ADDITION OF AN ETHYLCOPPER COMPLEX TO 1-OCTYNE:

(E)-5-ETHYL-1,4-UNDECADIENE

(1,4-Undecadiene, 5-ethyl-, (E)-)

$$EtMgBr \xrightarrow[\substack{Me_2S,\ Et_2O \\ -45^\circ C}]{CuBr[Me_2S]} EtCu[Me_2S]MgBr_2$$

$$EtCu[Me_2S]MgBr_2 \xrightarrow[-45^\circ C]{C_6H_{13}C \equiv CH} C_6H_{13}\overset{Et}{\diagdown}Cu[Me_2S]MgBr_2$$

$$C_6H_{13}\overset{Et}{\diagdown}Cu[Me_2S]MgBr_2 \xrightarrow[\substack{-30^\circ C \\ 2)\ NH_4Cl,\ H_2O}]{1)\ \diagup Br,\ (Me_2N)_3PO} C_6H_{13}\overset{Et}{\diagdown}$$
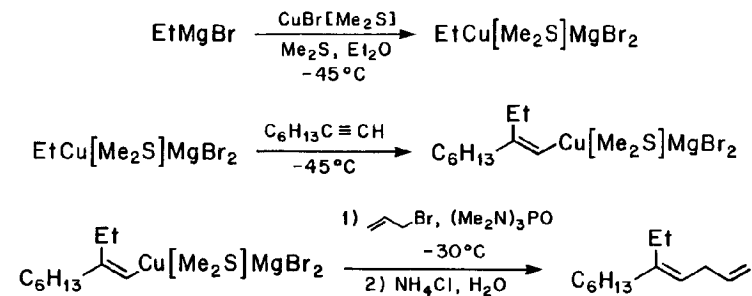
Submitted by Ramnath S. Iyer and Paul Helquist.[1]

Checked by Brian H. Johnston and Andrew S. Kende.
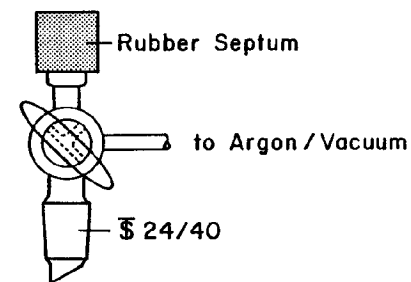
1. Procedure

Caution! This experiment should be performed in an efficient fume hood because of the unpleasant odor of dimethyl sulfide.

A dry, 1-L, one-necked, round-bottomed flask is equipped with a Teflon-coated magnetic stirring bar and a three-way stopcock bearing a rubber septum (Note 1), and the flask is charged with 25.2 g (0.123 mol) of the dimethyl sulfide complex of cuprous bromide (Note 2). An argon or nitrogen (Note 3) atmosphere is established in the flask by repeated cycles of evacuation with an oil pump and refilling with the inert gas. Through use of a syringe or cannula, 150 mL of diethyl ether (Note 4) and 120 mL of dimethyl sulfide

(Note 4) are added. After the mixture is stirred for a few minutes at 25°C, the resulting clear and colorless solution is cooled to -45°C (Notes 5,6). A 2.73 M solution (45.0 mL, 0.123 mol) of ethylmagnesium bromide in ether (Note 7) is added dropwise with a syringe or cannula over a period of 10 min. The suspension of yellow-orange solid is stirred at -45°C for 2 hr, and 1-octyne (16.0 mL, 0.109 mol; Note 4) is added with a syringe or cannula over a period of 2 min. After the solution is stirred at -45°C for 2 hr, it is cooled to -78°C (Note 5) and maintained at this temperature during the successive additions of hexamethylphosphoric triamide (40 mL, 0.229 mol; Note 4) (*Caution: Hexamethylphosphoric triamide is a potent carcinogen. Avoid inhalation of vapor, ingestion of the liquid, and contact with skin.*) and allyl bromide (11.4 mL, 0.131 mol; Note 4). The mixture is immediately warmed to -30°C and stirred at -30°C for 12 hr; it is warmed to 0°C and quenched by the addition of 30 mL of a saturated, aqueous solution of ammonium chloride adjusted to pH 8 with ammonium hydroxide. The mixture is stirred at 25°C in the air for 1.5 hr (Note 8) and is then shaken in a separatory funnel with a mixture of additional diethyl ether (50 mL) and water (50 mL). The dark blue aqueous layer is drawn off and the organic layer is washed with additional 50-mL portions of the ammonium chloride solution (pH 8) until the washings are colorless. The organic layer is washed separately with water (50 mL) and saturated aqueous sodium chloride solution (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated by rotary evaporation at 25°C (25 min). The residue consists of 17.6 g of yellow oil which is purified by distillation under reduced pressure through a 15-cm Vigreux column to give 16.6 g (85%) of (E)-5-ethyl-1,4-undecadiene as a clear, colorless liquid, bp 56°C (0.70 mm; Note 9).

2. Notes

1. The stopcock is constructed as shown below so that a source of inert gas and vacuum may be attached to the horizontal tubulation and liquid reagents and solutions may be transferred into the reaction flask with a syringe needle or cannula inserted through a rubber septum placed over the end of the vertical tubulation. In order to avoid air leaks through the septum into the reaction flask when reagents are not being added, the stopcock is normally turned to close off the vertical tubulation, but to leave the flask open to the argon source.

2. This complex is prepared from cuprous bromide and dimethyl sulfide according to the procedure of House.[2] The complex must be pure white. Slightly impure samples will produce pinkish solutions which are unsatisfactory for this procedure. Normally, the complex is dark red when it is first prepared, but the required state of purity can be achieved by two or three recrystallizations under a nitrogen atmosphere as described by House.[2] We have found, however, that if the initially-formed complex has a distinctly green appearance, it cannot be purified satisfactorily. Others have also been concerned about this matter of purification.[3]

3. The checkers found that the yields were diminished if the reaction was run under prepurified nitrogen, but did obtain the reported yields using argon. The submitters, however, have never experienced difficulty using the prepurified nitrogen available in their laboratory.

4. Commercially-obtained materials were purified before use as described below. Diethyl ether was distilled from a dark blue or dark purple solution of sodium benzophenone radical anion or dianion under nitrogen. This solution was obtained by dissolving 10 g of benzophenone in 1 L of commercial anhydrous ether, adding 10 g of freshly pressed sodium wire, and heating the mixture at reflux under nitrogen until the characteristic blue or purple color developed. Dimethyl sulfide (Aldrich Chemical Company, Inc.), 1-octyne (Chemical Samples Company or Albany International Chemicals), and allyl bromide (Columbia Organics) were distilled under nitrogen at atmospheric pressure. Hexamethylphosphoric triamide (Aldrich Chemical Company, Inc.) was distilled at aspirator pressure from calcium hydride.

5. Constant temperatures were maintained by using dry ice-acetone (-78°C) or dry ice-acetone-carbon tetrachloride baths (-25° to -45°C; the temperature tends toward the upper part of this range as the amount of acetone used is decreased) or more conveniently through the use of an acetone bath equipped with a Neslab CryoCool Model CC-100F low temperature unit, a Cole-Parmer Versa-Therm Model 2158 temperature controller, and a 500-W immersible heating coil. The temperature of the alkenylcopper solution must not be allowed to exceed -15°C; above this temperature rapid coupling to give a diene occurs.

6. When the solution of the cuprous bromide complex is cooled, a portion of the reagent may precipitate, but this behavior does not affect the overall results of the experiment.

7. The ethylmagnesium bromide solution was obtained from Alfa Products, Morton Thiokol, Inc. and was titrated before use by the method of Watson and Eastham.[4]

8. Stirring the mixture in the air simplifies the workup procedure because cuprous complexes are oxidized to cupric compounds that are highly soluble in water or the aqueous ammonia workup medium of this experiment.

9. The spectral characteristics of the final product are as follows: IR (neat) cm^{-1}: 3080, 2960, 2915, 2800, 1660, 1640, 1465, 1175, 940, and 910; H^1 NMR (80 MHz, $CDCl_3$) δ: 5.50-6.05 (m, 1 H, alkenyl C-H), 4.70-5.20 (m, 3 H, other alkenyl C-H's), 2.63 (t, 2 H, J = 6.5, $C=CH-CH_2-CH=CH_2$), 0.78-2.13 (several overlapping m, 18 H, other saturated C-H's); mass spectrum (70 eV) m/e (relative intensity) 181.1 (M + 1, 1.3), 180.1 (M, 9.2).

3. Discussion

The procedure that is described above provides an approach to trisubstituted alkenes, compounds that are very common among natural products and which serve as key intermediates in the synthesis of other types of compounds.[5] The methods that have been developed for the preparation of trisubstituted alkenes are far too numerous to discuss to any significant extent here, but they have been the subject of previous review articles.[6] Very briefly, however, a large portion of the available methods may be divided among the following categories:[7] (1) elimination or cleavage reactions of organic halides and other compounds bearing leaving groups; (2) carbonyl condensation reactions of phosphonium ylides and other carbanionic or at least nucleophilic organic intermediates; (3) cleavage or rearrangements of other systems; (4) substitution reactions of alkenyl halides and related compounds;
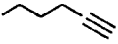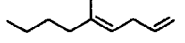
TABLE I

TRISUBSTITUTED ALKENES FROM ADDITION OF GRIGNARD-DERIVED

ALKYLCOPPER COMPLEXES TO ACETYLENES,

FOLLOWED BY REACTION WITH ELECTROPHILIC REAGENTS

Grignard Reagent	Acetylene	Electrophile	Product	Overall Yield (%)[a,b]
MeMgBr		Br		84
MeMgBr		Cl (O)		65
EtMgBr		O (epoxide)	OH	94
MgBr		CO_2	COOH	50
MgBr		O	O	73

[a]Since yields are sensitive to traces of oxygen during the reactions, the use of an argon atmosphere is strongly recommended.

[b]See refs. 7, 13.

(5) reactions of various allylmetal and other allylic systems; (6) reactions of various alkenylmetal species; and (7) addition reactions to acetylenes, 1,3-dienes, and allenes.

The reaction of organocopper reagents with simple, unactivated acetylenes, an example of the last class of methods in the preceding list, serves as the basis of the procedure described here. This addition reaction was first reported by Normant in 1971[8] and has been investigated extensively since that time by not only Normant,[9] but also by Vermeer,[10] Helquist,[7] Levy,[11] and others.[3b,12] An important modification[7] of the reaction which has been incorporated in the present preparation is the use of dimethyl sulfide as a ligand and co-solvent which permits much higher yields and a broader range of applicability than the originally reported procedure.[8]

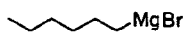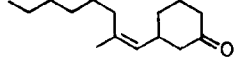The specific example reported here is one of several preparations that have been developed using the same general reaction sequence. A brief summary of other representative cases is given in Table I.[7,13] Notice that the alkenylcopper intermediates react with a variety of electrophilic reagents in addition to alkyl halides. It is especially noteworthy that the overall sequences leading to trisubstituted alkenes have been shown to proceed with greater than 99.9% stereoselectivity.[7] This unusually high degree of control of alkene configuration is of great value in natural products synthesis. The overall stereochemistry is indicative of *syn* addition of the alkylcopper complexes to acetylenes, a result which is observed for several types of carbometallation (or insertion) reactions.[9]

In summary, the procedure described in this chapter is representative of a very general, highly stereoselective approach to trisubstituted alkenes. The usefulness of this methodology has already been demonstrated in total synthesis.[7,12e,f,h,k,13]

1. Department of Chemistry, State University of New York, Stony Brook, NY 11794. Present address: Department of Chemistry, University of Notre Dame, Notre Dame, IN 46556.

2. House, H. O.; Chu, C.-Y.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460.

3. (a) Wuts, P. G. M. *Synth. Commun.*, **1981**, *11*, 139; (b) Theis, A. B.; Townsend, C. A. *Synth. Commun.* **1981**, *11*, 157.

4. Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

5. See reference 7 for an extensive discussion of the occurrence, synthetic applications, and methods of preparation of trisubstituted alkenes.

6. (a) Reucroft, J.; Sammes, P. G. *Quart. Rev., Chem. Soc.* **1971**, *25*, 135; (b) Faulkner, D. J. *Synthesis* **1971**, 175; (c) Arora, A. S.; Ugi, I. K. *Methoden Org. Chem. (Houben-Weyl)*, 4th Ed., **1972**, *5/1b*, 728; (d) Corey, E. J.; Long, A. K. *J. Org. Chem.* **1978**, *43*, 2208.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number):
(Registry Number)

1-Octyne (8,9); (629-05-0)

Dimethyl sulfide: Methyl sulfide (8); Methane, thiobis- (9); (75-18-3)

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

Allyl bromide: 1-Propene, 3-bromo- (8,9); (106-95-6)

2-ALKENYL CARBINOLS FROM 2-HALO KETONES: 2-E-PROPENYLCYCLOHEXANOL

(Cyclohexanol, 2-(1-propenyl)-, (E)-)

$$MeC \equiv CH \xrightarrow{\text{EtMgBr, THF, 10°C}} MeC \equiv CMgBr$$
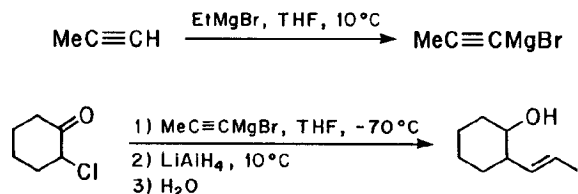
Submitted by P. A. Wender, D. A. Holt, and S. McN. Sieburth.[1]
Checked by Peggy A. Radel and Clayton H. Heathcock.

1. Procedure

A dry, 5-L, four-necked, round-bottomed flask is equipped with an air-driven stirrer (Note 1), 250-mL pressure-equalizing dropping funnel, thermometer, rubber septum, and a nitrogen inlet tube which, by means of a T-tube, is also connected to a gas bubbler. After being charged with 1200 mL of anhydrous tetrahydrofuran (Note 2), the flask is swept with dry nitrogen and maintained under an atmosphere of nitrogen throughout the remainder of the reaction. A solution of ethylmagnesium bromide in diethyl ether (1.1 mol, 380 mL, 2.9 M) is transferred to the flask and the flask is then cooled to below 10°C by means of an ice-water bath (Note 3). Propyne is bubbled through the cooled, stirred solution (Note 4) at such a rate that a small amount escapes through the nitrogen inlet/gas bubbler. Propyne addition is continued for 2.5 hr at which time approximately 100 g (2.5 mol) of propyne has been used (Note 5) and the internal temperature has risen 5-10°C. The ice-water bath is then replaced with a dry ice-acetone bath and the mixture is cooled to ca. -70°C. A solution of 2-chlorocyclohexanone (1 mol, 132.6 g) (Note 6) in 50 mL of tetrahydrofuran is added dropwise from the addition funnel over 1.5 hr so as to maintain the temperature below -65°C (Note 7). After stirring for an additional 1.5 hr at -70°C (Note 8), the dry ice-acetone bath is replaced with an ambient-temperature water bath and the reaction mixture is allowed to warm slowly. When the temperature reaches 10°C, a solution of lithium aluminum hydride in tetrahydrofuran (1 mol, 1000 mL, 1 M) is added by cannula (Note 9). After addition of the lithium aluminum hydride, the mixture is stirred at ambient temperature for 3-5 hr, at which time the solids have dissolved and reaction is complete (Notes 10, 11). The solution is then cooled to 5°C by means of an ice-water bath. The reaction is quenched by careful, dropwise addition of 38 mL of water over 2 hr so that the temperature remains below 20°C. The solution becomes somewhat cloudy at this point and 2000 mL of hexanes is added. The addition of 38 mL of aqueous 15% sodium hydroxide solution over 15 min is followed by the addition of 100 mL of water over 5 min. Some frothing occurs during the last addition of water and a large amount of white aluminum salts precipitates. After 5 min of stirring, 100 g of anhydrous sodium sulfate is added and stirring is continued for another 5 min. The thick mixture is then filtered by suction through Celite using a 200-mm diameter Büchner funnel. The solids are removed from the funnel, thoroughly washed with 1500 mL of hot tetrahydrofuran (Note 12), and re-filtered. This wash is repeated twice and the combined organic solutions are concentrated with a rotary evaporator (15 mm). The residual yellow liquid is distilled under reduced pressure to yield 118.8 g (85%) of 2-E-propenyl-cyclohexanol as a clear colorless liquid, bp 49-54°C (1 mm) (Note 13).

2. Notes

1. The use of a magnetic stirrer is more convenient than a mechanical stirrer for reactions conducted on small scale (<0.2 mol) or at low concentrations (<0.5 M). However, because of the difficulty encountered in stirring the sometimes thick suspensions associated with concentrated (e.g. 1 M) reaction mixtures, and because of the potentially disastrous results if a stir bar should fracture the flask wall during a large scale preparation, the submitters strongly recommend the use of an air-driven overhead mechanical stirrer for such large scale reactions. At a later stage in the reaction, when the propynylmagnesium bromide is cooled to -70°C, the THF solution becomes viscous and rather difficult to stir. The checkers recommend the use of a heavy-duty, air-driven stirrer such as the Fisher Scientific model 14-508-5. An electrically driven overhead stirrer should not be used, as the hydrogen released during the quench represents a considerable explosion hazard.

2. The submitters used 'Baker Analyzed' tetrahydrofuran (0.005% H_2O) without further purification or drying.

3. The submitters used ethylmagnesium bromide solution purchased from Aldrich Chemical Company, Inc., and found it most convenient to measure the required amount by transferring the solution by cannula to a nitrogen-flushed graduated cylinder fitted with a rubber septum. This measured amount of solution is then transferred to the flask by cannula. See reference 2 for general techniques for handling air-sensitive reagents in this manner. Some of the Grignard reagent precipitates at this temperature and concentration. There is a tendency for the ethylmagnesium bromide to clog the cannula. The checkers found it convenient to use a cannula made from 2-mm stainless steel tubing.

4. Propyne of 99.96% purity, purchased from Liquid Carbonic Company in a lecture bottle, was used without purification and was introduced to the flask by means of a Tygon tube which was attached to a 9-inch, 18-gauge hypodermic needle.

5. The amount of propyne used is conveniently determined by weighing the lecture bottle before and after addition. In this case the submitters used an excess of alkyne to insure complete consumption of the Grignard reagent. In cases where non-gaseous, non-volatile alkynes are to be used, stoichiometric amounts suffice.

6. The submitters used 2-chlorocyclohexanone purchased from Aldrich Chemical Company, Inc., without further purification. Alternatively, this compound can be easily prepared by chlorination of cyclohexanone.[3]

7. A flask should be used that is constructed in such a manner that the chloro ketone solution drips directly from the addition funnel into the reaction mixture. Any portion that flows along the sides of the flask will freeze.

8. Chloro alkoxide formation is essentially complete at this time and can be conveniently monitored by quenching a small aliquot and subjecting it to GLC analysis. Using a 50 m x 0.2 mm OV-1 capillary column at 110°C and a flow rate of 0.87 mL/min (H_2 carrier) the submitters found retention times of 3.2 min for 2-chlorocyclohexanone and 6.7 min and 7.2 min for trans- and cis-1-propynyl-2-chlorocyclohexanols, respectively.

9. Lithium aluminum hydride in tetrahydrofuran was purchased from Aldrich Chemical Company, Inc., and was handled in the fashion described above for the Grignard solution (see Note 3). While solid lithium aluminum hydride can be used (with appropriate changes in the amount of solvent initially used), the hazards of handling this flammable and even explosive reagent (see references 4 and 5) can be reduced by using the pre-prepared solution.

An excess of hydride reagent is necessary to facilitate complete reaction in a reasonable time. When only the stoichiomeric amounts of hydride reagent are used, the reaction is not complete even after several days at room temperature.

10. In reactions run at high concentration the reaction has a tendency to become slightly exothermic at some point, with the temperature increasing as much as 30°C. Although the reaction is usually complete in less time, and with no reduction in yield of product, this exothermic reaction can be prevented by keeping the flask in a large ambient-temperature water bath, thus buffering temperature changes that apparently initiate the exothermic reaction. The progress of the reaction can be conveniently monitored by TLC or GLC analysis of a quenched aliquot. Using the same GLC conditions as described in Note 8, the retention times for cis- and trans-2-E-propenylcyclo-hexanols are 4.1 min and 3.9 min, respectively.

11. The checkers noted that a homogeneous solution occurs after about 2 hr. However, TLC and GLC analysis showed that reaction was not complete until 3.5 to 5 hr.

12. The tetrahydrofuran used for washing the filter cake should be tested for peroxides before use, since the final distillation is carried out almost to dryness.

13. GLC analysis indicated a purity greater than 98% and a cis to trans ratio of 1:2. These isomers can be separated by column chromatography and give the following ^{1}H NMR spectra: (CDCl$_3$) δ: cis: 1.1-2.0 (m, 12 H, CH$_2$, CH$_3$, OH), 2.2 (m, 1 H, allylic CH), 3.75 (m, 1 H, carbinol CH), 5.4-5.6 (m, 2 H, CH=CH); trans: 1.0-2.2 (m, 10 H, CH$_2$, OH, allylic CH), 1.70 (d, 3 H, J = 4.9, CH$_3$), 3.1 (m, 1 H, carbinol CH), 5.0-5.8 (m, 2 H, CH=CH).

3. Discussion

A variety of approaches have been employed to effect the preparation of α-alkenyl ketones and carbinols, including reactions of metallo alkenes with epoxides,[6] α-halo ketones,[7] or enolonium ion equivalents[8] and the reactions of ketone enolates with vinyl cation equivalents.[9] The procedure described here offers several advantages over existing methodology. Starting materials and reagents are all commercially available at low cost. Manipulations are simple and the procedure can be carried out in a single operation, in a single flask, on a small or large (1 mol) scale and in high yield. In addition, as described in more detail elsewhere,[10] this method permits the use of cyclic as well as acyclic halo ketones, bromo ketones instead of chloro ketones, a variety of alkynes including acetylene, conjugated alkynes, and 3-silyloxy functionalized alkynes, and other aluminum hydride reagents such as diiso-butylaluminum hydride and lithium trimethoxyaluminum hydride. Furthermore, the method provides for complete control over alkene geometry and easy access to trisubstituted alkenes of defined stereochemistry.

Mechanistically, the reaction proceeds through an alkynyl chloro alkoxide which, when treated with the reducing agent, is hydroaluminated to yield the vinyl alanate, which subsequently undergoes a facile pinacol-like 1,2-rearrangement. Excess hydride reagent reduces the intermediate alkenyl ketone and the resulting 2-alkenyl carbinol is isolated upon aqueous workup (Scheme). Table I contains representative examples.

1. Department of Chemistry, Harvard University, Cambridge, MA 02138 and Department of Chemistry, Stanford University, Stanford, CA 94305.

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9. For example see: (a) Koppel, G. A.; Kinnick, M. D. *J. Chem. Soc., Chem. Commun.* **1975**, 473; (b) Kowalski, C. J.; Dung, J.-S. *J. Am. Chem. Soc.* **1980**, *102*, 7950; (c) Clive, D. L. J.; Russell, C. G.; Suri, S. C. *J. Org. Chem.* **1982**, *47*, 1632; (d) Hudrlik, P. F.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1981**, *103*, 6251; (e) Millard, A. A.; Rathke, M. W. *J. Am. Chem. Soc.* **1977**, *99*, 4833; (f) Chang, T. C. T.; Rosenblum, M.; Samuels, S. B. *J. Am. Chem. Soc.* **1980**, *102*, 5930.

10. Wender, P. A.; Holt, D. A.; Sieburth, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 3348.

Scheme
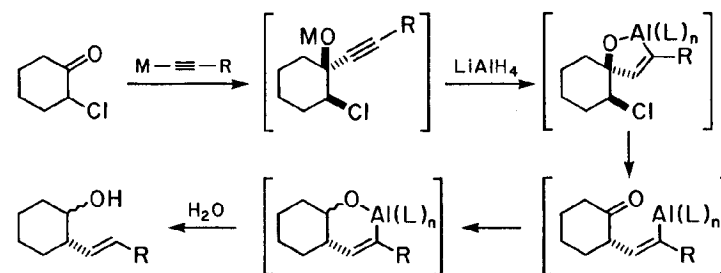
TABLE I

PREPARATION OF ALKENYL CARBINOLS

Carbonyl	Alkynylide	Alkenyl Carbinol	Yield (%)
	$-\!\equiv\!-MgBr$		85
	$\equiv\!-Li$		71
	$\equiv\!-Li$		76
	$\equiv\!-Li$		91
	$\equiv\!-Li$		46

α-AMINO ACETALS: 2,2-DIETHOXY-2-(4-PYRIDYL)ETHYLAMINE

(4-Pyridineethanamine, β,β-diethoxy)

Submitted by John L. LaMattina and R. T. Suleske.[1]

Checked by Paul Hebeisen and Andrew S. Kende.

1. Procedure

A. 4-Acetylpyridine oxime. Hydroxylamine hydrochloride (25.0 g, 0.36

mol) (Note 1) is dissolved in 50 mL of water, and the solution is added to 70

mL of 20% aqueous sodium hydroxide in a 500-mL Erlenmeyer flask. To this

magnetically stirred solution is added at one time 4-acetylpyridine (36.3 g,

0.30 mol) (Note 2); a precipitate forms rapidly. The reaction mixture is

stirred at 0-5°C for 2 hr; then the precipitate is collected by suction

filtration and washed with 500 mL of cold water.

The product (mp 122-146°C, 33-36 g, 81-88%) can be shown from its ^{1}H NMR spectrum (Note 3) to be a 5:1 mixture of the E- and Z-isomer of 4-acetylpyridine oxime. To obtain pure E-isomer (Note 4), the product is recrystallized twice as follows. The crude product is dissolved in 600 mL of hot water in a 2-L Erlenmeyer flask, the hot solution decanted from any undissolved residue, and the supernatant liquid is allowed to cool slowly to 30°C during 2-3 hr by placing the flask on a cork ring. The precipitate is collected at this temperature by suction filtration. A second crystallization by the same procedure yields pure E-oxime, which is dried under reduced pressure over Drierite to constant weight. The yield of E-4-acetylpyridine oxime, mp 154-157°C, (Note 5) is 27.1-28.3 g (66-69%).

B. *4-Acetylpyridine oxime tosylate.* Pure E-oxime (27.1 g, 0.20 mol) and p-toluenesulfonyl chloride (47.9 g, 0.22 mol) (Note 6) are added to 100 mL of anhydrous pyridine (Note 7) in a 1-L, round-bottomed flask fitted with a drying tube and a large magnetic stirring bar. The reaction mixture is stirred at 25°C for 24 hr; a precipitate of pyridine hydrochloride forms. A 500-mL portion of ice water is added with continued stirring. The initial precipitate dissolves and a voluminous white precipitate soon forms. This is collected by suction filtration, washed with three 150-mL portions of cold water and dried under reduced pressure and over Drierite to constant weight. The yield of pure tosylate, mp 79-81°C (Note 8), is 55.1 g (95%).

C. *2,2-Diethoxy-2-(4-pyridyl)ethylamine.* To a 2-L, round-bottomed flask containing 80 mL of absolute ethanol (Note 9) and fitted with a magnetic stirrer and a reflux condenser with a drying tube is slowly added potassium metal (7.60 g, 0.19 mol) (Note 10). When the metal has dissolved, the solution is cooled to 0-5°C and E-4-acetylpyridine tosylate (55.1 g, 0.19 mol) dissolved (with gentle warming) in 320 mL of absolute ethanol is added over 15 min through a dropping funnel to the stirred solution at 0-5°C. During this period a precipitate of potassium p-toluenesulfonate forms. The temperature of the stirred mixture is allowed to rise to room temperature for 1 hr. The mixture is diluted with 1 L of anhydrous ether and filtered by suction. The precipitate is quickly washed with 150 mL of anhydrous ether. The ether filtrates are combined, and hydrogen chloride gas is bubbled through the ether solution for 15 min. A precipitate forms immediately. The precipitate is collected by suction filtration, washed with three 170-mL portions of anhydrous ether and dried briefly under reduced pressure. The dihydrochloride thus obtained is dissolved in 200 mL of water, and powdered sodium carbonate is added until the mixture reaches a pH of >10. The mixture is extracted four times with 125-mL portions of chloroform. The combined chloroform extracts are dried over anhydrous magnesium sulfate and concentrated at reduced pressure to an oil. This orange-red oil is distilled at 0.2 mm to yield 29.7 g (74.5%) of the amine as a colorless oil, bp 93-95°C (Note 11).

2. Notes

1. Hydroxylamine hydrochloride 97% (mp 155-157°C), available from Aldrich Chemical Company, Inc. or Fisher Scientific Company, is suitable for use without further purification.

2. 4-Acetylpyridine (98%) from Aldrich Chemical Company, Inc. was distilled under reduced pressure (bp 103-104°C/14-16 mm) prior to use.

3. In dimethyl sulfoxide-d$_6$, the E- and Z-isomers show OH proton resonances at δ 11.65 and 10.97, respectively.

4. Use of the isomer mixture prevents isolation of oxime tosylate in crystalline form at the next step and leads to reduced overall yield of pure amine.

5. The lit[2] mp for the oxime is 158°C.

6. p-Toluenesulfonyl chloride was purified prior to use by the procedure of L. Fieser and M. Fieser in "Reagents for Organic Syntheses."[3]

7. Pyridine AR (Mallinckrodt, Inc.) was used directly.

8. The lit[2] mp for this compound is 80°C.

9. Ethanol was dried by reflux over magnesium ribbon.

10. For the safe handling and disposal of potassium metal, see *Org. Synth., Collect. Vol. IV* **1963**, 134.

11. This compound has the following 90 MHz ^{1}H NMR spectrum (CDCl$_3$) δ: 8.58 (d of d, 2 H, J = 2, 4.5, pyridine H$_2$ and H$_6$), 7.37 (d of d, 2 H, J = 2, 4.5, pyridine H$_3$ and H$_5$), 3.41 [m, 4 H, (OCH$_2$CH$_3$)$_2$], 2.97 (s, 2 H, CH$_2$NH$_2$), 1.20 [t, 6 H, J = 7, (CH$_3$CH$_2$O)$_2$], 0.75 (br s, 2 H, NH$_2$). Anal. Calcd for C$_{11}$H$_{18}$N$_2$O$_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.63; H, 8.52; N, 13.20.

3. Discussion

α-Amino ketones are useful intermediates for the preparation of a variety of heterocycles including imidazoles,[4] oxazoles,[5] and pyrazines.[6] Unfortunately, pyrazine formation can be a complicating side reaction because of the tendency of α-amino ketones to dimerize. One way to avoid this problem is to generate these intermediates in a protected form, specifically, as α-amino acetals.[7] Such derivatives allow one to manipulate the amino moiety as desired. The acetal can then be hydrolyzed at the appropriate interval to complete the synthesis.

α-Amino acetals have previously been prepared via catalytic hydrogenation of α,α-dialkoxynitriles,[8] a method which is limited by the availability of the appropriate starting material. The procedure here offers a more simple approach which involves the Neber rearrangement. Although this reaction is generally used to prepare α-amino ketones, use of an anhydrous ethanol medium readily results in acetal formation. A summary of other α-amino acetals prepared using this procedure appears in the Table.

This reaction, like all Neber rearrangements, is limited by availability of the appropriate oxime tosylate.[9] Substrates in which the aryl group contain an electron-donating function are unstable, since they have a propensity to undergo Beckmann rearrangement. However, this difficulty can be resolved by subsequent conversion of the α-amino acetals. For example, catalytic hydrogenation of 2,2-diethoxy-2-(p-bromophenyl)ethylamine yields the known parent compound, 2,2-diethoxy-2-phenylethylamine These two α-amino acetals readily undergo hydrolysis and should be protected from moisture.
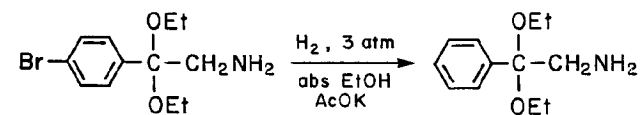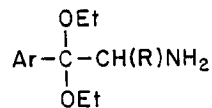
TABLE I

PREPARATION OF α-AMINO ACETALS

$$\begin{array}{c} \text{OEt} \\ | \\ \text{Ar}-\text{C}-\text{CH(R)NH}_2 \\ | \\ \text{OEt} \end{array}$$

Ar	R	Yield (%)	bp °C/mm	mp °C, HCl salt
2-pyridyl	H	58	82/0.2	150 (dec)[a]
3-pyridyl	H	53	84/0.2	187-188[a]
4-pyridyl	CH$_3$[b]	40	98/0.2	129-130[a]
4-O$_2$N-C$_6$H$_4$	H	78	c	116 (dec)
4-Br-C$_6$H$_4$	H	92	d	

a. Dihydrochloride salt.

b. For the preparation of this material in Step C, gaseous HCl is bubbled into the ethereal filtrate for 3 hr. Presumably the longer reaction time is necessary for steric reasons.

c. This material decomposes on distillation, and is purified by column chromatography (silica gel/chloroform).

d. This material decomposes on distillation and hydrolyzes when chromatographed on silica gel. However, ^{1}H-NMR analysis indicates that it is >95% pure.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

2,2-Diethoxy-2-(4-pyridyl)ethylamine: 4-Pyridineethanamine, β,β-diethyl (10); (74209-44-2)

4-Acetylpyridine: Ketone, methyl 4-pyridyl (8); Ethanone, 1-(4-pyridinyl)- (9); (1122-54-9)

Hydroxylamine hydrochloride (8); Hydroxylamine, hydrochloride (9); (5470-11-1)

4-Acetylpyridine oxime: Ketone, methyl 4-pyridyl oxime (8); Ethanone, 1-(4-pyridinyl)- oxime (9); (1194-99-6)

p-Toluenesulfonyl chloride (8); Benzenesulfonyl chloride, 4-methyl- (9);
(98-59-9)

4-Acetylpyridine oxime tosylate: Ethanone, 1-(4-pyridinyl)-0-
[(4-methylphenyl)sulfonyl]oxime (10); (74209-52-2)
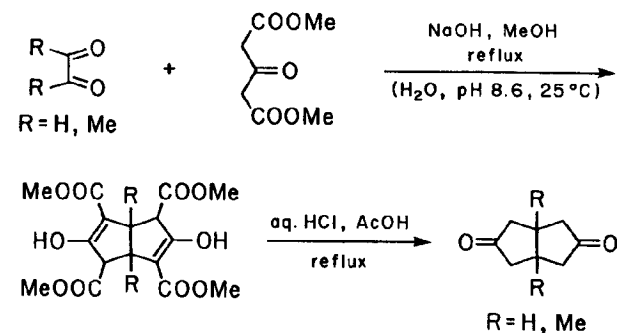
Submitted by Steven H. Bertz,[1] James M. Cook,[2] Ali Gawish,[2] and
Ulrich Weiss.[3]
Checked by Todd K. Jones, Scott E. Denmark, S. V. Govindan, and
Robert M. Coates.

1. Procedure

I. Specific procedure for glyoxal:

A.   *Tetramethyl 3,7-dihydroxybicyclo[3.3.0]octa-2,6-diene-2,4,6,8-tetra-
carboxylate.*   A 3-L, three-necked, round-bottomed flask is equipped with a
thermometer, mechanical stirrer, pressure-equalizing dropping funnel, reflux
condenser, and a heating mantle (Note 1). A solution of 64 g (1.60 mol) of

sodium hydroxide (Note 2) in 1.15 L of methanol is prepared in the flask, cooled in an ice bath, and stirred as 273 g (1.57 mol) of dimethyl 1,3-acetonedicarboxylate (Note 3) is added dropwise. The resulting slurry is stirred and heated to reflux at which point the white salt dissolves. The heating mantle is removed, and the solution is stirred rapidly while 128.5 g of aqueous 40% glyoxal (51.4 g, 0.886 mol) (Notes 3 and 4) is added at a rate sufficient to maintain the internal temperature at 65°C (Note 5). After the addition is completed (40-60 min, Note 6), the mixture is allowed to cool to room temperature and stirred overnight (Note 7). The precipitate is collected by suction filtration, washed with 500 mL of methanol (Note 8), and dried under reduced pressure. The yield of the white to light yellow disodium salt is 197-215 g (58-63%) (Note 9).

A 6-L Erlenmeyer flask equipped with a large magnetic stirring bar (Note 10) is charged with 1 L of chloroform and a solution of the disodium salt (0.46-0.50 mol) in 800 mL of water. The two phase mixture is stirred rapidly as 2.00 equiv (920-1000 mL, 0.92-1.00 mol) of cold 1 M hydrochloric acid is added. The layers are separated and the aqueous phase is extracted with three 500-mL portions of chloroform. The combined organic layers are washed once with saturated sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure by rotary evaporation keeping the water bath temperature at or below 40°C. Crystallization of the remaining waxy solid from 2:1 hexane-ethyl acetate affords 158-171 g (54-59% based on dimethyl 1,3-acetonedicarboxylate) of the tetraester, mp 97-100°C (Note 11).

B. *cis-Bicyclo[3.3.0]octane-3,7-dione.* A 3-L, three-necked, round-bottomed flask equipped with a heating mantle, two reflux condensers, and a magnetic stirrer (Note 12) is charged with 135 g (0.364 mol) of the tetraester, 66 mL of glacial acetic acid, and 600 mL of 1 M hydrochloric acid (Note 13). The mixture is stirred vigorously and heated at reflux for 2.5 hr (Note 14). The solution is cooled in an ice bath and the product is extracted with five 250-mL portions of chloroform. The chloroform extracts are combined, and the solution is concentrated by rotary evaporation (bath temperature at or below 40°C) until most of the acetic acid is removed. The residue is dissolved in 300 mL of fresh chloroform. The solution is washed with 60-mL portions of saturated sodium bicarbonate until the aqueous layer remains basic to litmus paper, dried with anhydrous sodium sulfate, and evaporated cautiously under reduced pressure. The yield of 44-45.5 g (88-90%) of white to light yellow solid, mp 84-85°C (Note 15). The product is sufficiently pure for most purposes; it may be purified by recrystallization from methanol or ethanol and/or by sublimation at 70°C (0.1 mm).

II. **General procedure using aqueous buffer:**

A. *Tetramethyl 3,7-dihydroxy-1,5-dimethylbicyclo[3.3.0]octa-2,6-diene-2,4,6,8-tetracarboxylate.* A freshly prepared solution (pH 8.3) of 5.6 g of sodium bicarbonate in 400 mL of water, 70 g (0.40 mol) of dimethyl 1,3-acetonedicarboxylate, and a magnetic stirring bar are placed in a 1-L Erlenmeyer flask. The resulting solution is stirred rapidly as 17.2 g (0.20 mol) of biacetyl (Note 3) is added in one portion. Stirring is continued for 24 hr during which time white crystals separate. The solid is collected by suction filtration and dried under reduced pressure to afford 60-62 g, mp 155-158°C. The filtrate is cooled in an ice bath, acidified to pH 5 (pHydrion paper) with dilute hydrochloric acid, and extracted with three 100-mL portions of chloroform. The chloroform extracts are combined, washed with saturated sodium chloride, and dried with anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gives another 2-4 g of crude product (Note 16). Recrystallization from hot methanol gives 58-60 g (73-75%) of the tetraester, mp 155-157°C, in two crops (Note 17).

B. *cis-1,5-Dimethylbicyclo[3.3.0]octane-3,7-dione*. A 1-L, one-necked, round-bottomed flask is equipped with a heating mantle, reflux condenser, and a magnetic stirring bar. The flask is charged with 200 mL of 1 M hydrochloric acid, 40 mL of glacial acetic acid, and 24 g (0.060 mol) of the tetraester from Part IIA. The mixture is stirred vigorously and heated at reflux for 3-6 hr (Note 18). The solution is cooled in an ice bath and the product is isolated as described in Part IB above. The yield of white to light yellow solid, mp 219-221°C, is 9.5-9.8 g (95-98%). Recrystallization from a minimum amount of hot ethanol affords 7.5-7.7 g (75-77%) of the diketone, mp 222-225°C, in one crop (Note 19).

2. Notes

1. The dropping funnel and the reflux condenser were connected to the same neck using a Claisen adapter.

2. The submitters recommend that a high-purity grade of sodium hydroxide be used. Otherwise insoluble impurities are formed that must be removed by filtration through a sintered glass Buchner funnel.

3. Dimethyl 1,3-acetonedicarboxylate, aqueous 40% glyoxal, and biacetyl were purchased from Aldrich Chemical Company, Inc. The submitters advise against using glyoxal solution that contains a significant amount of white solid.

4. The submitters report that the yield is decreased by 5% if exactly 0.5 equiv of glyoxal is used. The yield is improved to 75-76% in runs carried out on smaller scale (ca. 0.1 mol of glyoxal).

5. Heating should be resumed if necessary to maintain a temperature of 65°C. The submitters report that lower yields are obtained at lower temperatures (e.g., 37% at 25°C).

6. The submitters caution that the addition time is critical. In one run by the checkers with a 30-min addition time, the yield of the disodium salt was reduced to 49%.

7. Similar yields were obtained by the submitters when the reaction mixture was allowed to cool at room temperature for 2 hr and in an ice bath for another 2 hr.

8. The solid is washed first by allowing methanol to percolate through the filter cake with gentle suction until the brown color is removed. The product is suspended in methanol, filtered, and washed again by the percolation procedure.

9. The submitters obtained 411-430 g (61-64%) from reactions conducted on twice the scale described using a 2-hr addition time. Elemental analyses by the submitters and checkers indicate a variable degree of hydration (n = 1-2) for the product. The yield and molar quantities of the disodium salt are calculated assuming a monohydrate, $C_{16}H_{16}O_{10}Na_2H_2O$. For further characterization of this salt, see ref. 6.

10. The checkers used a mechanical stirrer to achieve more efficient mixing of the layers.

11. The submitters obtained 176-182 g (62-64%) of product, mp 103-105°C, after trituration with a minimum amount of cold methanol. Crystallization was facilitated by scraping the sticky solid with a silver spatula. The reported melting point is 104-107°C.[4] The crude product obtained initially by the checkers was a low melting solid, mp 70-75°C, that was conveniently transferred and purified by recrystallization from about 1 L of hot 2:1 hexane-ethyl acetate. Elemental analyses of the product by the submitters were within ±0.4% of the theoretical value. The spectral properties of the product are as follows: IR (CHCl$_3$) cm^{-1}: 1740, 1673, 1632, 1450, 1438, 1250,

1200, 1155; ^{1}H NMR (CDCl$_3$, 200 MHz) δ: 3.64 (apparent t, 2 H, J$_{app}$ = 2.4, two CH), 3.78 (s, 3 H, OCH$_3$), 3.81 (s, 3 H, OCH$_3$), 3.87 (apparent t, 2 H, J$_{app}$ = 2.4, two CH), 10.35 (broad s, 2 H, two enolic OH).

12. The volume of the flask should be at least three times larger than the volume of the solution to avoid losses from excessive foaming caused by rapid evolution of carbon dioxide. The checkers used a mechanical stirrer to facilitate stirring of the initially heterogeneous mixture.

13. The submitters point out that the disodium salt may be used directly provided that two additional equivalents of 1 M hydrochloric acid are employed. Acetic acid may be omitted to simplify the isolation procedure. In this case the reaction mixture remains heterogeneous throughout.

14. Progress of the reaction can be followed by observing the gas evolved through a bubbler connected to the top of the reflux condenser.

15. The product gave satisfactory elemental analyses: Calcd for C$_8$H$_{10}$O$_2$: C, 69.54, H, 7.30. Found: C, 69.42; H. 7.36. The literature melting point is 84-86°C.[4] The spectral properties of the product are as follows: IR (CHCl$_3$) cm^{-1}: 1738 (C=O), 1405, 1222, 1208, 1175, 792; ^{1}H NMR (CDCl$_3$, 220 MHz) δ: 2.16 (dd, 4 H, J = 4.2, 19.3, H$_A$ of CH$_A$H$_B$), 2.59 (dd, 4 H, J = 8.5, 19.3, H$_B$ of CH$_A$H$_B$), 3.04 (m, 2 H, CH); ^{13}C NMR (CDCl$_3$) δ: 35.5 (d, CH), 42.63 (t, CH$_2$), 217.2 (s, C=O); mass spectrum (70 eV) m/e (rel intensity): 138 (M$^+$, 41), 69 (36), 68 (58), 41 (100), 39 (53).

16. The checkers obtained ca. 19 g of a viscous red oil which, upon dissolution in ca. 150 mL of methanol, deposited 4 g of crude crystalline product.

17. The product gave a satisfactory elemental analysis: Calcd for C$_{18}$H$_{22}$O$_{10}$: C, 54.28; H, 5.53. Found: C, 54.00; H, 5.57. The melting point reported initially (167-169°C after sublimation)[5] is evidently incorrect. The spectral properties of the product are as follows: IR (KBr) cm^{-1}: 3539, 1742, 1664, 1425, 1340, 1260, 1235, 1070, 1020; ^{1}H NMR (CDCl$_3$) δ: 1.29 (s, 6 H, two CH$_3$), 3.75 (s, 6 H, two CO$_2$CH$_3$), 3.87 (s, 6 H, two CO$_2$CH$_3$), 3.94 (s, 2 H, two CHCO$_2$CH$_3$), 10.62 (br s, 2 H, two OH).

18. The checkers recovered a 1:1 mixture of tetraester and diketone from two runs conducted for 2.5 hr. When the reflux time was extended to 6 hr, complete conversion to product was attained. The reaction progress was monitored by gas evolution (Note 14). Some variability of reaction times is probably attributable to differences in stirring efficiency, temperature gradients, and/or particle size of the crystalline starting material.
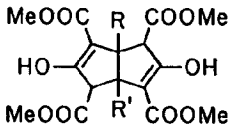
19. The recrystallized product was analyzed by the checkers. Calcd for C$_{10}$H$_{14}$O$_2$: C, 72.26; H, 8.49. Found: C, 72.45; H, 8.54. The spectral properties of the product are as follows: IR (KBr) cm^{-1}: 1736, 1390, 1245, 1210, 1180, 1145, 1070; ^{1}H NMR (CDCl$_3$, 360 MHz) δ: 1.22 (s, 6 H, two CH$_3$), 2.36 and 2.39 (AB q, 8 H, J = 18.5, four CH$_2$).

3. Discussion

Bicyclo[3.3.0]octane-3,7-dione has been prepared in five steps from dimethyl malonate and chloral in about 20% overall yield.[4] The direct formation of bicyclo[3.3.0]octane-3,7-diones by the 2:1 condensation of acetone-1,3-dicarboxylate and 1,2-dicarbonyl compound was discovered by Weiss and Edwards.[5] The variation described in Part I has been optimized for large-scale preparation of the parent diketone.[6] It is a good example of what Turner[7] has called a "point reaction," as it is very sensitive to experimental details such as temperature and stirring rate. The aqueous buffer procedure given in Part II is a "plateau reaction,"[7] and affords a general method for

preparing a variety of angularly-substituted bicyclo[3.3.0]octane-3,7-diones (Table I).[8-15] The parent dikeone can also be prepared by the aqueous buffer procedure (Part II), but chromatography is required to purify the product.[13] The mechanism of this novel annulation reaction involves a complex sequence of aldol condensations, dehydrations, and Michael additions,[9,16,17] the order of which may be pH dependent.[17] The isolation of γ-hydroxycyclopentenones in certain cases[9,16] implicates these reactive Michael acceptors as intermediates. A number of other interesting products have been isolated from reaction of glyoxal with acetonedicarboxylate.[17,18] The various bicyclic diketones prepared by this method have served as starting materials for syntheses of polycyclic compounds[19] and natural products.[20]

TABLE I

2:1 CONDENSATION OF DIMETHYL 1,3-ACETONEDICARBOXYLATE

WITH VARIOUS 1,2-DICARBONYL COMPOUNDS

		Yield (%)	Ref.
Glyoxal	R = R' = H	70	6,13
Pyruvaldehyde	R = H, R' = CH_3	52	5
Phenylglyoxal	R = H, R' = Ph	66	9
3-Cyclopentenylglyoxal	R = C_5H_7, R' = H	90	15
4-Cycloheptenylglyoxal	R = C_7H_{11}, R' = H	70	15
1-Phenyl-1,2-propanedione	R = CH_3, R' = Ph	68	15
4,5-Dioxopentanoic Acid	R = H, R' = $CH_2CH_2CO_2H$	80	8
Biacetyl	R = R' = CH_3	84	5
2,3-Pentanedione	R = CH_3, R' = CH_2CH_3	70	15
2,3-Hexanedione	R = CH_3, R' = $CH_2CH_2CH_3$	64	15
Cyclopentane-1,2-dione	R-R' = $(CH_2)_3$	45	5,14
Cyclohexane-1,2-dione	R-R' = $(CH_2)_4$	81	10
Cyclooctane-1,2-dione	R-R' = $(CH_2)_6$	80	11
Cyclooct-5-ene-1,2-dione	R-R' = $(CH_2)_2CHCH(CH_2)_2$	87	12
Cyclododecane-1,2-dione	R-R' = $(CH_2)_{10}$	94	11
Ninhydrin	R-R' = C_7H_4O	60	9

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

Dimethyl 1,3-acetonedicarboxylate: Glutaric acid, 3-oxo-, dimethyl ester (8); Pentanedioic acid, 3-oxo-, dimethyl ester (9); (1830-54-2)

Tetramethyl 3,7-dihydroxybicyclo[3.3.0]octa-2,6-diene-2,4,6,8-tetracarboxylate: 1,3,4,6-Pentalenetetracarboxylic acid, 1,3a,4,6a-tetrahydro-2,5-dihydroxy-, tetramethyl ester, (1α,3aα,4α,6aα)- (11); (82416-04-4)

Glyoxal (8); Ethanedial (9); (107-22-2)

cis-Bicyclo[3.3.0]octane-3,7-dione: 2,5(1H,3H)-Pentalenedione, tetrahydro-,

cis- (9); (51716-63-3)

Tetramethyl 3,7-dihydroxy-1,5-dimethylbicyclo-[3.3.0]octa-2,6-diene-2,4,6,8-

tetracarboxylate: 1,3,4,6-Pentalenetetracarboxylic acid, 1,3a,4,6a-

tetrahydro-2,5-dihydroxy-3a,6a-dimethyl-, tetramethyl ester (11); (79150-94-0)

Biacetyl: 2,3-Butanedione (8,9); (431-03-8)

cis-1,5-Dimethylbicyclo[3.3.0]octane-3,7-dione: 2,5(1H,3H)-Pentalenedione,

tetrahydro-3a,6a-dimethyl-, cis- (9); (21170-10-5)

CONVERSION OF EPOXIDES TO β-HYDROXY ISOCYANIDES.

TRANS-2-ISOCYANOCYCLOHEXANOL

(Cyclohexanol, 2-isocyanato-, trans-)
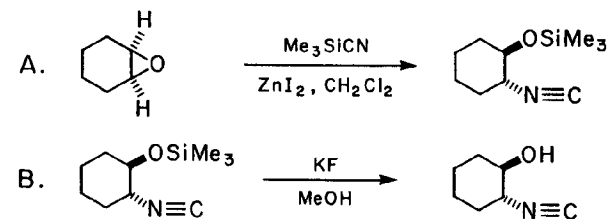
Submitted by Paul G. Gassman and Thomas L. Guggenheim.[1]

Checked by Curtis E. Adams and K. Barry Sharpless.

1. Procedure

Caution! Trimethylsilyl cyanide is very toxic. All reactions in this sequence should be carried out in a hood.

A. *[(trans-2-Isocyanocyclohexyl)oxy]trimethylsilane.* A 100-mL, three-necked flask equipped with a reflux condenser, constant pressure dropping funnel, magnetic stirring bar, and drying tube is charged with 20.2 g (204 mmol) of trimethylsilyl cyanide (Note 1), 60 mg (0.19 mmol) of anhydrous zinc iodide (Note 2) and 5 mL of dry methylene chloride (Note 3). The constant pressure dropping funnel is charged with 10.0 g (102 mmol) of cyclohexene oxide (Note 4) and 5 mL of dry methylene chloride. The reaction mixture is heated to reflux and the cyclohexene oxide - methylene chloride solution is added dropwise to the refluxing reaction mixture over a 30-min period. After the addition is complete, the reaction mixture is refluxed for 4 hr and then

allowed to cool to room temperature. The reaction mixture is transferred to a one-necked flask and the solvent and excess trimethylsilyl cyanide are removed under reduced pressure on a rotary evaporator (Note 5). The residue is vacuum distilled through a 3-inch Vigreux distillation column to yield 15.74 g (78%) of [(trans-2-isocyanocyclohexyl)oxy]trimethylsilane, bp 69-70°C (1.5 mm) (Note 6).

B. *trans-2-Isocyanocyclohexanol*. A 250-mL, one-necked, round-bottomed flask is charged with 13.72 g (70 mmol) of [(trans-2-isocyanocyclohexyl)oxy]-trimethylsilane, 12.12 g (210 mmol) of potassium fluoride (Note 7), and 100 mL of methanol. The reaction mixture is stirred magnetically for 5 hr at room temperature (23°C). The methanol is removed under reduced pressure on a rotary evaporator to yield a white slurry. This slurry is added to the top of a 250-g, 60-200 mesh silica gel chromatography column and the column is eluted with 20% ethyl acetate - 80% hexane solvent mixture (Note 8). The solvent is removed from those fractions containing the product under reduced pressure on a rotary evaporator to afford an oil which is redissolved in methylene chloride and the solution is filtered. The methylene chloride is removed from the filtrate under reduced pressure on a rotary evaporator to yield 8.46 g (68 mmol, 97%) of white, crystalline trans-2-isocyanocyclohexanol, mp 57.0-59.5°C (Note 9).

2. Notes

1. Trimethylsilyl cyanide was prepared shortly before use according to the procedure of Livinghouse, T. *Org. Synth.* **1980**, *60*, 126-132. The checkers used trimethylsilyl cyanide as supplied from Aldrich Chemical Company, Inc.

2. Anhydrous zinc iodide was purchased from Alfa Products, Morton/Thiokol, Inc., and used without further purification. In one run the checkers used 0.25 mmol of ZnI_2 and obtained a better yield than when they used 0.19 mmol of ZnI_2 (84% yield instead of 73%).

3. Commercial methylene chloride is dried by distillation from calcium hydride prior to use.

4. Cyclohexene oxide was purchased from Aldrich Chemical Company, Inc., and was used without purification.

5. The checkers also carried out this process in a fume hood. All glassware was rinsed afterwards with 10% KOH solution or rinsed with acetone and the rinses mixed with 10% KOH. The resulting KOH solutions were treated with Chlorox overnight before being discarded.

6. This pure, colorless liquid showed The following physical properties: IR (neat) cm^{-1}: 2950, 2870, 2145, 1454, 1267, 1255, 1144, 1114, 1065, 1028, 931, 894, 884, 844 and 758; ^{1}H NMR (60 MHz, CDCl$_3$/TMS) δ: 3.73-3.00 (br m, 2 H), 2.30-0.95 (br m, 8 H), 0.17 (s, 9 H); ^{1}H NMR (250 MHz, CDCl$_3$/CHCl$_3$ @ 7.24) δ: 3.56 (m, 1 H), 3.28 (m, 1 H), 2.13 (m, 1 H), 1.86 (m, 1 H), 1.67 (m, 2 H), 1.56 (m, 1 H), 1.25 (m, 3 H), 0.15 (s, 9 H); density 0.882 g/mL.

7. Potassium fluoride was purchased from the Fisher Scientific Company.

8. Approximately 100-mL fractions are collected. The progress of the chromatography is followed by analysis of the eluting fractions with thin-layer chromatography developed with iodine vapor. The checkers achieved equal success using 120 g of 70-230 mesh silica in a 30 x 250-mm column.

9. The product showed the following physical properties: IR (KBr) cm^{-1}: 3470, 3400, 2965, 2945, 2870, 2175, 1450, 1376, 1328, 1302, 1240, 1123, 1090, 1081, 1007, 919, 856, and 851; ^{1}H NMR (60 MHz, CDCl$_3$/TMS) δ: 3.90-3.00

(br m, 2 H), 2.85 (d, 1 H, J = 5), 2.40-0.70 (br m, 8 H); ^{1}H NMR (250 MHz, CDCl$_3$/CHCl$_3$ @ 7.24 ppm), 3.60 (m, 1 H), 3.30 (m, 1 H), 2.35 (d, 1 H, J = 4), 2.16 (m, 1 H), 2.02 (m, 1 H), 1.71 (m, 2 H), 1.56 (m, 1 H), 1.27 (m, 3 H).

3. Discussion

This method of preparation of trans-isocyanocyclohexanol is a version of our literature procedure.[2] It represents a general procedure which gives comparable yields with a wide variety of epoxides.[2] The method described is a new approach to the synthesis of isocyanides. Traditionally, isocyanides have been prepared by dehydration of formamides, the reaction of dihalocarbenes with primary amines, and the reaction of active halides and olefins with cyanides.[3-5]

Isocyanides are useful intermediates because of their diverse reactivity.[4] The β-hydroxy isocyanides which are prepared readily by our general procedure are particularly useful because of their straightforward conversion to β-amino alcohols in acids, and their catalyzed cyclization to oxazolines.[2]

1. Department of Chemistry, University of Minnesota, Minneapolis, MN 55455.
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Appendix

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

trans-2-Isocyanocyclohexanol: Cyclohexanol, 2-isocyanato-, trans- (10); (83152-97-0)

[(trans-2-Isocyanocyclohexyl)oxy]trimethylsilane: Silane, [(2-isocyano-cyclohexyl)oxy]trimethyl-, trans- (10); (83152-87-8)

Trimethylsilyl cyanide: Silanecarbonitrile, trimethyl- (8,9); (7677-24-9)
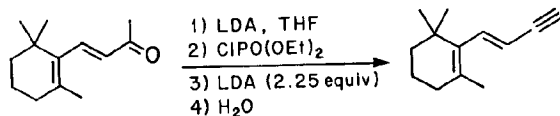
Zinc iodide (8,9); (10139-47-6)

Cyclohexene oxide: 7-Oxabicyclo[4.1.0]heptane (8,9); (286-20-4)

Potassium fluoride (8,9); (7789-23-3)

CONVERSION OF METHYL KETONES INTO TERMINAL ALKYNES.

(E)-BUTEN-3-YNYL-2,6,6-TRIMETHYL-1-CYCLOHEXENE

(Cyclohexene, 2-(1-buten-3-ynyl)-1,3,3-trimethyl-, (E)-)

Submitted by Ei-ichi Negishi, Anthony O. King, and James M. Tour.[1]
Checked by Weyton W. Tam and Robert V. Stevens.

1. Procedure

An oven-dried, 500-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum inlet, and an outlet connected to a mercury bubbler is flushed with nitrogen and charged with 100 mL of tetrahydrofuran (THF) (Note 1). To this are added sequentially at 0°C, diisopropylamine (Note 2) (10.6 g, 14.7 mL, 105 mmol) and butyllithium in hexane (Note 3) (2.22 M, 47.3 mL, 105 mmol). The reaction mixture is stirred for 30 min and cooled to -78°C. β-Ionone (Note 4) (19.2 g, 20.3 mL, 100 mmol) is slowly added. After stirring the mixture for 1 hr at -78°C, diethyl chlorophosphate (Note 5) (18.1 g, 15.2 mL, 105 mmol) is added, and the reaction mixture is allowed to warm to room temperature over 2-3 hr (Reaction mixture A) (Note 6).

Lithium diisopropylamide is prepared in a separate 1-L flask from diisopropylamine (22.8 g, 31.6 mL, 225 mmol), butyllithium in hexane (2.22 M,

101 mL, 225 mmol), and THF (200 mL), as described above. To this is added over ca. 45 min at -78°C Reaction mixture A prepared above via a 16-G double-ended needle under a slight pressure of nitrogen. The resulting mixture is allowed to warm to room temperature over 2-3 hr, and is quenched with water (200 mL) at 0°C. The organic layer is separated, and the aqueous layer is extracted with pentane (3 x 50 mL). The combined organic layer is treated with ice-cold hydrochloric acid (1 N, 200 mL), water (2 x 100 mL), and saturated aqueous sodium bicarbonate (100 mL) to pH ≥8 (Note 7). After drying over magnesium sulfate, the volatile compounds are evaporated using a rotary evaporator at ca. 20 mm. The residue is distilled at 0.7 mm to provide (E)-buten-3-ynyl-2,6,6-trimethyl-1-cyclohexene (Note 8) in one fraction boiling at 69-73°C (0.7 mm) (Note 9). The yield by isolation has ranged from 12.5 g (72%) to 14.8 g (85%) (Note 10). The purity of the product by GLC is 98%.

2. Notes

1. Tetrahydrofuran available from Aldrich Chemical Company, Inc. was purified by distillation from sodium and benzophenone.

2. The submitters used diisopropylamine (99%) available from Aldrich Chemical Company, Inc. without further purification.

3. The submitters used butyllithium in hexane available from Alfa Products, Morton/Thiokol Inc.

4. The submitters used 98% pure β-ionone available from Aldrich Chemical Company, Inc. without further purification.

5. The submitters used diethyl chlorophosphate available from Aldrich Chemical Company.

6. Reduced yields of product were obtained by the checkers when reaction time at room temperature was reduced from 2-3 hr to 1 1/2 hr.

7. After extraction with hydrochloric acid, the pentane layer, upon addition of 100 mL of water, formed a poorly separating emulsion. Checkers found that, by addition of 100 mL of saturated aqueous sodium bicarbonate to this pentane-water emulsion, two easily separable layers can be formed.

8. The distilled product was found to be slightly yellow, and deepened to orange at room temperature. Storage at -5°C maintained the initial coloration for several weeks.

9. The product displays the following data: n_D^{24} 1.5130; IR (neat) cm^{-1}: 3300 (s), 2920 (s), 2080 (m), 1770 (w), 1630 (w), 1600 (w), 1455 (s), 1380 (m), 1355 (m), 1200 (m), 1030 (m), 960 (s); ^{1}H NMR (CDCl$_3$, TMS) δ: 1.01 (s, 6 H), 1.2-1.8 (m with a singlet at 1.71, 7 H), 1.85-2.15 (m, 2 H), 2.90 (d, 1 H, J = 2), 5.42 (dd, 1 H, J = 17 and 2), 6.67 (d, 1 H, J = 17); ^{13}C NMR (CDCl$_3$, TMS) δ: 19.17, 21.48, 28.75, 33.07, 33.98, 39.59, 77.29, 83.10, 111.36, 131.38, 136.90, 142.33 ppm.

10. The GLC trace (SE-30) of the reaction mixture shows essentially one peak (>98%) in the product region. In separate 5-20 mmol scale experiments, the GLC yields observed by using a paraffin internal standard were 90-95%.

3. Discussion

This procedure is based on a study of conversion of methyl ketones into terminal alkynes.[2] The scope of the procedure may be indicated by the results summarized in Table I.

TABLE I

CONVERSION OF METHYL KETONES INTO TERMINAL ACETYLENES VIA ENOL PHOSPHATES

Ketone	Base[a]	Yield of Acetylene, %	
		GLC	Isolated
β-Ionone	LDA	95	85
Dihydro-β-ionone	LDA	90	85
Acetophenone	LDA	85	80
Pinacolone	LDA	90	78
Cyclohexyl methyl ketone	LDA	85	80
2-Octanone	LDA	23	--
2-Octanone	LTMP	75	--
6-Methyl-5-hepten-2-one	LDA	25	--
6-Methyl-5-hepten-2-one	LTMP	75	61

[a]LDA = lithium diisopropylamide. LTMP = lithium 2,2,6,6-tetramethylpiperidide.

As can be seen in the Table, lithium diisopropylamide (LDA) is a satisfactory base in cases where the carbon group (R) of a methyl ketone (RCOCH$_3$) either is bulky or does not contain an α-methylene or α-methine group. In the other cases, LDA is relatively ineffective. In such cases, however, the use of lithium 2,2,6,6-tetramethylpiperidide (LTMP) in place of LDA gives satisfactory results. The LTMP procedure appears to be the only documented method that is satisfactory for the conversion of the above-mentioned type.

The submitters have attempted the conversion of β-ionone into the desired dienyne by various known methods. In general, those involving acidic reagents or reaction conditions yielded the desired product in low yields (<50%) along with by-products, such as isomeric allenes, that appear near the product on GLC traces (SE-30). Such procedures include (a) PCl$_5$ in benzene, then NaNH$_2$ in NH$_3$,[3] (b) PCl$_5$ and 2,6-lutidine, then NaNH$_2$ in NH$_3$,[4] (c) POCl$_3$ in DMF, then NaOH,[5] and (d) (CF$_3$SO$_2$)$_2$O, CCl$_4$, pyridine, then heat.[6] Also unsatisfactory in the hands of submitters was a method involving the use of hydrazine in triethylamine, then iodine and triethylamine in THF, then methanolic potassium hydroxide.[7] A procedure involving the use of sodium ethoxide, then diethyl chlorophosphate, and finally NaNH$_2$ in NH$_3$,[8] on the other hand, converted β-ionone into the desired dienyne in <73% GLC yield. The procedure reported here may be viewed as a modification of the above method.

1. Department of Chemistry, Purdue University, West Lafayette, IN 47907.

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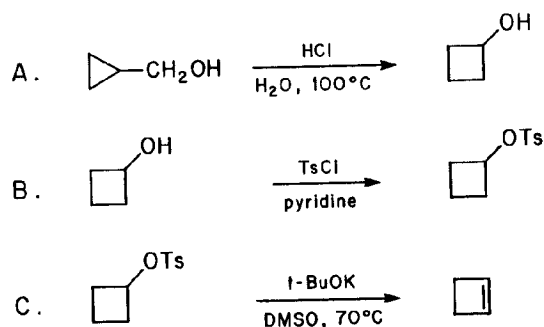
Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(E)-Buten-3-ynyl-2,6,6-trimethyl-1-cyclohexene: Cyclohexene, 2-(1-buten-3-ynyl)-1,3,3-trimethyl-, (E)- (10); (73395-75-2)

β-Ionone: 3-Buten-2-one, 4-(2,6,6-trimethyl-1-cyclohexen-1-yl)- (8,9); (14901-07-6)

Diethyl chlorophosphate: Phosphorochloridic acid, diethyl ester (8,9); (814-49-3)

CYCLOBUTENE

A. CH₂OH →[HCl][H₂O, 100°C] (OH on cyclobutane)

$$A. \quad \triangleright\!\!-CH_2OH \xrightarrow[\text{H}_2\text{O, 100°C}]{\text{HCl}} \square\text{-OH}$$

$$B. \quad \square\text{-OH} \xrightarrow[\text{pyridine}]{\text{TsCl}} \square\text{-OTs}$$

$$C. \quad \square\text{-OTs} \xrightarrow[\text{DMSO, 70°C}]{t\text{-BuOK}} \square\!\!\square$$

Submitted by J. Salaün and A. Fadel.[1]
Checked by Lawrence R. McGee and Bruce E. Smart.

1. Procedure

A. Cyclobutanol. A 1-L, three-necked, round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar is charged with 600 mL of water, 57.5 mL (ca. 0.68 mol) of concentrated hydrochloric acid, and 57.7 g (0.80 mol) of cyclopropylcarbinol (Note 1). The reaction mixture is stirred and refluxed for 3 hr. Cyclobutanol is only partially soluble in water and soon separates. The reaction mixture is allowed to cool to room temperature and the flask is then immersed in an ice bath. To the cold, stirred mixture is added 24 g (0.6 mol) of sodium hydroxide pellets, followed by 6.7 g (0.08 mol) of sodium bicarbonate to complete the neutralization. The mixture is saturated with sodium chloride and extracted for 30 hr with diethyl ether using a liquid-liquid continuous extraction apparatus. The ethereal extract

is dried over anhydrous sodium sulfate and the drying agent is removed by filtration. The bulk of the solvent is distilled from the filtrate to give 55.0 g of residual liquid containing 88% cyclobutanol and 12% 3-buten-1-ol by gas chromatography (Note 2). The crude product is carefully distilled through spinning band columns to give 32.8 g (57%) of cyclobutanol, bp 122-124°C. Gas chromatographic analysis of the product shows it to be 95% pure (Notes 2,3,4).

B. Cyclobutyl tosylate. A 500-mL, three-necked, round-bottomed flask fitted with a stirrer and a thermometer is charged with 200 mL of pyridine (Note 5) and 32.3 g (0.448 mol) of cyclobutanol. The solution is stirred and chilled to 0°C, and then 89.8 g (0.471 mol) of p-toluenesulfonyl chloride (Note 6) is added in portions over a 20-min period. The reaction mixture is allowed to warm to room temperature and is stirred for 16 hr. The mixture is recooled to 0°C, and poured into 260 mL of concentrated hydrochloric acid in 800 mL of ice water. The mixture is extracted with three 300-mL portions of ether and the combined ethereal extracts are dried over anhydrous magnesium sulfate. The drying agent is removed by filtration and the filtrate is concentrated on a rotary evaporator. The residue is held under high vacuum (0.03 mm) at room temperature for 3 hr to give 93.3 g (92%) of cyclobutyl tosylate as a pale yellow oil (Note 7).

C. Cyclobutene. A 500-mL, two-necked, round-bottomed flask is fitted with a 100-mL dropping funnel equipped with an argon-inlet tube, a magnetic stirring bar, and a water-cooled condenser. The outlet of the condenser is attached to an all glass transfer manifold. Two weighed traps fitted with gas-tight stopcocks and immersed in dry ice/acetone baths are attached to the manifold. A calcium chloride drying tube is attached to the exit of the second trap. While the system is continuously purged with a slow steam of argon, the flask is charged with 33.6 g (0.30 mol) of potassium tert-butoxide

and 120 mL of anhydrous dimethyl sulfoxide (Note 8), and a solution of 25.6 g (0.113 mol) of cyclobutyl tosylate in 30 mL of anhydrous dimethyl sulfoxide is placed in the dropping funnel. The potassium tert-butoxide suspension is stirred vigorously and heated to 70°C. The cyclobutyl tosylate solution is then added dropwise over a period of 10 min (Note 9). After the addition is completed, the reaction mixture is stirred at 70°C for an additional 2 hr. The manifold system is closed off from the reaction vessel and the material collected in the first trap is slowly warmed. The product distills at ca. 2°C into the second dry ice-cooled trap to give 4.3-5.1 g (70-84%) of cyclobutene [lit.[2] bp 2°C] (Notes 10 and 11).

2. Notes

1. The checkers obtained cyclopropylcarbinol from the Aldrich Chemical Company, Inc. It can be readily prepared by the reduction of cyclopropane-carboxylic acid with lithium aluminum hydride.[3]

2. A 25-m x 0.3-mm HP Ultra Silicone capillary column at 70°C with 30 psi helium head pressure was used for the chromatographic analysis: retention times of 3-buten-1-ol and cyclobutanol are 1.19 min and 1.35 min, respectively. The submitters used a 3-m x 0.3-cm 20 M carbowax column at 90°C/8 psi hydrogen and they reported retention times of 13 min and 20 min for 3-buten-1-ol and cyclobutanol, respectively.

3. The crude product was first distilled on a 50-cm x 0.8-cm spinning band column (reflux ratio 10:1) to give 19.6 g of cyclobutanol, bp 124°C. The forerun fractions, bp 66-123°C (23.0 g), were combined and redistilled on a 30-cm x 0.8-cm spinning band column (reflux ratio 25:1) to give an additional 13.2 g of cyclobutanol, bp 122-123°C. The major by-product, 3-buten-1-ol, boils at 112-114°C. Gas chromatographic analysis of the combined product fractions indicates a mixture of 95% cyclobutanol/3-buten-1-ol (99.7%/0.3%) and 5% unidentified compounds.

4. Cyclobutanol shows the following ^{1}H NMR spectrum (CDCl$_3$) δ: 4.54 (s, 1 H, OH), 4.16 (pentet, 1 H, J = 7.5), 1.1-2.4 (m, 6 H).

5. The pyridine was distilled from calcium hydride and stored over potassium hydroxide.

6. The p-toluenesulfonyl chloride was obtained from the Aldrich Chemical Company, Inc., and was recrystallized from hexane prior to use.

7. The product is >99% pure by NMR and shows the following spectrum: ^{1}H NMR (CDCl$_3$) δ: 7.79 (d, 2 H, J = 9.0), 7.32 (d, 2 H, J = 9.0), 4.77 (quintet, 1 H, J = 7.5), 2.47 (s, 3 H), 1.1-2.3 (m, 6 H).

8. Potassium tert-butoxide was obtained from the Aldrich Chemical Company, Inc. The dimethyl sulfoxide was distilled from calcium hydride and stored under argon.

9. The reaction mixture turns green, then blue indigo, and finally dark pink during the addition.

10. The submitters report obtaining 5.2 g of 99.2% pure cyclobutene. The product obtained by the checkers was pure by NMR spectroscopy and it shows the following ^{1}H NMR spectrum (CDCl$_3$) δ: 2.55 (s, 4 H), 6.00 (s, 2 H).

11. The cyclobutene can be converted to 1,2-dibromocyclobutane by distilling 4.3-7.3 g (0.079-0.135 mol) of cyclobutene into 100 mL of pentane chilled to -40°C, followed by adding a solution of 15.5-32.0 g (0.097-0.200 mol) of bromine in 30 mL of pentane. After the usual work-up with aqueous sodium thiosulfate and distillation, 14.3-25.3 g (84-87.5%) of pure 1,2-dibromocyclobutane, bp 60°C (6 mm), is obtained. It shows the following ^{1}H NMR spectrum (CDCl$_3$) δ: 1.90-3.03 (m, 4 H), 4.27-4.70 (m, 2 H). The 1,2-

dibromocyclobutane can be conveniently converted back to cyclobutene by debromination with zinc in ethanol.[4]

3. Discussion

Cyclobutene has been prepared (1) by pyrolysis of cyclobutyldimethylamine oxide[4-6] and cyclobutyltrimethylammonium hydroxide[4,6,7] (50-73% yield), which were prepared in eight steps from malonate esters (2.0-2.1% overall yield of cyclobutene contaminated with 1,3-butadiene), (2) by pyrolysis of the products of cycloaddition of dimethyl acetylenedicarboxylate with cyclooctatriene[8-10] (30-32% overall yield) or with cyclooctatetraene[11-13] (34-39% overall yield), (3) by photolysis of butadiene leading to cyclobutene (30% yield) and bicyclo[1.1.0]butane (5% yield),[14,15] (4) by oxidation of cyclobutylcarboxylic acid[16] with lead tetraacetate[17] (67% yield) (11.8% overall yield), (5) by fragmentation of 1,2-cyclobutyl thiocarbonate with trialkyl phosphite[18] (68% yield based on cis-1,2-dihydroxycyclobutane), (6) by ring expansion of cyclopropylcarbene[19] (7) from cyclobutylidene[20] and (8) by base induced ring-expansion of cyclopropylmethyl tosylate with potassium tert-butoxide in dimethyl sulfoxide leading to a 1:1 mixture of cyclobutene and methylene-cyclopropane.[21] None of these methods appears to be practical.

The present procedure offers in good yields a simple and ready preparation of pure cyclobutene from the easily available cyclopropyl-carbinol. The product is free of the impurities (e.g., 1,3-butadiene, bicyclobutane, methylenecyclopropane) usually obtained with the various methods so far reported. The procedure described for the synthesis of cyclobutanol is patterned after the acid-catalyzed rearrangement of cyclopropylcarbinol reported by Roberts[22] and Roček.[23]

1. Laboratoire des Carbocycles, U.A. 478, Bât. 420, Université de Paris-Sud, 91405 Orsay, France.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

Cyclobutene (8,9); (822-35-5)

Cyclobutanol (8,9); (2919-23-5)

Cyclopropylcarbinol: Cyclopropanemethanol (8,9); (2516-33-8)

Cyclobutyl tosylate: Cyclobutanol, p-toluenesulfonate (8); Cyclobutanol, 4-methylbenzenesulfonate (9); (10437-85-1)

p-Toluenesulfonyl chloride (8); Benzenesulfonyl chloride, 4-methyl- (9); (98-59-9)

Potassium tert-butoxide: tert-Butyl alcohol, potassium salt (8); 2-Propanol, 2-methyl-, potassium salt (9); (865-47-4)

DEOXYGENATION OF SECONDARY ALCOHOLS:

3-DEOXY-1,2:5,6-DI-O-ISOPROPYLIDENE-α-D-ribo-HEXOFURANOSE

(α-D-ribo-Hexofuranose, 3-deoxy-1,2:5,6-bis-O-(1-methylethylidene)-)

Submitted by S. Iacono and James R. Rasmussen.[1]

Checked by Peter J. Card and Bruce E. Smart.

1. Procedure

Caution! Carbon disulfide, iodomethane and tributyltin hydride are poisonous and should be handled in a well-ventilated hood.

A. 1,2:5,6-Di-O-isopropylidene-3-O-(S-methyl dithiocarbonate)-α-D-glucofuranose. A 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, nitrogen inlet adapter, pressure-equalizing addition funnel, and a stopper is charged with 26.0 g (0.10 mol) of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose, 25 mg of imidazole (Note 1), and 400 mL of anhydrous tetrahydrofuran (Note 2). The reaction vessel is flushed with

nitrogen and a nitrogen atmosphere is maintained during the ensuing steps. Over a 5-min period, 7.2 g (0.150 mol) of a 50% sodium hydride dispersion (Note 3) is added. Vigorous gas evolution is observed. After the reaction mixture is stirred for 20 min, 22.8 g (0.30 mol) of carbon disulfide is added all at once. Stirring is continued for 30 min, after which time 25.3 g (0.177 mol) of iodomethane is added in a single portion. The reaction mixture is stirred another 15 min, and 5.0 mL of glacial acetic acid is added dropwise to destroy excess sodium hydride. The solution is filtered (Note 4) and the filtrate is concentrated on a rotary evaporator. The semi-solid residue is extracted with three 100-mL portions of ether and the combined ether extracts are washed with two 100-mL portions of saturated sodium bicarbonate solution and two 100-mL portions of water. The ethereal solution is dried over anhydrous magnesium sulfate, the drying agent is removed by filtration, and the solvent is removed by rotary evaporation. The product is dried further at 0.05 mm overnight. The resulting orange syrup is distilled (Kugelrohr) to give 32.2-33.0 g (92-94%) of product, bp 153-160°C (0.5-1.0 mm) (Note 5).

B. 3-Deoxy-1,2:5,6-di-O-isopropylidene-α-D-ribo-hexofuranose. A dry, 1-L, round-bottomed flask is equipped with a magnetic stirring bar, and a reflux condenser to which a nitrogen inlet is attached. The apparatus is charged with 500 mL of anhydrous toluene (Note 6), 24.7 g (0.085 mol) of tributyltin hydride (Note 7) and 19.25 g (0.055 mol) of 1,2:5,6-di-0-isopropylidene-3-0-(S-methyl dithiocarbonate)-α-D-glucofuranose. The reaction mixture is heated at reflux under a nitrogen atmosphere until TLC analysis indicates the disappearance of starting materials (4-7 hr) (Note 8). During this time the reaction solution changes from deep yellow to nearly colorless. The toluene is removed on a rotary evaporator to yield a thick, oily residue that is

partitioned between 250-mL portions of petroleum ether and acetonitrile. The acetonitrile layer is separated and washed with three 100-mL portions of petroleum ether and is then concentrated on a rotary evaporator. The residual yellow oil is taken up in hexane/ethyl acetate (10:1) and filtered through a pad of silica gel (Note 9). The filtrate is concentrated and the residual oil is distilled to give 10.0 g (75%) of product as a colorless syrup, bp 72-73°C (0.2 mm); n_D^{25} 1.4474 (Note 10).

2. Notes

1.   1,2:5,6-Di-0-isopropylidene-α-D-glucofuranose and imidazole were purchased from Aldrich Chemical Company, Inc., and used without further purification. Alternatively, the glucofuranose starting material can be prepared by standard methods from D-glucose.[2]

2.   Reagent-grade tetrahydrofuran was freshly distilled from a purple solution of sodium and benzophenone.

3.   Sodium hydride, a 50% disperison in mineral oil, was purchased from Alfa Products, Morton/Thiokol Inc. It is not necessary to remove the mineral oil before conducting the reaction.

4.   The collected salts should be disposed of carefully by first rinsing with isopropyl alcohol to ensure that no sodium hydride remains.

5.   The submitters report pure product with bp 135-136°C (0.07 mm). The material obtained by the checkers is pure by NMR analysis. It shows ^{1}H NMR (CDCl$_3$) δ: 1.35 (s, 6 H), 1.42 (s, 3 H), 1.55 (s, 3 H), 2.60 (s, 3 H), 3.90-4.40 (m, 4 H), 4.68 (d, 1 H), 5.85-6.0 (m, 2 H).

6.   Reagent-grade toluene was dried by distilling the toluene-water azeotrope and then cooling the remaining liquid under an atmosphere of nitrogen.

7. Tributyltin hydride was purchased from Aldrich Chemical Company, Inc. and stored under nitrogen at 4°C.

8. An E. Merck Silica Gel 60 F-254 0.25-mm plate was used for the TLC analysis.

9. Silica Woelm TSC, obtained from Woelm Pharma, was used.

10. The product is pure by NMR and TLC analyses and shows ^{1}H NMR (CDCl$_3$) δ: 1.27 (s, 3 H), 1.31 (s, 3 H), 1.38 (s, 3 H), 1.46 (s, 3 H), 1.60-1.90 (m, 1 H), 2.05-2.30 (dd, 1 H), 3.65-4.25 (m, 4 H), 4.71 (t, 1 H), 5.77 d, 1 H).

3. Discussion

This procedure illustrates a simple, general method for the deoxygenation of secondary hydroxyl groups. It is particularly useful for reducing hindered alcohols. The method was first described by Barton and McCombie[3] who have reviewed a number of other examples.[4]

A variety of thiocarbonyl derivatives, in addition to xanthate esters, undergo reductive homolytic cleavage when treated with tributyltin hydride. These include thiobenzoates,[3] thiocarbonylimidazolides,[3,5] and phenyl thionocarbonate esters.[6] The S-methyl xanthate ester is a particularly convenient intermediate to prepare because of its ease of formation and the low cost of the reagents. Its use is precluded, however, by the presence of base-labile protecting groups and, in such cases, the thiocarbonylimidazolide or phenyl thionocarbonate ester will generally prove satisfactory. Additional methods for the radical deoxygenation of alcohols are described in a review by Hartwig.[7]

The tributyltin hydride reduction usually proceeds without complications. The most common byproduct is starting alcohol, which is postulated to be derived from a mixed thioacetal.[3] Use of the phenyl thionocarbonate ester has been reported to minimize this side reaction in cases where it is a problem.[6]

3-Deoxy-1,2:5,6-di-O-isopropylidene-α-D-ribo-hexofuranose has been prepared by a variety of other methods, the most widely used of which is the Raney nickel reduction of the 3-S-[(methylthio)carbonyl]-3-thioglucofuranose derivative.[8]

1. Department of Chemistry, Cornell University, Ithaca, NY 14853. Present address: Genzyme Corporation, 75 Kneeland Street, Boston, MA 02111.

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Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

3-Deoxy-1,2:5,6-di-0-isopropylidene-α-D-ribo-hexofuranose: D-ribo-

Hexofuranose, 3-deoxy-1,2:5,6-di-0-isopropylidene, α- (8); α-D-ribo-

Hexofuranose, 3-deoxy-1,2:5,6-bis-0-(1-methylethylidene)- (9); (4613-62-1)

1,2:5,6-Di-0-isopropylidene-α-D-glucofuranose: Glucofuranose, 1,2:5,6-di-0-

isopropylidene, α-D- (8); α-D-glucofuranose, 1,2:5,6-bis-0-(1-methyl-

ethylidene)- (9); (582-52-5)

1,2:5,6-Di-0-isopropylidene-3-0-(S-methyl dithiocarbonate)-α-D-

glucofuranose: Glucofuranose, 1,2:5,6-di-0-isopropylidene-, S-methyl

dithiocarbonate, α-D- (8,9); (16667-96-2)

Imidazole (8); 1 H-Imidazole (9); (288-32-4)

Sodium hydride (8,9); (7646-69-7)

Carbon disulfide (8,9); (75-15-0)

Iodomethane: Methane, iodo- (8,9); (74-88-4)

Tributyltin hydride: Stannane, tributyl- (8,9); (688-73-3)

DI-tert-BUTYL METHYLENEMALONATE

(Propanedioic acid, methylene-, bis(1,1-dimethylethyl)ester)

$$CH_2(COO\text{-}t\text{-}Bu)_2 + (CH_2O)_x \xrightarrow[\text{AcOH}]{\substack{\text{AcOK} \\ \text{Cu(OAc)}_2 \cdot H_2O}} CH_2{=}C(COO\text{-}t\text{-}Bu)_2$$
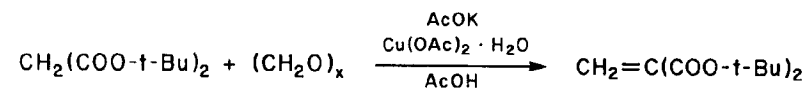
Submitted by Paloma Ballesteros and Bryan W. Roberts.[1]

Checked by Doreen L. Weller and James D. White.

1. Procedure

Caution! This reaction should be carried out in an efficient hood to prevent exposure to formaldehyde and acetic acid.

A 250-mL, one-necked, round-bottomed flask is equipped with a magnetic stirrer and a reflux condenser protected by a calcium chloride drying tube. Into the flask are placed 30.0 g (0.14 mol) of di-tert-butyl malonate (Note 1), 8.4 g (0.28 mol) of paraformaldehdye (Note 2), 1.4 g (0.014 mol) of potassium acetate, 1.4 g (0.007 mol) of cupric acetate monohydrate, and 70 mL of glacial acetic acid. The resulting green-white suspension is placed in an oil bath preheated to 90-100°C and stirred for 2 hr (Note 3). The reaction mixture is allowed to cool to room temperature, and the reflux condenser is replaced with a short-path distillation apparatus, the vacuum outlet of which is connected in sequence to a trap cooled in acetone-dry ice, a potassium hydroxide trap, another trap cooled in acetone-dry ice, and a vacuum pump. The receiving flask is cooled in acetone-dry ice, and the system is evacuated over approximately 1 hr to remove acetic acid and other volatile material

(Note 4). The bath temperature is increased to 40-50°C for 15 min and then is rapidly raised to 140-150°C to drive over crude product, which is collected over a boiling point range of 60-82°C (Note 5). When distillate ceases to come over, the bath temperature is increased to 170°C and distillate is collected over the same boiling point range until the reaction mixture turns from blue to green-brown. The total amount of crude product collected is 24.3 g. This material is dissolved in 50 mL of ether and washed with saturated aqueous sodium bicarbonate solution (4 x 20 mL) and water (25 mL). The combined aqueous fractions are extracted with 50 mL of ether, and the combined ether extracts are dried over magnesium sulfate for 10 min (Note 6). Filtration and evaporation on a rotary evaporator give 20.0 g of crude product which is distilled through an 8-cm Vigreux column. The di-tert-butyl methylenemalonate is collected at 60-67°C/0.1 mm and weighs 15.3 g (48%) (Note 7). The product is somewhat unstable and should be stored in Pyrex in the refrigerator.

2. Notes

1. Di-tert-butyl malonate was prepared according to the procedure of Johnson; see *Org. Synth., Collect. Vol. IV* 1963, 261.

2. Paraformaldehyde was obtained from Aldrich Chemical Company, Inc., and stored in a desiccator over phosphorus pentoxide.

3. After approximately 25 min, the suspension dissolves and the reaction mixture becomes blue-green.

4. At the beginning of the evaporation, the pressure is controlled to minimize bumping of the vigorously boiling mixture.

5. During this operation the pressure varies between 0.3 and 1.5 mm. As the temperature is raised, the reaction mixture turns blue and gas evolution is observed.

6. The procedure can be interrupted at this point and the ether extracts dried over magnesium sulfate overnight in the refrigerator.

7. The bath temperature should not exceed 100°C in order to prevent contamination of the product with the bis(hydroxymethyl) derivative of di-tert-butyl malonate. The product exhibits single peaks in the ^{1}H NMR spectrum (CDCl$_3$, 250 MHz) at 1.51 and 6.25 ppm and contains approximately 6% of di-tert-butylmalonate as indicated by a peak at 1.47 ppm. Contamination by the bis(hydroxymethyl) derivative is indicated by a peak at 1.48 ppm.

3. Discussion

Methylenemalonate esters are potentially useful activated alkenes which can serve as electrophilic partners in the Michael and cycloaddition reactions and, in the process, introduce a gem-diester functionality for further synthetic transformation. The simple esters, however, have a marked propensity toward spontaneous polymerization and, as a consequence, have been used only sparingly in the Michael reaction,[2] the Diels-Alder reaction,[3] [2 + 2] cycloaddition,[4] and [3 + 2] cycloaddition.[5] The recently prepared di-tert-butyl analog[6] is advantageous in being longer lived and suitable for conventional synthetic operations, and in introducing a readily cleaved diester moiety. In its most useful application thus far, the compound has been found to react under mild conditions with enamines with no added catalyst or with enol ethers and acetates under Lewis acid catalysis to give either cyclobutanes or Michael adducts, depending upon alkene structure.[7]

Di-tert-butyl methylenemalonate was originally prepared by phenyl-sulfenylation of di-tert-butyl methylmalonate and thermal elimination of the related sulfoxide.[6] Because methylenemalonate esters are customarily prepared by Knoevenagel-type condensation of malonic esters with formaldehyde equivalents, the considerably more convenient procedure described herein was subsequently adapted from Bachman and Tanner's study using paraformaldehyde under metal ion catalysis.[3a] The approximately 6% di-tert-butyl malonate accompanying the product has presented no interference in the aforementioned reactions with nucleophilic alkenes under neutral or acidic conditions, but its presence should be taken into consideration in other applications.

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

Di-tert-butyl methylenemalonate: Propanedioic acid, methylene-, bis(1,1-dimethylethyl) ester (11); (86633-09-2)

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

Paraformaldehyde: Poly(oxymethylene) (8,9); (9002-81-7)

THE STORK-DANHEISER KINETIC ALKYLATION PROCEDURE.

SYNTHESIS OF 3-ETHOXY-6-METHYL-2-CYCLOHEXEN-1-ONE
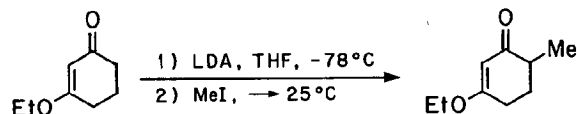
(2-Cyclohexen-1-one, 3-ethoxy-6-methyl-)

Submitted by Andrew S. Kende and Pawel Fludzinski.[1]

Checked by P. Wovkulich, F. Barcelos and Gabriel Saucy.

1. Procedure

A dry, 2-L, three-necked, round-bottomed flask is equipped with a magnetic stirrer, and two 500-mL pressure-equalizing dropping funnels. One of the dropping funnels is fitted with a rubber septum and the air in the system is replaced with dry nitrogen (Note 1). The flask is charged with 400 mL of anhydrous tetrahydrofuran (Note 2) and 51.6 g (71.5 mL, 0.51 mol) of anhydrous diisopropylamine (Note 3). The flask is cooled to 0° with an ice bath. A 1.7-M hexane solution of butyllithium (288 mL, 0.49 mol) is added dropwise with stirring over a 30-min period. The resulting lithium diisopropylamide is cooled to -78°C with a dry ice-acetone bath (Note 4). A solution of 53.9 g (0.385 mol) of 3-ethoxy-2-cyclohexen-1-one (Note 5) in 250 mL of anhydrous tetrahydrofuran is added dropwise with stirring at -78°C over a 1-hr period. The solution is stirred at -78°C for 30 min followed by the rapid addition of 114 g (50 mL, 0.80 mol) of methyl iodide (Note 6). After 5 min, the cooling

bath is removed, the mixture is allowed to warm to room temperature, and is stirred overnight. The reaction is quenched with 300 mL of water and the organic phase is separated. The aqueous phase is extracted four times with 75 mL of diethyl ether. The organic phases are combined and washed twice with 150 mL of water, once with 150 mL of brine, and dried over magnesium sulfate. Solvent removal on a rotary evaporator followed by distillation at reduced pressure affords 54-55 g (91-93%) of 3-ethoxy-6-methyl-2-cyclohexen-1-one as a colorless oil, bp 131-133°C (15 mm) (Notes 7, 8).

2. Notes

1. This is accomplished by alternately evacuating and filling the funnel with dry nitrogen two times; an oil bubbler is used to maintain a slight positive pressure throughout the reaction.

2. Tetrahydrofuran is freshly distilled from sodium and benzophenone.

3. Diisopropylamine is distilled from calcium hydride.

4. The flask is cooled with the dry ice-acetone bath for 1 hr before the next addition to insure complete cooling of the solution.

5. *Organic Synth., Coll. Vol. V* **1973**, 539.

6. Methyl iodide was obtained from Eastman Organic Chemicals and used directly from a fresh bottle.

7. Spectroscopic data for 3-ethoxy-6-methyl-2-cyclohexen-1-one are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.16 (d, 3 H, J = 7), 1.36 (t, 3 H, J = 6), 1.6-2.6 (m, 5 H), 3.92 (q, 2 H, J = 6), 5.32 (s, 1 H); IR (neat, cm^{-1}): 1670, 1600.

8. In the procedure as originally submitted, the authors used 1 equiv of base and distilled the product through a short path distillation apparatus with 75-80% yields. The checkers used excess lithium diisopropylamide (suggested by Professor Clayton Heathcock) as specified in this procedure, and distilled the product through a 15-cm Vigreux column to afford 1.7-1.9 g of forerun (97-98.5% pure by GC) and 54.1-55.3 g (91.4-93.4% yield) of main fraction. The short path distillation is probably quite adequate.

3. Discussion

The Stork-Danheiser[2] alkylation of 3-alkoxy-2-cyclohexenones under conditions of kinetic enolate formation at the 6-position has enjoyed extensive application in alicyclic synthesis. Such kinetic enolates have served as nucleophiles for a number of alkylations,[3-24] aldol condensations,[25-27] and Michael additions.[28,29] Reductive transposition of the resulting products to 4-substituted cyclohexenones has likewise found synthetic application.[30-33]

1. Department of Chemistry, University of Rochester, Rochester, NY 14627.

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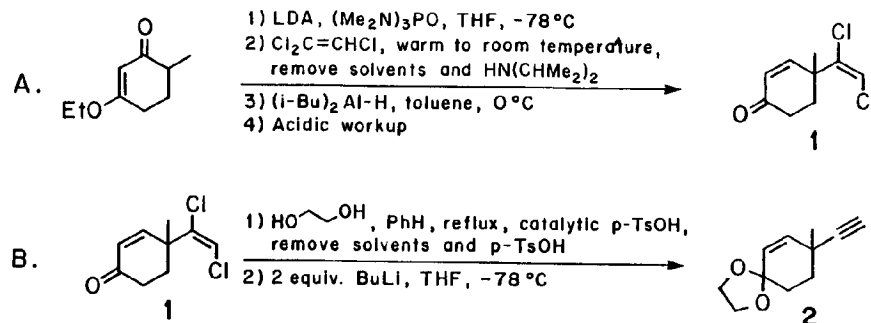27. Torii, S.; Okamoto, T.; Kadono, S. *Chem. Lett.* **1977**, 495.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

3-Ethoxy-6-methyl-2-cyclohexen-1-one: 2-Cyclohexen-1-one, 3-ethoxy-6-methyl- (10); (62952-33-4)

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

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

3-Ethoxy-2-cyclohexen-1-one: 2-Cyclohexen-1-one, 3-ethoxy- (8,9); (5323-87-5)

Methyl iodide: Methane, iodo- (8,9); (74-88-4)

DICHLOROVINYLATION OF AN ENOLATE. SYNTHESIS OF

8-ETHYNYL-8-METHYL-1,4-DIOXASPIRO[4.5]DEC-6-ENE

(1,4-Dioxaspiro[4.5]dec-6-ene, 8-ethynyl-8-methyl-)

A.
1) LDA, (Me₂N)₃PO, THF, −78°C
2) Cl₂C=CHCl, warm to room temperature, remove solvents and HN(CHMe₂)₂
3) (i-Bu)₂Al-H, toluene, 0°C
4) Acidic workup

B.
1) HO–OH, PhH, reflux, catalytic p-TsOH, remove solvents and p-TsOH
2) 2 equiv. BuLi, THF, −78°C

Submitted by Andrew S. Kende and Pawel Fludzinski.[1]

Checked by P. Wovkulich, F. Barcelos and Gabriel Saucy.

1. Procedure

Caution! Hexamethylphosphoric triamide and trichloroethylene are cancer-suspect agents. All operations with either one should be performed in an efficient hood. The use of disposable gloves is highly recommended. Glassware should be rinsed with copious amounts of water into separate waste containers before removal from the hood.

A. *4-(E-1,2-Dichlorovinyl)-4-methyl-2-cyclohexen-1-one* (1). A dry, 3-L, one-necked, round-bottomed flask is equipped with a magnetic stirrer and a 500-mL pressure-equalizing dropping funnel. The dropping funnel is fitted

with a rubber septum and the air in the system is replaced with dry nitrogen (Note 1). The flask is charged with 1500 mL of anhydrous tetrahydrofuran (Note 2) and 38.9 g (54 mL, 0.38 mol) of diisopropylamine (Note 3). The flask is cooled to 0°C with an ice bath. A 1.51-M hexane solution of butyllithium (255 mL, 0.38 mol) is added dropwise with stirring over a 30 min period. The resulting lithium diisopropylamide is cooled to -78°C with a dry ice-acetone bath (Note 4). A solution of 57.8 g (0.38 mol) of 3-ethoxy-6-methyl-2-cyclohexen-1-one (Note 5) in 400 mL of anhydrous tetrahydrofuran is added dropwise with stirring at -78°C over a 90-min period, followed immediately by the addition of 68 g (66 mL, 0.38 mol) of neat hexamethylphosphoric triamide (Note 6) over a 5-min period. The solution is stirred at -78°C for 45 min, followed by the dropwise addition of 52.6 g (36 mL, 0.40 mol) of neat trichloroethylene (Note 7). The solution is allowed to warm to room temperature slowly over a 6-hr period. As the solution warms, the color changes from pale yellow to olive green, to pale red, and finally to black. After 6 hr (Note 8) the solution is quenched with 1000 mL of water and the organic phase is separated. The aqueous phase is extracted four times with 250 mL of diethyl ether. The organic phases are combined and washed four times with 750 mL of water, twice with 750 mL of brine, and dried over magnesium sulfate. The solvent is removed on a rotary evaporator and recovered starting material is removed by fractional distillation at 91-93°C (1 mm) through a 15-cm Vigreux column. The residual crude 6-(E-1,2-dichlorovinyl)-3-ethoxy-6-methyl-2-cyclohexen-1-one (Note 9) is dissolved in 400 mL of toluene and placed in a dry, 2-L, one-necked, round-bottomed flask, equipped with a mechanical stirrer; a 500-mL pressure-equalizing dropping funnel is fitted with a rubber septum and the air in the system is replaced with dry nitrogen (Note 1). The solution is cooled to 0°C with an ice bath.

A 1-M hexane solution of diisobutylaluminum hydride (400 mL, 0.40 mol) (Note 10) is added dropwise with stirring at 0°C over a 1-hr period. The solution is stirred for 2 additional hr at 0°C. To quench the reaction 200 mL of methanol is carefully added to the stirred reaction mixture, followed slowly at first then more rapidly with 400 mL of water and then 300 mL of 10% sulfuric acid solution. After the mixture is stirred for 10 min, it is transferred to a separatory funnel and 500 mL of 10% sulfuric acid solution is added. The separatory funnel is shaken vigorously for 5 min and the organic phase is separated. The aqueous phase is extracted four times with 300 mL of diethyl ether. The organic phases are combined and washed twice with 300 mL of saturated sodium bicarbonate solution, twice with 300 mL of water, twice with 300 mL of brine, and dried over magnesium sulfate. Solvent removal on a rotary evaporator followed by short path distillation at reduced pressure affords 31-34 g (40-44%, based on 3-ethoxy-6-methyl-2-cyclohexen-1-one) of 4-(E-1,2-dichlorovinyl)-4-methyl-2-cyclohexen-1-one (1) as a colorless oil, bp 75-78°C (0.1 mm) (Note 11).

B. *8-Ethynyl-8-methyl-1,4-dioxaspiro[4.5]dec-6-ene* (2). A dry, 1-L, one-necked, round-bottomed flask is equipped with a magnetic stirrer, Dean-Stark trap and a reflux condenser. The flask is charged with 500 mL of benzene, 12.0 g (0.059 mol) of 4-(E-1,2-dichlorovinyl)-4-methyl-2-cyclohexen-1-one, 12.2 g (11 mL, 0.20 mol) of ethylene glycol and 40 mg (a catalytic amount) of p-toluenesulfonic acid. After the solution is refluxed for 24 hr, it is poured into 200 mL of saturated sodium bicarbonate solution. The organic phase is separated and the aqueous phase is extracted four times with 50 mL of diethyl ether. The organic phases are combined and washed twice with 100 mL of water, once with 100 mL of brine, and dried over magnesium sulfate. The solvent is removed on a rotary evaporator, and the resulting

crude 8-(E-1,2-dichlorovinyl)-8-methyl-1,4-dioxaspiro[4.5]dec-6-ene (Note 12) is dissolved in 200 mL of anhydrous tetrahydrofuran and placed in a dry, 1-L, one-necked, round-bottomed flask equipped with a magnetic stirrer and a 500-mL pressure-equalizing dropping funnel. The dropping funnel is fitted with a rubber septum and the air in the system is replaced with dry nitrogen (Note 1). The solution is cooled to -78°C with a dry ice-acetone bath (Note 4). A 1.51-M hexane solution of butyllithium (76 mL, 0.12 mol) is added dropwise with stirring at -78°C over a 30-min period. The solution is stirred at -78°C for 2 hr, the cold bath is removed, and stirring is continued for 90 min. The solution is poured into 100 mL of water and the organic phase is separated. The aqueous phase is extracted four times with 25 mL of diethyl ether. The organic phases are combined and washed twice with 75 mL of water, twice with 75 mL of brine, and dried over magnesium sulfate. Solvent removal on a rotary evaporator followed by short path distillation at reduced pressure yields 5.5-6.3 g (52-60%) of 8-ethynyl-8-methyl-1,4-dioxaspiro[4.5]dec-6-ene as a colorless oil, bp 88-90°C (1 mm) (Note 13).

2. Notes

1. This is accomplished by alternately evacuating and filling the funnel with dry nitrogen two times; an oil bubbler is used to maintain a slight positive pressure throughout the reaction.

2. Tetrahydrofuran is freshly distilled from sodium and benzophenone, as is all tetrahydrofuran used in this procedure.

3. Diisopropylamine is distilled from calcium hydride.

4. The flask is cooled with the dry ice-acetone bath for 1 hr before the next addition to insure complete cooling of the solution.

5. See *Organic Syntheses*, this volume p. 68.

6. Hexamethylphosphoric triamide is freshly distilled from calcium hydride.

7. Trichloroethylene is freshly distilled from phosphorus pentoxide.

8. On a smaller scale, the reaction warms to room temperature more quickly and can be worked up after 4 hr. Extended reaction times (e.g., overnight) lead to the formation of by-products.

9. Distillation is not necessary at this point. Spectroscopic data for 6-(E-1,2-dichlorovinyl)-3-ethoxy-6-methyl-2-cyclohexen-1-one is as follows: ^{1}H NMR (CDCl$_3$) δ: 1.38 (t, 3 H, J = 6), 1.48 (s, 3 H), 1.8-2.7 (m, 4 H), 3.96 (q, 2 H, J = 6), 5.44 (s, 1 H), 6.36 (s, 1 H). A purified sample (bp 140-142°C, 1 mm) gave satisfactory analysis. Anal. Calcd for $C_{11}H_{14}Cl_2O_2$: C, 53.02; H, 5.68. Found: C, 53.20; H, 5.43.

10. Diisobutylaluminum hydride was purchased from Aldrich Chemical Company, Inc. Since the reagent is not titrated, excess is used to insure complete reduction.

11. Spectroscopic data for 4-(E-1,2-dichlorovinyl)-4-methyl-2-cyclohexen-1-one are as follows: ^{1}H NMR (CDCl$_3$) δ: 1.50 (s, 3 H), 1.8-2.8 (m, 4 H), 5.92 (d, 1 H, J = 10), 6.34 (s, 1 H), 7.04 (d, 1 H, J = 10); ms (75 eV) m/e 204; IR (CHCl$_3$) cm^{-1}: 1680. Anal. Calcd $C_9H_{10}Cl_2O$: C, 52.71; H, 4.91. Found: C, 53.08, H, 5.03.

12. Spectroscopic data for 8-(E-1,2-dichlorovinyl)-8-methyl-1,4-dioxaspiro[4.5]dec-6-ene is as follows: ^{1}H NMR (CDCl$_3$) δ: 1.36 (s, 3 H), 1.6-2.6 (m, 4 H), 3.88-4.08 (m, 4 H), 5.56 (d, 1 H, J = 10), 6.08 (d, 1 H, J = 10), 6.28 (s, 1 H).

13. Spectroscopic data for 8-ethynyl-8-methyl-1,4-dioxaspiro[4.5]dec-6-ene are follows: ^{1}H NMR (CDCl$_3$) : 1.32 (s, 3 H), 1.6-2.2 (m, 4 H), 2.12 (s, 1 H), 3.88-4.04 (m, 4 H), 5.64 (AB q, 2 H, J = 10); ms (75 eV) m/e 178; IR (neat) cm^{-1}: 3290, 2100. Anal. Calcd for C$_{11}$H$_{14}$O$_2$: C, 74.13; H, 7.92. Found: C, 73.96; H, 7.78. ^{13}C NMR (CDCl$_3$) δ: 28.1 (C^{11}), 30.5 (C^9 or C^{10}), 31.4 (C^8), 34.6 (C^9 or C^{10}), 64.0 (C^2 or C^3), 64.3 (C^2 or C^3), 68.4 (C^{13}), 88.3 (C^{12}), 104.5 (C^5), 126.3 (C^6), 137.0 (C^7).
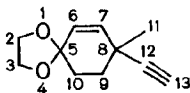
3. Discussion

Trichloroethylene serves as an effective reagent for the dichlorovinylation of lithium enolates of several conjugated ketones. Under similar reaction conditions, 2,6-dimethylcyclo-2-hexen-1-one and 2-ethyl-5-methoxy-1-tetralone give the analogous dichlorovinyl adduct in comparable yield.[2] This procedure represents an heretofore unknown, uncatalyzed[3] carbon-carbon bond forming reaction between enolates and a polychloroolefin which can subsequently provide access to α- and γ-acetylenic ketones.[4]

1. Department of Chemistry, University of Rochester, Rochester, NY 14627.

2. Kende, A. S.; Benechie, M.; Curran, D. P.; Fludzinski, P.; Swenson, W.; Clardy, J. *Tetrahedron Lett.* **1978**, 4513.

3. For examples of Ni-catalyzed vinylation and arylation of enolates by bromides and iodides, see Millard, A. A.; Rathke, M. W. *J. Am. Chem. Soc.* **1977**, *99*, 4833.

4. The trichloroethylene condensation has been shown to proceed by way of dichloroacetylene as an obligatory intermediate in a carbanion chain mechanism. See: Kende, A. S.; Fludzinski, P. *Tetrahedron Lett.* **1982**, *23*, 2369, 2373; Kende, A. S.; Fludzinski, P.; Hill, J. M.; Swenson, W.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 3551.

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

8-Ethynyl-8-methyl-1,4-dioxaspiro[4.5]dec-6-ene: 1,4-Dioxaspiro[4.5]dec-6-ene, 8-ethynyl-8-methyl (10); (73843-26-2)

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

Trichloroethylene: Ethylene, trichloro- (8); Ethene, trichloro- (9); (79-01-6)

4-(E-1,2-Dichlorovinyl)-4-methyl-2-cyclohexen-1-one: 2-Cyclohexen-1-one, 4-(1,2-dichloroethenyl)-4-methyl- (10); (73843-27-3)

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

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

3-Ethoxy-6-methyl-2-cyclohexen-1-one: 2-Cyclohexen-1-one, 3-ethoxy-6-methyl- (10); (62952-33-4)

6-(E-1,2-Dichlorovinyl)-3-ethoxy-6-methyl-2-cyclohexen-1-one: 2-Cyclohexen-1-one, 6-(1,2-dichloroethenyl)-3-ethoxy-6-methyl- (10); (73843-25-1)

Diisobutylaluminum hydride: Aluminum, hydrodiisobutyl- (8); Aluminum, hydro-bis(2-methylpropyl)- (9); (1191-15-7)

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

DIETHYL [(2-TETRAHYDROPYRANYLOXY)METHYL]PHOSPHONATE

(Phosphonic acid, [(tetrahydro-2H-pyran-2-yl)oxy]methyl-, diethyl ester)

$$(EtO)_2\overset{\overset{O}{\|}}{P}H + (CH_2O)_n + Et_3N \longrightarrow (EtO)_2\overset{\overset{O}{\|}}{P}CH_2OH$$

$$(EtO)_2\overset{\overset{O}{\|}}{P}CH_2OH + \underset{O}{\bigcirc} + POCl_3 \longrightarrow (EtO)_2\overset{\overset{O}{\|}}{P}CH_2O\text{-}\underset{O}{\bigcirc}$$
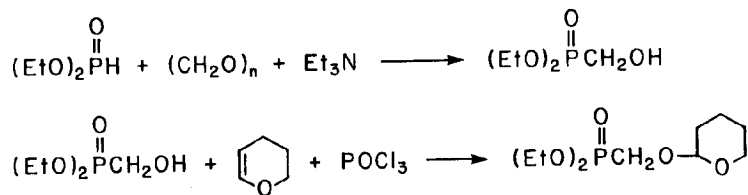
Submitted by Arthur F. Kluge.[1]

Checked by Ronaldo A. Pilli, Kenneth S. Kirshenbaum,

Clayton H. Heathcock, and K. Barry Sharpless.

1. Procedure

A. Diethyl hydroxymethylphosphonate. To a 250-mL, round-bottomed flask equipped with a magnetic stirring bar and an efficient reflux condenser are added 69 g (64.4 mL, 0.5 mol) of diethyl phosphite (Note 1), 15 g (0.5 mol) of paraformaldehyde, and 5.1 g (0.05 mol) of triethylamine. The mixture is placed in an oil bath preheated to 100-120°C. The temperature is increased to 120-130°C, and the mixture is stirred at this temperature for 4 hr. The stirring bar is removed, the flask is transferred to a rotary evaporator, and most of the triethylamine is removed by heating under reduced pressure of ca. 15 mm and with a bath temperature of ca. 80°C. Kugelrohr distillation at 125°C (0.05 mm) (Note 2) gives 41.4-54.9 g (49-65%) of material of sufficient purity for the next step (Notes 3 and 4).

B. Diethyl [(2-tetrahydropyranyloxy)methyl]phosphonate. A mixture of 33.63 g (0.2 mol) of diethyl hydroxymethylphosphonate, 21 g (0.25 mol) of dihydropyran, and 150 mL of diethyl ether is placed in a stoppered flask, and 20 drops of phosphorus oxychloride is added while the contents are swirled manually. After 3 hr at room temperature the reaction is monitored by TLC (Note 5). The mixture is diluted with diethyl ether, transferred into a separatory funnel, and shaken successively with 100 mL of saturated sodium bicarbonate solution, 100 mL of water, and 100 mL of saturated sodium chloride solution. The ether solution is dried over MgSO₄, filtered, and the ether is removed with a rotary evaporator. Kugelrohr distillation of the residue (110°C, 0.05 mm) gives 42.4-46.9 g (84-93%) of material of sufficient purity for use in homologation reactions (Notes 6 and 7).

2. Notes

1. Diethyl phosphite, paraformaldehyde, and triethylamine were obtained from Aldrich Chemical Company, Inc. Dihydropyran was obtained from MC and B Manufacturing Chemists.

2. Attempted isolation of diethyl hydroxymethylphosphonate by standard vacuum distillation technique is accompanied by extensive decomposition. The use of Kugelrohr apparatus allows the isolation to be accomplished at a lower temperature, and therefore the product is obtained in higher yield. Alternately, the checkers found that distillation using a 2" wiped-film molecular still (Pope Scientific, Inc.) significantly raised product yields, especially when the reaction was performed on a larger scale (Notes 3 and 6).

3. The checkers found that reactions run on up to four times the present scale and rectified using a molecular still (wall temperature 110-120°C, 0.10 mm) gave yields of 89-94%. *Warning*: On this larger scale (i.e., four times the present scale) a brief run-away was experienced and some material which escaped from the condenser was caught in a trap; however, the yield was still excellent (94%).

4. On TLC [silica, visualization with 1.5% phosphomolybdic acid spray and heating] the product has an R_f of ca. 0.1 with ethyl acetate development and ca. 0.3 with methanol-dichloromethane [5:95] development. The ^{1}H NMR spectrum (CDCl$_3$) is as follows δ: 1.31 (t, 6 H, J = 6.8), 3.87 (d, 2 H, J = 7), 4.13 (m, 4 H), 5.34 (br s, 1 H, OH).

5. Five drops of reaction mixture is added to a mixture of 20 drops of diethyl ether and 1 drop of triethylamine. On TLC (Note 4) the product has an R_f of ca. 0.4 with ethyl acetate development. If TLC indicates the presence of diethyl hydroxymethylphosphonate an additional 5 g of dihydropyran and 10 drops of phosphorus oxychloride are added. The reaction is checked by TLC for completeness after 1 hr and is worked up at that time.

6. The checkers found that reactions run on up to nine times the present scale could be effected with only a small reduction in yield. Molecular still distillation (wall temperature 105-115°C, 0.10 mm) gave yields of 81-83%.

7. GLC analysis [0.5 x 200 cm 3% OV-17, 170°C, He flow = 30 mL/min] shows the product with a retention time of 5 min and a purity greater than 97%. The ^{1}H NMR spectrum (CDCl$_3$) is as follows δ: 1.35 (t, 6 H, J = 7), 1.4-1.9 (m, 6 H), 3.4-4.45 (m, 8 H), 4.7 (m, 1 H).

3. Discussion

Diethyl [(2-tetrahydropyranyloxy)methyl]phosphonate is useful in the Wittig-Horner synthesis of enol ethers, which are intermediates in one-carbon homologations of carbonyl compounds.[2] This procedure is an adaptation of a general method for making dialkyl hydroxymethylphosphonates.[3] An O-tetrahydropyranyl derivative also has been made from dibutyl hydroxymethylphosphonate, and diethyl hydroxymethylphosphonate has been O-silylated with tert-butylchlorodimethylsilane and imidazole.[2] Another useful congener in this series has been prepared by an Arbuzov reaction of methoxyethoxymethyl (MEM) chloride and triethyl phosphite.[2]

1. Institute of Organic Chemistry, Syntex Research, Palo Alto, CA 94304
2. Kluge, A. F.; Clousdale, I. S. *J. Org. Chem.* **1979**, *44*, 4847.
3. Zaripov, R. K.; Abramov, V. S. *Tr. Khim.-Met. Inst., Akad. Nauk Kaz. S.S.R.* **1969**, *5*, 50; *Chem. Abstr.* **1970**, *72*, 21745y.

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

Diethyl [(2-tetrahydropyranyloxy)methyl]phosphonate: Phosphonic acid,

[[(tetrahydro-2H-pyran-2-yl)oxy]methyl]-, diethyl ester (10); (71885-51-3)

Diethyl hydroxymethylphosphonate: Phosphonic acid, (hydroxymethyl)-, diethyl

ester (8,9); (3084-40-0)

Diethyl phosphite: Phosphonic acid, diethyl ester (8,9); (762-04-9)

Paraformaldehyde: Poly(oxymethylene) (8,9); (9002-81-7)

Dihydropyran: 2H-Pyran, 3,4-dihydro- (8,9); (110-87-2)

Phosphorus oxychloride: Phosphoryl chloride (8,9); (10025-87-3)

β-DIMETHYLAMINOMETHYLENATION: N,N-DIMETHYL-N'-p-TOLYLFORMAMIDINE

(Methanimidamide, N,N-dimethyl-N'-(4-methylphenyl)-
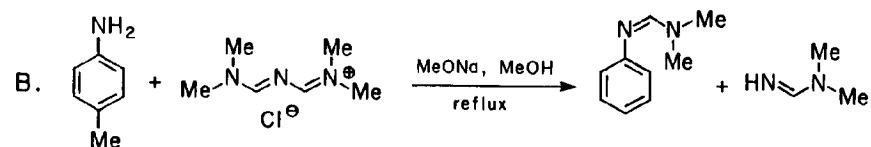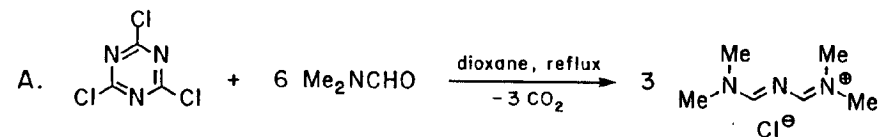
Submitted by John T. Gupton and Steven A. Andrews.[1]

Checked by T. V. RajanBabu and Bruce E. Smart.

1. Procedure

Caution! Cyanuric chloride is a lachrymator and causes burns on contact with the skin. All operations with this reagent should be carried out in a well-ventilated hood.

A. *[3-(Dimethylamino)-2-azaprop-2-en-1-ylidene]dimethylammonium chloride.* A 1-L, one-necked, round-bottomed flask is equipped with a Claisen adapter, mechanical stirrer, reflux condenser, and mineral oil bubbler (Note 1). The flask is charged with cyanuric chloride (73.8 g, 0.4 mol) (Note 2), N,N-dimethylformamide (175.4 g, 2.4 mol) (Note 3) and 1,4-dioxane (100 mL) (Note 4). The resulting solution is stirred and heated (at approximately 85°C) for 2-3 hr while a considerable amount of carbon dioxide is evolved

(Note 5). When gas evolution is minimal, the reaction mixture is allowed to cool to room temperature; the product rapidly solidifies. The flask which contains the solid product is connected to an isopropyl alcohol/dry ice trap and the solvent is removed by evacuating the system to approximately 0.05 mm pressure. The crude product weighs 186-187 g (95%) and melts at 95-103°C (Notes 6, 7, 8).

B. *N,N-Dimethyl-N'-p-tolylformamidine.* A 250-mL, three-necked, round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar coated with Teflon is placed under a positive nitrogen pressure and charged with 100 mL of methanol (Note 9). Sodium metal (1.4 g, 0.06 mol) (Note 10) is then added in small portions. After all of the sodium has reacted, p-toluidine (6.4 g, 0.06 mol) (Note 11) is added and the resulting solution is stirred for 5 min. The iminium salt (10.6 g, 0.065 mol) produced in part A is added in one portion and the resulting mixture is refluxed with stirring overnight. The reaction mixture is cooled to room temperature and the solvent is removed on a rotary evaporator. The residue is taken up in chloroform (100 mL) and extracted twice with a saturated, aqueous solution of sodium bicarbonate (2 x 30 mL). The chloroform phase is dried over anhydrous magnesium sulfate, filtered, and the solvent is removed on a rotary evaporator. The residual dark brown liquid is distilled using a Kugelrohr apparatus (Note 12); the major fraction boils at 85-100°C (oven temperature), 0.4 mm, and yields 9.1-9.2 g (94-95%) of a pale yellow liquid (Notes 13 and 14).

2. Notes

1. The bubbler is connected to the condenser to monitor carbon dioxide evolution.

2. Cyanuric chloride was purchased from Aldrich Chemical Co. and was used without additional purification.

3. N,N-Dimethylformamide was purchased from Aldrich Chemical Co. and was dried over 3 Å molecular sieves prior to use.

4. The 1,4-dioxane was reagent grade and obtained from Fisher Scientific Corp. It was dried over 3 Å molecular sieves prior to use.

5. The reaction becomes very exothermic with substantial evolution of carbon dioxide within 30-45 min after heating is initiated. It may be necessary to cool the mixture with ice water if the evolution of gas becomes too vigorous.

6. The checkers obtained material free of N,N-dimethylformamide after drying for at least 18 hr. The checkers found variable melting points that depended on the rate of heating. The submitters obtained 195 g (99%) of product which melted at 81-83°C after drying overnight at 1-6 mm of pressure, and indicated that the product may contain a small amount of N,N-dimethylformamide, but is suitable for use without additional purification. [3-(Dimethylamino)-2-azaprop-2-en-1-ylidene]dimethylammonium chloride is reported to melt at 101-103°C.[2]

7. The product is very hygroscopic and should be handled under a moisture-free environment. If the iminium salt is kept dry it has a substantial shelf life. The submitters recommend storing the product in a desiccator over anhydrous calcium sulfate.

8. The product has the following spectral characteristics: IR (CHCl$_3$) cm^{-1}: 1610 (C=N); ^{1}H NMR (CDCl$_3$) δ: 3.27 (s, 6 H, two CH$_3$), 3.43 (s, 6 H, two CH$_3$), 9.57 (s, 2 H, -CH=N).

9. The methanol which was used was reagent grade and was dried over 3 Å molecular sieves.

10. Sodium metal was obtained from Fisher Scientific Corp.

11. p-Toluidine was reagent grade and was obtained from the Eastman Chemical Co.

12. The Kugelrohr apparatus was obtained from the Aldrich Chemical Co.

13. The submitters obtained 8.3-9.1 g (86-94%) boiling at 85-107°C, 0.4 mm. The reported bp of N,N-dimethyl-N'-p-tolylformamidine is 163°C (30 mm).^{3} A gas chromatographic analysis of the product using a 1/4" x 10' column packed with 5% carbowax 20 M supported on 80-100 mesh chromosorb N exhibited a single peak with a retention time of 4.8 min at an oven temperature of 220°C with a flow rate of 60 cc/min. The checkers redistilled the product to obtain colorless material, bp 69.5°C (0.2 mm), which was analyzed. Anal. Calcd for C$_{10}$H$_{14}$N$_2$: C, 74.03; H, 8.70; N, 17.27. Found C, 73.57; H, 8.51; N, 17.50.

14. The product has the following spectral characteristics: IR (neat) cm^{-1}: 3030 (aromatic CH), 1635 (C=N), 1600 (C=C), ^{1}H NMR (CDCl$_3$) δ: 2.23 (s, 3 H, aromatic CH$_3$), 2.87 (s, 6 H, -N(CH$_3$)$_2$), 6.83 (d, 2 H, J = 8, aromatic CH), 7.06 (d, 2 H, J = 8, aromatic CH), 7.43 (s, 1 H, -CH=N-).

3. Discussion

[3-(Dimethylamino)-2-azaprop-2-en-1-ylidene]dimethylammonium chloride ("Gold's reagent"),[4] the preparation of which is described in part A of the procedure, is a general β-dimethylaminomethylenating agent which reacts successfully with amines (eq. 1) to produce amidines,[5] with ketones (eq. 2) to produce enaminones,[6] and with amides (eq. 3) to product acylamidines.[7]
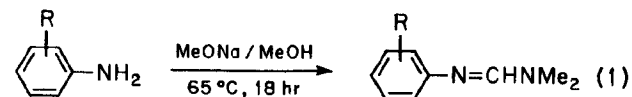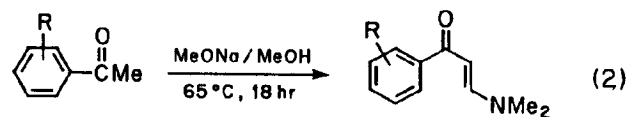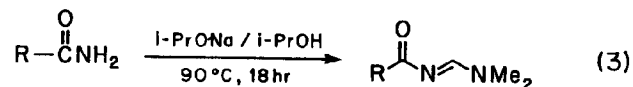
All reactions proceed in high yield and under mild conditions produce relatively pure products. The most effective β-dimethylamino methylenating agents currently available are the formamide acetals,[8] some of which are available commercially.[9] They are, however, expensive, moisture and heat

sensitive, and require potent, mutagenic alkylating agents for their preparation. Under some circumstances they also necessitate high reaction temperatures and long reaction times. Alternatively, "Gold's reagent" is prepared in a single step, and in nearly quantitative yield, without purification, from inexpensive raw materials. The reaction of "Gold's reagent" with an amine or other substrate can be carried out at relatively low temperatures (65-90°C) and moderate reaction times (12-24 hr).

The significance of the amino methylenated amines, ketones, and amides as important compounds and reaction intermediates is well-documented[5,6,7] and the use of "Gold's reagent," therefore, provides an efficient, economical, and clean method for obtaining such substances.

1. Department of Chemistry, University of Central Florida, P.O. Box 25000, Orlando, FL 32816.

2. Gold, H. *Angew. Chem.* **1960**, *72*, 956; *Chem. Abstr.* **1962**, *57*, 4542d.

3. Meerwein, H.; Florian, W.; Schon, N.; Stopp, F. *Justus Liebigs Ann. Chem.* **1961**, *641*, 1.

4. We have named this compound "Gold's Reagent" to simplify its common usage nomenclature.

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6. For a recent review of the synthetic importance of enaminones see: Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277.

7. (a) Lin, Y.; Lang, S. A.; Lovell, M. F.; Perkinson, N. A. *J. Org. Chem.* **1979**, *44*, 4160; (b) Lin, Y.; Lang, S. A.; Petty, S. R. *J. Org. Chem.* **1980**, *45*, 3750.

8. Abdulla, R.; Brinkmeyer, R. *Tetrahedron Lett.* **1979**, 1675; Simchen, G. In "Advances in Organic Chemistry: Methods and Results", Böhme, H. and Viehe, H., Eds.; Wiley: New York, 1979; Vol. 9, Pt. 2, pp. 393-526.

9. Aldrich Chemical Co., Milwaukee, Wisconsin.

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

Cyanuric chloride: s-Triazine, 2,4,6-trichloro- (8); 1,3,5-Triazine, 2,4,6-trichloro- (9); (108-77-0)

[3-(Dimethylamino)-2-azaprop-2-en-1-ylidene]dimethylammonium chloride: Ammonium, [[[(dimethylamino)methylene]amino]methylene]dimethyl-, chloride (8); Methanaminium, N-[[[(dimethylamino)methylene]amino]methylene]-N-methyl-, chloride (9); (20353-93-9)

p-Toluidine (8); Benzenamine, 4-methyl- (9); (106-49-0)

N,N-Dimethyl-N'-p-tolylformamidine: Formamidine, N,N-dimethyl-N'-p-tolyl- (8); Methanimidamide, N,N-dimethyl-N'-(4-methylphenyl)- (9); (7549-96-4)

1,3-DIMETHYLIMIDAZOLE-2-THIONE

(2H-Imidazole-2-thione, 1,3-dihydro-1,3-dimethyl-)
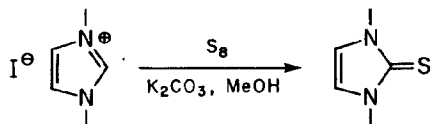
Submitted by Brian L. Benac,[1a] Edward M. Burgess,[2] and
Anthony J. Arduengo, III.[1b]

Checked by David R. Brittelli, Joseph Buriak, Jr., and Bruce E. Smart.

1. Procedure

In a dry, 500-mL, round-bottomed flask, equipped with a magnetic stirrer and a drying tube are placed 44.8 g (0.20 mol) of 1,3-dimethylimidazolium iodide (Note 1), 35.0 g (0.25 mol) of anhydrous potassium carbonate, 6.5 g (0.20 mol) of sulfur (Note 2) and 300 mL of methanol (Note 3). The mixture is stirred for 40 hr at room temperature. The cloudy yellow mixture is filtered through a pad of Celite (Note 4) and the filter cake is washed with 80 mL of dichloromethane. The combined mother liquor and wash is evaporated to dryness on a rotary evaporator. The orange residue is dissolved in 500 mL of hot water and the hot solution is filtered to remove insoluble impurities. The aqueous filtrate is reheated and the product crystallizes on cooling. The white needles are collected by filtration, washed with 50 mL of cold water and air dried for 1 hr. The mother liquor is concentrated to yield a second crop of crystals to give a total of 15-16 g (58-62%) of pure 1,3-dimethylimidazole-2-thione, mp 182-183.5°C (Note 5).

2. Notes

1. The imidazolium iodide salt is conveniently prepared by the following procedure: A 500-mL, three-necked, round-bottomed flask equipped with a dropping funnel, thermometer, water-cooled condenser, and a magnetic stirrer is charged with 200 mL of anhydrous methylene chloride and 82.1 g (1.0 mol) of 1-methylimidazole (from the Aldrich Chemical Company, Inc.). The solution is cooled and maintained at 5°C while 143.0 g (1.01 mol) of iodomethane in 75 mL of anhydrous methylene chloride is added dropwise over a period of 30 min. When the addition is completed, the cooling bath is removed and the reaction mixture is stirred for 30 min at room temperature. Methylene chloride is removed on a rotary evaporator to yield 213.6-216.7 g (95-97%) of 1,3-dimethylimidazolium iodide, mp 81-83°C, ^{1}H NMR (d_6-DMSO) δ: 3.89 (s, 6 H), 7.73 (s, 2 H), 9.16 (s, 1 H). The submitters report the following spectral data: ^{1}H NMR (d_6-DMSO) δ: 4.08 (s, 6 H), 7.75 (s, 2 H), 9.86 (s, 1 H); ^{13}C NMR (d_6-DMSO) δ: 36.10 (s), 123.04 (s), 136.69 (s).

The submitters report that the bromide and methyl sulfate salts of the 1,3-dimethylimidazolium cation gave similar yields in the thione synthesis.

2. Lac (precipitated) sulfur gives the best results. The checkers found that with sublimed sulfur (Fisher Scientific Company, Laboratory Grade) the yield of thione product is 12.5-12.8 g (49-50%).

Lac sulfur is prepared by boiling a suspension of 33 g of calcium oxide and 50 g of sublimed sulfur (Fisher Scientific Company) in 200 mL of water for 30 min, then filtering the hot solution and acidifying the clear filtrate to pH 5 with hydrochloric acid. The precipitated sulfur is collected, washed with water, and dried in a vacuum desiccator.

3. A.C.S. grade methanol from the Fisher Scientific Company was used without further purification. The submitters report that attempts to use ethanol or water as solvents were unsuccessful.

4. The reaction mixture has a distinct odor of sulfur and should be handled in a hood. The product is odorless.

5. The submitters report a mp of 182-184°C for material which was recrystallized from water or sublimed under reduced pressure. The product shows the following ^{1}H NMR spectrum (CDCl$_3$) δ: 3.58 (s, 6 H), 6.71 (s, 2 H). The submitters report the following spectral data: ^{1}H NMR (CDCl$_3$) δ: 3.6 (s, 6 H), 6.68 (s, 2 H); ^{13}C NMR (d$_6$-DMSO) δ: 34.34 (s), 117.82 (s), 161.87 (s); IR (CHCl$_3$) cm^{-1}: 2940 (C-H), 1450, and 1380.

3. Discussion

1,3-Dimethylimidazole-2-thione was first reported by Ansell, Forkey and Moore[3] who studied the X-ray crystal structure of this thione. No detailed synthesis of the thione has appeared in the chemical literature. This unusual thione has been used as a precursor to unusual thione ylides,[4,5] tricoordinate sulfuranes[6] and as a desulfurizing agent for a thiirane.[5] The thione also has remarkable anti-oxidant properties.[7] Compared to tetramethylthiourea, 1,3-dimethylimidazole-2-thione is remarkably resistant to desulfurization.

This procedure has been used to synthesize a variety of 1,3-dialkylimidazole 2-thiones. Other imidazole-2-chalcogenones (Se, Te) can be synthesized by similar procedures.

1. (a) Department of Chemistry, The Roger Adams Laboratory, University of Illinois-Urbana, IL 61801. (b) Present address: E. I. du Pont de Nemours & Co., Central Research and Development Department, E328/201, Wilmington, DE 19898.

2. Department of Chemistry, Georgia Institute of Technology, Atlanta, GA 30332.

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6. Arduengo, A. J.; Burgess, E. M. *J. Am. Chem. Soc.* **1977**, *99*, 2376.

7. Arduengo, A. J.; Burgess, E. M., unpublished results.

Appendix

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

1,3-Dimethylimidazole-2-thione: 4-Imidazoline-2-thione, 1,3-dimethyl- (8); 2H-Imidazole-2-thione, 1,3-dihydro-1,3-dimethyl (9); (6596-81-2)

1-Methylimidazole: Imidazole, 1-methyl- (8); 1H-Imidazole, 1-methyl- (9); (616-47-7)

Iodomethane: Methane, iodo- (8,9); (74-88-4)

Sulfur (S$_8$) (8); Octathiocane (9); (10544-50-0)

ELECTROPHILIC N-AMINATION OF IMIDE SODIUM SALTS WITH

O-DIPHENYLPHOSPHINYLHYDROXYLAMINE (DPH): 7-AMINOTHEOPHYLLINE

(1H-Purine-2,6-dione, 7-amino-3,7-dihydro-1,3-dimethyl-)

A. $Ph_2PCl + 2NH_2OH \longrightarrow Ph_2P-ONH_2 + NH_2OH \cdot HCl$

B.

C.
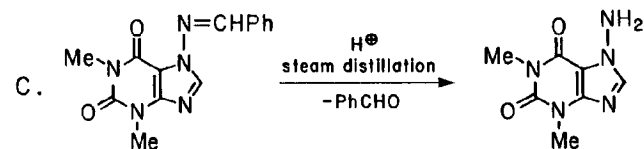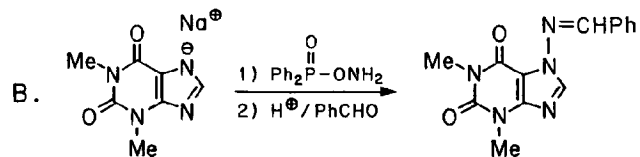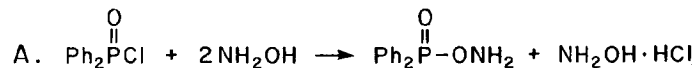
Submitted by W. Klötzer, J. Stadlwieser, and J. Raneburger.[1]

Checked by Michael J. Luzzio and Andrew S. Kende.

1. Procedure

A. O-Diphenylphosphinylhydroxylamine.[2] A 500-mL, round-bottomed flask, equipped with a reflux condenser, drying tube, an efficient mechanical stirrer, a dropping funnel and a nitrogen-inlet tube, is charged with 300 mL of anhydrous methylene chloride, 16.5 g (0.5 mol) of hydroxylamine base (Note 1), and 1.0 g of dry sodium bicarbonate. While the suspension is stirred vigorously at -30°C (bath temperature), a solution of 52.06 g (0.22 mol) of diphenylphosphinyl chloride (Note 2) in 70 mL of anhydrous methylene chloride

is added under a nitrogen atmosphere at a constant rate within 30 min. The resulting thick suspension is stirred at -30°C for 2 hr and for an additional 2 hr after the cooling bath is removed. The reaction mixture is filtered through a sintered-glass funnel (porosity 3) and the residue is washed with two 80-mL portions of methylene chloride. The methylene chloride is removed from the colorless solid by a stream of air for 2 hr. The dry solid, still on the funnel, is then mixed thoroughly with 200 mL of deionized water. The water is removed by suction. The same operation is performed sequentially with 150 mL of 5% aqueous sodium bicarbonate solution and then with two 150-mL portions of water. This solid, which retains water tenaciously, is dried by suction and by pressing down on the funnel for several hours, followed by drying in a phosphorus pentoxide-charged vacuum desiccator until its weight is constant (24 hr) to give 36 g (70%) of impure O-diphenylphosphinyl-hydroxylamine, mp 120°-135°C, with decomposition.

A 500-mL, two-necked flask, equipped with a reflux condenser and a drying tube, is charged with 240 mL of anhydrous ethanol. The solvent is preheated to 70°C and a 12-g portion of this finely powdered dry product is added all at once. The resulting suspension is refluxed for 2-3 min when almost all of the solid has dissolved. The hot solution is filtered as quickly as possible through a sintered-glass funnel (porosity 3) and the filtrate is chilled to 0°C for 30 min. Isolation of the crystalline deposit and washing with 20 mL of ether provides 7.8 g of pure product. Recrystallization of three 12-g portions furnishes 23.4 g (44%) of O-diphenylphosphinylhydroxylamine, mp >140°C, with decomposition (Note 3).

B. 7-Benzylideneaminotheophylline. A 2000-mL, round-bottomed flask, equipped with an efficient mechanical stirrer, thermometer, and drying tube, is charged with 600 mL of anhydrous N-methylpyrrolidone (Note 4) and 20.2 g

(0.1 mol) of anhydrous theophylline sodium salt (Note 5). The flask is cooled with an ice-salt bath to 0°C (internal temperature). Then 23.4 g (0.1 mol) of O-diphenylphosphinylhydroxylamine is added in three equal portions while the suspension is stirred vigorously. After the ice-salt bath is removed, the resulting viscous suspension is stirred for 6 hr at 20°C.

After the solution is diluted with 1200 mL of water, the pH is adjusted to 1-2 with concd hydrochloric acid and the mixture stirred at 5°C for 1 hr. The precipitated diphenylphosphinic acid is isolated by filtration and washed with 50 mL of water (Note 6). The filtrate is placed in a 2000-mL, round-bottomed flask, equipped with a reflux condenser and an efficient mechanical stirrer. A solution of 20 mL of benzaldehyde in 50 mL of ether is added and the mixture is stirred vigorously for 20 min. The precipitate that forms is isolated by filtration and washed sequentially with 50 mL of water and 50 mL of ether to yield 19.6 g (69%) of 7-benzylideneaminotheophylline, mp 207-209°C.[3] An analytical sample may be prepared by recrystallization from ethanol (mp 209°C).

C. *7-Aminotheophylline.* The reaction flask of a steam distillation apparatus is charged with 19.6 g (0.069 mol) of 7-benzylideneaminotheophylline and 100 mL (0.1 mol) of 1 N hydrochloric acid. The suspension is steam distilled until no more benzaldehyde is detected in the distillate (Note 7). The resulting clear solution in the reaction flask is concentrated by rotary evaporation to a volume of 30 mL, adjusted to pH 10 with concentrated ammonium hydroxide, transferred to a separatory funnel and extracted with five 60-mL portions of chloroform. The combined chloroform extracts are dried with anhydrous sodium sulfate, filtered and concentrated to dryness by rotary evaporation. The residue is recrystallized from 75 mL of water to afford 11.3 g (84%) of 7-aminotheophylline, mp 222°C.[3]

2. Notes

1. Hydroxylamine base has been prepared by the method of Lecher and Hofmann.[4] The free base can be stored in a tightly stoppered flask at -20°C for several days. The checkers found it expedient to prepare free hydroxylamine by a modification of the Lecher and Hofmann procedure in which a Schlenk tube under dry N_2 was used to filter the NaCl precipitate and the NH_2OH base was crystallized from the filtrate at -30°C, then isolated by inverting the Schlenk apparatus and filtering the product (74% yield from the hydrochloride).

2. Diphenylphosphinyl chloride can be purchased from Aldrich Chemical Company, Inc. or from EGA-Chemie, D-7924 Steinheim, West Germany (an Aldrich Chemical Company). Diphenylphosphinyl chloride can also be prepared by oxygen-mediated oxidation of diphenylchlorophosphine[5] (purchased from Fluka AG, CH-9470 Buchs, Switzerland).

3. The recrystallization should be performed as quickly as possible in portions below 15 g. Prolonged heating in ethanolic solution causes substantial losses. The pure, dry compound can be stored in a tightly stoppered flask at 0°C for at least 6 months without loss of aminating capacity. The submitters report that the pure compound showed no signs of spontaneous decomposition during 4 years of use, except when heated to >140°C, where the compound decomposes with effervescence.

4. N-Methylpyrrolidone (purum grade) was purchased from Fluka AG, CH-9470 Buchs, Switzerland, dried over calcium hydride, and vacuum distilled [bp 78-79°C (12 mm)].

5. The sodium salt of theophylline was obtained as follows: to a solution of 36.34 g (0.2 mol) of theophylline in 120 mL of 50% aqueous ethanol at 80°C was added 50 mL (0.2 mol) of aqueous 4 N sodium hydroxide. Chilling to 0°C, filtration of the precipitate, washing with 50 mL of 96% ethanol, then with 100 mL ether, and drying in a vacuum desiccator over phosphorus pentoxide provides 28.0 g of the anhydrous salt.

6. The recovered and dried diphenylphosphinic acid, 19.6 g (90%), is ready to be recycled to diphenylphosphinyl chloride.[6,7]

7. Traces of benzaldehyde can be detected with Brady's reagent (2,4-dinitrophenylhydrazine sulfate solution) or by its characteristic smell.

3. Discussion

Electrophilic N-aminations of imide salts have been performed with hydroxylamine-O-sulfonic acid (HOSA),[8,9,10] O-(2,4-dinitrophenyl)-hydroxylamine,[11,12] and O-mesitylenesulfonylhydroxylamine (MSH).[11] The use of HOSA is mainly restricted to aqueous reaction media.[8,9] O-(2,4-Dinitrophenyl)hydroxylamine, MSH, and O-diphenylphosphinylhydroxylamine (DPH) can be applied in anhydrous or even non-polar solvents. O-(2,4-Dinitrophenyl)hydroxylamine and MSH require N-protected hydroxylamine for their preparation.[11,12] MSH has been found to be explosive.[13,14] DPH has the advantage of being prepared directly from unprotected hydroxylamine and seems to have no tendency toward spontaneous decomposition. The possibility of recycling diphenylphosphinic acid may be regarded as a further advantage. The advantage of using unprotected hydroxylamine to prepare DPH is partially negated by the required somewhat delicate preparation and handling of the free hydroxylamine base. The large amount of solvent that is sometimes required

because of the low solubility of DPH and the resulting diphenylphosphinic acid salt may be regarded as a disadvantage too.

O-Diphenylphosphinylhydroxylamine has also been used to aminate carbanions,[15,16] tertiary phosphines, and thio ethers.[2]

TABLE

N-AMINO COMPOUNDS FROM IMIDE SODIUM SALTS AND DPH[a]

Educt Alkali Salt	Solvent[b]	Product	Yield	Lit.
Imidazole	DMF	1-Aminoimidazole	28%	3
2-Nitroimidazole	NMP	1-Amino-2-nitro-imidazole	40%	3
2-Methyl-4(5)-nitroimidazole	NMP	1-Amino-2-methyl-4-nitroimidazole	30%	3
Theobromine	DMF	1-Aminotheobromine	71%	3
Theophylline	NMP	7-Aminotheophylline	60%	3
Phthalimide	DMF	N-Aminophthalimide	90%	3

[a]DPH = O-diphenylphosphinylhydroxylamine.

[b]DMF = anhydrous dimethylformamide.

NMP = anhydrous N-methylpyrrolidone.

1. Institut für Organische und Pharmazeutische Chemie, Universität Innsbruck, A-6020 Innsbruck, Innrain 52a, Austria.

2. The method represents a modification of a recently published preparation: Harger, M. J. P. *J. Chem. Soc, Perkin Trans 1* 1981, 3284.

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16. Boche, G.; Bernheim, M.; Schrott, W. *Tetrahedron Lett.* **1982**, *23*, 5399.

Appendix

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

O-Diphenylphosphinylhydroxylamine: Hydroxylamine, O-(diphenylphosphinyl)- (10); (72804-96-7)

7-Aminotheophylline: 1H-Purine-2,6-dione, 7-amino-3,7-dihydro-1,3-dimethyl- (11); (81281-58-5)

Hydroxylamine hydrochloride (8,9); (5470-11-1)

Diphenylphosphinyl chloride: Phospinic chloride, diphenyl- (8,9); (1499-21-4)

7-Benzylideneaminotheophylline: 1H-Purine-2,6-dione, 3,7-dihydro-1,3-dimethyl-7-[(phenylmethylene)amino]- (11); (81281-59-6)

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

Theophylline (8); 1H-Purine-2,6-dione, 3,7-dihydro-1,3-dimethyl- (9); (58-55-9)

Diphenylphosphinic acid: Phosphinic acid, diphenyl- (8,9); (1707-03-5)

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

Diphenylchlorophosphine: Phosphinous chloride, diphenyl- (8,9); (1079-66-9)

ETHYL 4-HYDROXYCROTONATE

(2-Butenoic acid, 4-hydroxy-, ethyl ester, (E)-)

$$\text{HOOC} \diagdown \diagup \text{COOEt} \xrightarrow[\text{-10°C to room temperature}]{\text{BH}_3 \cdot \text{THF}} \text{HO} \diagdown \diagup \text{COOEt}$$
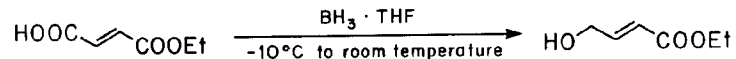
Submitted by Andrew S. Kende and Pawel Fludzinski.[1]

Checked by Cynthia McClure and Edwin Vedejs.

1. Procedure

A dry, 2-L, one-necked, round-bottomed flask is equipped with a 1-L pressure-equalizing funnel and a large magnetic stirring bar. The system is flame-dried under an internal atmosphere of dry nitrogen (Note 1). The flask is charged with 300 mL of anhydrous tetrahydrofuran (Note 2) and 100 g of monoethyl fumarate. The solution is then stirred under nitrogen and brought to about -5°C using an ice-salt/methanol bath (-10°C) (Note 3). A 1 M solution of 700 mL (0.70 mol) of borane-tetrahydrofuran complex (Note 4) is *cautiously* added dropwise (rapid H_2 evolution occurs) with rigorous temperature control to avoid an exothermic reaction. The ice-salt bath is maintained in position throughout the 90 min of addition. The stirred reaction mixture is then gradually allowed to warm to room temperature over the next 8-10 hr. The reaction is carefully quenched at room temperature by dropwise addition of 1:1 water-acetic acid (ca. 20 mL) with stirring until no more gas evolution occurs. The reaction is concentrated at room temperature and water pump pressure to a slurry by removal of most of the tetrahydrofuran. The slurry is carefully poured over a 20-min period into 300 mL of ice cold, saturated sodium bicarbonate solution with mechanical stirring to avoid precipitation of solids, and the product is extracted with 300 mL of ethyl acetate. The aqueous layer is again extracted with 100 mL of ethyl acetate. The organic layers are combined, washed once with 200 mL of saturated sodium bicarbonate, then dried well with anhydrous magnesium sulfate.

Solvent removal at reduced pressure gives 61 g (67% yield) of essentially pure ethyl hydroxycrotonate (Note 5).

An analytical sample may be prepared by quick distillation (or Kugelrohr distillation) at 117-120°C (15 mm), but there is significant loss of material because of decomposition in the distillation pot. From 1 g of product, 0.72 g of pure material is obtained in this way, and recovery decreases as scale of distillation increases.

2. Notes

1. This is accomplished by passing a stream of dry nitrogen through the reaction vessel. During the reaction, a slight positive pressure of nitrogen is maintained throughout the apparatus.

2. The tetrahydrofuran is freshly distilled from sodium and benzophenone.[2]

3. The flask is cooled with the ice-salt/methanol bath for 30 min before the next addition to insure complete cooling of the solution.

4. Borane-tetrahydrofuran is commercially available from Aldrich Chemical Company, Inc. When a fresh bottle is used, titration is not necessary.

5. NMR data for ethyl 4-hydroxycrotonate are as follows (100 MHz, $CDCl_3$): δ 1.30 (t, 3 H, J = 7), 3.58 (br s, 1 H), 4.17 (q, 2 H, J = 7), 4.30 (m, 2 H), 6.03 (dt, 1 H, J = 16), 6.98 (dt, 1 H, J = 16.

3. Discussion

Ethyl (or methyl) 4-hydroxycrotonate has previously been prepared in 51% yield by silver oxide-assisted solvolysis of methyl 4-bromocrotonate,[3] or in 94% yield by reaction of glycolaldehyde with (carbomethoxymethylene)tri-phenylphosphorane.[4] Both procedures require very expensive starting materials or reagents. Several multistep procedures for preparing the title compound have also been reported.[5] The procedure described above represents a convenient one-step alternative for preparing ethyl 4-hydroxycrotonate, requiring inexpensive starting materials and reagents. This procedure relies on the selective reduction of a carboxylic acid in the presence of a carboxylic ester with borane, which is well documented.[6]

Ethyl 4-hydroxycrotonate has proven to be a valuable intermediate in synthetic chemistry. It has been used in alkaloid synthesis[3] or as a dipolarophile in dipolar cycloadditions.[7] Furthermore, ethyl 4-hydroxycrotonate can be readily oxidized to ethyl 4-oxocrotonate,[4] which has also served as a valuable precursor in synthesis.[8]

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

Ethyl 4-hydroxycrotonate: Crotonic acid, 4-hydroxy-, ethyl ester, (E)- (8); 2-Butenoic acid, 4-hydroxy-, ethyl ester, (E)- (9); (10080-68-9)

Monoethyl fumarate: Fumaric acid, monoethyl ester (8); 2-Butenedioic acid (E)-, monoethyl ester (9); (2459-05-4)

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

ETHYL ISOCROTONATE

(Ethyl (Z)-crotonate)

A. $CH_3C\equiv CH \xrightarrow[\text{ether, -78°C}]{\text{BuLi}} \xrightarrow[\text{ether, 0°C}]{\text{ClCOOEt}} CH_3C\equiv CCOOEt$

B. $CH_3C\equiv CCOOEt \xrightarrow[\text{quinoline, ether}]{\text{H}_2\text{, Pd/BaSO}_4}$
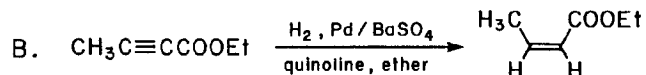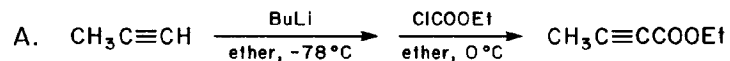
Submitted by Michael J. Taschner, Terry Rosen, and Clayton H. Heathcock.[1]
Checked by Judy Bolton and Ian Fleming.

1. Procedure

A. Ethyl tetrolate. A 3-L, three-necked, round-bottomed flask is equipped with an overhead mechanical stirrer and charged with 1000 mL of anhydrous ether (Note 1). One neck is fitted with a gas-inlet joint connected to a nitrogen line equipped with a mineral oil bubbler. The second neck is fitted with a low-temperature thermometer, and the third is closed with a rubber serum cap after nitrogen has been passed through the flask for a few minutes. The flask is then immersed in a dry ice-acetone bath. While the ether is cooling, 85 mL (60.0 g, 1.50 mol) of propyne (Note 2) is condensed into a flask (Note 3). The stopper is removed briefly, the cold (-78°C) propyne is poured into the flask through a powder funnel inserted into the neck, and stirring is commenced. The stopper is replaced, and 667 mL of a 1.5 M solution of butyllithium in hexane is introduced by syringe at such a rate that the internal temperature does not exceed -65°C (Notes 4, 5, 6). During

the butyllithium addition a copious white precipitate appears. The slurry is stirred at -78°C for 30 min, and 134 mL (152 g, 1.4 mol) of ethyl chloroformate (Note 7) is added. At this point, the acetone-dry ice bath is replaced by an ice bath and the reaction mixture is stirred overnight. During this time the ice bath will melt and the reaction mixture should eventually reach room temperature. The mixture is poured onto 400 g of crushed ice, the layers are separated, and the aqueous phase is extracted with two 200-mL portions of ether. The ether solutions are combined, washed with brine and dried over anhydrous $MgSO_4$. After filtration, the ether is removed with a rotary evaporator (Note 8). The residue is distilled at aspirator pressure to obtain 107-108 g (95-97%) of ethyl tetrolate, bp 60-64°C (20 mm) [lit.[2] 105°C (90 mm)] (Note 9).

B. Ethyl isocrotonate. An oven-dried, 500-mL hydrogenation flask equipped with a side arm fitted with a rubber serum cap and a magnetic stirring bar, is charged with 0.4 g of 5% palladium on barium sulfate (Note 10), 0.4 g of quinoline and 200 mL of anhydrous ether. The flask is attached to an atmospheric pressure hydrogenation apparatus (Note 11) and flushed with hydrogen. Ethyl tetrolate (23.2 mL, 22.4 g, 0.2 mol) is introduced into the hydrogenation flask with a syringe, and stirring is commenced. The progress of the reaction may be monitored by the uptake of hydrogen (theoretical ≅ 4500 mL), by gas chromatography, or by removing aliquots which are concentrated and analyzed by ^{1}H NMR, monitoring the disappearance of the methyl singlet at δ 1.95; a total hydrogenation time of 10-15 hr is required (Note 12). After hydrogenation is complete, the catalyst is removed by filtration of the reaction mixture through a Celite pad. The ether is removed with a rotary evaporator (Note 8) to obtain 21.1-22.4 g (93-98%) of ethyl isocrotonate as a light yellow liquid. This material contains traces of quinoline, but is of

suitable purity for many uses (Note 6, 13). The quinoline may be removed, if desired, by washing the ether solution with 1 M aqueous acetic acid, followed by aqueous sodium carbonate, or by distillation at atmospheric pressure, bp 128-132°C [lit.[3] bp 129-130.5°C] (Note 14).

2. Notes

1. Although stirring can be done with a large magnetic stirring bar, the reaction mixture becomes rather thick as the 1-lithiopropyne is formed, and effective stirring is difficult. The checkers found that the yield in this step is only 77% when a magnetic stirrer is used.

2. Methylacetylene (technical grade) from Linde Division of the Union Carbide Corporation was employed. The checkers used Matheson Lecture bottles.

3. The propyne is passed directly from the tank or lecture bottle to a cold-finger condenser filled with a slush of isopropyl alcohol and dry ice. The condenser is attached to a 200-mL, three-necked flask equipped with a gas-inlet adapter and a glass stopper. The flask has been previously calibrated to hold 85 mL of liquid.

4. Alternatively, the butyllithium solution may be forced into the reaction flask by means of an 18 gauge cannula inserted through the serum cap.

5. Butyllithium was obtained from Foote Mineral Co., Johnsonville, Tennessee. It may be standardized by a double titration procedure.[4]

6. If care is not taken in the formation of 1-lithiopropyne, the final product can be contaminated with as much as 10% of an impurity, which is presumed to be ethyl pentanoate. This impurity has a GLC retention time on conventional packed columns that is quite similar to that of ethyl (E)-crotonate. The by-product presumably results from the presence of butyl-lithium when the ethyl chloroformate is added. The submitters have not observed the formation of this product if care is taken to maintain the reaction temperature below -65°C during addition of the butyllithium to the propyne.

7. Ethyl chloroformate (practical grade) was obtained from Matheson Coleman & Bell Manufacturing Chemists, Inc., Cincinnati, Ohio 45212, and used without purification.

8. It is important that the rotary evaporator bath be kept at 5-10°C, or some of the product will be lost by evaporation.

9. The infrared spectrum (neat) has absorptions at 2250, 1700, and 1260 cm^{-1}. The ^{1}H NMR spectrum ($CDCl_3$) is as follows δ: 1.23 (t, 3 H, J = 7), 1.95 (s, 3 H), 4.07 (q, 2 H, J = 7).

10. The catalyst was obtained from The American Platinum Works, Newark, NJ.

11. The submitters employed an apparatus similar to that described by Wiberg.[5]

12. The hydrogenation can also be carried out without special apparatus by the following method. The ether solution is placed in a 500-mL, three-necked flask fitted with a fritted gas inlet tube, a rubber serum cap, an oil bubbler, and a magnetic stirring bar. The catalyst, quinoline and ethyl tetrolate are introduced, and the reaction flask is cooled in an ice bath. Hydrogen is bubbled through the cold solution at such a rate as to maintain atmospheric pressure in the flask as evidenced by the oil bubbler. When using this technique, it is necessary to monitor the course of hydrogenation by GLC or ^{1}H NMR. However, the rate of hydrogenation decreases rather abruptly after one molar equivalent has been absorbed, and there is little danger of over-hydrogenation.

13. Capillary GLC analysis (12 m, cross-linked methyl silicone, programmed, 45°C, 3°C/min, retention time of ethyl (Z)-crotonate, 2.5 min). Ethyl (E)-crotonate has a retention time of 2.95 min under the same conditions. Careful quantitative analysis reveals that the ratio of Z and E isomers is reproducibly in the range 58:1 to 59:1.

14. The infrared spectrum (neat) has absorptions at 3040, 1710, 1640, 1175, 1025, and 810 cm^{-1}. The ^1H NMR spectrum is as follows (CDCl$_3$) δ: 1.23 (t, 3 H, J = 7), 2.05 (dd, 3 H, J = 2, 7), 4.03 (q, 2 H, J = 7), 5.62 (dq, 1 H, J = 12, 2), 6.19 (dq, 1 H, J = 12, 7).

3. Discussion

A previous *Organic Syntheses* procedure for the preparation of isocrotonic acid involves the stereospecific Favorskii rearrangement of 1,3-dibromo-2-butanone.[6] However, the procedure is rather laborious and, in our hands, gives only a modest overall yield of acid. Isocrotonic acid has also been prepared by carbonation of cis-propenyllithium[7] and by sodium amalgam reduction of β-chloroisocrotonic acid.[8] The present procedure for semihydrogenation of ethyl tetrolate is based on early work of Bourguel[9] and of Allan, Jones and Whiting.[10] The procedure for acylation of propyne is general and may be employed for the preparation of other α,β-acetylenic esters.[11]

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

Ethyl isocrotonate: Crotonic acid, ethyl ester, (Z)- (8); 2-Butenoic acid, ethyl ester, (Z)- (9); (6776-19-8)

Ethyl tetrolate: Tetrolic acid, ethyl ester (8); 2-Butynoic acid, ethyl ester (9); (4341-76-8)

Propyne (8); 1-Propyne (9); (74-99-7)

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

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

FORMYL TRANSFER TO GRIGNARD REAGENTS: 3-PHENYLPROPIONALDEHYDE

(Benzenepropanal)

$$PhCH_2CH_2Cl + Mg \longrightarrow PhCH_2CH_2MgCl$$

$$PhCH_2CH_2MgCl + \text{(N-CHO)} \rightarrow PhCH_2CH_2CHO$$
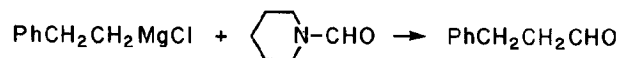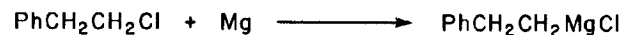
Submitted by George A. Olah and Massoud Arvanaghi.[1]

Checked by David Heiler and Martin F. Semmelhack.

1. Procedure

Magnesium (2.88 g, 0.12 mol), 300 mL of anhydrous tetrahydrofuran (Note 1), and 10 mg of iodine are placed in a 1-L, three-necked, round-bottomed flask fitted with a stirrer, dropping funnel with a pressure-equalizing tube and a reflux condenser connected to nitrogen flow line. Nitrogen is passed through the solvent for 15 min and a constant flow of nitrogen is maintained throughout the reaction. A solution of 14.06 g (0.1 mol) of (2-chloroethyl)benzene (Note 2) in 50 mL of tetrahydrofuran is placed in the dropping funnel. About 2 mL of this solution is added to the reaction mixture and the reaction is initiated by gently heating the flask (with a heat gun). Once the reaction has started, as evidenced by the disappearance of iodine color, the rest of the (2-chloroethyl)benzene solution is added dropwise at such a rate that a gentle reflux is maintained throughout the addition. The resulting solution is stirred for an additional 1 hr at 23°C, followed by heating at reflux for 8 hr. The reaction vessel is cooled to 0°C and a solution of 13.56 g (0.12 mol) of N-formylpiperidine (Note 3) in 50 mL of dry tetrahydrofuran is added dropwise (Note 4). The mixture is brought to 23°C and stirred for another 15 min.

The reaction mixture is quenched by the addition of 25 mL of ice water, and slowly acidified to pH 2 with 75 mL of 3 N hydrochloric acid. The organic layer is separated and the aqueous layer is extracted with three 75-mL portions of ether. The extracts are combined with the original ether layer, washed successively with 50 mL of water, two 50-mL portions of aqueous 10% sodium bicarbonate, and 50 mL of saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. After the magnesium sulfate is removed by filtration, the solvent is removed at aspirator vacuum on a rotary evaporator and the residue is distilled through a short column to give 8.8-10.2 g (66-76%) of 3-phenylpropionaldehyde, bp 87°C (1.0 mm) (Notes 5, 6, and 7).

2. Notes

1. Technical grade tetrahydrofuran was predried for a few days over sodium hydroxide. It was then heated under reflux over sodium wire with benzophenone until it developed a permanent blue color and distilled with exclusion of atmospheric moisture. (*Caution*: See p. 976 of *Org. Synth. Coll. Vol. V* for a warning regarding purification of tetrahydrofuran.)

2. The (2-chloroethyl)benzene was purchased from Eastman Organic Chemicals and used without further purification.

3. N-Formylpiperidine was obtained from Reilly Tar and Chemicals or from Aldrich Chemical Company and used without further purification.

4. Too rapid addition of N-formylpiperidine should be avoided as it can result in a cake-like solid which hinders mixing of the reaction mixture. Efficient stirring is crucial to optimum yields.

5. The reported[2] boiling point for 3-phenylpropionaldehyde is 104-105°C (13 mm).

6. The product exhibits the following carbon magnetic resonance spectrum (chloroform-d) δ: 201.4 (d, $-\overset{O}{\underset{}{C}}$-H), 140.2 (s, ipso), 128.5 (d, meta), 128.2 (d, ortho), 126.1 (d, para), 45.1 (t, $-CH_2-CHO$), 27.9 (t, $-CH_2-CH_2-CHO$); ^{1}H NMR (chloroform-d) δ: 9.80 (t, -CHO), 7.33-7.16 (m, aromatic), 2.95 (m, $-CH_2-CH_2-CHO$), 2.77 (m, $-CH_2-CHO$); infrared cm^{-1}: 2700, 1710.

7. (2-Bromoethyl)benzene can be used instead of (2-chloroethyl)benzene; anhydrous diethyl ether is used as the solvent instead of tetrahydrofuran.

3. Discussion

The procedure described here is a one-step conversion of (2-chloroethyl)benzene to 3-phenylpropionaldehyde. The method is general and characterized by good yields, mild conditions, and easy preparation of 3-phenylpropionaldehyde in pure form from readily available starting materials. Several methods are described in the literature for the preparation of 3-phenylpropionaldehyde, including dry distillation of calcium formate with calcium hydrocinnamate,[3] sodium amalgam reduction and deprotection of cinnamaldehyde dimethyl acetal,[4] or formation from heterocyclic system.[5,6] The present method has been shown[7] to be applicable to a wide variety of organolithium and Grignard reagents.

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

3-Phenylpropionaldehyde: Hydrocinnamaldehyde (8); Benzenepropanal (9); (104-53-0)

(2-Chloroethyl)benzene: Benzene, (2-chloroethyl)- (8,9); (622-24-2)

N-Formylpiperidine: 1-Piperidinecarboxaldehyde (8,9); (2591-86-8)

α-HYDROXY KETONES FROM THE OXIDATION OF ENOL SILYL ETHERS
WITH m-CHLOROPERBENZOIC ACID: 6-HYDROXY-3,5,5-TRIMETHYL-2-CYCLOHEXEN-1-ONE

(2-Cyclohexen-1-one, 6-hydroxy-3,5,5-trimethyl-)
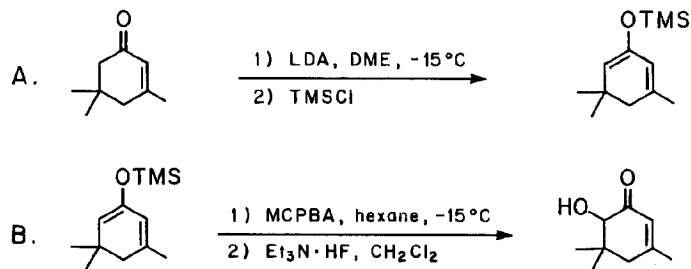
Submitted by George M. Rubottom, John M. Gruber, Henrik D. Juve, Jr.,
and Dan A. Charleson.[1]
Checked by Judy Bolton and Ian Fleming.

1. Procedure

A. *4,6,6-Trimethyl-2-trimethylsilyloxycyclohexa-1,3-diene.* A 500-mL,
three-necked, round-bottomed flask is fitted with a reflux condenser (center
neck), Teflon-covered magnetic stirring bar, ground-glass stopper, and a
rubber septum. The apparatus is connected, through the reflux condenser, to a
nitrogen source and a bubbler (Note 1). After the flask is flushed with
nitrogen, it is charged with 150 mL of dry dimethoxyethane (DME) (Note 2) and
11.25 mL (80.4 mmol) of freshly distilled diisopropylamine (Note 3). The
flask is immersed in a methanol-ice bath and cooled to an external temperature
of -15°C. Over a period of about 5 min, butyllithium, 49.8 mL (79.6 mmol)

(Note 4), is added, with continuous stirring, with a syringe through the
septum. After an additional 15 min of stirring, 10.0 g (72.4 mmol) of freshly
distilled isophorone (Note 5) is added neat over a 10-min period. The bright
yellow solution is stirred for an additional 10 min at -15°C. At this point,
17.5 mL (137.6 mmol) of freshly distilled chlorotrimethylsilane (TMSCl) (Note
6) is rapidly introduced through the septum. After the addition is complete
(ca. 20 sec), the white slurry is stirred for an additional 2 hr at room
temperature. The apparatus is then dismantled, the two outside necks of the
flask are stoppered with ground-glass stoppers, and the center neck is
attached to a rotary evaporator. Solvent is removed under reduced pressure
and the residue is treated with 100 mL of pentane. The slurry is filtered
through a sintered glass filter and the filtrate is concentrated on a rotary
evaporator. The residue is distilled at reduced pressure to give 13.5-13.9 g
(88-91%) of pure 4,6,6-trimethyl-2-trimethylsilyloxycyclohexa-1,3-diene, bp
54-57°C (1.5 mm), 37-39°C (0.01 mm) [lit.[2] bp 45-49°C (0.05 mm)] (Note 7).

B. *6-Hydroxy-3,5,5-trimethyl-2-cyclohexen-1-one.* A 500-mL, three-
necked, round-bottomed flask is fitted with an adapter with a stopcock
connected to a nitrogen source and a bubbler (center neck), two ground-glass
stoppers, and a Teflon-covered magnetic stirring bar (Note 1). After the
system is flushed with nitrogen, the flask is charged with 300 mL of dry
hexane (Note 8) and 10.0 g (47.5 mmol) of 4,6,6-trimethyl-2-
trimethylsilyloxycyclohexa-1,3-diene. The flask is immersed in a methanol-ice
bath and cooled to an external temperature of -15°C and then, with stirring,
the solution is treated with a slurry which contains 10.6 g (52.3 mmol) of m-
chloroperbenzoic acid (MCPBA) (Note 9) and 50 mL of dry hexane (Note 10).
When the addition is complete (ca. 1.5 min), the resulting slurry is stirred
at -15°C for 20 min and then at 30°C (water bath) for 2 hr. The mixture is

filtered through a sintered glass filter into a 500-mL, round-bottomed flask and the solvent is removed under reduced pressure using a rotary evaporator. If solid remains in the residue, 10-15 mL of pentane is added, filtration is repeated, and solvent is again removed under reduced pressure. The flask is fitted with a Teflon-covered stirring bar and the residue is treated with 150 mL of dry methylene chloride (Note 11) and 11.5 g (95.0 mmol) of triethylammonium fluoride (Et_3NHF) (Note 12). After the solution is stirred for 2 hr at room temperature, it is transferred to a separatory funnel and extracted with saturated aqueous sodium bicarbonate solution (2 x 100 mL), 100 mL of 1.5 N hydrochloric acid, and saturated aqueous sodium bicarbonate solution (2 x 50 mL). The organic layer is dried with anhydrous magnesium sulfate, filtered, and solvent is removed from the filtrate using a rotary evaporator. The residue is then freed of the last traces of solvent by pumping, *with stirring*, at reduced pressure (ca. 2.0 mm) (Note 13); the residue solidifies. The round-bottomed flask is attached to a short-path distillation apparatus and the residue is distilled at reduced pressure. After a small forerun, the main fraction, bp 73-75°C (1.3 mm), is collected (Note 14). This fraction solidifies and is triturated with 3-5 mL of petroleum ether (bp 30-60°C) at -15°C (ice-methanol) to remove traces of isophorone. When the crystalline residue is dried in a stream of nitrogen, pure 6-hydroxy-3,5,5-trimethyl-2-cyclohexen-1-one is obtained: 4.8-5.1 g (66-70%), mp 44.5-45°C [lit.[3] mp 45-46°C]. The forerun and the material left in the still head after distillation are combined (Note 15) and treated with the petroleum ether that was used to triturate the main fraction. Crystallization gives an additional 0.2-0.3 g (3-4%) of the hydroxy ketone, mp 44.5-45°C. Thus the total weight of the 6-hydroxy-3,5,5-trimethyl-2-cyclohexen-1-one is 5.1-5.4 g (70-73%) (Note 16).

2. Notes

1. All glassware was dried in an oven for 2 hr at 110°C before use. All reactions were carried out under an atmosphere of nitrogen. The checkers used a balloon filled with nitrogen rather than a bubbler.

2. Dimethoxyethane (DME) (Aldrich Chemical Company, Inc.) was dried over lithium aluminum hydride and distilled just before use. The submitters have found that DME is the solvent of choice in this reaction and is preferred over the more commonly used tetrahydrofuran (THF).

3. Diisopropylamine, bp 80-80.5°C (699 mm), (Aldrich Chemical Company, Inc.) was distilled under a static atmosphere of nitrogen just prior to use.

4. Butyllithium (Aldrich Chemical Company, Inc.) was a 1.6 M solution in hexane. The submitters used the method of Ronald[4] to check titer. It is essential to the success of the reaction that this value be checked with accuracy.

5. Isophorone, bp 85-87°C (10 mm), (Aldrich Chemical Company, Inc.) was distilled immediately before use.

6. Chlorotrimethylsilane (TMSCl), bp 54-55°C (699 mm), (Aldrich Chemical Company, Inc.) was distilled under a static atmosphere of nitrogen just prior to use.

7. The product has the following spectroscopic properties: n_D^{25} 1.4509; infrared (neat) cm^{-1}: 3040 (vinyl CH), 1660 (C=COTMS), 1610 (C=C); ^{1}H NMR ($CDCl_3$) δ: 0.21 (s, 9 H, $Si(CH_3)_3$), 0.98 (s, 6 H, two CH_3), 1.75 (broad s, 3 H, vinyl CH_3), 1.92 (broad s, 2 H, CH_2), 4.52 (broad s, 1 H, vinyl H on carbon 1), 5.40 (multiplet, 1 H, vinyl H on carbon 3); mass spectrum, m/z (relative abundance using 15 eV): 210 (M^+, 28), 196 (17), 195 (100), 179 (9); metastable (m^*): 164.3 (195 → 179). Anal. Calcd for $C_{12}H_{22}OSi$: C, 68.50; H,

10.54. Found: C, 68.50; H, 10.52. A gas chromatographic analysis using a 0.25" x 6.0' column packed with 12.5% SE 52 at a column temperature of 130°C and gas flow rate of 90 mL per minute showed the purity of the product to be greater than 95%. The impurities present were a small amount of unreacted isophorone and a trace of an unidentified material.

8. Hexane was purified in 1.5-L batches by sequential washing with concentrated sulfuric acid (5 x 50 mL) and water (3 x 100 mL), drying ($CaCl_2$), and distillation. The pure hexane is stored over Linde 4Å-molecular sieves.

9. m-Chloroperbenzoic acid (MCPBA) (Aldrich Chemical Company, Inc.) containing 15% m-chlorobenzoic acid was obtained commercially and used without purification.

10. It is convenient to stir the 85% MCPBA in hexane while the flask is being charged with the diene. Addition of the slurry with a pipet is the method used by the submitters. The checkers poured it in directly from a beaker, and washed the beaker with 10 mL of hexane.

11. Methylene chloride is dried by distillation from calcium chloride.

12 Triethylammonium fluoride is prepared by the method of Hünig.[5] The purity of this reagent seems to determine the amount of color that results in the crude hydroxy ketone. Stirring for a period of time greater than 2 hr results in lower yields and is to be avoided.

13. Stirring is crucial to prevent serious bumping when the crude hydroxy ketone solidifies. The checkers simply swirled the flask continuously without incident.

14. Taking a small forerun serves to concentrate residual isophorone in this fraction. Care must also be taken not to overcool the distillation head which may cause crystallization of the hydroxy ketone throughout the system.

15. A small amount of methylene chloride is used to wash the still head. This solvent is then removed (rotary evaporator) prior to the addition of the petroleum ether. Petroleum ether is used if recrystallization is needed.

16. The product has the following spectroscopic properties: infrared (Nujol mull) cm^{-1}: 3360 (OH), 3040 (vinyl CH), 1670, 1635 (C=C-C=O); ^{1}H NMR ($CDCl_3$) δ: 0.79 (s, 3 H, CH_3 on C-5 trans to OH), 1.14 (s, 3 H, CH_3 on C-5 cis to OH), 1.88 (s, 3 H, vinyl CH_3), 2.13 (d, 1 H, J = 18, AB doublet for H on C-4), 2.35 (d, 1 H, J = 18, AB doublet for H on C-4), 3.52 (d, 1 H, J = 2, OH), 3.78 (d, 1 H, J = 2, H on C-6), 5.70 (broad s, 1 H, vinyl H); mass spectrum, m/z (relative abundance using 15 eV): 154 (M^+, 24), 125 (10), 111 (14), 83 (100), 82 (96), 72 (44); metastables (m^*): 101.5 (154 → 125), 80.0 (154 → 111). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.81; H, 9.50. A gas chromatographic analysis using a 0.25" x 6.0' column packed with 12.5% SE-52 at a column temperature of 158°C and a gas flow rate of 90 mL per minute showed the purity of the product to be greater than 98%. In some runs, a trace of isophorone could be detected (ca. 2%).

3. Discussion

The preparation of α-hydroxy carbonyl compounds has been accomplished by the oxidation of enolates using both oxygen[6] and MoO_5·Py·HMPA·(MoOPh).[7] Acyl anion equivalents offer another route to this useful class of compounds.[8] The procedure presented here for the synthesis of 6-hydroxy-3,5,5-trimethyl-2-cyclohexen-1-one illustrates the use of MCPBA oxidation of an enol silyl ether as a method for obtaining an α-hydroxy enone. The procedure is a scaleup of a published synthesis.[9]

4,6,6-Trimethyl-2-trimethylsilyloxycyclohexa-1,3-diene has been reported by Conia[2] who used the standard "kinetic method" of House[10] for synthesis of the compound. The current method adapts this synthesis by employing DME as solvent and by using a non-aqueous workup which was previously noted by Ainsworth for the preparation of silyl ketene acetals.[11] These changes lead to higher yields of pure enol silyl ethers in general, and are recommended as a standard method.

6-Hydroxy-3,5,5-trimethyl-2-cyclohexen-1-one has been prepared in 22% yield by lead(IV) acetate oxidation of isophorone followed by hydrolysis of the resulting acetate.[3] The MCPBA method gives high yields of both α-hydroxy enones[12] and ketones[13] and is extremely general in scope. The method is also viable for the synthesis of α-hydroxy acids[14] and α-hydroxy esters.[15] The method fails with the enol silyl ethers of both lactones[15] and aldehydes.[16]

Since the double bond placement in enol silyl ethers is predictable and controllable,[13] the method allows the regiospecific introduction of α-hydroxy groups. Omission of the fluoride treatment permits isolation of α-trimethylsiloxy carbonyl compounds,[17] while treatment of enol silyl ethers, first with MCPBA, then with triethylammonium fluoride/acetic anhydride gives the corresponding α-acetoxy carbonyl compounds.[9] The probable mechanism of the MCPBA oxidation of enol silyl ethers has also been discussed.[18]

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HYDROXYLATION OF ENOLATES WITH

OXODIPEROXYMOLYBDENUM(PYRIDINE)(HEXAMETHYLPHOSPHORIC TRIAMIDE),

$MoO_5 \cdot Py \cdot HMPA$ (MoOPH): 1,7,7-TRIMETHYL-3-HYDROXYBICYCLO[2.2.1]HEPTAN-2-ONE

(Bicyclo[2.2.1]heptan-2-one, 3-hydroxy-1,7,7-trimethyl-)

A. $MoO_3 \xrightarrow[\text{2) } (Me_2N)_3PO]{\text{1) } H_2O_2} MoO_5 \cdot H_2O \cdot (Me_2N)_3PO$

B. $MoO_5 \cdot H_2O \cdot (Me_2N)_3PO \xrightarrow{0.2 \text{ mm}} MoO_5 \cdot (Me_2N)_3PO \xrightarrow{\text{pyridine}}$

$MoO_5 \cdot Py \cdot (Me_2N)_3PO$

C. $\xrightarrow[\text{2) } MoO_5 \cdot Py \cdot (Me_2N)_3PO]{\text{1) LDA}}$
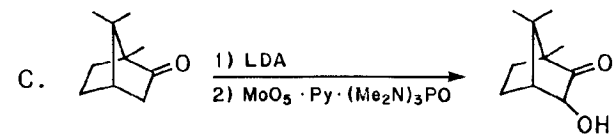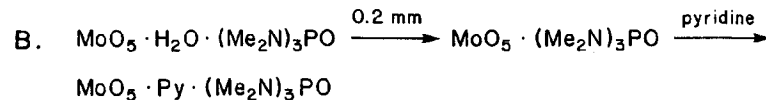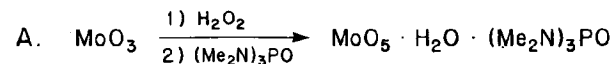
Submitted by Edwin Vedejs and S. Larsen.[1]

Checked by Gordon Hill and K. Barry Sharpless.

*Caution! Reactions using peroxides should be performed behind a safety
shield to minimize explosion hazards (Note 1). Hexamethylphosphoric triamide
(HMPA) and methanol are toxic and must be handled in a hood (Note 2).*

1. Procedure

*A.   Oxodiperoxymolybdenum(aqua)(hexamethylphosphoric triamide), $MoO_5 \cdot
H_2O \cdot HMPA$.*[2]   A 500-mL, three-necked flask is fitted with an internal
thermometer and a mechanical paddle stirrer.   The flask is charged, with
stirring, with 30 g (0.2 mol) of molybdenum oxide (MoO$_3$) (Note 3) and 150 mL
of 30% hydrogen peroxide (H$_2$O$_2$) (Note 4).   An oil bath equilibrated at 40°C is

placed under the reaction mixture and heating is continued until the internal temperature reaches 35°C. The heating bath is removed, and replaced by a water bath to control the mildly exothermic reaction so that an internal temperature of 35-40°C is maintained. After the initial exothermic period (approximately 30 min), the reaction flask is placed in the 40°C oil bath and stirred a total of 3.5 hr to form a yellow solution with a small amount of suspended white solid (Note 5).

After cooling to 20°C, the solution is filtered through a 1-cm mat of Celite pressed into a coarse-porosity sintered glass filter. The yellow filtrate is cooled to 10°C (with an ice bath and magnetic stirring) and 37.3 g (0.21 mol) of hexamethylphosphoric triamide (HMPA) (Note 2) is added dropwise over 5 min, resulting in the formation of a yellow crystalline precipitate. Stirring is continued for a total of 15 min at 10°C, and the product is filtered using a Büchner funnel and pressed dry with a spatula. After 30 min in the funnel (aspirator vacuum), the filter cake is transferred to a 1-L Erlenmeyer flask. Methanol (20 mL) is added and the mixture is stirred in the 40°C bath. More methanol is slowly added until the crystals have dissolved. Cooling the saturated solution in the refrigerator gives yellow needles. The crystal mass is broken up with a spatula, the product is filtered, and washed with 20-30 mL of cold methanol to give $MoO_5 \cdot H_2O \cdot HMPA$, 46-50 g, 59-64% (Notes 5, 6).

B. *Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide) $MoO_5 \cdot$ Py·HMPA = MoOPH.*[2] The recrystallized product from above is dried over phosphorus oxide (P_2O_5) in a vacuum desiccator, shielded from the light, for 24 hr at 0.2 mm to give a somewhat hygroscopic yellow solid, $MoO_5 \cdot HMPA$. A 36.0-g (0.101 mol) portion of $MoO_5 \cdot HMPA$ is dissolved in 150 mL of dry tetrahydrofuran (THF) (Note 7) and the solution is filtered through a Celite

mat, if needed, to remove a small amount of amorphous precipitate. The filtrate is then stirred magnetically in a 20°C water bath while 8.0 g (0.101 mol) of dry pyridine (Note 8) is added over 10 min. The crystalline, yellow product is collected on a Büchner funnel, washed with dry tetrahydrofuran (25 mL) and anhydrous ether (200 mL), and dried in a vacuum desiccator (1 hr, 0.2 mm) to yield 36-38 g (51-53% overall from MoO_3) of finely divided yellow crystalline $MoO_5 \cdot Py \cdot HMPA$ (Note 9).

The product is stored in a dark glass jar inside a second container partly filled with Drierite, and the container is kept in the refrigerator. Before opening the jar, the container is allowed to warm to room temperature to avoid condensation of moisture inside. Properly stored MoOPH is a freely flowing crystalline powder and can be used over a period of several months (Note 10).

C. *Hydroxylation of camphor: 1,7,7-Trimethyl-3-hydroxybicyclo[2.2.1]-heptan-2-one.* A solution of lithium diisopropylamide (LDA) is prepared as follows: A 250-mL, three-necked flask and magnetic stirrer are flame dried under a slow stream of nitrogen. After cooling, the flask is charged with 40 mL of approximately 1.5 M butyllithium in hexane (Note 11) under nitrogen flow using a syringe. The flask is cooled in a dry ice-acetone bath and 9.2 mL (66 mmol) of diisopropylamine (Note 8) is added by syringe, followed by 40 mL of dry THF (Note 7). The resulting LDA solution is allowed to reach room temperature under a slow flow of nitrogen. For titration, 0.312 g (2 mmol) of menthol is dissolved in 5 mL of dry THF with a few crystals of phenanthroline (Note 12) under nitrogen flow at -70°C. The LDA solution is added dropwise (using a nitrogen-purged syringe) to the stirred menthol solution until the yellow color of menthoxide-phenanthroline turns to the rust color of LDA - phenanthroline, (2.67 mL of LDA solution is needed, 0.75 M).

An aliquot of 47.1 mL (35.3 mmol) of LDA solution is transferred by nitrogen-filled syringe into a nitrogen-swept, 500-mL, three-necked flask equipped with a magnetic stirrer and a device for addition of solid MoOPH. The latter is an L-shaped glass tube with male joints at each end. A round-bottomed flask containing 20.9 g (48.1 mmol) of MoOPH is wired to the L-tube which is wired to the reaction vessel at such an angle that rotation of the L-tube causes addition of MoOPH to the enolate. The MoOPH container is temporarily suspended using clamps, and the entire apparatus is maintained under a slow flow of nitrogen. After the LDA solution is cooled in a dry ice-acetone bath, 4.88 g (32.1 mmol) of camphor (Note 13) in 200 mL of dry THF is added dropwise with stirring over 0.5 hr. Ten minutes later the reaction is placed in a dry ice - carbon tetrachloride bath and after 15 min the MoOPH is added over 1-2 min by rotating the L-tube and gently tapping to dislodge the powder. The reaction immediately turns orange and eventually fades to a pale tan (Note 14). Stirring is continued at approximately -23°C for 20 min, and the reaction is quenched by adding 100 mL of saturated aqueous sodium sulfite (Na_2SO_3). Vigorous stirring is maintained and the mixture is allowed to warm to room temperature. After 10 min at 20°C, the mixture is shaken with 100 mL of saturated sodium chloride solution, and the aqueous layer is extracted twice with 70 mL of ether. The combined organic layers are washed once with a mixture of 50 mL of 10% aqueous hydrochloric acid and 50 mL of saturated sodium chloride solution. The hydrochloric acid - sodium chloride aqueous layer is back-extracted with 50 mL of ether, the combined organic layers are dried over $MgSO_4$, filtered, and evaporated under an aspirator to yield a blue-green oil. Residual molybdenum salts are removed by filtration over 100 g of silica gel (Note 15) in a 2.5-cm column wet-packed and eluted with 1:1 ether-hexane. The product is eluted with approximately 750 mL of ether-hexane.

Evaporation (aspirator) yields a white semi-solid which is crystallized from 15 mL of hexane at -20°C and collected by washing with hexane cooled to -70°C. The mother liquors are crystallized in a similar manner from 2-4 mL of hexane to give a total of five crops, 4.14 g (77%) of colorless needles, mp 170-183°C, a 5:1 mixture of endo:exo isomers (Note 16). Recrystallization did not affect the isomer ratio (literature mp; endo, 192-195°C; exo, 210-211°C).[3]

2. Notes

1. There are no reports that $MoO_5 \cdot H_2O \cdot HMPA$, $MoO_5 \cdot HMPA$, or $MoO_5 \cdot Py \cdot HMPA$ are shock-sensitive. Upon heating on a hot plate, the crystalline solids ignite and burn, but do not detonate. These compounds can be stored in a refrigerator with precautions to exclude light. Prolonged storage at room temperature in the light may cause decomposition with gas evolution and an exotherm sufficient to crack a glass container.

2. Hexamethylphosphoric triamide is toxic and a cancer-suspect agent.

3. Molybdenum oxide was obtained from Mallinckrodt Inc.

4. Hydrogen peroxide was obtained from Mallinckrodt Inc.

5. Failure to maintain the internal temperature below 40°C results in formation of amorphous, insoluble products.

6. The purity of this material is decisive because the quality of subsequent products cannot be improved by recrystallization because of some decomposition.

7. Tetrahydrofuran was distilled from sodium-benzophenone and stored under nitrogen.

8. Pyridine was distilled from barium oxide.

9. The product melts with vigorous evolution of gas at 103-105°C.

10. Prolonged exposure to light, or failure to control exothermic reactions in prior steps, results in a sticky product which smells of pyridine. No method for purifying partly decomposed MoOPH has been found, and "sticky" product should not be used for enolate hydroxylation. Suspect material can be decomposed by stirring with aqueous sodium sulfite (Na_2SO_3) solution.

11. Butyllithium was obtained from the Foote Mineral Company.

12. Menthol and phenanthroline were obtained from the Aldrich Chemical Company, Inc.

13. Camphor was obtained from Eastman Organic Chemicals.

14. The colors are somewhat substrate dependent. Some enolate hydroxylations acquire a green-blue color.

15. Silica gel, 60-200 mesh, was obtained from Davison Chemical Division.

16. The endo:exo ratio is determined by comparing the NMR CHOH signal areas of the endo (4.21 ppm, d, J = 4.8 Hz) and exo (3.75 ppm, br s) isomers.

3. Discussion

Enolate hydroxylation is a problem of long standing. Direct oxygenation succeeds with the fully substituted enolates of certain α,α-disubstituted ketones[4] and a variety of carboxylic acid derivatives (ester anions, acid dianions, amide anions),[5] but the reaction of enolates, $RCH = C(O^-)R'$ or $CH_2 = C(O^-)R'$, with oxygen results in complex products of overoxidation. The stable molybdenum peroxide reagent $MoO_5 \cdot Py \cdot HMPA$ (MoOPH),[2] first prepared by Mimoun, allows the conversion of $RCH = C(OLi)R'$ into $RCH(OH)COR'$ in generally good yields (Table I).[6] In some cases, the α-diketone is formed as a byproduct.
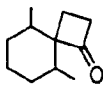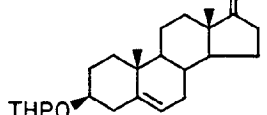
The MoOPH reagent also hydroxylates branched or unbranched ester, amide, and nitrile anions.[6,7] For unknown reasons, MoOPH hydroxylations often do not give complete conversion of enolates into products, and recovery of 5-15% of the starting carbonyl substrate is to be expected.

Methyl ketone enolates are hydroxylated by MoOPH, but the products tend to undergo condensation with the starting enolate, resulting in poor yields.[6] Methyl ketone hydroxylation has been described by Moriarty, using $C_6H_5I=O/CH_3OH-OH^\ominus$.[8]

Several indirect methods for conversion of enolates into α-hydroxycarbonyl compounds are known. The most versatile is the reaction of enol silanes with meta-chloroperbenzoic acid developed by Rubottom.[9] This technique is often successful with substrates which are oxidized inefficiently by the MoOPH technique.

The method described for MoOPH hydroxylation of the camphor enolate is representative for ketone enolate hydroxylations, but optimization in each individual case to determine the best temperature and concentration is recommended. Large scale oxidations may benefit from addition of reagent in several portions over time, and enolates which are sensitive to self-condensation may give higher yields if enolate is added slowly to excess MoOPH.

TABLE I

Ketone	Oxidation temp. (°C)	α-Hydroxy ketone	α-Diketone
valerophenone	-22	60 %	13%
	-44	62 %	<2%
deoxybenzoin	-44	34 %	26%
isobutyrophenone	-22	65 %	
α-tetralone	-22	48 %	
camphor	-22	77 %	<2 %
	-22 → 60, 16 hr	44 %	11%
4,4-diphenyl-cyclohexanone	-22	46 %	
2-phenylcyclohexanone	-44	70 %	<5%
	-22	81 %	
	-44	75 % (16α-OH)	

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Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide): Molybdenum, (hexamethylphosphoric triamide)oxodiperoxy(pyridine)- (8,9); (23319-63-3)

1,7,7-Trimethyl-3-hydroxybicyclo[2.2.1]heptan-2-one: Bicyclo[2.2.1]heptan-2-one, 3-hydroxy-1,7,7-trimethyl- (9); (10373-81-6)

endo-1,7,7-Trimethyl-3-hydroxybicyclo[2.2.1]heptan-2-one: Bicyclo[2.2.1]heptan-2-one, 3-hydroxy-1,7,7-trimethyl-, endo- (9); (21488-68-6)

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

Oxodiperoxymolybdenum(aqua)(hexamethylphosphoric triamide): Molybdenum, aqua(hexamethylphosphoric triamide)oxodiperoxy- (8,9); (23319-56-4)

Molybdenum oxide (8,9); (1313-27-5)

Hydrogen peroxide (8,9); (7722-84-1)

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

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

Oxodiperoxymolybdenum(hexamethylphosphoric triamide); Molybdenum, (hexamethylphosphoric triamide)oxodiperoxy- (8); Molybdenum, (hexamethylphosphoric triamide-O)oxodiperoxy- (9); (25377-12-2)

Camphor (8); Bicyclo[2.2.1]heptan-2-one, 1,7,7-trimethyl- (9); (76-22-2)

Lithium diisopropylamide: Diisopropylamine, lithium salt (8); 2-Propanamine, N-(1-methylethyl)-, lithium salt (9); (4111-54-0)

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

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

Menthol (8); Cyclohexanol, 5-methyl-2-(1-methylethyl)-, (1α, 2β, 5α)- (9); (89-78-1)

Phenanthroline: 1,10-Phenanthroline (8,9); (66-71-7)

Sodium sulfite: Sulfurous acid, disodium salt (8,9), (7757-83-7)

α-HYDROXYLATION OF A KETONE USING o-IODOSYLBENZOIC ACID:

α-HYDROXYACETOPHENONE VIA THE α-HYDROXY DIMETHYLACETAL

(Ethanone, 2-hydroxy-1-phenyl-)
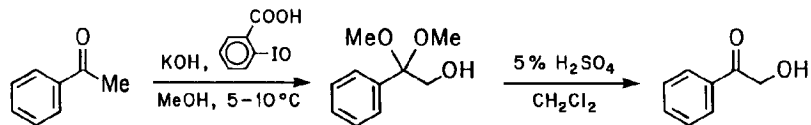
Submitted by Robert M. Moriarty, Kwang-Chung Hou, Indra Prakash, and S. K. Arora.[1]

Checked by Janice Klunder and K. Barry Sharpless.

1. Procedure

A 250-mL, two-necked, round-bottomed flask is equipped with a magnetic stirring bar, 100-mL pressure-equalized addition funnel to which is attached a drying tube, and a stopper. Anhydrous methanol (80 mL) (Note 1) is added to the flask, which is cooled to 5-10°C. Stirring is begun and 8.4 g (0.15 mol) of powdered potassium hydroxide is added. Acetophenone (6.0 g; 0.05 mol) (Note 2) dissolved in 20 mL of methanol is added dropwise over a period of 10 min. After the solution is stirred for 15 min, 14.52 g (0.055 mol) of o-iodosylbenzoic acid (Note 3) is added during 30 min. The ice bath is removed, and the resultant yellow-colored slurry is stirred overnight at room temperature to give a clear red solution (Note 4). The mixture is concentrated under reduced pressure in a rotary evaporator, until one-half of the methanol is removed, then 30 mL of water is added followed by extraction

with four 50-mL portions of dichloromethane. The combined dichloromethane extracts are washed with two 10-mL portions of water, and the combined organic extracts are dried over anhydrous magnesium sulfate for 1 hr. After filtration, the methylene chloride is removed under reduced pressure in a rotary evaporator, and the crude acetal is distilled to give a fraction at 73-76°C (0.4 mm) which weighs 6.0 g (65%) (Note 5). The acetal is of high purity, as shown by spectral analysis (Note 6).

α-Hydroxyacetophenone. In a 500-mL, round-bottomed flask equipped with a magnetic stirrer are placed 6.0 g (0.33 mol) of α-hydroxy dimethylacetal and 100 mL of dichloromethane. Stirring is begun and the flask is cooled to about 10°C with ice water. Aqueous 5% sulfuric acid (100 mL) is added dropwise from a pressure-equalized addition funnel and the mixture is stirred for another 30 min. The dichloromethane layer is separated and the aqueous layer is extracted twice with 25-mL portions of dichloromethane. The combined extracts are washed with two 10-mL portions of water, dried over anhydrous magnesium sulfate, and the solvent is removed under reduced pressure using a rotary evaporator. The resulting yellow crystalline solid is recrystallized from carbon tetrachloride to give a white crystalline material, mp 86-87.5°C (lit.[2] mp 86-87°C), yield 3.7 g (83%) (Note 7).

2. Notes

1. Anhydrous methanol is obtained by treatment with magnesium methoxide, obtained by refluxing 50 mL of methanol, 5 g of magnesium turnings, and 0.5 g of sublimed iodine together until the iodine color disappears. Then 1 L of methanol is added and the system is kept at reflux for 1 hr and distilled to yield purified methanol (bp 64.5°C).

2. Acetophenone was used as purchased from Fisher Scientific Company.

3. o-Iodosylbenzoic acid was used as purchased from Sigma Chemical Company.

4. TLC (ethyl acetate:hexane) shows residual starting material.

5. The α-hydroxy dimethylacetal obtained must be used immediately in the next step because at room temperature it undergoes a dimerization reaction by loss of two molecules of methanol.

6. The spectral properties of the product are as follows: IR (neat) cm^{-1}: 3470 (-OH); ^{1}H NMR (CDCl$_3$) δ: 1.83 (s, 1 H, OH), 3.23 (s, 6 H, (OCH$_3$)$_2$), 3.73 (s, 2 H, CH$_2$), 7.27-7.67 (m, 5 H, Ar H); ^{13}C NMR (CDCl$_3$) δ: 139.3 (s), 128.4 (d), 127.4, (d) 102.4 (s), 65.3 (t) 49.1 (q); mass spectrum: m/e 151 (M$^+$-OCH$_3$ 100%), 105 (29.7%), 91 (31.7%), 77 (7.0%).

7. The product has the following spectral properties: ^{1}H NMR (CDCl$_3$) δ: 3.63 (s, 1 H, OH), 4.86 (s, 2 H, CH$_2$), 7.25-7.90 (m, 5 H, Ar H); ^{13}C NMR (CDCl$_3$) δ: 198.6 (s), 134.4 (s), 129.1 (d), 127.8 (d), 65.6 (t).

3. Discussion

The procedure reported here provides a convenient method for the α-hydroxylation of ketones which form enolates under the reaction conditions. The reaction has been applied successfully to a series of para-substituted acetophenones, 1-phenyl-1-propanone, 3-pentanone, cyclopentanone, cyclohexanone, cycloheptanone, cyclododecanone, 2-methylcyclohexanone, 2-norbornanone and benzalacetone.[3] In the case of a steroidal example it was shown that a carbon-carbon double bond and a secondary hydroxyl group are not oxidized.[4] A primary amino function, as in the case of p-aminoacetophenone, is not affected.[5] Similarly, a tertiary amino ketone such as tropinone undergoes the α-hydroxylation reaction.[5]

The present procedure using o-iodosylbenzoic acid is an improvement over our original method which uses either iodosylbenzene or diacetoxyphenyliodine(III).[6,7,8] The advantage of the present method is the solubility of the product iodobenzoic acid under the basic reaction conditions. Thus the α-hydroxy dimethylacetal may be isolated by direct extraction. Using the original procedure both carboxylic acids and esters underwent high yield α-hydroxylation.[8]

The pathway by which the reactions are considered to occur involves attack of the enolate anion at the I=O bond of o-iodosylbenzoic acid followed by reductive elimination of o-iodobenzoic acid upon addition of methoxide to the carbonyl group. Ring opening of the epoxide thus formed yields the hydroxy dimethylacetal:
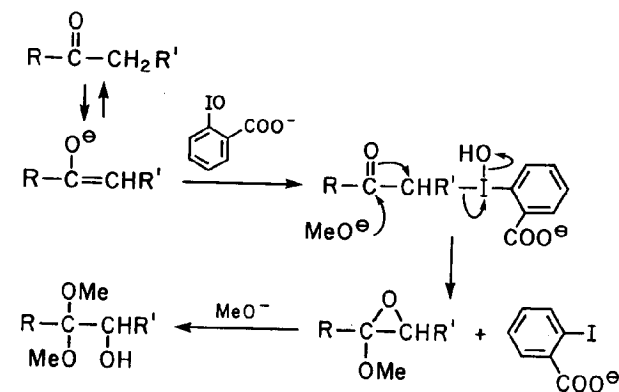
Other methods for α-hydroxy ketone synthesis are: addition of $^3O_2$ to an enolate followed by reduction of the α-hydroperoxy ketone using triethyl phosphite;[9] the molybdenum peroxide-pyridine-HMPA oxidation of enolates;[10] photooxygenation of enol ethers followed by triphenylphosphine reduction;[11] the epoxidation of trimethylsilyl enol ethers by peracid;[12] the oxidation of trimethylsilyl enol ethers by osmium tetroxide in N-methylmorpholine N-oxide;[13] and finally the classical method of hydrolysis of an α-bromo ketone.[14]

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

o-Iodosylbenzoic acid: Benzoic acid, o-iodoso- (8); Benzoic acid, 2-iodosyl- (9); (304-91-6)

α-Hydroxyacetophenone: Acetophenone, 2-hydroxy- (8); Ethanone, 2-hydroxy-1-phenyl- (9); (582-24-1)

Acetophenone (8); Ethanone, 1-phenyl- (9); (98-86-2)

α-Hydroxyacetophenone dimethyl acetal: Acetophenone, 2-hydroxy-, dimethyl acetal (8,9); (28203-05-6)

METHYL DIFORMYLACETATE

$$CH_2(COOMe)_2 \xrightarrow{KOH} MeOOCCH_2COOK \xrightarrow[POCl_3]{2\ DMF}$$
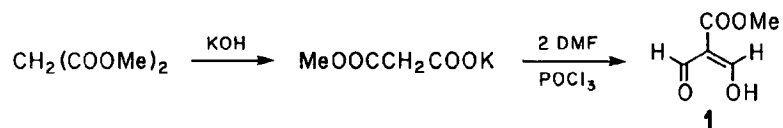
Submitted by C. R. Hutchinson, M. Nakane, H. Gollman, and P. L. Knutson.[1]
Checked by David J. Wustrow and Andrew S. Kende.

1. Procedure

A. Potassium monomethyl malonate. Dimethyl malonate (Note 1, 264.2 g, 2.0 mol) is dissolved in anhydrous methanol (Note 2, 1150 mL) contained in a dry, 3-L, one-necked flask containing a large magnetic stirring bar and protected from atmospheric moisture with a calcium sulfate-filled drying tube. The solution is stirred magnetically and cooled to ice-water bath temperature. Potassium hydroxide pellets (112.2 g, 2.0 mol) are added rapidly to the cold solution and the reaction mixture is allowed to warm to room temperature with stirring overnight. The colorless crystals of potassium monomethyl malonate which form are recovered by suction filtration through a Buchner funnel and washed with anhydrous diethyl ether. The combined filtrate and diethyl ether wash are concentrated at 30°C to a volume of ca. 750 mL on a rotary evaporator. The resulting crystalline precipitate is recovered as before by filtration and washing and combined with the first crop of crystals

to give 220 g (71%) of potassium monomethyl malonate as fine colorless needles, mp 204-207°C. These crystals are dried under vacuum (0.1 mm) before use in the following reaction.

B. Methyl diformylacetate. Freshly distilled phosphorus oxychloride (612 g, 4 mol) is added dropwise with constant stirring at ambient temperature (Note 3) to dimethylformamide (1460 g) contained in a 3-L, three-necked flask equipped with a mechanical paddle stirrer, immersion thermometer, and a 500-mL pressure-equalizing addition funnel fitted with a calcium chloride-filled drying tube. The reaction mixture warms up and turns to a dark reddish-brown color during addition of the phosphorus oxychloride and formation of the Vilsmeier reagent $[(CH_3)_2\overset{+}{N}=CHCl\ Cl^-]$. The addition funnel is replaced with a 10-inch long West condenser (Note 4) and then the reaction mixture is cooled to 0°C by immersing the reaction flask in an ice-salt water bath. The cooling bath is removed and potassium monomethyl malonate (206 g, 1.32 mol) is added to the stirred reaction mixture in ten equal portions over a thirty-minute period (Notes 3, 5), keeping the temperature of the mixture below 90°C. The dark brown mixture then is stirred and heated on a water bath at 90°C for 4 hr. Gas (CO_2 plus HCl) evolves initially from the reaction upon heating (Note 6). The thermometer is replaced with a glass stopper, the condenser is fixed for distillation by addition of a distilling head and vacuum distillation receiver, and the reaction solvent is removed from the reaction flask by distillation at ca. 2 mm on a steam bath (Note 7). The resulting dark brown liquid is poured onto ice (4 kg, Note 3). A saturated aqueous solution of potassium carbonate (1.3 kg) is added slowly to the ice-cold crude reaction product with constant stirring until the pH of the mixture stabilizes at ca. 11. Considerable foaming and gas evolution (CO_2) occur during the addition of the base. The resulting basic solution is stirred magnetically at ambient
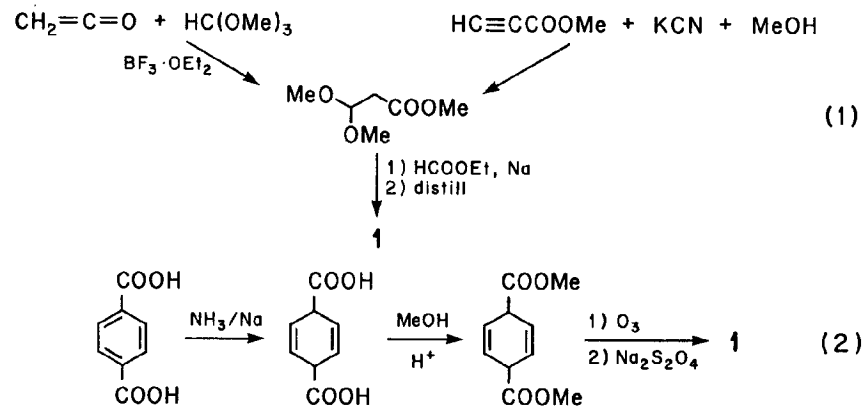
temperature for 48 hr and then extracted with ethyl acetate in four 1-L portions. The organic phases are discarded, and the aqueous phase is saturated with potassium chloride (500 g) by stirring at ambient temperature until no more salt dissolves. This mixture is mixed with ice (1 kg), slowly acidified to pH 1 with ice-cold 12 N hydrochloric acid, and then thoroughly extracted with four 2-L portions of diethyl ether (Note 8). The combined cold ether extracts are washed with a saturated aqueous solution of potassium chloride (4 L) and dried over anhydrous sodium sulfate (500 g) for 1 hr. The solution is decanted from the desiccant, combined with a 500-mL diethyl ether wash of the desiccant, concentrated under reduced pressure to ca. 500 mL, and redried over anhydrous sodium sulfate. After removal of the desiccant by gravity filtration, the diethyl ether is removed by rotary evaporation at water aspirator pressure and 25°C. Fractional distillation of the resulting liquid residue at 2 mm with a N_2 bleed capillary through a Claisen head first gives a little dimethylformamide. When dimethylformamide ceases to distill (Note 9), the receiver is cooled in a dry ice-ethanol bath and the methyl diformylacetate distilled at 58-61°C to give 86-94 g (50-55%) of a colorless, solid distillate, which melts at about 10°C (Notes 10, 11). Methyl diformylacetate prepared in this way is stable for at least 6 months if stored at -20°C.

2. Notes

1. All reagents are used as received from commercial suppliers unless stated otherwise.

2. Reagent grade methanol is made anhydrous by refluxing over $Mg(OCH_3)_2$ according to the method of Vogel.[2]

3. All of the following operations must be done in a hood.

4. The desiccant in the drying tube should be replaced with fresh calcium chloride and the drying tube fitted onto the top of the condenser.

5. The salt is added by replacing the condenser with a glass powder funnel, quickly pouring the crystalline solid through the funnel into the flask, and then replacing the powder funnel with the condenser.

6. The condenser can be cooled to prevent loss of solvent that is carried out of the reaction mixture by the escaping gases.

7. The volume of dimethylformamide distillate is ca. 1000 mL, and distillation is stopped when no more liquid distills from the reaction mixture.

8. The solvent extractions and washings should be done as rapidly as is possible since the crude methyl diformylacetate is not stable to small amounts of acid or base over long periods.

9. Dimethylformamide ceases to distill at a temperature less than 30°C.

10. Considerable product is lost if the receiver is not chilled to a low temperature.

11. The submitters have obtained the same yield when this procedure was done on scales from 0.5 to 1.3 mol.

3. Discussion

Methyl diformylacetate can be prepared from ketene and trimethyl orthoformate,[3] or methyl propiolate and methanol,[4] via formylation of the methyl 3,3-dimethoxypropanoate intermediate (eq. 1). The present procedure is better because it avoids the tedious preparation of ketene,[3] affords a superior yield,[3] or is much cheaper[4] than the other two methods. A fourth method[5] for its preparation (eq. 2) should permit the preparation of any ester of diformylacetic acid that is stable to Birch reduction and ozonolysis conditions. However, this method is not convenient for use above a 0.1-mole scale, nor recommended for reasons of safety because of the amount of an O_2/O_3 mixture needed at larger scales.

$$CH_2{=}C{=}O + HC(OMe)_3 \qquad HC{\equiv}CCOOMe + KCN + MeOH$$

$$BF_3 \cdot OEt_2 \searrow$$

$$MeO\!\!\diagdown\!\!\diagup COOMe \qquad\qquad (1)$$
$$OMe$$

1) HCOOEt, Na
2) distill

1

$$\text{(2)}$$

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

Methyl diformylacetate: 2-Propenoic acid, 2-formyl-3-hydroxy-, methyl ester (9); (39947-70-1)

Potassium monomethyl malonate: Propanedioic acid, monomethyl ester, potassium salt (9); (38330-80-2)

Dimethyl malonate: Malonic acid, dimethyl ester (8); Propanedioic acid, dimethyl ester (9); (108-59-8)

Phosphorus oxychloride: Phosphoryl chloride (8,9); (10025-87-3)

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

OZONOLYTIC CLEAVAGE OF CYCLOHEXENE TO TERMINALLY DIFFERENTIATED PRODUCTS:

METHYL 6-OXOHEXANOATE, 6,6-DIMETHOXYHEXANAL, METHYL 6,6-DIMETHOXYHEXANOATE

(Hexanoic acid, 6-oxo-, methyl ester; Hexanal, 6,6-dimethoxy-;

Hexanoic acid, 6,6-dimethoxy-, methyl ester)

A.

$$\text{1) O}_3\text{, MeOH, CH}_2\text{Cl}_2$$
$$\text{2) TsOH}$$
$$\text{3) NaHCO}_3$$
$$\text{4) Me}_2\text{S}$$

$\longrightarrow$ $(MeO)_2CH\diagdown\diagup\diagdown CHO$

B.

$$\text{1) O}_3\text{, MeOH, CH}_2\text{Cl}_2$$
$$\text{2) Ac}_2\text{O, Et}_3\text{N}$$

$\longrightarrow$ $MeOOC\diagdown\diagup\diagdown CHO$

C.

$$\text{1) O}_3\text{, MeOH, CH}_2\text{Cl}_2$$
$$\text{2) TsOH}$$
$$\text{3) Ac}_2\text{O, Et}_3\text{N}$$

$\longrightarrow$ $MeOOC\diagdown\diagup\diagdown CH(OMe)_2$
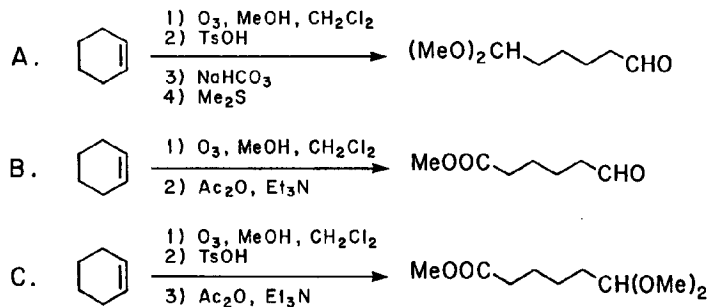
Submitted by Ronald E. Claus and Stuart L. Schreiber.[1]

Checked by Nakcheol Jeong and Martin F. Semmelhack.

1. Procedure

Caution! The ozonolysis reaction produces peroxidic intermediates which can present a potential explosion hazard. Accordingly, it is recommended that the following experiments be carried out in a hood and behind a safety shield.

A. A 500 mL, three-necked, round-bottomed flask is fitted with a glass tube to admit ozone, a calcium chloride drying tube, a glass stopper, and a magnetic stirring bar and is charged with 6.161 g of cyclohexene (0.075 mol), 250 mL of dichloromethane, and 50 mL of methanol (Note 1). The flask is cooled to ca. -78°C (2-propanol/dry ice) and ozone (Note 2) is bubbled through

the solution with stirring. When the solution turns blue, ozone addition is stopped. Nitrogen is passed through the solution until the blue color is discharged (Note 3) and then the cold bath is removed. The drying tube and ozone inlet are replaced with a stopper and rubber septum, and 1.215 g of p-toluenesulfonic acid (TsOH) (10% w/w) (Note 4) is added. The solution is allowed to warm to room temperature as it stirs under an atmosphere of nitrogen for 90 min. Anhydrous sodium bicarbonate (2.147 g, 4 mol-equiv) is added to the flask and the mixture is stirred for 15 min, and then 12 mL of dimethyl sulfide (0.150 mol) (Note 5) is added. After being stirred for 12 hr, the heterogeneous mixture is concentrated to approximately 50 mL by rotary evaporation. Dichloromethane (100 mL) is added and the mixture is washed with 75 mL of water (Note 6). The aqueous layer is extracted with two more 100-mL portions of dichloromethane, and the combined organic layers are washed with 100 mL of water. After extracting the aqueous layer with 100 mL of dichloromethane, the organic layers are dried over anhydrous magnesium sulfate, filtered and concentrated by rotary evaporation. Short path distillation of the crude product (Note 7) gives 8.2-8.4 g of 6,6-dimethoxyhexanal, 68-70%, bp 80-82°C/1.75 mm (Notes 8 and 9).

B. A round-bottomed flask equipped as in Procedure A is charged with 6.161 g of cyclohexene (0.075 mol), 250 mL of dichloromethane, 50 mL of methanol, and 2.0 g of anhydrous sodium bicarbonate (Notes 1 and 10). After the apparatus is cooled to ca. -78°C, ozone (Note 2) is bubbled through the solution as it is stirred. Ozone addition is stopped when the solution turns blue. Nitrogen is passed through the solution until the blue color is discharged (Note 3) and then the cold bath is removed. The solution is filtered into a 1-L, round-bottomed flask and 80 mL of benzene is added. The volume is reduced to approximately 50 mL by rotary evaporation (Note 11).

After dilution with 225 mL of dichloromethane the flask is cooled to 0°C and 16 mL of triethylamine (0.113 mol) and 21.24 mL of acetic anhydride (0.225 mol) are added via syringe (Note 12), and the solution is stirred under a nitrogen atmosphere for 15 min. The ice bath is removed and stirring is continued for 4 hr. The solution is washed with 150-mL portions of aqueous 0.1 N hydrochloric acid, aqueous 10% sodium hydroxide, and water. The organic layer is dried over anhydrous magnesium sulfate, filtered, and the solvent is removed by rotary evaporation. Short path distillation of the crude product yields methyl 6-oxohexanoate, (7.0-7.8 g, 65-72%), bp 83-86°C/1.5 mm (Note 13).

C. Cyclohexene, 6.161 g (0.075 mol), is stirred with ozone in dichloromethane and methanol, as above. The resulting solution is treated with p-toluenesulfonic acid and subsequently neutralized with sodium bicarbonate, as described in Procedure A. The solution is filtered into a 1-L, round-bottomed flask, 80 mL of benzene is added, and the volume is reduced to approximately 50 mL by rotary evaporation (Note 11). Dilution with dichloromethane, treatment with triethylamine and acetic anhydride, and workup as described in Procedure B followed by short path distillation provides methyl (6,6-dimethoxy)hexanoate, (11.2-11.8 g, 78-83%), bp 87-91°C/1.5 mm (Note 14).

2. Notes

1. Cyclohexene was purchased from Aldrich Chemical Company, Inc. and used without purification. Dichloromethane was distilled from calcium hydride. Methanol was distilled from magnesium.

2. Ozone was produced by a Welsbach Corporation Ozonator, style T-709, with the voltage set at 100 volts and oxygen pressure at 7 p.s.i. to give approximately 2% ozone concentration. The input oxygen was passed through a column of Hammond Drierite to ensure dryness.

3. The blue color indicates that cleavage of the olefin is complete. Excess ozone is removed to prevent over-oxidation.

4. Although the ozonolysis product exists in oligomeric form, the amount of acid used was calculated by assuming a theoretical yield of the corresponding monomeric aldehyde--methoxy hydroperoxide. p-Toluenesulfonic acid monohydrate, purchased from Aldrich Chemical Company, Inc., was not further purified.

5. The solution is neutralized to prevent bisacetal formation upon subsequent reduction. Dimethyl sulfide was purchased from Aldrich Chemical Company, Inc. and used without purification.

6. An aqueous workup facilitates the removal of dimethyl sulfoxide produced by the reduction of the peroxide.

7. Typically 12.4-13.0 g of crude product is obtained after solvent removal. Material of this quality is satisfactory for most subsequent reactions.

8. The distilled product is similar in purity to the crude material. A small amount of dimethyl sulfoxide and minor impurities remain. Purification of the crude product by flash chromatography (1:1 ether/hexanes) affords 6,6-dimethoxyhexanal that is pure by ^{1}H and ^{13}C NMR in 90-95% yield.

9. The following spectral properties of the product were observed: ^{1}H NMR (CDCl$_3$), δ: 9.7 (t, 1 H, J = 2.5), 4.3 (t, 1 H, J = 5.3), 3.3 (s, 6 H), 2.4 (t, 2 H, J = 7), 1.4-1.7 (m, 6 H). ^{13}C NMR (CDCl$_3$), ppm: 201.6, 103.9, 52.1, 43.2, 31.8, 23.7, 21.4 IR (film), cm^{-1}: 2700, 1720, 1100. MS, m/e (rel %): 113(95), 57(100).

10. Sodium bicarbonate serves to buffer the solution and prevent acetal formation.

11. Benzene is added to facilitate the removal of methanol. Although an aqueous wash will remove the methanol, azeotropic removal with benzene is simpler and provides a slightly higher yield.

12. Triethylamine, purchased from Aldrich Chemical Company, Inc., was distilled from calcium hydride. Acetic anhydride as supplied by Mallinckrodt, Inc. was distilled from phosphorus pentoxide.

13. The following spectral properties were observed: ^{1}H NMR (CDCl$_3$), δ: 9.7 (t, 1 H, J = 2.5), 3.6 (s, 3 H), 2.2-2.4 (m, 4 H), 1.5-1.7 (m, 4 H). ^{13}C NMR (CDCl$_3$), ppm: 201.4, 173.1, 51.0, 42.9, 33.2, 24.0, 21.1. IR (film), cm^{-1}: 2700, 1720, 1150. MS: m/e (rel. %): 159(1), 29(3), 75(100).

14. The following spectral properties were observed: ^{1}H NMR (CDCl$_3$), δ: 4.25 (t, 1 H, J = 5.5), 3.6 (s, 3 H), 3.2 (s, 6 H), 2.15 (t, 2 H, J = 8), 1.0-1.6 (m, 6 H). ^{13}C NMR (CDCl$_3$), ppm: 173.1, 103.9, 52.0,, 50.7, 33.4, 31.8, 24.3, 23.7. IR (film), cm^{-1}: 1735, 1050, MS: m/e (rel. %): 159(10), 127(30), 75(100).

3. Discussion

This procedure illustrates a recently published method for the ozonolytic cleavage of cycloalkenes to terminally differentiated products.[2] Other examples of the unsymmetrical cleavage of olefins have been reported.[3] In addition, the title compounds have been prepared by other routes. Methyl 6-oxohexanoate has been synthesized from the acid chloride of the half ester of adipic acid.[4] It has also been prepared from ε-caprolactone by methanolysis followed by oxidation.[4] Lead tetraacetate treatment of 2-hydroxy-cyclohexanone in methanol and subsequent acidification produces methyl 6,6-dimethoxyhexanoate.[5] A three step route from cyclohexanone enol acetate

(ozonolysis in methanol, reaction with dimethyl sulfide, then with trimethyl orthoformate) has been reported.[6] 6,6-Dimethoxyhexanal has been made by a multistep route.[7]

The present method utilizes commercially available cycloalkenes and proceeds under mild conditions to provide synthetically useful products. The method was shown to be general in the series of cycloalkenes investigated. Yields range from moderate (cyclopentene) to excellent (higher homologues).

The ozonolytic cleavage of cycloalkenes in the presence of methanol produces a chain with an aldehyde and a methoxy hydroperoxide group at the termini.[8] The unsymmetrical ozonolysis product is manipulated in several ways. Dehydration of the methoxy hydroperoxide group affords an ester (Procedure B). Alternatively, the aldehyde moiety is protected as an acetal. Under these conditions, the methoxy hydroperoxide is reduced[9] (Procedure A) or dehydrated (Procedure C).

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Appendix

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

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

Methyl 6-oxohexanoate: Hexanoic acid, 6-oxo-, methyl ester (9); (6654-36-0)

6,6-Dimethoxyhexanal: Hexanal, 6,6-dimethoxy- (9); (55489-11-7)

Methyl 6,6-dimethoxyhexanoate: Hexanoic acid, 6,6-dimethoxy-, methyl ester (9); (25176-55-0)

p-Toluenesulfonic acid monohydrate (8); Benzenesulfonic acid, 4-methyl- (9); (104-15-4)

Dimethyl sulfide: Methyl sulfide (8); Methan, thiobis- (9); (75-18-3)

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

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

PHENYL VINYL SULFONE AND SULFOXIDE

(Benzene, (ethenylsulfonyl)- and benzene, (ethenylsulfiny)-)

A.   PhSH $\xrightarrow[\text{2) BrCH}_2\text{CH}_2\text{Br}]{\text{1) EtONa, EtOH}}$ PhSCH$_2$CH$_2$Br

PhSCH$_2$CH$_2$Br $\xrightarrow[\text{EtOH}]{\text{EtONa}}$ PhSCH=CH$_2$

B.   PhSCH=CH$_2$ $\xrightarrow[\text{AcOH}]{\text{H}_2\text{O}_2}$ PhSO$_2$CH=CH$_2$

C.   PhSCH=CH$_2$ $\xrightarrow[\text{CH}_2\text{Cl}_2]{\text{MCPBA}}$ PhSOCH=CH$_2$
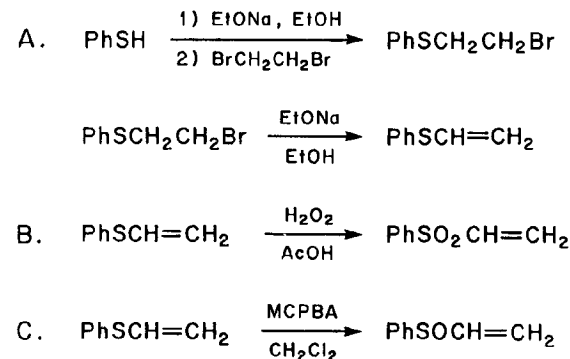
Submitted by Leo A. Paquette and Richard V. C. Carr.[1]

Checked by Wayne Schnatter and Martin F. Semmelhack.

1. Procedure

Caution! 1-Phenylthio-2-bromoethane is a powerful alkylating agent which causes severe skin blistering. Although the present one-pot procedure eliminates the cumbersome handling of this intermediate, due care must be exercised to avoid exposure to this substance.

A. Phenyl vinyl sulfide. In a 1-L, three-necked, round-bottomed flask fitted with magnetic stirrer, condenser, addition funnel, and nitrogen inlet tube is placed 400 mL of ethanol. Sodium metal (23 g, 1 g-atom), cut into small pieces, is added with stirring. When conversion to sodium ethoxide is

complete (5-15 min), the stopper of the addition funnel is removed under a positive flow of nitrogen, and benzenethiol (110 g, 1 mol) is poured into the addition funnel. The stopper is put in place, and the benzenethiol is added over 15-20 min to the cloudy, gray sodium ethoxide solution. The reaction mixture warms spontaneously and becomes clear brown. At 25°C this solution is transferred by stainless steel cannula (Note 1) over 45 min to a stirred solution of 1,2-dibromoethane (272 g, 1.45 mol) in ethanol (28 mL) contained in a 2-L, three-necked round-bottomed flask equipped with a mechanical stirrer, addition funnel, reflux condenser, nitrogen inlet tube, and internal thermometer (Note 2). The reaction temperature is maintained at 25-30°C by cooling with an ice bath. The mixture is stirred under nitrogen for 30 min and treated for an additional 30 min with ethanolic sodium ethoxide prepared from 40 g (2.17 g-atom) of sodium and 800 mL of ethanol (Note 3). The resulting mixture is stirred at the reflux for 8 hr (Note 4), cooled, and treated with 750 mL of benzene and 750 mL of water. The organic layer is separated, washed with water (2 x 50 mL) and brine (100 mL), and concentrated by rotary evaporation. The yellow oil which results is distilled to give 70-87 g (50-65%) of phenyl vinyl sulfide, bp 91-93°C/20 mm (Notes 5, 6).

B. Phenyl vinyl sulfone. In a 250-mL, three-necked, round-bottomed flask fitted with a magnetic stirrer, condenser, addition funnel, and thermometer is placed 19.7 g (0.145 mol) of phenyl vinyl sulfide dissolved in 70 mL of glacial acetic acid. Hydrogen peroxide (30%, 56 mL, 0.5 mol) is added slowly at such a rate to maintain a reaction temperature of 70°C (Note 7). The reaction mixture is heated at reflux for 20 min, cooled, and treated with ether (150 mL) and water (200 mL). The organic phase is separated, washed with water (50 mL) and brine (50 mL), and concentrated at 70°C/0.3 mm for 3 hr, to afford 18-19 g (74-78%) of phenyl vinyl sulfone as a colorless

solid, mp 64-65°C. Although this material is sufficiently pure for most purposes, recrystallization from hexane affords colorless crystals, mp 66-67°C (Note 8).

C. Phenyl vinyl sulfoxide. A 500 mL, three-necked, round-bottomed flask equipped with a dropping funnel and magnetic stirrer is charged with 20 g (0.147 mol) of phenyl vinyl sulfide and 250 mL of dichloromethane. The solution is stirred and cooled to -78°C while a solution of m-chloroperbenzoic acid (25.4 g, 1.0 equiv) in 200 mL of dichloromethane is added dropwise during a 30-min period. The mixture is stirred and warmed to room temperature for 1 hr in a water bath at 30°C. The mixture is then poured into 300 mL of saturated sodium bicarbonate solution, and the mixture is extracted with three 250-mL portions of dichloromethane. The combined organic extracts are washed with three 250-mL portions of water and dried over anhydrous magnesium sulfate. The solvent is removed by rotary evaporation and the residual liquid is distilled to afford 15-16 g (68-70%) of phenyl vinyl sulfoxide as a colorless liquid, bp 98°C/0.6 mm (Notes 9 and 10).

2. Notes

1. The cannula is a stainless steel tube, 16 gauge, sharpened to a needle at both ends, and 60 cm long. One end is placed through a rubber septum into the flask containing the 1,2-dibromoethane solution, while the other end is positioned under the surface of the benzenethiolate solution. Control of the nitrogen pressure allows slow transfer of the benzenethiolate solution.

2. The yield in the previously published method for the preparation of this sulfide is low, affording chiefly 1,2-bis(phenylthio)ethane.[2] The problem is overcome here by utilization of an inverse addition procedure.

3. Alternatively, dry, powdered sodium ethoxide may be substituted with a corresponding reduction of the reaction volume.

4. Thin layer chromatographic analysis at this stage shows that 1-phenylthio-2-bromoethane is absent.

5. This product has the following spectral properties: IR (neat) cm^{-1}: 3040, 1585, 1475, 1435, 1085, 1020, 950, 735, and 680; ^{1}H NMR (chloroform-d) δ: 5.25 (superimposed doublets, 2 H, J = 12 and 18, terminal vinyl), 6.50 (dd, 1 H, J = 12 and 18, olefinic), 7.32 (m, 5 H, aromatic).

6. When stored at room temperature, phenyl vinyl sulfide becomes yellow-colored within 1 day and a black syrup after 1 week. This decomposition can be substantially retarded by storage under a nitrogen or argon atmosphere in a freezer.

7. The submitter observed the temperature increase to 70°C during addition of the first 10 mL of hydrogen peroxide. The checkers noted that the mixture never rose in temperature to 70°C.

8. This product has the following spectral properties: IR (CHCl$_3$) cm^{-1}: 3020, 1445, 1380, 1315, 1145, 1080, and 965; ^{1}H NMR (chloroform-d) δ: 5.96 (d, 1 H, J = 10, olefinic), 6.33 (d, 1 H, J = 17, olefinic), 6.75 (dd, 1 H, J = 10 and 17, olefinic), 7.55 (m, 3 H, aromatic), 7.85 (m, 2 H, aromatic).

9. Earlier citations[3] report bp 105-110°C (1.5 mm) and 93-95°C (0.2 mm).

10. This product has the following spectral properties: IR (neat) cm^{-1}: 3025, 1720, 1680, 1480, 1440, 1045, 750, and 690; ^{1}H NMR (chloroform-d) δ: 5.63-6.17 (m, 2 H, olefinic H), 6.44-6.87 (m, 1 H, olefinic H), 7.10-7.55 (m, 5 H, aromatic H).

3. Discussion

The procedure for oxidation of the sulfide to the sulfone is based on that reported earlier by Bordwell and Pitt.[4] The synthetic utility of phenyl vinyl sulfone and sulfoxide derives not only from their ability to serve as excellent Michael acceptors toward such reagents as enolate anions and organometallics,[5-12] but also as moderately reactive dienophiles in Diels-Alder reactions.[13-16] The resulting adducts, in turn, can be chemically modified so that these electron-deficient olefins serve as useful synthons for acetylene,[13] ethylene,[14] terminal olefins,[15] vinylsilanes,[17] and ketene[18] in [4 + 2] cycloadditions. Phenyl vinyl sulfone undergoes ready cycloaddition to Danishefsky's diene in the first step of a protocol for the regiospecific γ-alkylation of 2-cyclohexenones.[19] Furthermore, the ready lithiation of phenyl vinyl sulfones[20] and sulfoxides[21] represents a convenient route to α-(phenylsulfonyl)- and α-(phenylsulfinyl)vinyllithium reagents.

The method described here for the preparation of phenyl vinyl sulfoxide is superior to that which involves reaction of ethyl phenyl sulfinate with vinylmagnesium bromide.[13]

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

Phenyl vinyl sulfone: Sulfone, phenyl vinyl (8); Benzene, (ethenylsulfonyl)- (9); (5535-48-4)

Phenyl vinyl sulfoxide: Sulfoxide, phenyl vinyl (8); Benzene, (ethenylsulfinyl)- (9); (20451-53-0)

Benzenethiol (8, 9); (108-98-5)

1,2-Dibromoethane: Ethane, 1,2-dibromo- (8, 9); (106-93-4)

Phenyl vinyl sulfide: Sulfide, phenyl vinyl (8); Benzene, (ethenylthio)- (9); (1822-73-7)

m-Chloroperbenzoic acid: Peroxybenzoic acid, m-chloro- (8); Benzenecarboperoxoic acid, 3-chloro- (9); (937-14-4)

SELECTIVE HYDROBORATION OF A 1,3,7-TRIENE: HOMOGERANIOL

(3,7-Nonadien-1-ol, 4,8-dimethyl-, (E)-)
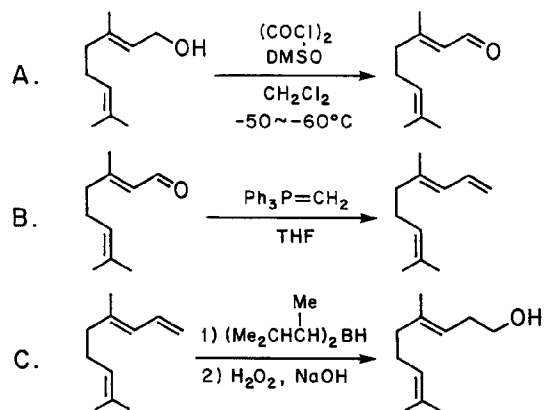
Submitted by Eric J. Leopold.[1]

Checked by Shridhar Hegde and Robert M. Coates.

1. Procedure

A. *Geranial.* A 2-L, three-necked, round-bottomed flask is dried in an oven and equipped with a mechanical stirrer, thermometer, Claisen adapter, and two pressure-equalizing dropping funnels. The flask is charged with 500 mL of dichloromethane (Note 1) and 20 mL (29.2 g, 0.23 mol) of oxalyl chloride (Note 2). The solution is stirred and cooled at -50 to -60°C as 34 mL (37.5 g, 0.48 mol) of dimethyl sulfoxide (Note 3) in 100 mL of dichloromethane is added dropwise at a rapid rate. After 5 min 30.8 g (0.2 mol) of geraniol (Note 4) is added dropwise over 10 min maintaining the temperature at -50 to -60°C.

After another 15 min, 140 mL of triethylamine is added dropwise while keeping the temperature at or below -50°C. Stirring is continued for 5 min after which the mixture is allowed to warm to room temperature and 700 mL of water is added. The aqueous layer is separated and extracted with two 300-mL portions of dichloromethane. The organic layers are combined, washed with two 100-mL portions of saturated sodium chloride, and dried over anhydrous magnesium sulfate. The filtered solution is concentrated to 500 mL by rotary evaporation and washed successively with 1% hydrochloric acid until no longer basic. The dichloromethane solution is washed with water, 5% sodium carbonate, water, and saturated sodium chloride before drying over anhydrous magnesium sulfate. Rotary evaporation of the solvent gives ca. 30 g of crude product. Distillation in a Kugelrohr apparatus (Note 5) with an oven temperature of 80-85°C (1 mm) affords 27.3-28.5 g (90-94%) of geranial, n_D^{24} 1.4870 (Note 6).

B. *(E)-4,8-Dimethyl-1,3,7-nonatriene.* A 1-L, three-necked, round-bottomed flask equipped with a pressure-equalizing dropping funnel, thermometer, magnetic stirring bar, and serum caps (Note 7) is charged with 50 g (0.12 mol) of methyltriphenylphosphonium iodide (Note 8) and 320 mL of tetrahydrofuran (Note 9) and is flushed with argon. The flask is cooled in an ice bath and the suspension is stirred under a positive pressure of argon, while about 0.2-0.6 mL of 2.05 M phenyllithium in 30:70 ether-cyclohexane (Notes 10 and 11) is added dropwise until the suspension develops a permanent yellow color (Note 12). Then 56 mL (0.115 mol) of 2.05 M phenyllithium is added dropwise over 10 min. The ice bath is removed, and the orange suspension containing excess phosphonium salt is stirred at room temperature for 30 min. The reaction mixture is stirred and cooled at 0 to 5°C, and 17.2 g (0.11 mol) of geranial in 50 mL of tetrahydrofuran is added dropwise over 10

min. The dropping funnel is rinsed with a small amount of tetrahydrofuran. The mixture is stirred at room temperature for 2 hr. The light orange mixture is hydrolyzed by adding 2 mL of methanol, and most of the solvent is removed on a rotary evaporator until a slurry results (Note 13). The slurry is diluted with 200 mL of petroleum ether (bp 60-68°C), and the supernatant solution is decanted and filtered through 150 g of Celite on a Büchner funnel. The solids remaining in the flask are heated with three 100-mL portions of hot petroleum ether and the supernatant solutions are also filtered through Celite. The filtrate is concentrated by rotary evaporation to a yellowish liquid which is filtered through 150 g of Florisil on a Büchner funnel, and the Florisil is washed with 300 mL of petroleum ether. Rotary evaporation of the eluate provides ca. 15 g of clear liquid which upon distillation in a Kugelrohr apparatus with an oven temperature of 60-70°C (2 mm) gives 13.1-13.5 g (77-80%) of the triene, n_D^{22} 1.4871 (Notes 14 and 15).

C. Homogeraniol. A 250-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, thermometer, pressure-equalizing dropping funnel, and a gas inlet tube to maintain a positive argon pressure within the apparatus (Note 7). The flask is charged with 102 mL (94.8 mmol) of 0.93 M diborane in tetrahydrofuran (Note 16), and the contents are cooled to -30°C. The diborane solution is stirred as 22.1 mL (0.21 mol) of 2-methyl-2-butene (Note 17) is added rapidly. Stirring is continued for 2 hr while maintaining the temperature at 0 to 2°C. A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, thermometer, pressure-equalizing dropping funnel, and a gas inlet tube to keep a positive pressure of argon (Note 7) is charged with 13.0 g (86.7 mmol) of (E)-4,8-dimethyl-1,3,7-nonatriene and 35 mL of tetrahydrofuran (Note 9). The contents are stirred and cooled at 0°C as the solution of disiamylborane in the first flask

is tranferred via cannula to the pressure-equalizing dropping funnel attached to the second flask. After approximtely 20 mL of disiamylborane is transferred to the dropping funnel via cannula, the dropwise addition of the disiamylborane is started while the transfer continues. The remainder of the disiamylborane solution in the first flask is kept at 0°C. Ater the 1-hr addition is completed, stirring is continued for 1 hr at 0°C and overnight at room temperature (15 hr). Excess disiamylborane is destroyed by adding 2 mL of ethanol, the mixture is cooled to 0°C, and 33 mL of 3 M sodium hydroxide is added rapidly. Stirring and cooling at -10°C are continued as 33 mL of chilled 30% hydrogen peroxide is slowly added (Note 18). The reaction mixture is stirred at room temperature for 3 hr, the layers are separated, and the aqueous layer is extracted with two 75-mL portions of ether (Note 19). The combined organic layers are washed with two 25-mL portions of saturated sodium chloride and dried over anhydrous magnesium sulfate. Evaporation of the solvent gives ca. 21 g of crude product which is purified by chromatography on 400 g of silica gel packed in a 7.5-cm by 20-cm column. The column is eluted with dichloromethane and 100-mL fractions are collected, the first two of which are discarded. Elution is continued by collecting the 100-mL fractions in a weighed flask and evaporating the solvent under reduced pressure until a constant weight of product is obtained (nine 100-mL fractions). Distillation of the residue in a Kugelrohr apparatus with an oven temperature of 150°C (0.02 mm) gives 12.6-13.2 g (88-91%) of homogeraniol, n_D^{21} 1.4740 (Note 20).

2. Notes

1. Dichloromethane was distilled from calcium hydride and stored over Linde Molecular Sieves Type 4A.

2. Oxalyl chloride was distilled immediately before use.

3. Dimethyl sulfoxide was distilled from calcium hydride and stored over Linde Molecular Sieves Type 3A.

4. Geraniol was obtained from Aldrich Chemical Company, Inc. (Gold Label) and used without purification.

5. Kugelrohr ovens are available from Rinco Instrument Co., Inc., 5035 Prairie St., P.O. Box 167, Greenville, IL 62246.

6. Thin-layer chromatographic analysis of the product by the submitter on silica gel with 20% ethyl acetate in hexane as developing solvent showed one spot, R_f 0.5. Gas chromatographic analysis showed the presence of 1.5% of the cis isomer by coinjection with 40:60 cis-trans citral mixture available from Aldrich Chemical Company, Inc. The ^{1}H NMR spectral data for the product are as follows δ: 1.61 (s, 3 H, CH$_3$), 1.69 (s, 3 H, CH$_3$), 2.17 (s, 3 H, CH$_3$), 2.19-2.23 (m, 4 H, CH$_2$CH$_2$), 5.06 (br s, 1 H, vinyl H at C-6), 5.88 (d, 1 H, J = 8, vinyl H at C-2), 9.99 (d, J = 8, CHO).

7. The glassware was dried in an oven at 150°C, assembled while still hot, and alternately evacuated and flushed with argon.

8. Methyltriphenylphosphonium iodide was prepared by the following procedure. Triphenylphosphine was recrystallized from ethanol and dried over phosphorus pentoxide under reduced pressure for 12 hr. A solution of 39 g (0.15 mol) of triphenylphosphine and 10.0 mL (22.8 g, 0.16 mol) of iodomethane in 105 mL of benzene was allowed to stir at room temperature for 12 hr. The precipitate was filtered, washed with benzene, and dried over phosphorus pentoxide under reduced pressure for 12 hr. The yield was 57 g (94%), mp 189°C (lit. [2] mp, 182°C). The reagent is also available from Aldrich Chemical Company, Inc.

9. Tetrahydrofuran was distilled from sodium-benzophenone ketyl.

10. The phenyllithium solution was purchased from Aldrich Chemical Company, Inc. The checkers used 64 mL (0.115 mol) of 1.8 M phenyllithium in 75:25 benzene-ether which was purchased from Alpha Products, Morton/Thiokol Inc.

11. The submitter states that the slight excesses of phenyllithium (5%) and methyltriphenylphosphonium iodide (10%) specified ensure complete conversion of the aldehyde and simplify the purification of the product since the excess phosphonium salt is readily removed during filtration through Florosil.

12. The addition of 0.2-0.6 mL of the phenyllithium solution presumably destroys small amounts of moisture or other impurities.

13. The submitter cautions against evaporating all of the solvent; the triphenylphosphine oxide will tenaciously occlude the product, and the yield will be reduced.

14. A gas chromatographic analysis of the product by the submitter on a 15-M capillary column coated with silicone oil SE-54 at 70°C showed one peak (98%).

15. An index of refraction of 1.4826 at 20°C is reported[3] for the product. The spectral properties of the product are as follows: IR (neat) cm^{-1}: 3080, 1645, 1600, 1345, 990, 900; ^{1}H NMR (CDCl$_3$) δ: 1.61 (3 H, CH$_3$), 1.68 (s, 3 H, CH$_3$), 1.76 (s, 3 H, CH$_3$ at C-4), 1.95-2.12 (broad, 4 H, CH$_2$CH$_2$), 4.80-5.15 (broad (3 H, vinyl H), 5.85 (d, 1 H, J = 10, vinyl H at C-3), 6.55 (3 d, J = 10, 10, 17, vinyl H at C-2).

16. The diborane solution was obtained from Aldrich Chemical Company, Inc. It was titrated[4] before use although the submitter states that this is not necessary. The solution was transferred from the stock solution to the reaction flask via a cannula. The checkers first transferred the diborane

solution via a cannula into a graduated cylinder that was capped with a rubber septum and purged with nitrogen. The specified volume was then transferred into the reaction vessel.

17. 2-Methyl-2-butene was obtained from Aldrich Chemical Company, Inc. and was distilled from calcium hydride.

18. The oxidation of organoboranes is exothermic, and efficient cooling and slow addition are necessary to keep the temperature near 0°C.[5]

19. The checkers observed the separation of a heavy, white precipitate presumed to be a borate salt during the addition of hydrogen peroxide. After the three-phase mixture had been stirred at room temperature for 3 hr, the liquid layers were decanted into a separatory funnel. The solid remaining in the flask was washed with two 75-mL portions of ether and these washings were used to extract the aqueous layer.

20. Indices of refraction of 1.4722 at 22°C and 1.4718 at 26°C are reported for homogeraniol.[6,7] The spectral properties of the product are as follows: IR (neat) cm^{-1}: 3330, 2960 (sh), 2920, 1448, 1435 (sh, m), 1374 (m), 1108 (w), 1045 (s), 875 (w); ^{1}H NMR (CDCl$_3$) δ: 1.60 (s, 3 H, CH$_3$ at C-4), 1.64 (s, 3 H, CH$_3$), 1.68 (s, 3 H, CH$_3$ at C-4), 1.95-2.15 (s, 4 H, CH$_2$CH$_2$), 2.30 (m, 2 H, CH$_2$CH$_2$OH), 3.60 (t, 2 H, J = 7, CH$_2$OH), 4.95-5.25 (m, 2 H, vinyl H).

3. Discussion

Homogeraniol is an important intermediate in syntheses of squalene,[6] aplysistatin,[8] dendrolasin,[9] and juvenile hormone analogues.[10] The present procedure affords an efficient, stereoselective method for preparing (E)-homogeraniol, contaminated by at most 1-2% of the Z isomer.

In Part A geraniol is oxidized to geranial (citral) by Swern's modification of the Moffat oxidation.[11] The stereoisomeric purity of the product is at least 98%. This procedure is readily conducted on a large-scale and requires only 4 hours' time including distillation of oxalyl chloride. The oxidation of geraniol to pure (E)-geranial may also be accomplished by Collin's oxidation with chromium trioxide-dipyridine complex,[12] or by use of activated manganese dioxide.[13] However, these methods require large amounts of reagents and solvents for 0.2-mol scale preparations.

The Wittig methylenation of geranial to (E)-4,8-dimethyl-1,3,7-nonatriene is best carried out with phenyllithium in tetrahydrofuran as described in Part B. The use of butyllithium in tetrahydrofuran or ether-hexane[3] affords the triene in only 50-60% yield. When the ylide was generated with sodium hydride or potassium tert-butoxide in dimethyl sulfoxide by the submitter, the Wittig reaction gave triene containing 10-20% of the Z isomer. Part C illustrates the selective hydroboration of a diene with disiamylborane.[14] The reaction is best carried out by adding preformed disiamylborane to the triene. Lower yields of homogeraniol were obtained by the submitter when the triene was added to the borane reagent.

Homogeraniol has been prepared by reduction of homogeranic acid with lithium aluminum hydride,[6] by cyclopropylcarbinol rearrangement to homogeranyl bromide and subsequent displacement of the bromide,[15] by zirconium-catalyzed cis addition of trimethylaluminum to an acetylene precursor followed by reaction with ethylene oxide,[7] and by hydroxymethylation of geranyl chloride with diisopropoxymethylsilylmethyl Grignard reagent.[16] Homogeranic acid has been prepared by base-catalyzed hydrolysis of the nitrile,[6,9,17] by copper-catalyzed S$_N$2-type alkylation of β-isopropenyl-β-propiolactone with dimethylallyl Grignard reagent,[18] by alkylation of methoxy(phenylthio)-

methyllithium with geranyl chloride and subsequent chromic acid oxidation,[19] and by carboxylation of geranyl phenyl sulfone followed by reductive desulfonation.[20] Although homogeranic acid prepared by nitrile hydrolysis and by β-isopropenyl-β-propiolactone alkylation[18] is a 70:30 mixture of E and Z isomers,[9,21a] the E form may be isolated by crystallization at -10°C[6] or by preparative gas chromatography of their tert-butyl esters.[21b] Homogeraniol prepared by acid-catalyzed cyclopropylcarbinyl to homoallyl rerrangement[15] is also a mixture of E and Z isomers.[22]

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Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

Homogeraniol: 3,7-Nonadien-1-ol, 4,8-dimethyl-, (E)- (9); (459-88-1)

Geranial: 2,6-Octadienal, 3,7-dimethyl- (8,9); (5392-40-5)

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

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

Geraniol: 2,6-Octadien-1-ol, 3,7-dimethyl-, (E)- (8,9); (106-24-1)

(E)- 4,8-Dimethyl-1,3,7-nonatriene: 1,3,7-Nonatriene, 4,8-dimethyl-, (E)- (8,9); (19945-61-0)

Methyltriphenylphosphonium iodide: Phosphorane, iodomethyltriphenyl- (9); (20667-19-0)

Phenyllithium: Lithium, phenyl- (8,9); (591-51-5)

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

2-Methyl-2-butene: 2-Butene, 2-methyl- (8,9); (513-35-9)

Disiamylborane: Borane, bis(1,2-dimethylpropyl)- (8,9); (1069-54-1)

STEREOCONTROLLED IODOLACTONIZATION OF ACYCLIC OLEFINIC ACIDS: THE TRANS AND CIS ISOMERS OF 4,5-DIHYDRO-5-IODOMETHYL-4-PHENYL-2(3H)-FURANONE
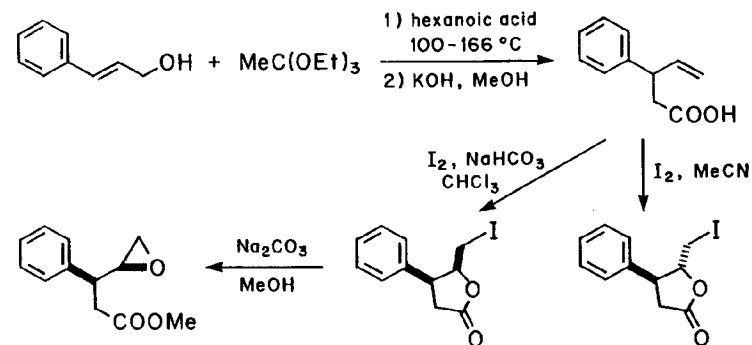
Submitted by F. Bermejo González and Paul A. Bartlett.[1]

Checked by Pauline J. Sanfilippo and Andrew S. Kende.

1. Procedure

A. 3-Phenyl-4-pentenoic acid. A mixture of 33.7 g (0.25 mol) of cinnamyl alcohol (Note 1), 46.1 mL (0.25 mol) of triethyl orthoacetate (Note 1), and 0.19 mL (1.5 mmol) of hexanoic acid (Note 2) is placed in a 250-mL, round-bottomed flask equipped with a thermometer, Claisen head, and condenser. The solution is heated in an oil bath with distillation of ethanol. After 3 hr, distillation of ethanol slows and another 0.1-mL portion of hexanoic acid is added. Additional portions (0.1 mL) of the catalyst are added again at 3.5 and 4.5 hr. After 6 hr, a total of 27 mL of ethanol, out of a theoretical 29.2 mL, has been collected, and GC analysis (Note 3)

indicates that no cinnamyl alcohol remains. Over this 6-hr period the internal temperature rises from 100°C to 166°C.

The solution is allowed to cool, and 19.7 g (0.35 mol) of potassium hydroxide in 25 mL of water and 75 mL of methanol is added. The mixture is heated under reflux for 1 hr under nitrogen. After the alkaline solution is allowed to cool to room temperature, it is washed with ether and acidified with concd HCl. The acidic solution is extracted with three 50-mL portions of ether, and the organic layer is dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The yield of crude 3-phenyl-4-pentenoic acid is 38-39 g (86-88%). This material is essentially pure by NMR analysis and can be used directly as starting material for the following iodolactonization reactions. The acid can be further purified by crystallization from hexane (86% recovery in two crops) to give product melting at 44-46°C.

B. Thermodynamically-controlled formation of the trans (4RS,5SR) isomer of 4,5-dihydro-5-iodomethyl-4-phenyl-2(3H)-furanone. In a 500-mL, round-bottomed flask equipped with a mechanical stirrer (Note 4) and immersed in an ice bath is placed a solution of 10 g (0.057 mol) of 3-phenyl-4-pentenoic acid in 200 mL of acetonitrile (Note 5). Solid iodine (44.5 g, 0.18 mol) (Note 6) is added, and the mixture is protected from light and stirred at 0°C under nitrogen for 24 hr. The mixture is partitioned between 100 mL of ether and 100 mL of saturated aq $NaHCO_3$. The organic layer is washed with 10% aq $Na_2S_2O_3$ until colorless, and with water and brine. It is then dried over $MgSO_4$, the solvent is removed at reduced pressure, and the crude trans iodolactone is obtained as a thick oil; weight 14.5-15.6 g (85-91%). NMR analysis indicates that the trans to cis ratio is at least 95:5 (Note 7).

C. Kinetically-controlled formation of the cis (4RS,5RS) isomer of 4,5-dihydro-5-iodomethyl-4-phenyl-2(3H)-furanone. A mixture of 10 g (0.057 mol)

of 3-phenyl-4-pentenoic acid, 9.1 g (0.11 mol) of $NaHCO_3$ and 200 mL of water is placed in a 1000-mL round-bottomed flask equipped with a mechanical stirrer (Note 4), and stirred until a homogeneous solution is obtained. Chloroform (200 mL) is added, the mixture is cooled in an ice bath, and 28.4 g (0.112 mol) (Note 8) of iodine is added. The mixture is stirred at 0°C for 6 hr, the layers are separated, and the organic phase is washed with 10% aq $Na_2S_2O_3$ until colorless, and with water and brine. The organic layer is dried over $MgSO_4$, the solvent is removed under reduced pressure, and the crude cis iodolactone is obtained as a semisolid: weight 15.5-16.3 g (91-95%), mp 75-90°C (Note 9). Direct recrystallization of this material from diisopropyl ether (Note 10) affords 9.0-9.5 g (52-55%) of material, mp 103-104°C, with a cis/trans ratio of 15-16:1. Further recrystallization from diisopropyl ether gives (in two crops) 8.3-8.9 g (48-52%) of product, mp 104-105°C, with a purity of >98%. Additional product can be obtained from the mother liquors.

2. Notes

1. The reagents employed were obtained from Aldrich Chemical Company and used as received.

2. Propionic acid may also be used as catalyst; however, its boiling point (141°C) is below that of the reaction temperature at the end of the reaction. The use of o-nitrophenol as catalyst resulted in a lower yield in this case.

3. GC analysis was performed on a Varian model 940 gas chromatograph equipped with a 6' x 1/8" column of 5% OV-101 on Gas-Chrom Q at a column temperature of 155°C.

4. A magnetic stirrer is not recommended because the mixture becomes very thick.

5. Mallinckrodt Inc. analytical reagent grade acetonitrile was used.

6. Two equivalents of iodine are required by the stoichiometry of the reaction, because of formation of HI_3. In our experience, however, the reaction does not proceed to completion without additional reagent.

7. The crude trans isomer obtained in this way is of suitable purity for conversion to the epoxy ester, as described below (see Discussion). It may be further purified by column chromatography; however, attempted vacuum distillation leads to considerable decomposition.

8. Two equivalents of iodine are required because of formation of NaI_3.

9. NMR analysis of the crude iodolactone indicates that the cis:trans ratio is about 3.4:1.

10. The recrystallization is performed using ca. 15 mL of diisopropyl ether per gram of crude product. Dichloromethane, 1-2%, is also added to the hot mixture to effect complete solution before cooling.

3. Discussion

Iodolactonization has become a useful reaction for the stereocontrolled introduction of chiral centers in both cyclic[2] and acyclic[3-9] systems. Depending upon the reaction conditions, the cyclization can be carried out under either kinetic or thermodynamic control.[3,10] The contrast between the stereochemical course of the two procedures is not always as dramatic as with 3-phenyl-4-pentenoic acid, as illustrated by the examples in Table I.[11]

Conversion of iodolactones into the corresponding epoxy esters is often one of the major steps in their utilization for the purposes of stereocontrol.[3-7,12] Methanolysis of the cis isomer of 4,5-dihydro-5-iodomethyl-4-phenyl-2(3H)-furanone to methyl (3RS,4RS)-4,5-epoxy-3-phenylpentanoate is a representative procedure for this transformation.

A mixture of 5.0 g (16.6 mmol) of (4RS,5RS)-4,5-dihydro-5-iodomethyl-4-phenyl-2(3H)-furanone (cis isomer), 75 mL of methanol, and 1.8 g (17.0 mmol) of finely powdered, anhydrous Na_2CO_3 is placed in a 250-mL, round-bottomed flask equipped with a mechanical stirrer, and heated under nitrogen at reflux for 8 hr. The resulting solution is concentrated under reduced pressure to a volume of 50 mL and partitioned between 100 mL of water and 100 mL of ether. The organic layer is washed with water and brine, dried over $MgSO_4$, and evaporated to give 3.1 g (91%) of crude product. This material, which shows only minor impurities by NMR spectroscopy, can be further purified by chromatography (silica gel/1:1 ether:hexane) (98% recovery) and bulb-to-bulb distillation (78°C/0.045 mm) (82% recovery).

TABLE I

IODOLACTONIZATION OF OLEFINIC ACIDS

Substrate	Trans:Cis Ratio [Yield (%)]	
	"Thermodynamic Control"	"Kinetic Control"
3-Methyl-4-pentenoic acid	10:1 (84)	1:3 (82)
4-Methyl-5-hexenoic acid	10:1 (77)	1:2.3 (83)
3-Methyl-5-hexenoic acid	1:6 (81)	1:3 (97)
2-Methyl-5-hexenoic acid	1.1:1 (68)	1.8:1 (78)
(2RS,4SR)-2,4-Dimethyl-5-hexenoic acid	20:1 (89)	3.5:1

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

trans-4,5-Dihydro-5-iodomethyl-4-phenyl-2(3H)-furanone: 2(3H)-Furanone, dihydro-5-(iodomethyl)-4-phenyl, trans- (10); (67279-69-0)

cis-4,5-Dihydro-5-iodomethyl-4-phenyl-2(3H)-furanone: 2(3H)-Furanone, dihydro-5-(iodomethyl)-4-phenyl-, cis- (10); (67279-70-3)

Cinnamyl alcohol (8); 2-Propen-1-ol, 3-phenyl- (9); (104-54-1)

Triethyl orthoacetate: Orthoacetic acid, triethyl ester (8); Ethane, 1,1,1-triethoxy- (9); (78-39-7)

Hexanoic acid (8,9); (142-62-1)

STEREOSPECIFIC REDUCTION OF PROPARGYL ALCOHOLS:

(E)-3-TRIMETHYLSILYL-2-PROPEN-1-OL

(2-Propen-1-ol, 3-(trimethylsilyl)-, (E)-)

A. $HC \equiv C-CH_2OH$ $\xrightarrow[\text{THF, 10°C}]{\text{EtMgBr}}$ $\xrightarrow[\text{5°→70°C}]{Me_3SiCl}$ $\xrightarrow[\text{45°C}]{\text{1.4 M } H_2SO_4}$

$Me_3Si-C \equiv C-CH_2OH$

B. $Me_3Si-C \equiv C-CH_2OH$ $\xrightarrow[\text{ether/toluene, 20°C}]{NaAlH_2(OCH_2CH_2OMe)_2}$
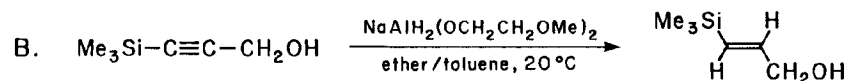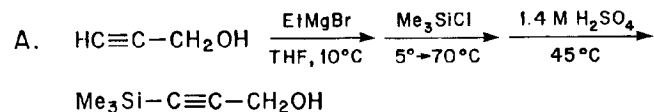
Submitted by Todd K. Jones and Scott E. Denmark.[1]
Checked by Steven M. Viti and K. Barry Sharpless.

1. Procedure

A. 3-Trimethylsilyl-2-propyn-1-ol. A 3-L, three-necked, round-bottomed flask (equipped with a mechanical stirrer and a thermometer) is fitted with a Claisen adapter on which is mounted a 250-mL pressure equalizing addition funnel and a reflux condenser (Note 1). The apparatus is flushed with nitrogen and then charged with 48.7 g (2.0 mol) of magnesium turnings and 1 L of dry tetrahydrofuran (Note 2). To the stirred suspension is added dropwise 149.5 mL (218.3 g, 2.0 mol) of bromoethane over 3 hr maintaining the temperature at 50°C or less. After complete addition, the gray-green solution is heated at 50°C for 1 hr and then cooled to 5°C on ice. A solution of 41.6 mL (40.5 g, 0.72 mol) of propargyl alcohol (Note 3) in 42 mL of tetrahydrofuran is cautiously added dropwise to the gray suspension over 2.25 hr

maintaining the temperature at 10°C or less (Note 4). The addition funnel is rinsed with 25 mL of tetrahydrofuran and the gray-green suspension is stirred overnight. The resulting solution is cooled to 5°C on ice and the addition funnel is charged with 254 mL (217 g, 2.0 mol) of chlorotrimethylsilane (Note 5). This is added dropwise to the stirred solution over 1 hr maintaining the temperature at 25°C or less by external cooling with ice. After complete addition, the mixture is heated to reflux for 2 hr with a heating mantle (Note 6). The suspension is cooled to 20°C on ice and then 800 mL of 1.4 M aqueous sulfuric acid is cautiously added over 0.75 hr so that the temperature remains below 45°C. The resulting solution is stirred for 5 min and then 600 mL of ether is added. Both phases are transferred to a 4-L separatory funnel and the layers are separated. The aqueous phase is extracted twice with 400-mL portions of ether and all ether layers are individually washed in series with two 1-L portions of water and once with 800 mL of saturated sodium chloride solution. The combined organic extracts are dried over magnesium sulfate and concentrated by rotary evaporation. The yellow-brown residue is purified by short path distillation to afford 82-86 g (91-94% yield) of 3-trimethylsilyl-2-propyn-1-ol as a clear, colorless liquid (Note 7), bp 76°C (20 mm) (Note 8).

B. (E)-3-Trimethylsilyl-2-propen-1-ol. A three-necked, 2-L, round-bottomed flask fitted with a thermometer, nitrogen inlet, 250-mL pressure-equalizing addition funnel, and a magnetic stirring bar is charged with 147 mL of a 3.4 M solution of sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH, Note 9) and 200 mL of anhydrous ether (Note 10). The SMEAH solution is cooled to 3°C on ice and then treated dropwise from the addition funnel with a solution of 40 g (0.31 mol) of 3-trimethylsilyl-2-propyn-1-ol in 180 mL of ether over 1.25 hr maintaining the temperature at 5°C or less. Ten minutes after complete addition the ice bath is removed and the reaction is complete

within 1 hr (Note 11). The mixture is cooled to 0°C and then quenched by the addition of 1 L of 3.6 M aqueous sulfuric acid (Note 12). The layers are separated in a separatory funnel and the aqueous phase is extracted twice with 200-mL portions of ether. All ether layers are individually washed in series with two 200-mL portions of water and once with 200 mL of saturated sodium chloride. The combined organic extracts are dried over magnesium sulfate and concentrated by rotary evaporation. Distillation of the yellow residue with a capillary bleed affords 27.7-29.0 g (68-71%) of (E)-3-trimethylsilyl-2-propen-1-ol (Note 13) as a clear, colorless liquid, bp 73-75°C (20 mm) (Note 14).

2. Notes

1. It is not necessary to flame or oven dry this apparatus but a nitrogen inlet on the reflux condenser is desirable. The size of the stirring paddle is critical because of the viscous nature of the solution during this protection step. A paddle at least 11 cm in length is recommended to ensure complete mixing.

2. Magnesium turnings and bromoethane are Mallinckrodt AR grade and are used without purification. Tetrahydrofuran is Aldrich Gold Label and is distilled from sodium benzophenone ketyl prior to use.

3. Propargyl alcohol is obtained from Aldrich Chemical Company, Inc., and is distilled from potassium carbonate.

4. Evolution of ethane can conveniently be monitored with a Nujol bubbler in the nitrogen line by turning off the nitrogen flow.

5. Chlorotrimethylsilane is purchased from Silar and used as received.

6. The progress of the reaction can be monitored by gas chromatography. Column: 5% Carbowax 12 M on acid-washed Chromosorb W, 6 ft x 1/8 in; temperature program: 70°C (2 min), 20°C/min, 200°C (5 min). Retention times: propargyl alcohol, 2.4 min; 3-trimethyl-2-propyn-1-ol, 4.8 min.

7. *CAUTION* - The distillation pot may ignite if it is exposed to air before it is allowed to cool. The product thus obtained is 94-98% pure by GC analysis and is of suitable purity for reduction. Further purification can be effected by distillation through a 6 in Vigreux column.

8. The product has the following spectral characteristics: ^{1}H NMR (90 MHz, $CDCl_3$) δ: 4.28 (s, 2 H, 2 H-C(1)); 1.65 (s, 1 H, OH); 0.27 (s, 9 H, $(CH_3)_3Si$).

9. Sodium bis(2-methoxyethoxy)aluminum hydride is obtained as a 70% solution in toluene from Aldrich Chemical Company, Inc. (Red-Al[R]). Iodometric titration gives a 3.6 M concentration.

10. Anhydrous ether is obtained from Mallinckrodt Inc. (AR grade) and used without purification.

11. The reaction can be monitored by gas chromatography (Note 6), temperature program: 70°C (2 min), 20°C/min, 150°C (2 min). Retention times: (E)-3-trimethylsilyl-2-propen-1-ol, 4.2 min; 3-trimethylsilyl-2-propyn-1-ol, 6.1 min.

12. A vigorous evolution of hydrogen accompanies the addition of the first milliliters of sulfuric acid. The reaction mixture becomes gelatinous and unstirrable, but clarifies upon further addition of acid.

13. The product is 100% E geometry by GC analysis.

14. The product has the following spectral characteristics: ^{1}H NMR (90 MHz, $CDCl_3$) δ: 6.23 (d of t, 1 H, J = 18 and 4, H-C(2)); 5.93 (d, 1 H, J = 18, H-C(3)); 4.22 (d of d, 2 H, J = 6 and 4, 2 H-C(1)); 1.5 (t, 1 H , J = 6, OH); 0.23 (s, 9 H, $(CH_3)_3Si$).

3. Discussion

The silylation of propargyl alcohol dianion[2a] described here is a further modification of the procedure recently reported.[2b] By replacing ether with tetrahydrofuran the reaction mixture is more manageable and the silyl ether can be hydrolyzed in situ obviating an unnecessary workup and distillation. The yield correspondingly improves up to 91-94%. Silylation of the dilithium salt in ether is reported[3] to proceed in 86% yield.

Reduction of 3-trimethylsilyl-2-propyn-1-ol exemplifies the problem of stereoselectivity in hydride reduction of acetylenic alcohols to E-allyl alcohols.[4] Early reports[5] that lithium aluminum hydride stereoselectively reduced acetylenic alcohols gave way to closer scrutiny which revealed a striking solvent dependence of the stereochemistry.[6] Specifically, the percentage of trans reduction is seen to increase with increasing Lewis basicity of solvent. Similarly, the addition of less Lewis acidic cations to the reducing mixture leads to improved trans/cis ratios.[7] Sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH)[8] makes use of these phenomena simultaneously (even in ether-toluene mixtures) and leads to completely stereospecific trans reduction where lithium aluminum hydride in various solvents or with sodium methoxide is less selective.[2b,9,10a,b] The use of SMEAH to reduce stereospecifically other acetylenic alcohols has been reported.[11]

(E)-3-Trimethylsilyl-2-propen-1-ol is a versatile intermediate used to introduce organosilicon functional groups into organic molecules.[9,12] The corresponding aldehyde has found use in the preparation of β-silyl divinyl ketones[13] and as a precursor for 1-trimethylsilyl-substituted dienes.[10]

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

(E)-3-Trimethylsilyl-2-propen-1-ol: 2-Propen-1-ol, 3-(trimethylsilyl)-, (E)- (9); (59376-64-6)

3-Trimethylsilyl-2-propyn-1-ol: 2-Propyn-1-ol, 3-(trimethylsilyl)- (9); (5272-36-3)

Bromoethane: Ethane, bromo- (8,9); (74-96-4)

Propargyl alcohol: 2-Propyn-1-ol (8,9); (107-19-7)

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

Sodium bis(2-methoxyethoxy)aluminum hydride: Aluminate (1-), dihydrobis(2-methoxyethanolato)-, sodium (8); Aluminate (1-), dihydrobis(2-methoxyethanolato-O,O')-, sodium (9); (22722-98-1)
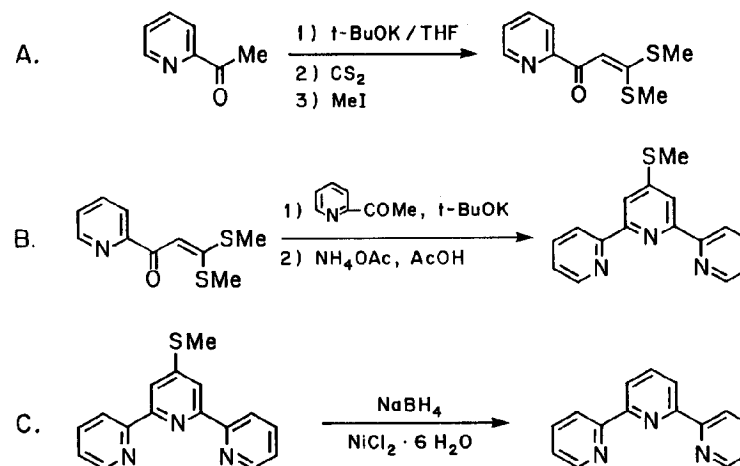
Submitted by Kevin T. Potts, Philip Ralli, George Theodoridis, and Paul Winslow.[1]

Checked by B. L. Chenard and Bruce E. Smart.

1. Procedure

A. 3,3-Bis(methylthio)-1-(2-pyridinyl)-2-propen-1-one. A 3-L, three-necked flask is equipped with an efficient mechanical stirrer, pressure equalizing dropping funnel with needle valve, and a reflux condenser fitted with a nitrogen gas inlet tube which is attached to a mineral oil bubbler. The system is flushed with nitrogen, and while the system is maintained under a static pressure of nitrogen, the flask is charged with 1000 mL of dry

tetrahydrofuran (Note 1) and 96.5 g (0.86 mol) of potassium tert-butoxide (Note 2). Freshly distilled 2-acetylpyridine (50.0 g, 0.41 mol) (Note 3) is then added dropwise over a period of 5-10 min (Note 4). To the resulting reaction mixture 32.7 g (0.43 mol) of carbon disulfide is added over a period of 30-35 min. After the addition is completed, 122.1 g (0.86 mol) of methyl iodide is added over 1 hr to the viscous, heterogeneous orange reaction mixture. After the tan reaction mixture is stirred for 12 hr at room temperature, it is poured into 2 L of iced water and allowed to stand for 4 hr. The solid that precipitates is collected by filtration and air dried to give 56 g (61%) of yellow crystals, mp 106-107°C. The filtrate is diluted with water to a total volume of 4 L, and chilled to afford an additional 16.5 g (18%) of product, mp 104-107°C (Note 5).

B. *4'-(Methylthio)-2,2':6',2"-terpyridine*. A 1-L, three-necked round-bottomed flask fitted with a mechanical stirrer and a gas inlet tube is flushed with nitrogen and charged with 500 mL of anhydrous tetrahydrofuran and 22.4 g (0.20 mol) of potassium tert-butoxide. Freshly distilled 2-acetyl-pyridine (12.1 g, 0.10 mol) (Note 3) is added, the solution is stirred for 10 min, and 22.5 g (0.1 mol) of 3,3-bis(methylthio)-1-(2-pyridinyl)-2-propen-1-one is then added. The mixture is stirred for 12 hr at room temperature, during which time it turns bright red and a red solid precipitates (Note 6). The mixture is next treated with 77 g (1.0 mol) of ammonium acetate and 250 mL of glacial acetic acid. A distillation head fitted with a thermometer is attached to the flask and the tetrahydrofuran is removed by distillation over a 2-hr period. The residual brown solution is chilled to 15°C, treated with 400 g of ice, and allowed to stand for 3 hr. Water (400 mL) is added, the mixture is chilled to 15°C, and the gray material that precipitates is collected by filtration, washed with iced water (3 x 200 mL), and air dried.

The crude product is taken up in 250 mL of boiling ethanol and filtered. The filtercake is rinsed with 50 mL of hot ethanol, and the hot filtrates are combined, diluted with 150 mL of water, concentrated to a volume of 400 mL, and allowed to cool to room temperature. After the mixture is thoroughly chilled in an ice bath, the precipitate is collected by filtration, washed with 50% aqueous ethanol, and dried under reduced pressure (23°C, 0.1 mm) to give 20.6-21.4 g (74-77%) of 4'-(methylthio)-2,2':6',2"-terpyridine as gray needles, mp 118-119°C (Note 7). This material is sufficiently pure for use in the following step.

C. *2,2':6',2"-Terpyridine*. A 1-L, four-necked flask equipped with a mechanical stirrer, pressure equalizing dropping funnel, thermometer, and a condenser fitted with a nitrogen gas inlet tube is flushed with nitrogen and charged with 300 mL of ethanol, 5.0 g (0.018 mol) of 4'-(methylthio)-2,2':6',2"-terpyridine, and 42.8 g (0.180 mol) of finely ground nickel chloride hexahydrate (Note 8). The resultant green heterogeneous mixture is chilled in an ice bath while the system is maintained under a static pressure of nitrogen. To this chilled (0-5°C) mixture, a solution of 20.4 g (0.54 mol) of sodium borohydride in 128 mL of 40% aqueous sodium hydroxide is added drop-wise over 4 hr (Note 9). After the addition is completed and the evolution of hydrogen subsides, the dark reaction mixture is refluxed for 12 hr. The hot mixture is then filtered through a Celite pad, and the pad is washed with hot ethanol (3 x 100 mL). The filtrates are combined and evaporated to dryness under reduced pressure to yield a gray solid residue (Note 10). This solid is suspended in 300-400 mL of water and chilled in an ice bath for 4 hr. The cold suspension is filtered and the gray solid is air-dried. The crude product is taken up in 100 mL of boiling hexane and filtered. The filtrate is

concentrated to 50 mL, chilled in an ice bath, and filtered to give 2.48-2.53 g (59-60%) of 2,2':6',2"-terpyridine as cream colored prisms, mp 84-86°C [lit.[2] mp 85-86°C] (Notes 11, 12). The mother liquor is concentrated to 10 mL to give a second crop of 0.37-0.40 g (8.8-9.5%), mp 81-84°C.

2. Notes

1. The checkers used tetrahydrofuran which was distilled from lithium aluminum hydride (*Caution*: see *Org. Synth.*, *Collect. Vol. V* **1973**, 976) and stored with a chip of sodium metal. Distillation from sodium/benzophenone is preferable.

2. Potassium tert-butoxide was obtained from the Aldrich Chemical Company, Inc.

3. The checkers obtained 2-acetylpyridine from the Aldrich Chemical Company, Inc. The submitters thank Reilly Tar & Chemical Corp. for a generous gift of 2-acetylpyridine used in their work.

4. A light yellow solid precipitates during this addition.

5. The product is pure by [1]NMR (CDCl$_3$) δ: 2.55 (s, 3 H), 2.65 (s, 3 H), 7.40 (d of d of d, 1 H, J = 1.5, 5.6, 7.5), 7.65 (s, 1 H), 7.85 (d of t, 1 H, J = 7.5, 2.0), 8.20 (d of t, 1 H, J = 7.5, 1.5), 8.65 (d of m, 1 H, J = 7.5); IR (KBr) cm^{-1}: 1484, 1471. Analytically pure material, mp 108-109°C, may be obtained by recrystallization from ethanol.

6. This solid is the potassium salt of the enedione intermediate:
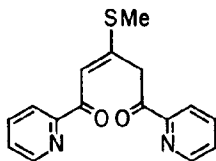
7. The checkers also obtained material with mp 116-118°C. The submitters report product of unspecified purity with mp 120-122°C. The material obtained by the checkers shows the following ^{1}H NMR (CDCl$_3$) δ: 2.0 (s, impurity), 2.67 (s, 3 H), 7.30 (d of d of d, 2 H, J = 1.8, 5.6, 8.0), 7.80 (d of t, 2 H, J = 1.8, 8.0), 8.35 (s, 2 H), 8.4-8.78 (m, 4 H). Mass spectrum m/e calculated: 279.0830. Found: 279.0815. IR (KBr) cm^{-1}: 1558, 1390. The combustion analyses for the products obtained by the checkers were within accepted limits for H, but off about 2% for C, and 0.6-0.8% for N.

8. Nickel chloride hexahydrate was obtained from the Fisher Scientific Company.

9. This reaction, which generates nickel boride,[3] is exothermic and evolves hydrogen. Frothing is prevented by keeping the reaction mixture at 0-5°C during addition of the sodium borohydride.

10. The submitters report obtaining tan material.

11. This material is analytically pure. Anal. Calcd for C$_{15}$H$_{11}$N$_3$: C, 77.23; H, 4.75; N, 18.01. Found C: 76.82; H, 4.69; N, 18.17. The product shows ^{1}H NMR (CDCl$_3$) δ: 7.33 (d of d of d, 2 H, J = 1.5, 5.0, 8.0), 7.86 (d of t, 2 H, J = 2.0, 8.0), 7.96 (t, 1 H, J = 8.0 H), 8.45 (d, 2 H, J = 8.0), 8.62 (d, 2 H, J = 8.0), 8.71 (d of m, 2 H).

12. The submitters report that 4'-(methylthio)-2,2':6',2"-terpyridine also can be conveniently reduced to 2',2":6',2"-terpyridine with Raney nickel in ethanol. The checkers found, however, that this procedure invariably gave product contaminated with 4'-ethoxy-2,2':6',2"-terpyridine. Raney nickel which was exhaustively washed with water to remove base still gave 15% of this byproduct.

3. Discussion

The procedure described here is by far the most efficient synthesis of terpyridine.[4] Previous preparations include the dehydrogenation of pyridine with ferric chloride,[2] the Ullman reaction of 2-bromopyridine and 2,6-dibromopyridine,[5] the action of copper on 2-bromopyridine and 6-bromo-2,2'-dipyridyl,[5] the reaction of iodine or ferric chloride with 2,2'-bipyridyl,[5] and the reaction of 2,2'-bipyridyl with 2-lithiopyridine (40% yield).[6]

Terpyridine is a very effective chelating agent.

1. Department of Chemistry, Rensselaer Polytechnic Institute, Troy, NY 12181.

2. Morgan, G.; Burstall, F. H. *J. Chem. Soc.* **1937**, 1649.

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6. Kauffmann, T.; König, J.; Woltermann, A. *Chem. Ber.* **1976**, *109*, 3864.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number):

(Registry Number)

Terpyridine: 2,2':6',2"-Terpyridine (8,9); (1148-79-4)

3,3-Bis(methylthio)-1-(2-pyridinyl)-2-propen-1-one: 2-Propen-1-one, 3,3-bis(methylthio)-1-(2-pyridinyl)- (9); (78570-34-0)

Potassium tert-butoxide: tert-Butyl alcohol, potassium salt (8); 2-Propanol, 2-methyl-, potassium salt (9); (865-47-4)

2-Acetylpyridine: Ethanone, 1-(pyridinyl)- (9); (30440-88-1)

Carbon disulfide (8,9); (75-15-0)

Methyl iodide: Methane, iodo- (8,9); (74-88-4)

4'-(Methylthio)-2,2':6,2"-terpyridine: 2,2':6',2"-Terpyridine, 4'-(methylthio)- (9); (78570-35-1)

Nickel chloride hexahydrate: Nickelbischofite (9); (70330-51-7)

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

(S)-(+)-2-(p-TOLUENESULFINYL)-2-CYCLOPENTENONE: PRECURSOR FOR ENANTIOSELECTIVE SYNTHESIS OF 3-SUBSTITUTED CYCLOPENTANONES

(2-Cyclopenten-1-one, 2-[(4-methylphenyl)sulfinyl]-, (S)-)

A.

B.

C.
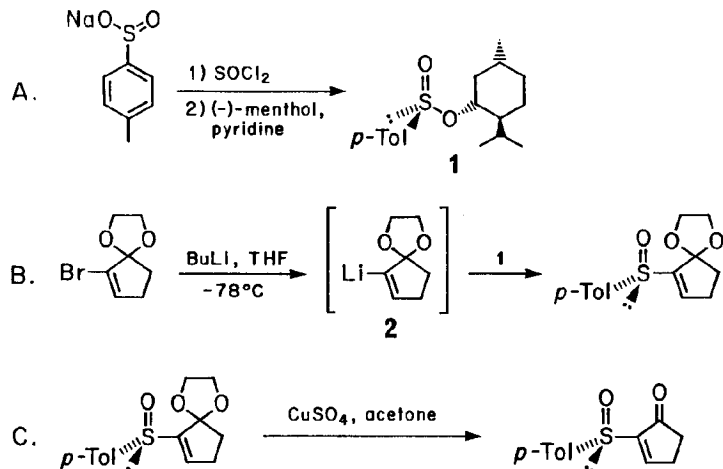
Submitted by Martin Hulce, John P. Mallamo, Leah L. Frye, Timothy P. Kogan, and Gary H. Posner.[1]

Checked by Ernest B. Clark, Michel Crevoisier, Han-Young Kang, and Robert M. Coates.

1. Procedure

Caution! Part A should be conducted in an efficient fume hood to avoid exposure to sulfur dioxide generated in the reaction.

A. *(S)-(-)-Menthyl p-toluenesulfinate.* In a dry, 250-mL, three-necked, round-bottomed flask equipped with a nitrogen inlet are placed a magnetic stirring bar and 65 g (40 mL, 0.55 mol) of thionyl chloride (Note 1). The liquid is stirred under a nitrogen atmosphere as 35.6 g (0.200 mol) of anhydrous sodium p-toluenesulfinate (Note 2) is added in portions over about 1 hr (Note 3). The solution immediately develops a yellow-green tinge as sulfur dioxide is liberated. After about three-fourths of the sulfinate has been added, 30 mL of benzene is added to facilitate stirring. The greenish slurry is stirred for another 1.5 hr, after which 75 mL of benzene is added. The mixture is transferred to a 500-mL, round-bottomed flask, along with 75 mL of benzene used to rinse the flask. Excess thionyl chloride and benzene are removed by rotary evaporation and gentle heating. Four 150-mL portions of benzene are added to the residue, and each portion is evaporated to complete the removal of the thionyl chloride. The flask is equipped with a magnetic stirring bar and a 125-mL, pressure-equalizing dropping funnel. The crude p-toluenesulfinyl chloride, sodium chloride, and residual benzene are dissolved in 150 mL of anhydrous diethyl ether. The resulting ethereal suspension is stirred and cooled in an ice bath as 31.3 g (0.200 mol) of (-)-menthol (Note 1) in 25 mL of pyridine is added over ca. 2 min. The mixture is allowed to stir overnight after which 70 g of ice is added. The layers are separated and the aqueous layer is extracted with one 100-mL portion of ether. The ethereal solutions are combined, washed three times with 50-mL portions of 20% aqueous hydrochloric acid, and dried with a mixture of anhydrous sodium sulfate and potassium carbonate. Filtration to separate the drying agents and rotary evaporation until a pressure of 3 mm is sustained leaves 57.5 g of crude menthyl p-toluenesulfinate as a clear liquid admixed with white crystals. The less soluble (S)-(-) diastereomer (1) is isolated in several crops by crystallization from 1.2 volumes of reagent-grade acetone at -20°C. After the first crop has been collected, 3 drops of concd hydrochloric acid is added to

the acetone mother liquor to effect equilibration of the sulfinate diastereomers. A total of 40.9-42.2 g of crystalline sulfinate is obtained in six crops. Recrystallization from acetone affords two crops of (S)-(-)-menthyl p-toluenesulfinate, mp 105-106°C, $[\alpha]_D^{25}$ -199.4 (acetone, c 1.5), weighing 36.9-38.2 g (63-65%) (Note 4).

B. (S)-(+)-2-(p-Toluenesulfinyl)-2-cyclopentenone ethylene ketal. A 250-mL, three-necked, round-bottomed flask equipped with two rubber septa, a nitrogen inlet, 125-mL pressure-equalizing dropping funnel, and a magnetic stirring bar is flame dried under nitrogen. After the apparatus cools to room temperature, the flask is charged with 70 mL of anhydrous tetrahydrofuran (Note 5) and cooled in an isopropyl alcohol-dry ice bath. Stirring is begun as 42 mL (60.8 mmol) of 1.45 M butyllithium in hexane (Note 6) is added slowly through the dropping funnel over 10-30 min. After another 10 min a solution of 11.3 g (55.1 mmol) of 2-bromo-2-cyclopentenone ethylene ketal (Note 7) is added from the dropping funnel over 30 min. The colorless or pale yellow solution is stirred and cooled at -78°C for 1.5 hr. A 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, two rubber septa and a stopcock connected to a bubbler gas exit is flushed with nitrogen and charged with 24.4 g (82.9 mmol) of (S)-(-)-menthyl p-toluenesulfinate and 460 mL of anhydrous tetrahydrofuran. The sulfinate suspension is stirred vigorously (Note 8) and cooled at -78°C as the vinyllithium reagent (2) in the first flask is then transferred into the second flask through a cooled cannula by means of nitrogen pressure (Note 9). As the 50-min transfer proceeds, the sulfinate suspension becomes yellow. The mixture is stirred for another 15 min at -78°C, the cooling bath is removed, and 125 mL of saturated aqueous sodium dihydrogen phosphate is added. When the contents have warmed to room temperature, the tetrahydrofuran is removed by rotary evaporation. The residue is partitioned between 300 mL of water and 200 mL of chloroform. The aqueous layer is extracted with three 100-mL portions of chloroform. The chloroform extracts are combined and dried over anhydrous potassium carbonate. Filtration of the drying agent and evaporation of the chloroform gives 40-55 g of a viscous brown oil consisting of the sulfinyl ketal, menthol, menthyl sulfinate, minor by-products, and residual chloroform. The sulfinyl ketal is isolated by modified flash chromatography on 500 g of Woelm silica gel (32-64 μ) packed in dry diethyl ether in a 6.5 cm x 45 cm column (Note 10). The crude product is applied to the column in 25 mL of chloroform and the column is eluted with ether under sufficient compressed air pressure to achieve a flow rate of 60 mL per min. After thirty 60-mL fractions are collected, the solvent is changed to ethyl acetate, and another forty 60-mL fractions are collected and analyzed by thin-layer chromatography (Note 11). Combination and evaporation of fractions 40-60 provides 9.05-9.75 g (62-67%) of crude (S)-(+)-2-(p-toluenesulfinyl)-2-cyclopentenone ethylene ketal as a pale, yellow oil, $[\alpha]_D^{25}$ +78° (CHCl$_3$, c 0.25) (Note 12).

C. (S)-(+)-2-(p-Toluenesulfinyl)-2-cyclopentenone. A magnetic stirring bar, 100 g of anhydrous copper(II) sulfate, and a solution of 9.05-9.75 g of the sulfinyl ketal in 300 mL of acetone are placed in a 500-mL Erlenmeyer flask. The flask is flushed with nitrogen and stoppered. The suspension is stirred vigorously overnight, the copper sulfate is separated by filtration, and the filter cake is washed thoroughly with 500-700 mL of acetone. Concentration of the combined filtrates by rotary evaporation gives 7.36-7.58 g of tan crystals. Recrystallization is carried out by dissolving the product in a minimum volume of ethyl acetate (ca. 80 mL) at room temperature, treating with Norite, diluting with an equal volume of diethyl ether, and cooling to -20°C. After the resulting crystals are collected, the mother liquor is

evaporated under reduced pressure at room temperature, and the procedure is repeated twice. The mother liquor is again evaporated and the residue (1.4-1.8 g) is purified by flash chromatography on 110 g of Woelm silica gel using ethyl acetate as eluant (Note 13). Combination of appropriate fractions, evaporation, and recrystallization affords two additional crops of crystalline product (0.4-0.7 g). The yield of (S)-(+)-2-(p-toluenesulfinyl)-2-cyclopentenone, mp 125-126°C, $[\alpha]_D^{25}$ +148° (CHCl$_3$, c 0.11), is 6.02-6.60 g (50-54% based on bromo ketal) (Notes 14 and 15).

2. Notes

1. This reagent was purchased from Aldrich Chemical Company, Inc.

2. Sodium p-toluenesulfinate hydrate purchased from Aldrich Chemical Company, Inc., was dried overnight in a vacuum oven at 140°C to remove the water of hydration. The weight loss amounts to 19-21%.

3. The checkers added the sodium sulfinate from a 100-mL, three-necked flask via a bent sidearm fitted to the reaction vessel. A stream of nitrogen flowing through the 100-mL flask prevented backflow of fumes from the reaction and caking of the sodium sulfinate powder.

4. Aldrich Chemical Company, Inc. is now preparing for sale the (S)-(-)- and the (R)-(+)-menthyl p-toluenesulfinates. The spectral properties of the (S)-(-) sulfinate are as follows: IR (CCl$_4$) cm^{-1}: 2958 (s), 2924 (s), 2870 (s), 1455 (m), 1135 (s), 961 (s), 919 (s), 853 (s); ^{1}H NMR (90 MHz, CDCl$_3$) δ: 0.72 (d, 3 H, J = 6, CHCH$_3$), 0.94 and 0.86 (2 d, 6 H, J = 7, CH(CH$_3$)$_2$), 2.37 (s, 3 H, ArCH$_3$), 4.08 (t of d, 1 H, J = 5, 10, CHOSO$_2$), 7.26 and 7.56 (2 d, 4 H, J = 8, ArH).

5. Tetrahydrofuran was dried by distillation from sodium-benzophenone ketyl before use.

6. Butyllithium in hexane is available from Aldrich Chemical Company, Inc. and Alfa Products, Morton/Thiokol Inc. The reagent was titrated with anhydrous diphenylacetic acid as described in the literature.[2]

7. 2-Bromo-2-cyclopentenone ethylene ketal was prepared according to a published procedure.[3] The compound is quite unstable and should be purified by distillation before use to remove impurities. The submitters stored the bromo ketal at -20°C over 3 Å molecular sieves and redistilled a portion in a Kugelrohr apparatus with an oven temperature of 38°C (0.1 mm) immediately before use. The checkers found it necessary to distill the bromo ketal a second time to increase its purity. The compound was stored at -20°C and used in Part B the next day.

8. The submitters caution that rapid stirring is essential to avoid local heating from the exothermic reaction, and as a consequence, diminished yields.

9. The checkers used a 61-cm, 16-gauge cannula with a single loop ca. 6 cm in diameter immersed in an isopropyl alcohol-dry ice bath. The submitters report that lower yields were obtained when the vinyllithium reagent was allowed to warm above -78°C briefly during the transfer.

10. The submitters purified the product by medium pressure liquid chromatography on a 60-cm x 5-cm column packed with 230-400 mesh silica gel 60 purchased from E. Merck. Ethyl acetate was used as eluant at a flow rate of 4.0 mL per min. Fractions (20 mL) were collected and analyzed by thin layer chromatography.

11. Thin layer chromatograms were obtained with silica gel as absorbent and ethyl acetate as developing solvent. The order of elution and R_f values of the major components are as follows: menthyl sulfinate (0.65), menthol (0.59), sulfinyl ketal (0.30).

12. The ^{1}H NMR spectral characteristics of the ketal are as follows (CDCl$_3$) δ: 2.0-2.2 (m, 2 H, CH$_2$), 2.3-2.6 (m, 2 H, C=CCH$_2$), 2.37 (s, 3 H, CH$_3$), 3.7-3.9 (m, 4 H, OCH$_2$CH$_2$O), 6.67 (t, 1 H, J = 2, C=CH), 7.24 and 7.57 (2 d, 4 H, J = 8, aryl H).

13. Flash chromatography was carried out according to a procedure in the literature.[4]

14. The spectral properties of the sulfinyl enone are as follows: IR (CCl$_4$) cm^{-1}: 2924 (m), 1715 (s), 1287 (m), 1152 (s), 1083 (s), 1054 (s), 728 (m); ^{1}H NMR (CDCl$_3$) δ: 2.2-2.5 (m, 2 H, CH$_2$), 2.30 (s, 3 H, CH$_3$), 2.6-2.8 (m, 2 H, C=CCH$_2$), 7.19 and 7.58 (2 d, 4 H, J = 8, aryl H), 8.03 (t, 1 H, J = 2, C=CH); mass spectrum (70 eV), m/z (rel intensity): 220 (M$^+$, 30), 172 (100), 139 (48), 129 (72). The product was analyzed by the submitters: Anal. Calcd. for C$_{12}$H$_{12}$SO$_2$: C, 65.43; H, 5.49; S, 14.56. Found: C, 65.53; H, 5.51; S, 14.72.

15. The submitters report that the sulfinyl ketone may be stored in vials in a desiccator at 0°C for more than 1 year without evidence of decomposition. Although storage under an inert atmosphere is not necessary, the checkers found that product exposed to the atmosphere at room temperature became discolored after several weeks.
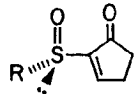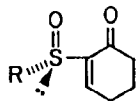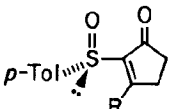
3. Discussion

Enantiomerically pure β-substituted carbonyl compounds serve as useful intermediates in the synthesis of many chiral organic compounds. The enantioselective synthesis of acyclic β-substituted carboxylic acids has been reported by Meyers,[5] Mukaiyama,[6] and Koga.[7] However, no effective, general method for the enantio-controlled preparation of β-substituted cycloalkanones was available prior to the investigations by the submitters.[8] For example, poor enantioselectivity was observed in conjugate additions of organometallic reagents to cyclic α,β-enones in the presence of optically active solvents[9] or chiral ligands.[10] In contrast, the submitters have found that conjugate addition to chiral cyclic α-sulfinyl α,β-enones occurs with high enantioselectivity.[11] Thus, the title compound is a useful intermediate for the synthesis of a variety of β-substituted cyclopentanones.

The preparation of (S)-(-)-menthyl p-toluenesulfinate described in Part A is based upon the procedure reported by Solladié.[12] 2-Bromo-2-cyclopentenone ethylene ketal is available from 2-cyclopentenone by the procedure of Smith and co-workers.[3] The present procedure has been used by the submitters to prepared analogous chiral α-sulfinyl α,β-enones (Table I).[11] The utility of these chiral synthons is enhanced by their stability, the facility of their conjugate addition reactions, and the capability of producing either enantiomeric β-substituted adduct by varying the reaction conditions.[13] Similar methodology has allowed conversion of some enantiomerically pure butenolide sulfoxides into the corresponding β-substituted butyrolactones.[14]

Both (S)-(-)- and (R)-(+)-menthyl 4-toluenesulfinates are now available from the Aldrich Chemical Company, Inc.

TABLE I

ENANTIOMERICALLY PURE α-SULFINYL-α,β-ENONES PREPARED FROM

ETHYLENE KETALS OF α-BROMO-α,β-ENONES

Sulfinyl enone	R	Yield (%)	mp (°C)	$[\alpha]_D^{25}$
	p-MeC$_6$H$_4$	50-54	125-126	+142°
	1-naphthyl	65	96.5-97.0	+292°
	p-MeOC$_6$H$_4$	76	120.5-121.5	+141°
	p-MeC$_6$H$_4$	66	101-102	+210°
	Me	38	90.5-91.0	+21.0°
	p-MeC$_6$H$_4$	35	132-133	-322°

1. Department of Chemistry, The John Hopkins University, Baltimore, MD 21218. Financial support from the National Science Foundation (CHE 79-15161) is gratefully acknowledged.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

(S)-(+)-2-(p-Toluenesulfinyl)-2-cyclopentenone: 2-Cyclopenten-1-one, 2-[(4-methylphenyl)sulfinyl]-, (S)- (9); (79681-26-8)

(S)-(-)-Menthyl p-toluenesulfinate: Menthol, (-)-, (S)-p-toluenesulfinate, (-)- (8); Benzenesulfinic acid, 4-methyl-, 5-methyl-2-(1-methylethyl)-cyclohexyl ester, [1R-[1α(S*), 2β, 5α]]- (9); (1517-82-4)

Thionyl chloride (8,9); (7719-09-7)

Sodium p-toluenesulfinate: p-Toluenesulfinic acid, sodium salt (8); Benzenesulfinic acid, 4-methyl-, sodium salt (9); (824-79-3)

(-)-Menthol: Menthol, (-)- (8); Cyclohexanol, 5-methyl-2-(1-methylethyl)-, [1R-(1α, 2β, 5α)]- (9); (2216-51-5)

(S)-(+)-2-(p-Toluenesulfinyl)-2-cyclopentenone ethylene ketal: 1,4-Dioxaspiro[4.4]non-6-ene, 6-[(4-methylphenyl)sulfinyl]-, (S)- (10); (82136-15-0)

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

2-Bromo-2-cyclopentenone ethylene ketal: 1,4-Dioxaspiro[4.4]non-6-ene, 6-bromo- (9); (68241-78-1)

Copper(II) sulfate: Sulfuric acid copper(2+) salt (1:1) (9); (7758-98-7)

A. $PhCHO + NH_2NHTs \longrightarrow PhCHNNHTs$

B. $PhCHNNHTs + MeONa \longrightarrow PhCHN\overset{\ominus}{N}Ts\ Na^{\oplus}$

$PhCHN\overset{\ominus}{N}Ts\ Na^{\oplus} \xrightarrow[vacuum]{heat} PhCHN_2 + TsNa$
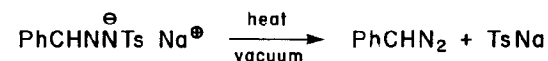
Submitted by Xavier Creary.[1]

Checked by Weyton W. Tam, Kim F. Albizati and Robert V. Stevens.

1. Procedure

Caution! Diazo compounds are presumed to be highly toxic and potentially explosive. All manipulations should be carried out in a hood. Although in numerous preparations we have never observed an explosion, all pyrolyses and distillations should routinely be carried out behind a safety shield.

A.   Benzaldehyde tosylhydrazone.   A 14.6-g sample (0.078 mol) of p-toluenesulfonylhydrazide (Note 1) was placed in a 125-mL Erlenmeyer flask and 25 mL of absolute methanol was added. The slurry was swirled as 7.50 g (0.071 mol) of freshly distilled benzaldehyde was added rapidly. A mildly exothermic reaction ensued and the p-toluenesulfonylhydrazide dissolved. Within a few minutes, the tosylhydrazone began to crystallize. After 15 min the mixture was cooled in an ice bath. The product was collected on a Büchner funnel,

washed with a small amount of cold methanol, and dried under an aspirator vacuum. The dry benzaldehyde tosylhydrazone, mp 124-125°C, weighed 16.97-18.19 g (87-93%) and was not further purified.

B. *Phenyldiazomethane (Vacuum pyrolysis method).* In a 200-mL, single-necked, round-bottomed flask is placed 13.71 g (0.05 mol) of benzaldehyde tosylhydrazone. A 1.0 M solution (51 mL) of sodium methoxide in methanol (0.051 mol) (Note 2) is added via syringe and the mixture is swirled until dissolution is complete (Note 3). The methanol is then removed by rotary evaporator. The last traces of methanol are removed by evacuation of the flask at 0.1 mm for 2 hr. The solid tosylhydrazone salt is broken up with a spatula and the flask is fitted with a vacuum take-off adaptor and a 50-mL receiver flask. The system is evacuated at 0.1 mm and the receiver flask is cooled in a dry ice-acetone bath to about -50°C. The flask containing the salt is immersed in an oil bath and the temperature is raised to 90°C (use a safety shield). At this temperature, red phenyldiazomethane first begins to collect in the receiver flask. The temperature is raised to 220°C over a 1-hr period (Note 4). During this time red phenyldiazomethane collects in the receiver flask (Note 5). The pressure increases to 0.35 mm over the course of the pyrolysis. On completion of the pyrolysis the pressure drops to less than 0.1 mm.

The apparatus is disconnected and the 50-mL receiver flask which contains the crude phenyldiazomethane is fitted with a water-cooled short-path distillation head and a receiver flask cooled to about -50°C in a dry ice-acetone bath. The pressure is lowered to 1.5 mm and a trace of methanol collects in the receiver. A new receiver flask is connected and cooled to -50°C and the pressure is lowered to less than 0.2 mm. Red phenyldiazomethane distills below room temperature (Note 6). The yield of phenyldiazomethane,

which is a liquid above -30°C, is 4.50-4.70 g (76-80%). The product should be used immediately or stored at a low temperature (-20 to -80°C) under nitrogen or argon (Notes 7-11); it is explosive at room temperature.

2. Notes

1. p-Toluenesulfonylhydrazide was obtained from Aldrich Chemical Company, Inc. and used without further purification.

2. The sodium methoxide solution was prepared by dissolving 2.30 g of sodium in absolute methanol and diluting it to 100 mL. If commercial sodium methoxide powder is used, it must be of high quality; otherwise the yield of phenyldiazomethane is lower.

3. Powdered sodium hydroxide can be used in place of sodium methoxide with no appreciable change in yield. Sodium hydroxide dissolves less readily in methanol.

4. When carried out on a small scale, pyrolysis is complete at lower temperatures (160°-200°C)

5. Phenyldiazomethane solidifies at dry ice-temperature. Care must be taken not to plug the vacuum take-off adapter; this occurs if the temperature of the receiver flask is too low. The receiver bath was maintained manually at about -50°C by addition of small pieces of dry ice to an acetone bath. We prefer to use this procedure rather than a chloroform-dry ice bath which freezes at -63°C, because of the toxic nature of chloroform and the disposal problems associated with this solvent.

6. Slight warming with an oil bath at 30°C allows distillation to proceed at a reasonable rate. The bath should not be heated above this temperature. Gutsche and Jason[2] report a boiling point of 37-41°C at 1.5

mm. Although in numerous distillations we have never experienced any difficulty, Gutsche and Jason[2] report that phenyldiazomethane "sometimes detonated violently during purification..." by distillation. Therefore we emphatically recommend that distillation be carried out below room temperature, behind a safety shield. On completion of the distillation, only a small amount of non-volatile residue remained.

7. The checkers reported that a sample that was allowed to stand at room temperature for approximately 1 hr and then exposed to air decomposed violently after 5 min. In numerous preparations, when distilled phenyldiazomethane was immediately stored at -20°C or at -80°C under nitrogen, we never experienced any difficulty. We emphasize the need to keep phenyldiazomethane cold, and under nitrogen.

8. In runs on smaller scales, yields ranged from 84-91%.

9. The infrared spectrum (CCl$_4$) shows an intense band at 4.83 μ (2060 cm^{-1}); ^{1}H NMR (CCl$_4$) δ: 4.79 (s, 1 H), 6.7-7.6 (m, 5 H).

10. Phenyldiazomethane shows no appreciable change on storage at -80°C for 3 months. Storage at -20°C led to significant decomposition after 2 weeks.

11. Traces of diazo compounds should be destroyed by addition to acetic acid.

3. Discussion
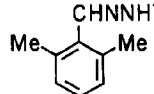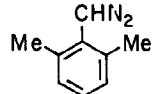
Diazo compounds have previously been prepared by a variety of methods. Some of these methods include hydrazone oxidations,[3] the reaction of diazomethane with acid chlorides,[4] the reaction of activated methylene compounds with tosyl azide,[5] decomposition of N-nitroso compounds,[6] diazotization of amines,[7] and pyrolysis of tosylhydrazone salts.[8-13] The present procedure for the preparation of phenyldiazomethane illustrates the vacuum pyrolysis method introduced by Shechter[12] for carrying out the Bamford-Stevens reaction.[9]

Phenyldiazomethane has been prepared by reaction of base with ethyl N-nitroso-N-benzylcarbamate,[13] N-nitroso-N-benzylurea[14] and N-nitroso-N-benzyl-N'-nitroguanidine.[15] Staudinger's preparation[16] and that of Gutsche and Jason[2] employed mercuric oxide oxidation of benzaldehyde hydrazone. Yates and Shapiro[17] prepared phenyldiazomethane by basic cleavage of azibenzil. Bamford and Stevens[9] prepared phenyldiazomethane by solution pyrolysis of the salt of benzaldehyde tosylhydrazone. Closs and Moss[10] and Farnum[11] used variations of this solution pyrolysis method for the preparation of phenyldiazomethane. The vacuum pyrolysis method employed by Shechter[12] has also been used to prepare phenyldiazomethane.

The present procedure uses sodium methoxide in methanol for generation of the tosylhydrazone salt. This procedure gives the highest reported yield and, unlike other procedures, also gives pure diazo compounds free from solvents. This vacuum pyrolysis method appears applicable to the formation of relatively volatile aryldiazomethanes from aromatic aldehydes. Table I gives yields of diazo compounds produced by this vacuum pyrolysis method. The yields have not been optimized. The relatively volatile diazo esters, ethyl α-diazopropionate[18] and ethyl α-diazobutyrate can also be prepared by this method.

TABLE I

FORMATION OF DIAZO-COMPOUNDS BY VACUUM PYROLYSIS OF SODIUM SALTS OF TOSYLHYDRAZONES
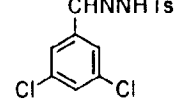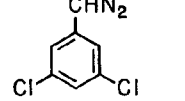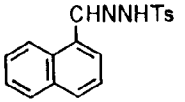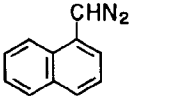
Tosylhydrazone	Product	Yield (%)
p-MeC$_6$H$_4$CHNNHTs	p-MeC$_6$H$_4$CHN$_2$	52
m-MeC$_6$H$_4$CHNNHTs	m-MeC$_6$H$_4$CHN$_2$	55
2,6-Me$_2$C$_6$H$_3$CHNNHTs (Me, Me on ring, CHNNHTs)	2,6-Me$_2$C$_6$H$_3$CHN$_2$ (Me, Me on ring, CHN$_2$)	69
p-FC$_6$H$_4$CHNNHTs	p-FC$_6$H$_4$CHN$_2$	59
m-FC$_6$H$_4$CHNNHTs	m-FC$_6$H$_4$CHN$_2$	84
Me-C(=NNHTs)-COOEt	Me-C(=N$_2$)-COOEt	87
Et-C(=NNHTs)-COOEt	Et-C(=N$_2$)-COOEt	65

The major limitation of the vacuum pyrolysis method appears to be thermal decomposition of less volatile diazo compounds during the pyrolysis. The vacuum pyrolysis method was unsuccessful for the preparation of 1-naphthyl diazomethane and 3,5-dichlorophenyldiazomethane. However, such diazo compounds could be prepared from the corresponding tosylhydrazone salts by pyrolysis in ethylene glycol and extraction of the aryldiazomethane into hexane or ether. This procedure, as described by Goh,[19] permits the periodic extraction of the potentially labile diazo compound into an organic solvent while leaving the unreacted tosylhydrazone salt dissolved in the immiscible ethylene glycol phase. This solution pyrolysis method can also be used to prepare aryl diazo esters in high yields. This method is quite useful since the starting keto esters can be readily prepared in large quantities by reaction of the corresponding arylmagnesium bromides with diethyl oxalate.[20]

In a typical procedure, 0.14 g of sodium was dissolved in 10 mL of ethylene glycol by heating to 70°C and 0.0041 mol of tosylhydrazone was added. After heating with vigorous stirring for 5 min at 70-80°C, the mixture was cooled to about 35°C and 15 mL of hexane or ether was added with continued stirring. The organic extract was removed by pipet and the procedure was repeated a total of 5 times. The combined organic extracts were washed with 30 mL of 5% sodium hydroxide solution, with a saturated sodium chloride solution, and dried over magnesium sulfate. After filtration, the solvent was removed on a rotary evaporator to leave the diazo compound. Table II gives yields of diazo compounds prepared by this solution pyrolysis method.

TABLE II

FORMATION OF DIAZO COMPOUNDS BY PYROLYSIS OF SODIUM SALTS OF

TOSYLHYDRAZONES IN ETHYLENE GLYCOL

Tosylhydrazone	Temperature (°C)	Product	Yield (%)
p-BrC$_6$H$_4$CHNNHTs	70[a]	p-BrC$_6$H$_4$CHN$_2$	80
p-ClC$_6$H$_4$CHNNHTs	80[a]	p-ClC$_6$H$_4$CHN$_2$	71
m-CF$_3$C$_6$H$_4$CHNNHTs	80[a]	m-CF$_3$C$_6$H$_4$CHN$_2$	79[c]
p-CF$_3$C$_6$H$_4$CHNNHTs	80[a]	p-CF$_3$C$_6$H$_4$CHN$_2$	88[c]
m-NCC$_6$H$_4$CHNNHTs	80[b]	m-NCC$_6$H$_4$CHN$_2$	45
p-NCC$_6$H$_4$CHNNHTs	80[b]	p-NCC$_6$H$_4$CHN$_2$	63
m-NO$_2$C$_6$H$_4$CHNNHTs	65[b]	m-NO$_2$C$_6$H$_4$CHN$_2$	56
CHNNHTs (3,5-dichlorophenyl)	80[a]	CHN$_2$ (3,5-dichlorophenyl)	90
CHNNHTs (naphthyl)	80[a]	CHN$_2$ (naphthyl)	77
Ph-C(=NNHTs)-COOEt	70[b]	Ph-C(=N$_2$)-COOEt	86
p-MeC$_6$H$_4$-C(=NNHTs)-COOEt	70[b]	p-MeC$_6$H$_4$-C(=N$_2$)-COOEt	88
p-MeOC$_6$H$_4$-C(=NNHTs)-COOEt	70[b]	p-MeOC$_6$H$_4$-C(=N$_2$)-COOEt	76
m-CF$_3$C$_6$H$_4$-C(=NNHTs)-COOEt	70[b]	m-CF$_3$C$_6$H$_4$-C(=N$_2$)-COOEt	94

[a]The salt in ethylene glycol was heated at this temperature, cooled, and extracted periodically with hexane.
[b]Ether extraction.
[c]This product was further purified by distillation at less than 0.1 mm. The other products were not distilled.

1. Department of Chemistry, University of Notre Dame, Notre Dame, IN 46556.

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19. Goh, S. H. *J. Chem. Soc. C* **1971**, 2275-2278.

20. Unpublished work from this laboratory. See also Nimitz, J. S.; Mosher, H. S. *J. Org. Chem.* **1981**, *46*, 211-213 for a synthesis of keto esters.

Appendix

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

Phenyldiazomethane: Toluene, α-diazo- (8); Benzene, diazomethyl- (9); (766-91-6)

Benzaldehyde tosylhydrazone: p-Toluenesulfonic acid benzylidenehydrazide (8); Benzenesulfonic acid, 4-methyl-, (phenylmethylene) hydrazide (9); (1666-17-7)

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

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

TRIFLUOROACETYL TRIFLATE

(Acetic acid, trifluoro-, anhydride with trifluoromethanesulfonic acid)

$$CF_3COOH + CF_3SO_3H \xrightarrow{P_2O_5} CF_3COOSO_2CF_3$$
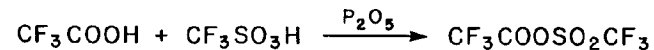
Submitted by Stephen L. Taylor, T. R. Forbus, Jr., and J. C. Martin.[1]

Checked by Thomas W. Panunto and Edwin Vedejs.

1. Procedure

Caution! The volatile product reacts rapidly with water to give corrosive strong acids. It also reacts rapidly with other nucleophiles. Care should therefore be exercised to avoid inhalation of its vapors. It should be handled in a well-vented fume hood.

To a 1-L flask containing 160 g (1.13 mol) of powdered phosphorus oxide (P_2O_5), thoroughly mixed with an equal volume of dried fine sand, is added a mixture of 85.5 g (0.75 mol) of trifluoroacetic acid (TFA) (Note 1) and 56.5 g (0.750 mol) of triflic acid (TfOH) at -20°C (Note 2). The stoppered flask (Note 3) is vigorously shaken for 5 min and then fitted for simple distillation, with the receiving flask cooled to -78°C, and allowed to stand at room temperature under a dry nitrogen atmosphere for 2.5 hr. The liquid is removed from the solid mixture by simple distillation at a bath temperature of 240°C (Note 4) for 3.5 hr (Note 5). The distillate is then carefully fractionally distilled (Note 6) from 5 g of powdered P_2O_5 (Note 7) with the receiving flasks cooled to -78°C. The colorless liquid collected at 62.5-63°C (760 mm)

(Note 8), 69 g (75%) of trifluoroacetyl triflate (TFAT), is of 99% purity (Note 9), as determined by fluorine magnetic resonance (Note 10).

2. Notes

1. The 99% TFA obtained from Aldrich Chemical Company, Inc., was used without further purification.

2. Triflic acid (TfOH) obtained from Minnesota Mining & Manufacturing Company, (3M), in kilogram quantities was used without further purification.

3. Ground glass joints were connected using Teflon sleeves or a chlorofluorocarbon stopcock grease.

4. High temperatures are needed to distill the products from P_2O_5. The use of temperatures higher than 250°C, however, causes the round-bottom flask to break when the temperature is lowered to near room temperature. Upon completion of the reaction, the P_2O_5 sand mixture can be removed from the flask by careful, slow addition of water. The checkers used an equilibrated bath of sand in a large heating mantle; the flask always broke after distillation.

5. The nitrogen outlet from the distillation apparatus should be well vented.

6. An 8-mm x 1-m jacketed column packed with a coiled tantalum wire was used by the submitters. The checkers used a Vigreux column of similar size.

7. Since the distillate contains 1-3% of the starting acids, P_2O_5 is added to prevent the reaction of TFA and TFAT, which gives trifluoroacetic anhydride (TFAA) and TfOH.

8. The first fraction is TFAA, bp 38.5-41°C (760 mm).

9. The impurity is TFAA.

10. The reactants and products show only singlets in their fluorine magnetic resonance spectra with the following chemical shifts (downfield from fluorotrichloromethane internal standard) δ: TFA, -76.3; TfOH, -77.3; TFAT, -73.3 and -74.8; TFAA, -75.9; triflic anhydride, -72.6 ppm.

3. Discussion

Trifluoroacetyl triflate is probably the most powerful trifluoro-acetylating agent known, as evidenced by its reactivity toward several types of nucleophiles under mild conditions. A sterically hindered base, 2,6-di-tert-butyl-4-methylpyridine,[2] may be used to scavenge the triflic acid produced in the reactions, since it does not react with TFAT under these conditions.

Trifluoroacetylation occurs at carbon in activated arenes such as anthracene[3] under milder conditions using TFAT than when using TFAA. Trifluoroacetate esters are formed from alcohols and phenols,[4] while ketones are acylated at oxygen to yield enol trifluoroacetates.[3] Amines[4] give the corresponding amides upon reaction with one equivalent of TFAT or imides upon reaction with two equivalents. Some covalent halides (fluorides[5] and chlorides[3]) are acylated at halogen by TFAT to yield the very volatile trifluoroacetyl halides and ionic triflates. It was recently reported that TFAT reacts with a thioketone to give a stable cation.[6] Reaction of TFAT with the methyl ester of glutaconic acid gives 2,6-dimethoxy pyrylium triflate, the first member of a new class of pyrylium salts[4] with alkoxy groups at positions 2 and 6.

The high reactivity of TFAT limits the number of solvents that can be used for its reactions. We have found that TFAT is unreactive towards saturated hydocarbons, benzene, and common halogenated solvents. It reacts only very slowly with nitromethane, but reacts relatively rapidly with ether, tetrahydrofuran, ethyl acetate, and acetonitrile.

1. Roger Adams Laboratory, University of Illinois, Urbana, IL 61801.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Numbers)

Trifluoroacetyl triflate: Acetic acid, trifluoro-, anhydride with trifluoromethanesulfonic acid (9); (68602-57-3)

Trifluoroacetic acid: Acetic acid, trifluoro- (8,9); (76-05-1)

Triflic acid: Methanesulfonic acid, trifluoro- (8,9); (1493-13-6)

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

Trifluoroacetic anhydride: Acetic acid, trifluoro-, anhydride (8,9); (407-25-0)

Triflic anhydride: Methanesulfonic acid, trifluoro-, anhydride (8,9); (358-23-6)

TRIS(DIMETHYLAMINO)SULFONIUM DIFLUOROTRIMETHYLSILICATE

(Sulfur(1+), tris(N-methylmethanaminato)-, difluorotrimethylsilicate(1-))

$$3 \ Me_3SiNMe_2 + SF_4 \ \xrightarrow[25°C]{ether} \ (Me_2N)_3S^{\oplus} \ F_2SiMe_3^{\ominus} + 2 \ FSiMe_3$$
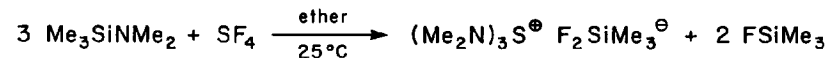
Submitted by William J. Middleton.[1]

Checked by Fred G. West and Edwin Vedejs.

1. Procedure

Caution! This procedure should be conducted in an efficient hood to avoid exposure to the toxic gas sulfur tetrafluoride.

A dry, 500-mL, four-necked flask equipped with a magnetic stirrer, dry-ice condenser, thermometer (-100° - 50°C) and a gas inlet tube is assembled as shown in Figure 1. The system is flushed with nitrogen through three-way stopcocks A and B, the four-necked flask is charged with 150 mL of dry ether (Note 1), and the dropping funnel is charged with 46.9 g (0.40 mol) of N,N-dimethylaminotrimethylsilane (Note 2). The reaction vessel is maintained under a positive nitrogen pressure using a bypass nitrogen stream and bubbler. Stopcock A is connected to the sulfur tetrafluoride (SF_4) tank (Note 3) and stopcock B is turned to vent directly into a nitrogen bypass line and bubbler. While the graduated cylinder C is cooled in acetone-dry ice, SF_4 is slowly passed into the cylinder until 7 mL (13 g at -70°C, 0.12 mol) of liquid SF_4 have condensed. Stopcock A is closed and B is vented directly into the three-necked flask. Removal of the cooling bath from graduated cylinder C allows distillation of SF_4 into the cooled reaction vessel.

A slow stream of nitrogen is passed into the reaction vessel through stopcock B and the N,N-dimethylaminotrimethylsilane is added to the stirred SF_4 solution at a rate sufficiently slow to keep the temperature below -60°C (about 30 min). The cooling bath is removed, the mixture is allowed to warm to room temperature, and the entire system is placed inside a nitrogen-flushed glove bag. The dropping funnel and condenser are replaced by stoppers, stopcock B is closed, and the closed system is stirred for 3 days with constant nitrogen flow through the glove bag (Note 4). During this time, the product separates as fine crystals. The crystals are collected in a nitrogen pressure filter, washed with 50-100 mL of dry ether, and dried by passing a stream of dry nitrogen through them to give 23-26 g (71-78% yield) of tris(dimethylamino)sulfonium difluorotrimethylsilicate as hygroscopic (Note 5), colorless needles, mp 98-101°C (Note 6).
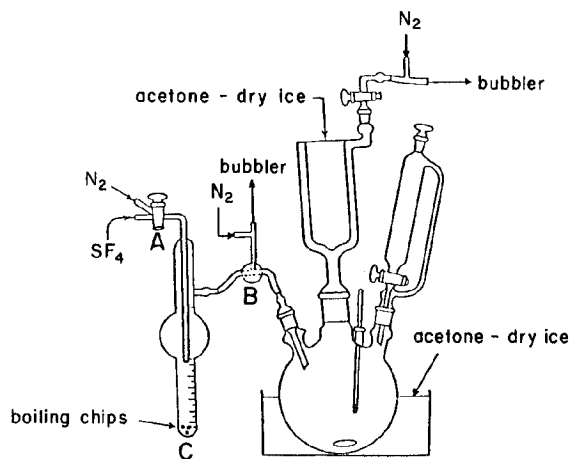
Figure 1

(Connections were all glass or polyethylene tubing.)

2. Notes

1. It is important that the ether be very dry (distilled from Na-benzophenone). Otherwise, the quality of the product and the yield will be substantially lower.

2. N,N-Dimethylaminotrimethylsilane is available from Petrarch Systems, Inc. Care should be taken to assure that there is no free dimethylamine present. Commercial samples can be purified by distillation through a 6"-Vigreux column, bp 86-87°C. The submitters used a spinning band column for removal of hexamethyldisiloxane, bp 99-100°C, which is present as a contaminant.

3. Sulfur tetrafluoride is available from Air Products and Chemicals, Inc. or Matheson Gas Products. Commercial SF_4 was used without purification.

4. The submitters obtained good yields without a glove bag, but the checkers encountered 30-40% yield reduction without this precaution. A dry box is also suitable.

5. Because tris(dimethylamino)sulfonium difluorotrimethylsilicate is very hygroscopic, it is best transferred in a dry atmosphere of nitrogen or argon (dry box or glove bag).

6. A brief exposure to moist air will appreciably lower the melting point. A melting point as low as 58-62°C can be obtained.

3. Discussion

Tris(dimethylamino)sulfonium difluorotrimethylsilicate is a source of soluble organic fluoride ion of high anionic reactivity. Fluoride ion from this salt and other tris(dialkylamino)sulfonium difluorotrimethylsilicates has

been used to displace halogen from carbon[2] and to cleave Si-O[3-7] and Si-C=O[7,8] bonds. Since these salts can be prepared in a rigorously anhydrous state, they have an advantage over quaternary ammonium fluorides which usually contain some water. Tris(dialkylamino)sulfonium difluorotrimethylsilicates have also been used to prepare other sulfonium salts with high nucleophilic reactivity, including $(R_2N)_3S^+$ enolates,[6] phenoxide,[5] cyanide, azides, and cyanates.[2]

This method has been used to prepare several different tris(dialkylamino)sulfonium difluorotrimethylsilicates, including salts with greater organic solubility such as the tris(diethylamino)sulfonium[2,3] and tris(pyrrolidine)sulfonium[2] difluorotrimethylsilicates. The tris(dimethylamino)sulfonium salt, however, is highly crystalline and thus has an advantage in ease of preparation and purification over these other salts.

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

Tris(dimethylamino)sulfonium difluorotrimethylsilicate: Sulfur(1+), tris(N-methylmethanaminato)-, difluorotrimethylsilicate (1-) (9); (59218-87-0)

N,N-Dimethylaminotrimethylsilane: Silylamine, pentamethyl- (8,9); (2083-91-2)

Sulfur tetrafluoride: Sulfur fluoride (8,9); (7783-60-0)

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