



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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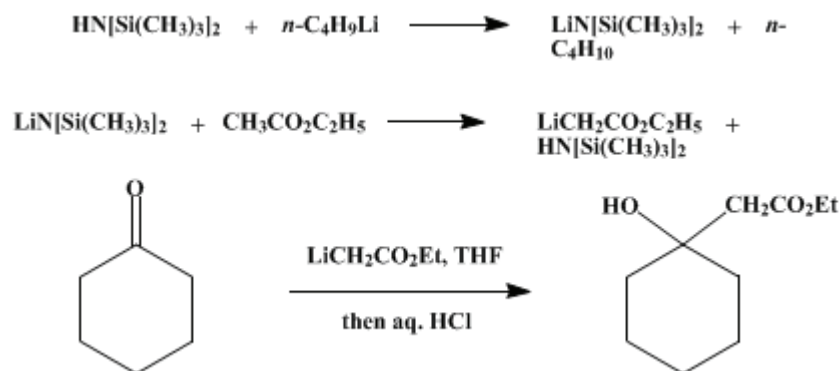
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 6, p.598 (1988); Vol. 53, p.66 (1973).

β -HYDROXY ESTERS FROM ETHYL ACETATE AND ALDEHYDES OR KETONES: ETHYL 1-HYDROXYCYCLOHEXYLACETATE

[Cyclohexaneacetic acid, 1-hydroxy, ethyl ester]



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1. Procedure

Caution! The first step of the reaction should be conducted in a well-ventilated hood since butane is liberated.

A. *Lithium bis(trimethylsilyl)amide* (Note 1). A dry, 500-ml., three-necked flask, fitted with a pressure-equalizing dropping funnel in the center neck and a stopcock in each side neck, is equipped for magnetic stirring and maintained under a static nitrogen pressure by attaching a nitrogen source to one stopcock and a mercury bubbler to the other. In the flask is placed 153 ml. of a hexane solution containing 0.250 mole of *n*-butyllithium (Note 2), and stirring is started. The flask is immersed in an ice-water bath, and 42.2 g. (0.263 mole) of hexamethyldisilazane (Note 3) is added dropwise over a period of 10 minutes. The ice-bath is removed, and the solution is stirred for 15 minutes longer. The hexane is removed under reduced pressure by replacing the mercury bubbler with heavy rubber tubing connected to a dry-ice condenser and an oil pump. During this step, the flask is immersed in a water bath at 40–50°, and stirring is continued as long as possible. After complete evaporation of the hexane, white crystals of lithium bis-(trimethylsilyl)amide appear. The flask is again subjected to a static pressure of nitrogen (Note 4), and 225 ml. of tetrahydrofuran (Note 5) is added to dissolve the crystals.

B. *Ethyl lithioacetate*. The reaction flask is immersed in an acetone–dry-ice bath, and the solution is stirred for 15 minutes to achieve thermal equilibration. After this time, 22.1 g. (0.250 mole) of ethyl acetate is added dropwise over a 10-minute period. Stirring is continued for an additional 15 minutes to complete formation of ethyl lithioacetate (Note 6).

C. *Ethyl 1-hydroxycyclohexylacetate*. A solution of 24.6 g. (0.250 mole) of cyclohexanone (Note 7) in 25 ml. of tetrahydrofuran is added dropwise to the reaction mixture over a 10-minute period. After an additional 5 minutes, the reaction mixture is hydrolyzed by adding 75 ml. of 20% hydrochloric acid in one portion (Note 8). The cooling bath is removed, and the stirred solution is allowed to reach room temperature.

The organic layer is separated, the aqueous layer is extracted with two 50-ml. portions of diethyl ether, and the combined extracts are dried over anhydrous sodium sulfate. The solvent is removed with a rotary evaporator (Note 9), and the almost-colorless residue is distilled under reduced pressure through

a 10-cm. Vigreux column, yielding 37–42 g. (79–90%) of the β -hydroxy ester as a colorless liquid, b.p. 77–80° (1 mm.); n_D^{24} 1.4555–1.4557 (Note 10).

2. Notes

1. The preparation of lithium bis(trimethylsilyl)amide is adapted from an earlier procedure.² The original procedure specifies addition of *n*-butyllithium to hexamethyldisilazane in diethyl ether followed by a reflux period. It is generally more convenient to add the hexamethyldisilazane to the *n*-butyllithium; satisfactory results are obtained without using ether or refluxing.
2. A 1.63 *M* solution of *n*-butyllithium in hexane was purchased from Foote Mineral Company.
3. Hexamethyldisilazane was obtained from Pierce Chemical Company and used without further purification.
4. Lithium bis(trimethylsilyl)amide is hydrolyzed rapidly by moist air. It is therefore essential to break the vacuum by admitting nitrogen rather than air.
5. The submitters used reagent grade tetrahydrofuran (available from Fisher Scientific Company) from a freshly opened bottle. The checkers used tetrahydrofuran purified by distillation from lithium aluminum hydride. See *Org. Synth.*, **Coll. Vol. 5**, 976 (1973) for warning regarding purification of this solvent.
6. Solutions of ethyl lithioacetate prepared by this method are stable indefinitely at –78°, but decompose rapidly if allowed to reach room temperature.
7. White label cyclohexanone (Eastman Organic Chemicals) was used without further purification.
8. The yield of the β -hydroxy ester is somewhat lower if the reaction mixture is allowed to reach room temperature prior to hydrolysis.
9. Continuing the evaporation process for some time after removal of the solvent is helpful in removing any residual hexamethyldisilazane (b.p. 125°) together with its hydrolysis product, hexamethyldisiloxane (b.p. 100°).
10. ¹H NMR (CDCl₃), δ 1.26 (t, $J = 7$ Hz., 3H, OCH₂CH₃), 1.52 (broad s, 10H, 5CH₂), 2.45 (s, 2H, CH₂CO₂), 3.33 (s, 1H, OH), 4.19 (q, $J = 7$ Hz., 2H, OCH₂CH₃).

3. Discussion

Ethyl 1-hydroxycyclohexylacetate has been prepared by the Reformatsky reaction of cyclohexanone with zinc and ethyl bromoacetate (56–71%)³ and by the condensation of ethyl acetate with cyclohexanone in liquid ammonia, using two equivalents of lithium amide (69%).⁴

This preparation illustrates a general method for the preparation of β -hydroxy esters from ethyl acetate and aldehydes or ketones.⁵ The procedure is simpler and less time-consuming than other methods and the yields are usually higher. In addition, the β -hydroxy esters are obtained in a high state of purity.

The procedure is especially suited to small-scale preparations (25 mmoles or less) where the necessity of evaporating hexane from the lithium bis(trimethylsilyl)amide is much less of a handicap. In such cases, it is convenient to equip the reaction vessel with a septum-inlet and transfer all reagents with a syringe.

References and Notes

1. Department of Chemistry, Michigan State University, East Lansing, Michigan 48823.
 2. E. H. Amonoo-Neizer, R. A. Shaw, D. O. Skovlin, and B. C. Smith, *J. Chem. Soc.*, 2997 (1965).
 3. R. L. Shriner, *Org. React.*, **1**, 17 (1942).
 4. W. R. Dunnivant and C. R. Hauser, *J. Org. Chem.*, **25**, 503 (1960).
 5. M. W. Rathke, *J. Am. Chem. Soc.*, **92**, 3222 (1970).
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Appendix

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

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

diethyl ether (60-29-7)

Cyclohexanone (108-94-1)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

zinc (7440-66-6)

Ethyl bromoacetate (105-36-2)

butane (106-97-8)

n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

lithium amide (7782-89-0)

hexane (110-54-3)

lithium bis-(trimethylsilyl)amide,
lithium bis(trimethylsilyl)amide (4039-32-1)

hexamethyldisiloxane (107-46-0)

Ethyl 1-hydroxycyclohexylacetate,
Cyclohexaneacetic acid, 1-hydroxy, ethyl ester (1127-01-1)

hexamethyldisilazane (999-97-3)

Ethyl lithioacetate