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.

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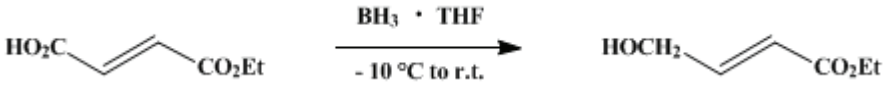
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.064.0104

Organic Syntheses, Coll. Vol. 7, p.221 (1990); Vol. 64, p.104 (1986).

ETHYL 4-HYDROXYCROTONATE

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



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. ^{1}H 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)triphenylphosphorane.[4] Both procedures require very expensive starting materials or reagents. Several multistep procedures for preparing the title compound have also been

reported.[5] [6] [7] [8] 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.[9]

Ethyl 4-hydroxycrotonate has proved to be a valuable intermediate in synthetic chemistry. It has been used in alkaloid synthesis[3] or as a dipolarophile in dipolar cycloadditions.[10] Furthermore, ethyl 4-hydroxycrotonate can be readily oxidized to ethyl 4-oxocrotonate,[4] which has also served as a valuable precursor in synthesis.[11] [12]

References and Notes

1. Department of Chemistry, University of Rochester, Rochester, NY 14627.
2. Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. "Purification of Laboratory Chemicals," 2nd ed.; Pergamon Press: New York, 1980.
3. Tufariello, J. J.; Tette, J. P. *J. Org. Chem.* **1975**, *40*, 3866. Rambaud, R. *Bull. Soc. Chim. Fr.* **1934**, 1317.
4. Witiak, D. T.; Tomita, K.; Patch, R. J. *J. Med. Chem.* **1981**, *24*, 788.
5. Ducher, S.; Journou, M. N. *Ann. Chim.* **1973**, *8*, 359;
6. Laporte, J. F.; Rambaud, R. *Bull. Soc. Chim. Fr.* **1969**, 1340;
7. McClure, J. D. *J. Org. Chem.* **1967**, *32*, 3888;
8. Kato, T.; Kimura, H. *Chem. Pharm. Bull.* **1977**, *25*, 2692.
9. Walker, E. R. H. *Chem. Soc. Rev.* **1976**, *5*, 23.
10. Padwa, A.; Ku, H. *J. Org. Chem.* **1979**, *44*, 255.
11. Naf, F.; Decorzant, R.; Thommen, W. *Helv. Chim. Acta* **1979**, *62*, 114;
12. Devos, M. J.; Hevesi, L.; Bayet, P.; Krief, A. *Tetrahedron Lett.* **1976**, 3911.

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

Ethyl (or methyl) 4-hydroxycrotonate

acetic acid (64-19-7)

ethyl acetate (141-78-6)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

Benzophenone (119-61-9)

sodium (13966-32-0)

monoethyl fumarate (2459-05-4)

magnesium sulfate (7487-88-9)

borane (7440-42-8)

Tetrahydrofuran (109-99-9)

ethyl 4-oxocrotonate (2960-66-9)

glycolaldehyde (141-46-8)

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

methyl 4-bromocrotonate (1117-71-1)

(carbomethoxymethylene)triphenylphosphorane (2605-67-6)