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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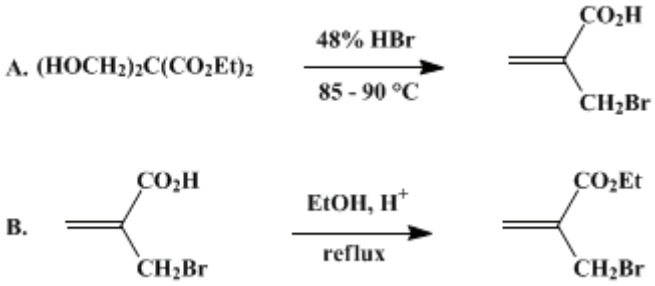
ETHYL α-(BROMOMETHYL)ACRYLATE

[2-Propenoic acid, 2-(bromomethyl)-,ethyl ester]



Submitted by K. Ramarajan, K. Ramalingam, D. J. O'Donnell, and K. D. Berlin[1].
Checked by H. S. Shou, E. Tsou, R. A. Hayes, and Orville L. Chapman.

1. Procedure

Caution! Ethyl α-(bromomethyl) acrylate is a potent vesicant and lachrymator and should be handled with care. All operations should be carried out in an efficiently ventilated hood in order to avoid contact.

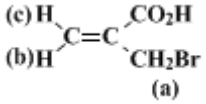
A. *α-(Bromomethyl)acrylic acid.* A 500-mL, three-necked, round-bottomed flask is equipped with a magnetic stirrer, fraction collector, cold-finger condenser, and two thermometers. Into the flask are placed 55.0 g (0.25 mol) of diethyl bis(hydroxymethyl)malonate (Note 1) and 142 mL (1.25 mol) of 47–49% hydrobromic acid (Note 2). The mixture is then heated and the temperature of the liquid maintained between 85 and 90°C. A mixture of ethyl bromide and water distills during the course of 1.5–2 hr. The residue is then boiled for 10 hr, maintaining the temperature between 85–90°C (Note 3). At the end of this period, the mixture is concentrated on a rotary evaporator at 65–70°C (10–15 mm). About 100 mL of water is removed. The residue is cooled in the refrigerator overnight. Crystals of α-(bromomethyl)acrylic acid are filtered in the cold (Note 4) to give, after drying (Note 5), 17.9 g (43%) of acid, mp 71–73°C (Note 6).

B. *Ethyl α-(bromomethyl)acrylate.* In a nitrogen-flushed, 1-L, round-bottomed flask equipped with a magnetic stirrer, Dean-Stark trap, and condenser are placed 42.0 g (0.25 mol) of α-(bromomethyl) acrylic acid and 300 mL of benzene. Approximately 50 mL of a binary azeotrope of benzene and water is distilled (Note 7). The Dean-Stark trap is removed and 100 mL of absolute ethanol (Note 8) and 1 mL of concentrated sulfuric acid are added slowly. The contents of the flask are boiled in a nitrogen atmosphere for 36 hr, the condensate being passed through 100 g of molecular sieves (Linde 3A) before being returned to the flask. About 125 mL of a mixture of benzene and ethanol is removed from the reaction mixture by distillation (at 67°C). Then 100 mL of benzene is added and another 125 mL of benzene-ethanol mixture distilled (67–75°C). The residue is poured into 200 mL of water and neutralized with solid sodium bicarbonate (ca. 10–15 g) until CO_2 evolution ceases. The resulting solution is extracted with three 75-mL portions of ether, and the combined extracts are dried over anhydrous sodium sulfate for 3 hr. The ether is removed under reduced pressure in a rotary evaporator, and crude ester distilled to give a fraction at 39–40°C (0.9 mm) that weighs 33–34 g (71%). The ester is of high purity, as evidenced by spectral analysis (Note 9).

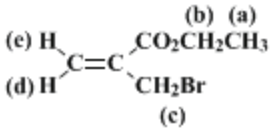
2. Notes

1. The checkers prepared this ester on a 0.7-mol scale by a modification of the previously published method.[2] The modification was effected as follows. The ethereal extract from the formaldehyde-diethyl malonate reaction, after drying over sodium sulfate for 3 hr, was concentrated in a rotary evaporator and the residue was stored in a refrigerator overnight. The crude ester was obtained as white crystals, mp

47–50°C; yield 85.6%. The checkers found that the ester prepared in this manner gave superior yields of the acrylic acid.
2. The submitters reported that the use of excess hydrobromic acid resulted in the formation of a mixture of dibromoisobutyric acid and α-(bromomethyl)acrylic acid as evidenced by NMR analysis.
3. Temperatures higher that 85–90°C gave a mixture of dibromoisobutyric acid and α-(bromomethyl) acrylic acid.
4. This was done at 4°C to improve the yield; otherwise considerable amounts of α-(bromomethyl) acrylic acid remain in solution.
5. The compound was air-dried for 3 days at room temperature.
6. The product was almost pure. It could be recrystallized from Skelly-solve-B (bp 60–80°C) and further purified by sublimation, mp 73–75°C (Anal. calcd. for $C_4H_5BrO_2$: C, 29.12; H, 3.05. Found: C, 29.07; H, 3.10). IR (KBr) cm^{-1}: 1689 (C=O), 1626 (C=CH_2), ^1H NMR ($CDCl_3$) δ: 4.18 (s, 2 H, H_a), 6.09 (s, 1 H, H_b), 6.49 (s, 1 H, H_c).



7. There was only about 1 mL of water in the distillate.
8. Absolute alcohol was prepared by boiling commercial absolute alcohol over magnesium turnings for 4 hr in a nitrogen atmosphere.
9. The spectral properties of ethyl α-(bromomethyl)acrylate are as follows: ^1H NMR ($CDCl_3$) δ: 1.26–1.40 (t, 3 H, H_a), 4.16–4.38 (quintet, 2 H, H_b), 4.19 (s, 2 H, H_c), 5.96 (s, 1 H, H_D), 6.32 (s, 1 H, H_e).



3. Discussion

The procedure described here is a modification of that of Ferris.[3] The overall yield has been increased from 17 to 30% by making changes as indicated in (Note 2) and (Note 3). In addition, the number of stages in the preparation of ethyl α-(bromomethyl)acrylate from diethyl malonate has been reduced from four to three.

Ethyl α-(bromomethyl)acrylate has proved to be an excellent reagent for conversion of aldehydes and ketones, both acyclic and cyclic, into the corresponding α-methylene-γ-butyrolactone derivatives[4,5,6,7,8,9] in a Reformatsky type reaction. The yield was excellent in the case of several spiro α-methylene-γ-butyrolactones.[10] Synthetic α-methylene-γ-butyrolactone derivatives have been shown to possess antitumor activity.[5,6,7,11,12,13] Ethyl α-(bromomethyl)acrylate has also proven of value in the synthesis of alkylated products of enol ethers of cyclohexane-1,3-dione.[14]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 265

References and Notes

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

formaldehyde-diethyl malonate

Skelly-solve-B

spiro α-methylene-γ-butyrolactones

enol ethers of cyclohexane-1,3-dione

alcohol,
ethanol (64-17-5)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

ether (60-29-7)

sodium bicarbonate (144-55-8)

magnesium turnings (7439-95-4)

HYDROBROMIC ACID (10035-10-6)

Ethyl bromide (74-96-4)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

CO_2 (124-38-9)

Acrylic acid (9003-01-4)

diethyl malonate (105-53-3)

benzene-ethanol (60-12-8)

Diethyl bis(hydroxymethyl)malonate (20605-01-0)

Ethyl α-(bromomethyl)acrylate,
2-Propenoic acid, 2-(bromomethyl)-,ethyl ester,
Ethyl α-(bromomethyl) acrylate (17435-72-2)

α-(Bromomethyl)acrylic acid (72707-66-5)

dibromoisobutyric acid