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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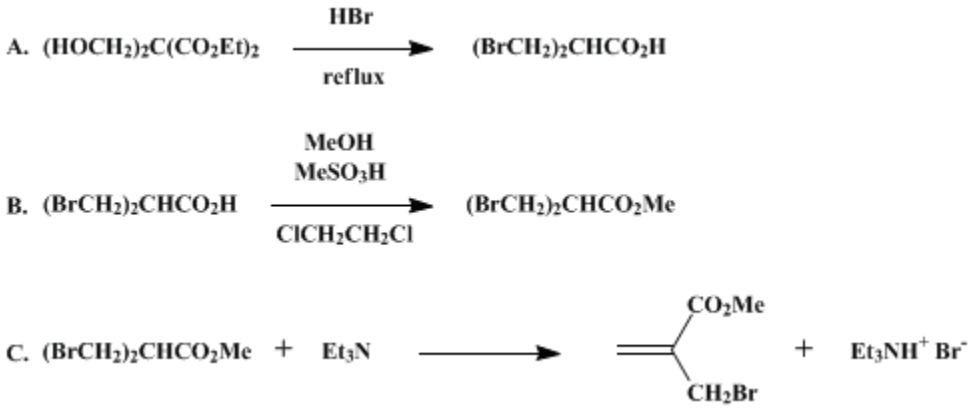
METHYL α-(BROMOMETHYL)ACRYLATE

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



Submitted by John M. Cassady, Gary A. Howie, J. Michael Robinson, and Ioannis K. Stamos[1].
Checked by Paul R. West and Orville L. Chapman.

1. Procedure

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

A. *β,β'-Dibromoisobutyric acid*. To a 5-L, single-necked flask, equipped with a heating mantle, 22-cm Vigreux distillation head, thermometer, 30-cm water-cooled condenser with adapter, and 1-L, ice-cooled receiving vessel (Note 1) is added 440 g (2.0 mol) of diethyl bis(hydroxymethyl)malonate (Note 2)[2] and (Note 3) and 3540 mL of concentrated aqueous hydrobromic acid (Note 4). Heating for 6 hr at vigorous reflux gives 2400 mL of aqueous distillate (Note 5). The undistilled concentrate is poured into a 3-L beaker, cooled overnight at −15°C (Note 6), and filtered through a 500-mL fritted-glass Büchner funnel using aspirator vacuum. After suction air drying for 6 hr, drying is continued for 6 days in a vacuum desiccator containing active Drierite and under 10 mm of initial vacuum (Note 7) to give 332 g (67.5%) of β,β'-dibromoisobutyric acid as a brown solid. Distillation of the filtrate to remove an additional 850 mL of aqueous hydrobromic acid (Note 8), followed by cooling and filtration, gives an additional 34.0 g (6.9%) of solid. Crude product, obtained in 74–85% yield (Note 9)[3], is suitable for use without further purification (Note 10).

B. *Methyl β,β'-dibromoisobutyrate*. In a 200-mL, round-bottomed flask fitted with a reflux condenser are placed 61.5 g (0.25 mol) of β,β'-dibromoisobutyric acid, 25 g (0.78 mol) of commercial methanol, 75 mL of ethylene dichloride, and 0.2 mL of methanesulfonic acid (Note 11)[4] and (Note 12). The reaction mixture is heated under reflux for 24 hr. The solution is cooled to room temperature, diluted with about 200 mL of methylene chloride, and neutralized with dilute, cold sodium bicarbonate solution (Note 13). The organic layer is dried over anhydrous sodium sulfate and concentrated on a rotary evaporator to remove most of the methylene chloride. Fractional distillation of this residue under reduced pressure (the receiver is cooled with an ice–salt mixture) yields 48.8 g (75%) of product, bp 64–65°C (0.3 mm).[3,5,6]

C. *Methyl α-(bromomethyl)acrylate*. In a dry, 250-mL three-necked flask, equipped with a mechanical stirrer, reflux condenser, and an addition funnel, 20 g (0.077 mol) of methyl β,β'-dibromoisobutyrate (Note 14)[5,6] in 50 mL of anhydrous benzene (Note 15)[7] is stirred vigorously. Triethylamine (Note 16)[8] and (Note 17) (7.7 g, 0.076 mol) in 50 mL of benzene is introduced dropwise at a rate of about 3 mL per min. After the addition is complete the mixture is stirred for an additional 1 hr at room temperature, refluxed for 1 hr, and then cooled to 20°C. The reaction mixture is filtered with suction and the amine salt washed twice with 20 mL of benzene. The filtrate and washings are

combined in a round-bottomed flask and concentrated on a rotary evaporator at 30–35°C to remove most of the benzene. The residue is transferred to a small distillation apparatus and fractionally distilled at reduced pressure using an oil bath at 50–55°C. The yield of ester collected at bp 35–37°C (1.3 mm) is 11.0 g (80%) (Note 18),(Note 19),(Note 20),(Note 21).

2. Notes

1. Cooling the receiving vessel greatly reduces loss of ethyl bromide.
2. Diethyl bis(hydroxymethyl)malonate was prepared up to an 8.0-mol scale by the method of Block.[2] After suction filtration to remove the drying agent, the dried diethyl ether extracts were concentrated directly on a Büchi rotary evaporator at aspirator vacuum using a bath temperature of 50°C; concentration was continued for ca. 2 hr after removal of the ether. The crude, oily diethyl bis (hydroxymethyl)malonate, obtained in 94–96% yield, solidified on standing and was suitable for use without further purification. The malonate can be stored at room temperature with no special precautions.
3. The checkers ran this reaction on a 20% scale [starting with 88 g (0.4 mol) of diethyl bis (hydroxymethyl)malonate]. At this scale, yields between 63 and 75% were realized.
4. Initial experiments used commercial 48% aqueous hydrobromic acid. In subsequent runs no decrease in yields was apparent when recovered distillate boiling at or above 110°C was substituted for the commercial acid.
5. Approximately 45 additional min of heating was required to reach distillation temperature. The first 780 mL (excluding ethyl bromide) of aqueous distillate boiled below 110°C and was discarded. The remaining distillate was recycled as described in (Note 4).
6. Cooling in a refrigerator freezing compartment is satisfactory. The beaker should be sealed (e.g., using Saran Wrap) to prevent escape of corrosive fumes.
7. After the solid was dried in the desiccator, weight reductions of up to 10% were observed.
8. Special care must be used toward the end of the distillation to avoid overheating caused by removal of too much solvent. Overheating can result in an intractable gummy residue.
9. Failure to distill the maximum amount of concentrated hydrobromic acid, higher crystallization temperatures, and/or washing with water may account for the lower (66%) reported[3] yield.
10. Storage at room temperature (under nitrogen or in a filled, sealed container) for periods in excess of 1 year resulted in no significant deterioration of the crude acid as judged by its suitability for use in step B. Preparation of acid was done on a 0.5–3.4-mol scale with no significant variation in yield.
11. These conditions are patterned after a general procedure for esterification reported by Clinton and Laskowski.[4]
12. The checkers ran this reaction on a 50% scale [starting with 30.75 g (0.125 mol) of β,β'-dibromoisobutyric acid] and obtained yields ranging from 66 to 67%.
13. A brown, emulsified layer, which separates on long standing, is formed between the organic and aqueous layers. This layer can also be taken up with an additional 200 mL of methylene chloride and dried with a sufficient amount of anhydrous sodium sulfate to recover the organic layer.
14. It is recommended that methyl β,β'-dibromoisobutyrate[5,6] that has been purified by fractional distillation be used, since the presence of acidic compounds reduces the yield and the presence of any hydroxyl function gives a product mixture that cannot be purified by simple distillation.
15. The preparation of anhydrous benzene has been described.[7]
16. Commercial triethylamine is conveniently purified by two distillations from a 2% solution of phenyl isocyanate.[8]
17. In a parallel experiment, ethyldiisopropylamine (9.82 g, purified as in (Note 16)) was mixed with a solution of 20 g of methyl β,β'-dibromoisobutyrate in 100 mL of dry benzene. The reaction mixture was stored at room temperature for 10 hr and gently refluxed for 1 hr under nitrogen in the dark. After workup and distillation the yield of the product was 80%.
18. Distillation at higher temperatures results in viscous residues with considerably reduced yields of the product. The receiver should be immersed in an acetone-dry ice bath in order to prevent loss of the product to the trap of the vacuum line.
19. The product is stable for long periods of time if kept under an inert atmosphere in the absence of light and in the refrigerator.
20. Ethyl α-(bromomethyl)acrylate is prepared similarly, bp 38–42°C (0.8 mm).
21. The checkers obtained a 76% yield.

3. Discussion

Although methyl and ethyl α-(bromomethyl)acrylate are used extensively as synthetic intermediates in the preparation of a variety of organic compounds,[9,10,11,12,13,14,15,16] many of biological importance, they are not commercially available and their preparation in good yield on a large scale is therefore of interest. The procedures outlined above represent useful modifications of published literature routes to these compounds.

The procedure for the elimination of HBr from the dibromo ester is a modification of the method of Lawton and co-workers for sui generis generation of the methyl[5,9] or ethyl ester[10] during a reaction. Methyl α-(bromomethyl)acrylate has also been prepared by bromination of methyl methacrylate in 700° C steam[17] and by dehydrohalogenation with sodium acetate in acetic acid.[6] Ethyl α-(bromomethyl) acrylate has been prepared by dehydrohalogenation with the monosodium salt of ethylene glycol[3,18] and ethyl diisopropylamine.[11] The latter reaction was reported by Öhler et al. with no experimental details for the elimination reaction. The use of triethylamine as reported in this procedure appears to be the most efficient and convenient method for dehydrobromination to these acrylate esters.

References and Notes

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

acetic acid (64-19-7)

Benzene (71-43-2)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

sodium acetate (127-09-3)

sodium bicarbonate (144-55-8)

HYDROBROMIC ACID (10035-10-6)

Ethyl bromide (74-96-4)

sodium sulfate (7757-82-6)

ethylene dichloride (107-06-2)

nitrogen (7727-37-9)

methylene chloride (75-09-2)

phenyl isocyanate (103-71-9)

triethylamine (121-44-8)

methanesulfonic acid (75-75-2)

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

methyl methacrylate (80-62-6)

ethyldiisopropylamine,
ethyl diisopropylamine (7087-68-5)

Ethyl α-(bromomethyl)acrylate (17435-72-2)

METHYL α-(BROMOMETHYL)ACRYLATE,
2-Propenoic acid, 2-(bromomethyl)-, methyl ester,
Methyl α-(bromomethyl) acrylate,
Methyl a-(bromomethyl)acrylate (4224-69-5)

β,β'-Dibromoisobutyric acid

Methyl β,β'-dibromoisobutyrate

monosodium salt of ethylene glycol