,** 569 (1975).
12. M. De Poortere, J. Marchand-Brynaert, and L. Ghosez, *Angew. Chem. Int. Ed. Engl.*, **13,** 268 (1974).

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Propenylamine, 1-chloro-*N,N*,2-trimethyl- (8); 1-Propen-1-amine, 1-chloro-*N,N*,2-trimethyl- (9); (26189-59-3)

1-Chloro-*N,N*,2-trimethylpropylideniminium chloride: Ammonium, (1-chloro-2-methylpropylidene)-*N,N*-dimethyl-, chloride (8); Methanaminium, *N*-(1-chloro-2-methylpropylidene)-*N*-methyl-, chloride (9); (52851-35-1)

Phosgene (8); Carbonic dichloride (9); (75-44-5)

N,N-Dimethylisobutyramide: Propionamide, *N,N*,2-trimethyl- (8); Propanamide, *N,N*,2-trimethyl- (9); (21678-37-5)

Triethylamine (8); Ethanamine, *N,N*-diethyl- (9); (121-44-8)

Triethylamine hydrochloride (8); Ethanamine, *N,N*-diethyl-, hydrochloride (9); (554-68-7)

Isobutyryl chloride (8); Propanoyl chloride, 2-methyl- (9); (79-30-1)

Dimethylamine (8); Methanamine, *N*-methyl- (9); (124-40-3)

2-Methylpropenylidenebis(dimethylamine): 1-Propene-1,1-diamine,*N,N,N',N'*,2-pentamethyl- (8, 9); (10596-50-6)

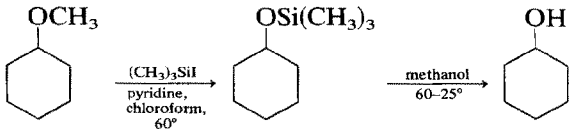
Phosphorus chloride (PCl_3) (8); Phosphorous trichloride (9); (7719-12-2)

Dichlorophenylphosphine: Phosphonous dichloride, phenyl- (8, 9); (644-97-3)

CLEAVAGE OF METHYL ETHERS WITH IODOTRIMETHYLSILANE: CYCLOHEXANOL FROM CYCLOHEXYL METHYL ETHER

(Silane, iodotrimethyl)

$$(CH_3)_3Si{-}O{-}Si(CH_3)_3 \xrightarrow[60\text{–}140^\circ]{Al,\ I_2} (CH_3)_3SiI$$



Submitted by MICHAEL E. JUNG and MARK A. LYSTER[1]
Checked by JOAN HUGUET, H. SHIBUYA, and
and S. MASAMUNE

1. Procedure

A. *Iodotrimethylsilane.* A 250-ml., two-necked, round-bottomed flask is equipped with a magnetic stirring bar, an addition funnel for solids (Note 1), and a reflux condenser bearing a nitrogen inlet. The flask is charged with 5.6 g. (0.21 mole) of aluminum powder (Note 2) and 16.2 g. (0.10 mole) of hexamethyldisiloxane (Note 3) and then purged with nitrogen. The mixture is stirred and heated with an oil bath at 60° as 50.8 g. (0.2 mole) of iodine is added slowly through the addition funnel over 55 minutes (Note 4). The bath temperature is raised to *ca.* 140°, and the mixture is heated at reflux for 1.5 hours. The reflux condenser is removed, and the flask is equipped for distillation at atmospheric pressure. The bath temperature is gradually raised from 140° to 210°, and the clear, colorless distillate is collected. The yield is 32.6–35.3 g. (82–88%) of iodotrimethylsilane, b.p. 106–109° (Notes 5 and 6).

B. *Cyclohexanol from cyclohexyl methyl ether.* In a 25-ml., oven-dried, round-bottomed flask is placed 1.722 g. (0.0151 mole) of cyclohexyl methyl ether (Note 7). The flask is purged with nitrogen and sealed with a rubber septum. By means of oven-dried syringes, 4 ml. of chloroform (Note 8), 0.5 g. (0.5 ml., 0.006 mole) of pyridine (Notes 8 and 9), and 4.8 g. (3.5 ml., 0.024 mole) of

freshly prepared iodotrimethylsilane are injected into the flask in the order specified. When the iodotrimethylsilane is added, the solution becomes slightly yellow and a precipitate appears. The mixture is heated without stirring at 60° for 64 hours, after which the reaction is normally complete (Note 10). Anhydrous methanol (2 ml.) is added, the mixture is cooled to room temperature, and the volatile components (Note 11) are removed on a rotary evaporator. Approximately 10 ml. of anhydrous ethyl ether (Note 12) is added, and the resulting suspension is filtered to remove pyridinium hydroiodide. The flask and the filter cake are washed thoroughly with *ca.* 50 ml. of anhydrous ethyl ether. The ether is evaporated, and the residual oil is purified by chromatography on 70 g. of silica gel packed in anhydrous ether in a 3×50 cm. glass column. The column is eluted with anhydrous ethyl ether, and 5–7 ml. fractions are collected and analyzed by thin-layer chromatography (Note 13). Fractions containing product are combined and evaporated, affording 1.26–1.35 g. (83–89%) of cyclohexanol (Note 14).

2. Notes

1. The submitters have used both an addition funnel with a worm gear delivery similar to those manufactured by Normag and an Erlenmeyer flask attached to the neck of the reaction vessel with a piece of Gooch rubber tubing. Normag addition funnels are available from Lab Glass, Inc., P. O. Box 610, Vineland, New Jersey 08360.

2. The submitters purchased aluminum powder from MC and B Manufacturing Chemists. The metal used by the checkers was supplied by J. T. Baker Chemical Company.

3. Hexamethyldisiloxane is available from Aldrich Chemical Company, Inc. The reagent may also be prepared by the procedure described in the following paragraph. The submitters have used chlorotrimethylsilane purchased from Aldrich Chemical Company, Inc., and Silar Laboratories, Inc. (10 Alplaus Road, Scotia, New York 12302) either as supplied or after distillation from calcium hydride. No appreciable difference in yield was noted between preparations using undistilled and distilled reagent.

A 250-ml., three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a pressure-equalizing dropping funnel, and a reflux condenser bearing a nitrogen inlet. The flask is charged with a solution of 7 g. (0.389 mole) of water in 72.7 g. (76 ml., 0.60 mole) of *N,N*-dimethylaniline and flushed with nitrogen. Stirring is begun, and 62.49 g. (73 ml., 0.575 mole) of chlorotrimethylsilane is added dropwise over 50 minutes. The mixture is heated under reflux in an oil bath at 125–130° for 1 hour. The reflux condenser is replaced by a distilling head, and the product is distilled at atmospheric pressure. The fraction boiling at 98–101° is collected, dried over anhydrous magnesium sulfate, and filtered, affording 43–44 g. (92–94%) of hexamethyldisiloxane as a clear colorless liquid.

4. In a similar procedure for the preparation of iodotrimethylsilane, aluminum, iodine, and hexamethyldisiloxane are combined, and the mixture is heated to reflux.[2] When this procedure was attempted by the submitters, violent exothermic reactions occurred at *ca.* 50–60°. The slow addition of iodine to the warm mixture described in the present procedure leads to a controlled, reproducible reaction.

5. The product is sometimes contaminated with a small amount of hexamethyldisiloxane. The amount of this contaminant is minimized by using longer reaction times and by careful handling to avoid contact with atmospheric moisture. The product may become discolored during storage, in which case it may be purified by distillation from copper powder. The proton magnetic resonance spectrum of iodotrimethylsilane in chloroform-*d* exhibits a singlet at δ 0.71 in the presence of benzene as internal standard.

6. The submitters obtained 69.4 g. (87%) of product when the scale was doubled.

7. Cyclohexyl methyl ether was prepared by the method of Stoocknoff and Benoiton.[3] A 250-ml., two-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum, and a reflux condenser mounted with a nitrogen inlet. The flask is purged with nitrogen and charged with 8 g. (0.2 mole) of a 60% dispersion of sodium hydride in mineral oil. The sodium hydride is washed free of mineral oil with pentane and suspended in 75 ml. of tetrahydrofuran. After 10 g. (0.1 mole) of cyclohexanol is added by syringe, the mixture is heated at reflux for 22 hours. A

28.4-g. (12.5 ml., 0.2 mole) portion of methyl iodide is injected into the flask, and the resulting mixture is heated under reflux for 18 hours. Water and chloroform are added to the cooled mixture. The aqueous layer is extracted with three 50-ml. portions of chloroform, the combined chloroform extracts are dried with anhydrous magnesium sulfate, and the solvents are evaporated. Distillation of the remaining liquid affords 7.1 g. (62%) of cyclohexyl methyl ether, b.p. 133–134°.

8. Chloroform and pyridine were dried over Linde type 4A molecular sieves.

9. Pyridine is added to neutralize small amounts of hydrogen iodide, which is often present in iodotrimethylsilane as a result of hydrolysis by contact with moisture. The amount of by-products, including cyclohexyl iodide, is reduced by the presence of pyridine. Hindered pyridine bases such as 2,6-di-*tert*-butyl-4-methylpyridine[4] have also been used for this purpose by the submitters. The pyridine bases do not appear to react with iodotrimethylsilane.

10. The progress of the reaction may be conveniently monitored by proton magnetic resonance spectroscopy. After 64 hours the signal at δ 3.25 for the methoxyl group of cyclohexyl methyl ether had usually decreased to less than 1% of its original intensity, and peaks for cyclohexyl iodide could not be discerned. Although the submitters found that the reaction time was decreased by using larger amounts of iodotrimethylsilane, 5–10% of cyclohexyl iodide was also produced.

11. The volatile components are chloroform, methanol, methyl iodide, methyl trimethylsilyl ether, and hexamethyldisiloxane.

12. When the submitters used technical-grade ethyl ether, the amount of iodine-containing by-products isolated from the chromatography was increased, and the yield of cyclohexanol was somewhat lower.

13. When an insufficient amount of iodotrimethylsilane was used by the submitters, cyclohexyl methyl ether remained at the end of the reaction and was eluted from the silica gel column before cyclohexanol. When present in the crude product, cyclohexyl iodide was also eluted from the column before cyclohexanol.

14. The identity and purity of the product were determined by gas chromatography, infrared spectroscopy, and proton magnetic resonance spectroscopy by both the submitters and the checkers.

3. Discussion

This procedure describes a convenient method for the preparation of iodotrimethylsilane and illustrates the use of this reagent for ether cleavage with the regeneration of cyclohexanol from cyclohexyl methyl ether.[5] Iodotrimethylsilane was first prepared in the laboratory of F. C. Whitmore by the reaction of trimethylphenylsilane with iodine.[6] The reagent has also been generated *in situ* by halide exchange between magnesium iodide and chlorotrimethylsilane.[7] The present procedure is essentially that reported by Voronkov and Khudobin,[2] with the modification of adding iodine slowly to a mixture of aluminum and hexamethyldisiloxane heated at 60° (see Note 4).

The use of methyl ethers as protecting groups for aliphatic alcohols has been hampered by the difficulty of liberating the alcohol from this inert derivative.[8,9] The cleavage of methyl ethers has been previously accomplished with boron reagents such as boron trichloride,[10] boron trifluoride in acetic anhydride,[11] and diborane or sodium borohydride in the presence of iodine.[12] Two recent modifications of early methods for cleavage of aliphatic methyl ethers utilize hydrogen iodide generated *in situ*[9] and magnesium bromide in acetic anhydride.[13]

The use of iodotrimethylsilane for this purpose provides an effective alternative to known methods. Thus the reaction of primary and secondary methyl ethers with iodotrimethylsilane in chloroform or acetonitrile at 25–60° for 2–64 hours affords the corresponding trimethylsilyl ethers in high yield.[5] The alcohols may be liberated from the trimethylsilyl ethers by methanolysis. The mechanism of the ether cleavage is presumed to involve initial formation of a trimethylsilyl oxonium ion which is converted to the silyl ether by nucleophilic attack of iodide at the methyl group. *tert*-Butyl, trityl, and benzyl ethers of primary and secondary alcohols are rapidly converted to trimethylsilyl ethers by the action of iodotrimethylsilane, probably via heterolysis of silyl oxonium ion intermediates. The cleavage of aryl methyl ethers to aryl trimethylsilyl ethers may also be effected more slowly by reaction with iodotrimethylsilane at 25–50° in chloroform or sulfolane for 12–125 hours,[5] with iodotrimethylsilane at 100–110° in the absence of solvent,[14,15] and with iodotrimethylsilane generated *in situ* from iodine and trimethylphenylsilane at 100°.[15,16]

Alkyl esters are efficiently dealkylated to trimethylsilyl esters with high concentrations of iodotrimethylsilane either in chloroform or sulfolane solutions at 25–80°[17] or without solvent at 100–110°.[14–16] Hydrolysis of the trimethylsilyl esters serves to release the carboxylic acid. Amines may be recovered from *O*-methyl, *O*-ethyl, and *O*-benzyl carbamates after reaction with iodotrimethylsilane in chloroform or sulfolane at 50–60° and subsequent methanolysis.[18] The conversion of dimethyl, diethyl, and ethylene acetals and ketals to the parent aldehydes and ketones under aprotic conditions has been accomplished with this reagent.[19] The reactions of alcohols (or the corresponding trimethylsilyl ethers) and aldehydes with iodotrimethylsilane give alkyl iodides[20] and α-iodosilyl ethers,[21] respectively. Iodomethyl methyl ether is obtained from cleavage of dimethoxymethane with iodotrimethylsilane.[22]

1. Contribution No. 3805 from the Department of Chemistry, University of California, Los Angeles, California 90024.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Disiloxane, hexamethyl- (8, 9); (107-46-0)

Silane, iodotrimethyl- (8, 9); (16029-98-4)

Cyclohexanol (8, 9); (108-93-0)

Ether, Cyclohexyl methyl (8); Cyclohexane, methoxy- (9); (931-56-6)

Silane, chlorotrimethyl- (8, 9); (75-77-4)

Aniline, *N*,*N*-dimethyl- (8); Benzenamine, *N*,*N*-dimethyl- (9); (121-69-7)

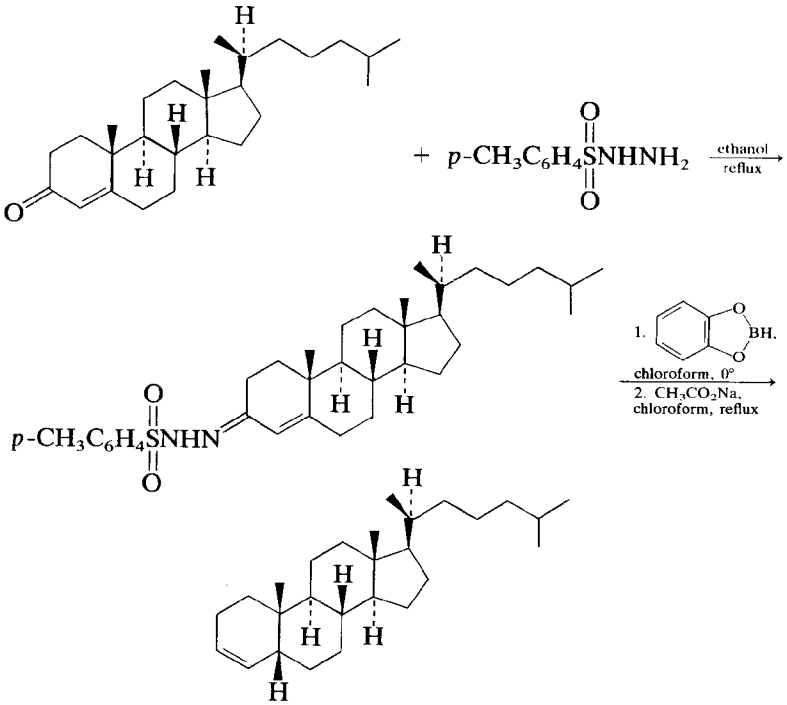
Cyclohexyl iodide: Cyclohexane, iodo- (8, 9); (626-62-0)

Pyridine, 2,6-di-*tert*-butyl-4-methyl- (8); Pyridine, 2,6-bis(1,1-dimethylethyl)-4-methyl- (9); (38222-83-2)

Methyl trimethylsilyl ether: Silane, methoxytrimethyl- (8, 9); (1825-61-2)

Silane, trimethylphenyl- (8, 9); (768-32-1)

CONJUGATE REDUCTION OF α,β-UNSATURATED *p*-TOLUENESULFONYLHYDRAZONES TO ALKENES WITH CATECHOLBORANE: 5β-CHOLEST-3-ENE



Submitted by GEORGE W. KABALKA,[1] ROBERT HUTCHINS,[2] NICHOLAS R. NATALE,[2] DOMINIC T. C. YANG,[3] and VICKY BROACH[3]
Checked by STEVEN J. BRICKNER and MARTIN F. SEMMELHACK

1. Procedure

A. *Cholest-4-en-3-one* p-*toluenesulfonylhydrazone.* A 100-ml., round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser is charged with 10.19 g. (0.0265 mole) of cholest-4-en-3-one (Note 1), 5.53 g. (0.0297 mole) of *p*-toluenesulfonylhydrazide (Note 1), and 17 ml. of 95% ethanol. The solution is stirred and heated at reflux for 10 minutes and

allowed to cool to room temperature. The precipitated solid is collected by filtration and recrystallized from 95% ethanol, affording 13.1–13.3 g (89–91%) of cholest-4-en-3-one *p*-toluenesulfonylhydrazone, m.p. 139–141° (Note 2), in two crops.

B. *5β-Cholest-3-ene.* A dry 100-ml., two-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum, and a reflux condenser connected to a mercury bubbler (Note 3). The flask is charged with 4.98 g. (0.009 mole) of cholest-4-en-3-one *p*-toluenesulfonylhydrazone and 20 ml. of chloroform, and the apparatus is evacuated with an aspirator and filled with nitrogen three times. The solution is stirred and cooled at 0° as 1.29 g. (1.21 ml., 0.0108 mole) of catecholborane (Note 4) is injected through the septum into the flask. Stirring and cooling are continued for 2 hours, after which 2.5 g. (0.018 mole) of sodium acetate trihydrate and 20 ml. of chloroform are added. The mixture is allowed to warm to room temperature over *ca.* 30 minutes, heated under reflux for 1 hour, cooled to room temperature, and filtered. The solid material on the filter is washed with 50 ml. of chloroform, and the combined filtrates are evaporated under reduced pressure. The remaining oil is purified by chromatography on a 5 × 50 cm. column packed with 200 g. of alumina (Note 5). The column is eluted with hexane and 200-ml. fractions are collected. Evaporation of the second 200-ml. fraction affords 2.76–2.95 g. (83–88%) of 5β-cholest-3-ene as a colorless oil which eventually crystallizes on standing, m.p. 48–50°, $[\alpha]_D^{24} = 19.6°$ ($c = 63$, chloroform) (Note 6).

2. Notes

1. Cholest-4-en-3-one and *p*-toluenesulfonylhydrazide are available from Aldrich Chemical Company, Inc. Procedures for the preparation of cholest-4-en-3-one and *p*-toluenesulfonylhydrazide are described in earlier volumes of this series.[4,5] The checkers used 5.70 g. of *p*-toluenesulfonylhydrazide, the purity of which was 97%.

2. The reported[6] melting point is 139–142°.

3. Nitrogen is introduced via a syringe needle that pierces the septum. A positive pressure of nitrogen is maintained in the apparatus during the following operations.

4. Catecholborane with a purity of 95% was purchased from Aldrich Chemical Company, Inc.

5. Activity grade I, neutral alumina was supplied by Brinckmann Instruments, Inc., Westbury, New York. The checkers used a 3×30 cm. column.

6. A thin-layer chromatographic analysis was carried out by the submitters on a precoated silica gel plate (type Q6) purchased from Quantum Industries, 341 Kaplan Drive, Fairfield, New Jersey 07006. The chromatogram was developed with cyclohexane and showed a single spot for the product after visualization by charring with concentrated sulfuric acid. 5β-Cholest-3-ene is reported[7] to melt at 48–49°. The spectral properties of the product are as follows: infrared (chloroform) cm.$^{-1}$: 2926, 1658, 1465, 831, 758, 678; proton magnetic resonance (chloroform-*d*) δ (multiplicity, number of protons, assignment): 0.66 (singlet, 3, C-18 CH_3), 0.82 (singlet, 3, CH_3), 0.92 (singlet, 3, CH_3), 0.94 (singlet, 3, C-19 CH_3), 5.2–5.7 (multiplet, 2, vinyl *H*); mass spectrum *m/e*: 370 (M^+).

The submitters prepared the dibromide derivative, 3α,4β-dibromo-5β-cholestane, m.p. 98–99°. The melting point of the dibromide is reported as 98–100°.[8] The mass spectrum of the dibromide exhibits three molecular ions at *m/e* (relative intensity, assignment): 532 (25%, $C_{27}H_{46}{}^{81}Br^{81}Br$), 530 (50%, $C_{27}H_{46}{}^{79}Br^{81}Br$), 528 (25%, $C_{27}H_{46}{}^{79}Br^{79}Br$).

3. Discussion

The reduction of the *p*-toluenesulfonylhydrazones of α,β-unsaturated ketones and aldehydes with aluminum[9] or boron hydride reagents[10–13] effects a formal "conjugate" hydride transfer and produces alkenes in which the double bond has migrated to the position between the α-carbon and the carbonyl carbon. The mechanism of the reaction is presumed to involve initial reduction of the C=N double bond, elimination of *p*-toluenesufinate to form an allyl diazene, and concerted fragmentation of the diazene with 1,5-hydrogen transfer. One or both of the last two steps may take place during a subsequent hydrolysis. The reductions have been carried out with excess lithium aluminum hydride in tetrahydrofuran,[9] with catecholborane in chloroform at 0° followed by hydrolysis at *ca.* 60° (Procedure A),[10] with sodium cyanoborohydride in 1:1 (v/v) *N,N*-dimethylformamide–sulfolane acidified with concentrated hydrochloric acid at 100–105° (Procedure B),[11,12] and with sodium borohydride in acetic acid at 70° (Procedure C).[13] A selection of examples of these reductions is given in Table I.

This method provides a convenient synthesis of alkenes with the double bond in a relatively unstable position. Thus reduction of the *p*-toluenesulfonylhydrazones of α,β-unsaturated aryl ketones and conjugated dienones gives rise to nonconjugated olefins. Unsaturated ketones with endocyclic double bonds produce olefins with double bonds in the exocyclic position. The reduction of *p*-toluenesulfonylhydrazones of conjugated alkynones furnishes a simple synthesis of 1,3-disubstituted allenes.[14]

The present procedure illustrates this method with the preparation of 5β-cholest-3-ene by reduction of cholest-4-en-3-one *p*-toluenesulfonylhydrazone using catecholborane as the reducing agent.[10,15] The advantages of catecholborane include its high solubility in common aprotic and nonpolar solvents, the low temperatures required for the reduction (0–25°), and the generally mild conditions used. Although the sodium cyanoborohydride and sodium borohydride procedures require higher temperatures, the use of polar solvents and protic conditions offers a valuable complement to the nonpolar, aprotic medium employed in the catecholborane procedure. However, the reduction of cholest-4-en-3-one *p*-toluene-sulfonylhydrazone with sodium cyanoborohydride (Procedure B) gave a 71% yield of a mixture consisting of 5β-cholest-3-ene (32.5%), 5β-cholestane (30.5%), 5α-cholestane (30.5%), and 5α-cholest-3-ene (6.5%).[16]

5β-Cholest-3-ene has been prepared previously by deamination of 5β-cholestan-3β-yl amine,[17] by reduction of a mixture of 4β-bromo-5β-cholestan-3α-ol and its 3β epimer with zinc in acetic acid,[7] and as component of a mixture of cholestenes by Wolff-Kishner reduction of cholest-4-en-3-one.[8]

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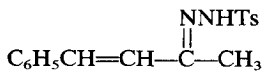
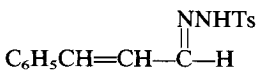
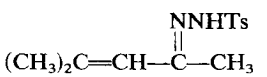
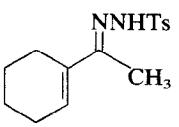
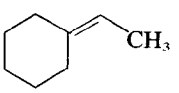
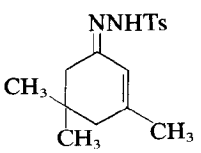
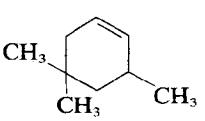
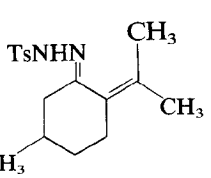
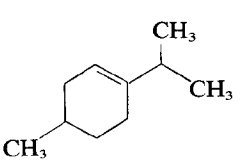
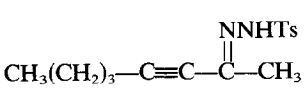
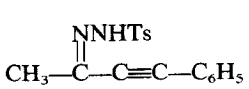
TABLE I

CONJUGATE REDUCTION OF α,β – UNSATURATED *p*-TOLUENESULFONYLHYDRAZONES TO ALKENES

p-Toluenesulfonylhydrazone[a,b]	Alkene[b]	Procedure[c]	Yield (%)
	$C_6H_5CH_2CH{=}CHCH_3$	A B C	72[d] 54 54
	$C_6H_5CH_2CH{=}CH_2$	A B C	53[d] 98[d] 42–56
	$(CH_3)_2CH{-}CH{=}CHCH_3$	A	65[d]
		A B C	77[d] 79 61–72
		A B C	66[e] 4[d,f] 18
		B C	70 51
	$CH_3(CH_2)_3{-}CH{=}C{=}CH{-}CH_3$	A	64
	$CH_3{-}CH{=}C{=}CH{-}C_6H_5$	A	75

[a] The abbreviation Ts stands for *p*-toluenesulfonyl.

[b] The *p*-toluenesulfonylhydrazones and alkenes with acyclic disubstituted double bonds are the *E* isomers.

[c] See text for descriptions of the procedures.

[d] Yield determined by gas chromatography.

[e] Yield determined by proton magnetic resonance spectroscopy.

[f] The cycloalkane was also formed in 32% yield.

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Catecholborane: 1,3,2-Benzodioxaborole (8, 9); (274-07-7)

Cholest-4-en-3-one (8, 9); (601-57-0)

5β-Cholest-3-ene (8); Cholest-3-ene, (5β)- (9); (13901-20-7)

Cholest-4-en-3-one *p*-toluenesulfonylhydrazone: *p*-Toluenesulfonic acid, cholest-4-en-3-ylidene hydrazide (8); Benzenesulfonic acid, 4-methyl-, cholest-4-en-3-ylidene hydrazide (9); (21301-41-7)

p-Toluenesulfonylhydrazide: *p*-Toluenesulfonic acid, hydrazide (8); Benzenesulfonic acid, 4-methyl-, hydrazide (9); (1576-35-8)

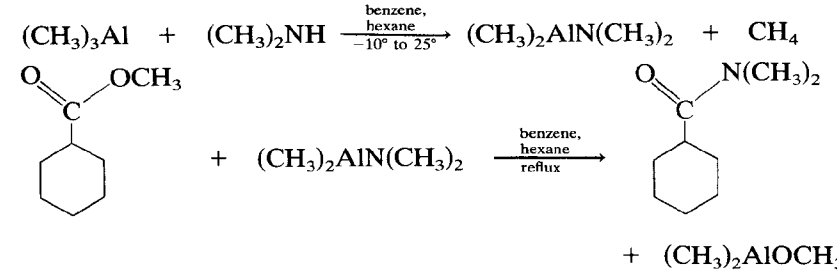
Sodium cyanoborohydride: Borate (1-), cyanotrihydro-, sodium (8); Borate (1-), (cyano-C)trihydro-, sodium, (T-4)- (9); (25895-60-7)

5β-Cholestan-3α-ol, 4β-bromo- (8); Cholestan-3-ol, 4-bromo-(4β, 3α, 5β) (9); (16375-30-7)

5β-Cholestane, 3α,4β-dibromo- (8); Cholestane, 3,4-dibromo-(3α, 4β, 5β) (9); (−)

5β-Cholestan-3β-yl amine: 5β-Cholestan-3β-amine (8); Cholestan-3-amine(3β, 5β) (9); (−)

CONVERSION OF ESTERS TO AMIDES WITH DIMETHYLALUMINUM AMIDES: *N,N*-DIMETHYLCYCLOHEXANECARBOXAMIDE



Submitted by MICHAEL F. LIPTON,[1] ANWER BASHA,[1] and STEVEN M. WEINREB[1,2]
Checked by CHARLES W. HUTCHINS and ROBERT M. COATES

1. Procedure

Caution! See warning regarding the use of benzene, Org. Syn., **58,** 168 (1978). *This procedure should be conducted in a well-ventilated hood.*

A dry 300-ml., two-necked, round-bottomed flask is equipped with a reflux condenser fitted with a nitrogen inlet at its top, a rubber septum, and a magnetic stirring bar. The flask is charged with 100 ml. of benzene (Note 1) and flushed briefly with nitrogen, after which 22 ml. (0.057 mole) of a 25% solution of trimethylaluminum in hexane (Note 2) is injected through the septum into the flask. The solution is stirred and cooled in an ice–salt bath at −10° to −15°, and 2.47 g. (3.64 ml., 0.055 mole) of dimethylamine (Note 3) is added slowly by means of a syringe. Twenty minutes after the addition is completed, the cooling bath is removed, and the contents of the flask are allowed to stir and warm slowly to room temperature over a 45-minute period. A solution of 7.10 g. (0.050 mole) of methyl cyclohexanecarboxylate (Note 4) in 20 ml. of benzene (Note 1) is injected through the septum. The resulting solution is heated under reflux for 22 hours, cooled to room temperature, and hydrolyzed by slow, cautious addition of 82.5 ml. (0.055 mole) of 0.67 *M* hydrochloric acid

(Note 5). The mixture is stirred for 30 minutes to ensure complete hydrolysis. The upper organic layer is separated, and the aqueous layer is extracted with three 25-ml. portions of ethyl acetate. The organic extracts are combined, washed with sodium chloride solution, dried with anhydrous magnesium sulfate, and evaporated under reduced pressure. Distillation of the residual liquid under reduced pressure through a 10-cm. Vigreux column affords a 0.1–0.6 g. forerun of unreacted ester and 6.40–7.25 g. (83–93%) of *N,N*-dimethylcyclohexanecarboxamide, b.p. 100° (5.5 mm.), 57–60° (0.08 mm.) (Note 6).

2. Notes

1. The benzene was dried by distillation from calcium hydride.

2. Trimethylaluminum in hexane solution was purchased from the Alfa Division, Ventron Corporation.

3. Dimethylamine was obtained in a cyclinder from the Linde Division, Union Carbide Chemical Corporation, and condensed in a dry, two-necked flask fitted with a rubber septum and cooled to −78° under nitrogen.

4. Cyclohexanecarboxylic acid is available from Aldrich Chemical Company, Inc., and conveniently esterified by the procedure of Harrison, Haynes, Arthur, and Eisenbraun.[3] A dry 500-ml., round-bottomed flask is charged with 225 ml. of anhydrous methanol, 1.0 ml. of concentrated sulfuric acid, and 41.0 g. (0.320 mole) of cyclohexanecarboxylic acid. The flask is fitted with a Soxhlet extractor containing 53 g. of Linde type 3A molecular sieves and a condenser bearing a calcium chloride drying tube at its top. The solution is heated at reflux for 19 hours and cooled to room temperature. The sulfuric acid is neutralized by adding 3.0 g. of sodium bicarbonate, the salts are filtered, and the filtrate is evaporated under reduced pressure. The remaining liquid is distilled through a 15-cm. Vigreux column at reduced pressure, affording 35.7–36.8 g. (79–81%) of methyl cyclohexanecarboxylate, b.p. 73–76° (13 mm.).

5. To avoid excessive foaming at the beginning of the hydrolysis, the checkers recommend that the hydrochloric acid solution be added 1 or 2 drops at a time. The rate of addition may be increased once the initially vigorous foaming subsides.

6. The spectral properties of the product are as follows: infrared (neat) $cm.^{-1}$: 1640 (C=O); proton magnetic resonance (chloroform-*d*) δ (multiplicity, number of protons, assignment): 1.05–1.95 (multiplet, 10, five CH_2, 2.50 (multiplet, 1, C*H*), 2.94 (singlet, 3, NCH_3), 3.06 (singlet, 3, NCH_3) A boiling point of 107–108° at 7 mm. has been reported for *N,N*-dimethylcyclohexanecarboxamide.[4]

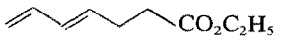
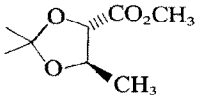
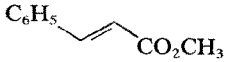
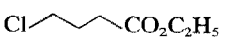
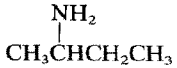
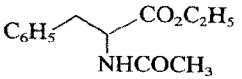
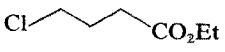
3. Discussion

This procedure,[5] which is based on the work of Ishii and co-workers,[6] affords a mild and general method for converting a wide variety of esters to primary, secondary, and tertiary amides (Table I). While the preparation of the tertiary amide, *N,N*-dimethylcyclohexanecarboxamide, described here is carried out in benzene, aluminum amides derived from ammonia and a variety of primary amines have been prepared by reaction with trimethylaluminum in dichloromethane and utilized for aminolysis in this solvent. Although 1 equivalent of the dimethylaluminum amides from amines was generally sufficient for high conversion within 5–48 hours, best results were obtained when 2 equivalents of the aluminum reagent from ammonia was used. Diethylaluminum amides can also effect aminolysis, but with considerably slower rates.

Although the preparation of carboxamides by direct aminolysis is a well-known and widely studied reaction,[7] the synthetic utility of this process is limited. The reactions generally require long heating periods at relatively high temperatures, and the reagents and catalysts used are usually strong bases.[8] The present procedure has the advantages of lower temperatures and moderate reaction times. The aluminum amides are conveniently prepared *in situ* and appear to be mild, nonbasic reagents compatible with many functional groups.[5] The isolation procedure is simple, since hydrolysis of the aluminum reagents and products affords only methane and acid-soluble aluminum salts. Another advantage is that amides from volatile amines may be prepared without the need to use sealed tubes.

N,N-Dimethylcyclohexanecarboxamide has been prepared by acylation of dimethylamine with cyclohexanecarbonyl chloride[9]

TABLE I
PREPARATION OF AMIDES FROM ESTERS BY AMINOLYSIS WITH DIMETHYLALUMINUM AMIDES[5]

Ester	Amine	Reaction Time (hours)[a]	Isolated Yield of Amide (%)
	NH_3	2[b]	70
	NH_3	16	69
	NH_3	12	86
		48	76
		45	74
		40	77
$CH_3CO_2(CH_2)_3CH_3$	$C_6H_5NH_2$	40	78
$C_6H_5CO_2C_2H_5$	$C_6H_5CH_2NH_2$	25	93
	$(CH_3)_3CNH_2$	45	79

[a] The solvent was dichloromethane except as noted.
[b] Benzene was used as solvent.

and by double alkylation of vinylidenebis(dimethylamine) with 1,5-diiodopentane to the cyclic amidinium salt followed by hydrolysis.[4]

1. This work was carried out at the Department of Chemistry, Fordham University, Bronx, New York 10458.
2. Present address: Department of Chemistry, Pennsylvania State University, University Park, Pennsylvania 16802.

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4. C. F. Hobbs and H. Weingarten, *J. Org. Chem.*, **39,** 918 (1974).
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7. A. L. J. Beckwith, in J. Zabicky, Ed., "The Chemistry of Amides," John Wiley & Sons, Wiley-Interscience, New York, 1970, p. 96.
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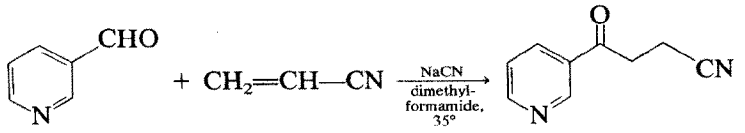
9. A. C. Cope and E. Ciganek, *Org. Syn.*, Coll. Vol. **4,** 339 (1963).

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Cyclohexanecarboxamide, *N,N*-dimethyl- (8, 9); (17566-51-7)
Aluminum, trimethyl- (8, 9); (75-24-1)
Dimethylamine (8); Methanamine, *N*-methyl- (9); (124-40-3)
Methyl cyclohexanecarboxylate: Cyclohexanecarboxylic acid, methyl ester (8, 9); (4630-82-4)
Cyclohexanecarboxylic acid (8, 9); (98-89-5)
Methanol (8, 9); (67-56-1)

CYANIDE-CATALYZED CONJUGATE ADDITION OF ARYL ALDEHYDES: 4-(3-PYRIDYL)-4-OXOBUTYRONITRILE

(3-Pyridinebutanenitrile, γ-oxo)



Submitted by H. STETTER, H. KUHLMANN, AND G. LORENZ[1]
Checked by BENJAMIN G. PADILLA AND GEORGE BÜCHI

1. Procedure

Caution! Sodium cyanide is highly toxic. Care should be taken to avoid direct contact of the chemical or its solutions with the skin, and impervious gloves should be worn to handle the reagent.

In a 1-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, a reflux condenser fitted with a potassium hydroxide drying tube, and a pressure-equalizing dropping funnel mounted with a nitrogen-inlet tube, are placed 4.9 g. (0.1 mole) of finely ground sodium cyanide (Note 1) and 500 ml. of dry *N,N*-dimethylformamide (Note 2). The flask is immersed in a water bath kept at 35°, stirring is begun, and the apparatus is purged thoroughly with dry nitrogen (Note 3). After 15 minutes 107.1 g. (1.0 mole) of 3-pyridinecarboxaldehyde (Note 4) is added dropwise over a period of 30 minutes. The dark brown solution is stirred for another 30 minutes (Note 5), after which 39.8 g. (0.75 mole) of freshly distilled acrylonitrile is added over 1 hour. The solution, now red-orange in color and quite viscous (Note 6), is stirred for 3 hours, 6.6 g. (0.11 mole) of acetic acid is added, and stirring is continued for 5 additional minutes. The solvent is removed with a rotary evaporator, the residue is dissolved in 500 ml. of water, and the solution is extracted continuously (Note 7) with 500 ml. of chloroform for 12 hours (Note 8). The solvent is evaporated under reduced pressure, and the residual liquid is distilled under reduced pressure in a short-path distillation apparatus. An initial fraction consisting mainly of 3-pyridinecarboxaldehyde collects in the cold trap. The product, which boils at 150–152° (0.1 mm.), solidifies in the condenser and is freed by heating the water in the cooling jacket to nearly 100°. The yield of the light-yellow, solid distillate amounts to 94–101 g. (78–84%). Recrystallization from 400 ml. of 2-propanol gives 77–82 g. (64–68% based on acrylonitrile) of 4-(3-pyridyl)-4-oxobutyronitrile as yellow-tinged white crystals, m.p. 70–72° (Note 9).

2. Notes

1. Analytical-grade (*pro analysi*) sodium cyanide was purchased by the submitters from Merck, Darmstadt, Germany, and dried for 24 hours in a vacuum desiccator containing potassium hydroxide pellets. The checkers obtained sodium cyanide from Fisher Scientific Company and dried the reagent in the same manner.

2. The submitters purified technical-grade *N,N*-dimethylformamide by distillation from powdered calcium hydride. The checkers used *N,N*-dimethylformamide that had been dried over Linde type 4A molecular sieves. A small amount of dimethylamine in the solvent does not interfere with the reaction.

3. The drying tube was connected to a Nujol bubbler. A nitrogen atmosphere was maintained during the reaction by passing nitrogen through the apparatus at a rate of *ca.* one bubble per second.

4. 3-Pyridinecarboxaldehyde (nicotinaldehyde) was supplied by Aldrich-Europe, Beerse, Belgium. The checkers purified this reagent by fractional distillation, b.p. 95–97° (15 mm.). The submitters stress that 3-pyridinecarboxaldehyde should be completely free from contamination by the acid. They stirred 150 g. of the aldehyde with 100 g. of potassium carbonate and 300 ml. of ethanol for 12 hours, filtered the suspended solid, and fractionally distilled the filtrate through a 30-cm. Vigreux column using a water aspirator. However, the checkers found that the recovery of aldehyde from this procedure was very low, and recommend vacuum distillation instead. 3-Pyridinecarboxaldehyde is a powerful skin irritant and should be handled with protective gloves.

5. The solution, in which some sodium cyanide remains suspended, becomes quite thick at this stage owing to formation of the benzoin-type dimer of 3-pyridinecarboxaldehyde. An adequate amount of *N,N*-dimethylformamide should be used as solvent to ensure that the dimer does not crystallize.

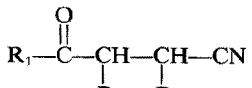
6. Although the solution becomes very viscous at this point, stirring is still possible and should be continued.

7. Continuous extraction is only necessary if the product is appreciably soluble in water. Products such as those shown in Table I may be isolated by extraction in a separatory funnel.

8. The submitters state that the solution need not be dried, since water is removed by azeotropic distillation as the chloroform is evaporated. However, the checkers dried the chloroform solution with anhydrous magnesium sulfate prior to evaporation.

9. The checkers dried the product in a vacuum desiccator for 24 hours to remove all the 2-propanol and obtained 77–79 g. (64–66%), m.p. 70–72°. The yield reported by the submitters was 82–89 g. (68–74%), m.p. 73–74°. The literature[2] melting point is 66–67°. The product has the following spectral properties: 90-MHz. proton magnetic resonance (chloroform-*d*): δ (multiplicity, number of protons, assignment, coupling constant J in Hz.): 2.84

TABLE I
γ-KETONITRILES PREPARED BY CYANIDE-CATALYZED CONJUGATE ADDITION OF ARYL ALDEHYDES TO α,β-UNSATURATED NITRILES



R_2	R_3	Distilled Yield (%)[a]	Recrystallized Yield (%)[b]	B.p. (°) (pressure, mm.)	M.p. (°)
$R_1 = C_6H_5$,	$R_2 = R_3 = H$	71	50[c]	131–134 (0.2)	72–73
$R_1 = C_6H_5$,	$R_2 = H$, $R_3 = CH_3$	73–76	34–37[d]	113–115 (0.1)	42–43
$R_1 = C_6H_5$,	$R_2 = CH_3$, $R_3 = H$	62–64	45–47[d]	111–113 (0.15)	58–59
$R_1 = R_2 = C_6H_5$,	$R_3 = H$	83	56[e]	157–159 (0.05)	83–84
$R_1 = p$-ClC_6H_4,	$R_2 = R_3 = H$	88–89	71–72[c]	152–154 (0.1)	70–71

[a] The distilled products were almost pure.
[b] The recrystallized products were pure, but considerable losses were entailed.
[c] Recrystallized from aqueous ethanol (decolorized with activated carbon).
[d] Recrystallized from ethyl acetate–petroleum ether at −30°.
[e] Recrystallized from 2-propanol.

(triplet, 2, CH_2CN, $J = 6.6$), 3.40 (triplet, 2, CH_2CH_2CN, $J = 6.6$), 7.49 (doublet of doublets, 1, H_5, $J = 4.4$ and 7.3), 8.24 (doublet of triplets, 1, H_4, $J = 2.0$ and 7.3), 8.82 (doublet of doublets, 1, H_6, $J = 2.0$ and 4.5), 9.16 (doublet, 1, H_2, $J = 2.0$); mass spectrum *m/e* (relative intensity): 160 (M^+, 8), 106 (74), 78 (100), 51 (100).

3. Discussion

4-(3-Pyridyl)-4-oxobutyronitrile has been prepared in three steps by Leete, Chedekel, and Bodem,[2] and in one step by Stetter and Schreckenberg[3] using a method closely related to the present procedure. This compound serves as precursor in syntheses of myosmine[2] and various nicotine analogs. Other general methods for the preparation of γ-keto nitriles include the addition of hydrogen cyanide to α,β-unsaturated ketones,[4] the reaction of potassium cyanide with the hydrochlorides of Mannich bases from ketones,[5] and a variety of new methods for nucleophilic acylation.[6]

The addition of 3-pyridinecarboxaldehyde to acrylonitrile is only one example of a wide range of reactions involving the conjugate addition of aldehydes to electron-deficient double bonds. The reaction is not limited to α,β-unsaturated nitriles.[3,7] For example,

γ-diketones[7,8] and γ-keto esters[7,9] may be similarly prepared by addition of aldehydes to α,β-unsaturated ketones and esters. Important advantages of this method are the simplicity of the procedure, the catalytic nature of the reaction, and the avoidance of costly reagents.

The γ-keto nitriles shown in Table I were prepared by the cyanide-catalyzed procedure described here. This procedure is generally applicable to the synthesis of γ-diketones, γ-keto esters, and other γ-keto nitriles. However, the addition of 2-furancarboxaldehyde is more difficult, and a somewhat modified procedure should be employed.[10] Although the cyanide-catalyzed reaction is generally limited to aromatic and heterocyclic aldehydes, the addition of aliphatic aldehydes to various Michael acceptors may be accomplished in the presence of thioazolium ions,[7,11] which are also effective catalysts for the additions.[7,12]

The mechanism of the cyanide- and thioazolium ion-catalyzed conjugate addition reactions[7] is considered to be analogous to the Lapworth mechanism for the cyanide-catalyzed benzoin condensation. Thus the cyano-stabilized carbanion resulting from deprotonation of the cyanohydrin of the aldehyde is presumed to be the actual Michael donor. After conjugate addition to the activated olefin, cyanide is eliminated to form the product and regenerate the catalyst.

1. Institut für Organische Chemie der Rheinisch-Westfälischen Technischen Hochschule Aachen, West Germany.
2. E. Leete, M. R. Chedekel, and G. B. Bodem, *J. Org. Chem.*, **37,** 4465 (1972).
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

4-(3-Pyridyl)-4-oxobutyronitrile: 3-Pyridinebutyronitrile, γ-oxo- (8); 3-Pyridinebutanenitrile, γ-oxo- (9); (36740-10-0)

Formamide, *N,N*-dimethyl- (8, 9); (68-12-2)

Nicotinaldehyde (8); 3-Pyridinecarboxaldehyde (9); (500-22-1)

Acrylonitrile (8); 2-Propenenitrile (9); (107-13-1)

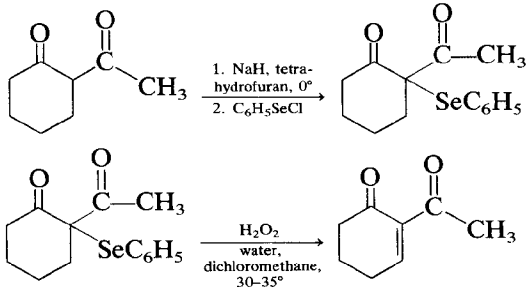
Dimethylamine (8); Methanamine, *N*-methyl- (9); (124-40-3)

Benzoin (8); Ethanone, 2-hydroxy-1,2-diphenyl- (9); (119-53-9)

Myosmine: Pyridine, 3-(1-pyrrolin-2-yl)- (8); Pyridine, 3-(3,4-dihydro-2*H*-pyrrol-5-yl)- (9); (532-12-7)

2-Furaldehyde (8); 2-Furancarboxaldehyde (9); (98-01-1)

α,β-DEHYDROGENATION OF β-DICARBONYL COMPOUNDS BY SELENOXIDE ELIMINATION: 2-ACETYL-2-CYCLOHEXEN-1-ONE



Submitted by JAMES M. RENGA and HANS J. REICH[1]
Checked by ALBERT W. M. LEE and ROBERT V. STEVENS

1. Procedure

Caution! Most selenium compounds are toxic; consequently care should be exercised in handling them. The hydrogen peroxide oxidation of selenides is highly exothermic, acid-catalyzed, and autocatalytic. The procedure given for adding the hydrogen peroxide solution should be carefully followed.

A. *2-Acetyl-2-phenylselenocyclohexanone.* A 500-ml., three-necked, round-bottomed flask is fitted with a mechanical stirrer, a pressure-equalizing dropping funnel, and a combined inlet-outlet assembly connected to a nitrogen source and a bubbler. The flask is charged with 3.36 g. (0.14 mole) of sodium hydride (Note 1), the apparatus is flushed with nitrogen, and 100 ml. of tetrahydrofuran (Note 2) is added. The suspension is stirred and cooled in an ice bath under a static nitrogen atmosphere as a solution of 14.02 g. (0.1 mole) of 2-acetylcyclohexanone (Note 3) and 15 ml. of tetrahydrofuran is added over a 15-minute period. The formation of the sodium enolate is complete when hydrogen evolution ceases and a thick suspension has developed. Stirring and cooling are continued for 20 minutes, after which a solution of 20.1 g. (0.105 mole) of benzeneselenenyl chloride (Note 4) and 20 ml. of tetrahydrofuran is rapidly added. The contents of the flask are stirred at 0° for 15 minutes and poured into a beaker in which a mixture of 200 ml. of 1:1 (v/v) ether–pentane, 50 ml. of aqueous 7% sodium bicarbonate, and 50 g. of ice is being stirred with a magnetic stirrer. The layers are separated, and the aqueous layer is extracted with 50 ml. of 1:1 (v/v) ether–pentane. The combined organic extracts are washed with 50 ml. of saturated aqueous sodium chloride and dried by filtering through a cone of anhydrous sodium sulfate. Evaporation of the solvents under reduced pressure gives 29.2–30 g. of crude, solid 2-acetyl-2-phenylselenocyclohexanone which is used in Part B without purification (Note 5).

B. *2-Acetyl-2-cyclohexen-1-one.* In a 500-ml., three-necked, round-bottomed flask equipped with a pressure-equalizing dropping funnel, a reflux condenser, and a thermometer are placed a magnetic stirring bar and a solution of 29.2–30 g. (*ca.* 0.1 mole) of crude 2-acetyl-2-phenylselenocyclohexanone in 100 ml. of dichloromethane (Note 6). The solution is stirred at room temperature, and a 2–3 ml. portion from a solution of 23.8 g. of 30% hydrogen peroxide (7.14 g., 0.21 mole) (Note 7) and 20 ml. of water is added to initiate the oxidation (*Caution!* Note 8). After the exothermic reaction begins, the mixture is stirred and cooled in an ice–salt bath as necessary to keep the temperature between 30 and 35° while the remainder of the hydrogen peroxide solution is added. When the oxidation is complete (Note 9), the ice–salt bath is removed, and vigorous stirring is continued for 15 minutes at

room temperature and 15 minutes at 0°. The chilled suspension of benzeneseleninic acid is filtered, and the filter cake is washed with 50 ml. of dichloromethane (Note 10). The dichloromethane layer from the filtrate is washed with 50 ml. of aqueous 7% sodium bicarbonate, dried by filtering through a cone of anhydrous sodium sulfate, and evaporated to provide 12.8–13.7 g. of crude product (Note 11). Distillation in carefully washed glassware (Note 12) at 0.1 mm. using a Kugelrohr apparatus (Note 13) with an oven temperature of 50–55° gives 11.0–11.9 g. (79–85%) of 2-acetyl-2-cyclohexen-1-one (Note 14).

2. Notes

1. A 57% dispersion of sodium hydride in mineral oil was purchased from Alfa Division, Ventron Corporation. A 5.90-g. portion of the dispersion was placed in the reaction vessel and washed free of mineral oil with three 50-ml. portions of pentane by decanting the supernatant pentane after each washing. The pentane that remains in the flask is evaporated as the assembled apparatus is purged with nitrogen prior to adding the tetrahydrofuran.

2. Tetrahydrofuran was purified by the submitters by distillation from the sodium ketyl of benzophenone.

3. 2-Acetylcyclohexanone was used as supplied by Aldrich Chemical Company, Inc.

4. Benzeneselenenyl chloride was prepared by the procedure of Reich, Cohen, and Clark, *Org. Syn.*, **59,** p. 141. A freshly prepared solution of 24.8 g. (0.105 mole) of benzeneselenenyl bromide[2] in 25 ml. of tetrahydrofuran may also be used.

5. The crude selenide is contaminated by volatile impurities including some 2-acetylcyclohexanone which may be removed by sublimation at 50–60° to a cold finger cooled with dry ice, or by recrystallization from ether–pentane. The purified product melts at 72–73° and exhibits the following spectral characteristics: infrared (carbon tetrachloride) cm^{-1}: 1693 strong, 1579 weak; proton magnetic resonance (carbon tetrachloride) δ (multiplicity, number of protons, assignment): 1.3–2.3 (multiplet, 7, seven ring protons), 2.30 (singlet, 3, CH_3), 2.5–2.8 (multiplet, 1, $CH_AH_BC{=}O$), 7.28 (multiplet, 5, C_6H_5Se). The product was analyzed by the submitters. Analysis calculated for $C_{14}H_{16}O_2Se$: C, 56.96; H, 5.46. Found: 57.12; H, 5.48.

6. Dichloromethane was used without purification.

7. A 30% solution of hydrogen peroxide in water was purchased from Mallinckrodt Chemical Works. The reaction requires 2 molar equivalents of hydrogen peroxide, the first to oxidize the selenide to the selenoxide and the second to oxidize the elimination product, benzeneselenenic acid, to benzeneseleninic acid. The submitters recommend that the hydrogen peroxide solution be taken from a recently opened bottle, or titrated to verify its concentration.

8. The oxidation is autocatalytic, being catalyzed by the product, benzeneseleninic acid.[3] If the temperature drops significantly below 30°, the addition of hydrogen peroxide should be stopped, and the ice–salt bath should be removed to maintain the rate of oxidation and avoid an accumulation of hydrogen peroxide in the flask.

9. The yellow dichloromethane solution turns colorless, and a precipitate of benzeneseleninic acid appears.

10. The benzeneseleninic acid weighs 14.4–16 g. (73–82%) and melts at 123–124°. It may be reconverted to diphenyl diselenide by reduction with sodium thiosulfate[2] or sodium bisulfite.[4]

11. The enol content of the product at this point is less than 2%. If the unenolized enedione is desired, the following distillation should be omitted and the product used without purification to avoid further isomerization.

12. The glassware was cleaned in a sodium dichromate–sulfuric acid bath, washed with aqueous 10% ammonium hydroxide, and rinsed with water. The extent of enolization apparently depends on the care taken in washing the glassware and conducting the distillation.

13. Kugelrohr distillation ovens manufactured by Büchi Glasapparatfabrik are available from Brinckmann Instruments, Inc., Westbury, New York.

14. The product is contaminated by 5–15% of 2-acetylcyclohexanone, which was present in the crude selenide. This imputity may be avoided by purifying the selenide as described in Note 5. The enol content of the product obtained by the submitters varied

from 5 to 50%. At equilibrium the enol content is 84%. The spectral properties of the enedione are as follows: infrared (carbon tetrachloride) cm.$^{-1}$: 1694 strong, 1602 weak; proton magnetic resonance (carbon tetrachloride) δ (multiplicity, number of protons, assignment, coupling constant J in Hz.): 1.9–2.2 (multiplet, 2, $CH_2CH_2CH_2$), 2.35 (singlet, 3, CH_3), 2.3–2.7 (multiplet, 4, $CH_2CH_2CH_2$), 7.56 (triplet, 1, $CH_2CH{=}C$, $J = 4.3$). The enol form of the product exhibits the following proton magnetic resonance absorptions in carbon tetrachloride: δ (multiplicity, number of protons, assignment, coupling constant J in Hz.): 2.07 (singlet, 3, CH_3), 2.1–2.7 (multiplet, 4, CH_2CH_2), 5.55 (doublet of triplets, 1, $CH_2CH{=}CH$), $J = 4.5$ and 10), 6.19 (doublet of triplets 1, $CH_2CH{=}CH$, $J = 1.5$ and 10), 15.8 (singlet, 1, OH).

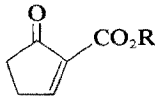
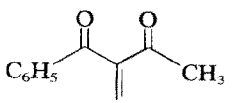
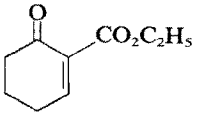
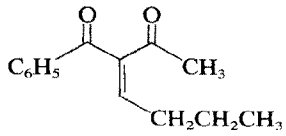
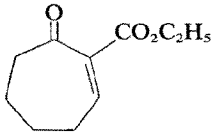
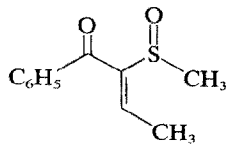
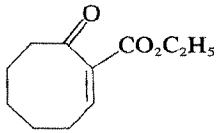
3. Discussion

The procedure described here serves to illustrate a new, general method for effecting the α,β-dehydrogenation of ketones,[2,5–7] aldehydes,[7] esters,[2,5,7] lactones,[7,8] nitriles,[9] sulfones, and related compounds.[2,10] The individual steps in the process are formation of an α-carbanion or enol derivative, phenylselenenylation with diphenyl diselenide or benzene selenenyl halides, oxidation of the resulting α-phenylseleno compound to the selenoxide, and thermal *syn*-elimination of benzeneselenenic acid. The advantages of this method include (*a*) the ease of introducing the α-phenylseleno group; (*b*) the rapid stoichiometric oxidation of the selenide with aqueous hydrogen peroxide at 25–35°, sodium metaperiodate in aqueous media, or ozone in dichloromethane at −78°; and (*c*) the fact that the elimination occurs at about room temperature under essentially neutral conditions.

The mild character of the reaction conditions is exemplified effectively here by the preparation of 2-acetyl-2-cyclohexen-1-one from 2-acetylcyclohexanone.[2] The crude product is initially isolated entirely in the less stable enedione form which is partially converted to the more stable enol form, 2-acetyl-1,3-cyclohexadien-1-ol,[11,12] during distillation at 45–55°. A series of α,β-unsaturated β-keto esters, β-diketones, and a β-keto sulfoxide have also been prepared in the unenolized form by this procedure (Table I).[2,5] In the case of the highly sensitive 2-ethoxycarbonyl-2-cyclopenten-1-one, the bicarbonate extraction must be omitted to avoid base-catalyzed decomposition during isolation.

TABLE I

α,β-UNSATURATED β-KETO ESTERS, β-DIKETONES, AND A β-KETO SULFOXIDE PREPARED BY SELENOXIDE ELIMINATION

α,β-Unsaturated Product	Yield (%)[a]	α,β-Unsaturated Product	Yield (%)[a]
	81[b]		74
	89		89
	84		55
	89		

[a] Overall yield from β-keto ester, β-diketone, or β-keto sulfoxide. The scale was 0.01–0.005 mole.

[b] The starting β-keto ester and the product were 2:1 mixtures of ethyl and methyl esters.

The enolized form of 2-acetyl-2-cyclohexen-1-one has been synthesized in low yield by dehydrochlorination of 2-acetyl-2-chlorocyclohexanone in collidine at 180°[11] and by elimination of acetamide from 3-acetamido-2-acetylcyclohexanone at 120–140°.[12] The preparation of other α,β-unsaturated β-dicarbonyl compounds has been attempted with varying degrees of success. The

dehydrogenation of 2-hydroxymethylene-3-keto steroids to 2-formyl-Δ^1-3-keto compounds with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone has been reported.[13] 2-Ethoxycarbonyl-2-cyclopenten-1-one has been prepared by selenium dioxide oxidation of the parent β-keto ester.[14] α-Acetoxylation of 3-methyl- and 3-isopropyl-2,4-pentanedione with lead tetraacetate followed by acetate pyrolysis provided the α,β-unsaturated β-diketones.[15] Chlorination and dehydrochlorination of 2-acetylcycloheptanone gave an enolic tautomer of 2-acetyl-2-cyclohepten-1-one.[11b] Numerous failures in attempts to synthesize these and other α,β-unsaturated β-dicarbonyl compounds by halogenation and dehydrohalogenation have been recorded as a consequence of competing Favorskii rearrangement, migration of halogen to the α'-position, and decomposition of the products from a combination of the high temperatures and basic conditions employed.[11,13–16] A number of α,β-unsaturated β-keto esters and β-diketones have been prepared by intermolecular aldol condensations under Knoevenagel conditions,[17] aldol cyclization,[16,18] and Robinson annelation.[19] All these procedures lead to equilibrium mixtures of keto and enol forms.

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2-Cyclohexen-1-one, 2-acetyl- (8, 9); (52784-38-0)

Cyclohexanone, 2-acetyl-2-phenylseleno- (8, 9); (57205-12-6)

Cyclohexanone, 2-acetyl- (8, 9); (874-23-7)

Benzeneselenenyl chloride (8, 9); (5707-04-0)

Benzeneseleninic acid (8, 9); (6996-92-5)

Lithium aluminum hydride: Aluminate (1-), tetrahydro-, lithium (8); Aluminate (1-), tetrahydro-, lithium, (T-4)- (9); (16853-85-3)

Benzeneselenenyl bromide (8, 9); (34837-55-3)

Benzeneselenenic acid (8, 9); (5818-99-5)

Phenyl diselenide (8); Diselenide, diphenyl (9); (1666-13-3)

2-Ethoxycarbonyl-2-cyclopenten-1-one: 1-Cyclopentene-1-carboxylic acid, 5-oxo-, ethyl ester (8, 9); (57020-97-0)

1,3-Cyclohexadien-1-ol, 2-acetyl-; Ethanone, 1-(2-hydroxy-1,5-cyclohexadien-1-yl)- (9); (37464-64-5)

Cyclohexanone, 2-acetyl-2-chloro- (8, 9); (64229-97-6)

3-Acetamido-2-acetylcyclohexanone (enol form): Acetamide, *N*-(2-acetyl-3-hydroxy-2-cyclohexen-1-yl)- (9); (35241-91-9)

2,4-Pentanedione, 3-methyl- (8, 9); (815-57-6)

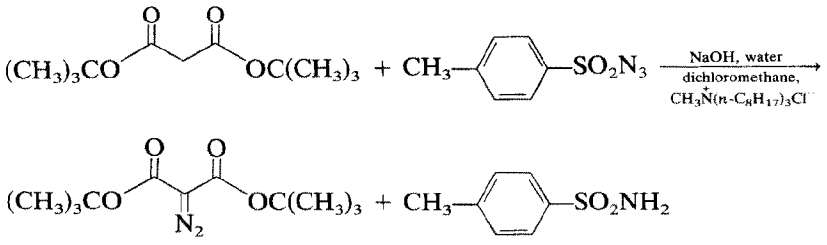
2,4-Pentanedione, 3-isopropyl- (8); 2,4-Pentanedione, 3-(1-methylethyl)- (9); (1540-38-1)

Cycloheptanone, 2-acetyl- (8, 9); (15419-61-1)

2-Cyclohepten-1-one, 2-acetyl- (8, 9); (−)

DIAZO TRANSFER BY MEANS OF PHASE-TRANSFER CATALYSIS: DI-*tert*-BUTYL DIAZOMALONATE

[Propanedioic acid, diazo-, bis(1,1-dimethylethyl) ester]



Submitted by HENRY J. LEDON[1]
Checked by STEVEN J. HOBBS and ROBERT M. COATES

1. Procedure

*Caution! Diazomalonic esters are toxic and potentially explosive. They must be handled with care. This preparation should be carried out in a well-ventilated hood, and the distillation of di-*tert*-butyl diazomalonate should be conducted behind a safety shield.*

A 500-ml., three-necked, round-bottomed flask is equipped with a reflux condenser, a dropping funnel, an argon inlet, and a Teflon-coated magnetic stirring bar. The flask is charged with 10.8 g. (0.05 mole) of di-*tert*-butyl malonate (Note 1), 9.9 g. (0.05 mole) of *p*-toluenesulfonyl azide (Note 2), 0.5 g. (0.0012 mole) of methyltri-*n*-octylammonium chloride (Note 3), and 200 ml. of dichloromethane (Note 4). The solution is stirred vigorously as the flask is flushed with argon for 10 minutes, then 10 ml. (0.1 mole) of aqueous 10*N* sodium hydroxide is added at once (Note 5). The mixture is stirred for 2 hours, during which time it changes from colorless to pale yellow. A 200-ml. portion of water is added. The organic layer is separated, washed with three 500-ml. portions of water (Note 6), and dried with anhydrous magnesium sulfate. After filtration of the drying agent, the solvent is removed on a rotary evaporator using a water bath kept at 30° (Note 7). The residual yellow-orange liquid is distilled at high vacuum (Note 8). The temperature of the heating bath is gradually raised to *ca.* 70° and kept at 70–75° during the distillation. After

separation of a small forerun, 7.2–7.6 g. (59–63%) of di-*tert*-butyl diazomalonate is collected, b.p. 44–45° (0.02 mm.), $n_D^{22} = 1.4568$ (Notes 9 and 10).

2. Notes

1. Di-*tert*-butyl malonate is available commercially either directly from Fluka AG, Buchs, Switzerland, or from its North American representative, Tridom Chemical Inc. Alternatively this compound may be prepared from malonic acid.[2]

2. *p*-Toluenesulfonyl azide was prepared according to the procedure of Regitz, Hocker, and Liedhegener.[3]

3. The submitter obtained methyltri-*n*-octylammonium chloride (Aliquat 336) from General Mills Company, Chemical Division, Kankakee, Illinois. The phase-transfer catalyst used by the checkers, which was supplied by Fluka AG through Tridom Chemical Inc., was a mixture in which the alkyl chains varied in length from *n*-octyl to *n*-decyl with the former predominating.

4. Reagent-grade dichloromethane was used without further purification.

5. The sodium hydroxide solution was deoxygenated by bubbling a stream of argon through it for 10 minutes.

6. The organic layer is washed with relatively large portions of water to avoid difficulty in separating the phases. The checkers found that vigorous shaking during the extractions gave intractable emulsions. The emulsions were avoided by gentle swirling of the dichloromethane–water mixtures.

7. To avoid foaming during the distillation, the checkers removed the last traces of solvent by evacuation at 0.1 mm. and room temperature for 12–24 hours.

8. The submitter recommends that the apparatus be purged with argon prior to the distillation.

9. The checkers collected foreruns amounting to 0.3–0.7 g., b.p. 50–58° (0.003 mm.) and 40–45° (0.0006 mm.). The product was collected in two or three fractions, b.p. 53–57° (0.002–0.011 mm.), 54–58° (0.002–0.003 mm.), and 45–52° (0.0004–0.0006 mm.). Inspection and integration of the proton magnetic resonance spectra of the foreruns indicated that the fractions were mainly di-*tert*-butyl diazomalonate contaminated with 16–35% of di-*tert*-butyl

malonate. The purest fractions usually crystallized on standing at room temperature to give a low-melting solid.

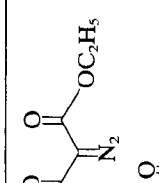
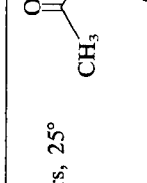
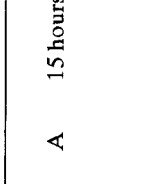
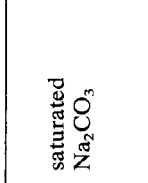
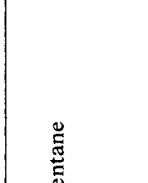
A gas chromatographic analysis on the product by the submitter, using an 0.3×80 cm. column packed with 10% silicone rubber (SE-30) supported on acid-washed, 60–80 mesh Chromasorb P at 80°, exhibited a single peak. The retention times of di-*tert*-butyl malonate, di-*tert*-butyl diazomalonate, and *p*-toluenesulfonyl azide were 2, 6, and 9 minutes, respectively. The purity of the product obtained by the checkers was estimated from proton magnetic resonance spectra to be *ca.* 94%, the remainder being di-*tert*-butyl malonate.

10. The spectral properties of the product are as follows: infrared (liquid film) $cm.^{-1}$: 2137 ($C{=}N_2$), 1751 ($C{=}O$), 1730 ($C{=}O$), 1686; ultraviolet (ethanol) nm. max. ($\log \varepsilon$): 255 (3.68); proton magnetic resonance (chloroform-*d*) δ (multiplicity, number of protons, assignment): 1.52 (singlet, 18, six CCH_3); carbon-13 magnetic resonance with proton decoupling (chloroform-*d*) δ (assignment): 28.5 (CH_3), 65.7 ($C{=}N_2$), 82.8 ($C(CH_3)_3$), 160.6 ($C{=}O$).

3. Discussion

The "diazo transfer reaction" between *p*-toluenesulfonyl azide and active methylene compounds is a useful synthetic method for the preparation of α-diazo carbonyl compounds.[3] However, the reaction of di-*tert*-butyl malonate and *p*-toluenesulfonyl azide to form di-*tert*-butyl diazomalonate proceeded to the extent of only 47% after 4 weeks with the usual procedure.[4] The present procedure, which utilizes a two-phase medium and methyltri-*n*-octylammonium chloride (Aliquat 336) as phase-transfer catalyst, effects this same diazo transfer in 2 hours and has the additional advantage of avoiding the use of anhydrous solvents.[5,6] This procedure has been employed for the preparation of diazoacetoacetates, diazoacetates, and diazomalonates (Table I).[6] Ethyl and *tert*-butyl acetoacetate are converted to the corresponding α-diazoacetoacetates with saturated sodium carbonate as the aqueous phase. When aqueous sodium hydroxide is used with the acetoacetates, the initially formed α-diazoacetoacetates undergo deacylation to the diazoacetates. Methyl esters are not suitable substrates, since they are too easily saponified under these conditions.

TABLE I
PREPARATION OF α-DIAZO CARBONYL COMPOUNDS VIA PHASE TRANSFER CATALYSIS[a]

Starting Material	Organic Phase	Aqueous Phase	Phase Transfer Catalyst[b]	Time and Temperature	Product	Yield (%)
Ethyl acetoacetate	pentane	saturated Na_2CO_3	A	15 hours, 25°		90
Ethyl acetoacetate	pentane	3*N* NaOH	A	15 hours, 25°		53
tert-Butyl acetoacetate	pentane	saturated Na_2CO_3	A	15 hours, 25°		77
	dichloromethane	3*N* NaOH	B	1 hour, 0°		92
tert-Butyl acetoacetate	pentane	3*N* NaOH	A	15 hours, 25°		89
Phenyl acetone	benzene	10*N* NaOH	A	15 hours, 0°		100

[a] These reactions were carried out with 0.005 mole of the carbonyl compound and 0.005 mole of *p*-toluenesulfonyl azide.
[b] A, tetrabutylammonium bromide; B, methyltri-*n*-octylammonium chloride (Aliquat 336).

Although the hazardous properties of di-*tert*-butyl diazomalonate are not known with certainty, it is reasonable to assume that they are similar to those of diazoacetic esters, which are considered to be moderate explosion hazards when heated.[7] Contact with rough or metallic surfaces should be avoided. The submitter has routinely distilled 10-g. quantities of di-*tert*-butyl diazomalonate under argon with no sign of decomposition.

Diazomalonic esters serve as intermediates for the synthesis of a wide variety of compounds including cyclopropanes,[8,9] cyclopropenes,[8,10] cycloheptatrienes,[11] sulfur ylides,[12] lactones,[13] and substituted malonates.[14]

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Di-*tert*-butyl diazomalonate: Malonic acid, diazo-, di-*tert*-butyl ester (8); Propanedioic acid, diazo-, bis(1,1-dimethylethyl)ester (9); (35207-75-1)

Di-*tert*-butyl malonate: Malonic acid, di-*tert*-butyl ester (8); Propanedioic acid, bis(1,1-dimethylethyl)ester (9); (541-16-2)

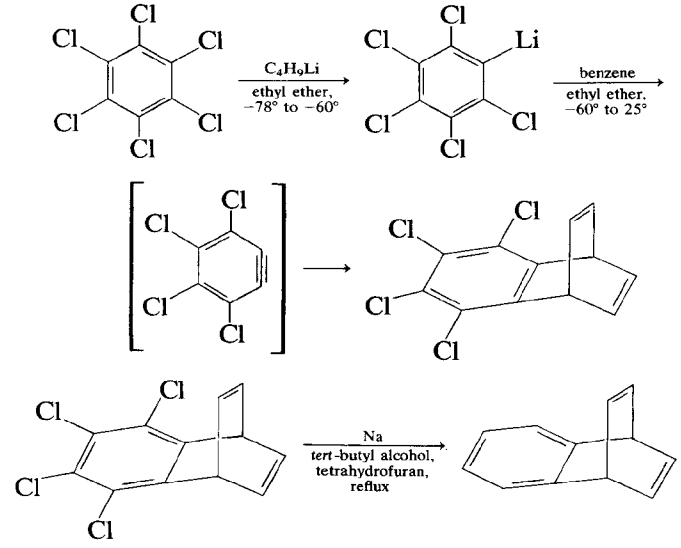
p-Toluenesulfonyl azide (8); Benzenesulfonyl azide, 4-methyl- (9); (941-55-9)

Methyltri-*n*-octylammonium chloride: Ammonium, methyltrioctyl-, chloride (8); 1-Octanaminium, *N*-methyl-*N,N,*-dioctyl-, chloride (9); (5137-55-3)

Malonic acid (8); Propanedioic acid (9); (141-82-2)

DIELS-ALDER ADDITION OF PERCHLOROBENZYNE: BENZOBARRELENE

(1,4-Ethenonaphthalene, 1,4-dihydro)



Submitted by NEIL J. HALES, HARRY HEANEY, JOHN H. HOLLINSHEAD, and PRITPAL SINGH[1]
Checked by G. CRASS, M. POHMAKOTR, and D. SEEBACH

1. Procedure

Caution! See benzene warning, Org. Syn., **58,** 168 (1978).

A. *Tetrachlorobenzobarrelene.* A carefully dried, 5-l., three-necked, round-bottomed flask is equipped with a large magnetic

stirring bar, a low-temperature thermometer, a 500-ml. pressure-equalizing dropping funnel bearing a gas-inlet tube at its top, and a Nujol bubbler (Note 1). The flask is charged with 28.5 g. (0.10 mole) of hexachlorobenzene (Note 2), the apparatus is flushed with argon or nitrogen (Note 3), and 600 ml. of dry ethyl ether (Note 4) is added. The resulting suspension is stirred and cooled to a temperature of −72° to −78° in a cooling bath holding *ca.* 4 l. of a dry ice–acetone slurry. A solution of butyllithium (0.110 mole) in hexane (Note 5) is added over a 30-minute period during which the temperature should not exceed −70° (Note 6), and the mixture is then allowed to warm to −60° over an additional 1.5 hours. Four liters of dry, thiophene-free benzene (Note 4) is added to the resulting solution of pentachlorophenyllithium (Note 7) over a 1-hour interval during which the temperature rises to *ca.* +10° (Note 8). The resulting mixture is allowed to warm slowly to room temperature over a period of at least 14 hours and then is heated at +30° for another 2 hours to ensure complete reaction (Note 9). A 10-g. portion of solid ammonium chloride is added, and 15 minutes later the contents of the flask are filtered through 20 g. of Celite. The volume of the filtrate is reduced to 75 ml. with a rotary evaporator, and 100 g. of alumina (Note 10) is added to the concentrate in a 250-ml. flask. The rotary evaporation is continued until the weight remains constant and a freely flowing consistency is attained. The material is placed on top of an 800-g. column of alumina and eluted with low-boiling petroleum ether (Note 11) while 200-ml. fractions are collected. The fractions are analyzed by gas chromatography or thin-layer chromatography (Note 6), and the appropriate fractions are combined and evaporated, providing 16.9–17.5 g. (58–60%) (Note 12) of essentially pure tetrachlorobenzobarrelene, m.p. 127–129° (Note 13).

B. *Benzobarrelene.* A dry 1-l., three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a combined gas-inlet tube and rubber septum, a 500-ml. pressure-equalizing dropping funnel, and a reflux condenser connected to a Nujol bubbler. The flask is charged with 500 ml. of dry tetrahydrofuran (Note 14) and 17 g. (0.74 mole) of sodium wire with a diameter of *ca.* 0.5 mm. The mixture is stirred and heated at reflux under an atmosphere of argon or nitrogen, and 50 ml. of freshly distilled *tert*-butyl alcohol is added. Immediately afterward a solution of 15 g. (0.051 mole) of tetrachlorobenzobarrelene in 200 ml. of tetrahydrofuran is added over a 15-minute period. After 4 hours under reflux (Note 15) the contents of the flask are cooled to room temperature and filtered through a plug of glass wool (Note 16) into 50 ml. of methanol contained in a 2-l. beaker. After any remaining small pieces of sodium have reacted with the methanol, 400 ml. of water is added, and the mixture is extracted with six 150-ml. portions of ethyl ether. The combined ether layers are washed with two 200-ml. portions of aqueous saturated sodium chloride, dried over magnesium sulfate, and evaporated with a rotary evaporator operated at water aspirator pressure and room temperature. The semicrystalline residue, which amounts to 7.3–8.1 g., is mixed with 40 g. of alumina (Note 10), and the resulting mixture is swirled at room temperature under reduced pressure until it attains a free-flowing consistency. The material is then placed on top of a column packed with 600 g. of alumina and eluted with low-boiling petroleum ether (Note 11). Fractions of *ca.* 200 ml. are collected, evaporated, and assayed by gas chromatography (Notes 15 and 17). Combination of the appropriate fractions affords 5.9–6.8 g. (75–86%) of benzobarrelene, m.p. 62–64.5° (Note 18).

2. Notes

1. The dropping funnel must be arranged so that the drops fall directly into the solution and not onto the side of the flask. The checkers used a 4-l., four-necked flask equipped with a mechanical stirrer and a ground-glass stirring assembly and carried out the reaction on four-fifth's scale.

2. Technical-grade hexachlorobenzene was purchased by the submitters from BDH Chemicals, Ltd., and recrystallized twice from benzene: m.p. 227°. The submitters found that if the technical-grade material is used without purification, some insoluble material remains after the reaction with butyllithium, though the yield of tetrachlorobenzobarrelene is only slightly reduced. The checkers used 22.8 g. (0.08 mole) of hexachlorobenzene of 98% purity, purchased as a fine powder from EGA-Chemie K. G., an affiliate of Aldrich Chemical Company, Inc., without further purification.

3. The flushing operation was accomplished by replacing the bubbler with a stopcock and alternately evacuating and filling the apparatus with inert gas three times. A slight outflow of inert gas should be maintained during all subsequent operations. When the flask is being cooled, it is necessary to increase the gas flow.

4. Dry ethyl ether and dry, thiophene-free benzene were prepared by the submitters according to procedures presented in ref. 2.

5. Butyllithium as 1.5–3.0 *M* solutions in hexane is available from the following firms: Pfizer, Ltd., Sandwich, England; Metallgesellschaft, Frankfurt, Germany; Alfa Division, Ventron Corporation. The appropriate volume of the solution is transferred with a 50-ml. syringe to the dropping funnel with care being taken to exclude air. An excess of butyllithium above the 10% recommended here may lead to the formation of dilithiotetrachlorobenzene.

6. The progress of the reaction of butyllithium and hexachlorobenzene and, later, the formation of tetrachlorobenzobarrelene may be monitored by gas chromatography or thin-layer chromatography. Samples withdrawn from the reaction mixture with a syringe are injected into a small amount of water, and the organic layer is analyzed. Gas chromatography was carried out by the submitters with flame ionization detection and with a 1.5 m. × 4 mm. (inside diameter) glass column packed with 3% silicone rubber (SE-30) supported on 80–100 mesh Gaschrom Q. With a column temperature of 150° and a nitrogen carrier gas flow rate of 45 ml. per minute, the retention times of pentachlorobenzene, hexachlorobenzene, and tetrachlorobenzobarrelene are *ca.* 2, 4, and 18 minutes, respectively. Normally trace amounts of hexachlorobenzene are still detectable at the end of the reaction with butyllithium. Thin-layer chromatography was performed on silica gel with 5% ether in pentane as developing solvent. The *Rf* value of tetrachlorobenzobarrelene is less than that of the chlorobenzenes.

7. A clear yellow solution is usually obtained at this stage; however, some suspended material may be present, particularly when technical-grade hexachlorobenzene is used.

8. For proper temperature control the cooling bath should be free from excess amounts of dry ice. The benzene should be added in the following manner (volume of benzene added, period of addition, final temperature reached): 0.5 l., 15 minutes, *ca.* −20°; 0.5 l., 15 minutes, *ca.* −10°; 3.0 l., 30 minutes, *ca.* +10°.

9. The reaction is relatively slow at a laboratory temperature of 18–20° and may require as much as 40 hours to reach completion.

10. The submitters used Activity I (Brockmann) Camag alumina, which was purchased from Hopkins and Williams. The checkers used comparable material obtained from E. Merck Darmstadt, Germany.

11. Low-boiling petroleum ether (b.p. 30–50° or 40–60°) was distilled from calcium chloride prior to use.

12. The submitters usually combined fractions 5–14 and obtained 18–19.5 g. (62–67%) of tetrachlorobenzobarrelene, m.p. 127–131°. The checkers, using a 3.5 cm. × 1 m. column for the chromatography, isolated 13.5–14 g. (58–60%) of product from fractions 10–25.

13. The proton magnetic resonance spectrum of the product in chloroform-*d* has the following absorptions: δ (multiplicity, number of protons, assignment): 5.45 (multiplet, 2, bridgehead *H*), 6.95 (multiplet, 4, vinyl *H*). A melting point of 125° is reported in the literature.[3]

14. The tetrahydrofuran was freshly distilled from lithium aluminum hydride. For a warning regarding this method of purifying tetrahydrofuran, see *Org. Syn.*, Coll. Vol. **5,** 976 (1973).

15. An aliquot may be removed at this stage and analyzed by either gas chromatography or thin-layer chromatography to ensure that the reaction is complete. Benzobarrelene has a retention time of *ca.* 5 minutes in a gas chromatographic analysis under the conditions stated in Note 6, but with a column temperature of 104°. The completion of the reaction is also indicated by a purple coloration of the precipitated sodium chloride.

16. The glass wool removes the larger pieces of unreacted sodium and much of the purple sodium chloride.

17. The dimensions of the column used by the checkers were the same as those specified in Note 12, and the product was obtained from fractions 10–20. The submitters evaporated the fractions with a rotary evaporator operated at water aspirator

pressure and room temperature (*ca.* 20°); however, the checkers caution that the product sublimes very readily.

18. The spectral properties of benzobarrelene are as follows: infrared (potassium iodide) cm.$^{-1}$, strong peaks: 1460, 1325, 790, 750, 690, 660; proton magnetic resonance (chloroform-*d*): δ (multiplicity, number of protons, assignment): 4.9 (multiplet, 2, bridgehead *H*), 6.8–7.3 (multiplet, 8, aryl and vinyl *H*). The reported melting point is 65.5–66°.[4] From 20 g. of tetrachlorobenzobarrelene the submitters obtained 8.3–8.8 g. (79–83%) of benzobarrelene, m.p. 64–65°.

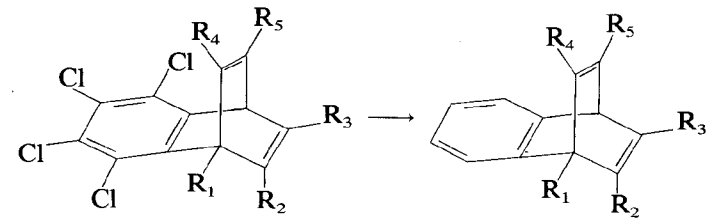
3. Discussion

Although benzobarrelene has been used in a number of recent studies, the best available published synthesis[4] starts with the Diels-Alder reaction of β-naphthol and maleic anhydride, affording benzobarrelene in *ca.* 1% yield after five further steps. Minor improvements allow small quantities of benzobarrelene to be prepared in an overall yield of *ca.* 10%.[5] The reaction of benzyne with benzene is relatively inefficient, giving benzobarrelene in *ca.* 2% yield.[6] When benzyne is generated by decomposition of benzenediazonium-2-carboxylate at high dilution in benzene, the yield of benzobarrelene is raised to 14%.[7] The reactions of benzyne with other aromatic substrates are equally inefficient.

Tetrahalobenzynes, however, react with a variety of aromatic compounds to afford tetrahalobenzobarrelene derivatives in good yields, frequently in the range of 55 to 75%.[8] The dehalogenation of a variety of alkenyl chlorides with alkali metals in tetrahydrofuran containing *tert*-butyl alcohol[9] suggested this approach to the dechlorination of tetrachlorobenzobarrelenes.

The generation of pentachlorophenyllithium by the reaction of butyllithium with hexachlorobenzene has been reported previously by Rausch, Tibbetts, and Gordon.[10] The present procedure for the preparation of benzobarrelene is based on the submitters' previously published note.[11] By this method 10-g. quantities of benzobarrelene may be obtained in *ca.* 3 working days without the use of large-scale apparatus. The generality of the procedure is shown by the examples given in Table I.

TABLE I
PREPARATION OF SUBSTITUTED BENZOBARRELENES



Tetrachlorobenzobarrelenes	Yield of Benzobarrelenes (%)
$R^1 = OMe$; $R^2 = R^3 = R^4 = R^5 = H$	100
$R^1 = OMe$; $R^2 = R^5 = Me$; $R^3 = R^4 = H$	90
$R^1 = OMe$; $R^2 = R^4 = Me$; $R^3 = R^5 = H$	95
$R^1 = OMe$; $R^2 = Me$; $R^3 = R^4 = R^5 = H$	95

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Benzobarrelene: 1,4-Ethenocaphthalene, 1,4-dihydro-(8, 9);(7322-47-6)

Tetrachlorobenzobarrelene: 1,4-Ethenonaphthalene, 5,6,7,8-tetrachloro-1,4-dihydro- (8, 9); (13454-02-9)

Benzene, hexachloro- (8, 9); (118-74-1)

Ethyl ether (8); Ethane, 1,1′-oxybis- (9); (60-29-7)

Lithium, butyl- (8, 9); (109-72-8)

tert-Butyl alcohol (8); 2-Propanol, 2-methyl- (9); (75-65-0)

Dilithiotetrachlorobenzene: Lithium, (tetrachlorophenyl)di-(8, 9); (−)

Benzene, pentachloro- (8, 9); (608-93-5)

Lithium, (pentachlorophenyl)- (8, 9); (6782-80-5)

β-Naphthol: 2-Naphthol (8); 2-Naphthalenol (9); (135-19-3)

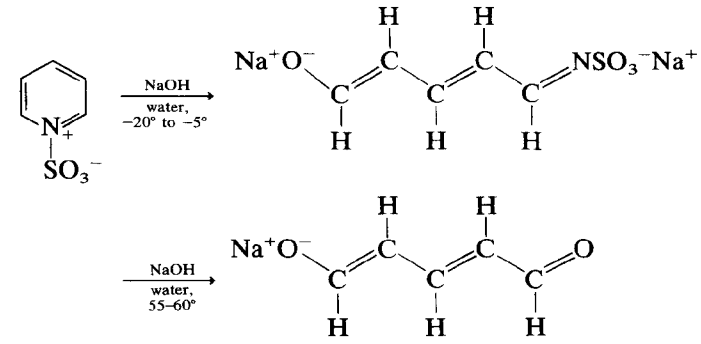
Maleic anhydride (8); 2,5-Furandione (9); (108-31-6)

Benzyne: 1,3-Cyclohexadien-5-yne (8, 9); (462-80-6)

Benzenediazonium-2-carboxylate: Benzenediazonium, *o*-carboxy-, hydroxide, inner salt (8); Benzenediazonium, 2-carboxy-, hydroxide, inner salt (9); (1608-42-0)

GLUTACONALDEHYDE SODIUM SALT FROM HYDROLYSIS OF PYRIDINIUM-1-SULFONATE

[2-Pentenedial, ion (1^-), sodium]



Submitted by JAN BECHER[1]
Checked by J. P. O'BRIEN, S. TEITEL, and G. SAUCY

1. Procedure

In a 500-ml., three-necked, round-bottomed flask fitted with a mechanical stirrer and a thermometer is placed 42 g. (1.05 mole) of sodium hydroxide dissolved in 168 ml. of water. The contents of the flask are cooled to −20° and stirred vigorously as 48 g. (0.30 mole) of pyridinium-1-sulfonate (Note 1), which has been previously chilled to −20°, is added in one portion. The mixture is stirred for 20 minutes while the temperature is kept below −5° (Note 2). The cooling bath is removed, and the mixture is stirred and warmed gradually to 20° over 20 minutes. The temperature of the dark orange mixture is then raised to 55–60° and after 1 hour is lowered again to −5°. The brown crystals that separate are filtered by suction, pressed into a compact filter cake, and washed with three 100-ml. portions of acetone (Note 3). The yield of this crude product amounts to 46–52 g. after drying on filter paper overnight or at 50° (1 mm.) for 1 hour. (Note 4).

If further purification is desired, the crude product is added to 1 l. of methanol in a 2-l., three-necked, round-bottomed flask equipped with a reflux condenser and a mechanical stirrer. The

mixture is stirred and heated under reflux for 30 minutes. A 10-g. portion of activated carbon is added, and after 5 minutes the hot mixture is filtered. The light yellow-red filtrate is concentrated to a volume of 50 ml. under reduced pressure and cooled to 0°. The resulting orange crystals are filtered, washed with two 25-ml. portions of acetone, and dried for 1 hour at 50° (1 mm.), affording 24–27 g. (50–58%) of glutaconaldehyde sodium salt dihydrate (Notes 5 and 6).

2. Notes

1. Pyridinium-1-sulfonate was prepared according to the procedure of Sisler and Audrieth.[2] The submitter reports that this procedure may be conveniently carried out at 5 times the specified scale. The reagent should be dry and used soon after its preparation. The checkers found that a technical grade of pyridinium-1-sulfonate (sulfur trioxide pyridine complex) purchased from Aldrich Chemical Company, Inc., gave substantially lower yields of product.

2. The initial exothermic reaction that occurs at this point produces the intermediate glutaconaldehyde iminesulfonate disodium salt shown in the scheme. It separates as a yellow, unstable precipitate that may be isolated by filtering, washing with ice-cold isopropyl alohol, and drying. The yield of the disodium salt is 64 g. (96%).

3. The acetone washes serve to remove colored by-products.

4. The crude product is relatively stable and sufficiently pure for most purposes.

5. The submitter advises that the product be dried at room temperature for 17 hours prior to analysis. An analysis including a Karl Fischer titration for water content was reported by the checkers. Analysis calculated for $C_5H_5O_2Na\cdot(H_2O)_2$: C, 38.46; H, 5.82; H_2O, 23.08. Found: C, 38.67; H, 5.91; H_2O, 23.40. The melting of the product is higher than 350° and its spectral characteristics are as follows: infrared (potassium bromide) cm.$^{-1}$: 3320 (H_2O), 1723, 1715 (C=O), 1530 (C—O); proton magnetic resonance (dimethyl sulfoxide-d_6) δ (multiplicity, number of protons, assignment, coupling constant J in Hz.): 5.07 (doublet of doublets, 2, H_2 and H_4, $J=9$ and 13), 7.03 (triplet, 1, H_3, $J=13$), 8.58 (doublet, 2, H_1, and H_5, $J=9$); ultraviolet (aqueous 0.1 M sodium hydroxide) nm. max. (log ε): 363 (4.75).

6. The water of hydration that accompanies the glutaconaldehyde sodium salt described in this procedure may interfere with applications requiring anhydrous conditions. Consequently the submitter has provided the following alternative procedure for preparing the anhydrous potassium salt. Pyridinium-1-sulfonate (108 g., 0.68 mole) is added to a solution of 155 g. (2.8 moles) of potassium hydroxide in 378 ml. of water in a 1-l. flask which is stirred and cooled to −20°. After 1 hour, the temperature is slowly raised to 20° over 4 hours. The mixture is heated at 30–40° for 30 minutes and cooled to 5°. The crude product that precipitates is filtered, washed with two 100-ml. portions of acetone, and dried in the air to give 120 g. of yellow-brown crystals. This material is heated at reflux in 2.5 l. of methanol, 5 g. of activated carbon is added, the carbon is filtered, and the filtrate is concentrated under reduced pressure to a volume of 100 ml. The pale yellow crystals of glutaconaldehyde potassium salt are collected, washed with acetone, and dried to give 53–57 g. (57–62%). Analysis of the potassium salt indicates the empirical formula $C_5H_5O_2K$, and the salt melts above 350°. The proton magnetic resonance spectrum is identical to that of the sodium salt, and the ultraviolet spectrum in aqueous 0.1 M potassium hydroxide solution exhibits a maximum at 362 nm. (log ε, 4.84).

The sodium and potassium salts of glutaconaldehyde are soluble only in polar solvents such as water, dimethyl sulfoxide, *N,N*-dimethylformamide, pyridine, and methanol. However, the stable tetrabutylammonium salt is soluble in relatively nonpolar solvents such as chloroform and ethyl acetate. It may be prepared from the potassium salt in the following manner. In a 1-l. Erlenmeyer flask equipped with a magnetic stirring bar are placed a solution of 13.6 g. (0.1 mole) of crude glutaconaldehyde potassium salt in 200 ml. of water and a solution of 33.9 g. (0.1 mole) of tetrabutylammonium hydrogen sulfate in 200 ml. of ice-cold water, the pH of which was adjusted to 10 by adding aqueous 2M sodium hydroxide. The resulting mixture is stirred for 5 minutes in an ice bath and extracted with three 400-ml. portions of dichloromethane that has been dried before use by filtration through anhydrous potassium

carbonate. The combined dichloromethane extracts are dried over 20 g. of anhydrous potassium carbonate and evaporated under reduced pressure. A 100-ml. portion of toluene is added, and the mixture is again evaporated under reduced pressure to remove residual water. The yield of dry, nearly colorless crystals of glutaconaldehyde tetrabutylammonium salt monohydrate is 23–25.1 g. (64–70%), m.p. 105–108°. Analysis corresponds to the empirical formula $C_{21}H_{41}NO_2 \cdot H_2O$, and the salt may be recrystallized from ethyl acetate.

3. Discussion

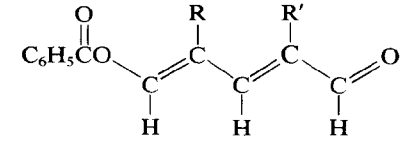
The sodium salt of glutaconaldehyde, first described by Baumgarten[3] in 1924, has been mentioned several times in the literature subsequently, but without full details of its preparation. The present procedure involves base-catalyzed hydrolysis of pyridinium-1-sulfonate at low temperature to glutaconaldehyde iminesulfonate dianion, followed by a second hydrolysis of the iminesulfonate at 55–60°, which affords glutaconaldehyde sodium salt as a dihydrate.[4] The anhydrous potassium salt[5] and the monohydrated tetrabutylammonium salt may be prepared by similar procedures (see Note 6). In additon to being anhydrous, the potassium salt is more stable than the sodium salt; however, the sodium salt has the advantage of being more soluble in dimethyl sulfoxide and *N,N*-dimethylformamide. Analogous glutaconaldehyde iminesulfonate dianions with methyl and methoxy substituents at the 4-position are obtained by regiospecific ring opening of 3-methyl and 3-methoxy pyridinium-1-sulfonates.[6]

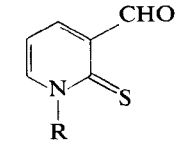
The reaction of glutaconaldehyde anion with benzoyl chloride and acetic anhydride gives the corresponding enol esters.[3,7] 4-Methyl- and 4-methoxyglutaconaldehyde enol benzoates are available by benzoylation of the corresponding iminesulfonate dianions and subsequent hydrolysis (Table I).[6] Halogenation of glutaconaldehyde anion or its enol benzoate gives a series of 2-halo and 2,4-dihalo derivatives (Table I).[6,8]

Glutaconaldehyde anion serves as an interesting intermediate for the synthesis of heterocyclic compounds. The parent pyrylium perchlorate has been prepared from glutaconaldehyde and 70% perchloric acid in ether at −55°.[9] The reaction of glutaconaldehyde anion with alkyl and aryl isothiocyanates and

TABLE I

GLUTACONALDEHYDE ENOL BENZOATES[6–8] AND 1-SUBSTITUTED 3-FORMYL-2(1*H*)-PYRIDINETHIONES[10] PREPARED FROM GLUTACONALDEHYDE ANION AND ITS DERIVATIVES





R	R′	M.p. (°)	Yield (%)	R	M.p. (°)	Yield (%)[d]
H	H	119–121	87	CH_3	126–128	58
CH_3	H	138–139	61[a]	C_2H_5	109–110	61
CH_3O	H	123–124	27[a]	C_3H_7	88–90	65
H	Br	128–129	72[b]	i-C_3H_7	113–115	75
H	Cl	126–128	55[c]	C_6H_5	180–182	95
H	I	131–141	58[c]	m-FC_6H_4	171–173	97
Cl	Cl	114–116	66[c]	p-FC_6H_4	191–193	82
Br	Br	98–100	65[c]			

[a] This ester was prepared by benzoylation of the corresponding glutaconaldehyde iminesulfonate dianion and subsequent hydrolysis.
[b] This ester was prepared by bromination of glutaconaldehyde enol benzoate.
[c] This ester was prepared by halogenation of glutaconaldehyde anion followed by benzoylation.
[d] The 3-formyl-2(1*H*)-pyridinethiones were prepared by reaction of glutaconaldehyde anion with the corresponding isothiocyanates (RN=C=S).

isoselenocyanates evidently occurs initially at the 2-position of the former, leading to a variety of *N*-substituted 3-formyl-2(1*H*)-pyridinethiones and the corresponding selenones (Table I).[10] A five-membered heterocycle, 2-isoxazolin-5-yl acetaldehyde oxime, is formed from reaction with hydroxylamine.[11]

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Glutaconaldehyde (8); 2-Pentenedial (9); (821-42-1)

Glutaconaldehyde, sodium salt, dihydrate: Glutaconaldehyde, ion (1^-) sodium (8); 2-Pentenedial, ion (1^-), sodium (9); (24290-36-6)

Pyridinium-1-sulfonate: Pyridinium, 1-sulfo-, hydroxide, inner salt (8, 9); (42824-16-8)

Glutaconaldehyde, potassium salt: Glutaconaldehyde, ion (1^-), potassium (8); 2-Pentenedial, ion (1^-), potassium (9); (62295-92-5)

Formamide, *N,N*-dimethyl- (8, 9); (68-12-2)

Dimethyl sulfoxide: Methyl sulfoxide (8); Methane, sulfinylbis- (9); (67-68-5)

Pyridine (8, 9); (110-86-1)

Tetrabutylammonium hydrogen sulfate: Ammonium, tetrabutyl-, sulfate (1:1) (8); 1-Butanaminium, *N,N,N*-tributyl-, sulfate (1:1) (9); (32503-27-8)

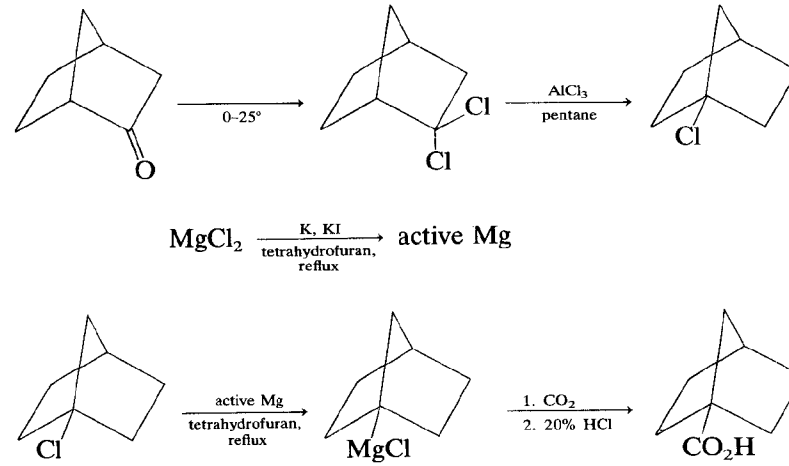
Pyrylium perchlorate (8, 9); (2567-32-0)

4-Methylglutaconaldehyde enol benzoate: 2,4-Pentadienal, 5-(benzoyloxy)-4-methyl, (*E,E*) (8, 9); (55546-49-1)

4-Methoxyglutaconaldehyde enol benzoate: 2,4-Pentadienal, 5-(benzoyloxy)-4-methoxy, (*E,Z*) (8, 9); (55546-51-5)

HIGHLY REACTIVE MAGNESIUM FOR THE PREPARATION OF GRIGNARD REAGENTS: 1-NORBORNANECARBOXYLIC ACID

(Bicyclo[2.2.1]heptane-1-carboxylic acid)



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Checked by DENNIS P. STACK and ROBERT M. COATES

1. Procedure

Caution! Potassium is highly reactive. Although it may be handled safely in air if it is covered with a hydrocarbon solvent such as heptane or mineral oil, it will spark and ignite flammable organic vapors on contact with water. The magnesium formed in this reaction is highly reactive and pyrophoric (Note 1). *Accordingly, Parts C and D of this procedure should be carried out behind a safety shield.*

A. *2,2-Dichloronorbornane.* A 1-l., round-bottomed flask equipped with a mechanical stirrer and a calcium sulfate drying tube is charged with 91.3 g. (0.665 mole) of phosphorous trichloride and 90.0 g. (0.817 mole) of norcamphor (Note 2). The solution is stirred and cooled to 0° in an ice–salt bath, then 193 g. (0.927 mole) of phosphorous pentachloride is added in portions

over a 1-hour period. The mixture is allowed to warm to room temperature and stand overnight. The contents of the flask are poured carefully onto 1000 g. of crushed ice. The mixture is thoroughly dispersed and extracted with four 500-ml. portions of pentane. The combined pentane layers are washed with two 600-ml. portions of water, and the aqueous layers are extracted with one 500-ml. portion of pentane. The pentane extracts are combined, dried with anhydrous sodium sulfate, and evaporated under reduced pressure. Distillation of the residual brown liquid affords 111–114 g. (82–85%) of 2,2-dichloronorbornane as a clear liquid, b.p. 70–74° (14 mm.), which solidifies on standing (Note 3).

B. 1-*Chloronorbornane.* A 5-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, a condenser fitted with a drying tube, and a stopper is charged with 230 g. (1.39 moles) of 2,2-dichloronorbornane and 3 l. of pentane (Note 4). The solution is stirred as 87.0 g. (0.652 mole) of aluminum chloride is added over 4.5 hours. The mixture is stirred for 40 hours, during which time hydrogen chloride gas is evolved and a brown sludge accumulates on the walls of the flask. The supernatant pentane solution is decanted, and the brown sludge remaining in the flask is thoroughly extracted with four 200-ml. portions of pentane. The combined pentane extracts are washed with three 600-ml. portions of water and one 600-ml. portion of saturated sodium chloride solution. The combined aqueous washes are extracted with two additional 500-ml. portions of pentane which are combined with the preceding pentane solution and dried over anhydrous sodium sulfate. The pentane solution is concentrated by distillation through a 3×30 cm. Vigreux column, and the residual liquid is distilled to afford 110–114 g. (60–63%) of 1-chloronorbornane as a colorless liquid, b.p. 70–74° (55 mm.), which solidifies on standing at room temperature (Note 5).

C. *Active magnesium.* A 200-ml., three-necked, round-bottomed flask is equipped with a Teflon-coated magnetic stirring bar, stopper, rubber septum, and condenser connected to an argon inlet (Note 6). The flask is charged with 1.5 g. (0.038 mole) of freshly cut potassium (Notes 7 and 8), 2.01 g. (0.0211 mole) of anhydrous magnesium chloride (Note 9), 3.55 g. (0.0214 mole) of anhydrous potassium iodide (Note 10), and 50 ml. of tetrahydrofuran (Note 11). The mixture is stirred vigorously (Note 12) and

heated to reflux by means of an electric heating mantle (Note 13). A black precipitate starts to form within a few minutes. After 3 hours at reflux temperature, the reduction should be complete (Note 14), producing active magnesium as a black powder that settles very slowly when the stirring is stopped (Note 15).

D. 1-*Norbornanecarboxylic acid.* The mixture of active magnesium metal and potassium salts is allowed to cool to room temperature, after which 1.25 g. (0.0096 mole) of 1-chloronorbornane is injected with a syringe through the septum into the flask (Note 16). The reaction mixture is heated under reflux for 6 hours and cooled to room temperature. A large excess of freshly sublimed dry ice chunks is added quickly to the Grignard reagent through the extra neck of the flask. The mixture is stirred vigorously, warmed to room temperature, acidified with 50 ml. of aqueous 20% hydrochloric acid, and extracted with three 100-ml. portions of ethyl ether. The combined ether layers are extracted with 100 ml. of aqueous 10% sodium hydroxide. The alkaline solution is acidified with concentrated hydrochloric acid, and the acidic solution is extracted with two 100-ml. portions of ether. The ether extracts are combined, washed with two 50-ml. portions of water, dried with anhydrous sodium sulfate, and evaporated to give 0.80–0.94 g. (60–70%) of 1-norbornanecarboxylic acid as a slightly yellow crystalline solid, m.p. 106–109° (Notes 17 and 18).

2. Notes

1. Although the submitters have never had a fire or explosion caused by active magnesium or other activated metals, they suggest extreme caution in working with these reactive materials, especially while the worker familiarizes him- or herself with the characteristics of each step in the procedure. If the active magnesium is wet with solvent when removed from the reaction vessel, it does not ignite spontaneously. If, however, the magnesium is allowed to dry first, it begins to glow when exposed to air. The submitters advise that the magnesium powder be kept under an argon atmosphere at all times.

2. The submitters purchased norcamphor from Aldrich Chemical Company, Inc. The checkers prepared this compound according to a literature procedure.[2]

3. The spectral characteristics of 2,2-dichloronorbornane are as follows: infrared (carbon tetrachloride) cm.$^{-1}$: 1449, 1307, 1072, 966, 933, 713; proton magnetic resonance (carbon tetrachloride) δ (number of protons): 1.1–2.8 (10).

4. Pentane was dried by distillation from aluminum chloride.

5. 1-Chloronorbornane has the following spectral properties: infrared (carbon tetrachloride) cm.$^{-1}$: 1451, 1310, 1298, 1037, 992, 947, 905, 838; proton magnetic resonance (carbon tetrachloride) δ (multiplicity, number of protons, assignment): 1.2–1.9 (broad multiplet, 10, five CH_2) and 2.2 (broad singlet, 1, one CH); carbon-13 magnetic resonance (chloroform-*d*): δ (off-resonance multiplicity, assignment): 31.0 (multiplet, C-2 and C-6 or C-3 and C-5), 34.8 (doublet, C-4), 38.4 (multiplet, C-2 and C-6 or C-3 and C-5), 46.8 (triplet, C-7), 70.0 (singlet, C-1).

6. The apparatus is dried in an oven and maintained under an argon atmosphere during the reaction. The submitters recommend against the use of nitrogen, since there are indications that nitrogen reacts with active magnesium. Argon, used as supplied by Matheson Gas Products or the Linde Division of Union Carbide Corporation, was delivered to the gas inlet through a combination of glass and Tygon tubing. A minimum of Tygon tubing is advised to avoid the diffusion of air into the argon stream.

7. Purified-grade potassium from J. T. Baker Chemical Company has been found by the submitters to give the most consistent results. The checkers used potassium metal from Allied Chemical Corporation. Very impure potassium or sodium generally gives magnesium powder with much reduced reactivity. Sodium may be used in place of potassium provided that the boiling point of the solvent chosen (Note 11) is higher than the melting point of the metal.

8. The potassium is usually cut into two or three pieces under hexane or heptane and placed wet in a tared flask that has been purged with argon. The flask is evacuated to remove the hydrocarbon, filled again with argon, and weighed to determine the exact amount of potassium. The amount of potassium used by the checkers varied from 1.4 to 1.6 g., the weights of the other reagents being adjusted proportionately. With this procedure the pieces of potassium are shiny and relatively free from oxide coating. Alternatively the potassium cuttings may be wiped free of solvent, quickly weighed in air, and placed in the flask. The submitters recommend that the first procedure be used.

9. Anhydrous magnesium chloride from Alfa Division, Ventron Corporation, was used as supplied by both the submitters and checkers. The submitters have subsequently had success with anhydrous magnesium chloride and bromide purchased from Cerac, Inc., P.O. Box 1178, Milwaukee, Wisconsin 53201. The checkers were unsuccessful in several attempts to prepare suitably active magnesium from analytical-grade anhydrous magnesium chloride purchased from Research Organic/Inorganic Chemical Corporation. The submitters stress that the reagent must be anhydrous. It may be stored in a desiccator containing anhydrous calcium sulfate and, if required, dried overnight in an oven at 120°. Anhydrous magnesium chloride cannot, however, be prepared by heating the hexahydrate under vacuum, since hydrogen chloride is released before dehydration is complete. The submitters have prepared active magnesium from anhydrous magnesium bromide and iodide; however, highly insoluble magnesium salts such as the fluoride or sulfate are not reduced. A small excess of magnesium chloride is used in this procedure to ensure that the potassium is completely consumed.

The submitters have also provided the following unchecked procedure, which is suitable for preparing both anhydrous magnesium chloride and bromide. The magnesium turnings and 1,2-dibromoethane used were purchased from J. T. Baker Chemical Company and Aldrich Chemical Company, Inc., respectively. A 200-ml., three-necked, round-bottomed flask is equipped with a magnetic stirring bar, two stoppers, and a condenser connected to an argon inlet (Note 6). The flask is charged with 0.35 g. (0.0144 mole) of magnesium turnings, 50 ml. of tetrahydrofuran (Note 11), and 3.0 g. (0.016 mole) of 1,2-dibromoethane. The suspension is warmed gently to initiate the reaction. After the initially exothermic reaction subsides, the mixture is heated at reflux for 50 minutes. The solvent is evaporated under a reduced pressure of argon or nitrogen, leaving a white solid. The flask is then evacuated and heated in an oil bath at 150° for 1 hour. The dry magnesium bromide is ready for preparing active magnesium in the same flask.

10. Potassium iodide (>99% purity) from Allied Chemical Cor-

poration or Mallinckrodt Chemical Works is finely ground with a mortar and pestle, dried overnight in an oven at 120°, and stored in a desiccator. The molar ratio of potassium iodide to magnesium chloride is not highly critical and may vary from 0.05 to 2.0. However, the optimum ratio is 1 : 1, as specified in the procedure. If the potassium iodide is omitted, the black magnesium powder produced reacts with bromobenzene at −78°. However, since the magnesium prepared in this way does not react with fluorobenzene in refluxing tetrahydrofuran, it is evidently less reactive than that produced in the presence of potassium iodide.

11. The submitters purified the tetrahydrofuran prior to use by distillation from lithium aluminum hydride. For a warning concerning potential hazards of this procedure, see *Org. Syn.*, Coll. Vol. **5**, 976 (1973). The checkers distilled the solvent from the sodium ketyl of benzophenone.

The submitters have found that diglyme and 1,2-dimethoxyethane are also effective solvents. The reactivity of the magnesium obtained with 1,2-dimethoxyethane as solvent is slightly reduced. Hydrocarbons, amines, and dioxane proved to be ineffective solvents owing to the insolubility of the magnesium salts and consequent incomplete reduction.

12. Efficient stirring is essential for the generation of highly reactive magnesium. If the stirring is not effective, the reduction may not be complete after the 3-hour reaction time. The remaining unreacted potassium is a fire hazard during the isolation of the product. If the scale of the reaction is increased, measures should be taken to ensure that effective stirring can be maintained throughout the reaction period. The submitters recommend that, as a precaution, the scale be increased gradually.

13. The mildly exothermic reduction may result in excessive foaming which carries potassium particles up into the condenser. This problem is avoided by using a relatively large flask (in this case, 200 ml. instead of 100 ml.) and by carefully controlling the temperature at the beginning of the reduction.

14. The reduction appears to be essentially complete in 30–45 minutes. However, a reaction time of 3 hours is recommended to ensure complete consumption of the potassium (Note 12).

15. Although the submitters have found that the active magnesium may be stored under argon for several days, they advise

that the preparation be used within a few hours to obtain the maximum reactivity. Most of the reactions carried out by the submitters with the active magnesium were performed in the same flask and solvent used for the reduction. Attempts to evaporate the tetrahydrofuran and replace it with different solvents resulted in magnesium suspensions of reduced reactivity. The active magnesium may be conveniently transferred to another reaction vessel, if desired, as a slurry under an atmosphere of argon.

16. The solid chloride was melted by warming on a steam bath and drawn into a syringe that had been warmed briefly in an oven.

17. The submitters reported a melting point of 114–116°. The checkers obtained analytically pure material with a recovery of 80% after decolorization with activated carbon and recrystallization from 2–3 ml. of hexane at 0°. The product was also purified with comparable efficiency by sublimation at 85–90° (10 mm.). A small amount of a yellow, volatile impurity was removed from the cold finger before the product began to sublime. The melting point of the product after purification by the checkers was 110–112°. The reported[3] melting point is 114–116°.

18. The spectral properties of the product are as follows: infrared (potassium bromide) $cm.^{-1}$: 2960 (OH), 1693 (C=O), 1422, 1312, 1262, 952, 734; proton magnetic resonance (carbon tetrachloride) δ (multiplicity, number of protons, assignment): 1.1–1.9 (multiplet, 10, five CH_2), 2.2 (broad singlet, 1, one CH), 12.5 (singlet, CO_2H); carbon-13 magnetic resonance (chloroform-*d*) δ (off-resonance multiplicity, assignment): 30.0 and 33.0 (multiplets, C-2, C-3, C-5, C-6), 37.8 (doublet, C-4), 42.4 triplet, C-7), 52.2 (singlet, C-1), 183.8 (singlet, carboxyl).

3. Discussion

The procedures for the preparation of 2,2-dichloronorbornane and 1-chloronorbornane are based on those of Bixler and Nieman.[3] The active magnesium generated in Part C of this procedure[4–6] is useful for the formation of Grignard reagents from alkyl and aryl halides that do not react, or react only slowly, with magnesium turnings or magnesium activated by previously known methods. Prior to the development of this procedure, four basic

modifications of the usual methods for preparing Grignard reagents were utilized for relatively unreactive halides: the use of (1) higher reaction temperatures by variation of the solvent, (2) more strongly coordinating solvents such as tetrahydrofuran,[7-9] (3) various procedures to activate the surface of the magnesium,[10-14] and (4) magnesium slurries prepared by cocondensation of magnesium vapor and solvent.[15]

Activation of the magnesium in the third method has been effected by reduction of the size of the metal particles[13] and chemical reactions. The Gilman procedure,[10] which consists of adding iodine to activate the magnesium surface, is representative of the latter technique. Ethyl bromide and 1,2-dibromoethane have been employed in catalytic amounts to activate the metal surface, and in stoichiometric proportions for entrainment.[11] Certain transition metal halides have also proven to be effective catalysts.[12] The magnesium preparations obtained by the cocondensation method are quite active, though considerably less active than those generated by the reduction process.[16] An alternative procedure has recently been published for the reduction of magnesium halides to activated magnesium with sodium naphthalene radical anion.[17]

Some results from an investigation into the reactions of the activated magnesium with various halides and dihalides, some of which react with difficulty under the conditions of normal Grignard preparations, are given in Table I.[6] A number of important features can be noted from the table, including the facile formation of di-Grignard reagents and allyl- and vinylmagnesium halides. Alkyl and aryl fluorides are easily converted to the corresponding magnesium fluorides. The formation of Grignard reagents may be effected at temperatures of $-78°$ or below with the active magnesium, thus allowing Grignard reactions to be carried out with unstable compounds.

The Grignard reagents prepared from the activated magnesium appear to react normally with electrophiles. Thus reactions with proton donors, ketones, and carbon dioxide afford hydrocarbons, alcohols, and carboxylic acids, respectively. The reductive coupling of ketones to pinacols had also been accomplished with the activated magnesium.[16]

1-Norbornanecarboxylic acid has been prepared by concurrent rearrangement and hydrogenolysis of *endo*-2-bromo-2-norbornanecarboxylic acid,[18] by sequential reduction and hydrolysis of *exo*-2-bromo-1-norbornanecarboxamide,[19] by ozonolysis of 1-(4-methoxyphenyl)norbornane,[20] and by carbonation of 1-norbornyllithium.[3]

TABLE I
REACTION OF VARIOUS HALIDES WITH ACTIVATED MAGNESIUM

Halide	Magnesium/ Halide[a] Ratio	Temperature (°)	Time (minutes)	Yield of Product (%) Mono-Grignard[b]	Di-Grignard[b]	Carboxylic Acid[c]
p-Dibromobenzene	4	25	15		100	
p-Bromochlorobenzene	4	25	15	100	10	
	4	25	120	100	100	
p-Dichlorobenzene	2	25	180	90	0	80
	4	25	120	100	30	
Fluorobenzene	4	66	60			69
t-Butyl chloride	2	25	10	100		52
1-Chloronorbornane	1.7	66	360	74		63
Methallyl chloride	2	25	60			82
2-Bromopropene	2	25	5	100		71

[a] With the aryl halides and 1-chloronornane the activated magnesium was formed in the presence of potassium iodide.
[b] Yield of hydrocarbon determined by gas chromatography after hydrolysis.
[c] Isolated yield based on halide after carbonation.

1. Department of Chemistry, University of Nebraska—Lincoln, Lincoln, Nebraska 68588. This work was supported in part by grants from the Research Corporation, National Science Foundation, North Carolina Board of Science and Technology, the Alfred P. Sloan Foundation, and the Army Research Office.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Norbornane, 2,2-dichloro- (8); Bicyclo[2.2.1]heptane, 2,2-dichloro- (9); (19916-65-5)

Phosphorus chloride (8); Phosphorous trichloride (9); (7719-12-2)

Norcamphor: 2-Norbornanone (8); Bicyclo[2.2.1]heptan-2-one (9); (497-38-1)

Phosphorous pentachloride: Phosphorus chloride (PCl_5) (8); Phosphorane, pentachloro- (9); (10026-13-8)

Norbornane, 1-chloro- (8); Bicyclo[2.2.1]heptane, 1-chloro- (9); (765-67-3)

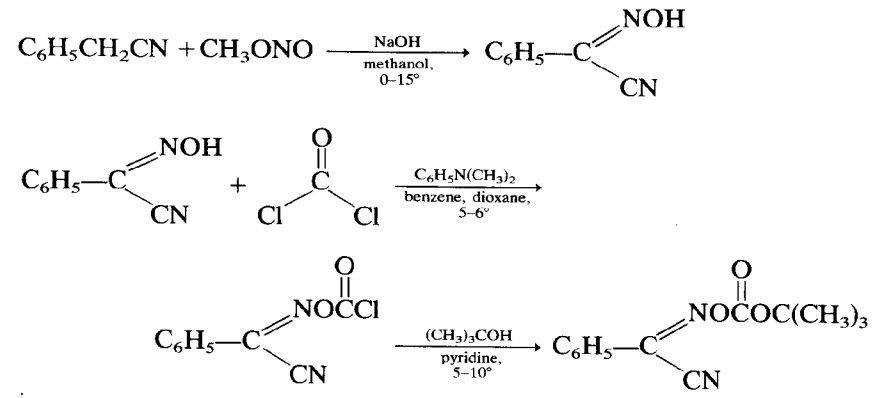
1-Norbornanecarboxylic acid (8); Bicyclo[2.2.1]heptane-1-carboxylic acid (9); (18720-30-4)

Benzene, bromo- (8, 9); (108-86-1)

Benzene, fluoro (8, 9); (462-06-6)

A NEW REAGENT FOR *tert*-BUTOXYCARBONYLATION: 2-*tert*-BUTOXYCARBONYLOXYIMINO-2-PHENYLACETONITRILE

(Benzeneacetonitrile, α-[[[(1,1-dimethylethoxy)carbonyl]oxy]imino]-)



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Checked by HIROYUKI ISHITOBI, TERUJI TSUJI, and WATARU NAGATA

1. Procedure

Caution! Phosgene is highly toxic. Part B should be performed in an efficient hood. For a warning regarding the use of benzene, see ref. 2.

A. 2-*Hydroxyimino*-2-*phenylacetonitrile.* A 1-l., round-bottomed flask is fitted with a mechanical stirrer, a calcium chloride drying tube, a thermometer, and a gas-inlet tube. In the flask are placed 117 g. (1.0 mole) of benzyl cyanide and a solution of 40.0 g. (1.0 mole) of sodium hydroxide in 300 ml. of methanol (Note 1). The resulting solution is stirred and cooled at 0° as methyl nitrite is introduced through the gas-inlet tube, which extends below the surface of the liquid. The methyl nitrite is generated by dropwise addition of a cold solution of 32 ml. of concentrated sulfuric acid in 65 ml. of water from a 100-ml., pressure-equalizing dropping funnel into a 300-ml. Erlenmeyer flask containing a suspension of 83 g. (1.2 moles) of sodium nitrite

in 53 ml. of methanol and 50 ml. of water (Note 2). The rate of generation of methyl nitrite is adjusted so that the reaction temperature does not exceed 15°. After the addition is complete (Note 3), stirring is continued for another 2 hours, and the solvent is removed under reduced pressure with a rotary evaporator. The residue is dissolved in 500 ml. of water, and the resulting solution is washed with two 100-ml. portions of toluene. The aqueous layer is acidified with concentrated hydrochloric acid and cooled in an ice bath. The resulting precipitate is filtered, washed thoroughly with cold water, and dried. The yield of 2-hydroxyimino-2-phenylacetonitrile is 111–120 g. (76–82%), m.p. 119–124° (Note 4). This material is used in Part B without further purification.

B. 2-tert-*Butoxycarbonyloxyimino*-2-*phenylacetonitrile.* A 200-ml., three-necked, round-bottomed flask is equipped with a dropping funnel, a mechanical stirrer, a thermometer, and a calcium chloride drying tube. The flask is charged with a solution of 10.9 g. (0.11 mole) of phosgene (Note 5) in 30 ml. of benzene. The contents of the flask are stirred and cooled in an ice bath while a solution of 14.6 g. (0.1 mole) of 2-hydroxyimino-2-phenylacetonitrile and 13.2 g. (0.11 mole) of *N,N*-dimethylaniline in 5 ml. of dioxane and 80 ml. of benzene (Note 6) is added dropwise over 1 hour at 5–6°. Stirring is continued for 6 hours at the same temperature, after which the mixture is allowed to stand overnight in an ice bath. A solution of 11.1 g. (0.15 mole) of *tert*-butyl alcohol and 12.0 ml. (0.15 mole) of pyridine (Note 7) in 30 ml. of benzene (Note 6) is added over 1 hour as the mixture is stirred and cooled at 5–10°. Stirring is continued for an additional 6 hours while the reaction temperature is allowed to rise to room temperature. The reaction mixture is allowed to stand overnight (Note 8) and is then mixed with 50 ml. of water and 50 ml. of benzene. The organic layer is separated and washed successively with three 30-ml. portions of cold 1*N* hydrochloric acid, 30 ml. of water, two 30-ml. portions of 5% sodium bicarbonate solution, and two 30-ml. portions of water. Each of the aqueous washings is extracted with 30 ml. of benzene. The organic layers are combined, dried with magnesium sulfate, and concentrated to dryness under reduced pressure at a temperature lower than 35°. The crystalline residue is triturated with 20 ml. of aqueous 90% methanol. The solid is filtered, washed with 30 ml. of aqueous 90% methanol, and

dried to give 15.8–17.0 g. of crude product, m.p. 84–86° (Note 9). Recrystallization from methanol (Note 10) affords 14.6–15.7 g. (59–64%) of 2-*tert*-butoxycarbonyloxyimino-2-phenylacetonitrile as white needles or plates, m.p. 84–86° (Note 11).

2. Notes

1. The submitters used reagent-grade solvents and reagents without further purification. The yield of 2-hydroxyimino-2-phenylacetonitrile was 76% when the checkers used technical-grade benzyl cyanide purchased from Wako Pure Chemical Industries, Ltd., Osaka, Japan. The yield was improved to 81% with distilled material, b.p. 75–77° (3 mm.). Benzyl cyanide is also available from Aldrich Chemical Company, Inc.

2. This method for the preparation of methyl nitrite is described in *Organic Syntheses.*[3]

3. The addition of sulfuric acid requires *ca.* 1 hour. Occasional swirling of the Erlenmeyer flask is recommended for smooth generation of methyl nitrite.

4. Material of this quality is satisfactory for most purposes; however, if further purification is necessary, it may be recrystallized from hot water to give a solid that melts at 126–128°. The checkers obtained product melting at 104–116° and 104–117° in the first and second runs, respectively. Evidently the product is a mixture of *syn* and *anti* isomers, the ratio of which was different in the material obtained by the submitters and the checkers. This difference in the isomer ratio might be attributed to a slight variation of experimental conditions. The submitters later informed the checkers that the methanol was evaporated at 70–80°. The checkers removed the solvent at 35–40°. On partial recrystallization from hot water, the checkers isolated both the less-soluble *anti* isomer, with a melting point at 127.5–129°, and the more soluble *syn* isomer, with a melting point of 97–99°. The melting points given in the literature for the *syn* and *anti* isomers are 129° and 99°, respectively.[4] The ultraviolet spectra of the *syn* and *anti* isomers in 95% ethanol show maxima at 274 nm. (log ε, 3.99) and 260 nm. (log ε, 4.05), respectively.

5. Phosgene can be replaced by a 0.5 molar equivalent of trichloromethyl chloroformate. This reagent may be purchased from

Hodogaya Chemical Company, Ltd., Tokyo, Japan, or prepared by the procedure of Kurita and Iwakura.[5]

6. *N,N*-Dimethylaniline, pyridine, *tert*-butyl alcohol, and the solvents were dried with Linde type 3A molecular sieves.

7. The use of a 0.5 molar excess of pyridine and *tert*-butyl alcohol is necessary in this case to obtain a satisfactory yield. However, when this procedure is applied to preparation of other alkoxycarbonates (Table II), an excess of the alcohol should be avoided since it may contaminate the product.

8. The yield was reduced to 46% in a run in which the product was isolated without the additional overnight reaction time.

9. The checkers obtained 12.8–13.0 g. (52–53%), m.p. 84–86°, in the first crop and 2.7–3.4 g. (11–14%), m.p. 52–62°, in the second crop. Recrystallization of the former from methanol gave 11.5 g. of crystals, m.p. 84–86°, suggesting that the first crop is a pure single isomer. A proton magnetic resonance spectrum in chloroform-*d* of the second crop shows two singlets at δ 1.62 and 1.64 for the *tert*-butyl groups. Thus this material is a mixture of *syn* and *anti* isomers. Both the first and second crops proved equally useful for *tert*-butoxycarbonylation of an amino acid.

10. Recrystallization from boiling methanol should be avoided owing to the thermal instability of the product.

11. The product has the following spectral properties: infrared (Nujol) cm.$^{-1}$: 1785 (C=O); proton magnetic resonance (chloroform-*d*) δ (multiplicity, number of protons, assignment): 1.62 (singlet, 9, three CCH_3), 7.2–8.2 (multiplet, 5, C_6H_5). A thin-layer chromatogram on silica gel (Merck precoated plate, 60 F_{254}) using ultraviolet detection and 10% methanol in chloroform as the developing solvent showed a major and a minor spot at an *Rf* value of 0.74 and 0.50, respectively. The minor spot arises from 2-hydroxyimino-2-phenylacetonitrile formed by partial hydrolysis of the product on the silica gel.

The submitters recommend that the product be stored in a stoppered brown bottle in a refrigerator. Although the material can be kept at room temperature for several weeks without noticeable decomposition, gradual evolution of carbon dioxide occurs over a period of several months, with the attendant risk of explosion. However, storage in the presence of a small amount of silica gel as a drying agent extends the shelf life of the material to more than a year.

3. Discussion

2-Hydroxyimino-2-phenylacetonitrile has been prepared from benzyl cyanide by reaction with nitrous acid,[6] with isoamyl nitrite and sodium ethoxide,[7] and with butyl nitrite and hydrogen chloride.[4]

The *tert*-butoxycarbonyl group is one of the most important amino protecting groups in peptide synthesis. Many *tert*-butoxycarbonylating reagents[8,9] have been prepared as substitutes for *tert*-butyl azidoformate,[10] which is toxic, shock-sensitive, and relatively unreactive.[11] 2-*tert*-Butoxycarbonyloxyimino-2-phenylacetonitrile,[12] one such reagent, possesses the following advantages: (1) it is stable, highly reactive, and ready for use; (2) *tert*-butoxycarbonylation of an amino acid is usually complete within 4–5 hours at room temperature in the presence of a 0.5 molar excess of triethylamine in 50% aqueous dioxane (Table I); and (3) the by-product, 2-hydroxyimino-2-phenylacetonitrile, is easily and completely removed by extraction into an organic solvent, leaving the *tert*-butoxycarbonylamino acid salt in the aqueous phase. The present procedure is also applicable to preparation of other amino-protecting reagents (Table II).

TABLE I

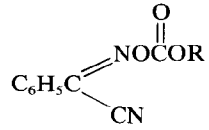
PREPARATION OF *N*-*tert*-BUTOXYCARBONYL-PROTECTED AMINO ACIDS WITH 2-*tert*-BUTOXYCARBONYLOXYIMINO-2-PHENYLACETONITRILE[a]

Amino Acid	Solvent[b]	Time (hours)	Yield (%)
Glycine	A	2	87
Alanine	B	4	80
S-Benzyl cysteine	A	3	94
Glutamic acid	A	3	78
Leucine	A	3	72
Methione	A	3	82
Phenylalanine	A	2	65
Proline	C	1.5	88
Threonine	A	3	100
Asparagine	A	20	86

[a] The reactions were carried out with 0.010 mole of the amino acid, 0.011 mole of 2-*tert*-butoxycarbonyloxyimino-2-phenylacetonitrile, and 0.015 mole of triethylamine at 20–25°.

[b] The solvents were as follows: A, aqueous dioxane; B, aqueous acetone; C, methanol–dioxane–water, 15:5:10.

TABLE II
OTHER ALKOXYCARBONYLATING REAGENTS PREPARED FROM 2-HYDROXYIMINO-2-PHENYLACETONITRILE



R	Solvent for Recrystallization	M.p. (°)	Yield (%)
$C_6H_5CH_2$—	ethyl acetate–hexane	73–75	62
p-$CH_3OC_6H_4CH_2$—	ethyl acetate–hexane	112–113	36
Cl_3CCH_2—	methanol	82–84	87

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11. For warnings regarding the use of *tert*-butyl azidoformate, see *Org. Syn.*, **57,** 122 (1977); P. Feyen, *Angew. Chem. Int. Ed. Engl.*, **16,** 115 (1977).
12. (a) M. Itoh, D. Hagiwara, and T. Kamiya, *Tetrahedron Lett.*, 4393 (1975); (b) M. Itoh, D. Hagiwara, and T. Kamiya, *Bull. Chem. Soc. Jap.*, **50,** 718 (1977).

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Phosgene (8); Carbonic dichloride (9); (75-44-5)

Acetonitrile, 2-hydroxyimino-2-phenyl- (8); Benzeneacetonitrile, α-(hydroxyimino)- (9); (825-52-5)

Benzyl cyanide: Acetonitrile, phenyl- (8); Benzeneacetonitrile (9); (140-29-4)

Methyl nitrite: Nitrous acid, methyl ester (8, 9); (624-91-9)

Acetonitrile, 2-*tert*-butoxycarbonyloxyimino-2-phenyl- (8); Benzeneacetonitrile, α-[[[(1,1-dimethylethoxy)carbonyl]oxy]imino]-(9); (58632-95-4)

Aniline, *N*,*N*-dimethyl- (8); Benzenamine, *N*,*N*-dimethyl- (9); (121-69-7)

tert-Butyl alcohol (8); 2-Propanol, 2-methyl- (9); (75-65-0)

Trichloromethyl chloroformate: Formic acid, chloro-, trichloromethyl ester (8); Carbonochloridic acid, trichloromethyl ester (9); (503-38-8)

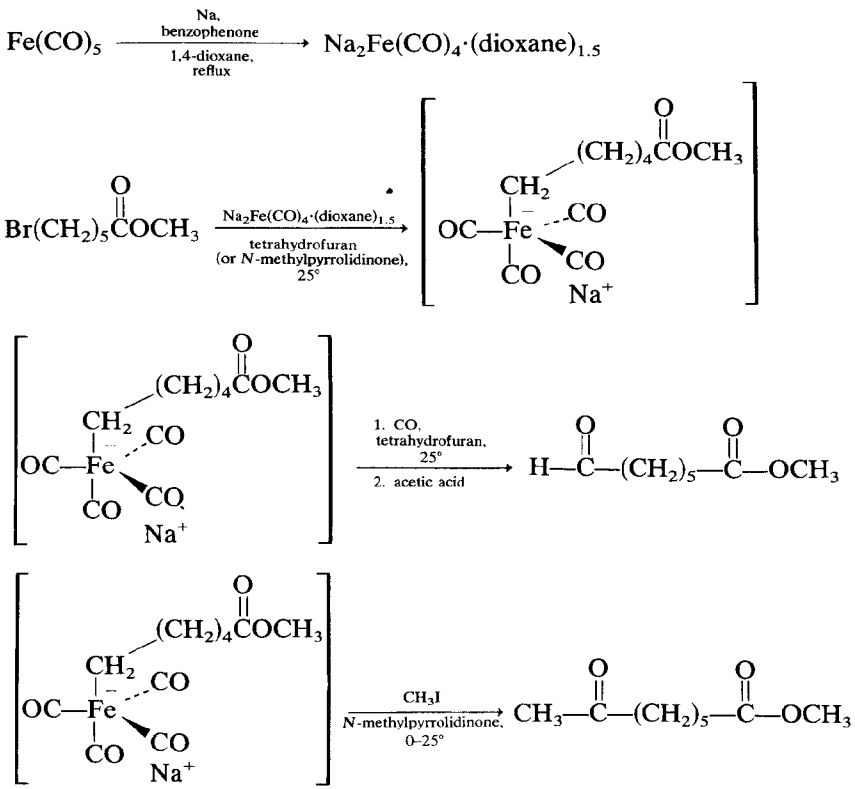
Isoamyl nitrite: Nitrous acid, isopentyl ester (8); Nitrous acid, 3-methylbutyl ester (9); (110-46-3)

Butyl nitrite: Nitrous acid, butyl ester (8, 9); (544-16-1)

Formic acid, azido-, *tert*-butyl ester (8); Carbonazidic acid, 1,1-dimethylethyl ester (9); (1070-19-5)

Triethylamine (8); Ethanamine, *N*,*N*-diethyl- (9); (121-44-8)

NUCLEOPHILIC ACYLATION WITH DISODIUM TETRACARBONYLFERRATE: METHYL 7-OXOHEPTANOATE AND METHYL 7-OXOOCTANOATE



Submitted by RICHARD G. FINKE[1,2] and THOMAS N. SORRELL[1,3]
Checked by RICHARD T. TAYLOR and MARTIN F. SEMMELHACK

1. Procedure

Caution! Iron pentacarbonyl, carbon monoxide, and methyl iodide are highly toxic; consequently all parts of this procedure should be carried out in a well-ventilated hood. Iron pentacarbonyl is easily recognized by its musty odor. Since disodium tetracarbonylferrate is very pyrophoric, the reagent must be kept under a dry inert atmosphere at all times.

A. *Disodium tetracarbonylferrate sesquidioxanate* (*Note* 1). A dry, 2-l., three-necked, round-bottomed flask is equipped with a mechanical stirrer (Note 2), a three-way stopcock with one branch connected to a nitrogen source, and a Y-shaped adapter fitted with a reflux condenser vented through an oil bubbler and with a pressure-equalizing dropping funnel capped by a rubber septum. The apparatus is flushed with nitrogen (Note 3) for 15 minutes and charged with 600 ml. of dry, deoxygenated dioxane (Notes 4 and 5), 10.6 g. (0.46 mole) of sodium, and 9.1 g. (0.05 mole) of benzophenone. The solution is stirred vigorously and heated under reflux with a heating mantle until the deep blue color of the benzophenone ketyl appears. By means of a gas-tight syringe, 45.3 g. (31 ml., 0.23 mole) of iron pentacarbonyl (Note 6) is injected into the dropping funnel. The blue solution is then titrated to a white or slightly yellow end point by adding iron pentacarbonyl to the refluxing solution over 2.5 hours (Note 7). The suspension is heated at reflux for another 45 minutes and then cooled to room temperature. Precipitation of the disodium tetracarbonylferrate sesquidioxanate as a white powder is completed by adding 600 ml. of dry, deoxygenated hexane (Notes 5 and 8). The Y-shaped adapter and the mechanical stirrer are removed under a rapid stream of nitrogen and quickly replaced by a tight-fitting rubber septum and a gas-dispersion tube with a fritted-glass tip (see Figure 1). The solvent is forced up the gas-dispersion tube and

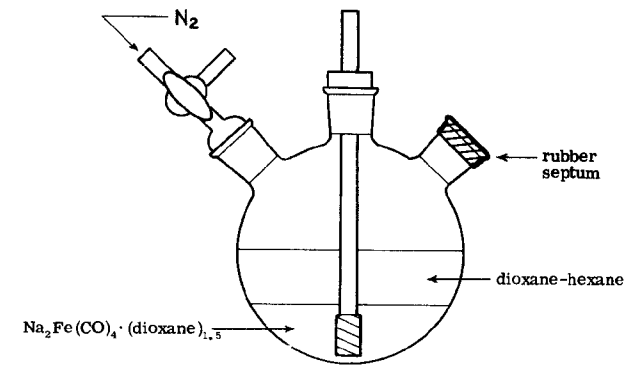


Figure 1

out of the flask by nitrogen pressure (Note 9). The product is washed in the flask with two 400-ml. portions of hexane added via cannula (Note 5), and the supernatant solvent is removed with nitrogen pressure in the same manner. The disodium tetracarbonylferrate sesquidioxanate is used directly in Parts B and C without drying or weighing (Note 10).

B. *Methyl 7-oxoheptanoate.* In the same three-necked, round-bottomed flask containing 72–78 g. (0.21–0.23 mole) of disodium tetracarbonylferrate sesquidioxanate, the gas-dispersion tube is replaced by a mechanical stirrer, and 1.5 l. of dry, deoxygenated tetrahydrofuran (Note 11) is added. The light tan suspension is stirred vigorously as 41.8 g. (0.2 mole) of methyl 6-bromohexanoate (Note 12) is added in one portion by syringe. The nitrogen is flushed from the flask with carbon monoxide (Notes 13 and 14) admitted through the other branch of the three-way stopcock, and the suspension is stirred under 10 p.s.i.g. of carbon monoxide for at least 14 hours during which time the solid dissolves. A rapid flow of nitrogen is swept through the flask while the septum is removed and replaced quickly by a pressure-equalizing dropping funnel. The dropping funnel is flushed with nitrogen and charged with 50 ml. of glacial acetic acid which is then added dropwise to the orange solution (Note 15). Stirring is continued for 20 minutes, after which the deep red solution is concentrated to a volume of *ca.* 400 ml. with a rotary evaporator in the hood (*Caution! Some iron pentacarbonyl is present*) and poured into 2 l. of water. The mixture is extracted with four 400-ml. portions of ethyl ether, and the combined organic solutions are washed with 400 ml. of water. The ethereal solution is mixed with 400 ml. of aqueous 2 *M* hydrochloric acid, and 68 g. of iron(III) chloride is added in small portions until carbon monoxide evolution subsides and the organic layer becomes green from triiron dodecacarbonyl. The organic layer is washed with successive 400-ml. portions of aqueous 2 *M* hydrochloric acid, water, saturated sodium bicarbonate, and saturated sodium chloride. After being dried with anhydrous sodium sulfate, the ethereal solution is concentrated to a green oil with a rotary evaporator. Iron-containing by-products such as triiron dodecacarbonyl and iron pentacarbonyl are removed by rapid chromatography on a 7 × 40 cm. column prepared in hexane with 400 g. of silica gel (Note 16). The green triiron dodecacarbonyl is first eluted with *ca.* 3 l. of hexane, and the product is then eluted with 3 l. of 2:1(v/v) ether–hexane. The ether–hexane eluate is dried with anhydrous magnesium sulfate and evaporated. Distillation of the residual oil through a 15-cm. Vigreux column at reduced pressure affords a small forerun amounting to 1 ml. or less and 17.9–20.0 g. (57–63%) of methyl 7-oxoheptanoate, b.p. 65–80° (0.1 mm.), n_D^{20} 1.4388 (Note 17).

C. *Methyl 7-oxooctanoate.* The 2-l., three-necked, round-bottomed flask containing 72–78 g. (0.21–0.23 mole) of disodium tetracarbonylferrate from Part A is flushed rapidly with nitrogen while the gas-dispersion tube is removed, a magnetic stirring bar is placed inside, and a pressure-equalizing dropping funnel is attached. The other branch of the three-way stopcock is connected to a bubbler, the dropping funnel is capped with a rubber septum, and 600 ml. of dry deoxygenated *N*-methylpyrrolidinone (Notes 5 and 18) is added. The suspension is stirred and maintained under a static nitrogen atmosphere as 41.8 g. (0.2 mole) of methyl 6-bromohexanoate (Note 12) is injected into the dropping funnel with a gas-tight syringe and added dropwise into the flask. The resulting solution (Note 19) is stirred for 30 minutes at room temperature and cooled in an ice bath before 64 g. (28 ml., 0.45 mole) of methyl iodide is added over 20 minutes. The ice bath is removed and stirring is continued for 20–40 hours (Note 14). The dark red mixture is poured into 3 l. of saturated aqueous sodium chloride and extracted with three 400-ml. portions of ether and one 400-ml. portion of hexane. The combined organic solutions are washed with one 400-ml. portion of water and one 400-ml. portion of saturated sodium chloride. After 400 ml. of aqueous 2 *M* hydrochloric acid is added, the iron by-products are oxidized with iron(III) chloride exactly as described in Part B. The etheral solution is evaporated under reduced pressure, the residual oil is applied to a column of silica gel packed in hexane, and the organic product is separated from the iron by-products by chromatography as described in Part B. The ether–hexane eluate is dried with anhydrous magnesium sulfate, the solvent is evaporated, and the remaining liquid is distilled at reduced pressure to give 24.0–24.8 g. (70–72%) of methyl 7-oxooctanoate, b.p. 112–127° (10 mm.), n_D^{20} 1.4360 (Note 20).

2. Notes

1. Approximately 4.5 hours are required to complete Part A.

2. A mechanical stirrer is necessary on any scale owing to the formation of a thick slurry toward the end of the reaction.

3. The submitters passed the nitrogen through *ca.* 100 g. of BASF catalyst R3-11 contained in a metal tube and heated at 160° to remove oxygen and through a column of Linde type 3A molecular sieves to remove water. The catalyst (catalog number 18-3000-00) and pertinent literature were obtained from Chemical Dynamics Corporation, P.O. Box 395, South Plainfield, New Jersey 07080. The checkers used "prepurified" nitrogen and argon in separate runs without additional drying or oxygen scavenging.

4. Dioxane was heated at reflux with sodium overnight under nitrogen, benzophenone was added, and the solvent was distilled after appearance of the deep blue color of the benzophenone ketyl.

5. The submitters recommend that the solvent be distilled under nitrogen into a two-necked receiving flask fitted with a three-way stopcock. The receiving flask is separated from the distillation apparatus under a rapid nitrogen flow and fitted quickly with a rubber septum. The solvent is then transferred to the reaction vessel by needlestock techniques.[4]

A stainless steel cannula with a 2-mm. inside diameter and both ends sharpened is inserted through the septum into the receiving flask above the surface of the liquid, and a stream of nitrogen is passed briefly through the stopcock and out the cannula to remove air. The other end of the cannula is then inserted through the septum on the reaction vessel, the end of the cannula in the receiver is pushed below the surface of the liquid, and the solvent is forced into the reaction vessel with nitrogen pressure.

6. Iron pentacarbonyl was purchased from PCR, Inc., Gainesville, Florida, and stored under nitrogen.

7. Approximately 95% of the iron pentacarbonyl is added within 2 hours, and the remaining 5% is then added dropwise over the next 30 minutes. The blue color should never be completely discharged prior to the end point, particularly toward the end of the reaction, since the remaining solution may be deactivated. Avoiding premature discharge of the blue color is especially important in small-scale preparations. At the end point 1 ml. or less of the iron pentacarbonyl remains in the dropping funnel.

The checkers carried out the reaction on a smaller scale in two runs, adding 13.1 g. (9 ml., 0.067 mole) of iron pentacarbonyl as a solution in 50 ml. of dry dioxane.

8. Reagent-grade hexane was dried and deoxygenated by distillation from calcium hydride under nitrogen.

9. Alternatively, 300–400 ml. of the dioxane may be transferred by this method into another flask before the hexane is added. The recovered dioxane may then be used in another preparation without purification.

10. The yield is typically 72–78 g. (90–100%). An excess of the reagent is not detrimental to the procedures in Parts B and C. The submitters have doubled the scale of this procedure with no change in the yield. For smaller-scale reactions the submitters recommend that the reagent be purchased from Alfa Division, Ventron Corporation. The checkers used the commercially available reagent successfully in one run, the material having been transferred to the reaction vessel in a dry box.

11. Tetrahydrofuran was dried and deoxygenated by distillation from calcium hydride under nitrogen.

12. 6-Bromohexanoic acid was purchased from Aldrich Chemical Company, Inc., and esterified with sulfuric acid and methanol. Methyl 6-bromohexanoate was obtained as a colorless liquid, b.p. 92–94° (5 mm.), n_D^{20} 1.4510, judged to be greater than 99% pure according to gas chromatographic analysis on dimethylsilicone (OV-101) as liquid phase.

13. A cylinder of carbon monoxide equipped with a suitable regulator calibrated in pounds per square inch (p.s.i.g.) is connected to the three-way stopcock. All joints and the septum must be secured with clamps or wire. A vertical tube containing mercury was connected to an exit tube from the reaction flask by the checkers. A pressure of carbon monoxide was maintained against a 500-mm. column of mercury.

14. Alkyl tetracarbonyl iron(0) reagents in solution decompose more rapidly with increasing concentration and temperature, especially above 0°. Carbon monoxide must be added without delay to convert this intermediate to the more stable acyl iron compound.

15. Subsequent operations may be conducted in air. However, the procedure should not be interrupted until the ethereal solution is drying over sodium sulfate.

16. Silica gel of mesh 60–200 was supplied by Davison Chemical Division, W. R. Grace and Company, Baltimore, Maryland, and was dried at 70° before use. The flow rate of hexane during the chromatography was 4 l. per hour.

17. The checkers obtained 13.6 g. (43%) of product, b.p. 65–75° (0.1 mm.). The submitters determined that the purity of the product was greater than 90% by gas chromatography using 10% dimethylsilicone (OV-101) as liquid phase at 200°. The proton magnetic resonance spectrum of the product in chloroform-*d* shows the following absorptions: δ (multiplicity, number of protons, assignment, coupling constant *J* in Hz.): 1.48 (multiplet, 6, three CH_2), 2.32 (triplet, 2, $CH_2CO_2CH_3$), 2.40 (triplet of doublets, 2, $CH_2CH{=}O$, $J = 2$ and 8), 3.65 (singlet, 3, CO_2CH_3), 9.62 (triplet, 1, $CH{=}O$, $J = 2$).

18. *N*-Methylpyrrolidinone was heated at reflux over calcium hydride under reduced pressure for at least 24 hours by the submitters and then distilled from the calcium hydride under reduced pressure. The checkers stirred the solvent in the presence of calcium hydride at 100° for 48 hours prior to distillation at 150 mm.

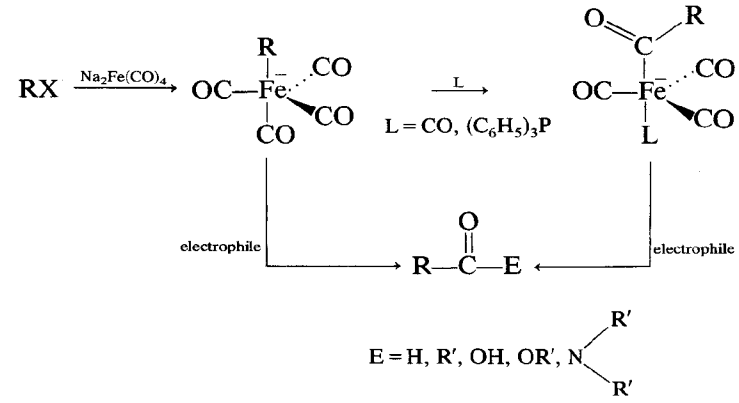
19. The homogeneous solution, if free of impurities, is bright yellow. Usually, however, the color is dark red or orange, evidently owing to the presence of trace amounts of impurities.

20. Starting with 13.1 g. (9 ml., 0.067 mole) of iron pentacarbonyl, the checkers obtained 7.3–7.4 g. (71–75%) of product, b.p. 92–95° (2 mm.). A gas chromatographic analysis by the submitters using dimethylsilicone (OV-101) as liquid phase at 200° showed the purity of the product to be greater than 95%. The spectral properties of the product are as follows: infrared (thin film) $cm.^{-1}$: 1735 (ester C=O), 1715 (ketone C=O); proton magnetic resonance (chloroform-*d*): δ (multiplicity, number of protons, assignment, coupling constant *J* in Hz.): 1.46 (multiplet, 6, three CH_2), 2.12 (singlet, 3, CH_2COCH_3), 2.32 (triplet, 2, $CH_2CO_2CH_3$, $J = 8$), 2.44 (triplet, 2, CH_2COCH_3, $J = 8$), 3.67 (singlet, 3, CO_2CH_3).

3. Discussion

This procedure describes the preparation of disodium tetracarbonylferrate sesquidioxanate by reduction of iron pentacarbonyl

with sodium and the use of the reagent for nucleophilic formylation and acetylation of the primary bromide, methyl 6-bromohexanoate. Disodium tetracarbonylferrate serves as a synthetic equivalent of carbon monoxide dianion, $\overset{O}{\overset{\|}{{}^{\ominus}C^{\ominus}}}$, in most preparations. Thus the reagent reacts with alkyl halides and *p*-toluenesulfonates to form anionic alkyltetracarbonyl iron(0) complexes which combine in a second step with various electrophiles to give carbonyl compounds.[5] The reagent donates the new carbonyl carbon, which becomes bonded to both the alkyl group and the electrophile in the final product. If the electrophile is a proton from acetic acid or an alkyl group from a second alkyl halide, the overall transformations amount to nucleophilic formylation[6] and acylation,[7] respectively. The preparation of carboxylic acids, esters, and amides by formal nucleophilic carboxylation is accomplished by use of oxygen and water (or sodium hypochlorite and water), iodine and alcohols, and iodine and amines, respectively, as the electrophiles.[8] The general reactions are summarized by the following equations and several specific examples[6–8] are presented in Table I.



The initial reaction between the alkyl halide (or *p*-toluenesulfonate) and disodium tetracarbonylferrate behaves as a typical S_N2-type substitution.[5,9] Thus this step proceeds smoothly with primary and secondary reactants, but the tertiary analogs fail

TABLE I

NUCLEOPHILIC ACYLATION AND CARBOXYLATION OF ALKYL HALIDES AND *p*-TOLUENESULFONATES WITH DISODIUM TETRACARBONYLFERRATE[6-8]

Alkyl Halide or *p*-Toluenesulfonate[a]	Electrophile	Product	Yield (%)
$C_6H_5(CH_2)_2Br$	CH_3CO_2H	$C_6H_5(CH_2)_2C(=O)H$	86[b]
$(CH_3)_2C{=}CH(CH_2)_2Br$	CH_3CO_2H	$(CH_3)_2C{=}CH(CH_2)_2C(=O)H$	81[b]
$CH_3(CH_2)_5CH(Br)CH_3$	CH_3CO_2H	$CH_3(CH_2)_5CH(CHO)CH_3$	50[b,c]
$CH_3(CH_2)_7Br$	CH_3CH_2I	$CH_3(CH_2)_7C(=O)CH_2CH_3$	80
$CH_3(CH_2)_5CH(OTs)CH_3$	CH_3I	$CH_3(CH_2)_5CH(COCH_3)CH_3$	79
$CH_3(CH_2)_5Br$	O_2, H_2O	$CH_3(CH_2)_5C(=O)OH$	82
$Cl(CH_2)_6Br$	O_2, H_2O	$Cl(CH_2)_6C(=O)OH$	84
$CH_3(CH_2)_7Br$	I_2, C_2H_5OH	$CH_3(CH_2)_7C(=O)OC_2H_5$	84
$CH_3(CH_2)_4Br$	$I_2, (C_2H_5)_2NH$	$CH_3(CH_2)_4C(=O)N(C_2H_5)_2$	80[b]

[a] The structural abbreviation Ts is used for *p*-toluenesulfonate.
[b] Yield determined by gas chromatography.
[c] Isomeric octenes identified as by-products.

owing to elimination. Allylic substrates are also incompatible, since this group undergoes elimination to form stable iron tricarbonyl-1,3-diene complexes. The initial substitution with secondary *p*-toluenesulfonates occurs more efficiently than with the corresponding halides, and the stereochemistry is clean inversion. The solvents used are generally either tetrahydrofuran or *N*-methylpyrrolidinone, the reactions being as much as 10^4 times faster in the latter. The initially formed alkyl iron intermediate rearranges to an acyl iron complex either prior to or during the subsequent reaction with the electrophile.[5-8,10] The presence of carbon monoxide or triphenylphosphine enhances the rate of rearrangement to the more stable acyl iron intermediate. The reactions show high selectivity and are compatible with functional groups such as chloro, cyano, and esters. The reagent reacts with acid chlorides to form the acyl iron complexes directly, and these may then be hydrolyzed to aldehydes or utilized for nucleophilic acylation.

The product of Part B of this procedure, methyl 7-oxoheptanoate, has previously been synthesized from cycloheptanone in two steps with a 42% overall yield.[11] 7-Oxooctanoic acid, the methyl ester of which is the product of Part C, has been prepared by base-induced ring cleavage of 2-acetylcyclohexanone.[12]

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Iron, pentacarbonyl- (8); Iron carbonyl ($Fe(CO)_5$) (TB-5-11)- (9); (13463-40-6)

Disodium tetracarbonylferrate sesquidioxanate: Ferrate(2-), tetracarbonyl (1,4-dioxane-O^1)-, disodium (9); (57398-59-1)

Dioxane: *p*-Dioxane (8); 1,4-Dioxane (9); (123-91-1)

Benzophenone (8); Methanone, diphenyl- (9); (119-61-9)

Benzophenone ketyl: Benzophenone, radical ion (1^-) (8); Methanone, diphenyl-, radical ion (1^-) (9); (16592-08-8)

Methyl 7-oxoheptanoate: Heptanoic acid, 7-oxo-, methyl ester (8, 9); (35376-00-2)

Methyl 6-bromohexanoate: Hexanoic acid, 6-bromo-, methyl ester (8, 9); (14273-90-6)

Triiron dodecacarbonyl: Iron dodecacarbonyl- (8); Iron, di-μ-decacarbonyltri-, *triangulo*- (9); (17685-52-8)

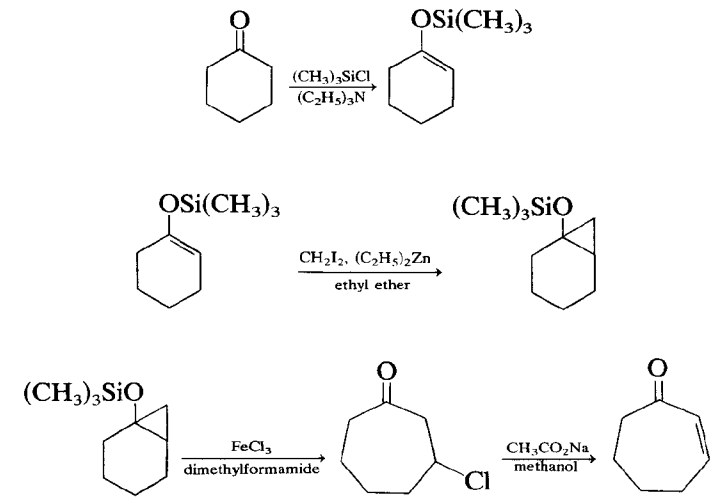
Methyl 7-oxooctanoate: Octanoic acid, 7-oxo-, methyl ester (8, 9); (16493-42-8)

N-Methylpyrrolidinone: 2-Pyrrolidinone, 1-methyl- (8, 9); (872-50-4)

Hexanoic acid, 6-bromo- (8, 9); (4224-70-8)

Disodium tetracarbonylferrate: Ferrate (2^-), tetracarbonyl-, disodium (8); Ferrate (2^-), tetracarbonyl-, disodium, (T-4)- (9); (14878-31-0)

ONE-CARBON RING EXPANSION OF CYCLOALKANONES TO CONJUGATED CYCLOALKENONES: 2-CYCLOHEPTEN-1-ONE



Submitted by YOSHIHIKO ITO, SHOTARO FUJII, MASASHI NAKATSUKA, FUMIO KAWAMOTO, and TAKEO SAEGUSA[1]
Checked by PETER SENTER, WILLIAM F. BURGOYNE, and ROBERT M. COATES

1. Procedure

Caution! Diethylzinc, which is used in Part B of this procedure, is highly pyrophoric. Accordingly this reagent must be kept under a nitrogen atmosphere, and exposure to air must be avoided during transfers.

A. 1-*Trimethylsilyloxycyclohexene.* In a 500-ml. three-necked, round-bottomed flask fitted with a mechanical stirrer, a reflux condenser protected with a calcium chloride tube, and a rubber septum are placed 100 ml. of *N,N*-dimethylformamide (Note 1) and 60.6 g. (0.60 mole) of triethylamine (Note 2). The solution is stirred while 32.6 g. (0.30 mole) of chlorotrimethylsilane (Note 3) and 24.5 g. (0.25 mole) of cyclohexanone are injected in succession through the septum into the flask. The resulting mixture is stirred and heated under reflux for 6 hours, cooled to room temperature,

and diluted with 300 ml. of pentane. The triethylamine hydrochloride that precipitates is removed by filtering through a coarse, sintered-glass Buchner funnel, and the filter cake is washed with three 100-ml. portions of pentane. The filtrates are combined and washed with three 300-ml. portions of ice-cold sodium bicarbonate solution. The organic layer is washed rapidly with 100 ml. of ice-cold 3% hydrochloric acid and 100 ml. of ice-cold sodium bicarbonate in succession. The pentane solution is washed with 50 ml. of sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated. The residual liquid is distilled at reduced pressure through a 10-cm. Vigreux column, affording, after separation of a small forerun, 33–35.5 g. (78–84%) of 1-trimethylsilyloxycyclohexene, b.p. 74–75° (20 mm.) (Note 4).

B. 1-*Trimethylsilyloxybicyclo*[4.1.0]*heptane.* A 250 ml., three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a pressure-equalizing dropping funnel, a reflux condenser bearing a nitrogen inlet at its top, and a rubber septum. The apparatus is purged with nitrogen, flamed dry, and allowed to cool (Note 5). The flask is charged with 130 ml. of ethyl ether (Note 6), 17.0 g. (0.10 mole) of 1-trimethylsilyloxycyclohexene, and 18.5 g. (0.15 mole) of diethylzinc (Note 7), each being added through the septum by means of a syringe. The solution is stirred and maintained at room temperature with a water bath while 40.2 g. (0.15 mole) of diiodomethane (Note 8) is added slowly from the dropping funnel over a 1-hour period (Note 9). The reaction mixture is stirred and heated under reflux for 8 hours (Note 10). After the reaction is complete (Note 11), the contents of the flask are stirred and cooled in an ice-water bath as 5.4 ml. of concentrated aqueous ammonium chloride is added over *ca.* 30 minutes. A large amount of gas is evolved, and a white solid is formed during the hydrolysis. The salts are separated by filtering through a sintered-glass Büchner funnel and washed with 100 ml. of a 1:1 ether–pentane solution. The combined filtrates are washed with four 50-ml. portions of ice-cold saturated aqueous ammonium chloride and two 100-ml. portions of ice-cold aqueous sodium chloride. The solution is filtered through a pad of anhydrous sodium sulfate and evaporated. The residual liquid is distilled through a 17.5-cm. Vigreux column under reduced pressure, affording a forerun of 2.1–3.5 g., b.p. 65–80° (12 mm.), and 14.2–15.2 g. (77–83%) of 1-trimethylsilyloxybicyclo[4.1.0]heptane, b.p. 80–82° (12 mm.) (Note 12).

C. 2-*Cyclohepten*-1-*one.* In a 250-ml., three-necked, round-bottomed flask equipped with a mechanical stirrer, a pressure-equalizing dropping funnel bearing a nitrogen inlet at its top, and a thermometer is placed 17.9 g. (0.110 mole) of anhydrous iron(III) chloride (Note 13). The flask is immersed in an ice-water bath, stirring is commenced, and 70 ml. of *N,N*-dimethylformamide (Note 1) is added slowly (Note 14). When all the iron(III) chloride has dissolved, a solution of 9.2 g. (0.050 mole) of 1-trimethylsilyloxybicyclo[4.1.0]heptane in 20 ml. of *N,N*-dimethylformamide is added dropwise through the dropping funnel over 1 hour while the internal temperature is maintained at 0–5°. After the addition is complete, the brown solution is stirred at room temperature for 2 more hours, then poured into *ca.* 200 ml. of ice-cold aqueous 1*N* hydrochloric acid. The aqueous solution is extracted with three 50-ml. portions of chloroform. The combined chloroform extracts are washed with 50-ml. portions of 1*N* hydrochloric acid, saturated sodium bicarbonate, and sodium chloride solution. The solution is dried by filtration through a pad of anhydrous sodium sulfate and evaporated. The remaining liquid (Note 15) is dissolved in 50 ml. of methanol saturated with sodium acetate, and the resulting mixture is heated at reflux for 3 hours. The volume is reduced to *ca.* 25 ml. by evaporation under reduced pressure, 50 ml. of water is added, and the mixture is extracted with three 30-ml. portions of ether. The combined extracts are dried over anhydrous sodium sulfate, the ether is evaporated, and the residual liquid is distilled under reduced pressure through a 17.5-cm. Vigreux column to provide, after separation of a 0.4–1.0 g. forerun, 4.3–4.5 g. (78–82%) of 2-cyclohepten-1-one as a colorless liquid, b.p. 73–76° (18 mm.) (Note 16).

2. Notes

1. *N,N*-Dimethylformamide was purified by distillation from calcium hydride under a nitrogen atmosphere and stored over Linde type 4A molecular sieves.

2. Triethylamine was distilled from lithium aluminum hydride.

3. Chlorotrimethylsilane is available from Aldrich Chemical Company, Inc. The reagent was distilled before use.

4. The product has the following spectral properties: infrared (neat) cm.$^{-1}$: 1675 (C=C); proton magnetic resonance δ (multiplicity, number of protons, assignment): 0.16 (s, 9, $Si(CH_3)_3$), 1.3–2.1 (multiplet, 8, four CH_2), 4.78 (multiplet, 1, vinyl *H*).

5. A slight positive pressure of nitrogen is maintained in the apparatus throughout this procedure.

6. Anhydrous ethyl ether from Mallinckrodt Chemical Works was distilled from sodium and benzophenone before use.

7. Diethylzinc in a cylinder pressurized with nitrogen was purchased from Alfa Division, Ventron Corporation, and distilled at atmospheric pressure under a nitrogen atmosphere before use, b.p. 118°. The distillate was collected in a two-necked receiver fitted with a rubber septum and kept under a nitrogen atmosphere. Aliquots of diethylzinc were withdrawn by means of a gas-tight syringe. The checkers destroyed excess or waste reagent by injecting it cautiously beneath the surface of ice-cold water through which argon was being vigorously bubbled.

8. Diiodomethane from both Eastman Organic Chemicals and Aldrich Chemical Company, Inc., was used by the checkers after distillation under reduced pressure, b.p. 68–70° (12 mm.).

9. The solution becomes somewhat cloudy as the diiodomethane is added.

10. The checkers found considerable variation in the rate of the reaction in different runs, the time required for its completion ranging from 3 to 10 hours. It is therefore advisable to monitor the progress of the reaction. For this purpose small aliquots (*ca.* 0.05 ml.) were withdrawn from the flask with a syringe and hydrolyzed by injection into a vial containing ether and saturated ammonium chloride. The relative amounts of enol silane and cyclopropoxy silane were determined by gas chromatography on an 0.6 cm. × 3.7 m. column of 3% OV-17 coated on 100–120 mesh Chromosorb W. With a column temperature of 120° and a carrier gas flow rate of 20 ml. per minute, the retention times for the enol silane and the cyclopropoxy silane are *ca.* 1.9 and 2.3 minutes, respectively.

11. In one run that was particularly slow, an additional 9.9 g. of diiodomethane was added. The reaction then proceeded quickly to completion.

12. The spectral properties of the product are as follows: infrared (neat) cm.$^{-1}$: 1250, 1209, 1010, 900, 865, 840; 220-MHz. proton magnetic resonance (chloroform-*d*) δ (multiplicity, number of protons, assignment, coupling constant *J* in Hz.): 0.13 (singlet, 9, three $SiCH_3$), 0.29 (triplet, 1, *endo* cyclopropyl *H* at C-7, $J = 5$), 0.84 (doublet of doublets, 1, *exo* cyclopropyl *H* at C-7, $J = 5$ and 11), 0.98–1.70 (multiplet, 6, cyclohexyl *H*), 1.82–2.18 (multiplet, 3, cyclohexyl *H*). A gas chromatographic analysis as described in Note 10 indicated the purity of the product to be *ca.* 95–98%, the remainder being 3-5% of unreacted enol silane.

13. Anhydrous iron(III) chloride was purchased by the submitters from Merck & Company, Inc. The checkers obtained the reagent from Aldrich Chemical Company, Inc. The reagent was dried at 60–70° under reduced pressure for several hours before use.

14. The dissolution of iron(III) chloride in N,N-dimethylformamide is exothermic.

15. A gas chromatographic analysis on the liquid by the submitters using a Carbowax 20 M (polyethylene glycol) column at 170° showed a major peak assigned to 3-chlorocycloheptanone and minor peak for 2-cycloheptenone. The spectral properties of 3-chlorocycloheptanone are as follows: infrared (neat) cm.$^{-1}$: 1705 (C=O); proton magnetic resonance (carbon tetrachloride) δ (multiplicity, number of protons, assignment): 1.4–2.3 (multiplet, 6, $CH_2CH_2CH_2CHCl$), 2.3–2.6 (multiplet, 4, $CH_2C(=O)CH_2$), 4.1–4.4 (multiplet, 1, CHCl); mass spectrum, *m/e* (intensity ratio): M^+, 146 and 148 (3:1).

16. A gas chromatographic analysis by the submitters as described in the preceding note indicated that the purity of the product was 98%. The purity of the product obtained by the checkers was estimated at 95% from a gas chromatographic analysis at 140° as described in Note 10. 2-Cyclohepten-1-one has the following spectral properties: infrared (neat) cm.$^{-1}$: 1700 (C=O), 1660 (C=C), 1445, 1090, 888; proton magnetic resonance δ (multiplicity, number of protons, assignment, coupling constant *J* in Hz.): 1.75 (multiplet, 4, $CH_2CH_2CH_2CH_2$), 2.45 (multiplet, 4, $CH_2CH_2CH_2CH_2$), 5.90 (doublet, 1, CH=CHC=O, $J = 13$), 6.52 (doublet of triplets, 1, CH=CH—C=O, $J = 5$ and 13).

3. Discussion

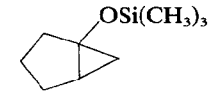
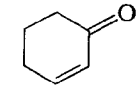
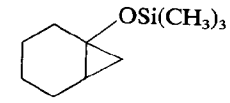
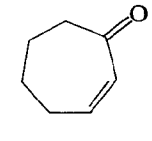
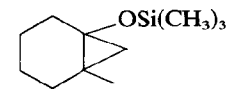
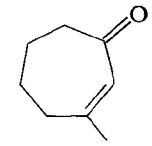
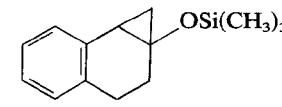
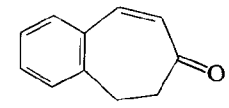
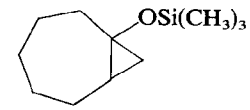
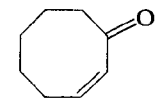
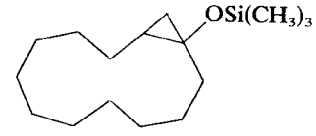
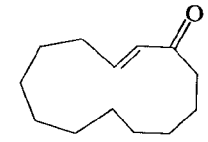
This procedure illustrates a new three-step reaction sequence for the one-carbon ring expansion of cyclic ketones to the homologous α,β-unsaturated ketones.[2] The key step in the sequence is the iron(III) chloride–induced cleavage of the central bond of trimethylsilyloxycyclopropanes which are obtained by cyclopropanation of trimethylsilyl enol ethers. The procedure for the preparation of 1-trimethylsilyloxycyclohexene from cyclohexanone described in Part A is that of House, Czuba, Gall, and Olmstead.[3]

The cyclopropanation of 1-trimethylsilyloxycyclohexene in the present procedure is accomplished by reaction with diiodomethane and diethylzinc in ethyl ether.[4] This modification of the usual Simmons–Smith reaction[5,6] in which diiodomethane and activated zinc are used has the advantage of being homogeneous and is often more effective for the cyclopropanation of olefins such as enol ethers which polymerize readily. However, in the case of trimethylsilyl enol ethers, the heterogeneous procedures with either zinc–copper couple[7] or zinc–silver couple[8] are also successful. Attempts by the checkers to carry out Part B in benzene or toluene at reflux instead of ethyl ether afforded the trimethylsilyl ether of 2-methylenecyclohexanol, evidently owing to zinc iodide–catalyzed isomerization of the initially formed cyclopropyl ether.[9] The preparation of 1-trimethylsilyloxybicyclo[4.1.0]heptane by cyclopropanation with diethylzinc and chloroiodomethane in the presence of oxygen has been reported.[10]

The ring-opening reaction with iron(III) chloride in *N,N*-dimethylformamide is effective with a series of 1-trimethylsilyloxybicyclo[*n*.1.0]alkanes, as shown by the examples presented in Table I.[2] The corresponding 3-chlorocycloalkanones are usually isolable intermediates which are separately subjected to dehydrochlorination with sodium acetate in methanol, as in the preparation of 2-cyclohepten-1-one described here. However, the reaction of 1-trimethylsilyloxybicyclo[3.1.0]hexane with iron(III) chloride at 0–5° afforded 2-cyclohexen-1-one directly. The slower ring opening of 1-trimethylsilyloxybicyclo[10.1.0]tridecane was carried out at 80°, conditions which also effected spontaneous dehydrochlorination to *trans*-2-cyclotridecenone. The regiospecific ring enlargement of the unsymmetrical ketones, 2-methylcyclo-

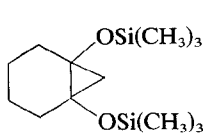
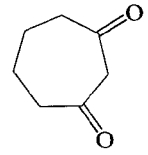
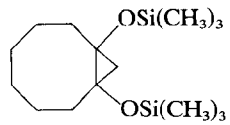
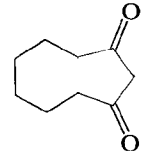
TABLE I

PREPARATION OF 2-CYCLOALKENONES AND CYCLOALKANE-1,3-DIONES BY IRON(III) CHLORIDE–INDUCED RING OPENING OF 1-TRIMETHYLSILYLOXY- AND 1,2-BIS(TRIMETHYLSILYLOXY)BICYCLO[*n*.1.0]ALKANES

Silyloxybicyclo-[*n*.1.0]alkane	2-Cycloalkenone or Cycloalkane-1,3-dione	Yield (%)[a]
		98
		80[b]
		83
		83
		92
		81[c]

[a] The scale was 0.002–0.005 mole except as noted.
[b] This reaction was conducted on a 0.05-mole scale.
[c] This compound was a mixture of *cis* and *trans* isomers.

TABLE 1 (*Continued*)

Silyloxybicyclo-[*n*.1.0]alkane	2-Cycloalkenone or Cycloalkane-1,3-dione	Yield (%)[a]
		68
		72

hexanone and β-tetralone, are of particular interest in view of the diversity of synthetic routes to trimethylsilyl enol ethers.[11]

The present procedure for ring expansion has also been applied to 1,2-bis(trimethylsilyloxy)bicyclo[*n*.1.0]alkanes,[2,12] which are prepared by cyclopropanation of 1,2-bis(silyloxy)cycloalkenes.[13] The latter are readily available from acyloin condensations in the presence of chlorotrimethylsilane.[14] This reaction provides a new route to cyclic 1,3-diketones and macrocyclic compounds containing two 1,3-diketone units in the ring.

The regiospecificity of the iron(III) chloride–induced ring cleavage contrasts with that observed in reactions of 1-silyloxybicyclo[*n*.1.0]alkanes with bromine[7c] and potassium *tert*-butoxide.[8b] Although the mechanism of the reaction is not known with certainty, it is reasonable to suppose that an alkoxy radical is involved, that this radical undergoes homolytic scission of the more highly substituted carbon–carbon bond of the cyclopropane ring, and that the resulting carbon radical abstracts a chlorine atom from iron(III) chloride.[15]

2-Cyclohepten-1-one has been prepared from cycloheptanone by dehydrohalogenation of the ethylene ketals of 2-chloro- and 2-bromocycloheptanone and subsequent hydrolysis.[16] The α,β-dehydrogenation of cycloheptanone has also been effected via the

α-phenylthio[17a] and α-phenylseleno[17b] ketones which are subjected to oxidation and thermal elimination. Another route to the title compound starts with cycloheptene, which is subjected to allylic bromination, hydrolysis, and chromic acid oxidation.[18]

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2-Cyclohepten-1-one (8, 9); (1121-66-0)

Zinc, diethyl- (8, 9); (557-20-0)

1-Trimethylsilyloxycyclohexene: Silane, (1-cyclohexen-1-yloxy)-trimethyl- (8, 9); (6651-36-1)

Silane, chlorotrimethyl- (8, 9); (75-77-4)

Cyclohexanone (8, 9); (108-94-1)

1-Trimethylsilyloxybicyclo[4.1.0]heptane: Silane, (bicyclo[4.1.0]-hept-1-yloxy)trimethyl- (8, 9); (38858-74-1)

Methane, diiodo- (8, 9); (75-11-6)

Cycloheptanone, 3-chloro- (8, 9); (21430-13-7)

Trimethylsilyl ether of 2-methylenecyclohexanol: Silane, trimethyl-[(2-methylenecyclohexyl)oxy]- (8, 9); (52389-13-6)

1-Trimethylsilyloxybicyclo[3.1.0]hexane: Silane, (bicyclo[3.1.0]-hex-1-yloxy)trimethyl- (8, 9); (50338-46-0)

2-Cyclohexen-1-one (8, 9); (930-68-7)

1-Trimethylsilyloxybicyclo[10.1.0]tridecane: Silane, (bicyclo-[10.1.0]tridec-16-yloxy)trimethyl- (8, 9); (59454-27-2)

trans-2-Cyclotridecenone: 2-Cyclotridecen-1-one (8, 9); (59454-32-9)

PENTAFLUOROPHENYLCOPPER TETRAMER, A REAGENT FOR SYNTHESIS OF FLUORINATED AROMATIC COMPOUNDS

[Copper, tetrakis(pentafluorophenyl)tetra]

$$C_6F_5Br \xrightarrow[\text{ether}]{Mg} C_6F_5MgBr \xrightarrow[\text{2. dioxane}]{\text{1. CuBr}} (C_6F_5Cu)_2\cdot\text{dioxane}$$

$$(C_6F_5Cu)_2\cdot\text{dioxane} \xrightarrow[10^{-6}\text{ mm.}]{100\text{–}128^\circ} (C_6F_5Cu)_4$$

Submitted by ALLAN CAIRNCROSS WILLIAM A. SHEPPARD, and EDWARD WONCHOBA[1]
Checked by WILLIAM J. GUILFORD, CYNTHIA B. HOUSE, and ROBERT M. COATES

1. Procedure

A 1-l., four-necked, round-bottomed flask fitted with a condenser bearing a nitrogen inlet, a pressure-equalizing dropping funnel, a thermometer, and a mechanical stirrer is charged with 5.40 g. (0.22 mole) of magnesium turnings (Note 1). The flask is flame dried while being flushed with nitrogen and is kept dry and

oxygen-free throughout the preparation with a static nitrogen atmosphere (Note 2). After 150 ml. of ethyl ether (Note 3) is introduced into the flask with a syringe, 54.9 g. (28.2 ml., 0.222 mole) of bromopentafluorobenzene (Note 4) is added dropwise over *ca.* 45 minutes at a rate that maintains a gentle reflux. The reflux is maintained for another 15 minutes by heating at 35° (Note 1). The resulting black solution is cooled to room temperature, and 63.1 g. (0.44 mole) of powdered, anhydrous copper(I) bromide (Note 5) is added in three 21-g. portions at 1-minute intervals. An exothermic reaction occurs after each addition (Note 6). The brown mixture is stirred for 30 minutes, 100 ml. of ether is added, and the mixture heated at reflux for another 30 minutes. The brown suspension is diluted with 400 ml. of ether, after which 100 ml. of *p*-dioxane (Note 7) is added carefully over 15 minutes in order to moderate the mildly exothermic reaction. The light gray suspension is stirred for 30 minutes.

The dropping funnel is replaced by a three-way stopcock with an attached nitrogen source and a bubbler open to the system (see Figure 1). The thermometer and mechanical stirrer are replaced with ground-glass plugs (Note 8), and the condenser is replaced by a 1-l., 90-mm., medium-porosity fritted-disk nitrogen pressure funnel attached to a 1-l., round-bottomed, two-necked flask fitted with a three-way stopcock on the side arm (Figure 1). All joints are either clamped or taped together, and the apparatus is carefully inverted to pour the slurry into the funnel. The mixture is filtered with nitrogen pressure into the 1-l. receiving flask (Note 9), which is maintained under a nitrogen atmosphere. The solid filter cake is rinsed with three 50-ml. portions of 4:1 (v/v) ether–dioxane injected with a long needle syringe through the three-way stopcock. The four-necked flask is rinsed by manipulation of the needle, and the apparatus and the solids are dispersed in each rinse. The pale yellow filtrate is evaporated to dryness under reduced pressure with a warm water bath at 40°, and the powdery white solid is dried at 10-mm. pressure for 4 hours at 25° to yield 38.3–48.8 g. (63–80%) of bis(pentafluorophenylcopper)dioxane complex (Note 10). The color of this dioxane complex varies from tan to white. The complex is transferred to a 200-ml., round-bottomed flask under a nitrogen atmosphere. The flask is evacuated to a pressure of 0.001 mm., immersed in an oil bath, and slowly heated to 100°

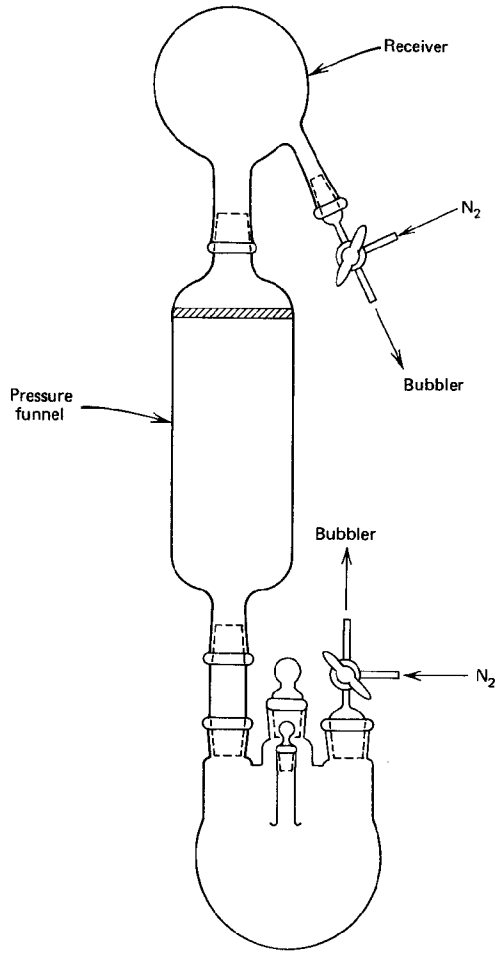

Figure 1

over 1 hour (Note 11). The temperature is slowly and constantly increased to 128° during a second hour and maintained at 128° for 4 hours (Note 12). Pure pentafluorophenylcopper tetramer is obtained as a gray to tan powder weighing 29.8–34.7 g. (58–68%) (Note 13).

2. Notes

1. Magnesium metal turnings from Fisher Scientific Company or Mallinckrodt Chemical Works were used. Excess magnesium or incomplete formation of the Grignard must be avoided, since any

free magnesium reacts when the copper salts are added to produce a dark product in lower yield and of questionable purity.

2. All glassware must be flame dried, and an absolute nitrogen atmosphere must be maintained during each step, since pentafluorophenylcopper hydrolyzes easily and undergoes oxidative coupling in air. The checkers used dry-grade nitrogen from a cylinder supplied by the Linde Division, Union Carbide Corporation.

3. Anhydrous ethyl ether purchased from Fisher Scientific Company or Mallinckrodt Chemical Works was dried over Linde type 3A molecular sieves. The checkers degassed the solvent immediately before use by evacuating and filling the container with nitrogen three times.

4. Bromopentafluorobenzene obtained from either PCR, Inc., or Columbia Organic Chemicals Company, Inc., was used without purification.

5. Anhydrous copper(I) bromide from Fisher Scientific Company was powdered and used without drying by the submitters. The checkers dried the copper(I) bromide at 140° for 2 hours under reduced pressure before use.

6. The copper(I) bromide can also be added gradually from a solid addition apparatus such as a 50-ml. Erlenmeyer flask connected to a ground-glass adapter with a short piece of gouch tubing.

7. Spectral-grade *p*-dioxane from MC and B Manufacturing Chemists or Mallinckrodt Chemical Works was dried over Linde type 4A molecular sieves. The checkers degassed the solvent prior to use as described in Note 3.

8. The checkers used rubber septa that were secured with wire bands.

9. The filtering operation can also be conveniently done in a high-quality nitrogen atmosphere dry box by vacuum filtration through a 90-mm., 60-ml., medium-porosity fritted-disk Büchner funnel.

10. Pentafluorophenylcopper is first isolated as a 1:1 complex with dioxane which is usually white. Half of the complexed dioxane is very labile and is usually lost during vacuum drying, giving the 2:1 complex. Excessive heating can cause loss of additional dioxane (lower apparent yield) and eventually decomposition of the product.

If the product is isolated in a nitrogen dry box, the filtrate is evaporated without heat until a small amount of solvent remains. The precipitate is collected cold and rinsed with cold ethyl ether. The 1:1 pentafluorophenylcopper·dioxane complex is obtained with no significant loss of yield and is nearly white.

11. The rate of heating is critical. The temperature must be increased very gradually to remove the dioxane without causing decomposition of the product.

12. If the product is heated to 130° or higher, decomposition of product occurs with the formation of a copper mirror.

13. The spectral properties of pentafluorophenylcopper tetramer are as follows: infrared (Nujol) cm.$^{-1}$: 1630 medium; 1391 medium; 1353 medium; 1275 medium; 1090, 1081, and 1071 strong triplet; 978 strong; 785 medium; fluorine magnetic resonance (tetrahydrofuran with trichlorofluoromethane as internal reference): δ (multiplicity, number of fluorines, assignment, coupling constant J in Hz.): 107.2 (20-line multiplet, 2, ortho F), 153.4 (triplet of triplets, 1, para F, $J = \sim 1.3$ and 20), 162.3 (17-line multiplet, 2, meta F). Absorptions at 820–900, 1100–1125, and 1290 cm.$^{-1}$ in the infrared spectrum and at δ 3.05 in the proton magnetic resonance spectrum indicate that dioxane is still present.

The pentafluorophenylcopper tetramer is usually analytically pure as isolated and melts at 200° with decomposition. If any significant decomposition occurs during the final drying, the product can be purified by dissolution in ether, filtration to remove copper metal, and precipitation by addition of hexane. It can also be recrystallized from benzene. When kept in a sealed container under nitrogen at room temperature, pentafluorophenyl copper tetramer appears to be stable for reasonable periods. It can be stored indefinitely at −78° under an atmosphere of carbon dioxide.

3. Discussion

Pentafluorophenylcopper is representative of a series of fluorinated organocopper compounds that are highly soluble in organic solvents, more thermally stable than their hydrocarbon analogs, and useful as synthetic intermediates.[2–4] Pentafluorophenylcopper has been used to introduce the pentafluorophenyl group[5,6] and as a reagent for an improved Ullman diphenyl ether synthesis.[7] It is

also an effective catalyst for decarboxylation of aromatic acids,[8,9] rearrangement of bicyclic hydrocarbons,[10] and decomposition of alkyldiazo compounds.[2,3] It also is an excellent reagent for the preparation of anhydrous copper salts of carboxylic acids[8] and can be used for coating substrates with copper by thermal decomposition.[11]

Pentafluorophenylcopper exists as a tetramer.[12] It forms complexes with a variety of reagents and solvents as well as "ate" complexes; a representative list is given in Table I. For many syntheses the crude reaction mixtures of cuprous halide with either pentafluorophenylmagnesium bromide, or pentafluorophenyllithium,[6] or the pentafluorophenylcopper·dioxane complex[5] react as well as the solvent-free tetramer.

A selection of synthetic uses of pentafluorophenylcopper is given in Table II. Two unchecked experimental procedures illustrating the use of pentafluorophenylcopper tetramer and dioxane complex to introduce the pentafluorophenyl group are given below. In coupling reactions hexane is usually the preferred solvent, particularly with alkyl halides that can readily form carbonium ion intermediates. Aromatic solvents are often alkylated during coupling, giving undesired by-products.

A. *(Pentafluorophenyl)benzene.* A 100-ml., round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser bearing a nitrogen inlet is flushed with nitrogen. The flask is charged with a solution of 2.40 g. (0.0026 mole) of pentafluorophenylcopper tetramer in 25 ml. of benzene, and 2.12 g.

TABLE I
COMPLEXES OF PENTAFLUOROPHENYLCOPPER[2,3]

Complex	Properties
C_6F_5Cu·benzonitrile	m.p. 101°
C_6F_5Cu·tributylamine	liquid at room temperature
$(C_6F_5Fu)_2$·dioxane	m.p. 200–220° (dec.)
C_6F_5Cu·quinoline	m.p. 170–176°
$(C_6F_5Cu)_2$·1,5-cyclooctadiene	dec. 160°
C_6F_5Cu·dimethylacetylene	dec. 145°
$(C_6F_5Cu)_2$·butadiene	dec. 215°
C_6F_5Cu·tetraethylammonium cyanide	dec. 160°

TABLE II

SUMMARY OF REACTIONS OF PENTAFLUOROPHENYLCOPPER

Reactant	Form of C_6F_5Cu[a]	Conditions	Product (% yield)	Reference
H_2O	B	ether, 25°, 1 hour	C_6F_5H (87)	3
None	B	200°	$C_6F_5—C_6F_5$ (60)	3
Br_2	B	hexane, 0°	C_6F_5Br(4) + $C_6F_5—C_6F_5$ (47)	2a
CuBr	B	hexane, reflux	$C_6F_5—C_6F_5$ (68)	2a
CO_2	A or B	neat or aprotic solvent, −78° to 25°	no reaction	2a
CH_3I	A	hexane, 25°, 5 days	$CH_3—C_6F_5$ (39)	2a
$C_6H_5CH_2Br$	B	ether, 25°, 4 hours	$C_6H_5CH_2C_6F_5$ (40)	2a
1-Bromobicyclo-[2.2.2]octane	A	hexane, reflux, 20 hours	1-pentafluorophenylbicyclo[2.2.2]octane (83)	2
$C_2H_5O_2CCHN_2$	A	tetrahydrofuran, 0°; hydrolysis	$C_2H_5O_2CCH_2C_6F_5$ (43)	2a
C_6H_5I	A	benzene, reflux, 2 hours	$C_6F_5—C_6H_5$ (87)	2a
m-FC_6H_4I	B	benzene, reflux, 2 hours	*m*-$FC_6H_4—C_6F_5$ (73)	5
$O_2NC_6H_4I$	B	*meta*: benzene, reflux, 2 hours	$O_2NC_6H_4C_6F_5$ *meta* (85)	5
		para: benzene, reflux, 2 hours	*para* (85)	5
		ortho: ether, reflux (exothermic)	*ortho* (73)	3
p-$(CH_3)_2NC_6H_4I$	B	benzene, reflux, 2 hours	*p*-$(CH_3)_2NC_6H_4C_6F_5$ (26)	5
p-$C_2H_5O_2CC_6H_4I$	B	benzene, reflux, 2 hours	*p*-$C_2H_5O_2CC_6H_4C_6F_5$ (97)	5
$CF_2=CFI$	C	tetrahydrofuran, 25–55°, 5 hours	$C_6F_5CF=CF_2$ (55)	13
$CBr_2=CHBr$	C	tetrahydrofuran, −5°, 3 hours	$C_6F_5C\equiv CC_6F_5$ (43)	14
$CH_3\overset{O}{\overset{\|}{C}}Cl$	D	tetrahydrofuran–hexane, 0°, several hours	$C_6F_5\overset{O}{\overset{\|}{C}}CH_3$ (84)	6b
$ClC(=O)C(=O)Cl$	D	tetrahydrofuran, 0° (exothermic)	$(C_6F_5\overset{O}{\overset{\|}{C}})_2$ (71)	15
$-(CH_2\overset{O}{\overset{\|}{C}}Cl)_2$	C	tetrahydrofuran, −5°, 3 hours	$(C_6F_5\overset{O}{\overset{\|}{C}}CH_2)_2$ (71)	14
C_6H_5I	C	tetrahydrofuran, 66°, 10 hours	$C_6H_5—C_6F_5$ (74)	13
$C_6H_5\overset{O}{\overset{\|}{C}}Cl$	C	tetrahydrofuran, −5°, 3 hours	$C_6F_5\overset{O}{\overset{\|}{C}}C_6H_5$ (77)	14
$(C_2H_5)_3SiC\equiv CBr$	C	tetrahydrofuran, 25°, 1 hour; reflux, 10 hours	$(C_2H_5)_3SiC\equiv CC_6F_5$ (85)	16

[a] A, $(C_6F_5Cu)_4$; B, $(C_6F_5Cu)_2$·dioxane; C, reagent prepared *in situ* from C_6F_5MgX and CuX; D, reagent prepared *in situ* from C_6F_5Li and CuX.

(0.0104 mole) of iodobenzene is added. A static nitrogen atmosphere is maintained in the flask as the solution is heated to reflux. Copper(I) iodide starts to precipitate almost immediately. After 2 hours at reflux, the mixture is cooled and filtered to separate 1.67 g. of copper(I) iodide. The filtrate is evaporated, and the remaining pale brown residue is sublimed at 100° (0.1 mm.), affording 2.01 g. (79%) of (pentafluorophenyl)benzene as a colorless solid, m.p. 110.0–112.4°. The presence of about 3% of decafluorobiphenyl in the product is revealed by gas chromatographic analysis. (Pentafluorophenyl)benzene may be further purified by column chromatography on acid-washed alumina (Woelm, activity grade I) with hexane as an eluent, the decafluorobiphenyl impurity being eluted first. The purified product melts at 111.3–112.0°.

B. 1-(*Pentafluorophenyl*)*adamantane*. A 500 ml., three-necked flask is equipped with a thermometer, a magnetic stirring bar, and a reflux condenser bearing a nitrogen inlet. The flask is maintained under nitrogen and charged with 32.5 g. (0.061 mole) of bis(pentafluorophenylcopper)·dioxane complex, 24.9 g. (0.116 mole) of 1-bromoadamantane, and 175 ml. of spectral-grade hexane. The mixture is stirred and slowly warmed until the onset of an exothermic reaction which causes the mixture to reflux for approximately 15 minutes. After the exothermic reaction subsides, the mixture is heated at reflux overnight, stirred briefly with 3 ml. of water, and filtered to separate 17.0 g. of copper(I) bromide. The filtrate is concentrated, and the residue is recrystallized from ethanol, affording 32.6 g. (93%) of colorless crystals of 1-pentafluorophenyladamantane. After sublimation at 100° (0.1 mm.) the product melts at 109.9–111.0°.

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Pentafluorophenylcopper tetramer: Copper, tetrakis(pentafluorophenyl)tetra- (8, 9); (34077-61-7)

Benzene, bromopentafluoro- (8, 9); (344-04-7)

p-Dioxane (8); 1,4-Dioxane (9); (123-91-1)

Copper, (pentafluorophenyl)- (8, 9); (18206-43-4)

Pentafluorophenylmagnesium bromide: Magnesium, bromo(pentafluorophenyl)- (8, 9); (879-05-0)

Lithium, (pentafluorophenyl)- (8, 9); (1076-44-4)

(Pentafluorophenyl)benzene: Biphenyl, 2,3,4,5,6-pentafluoro- (8); 1,1′-Biphenyl, 2,3,4,5,6-pentafluoro- (9); (784-14-5)

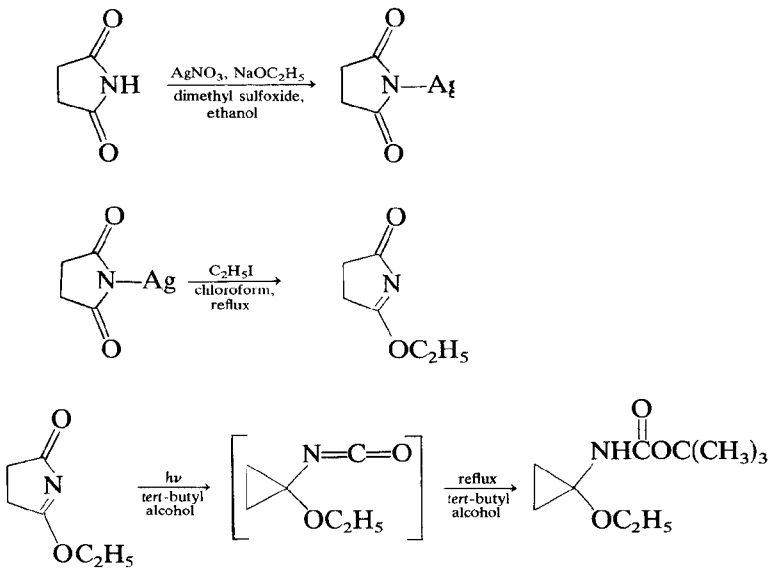
Biphenyl, decafluoro- (8); 1,1′-Biphenyl, 2,2′,3,3′,4,4′,5,5′,6,6′-decafluoro- (9); (434-90-2)

Adamantane, 1-(pentafluorophenyl)- (8); Tricyclo[3.3.1.$1^{3,7}$]decane, 1-(pentafluorophenyl)- (9); (281-23-2)

Adamantane, 1-bromo- (8); Tricyclo[3.3.1.$1^{3,7}$]decane, 1-bromo- (9); (768-90-1)

PHOTOCHEMICAL RING CONTRACTION OF 2-ETHOXYPYRROLIN-5-ONES TO CYCLOPROPANONE DERIVATIVES: *tert*-BUTYL *N*-(1-ETHOXYCYCLOPROPYL)CARBAMATE

[Carbamic acid, (1-ethoxycyclopropyl)-, 1,1-dimethylethyl ester]



Submitted by GEOFFREY C. CROCKETT and TAD H. KOCH[1]
Checked by S. BOETTGER and M. F. SEMMELHACK

1. Procedure

Caution! The photochemical reaction in Part C should be carried out behind a light-absorbent cover or shield. Protective goggles should be worn to avoid exposure of the eyes to ultraviolet light.

A. *Succinimide silver salt* (*Note* 1). A 3-l., two-necked, round-bottomed flask equipped with a mechanical stirrer and a pressure-equalizing dropping funnel is charged with a solution of 28.9 g. (0.292 mole) of succinimide (Note 2) in 1.2 l. of absolute ethanol (Note 3). A solution of 48.58 g. (0.286 mole) of silver nitrate in 200 ml. of dimethyl sulfoxide (Note 4) is added in one portion. The resulting solution is stirred as 700 ml. (0.280 mole) of 0.4 *M*

sodium ethoxide in ethanol (Notes 5 and 6) is added dropwise over 1.5 hours. The off-white silver salt begins to precipitate after *ca.* 140 ml. of the sodium ethoxide solution has been added. Stirring is continued for 45 minutes after the addition is completed, and the reaction mixture is then stored in a refrigerator at *ca.* 5° overnight to complete the precipitation and aggregation of the product.

The precipitate is collected on filter paper (Note 7) in a Büchner funnel by vacuum filtration and is washed with 100 ml. of absolute ethanol. The solid is slurried in three 75-ml. portions of distilled water (Note 8), 100 ml. of absolute ethanol, two 100-ml. portions of reagent-grade acetone, and two 100-ml. portions of anhydrous ethyl ether. The filter cake is pressed dry in the funnel with suction by means of a piece of rubber dam, transferred to a tared, 500-ml., round-bottomed flask, and dried under reduced pressure (0.01 mm.) at room temperature for 24 hours (Note 9). The weight of the dry silver salt of succinimide is 51–54 g. (88–94%).

B. 2-*Ethoxypyrrolin*-5-*one*. The flask containing 51–54 g. (0.25–0.26 mole) of succinimide silver salt is equipped with a magnetic stirring bar (Note 10), a heating mantle, and reflux condenser bearing a silica gel drying tube. The solid is suspended in 295 ml. of dry chloroform (Note 11), and 51.4 g. (26.4 ml., 0.330 mole) of ethyl iodide is added in one portion. The flask is covered with aluminum foil, and the mixture is stirred vigorously and heated under reflux for 48 hours. The mixture is cooled, the silver iodide is removed by vacuum filtration through Celite, and the filter cake is washed well with dry chloroform. The filtrate is concentrated by rotary evaporation to a mixture of a dark liquid and a white solid identified as succinimide. Anhydrous ethyl ether is added to dissolve the liquid, and the resulting suspension is filtered through a plug of glass wool to separate 7.7–11.5 g. of succinimide. The ether is removed from the filtrate by rotary evaporation at aspirator vacuum, and the residual liquid is distilled under reduced pressure with a short-path distillation apparatus. The product is collected at 74–82° (0.01 mm.) as a faintly yellow oil which crystallizes in the freezer. The yield is 11.5–16.7 g. (32–46% based on sodium ethoxide in Part A) (Notes 12 and 13).

C. tert-*Butyl* N-(1-*ethoxycyclopropyl*)*carbamate*. A three-necked, cylindrical irradiation vessel is equipped with a magnetic stirring bar, a water-jacketed quartz immersion well, an inert gas inlet,

and a gas-exit tube connected to a bubbler (Note 14). The vessel is charged with 6.26 g. (0.049 mole) of redistilled 2-ethoxypyrrolin-5-one (Note 20) and 180 ml. of dry *tert*-butyl alcohol (Note 15). The solution is stirred and degassed by bubbling nitrogen or argon through the gas-inlet tube for 15 minutes. The degassed solution is stirred and irradiated with ultraviolet light from a 450-watt Hanovia medium-pressure mercury lamp filtered through a Vycor glass sleeve. During the irradiation an atmosphere of nitrogen or argon is maintained, and the lamp is cooled with warm water (35–40°) circulated through the cooling jacket of the immersion well. The progress of the irradiation is monitored by gas chromatography (Note 16). When 90% of the 2-ethoxypyrrolin-5-one has reacted, the irradiation is stopped. The solution (Note 17) is transferred to a 250-ml., round-bottomed flask equipped with a magnetic stirring bar and an air-cooled reflux condenser mounted with a T-shaped nitrogen inlet. Nitrogen is passed through the apparatus for 30 minutes, after which the solution is stirred and heated at reflux under a nitrogen atmosphere for 20 hours (Note 18). The solvent is removed by rotary evaporation, and the residual orange oil is refrigerated to induce crystallization. Sublimation of the solid at 35–40° (0.05 mm.) affords 5.5–6.3 g. (56–64%) of the carbamate as white needles, m.p. 38–40° (Notes 19 and 20).

2. Notes

1. In parts A and B care should be taken to minimize the exposure of silver-containing reactants and products to light.

2. Succinimide purchased from MC and B Manufacturing Chemists was used without purification.

3. Absolute ethanol from a commercial supplier was used.

4. A mixture of silver nitrate and dimethyl sulfoxide is stirred vigorously for *ca.* 1 hour to dissolve all of the salt. Reagent-grade dimethyl sulfoxide was used without purification.

5. The sodium ethoxide solution is prepared from the reaction of 9.2 g. (0.40 mole) of sodium with 1 l. of absolute ethanol and is standardized by titration with aqueous 0.1 *N* hydrochloric acid. The appropriate volume of the solution to give 0.280 mole of base is used.

6. Slightly less than equivalent amounts of both silver nitrate and sodium ethoxide are used to minimize the formation of silver oxide which imparts a brown color to the product.

7. The submitters state that the use of a sintered-glass funnel may cause discoloration of the product. However, the checkers used a sintered glass funnel in one run with no adverse effect on the yield or purity of the product.

8. A considerable amount of sodium nitrate is present in the precipitate. Although the presence of sodium nitrate did not hinder small-scale alkylation reactions (*ca.* 250 mg.), the submitters recommend that it be removed in larger runs to facilitate the isolation and drying of the silver salt.

These washings are most easily done without removing the material from the filter. However, the solid must be slurried thoroughly in each portion of solvent, particularly with acetone and ether. Care must be taken to ensure that the filter paper is not lifted from the bottom of the funnel. The submitters accomplished this by holding the filter paper in the funnel with a ring of flexible polyvinyl chloride (inside diameter 0.64 cm.), the ends of which were joined by a small piece of rigid polyethylene tubing. The ring was expanded to fit snugly in the bottom of the funnel over the paper.

9. Silver salts may be unstable when heated. An explosion occurred while the silver salt of isatin was being dried under reduced pressure at *ca.* 100°.

10. The checkers found that the heavy suspension could not be stirred effectively with a magnetic stirring bar and recommend that a mechanical stirrer be used.

11. Reagent-grade chloroform was dried by filtering through alumina (50 g. per l. of solvent).

12. The checkers' data are given. The submitters recovered 4.7–11.4 g. of succinimide and collected 15.6–21.2 g. (44–60% based on sodium ethoxide in Part A) of product, b.p. 65–70° (0.05 mm.). Based on the amount of unrecovered succinimide, the yield of product obtained by the checkers and submitters was 49–61% and 68–69%, respectively. The product is best stored in a freezer. If sufficient care is taken to exclude moisture, 2-ethoxypyrrolin-5-one is stable indefinitely.

13. The product obtained by the submitters was contaminated

with impurities amounting to *ca.* 10% which were primarily succinimide and *N*-ethylsuccinimide. Although this material was considered to be of satisfactory purity for use in Part C, further purification can be accomplished, if desired, by redistillation to give product boiling at 72–74° (0.05 mm.). The checkers found it necessary to redistil the 2-ethoxypyrrolin-5-one to obtain product with the reported melting point in Part C (Note 20). The spectral characteristics of 2-ethoxypyrrolin-5-one are as follows: infrared (neat) cm.$^{-1}$: 2940, 1748, 1562; proton magnetic resonance (chloroform-*d*) δ (multiplicity, number of protons, assignment, coupling constant J in Hz.): 1.4 (triplet, 3, OCH_2CH_3, $J=7$), 2.4–3.0 (multiplet, 4, CH_2CH_2), 4.45 (quartet, 2, OCH_2CH_3, $J=7$); ultraviolet (cyclohexane) nm. max. (ε): 273 (55).

14. The irradiation apparatus was similar to one depicted in an earlier volume of this series (section A, Figure 2): *Org. Syn.*, **55,** 17 (1976). The height and inside diameter of the irradiation vessel used by the submitters were approximately 35 cm. and 6.2 cm., respectively. Two short necks with ℱ 14/20 outer joints were located on the shoulder of the vessel just below the ℱ 60/50 center joint. One neck was capped with a rubber septum and the other was connected to the exit bubbler. The nitrogen inlet was a syringe needle passing through the septum and connected to a section of Teflon tubing that extended to the bottom of the vessel. The checkers used a similar 23 × 7.5 cm. irradiation vessel that had a fritted-glass inlet for argon situated at the base as shown in the figure referred to above. The solution was agitated during the irradiation by a continual flow of argon rather than by magnetic stirring.

The apparatus is dried in an oven at 140° overnight and cooled under nitrogen or argon prior to the irradiation. A Vycor filter sleeve and a 450-watt medium-pressure mercury lamp are placed in the immersion well. The Vycor filter, the quartz immersion well (catlog No. 19434), the 450-watt mercury lamp (catalog No. 679A36), and the requisite transformer are all available from Hanovia Lamp Division, Canrad-Hanovia Inc., 100 Chestnut Street, Newark, New Jersey 07105.

15. Reagent-grade *tert*-butyl alcohol was distilled from calcium hydride prior to use. The scale described is that used by the checkers. The submitters irradiated 4.0 g. (0.032 mole) of 2-ethoxypyrrolin-5-one in 115 ml. of dry *tert*-butyl alcohol.

16. The submitters used a 2.1 m. × 0.64 cm. column with 5% fluorosilicone (FS-1265) supported on Diatoport S as stationary phase. With a column temperature of 170° and a helium flow rate of 60 ml. per minute, 2-ethoxypyrrolin-5-one has a retention time of 2.2 minutes. The analysis was carried out at 160° by the checkers, using a column of 5% diethylene glycol succinate–Bentone[34] supported on Diatoport S. The starting material had a retention time of 3.9 minutes under these conditions. Bentone[34] is available from Applied Sciences Laboratory, Box 440, State College, Pennsylvania 16801.

17. At this point the product consisted mostly of the isocyanate, since the reaction with *tert*-butyl alcohol is relatively slow at 35–40°. If the photolysis is carried out in an aprotic solvent such as tetrahydrofuran, the isocyanate may be isolated.[2] However, care must be exercised to avoid losses of this rather volatile and moisture-sensitive compound.

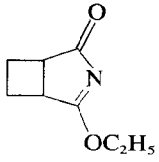
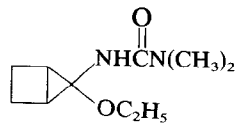
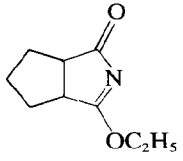
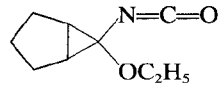
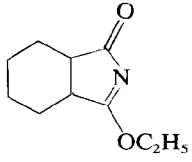
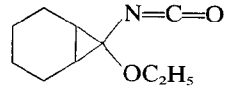
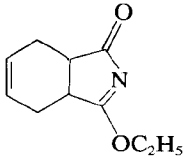
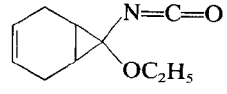
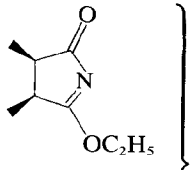
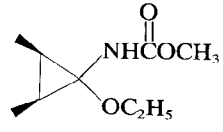
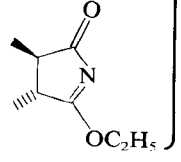
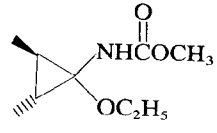
18. The isocyanate is completely consumed at this time, as evidenced by the disappearance of the absorption band at 2250 cm.$^{-1}$ in the infrared spectrum.

19. Alternatively, the product may be distilled at 40° (0.05 mm.). However, the distillate tends to crystallize in the condenser and plug the apparatus.

20. The checkers found that product with the reported melting point was obtained only when the starting 2-ethoxypyrrolin-5-one was redistilled carefully and was largely free of the *N*-ethyl isomer and succinimide. With 2-ethoxypyrrolin-5-one purified by a single distillation, the product was obtained as a gummy solid that was difficult to purify. Nevertheless, the infrared and proton magnetic resonance spectra of this material were essentially identical to those of pure *tert*-butyl *N*-(1-ethoxycyclopropyl)carbamate. The submitters obtained 4.4–4.8 g. (70–76%) of carbamate, m.p. 40–42°, from 4.0 g. of 2-ethoxypyrrolin-5-one. The product has the following spectral characteristics: infrared (neat) cm.$^{-1}$: 3333, 2940, 1754 (C=O); proton magnetic resonance (chloroform-*d*) δ (multiplicity, number of protons, assignment, coupling constant J in Hz.): 0.80–1.15 (multiplet, 4, cyclopropyl *H*), 1.13 (triplet, 3, OCH_2CH_3, $J=7$), 1.47 (singlet, 9, *tert*-butyl *H*) 3.68 (quartet, 2, OCH_2CH_3, $J=7$), 5.75 (broad, 1, N*H*).

TABLE I

PREPARATION AND IRRADIATION OF 2-ETHOXYPYRROLIN-5-ONES

2-Ethoxy-pyrrolin-5-one	Yield (%)	Photoproduct or Its Derivative	Yield (%)
	46[a]		43[b]
	59		76[b]
	89		64[b]
	74		53[b]
	88[c]		58[d]
			60

[a] The yield was 84% based on unrecovered imide.
[b] The product is a mixture of *endo* and *exo* isomers.
[c] The isomers were separated by preparative gas chromatography.
[d] The product is a mixture of *cis* and *trans* isomers.

3. Discussion

The procedure described here for the preparation of succinimide silver salt is a modification of one reported for the formation of the silver derivative of maleimide.[3] The alkylation step is modeled after the procedure of Comstock and Wheeler,[4] who prepared 2-ethoxypyrrolin-5-one in unspecified yield, and is an improvement over a later procedure developed in the laboratories of the submitters.[2] The general scheme has been successfully applied to the preparation of a variety of 2-ethoxypyrrolin-5-ones (Table I)[5-7] as well as 6-ethoxy- and 6-propoxy-4,5-dihydro-2(3*H*)-pyridone from the corresponding five- and six-membered cyclic imides.[2]

The photochemical rearrangement of substituted 2-ethoxypyrrolin-5-ones is a general reaction of synthetic utility and high stereoselectivity, which affords the corresponding 1-ethoxycyclopropyl isocyanates and their derivatives in useful yields (Table I).[6,7] The procedure reported here is the only known preparation of *tert*-butyl *N*-(1-ethoxycyclopropyl)carbamate, a precursor of 1-aminocyclopropanol and 1-ethoxycyclopropylamine.[8] 1-Aminocyclopropanol has previously been prepared in low yield by the addition of ammonia to cyclopropanone.[8] The photorearrangement of 2-ethoxypyrrolin-5-one to *tert*-butyl *N*-(1-ethoxycyclopropyl)carbamate followed by hydrolysis to 1-aminocyclopropanol is a key step in the synthesis of the alkaloid coprine.[8] Cyclopropanone derivatives have been used as precursors for a variety of compounds[9] such as β-lactams,[10] cyclobutanones,[11] and cyclopropanols.[12]

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Succinimide, silver salt (8); 2,5-Pyrrolidinedione, silver (1^+) salt (9); (55047-82-0)

Succinimide (8); 2,5-Pyrrolidinedione (9); (123-56-8)

Dimethyl sulfoxide: Methyl sulfoxide (8); Methane sulfinylbis- (9); (67-68-5)

2-Ethoxypyrrolin-5-one: 1-Pyrrolin-5-one, 2-ethoxy- (8); 2*H*-Pyrrol-2-one, 5-ethoxy-3,4-dihydro- (9); (29473-56-1)

tert-Butyl *N*-(1-ethoxycyclopropyl)carbamate: Cyclopropanecarbamic acid, 1-ethoxy-, *tert*-butyl ester (8); Carbamic acid, (1-ethoxycyclopropyl)-, 1,1-dimethylethyl ester (9); (28750-48-3; 41879-49-6)

tert-Butyl alcohol (8); 2-Propanol, 2-methyl- (9); (75-65-0)

Succinimide, *N*-ethyl- (8); 2,5-Pyrrolidinedione, 1-ethyl- (9); (2314-78-5)

2(3*H*)-Pyridone, 6-ethoxy-4,5-dihydro- (8); 2(3*H*)-Pyridinone, 6-ethoxy-4,5-dihydro- (9); (41879-47-4)

2(3*H*)-Pyridone, 4,5-dihydro-6-propoxy- (8); 2(3*H*)-Pyridinone, 4,5-dihydro-6-propoxy- (9); (41879-48-5)

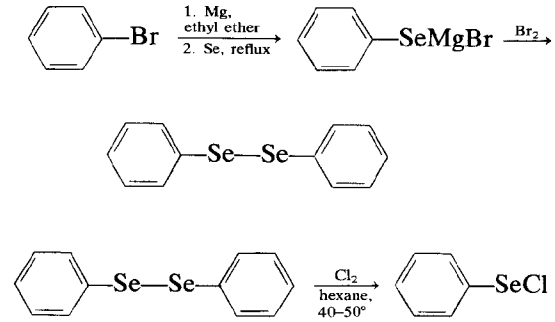
Cyclopropanol, 1-amino- (8, 9), hydrochloride (58939-46-1)

Cyclopropylamine, 1-ethoxy- (8); Cyclopropanamine, 1-ethoxy- (9), hydrochloride (58939-48-3)

Cyclopropanone (8, 9); (5009-27-8)

Coprine: Glutamine, *N*-(1-hydroxycyclopropyl)-, *L*- (8); *L*-Glutamine, *N*-(1-hydroxycyclopropyl)- (9); (58919-61-2)

REAGENTS FOR SYNTHESIS OF ORGANOSELENIUM COMPOUNDS: DIPHENYL DISELENIDE AND BENZENESELENENYL CHLORIDE



Submitted by HANS J. REICH, MARTIN L. COHEN, and PETER S. CLARK[1]
Checked by ANNA VINOGRADOFF, ALBERT W. M. LEE, and ROBERT V. STEVENS

1. Procedure

Caution! Most selenium compounds are toxic; care should be exercised to avoid contact with skin. All operations in this procedure should be conducted in a well-ventilated hood.

A. *Diphenyl diselenide.* A 2-l., three-necked, round-bottomed flask is equipped with a mechanical stirrer, a pressure-equalizing dropping funnel, and an efficient reflux condenser mounted with a combined inlet-outlet assembly connected to a nitrogen source and a bubbler. The apparatus is flamed dry while a slow stream of nitrogen is passed through the system. In the cooled flask a solution of phenylmagnesium bromide is prepared from 160 g. (1.02 mole) of bromobenzene, 24.0 g. (0.99 g.-atom) of magnesium, and 550 ml. of anhydrous ethyl ether. The dropping funnel is removed, and an Erlenmeyer flask containing 70 g. (0.89 g.-atom) of selenium (Note 1) is attached to the neck of the flask with a section of nylon tubing (Note 2). The selenium is added in portions at a rate sufficient to maintain a vigorous reflux (Note 3). The addition requires 15–30 minutes, after which the mixture is stirred and heated at reflux for another 30 minutes. The Erlenmeyer flask and nylon tubing are removed, and 3 g. (0.17 mole) of

water is added to hydrolyze any excess Grignard reagent. The mixture is stirred and cooled in an ice bath while 74.3 g. (23.8 ml., 0.465 mole) of bromine is added dropwise at a rate such that the ether does not reflux (Note 4). Cooling and stirring are continued as a solution of 53.5 g. (1.0 mole) of ammonium chloride in 140 ml. of water is added slowly. The mixture is filtered by gravity into a 1-l., round-bottomed flask, and the granular precipitate is washed thoroughly with three 100-ml. portions of ether. The combined filtrates are evaporated, the remaining solid is dissolved insofar as possible in 500 ml. of hot hexane, and a small amount of insoluble material is separated by gravity filtration. The filtrate is allowed to crystallize at room temperature and then at 6°. The yellow microcrystalline solid is collected, washed with 30 ml. of pentane, and dried in the air. The yield of diphenyl diselenide, m.p. 60–62°, is 89–97 g. (64–70%) (Notes 5 and 6).

B. *Benzeneselenenyl chloride.* A 1-l., three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a thermometer, a gas-inlet tube, and a reflux condenser. The flask is charged with 50 g. (0.16 mole) of diphenyl diselenide and 350 ml. of hexane (Note 7), and the mixture is warmed to 40–50° to dissolve the solid. The resulting solution is stirred while chlorine gas is passed through the gas-inlet tube into the flask 1 cm. above the surface of the liquid at a rate sufficient to maintain the temperature between 40° and 50°. Chlorination is continued until 11.3 g. (0.16 mole) of the gas is absorbed (Note 8). The solution is heated to reflux, filtered by gravity, and allowed to cool slowly at room temperature and then at 6° (Note 9). The mother liquor is decanted, the large, deep orange crystals are washed with 25 ml. of pentane, and the residual solvent is evaporated by passing a slow stream of nitrogen over the crystals for 30 minutes. The benzeneselenenyl chloride weighs 51–54 g. (84–88%) and melts at 60–62°. (Note 10).

2. Notes

1. The gray powdered form of selenium should be used. The submitters purchased this material from Research Organic/Inorganic Chemical Corporation, 11686 Sheldon Street, Sun Valley, California 91352, and from Var-lac-oid Chemical Company, 666 South Front Street, Elizabeth, New Jersey 07202.

2. Alternatively the flask may be equipped with a Y-shaped adapter bearing a straight condenser on its vertical branch and fitted with a nitrogen inlet in its lower branch. A slow stream of nitrogen is passed through the nitrogen inlet while the portions of selenium are added through the top of the condenser. The top of the condenser is stoppered between additions.

3. Careful exclusion of oxygen during this operation is important.

4. The addition of bromine requires about 30 minutes, after which the maintenance of a nitrogen atmosphere is no longer necessary.

5. The submitters have carried out this procedure on a 3-mole scale and obtained similar yields. A melting point of 63.5° is reported[2] for diphenyl diselenide.

6. The appearance of a red coloration in the product indicates the presence of excess selenium. Free selenium begins to separate when the product is contaminated by more than *ca.* 1% of diphenyl triselenide. Even material that crystallizes as a brick-red solid may contain only 5% excess selenium. The procedure described here gives diphenyl diselenide containing less than 0.5% free selenium. More of this contaminant will be present, however, if the formation of the Grignard reagent is incomplete, or if oxygen is allowed to enter the flask during the addition of selenium.

7. Technical-grade hexane is adequate.

8. The amount of chlorine absorbed can be measured by the increased weight of the flask. The progress of the reaction can also be monitored in the following manner. A white ring of phenylselenium trichloride forms on the wall of the flask just above the surface of the liquid during the chlorination. If diphenyl diselenide remains in the solution, the solid dissolves when the flask is tipped slightly to immerse the phenylselenium trichloride below the surface of the solution. The solid no longer dissolves after the reaction is complete. The remaining ring of phenylselenium trichloride can be removed by adding another small portion of diphenyl diselenide.

9. The solution should not be cooled below 0°, since impurities, including diphenyl selenide dichloride, may also crystallize.

10. The submitters obtained 54–57 g. (88–93%) of product which melted at 62–64°. The reported[3] melting point for benzeneselenenyl chloride is 64–65°.

3. Discussion

Diphenyl diselenide has been prepared by disproportionation of phenyl selenocyanate in the presence of potassium hydroxide[4,5] or ammonia,[4] and by air oxidation of benzeneselenol.[6,7] The preparation of benzeneselenol is described in an earlier volume in this series.[8] In the present procedure phenylselenomagnesium bromide formed from phenylmagnesium bromide and selenium[8] is oxidized directly to diphenyl diselenide with bromine.[9] Thus the liberation of the malodorous and toxic hydrogen selenide and benzeneselenol is avoided. Benzeneselenenyl chloride has been prepared by thermal elimination of ethyl chloride from ethyl phenyl selenide dichloride,[3,10] by thermal elimination of chlorine from phenylselenium trichloride,[11] and by chlorinolysis of diphenyl diselenide with either sulfuryl chloride[12,13] or chlorine.[9,13]

Diphenyl diselenide and benzeneselenenyl chloride have been utilized as intermediates for the preparation of several phenyl-substituted organoselenium reagents (Table I).[14] Benzeneselenenyl bromide is available by direct brominolysis of diphenyl diselenide.[9,15] The reaction of benzeneselenenyl halides with silver acetate and silver trifluoroacetate has been employed to generate benzeneselenenyl acetate[13] and trifluoroacetate[16] *in situ*. *N,N*-Dialkyl benzeneselenenamides have been isolated from the reaction of secondary amines with benzeneselenenyl chloride or bromide.[17] Oxidation of benzeneselenenyl chloride and diphenyl diselenide with ozone affords benzeneseleninyl chloride and benzeneseleninic anhydride, respectively.[9,18] The highly nucleophilic selenenylating reagent, selenophenoxide, is liberated in solution readily by reduction of diphenyl diselenide with sodium borohydride in ethanol[19] or with other reducing agents.[14] Solutions of selenophenol are conveniently prepared by reduction with hypophosphorous acid.[20]

Diphenyl diselenide, benzeneselenenyl chloride, and organoselenium compounds derived from them have served as convenient reagents for introducing the phenylseleno group in synthesis. The reaction of organolithium and Grignard reagents with diphenyl diselenide affords phenyl selenides.[21] The phenylseleno group has been introduced into the α-position of aldehydes, ketones, esters, nitriles, sulfones, and related compounds by reaction of enol derivatives, enolate anions, or carbanions with

TABLE I
ORGANOSELENIUM REAGENTS PREPARED FROM DIPHENYL DISELENIDE OR BENZENESELENENYL CHLORIDE

Organoselenium Reagent	M.p. or B.p. (·)	Reference(s)
C_6H_5SeBr	62	4, 9, 15
$C_6H_5SeOCCH_3$ (O above C)	[a]	13
$C_6H_5SeOCCF_3$ (O above C)	[a]	16
$C_6H_5SeN(CH_3)_2$	39–40 (0.1 mm.)	17
C_6H_5—Se(O)—Cl	75	9, 18
$C_6H_5Se(O)OSe(O)C_6H_5$	120–122	18
C_6H_5SeNa	[a]	14, 19, 20
C_6H_5SeH	[a]	20

[a] This reagent was generated in solution and used without isolation.

diphenyl diselenide or benzeneselenenyl chloride.[9,14,15a] The addition of benzeneselenenyl halides,[13,22] acetate,[13] and trifluoroacetate[16] to olefins affords alkyl phenyl selenides substituted in the β-position with halo, acetoxy, and trifluoroacetoxy groups.

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Phenyl diselenide (8); Diselenide, diphenyl (9); (1666-13-3)

Benzeneselenenyl chloride (8, 9); (5707-04-0)

Phenylmagnesium bromide: Magnesium, bromophenyl- (8, 9); (100-58-3)

Phenylselenium trichloride: Selenium, trichlorophenyl- (8); Selenium, trichlorophenyl-, (T-4)- (9); (42572-42-9)

Benzeneselenol (8, 9); (645-96-5)

Phenylselenomagnesium bromide: Magnesium, (benzeneselenolato)bromo- (9); (42778-03-0)

Benzeneselenenyl bromide (8, 9); (34837-55-3)

Benzeneseleninic anhydride (8, 9); (17697-12-0)

Benzeneseleninyl chloride (8, 9); (57204-85-0)

Benzeneselenenyl trifluoroacetate: Ethane(selenoperoxoic) acid, trifluoro-, *OSe*-phenyl ester (9); (51558-78-2)

Benzeneselenenyl acetate: Ethane(selenoperoxoic) acid, *OSe*-phenyl ester (9); (−)

Diphenyl selenide dichloride: Selenium, dichlorodiphenyl- (8); Selenium, dichlorodiphenyl-, (T-4)- (9); (2217-81-4)

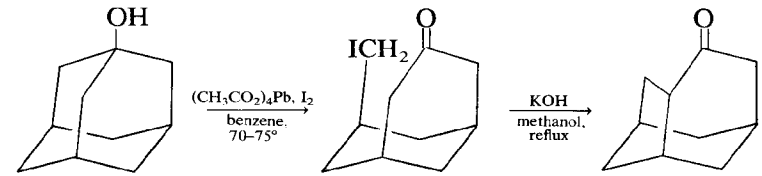
Phenyl selenocyanate: Selenocyanic acid, phenyl ester (8, 9); (2179-79-5)

Ethyl phenyl selenide dichloride: Selenium, dichloroethylphenyl- (8, 9); (−)

Selenophenoxide: Benzeneselenol ion (1-) (8, 9); (14971-39-2)

REARRANGEMENT OF BRIDGEHEAD ALCOHOLS TO POLYCYCLIC KETONES BY FRAGMENTATION-CYCLIZATION: 4-PROTOADAMANTANONE

(2,5-Methano-1*H*-inden-7(4*H*)-one, hexahydro)



Submitted by ZDENKO MAJERSKI[1] and ZDENKO HAMERŠAK[1]
Checked by THOMAS P. DEMUTH and ANDREW S. KENDE

1. Procedure

Caution! See benzene warning, Org. Syn., **58,** 168 (1978).

A. endo-7-*Iodomethylbicyclo*[3.3.1]*nonan*-3-*one.* A 2-l., three-necked, round-bottomed flask equipped with an efficient mechanical stirrer and a reflux condenser is charged with 600 ml. of dry benzene (Note 1). The flask is immersed in a water bath, stirring is initiated, and 58.3 g. (0.132 mole) of lead tetraacetate (Note 2), 37.4 g. (0.147 mole) of iodine, and 10.0 g. (0.066 mole) of 1-adamantanol (Note 3) are added (Note 4). The bath temperature is gradually raised to 80° over a 20-minute period and is then allowed to cool to 70–75°. Stirring is continued for 2 hours at 70–75° (Note 5) and for an additional hour while the mixture is cooled to room temperature. The inorganic salts are filtered and carefully washed with five 50-ml. portions of ethyl ether. The

benzene filtrate and ether washings are combined in a 2-l. separatory funnel and shaken with 500 ml. of saturated aqueous sodium bisulfite (Note 6) until the dark red color disappears. The layers are *not* separated. If the color reappears within 10–15 minutes, the mixture is shaken again until colorless. This procedure is repeated as many times as necessary. The layers are then separated, and the organic layer is washed with 500 ml. of water and 250 ml. of saturated aqueous sodium bicarbonate. The benzene–ether solution is dried over anhydrous magnesium sulfate for 1 hour and concentrated in a 500-ml., round-bottomed flask with a rotary evaporator (Note 7). The resulting crude, oily iodo ketone weighs 14–16 g. (Note 8) and is used immediately in Part B.

B. 4-*Protoadamantanone.* The flask containing the crude iodo ketone is equipped with a magnetic stirring bar and a reflux condenser. A solution of 7 g. (0.125 mole) of potassium hydroxide in 150 ml. of methanol is added, and the mixture is stirred and heated at reflux for 3 hours. The contents of the flask are allowed to cool to room temperature and poured into 300 ml. of ice-water. The resulting mixture is extracted with five 100-ml. portions of ether. The combined extracts are dried over anhydrous magnesium sulfate and evaporated under reduced pressure, leaving 8.6–9.1 g. of a yellow solid (Note 9). A solution of this crude product in 3 ml. of chloroform is allowed to percolate onto a chromatography column packed with 200 g. of activity III, neutral alumina in pentane (Note 10). The column is eluted first with 100 ml. of pentane and then with 500 ml. of 3:7 (v/v) ether–pentane as 25-ml. fractions are collected and analyzed by gas chromatography (Note 11). Those fractions containing product whose purity is judged to be 98% or greater are combined and evaporated, affording 7.0–8.1 g. (71–82% based on 1-adamantanol) of 4-protoadamantanone as a colorless or pale yellow solid, m.p. 202–204° (Note 12).

2. Notes

1. Solvent-grade benzene was dried over sodium wire prior to use. If the benzene is wet, a considerable amount of starting 1-adamantanol remains unreacted owing to hydrolysis of lead tetraacetate.

2. Lead tetraacetate, both purchased from Fluka AG, Buchs, Switzerland, and prepared according to a literature procedure,[2] were used by the submitters without any noticeable difference. Lead tetraacetate was dried prior to use for at least 12 hours over potassium hydroxide and phosphorus pentoxide in an evacuated desiccator (12 mm.) that was protected from direct light. If well protected from moisture, lead tetraacetate can be kept for weeks in this way. However, after exposure to moisture in the air, lead tetraacetate usually turns brown from hydrolysis to lead hydroxide. The reactivity of such lead tetraacetate is diminished somewhat, but it can still be used. If the lead tetraacetate has turned black, the reagent should be recrystallized from glacial acetic acid and dried prior to use as described above.

3. 1-Adamantanol is available from the following three suppliers: Aldrich Chemical Company, Inc., Fluka AG, Buchs, Switzerland; E. Merck, Darmstadt, Germany. It may also be prepared from adamantane by bromination to 1-bromoadamantane and hydrolysis.[3] Adamantane is sold by the same three suppliers.

4. The resulting solution is dark red in color.

5. The temperature of the bath should be *carefully* maintained in this range. At temperatures below 70° the reaction is much slower and increased amounts of unreacted 1-adamantanol will contaminate the product. At temperatures above 75° the amount of tar in the product is increased.

6. Other reducing agents such as sodium thiosulfate or sodium metabisulfite may be used as well.

7. Most of the solvent was evaporated with a bath temperature of 40–50°. The last 40–50 ml. was removed without heating. *endo*-7-Iodomethylbicyclo[3.3.1]nonan-3-one should be handled as quickly as possible, since this iodo ketone is thermally unstable. In the absence of solvent, decomposition may be rapid even at room temperature.

8. The crude iodo ketone usually contains up to 10% benzene, which does not interfere with the cyclization step (Part B). Complete removal of the benzene takes time, during which a considerable proportion of the iodo ketone may decompose.

9. A gas chromatographic analysis on the crude product was carried out by the submitters using a 1.5 m. × 3.2 mm. column packed with 10% diethylene glycol succinate supported on 60/80 mesh Chromosorb W and heated at 140°. The chromatogram

showed peaks for product, 1–3% unreacted 1-adamantanol, and a total of 1–2% of several other minor by-products.

10. Activity III alumina is prepared by adding 6% (w/w) of water to neutral alumina of activity grade I. The submitters used a 50×3 cm. glass column for the chromatography.

11. The conditions for gas chromatography are given in Note 9. The product was found mainly in fractions 2–20 by the submitters. The first 25-ml. fraction contained considerable amounts of by-products, while fractions 21 and higher contained 1-adamantanol. The checkers collected 10-ml. fractions with an automatic fraction collector.

12. Recrystallization from aqueous methanol raised the melting point to 207–210°. The reported[4] melting point is 210–212°. The product obtained by the checkers was analytically pure. Analysis calculated for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 80.19; H, 9.31. The spectral characteristics of 4-protoadamantanone are as follows: infrared (potassium bromide) cm.$^{-1}$: 2920, 2860, 1710 (C=O), 1322, 1235; proton magnetic resonance (chloroform-*d*) δ (multiplicity, number of protons): 1.0–2.0 (multiplet, *ca.* 7), 2.0–3.0 (multiplet, *ca.* 7); carbon-13 magnetic resonance (chloroform-*d*) δ (assignment): 216.2 (*C*=O), 51.1 (*C*H), 45.0 (CH_2), 41.4 (CH_2), 38.2 (CH_2), 37.3 (CH_2 and *C*H), 37.2 (*C*H), 34.9 (CH_2), 29.6 (*C*H); mass spectrum *m/e* (relative intensity): 150 (M^+, 100), 95 (63), 93 (23), 81 (24), 80 (40), 79 (46), 67 (30), 66 (40).

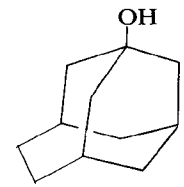
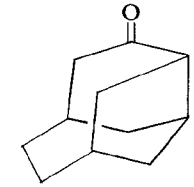
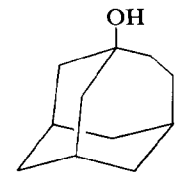
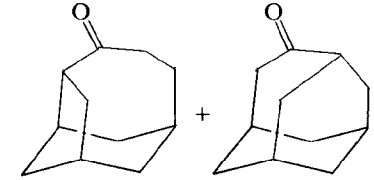
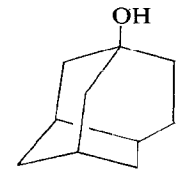
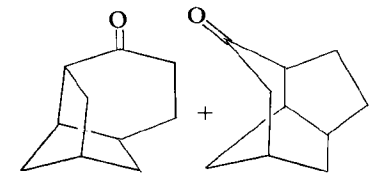
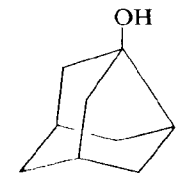
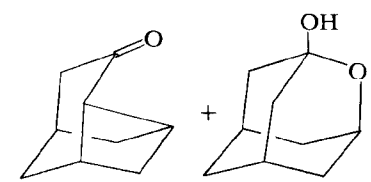
3. Discussion

4-Protoadamantanone is a versatile intermediate for the synthesis of not only protoadamantane derivatives,[5–7] but also 1,2- and 2,4-disubstituted adamantanes,[8–10] 2-substituted noradamantanes,[11] and 4(5)-substituted 4-homoprotoadamantanes.[12]

4-Protoadamantanone has been prepared by the nitrous acid deamination of 2-amino-1-adamantanol (77%),[5] by aprotic diazotization of *endo*-7-aminomethylbicyclo[3.3.1]nonan-3-one in benzene with an equivalent amount of acetic acid (67%),[13] and by thermolysis of 1-adamantyl hypohalites followed by base-promoted cyclization of the resulting halo ketones (32–37%).[4,14,15] In spite of low and erratic yields, the last reaction sequence has provided the most convenient route to the protoadamantanes, since the other two approaches require lengthy syntheses of the starting materials.

The procedure described here is a modification of one involving the thermal fragmentation of 1-adamantyl hypoiodite and cyclization of the resulting iodo ketone.[4,14,16] By means of this procedure, 4-protoadamantanone is obtained from 1-adamantanol with consistent yields in the range of 71 to 82% and a purity greater than 98%. This method is also applicable to the preparation of other polycyclic ketones from the related bridgehead alcohols with α-bridges of zero, one, or two carbon atoms (see Table I).

TABLE I
REARRANGED POLYCYCLIC KETONES PREPARED BY FRAGMENTATION AND RECYCLIZATION OF BRIDGEHEAD ALCOHOLS

Alcohol	Product(s)	Ratio	Yield (%)	Reference
		—	74	16
		2:3	78	17
		1:1	69	18
		2:1[a]	30	18

[a] The base-catalyzed cyclization was carried out in aqueous 70% dioxane at reflux.

With unsymmetrical bridgehead alcohols the structure of the product depends on the regioselectivity of both the fragmentation and intramolecular alkylation reactions. The position of the bond cleavage in the fragmentation step appears to be controlled by the stability of the keto free radical intermediates which subsequently react with iodine to produce the iodo ketones. The course of the cyclization is probably governed by preferential enolization toward one α-methylene group and by a more favorable position of the iodomethyl group with respect to one of the two α-carbons in the enolate anions.

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

4-Protoadamantanone: 2,5-Methanoindan-7(4*H*)-one, tetrahydro- (8); 2,5-Methano-1*H*-inden-7(4*H*)-one, hexahydro- (9); (27567-85-7)

Bicyclo[3.3.1]nonan-3-one, 7-(iodomethyl)-, *endo*- (8, 9); (29817-49-0)

Lead tetraacetate: Lead, tetrakis(acetato)- (8, 9); (−)

Iodine (8, 9); (7553-56-2)

1-Adamantanol (8); Tricyclo[3.3.1.1^{3,7}]decan-1-ol (9); (768-95-6)

Ethyl ether (8); Ethane, 1,1′-oxybis- (9); (60-29-7)

Adamantane (8); Tricyclo[3.3.1.1^{3,7}]decane (9); (281-23-2)

Adamantane, 1-bromo- (8); Tricyclo[3.3.1.1^{3,7}]decane, 1-bromo- (9); (768-90-1)

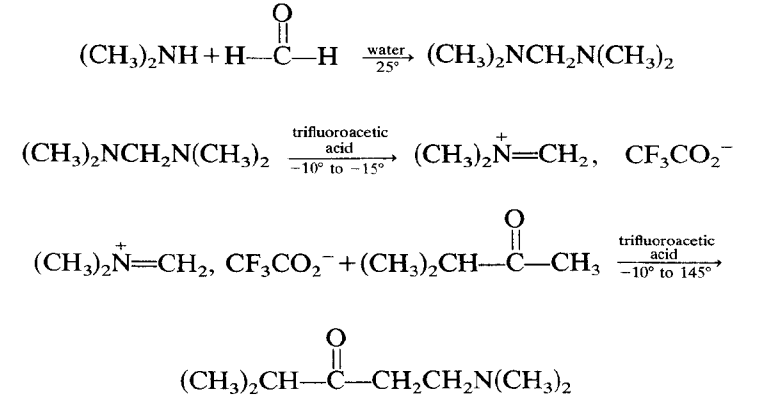
1-Adamantanol, 2-amino- (8); Tricyclo[3.3.1.1^{3,7}]decan-1-ol, 2-amino- (9); (17744-02-4)

Bicyclo[3.3.1]nonan-3-one, 7-(aminomethyl)-, *endo*- (8, 9) (34650-78-7)

1-Adamantyl hypoiodite: 1-Adamantanol, hypoiodite (8); (29844-68-6)

REGIOSELECTIVE MANNICH CONDENSATION WITH DIMETHYL(METHYLENE)AMMONIUM TRIFLUOROACETATE: 1-DIMETHYLAMINO-4-METHYL-3-PENTANONE

[3-Pentanone, 1-(dimethylamino)-4-methyl-]



Submitted by Michel Gaudry, Yves Jasor, and Trung Bui Khac[1]
Checked by Bernard L. Müller and George Büchi

1. Procedure

Caution! Trifluoroacetic acid is highly toxic; consequently Part B of this procedure must be conducted in a well-ventilated hood.

A. *Bis(dimethylamino)methane.* A 500-ml., round-bottomed flask equipped with a magnetic stirring bar and a dropping funnel is charged with 100 g. (1 mole) of aqueous 30% formaldehyde (Note 1). The solution is stirred and cooled in an ice bath as 225 g. (2 moles) of a 40% solution of dimethylamine (Note 1) in water is added dropwise. The resulting aqueous solution is allowed to stand overnight at room temperature, after which it is saturated with solid potassium hydroxide. The two layers are separated, the upper layer is dried over potassium hydroxide pellets, and the drying agent is removed. Distillation at atmospheric pressure through a Vigreux column gives 85–88 g. (83–86%) of bis(dimethylamino)methane, b.p. 81.5–83°.

B. *1-Dimethylamino-4-methyl-3-pentanone.* A 100-ml., two-necked, round-bottomed flask equipped with a magnetic stirring bar and a pressure-equalizing dropping funnel bearing a calcium chloride drying tube is charged with 50 ml. of anhydrous trifluoroacetic acid (Note 2). The trifluoroacetic acid is stirred and cooled in an ice–salt bath at −10° to −15° while 10.2 g. (0.10 mole) of bis(dimethylamino)methane is added during a 50-minute period (Note 3). The temperature of the resulting solution of dimethyl(methylene)ammonium trifluoroacetate is kept below −10° as 8.6 g. (0.10 mole) of 3-methyl-2-butanone (Note 4) is gradually added. The cooling bath is removed and the solution is heated in an oil bath at 65° for 1.5 hours (Note 5). The temperature of the oil bath is then raised to 145° (Note 6). After 1.5 hours the solution is cooled and the trifluoroacetic acid is neutralized by adding the contents of the flask dropwise to an ice-cold solution of 100 g. of potassium carbonate in 100 ml. of water (Note 7). The crystals are collected by filtering through a sintered-glass Büchner funnel and washed with two 50-ml. portions of dichloromethane. The aqueous filtrate is extracted with four 50-ml. portions of dichloromethane. The dichloromethane extracts are combined, washed with 50 ml. of water, dried over anhydrous sodium sulfate, and concentrated with a rotary evaporator. The concentrate, which amounts to 12.7 g. (Note 8), is distilled under reduced pressure through an 18-cm. column packed with Raschig rings (Note 9), affording 7.0–8.2 g. (49–57%) of 1-(dimethylamino)-4-methyl-3-pentanone, b.p. 49° (3 mm.) (Note 10).

2. Notes

1. Formaldehyde and dimethylamine are available as aqueous 37% and 40% solutions, respectively, from Aldrich Chemical Company, Inc.

2. The submitters purchased trifluoroacetic acid from Prolabo, Paris, France, or E. Merck, Darmstadt, Germany, and distilled it from phosphorous pentoxide. This reagent is also available from Aldrich Chemical Company, Inc., and J. T. Baker Chemical Company.

3. The reaction between bis(dimethylamino)methane and trifluoroacetic acid is very exothermic. If the temperature is carefully controlled, a colorless solution remains when the addition is complete.

4. 3-Methyl-2-butanone was purchased from Eastman Organic Chemicals and distilled before use.

5. The progress of the reaction can be monitored by taking proton magnetic resonance spectra at appropriate intervals. The following absorptions for dimethyl(methylene)ammonium trifluoroacetate in trifluoroacetic acid disappear as the reaction progresses: δ (multiplicity, number of protons, assignment): 3.89 (broad multiplet, 6, two NCH_3), 8.07 (broad multiplet, 2, $N{=}CH_2$).

6. At this temperature 4-(dimethylamino)-3,3-dimethyl-2-butanone, which is formed initially, isomerizes to 1-(dimethylamino)-4-methyl-3-pentanone.

7. Removing the trifluoroacetic acid by evaporation is tedious. The neutralization procedure given here produces insoluble salts that are readily separated by filtration.

8. The ratio of the isomeric amino ketones in the crude product can be determined from the relative intensities of the signals for the $(CH_3)_2C$ grouping in a proton magnetic resonance spectrum taken in trifluoroacetic acid (see Note 10). In chloroform-*d* these absorptions overlap.

9. To minimize losses of products during the distillation, the submitters used a circulating device to chill the condenser cooling

water to 5–10°. In addition, the outlet to the vacuum line was located as far as possible from the drip tip, and the receivers were cooled in an ice bath.

10. The proton magnetic resonance spectrum of the product in trifluoroacetic acid shows that the isomeric purity is greater than 90%. The proton magnetic resonance spectral properties for the isomeric amino ketones in both trifluoroacetic acid and chloroform-*d* are as follows: (solvent) δ (multiplicity, number of protons, assignment, coupling constant J in Hz.); 1-(dimethylamino)-4-methyl-3-pentanone (trifluoroacetic acid): 1.16 (doublet, 6, two CCH_3, $J=7$), 2.98 (doublet, 6, two NCH_3, $J=5$), 3.31 (multiplet, 4, CH_2CH_2); (chloroform-*d*): 1.10 (doublet, 6, two CCH_3, $J=7$), 2.23 (singlet, 6, two NCH_3), 2.60 (singlet, 4, CH_2CH_2); 4-(dimethylamino)-3,3-dimethyl-2-butanone (trifluoroacetic acid): 1.53 (singlet, 6, two CCH_3), 2.45 (singlet, 3, $C(=O)CH_3$), 3.15 (doublet, 6, two NCH_3, $J=5$), 3.40 (doublet, 2, CH_2N, $J=5$); (chloroform-*d*): 1.12 (singlet, 5, two CCH_3), 2.13 (singlet, 3, $C(=O)CH_3$), 2.18 (singlet, 6, two NCH_3), 2.41 (singlet, 2, CH_2N).

3. Discussion

The Mannich condensation has traditionally been carried out in the presence of water as a three-component condensation involving a carbonyl compound (or related carbon nucleophile), formaldehyde, and a primary or secondary amine.[2] The initial step is a condensation between the latter two reactants to form a mono- or dialkyl(methylene)ammonium ion which subsequently serves as the electrophilic partner in the reaction. With unsymmetrical ketones aminomethylation generally occurs at both positions to give mixtures of isomeric β-amino ketones. The ratio of the isomers depends strongly on the structure of the ketone,[3] and the more highly branched β-amino ketone usually predominates.

In recent years a number of methods have been developed for the preparation of dialkyl(methylene)ammonium salts (Mannich reagents),[4-8] and their use in Mannich-type condensation reactions under anhydrous conditions has improved the scope and efficiency of this important synthetic process.[5-12] However, the orientation of the Mannich reaction may nevertheless be difficult to control. Apart from the work of the submitters, the preparation of isomerically pure Mannich bases has only been achieved by indirect

methods in which specific enol derivatives are generated and allowed to react with dialkyl(methylene)ammonium salts.[9,11,13] The Mannich reaction of β-keto esters affords isomerically pure β-dimethylamino β'-keto esters which may in turn be converted to specific α-methylene ketones.[14] However, the β-amino ketones themselves are not as yet available by this method.

The submitters have found that the orientation of the reaction of Mannich reagents with unsymmetrical ketones in anhydrous solvents is highly dependent on the experimental conditions, the solvent, and the structures of the ketone and iminium ion reactants.[10] Under conditions of kinetic control, the reaction of methyl ketones with dimethyl(methylene)ammonium trifluoroacetate in trifluoroacetic acid leads to amino ketones in which the more highly substituted isomer predominates ($\geq 85\%$ when the α'-position is tertiary and 80% when the α'-position is secondary). In contrast, reaction with diisopropyl(methylene)ammonium perchlorate in acetonitrile gives almost exclusively the less highly substituted isomer (100% when the α'-position is tertiary and 90% when it is secondary). Although the latter method directly affords the less highly substituted Mannich bases in yields greater than 80%, it cannot be utilized safely in large-scale preparative reactions owing to the hazardous nature of perchlorate salts.

The less highly substituted Mannich bases can also be prepared directly from ketones and dimethyl(methylene)ammonium trifluoroacetate by the procedure reported here, which takes advantage of the isomerization of Mannich bases in trifluoroacetic acid.[10] (In acetic acid the Mannich bases undergo elimination of dimethylamine to give α-methylene ketones.) This method is rapid and affords products having an isomeric purity of at least 90% without difficult separations. The 49–57% yield of 1-(dimethylamino)-4-methyl-3-pentanone obtained with this procedure compares favorably with the overall yields of amino ketones prepared by the indirect routes mentioned previously.

1-(Dimethylamino)-4-methyl-3-pentanone has been prepared by addition of isopropylmagnesium bromide to methyl 3-(dimethylamino)propionate,[15] by reduction of 1-(dimethylamino)-4-methyl-1-penten-3-one with lithium aluminum hydride,[16] and by displacement of chloride from 1-chloro-4-methyl-3-pentanone with dimethylamine.[17] Although the preparation of 1-(dimethylamino)-4-methyl-3-pentanone by Mannich condensation

of 3-methyl-2-butanone with dimethylamine hydrochloride and formaldehyde has been reported,[18] the product evidently is a mixture of the two isomeric β-dimethylamino ketones.[3,17]

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

3-Pentanone, 1-(dimethylamino)-4-methyl- (8, 9); (5782-64-9)

Bis(dimethylamino)methane; Methanediamine, *N,N,N′,N′*-tetramethyl- (8, 9); (51-80-9)

Formaldehyde (8, 9); (50-00-0)

Dimethylamine (8); Methanamine, *N*-methyl- (9); (124-40-3)

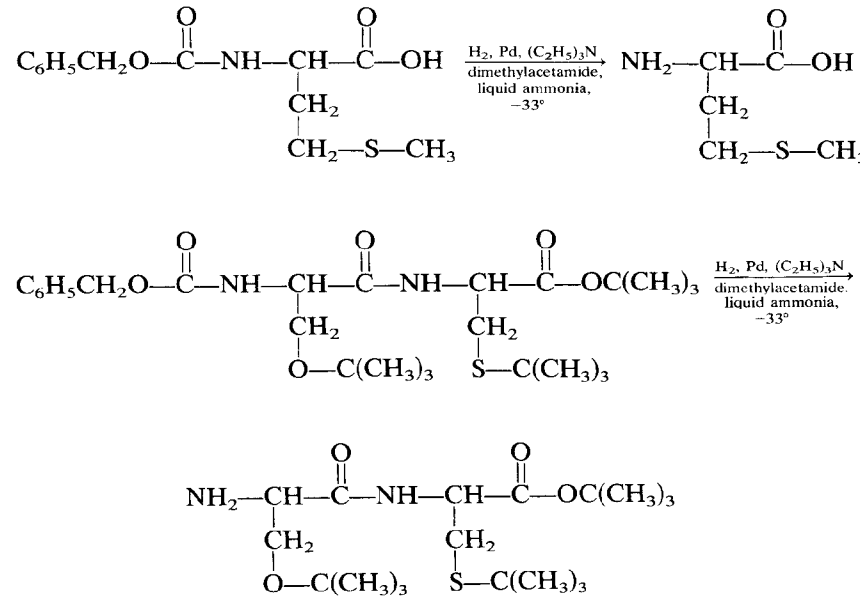
2-Butanone, 3-methyl- (8, 9); (563-80-4)

2-Butanone, 4-(dimethylamino)-3,3-dimethyl- (8, 9); (53921-82-7)

Dimethyl(methylene)ammonium trifluoroacetate: Ammonium, dimethylmethylene-, salt with trifluoroacetic acid (1:1) (8); Methanaminium, *N*-methyl-*N*-methylene-, salt with trifluoroacetic acid (1:1) (9); (25468-31-9)

Diisopropyl(methylene)ammonium perchlorate: Ammonium, diisopropylmethylene-, perchlorate (8); 2-Propanaminium, *N*-methylene-*N*-(1-methylethyl)-, perchlorate (9); (28746-66-9)

REMOVAL OF N^{α}-BENZYLOXYCARBONYL GROUPS FROM SULFUR-CONTAINING PEPTIDES BY CATALYTIC HYDROGENATION IN LIQUID AMMONIA: *O-tert*-BUTYL-L-SERYL-*S-tert*-BUTYL-L-CYSTEINE *tert*-BUTYL ESTER



Submitted by ARTHUR M. FELIX, MANUEL H. JIMENEZ, and JOHANNES MEIENHOFER[1,2]
Checked by LÁSZLÓ RÉVÉSZ and G. BÜCHI

1. Procedure

Caution! All operations described in these procedures must be carried out in a well-ventilated hood, since ammonia is highly toxic, hydrogen is extremely flammable, and palladium black is pyrophoric.

A. L-*Methionine.* A dry, 1-l., three-necked, round-bottomed flask is equipped with a dry ice reflux condenser (Note 1), a gas-inlet tube, and a magnetic stirring bar as illustrated in Figure 1. The reaction vessel is immersed in a dry ice–acetone bath, and a total of 300 ml. of ammonia (Note 2) is passed through a drying tower containing potassium hydroxide pellets and then collected in the flask. The dry ice–acetone bath is removed to permit the reaction to proceed at the boiling point of ammonia (−33°), and a gentle stream of dry nitrogen (Note 2) is bubbled into the flask. A solution of 0.708 g. (0.0025 mole) of *N*-benzyloxycarbonyl-L-methionine (Note 3) in 10 ml. of *N,N*-dimethylacetamide (Note 4), 1.02 g. (1.40 ml., 0.010 mole) of triethylamine (Note 5), and 1.25 g. of freshly prepared palladium black (Note 6) are added. The nitrogen stream is discontinued and replaced by a stream of hydrogen (Note 2) that has been passed through a concentrated sulfuric acid scrubber. The mixture is stirred under reflux for 5.5

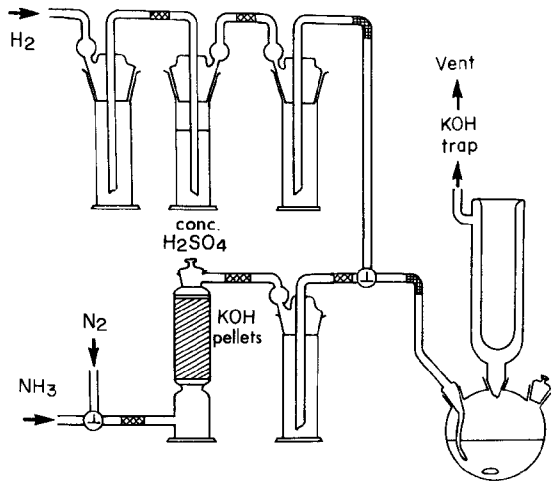


Figure 1

hours to effect the hydrogenolysis (Note 1). The hydrogen stream is then discontinued, a flow of nitrogen is resumed, and the dry ice is removed from the reflux condenser to permit rapid evaporation of ammonia (Note 7). The flask is attached to a rotary evaporator (Note 8), and the mixture is evaporated to dryness under reduced pressure. The residue is dissolved in water and filtered through a sintered funnel of medium porosity to remove the catalyst. The filtrate is evaporated to dryness, and the residue (354 mg., 95%) is crystallized from water–ethanol. The white crystalline product, after drying under reduced pressure at 25°, weighs 272–305 mg. (73–82%), m.p. 280–282° (dec.) (Note 9), $[\alpha]_D^{25}$ +23.1° ($c = 1$, aqueous 5*N* hydrochloric acid) (Note 10).

B. *O*-tert-*Butyl*-L-*seryl*-*S*-tert-*butyl*-L-*cysteine* tert-*butyl ester.* A dry 1-l., three-necked, round-bottomed flask is equipped with a dry ice reflux condenser (Note 1), a gas-inlet tube, and a magnetic stirring bar as illustrated in Figure 1. The reaction vessel is immersed in a dry ice–acetone bath, and a total of 300 ml. of ammonia (Note 2) is passed through a drying tower containing potassium hydroxide pellets and then collected in the flask. The dry ice–acetone bath is removed, and a gentle stream of nitrogen (Note 2) is bubbled into the flask. A solution of 200 mg. (0.000392 mole) of N^{α}-benzyloxycarbonyl-*O*-*tert*-butyl-L-seryl-*S*-*tert*-butyl-L-cysteine *tert*-butyl ester (Note 11) in 4 ml. of *N,N*-dimethylacetamide (Note 4), 0.160 g. (0.22 ml., 0.00158 mole) of triethylamine (Note 5), and 200 mg. of palladium black freshly prepared from 333 mg. (0.00188 mole) of palladium(II) chloride (Note 6) are added. The nitrogen stream is discontinued and replaced by a stream of hydrogen (Note 2) that has been passed through a concentrated sulfuric acid scrubber. The mixture is stirred and hydrogenated at reflux temperature for 6 hours (Note 1). The hydrogen stream is discontinued, a stream of nitrogen is again passed into the flask, and the dry ice is removed from the reflux condenser to permit rapid evaporation of ammonia (Note 7). The flask is attached to a rotary evaporator (Note 8) and evaporated to dryness under reduced pressure. The residue is dissolved in 50 ml. of methanol (Note 12), and the suspension is filtered through a 5×25-mm. bed of Celite (Note 13) to remove the catalyst. The Celite bed is washed thoroughly with three 20-ml. portions of methanol. The filtrate is evaporated to dryness, and the

residue is recrystallized from petroleum ether (b.p. 60–90°). The white crystalline product, after drying under reduced pressure at 25°, weighs 121–127 mg. (82–86%), m.p. 71–73° (Note 14), $[\alpha]_D^{25}$ −5.8° ($c = 1$, methanol) (Note 15).

2. Notes

1. The condenser is filled with crushed dry ice (no solvent). More dry ice is added periodically as necessary throughout Parts A and B.

2. Anhydrous ammonia, prepurified nitrogen, and prepurified hydrogen were all purchased from Matheson Gas Products.

3. *N*-Benzyloxycarbonyl-L-methionine was obtained from Bachem, Inc., 3132 Kashiwa Street, Torrance, California 90505.

4. Spectrophotometric-grade *N,N*-dimethylacetamide was purchased from Aldrich Chemical Company, Inc., and stored over molecular sieves.

5. Sequanal-grade triethylamine, obtained from Pierce Chemical Company, Rockford, Illinois, was distilled under nitrogen from ninhydrin, which was also purchased from Pierce Chemical Company.

6. The catalyst is prepared as follows[3,4] with palladium(II) chloride and 97–100% formic acid, which were purchased from Engelhard Industries Division (Engelhard Minerals and Chemicals Corporation) and MC and B Manufacturing Chemists, respectively. A 10.4-ml. aliquot containing 2.08 g. (0.0117 mole) of palladium(II) chloride from a stock solution of palladium(II) chloride in aqueous 2*N* hydrochloric acid (10 g. per 50 ml.) is added to 104 ml. of boiling water in a 600-ml. beaker. A 0.51-g. (0.42 ml., 0.011 mole) portion of formic acid and 33 ml. of aqueous 10% potassium hydroxide are added to the boiling solution. The pH of the resulting slightly alkaline solution (pH ~ 8) is adjusted to 6–7 by adding formic acid, after which the mixture is allowed to boil for an additional 5 minutes. The catalyst is isolated by careful suction filtration. *Caution! The palladium catalyst is pyrophoric and must always be kept wet with water or methanol to prevent contact with air.*

To minimize the danger in handling palladium black, the submitters recommend that the filtration, washing, and transfer of the catalyst be performed with a "syringe filter."[5] This device was fashioned from a 10-ml. Plastipak syringe purchased from Becton-Dickinson and Company, Rutherford, New Jersey, by cutting off the tip at the end of the cylindrical barrel and forcing a tight-fitting, porous disk of polypropylene into its place. The use of this "syringe filter" permits the removal of most of the solvent and the safe transfer of the catalyst to the flask with little danger of ignition or moisture absorption.

The catalyst is washed thoroughly with 100 ml. of water and with 200 ml. of absolute methanol to remove all traces of water, after which it is transferred to the flask under nitrogen with a minimal amount of absolute methanol. To be effective the catalyst must be pyrophoric, and extreme care must be taken during this operation to prevent ignition of the methanol or ammonia. The catalyst must not be allowed to become dry or to collect on the wall of the flask above the surface of the liquid ammonia.

7. Evaporation of the ammonia generally requires several hours. Toward the end of the evaporation, it is advantageous to immerse the flask in an acetone bath, taking care to avoid bumping.

8. *N,N*-Dimethylacetamide remains in the flask and is removed by rotary evaporation under reduced pressure with a water bath kept at a temperature lower than 35°. The submitters recommend that the evaporation be carried out directly in the same three-necked flask by stoppering the two side arms and adjusting the angle of the rotary evaporator.

9. The melting point is corrected. The reported[6] melting point is 280–281° (dec.).

10. The literature[7] reports $[\alpha]_D^{25}$ +23.2° ($c = 1$, aqueous 5*N* hydrochloric acid). The product was analyzed by the submitters. Analysis calculated for $C_5H_{11}NO_2S$: C, 40.25; H, 7.43; N, 9.39; S, 21.49. Found: C, 40.14; H, 7.42; N, 9.50; S, 21.52. The product was homogeneous according to thin-layer chromatograms on precoated silica gel G plates purchased from Analtech, Inc., Newark, Delaware, and developed with the following two solvent systems (solvents, volume ratios of solvents in the same order): 1-butanol–acetic acid–ethyl acetate–water, 1 : 1 : 1 : 1, *Rf* 0.49; 1-butanol–acetic acid–pyridine–water, 15 : 3 : 10 : 12, *Rf* 0.51.

11. The protected dipeptide was prepared by the procedure

described in the following paragraph using *N*-benzyloxycarbonyl-*O*-*tert*-butyl-L-serine purchased from Chemical Dynamics Corporation (P. O. Box 395, South Plainfield, New Jersey 07080), tetrahydrofuran distilled from lithium aluminum hydride [*Caution!* For a warning regarding this method for purifying tetrahydrofuran, see *Org. Syn.*, Coll. Vol. **5,** 976 (1973)], and *N*-methylmorpholine distilled from ninhydrin. *S*-*tert*-Butyl-L-cysteine *tert*-butyl ester[8] was prepared as follows: To a suspension of 10 g. (0.082 mole) of L-cysteine in 75 ml. of dry dioxane in a 200-ml. pressure bottle cooled in an ice bath are added 10.0 ml. of concentrated sulfuric acid and 56 g. (95 ml., 1.00 mole) of isobutylene. The pressure bottle is stoppered and shaken at room temperature for 18 hours. The mixture is cooled to 0°, the pH is adjusted to 10 by adding 160 ml. of aqueous 2*N* sodium hydroxide, and the product is extracted with three 100-ml. portions of ethyl ether. The ethereal solution is washed with three 80-ml. portions of aqueous 5% sodium bicarbonate and three 80-ml. portions of water, dried with anhydrous magnesium sulfate, and concentrated to a volume of *ca.* 200 ml. The concentrate is stirred and cooled at 0° as 90.8 ml. (0.091 mole) of 1 *M* hydrogen chloride in ethyl ether is added. The resulting mixture is stirred for several minutes, the precipitated hydrochloride is filtered, and the filter cake is washed with ether. The white crystalline product weighs 18.1 g. (81%) and is used without further purification. The submitters caution that the hydrochloride sublimes under reduced pressure. Recrystallization from chloroform–petroleum ether afforded an analytical sample, double m.p. 187° and 219–222°, $[\alpha]_D^{25}$ +5.85° ($c = 1$, methanol). Analysis calculated for $C_{11}H_{23}NO_2S \cdot HCl$: C, 48.96; H, 8.96; N, 5.19; S, 11.88; Cl, 13.14. Found: C, 49.07; H, 9.25; N, 5.13; S, 12.06; Cl, 13.07. The free base is obtained by dissolving the hydrochloride in aqueous 10% sodium carbonate, extracting the mixture with ether, and evaporating the ethereal solution under reduced pressure.

A dry, three-necked, round-bottomed flask is equipped with a mechanical stirrer, a rubber septum, and a 200-ml. pressure-equalizing dropping funnel mounted with a T-shaped gas inlet that is connected to both a nitrogen source and a bubbler serving as a gas exit. The flask is charged with a solution of 14.9 g. (0.0506 mole) of N^{α}-benzyloxycarbonyl-*O*-*tert*-butyl-L-serine in 100 ml. of tetrahydrofuran and is purged with nitrogen. The solution is stirred and cooled at −15° as 5.12 g. (5.67 ml., 0.0506 mole) of *N*-methylmorpholine and 6.91 g. (6.61 ml., 0.0506 mole) of isobutyl chloroformate are added rapidly through the septum by means of syringes. One minute after the addition is completed, a precooled (−20°) solution of 11.8 g. (0.0506 mole) of *S*-*tert*-butyl-L-cysteine *tert*-butyl ester in 100 ml. of tetrahydrofuran is added dropwise at −15°. The contents of the flask are stirred for 1 hour at −15° and for 3 hours at room temperature. The mixture is then evaporated to dryness under reduced pressure, and the residue is dissolved in 150 ml. of ethyl acetate. The solution is washed with three 50-ml. portions of each of the following: 5% sodium bicarbonate in water, water, 1 *M* citric acid in water, and water. The ethyl acetate solution is then dried over anhydrous magnesium sulfate, the solvent is evaporated, and the remaining solid is recrystallized from ethyl acetate–petroleum ether (b.p. 35–60°). The white crystalline product, after drying under reduced pressure at 25°, weighs 25.5 g. (98.6%), m.p. 94.5–95°, $[\alpha]_D^{25}$ −2.47° ($c = 1$, methanol). Thin-layer chromatograms of the product on plates precoated with silica gel G and purchased from Analtech, Inc., Newark, Delaware, each showed a single spot when developed with the following three solvent systems (solvents, volume ratio of solvents in the same order): 1-butanol–acetic acid–ethyl acetate–water, 1:1:1:1, *Rf* 0.90; 1-butanol–acetic acid–water, 4:1:1, *Rf* 0.81; 1-butanol–acetic acid–pyridine–water, 15:3:10:12, *Rf* 0.81. Analysis calculated for $C_{26}H_{42}N_2O_6S$: C, 61.15; H, 8.29; N, 5.49; S, 6.28. Found: C, 61.15; H, 8.52; N, 5.42; S, 6.44.

12. Other solvents including *N*,*N*-dimethylformamide and water may also be used to dissolve the products.

13. In some cases the catalyst was not entirely removed, and the filtrate contained trace amounts of palladium. In those instances the submitters evaporated the filtrate to a small volume and repeated the filtration using a large bed of Celite.

14. The melting point was taken on a Reichert hot stage microscope. This instrument is available from William J. Hacker and Company, Inc., P.O. Box 646, West Caldwell, New Jersey 07006.

15. The recrystallized product was analyzed by the submitters.

Analysis calculated for $C_{18}H_{36}N_2O_4S$: C, 57.41; H, 9.63; N, 7.43; S, 8.51. Found: C, 57.60; H, 9.66; N, 7.37; S, 8.25. Thin-layer chromatograms (Note 10) run by the submitters showed a single spot for the product in each of three following solvent systems (solvents, volume ratio of solvents in the same order): chloroform–methanol–acetic acid, 85:10:5, *Rf* 0.60; 1-butanol–acetic acid–water, 4:1:1, *Rf* 0.58; 1-butanol–acetic acid–pyridine–water, 15:3:10:12, *Rf* 0.71.

3. Discussion

The protection of the amino terminus of a peptide with the benzyloxycarbonyl group combined with protection of the carboxyl terminus and all side-chain functions with *tert*-butyl-derived groups[9] enables totally selective liberation of the terminal amino function by catalytic hydrogenolysis. This combination of protecting groups is currently considered "ideal" for peptide synthesis,[10] except for the rather serious limitation that catalyst poisoning has prevented its application to the preparation of peptides that contain cysteine, methionine, or other residues bearing divalent sulfur groups. The submitters have recently discovered[11] that catalyst poisoning is greatly diminished when liquid ammonia is used as solvent for palladium-catalyzed hydrogenation. This solvent enables quantitative cleavage of N^{α}-benzyloxycarbonyl groups on many protected peptides bearing *S*-protected cysteine residues. The method has been used successfully in syntheses of oxytocin[12] and somatostatin.[13]

The present procedures illustrate this method with the regeneration of L-methionine and the preparation of the *tert*-butyl ester of *O*-*tert*-butyl-L-seryl-*S*-*tert*-butyl-L-cysteine[13] from their respective N^{α}-benzyloxycarbonyl derivatives. No other procedures for the preparation of this protected dipeptide have been reported. These preparations and other peptide syntheses have served to establish the complete stability of the *S*-methyl substituent and various protecting groups including the *tert*-butyl ester (OBu^t), *tert*-butyl ether (Bu^t), *N*-*tert*-butyloxycarbonyl (Boc), *S*-*tert*-butyl (Bu^t), *S*-benzyl (Bzl), and *S*-acetamidomethyl (Acm) groups.[14] Table I summarizes the results of hydrogenations carried out with sulfur-containing peptides having chain lengths varying from 6 to 13

TABLE I
REMOVAL OF N^{α}-BENZYLOXYCARBONYL GROUPS FROM SULFUR-CONTAINING PEPTIDES

Peptide[a]	Amount (g.) (mmole.)	Dimethylacetamide (ml.)	Ammonia (ml.)	Triethylamine (mmole.)	Palladium(II) Chloride (g.)	Yield[b] (%)
Z-R	3.05 (2.54)	10.0	300	40	2.08	98
Z-Phe-Trp-R	0.418 (0.272)	3.0	35	4.0	0.227	81
Z-Phe-Phe-Trp-R	0.263 (0.160)	3.5	30	4.0	0.133	91
Z-Asn-Phe-Phe-Trp-R	0.305 (0.170)	3.0	60	4.7	0.532	100
Z-Lys-Asn-Phe-Phe-Trp-R (Boc)	0.368 (0.182)	3.0	70	4.7	0.596	89
Z-Cys-Lys-Asn-Phe-Phe-Trp-R (Bu^t, Boc)	0.281 (0.129)	2.0	40	10.0	0.596	86
Z-Gly-Cys-Lys-Asn-Phe-Phe-Trp-R (Bu^t, Boc)	0.178 (0.080)	1.3	40	10.0	0.380	85

[a] Protecting group abbreviations are as follows: *N*-benzyloxycarbonyl (Z), *N*-*tert*-butyloxycarbonyl (Boc), *tert*-butyl ether (Bu^t), and *S*-*tert*-butyl (Bu^t).

[b] The reaction time was 5.0–6.0 hours in all entries.

amino acid residues, demonstrating the stability of various protecting groups to this procedure for hydrogenolysis. In each case the N^{α}-benzyloxycarbonyl (Z) group was removed quantitatively, and the *tert*-butyl based protecting groups were completely stable. As a result of these findings, sulfur-containing amino acids may now be used in peptide synthesis by the "ideal" combination of amino-terminal benzyloxycarbonyl protection with *tert*-butyl-type blocking groups on all other functions.

Since the use of *N,N*-dimethylacetamide and triethylamine improved the rate and extent of cleavage of the *N*-benzyloxycarbonyl group in several difficult cases, these additives have been incorporated into the submitters' standard procedure and are included in the present procedures. Deprotection with this method has been carried out with as much as 25 g. of the protected peptide.

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14. A procedure for *S*-acetamidomethylation is described in this volume, p. 190.

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

L-Methionine (8, 9); (63-68-3)

N-Benzyloxycarbonyl-L-methionine: L-Methionine, *N*-carboxy-, *N*-benzyl ester (8); L-Methionine, *N*-[(phenylmethoxy)carbonyl]- (9); (1152-62-1)

Acetamide, *N,N*-dimethyl- (8, 9); (127-19-5)

Triethylamine (8); Ethanamine, *N,N*-diethyl- (9); (121-44-8)

N-Benzyloxycarbonyl-*O*-*tert*-butyl-L-seryl-*S*-*tert*-butyl-L-cysteine *tert*-butyl ester; (−)

N^{α}-Benzyloxycarbonyl-*O*-*tert*-butyl-L-serine: Alanine, 3-*tert*-butoxy-*N*-carboxy-, *N*-benzyl ester, L- (8); L-Serine, *O*-(1,1-dimethylethyl)-*N*-[(phenylmethoxy)carbonyl]- (9); (1676-75-1)

Morpholine, 4-methyl- (8, 9); (109-02-4)

Isobutyl chloroformate: Formic acid, chloro-, isobutyl ester (8); Carbonochloridic acid, isobutyl ester (9); (543-27-1)

S-*tert*-Butyl-L-cysteine *tert*-butyl ester: L-Cysteine, *S*-(1,1-dimethylethyl), 1,1-dimethylethyl ester (9); (−); acetate: (38024-19-0); hydrochloride: (2481-11-0)

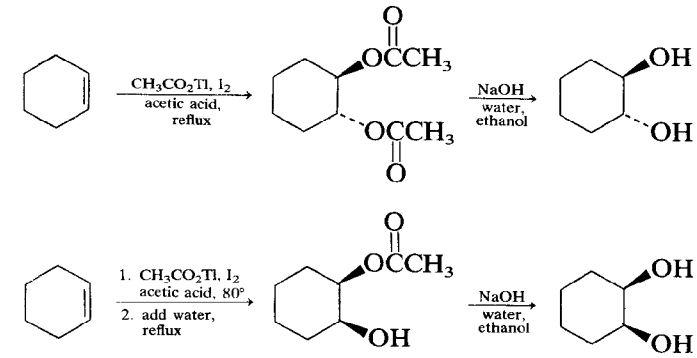
Formamide, *N,N*-dimethyl- (8, 9); (68-12-2)

Oxytocin (8, 9); (50-56-6)

Somatostatin: Growth hormone-release inhibiting factor (8, 9); (51110-01-1)

O-*tert*-Butyl-L-seryl-*S*-*tert*-butyl-L-cysteine *tert*-butyl ester: (−)

STEREOSELECTIVE HYDROXYLATION WITH THALLIUM(I) ACETATE AND IODINE: *trans*- AND *cis*-1,2-CYCLOHEXANEDIOLS



Submitted by R. C. CAMBIE and P. S. RUTLEDGE[1]
Checked by D. SEEBACH, M. LIESNER, and E.-M. WILKA

1. Procedure

Caution! Thallium salts are very toxic. These procedures should be carried out in a well-ventilated hood, and rubber gloves should be worn. For disposal of thallium wastes, see ref. 2.

A. trans-1,2-*Cyclohexanediol.* In a 100-ml., round-bottomed flask equipped with a reflux condenser protected with a drying tube are placed a magnetic stirring bar, 17.56 g. (0.0667 mole) of thallium(I) acetate (Note 1), and 40 ml. of dried acetic acid (Note 2). The mixture is stirred and heated at reflux for 1 hour. To the cooled mixture are added 2.84 g. (3.5 ml., 0.0346 mole) of cyclohexene (Note 3) and 8.46 g. (0.0333 mole) of iodine (Note 4). The resulting suspension is stirred and heated at reflux for 9 hours (Note 5), and then cooled to room temperature. The yellow precipitate of thallium(I) iodide is filtered and washed thoroughly with ethyl ether. The filtrates are combined, the solvents are removed under reduced pressure with a rotary evaporator (Note 6), and the residual liquid is dissolved in dry ethyl ether. The turbid solution is dried with anhydrous potassium carbonate, and the solvent is again removed by rotary evaporation (Note 6), affording 5.4–6.3 g. of *trans*-1,2-cyclohexanediol diacetate as a mobile, brown liquid (Note 7).

The diacetate is dissolved in 25 ml. of 95% ethanol, a solution of 2.9 g. (0.073 mole) of sodium hydroxide in 11 ml. of water is added, and the resulting mixture is heated under reflux for 3 hours. The solution is concentrated by rotary evaporation under reduced pressure, and the remaining syrup is extracted with six 50-ml. portions of chloroform. The combined extracts are dried over anhydrous magnesium sulfate and evaporated, providing 3.1–3.3 g. of a pale brown crystalline solid that melts at 97–103°. Recrystallization from carbon tetrachloride gives 2.5–2.7 g. (65–70% based on iodine) of *trans*-1,2-cyclohexanediol, m.p. 103–104° (Note 8).

B. cis-1,2-*Cyclohexanediol.* A 500-ml., round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar is charged with 17.56 g. (0.0667 mole) of thallium(I) acetate (Note 1), 160 ml. of glacial acetic acid, 3.0 g. (3.7 ml., 0.0365 mole) of cyclohexene (Note 3), and 8.46 g. (0.0333 mole) of iodine (Note 4) in the order given. The suspension is stirred and warmed in a heating bath at 80° for 30 minutes. An 80-ml. portion of water is added, stirring is continued, and the mixture is heated at reflux for 9 hours. The product is isolated and hydrolyzed as described in Part A, affording 3.2–4.9 g. of *cis*-1,2-cyclohexanediol, m.p. 88–95° (Note 9). Recrystallization from carbon tetrachloride gives 2.7–2.9 g. (70–75% based on iodine) of *cis*-1,2-cyclohexanediol, m.p. 97–98° (Note 10).

2. Notes

1. Thallium(I) acetate purchased from BDH Chemicals Ltd., Poole, England, or Fluka AG, Buchs, Switzerland, was used without further purification. This reagent is also available from Alfa Division, Ventron Corporation.

2. The submitters purchased glacial acetic acid from Showa Denko K. K., Tokyo, Japan, and acetic anhydride from Riedel de Haen AG, Seelze-Hannover, Germany. A solution prepared from 4 volumes of glacial acetic acid, 1 volume of acetic anhydride, and a catalytic amount of *p*-toluenesulfonic acid was heated under reflux for 24 hours and distilled. The distillate, which contained 5% water and 4% acetic anhydride according to analysis of the proton magnetic resonance spectrum, was then used by the submitters. The water content was determined from the chemical shift of the hydroxyl proton.[3]

The checkers purchased analytical-grade (*pro analysi*) glacial acetic acid and acetic anhydride from E. Merck, Darmstadt, Germany. A solution of glacial acetic acid and acetic anhydride (4:1, v/v) containing 500 mg. of *p*-toluenesulfonic acid per l. was heated at reflux for 24 hours and then distilled. A forerun amounting to 25% of the solution was discarded, and a main fraction of acetic acid amounting to 60% of the solution was collected. The main fraction, containing 17% acetic anhydride and 1% or less water as determined from its proton magnetic resonance spectrum, was used by the checkers.

3. Cyclohexene was purchased from BDH Chemicals Ltd., Poole, England, by the submitters and used without purification. This reagent was purchased by the checkers from Fluka AG, Buchs, Switzerland, and distilled before use.

4. Iodine purchased from Riedel de Haen AG, Seelze-Hannover, Germany, was sublimed before use by the submitters. The checkers used iodine from Siegfried AG, Zofingen, Switzerland, without purification.

5. After *ca.* 30 minutes the initially black-green solid becomes yellow.

6. The checkers recommend that excessive heating and evacuation be avoided during rotary evaporation to minimize the loss of product during this operation. They kept the heating bath temperature below 80° and used a water aspirator.

7. The diacetate was judged to be virtually pure by the submitters on the basis of a gas chromatographic analysis carried out at 150° using a glass column packed with 3% OV 17 (1:1 methylphenyl silicone) supported on 70–80 mesh Chromosorb W.

8. The submitters obtained 2.9 g. (75%) of product that melted at 103–105°. The reported[4a] melting point is 104°.

9. The unrecrystallized product obtained by the submitters melted at 91–95°. The purity of this material is estimated to be 96% on the basis of the melting point.[4a]

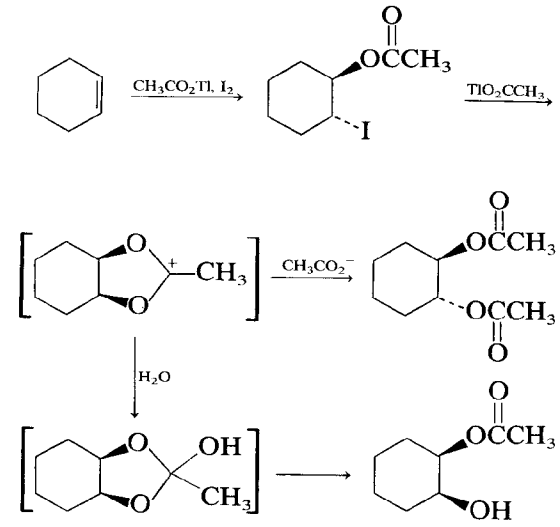
10. The submitters obtained 3.0 g. (78%) of product which melted at 99–100°. The melting point of 97–98° shown above was obtained by the checkers using a Tottoli melting point apparatus (Büchi) equipped with a 50° range *Anschütz* thermometer. A melting point of 98° has been reported[4b]

3. Discussion

The present procedure offers a convenient alternative to the Prévost reaction[5] and the Woodward modification of the Prévost reaction[6] in which silver carboxylates are used instead of thallium(I) carboxylates. Thallium(I) salts have the advantages of being generally stable crystalline solids that can be readily prepared in high yield by neutralization of the appropriate carboxylic acid with thallium(I) ethoxide.[7] Silver salts, on the other hand, are frequently unstable and difficult to dry. Thallium and its compounds are, however, extremely toxic, and great care must therefore be taken in the use and disposal of thallium salts.[2,8,9]

The mechanisms of these reactions are presumably analogous to those of the Prévost and Woodward-Prévost reactions.[5,6] In the first step of the reaction of iodine and thallium(I) acetate with cyclohexene in both parts A and B of this procedure, *trans*-2-iodocyclohexyl acetate is formed. The second equivalent of thallium(I) acetate scavenges iodide ion during formation of the 1,3-

dioxolan-2-ylium ion intermediate. Under the anhydrous conditions in Part A, the carbonium ion reacts with acetate ion at a ring carbon with inversion to give the diacetate. In part B the ion is captured by water, and the resulting ortho ester undergoes ring opening to the *cis*-diol monoacetate. No appreciable reaction occurs unless thallium(I) acetate, iodine, and cyclohexene are all present. Thus, in contrast to the Prévost and Woodward–Prévost procedures, acetyl hypoiodite evidently cannot be prepared separately from thallium(I) acetate and iodine. The precise reasons for this difference are not clear.



trans-2-Iodocyclohexyl acetate can be isolated in essentially quantitative yield from the reaction of thallium(I) acetate, iodine, and cyclohexene in a 1:1:1 molar ratio in refluxing chloroform.[10] Iodo acetates from a representative series of alkenes including cyclohexene have been similarly prepared in 80–98% yield[11] in glacial acetic acid which was not dried as described in this procedure. The corresponding iodo benzoates are obtained in comparable yields from reaction with thallium(I) benzoate and iodine in benzene. The deactivated olefin methyl cinnamate did not react under these conditions, and *o*-allylphenol underwent ring iodination to

give 2-allyl-6-iodophenol.[12] The diterpenes, phyllocladene and isophyllocladene, upon reaction with thallium(I) benzoate and iodine,[13] afford the same mixture of allylic benzoates obtained from a Woodward–Prévost reaction. With the exception of 3-phenylpropene, the formation of iodo carboxylates from unsymmetrical alkenes occurs regioselectively in a Markovnikov sense.

Vicinal iodo carboxylates may also be prepared from the reaction of olefins either with iodine and potassium iodate in acetic acid,[14a] or with *N*-iodosuccinimide and a carboxylic acid in chloroform.[14b] A number of new procedures for effecting the hydroxylation or acyloxylation of olefins in a manner similar to the Prévost or Woodward–Prévost reactions include the following: iodo acetoxylation with iodine and potassium chlorate in acetic acid followed by acetolysis with potassium acetate[14c]; reaction with *N*-bromoacetamide and silver acetate in acetic acid[15]; reaction with thallium(III) acetate in acetic acid[16]; and reaction with iodine tris(trifluoroacetate) in pentane.[17]

The preparation of *trans*-1,2-cyclohexanediol by oxidation of cyclohexene with peroxyformic acid and subsequent hydrolysis of the diol monoformate has been described,[18] and other methods for the preparation of both *cis*- and trans-1,2-cyclohexanediols were cited. Subsequently the trans diol has been prepared by oxidation of cyclohexene with various peroxy acids,[19] with hydrogen peroxide and selenium dioxide,[20] and with iodine and silver acetate by the Prévost reaction.[21] Alternative methods for preparing the trans isomer are hydroboration of various enol derivatives of cyclohexanone[22] and reduction of *trans*-2-cyclohexen-1-ol epoxide with lithium aluminum hydride.[23] *cis*-1,2-Cyclohexanediol has been prepared by *cis* hydroxylation of cyclohexene with various reagents or catalysts derived from osmium tetroxide,[24] by solvolysis of *trans*-2-halocyclohexanol esters in a manner similar to the Woodward-Prévost reaction,[14c,15,17,21,25] by reduction of *cis*-2-cyclohexen-1-ol epoxide with lithium aluminum hydride,[23] and by oxymercuration of 2-cyclohexen-1-ol with mercury(II) trifluoroacetate in the presence of chloral and subsequent reduction.[26]

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1,2-Cyclohexanediol, *trans*- (8, 9); (1460-57-7)
1,2-Cyclohexanediol, *cis*- (8, 9); (1792-81-0)

Thallium(I) acetate: Acetic acid, thallium salt (8, 9); (15843-14-8); Acetic acid, thallium (1+) salt (8, 9); (563-68-8)

1,2-Cyclohexanediol diacetate, *trans*- (8, 9); (1759-71-3)

Thallium(I) ethoxide: Ethyl alcohol, thallium (1+) salt (8); Ethanol, thallium (1+) salt (9); (20398-06-5)

trans-2-Iodocyclohexyl acetate: Cyclohexanol, 2-iodo-, acetate, *trans*- (9); (43084-75-9)

Thallium(I) benzoate: Benzoic acid, thallium salt (8, 9); (41830-88-0); Benzoic acid, thallium (1+) salt (8, 9); (5630-31-9)

Succinimide, *N*-iodo- (8); 2,5-Pyrrolidinedione, 1-iodo- (9); (516-12-1)

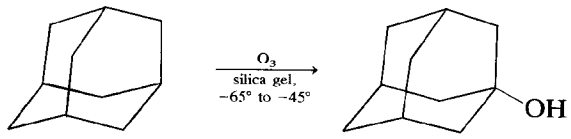
Acetamide, *N*-bromo- (8); (79-15-2)

Thallium(III) acetate: Acetic acid, thallium (3+) salt (8, 9); (2570-63-0)

Iodine tris(trifluoroacetate): Acetic acid, trifluoro-, trianhydride with iodous acid (H_3IO_3) (8, 9); (14353-86-7)

TERTIARY ALCOHOLS FROM HYDROCARBONS BY OZONATION ON SILICA GEL: 1-ADAMANTANOL

(Tricyclo[3.3.1.1^{3,7}]decan-1-ol)



Submitted by Zvi Cohen, Haim Varkony, Ehud Keinan, and Yehuda Mazur[1]
Checked by Frank E. Blaney and Robert M. Coates

Caution! Ozone is toxic and potentially explosive. This procedure should be carried out in an efficient hood and behind a suitable protective shield.

1. Procedure

A solution of 6 g. (0.044 mole) of adamantane (Note 1) in 100 ml. of pentane and 500 g. of silica gel (Note 2) are placed in a 2-l., round-bottomed flask (Note 3). The pentane is removed by rotary evaporation at room temperature under reduced pressure (20 mm.), and the resulting dry silica gel is allowed to rotate for an additional 2 hours (Note 4). The adamantane–silical gel dispersion is poured through a powder funnel into the ozonation vessel (Note 5), which is then immersed in a 2-propanol–dry ice bath at −78°. A flow of oxygen is passed through the vessel at a rate of 1 l. per minute for 2 hours, after which the internal temperature reaches −60 to −65° (Note 6). The ozone generator (Note 7) is turned on, and the ozone–oxygen mixture is passed through the vessel for *ca.* 2 hours, causing the silica gel to become dark blue (Notes 8 and 9). The cooling bath is removed, and the vessel is allowed to warm to room temperature in the hood over a 3-hour period. The silica gel is then transferred to a chromatography column, and the organic material is eluted with 3 l. of ethyl acetate. Evaporation of the solvent affords 6.1–6.4 g. of crude adamantanol (Note 10), which is dissolved in 200 ml. of 1:1 (v/v) dichloromethane–hexane by heating on a steam bath. The solution is filtered, concentrated to incipient crystallization and placed in a freezer at −20°. A crop of fine white needles amounting to 3.0–3.2 g., m.p. 280–282° (sealed capillary), is collected. The mother liquor is concentrated and cooled to separate two additional crops, which amount to 2.2–2.6 g. and have melting point ranges of 270–274° to 275–280° (sealed capillary) (Note 11). The total yield of 1-adamantanol is 5.4–5.6 g. (81–84%) (Note 12).

2. Notes

1. Adamantane is available from Aldrich Chemical Company, Inc., and Fluka AG, Buchs, Switzerland.

2. Silica gel 60 having particle sizes ranging from 0.063 to 0.200 mm. (70–230 mesh) is suitable. It may be purchased from Brinkmann Instruments, Inc., or E. Merck, Darmstadt, Germany. The submitters report that silica gel of this type normally contains *ca.* 5% water, which may be removed by drying at 300° for several hours. Somewhat better yields are obtained when the silica gel is dried in this manner before use.

3. The submitters have found that the adsorption of adamantane on silica gel may also be accomplished by mixing the dry solids in a closed flask for a few hours.

4. Heating should be avoided to prevent loss of some of the adamantane through sublimation.

5. The submitters have used both a tightly closed, 1-l. gas-washing bottle and the apparatus shown in Figure 1 for ozonation vessels. They recommend that the glass joints not be greased. The apparatus used by the checkers consisted of a cylindrical, two-necked vessel having the same dimensions as that in Figure 1. One neck of the vessel was fitted with a Claisen distillation head and the

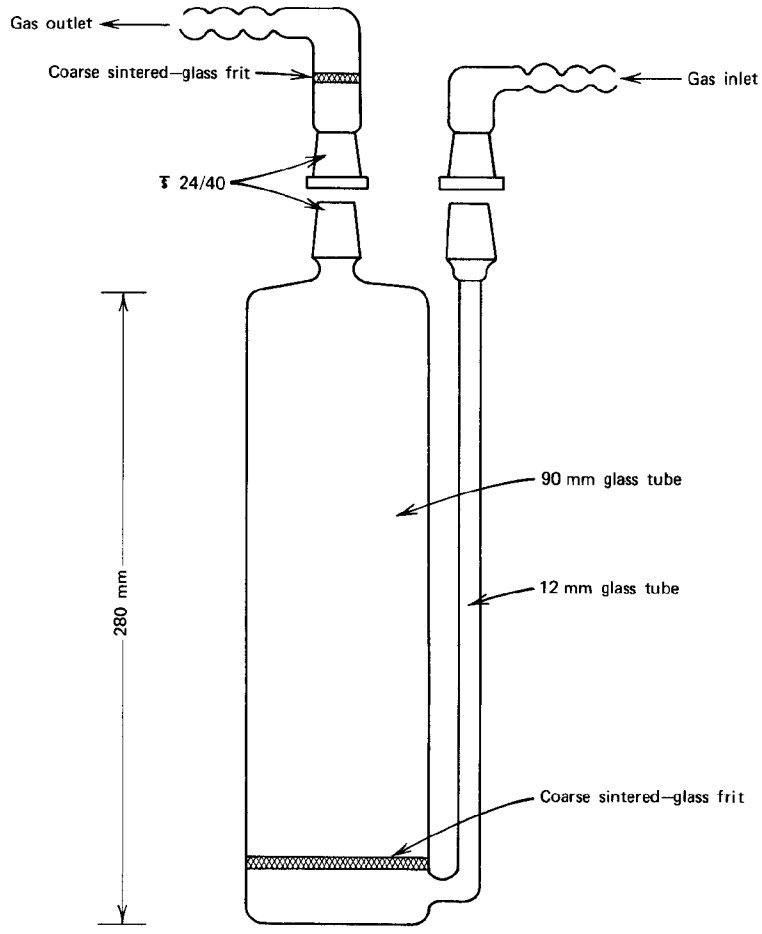


Figure 1

other with a thermometer with its bulb positioned in the middle of the vessel. A bent gas-dispersion tube with an extra-coarse sintered-glass frit extending through the vertical branch of the Claisen head to within 2–3 mm. of the center of the bottom of the flask served as the gas inlet. The curved branch of the Claisen head was fitted with a drying tube and this functioned as the gas exit.

6. The checkers found that the maintenance of a flow of oxygen during the cooling period prevented clogging of the glass frit and a building up of pressure in the gas-inlet tube in their apparatus.

7. A Welsbach T-816 Ozonator purchased from the Welsbach Corporation, Philadelphia, Pennsylvania, was used. The oxygen stream was dried by passage through dry silica gel and molecular sieves and then introduced into the ozonator with the operating voltage set at 115 V., the gas pressure at 8 p.s.i.g., and the gas flow rate at 1 l. per minute. The resulting ozone flow rate was 0.00245 mole per minute, as determined by titration of a potassium iodide trap.[2]

8. In the apparatus used by the checkers, the internal temperature was between $-45°$ and $-65°$ while ozone was being passed through the silica gel. The use of lower bath temperatures results in the adsorption of a greater quantity of ozone on the silica gel; consequently shorter reaction times and higher conversions may be realized in the ozonation. *However, since ozone liquifies at* $-112°$, *there is a serious danger of explosion.*

9. The ozone flow is stopped when the silica gel reaches a constant, dark blue color. The time required for saturating the silica gel with ozone depends on the type of silica gel used and on whether it has been dried (Note 2).

10. A gas chromatographic analysis on the crude adamantanol was carried out by the checkers using a 1.8 m. × 3 mm. column packed with 5% silicone oil (SE-30) supported on Chromosorb W and the following column temperature program: hold at 120° for 6 minutes and then increase at *ca.* 8° per minute. The chromatogram of the product from one run showed a major peak at retention time of 10 minutes and three minor peaks with retention times of 11.2, 12, and 13.7 minutes and relative areas amounting to 1.5, 1.6, and 4% of the major peak, respectively. A gas chromatographic analysis by the submitters with 5% diethylene glycol succinate supported on Chromosorb W as stationary phase at 110–160°

showed peaks for adamantane-1,3-diol and adamantanone as by-products totaling 7% in addition to the peak for 1-adamantanol.

11. A gas chromatographic analysis by the checkers (see Note 10) on the material in the third crop from one run showed a major peak for 1-adamantanol and a second minor peak having an area *ca.* 12% of that of the major peak. In another run the area of the peak from this by-product in the third crop was less than 2% relative to that of 1-adamantanol.

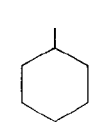
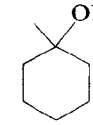
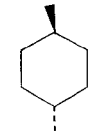
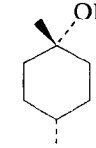
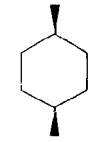
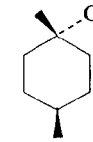
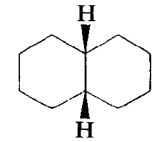
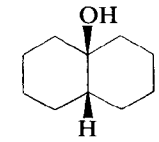
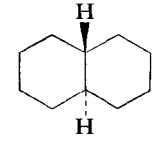
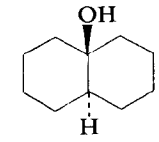
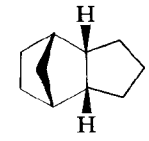
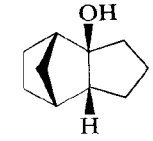
12. A yield of 5.8 g. (87%), m.p. 280–282°, was obtained by the submitters. The infrared spectrum, proton and carbon-13 magnetic resonance spectra, and mass spectrum of the product were identical to those of an authentic sample of 1-adamantanol. A mixed melting point with an authentic sample of 1-adamantanol showed no depression.

The spectral characteristics of the product are as follows: infrared (potassium bromide) cm.$^{-1}$: 3350(OH), 1455, 1352, 1302, 1118, 1088; proton magnetic resonance (chloroform-*d*)δ (multiplicity, number of protons, assignment): 1.53 (singlet, 1, O*H*), 1.55–1.80 (multiplet, 12, six CH_2), 2.17 (broad singlet, 3, three C*H*); carbon-13 magnetic resonance (chloroform-*d*) δ (assignment): 30.7 (three *C*H), 36.1 (three *C*H), 36.1 (three *C*H_2), 45.4 (three *C*H_2), 68.2 (one *C*OH).

3. Discussion

This "dry ozonation" procedure is a general method for hydroxylation of tertiary carbon atoms in saturated compounds (Table I).[3] The substitution reaction occurs with predominant retention of configuration. Thus *cis*-decalin gives the *cis*-1-decalol, whereas *cis*- and *trans*-1,4-dimethylcyclohexane afford *cis*- and *trans*-1,4-dimethylcyclohexanol, respectively. The amount of epimeric alcohol formed in these ozonation reactions is usually less than 1%. The tertiary alcohols may be further oxidized to diols by repeating the ozonation; however, the yields in these reactions are poorer. For instance, 1-adamantanol is oxidized to 1,3-adamantanediol in 43% yield. Secondary alcohols are converted to the corresponding ketone. This method has been employed for the hydroxylation of tertiary positions in saturated acetates and bromides.

TABLE I
PREPARATION OF TERTIARY ALCOHOLS FROM HYDROCARBONS WITH OZONE ON SILICA GE

Hydrocarbon	Tertiary Alcohol	Conversion (%)	Yield (%)[a]
		>99.5	65[b]
		72	79[c]
		92	76[d]
		>99.5	99
		88	72[e]
		>99.5	90

[a] Based on the amount of hydrocarbon consumed, as determined by gas chromatography.
[b] A mixture of the three methyl cyclohexanones was also formed to the extent of 34%.
[c] The epimeric alcohol was also present to the extent of 0.6%.
[d] The epimeric alcohol was also present to the extent of 3.5%.
[e] *trans*-1-Decalone (10%) and *trans*-2-decalone (16%) were also formed.

1-Adamantanol has been prepared by oxidation of adamantane with peroxyacetic acetic[4] and by hydrolysis of 1-bromoadamantane with silver nitrate[5] or hydrochloric acid.[6]

1. Department of Organic Chemistry, Weizmann Institute of Science, Rehovot, Israel.

2. P. S. Bailey and R. E. Erickson, *Org. Syn.*, Coll. Vol. **5,** 489 (1973); P. S. Bailey, *Chem. Rev.*, **58,** 986 (1958).
3. (a) Z. Cohen, E. Keinan, Y. Mazur, and T. H. Varkony, *J. Org. Chem.*, **40,** 2141 (1975); (b) Z. Cohen, E. Keinan, Y. Mazur, and A. Ulman, *J. Org. Chem.*, **41,** 2651 (1976); (c) E. Keinan and Y. Mazur, *Synthesis*, 523 (1976).
4. P. von R. Schleyer and R. D. Nicholas, *J. Amer. Chem. Soc.*, **83,** 182 (1961).
5. H. Stetter, M. Schwarz, and A. Hirschhorn, *Chem. Ber.*, **92**, 1629 (1959).
6. H. W. Geluk and J. L. M. A. Schlatmann, *Tetrahedron*, **24**, 5361 (1968).

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Adamantane (8); Tricyclo[3.3.1.1^{3,7}]decane (9); (281-23-2)

1-Adamantanol (8); Tricyclo[3.3.1.1^{3,7}]decan-1-ol (9); (768–95–6)

cis-Decalin: Naphthalene, *cis*-decahydro- (8, 9); (493-01-6)

cis-1-Decalol: 4a(2*H*)-Naphthol, *cis*-octahydro- (8); 4a(2*H*)-Naphthalenol, *cis*-octahydro- (9); (3574-58-1)

Cyclohexane, 1,4-dimethyl-, *cis*- (8, 9); (624-29-3)

Cyclohexane, 1,4-dimethyl-, *trans*- (8, 9); (2207-04-7)

Cyclohexanol, 1,4-dimethyl-, *cis*- (8, 9); (16980-60-2)

Cyclohexanol, 1,4-dimethyl-, *trans*- (8, 9); (16980-61-3)

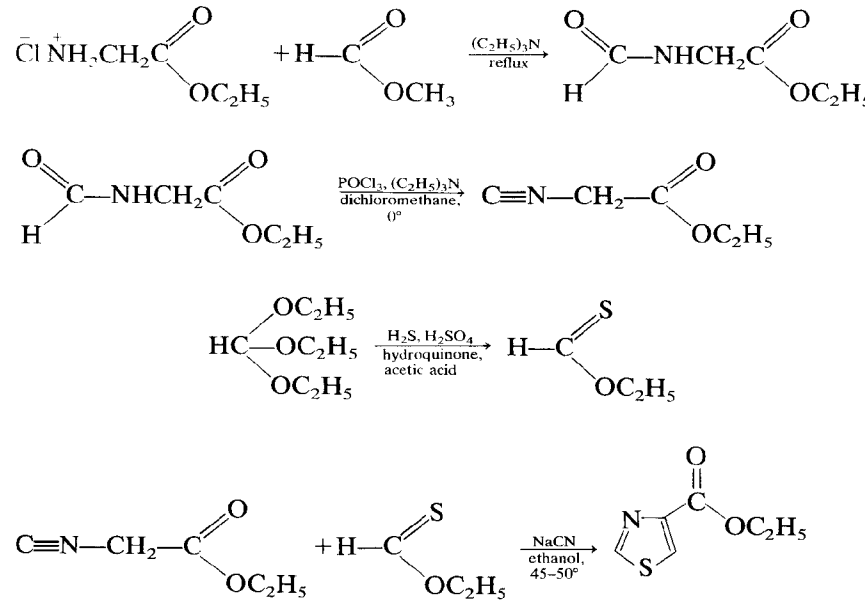
1,3-Adamantanediol (8); Tricyclo[3.3.1.1^{3,7}]decane-1,3-diol (9); (5001-18-3)

Peroxyacetic acid (8); Ethaneperoxoic acid (9); (79-21-0)

Adamantane, 1-bromo- (8); Tricyclo[3.3.1.1^{3,7}]decane, 1-bromo- (9); (768-90-1)

THIAZOLES FROM ETHYL ISOCYANOACETATE AND THIONO ESTERS: ETHYL THIAZOLE-4-CARBOXYLATE

(4-thiazolecarboxylic acid, ethyl ester)



Submitted by G. D. HARTMAN and L. M. WEINSTOCK[1]
Checked by LOUIS E. BENJAMIN, SR., NORMAN W. GILMAN, and GABRIEL SAUCY

1. Procedure

A. N-*Formylglycine ethyl ester.* A 1-l., three-necked, round-bottomed flask fitted with a mechanical stirrer, a pressure-equalizing dropping funnel, and a reflux condenser bearing a calcium chloride drying tube is charged with 69.5 g. (0.5 mole) of glycine ethyl ester hydrochloride and 250 ml. of methyl formate (Note 1). The suspension is stirred and heated at reflux while 55.0 g. (0.54 mole) of triethylamine (Note 1) is added. The resulting mixture is stirred and heated under reflux for 20 hours, cooled to room temperature, and filtered through a Büchner funnel to remove triethylamine hydrochloride. The filtrate is concentrated

on a rotary evaporator, and the remaining clear oil is distilled under reduced pressure. The yield of *N*-formylglycine ethyl ester, b.p. 94–97° (0.05 mm.), is 51.7–61.5 g. (79–94%) (Note 2).

B. *Ethyl isocyanoacetate.* A 3-l., three-necked, round-bottomed flask is equipped with a thermometer, a mechanical stirrer, and a pressure-equalizing dropping funnel bearing a nitrogen inlet. The flask is charged with 65.5 g. (0.5 mole) of *N*-formylglycine ethyl ester, 125.0 g. (1.24 moles) of triethylamine, and 500 ml. of dichloromethane, and the apparatus is flushed with nitrogen. The resulting solution is stirred and cooled to 0° to −2° in an ice–salt bath, and 76.5 g. (0.5 mole) of phosphoryl chloride (Note 3) is added dropwise over 15–20 minutes while the temperature is kept at 0°. The mixture becomes reddish brown as it is stirred and cooled at 0° for an additional 1 hour. The ice–salt bath is removed and replaced by an ice-water bath. Stirring is continued as a solution of 100 g. of anhydrous sodium carbonate in 400 ml. of water is added dropwise at a rate such that the temperature of the mixture is maintained at 25–30° (Note 4). The two-phase mixture is stirred for another 30 minutes, after which water is added until the volume of the aqueous layer is brought to 1 l. The aqueous layer is separated and extracted with two 250-ml. portions of dichloromethane. The dichloromethane solutions are combined, washed with saturated sodium chloride solution, and dried over anhydrous potassium carbonate. Evaporation of the solvent under reduced pressure and distillation of the remaining brown oil afford 43–44 g. (76–78%) of ethyl isocyanoacetate, b.p. 89–91° (11 mm.) (Note 5).

C. *O-Ethyl thioformate. Caution! Hydrogen sulfide gas is highly toxic; this procedure should be conducted in a well-ventilated hood.* A 1-l., three-necked, round-bottomed flask is equipped with a mechanical stirrer, a gas-inlet tube with a fritted-glass tip extending near to the bottom of the flask, and a gas outlet connected to a scrubber flask containing 0.5–1.0 l. of aqueous 20% sodium hydroxide (Note 6). The flask is charged with 333 g. (2.25 moles) of triethyl orthoformate (Note 7), 330 ml. of glacial acetic acid, 3.2 g. of hydroquinone, and 0.4 ml. of concentrated sulfuric acid. The resulting solution is stirred and cooled in an ice bath as hydrogen sulfide gas is passed through the gas-inlet tube into the solution (Note 8). After the solution becomes saturated with hydrogen

sulfide, the contents of the flask are poured into a 4-l. beaker containing a mixture of 2.3 l. of ice and 340 ml. of ethyl ether which is being stirred with a mechanical stirring assembly. The mixture is poured into a separatory funnel, and the layers are separated. The organic layer is washed with two 100-ml. portions of aqueous saturated sodium bicarbonate solution, two 100-ml. portions of water, three 80-ml. portions of aqueous saturated sodium bicarbonate, and two 80-ml. portions of aqueous saturated sodium chloride. The solution is dried with anhydrous sodium sulfate and distilled at atmospheric pressure through a 45-cm. Vigreux column, affording 60–76.7 g. (30–38%) of *O*-ethyl thioformate as a yellow liquid, b.p. 87–89° (Notes 9 and 10).

D. *Ethyl thiazole-4-carboxylate.* A 250-ml., three-necked, round-bottomed flask fitted with a thermometer, a mechanical stirrer, and a pressure-equalizing dropping funnel bearing a calcium chloride drying tube is charged with 0.25 g. (0.005 mole) of sodium cyanide and 10 ml. of absolute ethanol. The suspension is stirred vigorously at room temperature as a solution of 4.52 g. (0.04 mole) of ethyl isocyanoacetate and 3.60 g. (0.04 mole) of *O*-ethyl thioformate in 15 ml. of absolute ethanol is added slowly. The reaction is exothermic. The temperature of the mixture should be kept below 45° by adjusting the addition rate and, if necessary, cooling the flask in an ice bath (Note 11). When the addition is completed, the contents of the flask are stirred and heated at 50° for another 30 minutes. The solvent is removed by rotary evaporation, and the resulting dark oil is extracted with three 60-ml. portions of hot hexane (Note 12). The combined hexane extracts are concentrated with a rotary evaporator until the product begins to separate, and the concentrate is then cooled in an ice bath. The yield of off-white needles of ethyl thiazole-4-carboxylate is 5.1–5.5 g. (81–87%), m.p. 52–53° (Note 13).

2. Notes

1. Glycine ethyl ester hydrochloride, methyl formate, and triethylamine were purchased from Aldrich Chemical Company, Inc., and were used without purification.

2. The submitters obtained 63 g. (96%), b.p. 104–106° (0.1 mm).

3. The submitters recommend that phosphoryl chloride either be taken from a previously unopened bottle or distilled before use.

4. Foaming generally occurs during the addition.

5. Essentially no forerun need be taken prior to collection of the product. The last few milliliters of distillate were slightly yellow, and 2–3 g. of intractable material remained in the distillation flask. A boiling point of 76–78° (4 mm.) has been reported[2] for ethyl isocyanoacetate. The submitters have found the distilled product to be stable for up to 6 months when stored under nitrogen in a freezer at −20°.

6. The checkers used a gas-inlet tube without a fritted-glass tip and aqueous 30% sodium hydroxide as scrubber solution.

7. Triethyl orthoformate is available from Aldrich Chemical Company, Inc.

8. Hydrogen sulfide is admitted into the flask slowly at first, with bubble formation kept to a minimum. Initially the gas dissolves readily. As the solution becomes saturated, more bubbling action is apparent in the flask and the scrubber.

9. The submitters reported a yield of 56.5 g. (28%), b.p. 90–92°. The product is often contaminated with *ca.* 5% of ethyl formate; however, this impurity does not interfere with Part D. The submitters state that the product is stable when stored under nitrogen in a freezer at −20°.

10. The checkers found that glassware in which the product was stored acquired a disagreeable odor that was difficult to remove with aqueous sodium hydroxide solution.

11. Controlling the temperature in this manner prevents discoloration of the final product and improves its yield.

12. The product was obtained as tan needles when boiling hexane was used by the checkers. Off-white needles were isolated when the temperature of the hexane was 50–55°.

13. The submitters reported a yield of 5.8 g. (92%) of product as white needles, m.p. 53–54°. However, the checkers obtained colourless needles only after recrystallizing the product from hexane. The melting points of the discolored needles obtained initially by the checkers and the recrystallized material were the same. Melting points of 57° and 52–54° are recorded in the literature for ethyl thiazole-4-carboxylate.[3,4] The spectral properties of the product are as follows: infrared (chloroform) cm.$^{-1}$: 3130, 3030, 1724 (C=O), 1500, 1270; proton magnetic resonance (chloroform-*d*): δ (multiplicity, number of protons, assignment, coupling constant *J* in Hz.): 1.39 (triplet, 3, OCH_2CH_3, $J = 7$), 4.43 (quartet, 2, OCH_2CH_3, $J = 7$), 8.33 (doublet, 1, *H* at C-5, $J = 2.5$), 8.98 (doublet, 1, *H* at C-2, $J = 2.5$).

3. Discussion

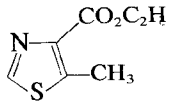
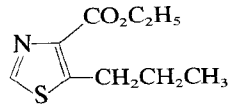
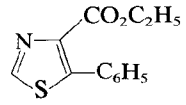
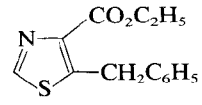
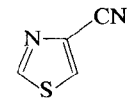
Ethyl thiazole-4-carboxylate has been prepared by hydrogenolysis of ethyl 2-bromothiazole-4-carboxylate with Raney nickel in ethanol,[3] by desulfurization of ethyl 2-mercaptothiazole-4-carboxylate with hydrogen peroxide in concentrated hydrochloric acid,[4] and by condensation of ethyl bromopyruvate with thioformamide in ether.[5,6]

The present procedure is illustrative of a mild and general method for preparing thiazoles substituted in the 4-position with electron-withdrawing substitutents such as carbethoxy,[7] cyano,[7] and *p*-toluenesulfonyl.[8] Thus condensation of ethyl isocyanoacetate with various thiono esters affords the parent ethyl thiazole-4-carboxylate as well as a series of analogs bearing substituents in the 5-position (Table I).[7] A similar reaction of α-isocyanoacetonitrile with *O*-ethyl thioformate gave the cyano analog in 23% yield. However, the instability of the latter isocyanide hampers the utility of this reaction.

The mechanism of the condensation in Part D probably involves thioformylation of the metallated isocyanoacetate followed by intramolecular 1,1-addition of the tautomeric enethiol to the isonitrile. This thiazole synthesis is analogous to the formation of oxazoles from acylation of metallated isonitriles with acid chlorides or anhydrides.[9,10] Interestingly, ethyl formate does not react with isocyanoacetate under the conditions of this procedure. Ethyl and methyl isocyanoacetate have been prepared in a similar manner by dehydration of the corresponding *N*-formylglycine esters with phosgene[2] and trichloromethyl chloroformate,[11] respectively. The phosphoryl chloride method described here was provided to the submitters by Professor U. Schöllkopf[12] and is based on the procedure of Böhme and Fuchs.[13] The preparation of *O*-ethyl thioformate in Part C was developed from a report by Ohno, Koizuma, and Tsuchihaski.[14]

TABLE I

THIAZOLES FROM CONDENSATION OF ETHYL ISOCYANOACETATE AND α-ISOCYANOACETAMIDE WITH THIONO ESTERS

Thiazole	M.p. or B.p. (°)	Yield (%)
	89–90	82
	85–87 (0.15 mm.)	68
	183–185	22
	49–50	75
	55–56	23

4-Substituted thiazoles are important chemical intermediates, for example, in the synthesis of thiabendazole [2-(4-thiazolyl)-benzimidazole], which is a leading anthelminthic utilized for control of gastrointestinal nematodes in ruminants.[15] Other thiazoles have displayed significant pharmacologic activity as antiinflammatory[16] and antibacterial agents.[17] Recently, 4-substituted thiazoles were implicated as intermediates in the energy transfer mechanism of firefly bioluminescence.[18]

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Numbers)

Ethyl thiazole-4-carboxylate: 4-Thiazolecarboxylic acid, ethyl ester (8, 9); (14527–43–6)

Glycine, *N*-formyl-, ethyl ester (8, 9); (3154–51–6)

Glycine, ethyl ester, hydrochloride (8, 9); (623–33–6)

Methyl formate: Formic acid, methyl ester (8, 9); (107–31–3)

Ethyl isocyanoacetate: Acetic acid, isocyano-, ethyl ester (8, 9); (2999–46–4)

Triethylamine (8); Ethanamine, *N,N*-diethyl- (9); (121–44–8)

Phosphoryl chloride (8, 9); (10025–87–3)

O-Ethyl thioformate: Formic acid, thio-, *O*-ethyl ester (8); Methanethioic acid, *O*-ethyl ester (9); (29392–46–9)

Triethyl orthoformate: Orthoformic acid, triethyl ester (8); Ethane, 1,1′, 1″-[methylidynetris(oxy)]tris- (9); (122–51–0)

Hydroquinone (8); 1,4-Benzenediol (9); (123–31–9)

Formamide, thio- (8); Methanethioamide (9); (115-08-2)

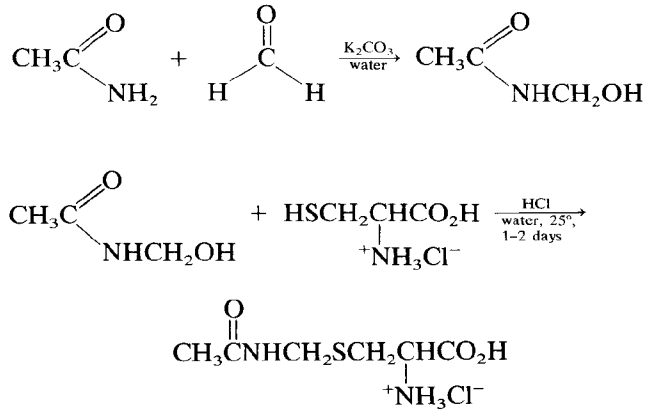
Ethyl bromopyruvate: Pyruvic acid, bromo-, ethyl ester (8); Propanoic acid, 3-bromo-2-oxo-, ethyl ester (9); (70–23–5)

Phosgene (8); Carbonic dichloride (9); (75–44–5)

Thiabendazole: Benzimidazole, 2-(4-thiazolyl)- (8); 1*H*-Benzimidazole, 2-(4-thiazolyl)- (9); (148–79–8)

THIOL PROTECTION WITH THE ACETAMIDOMETHYL GROUP: S-ACETAMIDOMETHYL-L-CYSTEINE HYDROCHLORIDE

(L-Cysteine, *S*-[(acetylamino)methyl]-, monohydrochloride)



Submitted by JOHN D. MILKOWSKI,[1] DANIEL F. VEBER,[2] and RALPH HIRSCHMANN[2]
Checked by A. PEARCE and G. BÜCHI

1. Procedure

A. N-(*Hydroxymethyl*)*acetamide.* A solution of 10 g. (0.07 mole) of anhydrous potassium carbonate in 137 g. of a 36–38% solution of formaldehyde (1.7 moles) in water (Note 1) is prepared in a 2-l., round-bottomed flask, and 100 g. (1.7 moles) of

acetamide (Note 2) is added. The mixture is swirled, heated on a steam bath for 3 minutes, and allowed to stand overnight at room temperature. Several pieces of crushed dry ice are added (Note 3), after which the mixture is evaporated under reduced pressure with a heating bath kept below 40° (Note 4). A 128-g. portion of anhydrous sodium sulfate is added to the remaining colorless oil, which may have some precipitated salt suspended in it. After several hours the oil is dissolved in 1 l. of acetone, the suspended drying agent and salts are filtered, and the filtrate (Note 5) is dried further with additional anhydrous sodium sulfate. The suspension is filtered, and the clear filtrate is evaporated under reduced pressure. The yield of *N*-(hydroxymethyl)acetamide, a colorless hygroscopic oil at this point, is 148–151 g. (98–100%) (Note 6). The oily product, which may solidify (Note 7) on standing for several days, is used directly in step B.

B. S-*Acetamidomethyl*-L-*cysteine hydrochloride.* A 1-l., round-bottomed flask is charged with 127 g. (1.43 moles) of *N*-(hydroxymethyl)acetamide, 228 g. (1.3 moles) of L-cysteine hydrochloride monohydrate (Note 8), and 350 ml. of water. The resulting solution is swirled and cooled in an ice bath as 50 ml. of concentrated hydrochloric acid is slowly added (Note 9). The flask is flushed with nitrogen, capped with a nitrogen-filled balloon, and allowed to stand for 1–2 days at room temperature. The progress of the reaction is monitored by thin-layer chromatography (Note 10). When L-cysteine hydrochloride is no longer detectable, the flask is connected to a rotary evaporator, and the solution is evaporated under reduced pressure with a bath temperature of *ca.* 40°. The remaining solid is suspended in a small amount of absolute ethanol, and the mixture is again carefully evaporated to avoid bumping. This entrainment procedure with absolute ethanol is repeated several times to remove traces of water. The dry solid is dissolved in the minimum amount of methanol (Note 11), and anhydrous ether is added until the cloud point is reached. The cloudy solution is allowed to stand in a refrigerator at *ca.* 4–5° for 1 week, during which the crystalline mass is broken up several times. The white crystalline product is collected, washed with ether, and dried under reduced pressure. The yield is 152–190 g. (51–64%) of *S*-acetamidomethyl-L-cysteine hydrochloride, dec. 159–163°, $[\alpha]_D^{25°}$ 30.7° (*c* 1, water) (Notes 12–14).

2. Notes

1. A 37% solution of formaldehyde in water is available from Aldrich Chemical Company, Inc.

2. The submitters obtained acetamide from Merck & Company, Inc. Acetamide was purchased by the checkers from Fisher Scientific Company.

3. The submitters state that the failure to add dry ice at this point may result in greatly reduced yields. The purpose of the dry ice is presumably to lower the pH of the solution by converting potassium carbonate to potassium bicarbonate.

4. When the mixture was heated above 40° by the submitters, it became discolored and an insoluble precipitate was formed.

5. The filtrate may be cloudy.

6. Apparent yields in excess of the theoretical amount may be observed owing to the presence of a small proportion of water. The oily product may be dried at high vacuum over phosphorous pentoxide for several days.

7. A melting point of 50–52° is reported for *N*-(hydroxymethyl)acetamide.[3]

8. The submitters purchased L-cysteine hydrochloride monohydrate from Schwartz/Mann Division, Becton, Dickinson, and Company, Mountain View Avenue, Orangeburg, New York 10962. The checkers used material supplied by Aldrich Chemical Company, Inc.

9. The pH of the solution is *ca.* 0.5.

10. The balloon was removed briefly while aliquots were taken. The flask was flushed again with nitrogen and the balloon was then replaced. Thin-layer chromatographic analyses were carried out on glass plates coated with silica gel G which were purchased from Analtech, Newark, Delaware. With a 10:2:3 (v/v/v) solution of 1-butanol, acetic acid, and water as developing solvent, the *Rf* values for the product and L-cysteine hydrochloride are 0.19 and 0.25, respectively.

11. The submitters dissolved the solid in methanol at room temperature. However, the solid obtained by the checkers was not very soluble in methanol at room temperature. Consequently, the material was dissolved in approximately 2–3 l. of methanol by gentle warming on a steam bath.

12. The product obtained by the checkers had $[\alpha]_D^{25°}$ −28° ($c = 1$, water). The spectral properties of the product are as follows: infrared (Nujol) $cm.^{-1}$: 1715 (C=O), 1580 (C=O); proton magnetic resonance (deuterium chloride in deuterium oxide) δ (multiplicity, number of protons, assignment): 2.05 (singlet, 3, CH_3), 3.2–3.4 (multiplet, 2, CH_2CH), 4.3–4.5 (multiplet, 1, CH_2CH), 4.39 (singlet, 2, NCH_2S).

13. On several occasions the product isolated by the submitters was contaminated with L-cystine dihydrochloride, which was not easily removed by recrystallization. In this event the product was converted to the zwitterionic form and recrystallized in the following manner. The pH of a solution of the product in water was adjusted to 6 with aqueous 2.5*N* potassium hydroxide. The neutralized solution was evaporated to dryness under reduced pressure at *ca.* 40°. The residue was dissolved in a minimum amount of hot water, and two volumes of 95% ethanol were added to precipitate *S*-acetamidomethyl-L-cysteine monohydrate, dec. 187°, $[\alpha]_{589}^{25}$ −42.5° ($c = 1$, water).

14. The following unchecked procedure for liberating L-cysteine from *S*-acetamidomethyl-L-cysteine was provided by the submitters as a model for removing the *S*-acetamidomethyl group from peptides. The pH of a solution of 96.1 mg. (0.0005 mole) of *S*-acetamidomethyl-L-cysteine in 10.0 ml. of water is adjusted to 4.0 with aqueous 0.25*N* hydrochloric acid. The solution is stirred, 159.3 mg. (0.0005 mole) of mercury(II) acetate is added, and the pH is readjusted to 4.0 by adding more 0.25*N* hydrochloric acid. The resulting suspension is stirred for 1 hour at room temperature and is then diluted with an equal volume of water. Hydrogen sulfide gas is introduced to complete the precipitation of mercury from solution, the mixture is filtered, and the aqueous filtrate is evaporated to dryness under reduced pressure. A thin-layer chromatographic analysis on the residue as described in Note 10 showed the presence of L-cysteine and the absence of *S*-acetamidomethyl-L-cysteine.

3. Discussion

The present procedure provides a convenient method for preparing *S*-acetamidomethyl-L-cysteine hydrochloride.[4] The zwitterionic form may be obtained readily from the hydrochloride by

the procedure described in Note 13, by ion-exchange chromatography,[5] or by precipitation from 2-propanol with pyridine.[6] *S*-Acetamidomethyl-L-cysteine has also been prepared from *N*-(hydroxymethyl)acetamide under anhydrous conditions in liquid hydrogen fluoride[4] and in trifluoroacetic acid.[7] The preparation of *N*-(hydroxymethyl)acetamide described in Part A is based on the procedure of Einhorn.[3]

The acetamidomethyl group serves as a useful thiol-protecting group for cysteine during peptide synthesis.[4,7–9] The protecting group is stable to the conditions generally prevailing in peptide synthesis, including not only typical solution and solid-phase procedures but also reactions carried out in liquid hydrogen fluoride.[4] Peptides containing *S*-acetamidomethyl-L-cysteine generally have good water solubility[8] and are not prone to racemization at the α-position of the cysteine residue.[4] The acetamidomethyl protecting group may be easily removed by reaction either with mercury(II) acetate at pH 4 as described in Note 14 or with iodine.[7,8] *S*-Acetamidomethylation of the cysteine residues of proteins may be accomplished in liquid hydrogen fluoride, and the group may be removed by reaction with mercury(II) ion.[4] The thiol group of β-mercaptopropionic acid has also been protected by formation of the *S*-acetamidomethyl derivative.[7]

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Acetamide, *N*-(hydroxymethyl)- (8, 9); (625-51-4)

Acetamide (8, 9); (60-35-5)

S-Acetamidomethyl-L-cysteine hydrochloride: Alanine, 3-[(acetamidomethyl)thio]-, monohydrochloride, L- (8); L-Cysteine, *S*-[(acetylamino)methyl]-, monohydrochloride (9); (28798-28-9)

L-Cysteine hydrochloride, monohydrate (8, 9); (7048-04-6)

Mercury(II) acetate: Acetic acid, mercury (2^+) salt (8, 9); (1600-27-7)

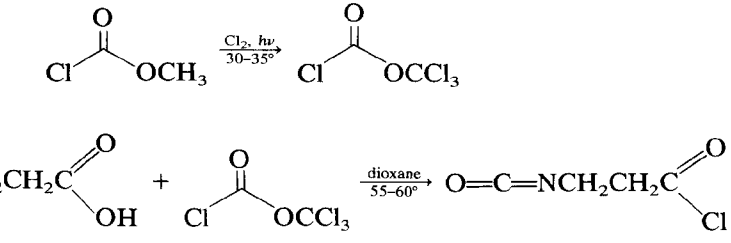
Acetic acid, trifluoro- (8, 9); (76-05-1)

Cysteine (8, 9); (4371-52-2); L-Cysteine (8, 9); (52-90-4)

β-Mercaptopropionic acid: Propionic acid, 3-mercapto- (8, 9); (107-96-0)

TRICHLOROMETHYL CHLOROFORMATE AS A PHOSGENE EQUIVALENT: 3-ISOCYANATOPROPANOYL CHLORIDE

(Carbonochloridic acid, trichloromethyl ester, and propanoyl chloride, 3-isocyanato-)



Submitted by KEISUKE KURITA and YOSHIO IWAKURA[1]
Checked by WILLIAM F. BURGOYNE, CHRISTOPHER VANCANTFORT, and ROBERT M. COATES

1. Procedure

Caution! Trichloromethyl chloroformate is toxic. These reactions should both be carried out in a well-ventilated hood (*Note* 1).

A. *Trichloromethyl chloroformate.* A 100-ml., three-necked, round-bottomed Pyrex flask is equipped with a thermometer, a reflux condenser protected at the top with a calcium chloride tube, and a gas-inlet tube with a coarse fritted-glass tip extending almost to the bottom of the flask. In the flask are placed 37.8 g. (0.4 mole) of freshly distilled methyl chloroformate (Note 2) and a Teflon-coated magnetic stirring bar. The flask is illuminated with a 100-W. high-pressure, mercury-vapor lamp (Note 3) which is placed beside

it (Notes 4 and 5). The methyl chloroformate is stirred and irradiated as a slow stream of chlorine (Note 6) is passed into the flask through the gas-inlet tube (Note 7). When the temperature reaches 30° from the exothermic reaction, the flask is immersed in a water bath (Note 8). The chlorine is then passed into the solution more rapidly so as to maintain the temperature at 30–35° (Note 9). After *ca.* 6.5–7 hours the colorless solution assumes the pale yellow-green color of chlorine, which indicates that the end point of the reaction has been reached (Note 10). Distillation under reduced pressure affords 65–72 g. (82–91%) of trichloromethyl chloroformate as a colorless liquid, b.p. 53–55° (53 mm.) (Note 11).

B. 3-*Isocyanatopropanoyl chloride.* A 500-ml., two-necked flask is equipped with a thermometer and a reflux condenser protected at its top by a calcium chloride tube. A Teflon-coated magnetic stirring bar, 250 ml. of anhydrous dioxane (Note 12), 12.6 g. (0.1 mole) of finely pulverized 3-aminopropanoic acid hydrochloride (Note 13), and 23.8 g. (14.4 ml., 0.12 mole) of trichloromethyl chloroformate (Note 14) are placed in the flask in the order specified. The mixture is stirred and heated at 55–60°. After *ca.* 5 hours, the solid has completely dissolved, leaving a clear solution. The heating is discontinued after a total of 7 hours (Note 15), and the solvent is removed under reduced pressure. The residual oil is distilled rapidly under reduced pressure and a distillate amounting to 11.2–12.4 g. (84–93%) is collected at 75–85° (20 mm.) (Note 16). Redistillation affords 10.5–11.8 g. (79–88%) of 3-isocyanatopropanoyl chloride as a colorless liquid, b.p. 92–94° (25 mm.) (Note 17).

2. Notes

1. Vapors of all of the polychlorinated methyl chloroformates are toxic.[2–4] Trichloromethyl chloroformate has a phosgene-like odor and is known to decompose to phosgene at elevated temperature[5] or on contact with ferric oxide or charcoal.[6]

2. Methyl chloroformate is available from Aldrich Chemical Company, Inc.

3. The checkers used a 200-W., high-pressure, mercury-vapor lamp and the corresponding transformer which are available from the Hanovia Lamp Division, Canrad-Hanovia, Inc., 100 Chestnut St., Newark 5, New Jersey 07105. The lamp was suspended vertically in a cylindrical, double-walled, Pyrex jacket cooled by flowing water. The inside diameter, outside diameter, and length of the cooling jacket were 3, 4, and 22 cm., respectively. The cooling jacket was clamped in place *ca.* 5 cm. from the reaction vessel to allow the cooling bath to be raised into position. The use of the 200-W. lamp did not alter the reaction time.

4. It is advisable to wrap the entire apparatus with aluminum foil to avoid exposure to ultraviolet light. The reaction solution can be observed through a small hole in the aluminum foil which is shielded from the direct radiation of the lamp.

5. The irradiation should be started before the flow of chlorine gas is begun to avoid the risk of explosion.

6. The checkers used chlorine from a lecture bottle supplied by the Linde Division, Union Carbide Chemical Corp.

7. Chlorine should be introduced slowly at first to prevent an accumulation of unreacted chlorine in the solution and to avoid the risk of a rapid, exothermic reaction. The accumulation of chlorine is indicated by the appearance of its characteristic yellow-green color.

8. The checkers used a 15×7.5 cm. Pyrex crystallizing dish as a transparent water bath.

9. Once the chlorine gas flow is properly adjusted, the solution remains colorless and the temperature stays in the 30–35° range without further adjustment until the end point is approached. However, the color and temperature should be observed frequently during the 6.5- to 7-hour reaction time.

Although this reaction can be carried out at higher temperatures, the yields are reduced, probably owing to loss of the volatile methyl chloroformate, b.p. 71°, and/or decomposition of the product. For example, the yields of trichloromethyl chloroformate are *ca.* 75% and 55% when the chlorination is carried out at 50–55° and 85–90°, respectively.

10. The checkers judged that the end point had been reached when the yellow-green color persisted for 2–3 minutes after the chlorine flow had been stopped. At the first appearance of the yellow-green color, the gas stream was shut off, and the color faded within *ca.* 15 sec. The chlorine flow was resumed at a slow rate until the end point was reached.

11. The product has the following spectral properties: infrared

(neat liquid) cm.$^{-1}$: 1815 (C=O), 1054, 968, 912, 814, 764; carbon-13 nuclear magnetic resonance (chloroform-*d*) δ (assignment): 108.37 (CCl_3), 143.93 (*C*=O). Trichloromethyl chloroformate is stable at room temperature, but decomposes to phosgene when heated above 300°[5] or on contact with ferric oxide or charcoal.[6] Decomposition to carbon tetrachloride and carbon dioxide occurs on exposure to alumina, aluminum chloride, or ferric chloride.[5-8]

12. The checkers dried and purified the dioxane by distillation from the sodium–benzophenone ketyl.

13. 3-Aminopropanoic acid (β-alanine) is available from Aldrich Chemical Company, Inc., and from the Nutritional Biochemical Division, ICN Products. The hydrochloride salt is prepared in the following manner. A solution of 89 g. (1.0 mole) of 3-aminopropanoic acid in 200 ml. of water is acidified by addition of 100 ml. (1.2 mole) of concentrated hydrochloric acid and then concentrated to a white solid with a rotary evaporator. The solid is pulverized to a fine powder and dried at 60° under reduced pressure. The yield of 3-aminopropanoic acid hydrochloride amounts to 113–125 g. (90–100%).

14. Although the reaction can be carried out with an equimolar amount of trichloromethyl chloroformate, a longer time (15–20 hours) is required to reach completion, and the yield is reduced somewhat. If a 1.5–2.0-fold excess of trichloromethyl chloroformate is used, the reaction time is decreased to *ca.* 5 hours and the yield is increased to 90–95%.

15. The checkers heated the suspension for a total of 10 hours, 7–8 hours having been required to dissolve the solid completely. The reaction time may depend on the particle size of the hydrochloride salt and the rate of stirring.

16. The submitters advise that the distillation be carried out rapidly to avoid the formation of a tarry residue.

17. The spectral properties of 3-isocyanatopropanoyl chloride are as follows: infrared (liquid film) cm.$^{-1}$: 2278 (N=C=O), 1795 (O=C—Cl); proton magnetic resonance (chloroform-*d*) δ (multiplicity, number of protons, assignment, coupling constant *J* in Hz.): 3.17 (triplet, 2, CH_2CH_2N=C=O, $J = 6$), 3.67 (triplet, 2, CH_2N=C=O, $J = 6$); carbon-13 magnetic resonance (chloroform-*d*) δ (assignment); 38.3 (CH_2N=C=O), 47.6 (CH_2CH_2N=C=O), 123.0 (N=*C*=O), 171.6 (O=*C*—Cl). A small peak at δ 67.1 in the carbon-13 magnetic resonance spectrum of the product obtained by the checkers was attributed to a small amount of dioxane.

3. Discussion

The chlorination of methyl chloroformate in sunlight was first reported by Hentschel, but without a detailed description of either the procedure or the results.[5] The first step of the present procedure for the preparation of trichloromethyl chloroformate utilizes an ultraviolet light source and affords a simple and reproducible way to obtain this reagent. Although trichloromethyl chloroformate may also be synthesized by photochemical chlorination of methyl formate,[9-11] the volatility of methyl formate causes losses during the reaction and increases the hazard of forming an explosive mixture of its vapor and chlorine gas. The preparation of trichloromethyl chloroformate by chlorination of methyl chloroformate in the dark with diacetyl peroxide as initiator has been reported.[12] However, the procedure consists of several steps, and the overall yield is rather low.

Trichloromethyl chloroformate is useful in synthesis as a substitute for phosgene, which, owing to its high volatility and toxicity, presents a severe hazard in the laboratory. Although trichloromethyl chloroformate is toxic, it is a dense and less volatile liquid, b.p. 128°, d_{15}^{15} 1.65, having a vapor pressure of only 10 mm. at 20°. Consequently it is more easily handled in a safe manner than phosgene.

Trichloromethyl chloroformate has proven effective in the preparation of *N*-carboxy-α-amino acid anhydrides from amino acids,[13] and various compounds having isocyanate, acid chloride, and chloroformate groups.[14,15] For example, trichloromethyl chloroformate may be used instead of phosgene in the preparation of 2-*tert*-butoxycarbonyloxyimino-2-phenylacetonitrile.[15] The use of this reagent is illustrated here by the synthesis of 3-isocyanatopropanoyl chloride from 3-aminopropanoic acid hydrochloride.

3-Isocyanatopropanoyl chloride has also been prepared by the reaction of 3-aminopropanoic acid hydrochloride with phosgene.[16]

However, the yield is only 36%, and hydrogen chloride must be introduced to increase the yield to 92%. The present procedure effects this reaction without additional hydrogen chloride and avoids the hazards of handling phosgene. This procedure has been successful in the synthesis of isocyanato acid chlorides and isocyanato chloroformates from amino acids and amino alcohols, respectively.[14] For example, 6-isocyanatohexanoyl chloride can be prepared in good yield with trichloromethyl chloroformate, although it is obtained in only trace amounts with phosgene unless additional hydrogen chloride is used. Isocyanato acid chlorides such as 3-isocyanatopropanoyl chloride, having two different, highly reactive electrophilic groups, are novel reagents for introducing amino acid residues into organic compounds[14] and polymers.[17]

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Trichloromethyl chloroformate: Formic acid, chloro-, trichloromethyl ester (8); Carbonochloridic acid, trichloromethyl ester (9); (503-38-8)

Isocyanic acid, 2-(chloroformyl)ethyl ester (8); Propanoyl chloride, 3-isocyanato- (9); (3729-19-9)

Methyl chloroformate: Formic acid, chloro-, methyl ester (8); Carbonochloridic acid, methyl ester (9); (79-22-1)

Dioxane: *p*-Dioxane (8); 1,4-Dioxane (9); (123-91-1)

3-Aminopropanoic acid hydrochloride: β-Alanine, hydrochloride (8, 9); (6057-90-5)

Phosgene (8); Carbonic dichloride (9); (75-44-5)

Sodium benzophenone ketyl: Benzophenone, radical ion (1−), sodium (8); Methanone, diphenyl-, radical ion (1-), sodium (9); (3463-17-0)

3-Aminopropanoic acid: β-Alanine (8, 9); (107-95-9)

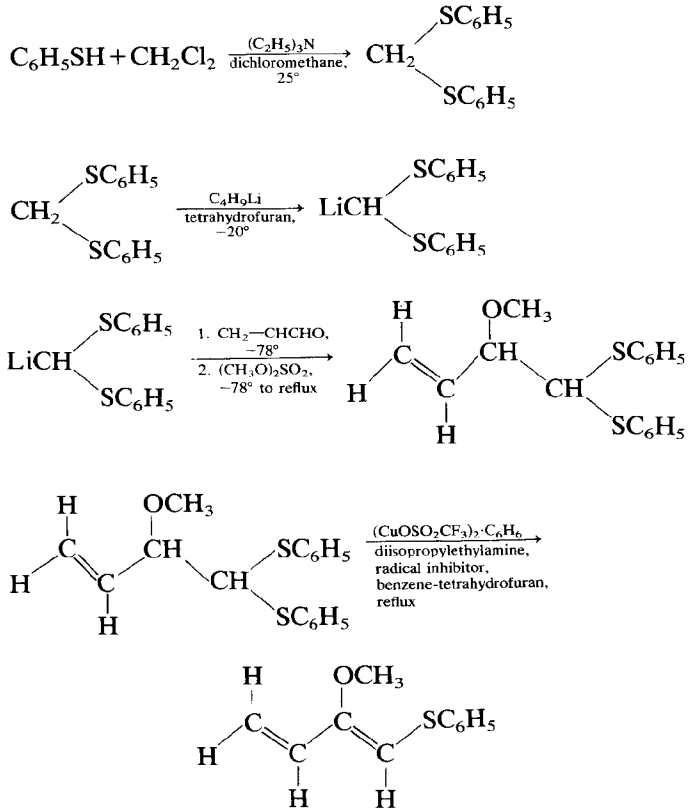
Methyl formate: Formic acid, methyl ester (8, 9) (107-31-3)

Acetyl peroxide (8); Peroxide, diacetyl (9); (110-22-5)

Hexanoyl chloride, 6-isocyanato- (8, 9); (3729-18-8)

VINYL SULFIDES FROM THIOACETALS WITH COPPER(I) TRIFLUOROMETHANESULFONATE: (Z)-2-METHOXY-1-PHENYLTHIO-1,3-BUTADIENE

(Benzene, [(2-methoxy-1,3-butadienyl)thio]-, (Z)-)



Submitted by THEODORE COHEN, ROBERT J. RUFFNER, DAVID W. SHULL, ELAINE R. FOGEL, and J. R. FALCK[1]
Checked by J. BISAHA and M. F. SEMMELHACK

1. Procedure

Caution! Part A should be carried out in an efficient hood to minimize exposure to the foul-smelling thiophenol. See benzene warning, Org. Syn., **58,** 168 (1979).

A. *Bis(phenylthio)methane.* A dry 2-l., one-necked flask is equipped with a magnetic stirring bar and a 250-ml. pressure-equalizing dropping funnel mounted with a combined inlet-outlet assembly for introducing argon (Note 1). The flask is charged with 1.5 l. of distilled dichloromethane and 79.9 g. (110 ml., 0.791 mole) of triethylamine (Note 2) and is purged with argon. The solution is stirred and cooled in an ice bath as 87 g. (81 ml., 0.79 mole) of thiophenol (Note 3) is added over 20–30 minutes. The mixture is allowed to warm to 20° and is stirred at this temperature for another 3 hours. The precipitate of triethylamine hydrochloride is removed by filtration through a fritted-glass Büchner funnel. The filtrate is washed with two 200-ml. portions of aqueous 10% sodium hydroxide, two 200-ml. portions of aqueous 2*N* hydrochloric acid, and one 300-ml. portion of water. The dichloromethane solution is dried with anhydrous magnesium sulfate and evaporated under reduced pressure. Recrystallization of the residue from petroleum ether gives 51.2–59.6 g. (56–65%) of bis(phenylthio)methane as white crystals, m.p. 35–37° (Note 4).

B. 4,4-*Bis(phenylthio)*-3-*methoxy*-1-*butene.* A 250-ml., two-necked, round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and a reflux condenser bearing an inlet-outlet assembly for argon (Note 1) is dried in an oven at 110° and cooled under a stream of argon passed through the septum with a syringe needle and vented through the argon bubbler. A solution of 5.00 g. (0.0215 mole) of bis(phenylthio)methane in 150 ml. of tetrahydrofuran (Note 5) is placed in the flask and is cooled to −20° with a carbon tetrachloride–dry ice bath. A 15.8-ml. (0.0217 mole) aliquot from a 1.37 *M* solution of butyllithium in hexane (Note 6) is injected through the septum by means of a syringe. The resulting deep yellow solution is stirred and cooled at −20° for 1 hour and then is cooled to −78° with a dry ice–acetone bath. The color of the solution is discharged immediately when 1.4 g. (1.7 ml., 0.025 mole) of acrolein (Note 7) is added by syringe at −78°. Stirring and cooling are continued for 15 minutes, after which 2.90 g. (2.19 ml., 0.023 mole) of dimethyl sulfate (Note 8) is added, and the cooling bath is removed. The solution is stirred at room temperature for 16 hours and heated at reflux for 2 hours. A 3-ml. portion of water is added to the cooled mixture, most of the tetrahydrofuran is removed by rotary evaporation, and the con-

centrate is partitioned between 30 ml. of water and 30 ml. of ethyl ether. The organic layer is washed three times with 10-ml. portions of aqueous concentrated ammonia and once with water. The ethereal solution is dried with anhydrous magnesium sulfate and evaporated under reduced pressure. Crystallization of the viscous yellow residue from 30 ml. of 95% ethanol at −20° gives 3.11–3.36 g. (48–52%) of 4,4-bis(phenylthio)-3-methoxy-1-butene as a light yellow solid, m.p. 45–48°, which is of adequate purity for use in the next step (Note 9).

C. (Z)-2-*Methoxy*-1-*phenylthio*-1,3-*butadiene*. A 250-ml., two-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum, and a reflux condenser bearing a combined inlet-outlet assembly for argon (Note 1). The flask is flushed with argon and charged with 3.27 g. [0.0065 mole, 0.013 g.-atom of copper(I)] of bis[copper(I) trifluoromethanesulfonate] benzene complex (Note 10), 0.036 g. (0.0001 mole) of 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide (Note 11), and 70 ml. of benzene (Note 12). By means of syringes 1.20 g. (0.00397 mole) of 4,4-bis(phenylthio)-3-methoxy-1-butene, 1.33 g. (1.80 ml., 0.0103 mole) of *N,N*-diisopropylethylamine (Note 13), and 14 ml. of tetrahydrofuran (Note 5) are injected through the septum into the flask. The suspension is stirred and heated under reflux for 4.75 hours (Note 14), after which the starting thioacetal has completely reacted, as judged from thin-layer chromatograms (Note 15). Two milliliters of water is added to the cooled mixture, the insoluble material is removed by filtration through Celite, and the flask is rinsed with several portions of ether. A 40-ml. portion of water is added to the filtrate, the layers are separated, and the aqueous layer is extracted with three 25-ml. portions of ethyl ether. The organic solutions are combined, dried with anhydrous magnesium sulfate, and evaporated under reduced pressure. Bulb-to-bulb distillation of the residual brown oil (0.782 g.) in a Kugelrohr apparatus (Note 16) with an oven temperature of 85–95° (0.005 mm.) provides 0.421–0.486 g. (55–64%) of (*Z*)-2-methoxy-1-phenylthio-1,3-butadiene as a light yellow oil (Notes 17 and 18).

2. Notes

1. The inlet-outlet assembly is connected to both a source of argon and a bubbler which serves as exit for the inert gas. Argon is passed through the apparatus for 30 minutes, and the system is then kept under a slight positive pressure of inert gas by maintaining a slow flow of argon through the bubbler.

2. Triethylamine was purchased from Eastman Organic Chemicals and distilled from calcium hydride before use.

3. Thiophenol was purchased from Aldrich Chemical Company, Inc., and distilled, b.p. 75–77° (30 mm.), 168–169° (760 mm.).

4. The submitters obtained 59.6–64.1 g. (65–70%) of product melting at 36–37° after recrystallization from ethanol. Reported melting points for bis(phenylthio)methane are 34–35°,[2] 38–40°,[3] and 39.5–40.5°.[4] The proton magnetic resonance spectrum of the product in carbon tetrachloride exhibits a two-proton singlet at δ 4.30 and a 10-proton multiplet at δ 7.10–7.56.

5. Tetrahydrofuran was distilled from lithium aluminum hydride by the submitters and collected in a flask containing molecular sieves. For a warning regarding this method of purifying tetrahydrofuran, see *Org. Syn.*, Coll. Vol. **5,** 976 (1973).

6. Butyllithium in hexane was purchased from Alfa Division, Ventron Corporation.

7. Acrolein was purchased by the submitters from Cationics, Division of Columbia Organic Chemicals Company, Inc. (Columbia, South Carolina) and distilled immediately before use, b.p. 51–53°.

8. Dimethyl sulfate was used as supplied by Eastman Organic Chemicals. The submitters obtained lower yields when methyl iodide was substituted for dimethyl sulfate.

9. The yield and melting point data given are those of the checkers. The purity of the product was estimated to be at least 98% from analysis of its proton magnetic resonance spectrum. The submitters report that the crude product crystallized on standing in a freezer and that one recrystallization from absolute ethanol afforded 3.6–4.1 g. (55–63%) of product that melted at 49.5–51°. The proton magnetic resonance spectrum of the product in carbon tetrachloride exhibits the following absorptions δ (multiplicity, number of protons, assignment, coupling constant *J* in Hz.): 3.23 (singlet, 3, OCH_3), 3.48–3.97 (multiplet, 1, $CHOCH_3$), 4.37 (doublet, 1, $C_6H_5SCHSC_6H_5$, $J = 4.0$), 5.03–5.43 (multiplet, 2, $-CH{=}CH_2$), 5.67–6.13 (multiplet, 1, $-CH{=}CH_2$), 6.90–7.57 (multiplet, 10, two $-SC_6H_5$).

10. Bis[copper(I) trifluoromethanesulfonate] benzene complex

was prepared by a modification of a procedure reported by Salomon and Kochi[5] as described in the following paragraph. The copper(I) oxide used was purchased from J. T. Baker Chemical Company, and trifluoromethanesulfonic anhydride was prepared by the procedure of Hanack, Dehesch, Hummel, and Nierth.[6] The submitters have found once-distilled anhydride to be satisfactory provided that the weight of phosphorous pentoxide used was approximately equal to the weight of sulfonic acid, and the reaction mixture was stirred vigorously. When twice-distilled anhydride was used in the procedure below, reaction times as long as 13 hours were required before decolorization occurred. The submitters suggest that the enhanced rates observed with once-distilled anhydride may be attributed to the presence of the sulfonic acid. Although trifluoromethanesulfonic anhydride is available from Aldrich Chemical Company, Inc., the commercial reagent has not been used in this procedure.

A dry 1-l., two-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum, and a reflux condenser bearing a combined inlet-outlet assembly for argon (Note 1). The flask is purged with argon and charged with 18.0 g. (0.126 mole) of copper(I) oxide and 600 ml. of degassed benzene (Note 12). By means of a syringe, 42.7 g. (25.5 ml., 0.151 mole) of trifluoromethanesulfonic anhydride is injected through the septum into the flask. The suspension is stirred and heated under reflux until nearly all of the red copper(I) oxide has dissolved. Although 3–5 hours is normally sufficient, reaction times as long as 19 hours were required on some occasions (see preceding paragraph). The hot suspension is filtered through a Büchner funnel in an argon-filled glove bag kept dry with a dish of phosphorous pentoxide. The filtrate is allowed to cool in the glove bag for 1 hour, after which the crop of fine white crystals is collected on a fritted-glass Büchner funnel. The funnel is tightly covered with aluminum foil and then placed in a vacuum desiccator containing anhydrous calcium sulfate and phosphorous pentoxide. The desiccator is removed from the glove bag, evacuated overnight, filled with argon again, and returned to the glove bag. The dry bis[copper(I) trifluoromethanesulfonate] benzene complex, which weighs 37.6–49.5 g. (60–79%), is transferred to vials in the glove bag. The

product maintains its activity indefinitely when protected from moisture and air.

The procedure described above provides a sufficient quantity of bis[copper(I) trifluoromethanesulfonate] benzene complex for several reactions at the scale used in Part C. If bis[copper(I) trifluoromethanesulfonate] benzene complex for a single reaction is desired, the same procedure can be followed at the appropriate scale without the use of the glove bag. In this case, the decolorized solution is not filtered but instead is cooled, and the product is allowed to crystallize in the reaction vessel. The supernatant benzene is decanted, and the crystals are washed in the flask with fresh benzene. The bis[copper(I) trifluoromethanesulfonate] benzene complex is then used without drying in the same flask.

11. 3-*tert*-Butyl-4-hydroxy-5-methylphenyl sulfide was purchased from Aldrich Chemical Company, Inc. This material serves as a radical inhibitor to prevent the polymerization of the product. Lower yields of product were obtained when hydroquinone was used as the inhibitor.

12. Benzene was freshly distilled from calcium hydride and collected in a flask containing molecular sieves.

13. *N,N*-Diisopropylethylamine supplied by Aldrich Chemical Company, Inc., was distilled prior to use. The amine is added to prevent polymerization of the diene by acid generated during the reaction. If the product is not sensitive to acid, the amine may be omitted.

14. The temperature at which elimination of thiophenol occurs depends on the substituents on the sulfur-bearing carbon.[7] Thioketals react rapidly at 25°. In some cases the elimination of thiophenol from the less reactive thioacetals may also be performed at 25°. However, in the present case the combined inductive effects of the vinyl and methoxy groups evidently destabilize the incipient carbonium ion and necessitate a higher temperature for the reaction.

15. Thin-layer chromatograms were run on plates coated with silica gel using 1:10 (v/v) ether–hexane as developing solvent.

16. Kugelrohr distillation ovens manufactured by Büchi Glasaparatefabrik are available from Brinkmann Instruments, Inc., Westbury, New York.

17. The yields and boiling point range given are those reported by

the checkers. When the checkers used starting thioacetal that had been purified by both column chromatography and recrystallization (m.p. 50–52°), the yield was 0.486 g. (64%). Using recrystallized thioacetal, m.p. 49.5–51°, the submitters obtained 0.532–0.646 g. (70–85%) of product.

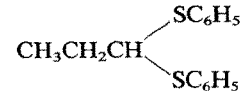
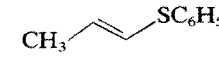
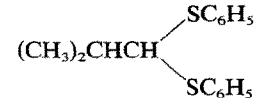
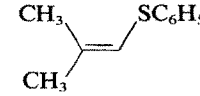
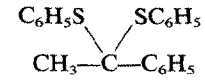
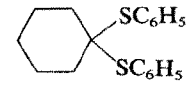
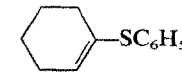
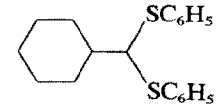
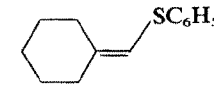
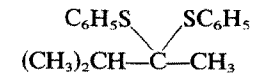
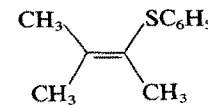
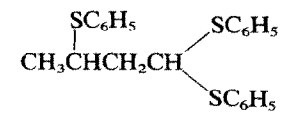
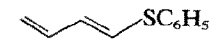
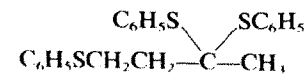
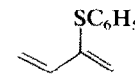
The proton magnetic resonance spectrum of the diene in carbon tetrachloride exhibits the following absorptions: δ (multiplicity, number of protons, assignment): 3.70 (singlet, 3, OCH_3), 4.87–5.52 (multiplet, 2, $—CH=CH_2$), 5.64 (singlet, 1, $=CHSC_6H_5$), 5.83–6.31 (multiplet, 1, $—CH=CH_2$), 6.98–7.37 (multiplet, 5, $—SC_6H_5$). A thin-layer chromatogram on silica gel with 3:2 (v/v) benzene–hexane as developing solvent showed a single spot. The single sharp peak for the methoxy group in the proton magnetic resonance spectrum and the absence of a spot at a high *Rf* value on the thin-layer chromatogram established that the product was not contaminated by its *E*-isomer. A mixture of the two isomers in which the *E*-isomer predominates can be prepared by heating a solution of the product in dichloromethane at reflux for 4 hours. The stereochemistry of the original product is assigned as *Z* on the basis of its high reactivity in Diels-Alder reactions and on the exclusive formation of an adduct with *cis* stereochemistry from reaction with methyl vinyl ketone.[8] The *E*-isomer undergoes Diels-Alder reactions much more slowly.[9]

18. The product is stable for months when mixed with a small amount of the radical inhibitor, 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide, and stored in a freezer. In the absence of the inhibitor, it isomerizes to a mixture of *E*- and *Z*-isomers over a period of some months.

3. Discussion

Part C of the present procedure illustrates a mild method for effecting the elimination of thiophenol from thioacetals and thioketals under essentially neutral conditions. The reaction of simple thioacetals and thioketals with bis[copper(I) trifluoromethanesulfonate] benzene complex in benzene-tetrahydrofuran at room temperature affords vinyl sulfides in high yield (Table I).[7,8] The reaction presumably occurs by coordination of the thiophilic copper(I) reagent with sulfur, heterolysis to a phenylthio-stabilized

TABLE I
VINYL SULFIDES FROM THIOACETALS AND THIOKETALS WITH COPPER(I) TRIFLUOROMETHANESULFONATE

Thioacetal or Thioketal	Vinyl Sulfide	Yield (%)
		91
		85
		85
		92
		92
		94
		84
		76

carbonium ion with formation of the insoluble copper(I) thiophenoxide, and finally proton loss to give the vinyl sulfide. Since trifluoromethanesulfonic acid is generated in stoichiometric quantity during the reaction, the medium becomes highly acidic. If the reactant or product is unstable to acid, as is the case in the present procedure, the pH can be kept neutral by adding *N,N*-diisopropylethylamine.

The reaction of crotonaldehyde and methyl vinyl ketone with thiophenol in the presence of anhydrous hydrogen chloride effects conjugate addition of thiophenol as well as acetal formation. The resulting β-phenylthio thioacetals are converted to 1-phenylthio- and 2-phenylthio-1,3-butadiene, respectively, upon reaction with 2 equivalents of copper(I) trifluoromethanesulfonate (Table I).[8] The copper(I)-induced heterolysis of carbon–sulfur bonds has also been used to effect pinacol-type rearrangements of bis(phenylthio)methyl carbinols.[10] Thus the addition of bis(phenylthio)methyllithium to ketones and aldehydes followed by copper(I)-induced rearrangement results in a one-carbon ring expansion or chain-insertion transformation which gives α-phenylthio ketones. Monothioketals of 1,4-diketones are cyclized to 2,5-disubstituted furans by the action of copper(I) trifluoromethanesulfonate.[7,11]

The most common procedure previously employed to effect the elimination of thiols from thioacetals has been heating in the presence of a protic acid.[12] For example, propionaldehyde diethyl thioacetal is converted to 1-ethylthio-1-propene on heating at 175° in the presence of phosphoric acid.[12a] The relatively high temperature and acidic conditions of such procedures are, however, distinct disadvantages of this method. Another approach consists of oxidation of a thioacetal to the mono *S*-oxide and thermal elimination of a sulfenic acid at 140–150°.[13]

Vinyl sulfides have found numerous applications in synthesis in the recent literature. Vinyl sulfides unsubstituted in the 1-position are metallated readily, and the resulting 1-phenythio- or 1-alkylthiovinyllithium reagents have been utilized for nucleophilic acylation and other applications.[14,15] The phenylthio-substituted 1,3-butadienes serve as interesting functionalized dienes in Diels-Alder reactions.[8,16,17] For example, (*Z*)-2-methoxy-1-phenylthio-1,3-butadiene and methyl vinyl ketone afford an adduct with the

normally inaccessible "meta" relationship between the methoxy and acetyl substituents.[8] The isomeric 2-methoxy-3-phenylthio- and 1-methoxy-4-phenylthio-1,3-butadienes have been recently prepared by thermal ring opening of the appropriate cyclobutenes.[17]

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Methane, bis(phenylthio)- (8); Benzene, 1,1′-[methylenebis(thio)]-bis- (9); (3561-67-9)

Thiophenol: Benzenethiol (8, 9); (108-98-5)

4,4-Bis(phenylthio)-3-methoxy-1-butene: Benzene, 1,1′-[(2-methoxy-3-butenylidene)bis(thio)]bis- (9); (60466-65-1)

Acrolein (8); 2-Propenal (9); (107-02-8)

(*Z*)-2-Methoxy-1-phenylthio-1,3-butadiene: Benzene, [(2-methoxy-1,3-butadienyl)thio]-, (*Z*)- (9); (60466-66-2)

Bis[copper(I) trifluoromethanesulfonate] benzene complex: Copper, [μ-(benzene)]bis(trifluoromethanesulfonato-*O*)di- (9); (37234-97-2)

Trifluoromethanesulfonic anhydride: Methanesulfonic acid, trifluoro-, anhydride (8, 9); (358-23-6)

Propionaldehyde diethyl thioacetal: Propane, 1,1-bis(ethylthio)- (9); (7282-08-8)

Sulfide, ethyl propenyl (8); 1-Propene, 1-(ethylthio)- (9); (36784-55-1)

1-Phenylthio-1,3-butadiene: Benzene, (1,3-butadienylthio)-(9); (53097-28-2); (*E*)-; (36715-51-2); (*Z*)-; (20664-21-5)

2-Methoxy-3-phenylthio-1,3-butadiene: Benzene, [(2-methoxy-1-methylene-2-propenyl)thio]- (9); (60603-16-9)

2-Phenylthio-1,3-butadiene: Sulfide, 1-methyleneallyl phenyl (8); Benzene, [(1-methylene-2-propenyl)thio]- (9); (7326-64-9)

Lithium, [bis(phenylthio)methyl]- (8, 9); (13307-76-1)

1-Methoxy-4-phenylthio-1,3-butadiene: Benzene, [(4-methoxy-1,3-butadienyl)thio]- (9); (*E,E*); (67700-13-4); (*E,Z*); (67700-14-5); (*Z,E*); (67700-15-6)

CUMULATIVE AUTHOR INDEX FOR VOLUMES 55 TO 59

This index comprises the names of contributors to Volumes **55** through **59**. A number in **boldface type** denotes the volume; a number in ordinary type indicates the page of that volume. For authors to previous volumes, see the cumulative index in Volume **54** which covers Volumes **50** through **54**, and either the indices in Collective Volumes I through V or the single volume entitled "Organic Syntheses, Collective Volumes I, II, III, IV, V, Cumulative Indices," edited by R. L. Shriner and R. H. Shriner.

CUMULATIVE SUBJECT INDEX FOR VOLUMES 55 TO 59

This index comprises subject matter from Volumes 55 through 59. For subjects in previous volumes, see the cumulative index in Volume 54 which covers Volumes 50 through 54, and either the cumulative indices in each of the Collective Volumes I-V, or the single volume entitled "Organic Syntheses, Collective Volumes I, II, III, IV, V, Cumulative Indices," edited by R. L. Shriner and R. H. Shriner.

This index is divided into two parts. **Part I** gives the names of compounds as used in these volumes as well as general terms for classes of compounds, types of reactions, synthetic applications, special apparatus, and unfamiliar methods. The complete names of all specific compounds are given in normal order as written in the text (e.g., ethyl cyanoacetate appears under ethyl). Some entries are common names and others are systematic *Chemical Abstracts* names, whichever was used in the text.

Most chemicals used in the procedure will appear in the index. Thus, there will generally be entries for all starting materials, reagents, intermediates, important by-products, and final products. Most products shown in the Tables in the discussion sections of this volume are included unless the compounds are quite similar in which case a general descriptive name was entered. Chemicals generally not indexed included common solvents, standard inorganic acids and bases, reactants shown in the Tables, and compounds cited in the discussion section in connection with other methods of preparation.

Part II consists entirely of systematic names of specific compounds according to *Chemical Abstracts* nomenclature (see the Index Guide in *Chemical Abstracts,* Volume **76,** 1972). Each compound is listed under the parent name as it would appear in *Chemical Abstracts,* and each entry from Volumes **56** through **59** is followed by the registry number in brackets. Entries from Volumes **58** and **59** are, for the most part, taken from the appendices which follow the procedures. When the *Chemical Abstracts'* name differs in Collective Indices **8** and **9,** both names have been included. Some compounds in the appendices of this volume have been omitted from the index in accord with the guidelines given for **Part I.**

Each entry in both **Part I** and **Part II** is followed by the volume number or numbers in **bold-face type** and the page number on which the compound or subject is to be found. Entries in capital letters indicate compounds, reactions, or methods appearing in the title of the preparation.

PART I

(Names Used in These Volumes)

PART II

(Chemical Abstracts Systematic Nomenclature)

ORGANIC SYNTHESES

AN ANNUAL PUBLICATION OF SATISFACTORY METHODS FOR THE PREPARATION OF ORGANIC CHEMICALS

VOLUME 59

1979

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