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.

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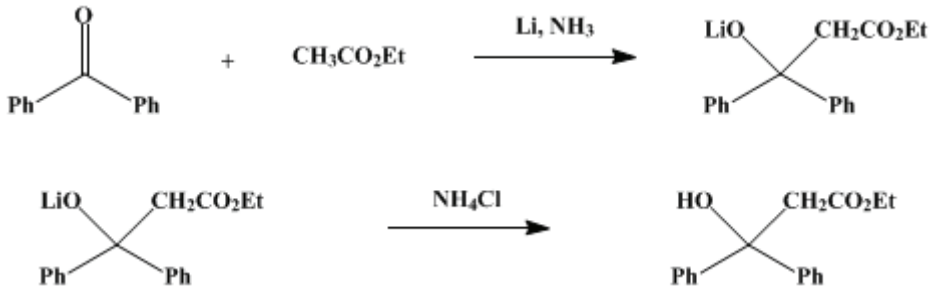
ETHYL β-HYDROXY-β,β-DIPHENYLPROPIONATE

[Hydracrylic acid, 3,3-diphenyl, ethyl ester]



Submitted by W. R. Dunnavant and Charles R. Hauser[1].
Checked by William E. Parham and J. E. Burcsu.

1. Procedure

Caution! This preparation should be carried out in a hood to avoid exposure to ammonia.

A Suspension of lithium amide (0.25 mole) (Note 1) in liquid ammonia is prepared in a 1-l. three-necked flask equipped with a condenser, a ball-sealed mechanical stirrer, and a dropping funnel. In the preparation of this reagent commercial anhydrous liquid ammonia (500 ml.) is introduced from a cylinder through an inlet tube. To the stirred ammonia is added a small piece of clean lithium metal. After the appearance of a blue color a few crystals of ferric nitrate hydrate (about 0.25 g.) are added, followed by small pieces of freshly cut lithium metal (Note 2) until 1.73 g. has been added. After all the lithium has been converted to the amide (Note 3), 17.6 g. (0.2 mole) of ethyl acetate (Note 4) is added, and the gray suspension is stirred for about 30 seconds. To the gray suspension is added 36.4 g. (0.2 mole) of benzophenone (Note 4) dissolved in 100 ml. of anhydrous ether. The mixture is stirred for 30 minutes and is then neutralized by the addition of 13.4 g. (0.25 mole) of ammonium chloride. The liquid ammonia is then removed by use of a steam bath while 200–300 ml. of ether is being added (Note 5). When the ammonia has been removed, 200 ml. of cold water is added. The ether layer is separated, and the aqueous layer is further extracted with two 100-ml. portions of ether. The combined ether extract is dried over magnesium sulfate and filtered, and the solvent is evaporated. The residue is dissolved in 50 ml. of hot 95% ethanol, treated with Norit®, filtered, and allowed to cool. The yield of ethyl β-hydroxy-β,β-diphenylpropionate, obtained as colorless, needle-like crystals melting at 85–86°, is 40.5–45.5 g. (75–84%). The filtrate, on reduction in volume and cooling, yields small amounts of benzophenone, m.p. 46–47°.

2. Notes

1. This preparation may be accomplished by using one molecular equivalent of lithium amide; special reaction procedures must be employed, however, and the yields are not reproducible.[2] The preparation may also be accomplished (with reduced yield) by using sodium amide, but only under special reaction conditions.[3]
2. The lithium wire or ribbon is cut in about 0.25-g. pieces, stored under kerosene, and blotted with filter paper before addition.
3. Conversion is indicated by the discharge of the blue color.
4. Ethyl acetate and benzophenone as supplied by the Eastman Kodak Company were used without further purification.
5. The checkers added ether and permitted the ammonia to evaporate overnight. If a steam bath is employed, care must be exercised to prevent charring of the product.

3. Discussion

This procedure is an adaptation of ones described by Dunnavant and Hauser.[2,4] Ethyl β-hydroxy-β,β-diphenylpropionate has been prepared previously using the Reformatsky reaction by condensing ethyl α-bromoacetate with benzophenone by means of zinc metal.[5]

4. Merits of the Preparation

This procedure illustrates the use of lithio esters for the preparation of β-hydroxy esters. Isopropyl and *t*-butyl β-hydroxy-β,β-diphenylpropionate may be prepared in approximately 80% yields by using isopropyl or *t*-butyl acetates in place of ethyl acetate.[2] This procedure is generally more convenient than the Reformatsky reaction for the preparation of such esters. Under similar conditions ethyl acetate may conveniently be condensed with various aldehydes or ketones to give the corresponding β-hydroxy esters.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 509

References and Notes

1. Department of Chemistry, Duke University, Durham, North Carolina. This work was supported by the Army Research Office (Durham).
2. W. R. Dunnavant and C. R. Hauser, *J. Org. Chem.*, **25**, 1693 (1960).
3. C. R. Hauser and W. R. Dunnavant, *J. Org. Chem.*, **25**, 1296 (1960).
4. W. R. Dunnavant and C. R. Hauser, *J. Org. Chem.*, **25**, 503 (1960).
5. H. Rupe and E. Busolt, *Ber.*, **40**, 4537 (1907).

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

Isopropyl and t-butyl β-hydroxy-β,β-diphenylpropionate

isopropyl or t-butyl acetates

ethanol (64-17-5)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

ether (60-29-7)

ammonium chloride (12125-02-9)

Norit (7782-42-5)

Benzophenone (119-61-9)

zinc (7440-66-6)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

ethyl α-bromoacetate (105-36-2)

sodium amide (7782-92-5)

lithium amide (7782-89-0)

ferric nitrate hydrate

Ethyl β-hydroxy-β,β-diphenylpropionate,
Hydracrylic acid, 3,3-diphenyl, ethyl ester (894-18-8)