ACID CHLORIDES FROM α-KETO ACIDS WITH α,α-DICHLOROMETHYL METHYL ETHER: PYRUVOYL CHLORIDE
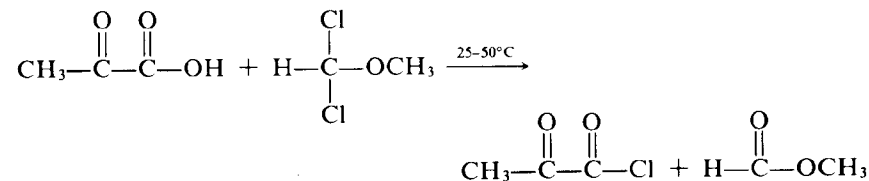
(Propanoyl chloride, 2-oxo-)

$$CH_3-\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}-OH \; + \; H-\underset{\underset{Cl}{|}}{\overset{\overset{Cl}{|}}{C}}-OCH_3 \xrightarrow{25-50°C}$$

$$CH_3-\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}-Cl \; + \; H-\overset{\overset{O}{\|}}{C}-OCH_3$$

Submitted by HARRY C. J. OTTENHEIJM and MARIANNE W. TIJHUIS[1]
Checked by LARRY A. LAST and ROBERT M. COATES

1. Procedure

A 100-mL, two-necked, round-bottomed flask is equipped with a magnetic stirrer, pressure-equalizing dropping funnel, and a 1.2- by 24-cm vacuum-jacketed Vigreux column which is connected to a condenser, vacuum-takeoff adapter, and fraction collector with three receiving flasks (Note 1). The vacuum-takeoff adapter is attached to a calcium chloride drying tube which is connected to a water aspirator, and the flask is charged with 35.2 g (28.6 mL, 0.40 mol) of pyruvic acid (Note 2). The pyruvic acid is stirred at room temperature as 46.4 g (36.1 mL, 0.40 mol) of α,α-dichloromethyl methyl ether (Note 3) is added slowly over 30 min. Evolution of hydrogen chloride begins after a few minutes. When the addition is complete, the dropping funnel is removed and replaced by a glass stopper. The solution is stirred and heated at 50°C in an oil bath for 30 min (Note 4) while a few drops of methyl formate are collected as the first fraction (Note 5). The condenser is then cooled to −30°C (Note 6) and the receiving flasks are cooled to −50°C with chilled acetone. The aspirator is turned on and the pressure is adjusted to 190 mm. With the oil bath at 50°C, a second fraction, bp 25–35°C (190 mm), is collected. As soon as the head temperature begins to drop, the pressure is reduced to 120 mm and the temperature of the oil bath is raised slowly to 75°C. A third fraction, bp 35–40°C (120 mm), consisting mainly of pyruvoyl chloride is collected (Notes 7 and 8). The second and third

fractions are combined to give 33–41 g of a mixture of pyruvoyl chloride and methyl formate which is redistilled through a 1.4- by 18-cm vacuum-jacketed Vigreux column (Note 1). The condenser and the receiving flasks are cooled to −5°C with chilled acetone. The first fraction, weighing 2.3–11.4 g and consisting mainly of methyl formate, is collected at 25–30°C (190 mm) with an oil bath temperature of 60°C. When the pressure is reduced to 120 mm and the oil bath is maintained at 60°C, 18.6–21.2 g (44–50%) of pyruvoyl chloride, bp 43–45°C (120 mm), distills into the receiver as a light yellow liquid, n_D^{20} 1.4165 (Notes 9 and 10).

2.   Notes

1. The glassware was dried for 16 hr in an oven at ca. 125°C and assembled while still warm. The checkers used a 27-cm Vigreux column insulated with glass wool instead of the vacuum-jacketed column.

2. Pyruvic acid, supplied by Aldrich Chemical Company, Inc., was freshly distilled: bp 59–62°C (14 mm).

3. α,α-Dichloromethyl methyl ether was purchased from Aldrich Chemical Company, Inc., and redistilled prior to use: bp 83–84°C. The reagent may also be prepared from methyl formate and phosphorus pentachloride.[2] Unlike chloromethyl methyl ether and bis(chloromethyl) ether, α,α-dichloromethyl methyl ether is reported to have no significant carcinogenic activity.[3] However, as a precaution, the compound should be handled with care in a well-ventilated hood.

4. At this temperature the intermediate, chloromethoxymethyl pyruvate, decomposes to pyruvoyl chloride and methyl formate.[4]

5. The submitters made no effort to collect methyl formate quantitatively. The checkers did not observe the formation of any condensate at this point.

6. This was accomplished by the checkers by passing acetone chilled with dry ice slowly through the condenser jacket. The coolant was contained in a 1-L separatory funnel which was connected to the condenser inlet with a section of Tygon tubing. The effluent was collected in a beaker and periodically returned to the separatory funnel reservoir.

7. Fractions 2 and 3 weighed 10.1–13.4 and 23.6–30.0 g, respectively. Proton NMR spectra of fraction 2 indicated a composition of 70–84% of methyl formate, 16–20% of pyruvoyl chloride, and 0–10%

of unreacted starting materials. The composition of fraction 3 was 21–28% of methyl formate, 60–70% of pyruvoyl chloride, and 1–20% of starting materials. The two fractions collected by the checkers boiled at 25–26°C (190 mm) and 40–46°C (120 mm).

8. For some reactions, such as simple esterification, it is not necessary to distill the acid chloride. The crude reaction mixture may be used provided the hydrogen chloride present is neutralized with an appropriate base.[5]

9. The submitters found that pyruvoyl chloride may be stored at −20°C in carbon tetrachloride solution or as the pure liquid in a sealed tube.

10. The product obtained by the checkers boiled at 48–51°C (120 mm) and was contaminated with ca. 5–10% of methyl formate and unreacted starting materials. The spectral properties of the product are as follows: IR (liquid film) cm^{-1}: 2900 (w), 1770 (s, broad), 1415 (m), 1355 (s), 1195 (s), 1130 (m), 1095 (m), 1005 (s), 875 (s); ^{1}H NMR (CDCl$_3$) δ: 2.51 (s, 3 H). The compound may be characterized as the p-nitroanilide derivative.[6]

3.   Discussion

Most of the conventional reagents for the synthesis of acid chlorides from carboxylic acids are unsatisfactory for the preparation of α-keto acid chlorides. For example, the reaction of pyruvic acid with phosphorus halides does not give pyruvoyl chloride[7] whereas the use of phosgene[8] or oxalyl chloride[9,10] affords ether solutions of the acid chloride in low yield. Recently a useful preparation of pyruvoyl chloride from trimethylsilyl pyruvate and oxalyl chloride has been described.[11]

The use of α,α-dichloromethyl alkyl ethers for the conversion of carboxylic acids to acid chlorides was first reported by Heslinga et al. in 1957.[4] The submitters have found that the readily available α,α-dichloromethyl methyl ether[2] is the reagent of choice for the preparation of pyruvoyl chloride.[6] This simple and economical procedure has been used in other laboratories,[5,12,13] and the submitters have applied the method to the preparation of three other α-keto acid chlorides: 2-oxobutanoyl chloride (32%), 3-methyl-2-oxobutanoyl chloride (10%), and phenylglyoxylyl chloride (78%).[6]

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

Pyruvic acid (8); Propanoic acid, 2-oxo- (9); (127-17-3)

α,α-Dichloromethyl methyl ether: Ether, dichloromethyl methyl (8); Methane, dichloromethoxy- (9); (4885-02-3)

Methyl formate: Formic acid, methyl ester (8,9); (107-31-3)

Pyruvoyl chloride (8); Propanoyl chloride, 2-oxo- (9); (5704-66-5)

ALIPHATIC AND AROMATIC β-KETOESTERS FROM MONOETHYL MALONATE: ETHYL 2-BUTYRYLACETATE

(Pentanoic acid, 4-methyl-3-oxo-, ethyl ester)

$$HO_2CCH_2CO_2C_2H_5 \xrightarrow[\text{(2) } (CH_3)_2CHCOCl]{\text{(1) } n\text{-BuLi, THF}} (CH_3)_2CHCOCH_2CO_2C_2H_5$$

Submitted by W. Wierenga and H. I. Skulnick[1]
Checked by Stefan Blarer, Daniel Wasmuth, and Dieter Seebach

1. Procedure

Ethyl 2-butyrylacetate. In a 1-L, three-necked, round-bottomed flask fitted with a mechanical stirrer, dry nitrogen inlet, and thermometer is placed 19.8 g (0.150 mol) of monoethyl malonate (Note 1), 350 mL of dry tetrahydrofuran (THF, Note 2), and 5 mg of 2,2′-bipyridyl. The solution is cooled to approximately −70°C (in an isopropyl alcohol–dry ice bath) and a 1.6 *M* solution of *n*-butyllithium in hexane is added from a dropping funnel while the temperature is allowed to rise to approximately −10°C. Sufficient *n*-butyllithium is added (approx. 190 mL) until a pink color persists for several minutes (Note 3). The heterogeneous solution is recooled to −65°C and 7.90 mL (7.98 g, 75 mmol) of isobutyryl chloride (Note 4) is added dropwise over 5 min. The reaction solution is stirred for another 5 min (Note 5) and then poured into a separatory funnel containing 500 mL of ether and 300 mL of cold, 1 *N* hydrochloric acid (Note 6). The funnel is shaken, the layers are separated, and the organic phase is washed with two 150-mL portions of saturated aqueous sodium bicarbonate, followed by 150 mL of water, and dried over anhydrous sodium sulfate. Removal of the solvents under reduced pressure leaves 11.70 g (98%) of ethyl 2-butyrylacetate (Note 7). The crude product can be distilled at 70–74°C (7 mm) (80% yield, 96% purity by GLC).

2. Notes

1. The potassium salt of monoethyl malonate, available from the Aldrich Chemical Company, Inc., can be used after neutralization. Direct

use of the potassium salt with only 1 equiv. of *n*-butyllithium gave substantially lower yields. Alternatively, monoethyl malonate can be conveniently prepared in high yield from diethyl malonate.[2]

2. For smaller-scale reactions, THF was dried and used directly by distillation from sodium/benzophenone, or first from KOH and then from LiAlH$_4$. The checkers used only dry THF for the present, large-scale procedure as well.

3. Initially, *n*-butyllithium can be added rapidly (20 mL/min) while the cooling bath is removed. A slightly exothermic reaction is noted. Toward the end of the reaction, dropwise addition should be used; the pink color will form and then dissipate. The checkers found it more convenient to use the calculated amount of a freshly titrated[3] solution of *n*-butyllithium.

4. Isobutyryl chloride was used as purchased from Aldrich Chemical Company, Inc., or Fluka AG.

5. Reaction times and temperatures vary, depending on the substrate acid chloride (see Table I).

6. For acid chlorides that contain a basic nitrogen, the aqueous phase is adjusted to approximately pH 7 by limiting the concentration of the hydrochloric acid.

7. Gas chromatographic analysis using a 3-ft, 3% OV-17 column at 90°C indicated a purity of 92% (retention time was 3.2 min) with GC–mass spectrometric identification showing M$^+$ *m/e* 158 (27%) and the base peak (100%) at *m/e* 113 (C$_6$H$_9$O$_2$). The ^{1}H NMR spectrum of undistilled material indicates impurities with resonances in the aliphatic region (δ : 1.5–1.0). The checkers recommend distillation of the crude product.

3. Discussion

Since the β-ketoester group is often a key moiety in organic syntheses, a general and efficient route to these 1,3-dicarbonyl compounds is highly desirable. We feel that the one-pot preparation from monoethyl malonate described here[4] represents an attractive alternative to previous methods[5] because of the following characteristics: (1) the reaction is general, as demonstrated by the diversity of examples in Table I; (2) the starting materials, (monoethyl malonate and the acid chlorides) are readily available and inexpensive; (3) the yields are high and therefore omission of

purification is possible in many instances; and finally (4) the reaction is simple and easy to scale up.

The optimum ratio for high yields of β-ketoester is 1.7 (monoethyl malonate : acid chloride). A nonstoichiometric reaction for optimum yield is not a serious drawback in this case since the reagent in excess is the inexpensive dilithio monoethyl malonate. Our results show that lowering the ratio also lowers the yield, whereas an increase in the ratio beyond 1.7 has little effect.

TABLE I
REACTION OF ACID CHLORIDES WITH DILITHIO MONOETHYL MALONATE
RCOCl → RCOCH$_2$CO$_2$C$_2$H$_5$

R	Reaction Time (min)/ Temperature (°C)	Yield (%)[a]
CH$_3$CH$_2$CH$_2$	5/ − 65	95
PhCH$_2$	5/ − 65	99
Ph	30/ − 65	97
4-CH$_3$OC$_6$H$_4$	60/ − 65	90
4-ClC$_6$H$_4$	30/ − 65	96
2-ClC$_6$H$_4$	30/ − 65	95
2-C$_{10}$H$_7$	30/ − 65	95
3-Furyl	15/ − 65, 60 to 0	97
2-Pyrazinyl	15/ − 65, 60 to 0	91

[a]The purity of all products isolated is higher than 90% as determined by GLC or ^{1}H NMR. The only contaminants appear to be hydrocarbons including *n*-octane.

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

Ethyl 2-butyrylacetate: Pentanoic acid, 4-methyl-3-oxo-, ethyl ester (9); (7152-15-0)

Monoethyl malonate: Malonic acid, monoethyl ester (8); Propanedioic acid, monoethyl ester (9); (1071-46-1)

2,2′-Bipyridyl: Bipyridine; 2,2′-Bipyridine (8); 2,2′-Bipyridine (9); (366-18-7)

n-Butyllithium: Lithium, butyl (8,9); (109-72-8)

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

Potassium monoethylmalonate: Malonic acid, monoethyl ester, potassium salt (8); Propanedioic acid, monoethyl ester, potassium salt (9); (6148-64-7)

PREPARATION OF 4-ALKYL- AND 4-HALOBENZOYL CHLORIDES: 4-PENTYLBENZOYL CHLORIDE

(Benzoyl chloride, 4-pentyl-)
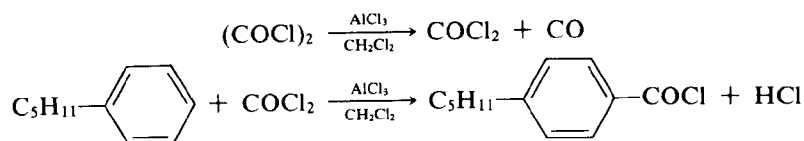
Submitted by MARY E. NEUBERT and D. L. FISHEL[1]
Checked by VINAY CHOWDHRY and R. E. BENSON

1. Procedure

Caution! Operations prior to vacuum distillation of the product should be done in a good hood since phosgene, carbon monoxide, and hydrogen

chloride are present (Note 1). Rubber gloves should also be used to avoid contact with the reagents.

A 100-mL, three-necked, round-bottomed flask is fitted with a mechanical stirrer, 100-mL pressure-equalized addition funnel (Note 2) to which is attached a drying tube (Note 3), and a rubber septum. Dry methylene chloride (27 mL, Note 4) and 8.9 g (0.067 mol) of aluminum chloride (Note 5) are added to the flask, stirring is begun, and 17.1 g (11.5 mL, 0.135 mol) of oxalyl chloride (Note 6) is added over 5 min by means of a syringe introduced through the septum (Note 7). The septum is replaced by a thermometer and a solution of 10 g (11.6 mL, 0.067 mol) of amylbenzene (Note 8) in 40 mL of dry methylene chloride is added dropwise over 1 hr with stirring while the temperature is maintained at 20–25°C. The reaction mixture is reduced to about half of the original volume by distillation of solvent and excess oxalyl chloride and/or phosgene (Note 9). Approximately 40 mL of fresh dry methylene chloride is added to the flask and the solution is cooled to 0°C in an ice–salt bath. The cold solution is slowly poured onto a stirred mixture of 170 g of crushed ice and 10 g of calcium chloride at a rate to maintain the temperature below 5°C (Note 10). The organic layer is rapidly separated from the aqueous layer and dried over anhydrous sodium sulfate. The mixture is filtered and the solvent is removed by distillation at reduced pressure. The residual liquid is dissolved in 50 mL of ether, and the resulting solution is cooled to 0°C, extracted with 5 mL of cold (0°C) 5% potassium hydroxide solution, and then washed twice with 15-mL portions of cold (0°C) water (Note 11). The ether solution is separated and dried over anhydrous sodium sulfate. The mixture is filtered and the solvent is removed by distillation at reduced pressure (Note 12). Distillation through a Vigreux column affords a small forerun and then 7.80–7.82 g (55%) of pure 4-pentylbenzoyl chloride, bp 95°C (0.20 mm) (Notes 13, 14). The acid chloride is stable if kept in a sealed container to prevent hydrolysis.

2. Notes

1. Both phosgene and carbon monoxide were identified in IR spectra of gases generated from an equimolar mixture of oxalyl chloride and aluminum chloride at room temperature.

2. The submitters used a constant addition funnel.

3. Molecular sieves 4A available from Davison Chemical Co. were used.

4. The submitters state that the use of predried methylene chloride (stored overnight over 4A molecular sieves) gave the best results.

5. Use of either an excess of aluminum chloride or partially hydrolyzed aluminum chloride gives larger amounts of the by-product diaryl ketone at the expense of the acid chloride. The checkers used freshly opened containers of the anhydrous material available from Fisher Scientific.

6. Oxalyl chloride should be distilled if it is colored or contains solid. Studies by the submitters have shown that an excess of oxalyl chloride is needed for maximum conversion of the alkylbenzene to acid chloride. The checkers used oxalyl chloride available from Eastman Organic Chemicals.

7. The submitters added the oxalyl chloride through the funnel used to add amylbenzene.

8. The checkers used product available from Aldrich Chemical Company, Inc.

9. If excess oxalyl chloride (and/or phosgene) is not removed, the vigorous reaction with water during decomposition of the aluminum chloride complex contributes to hydrolysis of the product acid chloride by increasing the time needed to complete this step. The more dilute solution achieved by additional solvent helps to prevent this hydrolysis as does maintenance of a low temperature during decomposition of the complex.

10. The calcium chloride–ice mixture helps to maintain a low temperature.

11. Changing the solvent to ether prior to the base extraction step (to remove carboxylic acid formed by hydrolysis) inhibits emulsion formation, particularly with the higher aliphatic-substituted products.

12. The procedure may be interrupted at this point if the crude acid chloride is protected from moisture, although highest yields are obtained if distillation is done at once. Failure to remove water (even that associated with the sodium sulfate drying agent) before storage may result in anhydride formation during distillation because of the presence of free carboxylic acid.

13. Infrared analysis (neat, film) shows a carbonyl doublet at 1740, 1770 cm^{-1}, typical of 4-substituted benzoyl chlorides and thought to be due to Fermi resonance.[2,3] Contamination of the product with the anhydride can be detected by a doublet at 1720 and 1780 cm^{-1}, with the ketone by a singlet at 1650 cm^{-1}, and with the acid by a singlet at 1690 cm^{-1}.

14. The submitters obtained the product in 75% yield.

3. Discussion

This method is based on that of Fahim,[4] who isolated 4-alkylbenzoic acids in 40–60% yields by hydrolysis of the corresponding acid chlorides. The present improved procedure includes those conditions believed to be optimum for a one-step synthesis of 4-substituted benzoyl chlorides in good yields and apparently free of positional isomers, as indicated by gas chromatography/mass spectroscopy as well as ^{1}H and ^{13}C NMR analyses. The procedure has been used successfully for the synthesis of 4-halobenzoyl chlorides and several other aryl acid chlorides,[5,6] as well as for 4-alkylbenzoyl chlorides up through the decyl derivative. Some of these results are summarized in Table I. The reaction has been run on a 1-mol scale by the submitters with no difficulty.

The major by-product that can be isolated (3–6%) from the residue after distillation is the 4,4'-disubstituted benzophenone; formation of the ketone is minimized by using excess oxalyl chloride and by slow addition of a dilute solution of the alkylbenzene to the acylating agent. Ambient temperatures (20–25°C) appear to give optimum results; higher temperatures favor ketone formation and lower temperatures result in incomplete reaction reasonable reaction times. This method cannot be used to prepare acid chlorides of aromatic systems which contain substituents strongly activating for electrophilic substitution such as alkoxy groups (major product is ketone), deactivating ring substituents (no reaction), or those

TABLE I
4-Substituted Benzoyl Chlorides from
Substituted Benzenes

Substituent	Yield (%)	bp (°C) (mm)
C_4H_9	66.5	113 (1.7)
i-C_4H_9	77.5	115 (1.6)
C_5H_{11}	75.3	136 (3.2)
C_6H_{13}	80.3	143 (1.3)
C_7H_{15}	79.3	160 (5)
C_9H_{19}	71.8	182 (2.6)
$C_{10}H_{21}$	68.0	169 (0.6)
F	84.4	50 (1.1)
Cl	77.7	86 (2.1)
Br	75.9	103 (2.5)
I	74.1	100 (0.7)

that form stable acylium ions (major product is carboxylic acid). Mesitoic acid rather than the acid chloride was isolated from the acylation of mesitylene using these conditions, which confirms the results previously reported using similar conditions.[7]

Previously, the most widely used method for preparation of 4-alkylbenzoyl chlorides on a laboratory scale has been from the benzoic acids obtained by oxidation of aromatic ketones, usually 4-alkylacetophenones.[8-14] The latter are usually prepared by acylating alkylbenzenes. Although this sequence gives high yields, it is lengthy (three completely separate steps) and the scale is restricted in the second step because of the large volumes required. The submitters state that they were unable to repeat the reported alkylation of toluic acid.[15] Methods that lead to formation of ortho and para isomeric intermediates are inconvenient since they require that the isomers be separated.[16-19]

This method provides easy access to 4-alkylbenzoyl chlorides, which are useful intermediates in the preparation of diaryl esters that have mesomorphic properties.[20] Benzoyl chlorides substituted in the 4-position also serve as starting materials for the preparation of aromatic aldehydes[21] and nitriles,[6,22] whereas the acids, derivable quantitatively from the acid chlorides, are good precursors via the Schmidt reaction to 4-substituted anilines.[23]

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

Oxalyl chloride (8); Ethanedioyl dichloride (9); (79-37-8)

Aluminum chloride (8, 9); (7446-70-0)

Benzene, pentyl (8, 9); (538-68-1)

Benzoyl chloride, 4-pentyl- (9); (49763-65-7)

BENZYL ISOCYANIDE: OXIDATION OF 5-AMINOTETRAZOLES

(Benzene, isocyanomethyl)
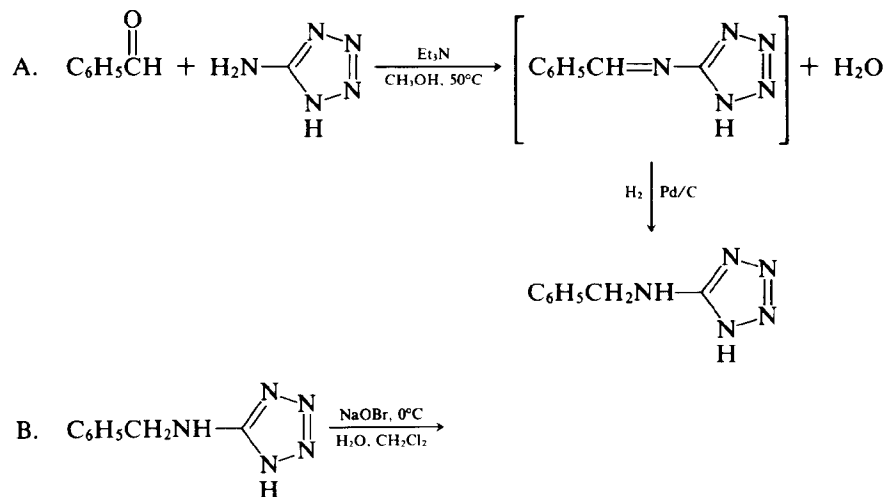
Submitted by Gerhard Höfle and Bernd Lange[1]
Checked by Orville L. Chapman and Thomas C. Hess

1. Procedure

Caution! This preparation should be conducted in an efficient hood because of the obnoxious odor of the isocyanide.

A. 5-Benzylaminotetrazole. Freshly distilled benzaldehyde (21.2 g, 0.2 mol) is added in one portion to a warm (50°C) solution of 5-aminotetrazole (17.2 g, 0.2 mol) (Note 1) and triethylamine (20.2 g, 0.2 mol) in 100 mL of absolute methanol. After 15 min the reaction mixture is cooled to room temperature, transferred to an autoclave, and hydrogenated with agitation at room temperature over Pd (10%) on carbon (1 g) for 18 hr at 500 psi of hydrogen. The catalyst is removed by filtration and all volatile material is removed at 60°C under aspirator pressure. The gummy tan solid is triturated with 250 mL of hot water. Aqueous 20% HCl is added until pH 3 is reached. The mixture is cooled to room temperature and the solid collected, washed with water, and dried over-

night at room temperature under reduced pressure (100 μ); yield: 27.5 g (80%), mp 183.5–185°C (lit.[2] mp 183°C).

B. Benzyl isocyanide. In a 500-mL, round-bottomed flask equipped with a magnetic stirring bar and a pressure-equalizing funnel are placed 5-benzylaminotetrazole (10.5 g, 60 mmol), 100 mL of 10% sodium hydroxide solution, and 70 mL of dichloromethane. The mixture is cooled to 0°C and a solution of NaOBr in water (165 mL, 65 mmol) (Note 2) is added with vigorous stirring over a 15-min period (Note 3). The dichloromethane layer is separated and the aqueous phase extracted with five 50-mL portions of dichloromethane. The combined dichloromethane extracts are dried over anhydrous MgSO₄, the drying agent is removed by filtration, and the dichloromethane is removed by simple distillation. The pressure is then reduced to ~20 mm with an aspirator and benzyl isocyanide is distilled at 98–100°C; yield: 5.91 g (84%) (Notes 4 and 5).

2. Notes

1. 5-Aminotetrazole monohydrate is available from Aldrich Chemical Company, Inc.; it was dehydrated by heating over P_2O_5 at 100°C under reduced pressure (100 μ) for 4 hr.

2. The NaOBr solution was prepared according to a procedure described in *Organic Syntheses*.[3] Bromine [12.6 g (4 mL, 79 mmol)] was added dropwise with vigorous stirring to 150 mL of a 10% NaOH solution at −10°C. Enough 10% NaOH solution was added to the yellow solution to give 200 mL of reagent.

3. During addition of the NaOBr solution the mixture warms to 20°C. The reaction is virtually instantaneous and can be monitored by the liberated nitrogen.

4. The product was pure by IR and NMR spectroscopy. The IR spectrum showed a very strong band at 2150 cm⁻¹, the NMR spectrum a broad singlet at δ 7.3 (5 H) and a distorted triplet at δ 4.5 (2 H).

5. Glassware can be freed from the odor of isocyanide by rinsing with a 1 : 10 mixture of concentrated hydrochloric acid and methanol.

3. Discussion

By this method high yields of isocyanides are obtained by an oxidation process. Since this oxidation can also be performed anodically or with

TABLE I

PREPARATION OF ISOCYANIDES (R—N≡C) BY OXIDATION OF 5-AMINOTETRAZOLES

| R | NaOBr[a] | Yield (%) | | Anodic Oxidation[a] |
		Pb(OAc)$_4$/NEt$_3$[b]	Br$_2$/NEt$_3$[b]	
C$_6$H$_5$	92	70	43	39
C$_4$H$_9$	75			
C$_6$H$_5$CH$_2$	84			48

[a] In 2 N sodium hydroxide solution.
[b] In dichloromethane.

bromine or lead tetraacetate and triethylamine in the absence of water (see Table I),[4] it represents a valuable alternative to other procedures: dehydration reactions,[5–7] the alkylation of silver cyanide[8,9] or the carbylamine (isocyanide) reaction.[10] The starting materials, 5-aminotetrazoles, can be readily obtained by reductive alkylation of 5-aminotetrazole[2] or from monosubstituted thioureas and sodium azide.[11] A limitation of the reaction is that the substituent R must be stable toward oxidation. From a mechanistic point of view the oxidation of 5-aminotetrazoles is a two-step process with a pentaazafulvene as an unstable, undetectable intermediate.

Benzyl isocyanide is a useful precursor of compounds containing the α-benzylamino moiety. Substituted styrenes, vinyl isocyanides, 2-oxazolines, 1-pyrrolines, imidazoles, and α-amino acids and ketones can be obtained by metalation of isocyanides with butyllithium[12] or copper salts,[13] and subsequent reaction with various electrophiles.[12]

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

Benzyl isocyanide (8); Benzene, (isocyanomethyl)- (9); (10340-91-7)

5-Benzylaminotetrazole: 1H-Tetrazole, 5-(benzylamino)- (8); 1H-Tetrazol-5-amine, N-(phenylmethyl)- (9); (14832-58-7)

5-Aminotetrazole: 1H-Tetrazole, 5-amino-(8); 1H-Tetrazol-5-amine (9); (4418-61-5)

5-Aminotetrazole monohydrate: 1H-Tetrazole, 5-amino-, monohydrate (8,9); (15454-54-3)

BIS(2,2,2-TRICHLOROETHYL) AZODICARBOXYLATE
[Diazenedicarboxylic acid, bis(2,2,2-trichloroethyl) ester]

A. $H_2NNH_2 \cdot H_2O + 2\ ClCO_2CH_2CCl_3 + Na_2CO_3 \rightarrow$
$$Cl_3CCH_2O_2CNHNHCO_2CH_2CCl_3 + 2\ NaCl + CO_2 + 2\ H_2O$$

B. $Cl_3CCH_2O_2CNHNHCO_2CH_2CCl_3 \xrightarrow[\substack{HNO_3 \\ (fuming)}]{[O]} Cl_3CCH_2O_2CN{=}NCO_2CH_2CCl_3$
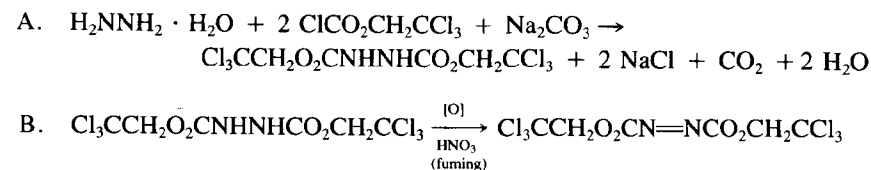
Submitted by R. DANIEL LITTLE and MANUEL G. VENEGAS[1,2]
Checked by SANDY BANKS and ORVILLE L. CHAPMAN

1. Procedure

A. Bis(2,2,2-trichloroethyl) hydrazodicarboxylate. In a 500-mL, three-necked flask equipped with mechanical stirrer, thermometer, and 250-mL and 125-mL dropping funnels (Note 1) is placed a solution of 13.34 g (0.23 mol) of 64% hydrazine hydrate (Note 2) in 60 mL of 95% ethanol. The reaction flask is cooled in an ice bath and 96 g (0.46 mol) of 2,2,2-trichloroethyl chloroformate (Note 3) is added dropwise so that

the temperature is kept below 20°C. During the addition of 1 equiv of the chloroformate, a white precipitate is formed. After exactly one-half of the chloroformate has been added, a solution of 25 g (0.24 mol) of sodium carbonate in 100 mL of water is added dropwise along with the remaining chloroformate. The rate of addition of these two reagents is such that the flow of the chloroformate is faster than that of the sodium carbonate so that there is always an excess of chloroformate present; the temperature is kept below 20°C during the addition. As the second equivalent of chloroformate is added the white precipitate dissolves.

After the addition of the reactants is complete, the reaction is allowed to stir for an additional 30 min while the solution warms to room temperature. The reaction mixture is then transferred to a separatory funnel. The viscous organic bottom layer is separated from the aqueous layer and is dissolved in 200 mL of ether. The reaction vessel is washed with 100 mL of ether, and this ether portion is used to extract further the aqueous layer. The ether layers are combined, dried over magnesium sulfate, and filtered, and the solvent is removed under reduced pressure. The viscous oil is allowed to crystallize in an ice bath (0°C). The crystals are collected on a Büchner funnel, washed with 500 mL of water, and dried in a vacuum desiccator at 0.5 mm for 48 hr. 80.8 g (93%) of white crystalline bis(2,2,2-trichloroethyl) hydrazodicarboxylate (mp 85–89°C) is obtained. This material is sufficiently pure for the next preparation. However, further purification can be achieved using an Abderhalden drying apparatus (refluxing 95% EtOH for 12 hr at 0.05 mm; MgSO$_4$ desiccant). Material purified in this way melted at 96.5–97.5°C (Notes 4 and 5).

B. *Bis(2,2,2-trichloroethyl) azodicarboxylate Caution! Large amounts of nitrogen oxides are evolved during the oxidation with fuming nitric acid. Therefore, operations should be conducted in an efficient fume hood.*

In a 500-mL, three-necked flask equipped with mechanical stirrer, thermometer, pressure-equalizing dropping funnel, and gas outlet tube is added 78.55 g (0.21 mol) of bis(2,2,2-trichloroethyl) hydrazodicarboxylate dissolved in 180 mL of chloroform (Note 6). The solution is cooled to 0°C and 53.2 mL (1.26 mol) of fuming nitric acid (Notes 7 and 8) is added so that the temperature of the solution does not rise above 5°C. The reaction mixture is then allowed to warm slowly to room temperature over 4 hr (Note 9). After an additional 2 hr at room temperature, the material is transferred to and shaken in a 1-L separatory funnel half filled

with ice chips. The two layers are allowed to separate and the bottom organic layer is removed. The aqueous layer is extracted with 250 mL of chloroform. The organic layers are combined and washed with 300 mL of water, 300 mL of aqueous 5% sodium bicarbonate, and again with 300 mL of water. The organic layer is dried with magnesium sulfate, filtered, and the solvent is removed under reduced pressure. The yellow crystals that form are collected on a Büchner funnel and washed with pentane. The pentane filtrate is concentrated under reduced pressure to afford more crystalline material which is again collected on a Büchner funnel and washed with more pentane. The cycle is repeated until no more crystals appear after removal of pentane. The yellow crystals so obtained are air dried for 1 hr to afford 59.2 g (75.8%) of bis(2,2,2-trichloroethyl) azodicarboxylate which melts at 108–110°C. Further drying using an Abderhalden drying apparatus (refluxing 95% EtOH for 12 hr at 0.5 mm; MgSO$_4$ desiccant) affords a compound that melts at 109–110.5°C (Notes 10 and 11).

2. Notes

1. The thermometer is fitted into one of the necks of the flask so that when it is immersed in the solution, the range between 10 and 20°C is easily visible. A two-necked adapter is used for the dropping funnels.

2. Hydrazine hydrate, 64%, practical grade, was obtained from Matheson, Coleman, and Bell.

3. 2,2,2-Trichloroethyl chloroformate (96%) is commercially available from Aldrich Chemical Company, Inc., and is used without further purification.

4. The average yield obtained for five runs performed by three different people was 83%.

5. The spectral properties of bis(2,2,2-trichloroethyl) hydrazodicarboxylate are as follows: ^{1}H NMR (CDCl$_3$) δ: 4.80 (s, 4 H, CH$_2$CCl$_3$), 7.0–7.6 (s, br, 2 H, −NH, the position is concentration dependent).

6. The solution can be warmed gently without harm to facilitate solution of the hydrazo compound.

7. Mallinckrodt fuming nitric acid (90–95%, d 1.5) was used.

8. The reaction seems to be surprisingly dependent on the amount of nitric acid used. A run with 78.6 g of hydrazo compound and a sixfold excess of nitric acid was quenched after 22 hr and afforded 100% conversion to the desired azo compound (NMR analysis). Another run with

80.0 g of hydrazo compound and a fivefold excess of nitric acid gave only 92% conversion after 25 hr. In another run with 2.0 g of hydrazo compound and a sixfold excess of nitric acid the reaction was complete after 4 hr. In addition, the oxidation was found to be temperature dependent. For example, in a run in which the temperature was maintained between 0 and 5°C for 3 hr and the solution was not allowed to warm to room temperature, only 18% yield was obtained (NMR analysis).

9. The evolution of large amounts of nitrogen oxides was noticed after approximately 1.5 hr (the temperature had reached 13°C).

10. Yields ranged from 76 to 94% (six runs performed by three different people).

11. The NMR spectrum (CDCl$_3$) for bis(2,2,2-trichloroethyl) azodicarboxylate shows only a singlet at δ 5.05.

3. Discussion

Bis(2,2,2-trichloroethyl) azodicarboxylate has been prepared by oxidation of bis(2,2,2-trichloroethyl) hydrazodicarboxylate with dinitrogen tetroxide.[3]

Bis(2,2,2-trichloroethyl) azodicarboxylate is a yellow crystalline material which is stable indefinitely in a vacuum desiccator stored in the dark. This compound offers a number of important advantages over diethyl and dimethyl azodicarboxylate for the synthesis of azo compounds. Probably the most important advantage is that in contrast to the ethyl and methyl esters, the trichloroethyl ester grouping can be removed under neutral conditions—a requirement when the product of the transformation is acid or base labile.[4] Furthermore, in contrast to dimethyl azodicarboxylate and diethyl azodicarboxylate, which have been known to explode when heated and which require distillation for purification, bis(2,2,2-trichloroethyl) azodicarboxylate is isolated as a crystalline solid requiring no heating whatsoever. Another advantage is that Diels-Alder cycloadducts with bis(2,2,2-trichloroethyl) azodicarboxylate are often crystalline solids which can be purified by recrystallization. This is in marked contrast to the viscous oils that are often obtained when the commercially available diethyl azodicarboxylate is used. Finally, we have found that Diels-Alder cycloadditions using bis(2,2,2-trichloroethyl) azodicarboxylate often proceed faster and at a lower temperature than that required for the dimethyl and diethyl analogues (e.g., reaction with 6,6-dimethylfulvene and 6-acetoxyfulvene).

1. Department of Chemistry, University of California, Santa Barbara, CA 93106.
2. The authors wish to thank Ahmed Bukhari for the data which he supplied for this publication.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Numbers)

Bis(2,2,2-trichloroethyl) azodicarboxylate: Diazenedicarboxylic acid, bis(2,2,2-trichloroethyl) ester (9); (38857-88-4)

Hydrazine hydrate: Hydrazine monohydrate (8, 9); (7803-57-8)

2,2,2-Trichloroethyl chloroformate: Formic acid, chloro-, 2,2,2-trichloroethyl ester (8); Carbonochloridic acid, 2,2,2-trichloroethyl ester (9); (17341-93-4)

Bis(2,2,2-trichloroethyl) hydrazodicarboxylate: 1,2-Hydrazinedicarboxylic acid, bis(2,2,2-trichloroethyl) ester (9); (38858-02-5)

SUBSTITUTED γ-BUTYROLACTONES
FROM CARBOXYLIC ACIDS AND OLEFINS:
γ-(*n*-OCTYL)-γ-BUTYROLACTONE

(2(3*H*)-Furanone, dihydro-5-octyl-)

$$4Mn(OAc)_2 \cdot 4H_2O + KMnO_4 + 8CH_3CO_2H \longrightarrow$$
$$5Mn(OAc)_3 \cdot 4H_2O + KOAc$$

$$Mn(OAc)_3 \cdot 4H_2O + 3(CH_3CO)_2O \longrightarrow Mn(OAc)_3 \cdot H_2O + 6CH_3CO_2H$$

$$2Mn(OAc)_3 \cdot H_2O + C_8H_{17}CH = CH_2 \xrightarrow{\text{NaOAc}}$$

$$+ 2Mn(OAc)_2 \cdot H_2O + HOAc$$
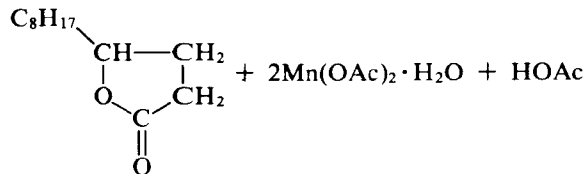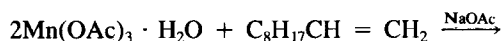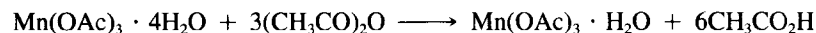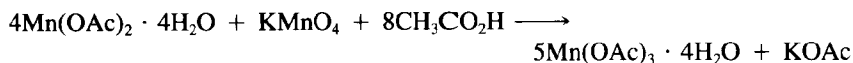
Submitted by E. I. Heiba, R. M. Dessau, A. L. Williams and P. G. Rodewald[1]
Checked by Gerald E. Lepone and Orville L. Chapman

1. Procedure

A 1-L, four-necked flask is fitted with a nitrogen inlet tube, stirrer, dropping funnel, and thermometer. Acetic acid (558 g) is introduced and 107.6 g (0.439 mol) of manganese acetate tetrahydrate (Note 1) is added with stirring and heating under nitrogen. When the temperature reaches 90°C, 16.5 g of solid potassium permanganate (0.104 mol) is added. After the temperature has again fallen to 90°C, 175 mL (189 g, 1.86 mol) of acetic anhydride (Note 2) is added. When the temperature rise has ceased, 44.0 g of 1-decene (0.312 mol) (Note 3) is introduced, followed at once by 250 g of anhydrous sodium acetate. The reaction mixture is then heated to reflux (134°C pot temperature). After 2 hr of reflux under nitrogen the reaction mixture, now clear yellow, is diluted with 1-L of water. The crude product is extracted into 200 mL of benzene, and the aqueous layer again washed with 100 mL of benzene. Benzene is distilled from the combined extracts to give 55.1 g of lactone and 1-decene. 1-Decene is removed by vacuum distillation, followed by the lactone, which distills at 98–99°C (0.05 mm) (Note 4). The yield of γ-(*n*-octyl)-γ-butyrolactone is 34.1 g (66% based on potassium perman-

ganate. However, the lactone yield based on olefin consumed is greater than 95%.)

2. Notes

1. The checkers used manganous acetate tetrahydrate obtained from Fisher Scientific Company. This compound is more readily available than manganous acetate dihydrate used by the submitters and obtained from the Harshaw Chemical Company.
2. If the dihydrate is used, only 76.7 g (0.751 mol) of acetic anhydride is required.
3. 1-Decene was used as obtained from the Humphrey Chemical Company.
4. The checkers found the yield based upon olefin consumed to be 85%. This discrepancy could be accounted for by losses due to the high volatility of 1-decene at reduced pressure.

3. Discussion

This method has the advantage that it does not require the preparation and purification of solid manganic acetate dihydrate. Dehydration by various ratios of acetic anhydride to manganese shows that in this procedure the yield (35%) from the monohydrate is greater than that from the manganic acetate dihydrate. Further removal of all water from the manganic acetate by means of acetic anhydride does not improve the yield (66%).

This general procedure can be used to prepare a wide variety of substituted γ-butyrolactones which depend on the structure of the olefin and the aliphatic acid used. The free radical mechanism and scope of this reaction are described in detail in a paper by Heiba, Dessau, and Rodewald.[2]

$$+ R_5CH_2COOH + 2Mn(OAc)_3 \longrightarrow$$

$$+ 2Mn(OAc)_2$$
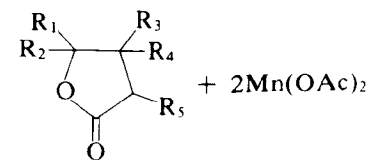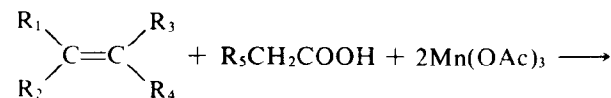
1. Mobil Research and Development Corporation, Central Research Division, P.O. Box 1025, Princeton, NJ 08540.
2. Heiba, E. I.; Dessau, R. M.; Rodewald, P. G. *J. Am. Chem. Soc.* **1974**, *96*, 7877–7981.

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

γ-(*n*-Octyl)-γ-butyrolactone: 2(3*H*)-Furanone, dihydro-5-octyl- (8, 9); (2305-05-7)

Acetic acid (8, 9); (64-19-7)

Manganese acetate tetrahydrate: Acetic acid, manganese(2 +) salt, tetrahydrate (8, 9); (6156-78-1)

Potassium permanganate; (7722-64-7)

Acetic anhydride (8); Acetic acid anhydride (9); (108-24-7)

1-Decene (8, 9); (872-05-9)

CHIRAL MEDIA FOR ASYMMETRIC SOLVENT INDUCTIONS. (*S,S*)-(+)-1,4-BIS(DIMETHYLAMINO)-2,3-DIMETHOXYBUTANE FROM (*R,R*)-(+)-TARTARIC ACID DIETHYL ESTER

(1,4-Butanediamine, 2,3-dimethoxy-*N,N,N',N'*-tetramethyl-[S,S]-)
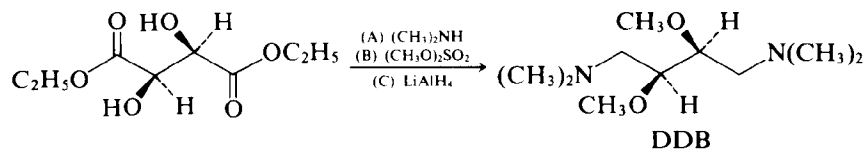
Submitted by Dieter Seebach, Hans-Otto Kalinowski, Werner Langer, Gerhard Crass, and Eva-Maria Wilka[1]

Checked by M. F. Semmelhack and Diane Facciolo

1. Procedure

A. (R,R)-(+)-N,N,N',N'-Tetramethyltartaric acid diamide.   Into a mixture of 618 g (3 mol) of diethyl tartrate (Note 1) and 600 mL of freshly distilled methanol in a 2-L Erlenmeyer flask is poured at least

450 mL (7 mol) of liquid, anhydrous, cold (− 78°C) dimethylamine (Note 2). The mixture is swirled briefly, and then allowed to stand in a hood for 3 days with a drying tube in place. After seeding (Note 3) and cooling in a refrigerator overnight, the massive crystals are collected by suction filtration. The filtrate is concentrated, seeded, and cooled to yield a second crop. The combined crystals are washed with cold methanol (− 30°C) and dried under reduced pressure at 70–100°C (oil bath). The diamide thus obtained is sufficiently pure to be used in the following step. The yield is 570–580 g (93–95%). Recrystallization from methanol/ethyl acetate furnishes an analytically pure sample, mp 189–190°C, [α]$_D$ +43° (ethanol, *c* 3.0)

B. (R,R)-(+)-2,3-Dimethoxy-N,N,N',N'-tetramethylsuccinic acid diamide.   Into a 4-L, three-necked, round-bottomed flask, fitted with a mechanical stirrer, reflux condenser, and stopper, are introduced 240 mL of 50% aqueous sodium hydroxide (3 mol), 1.5 L of methylene chloride, 0.2 g of benzyltriethylammonium chloride (TEBA), and then 260 g (2.06 mol) of dimethyl sulfate (Note 4). The mixture is stirred vigorously (Note 5), and a total of 204 g (1 mol) of the powdered tartaric acid diamide is added in portions at such a rate as to maintain refluxing (Note 6). Stirring is continued for 24 hr without heating, whereupon 1 L of water is added. Separation of the organic phase, extraction of the aqueous layer with three 300-mL portions of methylene chloride, drying of the combined organic solutions over sodium sulfate, and removal of the solvent in a rotary evaporator (bath temperature below 80°C, water aspirator vacuum) furnishes a slightly yellow oil which crystallizes at 25°C and is sufficiently pure for use in the following reduction step. Recrystallization from cyclohexane/benzene yields 220 g (95%, Note 7) of colorless prisms, mp 63.2–63.5°C, [α]$_D$ +116° (benzene, *c* 3).

C. (S,S)-(+)-1,4-Bis(dimethylamino)-2,3-dimethoxybutane (DDB). A 4-L, three-necked, round-bottomed flask is fitted with a heating jacket, mechanical stirrer, reflux condenser with drying tube, and a stoppered, pressure-equalizing dropping funnel, flushed with nitrogen or argon, and charged with 2.2 L of dry tetrahydrofuran (THF, Note 8) and 60 g (1.6 mol) of lithium aluminum hydride (LiAlH$_4$, Note 9). A mixture of 250 mL of THF and 232 g (1.0 mol) of the diamide is added, with stirring, at a rate sufficient to reach and maintain refluxing. After the addition is completed, the reaction mixture is kept boiling for 2 hr. The flask is immersed in an ice bath, and 60 mL of water, 180 mL of 10% aqueous potassium hydroxide, and again 60 mL of water are added cautiously with very vigorous stirring. The hydrogen gas that is generated is led

well above the stirring motor into the hood exhaust. Temporarily, the slurry becomes viscous and difficult to stir; during this period addition has to be made extremely carefully. The pale yellow, completely hydrolyzed slurry is filtered by suction, the filter cake extracted twice by refluxing with THF in a round-bottomed flask, and the combined solutions are concentrated in a rotary evaporator. The residual liquid is distilled through a 20-cm Vigreux column; bp 62–64°C (3 mm), yield 180 g (88%). For use in organometallic reactions, DDB is freshly distilled from LiAlH$_4$, $[\alpha]_D$ + 14.7° (neat), d_4^{20} 0.896 (Note 10).

2. Notes

1. Commercial (R,R)-$(+)$-diethyl tartrate can be used. The submitters prepared it from (R,R)-$(+)$-tartaric acid (Firma Benckiser, D-Ludwigshafen or Firma Boehringer, D-Ingelheim), $[\alpha]_D$ + 12.7° (water, c 17): a 4-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, water separator for organic solvents heavier than water, and a stopper is charged with 1.5 kg (10 mol) of tartaric acid, 1.5 L (26 mol) of 96% ethanol, 1 L of chloroform, and 30 g of freshly activated (1 N HCl), highly acidic ion exchange resin (Lewatit 3333). The stirred mixture is heated at reflux until no more water separates (up to 60 hr). Filtration, evaporation, and vacuum distillation (oil bath temperature must not exceed 145°C, no column, fast distillation) yield 1.85 kg (90%) of the ester, $[\alpha]_D$ + 8.16° (neat).

2. Dimethylamine (bp 6°C) is condensed into a 1-L flask cooled to −78°C and fitted with an inlet tube and an opening protected from atmospheric moisture with a silica gel drying tube. It is either taken from a cylinder or freed from 1.5 L of a stirred 40% aqueous solution by heating at 60–80°C with 50 g of potassium hydroxide and leading the amine vapors first through a reflux condenser, then through a 50-cm (2 cm I.D.) drying tube filled with potassium hydroxide pellets, and finally into the receiver flask cooled to −78°C.

3. Sometimes spontaneous crystallization occurs; if it does not, a small amount of the solution is withdrawn and evaporated on a watch glass, and the crystals that are obtained by scratching with a glass rod are used for seeding.

4. Dimethyl sulfate was purchased from Riedel de Haen, D-Seelze-Hannover, and used without purification. Because of its high toxicity and carcinogenicity, it should be handled only in a well-ventilated hood.

5. Since the reaction mixture becomes very gelatinous upon addition of the tartaric acid amide, a powerful motor and a large stirring blade are necessary.

6. Since dimethyl sulfate decomposes rapidly in concentrated alkaline medium, addition of the powdered tartaric acid amide must begin *immediately* after the dimethyl sulfate is introduced. The amide should be added *as fast as possible* (ca. 20–30 min) within the limits of the capacity of the reflux condenser and the mechanical stirrer. The amount of dimethyl sulfate can be increased up to 2.5 equivalents and fresh benzyltriethylammonium chloride can be added toward the end of the addition. With less rapid addition and stirring, the yield drops to 45–55%.

7. The yield obtained by the checkers was 78%.

8. Tetrahydrofuran (THF) was obtained from BASF AG, D-Ludwigshafen, and was distilled twice from potassium hydroxide pellets.

9. Lithium aluminum hydride (LiAlH$_4$) was used as a white powder purchased from the Metallgesellschaft AG, D-Frankfurt.

10. The specific rotation is highly sensitive to the water content of the DDB; only material distilled from LiAlH$_4$ shows this value.

3. Discussion

The three compounds whose syntheses are described in the present procedure have been reported previously by the submitters.[2,3]

The amino ether DDB has been used extensively as a chiral solvent for asymmetric syntheses.[2-8] It is readily available on a large scale in both enantiomeric forms: starting from the unnatural (S,S)-$(-)$-tartaric acid,[9] $(-)$-DDB is equally accessible[3] following the procedures described herein.

As demonstrated by the examples listed in Table I, DDB induces chirality in enantioface, enantiotope, and enantiomer differentiating[10] reactions in which it acts as a metal (Li, Mg, Cu, Zn) complexing ligand, as a hydrogen-bond mediating component, and as a base catalyst. It can be used at temperatures as low as −150°C if mixed with appropriate cosolvents.[3] It is readily recovered and separated from products by acid extraction during work-up. The enantiomeric excess (e.e.) obtained in this asymmetric induction is generally in the range of 10–20%; in optimized and/or fortuitous cases, optical yields of up to 50% have been obtained. The chemical yields are as high as in conventional achiral solvent systems. An application of DDB is described in the following *Organic Syntheses* procedure.

TABLE I
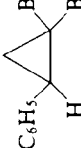### Asymmetric Syntheses with (+)-DDB as a Chiral Auxiliary Agent[2-8]
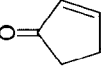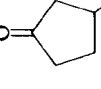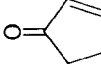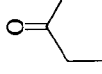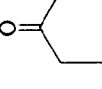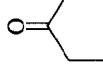
Reagents	Conditions (DDB : Reagent, Temp. °C, Solvent)	Product	$[\alpha]_D$ (Solvent, c) (%, e.e)
$C_6H_5CHO + Bu_2Mg$	2 : 1, −78, ether	$C_6H_5\overset{OH}{\underset{}{C}}HC_4H_9$	−2.5° (C_6H_6, 7.0) (8)
$C_6H_5CHO + BuLi$	10 : 1, −150, pentane	$C_6H_5\overset{OH}{\underset{}{C}}HC_4H_9$	+7° (neat) (40)
$C_6H_5CHO + i\text{-}PrLi$	4 : 1, −120, pentane	$C_6H_5\overset{OH}{\underset{}{C}}H\text{-}i\text{-}Pr$	+6.1° (ether, 7.5) (14)
$C_6H_5CHO + (C_6H_5S)_3CLi$	10 : 1, −78, pentane	$C_6H_5\overset{OH}{\underset{}{C}}HC(SC_6H_5)_3$	+23° (C_6H_6, 1.03) (12)
$C_6H_5CHO + CH_3\overset{NO}{\underset{}{N}}CH_2Li$	10 : 1, −78, pentane	$C_6H_5\overset{OH}{\underset{}{C}}HCH_2\overset{NO}{\underset{}{N}}CH_3$	+6.5 (CH_2Cl_2, 3.0) (14.8)
$C_6H_5CHO + CH_2{=}\overset{OLi}{\underset{}{C}}\!-\!O\text{-}t\text{-}Bu$	10 : 1, −78, pentane	$C_6H_5\overset{OH}{\underset{}{C}}HCH_2\overset{O}{\underset{}{C}}\!-\!O\text{-}t\text{-}Bu$	+5.1° (C_6H_6, 11.1)
$C_6H_5CHO + CH_2{=}\overset{OLi}{\underset{}{C}}NMe_2$	10 : 1, −78, pentane	$C_6H_5\overset{OH}{\underset{}{C}}HCH_2\overset{O}{\underset{}{C}}NMe_2$	+9.1° (C_6H_6, 12.4) (14)
$(C_6H_5)_2CO + CH_3CH{=}\overset{OLi}{\underset{}{C}}NMe_2$	10 : 1, −78, pentane	$(C_6H_5)_2\overset{OH}{\underset{}{C}}\!-\!\overset{CH_3}{\underset{}{C}}\!-\!\overset{O}{\underset{}{C}}\!-\!NMe_2$	+8.5° (C_6H_6, 11.3) (~22)
$C_6H_5COCH_3 + LiAlH_4$	−78, pentane	$C_6H_5\overset{OH}{\underset{}{C}}HCH_3$	+4.7° (neat) (11)
$C_6H_5CH{=}NC_6H_5 + $	3 : 1, −30, hexane		+15.5° (CH_2Cl_2, 18.7)
$+ Bu_2CuLi$	10 : 1, −78, ether		−10° (C_6H_6, 5.9)
$+ Bu_3ZnLi$	10 : 1, −78, ether		+6.9° (C_6H_6, 6.8)
$+ Bu_2CuLi$	10 : 1, −78, ether		−0.9° (C_6H_6, 11.5)
$+ Me_2CuLi$	10 : 1, −78, ether		−1.7° (neat) (13.6)

TABLE I (Continued)
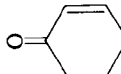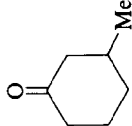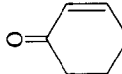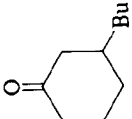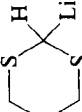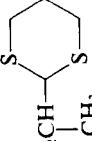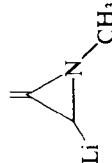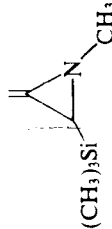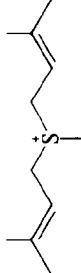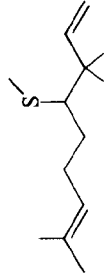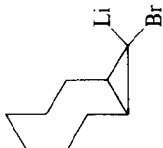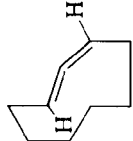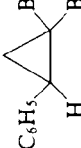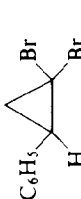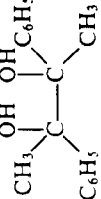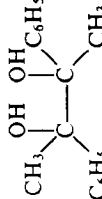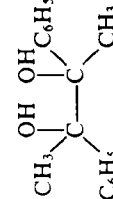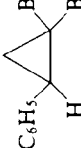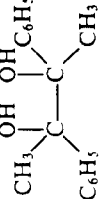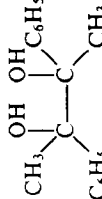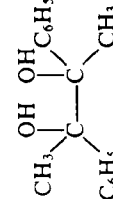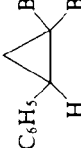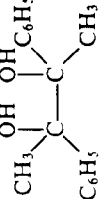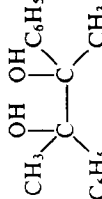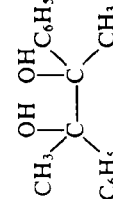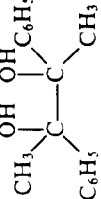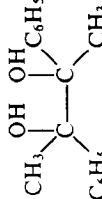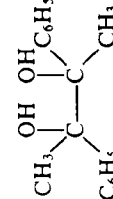
Reagents	Conditions (DDB : Reagent, Temp. °C, Solvent)	Product	$[\alpha]_D$ (Solvent, c) (%, e.e)
cyclohex-2-enone + Me$_3$ZnLi	10 : 1, −78, ether	3-methylcyclohexanone	−0.74° (C$_6$H$_6$, 6)
cyclohex-2-enone + Bu$_3$ZnLi	10 : 1, −78, ether	3-butylcyclohexanone	−1.0° (C$_6$H$_6$, 4.3)
CH$_3$CH=CHNO$_2$ + BuLi	10 : 1, −78, pentane	O$_2$NCH$_2$CHC$_4$H$_9$ / CH$_3$	+0.9° (C$_6$H$_6$, 10.4) (28)
CH$_3$CH=CHNO$_2$ + 1,3-dithiane (2-Li)	10 : 1, −78, pentane	O$_2$NCH$_2$CH(dithian-2-yl)CH$_3$	−4.3° (C$_6$H$_6$, 7.5) (45)
CH$_3$CH=CHNO$_2$ + H$_2$C=C(OLi)NMe$_2$	10 : 1, −78, pentane	O$_2$NCH$_2$CHCH$_2$CONMe$_2$ / CH$_3$	+0.7° (C$_6$H$_6$, 5.4) (10)
(CH$_3$)$_3$SiCl + N-methyl methyleneaziridinyllithium	9 : 1, −125, pentane	(CH$_3$)$_3$Si-substituted N-methyl methyleneaziridine	−27.5° (C$_6$D$_6$, 4.9) (12.4)
sulfonium ylide (CF$_3$) + C$_6$H$_5$CHOLi	−20, THF	allyl thioether product	+2.9 ± 0.3° [365 nm] (CHCl$_3$, 0.62) (12)
bicyclic Li/Br	10 : 1, −78, pentane	bicyclic H product	+8.2° (neat) (5)
C$_6$H$_5$,H-cyclopropane Br + ½ BuLi + H$_2$O	10 : 1, −100, pentane	C$_6$H$_5$,H-cyclopropane Br	+1.9° (neat)
C$_6$H$_5$COCH$_3$ + $h\nu$	7.5 : 1, −72, pentane	pinacol (OH OH / C$_6$H$_5$, CH$_3$)	+8.0° (C$_2$H$_5$OH, 5.0) (23.5)
C$_6$H$_5$COCH$_3$ + cathodic, electrochemical reduction	24, methanol	pinacol (OH OH / C$_6$H$_5$, CH$_3$)	+2.2° (C$_2$H$_5$OH, 5.0) (6.4)
C$_6$H$_5$COCH$_3$ + Li/naphthalene	6 : 1, 25,	pinacol (OH OH / C$_6$H$_5$, CH$_3$)	2.5° (C$_2$H$_5$OH, 5.0) (7.3)

TABLE I (Continued)

Reagents	Conditions (DDB : Reagent, Temp. °C, Solvent)	Product	$[\alpha]_D$ (Solvent, c) (%, e.e)
$C_6H_5CO\text{-}t\text{-}Bu + h\nu$	−30, neat DDB		$-1.2°[(C_2H_5)_2O, 5.0]$
(tetralone) $+ h\nu$	−35, pentane		$+22.3° (CHCl_3, 5.0)$
C_6H_5CO (pyridyl) $+ h\nu$	−15, neat DDB		$-20.0° (CH_3SOCH_3, 2.0)$
$C_6H_5CHO + C_6H_5CH_2COOH + AcOAc$	6 : 1, −25	$C_6H_5\overset{OAc}{C}H\underset{C_6H_5}{C}HCOOH$	diastereomer a $+5.0°$, diastereomer b $+26.0°$ (C_2H_5OH, 3)

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TABLE II

Comparison of TMB[a] with DDB[b] Used as Cosolvents in the Addition of n-Butyllithium to Various Aldehydes at −78°C in Pentane[3]

$$RCHO + C_4H_9Li \rightarrow RCH(OH)C_4H_9$$

R	e.e. (%)		Sense of Rotation, Absolute Configuration
	with TMB[a]	with DDB[b]	
CH_3	1.2	7.5	(+)-S
C_2H_5	8.8	11.5	(+)-S
$i\text{-}C_3H_7$	18.0	19.0	(+)-R
$t\text{-}C_4H_9$	22.8	13.5	(+)-R
$(C_2H_5)_2CH$	20.0	19.0	(+)
$c\text{-}C_6H_{11}$	25.0	22.5	(+)-R
C_6H_5	30.0	19.0	(+)-R
$4\text{-}CH_3\text{-}C_6H_4$	32.5	11.5	(+)
$2\text{-}CH_3\text{-}C_6H_4$	45.3	10.5	(+)
$2,4,6\text{-}(CH_3)_3\text{-}C_6H_2$	23.0	2.3	(+)

[a]TMB = $(S,S)\text{-}(-)\text{-}1,2,3,4$-tetramethoxybutane.
[b]DDB = $(S,S)\text{-}(+)\text{-}1,4$-bis(dimethylamino)-2,3-dimethoxybutane.

Another chiral cosolvent, which is less readily separated from low boiling and/or water soluble products and which is somewhat less stable toward organolithium reagents, is $(S,S)\text{-}(-)\text{-}1,2,3,4$-tetramethoxybutane (TMB).[3] As is shown in Table II, it is a cosolvent that is superior to DDB in differentiating between the enantiotopic faces of aldehydes with organolithium reagents.[3] Finally, the octamethyl-1,4-diamino-2,3-bis(2-aminoethoxy)butane (DEB)[5] can be used in a 2 : 1 ratio with alkyllithium reagents to produce carbinols in even higher enantiomeric yields.

DDB, TMB, and DEB are far superior to other neutral chiral auxiliary agents used in the same reactions.[3,10–13]

1. Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, ETH-Zentrum, Universitätstrasse 16, CH-8092-Zürich and Institut für Organische Chemie der Justus Liebig-Universität, Giessen, Fachbereich 14, Heinrich-Buff-Ring 58, D-6300-Giessen.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); Registry Number

(*S,S*)-(+)-1,4-Bis(dimethylamino)-2,3-dimethoxybutane [DDB]: 1,4-Butanediamine-2,3-dimethoxy-*N,N,N',N'*-tetramethyl-,(*S,S*)-(+)- (8): 1,4-Butanediamine, 2,3-dimethoxy-*N,N,N',N'*-tetramethyl-[*S,S*]- (9); (26549-21-3)

(*R,R*)-(+)-Tartaric acid diethyl ester; Diethyl tartrate: Tartaric acid, diethyl ester, (*R*)-(+)-; Tartaric acid, diethyl ester, (+)- (8); (608-84-4)

(*R,R*)-(+)-*N,N,N',N'*-Tetramethyltartaric acid diamide: Tartramide, *N,N,N',N'*-tetramethyl-(+)- (8); Butanediamide,2,3-dihydroxy-*N,N,N',N'*-tetramethyl-[*R*-[*R,R*]- (9); (26549-65-5)

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

(*R,R*)-(+)-2,3-Dimethoxy-*N,N,N',N'*-tetramethylsuccinic acid diamide: Succinamide, 2,3-dimethoxy-*N,N,N',N'*-tetramethyl-(+)- (8); Butanediamide, 2,3-dimethoxy-*N,N,N',N'*-tetramethyl-[*R,R*]- (9): (26549-29-1)

Benzyltriethylammonium chloride: Ammonium, benzyltriethyl-, chloride (8); Benzenemethanaminium, *N,N,N*-triethyl-, chloride (9); (56-37-1)

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

(*R,R*)-(+)-Tartaric acid: L-(+)-Tartaric acid; (+)-Tartaric acid (8); (87-69-4)

(*S,S*)-(−)-Tartaric acid (8); Butanedioic acid, 2,3-dihydroxy-[*S,S*]- (9); (147-71-7)

CYANIC ACID ESTERS FROM PHENOLS: PHENYL CYANATE

(Cyanic acid, phenyl ester)

$$\text{Br}_2 + \text{NaCN} \xrightarrow[-5 \text{ to } 5^\circ\text{C}]{\text{H}_2\text{O}} \text{BrCN}$$

$$\text{BrCN} + \text{C}_6\text{H}_5\text{OH} \xrightarrow[\text{CCl}_4, -5 \text{ to } 10^\circ\text{C}]{(\text{C}_2\text{H}_5)_3\text{N}} \text{C}_6\text{H}_5\text{OCN}$$
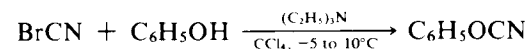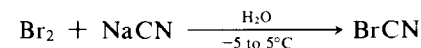
Submitted by D. Martin[1] and M. Bauer
Checked by E. R. Holler, Jr. and R. E. Benson

1. Procedure

Caution! These operations, which involve toxic reagents, should be conducted in an efficient hood.

A 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, thermometer, and a 200-mL pressure-equalizing dropping funnel with a stopper is charged with 160 g (50.9 mL, 1.0 mol) of bromine (Note 1) and 150 mL of water. The mixture is stirred rapidly while cooling in an ice–salt bath to −5°C, and a solution of 49.0 g (1.0 mol) of sodium cyanide in 150 mL of water is added dropwise over a 40–50 min period while maintaining the temperature of the reaction mixture at −5 to 5°C. The resulting solution is stirred an additional 5–10 min (Note 2). A solution of 89.5 g (0.95 mol) of phenol in 300 mL of tetrachloromethane (Note 3) is added in one portion to the flask. The resulting mixture is stirred vigorously while 96.0 g (131 mL, 0.95 mol) of triethylamine is added dropwise over a 30–40 min period at such a rate that the temperature does not exceed 5–10°C. After an additional 15 min of stirring, the mixture is transferred to a separatory funnel, the organic phase is separated and the aqueous layer is extracted twice with 50-mL portions of tetrachloromethane. The organic phases are combined and washed three times with 50-mL portions of water and then dried over polyphosphoric anhydride (Note 4). The drying agent is removed by filtration and the solvent is removed by distillation under reduced pressure using a rotary evaporator at 20°C (25 mm). A few drops of polyphosphate ester (Note 5) are added to the remaining liquid and the product is distilled through a 20-cm Vigreux column to give 85–96 g (75–85%) of phenyl cyanate,

bp 77–79° (13 mm), n_D^{20} 1.5094–1.5100, d_4^{20} 1.096. The product is a colorless liquid with a pungent odor (Note 6).

2. Notes

1. The chemicals used were commercially available products and were used without further purification. The checkers used sodium cyanide, phenol, and tetrachloromethane from Fischer Scientific Company, bromine from Matheson, Coleman and Bell, phosphoric anhydride from J. T. Baker Chemical Co., and triethylamine from Eastman Organic Chemicals.

2. The solution should develop a yellowish color.

3. The procedure can also be conducted using other water immiscible solvents such as ether, trichloromethane, and benzene.[2]

4. Other drying agents such as anhydrous calcium chloride can also be used. The desiccation must be done carefully since water is soluble in the product in the presence of phenol and may cause trimerization of the cyanate to a 1,3,5-triazine derivative.

5. A few drops of polyphosphate ester are a good drying agent and stabilizer.[3] The ester may be prepared by heating polyphosphoric anhydride in dry ether and trichloromethane for 40 hr followed by removal of the solvent.[4] The checkers found that the use of polyphosphate ester was essential to obtain the described yield.

6. The spectral properties of phenyl cyanate are as follows. IR(CCl$_4$) cm^{-1}: 2235 (m), 2261 (m), 2282 (S) ($\nu_{C\equiv N}$).[5] UV (cyclohexane) nm max (log ϵ): 216 (3.21), 256 (2.58), 262 (2.75), and 268 (2.67).[6] The product was further characterized by vapor phase chromatography analysis using a 200-cm column containing 10% SE 52 on Chromosorb W/AW/DMCS at 140°C with a hydrogen flow rate of 70 mL/min and a retention time of 1.47 min.

3. Discussion

Although isocyanates have been known for some time, the isomeric cyanates were unknown until 1964. The latter were first prepared almost simultaneously by two different methods: (1) thermolysis of 5-aryl- or 5-alkyloxy-1,2,3,4-thiatriazoles[6,7] and (2) by reaction of phenols or alcohols with cyanogen halides.[8] Since their synthesis, cyanates have ac-

quired considerable synthetic significance.[9–14] The simplified procedure described here for preparation of phenyl cyanate is a combination of the preparation of cyanogen bromide[15] and the cyanation of phenol in the presence of a base.[8] This procedure is also applicable to many other phenols, bisphenols, naphthols, and some acidic alcohols. Examples are given in Table I.

Aryl cyanates have activated cyano groups and undergo many reactions.[14] They are effective dehydrating and hydrogen sulfide-bonding agents in organic synthesis.[9–11,13,14] N-, O-, and S-nucleophiles (HX) add to the carbon atom of the cyano group to form the corresponding carbonic

$$\overset{\displaystyle X}{\underset{|}{}}$$

acid imide esters (ArO—C=NH).[9–11,13,14] Transfer of the cyano group to a number of carbon nucleophiles also occurs.[9–11,13,14] Acyl halides (AcCl) add to the nitrogen atom of the cyano group to give N-acylated carbonic

$$\overset{\displaystyle Cl}{\underset{|}{}}$$

acid imide chlorides (ArO—C=N—Ac).[12–14] These compounds are useful starting materials for syntheses of heterocyclic compounds. The cyanates also undergo 1,3- and 1,4-dipolar cycloadditions involving the cyano group to give substituted azoles and azines.[9–11,13,14] Polycyclic trimerization of dicyanates to poly-s-triazines is of considerable importance.[16–18]

TABLE I
CYANATES FROM HYDROXY COMPOUNDS

Hydroxy Compound	Cyanate	mp (°C) (bp, °C/mm)	Yield (%)
2-CH$_3$C$_6$H$_4$OH	2-CH$_3$C$_6$H$_4$OCN	(88–90/10)	81
4-CH$_3$C$_6$H$_4$OH	4-CH$_3$C$_6$H$_4$OCN	(90–91/10)	87
4-CH$_3$OC$_6$H$_4$OH	4-CH$_3$OC$_6$H$_4$OCN	22–26 (118–119/10)	91
2-ClC$_6$H$_4$OH	2-ClC$_6$H$_4$OCN	(112–113/13)	81
4-ClC$_6$H$_4$OH	4-ClC$_6$H$_4$OCN	38–39 (100–101/10)	87
2-CH$_3$OCOC$_6$H$_4$OH	2-CH$_3$OCOC$_6$H$_4$OCN	58–60	84
2-Naphthyl-OH	2-Naphthyl-OCN	(162–164/12)	95
4-NCOC$_6$H$_4$OH	4-NCOC$_6$H$_4$OCN	107–109	98
CCl$_3$CH$_2$OH	CCl$_3$CH$_2$OCN	(77–78/10)	75
CF$_3$CH$_2$OH	CF$_3$CH$_2$OCN	(29–30/13)	81

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

Bromine (8, 9); (7726-95-6)

Sodium cyanide (8, 9); (143-33-9)

Cyanogen bromide (CNBr) (8, 9); (506-68-3)

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

Carbon tetrachloride (8); Methane, tetrachloro- (9); (56-23-5)

Phenol (8, 9); (108-95-2)

Cyanic acid, phenyl ester (8, 9); (1122-85-6)

Phosphorus pentoxide [P₂O₅]: Phosphorus oxide (8, 9); (1314-56-3)

1,6-DIMETHYLTRICYCLO[4.1.0.0²·⁷]HEPT-3-ENE
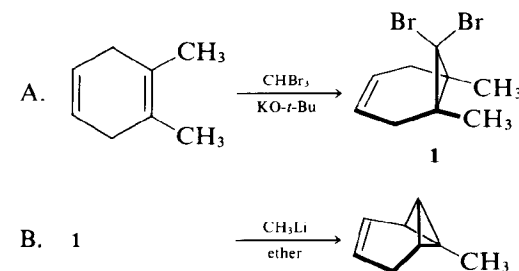
Submitted by R. T. TAYLOR[1] and L. A. PAQUETTE[1]
Checked by DAVID A. CORTES and M. F. SEMMELHACK

1. Procedure

A. *7,7-Dibromo-*1*,6-dimethylbicyclo*[4.1.0]*hept-3-ene.*   Into a 3-L, three-necked flask equipped with an overhead stirrer, 1-L addition funnel, and reflux condenser capped with a nitrogen inlet tube are introduced 44.8 g (0.4 mol) of powdered potassium *tert*-butoxide (Note 1) and 1 L of olefin-free petroleum ether (bp 35–55°C; Note 2). To this stirred mixture is added a solution containing 38.0 g (0.35 mol) of 1,2-dimethyl-1,4-cyclohexadiene (Note 3) in 200 mL of the same solvent. With external cooling from an ice bath and under nitrogen, 102.4 g (0.4 mol) of bromoform in 400 mL of petroleum ether is added dropwise during 1 hr. The ice bath is removed and the resultant slurry is stirred at room temperature under nitrogen for 6 hr. Water (500 mL) is added and the mixture is poured into a 3-L separatory funnel containing 300 mL of benzene. The organic layer is washed with four 500-mL portions of water, dried over anhydrous magnesium sulfate, and concentrated on a rotary evaporator (Note 4). Further evacuation at 0.5 mm produces a solid which is recrystallized from ether–petroleum ether (1 : 3) to afford 55–62 g (56.5–63.5%) of colorless solid, mp 95–98°C (Note 5).

B. 1*,6-Dimethyltricyclo*[4.1.0.0²·⁷]*hept-3-ene.*   A solution of 20.95 g (0.075 mol) of 7,7-dibromo-1,6-dimethylbicyclo[4.1.0]hept-3-ene in 500 mL of anhydrous ether is placed in a 1-L, three-necked flask equipped with a magnetic stirring bar, reflux condenser, addition funnel, and nitrogen inlet tube. With stirring under nitrogen and external cooling in an

ice bath, 50mL of 1.6 M ethereal methyllithium (Note 6) in 70 mL of ether (0.08 mol) is introduced by dropwise addition during 30 min. The ice bath is removed and the mixture is stirred at room temperature for 1 hr. After 100 mL of water has been cautiously introduced, the mixture is transferred to a separatory funnel and the organic layer is separated. This solution is washed with water (3 × 100 mL), dried over anhydrous sodium sulfate (Note 7), and carefully concentrated by slow distillation through a 40-cm Vigreux column at atmospheric pressure, heating at <60°C (Note 8). The residual liquid is distilled through a short, unpacked column to give 4.2–4.4 g (46–49%) of colorless oil, bp 48–49°C (23 mm) (Note 9). Under the proper conditions, this hydrocarbon can be stored for 2 weeks at −5°C without deterioration.

2. Notes

1. Potassium *tert*-butoxide can be obtained commercially from MSA Research Corporation, Callery, Pennsylvania. The checkers used a sample from Aldrich Chemical Company, Inc.

2. A liter of technical grade petroleum ether was treated in a separatory funnel with 200 mL of concentrated sulfuric acid, washed with water, and dried over anhydrous magnesium sulfate.

3. This diene was prepared by the procedure of Paquette and Barrett[2]; satisfactory results can be realized with material of 70–85% purity (15–30% contamination by *o*-xylene) since the aromatic impurity does not react subsequently and is easily removed.

4. Any residual *o*-xylene should be removed prior to crystallization because the dibromide is exceedingly soluble in aromatic solvents.

5. Further recrystallization is not necessary, but pure crystals, mp 107–108°C, can be obtained in the manner described by Vogel and co-workers.[3]

6. The ethereal methyllithium solutions were purchased from Alfa Inorganics. The concentration of methyllithium in such solutions may be conveniently determined by a procedure described elsewhere[4,5] in which the lithium reagent is titrated with *sec*-butyl alcohol, utilizing the charge transfer complex formed from bipyridyl or *o*-phenanthroline and the lithium reagent as indicator.

7. Anhydrous magnesium sulfate is too acidic for this purpose and promotes rearrangement of the hydrocarbon.

8. All glassware that is to contain the cyclized product should be washed in base and dried (where necessary) prior to use.

9. The checkers found bp 55–56°C/ 30 mm. Attempted distillation at

ca. 50 mm (bp 75°C) led to significant rearrangement to a dimethylcycloheptatriene. The product exhibits the following ^{1}H NMR spectrum (CDCl$_3$) δ:1.08 (s, 3 H, CH$_3$), 1.33 (d, 1 H, $J = 2$, methine C—H), 1.52 (s, 3 H, CH$_3$), 2.15–1.80 (m, 3 H, allylic methylene and methine), 5.50–5.15 (m, 1 H, olefinic C—H), 6.10–5.70 (m, 1 H, olefinic C—H).

3. Discussion

The tricyclo[4.1.0.0^{2,7}]hept-3-ene ring system, with its conjugated bicyclobutane ring and double bond and its isomeric relationship to cycloheptatriene, has recently commanded attention as a precursor of yet more highly strained molecules. However, the preparation of the parent hydrocarbon by reaction of 7,7-dibromo-3-norcarene with methyllithium at 0°C, first reported by Klummp and Vrielink,[6] does not proceed in yields above 1–5%.[6,7] Placement of a single methyl group at a ring juncture position of the transient norcarenylidene intermediate is, however, adequate to promote efficient ring closure through C—H alpha insertion.[7,8] The procedure described above is exemplary. Although two alternative routes to tricyclo[4.1.0.0^{2,7}]hept-3-enes are currently available,[6,9] alkyllithium-promoted cyclization of readily available 7,7-dibromobicyclo[4.1.0]hept-3-enes constitutes the most direct and efficient approach. In addition, this procedure illustrates an entirely general method for converting norcarane derivatives to *endo,endo*-1,3-bridged bicyclobutanes.[10–12]

Exposure of tricyclo[4.1.0.0^{2,7}]hept-3-enes to catalytic amounts of Ag$^+$ leads instantaneously and quantitatively to cycloheptatriene derivatives.[7] Promise of their usefulness as synthetic intermediates is growing rapidly.[13,14]

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

1,6-Dimethyltricyclo[4.1.0.0^{2,7}]hept-3-ene (9); ($-$)

Methyllithium (8, 9); (917-54-4)

1,2-Dimethyl-1.4-cyclohexadiene: 1,4-Cyclohexadiene, 1,2-dimethyl- (8, 9); (17351-28-9)

7,7-Dibromo-1,6-dimethylbicyclo[4.1.0]hept-3-ene: Bicyclo[4.1.0]hept-3-ene, 7,7-dibromo-1,6-dimethyl- (9); (38749-43-8)

Bromoform: Methane, tribromo- (8, 9); (75-25-2)

ENANTIOSELECTIVE ADDITION OF BUTYLLITHIUM
IN THE PRESENCE OF THE CHIRAL COSOLVENT DDB.
(+)-(R)-PHENYL-1-PENTANOL

[Benzenemethanol, α-butyl-, (R)-]
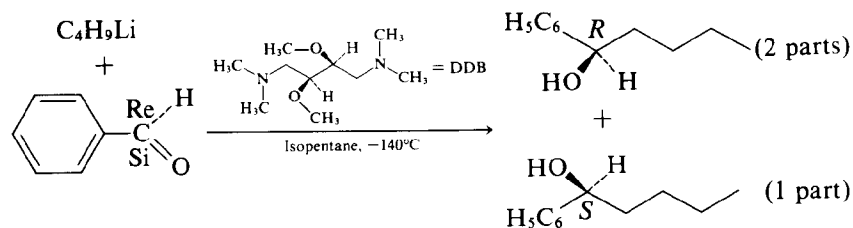
Submitted by DIETER SEEBACH and AUGUST HIDBER[1]
Checked by M. F. SEMMELHACK and CHARLES SHUEY

1. Procedure

As shown in Figure 1, a dry, 1-L, three-necked flask is equipped with an overhead stirrer bearing a four-bladed propeller of ca. 2.5-cm diameter

driven by a strong, safely connected motor A (Note 1), a rubber septum, and a three-way stopcock. The air in the flask is replaced by dry argon or nitrogen, the pressure of which is maintained during the reaction at ca. 50 mm above atmospheric pressure with a mercury bubbler (Note 2). A second stirrer (motor B, Figure 1) to agitate the baths is attached next to the flask with the propeller just below the bottom of the flask. Finally, a 4.5- × 20-cm test tube is held next to the bath stirrer. The entire apparatus (Figure 1) is mounted well above the bench to allow for immersion of the flask, bath stirrer, and tube into cooling baths and for exchange of bulky bath containers with the aid of a lab-jack. The flask
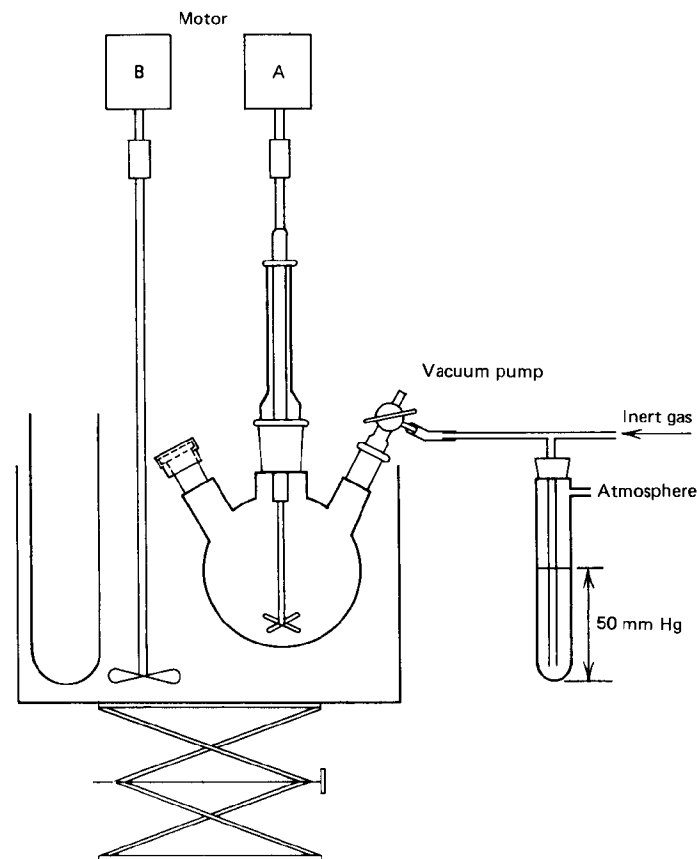
Figure 1

is charged (Note 3) with 400 mL of 2-methylbutane (isopentane) (Note 4) and 24.6 g (27.5 mL, 0.12 mol) of (S,S)-$(+)$-N,N,N',N'-tetramethyl-1,4-diamino-2,3-dimethoxybutane (DDB) (Note 5). A methanol–dry ice bath is raised to immerse the flask and cool the contents to $-78°C$ with slow stirring, whereupon 0.021 mol of butyllithium (13.5 mL of a 1.56 M solution in hexane) (Note 6) is added within a few minutes. A second cooling bath is prepared in a ca. 7-L Dewar cylinder (Note 7) by pouring liquid nitrogen into a stirred (glass rod) mixture of methylcyclohexane/isopentane (3 : 2) (Note 8) until about half of the liquid has solidified and a slush has been formed, the temperature of which is ca. $-140°C$ (Note 9). The reaction flask is cooled to the lower temperature by exchanging baths and waiting for 15 min with bath stirring. The bath is temporarily lowered and cooled until again half frozen by pouring in liquid nitrogen with manual agitation (Note 10). From now on, cooling is kept constant by filling the tube in the stirred bath at intervals with liquid nitrogen (Note 10). A solution of 2.12 g (0.020 mol) of benzaldehyde (Note 11) in 20 mL of isopentane (Note 4) is added dropwise (Note 12) over 15 min to the vigorously stirred (ca. 1000 rpm) reaction mixture. After completion of the addition (ca. 0.5 hr), the bath is removed, the flask is warmed to ca. 0°C (Note 13), and the contents are poured into a 1-L separatory funnel containing 150 mL of ice-cold 2 N aqueous hydrochloric acid. The aqueous layer is extracted twice with 70 mL of hexane and saved for recovery of the chiral auxiliary agent DDB (Note 14). The combined organic layers are sequentially washed with saturated aqueous bicarbonate and sodium chloride solutions and concentrated in a rotary evaporator to ca. 200 mL. The solution is then transferred to a 500-mL separatory funnel and vigorously shaken with 40 mL of a saturated aqueous sodium bisulfite solution to precipitate the bisulfite adduct of unreacted benzaldehyde (Note 15). After filtration (if necessary) the residue and the aqueous phase are washed with hexane. The combined organic solution is dried over anhydrous magnesium sulfate and concentrated by rotary evaporation. Simple distillation yields 2.60–2.95 g (80–90%) of 1-phenyl-1-pentanol, bp 54–56°C (0.02 mm)$[\alpha]_D = 6.13°$ (neat) (Note 16), optical yield 30% (Note 17).

2. Notes

1. The checkers used a conventional, flat, crescent-shaped Teflon blade, 8 cm long.

2. This is done as previously described in *Organic Syntheses* procedures: Seebach, D.; Beck, A. K. *Org. Synth.* **1971**, *51*, 39, 76; Enders, D.; Pieter, R.; Seebach, D. *Org. Synth.* **1978**, *58*, 113. All connections should be securely fastened.

3. All additions of solvents and reagents are carried out through the rubber septum with dry, appropriately sized, and argon-flushed syringes with hypodermic needles. Because of its low boiling point, it is advantageous to force isopentane into the 100-mL syringe by applying pressure to the storage flask.

4. Isopentane (bp 28°C, ~95% 2-methylbutane), was purchased from Fluka AG, freshly distilled from P_2O_5, and stored under inert gas pressure.

5. DDB is presently available from Aldrich Chemical Company, Inc. For its preparation, see the accompanying procedure: Seebach, D.; Kalinowski, H.-O.; Langer, W.; Crass, G.; Wilka, E.-M. *Org. Synth.* **1982**, *61*, previous prep 2097. DDB is hygroscopic and must be refluxed for some time and freshly distilled from lithium aluminum hydride (bp 38°C/0.01 mm) prior to use. The submitters used material with $[\alpha]_D$ 14.7°; the checkers' sample showed $[\alpha]_D$ 14.3°.

6. Butyllithium was purchased from Metallgesellschaft, Frankfurt, and titrated for active alkyllithium using diphenylacetic acid as an indicator: Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

7. If no such Dewar container is available, two appropriately sized plastic buckets with a layer of styrofoam particles between the inner and outer bucket can be used.

8. The mixture was used as purchased from Fluka AG. The submitters have occasionally used, as a bath liquid, petroleum ether (bp 40–60°C) of unknown composition or pure isopentane (mp $-160°C$). In such cases, temperature control is necessary; it was achieved with a platinum temperature sensor inside the reaction mixture.

9. The checkers used a thermocouple to verify the temperature of the cooling bath.

10. The coolant must not be poured directly into the bath, because local overcooling can cause partial freezing of the reaction mixture, which is clear and homogeneous before addition of the aldehyde. If freezing should occur, the flask is temporarily warmed slightly by removing the bath.

11. Benzaldehyde was obtained from Fluka AG or Aldrich Chemical Company, Inc., and freshly distilled under reduced pressure (40°C/3 mm).

12. Clear drops of the aldehyde solution must fall from the tip of the

needle directly into the reaction mixture. If the needle is inserted too far, the aldehyde can freeze and clog the needle; it is thawed by extracting the needle tip into the upper, warmer part of the neck.

13. A slow method is to wait until the ice that has condensed on the walls of the flask has all melted. Alternatively, the flask may be immersed in a methanol bath.

14. The combined aqueous layers of several runs are saturated with potassium hydroxide by adding KOH pellets with cooling. DDB separates on top of the aqueous phase and is extracted with ether. Distillation leads to ~90% recovery (bp 42–43°C/0.05 mm).

15. The checkers observed no precipitate formation at this point.

16. In five runs carried out by the submitters at temperatures between −140 and −150°C, the specific rotations of phenylpentanol (d_4^{20} 0.967) ranged from $[\alpha]_D$ 5.95 to 7.0° (29–34% optical yield; see Note 17). At dry ice temperature, the optical yields are only half as high.[2] The checkers obtained specific rotations of $[\alpha]_D$ 5.87° and 6.05° (28 and 29% optical yield).

17. For optically pure 1-phenyl-1-pentanol a specific rotation of $[\alpha]_D^{25}$ 20.7° (neat) is reported.[3]

3. Discussion

The optically active form of 1-phenyl-1-pentanol has been prepared by a variety of methods.[4,5] The present procedure is a modification and extended description of our previously published[2] chiral solvent method. DDB and other auxiliary agents from tartaric acid lead to a wide range of optically active products from achiral components with prochiral centers (enantioselective syntheses). A list of examples of DDB applications is found in the accompanying procedure describing its preparation from tartaric acid.

1. Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, ETH-Zentrum, Universitätstrasse 16, CH-8092 Zürich, Switzerland.
2. Seebach, D.; Kalinowski, H.-O.; Bastani, B.; Crass, G.; Daum, H.; Dörr, H.; DuPreez, N. P.; Ehrig, V.; Langer, W.; Nüssler, C.; Oei, H.-A.; Schmidt, M. *Helv. Chim. Acta* **1977**, *60*, 301; Langer, W.; Seebach, D. *Helv. Chim. Acta* **1979**, *62*, 1701, 1710; Seebach, D.; Crass, G.; Wilka, E.-M.; Hilvert, D.; Brunner, E. *Helv. Chim. Acta* **1979**, *62*, 2695.
3. Horeau, J.; Guetté, J. P.; Weidmann, R. Bull. Soc. Chim. Fr. *1966*, 3513.
4. For reviews of asymmetric syntheses, see: (a) Morrison, J. D.; Mosher, H. S. "Asymmetric Organic Reactions, "Prentice Hall: Englewood Cliffs, NJ, 1971; (b) Izumi, Y.; Tai, A. "Stereo-

Differentiating Reactions,'' Academic Press: New York, 1977; (c) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1978**, *10*, 175.
5. Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455.

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

(+)-(R)-1-Phenyl-1-pentanol: Benzenemethanol, α-butyl-, (R)-; (19641-53-3)

n-Butyllithium: Lithium, butyl (8, 9); (109-72-8)

(S,S)-(+)-N,N,N',N'-Tetramethyl-1,4-diamino-2,3-dimethoxybutane [DDB]: 1,4-Butanediamine-2,3-dimethoxy-N,N,N',N'-tetramethyl-, (S,S)-(+)- (8); 1,4-Butanediamine, 2,3-dimethoxy-N,N,N',N'-tetramethyl-[S-(R*,R*)]- (9); (26549-21-3)

Benzaldehyde (8, 9); (100-52-7)

Phosphorus pentoxide [P₂O₅]: Phosphorus oxide (8, 9); (1314-56-3)

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

Diphenylacetic acid: Acetic acid, diphenyl- (8); Benzeneacetic acid, α-phenyl- (9); (117-34-0)

1-Phenyl-1-pentanol: Benzenemethanol, α-butyl- (9); (583-03-9)

(S)-1-Phenyl-1-pentanol: Butanemethanol, α-butyl-, (S)- (9); (33652-83-4)

PREPARATION OF *O*-ESTERS FROM THE CORRESPONDING THIOL ESTERS

(Cyclohexanecarboxylic acid, 1,1-dimethylethyl ester)
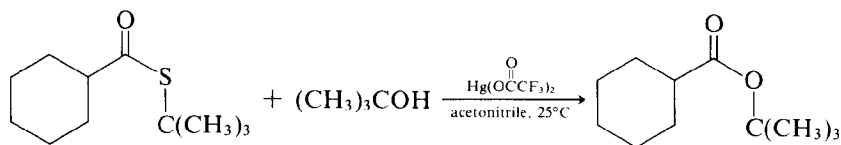
Submitted by WAN KIT CHAN,[1] S. MASAMUNE,[1] and GARY O. SPESSARD[2]
Checked by TRINA KITTREDGE and ROBERT V. STEVENS

1. Procedure

A 500-mL, round-bottomed flask equipped with a magnetic stirring bar is flushed with nitrogen. The flask is then charged with 5.56 g (0.028 mol) of *S-tert*-butyl cyclohexylmethanethioate (Note 1), 5.55 g (0.075 mol) of *tert*-butyl alcohol, and 250 mL of anhydrous acetonitrile (Note 2). The mixture is stirred vigorously and 23.7 g (0.056 mol) of mercury(II) trifluoroacetate (Note 3) is added in one portion. The resulting mixture is stirred vigorously for 45 min and then concentrated to approximately 50–75 mL on a rotary evaporator (Note 4). To this concentrated mixture is added 250 mL of hexane and the orange solid that forms is removed by filtration. The filter pad is then washed with 50 mL of hexane. The filtrate and washings are combined and washed with a 50 mL portion of aqueous saturated sodium chloride, dried over anhydrous sodium sulfate, and concentrated on a rotary evaporator to give a pale yellow liquid (Note 4).

The crude product is purified by passing it through a column (4.5 cm × 30 cm) of neutral alumina (Note 5) using chloroform as eluant. The desired product moves with the solvent front, and the first 300–350 mL of eluant contains all of the product. Removal of the solvent gives 4.96 g. The product, which contains a small amount of *tert*-butyl alcohol, can be further purified by distillation through a short-path apparatus to give 4.6 g (90%) of pure *O*-ester, bp 91°C (25 mm) (Notes 4 and 6).

2. Notes

1. This reagent is prepared according to *Org. Synth.*, **1982**, *61*, 134.
2. Acetonitrile, obtained from J. T. Baker Chemical Co., was refluxed overnight with phosphorus pentoxide and then distilled under nitrogen onto freshly activated Linde 4A molecular sieves. The acetonitrile was stored over the molecular sieves for 24 hr before use.
3. Although mercury(II) trifluoroacetate may be obtained commercially, the submitters recommend that it be freshly prepared. A mixture of red mercury(II) oxide (108.3 g, 0.5 mol) (obtained from BDH Chemicals Ltd.) and freshly distilled trifluoracetic acid (137.0 g, 1.2 mol) (purchased from J. T. Baker Chemical Co.) was heated at 80°C for 30 min. The excess trifluoroacetic acid and the water formed in the reaction were removed under reduced pressure. The white crystalline residue was then dried (50°C, 0.01 mm) for 48 hr to give a quantitative yield of product.
4. The temperature of the water bath was kept below 28°C during evaporation of the acetonitrile.
5. Woelm neutral alumina, activity grade 1, (300 g) was used. The column was packed using hexane.
6. The spectral properties of the product are as follows: IR (neat) cm^{-1}: 1735 (strong); ^{1}H NMR (CDCl$_3$) δ: 1.38 [singlet, 9 H, C(CH$_3$)$_3$] 1.0–2.4 (multiplet, 11 H, cyclohexane protons).

3. Discussion

In recent years much attention has been directed toward efficient ester (and lactone) formation in connection with the synthesis of naturally occurring macrolides.[3,4] Four principal methods for such a reaction have emerged from these studies:

Method 1. Use of a thiophilic metal ion to activate an alkane- or arenethiol ester for nucleophilic displacement by an alcohol is applicable to both ester and lactone formation.[5]

Method 2. Corey's "double activation" method for lactone formation is patterned after Mukaiyama's procedure for peptide formation and involves refluxing a solution of the 2-pyridinethiol ester of a hydroxy acid in a high-boiling solvent for a prolonged period of time.[6]

Method 3. Gerlach's modification of Method 2 uses $AgClO_4$ or $AgBF_4$ to catalyze the cyclization.[7]

Method 4. Mitsunobu's method uses a combination of diethyl azodicarboxylate and triphenylphosphine as a condensing agent.[8]
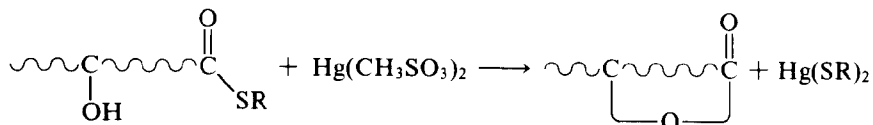
Method 1
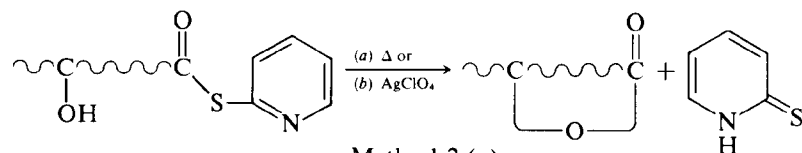
Method 2 (*a*)
Method 3 (*b*)

Method 1 offers some distinct advantages. First, an ester such as the 1,1-dimethylethylthiol ester serves as an excellent protective group, surviving both relatively mild alkaline and acid conditions, and has been used successfully in the synthesis of many macrolide natural products.[4b,g,j,n,o,q] Second, reaction of a metal ion such as Hg(II) with the thiol ester formally creates a highly reactive trivalent sulfur species, and thus ester (and lactone) formation proceeds very rapidly at room temperature or below. More importantly, bulky substituents or double bonds located near the reaction centers (i.e., near the hydroxy and acyl groups) do not impede the reaction (see Table I).[4j] Thus *tert*-butyl pivalate and *tert*-butyl crotonate are prepared in excellent yields. In the absence of alcohols, *tert*-butyl cyclohexanemethanethioate reacts with $Hg(CF_3CO_2)_2$ to form cyclohexanecarboxylic trifluoroacetic anhydride. Reaction of this anhydride with *tert*-butyl alcohol to give the ester, however, proceeds ca. 10 times more slowly than the Hg(II)-catalyzed ester formation described above.[9] The intermediacy of the corresponding ketene has been eliminated by use of an appropriately deuterated compound[9] and pivalic acid. Thus the metal-catalyzed ester formation appears to proceed for the most part through coordination of the alcohol to the metal, as shown in a possible intermediate (**1**), followed by collapse into the ester and mercuric salts with retention of stereochemistry at the carbon atom alpha to the carboxy group.
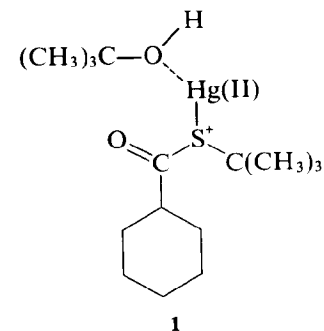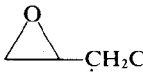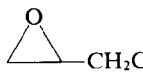
1

This method is not free from disadvantages: the electrophilicity of Hg(II) toward reactive alkanes may sometimes be a problem. However, in most cases the reactivity of Hg(II) with sulfur significantly exceeds that with ordinary or electron-deficient ($C\!=\!C\!-\!C\!=\!O$) double bonds, and other combinations of thiol esters and thiophilic metals may be used to overcome this problem. The more acidic the reacting thiol, the less thiophilic is the metal needed to effect the reaction, and in some cases Cu(I), Cu(II), and Ag(I) are superior to Hg(II). For example, the combination of $Ag(I)CF_3CO_2$ [but not $Ag(I)ClO_4$ or $Ag(I)BF_4$] and a benzenethiol ester is very efficient for ester formation. The presence of electron-withdrawing groups such as the $C\!=\!C$ bond and protected hydroxy groups

TABLE I
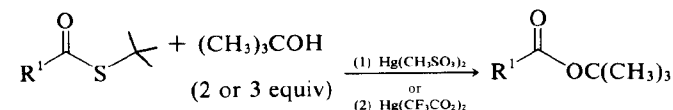
R^1	Reagent	Buffer	Yield (%)[a]
$c\!-\!C_6H_{11}\!-\!$	1 or 2	Na_2HPO_4 (or none)	100
$(CH_3)_3C\!-\!$	1	![epoxide]—CH_2Cl	90
$(E)\!-\!CH_3CH\!=\!CH\!-\!$	1 or 2	![epoxide]—CH_2Cl	85
$(Z)\!-\!CH_3CO_2C(CH_3)\!=\!CH\!-\!$	1	Na_2HPO_4	90

[a] The yields are estimated by GC analysis.

somewhat retards the ester formation. A few examples are shown in Table II.[4j] All these observations appear to conform with the hard and soft acid and base principle of Pearson. Further, it is clear that Gerlach's report of the use of Ag(1) to activate 2-pyridinethiol esters (Method 3) is fully in accord with this trend.

Corey's "double activation" procedure (Method 2) does not use an external reagent to activate the functional group, but effects cyclization by heating a solution of the 2-pyridinethiol ester of a hydroxy acid for a prolonged period. Several pieces of evidence point to the intermediacy of **2** in this lactonization.[10] If one accepts this intermediate, it follows that a hydroxy(2-pyridinethiol) ester, heavily substituted near the reaction centers (i.e., near the hydroxyl and acyl groups), would encounter a high

2
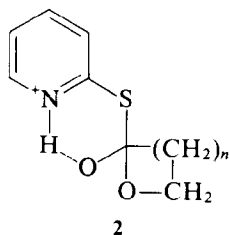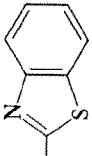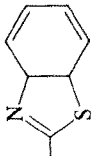
energy barrier in the process leading to **2**. This inference has been confirmed by measuring the approximate rates of reaction of 2-pyridine- and 2-benzothiazolethiol esters of cyclohexanecarboxylic acid with primary, secondary, and tertiary alcohols.[3a,9] This steric retardation of the reaction may constitute a major drawback to Method 2. A marked improvement has been made, however, and the latest version of this method[11] involves use of the 1-methyl- or 1-isopropyl-4-*tert*-butylimidazole-2-thiol ester of the hydroxy acid which undergoes cyclization ~100 times faster than the corresponding 2-pyridinethiol ester. This improved method has been used in syntheses of erythronolide A[4m] and B.[4k]

Lactonization of aliphatic hydroxy acids proceeds with the aid of two reagents, diethyl azodicarboxylate and triphenylphosphine. This fourth procedure has been selected as a method of choice for the final cyclization to yield vermiculine[4i] and pyrenophorin.[4h]

Several other methods to effect ester and lactone formation are now available. Mukaiyama uses 2-chloro-N-methylpyridinium iodide and its derivatives as a condensing agent.[12] Staab's imidazole method,[13] suc-

TABLE II

$$R^1-\overset{O}{\overset{\|}{C}}-SR^2 + MX \xrightarrow[25°C]{(CH_3)_3COH} R^1-\overset{O}{\overset{\|}{C}}-O-C(CH_3)_3$$
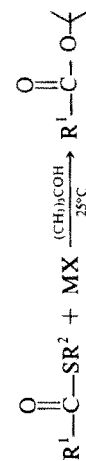
R¹	R²	MX	Solvent	Time	Yield (%)
c-C₆H₁₁—	—C₆H₅	Cu(CF₃SO₃)	C₆H₆/THF	10 min	95
c-C₆H₁₁—	benzothiazol-2-yl	Ag(CF₃CO₂)	C₆H₆	10 min	100
(E)-CH₃CH=CH—	—C₆H₅	Cu(CF₃SO₃)	C₆H₆/THF	5 hr	80
(E)-C₆H₅CH=CH—	—C₆H₅	Cu(CF₃SO₃)₂	CH₃CN	1.5 hr	24
		Ag(CF₃CO₂)	C₆H₆(Δ)	1.5 hr	100
		AgBF₄	C₆H₆(Δ)	1 hr	<5
C₆H₅—	benzothiazol-2-yl	Ag(CF₃CO₂)	C₆H₆(Δ)	1.5 hr	100
		Cu(CF₃SO₃)	C₆H₆/THF	5 hr	90
		Cu(CF₃SO₃)₂	CH₃CN	30 min	100

cessfully utilized in a synthesis of pyrenophorin[4c] and a model study for erythronolide B,[14] requires a catalytic amount of strong base, and thus is applicable only to compounds stable under such conditions. The mixed anhydride of a hydroxycarboxylic acid and 2,4,6-trichlorobenzoic acid is efficiently cyclized to provide the corresponding lactone.[41,15] Similarly, the use of a reactive phosphoric acid anhydride intermediate is equally effective.[16] Some other methods for carboxyl activation have also appeared recently.[17]

The above discussion is a summary of the lactonization methods known at present; newer methods continue to be explored. The selection of a method for an individual case depends to a large extent on the structure and functionalities of the substrate. Detailed comments in this respect are reserved until more information has accumulated.

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3. For recent reviews, see (a) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585; (b) Nicolaou, K.C. *Tetrahedron* **1977**, *33*, 683; (c) Back, T. G. *Tetrahedron* **1977**, *33*, 3041.
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Appendix
Chemical Abstracts Nomenclature (Collective Volume Number); (Registry Number)

Cyclohexanecarboxylic acid, 1,1-dimethylethyl ester: Cyclohexanecarboxylic acid, *tert*-butyl ester (8); Cyclohexanecarboxylic acid, 1,1-dimethylethyl ester (9); (16537-05-6)

S-tert-Butyl cyclohexylmethanethioate: Cyclohexanecarbothioic acid, *S*-(1,1-dimethylethyl) ester (9); (54829-37-7)

Mercury(II) trifluoroacetate: Acetic acid, trifluoro-, mercury(2 +) salt (8, 9); (13257-51-7)

Red mercury(II) oxide: Mercury oxide (8, 9); (21908-53-2)

ETHYL α-(BROMOMETHYL)ACRYLATE

(2-Propenoic acid, 2-(bromomethyl)-,ethyl ester)

A. $(HOCH_2)_2C(CO_2C_2H_5)_2 \xrightarrow[85-90°C]{48\% \ HBr} CH_2{=}C{-}CO_2H$
$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$
$\qquad\qquad\qquad\qquad\qquad\qquad\qquad CH_2Br$

B. $CH_2{=}C{-}CO_2H \xrightarrow[reflux]{C_2H_5OH, \ H^+} CH_2{=}C{-}CO_2C_2H_5$
$\qquad\quad |\qquad\qquad\qquad\qquad\qquad\qquad\quad |$
$\qquad\quad CH_2Br\qquad\qquad\qquad\qquad\quad CH_2Br$
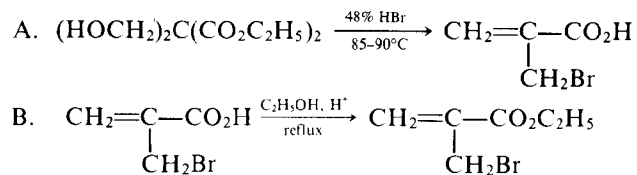
Submitted by K. RAMARAJAN, K. RAMALINGAM, D. J. O'DONNELL, and K. D. BERLIN[1]
Checked by H. S. SHOU, E. TSOU, R. A. HAYES, and ORVILLE L. CHAPMAN

1. Procedure

A. α-(Bromomethyl)acrylic acid. A 500-mL, three-necked, round-bottomed flask is equipped with a magnetic stirrer, fraction collector, cold-finger condenser, and two thermometers. Into the flask are placed 55.0 g (0.25 mol) of diethyl bis(hydroxymethyl)malonate (Note 1) and 142 mL (1.25 mol) of 47–49% hydrobromic acid (Note 2). The mixture is then heated and the temperature of the liquid maintained between 85–90°C. A mixture of ethyl bromide and water distills during the course of 1.5–2 hr. The residue is then boiled for 10 hr, maintaining the temperature between 85–90°C (Note 3). At the end of this period, the mixture is concentrated on a rotary evaporator at 65–70°C (10–15 mm). About 100 mL of water is removed. The residue is cooled in the refrigerator overnight. Crystals of α-(bromomethyl)acrylic acid are filtered in the cold (Note 4) to give, after drying (Note 5), 17.9 g (43%) of acid, mp 71–73°C (Note 6).

B. Ethyl α-(bromomethyl)acrylate. In a nitrogen-flushed, 1-L, round-bottomed flask equipped with a magnetic stirrer, Dean–Stark trap, and condenser are placed 42.0 g (0.25 mol) of α-(bromomethyl)acrylic acid and 300 mL of benzene. Approximately 50 mL of a binary azeotrope of benzene and water is distilled (Note 7). The Dean–Stark trap is removed and 100 mL of absolute ethanol (Note 8) and 1 mL of concentrated sulfuric acid are added slowly. The contents of the flask are boiled in a nitrogen atmosphere for 36 hr, the condensate being passed through 100 g of molecular sieves (Linde 3A) before being returned to the flask. About 125 mL of a mixture of benzene and ethanol is removed from the reaction

mixture by distillation (at 67°C). Then 100 mL of benzene is added and another 125 mL of benzene–ethanol mixture distilled (67–75°C). The residue is poured into 200 mL of water and neutralized with solid sodium bicarbonate (ca. 10–15 g) until CO_2 evolution ceases. The resulting solution is extracted with three 75-mL portions of ether, and the combined extracts are dried over anhydrous sodium sulfate for 3 hr. The ether is removed under reduced pressure in a rotary evaporator, and crude ester distilled to give a fraction at 39–40°C (0.9 mm) which weighs 33–34 g (71%). The ester is of high purity, as evidenced by spectral analysis (Note 9).

2. Notes

1. The checkers prepared this ester on a 0.7-mol scale by a modification of the previously published method.[2] The modification was effected as follows. The ethereal extract from the formaldehyde–diethyl malonate reaction, after drying over sodium sulfate for 3 hr, was concentrated in a rotary evaporator and the residue was stored in a refrigerator overnight. The crude ester was obtained as white crystals, mp 47–50°C; yield 85.6%. The checkers found that the ester prepared in this manner gave superior yields of the acrylic acid.

2. The submitters reported that the use of excess hydrobromic acid resulted in the formation of a mixture of dibromoisobutyric acid and α-(bromomethyl)acrylic acid as evidenced by NMR analysis.

3. Temperatures higher than 85–90°C gave a mixture of dibromoisobutyric acid and α-(bromomethyl)acrylic acid.

4. This was done at 4°C to improve the yield; otherwise considerable amounts of α-(bromomethyl)acrylic acid remain in solution.

5. The compound was air-dried for 3 days at room temperature.

6. The product was almost pure. It could be recrystallized from Skellysolve-B (bp 60–80°C) and further purified by sublimation, mp 73–75°C (Anal. Calcd. for $C_4H_5BrO_2$: C, 29.12; H, 3.05. Found: C, 29.07; H, 3.10). IR (KBr) cm^{-1}: 1689 (C=O), 1626 (C=CH$_2$); ^1H NMR (CDCl$_3$) δ: 4.18 (s, 2 H, H$_a$), 6.09 (s, 1 H, H$_b$), 6.49 (s, 1 H, H$_c$).

(c) H$\qquad$CO$_2$H
$\qquad\diagdown\qquad\diagup$
$\qquad\quad$C=C
$\qquad\diagup\qquad\diagdown$
(b) H$\qquad\quad$CH$_2$Br

(a)
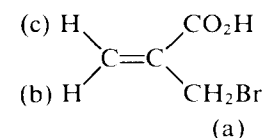
7. There was only about 1 mL of water in the distillate.

8. Absolute alcohol was prepared by boiling commercial absolute alcohol over magnesium turnings for 4 hr in a nitrogen atmosphere.

9. The spectral properties of ethyl α-(bromomethyl)acrylate are as follows: ^{1}H NMR (CDCl$_3$) δ: 1.26–1.40 (t, 3 H, H$_a$), 4.16–4.38 (quintet, 2 H, H$_b$), 4.19 (s, 2 H, H$_c$), 5.96 (s, 1 H, H$_d$), 6.32 (s, 1 H, H$_e$).
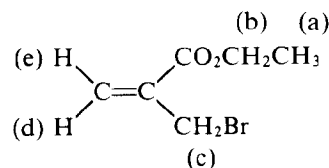
3. Discussion

The procedure described here is a modification of that of Ferris.[3] The overall yield has been increased from 17 to 30% by making changes as indicated in Notes 2 and 3. In addition, the number of stages in the preparation of ethyl α-(bromomethyl)acrylate from diethyl malonate has been reduced from four to three.

Ethyl α-(bromomethyl)acrylate has proved to be an excellent reagent for conversion of aldehydes and ketones, both acyclic and cyclic, into the corresponding α-methylene-γ-butyrolactone derivatives[4-9] in a Reformatsky type reaction. The yield was excellent in the case of several spiro α-methylene-γ-butyrolactones.[10] Synthetic α-methylene-γ-butyrolactone derivatives have been shown to possess antitumor activity.[5,6,7,11,12] Ethyl α-(bromomethyl)acrylate has also proven of value in the synthesis of alkylated products of enol ethers of cyclohexane-1,3-dione.[13]

1. Department of Chemistry, Oklahoma State University, Stillwater, OK 74078. We gratefully acknowledge partial support of this work by a grant from the National Cancer Institute, CA 14343.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Ethyl α-(bromomethyl)acrylate: Acrylic acid, 2-(bromomethyl)-, ethyl ester (8); 2-Propenoic acid, 2-(bromomethyl)-, ethyl (9); (17435-72-2) Diethyl bis(hydroxymethyl)malonate: Malonic acid, bis(hydroxymethyl)-, diethyl ester (8); (20605-01-0)

2-HEPTYL-2-CYCLOHEXENONE: ALKYLATION OF THE ANION FROM BIRCH REDUCTION OF *o*-ANISIC ACID
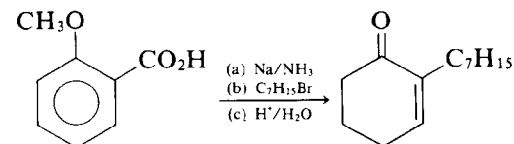
Submitted by D. F. Taber, B. P. Gunn, and I-Ching Chiu[1]
Checked by M. F. Semmelhack and E. Stelter

1. Procedure

Caution! Liquid ammonia should be used only in a well-ventilated hood.

2-Heptyl-2-cyclohexenone. A 1-L, three-necked, round-bottomed flask is charged with 15.2 g (0.1 mol) of *o*-anisic acid (Note 1) and 100 mL of tetrahydrofuran (Note 2). An acetone–dry ice condenser and mechanical stirrer are put in place, the flask is immersed in an acetone–dry

ice bath, and 400 mL of ammonia is distilled in (Notes 3, 4). The resulting thick white suspension (the ammonium salt of the acid) is stirred mechanically. Sodium, washed sequentially with xylenes and ether, is added in small pieces. The suspension dissolves to give a pale yellow solution which, upon introduction of more sodium, changes to the characteristic blue color of excess sodium. When the deep blue color persists, a mixture of 1-bromoheptane (21.49 g, 0.12 mol) and 1.0 mL (2.4 mmol) of 1,2-dibromoethane is added in one portion. The blue color is discharged immediately, leaving a yellow solution. The acetone–dry ice bath and the condenser are removed, and the ammonia is allowed to evaporate under a gentle stream of nitrogen.

The residue is diluted with 700 mL of water, and the resulting aqueous solution is washed with three 40-mL portions of dichloromethane, acidified with cold concentrated HCl, and extracted with five 40-mL portions of 1,2-dichloroethane. The combined 1,2-dichloroethane extracts are placed in a 500-mL, one-necked, round-bottomed flask bearing a reflux condenser; water (50 mL), concentrated HCl (50 mL), and hydroquinone (300 mg) are added; and the mixture is heated at reflux under a positive pressure of nitrogen for 30 min. The mixture is cooled to 25°C, the layers are separated, and the organic layer is washed with 60 mL of 0.5 M aqueous sodium bicarbonate solution. The organic phase is dried over anhydrous potassium carbonate, concentrated by rotary evaporation at aspirator vacuum, and distilled through a 10-cm Vigreux column to yield a center cut, bp 100–104°C (0.02 mm), 9.0–11.5 g (46–59%) (Notes 5, 6).

2.   Notes

1. *o*-Anisic acid was obtained from Aldrich Chemical Company, Inc.

2. Tetrahydrofuran was dried and made oxygen-free by boiling over sodium/benzophenone ketyl under argon, and distilling just before use.

3. Reduction in refluxing liquid ammonia (-33°C) led to substantial cleavage of the methoxyl group with resultant formation of alkylated dihydrobenzoic acid.

4. Arrangements for cooling or condensing the liquid ammonia over sodium in a preliminary drying operation could be made, but were not necessary. The results reported here were achieved by simply passing ammonia gas from a cylinder into the cold reaction system through heavy Tygon tubing.

5. The spectral properties of 2-heptyl-2-cyclohexenone are as follows: IR (CCl$_4$) cm^{-1}: 2920, 2860, 1670, 1455, 1435, 1370, 1170, 1120, 1095, 905; ^{1}H NMR (CDCl$_3$) δ: 0.85 (br t, 3 H, $J = 7$), 1.28 (br s, 10 H), 1.8–2.6 (m, 8 H), 6.70 (br s, 1 H); n_D^{26} 1.4738.

6. Before distillation, the crude enone contained substantial amounts of the β,γ-isomer. As an alternative to equilibration on distillation, this mixture could be converted to the α,β-isomer by stirring with 0.1 M sodium methoxide in methyl alcohol under nitrogen at 0°C for 2 hr.

3.   Discussion

Cyclohexenones with 2-alkyl substituents are usually prepared by alkylation of dihydroresorcinol followed by enol ether formation, reduction, and hydrolysis.[2b] A variety of other approaches have been employed.[2] The procedure outlined here is simple, occurring in essentially one pot, using commercially available starting materials. The alkylating agent can equally well be an alkyl iodide or *p*-toluenesulfonate ester. A variety of other alkylating agents have been employed using an earlier, unoptimized version of this procedure.[3,4]

1. Department of Pharmacology, School of Medicine, Vanderbilt University, Nashville, TN 37232.
2. (a) Alkylation of cyclohexenone: Conia, J.-M.; Le Craz, A. *Bull. Soc. Chim. Fr.* **1960**, 1934. (b) Alkylation of cyclohexane-1,3-dione followed by enol ether formation, reduction, and hydrolysis: Angell, M. F.; Kafka, T. M. *Tetrahedron* **1969**, *25*, 6025. (c) Bromination-dehydrobromination of a 2-alkylcyclohexanone: Warnhoff, E. W.; Martin, D. G.; Johnson, W. S. *Org. Synth.* **1957**, *37*, 8. (d) Sulfenylation of a 2-alkylcyclohexanone followed by oxidation and elimination: Trost, B. M.; Salzmann, T. N. *J. Am. Chem. Soc.* **1973**, *95*, 6840. (e) Selenation of a 2-alkylcyclohexanone followed by oxidation and elimination: Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434. (f) Reduction of a 2-alkylpyridine followed by hydrolysis and aldol condensation: Danishefsky, S.; Cain, P. *J. Org. Chem.* **1975**, *40*, 3607. (g) Oxidation of a 1-alkylcyclohexene: Belyaev, V. F. *Zhidkofaznoe Okislenie Nepredel'nykh Organ. Soedin., Sb.* **1961**, *No. 1*, 97–104; *Chem. Abstr.* **1963**, *58*, 4435d.
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4. Note added in proof: Professor L. N. Mander has recently advised us that addition of 1.0 equivalent of potassium *t*-butoxide prior to addition of sodium metal significantly improved the yield of this procedure.

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

o-Anisic acid (8); Benzoic acid, 2-methoxy- (9); (579-75-9)

1-Bromoheptane: Heptane, 1-bromo- (8, 9); (629-04-9)

Cyclohexane-1,3-dione: 1,3-Cyclohexanedione (8, 9); (504-02-9)

HEXAMETHYL DEWAR BENZENE

(Bicyclo[2.2.0]hexa-2,5-diene, 1,2,3,4,5,6-hexamethyl-)
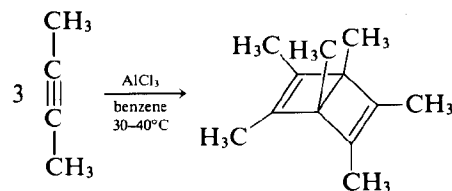
Submitted by SAMI A. SHAMA and CARL C. WAMSER[1]
Checked by RETO NAEF, DIETER SEEBACH, and BEAT WEIDMANN

1. Procedure

Caution! See benzene warning, Org. Synth. **1978,** *58,* 168. *This preparation should be conducted in an efficient hood and the operator should wear protective gloves.*

A 250-mL, three-necked, round-bottomed flask containing a 2.5-cm magnetic stirring bar is equipped with a Dewar-type reflux condenser containing ice, a dropping funnel, and a gas inlet tube. A calcium chloride drying tube is attached to the condenser and the apparatus is flushed with dry deoxygenated nitrogen (Note 1). The gas inlet tube is then replaced by a thermometer, and a suspension of 5.0 g of aluminum trichloride in 50 mL of benzene is introduced into the flask (Note 2). A solution of 100 g (1.85 mol) of 2-butyne (Notes 3 and 4) in 50 mL of cold dry benzene is added, with vigorous stirring, through the dropping funnel, over a period of 1 hr. During the addition, the temperature of the reaction mixture is kept between 30 and 40°C through the use of a water bath. Stirring is continued for 5 hr at 30–40°C after the addition has been completed. The catalyst is then decomposed by pouring the mixture onto 50 g of crushed ice in a 500-mL separatory funnel, whereupon the dark brown color turns pale yellow. When the ice has melted completely, the organic layer is separated, washed with two 25-mL portions of cold water, dried over anhydrous potassium carbonate, and filtered. Benzene and unreacted butyne (Note 5) are removed in a rotary evaporator using a water bath at 40°C and a water aspirator vacuum. The residual liquid is distilled through a short-path distillation head under reduced pressure using a capillary. The yield is 38–50 g (38–50%) of hexamethyl Dewar benzene, bp 43°C/10 mm, mp 7–8°C, n_D^{20} 1.4480 (Notes 6 and 7).

2. Notes

1. Commercial nitrogen is deoxygenated by bubbling it through a trap containing an alkaline pyrogallol solution.[2] The gas is then dried by passing it through a potassium hydroxide tower. The checkers used argon as an inert atmosphere.

2. Aluminum trichloride is purified by sublimation under reduced pressure and the benzene is dried over sodium wire before use. The checkers used sublimed $AlCl_3$ as supplied by Merck (Darmstadt).

3. 2-Butyne was purchased from Chemical Samples Company or from Fluka AG.

4. The bottle containing 2-butyne (bp 27°C) should be chilled thoroughly before opening.

5. About 20 g of 2-butyne may be collected in an ice-cooled receiver if the dried solution is concentrated by distillation through a 25-cm Vigreux column rather than by evaporation. The checkers do not recommend this mode of work-up, nor did they use a column for distilling the Dewar benzene, to avoid prolonged heating of the bicyclic system.

6. The spectral properties of hexamethyl Dewar benzene are as follows: ^1H NMR ($CDCl_3$) δ: 1.07 (s, 6 H), 1.58 (s, 12 H).

7. Hexamethyl Dewar benzene undergoes thermal isomerization[3,4] and reacts with acids[5] and transition metal ions.[6] It should be stored in a freezer in a tightly sealed bottle. Hexamethyl Dewar benzene is reportedly a carcinogen,[7] and care must be taken to avoid contact with the skin or inhalation of its vapor.

3. Discussion

The present procedure is that of Schäfer[8,9] and is the first method available for large-scale preparation of a Dewar benzene. Other syntheses of compounds containing the Dewar benzene skeleton have generally involved photochemical isomerization of the corresponding benzene isomer.[10]

The present procedure represents a novel reaction, bicyclotrimerization. The intermediate dimeric complex of $AlCl_3$ with tetramethylcyclobutadiene has been isolated, and addition of different alkynes to this complex provides a synthetic route to a variety of substituted Dewar benzenes.[11]

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

Hexamethyl Dewar benzene: Bicyclo[2.2.0]hexa-2,5-diene, 1,2,3,4,5,6-hexamethyl- (8, 9); (7641-77-2)

2-Butyne (8, 9); (503-17-3)

2-HYDROXYMETHYL-2-CYCLOPENTENONE
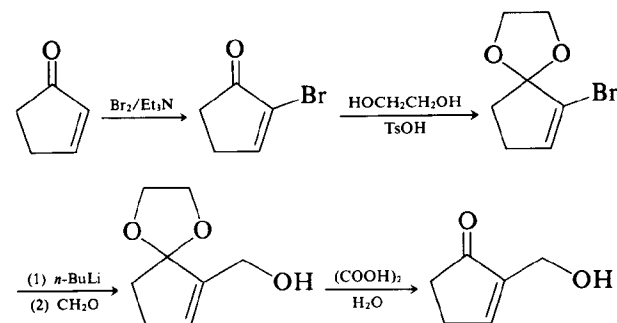
Submitted by AMOS B. SMITH, III, STEPHEN J. BRANCA, MICHAEL A. GUACIARO, PETER M. WOVKULICH, and ABNER KORN[1]

Checked by F. PIGOTT and G. SAUCY

1. Procedure

A. 2-Bromo-2-cyclopentenone. In a well-ventilated hood, a solution of 18.98 g (231.2 mmol) of 2-cyclopentenone (Note 1) in 150 mL of carbon tetrachloride is added to a 1-L, three-necked, round-bottomed flask fitted with a mechanical stirrer, thermometer, and an addition funnel. The solution is chilled to 0°C with an ice bath and a solution of 40.5 g (253.4 mmol, 13.0 mL) of bromine in 150 mL of carbon tetrachloride is added dropwise during 1 hr. Then a solution of 35.1 g (346.8 mmol, 48.3 mL) of triethylamine in 150 mL of carbon tetrachloride is added dropwise over 1 hr with vigorous stirring while the reaction is held at 0°C. Stirring is continued for an additional 2 hr at room temperature; the resulting dark suspension is filtered with suction and the filter cake washed with carbon tetrachloride. The filtrate and washings are combined and washed with two 100-mL portions of 2 N hydrochloride acid, one 100-mL portion of saturated sodium bicarbonate solution, one 100-mL portion of water, and one 100-mL portion of saturated sodium chloride solution. The resultant solution is dried over anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure. Distillation of the resultant oil (69–78°C, 1.0 mm) afforded 23.7 g (147.2 mmol, 64%) (Note 2) of a white crystalline solid (mp 36–37°C, lit.[2] mp 39–39.5°C) (Note 3).

B.   2-Bromocyclopentenone ethylene ketal.   A solution of 22.00 g (136.7 mmol) of freshly distilled 2-bromo-2-cyclopentenone, 21.80 g (351.2 mmol) of ethylene glycol, 1.5 L of benzene (Note 4), and 60 mg of *p*-toluenesulfonic acid monohydrate is refluxed for 64 hr (Note 5), with azeotropic removal of water, in a 3-L, round-bottomed flask, equipped with a Dean-Stark trap, condenser, and Drierite drying tube. The solution is cooled to room temperature, dried with potassium carbonate, and filtered by vacuum through 15 g of Celite. The filter cake is washed with 150 mL of benzene. Removal of the solvent under reduced pressure yields a mobile yellow oil. Distillation (65–67°C, 0.7 mm) affords 22.4 g (109.0 mmol, 80%) (Note 6) of the ketal (Note 7).

C.   2-Hydroxymethyl-2-cyclopentenone.   The apparatus, as illustrated in Figure 1 (Note 8), is flame-dried while dry nitrogen is passed through. Paraformaldehyde (13 g, 433 mmol) (Note 9) is then added to the 250-mL flask (the generator) and 19.4 g (94.6 mmol) of freshly distilled 2-bromo-2-cyclopentenone ethylene ketal in 300 mL of dry tetrahydrofuran containing 2 mg of 2,2'-bipyridyl (Note 10) is added to the 500-mL flask (the reaction flask). The reaction flask is chilled to −78°C with an acetone/dry ice bath and 46.0 mL (105.8 mmol) of *n*-butyllithium (2.3 *M* in hexane) (Note 11) is added dropwise by syringe through the rubber septum during 1 hr. The resultant red solution is stirred for 1 hr and then warmed to −30°C using a methanol–water (2 : 3)/dry ice bath. An oil bath previously heated to 160°C is applied to the generator and the monomeric formaldehyde thus generated is bubbled into the reaction

Figure 1

mixture via a steady stream of dry nitrogen until the red color of the indicator is discharged (approximately 45 min). The reaction is quenched by the addition of 10 mL of saturated ammonium chloride solution and the resultant mixture is poured into 100 mL of a saturated sodium chloride solution. This mixture is extracted four times with 100-mL portions of methylene chloride; the methylene chloride extracts are combined and dried over magnesium sulfate. After filtration, evaporation of the solvent under reduced pressure affords 8.1–10.7 g (Note 12) of crude 2-hydroxymethyl-2-cyclopentenone ethylene ketal as a viscous liquid (Note 13).

Without purification, 8.1 g of the above crude ketal is added to a solution consisting of 1.0 g of oxalic acid, 5 mL of water, and 40 mL of methylene chloride. The resultant mixture is stirred for 5 hr at room temperature. At the end of this period the solution is filtered through 50 g of magnesium sulfate impregnated with 1.0 g of potassium carbonate (Note 14). Evaporation of the solvent from the filtrate affords a solid which, after purification by short-path distillation (70–80°C, 0.1 mm) (Note 15), gives 4.9 g (46%, based on bromoketal) (Note 16) of pure 2-hydroxymethyl-2-cyclopentenone, mp 68–69°C (off-white crystals) (Notes 17 and 18).

2.   Notes

1. Cyclopentenone is commercially available from the Aldrich Chemical Company, Inc., or may be prepared according to the procedure of DePuy; see *Org. Synth. Collect. Vol.* **1973**, *V*, 326.

2. The checkers obtained somewhat higher yields (i.e., 66 and 77%).

3. Pure 2-bromo-2-cyclopentenone obtained by recrystallization from diethyl ether–hexane (Ref. 2) displayed the following spectroscopic properties: IR (CCl$_4$) cm^{-1}: 1720 (s), 1595 (m); ^{1}H NMR (CCl$_4$, 60 MHz) δ: 2.35–2.60 (m, 2 H), 2.60–2.91 (m, 2 H), 7.40 (t, 1 H, *J* = 2).

4. Benzene is a potential carcinogen!

5. The reaction progress was monitored by TLC analysis (silica gel) using hexane–ethyl acetate (4 : 1, v/v) with 3.5% methanolic phosphomolybdic acid as indicator: bromoketal, R_f 0.37, bromoketone, R_f 0.15.

6. The bromoketal appears to be somewhat unstable and should be used as soon as possible after preparation. Some decomposition was observed during distillation.

7. Pure 2-bromo-2-cyclopentenone ethylene ketal displayed the following spectroscopic properties: IR (CCl$_4$) cm^{-1}: 2975 (s), 2950 (s), 2880
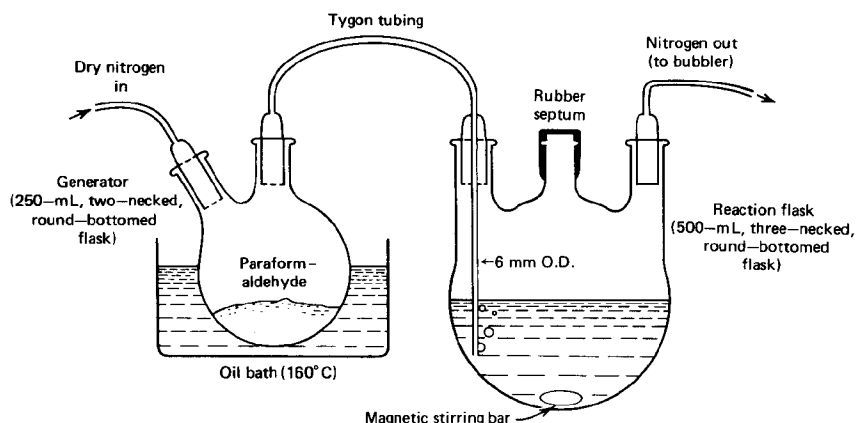
(s), 1615 (w); ^{1}H NMR (CCl$_4$, 60 MHz) δ: 1.95–2.55 (m, 4 H), 3.71–4.01 (m, 2 H), 4.01–4.33 (m, 2 H), 6.05 (t, 1 H, $J = 2$).

8. The checkers found that it is important to employ tubing of wide bore (6 mm O.D.) to conduct the gaseous formaldehyde from the generation flask into the reaction flask to avoid the possibility of the tube becoming plugged.

9. Prior to use paraformaldehyde was dried overnight in high vacuum (0.1 mm) over phosphorus pentoxide.

10. The reagent 2,2′-bipyridyl, available from the Aldrich Chemical Company, Inc., appears red in solutions containing organolithium and organomagnesium reagents[3] and is thereby an excellent indicator. Its use here allows addition of the precise amount of gaseous formaldehyde.

11. *n*-Butyllithium is available commercially from Alfa Products, Ventron Corporation.

12. The checkers found this crude product to contain 84.5% of the desired ketal, based on GC analysis.

13. Although 2-hydroxymethyl-2-cyclopentenone ethylene ketal could be purified by Kugelrohr distillation (88–100°C, 0.10 mm) this was not necessary for successful completion of the subsequent hydrolysis step. Pure 2-hydroxymethyl-2-cyclopentenone ethylene ketal possesses the following spectroscopic properties: IR (CCl$_4$) cm^{-1}: 3470–3500 (s), 1616 (w); ^{1}H NMR (CCl$_4$, 60 MHz) δ: 1.68–2.17 (m, 2 H), 2.17–2.58 (m, 2 H), 2.58–2.93 (br s, 1 H), 3.87 (s, 4 H), 3.98–4.16 (m, 2 H), 5.81–6.03 (m, 1 H).

14. The function of the potassium carbonate is to neutralize the oxalic acid[10] as the solution passes through.

15. The short-path distillation of 2-hydroxymethyl-2-cyclopentenone is carried out without a water condenser. Furthermore, to prevent solidification of the distillate in the condenser, gentle warming of the condenser with a heat gun may be necessary.

16. The submitters had obtained a 70% yield for this two-step sequence, the crucial step being the reaction with formaldehyde.

17. Pure 2-hydroxymethyl-2-cyclopentenone displayed the following spectroscopic properties: IR (CHCl$_3$) cm^{-1}: 3400–3450 (s), 1680 (s), 1630 (m); ^{1}H NMR (CDCl$_3$, 60 MHz) δ: 2.27–2.84 (m, 4 H), 3.00 (br s, 1 H), 4.33 (d, 2 H, $J = 1$), 7.60 (m, 1 H).

18. The overall yield from cyclopentenone to 2-hydroxymethyl-2-cyclopentenone over a number of runs was found to be in the range of 23–28%. The submitters had obtained 34.5%.

3. Discussion

The procedure reported here provides an efficient method for the construction of a wide variety of α,β-unsaturated ketones directly from the parent enone (i.e., $1 \rightarrow 2$), which does not require intervention of the thermodynamic dienolate. To our knowledge, a *general* solution for this recurring synthetic problem is unavailable, although Corey et al.,[4] Fuchs,[5] and Stork and Panaras[6] have independently developed a reverse polarity (umpolung) strategy for α-arylation of α,β-unsaturated ketones. Central to their approach was the generation of an effective latent equivalent for α-ketovinyl cation 3. Such a strategy, however, is limited in that it depends critically upon the availability of the requisite alkyl or aryl organocuprate or magnesium reagent.

1   2   3   4
α-Ketovinyl cation   α-Ketovinyl anion
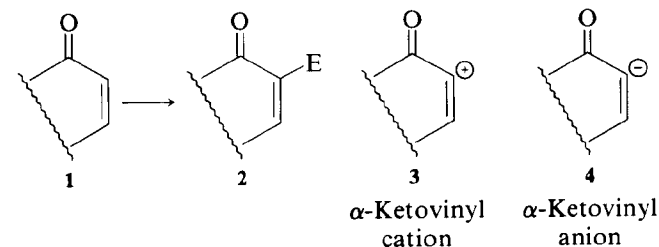
A more versatile, as well as a more direct approach for the conversion of 1 to 2 employs the ethylene ketal of α-bromo-α,β-enones (e.g., 5) as a latent equivalent of α-ketovinyl anion 4.[7] Indeed, independent studies by Ficini and Depezay,[8] House and McDaniel,[9] and Manning et al.[10] as well as our own[11] suggested that such a general strategy would be viable. To illustrate this approach, we record here the preparation of the very useful synthon α-hydroxymethyl-2-cyclopentenone:

5   6   7   8
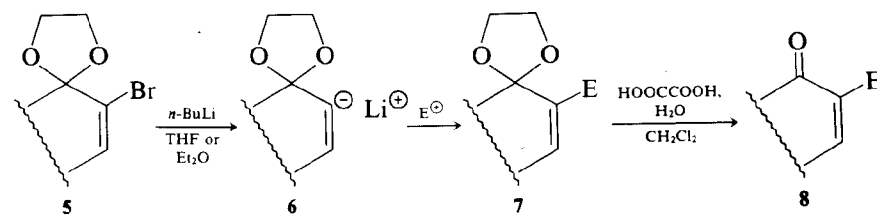
The overall efficiency of this sequence demonstrates, we believe, the considerable promise that α-bromoketals of α,β-enones hold as latent α-

ketovinyl anion equivalents. In particular, we note the feasibility of introducing the very useful trimethylsilyl, tri-*n*-butyltin, and phenylselenenyl substituents.

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

2-Bromo-2-cyclopentenone: 2-Cyclopenten-1-one, 2-bromo- (8); (10481-34-2)

2-Cyclopentenone: 2-Cyclopenten-1-one (8, 9); (930-30-3)

Ethylene glycol (8); 1,2-Ethanediol (9); (107-21-1)

Paraformaldehyde (9); (30525-89-4)

2,2'-Bipyridyl: 2,2'-Bipyridine (8, 9); (366-18-7)

o-ISOTHIOCYANATO-(*E*)-CINNAMALDEHYDE
(2-Propenal, 3-(2-isothiocyanatophenyl)-, (*E*)-)
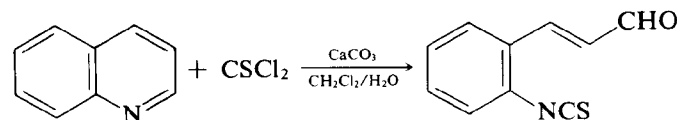
Submitted by R. FARRAND and R. HULL[1]
Checked by K. E. FAHRENHOLTZ and G. SAUCY

1. Procedure

Caution! This reaction should be carried out in a good hood.

A 1000-mL (Note 1), multinecked flask is provided with an efficient stirrer, vented outlet, thermometer, and 250-mL dropping funnel. The flask is surrounded by an ice/water bath and charged with 62.5 mL (68.4 g, 0.53 mol) of quinoline, 250 mL of dichloromethane, 55 g (0.55 mol) of finely powdered calcium carbonate, and 250 mL of water. The mixture is stirred vigorously, cooled to 10°C, and maintained at 10–15°C as a solution of 37.5 mL (56.5 g, 0.49 mol) of thiophosgene (Note 2) in 120 mL of dichloromethane is added over 15 min. There is very little exotherm or foaming. The cooling bath is removed and the reaction mixture is stirred vigorously at ambient temperature overnight. The reaction is then filtered through a bed of filter aid. The layers are separated and the aqueous layer is extracted with 50 mL of dichloromethane. The combined organic layers are washed twice with 150 mL of 2 *N* hydrochloric acid (Note 3), then with 150 mL of water, and dried over anhydrous magnesium sulfate. Concentration under reduced pressure gives 95–103 g of crude material (Note 4). This is dissolved with heating in 400 mL of cyclohexane, decolorizing carbon is added, and the mixture is filtered through a bed of filter aid. The filtrate is heated under reflux for 2 hr (Note 5) and allowed to cool with stirring (Note 6). The resulting solid is isolated by filtration, washed with cyclohexane, and dried in a vacuum oven at 40°C to give 78–83 g (84–89%) of *o*-isothiocyanato-(*E*)-cinnamaldehyde as cream crystals, mp 77–79°C (Note 7).

2. Notes

1. The reaction has been carried out on 10 times these quantities with no difficulty.

2. The checkers used an older bottle of thiophosgene and obtained an 84% yield (based on thiophosgene). A subsequent run was carried out with Aldrich "85% in CCl$_4$" thiophosgene found by analysis to contain 63% thiophosgene (therefore 89.4 g was used) and an 89% yield was obtained. A subsequent run on an unanalyzed bottle of the same lot number using 89.4 g gave a 100% yield (92% based on quinoline). It is suggested that thiophosgene be analyzed before use (Note 8).

3. These two washes remove unreacted quinoline.

4. The crude material consists of a mixture of Z and E isomers, with Z predominating. If work-up of the reaction is delayed, more of the less soluble E isomer is formed, complicating subsequent filtration.

5. This additional heating completes the isomerization of the Z to the E isomer.

6. Subsequent breakup and filtration of the solid are facilitated if this solution is transferred and allowed to cool with stirring in a large-mouth container such as a beaker.

7. Melting points were taken in open capillaries on a Thomas-Hoover melting point apparatus. The crude material can be purified by dissolving it in dichloromethane, passing the solution over a plug of silica gel, and concentrating the solution with the addition of ether. The recrystallized material has essentially the same melting point and is colorless. The spectral properties of o-isothiocyanato-(E)-cinnamaldehyde are as follows: IR (Nujol) cm^{-1}: 2075 (NCS) and 1670 (conjugated CHO); ^{1}H NMR (CDCl$_3$) δ: 6.75 (d of d, 1 H, J = 16 and 7.5, CH=CHCHO), 7.4 (m, 4 H, aromatic H), 7.8 (d, 1 H, J = 16, ArCH=CH), 9.78 (d, 1 H, J = 7.5, CHO).

8. Thiophosgene mixed with CCl$_4$ can be analyzed as follows: a 0.5-mL aliquot of the reagent is mixed with a warm mixture of 15 mL of 30% hydrogen peroxide and 15 mL of 1 N sodium hydroxide. The mixture is shaken occasionally during 20 min (overnight gives the same titer) and diluted to 200 mL with water. Liberated Cl$^-$ is then titrated with mercuric nitrate.

3. Discussion

This procedure is an example of a simple fission reaction of N-heterocyclic compounds by thiophosgene and base[2] wherein the dihydro intermediate 1 undergoes ring fission to yield the Z-isothiocyanate 2 which isomerizes in situ to the E-isomer 3. The reaction may be applied to

1   2   3
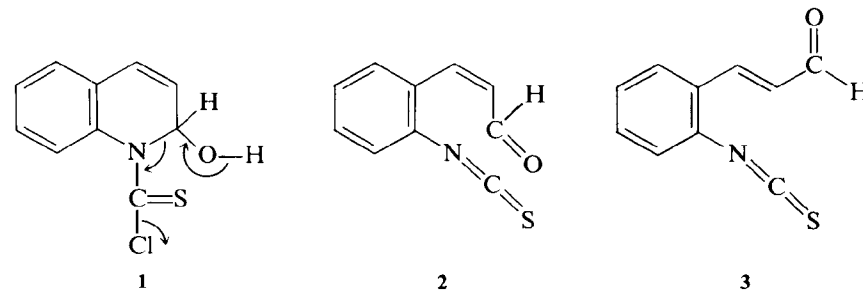
certain substituted quinolines,[3,4] isoquinoline,[2] pyridine,[5] benzoxazole,[6] benzimidazole,[6,7] and oxazole[8] derivatives, but not to benzothiazole.[6]

The ortho-substituted isothiocyanates are valuable intermediates for the preparation of a variety of heterocyclic compounds; for example, o-isothiocyanato-(E)-cinnamaldehyde with sodio diethyl malonate undergoes facile cyclization to 3-formylquinoline-2(1H)-thione,[9] which in turn may be used for the preparation of tricyclic[9,10] and large ring heterocyclic compounds.[11]

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

o-Isothiocyanato-(E)-cinnamaldehyde: Isothiocyanic acid, o-(2-formyl-vinyl)phenyl ester, (E)- (8); 2-Propenyl, 3-(2-isothiocyanatophenyl)-, (E)- (9); (19908-01-1)
Quinoline (8, 9); (91-22-5)
Thiophosgene (8); Carbonothioic dichloride (9); (463-71-8)
o-Isothiocyanato-(Z)-cinnamaldehyde: Isothiocyanic acid, o-(2-formyl-vinyl)phenyl ester, (Z)- (8); (19908-02-2)
Sodio diethyl malonate: Malonic acid, diethyl ester, ion(1−), sodium (8); Propanedioic acid, diethyl ester, ion(1−), sodium (9); (996-82-7)
3-Formylquinoline-2(1H)-thione: 3-Quinolinecarboxaldehyde, 1,2-dihydro-2-thioxo- (9); (51925-41-8)

MERCAPTANS FROM THIOKETALS:
CYCLODODECYL MERCAPTAN
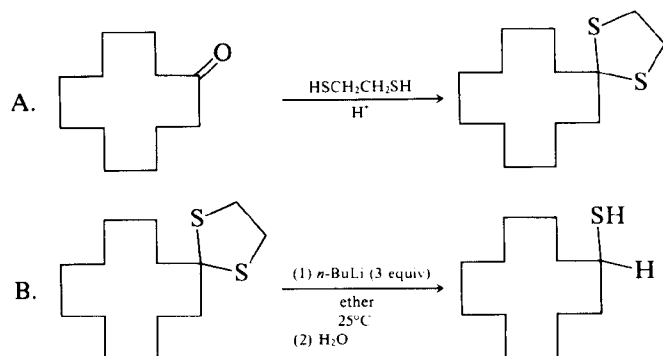
Submitted by S. R. Wilson[1] and G. M. Georgiadis[1]
Checked by E. Vedejs, P. C. Conrad, and M. W. Beck

1. Procedure

Caution! This procedure should be carried out in an efficient hood to prevent exposure to alkane thiols or benzene.

A. 1,4-Dithiaspiro[4.11]hexadecane.   A mixture of 46.5 g (0.26 mol) of cyclododecanone (Note 1), 24.1 g (21.5 mL, 0.26 mol) of 1,2-ethanedithiol (Note 1), and 0.75 g (0.004 mol) of p-toluenesulfonic acid monohydrate (Note 2), in 200 mL of benzene (Note 3) is placed in a 500-mL, three-necked reaction flask equipped for reflux under a water separator.[2] The mixture is heated at reflux for several hours until the theoretical amount of water (0.26 mol = 4.6 mL) has collected in the Dean–Stark trap. The reaction mixture is cooled and transferred to a separatory funnel. The mixture is washed with water, the benzene is removed on a rotary evaporator, and the residue is placed under reduced pressure (<0.1 mm) for several hours to remove traces of solvent. Approximately 66 g (99%) of a white solid is recovered (0.26 mol, mp 84–86°C). The crude material is pure by GLC and TLC, and is used in the next step with no further purification.

B. Cyclododecyl mercaptan.   In a 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer and nitrogen inlet and outlet stopcocks are placed 25.8 g (0.10 mol) of 1,4-dithiaspiro[4.11]hexadecane and 300 mL of ether, freshly distilled from sodium. The mixture is purged with nitrogen, cooled to 0°C with an ice bath, and 125 mL (0.30 mol, 2.4 M in hexane) of butyllithium is added by syringe (Notes 4, 5) under a slow flow of nitrogen. The light yellow mixture is then allowed to warm to room temperature and stirred overnight with nitrogen stopcocks closed (Note 6). The reaction mixture is cooled to 0°C and 50 mL of water is added slowly and very carefully (Note 7). The resulting light brown solution is poured into 200 mL of water in a separatory funnel and, after shaking, the organic layer is separated. The solution is dried over $MgSO_4$, concentrated (aspirator), and distilled through a 10-cm Vigreux column at 103–108°C (1 mm) to give 17.2–17.9 g (86–90%) of pure cyclododecyl mercaptan (Notes 8, 9). A small forerun, bp < 95°C, (ca. 2 mL) is discarded.

2. Notes

1. The submitters used cyclododecanone and 1,2-ethanedithiol obtained from Aldrich Chemical Company, Inc.
2. The submitters used p-toluenesulfonic acid monohydrate from Matheson, Coleman, and Bell.
3. The checkers used toluene in place of benzene.

4. The submitters used butyllithium from Alfa Products, Ventron Corporation.

5. The reaction also occurs well with only 2 mol of butyllithium, but traces of starting material remain.

6. The reaction is complete in about 6 hr.

7. *Caution! Quenching of excess butyllithium is exothermic.*

8. By GLC analysis, the distilled cyclododecyl mercaptan is >95% pure. Sometimes the product is pale pink.

9. The distilled cyclododecyl mercaptan has the following spectral data: ^{1}H NMR (CCl$_4$) δ: 1.1 (d, 1 H, $J = 6$, S-*H*), 1.32 (broad s, 20 H), 1.64–1.82 (m, 2 H), 2.81 (m, 1 H, C*H*SH); IR (neat, μ) 3.4, 6.82, 6.94. Anal. Calcd for C$_{12}$H$_{24}$S: C, 71.93; H, 12.07; S, 16.00. Found: C, 71.83; H, 12.19; S, 16.03.

3. Discussion

Mercaptans are generally prepared by displacement reactions.[3] However, secondary or hindered mercaptans are more difficult to obtain. The dithiolane cleavage reaction[4] is a convenient "in situ" generation of thioketones which are known to be reduced[5] with butyllithium to secondary mercaptans by β-hydrogen transfer. Table I shows a number of mercaptans prepared from *saturated* thioketals in 78–90% yields. The aryl example gives lower yields partly because of ring metalation.

TABLE I
MERCAPTANS FROM ETHYLENE THIOKETAL CLEAVAGE/REDUCTION

Ketone Thioketal	Bp/mp (°C)	Yield (%)
Cyclododecanone	103–108 (1 mm)	90
4-*tert*-Butylcyclohexanone	~100 (0.5 mm)	90[a]
2-Adamantanone	mp 139–142	79
4-Heptanone	127–135 (760)	81
Acetophenone	70–75 (0.5 mm)	36[b]
Cyclohexanone	130–140 (760)	78[c]
Estrone	mp 170–175	90[d]
Pregnenolone	mp 108–113	65[d]
Undecan-5-one	110–120 (0.3 mm)	93

[a]Axial : equatorial ratio, 2 : 1.
[b]By extraction into KOH (purity = 85–93%).
[c]Distillation could not cleanly separate thiol from octane (formed from the butyllithium).
[d]Mixture of isomers.

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

1,4-Dithiaspiro[4.11]hexadecane (9); (16775-67-0)
Cyclododecanone (8, 9); (830-13-7)
1,2-Ethanedithiol (8, 9); (540-63-6)
Butyllithium: Lithium, butyl- (8, 9); (109-72-8)

METHYL α-(BROMOMETHYL)ACRYLATE

(2-Propenoic acid, 2-(bromomethyl)-, methyl ester)

A. $(HOCH_2)_2C(CO_2C_2H_5)_2 + HBr \xrightarrow[6 \text{ hr}]{\text{reflux}} (BrCH_2)_2CHCO_2H$

B. $(BrCH_2)_2CHCO_2H + CH_3OH \xrightarrow[ClCH_2CH_2Cl]{CH_3SO_3H} (BrCH_2)_2CHCO_2CH_3$

C. $(BrCH_2)_2CHCO_2CH_3 + (CH_3CH_2)_3N \longrightarrow$

$$CH_2{=}CCO_2CH_3 + (CH_3CH_2)_3NH^+Br^-$$
$$|$$
$$CH_2Br$$
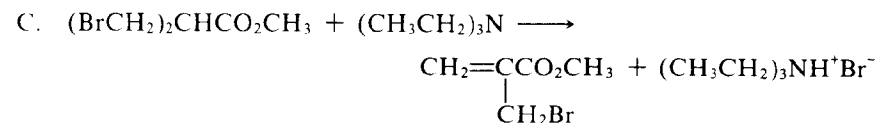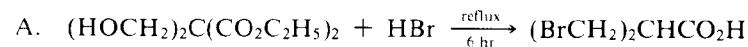
Submitted by JOHN M. CASSADY, GARY A. HOWIE, J. MICHAEL ROBINSON, and IOANNIS K. STAMOS[1]

Checked by PAUL R. WEST and ORVILLE L. CHAPMAN

1. Procedure

Caution! Methyl α-(bromomethyl)acrylate is a potent vesicant and lachrymator and should be handled with care. All operations should be carried out in an efficient hood in order to avoid contact.

A. β,β'-Dibromoisobutyric acid. To a 5-L, single-necked flask, equipped with a heating mantle, 22-cm Vigreux distillation head, thermometer, 30-cm water-cooled condenser with adapter, and 1-L, ice-cooled receiving vessel (Note 1) is added 440 g (2.0 mol) of diethyl bis(hydroxymethyl)malonate (Notes 2^2 and 3) and 3450 mL of concentrated aqueous hydrobromic acid (Note 4). Heating for 6 hr at vigorous reflux gives 2400 mL of aqueous distillate (Note 5). The undistilled concentrate is poured into a 3-L beaker, cooled overnight at $-15°C$ (Note 6), and filtered through a 500-mL fritted-glass Büchner funnel using aspirator vacuum. After suction air drying for 6 hr, drying is continued for 6 days in a vacuum desiccator containing active Drierite and under 10 mm of initial vacuum (Note 7) to give 332 g (67.5%) of β,β'-dibromoisobutyric acid as a brown solid. Distillation of the filtrate to remove an additional 850 mL of aqueous hydrobromic acid (Note 8), followed by cooling and filtration, gives an additional 34.0 g (6.9%) of solid. Crude product, obtained in 74–85% yield (Note 9^3), is suitable for use without further purification (Note 10).

B. Methyl β,β'-dibromoisobutyrate. In a 200-mL, round-bottomed flask fitted with a reflux condenser are placed 61.5 g (0.25 mol) of β,β'-dibromoisobutyric acid, 25 g (0.78 mol) of commercial methanol, 75 mL of ethylene dichloride, and 0.2 mL of methanesulfonic acid (Notes 11^4 and 12). The reaction mixture is heated under reflux for 24 hr. The solution is cooled to room temperature, diluted with about 200 mL of methylene chloride, and neutralized with dilute, cold sodium bicarbonate solution (Note 13). The organic layer is dried over anhydrous sodium sulfate and concentrated on a rotary evaporator to remove most of the methylene chloride. Fractional distillation of this residue under reduced pressure (the receiver is cooled with an ice–salt mixture) yields 48.8 g (75%) of product, bp 64–65°C (0.3 mm).^{3,5,6}

C. Methyl α-(bromomethyl)acrylate. In a dry, 250-mL three-necked flask, equipped with a mechanical stirrer, reflux condenser, and an addition funnel, 20 g (0.077 mol) of methyl β,β'-dibromoisobutyrate (Note $14^{5,6}$) in 50 mL of anhydrous benzene (Note 15^7) is stirred vigorously. Triethylamine (Notes 16^8 and 17) (7.7 g, 0.076 mol) in 50 mL of benzene is introduced dropwise at a rate of about 3 mL per min. After the addition is complete the mixture is stirred for an additional 1 hr at room temperature, refluxed for 1 hr, and then cooled to 20°C. The reaction mixture is filtered with suction and the amine salt washed twice with 20 mL of benzene. The filtrate and washings are combined in a round-

bottomed flask and concentrated on a rotary evaporator at 30–35°C to remove most of the benzene. The residue is transferred to a small distillation apparatus and fractionally distilled at reduced pressure using an oil bath at 50–55°C. The yield of ester collected at bp 35–37°C (1.3 mm) is 11.0 g (80%) (Notes 18–21).

2. Notes

1. Cooling the receiving vessel greatly reduces loss of ethyl bromide.

2. Diethyl bis(hydroxymethyl)malonate was prepared up to an 8.0-mol scale by the method of Block.^{2} After suction filtration to remove the drying agent, the dried diethyl ether extracts were concentrated directly on a Büchi rotary evaporator at aspirator vacuum using a bath temperature of 50°C; concentration was continued for ca. 2 hr after removal of the ether. The crude, oily diethyl bis(hydroxymethyl)malonate, obtained in 94–96% yield, solidified on standing and was suitable for use without further purification. The malonate can be stored at room temperature with no special precautions.

3. The checkers ran this reaction on a 20% scale [starting with 88 g (0.4 mol) of diethyl bis(hydroxymethyl)malonate]. At this scale, yields between 63 and 75% were realized.

4. Initial experiments used commercial 48% aqueous hydrobromic acid. In subsequent runs no decrease in yields was apparent when recovered distillate boiling at or above 110°C was substituted for the commercial acid.

5. Approximately 45 additional min of heating was required to reach distillation temperature. The first 780 mL (excluding ethyl bromide) of aqueous distillate boiled below 110°C and was discarded. The remaining distillate was recycled as described in Note 4.

6. Cooling in a refrigerator freezing compartment is satisfactory. The beaker should be sealed (e.g., using Saran Wrap) to prevent escape of corrosive fumes.

7. After the solid was dried in the desiccator, weight reductions of up to 10% were observed.

8. Special care must be used toward the end of the distillation to avoid overheating caused by removal of too much solvent. Overheating can result in an intractable gummy residue.

9. Failure to distill the maximum amount of concentrated hydro-

bromic acid, higher crystallization temperatures, and/or washing with water may account for the lower (66%) reported[3] yield.

10. Storage at room temperature (under nitrogen or in a filled, sealed container) for periods in excess of 1 year resulted in no significant deterioration of the crude acid as judged by its suitability for use in step B. Preparation of acid was done on a 0.5 – to 3.4 – mol scale with no significant variation in yield.

11. These conditions are patterned after a general procedure for esterification reported by Clinton and Laskowski.[4]

12. The checkers ran this reaction on a 50% scale [starting with 30.75 g (0.125 mol) of β,β′-dibromoisobutyric acid] and obtained yields ranging from 66 to 67%.

13. A brown, emulsified layer, which separates on long standing, is formed between the organic and aqueous layers. This layer can also be taken up with an additional 200 mL of methylene chloride and dried with a sufficient amount of anhydrous sodium sulfate to recover the organic layer.

14. It is recommended that methyl β,β′-dibromoisobutyrate[5,6] which has been purified by fractional distillation be used, since the presence of acidic compounds reduces the yield and the presence of any hydroxyl function gives a product mixture that cannot be purified by simple distillation.

15. The preparation of anhydrous benzene has been described.[7]

16. Commercial triethylamine is conveniently purified by two distillations from a 2% solution of phenyl isocyanate.[8]

17. In a parallel experiment, ethyldiisopropylamine (9.82 g, purified as in Note 16) was mixed with a solution of 20 g of methyl β,β′-dibromoisobutyrate in 100 mL of dry benzene. The reaction mixture was stored at room temperature for 10 hr and gently refluxed for 1 hr under nitrogen in the dark. After work-up and distillation the yield of the product was 80%.

18. Distillation at higher temperatures results in viscous residues with considerably reduced yields of the product. The receiver should be immersed in an acetone–dry ice bath in order to prevent loss of the product to the trap of the vacuum line.

19. The product is stable for long periods of time if kept under an inert atmosphere in the absence of light and in the refrigerator.

20. Ethyl α-(bromomethyl)acrylate is prepared similarly, bp 38–42°C (0.8 mm).

21. The checkers obtained a 76% yield.

3. Discussion

Although methyl and ethyl α-(bromomethyl)acrylate are used extensively as synthetic intermediates in the preparation of a variety of organic compounds,[9,16] many of biological importance, they are not commercially available and their preparation in good yield on a large scale is therefore of interest. The procedures outlined above represent useful modifications of published literature routes to these compounds.

The procedure for the elimination of HBr from the dibromo ester is a modification of the method of Lawton and co-workers for *sui generis* generation of the methyl[5,9] or ethyl ester[10] during a reaction. Methyl α-(bromomethyl)acrylate has also been prepared by bromination of methyl methacrylate in 700°C steam[17] and by dehydrohalogenation with sodium acetate in acetic acid.[6] Ethyl α-(bromomethyl)acrylate has been prepared by dehydrohalogenation with the monosodium salt of ethylene glycol[3,18] and ethyl diisopropylamine.[11] The latter reaction was reported by Öhler et al. with no experimental details for the elimination reaction. The use of triethylamine as reported in this procedure appears to be the most efficient and convenient method for dehydrobromination to these acrylate esters.

1. Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, IN 47907.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Methyl α-(bromomethyl)acrylate: Acrylic acid, 2-(bromomethyl)-, methyl ester (8); 2-Propenoic acid, 2-(bromomethyl)-, methyl ester (9); (4224-69-5)

β,β'-Dibromoisobutyric acid: Propanoic acid, 3-bromo-2-(bromo-methyl)- (9); (41459-42-1)

Diethyl bis(hydroxymethyl)malonate: Malonic acid, bis(hydroxymethyl)-, diethyl ester (8); (20605-01-0)

Methyl β,β'-dibromoisobutyrate: Propionic acid, 3-bromo-2-(bromo-methyl)-, methyl ester (8, 9); (22262-60-8)

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

2-METHYL-3-PHENYLPROPANAL
(Benzenepropanal, α-methyl-)

$$C_6H_5I + CH_2{=}\overset{\overset{\displaystyle CH_3}{|}}{C}CH_2OH + Et_3N \xrightarrow{Pd(OCOCH_3)_2} C_6H_5CH_2\overset{\overset{\displaystyle CH_3}{|}}{C}HCHO + Et_3\overset{+}{N}H\ I^-$$
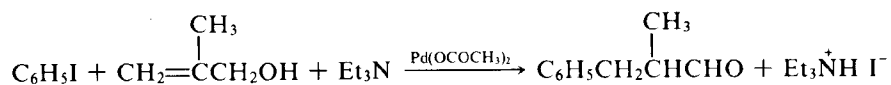
Submitted by S. A. Buntin and R. F. Heck[1]
Checked by C. M. Tice and C. H. Heathcock

1. Procedure

A 250-mL, three-necked, round-bottomed flask, equipped with a mechanical stirrer and a reflux condenser, is charged with 0.49 g (2.2 mmol) of palladium acetate (Note 1), 20.4 g (100 mmol) of iodobenzene, 9.0 g (125 mmol) of 2-methyl-2-propen-1-ol, 12.6 g (125 mmol) of triethylamine, and 32.5 mL of acetonitrile (Note 2). The reaction vessel is placed in an oil bath at 100°C and the solution is heated to reflux for 11 hr under a nitrogen atmosphere. The reaction mixture is allowed to cool to room temperature and transferred to a 500-mL separatory funnel with the aid of 100 mL of ether and 100 mL of water. The organic layer is washed five times with 100 mL portions of water. The combined aqueous layers are reextracted with 100 mL of ether. The organic layers are combined, dried over anhydrous sodium carbonate, and filtered. The organic layer is concentrated and distilled under reduced pressure. The product, 2-methyl-3-phenylpropanal, 12.05 g (82%), has a boiling range of 52–58°C at 0.40 mm (Note 3).

2. Notes

1. Palladium acetate was prepared by the method of Stephenson et al.[2] A suitable material is also available from the Strem Chemical Company or Alfa Inorganics.

2. Iodobenzene, 2-methyl-2-propen-1-ol, and triethylamine were obtained from the Aldrich Chemical Company, Inc. Acetonitrile was obtained from the J. T. Baker Chemical Company. All these reagents were used as received.

3. The 2-methyl-3-phenylpropanal is 90% pure by GLC. The product mixture contains 6% of another isomer, 2-methyl-2-phenylpropanal, and a small amount of 2-phenyl-2-propen-1-ol. A completely pure sample of the aldehyde is readily obtained by stirring the crude aldehyde with excess saturated aqueous sodium bisulfite solution for several hours, filtering the solid bisulfite adduct, washing with ether, and liberating the aldehyde with excess aqueous sodium bicarbonate. Redistillation gives the completely pure aldehyde in about 60% yield.

3. Discussion

The reaction of allylic alcohols and aryl halides in the presence of a palladium catalyst has been used in the past to prepare various β-arylaldehydes. The procedure described here is essentially that of Heck and Melpolder.[3] A similar reaction has been carried out with bromobenzene and 2-methyl-2-propen-1-ol in hexamethylphosphoric triamide (HMPT) as solvent with sodium bicarbonate as base. A variety of other bases have also been used.[4] 2-Methyl-3-phenylpropanal has been prepared by reacting palladium acetate and phenylmercuric acetate with 2-methyl-2-propen-1-ol.[5]

The aldehyde is also obtained by the hydroformylation of allylbenzene.[6] An alternative method involves benzylation of 2-ethylthiazoline followed by reduction with aluminum amalgam and cleavage with mercuric chloride.[7] A sixth method of preparation is the phenylation of 2-vinyl-5,6-

dihydro-1,3-oxazine with phenylmagnesium bromide followed by methylation and hydrolysis.[8] Finally, arylation of 2-methyl-2-propen-1-ol with phenyldiazonium salts catalyzed by zero-valent palladium complexes give the title aldehyde.[9]

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

2-Methyl-3-phenylpropanal: Hydrocinnamaldehyde, α-methyl- (8); Benzenepropanal, α-methyl- (9); (5445-77-2)

Palladium acetate: Acetic acid, palladium(2+) salt (8, 9); (3375-31-3)

Iodobenzene: Benzene, iodo- (8, 9); (591-50-4)

2-Methyl-2-propen-1-ol: 2-Propen-1-ol, 2-methyl- (8, 9); (513-42-8)

Phenylmercuric acetate: Mercury, (aceto)phenyl- (8); Mercury, (aceto-O)phenyl- (9); (62-38-4)

OSMIUM-CATALYZED VICINAL OXYAMINATION OF OLEFINS BY CHLORAMINE-T: cis-2-(p-TOLUENESULFONAMIDO)CYCLOHEXANOL AND 2-METHYL-3-(p-TOLUENESULFONAMIDO)-2-PENTANOL

[Benzenesulfonamide, N-(2-hydroxycyclohexyl)-4-methyl-, cis-]

A. $TsNClNa \cdot 3H_2O$ + [cyclohexene] $\xrightarrow[\text{phase-transfer conditions}]{1\% OsO_4, CHCl_3/H_2O, 60°C}$ [product] + NaCl

B. $TsNClNa \cdot 3H_2O$ + [olefin] $\xrightarrow{1\% OsO_4, \text{tert-butyl alcohol, 60°C}}$ [product] + NaCl
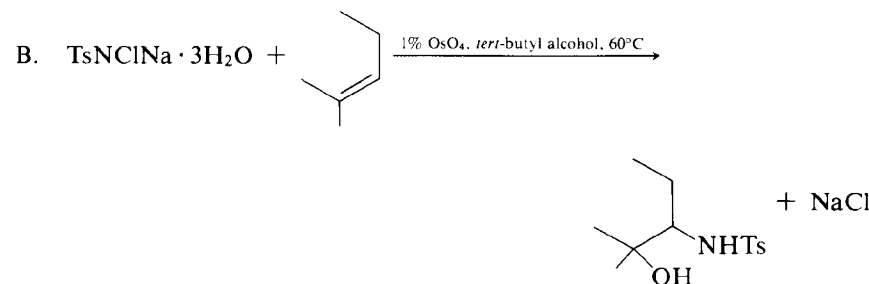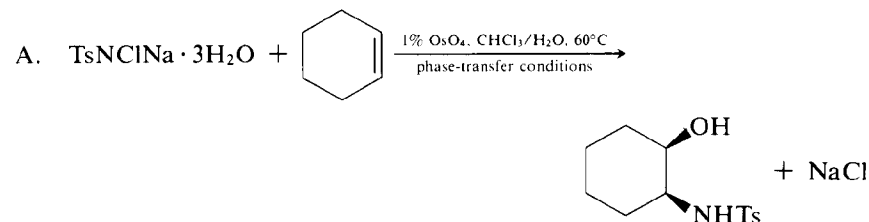
Submitted by Eugenio Herranz and K. Barry Sharpless[1]
Checked by Rita Locher, Thomas Weller, and Dieter Seebach

Caution! Because of the volatility and toxic nature of OsO_4, these reactions should be carried out in a well ventilated hood.

1. Procedure

A. cis-2-p-(Toluenesulfonamido)cyclohexanol. A 1-L, three-necked, round-bottomed flask is equipped with an efficient mechanical stirrer, thermometer, and reflux condenser. The flask is charged with 8.2 g (0.1 mol) of cyclohexene (Note 1), 250 mL of reagent grade chloroform (Note

2), and 10 mL (1 mmol) of osmium tetroxide catalyst solution (Note 3). To the resulting black solution is added a solution of 35.2 g (0.125 mol) of chloramine-T trihydrate (Note 4) and 1.1 g (5 mmol) of benzyltriethylammonium chloride (Note 5) in 250 mL of distilled water. Vigorous stirring is begun, and the reaction mixture is brought to 55–60°C by means of a heating mantle.

After 10 hr at 55–60°C, 14.2 g (0.1 mol) of sodium sulfite (Note 6) is added and the mixture is refluxed for 3 hr. The hot reaction mixture (Note 7) is transferred to a 1-L separatory funnel and allowed to stand for 10 min. The organic layer is collected in a 500-mL, round-bottomed flask. The aqueous layer is extracted once with 25 mL of $CHCl_3$ which is then combined with the original organic layer. Removal of solvent with a rotary evaporator provides a residue (Note 8) that is transferred to a 350-mL fritted-glass funnel and triturated successively with 200 mL and 100 mL of saturated sodium chloride solution containing 1% sodium hydroxide (Note 9) and finally with two 50-mL portions of distilled water.

The resulting solid is placed in a 500-mL Erlenmeyer flask and dissolved in a mixture of 250 mL of $CHCl_3$ and 25 mL of CH_3OH. Anhydrous magnesium sulfate (ca. 8–10 g) is added and the resulting suspension is stirred magnetically for 5 min. Filtration of this suspension through a Celite mat on a sintered-glass funnel (Note 10), followed by evaporation of the solvent, affords (after drying under reduced pressure) 20.3–22 g (75–81.2%) of almost pure *cis*-2-(*p*-toluenesulfonamido)cyclohexanol, mp 155–157°C (Note 11). The oxyaminated product may be purified further by washing with toluene to give 20–21.8 g (74.3–80.9%); mp 157–158°C (Note 12).

B. 2-Methyl-3-(p-toluenesulfonamido)-2-pentanol. A 500-mL, three-necked, round-bottomed flask is equipped with an efficient mechanical stirrer, thermometer, and reflux condenser. The flask is charged with 8.4 g (0.1 mol) of 2-methyl-2-pentene (Note 1), 100 mL of reagent grade *tert*-butyl alcohol (Note 2), 10 mL (1 mmol) of osmium tetroxide catalyst solution (Note 3), and 35.2 g (0.125 mol) of chloramine-T trihydrate (Note 4). Vigorous stirring is begun, and the reaction mixture is brought to 55–60°C by means of a heating mantle.

After ca. 20 hr at 55–60°C, the mixture is cooled to room temperature using a water bath, and then 1.1 g (0.03 mol) of sodium borohydride is

added (Note 6). Stirring is continued at room temperature for about 1 hr. Removal of the solvent on a rotary evaporator gives an oil which is taken up in 100 mL of ethyl acetate and washed once with a solution that is prepared by mixing 100 mL of saturated sodium chloride solution containing 1% sodium hydroxide (Note 13) with 25 mL of distilled water. The organic layer is washed twice more with 200 mL of saturated sodium chloride solution containing 1% sodium hydroxide and finally with 100 mL of saturated sodium chloride solution (Notes 9 and 14). Addition of anhydrous magnesium sulfate, filtration through a column of 75 g of silica gel (Note 15), elution with ethyl acetate (Note 16), and evaporation of the solvent on a rotary evaporator provides 21.5 g of the crude oxyaminated product (Note 17). The solid is then washed twice with ether (Note 18) to give 13.8–14.9 g (51–55%) of white, crystalline 2-methyl-3-(*p*-toluenesulfonamido)-2-pentanol, mp 96–97°C. Concentration of the ether yields an additional 4.0–5.0 g (15–18%) of oxyaminated product, mp 95–97°C (Note 19).

2. Notes

1. Cyclohexene and 2-methyl-2-pentene were used as commercially available.

2. The amount of solvent used is not critical. Several experiments have been performed at higher and lower concentrations and in all cases the yields were very much alike.

3. Osmium tetroxide was supplied commercially in 1-g amounts in sealed glass ampuls. The procedure we describe below should be followed to prepare the osmium tetroxide catalyst solution. Work in a well-ventilated hood. One ampul is scored in the middle, broken open, and the two halves are dropped into a clean brown bottle containing 39.8 mL of reagent grade *tert*-butyl alcohol and 0.20 mL of 70 or 90% *tert*-butyl hydroperoxide. The bottle is capped (use caps with Teflon liners) and then swirled to ensure dissolution of the OsO_4. Each milliliter of this stock solution contains 25 mg (ca. 0.1 mmol) of OsO_4. These solutions are stored in the hood at room temperature and seem to be very stable. We have also prepared five times more dilute solutions of OsO_4 in *tert*-butyl alcohol which we use in the case of small scale experiments.[2]

4. Chloramine-T trihydrate (CT) was obtained commercially. Excess chloramine-T is used because we have observed traces of the α-ketosulfonamide in those cases where the oxyaminated product contains a secondary hydroxyl group. We have also observed that these α-ketosulfonamides are further oxidized under the reaction conditions in a process which consumes several moles of chloramine-T.

5. Benzyltriethylammonium chloride was used as purchased.

6. The rates of reduction of the osmate esters vary considerably. We found that although the sulfite method (in the past we have also used sodium bisulfite) would reduce osmate esters from monosubstituted and 1,2-disubstituted olefins, however, osmate esters derived from trisubstituted and 1,1-disubstituted olefins were more inert to this treatment. Sodium borohydride reduces even these more hindered osmate esters rapidly at room temperature.

7. The oxyaminated product derived from cyclohexene is highly crystalline and begins to crystallize if the chloroform phase is allowed to cool.

8. The residue is dried under reduced pressure to remove the last traces of chloroform and *tert*-butyl alcohol, and then pulverized with a mortar and pestle.

9. In this way the *p*-toluenesulfonamide by-product along with some other impurities are removed from the oxyaminated product.

10. This treatment removes the suspended osmium particles from the solution.

11. GLC analysis revealed a purity of 99%.

12. The product obtained by this procedure is pure enough for most purposes. Its melt, however, is faintly cloudy. A product of higher purity, giving a clear melt, mp 158–159°C, can be obtained by recrystallization from about 10 mL of CHCl$_3$ per gram of oxyaminated product. The structural characterization of *cis*-2-(*p*-toluenesulfonamido)cyclohexanol, mp 158–159°C, is as follows. Anal. Calcd. for C$_{13}$H$_{19}$NO$_3$S: C, 57.97; H, 7.11; N, 5.20. Found: C, 57.81; H, 6.98; N, 5.19. ^{1}H NMR (CDCl$_3$) δ: 1.2–1.9 (m, 8 H, C*H*), 2.26 (d, 1 H, $J = 4$, O*H*), 2.44 (s, 3 H, Ar C*H*$_3$), 3.30 (m, 1 H, NC*H*), 3.80 (m, 1 H, OC*H*), 5.30 (d, 1 H, $J = 7$, N*H*), 7.55 (AA'BB' pattern, 4 H, $J = 8$, Ar*H*); IR (KBr pellet) cm^{-1}: 3420, 3150, 1305, 1285, 1145, 1085, 550 all (s); 2920, 2850, 1440, 970, 930, 890, 815, 660 all (m); 1590, 1370, 1250, 1195, 1185, 1060,

1000 all (w). GC analysis was carried out using the following conditions: 6-ft × 2-mm glass column, packed with 5% OV-17 on 80/100 Gas-Chrom Q, at 70 → 250°C (32°C/min), retention time 9.50–9.60 min.

13. First a 1% solution of NaOH is prepared and then sodium chloride is added until saturation is reached. For the first washing, 25 mL of distilled water is added to 100 mL of the above solution in order to dissolve the inorganic salts present in the reaction mixture.

14. When ethyl acetate is used as the extracting solvent, rapid separation of the two phases was achieved. If a slight emulsion forms at the interphase during the last wash, the addition of celite and subsequent filtration improves the separation.

15. Silica Gel 60 (70–230 mesh ASTM) was used as obtained commercially. A column 50 cm long by 3.5 cm in diameter was used.

16. Approximately 700 mL of EtOAc was necessary to elute all the oxyaminated product from the silica gel column (monitoring by TLC elution with EtOAc is continued until a UV active spot does not appear on TLC). To speed up filtration a slight pressure of 4 psi is applied.

17. The product is a yellowish-brown solid that usually crystallizes when the last traces of EtOAc are removed on the rotary evaporator. If problems are encountered in inducing crystallization, either high vacuum or addition of ether followed by concentration should yield the desired solid.

18. The solid was washed in a 60-mL, sintered-glass funnel, the first time with 30 mL of ether and the second time with 25 mL.

19. The product obtained by this procedure is relatively pure. However, a product of higher purity, giving a clear melt, mp 99–100°C, can be obtained by recrystallization from about 1 mL of toluene per gram of oxyaminated product.

3. Discussion

This osmium-catalyzed procedure provides the first practical and direct means for the *cis* addition of a hydroxyl group and an arylsulfonamido moiety (ArSO$_2$NH) to an olefinic bond. The resulting vicinal hydroxy arylsulfonamides may in some cases be useful in their own right, but they are easily transformed in a variety of selective and potentially useful

ways. Some of the interesting transformations that we[3] have observed are shown below:
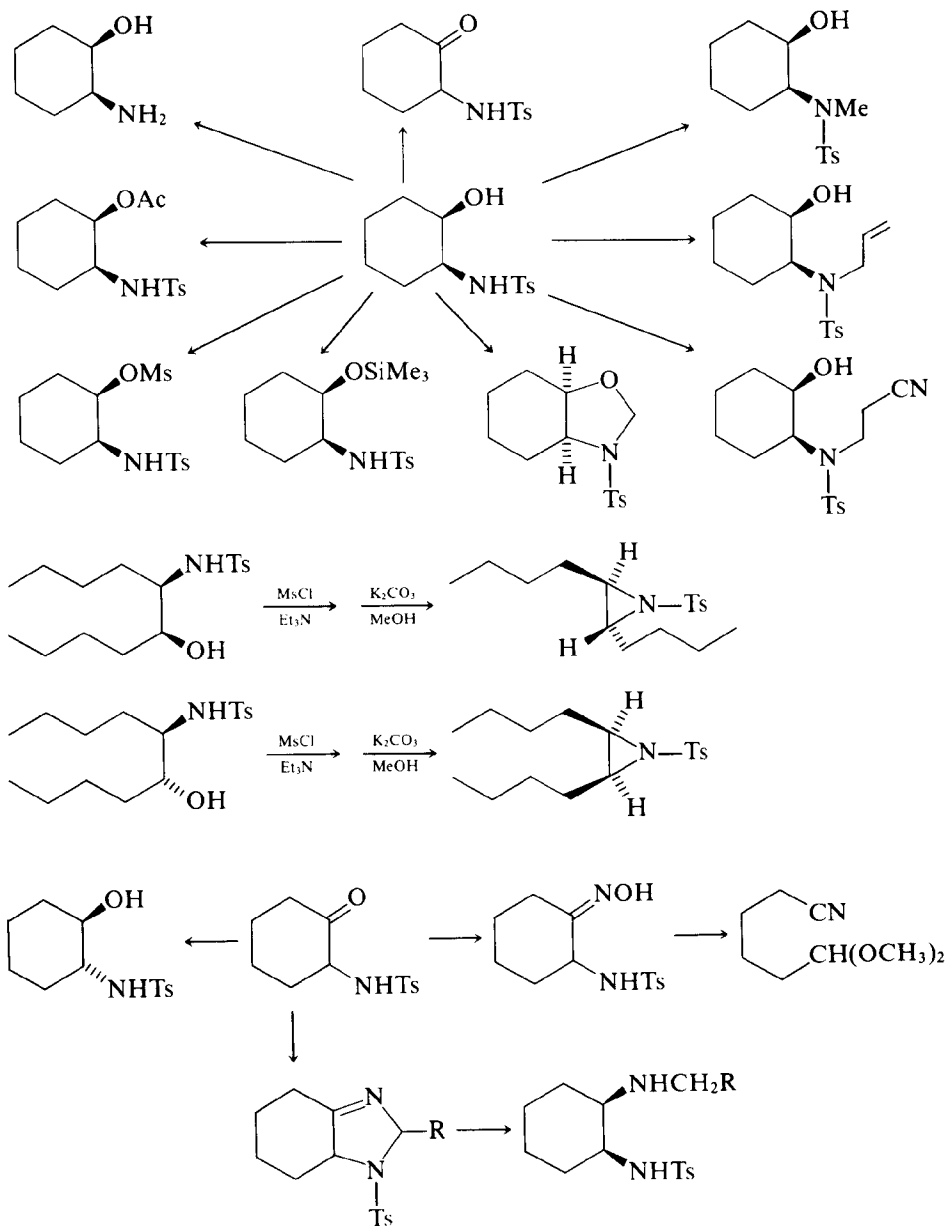
Procedure A is very effective for most monosubstituted and 1,2-disubstituted olefins. This method,[2] using phase-transfer conditions (PTC), has been developed recently in our laboratory and represents a substantial improvement over our former procedures.[4] Cyclooctene, (Z)-5-decene, stilbene, ethyl crotonate, and 1-decene are among the olefins that are readily oxyaminated under the conditions described in procedure A.

It is important to point out that the work-up we have used in the case of cyclohexene is a peculiar one because of the exceptional crystallinity of the oxyamination product. Generally, removal of the p-toluenesulfonamide is accomplished by shaking the chloroform layer with a saturated sodium chloride solution containing 1% sodium hydroxide.

The chloramine derivatives (ArSO$_2$NClNa) of a variety of other arylsulfonamides (Ar = phenyl, o-tolyl, p-chlorophenyl, p-nitrophenyl, and o-carboalkoxyphenyl) have been used successfully in these catalytic oxy-aminations. Since only chloramine-T (Ar = p-tolyl) and chloramine-B (Ar = phenyl) are commercially available, we have developed a convenient procedure for generating the chloramines in situ for use in the modification involving phase-transfer catalysis. One simply stirs a suspension of the arylsulfonamide with an equivalent of sodium hypochlorite (Clorox) until a homogeneous solution is obtained. When this solution is used in the PTC method (see Ref. 2 for experimental details), the yields of oxyaminated product are comparable with those obtained with isolated chloramine salts.

The PTC method gives poor results with trisubstituted and 1,1-disubstituted olefins. The oxyamination product may still form, but it is accompanied by a number of by-products. Fortunately, this class of olefins is successfully oxyaminated by the alternative procedure (B). Methylcyclohexene, α-methylstyrene, 2-methyl-2-hepten-6-one, and its ketal are examples of olefins that give oxyamination products in good yield following procedure B.

Addition of a phase-transfer catalyst such as dicyclohexyl-18-crown-6 to the reaction mixture (in procedure B) results in a faster reaction rate. However, there are no significant changes in the final yield of oxyamination product.

We have carried out experiments on a 1-mol scale in the case of cyclohexene and α-methylstyrene (in the cyclohexene 1-mol experiment, the reaction mixture was 2.5 times more concentrated than described here), and have realized 70–80% and 65–75% yields, respectively, of the oxyaminated products.

Procedure A does not succeed with diethyl fumarate and 2-cyclohexen-1-one. Both chloramine-T and part of the olefin are consumed, but the oxyamination product has not been detected in the reaction mixtures. It seems likely that it forms, but is unstable to the reaction conditions. Both of these olefins do form isolable oxyamination products under the milder conditions (room temperature) of a more recent oxyamination procedure.[5]

Procedure B does not succeed with tetramethylethylene and cholesterol and it seems reasonable to anticipate negative results with most hindered tri- and tetrasubstituted olefins. No reaction occurs, and chloramine-T is not consumed.

The sulfonamide protecting group on the nitrogen may be undesirable in some cases. For this reason we have developed an analogous osmium-catalyzed procedure which effects cis addition of hydroxyl and carbamate (ROCONH) moieties across the olefinic linkage.[5] β-Amino alcohols with benzyloxycarbonyl (Z or CBZ) and tert-butoxycarbonyl (BOC) protecting groups on the nitrogen are accessible directly from the corresponding olefins by the new method.[5]

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

Chloramine-T trihydrate: p-Toluenesulfonamide, N-chloro-, sodium salt (8); Benzenesulfonamide, N-chloro-4-methyl-, sodium salt, trihydrate (9); (7080-50-4)

cis-2-(p-Toluenesulfonamido)cyclohexanol: Benzenesulfonamide, N-(2-hydroxy-cyclohexyl)-4-methyl-, cis- (9); (58107-40-7)

Cyclohexene (8, 9); (110-83-8)

Benzyltriethylammonium chloride: Ammonium, benzyltriethyl-, chloride (8); Benzenemethanaminium, N,N,N-triethyl-, chloride (9); (56-37-1)

2-Methyl-2-pentene: 2-Pentene, 2-methyl- (8, 9); (625-27-4)

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

Osmium tetroxide: Osmium oxide (8); Osmium oxide, (T-4)- (9); (20816-12-0)

Sodium borohydride: Borate(1 −), tetrahydro-, sodium (8, 9); (16940-66-2)

Cyclooctene (8, 9); (931-88-4)

(Z)-5-Decene: 5-Decene, (Z)- (8, 9); (7433-78-5)

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

Ethyl crotonate: Crotonic acid, ethyl ester, (E)- (8); 2-Butenoic acid, ethyl ester, (E)- (9); (623-70-1)

1-Decene (8, 9); (872-05-9)

OSMIUM-CATALYZED VICINAL OXYAMINATION OF OLEFINS BY N-CHLORO-N-ARGENTOCARBAMATES: ETHYL threo-[1-(2-HYDROXY-1,2-DIPHENYL-ETHYL)]CARBAMATE

[Carbamic acid (2-hydroxy-1,2-diphenylethyl),- ethyl ester, (R*R*)-]

$$EtOCONH_2 + t\text{-}BuOCl \xrightarrow{CH_3OH} EtOCONHCl + t\text{-}BuOH$$

$$EtOCONHCl + NaOH \xrightarrow{CH_3OH} EtOCONClNa + H_2O$$

$$Ph\diagdown\diagup Ph + EtOCONClNa + AgNO_3 + H_2O \xrightarrow[CH_3CN]{1\% OsO_4}$$

$$Ph\diagdown\overset{\displaystyle OH}{\underset{\displaystyle NHCOOEt}{\diagup}} Ph + AgCl + NaNO_3$$
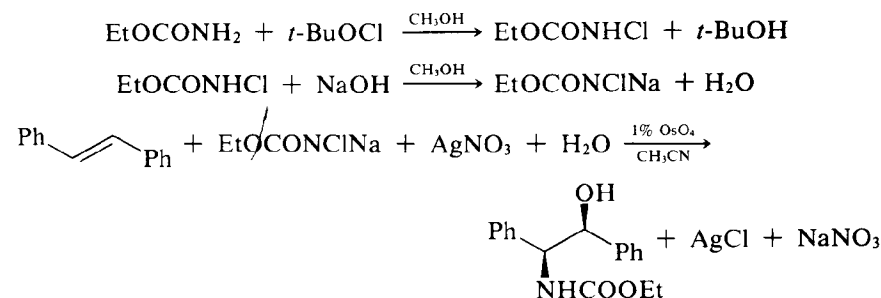
Submitted by Eugenio Herranz and K. Barry Sharpless[1]
Checked by Steven D. Young and Clayton H. Heathcock

1. Procedure

A 1-L, one-necked, round-bottomed flask is equipped with a magnetic stirring bar and a 100-mL addition funnel. The flask is placed in an ice

bath and charged with 13.36 g (0.15 mol) of ethyl carbamate (Note 1) and 100 mL of reagent grade methanol. Vigorous stirring is begun and to the ice-cold solution is carefully added 16.9 mL (16.2 g, 0.15 mol) of *tert*-butyl hypochlorite (Note 2). Fifteen minutes after the addition of the *tert*-butyl hypochlorite is complete, a methanolic solution (75 mL) of sodium hydroxide (6.43 g, 0.158 mol) is added dropwise over a period of several minutes (Note 3). After addition of the sodium hydroxide is complete, the ice bath is removed and stirring is continued for a further 10 min. The solvent is removed using a rotary evaporator (bath <60°C) to give the crude ethyl *N*-chloro-*N*-sodiocarbamate as a white solid (Note 4). Addition of 400 mL of reagent grade acetonitrile and 26.33 g (0.1 mol) of silver nitrate (Note 5) results in the gradual appearance of a brown suspension. The solution is stirred for 5 min at room temperature; 18.23 g (0.1 mol) of (*E*)-stilbene (Note 6), 10 mL (~1.0 mmol) of a solution of OsO₄ in *tert*-butyl alcohol (Note 7), and 8.1 mL (0.45 mol) of water are then added. The milky brown suspension that results is stirred for 18 hr at room temperature. Filtration of the reaction mixture through a Celite mat on a sintered-glass funnel gives a yellow-brown solution (Note 8). The filtrate is refluxed for 3 hr with 200 mL of 5% aqueous sodium sulfite (Note 9). The resulting mixture is concentrated at aspirator pressure using a rotary evaporator until acetonitrile no longer distills. The residue, which is primarily aqueous, is extracted with two 60 mL portions of methylene chloride (Note 10). The organic phase is dried (MgSO₄) and concentrated to give 24.6 g of crude product as a pale yellow solid. Crystallization from 50 mL of hot toluene affords 18.6–19.8 g (66–69%) of almost pure ethyl *threo*-1-(2-hydroxy-1,2-diphenylethyl)carbamate, mp 120–122°C (Note 11). Concentration of the mother liquors yields an additional 0.6–0.8 g of the hydroxy carbamate (Note 12).

2. Notes

1. Ethyl carbamate was obtained from the Aldrich Chemical Company, Inc.

2. *tert*-Butyl hypochlorite was obtained from Frinton Laboratories.

3. A 5% excess of sodium hydroxide was used to make sure that the *N*-chloro-*N*-sodiocarbamate was in a basic environment. The sodium hydroxide was obtained from J. T. Baker Chemical Company; it was 97.9% pure.

4. To remove the last traces of methanol the crude *N*-chloro-*N*-sodiocarbamate is placed under high vacuum (0.1 mm) for 15 min. Slightly higher yields of final product are obtained if the crude *N*-chloro-*N*-sodiocarbamate is purified by trituration with ether.

5. Silver nitrate was obtained from Apache Chemicals Inc.

6. (*E*)-Stilbene was used as obtained from Aldrich Chemical Company. The olefin should be added in small portions to avoid overheating of the reaction mixture.

7. Osmium tetroxide was supplied by Matthey-Bishop, Inc. in 1-g amounts in sealed glass ampuls. The procedure that we describe below should be followed to prepare the osmium tetroxide catalyst solution. Work in a well-ventilated hood. One ampul is scored in the middle, broken open, and the two halves are dropped into a clean, brown bottle containing 39.8 mL of reagent grade *tert*-butyl alcohol and 0.20 mL of 70 or 90% *tert*-butyl hydroperoxide (Aldrich). The bottle is capped (use caps with Teflon liners) and then swirled to ensure dissolution of the OsO₄. These solutions are stored in the hood at room temperature and seem to be very stable.

8. In this way the silver salts (AgCl) are removed from the reaction mixture. The precipitate is washed twice with 20-mL portions of acetonitrile.

9. The purpose of this sulfite treatment is to reduce and thereby remove the small amount of osmium that is bound to the organic products.

10. If an emulsion forms, addition of Celite and subsequent filtration through a sintered-glass funnel gives a clear separation of the two phases. The checkers found that extraction with three 100-mL portions of methylene chloride avoids emulsion formation.

11. Crystallization occurs at room temperature over a period of ca. 12 hr. The crystals are washed once with 15 mL of toluene or 50 mL of petroleum ether (bp 40–60°C). The product is quite pure. A product of higher purity, however, mp 122–123.5°C, can be obtained by a second crystallization from toluene.

12. After 24 hr at high vacuum (0.1 mm), some crystals appear. Addition of 15 mL of ether, filtration, and washing with 10 mL of ether give more product, mp 110–121°C. The checkers found that a higher overall yield was obtained if the mother liquors from the first recrystallization were dissolved in 50 mL of boiling diethyl ether. The solution is then brought to cloudiness by addition of petroleum ether (bp 40–

60°C). When this mixture is stored at 0°C overnight, brown crystals are deposited. Recrystallization of this material from 10 mL of hot toluene provides an additional 2.25–3.51 g of hydroxy carbamate, mp 114–117°C.

3. Discussion

This new procedure[2] for vicinal, cis addition of an oxygen and a nitrogen to an olefinic bond constitutes a major improvement over earlier methods,[3,4] since the nitrogen is introduced bearing an easily removed protecting group. Although the procedure described here employs ethyl carbamate, both *tert*-butyl carbamate and benzyl carbamate can also be used. In fact, in most cases, higher yields are realized in oxyaminations using the latter carbamates.

N-Chloro-*N*-argentocarbamates are generated *in situ* by reaction of the corresponding *N*-chlorosodiocarbamates with silver nitrate in acetonitrile. The *N*-chlorosodiocarbamates are prepared from the carbamates according to the method of Campbell and Johnson.[5] There are conflicting statements in the literature about the stability of these *N*-chlorosodiocarbamates.[6] On one occasion, when EtOCONNaCl was prepared by the submitters on a 250-mmol scale, it decomposed rapidly (but not explosively), turning dark and releasing heat and gases. However, this same chloramine salt has been prepared on a 100-mmol scale without incident. The submitters have found that acidic conditions (which lead to contamination by the *N*-chlorocarbamate) are responsible for the spontaneous decomposition of these salts at room temperature. A simple modification of Campbell's procedure for preparing *N*-chloro-*N*-sodiocarbamates avoids this problem. By adding 5% more sodium hydroxide than the calculated amount, it is assured that all the *N*-chlorocarbamate in the reaction mixture is neutralized. No spontaneous decomposition has occurred in the batches of *N*-chloro-*N*-sodiocarbamates prepared in this way.

The regioselectivity of this new procedure toward terminal olefins is considerably better than that realized with the earlier catalytic oxyamination procedures based on chloramine-T.[3] However, the catalytic procedure cannot compete with the regiospecificity exhibited by the stoichiometric *tert*-alkyl imido osmium reagents.[3]

This new catalytic procedure shows a different range of reactivity when compared with the chloramine-T based procedures, being very effective for mono- and 1,2-disubstituted olefins, especially electron-deficient ole-

fins such as dimethyl fumarate and (*E*)-stilbene. However, when the steric hindrance of the olefin increases (trisubstituted olefins), the oxyamination reaction proceeds slowly and affords mixtures of products. Very recently we have been able to oxyaminate trisubstituted olefins (2-methyl-2-heptene, 1-methylcyclohexene, 1-phenylcyclohexene, 3-methyl-2-cyclohexenone) using other *N*-chloro-*N*-metallocarbamates in conjunction with the addition of tetraethylammonium acetate (Et_4NOAc).[7]

1. Department of Chemistry, Stanford University, Stanford, CA 94305. Present address: Department of Chemistry, Massachusetts Institute of Technology, Cambridge Mass., 02139.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

Ethyl *threo*-[1-(2-hydroxy-1,2-diphenyl)ethyl]carbamate: Carbamic acid (2-hydroxy-1,2-diphenylethyl)-, ethyl ester, (*R**,*R**)- (9); (73197-89-4)

Ethyl carbamate: Carbamic acid, ethyl ester (8, 9); (51-79-6)

Ethyl *N*-chloro-*N*-sodiocarbamate: Carbamic acid chloro-, ethyl ester, sodium salt; (8, 9); (17510-52-0)

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

1,3-OXAZEPINES VIA PHOTOISOMERIZATION OF HETEROAROMATIC *N*-OXIDES: 3,1-BENZOXAZEPINE
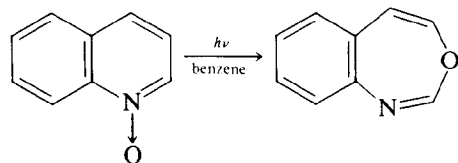
Submitted by ANGELO ALBINI, GIAN FRANCO BETTINETTI, and GIOVANNA MINOLI[1]
Checked by PATRICK MACMANUS and ROBERT M. COATES

1. Procedure

Caution! 3,1-Benzoxazepine is a strong lacrimator and a moderate skin irritant. The preparation should be carried out in a well-ventilated hood. See benzene warning, Org. Synth. **1978,** *58, 168. The apparatus should be shielded to avoid exposure to ultraviolet light.*

Irradiation is carried out in a round-bottomed, cylindrical, Pyrex vessel (Note 1) equipped with a Pyrex immersion well (Note 2), nitrogen inlet, distillation sidearm, a small sidearm fitted with a rubber septum for removing aliquots, and a magnetic stirring bar. The flask is charged with 12 g (0.066 mol) (Note 3) of quinoline *N*-oxide dihydrate (Note 4) and 1.3 L of dry benzene (Note 5). The mixture is stirred and heated to boiling with a heating mantle as a slow stream of nitrogen (Note 6) is bubbled into the vessel. Benzene is distilled through the sidearm until the distillate is perfectly clear (Note 7). The lamp (Note 8) is placed in the immersion well, water is circulated through the cooling jacket, and the nitrogen flow is adjusted as necessary to maintain an outward flow of gas while the light yellow solution cools to room temperature (Note 9). The solution is stirred vigorously (Note 10) and irradiated for 2.5–3 hr at which time the *N*-oxide is largely consumed (Note 11). The orange solution is transferred to a 1-L, round-bottomed flask, and the benzene is removed by rotary evaporation at room temperature. The red-orange oily residue which contains some solid is extracted with three 40-mL portions of dry cy-

clohexane, the combined cyclohexane extracts are evaporated under reduced pressure at room temperature, and the extraction operation is repeated on the oil thus obtained (Note 12). Evaporation of the combined cyclohexane extracts affords 6.1–6.3 g (63–65%) of crude 3,1-benzoxazepine (Note 13). Bulb-to-bulb distillation in a Kugelrohr apparatus at 0.2 mm with an oven temperature of 80°C affords 4.7–4.8 g (49–50%) of 3,1-benzoxazepine as a pale yellow oil, n_D^{24} 1.6074 (Notes 14 and 15).

2. Notes

1. The apparatus used by the checkers for irradiations at a 9-g scale was 33 cm high and 9 cm in diameter and had a 60/50 ℸ joint at the top for the immersion well. The joints for the distillation and sampling sidearms were 24/40 and 14/20, respectively. The gas inlet was located about 6 cm from the bottom of the vessel to accommodate the use of a heating mantle. A disk of coarse, sintered glass was sealed into the gas inlet near its point of attachment. The capacity of the vessel with the immersion well in place was ca. 900 mL. The submitters used a similar but flat-bottomed apparatus of 1.2-L capacity. The flat-bottomed vessel facilitates vigorous stirring, but it does not fit as well into the heating mantle and may therefore be somewhat hazardous to use.

2. The checkers used a Vycor immersion well and a Pyrex filter sleeve. The immersion well, 450-W mercury lamp, and the requisite transformer are available from Hanovia Lamp Division, Canrad-Hanovia Inc, 100 Chestnut Street, Newark, NJ 07105.

3. The checkers carried out the irradiation on a 9-g scale in 750 mL of benzene after azeotropic distillation.

4. Quinoline *N*-oxide dihydrate is supplied by Aldrich Chemical Company, Inc. and EGA Chemie KG, Steinheim/Albuch, Germany. The submitters prepared the compound by the procedure of Hayashi[2] with minor modifications. The water of hydration may be removed under reduced pressure in a drying pistol. However, since the anhydrous *N*-oxide is very hygroscopic, the submitters have found that it is more expedient to use the dihydrate and remove the water by azeotropic distillation in the irradiation vessel.

5. The checkers dried the benzene by distillation from calcium hydride immediately before use. The submitters report that toluene may be

used instead of benzene; however, since the product is not very thermally stable, they advise that the toluene should be evaporated without heating during the isolation.

6. Other dry gases may be used. The submitters report that the reaction is not quenched by oxygen.

7. A total of ca. 150–300 mL was collected. The distillation time may be reduced by insulating the vessel and sidearm with glass wool.

8. The submitters used a Helios Italquartz 500-W lamp which has emission characteristics similar to those of the Hanovia 450-W medium pressure mercury lamp used by the checkers.

9. The checkers noticed that a thin film of oil which was evidently quinoline N-oxide deposited on the surface of the immersion well and irradiation vessel during cooling.

10. Vigorous stirring is essential for optimum yields. The checkers obtained lower isolated yields (ca. 32–33%) in two runs in which a relatively slow stirring rate was employed. The low yields were probably caused in part by deposition of oil on the surface of the immersion well and the resulting interference with the transmission of ultraviolet light into the solution.

11. The submitters emphasize the importance of terminating the irradiation before all of the N-oxide is consumed. Overirradiation gives rise to a more complicated mixture of products from which the product can no longer be isolated by the simple extraction procedure described.

The progress of the irradiation was determined by the checkers by proton NMR analysis. At appropriate intervals 5-mL aliquots were removed, the solvent was evaporated, and hexamethylbenzene was added as an internal standard. The ratio of N-oxide, benzoxazepine, and hexamethylbenzene was determined from integration of the resonances at δ 8.46 (d, 1 H, J = 6), 5.55 (d, 1 H, J = 6), and 2.26 (s, 18 H), respectively, in chloroform-d. After 2.5–3 hr of irradiation the amount of benzoxazepine present was ca. 60–68% of theoretical and ca. 10% of starting N-oxide remained.

The submitters followed the course of the irradiation by TLC analysis on silica gel with 5% (v/v) methanol in chloroform as developing solvent. Since some by-products have R_f values coincident with the N-oxide, this spot will not completely disappear and caution must be exercised to avoid overirradiation.

12. This extraction procedure separates most of the carbostyril, that is, 2(1H)-quinolinone, which is formed to the extent of ca. 20% in the irradiation. The submitters have isolated the carbostyril by-product by crystallization of the extraction residue from 95% ethanol in runs carried out to high conversion. Alternatively, the carbostyril may be isolated by chromatography of the crude product on silica gel with 5% methanol–chloroform as eluant. However, the benzoxazepine cannot be obtained by this method since it undergoes hydrolysis during the chromatography.

13. The purity of the crude product is about 90% according to NMR analysis, the remaining material being mostly unchanged N-oxide.

14. The spectral properties of the product are as follows: IR (liquid film) cm^{-1}: 1665 (C=N), 1630 (C=C), 1480 (sharp), 1440 (sharp), 1035 (strong), 765 (strong); ^{1}H NMR (CDCl$_3$) δ: 5.55 (d, 1 H, J = 6, CH=CH—O), 5.84 (d, 1 H, J = 6, CH=CH—O), 6.44 (s, 1 H, O—CH=N), 6.96 (m, 4 H, aromatic protons).

15. Samples of the product stored in tightly stoppered flasks in a freezer at −20°C for several weeks showed no sign of decomposition.

3. Discussion

The preparation of 3,1-benzoxazepines by photochemical isomerization of quinoline N-oxides constitutes a rather general entry into this class of seven-membered heterocycles. Since the structure of the photoisomer of 2-phenylquinoline N-oxide was first recognized as 2-phenyl-3,1-benzoxazepine by Buchardt et al.,[3] the scope of this method for oxidative ring expansion of six-membered heterocyclic N-oxides to 1,3-oxazepines has been extensively explored.[4] For example, irradiation of 2-cyano-, 2-phenyl-, and 2-methoxyquinoline N-oxides affords the corresponding 2-substituted 3,1-benzoxazepines in 70–90% yield.[5] However, isolation of the moisture-sensitive parent compound was only recently accomplished in the submitters' laboratories.[6]

Related 1,3-oxazepines have been obtained from irradiation of many other heterocyclic N-oxides including pyridine N-oxides, isoquinoline N-oxides, quinoxaline N-oxides, quinazoline N-oxides, phenanthridine N-oxides, benzophenazine N-oxides, and acridine N-oxides.[4] However, the reported yields are variable and have generally been higher for phenyl and other aryl-substituted derivatives.
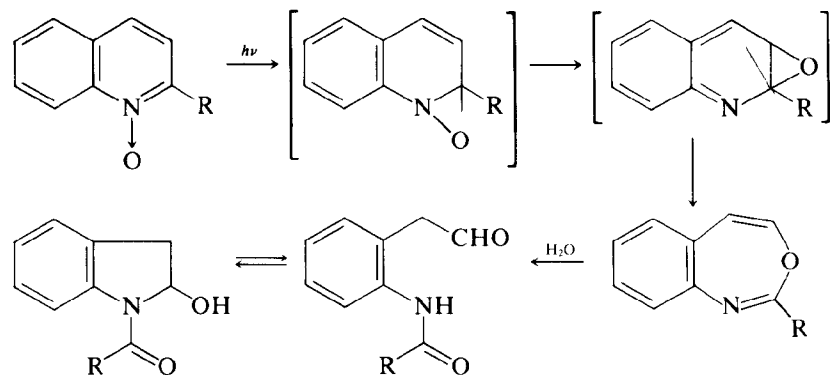
A mechanism involving initial cyclization to an oxaziridine, [1,5] sigmatropic rearrangement to an imino epoxide, and electrocyclic ring opening was originally proposed for the photochemical isomerization.[4] However, since later attempts to detect intermediates by flash photolysis were unsuccessful,[7] ground-state oxaziridines, if formed at all, must have exceedingly short lifetimes. The benzoxazepines undergo facile hydrolysis to o-(N-acylamino)phenylacetaldehydes which frequently exist as the cyclic carbinol amide tautomers. If water is present during the irradiation from use of the N-oxide hydrate or moist solvent, the hydrolysis products may be isolated instead of the benzoxazepines. Dehydration of the carbinol amide to N-acyl indoles may also occur during irradiation and/or purification of the products. The formation of carbostyrils is sometimes an important competing reaction in the irradiation of quinoline N-oxides and this by-product is in fact formed to the extent of ca. 20% in the present procedure. The use of polar protic solvents such as water or alcohols favors carbostyril formation in contrast to aprotic solvents such as benzene or acetone in which the pathway leading to benzoxazepines usually predominates.

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

3,1-Benzoxazepine (8, 9); (15123-59-8)
Quinoline N-oxide: Quinoline 1-oxide (8, 9); (1613-37-2)
Hexamethylbenzene: Benzene, hexamethyl- (8, 9); (87-85-4)
Carbostyril (8) (493-62-9); 2(1H)-Quinolinone (9) (59-31-4)

PERHYDRO-9b-BORAPHENALENE
AND PERHYDRO-9b-PHENALENOL

(9b-Boraphenalene, dodecahydro-) and [Phenalen-9bα(2H)-ol, 3,3aα,4,5,6,6aα,7,8,9,9aβ-decahydro-]

$$+ NaB(OH)_4 + (CH_2OH)_2$$
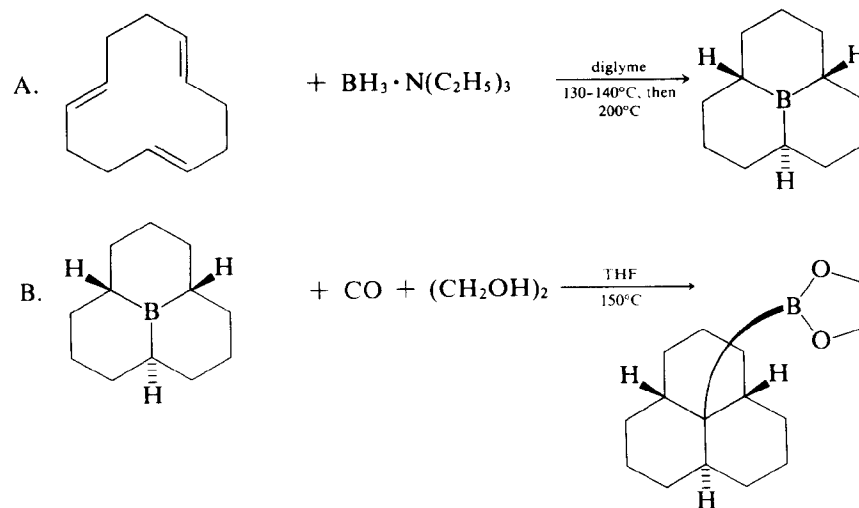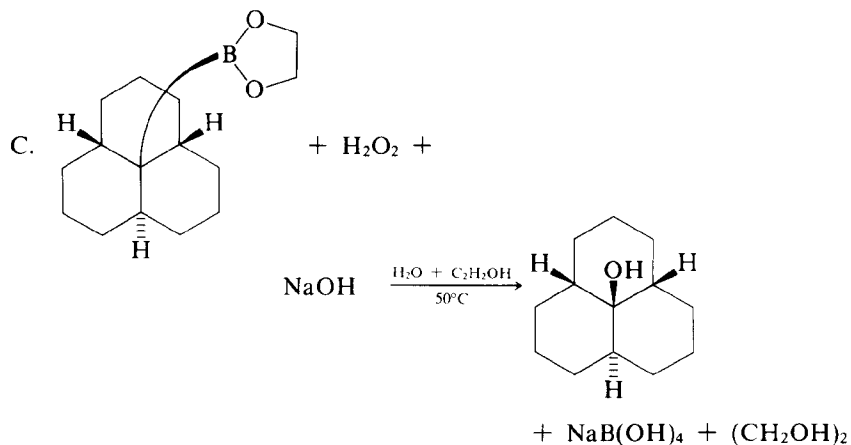
Submitted by El-ICHI Negishi[1,3] and Herbert C. Brown[2,3]
Checked by A. J. Cocuzza and R. E. Benson

1. Procedure

Caution! The products used and formed in Step A are extremely pyrophoric. Great care should be taken in conducting this step.

A. *cis,trans-Perhydro-9b-boraphenalene.* A 1-L, three-necked, round-bottomed flask is fitted with a septum, thermometer, magnetic stirring bar, and a 12-cm Vigreux column. A 2-L, two-necked receiving flask is attached to the Vigreux column and fitted with a nitrogen inlet tube that is attached to a mercury bubbler device to permit a positive pressure on the system (Note 1). The entire system is flushed with nitrogen and, while the system is maintained under a static pressure of nitrogen, 500 mL (0.050 mol) of a 1.0 M solution of borane in tetrahydrofuran (THF, Note 2) is added to the reaction flask by means of a syringe. The flask is immersed in an ice-water bath, stirring is begun, and 50.6 g (0.50 mol) of triethylamine (Note 3) is added slowly over 15 min. After the addition is completed, the THF is removed by distillation at atmospheric pressure and 300 mL of dry diglyme (Note 4) is added. The resulting solution is heated to 130–140°C and a solution of 81 g (0.50 mol) of *trans,trans,trans*-1,5,9-cyclododecatriene (Note 5) in 100 mL of dry diglyme (Note 6) is added over 2 hr. At the end of this time, the diglyme is removed by distillation at atmospheric pressure and the residual oil is

heated at 200°C for 6 hr (Note 7). After the reaction is cooled, the thermally treated product is used directly in Step B (Note 8). Product free of polymeric impurity can be obtained by distillation (Notes 9, 10).

B. *cis,cis,trans-2-(Perhydro-9'b-phenalyl)-1,3,2-dioxaborole.* The 250-mL pressure vessel (Note 11) is fitted with a cap bearing a rubber septum. Two hypodermic needles are inserted into the vessel through the septum, one with the end close to the bottom of the vessel and the other with the end close to the top. The vessel is flushed with nitrogen, with the exit gas passing through a mercury bubbler device. One-fifth of the thermally treated, undistilled product obtained from Step A is dissolved in 50 mL of dry THF (Note 12) and added to the vessel by means of a syringe while a static pressure of nitrogen is maintained on the vessel. Ethylene glycol (18.6 g, 16.8 mL, 0.30 mol) (Note 13) is then added. The rubber septum is removed and the vessel is quickly connected to a cylinder of carbon monoxide (Note 14) and placed in a heating device capable of agitation. The vessel is agitated and the pressure increased with carbon monoxide to ca. 70 atm (ca. 1000 psi); the temperature is raised to 150°C. The vessel is maintained at this temperature for 2 hr and then cooled to room temperature and opened to the air. The contents of the vessel are transferred to a flask; the vessel is rinsed with two 50-mL portions of pentane, and the pentane is added to the product. The resulting solution is washed with 50 mL of water and dried over magnesium sulfate. The drying agent is removed by filtration, and the pentane removed by distillation to give 19.4 g of *cis,cis,trans*-2-(perhydro-9'b-phenalyl)-1,3,2-dioxaborole, a solid that can be further purified by recrystallization from pentane, mp 101–102°C (Note 15).

C. *cis,cis,trans-Perhydro-9b-phenalenol.* A 500-mL, three-necked, round-bottomed flask is fitted with a septum, thermometer, magnetic stirring bar, and a reflux condenser, which is connected to a nitrogen inlet and a mercury bubbler device. The system is flushed with nitrogen, and 50 mL of THF, 100 mL of 95% ethanol, and 19.4 g (0.0782 mol) of *cis,cis,trans*-2-(perhydro-9'b-phenalyl)-1,3,2-dioxaborole from step B are added to the flask together with 37 mL (0.220 mol, 120% excess) of 6 N sodium hydroxide. The solution is stirred and, by means of a dropping funnel, 37 mL (~0.326 mol) of 30% hydrogen peroxide (Note 16) is added at such a rate that the temperature of the reaction mixture does not exceed 40°C. After the initial reaction has subsided, the reaction mixture is heated for 2 hr at 50°C to assure complete oxidation (Note

17). At the end of this time, 300 mL of pentane is added. The mixture is transferred to a separatory funnel, and the organic layer is separated and washed three times with 50-mL portions of water and then dried over magnesium sulfate. The mixture is filtered, and the solvent is removed by distillation to yield a solid (Note 18) which is recrystallized from cold pentane to give 10.9 g (71.7%) of cis,cis,trans-perhydro-9b-phenalenol, mp 75–76°C (Note 19).

2. Notes

1. All joints must be well greased and securely clamped. Even a minor leak is a fire hazard.

2. The checkers used a reagent available from Aldrich Chemical Company, Inc. Borane–THF was prepared by the submitters.[2] The direct use of borane–THF for hydroboration results in the formation of a polymeric, insoluble intermediate, which can be depolymerized by heating.

3. The checkers refluxed triethylamine, available from Eastman Organic Chemicals, with phenyl isocyanate and then isolated the amine by distillation. The submitters used a reagent available from Aldrich Chemical Company, Inc.

4. The checkers used a reagent available from Aldrich Chemical Company, Inc. The diglyme was distilled from sodium benzophenone ketyl prior to use. The submitters used a reagent available from the same source and distilled it from lithium aluminum hydride prior to use.

5. The checkers and the submitters used reagent available from Chemical Samples Co. The submitters state that other isomers such as trans,trans,cis-1,5,9-cyclododecatriene or a mixture of isomers can be used.[3] In this case a slightly different isomer distribution is observed, and the yields of isolated product are somewhat lower. The checkers confirmed this observation, using trans,trans,cis reagent available from Aldrich Chemical Company, Inc.

6. A syringe pump was used with the syringe well greased with a polyhalo hydrocarbon lubricant. Alternatively, a pressure-equalizing dropping funnel can be used.

7. It is essential to heat the initially formed product to 200°C to achieve isomerization of the other isomers present to cis,trans-perhydro-9b-boraphenalene. When this thermal treatment is omitted, the desired product is contaminated with one major (30–40%) and several minor, unidentified, isomeric substances.

8. Perhydro-9b-boraphenalene is highly flammable. The transfer must be carried out with caution. The use of gloves is recommended to avoid direct contact with the organoborane. The transfer is most conveniently done under a slightly positive pressure of nitrogen using a broad gauge (18G), double-tipped needle.

9. The crude product is diluted with a small amount of dry THF and the solution transferred to a 100-mL distillation flask. Distillation through a 12-cm Vigreux column gives 58.0–60.1 g (66–68% yield) of a mixture of cis,trans- and cis,cis-perhydro-9b-boraphenalene, bp 113–114°C (9.5 mm), ^{1}H NMR (CDCl$_3$) δ: 0.7–2.2.

10. The submitters state that the composition of the distillate is 92 : 8 cis,trans : cis,cis isomer, based on GC analyses using an SE-30 column. The assigned stereochemistry is supported by the ^{1}H NMR spectrum of the pyridine complex.[3]

11. The checkers used a 250-mL Hastelloy pressure vessel. The submitters used a 250-mL autoclave available from American Instrument Co.

12. The checkers used a reagent available from Fisher Scientific Company. The submitters used a reagent available from Aldrich Chemical Company, Inc.

13. The checkers distilled the reagent available from E.I. du Pont de Nemours & Co. The submitters used a reagent available from Aldrich Chemical Company, Inc.

14. The checkers and submitters used a reagent available from Matheson Gas Products.

15. The checkers obtained the product in 87% crude yield using distilled boraphenalene. Recrystallization from pentane gave product in 66% yield, mp 101–102°C, with the following spectral characteristics: IR (KBr) cm^{-1}: 1185, 1200, 1250, 1310, 1385, 2860, and 2900–2950; ^{1}H NMR (CDCl$_3$) δ: 1.0–1.9 (m, 21 H), 4.11 (s, 4 H). The structure of the product has been confirmed by X-ray crystallography.[3]

16. The checkers and the submitters used reagent available from Fisher Scientific Company.

17. The submitters state that oxidation of the dioxaborole is unusually sluggish and urge the use of ethanol as a cosolvent and an excess of 6 N sodium hydroxide. They also urge monitoring of the reaction by GC. The checkers monitored the reaction by both GC and TLC analyses. GC analysis by the checkers was conducted using the following column and conditions: 3.2-mm by 2-m column, 7% SE 30/3% Silar on Gas

Chrom Q (60–80 mesh), 170°C, 50 mL of nitrogen per min. The retention times for the perhydrophenalenol and dioxaborole are 6.4 and 15.2 min, respectively. For TLC analyses, Analtech silica gel plates bearing the material were eluted by 1 : 2 methylene chloride–petroleum ether, and visualized with phosphomolybdic acid: perhydrophenalenol, R_f 0.4; dioxaborole, R_f 0.9. The checkers found that the reaction was essentially complete after addition of the hydrogen peroxide. Additional heating did not lower the yield of product.

18. The submitters state that GC analysis of the solid indicates a 92 : 8 mixture of the cis,cis,trans and cis,cis,cis isomers.

19. Using recrystallized borazole from Step B, the checkers obtained product, recrystallized from pentane, mp 75–76°C, in 85% yield, having the following spectral characteristics: IR (KBr) cm^{-1}: 1450 (s), 2860 (m), 2930 (s), and 3460 (m); ^{1}H NMR (CDCl$_3$) δ: 1.0–2.3; ^{13}C NMR (CDCl$_3$) δ: 73.24 (s), 44.32 (d), 33.86 (d), 29.12 (t), 29.79 (t), 27.42 (t), 26.52 (t), 21.25 (t) (undecoupled spectrum).

3. Discussion

Preparation of the two stereoisomers of perhydro-9b-boraphenalene was originally reported by Köster and Rotermund,[6] and the present procedure (part A) is largely based on the procedure described by these authors. However, the original stereochemical assignment was incorrect and has been reversed.[3,7] Furthermore, these authors did not use the thermal treatment described above, which appears essential to achieve isomerization of other constitutional isomers into perhydro-9b-boraphenalene.[3] The original procedure for isomerization of the cis,trans isomer to the all cis isomer has been satisfactory. Contrary to the claim made by these authors,[6] however, this isomerization does not lead quantitatively to the all cis isomer, but reaches an equilibrium, which consists of the all cis and cis,trans isomers in the ratio of 88 : 12; this ratio was also confirmed by reverse isomerization of the pure all cis isomer.[5]

cis,trans-Perhydro-9b-boraphenalene has been converted to lithium cis,cis,trans-perhydro-9b-boraphenalyl hydride by reaction with lithium hydride.[8] The tricyclic organoborane reported here has been converted to bicyclo[7.3.1]dodecane-1,5-diol[9] and trans-13-azabicylo[7.3.1]tridecan-5-ol.[10] The latter has been converted to cis,trans-perhydro-9b-azaphenalene.[10]

Scheme 1

The procedure reported here (parts B and C) has been applied with minor modifications to the syntheses of the cis,cis,cis isomers of the 1,3,2-dioxaborole and perhydro-9b-phenalenol.[7] The two other stereo-isomers, cis,trans,trans and trans,trans,trans, have been prepared from cis,cis,trans-perhydro-9b-phenalenol via the cis and trans isomers of $\Delta^{3a,9b}$-perhydrophenalene.[5] In addition, a few isomers of perhydrophenalenol and of perhydrophenalene and cis,cis,trans-9b-chloroperhydrophenalene have also been prepared from cis,cis,trans-perhydro-9b-phenalenol.[5] Some of the representative transformations are summarized in Scheme 1. (The numbers in parentheses refer to references.)

1. Department of Chemistry, Syracuse University, Syracuse, NY 13210. The current address is the same as Ref. 2.
2. Richard B. Wetherill Laboratory, Purdue University, West Lafayette, IN 47907.
3. The results described here were previously reported as a Communication: Brown, H. C.; Negishi, E. J. Am. Chem. Soc. **1967**, 89, 5478–5480. A similar procedure has also been described elsewhere.[4]
4. Brown, H. C. "Organic Syntheses via Boranes," Wiley: New York, 1975.
5. Dickason, W. C. Ph.D. Thesis, Purdue University, 1970.
6. Köster, R.; Rotermund, G. Angew Chem. **1960**, 72, 563; Rotermund, G. W.; Köster, R. Liebigs Ann. Chem. **1965**, 686, 153–166.
7. Brown, H. C.; Dickason, W. C. J. Am. Chem. Soc. **1969**, 91, 1226–1228.
8. Brown, H. C.; Dickason, W. C. J. Am. Chem. Soc. **1970**, 92, 709–710.
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10. Mueller, R. H. Tetrahedron Lett. **1976**, 2925–2926.

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

Perhydro-9b-boraphenalene: 9b-Boraphenalene, dodecahydro- (8, 9); (16664-33-8); cis,cis-; (3aα, 6aα, 9aα), (1130-59-2): cis,trans-: (3aα, 6aα, 9aβ), (2938-53-6)

Perhydro-9b-phenalenol: Phenalen-9b(2H)-ol, decahydro-cis,cis,trans- (8); Phenalen-9bα(2H)-ol, 3,3aα,4,5,6,6aα,7,8,9,9aβ-decahydro- (9); (16664-34-9)

Borane–tetrahydrofuran: Furan, tetrahydro-, compd. with borane (1 : 1) (8, 9); (14044-65-6)

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

Diglyme: Ether, bis(2-methoxyethyl) (8); Ethane 1,1'-oxybis(2-methoxy)- (9); (111-96-6)

1,5,9-Cyclododecatriene (8, 9); (4904-61-4); trans,trans,trans-: (E,E,E)-; (676-22-2); trans,trans,cis-: (E,E,Z)-; (706-31-0); trans,cis,cis-: (E,Z,Z)-; (2765-29-9); cis,cis,cis-: (Z,Z,Z)-; (4736-48-5)

2-(Perhydro-9'b-phenalyl)-1,3,2-dioxaborole: Phenalene-9b(2H)-boronic acid, decahydro-, cyclic ethylene ester (8); (18604-57-4)

Ethylene glycol (8); 1,2-Ethanediol (9); (107-21-1)

Lithium perhydro-9b-boraphenalyl hydride: Borate (1-), cyclododecane-1,5,9-triylhydro-, lithium (8); Borate (1-), 1,5,9-cyclododecane triylhydro-, lithium (T-4)- (9); (36005-35-3)

Bicyclo[7.3.0]dodecane-1,5-diol: 3a,7(1H)-Cyclopentacyclononenediol, decahydro- (9); (52318-91-9)

13-Azabicyclo[7.3.1]tridecan-5-ol, stereoisomer (9); (61714-12-3)

Perhydro-9b-azaphenalene: Pyrido(2,1,6-de)quinolizine, dodecahydro- (9): cis,cis-: (3aα,6aα,9aα)-; (57147-57-6); cis,trans-: (3aα,6aα,9aβ)-: (57194-67-9)

Perhydrophenalene: 1H-Phenalene, dodecahydro- (8); (2935-07-1); 1H-Phenalene, dodecahydro-, (3aα,6aα,9aα,9bβ)- (9); (40250-64-4)

9b-Chloroperhydrophenalene: Phenalene, 9bα-chloro-2,3,3aα,4,5,6,6aα, 7,8,9,9aβ,9b-dodecahydro- (8); (33343-40-7); 1H-Phenalene, 9b-chlorododecahydro-, cis,cis,trans-: (3aα,6aα,9aα,9bβ)- (9); (52079-56-8)

PHOTOPROTONATION OF CYCLOALKENES:
LIMONENE TO *p*-MENTH-8-EN-1-YL
METHYL ETHER

(Cyclohexene, 1-methyl-4-(1-methylethenyl)-) to (Cyclohexane, 1-methoxy-1-methyl-4-(1-ethenyl-1-methyl-)
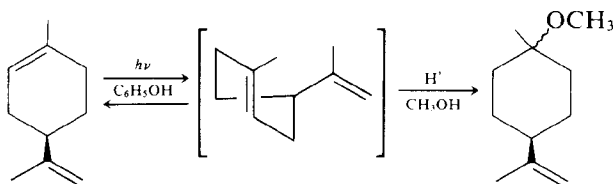
Submitted by F. P. Tise and P. J. Kropp[1]
Checked by R. L. Amey and R. E. Benson

1. Procedure

A 250-mL photochemical reactor (see Figure 1) is fitted with a cylindrical Vycor filter sleeve, a 450-W Hanovia mercury lamp, and a water-cooled condenser which is connected to a mineral oil bubbler. Tubing attachments are made so that water is circulated through the condenser and then through the Vycor filter sleeve. The tube leading from the bottom of the reaction vessel and containing the glass frit is connected in series to a trap fitted with a fritted filter stick and then to a trap that is connected to a nitrogen source. The system is flushed with nitrogen, and sufficient anhydrous methanol is placed in the trap containing the fritted stick to provide for a methanol-saturated gas stream during the course of the reaction (Note 1).

The nitrogen-flushed reactor is charged with a solution of 20.0 g (147 mmol) of (+)-limonene (Note 2), 5.0 g (53 mmol) (Note 3) of phenol, and 5 drops of concentrated sulfuric acid in 210 mL (167 g, 5.2 mol) of anhydrous methanol (Note 4). Water flow through the condenser is started (Note 5), and the nitrogen flow is adjusted to provide good agitation of the contents of the vessel. After 15 min, irradiation is started and the reaction followed by GLC (Note 6), with 48 hr being the approximate time needed for essentially complete conversion (Note 7).

The solution is poured into 900 mL of 5% aqueous sodium hydroxide solution containing 125 g of sodium chloride, and the mixture is extracted with two 100-mL portions of ether. The ether layers are combined, washed with 50 mL of saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The drying agent is removed by filtration and the filtrate is concentrated with a Buchi rotary evaporator. After a preliminary distillation to separate the product from a small amount of nonvolatile material, the liquid is distilled at reduced pressure through a Teflon spinning band column (47 cm × 7 mm). The material that distills at 90–95°C (10 mm) is collected to give 12.8–13.2 g (52–53%) of a mixture of *cis*- and *trans*-*p*-menth-8-en-1-yl methyl ether (Notes 8–10).
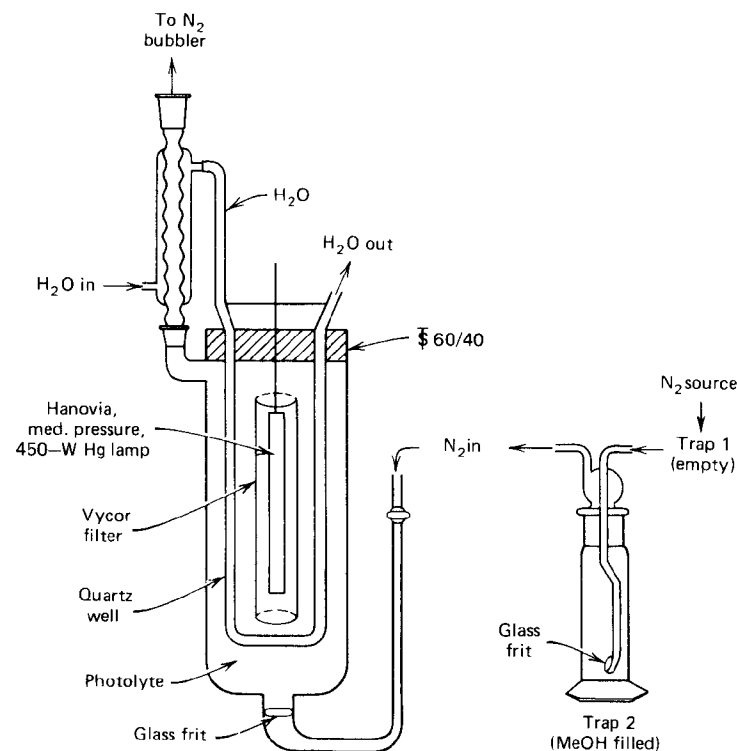
Figure 1

2. Notes

1. The submitters used a reactor with a joint which was capped with a rubber septum fitted with two syringe needles, which were attached by means of a Y-tube to a single nitrogen line. To one of these needles is attached a piece of 1.70-mm O.D. polyethylene tubing of sufficient length to reach to the bottom of the reaction vessel. By use of pinchcocks, nitrogen can be passed through either of the two needles. The solution was stirred with a magnetic stirring bar.

2. (+)-Limonene was obtained from Aldrich Chemical Company, Inc. and distilled before use.

3. The checkers used reagent available from Fisher Scientific Company.

4. The checkers used fresh, acetone-free, absolute methanol available from Fisher Scientific Company.

5. For best results the cooling water should pass through the condenser first and then through the immersion well. This arrangement lessens evaporation of methanol.

6. The submitters used a 3-m × 3.2-mm stainless steel column packed with 20% SF-96 on Chromasorb W (60–80 mesh) and a He flow rate of 60 mL/min. With a temperature program of 4 min at 50°C followed by an increase of 10°C per min to a maximum of 200°C, the retention times were 17.9 and 18.7 min.

7. The checkers found that the reaction was impeded by the formation of a yellow film on the immersion well with very little further conversion occurring after 30 hr of irradiation.

8. The checkers used a 2.4-m × 3.2-mm column packed with 7% SE-30 and 3% Silar on Chromasorb W (60–80 mesh) at 160°C. The retention time was 1.56 min for the trans isomer and 1.81 min for the cis isomer at a He flow rate of 55 mL/min.

9. The spectral properties of the product (approximately 60% cis : 40% trans isomers) are as follows: IR (neat) cm^{-1}: 3080 (=C—H); 2964, 2939, 2860, 2825, (C—H); 1645 (C=C); 1464, 1453, and 1442 (overlapping peaks); 1370, 1124, and 1082 (C—OC); 885 (=CH). ^{1}H NMR (CDCl$_3$) δ: 1.10 [s, 3 H, CH$_3$ (trans)], 1.19 [s, 3 H, CH$_3$ (cis)], 1.30–2.00 (8 H, —CH$_2$-), 1.71 [s, 3 H, CH$_3$ (cis/trans)], 3.14 [s, 3 H, OCH$_3$ (trans)], 3.21 [s, 3 H, OCH$_3$ (cis)], 4.69 [s, 2 H, =CH$_2$ (cis/trans)].

10. The submitters state that similar irradiation of 20.0 g of cyclo-hexene, 5.0 g of phenol, and 1.5 mL of concentrated sulfuric acid for 24 hr afforded cyclohexyl methyl ether in 70% yield.

3. Discussion

Acid-catalyzed, ground state additions to limonene generally afford a mixture of products resulting from competing protonation of both double bonds.[2] In one case in which selective reaction was observed, attack occurred at the acyclic C$_8$–C$_9$ double bond.[3]

The photoprotonation of cycloalkenes, described in this procedure, is believed to proceed via initial light-induced cis → trans isomerization of the alkene.[4] The resulting highly strained trans isomer undergoes facile protonation. This procedure permits the protonation of cyclohexenes and cycloheptenes under neutral or mildly acidic conditions.[5] Since the process is irreversible, high levels of conversion to addition products can be achieved.

Photoprotonation is generally specific for cyclohexenes and cycloheptenes. Smaller-ring cycloalkenes are incapable of undergoing cis → trans isomerization, and the trans isomers of larger-ring or acyclic analogues have insufficient strain to undergo ready protonation. Thus, in addition to facilitating protonation of cycloalkenes, the procedure affords a means of selectively protonating a double bond contained in a six- or seven-membered ring in the presence of another double bond contained in an acyclic, exocyclic, or larger-ring cyclic environment.[6] When conducted in non-nucleophilic media, the photoprotonation procedure is also useful for effecting the isomerization of 1-alkylcyclohexenes and -heptenes to their exocyclic isomers.[4]

1. Department of Chemistry, University of North Carolina, Chapel Hill, NC 27514.
2. For a review of the chemistry of limonene, see Verghese, J. *Perfum. Essent. Oil Rec.* **1968,** *59,* 439–454.
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5. There is a fine balance between the acidity of the alcohol and the basicity of the trans olefin. For example, 1-methylcyclohexenes undergo photoprotonation in methanol whereas cyclohexenes require the addition of small amounts of acid. In the present example, the addition of a small quantity of acid reduces the competing formation of the exocyclic isomer, *p*-mentha-1(7),8-diene.
6. For an earlier report on the photoprotonation of (+)-limonene, see Kropp, P. J. *J. Org. Chem.* **1970,** *35,* 2435–2436.

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

Limonene: (+)-*p*-Mentha-1,8-diene (8); Cyclohexene, 1-methyl-4-(1-methylethyl)- (9); (5989-27-5)

Methanol (8, 9); (67-56-1)

cis-p-Menth-8-en-1-yl methyl ether: Ether, *p*-menth-8-en-1-yl methyl, *cis-* (8); Cyclohexane, 1-methoxy-1-methyl-4-(1-ethenyl-1-methyl)- *cis-* (9); (24655-71-8)

trans-p-Menth-8-en-1-yl methyl ether: Ether, *p*-menth-8-en-1-yl methyl, *trans-* (8); Cyclohexane, 1-methoxy-1-methyl-4-(1-ethenyl-1-methyl)-, *trans-* (9); (24655-72-9)

REDUCTIVE CLEAVAGE OF VINYL PHOSPHATES:
PREPARATION OF 17β-*tert*-BUTOXY-5α-ANDROST-2-ENE
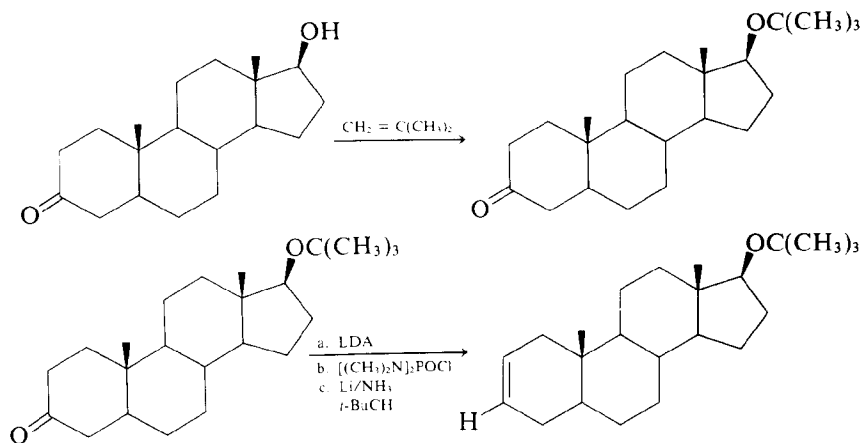
Submitted by ROBERT E. IRELAND, THOMAS H. O'NEIL, and GLEN L. TOLMAN[1]
Checked by M. F. SEMMELHACK and JAMES W. HERNDON

1. Procedure

A. Protection of the 17-hydroxyl group. A solution of androstan-olone (Note 1, 4.10 g, 14 mmol) in 30 mL of dichloromethane in a 250-mL, one-necked round-bottomed flask equipped with a magnetic stirring bar and a rubber septum bearing two syringe needles (argon inlet and exit) is cooled to −20°C (refrigerated bath). Argon is allowed to pass over the surface of the mixture for 15 min and then boron trifluoride etherate (Note 2, 0.125 mL, 0.90 mmol) is added rapidly, via syringe, followed by anhydrous phosphoric acid (Note 3, 0.053 mL, 1.0 mmol). Isobutene (Note 4) is added as a gas through a large-bore syringe needle until approximately 100 mL has condensed. The steroid precipitates during addition of the isobutene and redissolves as the reaction proceeds. The drying tube is replaced with a stopper, the tightly sealed flask is allowed to warm to 25°C, and the mixture is stirred at this temperature for 4 hr (Note 5). The flask is cooled to 0°C, opened, and warmed to 25°C to allow excess isobutene to evaporate. The residue is poured into 2 *N* aqueous ammonium hydroxide (100 mL) and ethyl acetate (75 mL) is added. After the layers are vigorously shaken, the aqueous solution is washed with a second portion of ethyl acetate. The combined organic extracts are washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation. The residue is recrystallized from hexane to give colorless crystals, mp 146–148°C, 4.10 g (86%, Note 6).

B. Preparation of N,N,N',N'-tetramethyldiamidophosphorochloridate. In a dry, 2-L, three-necked flask equipped with overhead stirrer, thermometer, argon outlet, and pressure-equalizing addition funnel is placed 400 mL of diethyl ether (Note 7). The flask is cooled in an isopropyl alcohol/dry ice bath while 100 g (2.2 mol) of anhydrous dimethylamine is added in one portion. A solution of 85 g (0.56 mol) of phosphoryl chloride in 200 mL of diethyl ether is added at a rate to maintain the temperature at −35 ± 5°C. The addition time is approximately 1.5 hr. After the addition is complete, the bath is removed, and stirring is continued for 4 hr. The thick white slurry is filtered through a coarse frit and the filter cake is washed with 4000 mL of diethyl ether. The combined filtrates are concentrated under aspirator pressure on a rotary evaporator. Fractional distillation of the concentrate through a 10-cm Vigreux column gives 71–80 g (74–84%) of the *N,N,N',N'*-tetramethyldiamidophosphorochloridate, bp 58.5–59°C (0.6 mm) (Note 8).

C. Preparation and reductive cleavage of the vinyl phosphoroimidate. A dry, 250-mL flask equipped with magnetic stirrer, syringe port (Note 9), and argon outlet is flushed three times with argon. To the flask

are added 40 mL of dry tetrahydrofuran (THF) and 1.17 mL (8.4 mmol) of dry diisopropylamine (Note 10). The flask is cooled in an acetone/dry ice bath while 7.4 mmol of butyllithium in hexane (Note 11) is added dropwise with stirring. After the addition is complete, the solution is allowed to warm for 15 min. The flask is then cooled in an ice/water bath. To this solution is added 1.61 g (4.6 mmol) of 17β-*tert*-butoxy-5α-androstan-3-one in 30 mL of 2 : 1 THF/hexamethylphosphorictriamide solution. The reaction mixture is stirred with ice cooling for 15 min. *N,N,N',N'*-Tetramethyldiamidophosphorochloridate, 5.83 mL (0.038 mol), is added dropwise with stirring. After 15 min, the bath is removed; the flask is allowed to warm to 25°C and is stirred for an additional 2 hr. The excess reagent is hydrolyzed by slow addition of 30 mL of saturated aqueous sodium bicarbonate solution and stirring for 30 min. After three extractions with 100-mL portions of diethyl ether, the combined organic layers are washed twice with 100 mL water and 100 mL of saturated sodium chloride solution. The solution is dried over anhydrous magnesium sulfate and the ether is removed under reduced pressure on a rotary evaporator to afford 2.9–3.0 g of a crude yellow solid (Note 12). The crude phosphoroamidate is dissolved in 40 mL of dry THF and added to a dry, three-necked, 250-mL flask equipped with overhead stirrer, cold finger condenser (acetone/dry ice), argon bubbler, and acetone/dry ice bath. Dry ammonia is distilled into the flask until the phosphorodiamidate begins to precipitate. The bath is removed and the solution is allowed to warm to reflux. Dry *tert*-butyl alcohol (1.75 mL, Note 13) is added in one portion. To the clear solution is added 1.5 cm of ⅛-in., cleaned lithium wire in 0.3-cm portions. The blue color is maintained (by the addition of lithium wire if necessary) with stirring for 2 hr. Sodium benzoate is added in 25-mg portions until the blue color is discharged. Ammonium chloride (0.50 g) is added in one portion, the condenser removed, and the ammonia allowed to evaporate. The residue is taken up in 100 mL of diethyl ether and 100 mL of water. The layers are separated and the aqueous phase is extracted with 100 mL of diethyl ether. The combined organic layers are washed with 100 mL of saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and filtered. The ether is removed under reduced pressure on a rotary evaporator. The crude olefin is filtered through 15 g of silica gel (Note 14) using benzene/ethyl acetate (2 : 1) as eluant, to give an off-white solid that is recrystallized from a minimum amount of absolute ethanol

to give, after drying, 1.1–1.2 g (71–78%) of 17β-*tert*-butoxy-5α-androst-2-ene, mp 115–117°C (Note 15).

2. Notes

1. Androstanolone was obtained from Aldrich Chemical Company, Inc., and used without purification.

2. Boron trifluoride etherate was distilled before use.

3. Anhydrous phosphoric acid was prepared by slow addition of 5 g of 15% phosphoric acid to 2 g of phosphorus pentoxide.[2]

4. Isobutene, reagent grade, was obtained from Phillips Company.

5. The flask was stoppered with a greased ⊥ 24/40 ground-glass stopper held in place by rubber bands stretched over appropriately placed wire hooks. The pressure at 25°C was slightly more than 1 atm.

6. The spectral properties are as follows: ^{1}H NMR (CDCl$_3$) δ: 0.74 (s, 3 H), 1.02 (s, 3 H), 1.13 (s, 9 H), 3.36 (m, 1 H); IR (CHCl$_3$) cm^{-1}: 1715 (C=O), 1255, 1205.

7. Diethyl ether (anhydrous) from Mallinckrodt Inc., dimethylamine (anhydrous from Eastman Chemical Co.) and phosphoryl chloride "Baker Analyzed Reagent" from J. T. Baker Chemical Co. were used without further purification.

8. Physical and spectral data are as follows: d 1.126; IR (neat) cm^{-1}: 1470, 1450, 1290, 1230, 980; ^{1}H NMR (neat) δ: 2.69 (d, J_{P-H} = 13).

9. All solutions were added via glass syringes under rigorously anhydrous conditions.

10. Diisopropylamine and hexamethylphosphorictriamide (Aldrich Chemical Company, Inc.) were distilled from calcium hydride.

11. Butyllithium in hexane was obtained from Alfa Products, Ventron Corporation or Foote Mineral Company. The checkers titrated the solution before[3] use.

12. Spectral data are as follows: IR (CCl$_4$) cm^{-1}: 1660, 1350, 1215; ^{1}H NMR (CDCl$_3$) δ: 0.69 (s, 3 H, CH_3), 0.78 (s, 3 H, CH_3), 1.11 (s, 9 H, CH_3), 2.60 (d, 3 H, J_{P-H} = 10, N—CH_3), 3.28 (m, 3 H, CH_3O), 5.12 (m, 2 H, C=CH_2).

13. *tert*-Butyl alcohol was dried by distillation from calcium hydride.

14. Silica gel 60 (particle size 0.063–0.200 μm) is available from E. Merck, A.G.

15. Spectral data are as follows: ^{1}H NMR (CDCl$_3$) δ: 0.63 (s, 3 H,

CH_3), 0.67 (s, 3 H, CH_3), 1.02 (s, 9 H, CH_3), 3.28 (s, 1 H, OCH), 5.43 (m, 2 H, vinyl H); IR (CHCl$_3$): The product was characterized by cleavage of the *tert*-butyl ether (CF$_3$CO$_2$H, CH$_2$Cl$_2$, 0°C) to give 17β-hydroxy-5α-androst-2-ene, mp 161–162°C, lit.[4] mp 163–165°C.

3. Discussion

The reduction of a carbonyl group to an olefin has been accomplished by the Shapiro modification[5] of the Bamford-Stevens reaction and by the hydride reduction of the corresponding enol ether,[6] enol acetate,[7] or enamine.[8] The nickel reduction of the thioketal has also been used successfully.[9]

The lithium/amine reduction of *N,N,N',N'*-tetramethylphosphorodiamidates is a general method for the cleavage of the C–O bond.[10] In addition to the reductive deoxygenation of carbonyl compounds to generate olefins, the phosphorodiamidates of alcohols are reduced in high yield to give alkanes. Alcohols in which the hydroxyl group is greatly hindered could be unreactive toward *N,N,N',N'*-tetramethyldiaminophosphorochloridate. In such cases, treatment of the alcohols with butyllithium and *N,N*-dimethylphosphoramidic dichloride in 1,2-dimethoxyethane and *N,N,N',N'*-tetramethylethylenediamine followed by addition of dimethylamine gave rise to *N,N,N',N'*-tetramethylphosphorodiamidates in good yields.[11] Combined in a two-step process (e.g., RCOR′ → RCHOHR′ → RCH$_2$R′), the method allows the reductive removal of a carbonyl functionality. This two-step process compares favorably with the analogous Wolff-Kishner reduction. Additionally, reduction of the enol phosphorodiamidate by dialkyl cuprate reagents generates a substituted olefin.[12]

The phosphorodiamidate group can also serve as a protecting group for the hydroxyl function, since it is stable to CH$_3$Li, LiAlH$_4$, KOH, and 0.2 N aqueous HCl, but is quantitatively cleaved by butyllithium/TMEDA (tetramethylethylenediamine).[10]

1. The Chemical Laboratories of the California Institute of Technology, Pasadena, CA 91125, Contribution No. 5718. This work was made possible in part by a grant from the National Institutes of Health.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Androstanolone: 5α-Androstan-3-one, 17β-hydroxy- (8); Androstan-3-one, 17-hydroxy-, (5α,17β)- (9); (521-18-6)

Boron trifluoride etherate: Ethyl ether, compd. with boron fluoride (BF$_3$) (1 : 1) (8); Ethane, 1,1'-oxybis-, compd. with trifluoroborane (1 : 1) (9); (109-63-7)

Phosphorus pentoxide: Phosphorus oxide (8, 9); (1314-56-3)

Isobutene: Propene, 2-methyl- (8); 1-Propene, 2-methyl- (9); (115-11-7)

Phosphorus oxychloride [POCl$_3$]: Phosphoryl chloride (8, 9); (10025-87-3)

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

N,N,N',N'-Tetramethyldiamidophosphorochloridate: Phosphorodiamidic chloride, tetramethyl- (8, 9); (1605-65-8)

Diisopropylamine (8); 2-Propanamine, *N*-(1-methylethyl)- (9); (108-18-9)

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

Hexamethylphosphorictriamide: Phosphoric triamide, hexamethyl- (8, 9); (680-31-9)

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

17β-Hydroxy-5α-androst-2-ene: 5α-Androst-2-en-17β-ol (8); Androst-2-en-17-ol, (5α,17β)- (9); (2639-53-4)

N,N-Dimethylphosphoramidic dichloride: Phosphoramidic dichloride, dimethyl- (8, 9); (677-43-0)

N,N,N',N'-Tetramethylethylenediamine: Ethylenediamine, *N,N,N',N'*-tetramethyl- (8); 1,2-Ethanediamine, *N,N,N',N'*-tetramethyl- (9); (110-18-9)

SILYLATION OF KETONES WITH ETHYL TRIMETHYLSILYLACETATE: (Z)-3-TRIMETHYLSILOXY-2-PENTENE

(Silane, [(1-ethyl-1-propenyl)oxy]trimethyl-, (Z)-)

A. $\quad BrCH_2COOC_2H_5 \xrightarrow[C_2H_5OC_2H_5, C_6H_6]{(CH_3)_3SiCl, Zn(Cu)} (CH_3)_3SiCH_2COOC_2H_5$

B. $\quad CH_3CH_2\overset{\overset{\displaystyle O}{\|}}{C}CH_2CH_3 + (CH_3)_3SiCH_2COOC_2H_5 \xrightarrow[C_4H_8O]{(C_4H_9)_4N^+F^-}$

$$CH_3CH_2\overset{\overset{\displaystyle OSi(CH_3)_3}{|}}{C}=CHCH_3$$
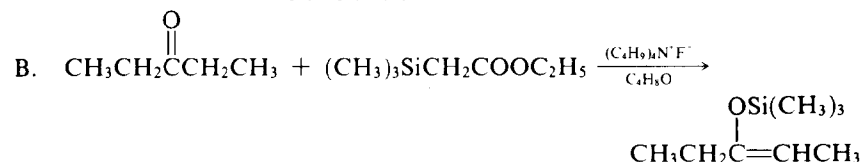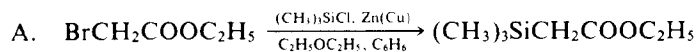
Submitted by Isao Kuwajima, Eiichi Nakamura, and Koichi Hashimoto[1]
Checked by Peter J. Card and Richard E. Benson

1. Procedure

Caution! Ethyl bromoacetate is intensely irritating to eyes and skin. The preparation of this ester should be carried out in an efficient hood.

A. Ethyl trimethylsilylacetate (Note 1). In a 3-L, three-necked flask fitted with a 1-L pressure-equalizing dropping funnel, mechanical stirrer, and efficient condenser which is connected to a nitrogen source are placed 97.5 g (1.5 mol) of zinc powder (Note 2) and 14.9 g (0.15 mol) of cuprous chloride (Note 3). After the reaction vessel is flushed with nitrogen, a static nitrogen atmosphere is maintained for the remainder of the reaction. A mixture of 150 mL of ether (Note 4) and 550 mL of benzene (Note 5) is added to the flask, and the resulting mixture is refluxed with stirring for 30 min with the aid of an electric heating mantle. Heating is discontinued and a solution of 109 g (128 mL, 1.0 mol) of chlorotrimethylsilane (Note 6) and 184 g (123 mL, 1.1 mol) of ethyl bromoacetate (Note 7) in a mixture of 90 mL of ether and 350 mL of benzene is promptly added through the dropping funnel at such a rate as to maintain the reaction at gentle reflux. The addition takes about 1 hr. After the addition is complete, the mixture is heated at reflux for 1 hr and then cooled in an ice bath. While the mixture is stirred, 300 mL of aqueous 5% hydrochloric acid is added through the dropping funnel over a 10-min period. The liquid layer is decanted into a 3-L separatory funnel and

the flask is washed with two 100-mL portions of ether. The ether solutions are added to the separatory funnel, the organic layer is separated, and the aqueous layer is extracted with two 200-mL portions of ether. The organic phases are combined and washed twice with 200-mL portions of saturated aqueous sodium chloride, twice with 200-mL portions of saturated aqueous sodium bicarbonate, and finally with 200 mL of saturated aqueous sodium chloride. The organic layer is dried over anhydrous magnesium sulfate, the mixture is filtered, and the filtrate is concentrated on a rotary evaporator to a volume of about 400 mL. The residual yellow liquid is distilled in a 30-cm vacuum-jacketed Vigreux column at atmospheric pressure until the boiling point is 90°C. The remaining liquid is distilled at reduced pressure to give, after a small forerun, 101–118 g (63–74%, Note 8) of ethyl trimethylsilylacetate, bp 93–94°C (104 mm), n_D^{20} 1.4152–1.4154 (Note 9).

B. (Z)-3-Trimethylsiloxy-2-pentene. In a dry, 200-mL flask (Note 10) equipped with a Teflon-coated magnetic stirring bar and a three-way stopcock, one exit of which is capped with a small rubber septum, is quickly placed 1.5 g (ca. 6 mmol) of dried tetrabutylammonium fluoride hydrate (Note 11). With the aid of a hypodermic syringe, 50 mL of dry tetrahydrofuran (THF, Note 12) is added through the septum, and the clear solution is stirred. After 5 min, the reaction vessel is immersed in a hexane/dry ice bath, and 38.4 g (0.240 mol) of ethyl trimethylsilylacetate is added during 10 min through a syringe which is rinsed with 15 mL of dry THF. After 10 min a solution of 17.2 g (0.200 mol) of 3-pentanone (Note 13) in 15 mL of dry THF is introduced during 10 min to the stirred solution with the aid of a syringe, which is then rinsed with 5 mL of dry THF. The clear solution is stirred for 3 hr, then warmed gradually to 0°C over about 1 hr and finally the temperature is held at 0°C for 2–4 hr (Note 14). Meanwhile, 400 mL of pentane (Note 15) in a dry, nitrogen-filled, 1-L flask equipped with a drying tube and a magnetic stirring bar is cooled with stirring in a hexane/dry ice bath, and the dark orange reaction mixture is poured into it. The reaction vessel is rinsed with three 50-mL portions of pentane. The pentane rinses are added to the reaction solution and the resulting mixture is filtered through a pad of Hyflo Super Cell on a sintered-glass filter, and the filtrate is washed with 100 mL of saturated aqueous sodium bicarbonate and 100 mL of saturated aqueous sodium chloride. The organic layer is dried over magnesium sulfate, the drying agent is removed by filtration, and the resulting solution is concentrated on a rotary evaporator at room temperature to a

volume of 150 mL. The remaining liquid is distilled through a 10-cm Vigreux column. After a very small amount of forerun (<1 g), 21.9–24.1 g (69–76%) of 3-trimethylsiloxy-2-pentene is obtained, bp 139–142°C; n_D^{20} 1.4133–1.4135 (Note 16).

2. Notes

1. This procedure is based on a report by Fessenden and Fessenden.[2a] Cuprous chloride[3] is a more efficient initiator than iodine as specified in the original procedure.

2. The submitters used zinc powder purchased from Koso Chemical (Japan) without any purification. The checkers used product available from Fisher Scientific Company. It is essential to use excess zinc to ensure complete consumption of ethyl bromoacetate which interrupts the catalytic cycle in step B of the present silylation reaction.

3. The submitters used cuprous chloride purchased from Koso Chemical Co. Ltd. without purification. The checkers used cuprous chloride available from Fisher Scientific Company.

4. The submitters used diethyl ether, obtained from Showa Ether, after distillation from sodium wire. The checkers distilled the product obtained from Fisher Scientific Company from lithium aluminum hydride.

5. Benzene was distilled over sodium wire before use.

6. The submitters used chlorotrimethylsilane obtained from Nakarai Chemical. The material was distilled from calcium hydride or sodium wire before use. The checkers used product available from Aldrich Chemical Company, Inc.

7. The submitters used ethyl bromoacetate (GR grade) obtained from Tokyo Kasei and distilled it before use in an efficient hood. The checkers used product available from Aldrich Chemical Company, Inc.

8. The submitters state that the yield ranged from 68 to 70% for runs made on a 1.5-mol scale.

9. Ethyl trimethylsilylacetate is stable to the usual manipulations, and can be stored in glass containers for years without change of physical and spectral properties. IR (liquid film) cm^{-1}: 1720, characteristic of α-silyl esters. The reported physical constants are bp 76–77°C (40 mm), n_D^{25} 1.4136,[2a] n_D^{20} 1.4149.[2b] ^{1}H NMR (CCl$_4$) δ: 0.17 (s, 9 H, CH$_3$Si), 1.31 (t, 3 H, J = 7, CH$_3$CH$_2$), 1.88 (s, 2 H, SiCH$_2$), and 4.14 (q, 2 H, J = 7, CH$_2$O).

10. Tetrabutylammonium fluoride is very hygroscopic. A drybox may be used to avoid rapid manipulation of the fluoride in the atmosphere and exposure of the reagent in the storage vessel to moisture. Alternatively, hydrated tetrabutylammonium fluoride (Note 11) can be dried in the reaction vessel and used directly.

11. Tetrabutylammonium fluoride trihydrate obtained from Fluka AG was dried over phosphorus pentoxide for 48 hr at a pressure of ~0.1 mm. The hygroscopic fluoride was pulverized with the aid of a spatula in a dry atmosphere. The checkers prepared the dry salt by this method using material obtained from Tridom Chemical, Inc.

Alternatively, the fluoride can be prepared as follows: A 10–40% aqueous or alcoholic solution of tetrabutylammonium hydroxide available from several sources is placed in a glass flask fitted with a Teflon-coated magnetic stirring bar and stirred gently. The pH of the solution is adjusted to about 8 by rapid addition of an almost theoretical amount of 48% aqueous hydrofluoric acid with the aid of a plastic pipet. *Caution: Hydrofluoric acid in contact with the skin produces extremely painful burns. Long, acid-resistant gloves should be worn.* Final adjustment of the pH to 7–8, measured with a pH meter, is achieved by addition of 5% aqueous acid. The bulk of the solvent is removed by distillation on a rotary evaporator at ~30°C (1 mm). The resulting white paste is further dried as described above to give the salt as a white mass.

The submitters state that in some cases, probably depending on the source of the hydroxide, the dried salt did not solidify. On such an occasion, the aqueous solution was diluted with deionized water to obtain a ~0.5 M aqueous solution. The resulting solution was cooled to 5–10°C and allowed to stand to give a white clathrate. The supernatant liquid was removed by a pipet and the clathrate was washed once with cold water. When the clathrate was dried as described above the fluoride was obtained as a solid.[4]

12. Tetrahydrofuran was distilled successively from cuprous chloride and sodium wire,[5] and further purified by distillation from sodium benzophenone ketyl in a recycling still. The checkers used product obtained from Fisher Chemical Company that was distilled from lithium aluminum hydride prior to use.

13. 3-Pentanone obtained from Tokyo Kasei (GR grade) was distilled before use. The checkers used product available from Aldrich Chemical Company, Inc.

14. The reaction is normally complete at $-78°C$, affording a product of 99.5% isomeric purity. It is advisable, however, to raise the reaction temperature finally to 0°C, since some unknown factors occasionally retard this catalyzed reaction. Development of an orange to red color of the mixture usually indicates the progress of the reaction.

15. Pentane was stored over sodium wire. The checkers used product available from Eastman Organic Chemicals.

16. The spectral properties of 3-trimethylsiloxy-2-pentene are as follows: ^{1}H NMR (CCl$_4$) δ: 0.18 (s, 9 H, SiCH$_3$), 1.03 (t, 3 H, $J = 7$, CH$_3$CH$_2$), 1.48 (d of t, 3 H, CH$_3$C=CH, $J = 1$ and 6.5), 2.02 (unresolved quartet, 2 H, CH$_2$CH$_3$, $J = 7$), 4.47 (q, 1 H, $J = 7$, CH$_3$CH=C). IR spectrum (liquid film) cm^{-1}: 1678, 1250, and 835. The isomeric purity was 96–99.5% of Z isomer as determined by the submitters by GLC comparison with an authentic E-[6,7] or Z-enriched[7] mixture. The GLC analysis was carried out using the following column and conditions: 3-mm × 6-m stainless steel column, 5% XE-60 on 60–80 mesh Chromosorb P(AW), 80°C, 45 mL of nitrogen per min. The retention times for the E-isomer, the Z-isomer, 3-pentanone, and ethyl trimethylsilylacetate are 5.2, 5.6, 6.2, and 15.9 min, respectively.

3. Discussion

Enol trimethylsilyl ethers belong to a most important class of enol derivatives,[8] and serve as good precursors of isomerically pure enolate anions.[7,9] The double bond also resembles that of electron-rich olefins in reactions with electrophiles, and sometimes is reactive in electrocyclic reactions.

Among the methods for their preparations, two reactions described by House have been employed widely:[7] a thermodynamically controlled silylation with chlorotrimethylsilane/triethylamine in hot dimethylformamide or a kinetically controlled reaction which involves lithiation with a lithium dialkylamide followed by quenching with the chlorosilane. Each method has its own merits and drawbacks with respect to three important factors: regio-, stereo-, and chemoselectivities.

The present silylation reaction[10a,b] represents a new procedure based on metathetical generation of reactive enolate species,[11] and some characteristic features described below make this reaction complementary to the previous methods.

The excellent stereoselectivity as described in the present example is

one of the advantages that merits attention.[10b] The reaction affords only Z-enol silyl ethers when applied to acyclic ketones. For instance, silylation of 5-nonanone and 2-octanone gave (Z)-5-trimethylsiloxy-4-nonene and (Z)-2-trimethylsiloxy-2-octene (together with 14% of its regio isomer), both in 91% yield.

Chemoselectivity of the reaction constitutes another point of interest. Ketones can be silylated in the presence of functional groups which include oxiranes, esters, nitriles,[10a] and even ketones. Thus silylation of one ketone can be performed in the presence of another. The equation shown below illustrates this selectivity.[12]

73%   100% recovery
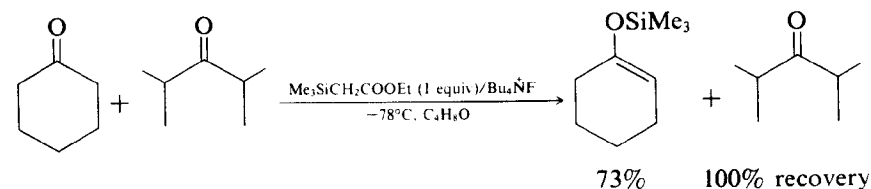
Alkyl halides[11] and aldehydes[13] are not compatible with the present silylation reaction.

Kinetic selectivity of the silylation reaction is high with methyl isopropyl ketone (99.5% of the less highly substituted isomer),[12] and methyl isobutyl ketone (~90%), and fair with 2-methylcyclohexanone (~80%).[10a] The nature of the regioselectivity of this reaction appears different from that with lithium dialkylamide for which steric factors may influence the regioselectivity. In fact, silylation of 3-phenylthio-2-butanone with ethyl trimethylsilylacetate at 0°C produced 2-phenylthio-3-trimethylsiloxy-2-butene, whereas treatment with lithium diisopropylamide followed by quenching with chlorotrimethylsilane gave mainly the less highly substituted regio isomer.[12]

7:3
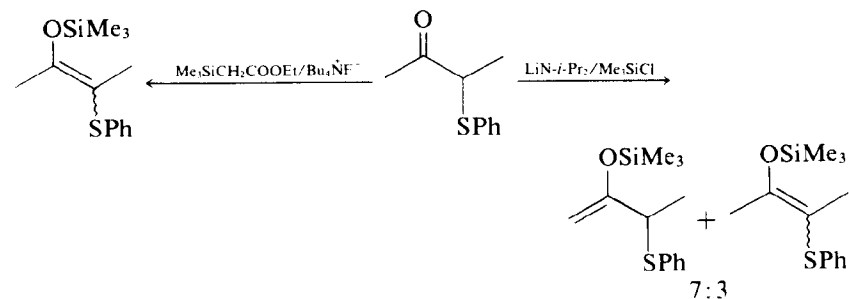
Since the only by-product of the reaction is ethyl acetate, the silylated product can be employed for further reactions without purification. Examples include the fluoride-catalyzed aldol reaction[14] and bromination with N-bromosuccinimide.[10a]

The present reaction can be applied to a variety of ketones including four- to eight-membered and twelve-membered cycloalkanones and acyclic and α,β-unsaturated ketones.[10a] It has also been used for primary, secondary, and tertiary alcohols,[15] alkanethiols,[15] phenols,[15] and arylacetylenes.[10a]

Ethyl trimethylsilylacetate has also been used for the synthesis of α,β-unsaturated esters.[16] The chemistry of tetrabutylammonium fluoride as a base with mild reactivity has been reviewed.[17]

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

(Z)-3-Trimethylsiloxy-2-pentene: Silane, [(1-ethyl-1-propenyl)oxy]trimethyl-, (Z)-(9); (51425-54-8)

Ethyl trimethylsilylacetate: Acetic acid, (trimethylsilyl)-, ethyl ester (8, 9); (4071-88-9)

Zinc (8, 9); (7440-66-6)

Cuprous chloride: Copper chloride (8); Copper chloride (CuCl) (9); (7758-89-6)

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

Ethyl bromoacetate: Acetic acid, bromo-, ethyl ester (8, 9); (105-36-2)

Tetrabutylammonium fluoride hydrate: Ammonium, tetrabutyl-, fluoride, hydrate (8); (22206-57-1)

3-Pentanone (8, 9); (96-22-0)

Tetrabutylammonium hydroxide: Ammonium, tetrabutyl-, hydroxide (8); 1-Butanaminium, N,N,N-tributyl-, hydroxide (9); (2052-49-5)

SPIRO[5.7]TRIDECA-1,4-DIEN-3-ONE
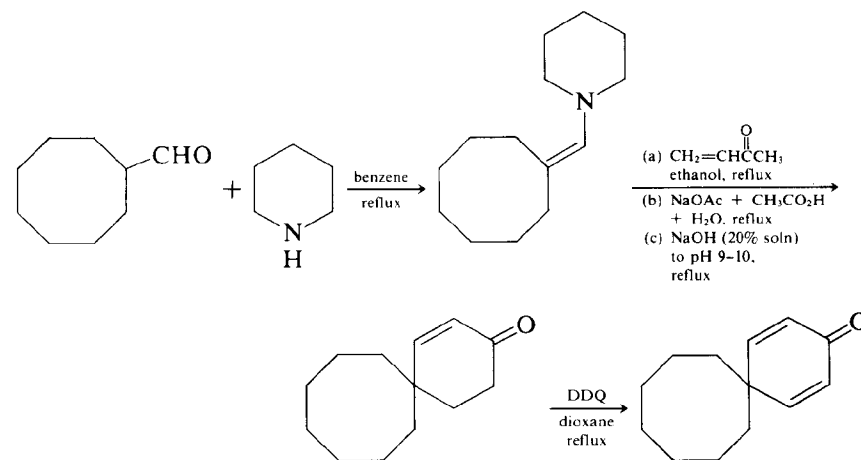
Submitted by VINAYAK V. KANE and MAITLAND JONES, JR.[1]
Checked by R. V. STEVENS and R. P. POLNIASZEK

1. Procedure

Caution! The following reactions should be performed in an efficient hood to protect the experimentalist from noxious vapors (piperidine and methyl vinyl ketone).

A. 1-(*Cyclooctylidenemethyl*)*piperidine.* Cyclooctanecarboxaldehyde (12.5 g, 0.089 mol) (Note 1) and piperidine (8.35 g, 0.098 mol) are dissolved in 115 mL of toluene and placed in a 250-mL, one-necked flask equipped with a magnetic stirring bar and Dean–Stark water separator on top of which is a condenser fitted with a nitrogen inlet tube. The reaction mixture is placed under a nitrogen atmosphere, then brought to and maintained at reflux with stirring for 6 hr, at which time the theoretical amount of water (1.75 mL) has been collected. The reaction mixture is cooled and fractionally distilled under reduced pressure (Note 2): toluene and excess piperidine are removed at 40°C (0.5 mm), and the enamine product is distilled as a colorless liquid to yield 17.30 g (0.084 mol, 93.6%) of 1-(cyclooctylidenemethyl)piperidine, bp 81–83°C (0.5 mm).

B. *Spiro*[5.7]*tridec-1-en-3-one.* A dry, 1-L, three-necked flask is equipped with a Teflon stirring bar, condenser, pressure-equalizing dropping funnel, and nitrogen inlet tube. To this flask are introduced absolute ethanol (460 mL) (Note 3) and 1-(cyclooctylidenemethyl)piperidine (17.3 g, 0.084 mol). After the solution has been stirred for 5 min, methyl vinyl ketone (6.44 g, 0.092 mol) (Note 4) is added dropwise over a period of 5 min. The solution is refluxed for 20 hr using a heating mantle. The mixture is cooled and anhydrous sodium acetate (15.0 g), acetic acid (25.5 mL), and water (46 mL) are added. The mixture is brought to and maintained at reflux for 8 hr. The heat is removed and the solution is cooled with ice water; aqueous sodium hydroxide (20% solution, approximately 65 mL) is added until pH 9–10 is attained. The solution is refluxed for another 15 hr; at the end of this period the reaction mixture is cooled. The reaction mixture (600 mL) is divided equally into two 2-L separatory funnels and each portion is diluted with 600 mL of ice-cold water. Each separatory funnel is extracted with ether (3 × 125 mL). The ether extract is washed successively with aqueous 5% hydrochloric acid (125 mL) and saturated brine (3 × 170 mL), dried over anhydrous magnesium sulfate, and filtered. The solvent is removed on a rotary evaporator and the product is distilled under vacuum (Note 5) as a colorless liquid to yield 7.05–7.75 g (44–49%) of spiro[5.7]tridec-1-en-3-one, bp 95–125°C (0.5 mm) (Note 6).

C. *Spiro*[5.7]*trideca*-1,4-*dien*-3-*one.* Spiro[5.7]tridec-1-en-3-one (3.63 g, 0.0189 mol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (8.90 g, 0.0392 mol) (Note 7) are dissolved in 50 mL of dioxane (Note 8) in a 250-mL, one-necked flask equipped with a magnetic stirring bar fitted with a condenser and drying tube. The reaction mixture is brought to and maintained at reflux with stirring for 6 hr. The mixture is cooled, filtered, and the dioxane removed in a rotary evaporator. The product is taken up in ether (125 mL), and the ether layer is washed with aqueous sodium hydroxide (15%, 4 × 60 mL). The combined aqueous layers are further extracted with ether (3 × 60 mL). The ether layers are combined and washed with saturated sodium chloride (4 × 60 mL), dried over anhydrous magnesium sulfate and filtered. The solvent is removed on the rotary evaporator to afford a crude yellow liquid. To this crude product are added silica gel (6.25 g) (Note 9) and enough ether to cover the silica gel. The ether is removed with a rotary evaporator so as to absorb the crude product on the silica gel. This silica gel dry powder is poured onto a column (12 in. long × 1.0 in. diameter) containing silica gel (50 g) in hexane. The column is eluted with hexane (70 mL) and then with an increasing amount of ethyl acetate/hexane (Note 10). The desired fractions are combined (Note 11) and solvent is removed under reduced pressure to afford spiro[5.7]trideca-1,4-dien-3-one (2.65 g, 73.7%), (Note 12).

2. Notes

The checkers performed all reactions on ¼ the scale reported by the submitters.

1. Cyclooctanecarboxaldehyde was obtained from Aldrich Chemical Company, Inc., and used without purification.

2. 1-(Cyclooctylidenemethyl)piperidine is typical of most enamines in that it discolors rapidly when exposed to air and therefore must be handled under an inert atmosphere, preferably nitrogen.

3. Absolute ethanol, distilled and stored over molecular sieves, was used.

4. Methyl vinyl ketone (bp 35–36°C at 140 mm) was obtained from Aldrich Chemical Company, Inc. and distilled immediately before use.

5. A heating mantle was used for this distillation. A forerun of 25–95°C (0.5 mm) was discarded. The exact boiling point of spiro[5.7]tridec-1-en-3-one is 86°C (0.1 mm).

6. The product has the following spectral properties: ^{1}H NMR (CCl$_4$)

δ: 1.62 (s, 14 H), 1.85 (br d, 2 H), 2.25 (m, 2 H), 5.68 (d, 1 H, $J = 10$ Hz), 6.75 (d, 1 H, $J = 10$ Hz).

7. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone, supplied by Aldrich Chemical Company, Inc., was used without further purification.

8. Dioxane was refluxed over potassium hydroxide pellets, distilled, and stored over molecular sieves.

9. Silica gel analytical reagent (60–200 mesh) was obtained from the J. T. Baker Chemical Co.

10. The silica gel column was eluted starting with hexane (70 mL), followed by 2% ethyl acetate/hexane (100 mL); 5% ethyl acetate/hexane (100 mL); 10% ethyl acetate/hexane (600 mL). The fractions were monitored with 20% ethyl acetate/hexane, using silicon 7 GF plates (purchased from Analtech, Inc.), thickness 250 μm, 20 cm long × 5 cm wide. The plates were sprayed with 3% ceric sulfate and heated at 350°C to detect dienone and monoenone. Alternatively, silica gel 60 F-254 plates (purchased from EM Laboratories, Inc.), thickness 25 mm, 20 cm long × 5 cm wide may be used. Detection may be made with ultraviolet light. The ratio of 1 g of crude dienone to 15 g of silica gel is adequate for obtaining pure spiro[5.7]trideca-1,4-dien-3-one.

11. When 20% ethyl acetate/hexane is used, the monoenone, R_f 0.57, and the dienone, R_f 0.47 (Analtech Uniplate − Silica 7 GF), are obtained.

12. The product has the following spectral properties: ^{1}H NMR (CCl$_4$) δ: 1.65 (s, 14 H), 6.10 (d, 2 H, $J = 10$ Hz), 6.98 (d, 2 H, $J = 10$ Hz).

3. Discussion

This procedure illustrates a general method for preparing a wide range of spirocyclohexenones and hence spirocyclohexadienones. A number of intramolecular and intermolecular reactions are known to give spirodienones; however, these methods have limited synthetic application.[2] This procedure is superior[3] to that developed by Bordwell and Wellman,[4] for side reactions such as aldol condensation of the aldehyde and polymerization of methyl vinyl ketone are avoided. These spirodienones are useful intermediates in the synthesis of paracyclophanes.[5,6]

Cyclopentanecarboxaldehyde (47%), cyclohexanecarboxaldehyde (41%), 1,2,5,6-tetrahydrobenzaldehyde (43%), cycloheptanecarboxaldehyde (41%), cyclooctanecarboxaldehyde (42%), cycloundecanecarboxaldehyde (36%), 5-norbornene-2-carboxaldehyde (32%), adamantanecarbox-

aldehyde (20%), and 1,2,3,4-tetrahydro-1-naphthylaldehyde (40%) gave corresponding spiroenones.[7] Spiroenones obtained from cyclohexanecarboxaldehyde, cycloheptanecarboxaldehyde and cyclooctanecarboxaldehyde were converted to the corresponding dienones using the dichlorodicyanobenzoquinone (DDQ). The yields for all three dienones are in the range of 56 to 58%.

1. Department of Chemistry, Princeton University, Princeton, NJ 08544.
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7. Yields are for the overall conversion.

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

Spiro[5.7]trideca-1,4-dien-3-one (8, 9); (41138-71-0)

Cyclooctanecarboxaldehyde (8, 9); (6688-11-5)

Spiro[5.7]tridec-1-en-3-one (9); (60033-39-8)

Piperidine (8, 9); (110-89-4)

Methyl vinyl ketone: 3-Buten-2-one (8, 9); (78-94-4)

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone [DDQ]: 1,4-Cyclohexadiene-1,2-dicarbonitrile, 4,5-dichloro-3,6-dioxo- (8, 9): (84-58-2)

Cyclopentanecarboxaldehyde (8, 9); (872-53-7)

Cyclohexanecarboxaldehyde (8, 9); (2043-61-0)

1,2,5,6-Tetrahydrobenzaldehyde: 3-Cyclohexene-1-carboxaldehyde (8, 9); (100-50-5)

Cycloheptanecarboxaldehyde (8, 9); (4277-29-6)

Cycloundecanecarboxaldehyde (9); (4373-07-3)

5-Norbornene-2-carboxaldehyde (8); (5453-80-5)

Adamantanecarboxaldehyde: 1-Adamantanecarboxaldehyde (8); Tricyclo[3.3.1.1^{3,7}]decane-1-carboxaldehyde (9); (2094-74-8)

1,2,3,4-Tetrahydro-1-naphthylaldehyde: 1-Naphthaldehyde, 1,2,3,4-tetrahydro- (8); 1-Naphthalenecarboxaldehyde, 1,2,3,4-tetrahydro- (9); (18278-24-50)

PREPARATION OF THIOL ESTERS:
THE 2-METHYLPROPANE-2-THIOL ESTERS OF
CYCLOHEXANECARBOXYLIC ACID AND CHOLIC ACID

A. $(CH_3)_3CSH + TlOC_2H_5 \xrightarrow{\text{benzene}} TlSC(CH_3)_3 + C_2H_5OH$

B.

C.
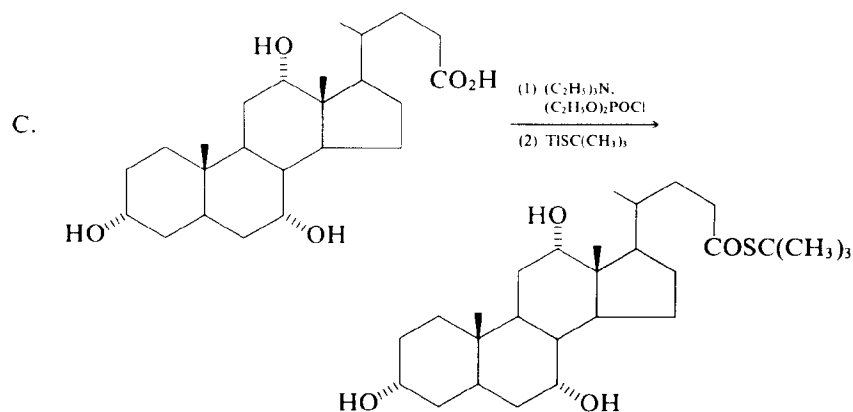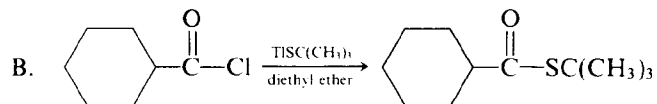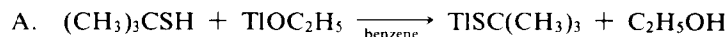
Submitted by GARY O. SPESSARD,[1] WAN KIT CHAN,[2] and S. MASAMUNE[2]
Checked by TRINA KITTREDGE and ROBERT V. STEVENS

1. Procedure

Caution! Thallium compounds are very toxic. However, they may be safely handled if prudent laboratory practices are followed. Rubber gloves and laboratory coats should be worn, and reactions should be carried out in an efficient hood. Thallium wastes should be collected and disposed of separately.[3]

A. *Thallium(I) 2-methylpropane-2-thiolate.* A 500-mL, round-bottomed flask equipped with a magnetic stirring bar and a pressure-equalizing dropping funnel to which a nitrogen inlet adapter is attached is charged with 47.2 g (0.189 mol) of thallium(I) ethoxide (Note 1) and 200 mL of anhydrous benzene (Note 2). Over a period of 15 min 19.2 g (24 mL, 0.213 mol) of 2-methylpropane-2-thiol (Note 1) is added. The

reaction mixture is stirred under a nitrogen atmosphere for 1 hr and the resulting precipitate is collected by filtration. After washing with three 100-mL portions of anhydrous pentane (Note 3), 48.5–51.2 g (90–95%) of the product is obtained as bright yellow crystals, mp 165–170°C dec (Note 4). This material is sufficiently pure for use in the following steps.

B. *S-tert-Butyl cyclohexylmethanethioate.* A solution of 4.38 g (0.030 mol) of cyclohexanecarboxylic acid chloride (Note 5) in 150 mL of ether (Note 6) is placed in a dry, 500-mL, round-bottomed flask equipped with a magnetic stirring bar and a gas inlet. The system is flushed with nitrogen and the solution is cooled in an ice bath. Stirring is initiated and 8.82 g (0.031 mol) of the thallium(I) 2-methylpropane-2-thiolate prepared in Step A is added. After the resulting milky suspension is stirred for 2 hr at room temperature, the fine precipitate is removed by filtration through Celite (Note 7) and washed thoroughly with four 50-mL portions of ether. The combined filtrate and washings are concentrated on a rotary evaporator to give a pale yellow oil which is distilled under reduced pressure through a 5-cm Vigreux column. After separation of a forerun, 5.36–5.44 g (90–91%) of the colorless thiol ester is collected, bp 100°C (7 mm) (Note 8).

C. *S-tert-Butyl ester from cholic acid.* A dry, 250-mL, one-necked, round-bottomed flask is equipped with a magnetic stirring bar and a nitrogen inlet adapter; the system is purged with, and maintained under, dry nitrogen. After 4.90 g (0.0120 mol) of cholic acid (Note 9), 1.33 g (0.0131 mol) of triethylamine (Note 10), and 60 mL of dry tetrahydrofuran (THF, Note 11) are placed in the flask, a stoppered, pressure-equalizing dropping funnel charged with a solution of 2.18 g (0.0127 mol) of diethyl phosphorochloridate (Note 9) in 30 mL of dry THF is attached to the top of the nitrogen inlet adaptor (see Figure 1). The solution is added to the stirred reaction mixture over a period of 5 min and stirring is continued for 3.5 hr at room temperature. The dropping funnel is removed, and the reaction mixture is taken up into a dry, 100-mL syringe and transferred to a dry filtering apparatus. This apparatus is shown in Figure 2. The glass-fritted filter funnel of medium porosity with a built-in vacuum adapter is connected to the middle neck of a 500-mL, three-necked, round-bottomed flask. A calcium chloride drying tube is connected to the vacuum adapter and a nitrogen inlet adapter is attached to the top of the filter funnel. The precipitated triethylamine hydrochloride is now removed from the reaction mixture by stoppering the nitrogen inlet adapter and using the positive nitrogen pressure to force the solution through the glass frit.
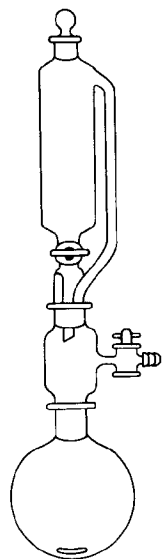
Figure 1

Dry tetraheydrofuran, 40 mL, is used to rinse the original reaction flask. The stopper of the nitrogen inlet adapter (Figure 2) is removed and this washing is transferred via the same syringe to the filtering apparatus and forced through the filter in the same manner described above. One of the stoppers of the three-necked flask is replaced by a nitrogen inlet adapter and the filter funnel is replaced by a mechanical stirrer. As the filtrate is stirred at room temperature, the remaining stopper is removed and 3.90 g (0.0133 mol) of thallium(I) 2-methylpropane-2-thiolate is added. After the addition is complete, the neck is restoppered, and the resulting mixture is vigorously stirred under nitrogen at room temperature overnight. The precipitate is removed by suction filtration through Celite filter aid (Note 7) and washed with three 30-mL portions of THF. The filtrate and washings are combined and concentrated under reduced pressure, and the resulting residue is dissolved in 160 mL of ethyl acetate. This solution is washed with two 100-mL portions of aqueous 5% $NaHCO_3$, then with 50 mL of aqueous saturated NaCl, and finally is dried over anhydrous Na_2SO_4. The solvent is removed by rotary evaporator to afford a white, gummy paste which crystallizes upon trituration with 20 mL of acetonitrile. The crystals are collected by suction filtration to afford 4.2 g of
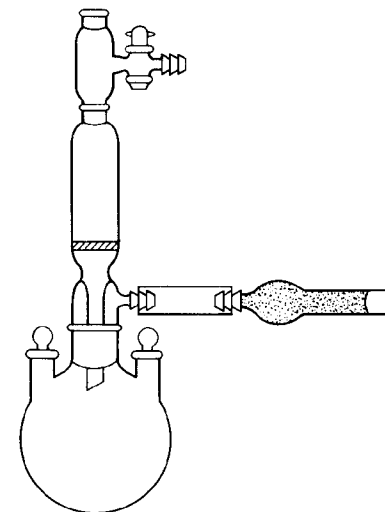
Figure 2

crude product. Recrystallization from 90 mL of hot acetonitrile provides 3.5 g of the thiol ester as small white needles, mp 166–167°C (Note 12). A second crop of 0.5 g, mp 165–166°C, can be obtained upon concentration of the mother liquor to approximately 30 mL, for a combined yield of 70%.

2.   Notes

1. Thallium(I) ethoxide and 2-methylpropane-2-thiol were purchased from Aldrich Chemical Company, Inc.

2. Benzene, reagent grade, was purified and dried by first removing the benzene–water azeotrope by simple distillation and then collecting the remaining liquid under an atmosphere of nitrogen.

3. Dry pentane was obtained by allowing practical grade pentane to be shaken with and then distilled from concentrated sulfuric acid.

4. The product should be stored in a dark bottle under an atmosphere of argon to prevent discoloration and possible decomposition.

5. Cyclohexanecarboxylic acid chloride may be prepared in the following way: a pressure-equalizing addition funnel fitted with a nitrogen inlet tube is attached to a 500-mL round-bottomed flask which is equipped

with a magnetic stirring bar and also charged with 12.8 g (0.100 mol) of cyclohexanecarboxylic acid (purchased from Aldrich Chemical Company, Inc.) and 250 mL of anhydrous ether. (Anhydrous benzene may also be used.) The ethereal solution is cooled to ice-bath temperature and 25.4 g (0.200 mol) of oxalyl chloride (purchased from Aldrich Chemical Company, Inc.) is added over a period of 20 min. Under nitrogen, the resulting solution is stirred for 26 hr before it is concentrated on a rotary evaporator to afford a pale yellow oil. Distillation of the oil yields 13.5 g (92%) of cyclohexanecarboxylic acid chloride as a clear, colorless liquid, bp 75°C (30 mm); IR (liquid film) cm^{-1}: 1800 (strong).

6. Anhydrous ether was obtained from Mallinckrodt Inc. and used without further purification.

7. Celite (C-211), purchased from Fisher Scientific Company, was washed thoroughly with ether.

8. The spectral characteristics of the product are as follows: IR (liquid film) cm^{-1}: 1675 (strong); ^{1}H NMR (neat) δ: 1.42 [s, 9 H, C(CH$_3$)$_3$], 1.0–2.0 (m, 10 H, all CH$_2$ in cyclohexane portion), 2.3 (m, 1 H, CH).

9. Cholic acid and diethyl phosphorochloridate were obtained from Aldrich Chemical Company, Inc.

10. Triethylamine was purchased from Eastman Organic Chemicals.

11. Tetrahydrofuran, reagent grade, was refluxed over and distilled from lithium aluminum hydride immediately prior to use.

12. The spectral properties of the product are as follows: IR (CHCl$_3$) cm^{-1}: 3600 (sharp, weak), 3430 (broad, medium), 1675 (strong), no absorption at 1700.

3. Discussion

Methods available before 1971 for the preparation of thiol esters are briefly summarized in a review article.[4] Since then, several newer techniques have been developed, to meet a certain set of criteria required for recent synthetic operations. This development may be summarized as follows. Whenever an acid chloride is available, the reaction of the Tl(I) salt of a thiolate of virtually any kind, including alkane-, benzene-, 2-benzothiazoline-, and 2-pyridinethiol, proceeds efficiently and near-quantitatively. However, if selective thiol ester formation in the presence of hydroxy or other functional groups in the same molecule is required, three main procedures are available. First, reaction of an acid (1), with
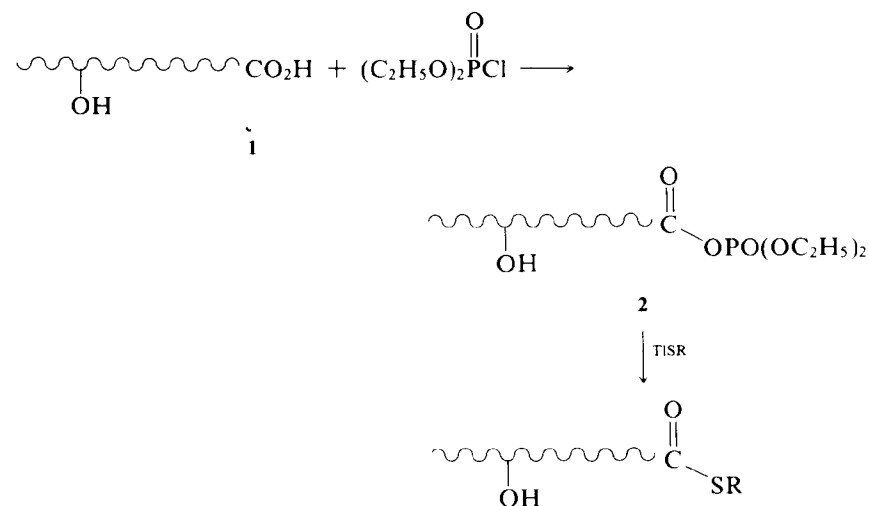
a dialkyl or diphenyl phosphorochloridate affords the anhydride (2) (with the hydroxy groups intact) which is subsequently converted to the thiol ester.[5] This method can be applied to any type of thiol and a variety of hydroxy acids (except for β-hydroxy acids[6]). A mixed anhydride method using ethyl chloroformate and pyridine also effects selective thiol ester formation in many cases.[7] Secondly, the imidazolide of an acid which is prepared from 1 and N,N-carbonyldiimidazole reacts efficiently with relatively acidic thiols such as benzenethiol to yield the thiol ester.[6,8] Thirdly, use of a disulfide and triphenylphosphine effects the selective formation of thiol esters, but this technique is only applicable to relatively reactive disulfides such as those derived from 2-benzothiazole-, 2-pyridinethiol,[9,10] and 4-tert-butyl-N-isopropylimidazole-2-thiol.[11]

Other methods that can be used to prepare thiol esters from carboxylic acids include the use of aryl thiocyanates,[12] thiopyridyl chloroformate,[13] 2-fluoro-N-methylpyridinium tosylate,[14] 1-hydroxybenzotriazole,[15] and boron thiolate.[16] Direct conversion of O-esters to S-esters can also be effected via aluminum and boron reagents.[17] However, the applicability of these [12-17] and other more recent methods[18] to the selective thiol ester formation discussed above has not been clearly defined.

Thiol esters have recently been utilized, with and without activation, for the preparation of O-esters for lactones, in particular, in macrolide syntheses. The accompanying procedure illustrates this conversion.[19]

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2. Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada, T6G 2G2. The present address of S. Masamune is the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

Thallium(I) 2-methylpropane-2-thiolate: 2-Propanethiol, 2-methyl-, thallium(I) salt (10); (56393-79-4)

Thallium(I) ethoxide: Ethanol, thallium (1 +) salt (8, 9); (20398-06-5)

2-Methylpropane-2-thiol: 2-Propanethiol, 2-methyl- (8, 9); (75-66-1)

S-*tert*-Butyl cyclohexylmethanethioate: Cyclohexanecarbothioic acid, S-(1,1-dimethylethyl) ester (9); (54829-37-7)

Cyclohexanecarboxylic acid (8, 9); (98-89-5)

Oxalyl chloride (8); Ethanedioyl dichloride (9); (79-37-8)

S-*tert*-Butyl ester of cholic acid: Cholane-24-thioic acid, 3,7,12-trihydroxy-S-(1,1-dimethylethyl) ester, (3α,5β,7α,12α)- (9); (58587-05-6)

Cholic acid (8); Cholan-24-oic acid, 3,7,12-trihydroxy-, (3α,5β,7α,12α) (9); (81-25-4)

Diethyl phosphorochloridate: Phosphorochloridic acid, diethyl ester (8, 9); (814-49-3)

GENERATION AND REACTIONS
OF VINYLLITHIUM REAGENTS:
SYNTHESIS OF 2-BUTYLBORNENE
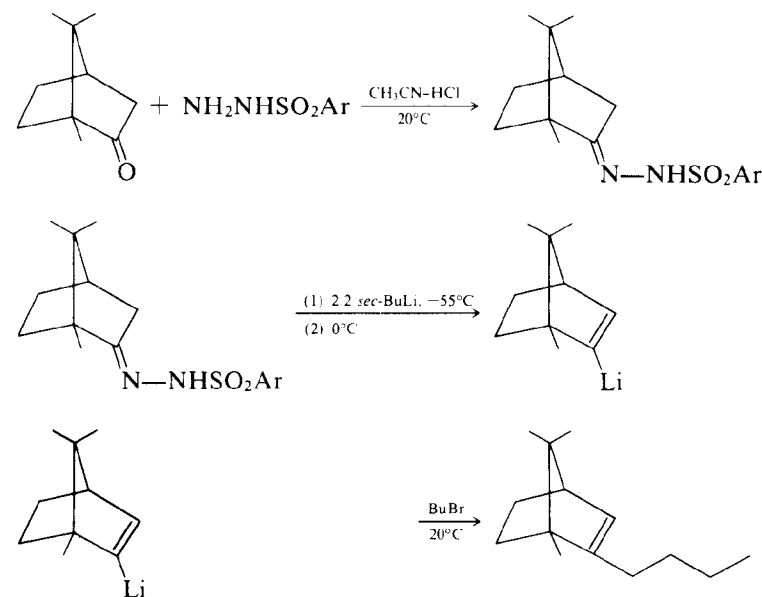
Submitted by A. RICHARD CHAMBERLIN, ELLEN L. LIOTTA, and F. THOMAS BOND[1]
Checked by HIROKO MASAMUNE and ROBERT V. STEVENS

1. Procedure

A.   d-Camphor 2,4,6-triisopropylbenzenesulfonylhydrazone.   In a 500-mL Erlenmeyer flask equipped with a magnetic stirring bar is placed 66.0 g (0.22 mol) of 2,4,6-triisopropylbenzenesulfonylhydrazide (Note

1), 30.4 g (0.20 mol) of *d*-camphor (Note 2), 100 mL of freshly distilled acetonitrile, and 20.0 mL (0.24 mol) of concentrated hydrochloric acid. The resulting solution is stirred overnight while a granular solid precipitates. The white crystals are cooled at −10°C for 4 hr and collected by suction filtration, dissolved in 175 mL of dichloromethane, filtered to remove a small amount of insoluble material, and concentrated under reduced pressure on a rotary evaporator to give 60.8–63.4 g (70–73%) of a white solid, mp 196–199°C (dec) (Note 3).

B.   2-Butylbornene.   A 1-L, three-necked flask is equipped with a 250-mL addition funnel (sealed with a rubber septum), a mechanical stirrer, and a rubber septum. The system is vented (via a hypodermic needle inserted through the addition funnel septum) through a mineral oil bubbler, and the apparatus is flame-dried while it is flushed with pre-purified nitrogen introduced through the septum of the flask. The flask is charged with 40.0 g (0.092 mol) of *d*-camphor 2,4,6-tri-isopropylbenzenesulfonylhydrazone, resealed, and again flushed with nitrogen. Hexane, 200 mL, (Note 4), and 200 mL of tetramethylethylenediamine (Note 5), are added, and the stirred solution, under an atmosphere of nitrogen, is cooled to approximately −55°C with an ethanol-water(2 : 1)/dry ice bath. Using a Luer-Lok syringe, 158 mL (0.20 mol) of 1.29 *M sec*-butyllithium (Note 6) is transferred to the addition funnel. The solution is stirred rapidly and the *sec*-butyllithium added over a period of 15–20 min. The resulting orange solution is stirred for 2 hr, and the cold bath removed. After 20 min the flask is immersed in an ice bath until nitrogen evolution ceases (approximately 10 min).

To this stirred solution of 2-lithiobornene is added, via syringe, 15.2 g (0.11 mol) of butyl bromide (Note 7) over a 1-min period. The ice bath is then removed, and the reaction mixture is stirred at room temperature overnight. The mixture is poured into 500 mL of water. The layers are separated and the aqueous layer extracted with two 100-mL portions of ether. The combined organic extracts are washed with five 200-mL portions of water, one 50-mL portion of 1 *N* hydrochloric acid, and two 200-mL portions of water. The solution is dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator at aspirator pressure and room temperature. Distillation of the residual yellow liquid through a 20-cm Vigreux column affords 8.9–9.4 g (50–53%) of product as a colorless liquid, bp 57–59°C (0.5 mm), n_D^{25} 1.4664, $[\alpha]_D^{25}$ −10.7° (*c* MeOH, 0.0747) (Note 8).

2.   Notes

1. The submitters used material prepared following a literature procedure.[2]

2. *d*-Camphor was purchased from Eastman Kodak Co., $[\alpha]_D^{25}$ +39.5°.

3. The ^{1}H NMR spectrum is as follows: δ: 0.61 (s, 3 H), 0.86 (s, 6 H), 1.26 (overlapping doublets, *J* = 6.7, 18 H), 1.4–2.2 (m, 7 H), 2.90 (septuplet, *J* = 7, 1 H), 4.20 (septuplet, *J* = 7, 2 H), 7.15 (s, 2 H).

4. Matheson, Coleman, and Bell reagent grade hexane was distilled from lithium aluminum hydride.

5. This compound was purchased from Aldrich Chemical Company, Inc., and distilled from lithium aluminum hydride.

6. The *sec*-butyllithium was purchased from Alfa Products, Ventron Corp., and standardized by double titration or diphenylacetic acid titration. Other alkyllithium bases such as butyllithium and methyllithium cannot be substituted for the stronger *sec*-butyllithium since larger amounts of bornylene are formed because of incomplete dianion formation. Careful attention must be paid to stoichiometry in this reaction; failure to do so also results in increasing the amount of bornylene formed.

Even under ideal conditions the NMR of crude product shows 20–30% bornylene, which, however, is easily separated from the desired product during distillation as a "forerun" which sublimes into the vacuum pump trap.

7. Analytical reagent material was purchased from Mallinckrodt, Inc., and distilled from calcium hydride.

8. The ^{1}H NMR spectrum (CDCl$_3$) is as follows: δ 0.74 (s, 3 H), 0.76 (s, 3 H), 0.94 (s, 3 H), 0.7–1.0 (broad m, 7 H), 1.4 (m, 4 H), 1.9 (m, 2 H), 2.19 ("t", *J* = 4,1 H), 5.51 (m, 1 H).
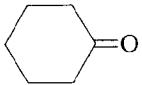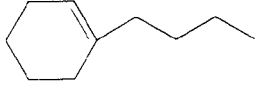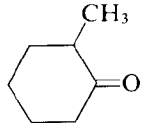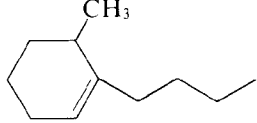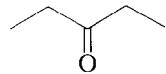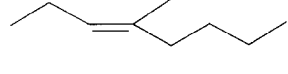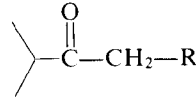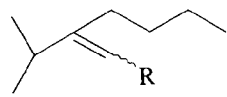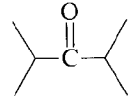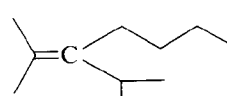
3.   Discussion

The sequence described here illustrates a general procedure for converting ketones into alkylated olefins:
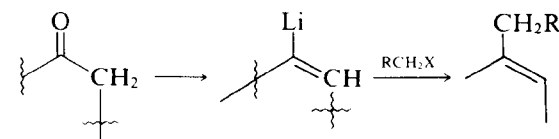
It is a modification of the Shapiro olefin synthesis[3] which allows the vinyl anion intermediate to be trapped with primary halides and other electrophiles. Use of triisopropylbenzenesulfonylhydrazones as the vinyllithium precursor[4] is an improvement over previously[4] used toluenesulfonylhydrazones,[5,6] which can be employed in the sequence provided excess *sec*-butyllithium (typically 4.5 equiv) and alkyl halide (3.0 equiv) are used. Methyl ketones (e.g., acetone, acetophenone, 2-octanone) can also be used and can be converted into their dianions using 2.2 equiv of the weaker base, *n*-butyllithium. The conditions described above, with the slight modifications noted, have been used for a variety of ketones as shown in Table I.

TABLE I
KETONE TO BUTYLALKENE CONVERSIONS

Ketone	Product	
		a
		a,b
		a
		a,c
		d

[a] *sec*-Butyllithium is added at −8°C.
[b] Approximately 2% of the isomeric 1-butyl-2-methylcyclohexene is formed.
[c] A mixture of (Z) and (E) isomers is formed.
[d] Tertiary hydrogen removal is slower. *sec*-Butyllithium (3.0 equiv) is added at −78°C; the solution is immediately warmed to room temperature and stirred for 1–2 hr before butyl bromide (2.0 equiv) is added.

The submitters have found that the hexane–tetramethylethylenediamine solvent system described above, which is required for toluenesulfonylhydrazones, may be replaced with tetrahydrofuran when triisopropylbenzenesulfonylhydrazones are used, provided that the electrophilic reagent is added to the vinyllithium species as soon as it is formed (as indicated by cessation of nitrogen evolution).

Primary alkyl bromides react well in this sequence except for particularly reactive compounds (e.g., methyl bromide, allyl bromide) which give the vinyl halide by metal–halogen exchange. Secondary halides, as expected, suffer from elimination as a side reaction. Other electrophiles have been used successfully including D$_2$O, aldehydes and ketones, dimethylformamide,[4,7] chlorotrimethylsilane,[4,8] 1,2-dibromoethane,[4] and
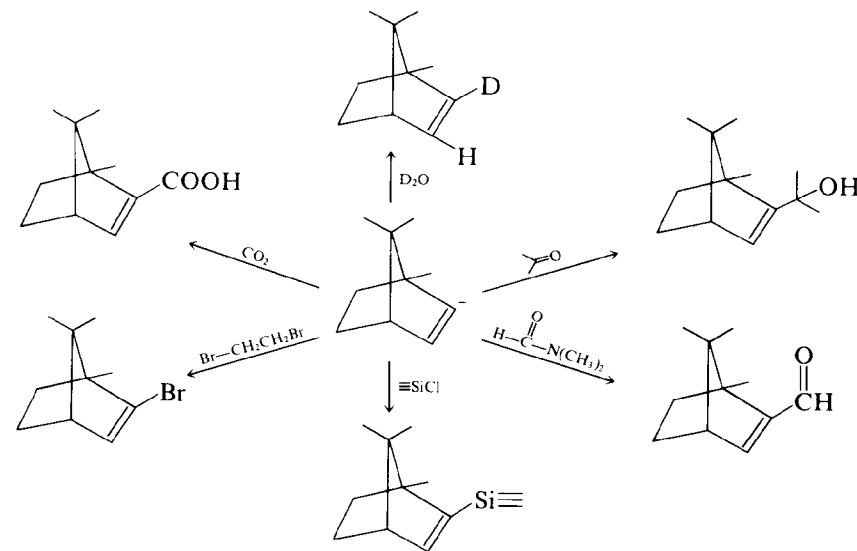
carbon dioxide. Such sequences allow for relatively straightforward preparation of deuterated olefins, allylic alcohols, α,β-unsaturated aldehydes, vinylsilanes, vinyl bromides, and α,β-unsaturated acids. The major advantages of this route to vinyllithium reagents[9] lie in the availability of the ketone precursors and the regiospecificity of the Shapiro reaction.[3,10] There are numerous alternative routes to trisubstituted olefins.[11]

1. Department of Chemistry, University of California, San Diego, La Jolla, CA 92093.
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Appendix

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

2,4,6-Triisopropylbenzenesulfonylhydrazide: Benzenesulfonic acid, 2,4,6-tris(1-methylethyl)-, hydrazide (9); (39085-59-1)

d-Camphor: Camphor (1*R*, 4*R*)-(+)- (8); Bicyclo[2.2.1]heptan-2-one, 1,7,7-trimethyl-, (1*R*)- (9); (464-49-3)

Tetramethylethylenediamine: Ethylene, *N,N,N',N'*-tetramethyl- (8); 1,2-Ethanediamine, *N,N,N',N'*-tetramethyl- (9); (110-18-9)

sec-Butyllithium: Lithium, *sec*-butyl- (8); Lithium, (1-methylpropyl)- (9); (598-30-1)

Butyl bromide: Butane, 1-bromo- (8, 9); (109-65-9)

PREPARATION AND DIELS–ALDER REACTION OF A HIGHLY NUCLEOPHILIC DIENE: *trans*-1-METHOXY-3-TRIMETHYLSILOXY-1,3-BUTADIENE

(Silane, [(3-methoxy-1-methylene-2-propenyl)oxy]trimethyl-)
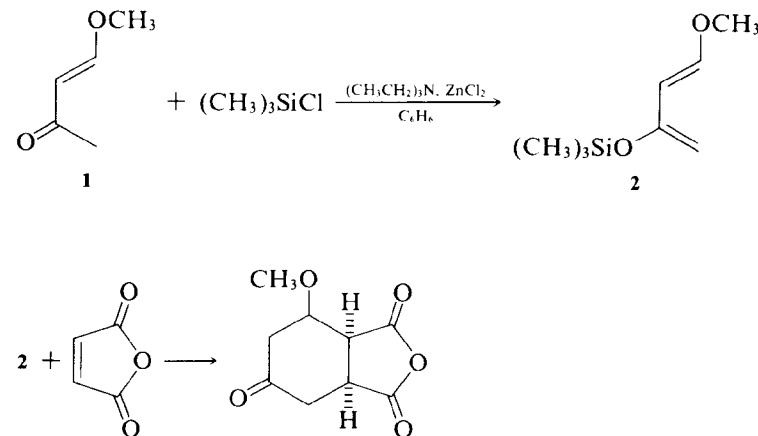
Submitted by SAMUEL DANISHEFSKY, TAKESHI KITAHARA, and PAUL F. SCHUDA[1]
Checked by DENNIS GOLOB, JOHN DYNAK, and ROBERT V. STEVENS

1. Procedure

A. Preparation of the zinc chloride. Reagent grade zinc chloride (50 g) is placed in an evaporating dish and heated in a fume hood with a Fisher burner until no more water vapor is driven off. The hot dish is rapidly transferred to a glove bag which has been maintained under nitrogen. After the zinc chloride has cooled to a transparent glassy solid, it is ground to a fine powder with a mortar and pestle. The solid is transferred to a tightly stoppered bottle and stored in a desiccator over Drierite.

B. Preparation of 1-methoxy-3-trimethylsiloxy-1,3-butadiene. Triethylamine (575 g, 5.7 mol) is stirred mechanically in a three-necked flask (Note 1). To it is added 10.0 g (0.07 mol) of zinc chloride prepared as described above. The mixture is stirred at room temperature under nitrogen for 1 hr. A solution of 250 g (2.50 mol) of 4-methoxy-3-buten-

2-one (from Aldrich Chemical Company, Inc.) in 750 mL of benzene is added all at once. Mechanical stirring is continued for 5 min. Chlorotrimethylsilane (542 g, 5.0 mol) is added rapidly. The reaction mixture first turns pink, then red, and finally brown. Heat is evolved and the reaction is kept below 45°C by cooling in an ice bath. After 30 min, the mechanically stirred solution is heated by a heating mantle to 43°C (Note 2). This temperature is maintained for 12 hr. The reaction mixture becomes very thick during this time. After the mixture cools to ambient temperature, it is poured, with mixing, into 5 L of ether. The solid material is filtered through Celite. The Celite and solid material are removed and stirred with 4 L more of ether and refiltered through Celite. The combined ether washings are evaporated under reduced pressure (rotary evaporator) to a brown, sweet-smelling oil. The oil is transferred to a 1-L, single-necked flask equipped with an 18-in. Vigreux column (Note 3). Careful fractional distillation under water vacuum affords a forerun of approximately 16 g which boils at 70–78°C (22 mm). This fraction consists of impure diene which contains 4-methoxy-3-buten-2-one. The main fraction boils at 78–81°C (23 mm) and consists of 245 g of diene (Note 4) with approximately 5–10% of 4-methoxy-3-buten-2-one (Note 5). This material is suitable for most purposes. If higher purity is desired, the second fraction may be redistilled under reduced pressure through an 18-in. Vigreux column to afford 200 g (46%) of *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Note 6).

C. 5β-*Methoxycyclohexan*-1-*one*-3β,4β-*dicarboxylic acid anhydride*. To 3.00 g (0.174 mol) of 1-methoxy-3-trimethylsiloxy-1,3-butadiene at 0°C (ice bath) is added a total of 980 mg (0.01 mol) of freshly sublimed maleic anhydride in portions of 70–80 mg each over a period of 25 min. When the addition is complete, the ice bath is removed and the clear solution is stirred for 15 min at room temperature (Note 7). Three 5-mL portions of a solution of tetrahydrofuran (35 mL) and 0.1 N hydrochloric acid (15 mL) are added and the solution is stirred for 1 min. The remaining acid solution (35 mL) is added all at once and the resulting solution is poured into 100 mL of chloroform and treated with 25 mL of water. The organic layer is separated and the aqueous layer is extracted four times with 100-mL portions of chloroform. The extracts are combined and dried over anhydrous magnesium sulfate. The solvent is then removed under reduced pressure (Note 8) to provide 2.0 g of an oil which solidifies. Pentane (10 mL) is added to the oily solid and small portions

of ether (total of 6 mL) are added; trituration is continued until the crystals become free flowing. The crystals are isolated by filtration and washed with 10 mL of 2 : 1 pentane/ether to afford 1.75 g (90%) of the anhydride, mp 87–89°C. Further recrystallization affords an analytically pure sample, mp 97–98°C.

2. Notes

1. The checkers dried all reagents by allowing them to stand over molecular sieves (Type 4A), with the exception of triethylamine, which was dried over potassium hydroxide pellets. The reaction flask was flame-dried. Because of evolution of triethylamine hydrochloride that was encountered during addition of the chlorotrimethylsilane and in the work-up, the reaction should be carried out in a hood.

2. The checkers did not cool the reaction, which allowed the temperature to rise to 55°C. After 30 min, the solution was heated overnight with a heating mantle. After 12 hr, the reaction temperature was 67°C.

3. A 16-in. Widmer column packed with 3-mm glass helices may also be used for the distillation.

4. *Caution! When the temperature begins to drop, heating must be stopped. Otherwise, on occasion, a violent reaction may occur with formation of a gas and rapid expansion of the residual tars.*

5. The checkers performed this distillation at a lower pressure (1–10 mm) through a similar Vigreux column to yield 225 g of clear liquid containing fluffy white material (triethylamine hydrochloride) which could not be removed by filtration. The purity of this distillate, determined by NMR, was 90 : 10 (dien : ketone). No forerun was obtained which contained more than 15% ketone.

6. The checkers carefully redistilled the impure distillate through the same previously mentioned distillation apparatus under water vacuum. Six fractions of various amounts were collected and combined to yield (1) a forerun of 64 g, bp 70–78°C (23–25 mm), purity 77 : 23 (diene : ketone); and (2) 145 g of pure diene, bp 78–81°C (23–25 mm). This second distillation seemed to remove the triethylamine hydrochloride from the product.

7. The reaction mixture is initially yellow, but turns colorless when the solution is warmed to room temperature.

8. When the chloroform extract is concentrated, care must be exercised to avoid overheating. The temperature should be no greater than 40°C.

3. Discussion

The procedure described here is a scale-up of the published method[2] for the preparation of 1-methoxy-3-trimethylsiloxy-1,3-butadiene (2) from readily available reagents. The preparation of this diene has recently been complemented by a report of the preparation of 1,3-bis(trimethysiloxy)-1,3-butadiene,[3] and earlier by a reported synthesis of a 1,3-dialkoxy-1,3-butadiene.[4]

The electron-donating nature of this diene confers high reactivity and orientational specificity in its reaction with unsymmetrical dienophiles.[5] This fact, coupled with the readily available conversion to the α,β-unsaturated ketone from the imparted functionality, makes 1-methoxy-3-trimethylsiloxy-1,3-butadiene (2) a potentially very valuable reagent in organic synthesis. The general reaction scheme is illustrated below:
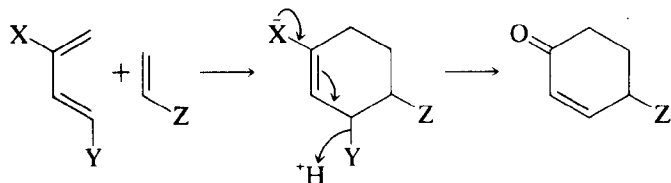
The high reactivity of the diene is shown by reaction with notoriously unreactive dienophiles such as 1-carbomethoxycyclohexene, 2,5-dihydrobenzoic acid methyl ester,[6] and 2-methylcyclohex-2-en-1-one to give, after mild work-up, the corresponding α,β-unsaturated ketones in quite respectable yields.[5]

The Diels–Alder reaction with maleic anhydride is illustrative of the high reactivity and potential utility of this diene.

1. Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

trans-1-Methoxy-3-trimethylsiloxy-1,3-butadiene: Silane, [(3-methoxy-1-methylene-2-propenyl)oxy]trimethyl- (9); 59414-23-2

4-Methoxy-3-buten-2-one: 3-Buten-2-one, 4-methoxy- (8, 9); 4652-27-1

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

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

CUMULATIVE AUTHOR INDEX
FOR VOLUMES 60 AND 61

This index comprises the names of contributors to Volumes **60** and **61** only. For authors to previous volumes, see cumulative indices in Volume **59**, which covers Volumes **55** through **59**, and Volume **54**, which covers Volumes **50** through **54**, and either indices in Collective Volumes I through V or 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 60 AND 61

This index comprises subject matter for Volumes **60** and **61** only. For subjects in previous volumes, see the cumulative indices in Volume **59**, which covers Volumes **55** through **59**, and Volume **54**, which covers Volumes **50** through **54**, and either the indices in Collective Volumes 1 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.

The index lists the names of compounds in two forms. The first is the name used commonly in procedure. The second is the systematic name according to **Chemical Abstracts** nomenclature, accompanied by its registry number in brackets. Also included are general terms for classes of compounds, types of reactions, special apparatus, and unfamiliar methods.

Most chemicals used in the procedure will appear in the idnex as written in the text. There generally will be entries for all starting materials, reagents, intermediates, important by-products, and final products. Entries in capital letters indicate compounds, reactions, or methods appearing in the title of the preparation.

ORGANIC SYNTHESES

AN ANNUAL PUBLICATION OF SATISFACTORY
METHODS FOR THE PREPARATION
OF ORGANIC CHEMICALS

VOLUME 61

1983

BOARD OF EDITORS

ROBERT V. STEVENS, *Editor-in-Chief*

NOMENCLATURE

Both common and systematic names of compounds are used throughout this volume, depending on which the Editor-in-Chief felt was more appropriate. Preparations appear in alphabetical order of titles of the synthetic procedures. The *Chemical Abstracts* indexing name for each title compound, if it differs from the title name, is given as a subtitle. Systematic *Chemical Abstracts* nomenclature, used in both the 8th and 9th Collective Indexes for the title compound and a selection of other compounds mentioned in the procedure, is provided in an appendix at the end of each preparation. Registry numbers, which are useful in computer searching and identification, are also provided in these appendixes. Whenever two names are concurrently in use and one name is the correct *Chemical Abstracts* name, that name is adopted. For example, both diethyl ether and ethyl ether are normally used. Since ethyl ether is the established *Chemical Abstracts* name for the 8th Collective Index, it has been used in this volume. The 9th Collective Index name is 1,1'-oxybisethane, which the Editors consider too cumbersome. The prefix *n*-is deleted from *n*-alkanes and *n*-alkyls. All reported dimensions are now expressed in Système International units.

SUBMISSION OF PREPARATIONS

Chemists are invited to submit for publication in *Organic Syntheses* procedures for the preparation of compounds that are of general interest, as well as procedures that illustrate synthetic methods of general utility. It is fundamental to the usefulness of *Organic Syntheses* that submitted procedures represent optimum conditions, and the procedures should be checked carefully by the submitters, not only for yield and physical properties of the products, but also for any hazards that may be involved. Full details of all manipulations should be described, and the range of yield should be reported rather than the maximum yield obtainable by an operator who has had considerable experience

with the preparation. For each solid product the melting-point range should be reported, and for each liquid product the boiling-point range and refractive index should be included. In most instances it is desirable to include additional physical properties of the product, such as ultraviolet, infrared, mass, or nuclear magnetic resonance spectra, and criteria of purity such as gas chromatographic data. In the event that any of the reactants are not commercially available at reasonable cost, their preparation should be described in as complete detail and in the same manner as the preparation of the product of major interest. The sources of the reactants should be described in the Notes section, and physical properties such as boiling point, index of refraction, and melting point of the reactants should be included except where standard commercial grades are specified.

Beginning with Volume 49, Methods of Preparation (Sec. 3) and Merits of the Preparation (Sec. 4) have been combined into Discussion (Sec. 3). This section should include descriptions of related and practical methods. Other published methods that have no practical synthetic value do not need to be mentioned. Those features of the procedure that recommend it for publication in *Organic Syntheses* should be cited (synthetic method of considerable scope, specific compound of interest not likely to be made available commercially, method that gives better yield or is less laborious than other methods, etc.). If possible, a brief discussion of the scope and limitations of the procedure as applied to other examples, as well as a comparison of the particular method with the other methods cited, should be included. If necessary to the understanding or use of the method for related syntheses, a brief discussion of the mechanism may be placed in this section. The present emphasis of *Organic Syntheses* is on model procedures rather than on specific compounds (although the latter are still welcomed), and the Discussion should be written to help readers decide on the value of the procedure in their research. Three copies of each procedure should be submitted to the Secretary of the Editorial Board. An accompanying letter setting forth the features of the preparations that are of interest or value is helpful to the Board.

Additions, corrections, and improvements to the preparations previously published are welcomed; these should be directed to the Secretary.

CARL ROBERT NOLLER

November 10, 1900–October 20, 1980

Carl Robert Noller, one of the early members of the Board of *Organic Syntheses* and Editor-in-Chief of Volume 15, died at the age of 79 on October 20, 1980 at the Stanford Hospital after a heart attack followed by open heart surgery.

His close colleagues at Stanford University, Professors William A. Bonner, Richard H. Eastman, and Harry S. Mosher write about him as follows.

"Carl was born November 10, 1900 in St. Louis, Missouri. His father, a wagon maker, and his mother, maiden name Laessig, were of German descent. He grew up in St. Louis and obtained his B.S. and M.S. degrees, 1922 and 1923, at Washington University in St. Louis and his Ph.D. degree, 1926, under professor Roger Adams at the University of Illinois. After being an instructor at Northwestern University in 1926–1927 with Frank Whitmore, he spent two years with Eastman Kodak Company in Rochester; then in 1929 he accepted an appointment as Assistant Professor at Stanford. He was awarded a Guggenheim fellowship for six months' study in Munich and Zürich in 1933. During the academic year of 1938–1939, he was a Visiting Lecturer at Harvard. . . ."

"Professor Noller was most widely known for his textbooks in organic chemistry. His text for majors, *Chemistry of Organic Compounds*, was first published in 1951, followed by second and third editions in 1957 and 1965. There were also two shorter versions, his *Textbook of Organic Compounds* (also three editions) and *Structure and Properties of Organic Compounds*. Approximately 10,000 Stanford students between 1951 and 1970 were introduced to organic chemistry through his books. His texts were rapidly adopted for the organic chemistry courses in a large number of universities in the United States. These books held their favored position for many years. They were recognized internationally by editions in Spanish (Argentine and Mexican editions), Chinese (Asian edition), Yugoslavian, and German. Noller's was the first text to embrace modern molecular orbital treatment of

chemical bonding. This had an immediate and worldwide impact on the teaching of organic chemistry. His majors text included a wide range of examples of industrial products and processes. By use of special topics chapters and generous footnotes, this volume was encyclopedic in its scope. Because of these features and the meticulously prepared index, it also served as a major reference work and is still widely used for this purpose. These texts have served his students and colleagues as models of clarity, factural integrity, nomenclature, and style for scientific writing. . . .''

"Professor Noller co-authored over one hundred scientific papers with his students. The subjects of these studies evolved over the years, but the central theme interwoven into his broad-ranging research endeavors was the investigation of natural products of plant origin. This interest began with his Ph.D. thesis problem, which dealt with the proof of structure and synthesis of chaulmoogric acid, a substance isolated from chaulmoogra oil which was being used at that time as a topical treatment for leprosy. Subsequent studies included the first total synthesis of oleic and elaidic acids and the isolation of erucic acid from rapeseed oil. Noller then undertook investigations in the areas of steroidal sapogenins and triterpenes. His final major research effort in the natural product field was the investigation of the toxic, bitter constituent of manroot (*Echinocystis fabracea*), a member of the gourd family that was "mined" by Carl and his students along the banks of San Francisquito Creek. Extracts of this plant reportedly were used by the Californian Indians as fish poisons. The active component proved to be the cucurbitacins, which are both chemically and pharmacologically most interesting. They have highly oxygenated steroid-like structures but lack the angular methyl group at C-10 common to other steroids. His interest in the chemistry of plant products and in gardening led Professor Noller to become an amateur botanist with a broad knowledge of the scientific names of the local flora. Along with this natural product research, he and his students conducted experiments on the nature of the Grignard reagent; the mechanism of the Friedel-Crafts reaction, ozonolysis, and catalytic reduction reactions; basic problems in stereochemistry; the synthesis of pyridine and piperidine derivatives; and the use of zinc alkyls, mercury alkyls, and phosphate esters in organic synthesis. He also published several articles on effective lecture demonstrations, especially in the area of stereochemistry."

In addition to his impact internationally on science and education through his textbooks and research publications, Carl Noller played an important domestic role as an educator and scholar. He is remembered particularly for the very high standards of performance he demanded of himself as well as of his students. His intolerance of unscientific thinking and sloppy work was strongly influential in establishing a no-nonsense attitude of scholarly integrity which prevailed in the Stanford Chemistry Department.

WILLIAM S. JOHNSON

December 1982

PREFACE

This volume contains 30 checked procedures. The vast majority of these deal with new synthetic methods and methodology of a general nature. A broad range of synthetic transformations is covered.

The synthesis of PYRUVOYL CHLORIDE from the corresponding acid not only represents the method of choice for the preparation of this substance, but can be applied to other acids as well. A one-pot procedure for the preparation of ETHYL 2-BUTYRYLACETATE illustrates another general method for the synthesis of β-ketoesters. The synthesis of 4-PENTYLBENZOYL CHLORIDE by direct electrophilic substitution of 4-pentylbenzene with phosgene, derived *in situ* from oxalyl chloride, can likewise be applied to other aromatic substrates.

The synthesis of BENZYL ISOCYANIDE from benzaldehyde via reductive amination with 5-aminotetrazole followed by oxidation of the resultant amine with sodium hypobromite provides a general method for the synthesis of isocyanides. The preparation of BIS(2,2,2-TRICHLOROETHYL) AZODICARBOXYLATE makes available an alternative to dimethyl azodicarboxylate that is not only more reactive in Diels–Alder reactions but whose ester groups can be removed under neutral conditions.

A wide variety of substituted γ-butyrolactones can be prepared directly from olefins and aliphatic carboxylic acids by treatment with manganic acetate. This procedure is illustrated in the preparation of γ-(n-OCTYL)-γ-BUTYROLACTONE. Methods for the synthesis of chiral molecules are presently the target of intensive investigation. One such general method developed recently is the employment of certain chiral solvents as auxiliary agents in asymmetric synthesis. The preparation of (S,S)-(+)-1,4-BIS(DIMETHYLAMINO)-2,3-DIMETHOXY-BUTANE FROM TARTARIC ACID DIETHYL ESTER provides a detailed procedure for the production of this useful chiral media; an example of its utility in the synthesis of (+)-(R)-1-PHENYL-1-PENTANOL from benzaldehyde and butyllithium is provided.

In contrast to isocyanates, the isomeric cyanates were unknown until recently. These substances undergo a number of useful transfor-

mations. A simple procedure that can be applied to a number of phenols and some acidic alcohols is illustrated in the preparation of PHENYL CYANATE. A procedure which illustrates a general method for converting norcarane derivatives to *endo,endo*-1,3-bridged bicyclobutanes via a carbenoid insertion is shown in the synthesis of 1,6-DIMETHYLTRICYCLO[4.1.0.0^{2,7}]HEPT-3-ENE.

Thiol esters have recently found broad applications in organic synthesis. Two methods for their preparation from acid chlorides and acids are described in the preparation of 2-METHYLPROPANE-2-THIOL ESTERS OF CYCLOHEXANECARBOXYLIC ACID AND CHOLIC ACID. Conversion of the former thiol ester to the corresponding *O-t*-butyl ester illustrates a general method for the preparation of *O*-ESTERS FROM THE CORRESPONDING THIOL ESTERS.

The synthesis of ETHYL α-(BROMOMETHYL)ACRYLATE and METHYL α-(BROMOMETHYL)ACRYLATE makes these valuable intermediates readily available for the synthesis of α-methylene-γ-butyrolactone derivatives and other substances as well. A simple procedure for the preparation of 2-alkyl-2-cyclohexenones by reductive alkylation of *o*-anisic acids is demonstrated in the preparation of 2-HEPTYL-2-CYCLOHEXENONE. A remarkable large-scale preparation of a Dewar benzene derivative is illustrated by the preparation of HEXAMETHYL DEWAR BENZENE from dimethylacetylene.

The synthesis of 2-HYDROXYMETHYL-2-CYCLOPENTENONE from cyclopentenone illustrates a general strategy and method for the synthesis of an effective latent synthon of an α-ketovinyl anion. The synthesis of CYCLODODECYL MERCAPTAN from cyclodecanone provides a method for the preparation of secondary or hindered mercaptans which cannot be prepared by traditional displacement reactions.

Emphasis on the employment of transition metal catalysts to achieve useful synthetic transformations is illustrated by three procedures in this volume. The reaction of allylic alcohols with aryl halides in the presence of a palladium derived catalyst can be used to prepare various β-arylaldehydes. This is illustrated by the preparation of 2-METHYL-3-PHENYLPROPANAL. OSMIUM-CATALYZED VICINAL OXYAMINATION OF OLEFINS BY CHLORAMINE-T is a novel and useful procedure for the preparation of vicinal hydroxy arylsulfonamides which in turn can be employed in the synthesis of a host of sub-

stances. A closely related procedure illustrated by the synthesis of ETHYL *threo*-[1-(2-HYDROXY-1,2-DIPHENYLETHYL)]CARBAMATE is also provided.

A practical synthesis of 1,3-OXAZEPINES VIA PHOTOISOMERIZATION OF HETEROAROMATIC *N*-OXIDES is illustrated for 3,1-BENZOXAZEPINE. A hydroboration procedure for the synthesis of PERHYDRO-9b-BORAPHENALENE AND PERHYDRO-9b-PHENALENOL illustrates beautifully the power of this methodology in the construction of polycyclic substances. The conversion of LIMONENE TO *p*-MENTH-8-EN-YL METHYL ETHER demonstrates a regio- and chemoselective method for the PHOTOPROTONATION OF CYCLOALKENES. An efficient method for the conversion of a ketone to an olefin involves REDUCTIVE CLEAVAGE OF VINYL PHOSPHATES. A mild method for the conversion of a ketone into the corresponding trimethylsiloxy enol ether using trimethylsilyl acetate is shown for the synthesis of (*Z*)-3-TRIMETHYLSILOXY-2-PENTENE.

A procedure which illustrates a general method for preparing a wide range of spirocyclohexenones and spirocyclohexadienones is provided for SPIRO[5.7]TRIDECA-1,4-DIEN-3-ONE. A detailed procedure for the preparation of *trans*-1-METHOXY-3-TRIMETHYLSILOXY-1,3-BUTADIENE and its employment as a diene in the Diels–Alder reaction illustrates the high nucleophilicity of this important intermediate. A method for the GENERATION AND REACTIONS OF VINYLLITHIUM REAGENTS from ketones via triisopropylbenzenesulfonylhydrazones is presented. Finally, a neat procedure for the fission of *N*-heterocyclic compounds with thiophosgene and base is illustrated in the preparation of *o*-ISOTHIOCYANATO-(*E*)-CINNAMALDEHYDE from quinoline.

The Board of Editors welcomes both the submission of preparations for future volumes and suggestions for change that will enhance the usefulness of *Organic Syntheses*. Submitters are kindly asked to examine the instructions on pages v and vi that describe the type of preparations we wish to receive and also the information to be included in each contribution. A style guide for preparing manuscripts is available from the Secretary to the Board, and submitters are requested to follow its instructions.

Professor Jeremiah P. Freeman, current Secretary to the Board, has carried on the voluminous correspondence with the submitters and

checkers behind the scenes and provided valuable guidance to the Editor-in-Chief. The *Chemical Abstracts* names and registry numbers in the appendix following each procedure were found and compiled by Dr. Theodora W. Greene who also helped edit this volume. Finally, I would like to acknowledge my secretary, Mandy Ceccarelli, for her skill and diligence in compiling this volume.

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