Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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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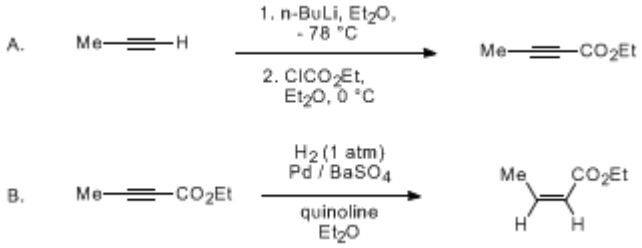
ETHYL ISOCROTONATE

[Ethyl (*Z*)-crotonate]



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Checked by Judy Bolton and Ian Fleming.

1. Procedure

A. *Ethyl tetrolate*. A 3-L, three-necked, round-bottomed flask is equipped with an overhead mechanical stirrer and charged with 1000 mL of anhydrous ether (Note 1). One neck is fitted with a gas inlet joint connected to a nitrogen line equipped with a mineral oil bubbler. The second neck is fitted with a low-temperature thermometer, and the third is closed with a rubber serum cap after nitrogen has been passed through the flask for a few minutes. The flask is then immersed in a dry ice–acetone bath. While the ether is cooling, 85 mL (60.0 g, 1.50 mol) of propyne (Note 2) is condensed into a flask (Note 3). The stopper is removed briefly, the cold (−78°C) propyne is poured into the flask through a powder funnel inserted into the neck, and stirring is commenced. The stopper is replaced, and 667 mL of a 1.5 M solution of butyllithium in hexane is introduced by syringe at such a rate that the internal temperature does not exceed −65°C (Note 4)–(Note 6). During the butyllithium addition a copious white precipitate appears. The slurry is stirred at −78°C for 30 min, and 134 mL (152 g, 1.4 mol) of ethyl chloroformate (Note 7) is added. At this point, the acetone–dry ice bath is replaced by an ice bath and the reaction mixture is stirred overnight. During this time the ice bath will melt and the reaction mixture should eventually reach room temperature. The mixture is poured onto 400 g of crushed ice, the layers are separated, and the aqueous phase is extracted with two 200-mL portions of ether. The ether solutions are combined, washed with brine and dried over anhydrous $MgSO_4$. After filtration, the ether is removed with a rotary evaporator (Note 8). The residue is distilled at aspirator pressure to obtain 107–108 g (95–97%) of ethyl tetrolate, bp 60–64°C (20 mm) [lit.[2] 105°C (90 mm)] (Note 9).

B. *Ethyl isocrotonate*. An oven-dried, 500-mL hydrogenation flask equipped with a sidearm fitted with a rubber serum cap and a magnetic stirring bar is charged with 0.4 g of 5% palladium on barium sulfate (Note 10), 0.4 g of quinoline, and 200 mL of anhydrous ether. The flask is attached to an atmospheric-pressure hydrogenation apparatus (Note 11) and flushed with hydrogen. Ethyl tetrolate (23.2 mL, 22.4 g, 0.2 mol) is introduced into the hydrogenation flask with a syringe, and stirring is commenced. The progress of the reaction may be monitored by the uptake of hydrogen (theoretical ≅ 4500 mL), by gas chromatography, or by removing aliquots that are concentrated and analyzed by ^1H NMR, monitoring the disappearance of the methyl singlet at δ 1.95; a total hydrogenation time of 10–15 hr is required (Note 12). After hydrogenation is complete, the catalyst is removed by filtration of the reaction mixture through a Celite pad. The ether is removed with a rotary evaporator (Note 8) to obtain 21.1–22.4 g (93–98%) of ethyl isocrotonate as a light-yellow liquid. This material contains traces of quinoline but is of a purity suitable for many uses (Note 6) and (Note 13). The quinoline may be removed, if desired, by washing the ether solution with 1 *M* aqueous acetic acid, followed by aqueous sodium carbonate, or by distillation at atmospheric pressure, bp 128–132°C [lit.[3] bp 129–130.5°C] (Note 14).

2. Notes

1. Although stirring can be done with a large magnetic stirring bar, the reaction mixture becomes rather thick as the 1-lithiopropyne is formed, and effective stirring is difficult. The checkers found that the yield in this step is only 77% when a magnetic stirrer is used.
2. Methylacetylene (technical grade) from Linde Division of the Union Carbide Corporation was employed. The checkers used Matheson Lecture bottles.
3. The propyne is passed directly from the tank or lecture bottle to a cold-finger condenser filled with a slush of isopropyl alcohol and dry ice. The condenser is attached to a 200-mL, three-necked flask equipped with a gas inlet adapter and a glass stopper. The flask has been previously calibrated to hold 85 mL of liquid.
4. Alternatively, the butyllithium solution may be forced into the reaction flask by means of an 18-gauge cannula inserted through the serum cap.
5. Butyllithium was obtained from Foote Mineral Co., Johnsonville, Tennessee. It may be standardized by a double titration procedure.[4]
6. If care is not taken in the formation of 1-lithiopropyne, the final product can be contaminated with as much as 10% of an impurity, which is presumed to be ethyl pentanoate. This impurity has a GLC retention time on conventional packed columns that is quite similar to that of ethyl (*E*)-crotonate. The by-product presumably results from the presence of butyllithium when the ethyl chloroformate is added. The submitters have not observed the formation of this product when care was taken to maintain the reaction temperature below −65°C during addition of the butyllithium to the propyne.
7. Ethyl chloroformate (practical grade) was obtained from MCB, Inc., Cincinnati, Ohio 45212, and used without purification.
8. It is important that the rotary evaporator bath be kept at 5–10°C, or some of the product will be lost by evaporation.
9. The IR spectrum (neat) has absorptions at 2250, 1700, and 1260 cm^{-1}. The ^1H NMR spectrum ($CDCl_3$) is as follows δ: 1.23 (t, 3 H, $J = 7$), 1.95 (s, 3 H), 4.07 (q, 2 H, $J = 7$).
10. The catalyst was obtained from The American Platinum Works, Newark, NJ.
11. The submitters employed an apparatus similar to that described by Wiberg.[5]
12. The hydrogenation can also be carried out without special apparatus by the following method. The ether solution is placed in a 500-mL, three-necked flask fitted with a fritted-gas inlet tube, a rubber serum cap, an oil bubbler, and a magnetic stirring bar. The catalyst, quinoline, and ethyl tetrolate are introduced, and the reaction flask is cooled in an ice bath. Hydrogen is bubbled through the cold solution at such a rate as to maintain atmospheric pressure in the flask as evidenced by the oil bubbler. When using this technique, it is necessary to monitor the course of hydrogenation by GLC or ^1H NMR. However, the rate of hydrogenation decreases rather abruptly after one molar equivalent has been absorbed, and there is little danger of overhydrogenation.
13. Capillary GLC analysis (12 m, cross-linked methyl silicone, programmed, 45°C, 3°C/min, retention time of ethyl (*Z*)-crotonate, 2.5 min). Ethyl (*E*)-crotonate has a retention time of 2.95 min under the same conditions. Careful quantitative analysis reveals that the ratio of *Z* and *E* isomers is reproducibly in the range 58 : 1 to 59 : 1.
14. The IR spectrum (neat) has absorptions at 3040, 1710, 1640, 1175, 1025, and 810 cm^{-1}. The ^1H NMR spectrum is as follows ($CDCl_3$) δ: 1.23 (t, 3 H, $J = 7$), 2.05 (dd, 3 H, $J = 2, 7$), 4.03 (q, 2 H, $J = 7$), 5.62 (dq, 1 H, $J = 12, 2$), 6.19 (dq, 1 H, $J = 12, 7$).

3. Discussion

A previous *Organic Syntheses* procedure for the preparation of isocrotonic acid involves the stereospecific Favorskii rearrangement of 1,3-dibromo-2-butanone.[6] However, the procedure is rather laborious and, in our hands, gives only a modest overall yield of acid. Isocrotonic acid has also been prepared by carbonation of *cis*-propenyllithium[7] and by sodium amalgam reduction of β-chloroisocrotonic acid.[8] The present procedure for semihydrogenation of ethyl tetrolate is based on early work of Bourguel[9] and of Allan, Jones, and Whiting.[10] The procedure for acylation of propyne is general and may be employed for the preparation of other α,β-acetylenic esters.[11]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 375

References and Notes

1. Department of Chemistry, University of California, Berkeley, CA 94720.
2. In "Handbook of Chemistry and Physics," 52nd ed.; Weast, R. C., Ed.; Chemical Rubber Company: Cleveland, 1971; p. C-227.
3. von Auwers, K. *Liebigs Ann. Chem*. **1923**, *432*, 46.
4. Jones, R. G.; Gilman, H. *Org. React*. **1951**, *6*, 353.
5. Wiberg, K. B. "Laboratory Technique in Organic Chemistry"; McGraw-Hill: New York, 1960; p. 228.
6. Rappe, C. *Org. Synth., Coll. Vol. VI* **1988**, 711.
7. Seyferth, D.; Vaughan, L. G. *J. Am. Chem. Soc*. **1964**, *86*, 883.
8. Plisov. A. K.; Bogatsky, A. V. *Zhur. Obshchei Khim*. **1957**, *27*, 360; *Chem. Abstr*. **1957**, *51*, 15401c.
9. Bourguel, M. *Bull. Soc. Chim. Fr. (4)* **1929**, *45*, 1067.
10. Allan, J. L. H.; Jones, E. R. H.; Whiting, M. C. *J. Chem. Soc*. **1955**, 1862.
11. Brandsma, L. "Preparative Acetylene Chemistry"; Elsevier: Amsterdam, 1971; p. 80.

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

brine

methyl silicone

acetic acid (64-19-7)

ether (60-29-7)

hydrogen (1333-74-0)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

barium sulfate (7727-43-7)

sodium (13966-32-0)

isopropyl alcohol (67-63-0)

palladium (7440-05-3)

Quinoline (91-22-5)

ethyl chloroformate (541-41-3)

$MgSO_4$ (7487-88-9)

butyllithium (109-72-8)

hexane (110-54-3)

Ethyl (Z)-crotonate,
ethyl (E)-crotonate (623-70-1)

propyne,
methylacetylene (74-99-7)

Isocrotonic acid (503-64-0)

1,3-Dibromo-2-butanone (815-51-0)

Ethyl isocrotonate (6776-19-8)

Ethyl tetrolate (4341-76-8)

1-lithiopropyne (4529-04-8)

ethyl pentanoate (539-82-2)

β-chloroisocrotonic acid

cis-propenyllithium