



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.

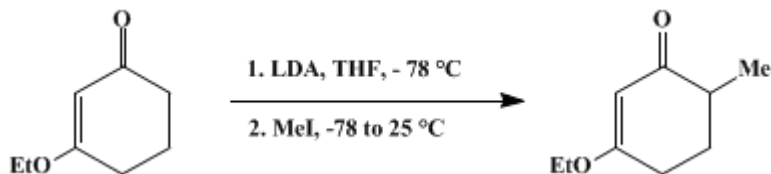
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 7, p.208 (1990); Vol. 64, p.68 (1986).

THE STORK–DANHEISER KINETIC ALKYLATION PROCEDURE: 3-ETHOXY-6-METHYL-2-CYCLOHEXEN-1-ONE

[2-Cyclohexen-1-one, 3-ethoxy-6-methyl-]



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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°C 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 and 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) (Note 7) and (Note 8).

2. Notes

- The procedure described above 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.
- Tetrahydrofuran is freshly distilled from sodium and benzophenone.
- Diisopropylamine is distilled from calcium hydride.
- The flask is cooled with the dry ice–acetone bath for 1 hr before the next addition to ensure complete cooling of the solution.
- Org. Synth., Coll. Vol. V 1973, 539.*
- Methyl iodide was obtained from Eastman Organic Chemicals and used directly from a fresh bottle.
- Spectroscopic data for 3-ethoxy-6-methyl-2-cyclohexen-1-one are as follows: ¹H NMR (CDCl₃) 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.
- 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-Danheiser² 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,^{3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24} aldol condensations,^{25,26,27} and Michael additions.^{28,29} Reductive transposition of the resulting products to 4-substituted cyclohexenones has likewise found synthetic application.^{30,31,32,33}

This preparation is referenced from:

- *Org. Syn. Coll. Vol. 7*, 241
- *Org. Syn. Coll. Vol. 8*, 235

References and Notes

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

brine

diethyl ether (60-29-7)

nitrogen (7727-37-9)

Benzophenone (119-61-9)

sodium (13966-32-0)

Methyl iodide (74-88-4)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

calcium hydride (7789-78-8)

3-ethoxy-2-cyclohexen-1-one (5323-87-5)

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

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