Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.
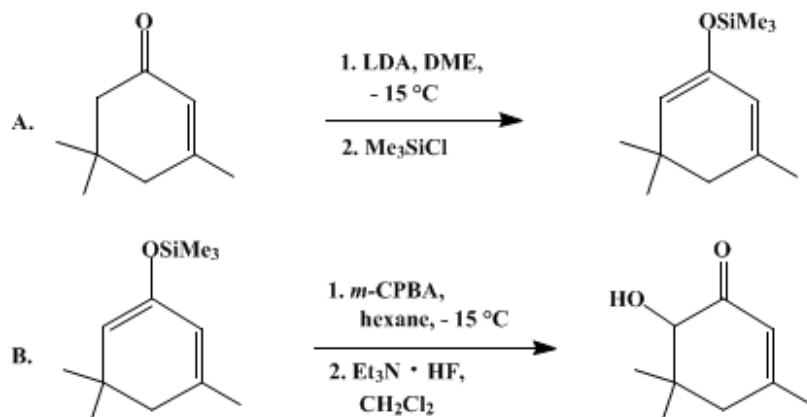
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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-]

A. 1. LDA, DME, - 15 °C 2. Me₃SiCl → OSiMe₃

B. OSiMe₃ 1. *m*-CPBA, hexane, - 15 °C 2. Et₃N · HF, CH₂Cl₂ → HO

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Checked by Judy Bolton and Ian Fleming.

1. Procedure

> *Caution! Reactions and subsequent operations involving peracids and peroxy compounds should be run behind a safety shield. Peroxy compounds should be added to the organic material, never the reverse. For relatively fast reactions, the rate of addition of the peroxy compound should be slow enough so that it reacts rapidly and no significant unreacted excess is allowed to build up. The reaction mixture should be stirred efficiently while the peroxy compound is being added, and cooling should generally be provided since many reactions of peroxy compounds are exothermic. New or unfamiliar reactions, particularly those run at elevated temperatures, should be run first on a small scale. Reaction products should never be recovered from the final reaction mixture by distillation until all residual active oxygen compounds (including unreacted peroxy compounds) have been destroyed. Decomposition of active oxygen compounds may be accomplished by the procedure described in Korach, M.; Nielsen, D. R.; Rideout, W. H. Org. Synth. 1962, 42, 50 (Org. Synth. 1973, Coll. Vol. 5, 414). [Note added January 2011].*

A. *4,6,6-Trimethyl-2-trimethylsiloxycyclohexa-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 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-trimethylsiloxycyclohexa-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-trimethylsiloxycyclohexa-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 × 100 mL), 100 mL of 1.5 *N* hydrochloric acid, and saturated aqueous sodium bicarbonate solution (2 × 50 mL). The organic layer is dried with anhydrous magnesium sulfate, and 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 petrolum 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 (TMSCI), 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; IR (neat) cm^{-1}: 3040 (vinyl CH), 1660 (C=COTMS), 1610 (C=C); ^{1}H NMR ($CDCI_3$) δ: 0.21 [s, 9 H, $Si(CH_3)_3$], 0.98 (s, 6 H, 2 CH_3), 1.75 (broad s, 2 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 C-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-in. × 6.0-ft column packed with 12.5% SE-52 at a column temperature of 130°C and gas flow rate of 90 mL/min 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 × 50 mL) and water (3 × 100 mL), drying ($CaCl_2$), and distillation. The pure hexane is stored over Linde 4A 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 pipette 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 overcoolthe distillation head which may cause crystallization of the hydroxy ketonethroughout 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: IR (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$_9$H$_{14}$O$_2$: C, 70.10; H, 9.15. Found: C, 69.81; H, 9.50. A gas chromatographic analysis using a 0.25-in. × 6.0-ft 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 scale-up of a published synthesis.[9]

4,6,6-Trimethyl-2-trimethylsiloxycyclohexa-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 nonaqueous 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] [13] and ketones[14] [15] and is extremely general in scope. The method is also viable for the synthesis of α-hydroxy acids[16] and α-hydroxy esters.[17] The method fails with the enol silyl ethers of both lactones[17]15 and aldehydes.[18]

Since the double-bond placement in enol silyl ethers is predictable and controllable,[14,15] the method allows the regiospecific introduction of α-hydroxy groups. Omission of the fluoride treatment permits isolation of α-trimethylsiloxy carbonyl compounds,[19] [20] [21] 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.[22]

References and Notes

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

petroleum ether

m-chloroperbenzoic acid (MCPBA)

petrolum ether

DME

drying (CaCl$_2$)

MoO$_5$ · Py · HMPA · (MoOPH)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic anhydride (108-24-7)

sodium bicarbonate (144-55-8)

oxygen (7782-44-7)

nitrogen (7727-37-9)

Pentane (109-66-0)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

dimethoxyethane (534-15-6)

fluoride (16984-48-8)

isophorone

diisopropylamine (108-18-9)

CHLOROTRIMETHYLSILANE (75-77-4)

6-HYDROXY- 3,5,5-TRIMETHYL-2-CYCLOHEXEN-1-ONE,
2-Cyclohexen-1-one, 6-hydroxy-3,5,5-trimethyl-,
6-Hydroxy-3,5,5-trimethyl-2-cyclohexen-1-one (61592-66-3)

4,6,6-Trimethyl-2-trimethylsiloxycyclohexa-1,3-diene (54781-28-1)

triethylammonium fluoride

lead(IV) acetate (546-67-8)

m-Chloroperbenzoic acid,
MCPBA (937-14-4)

m-chlorobenzoic acid (535-80-8)