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.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

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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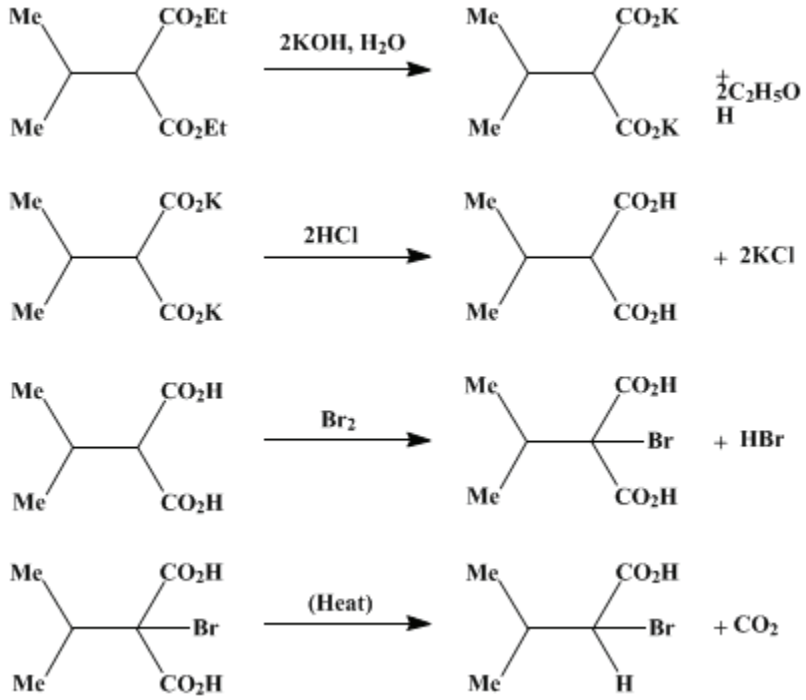
Organic Syntheses, Coll. Vol. 2, p.93 (1943); Vol. 11, p.20 (1931).

α-BROMOISOVALERIC ACID

[Isovaleric acid, α-bromo-]



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1. Procedure

A solution of 200 g. (3.6 moles) of potassium hydroxide in 200 cc. of water is placed in a 2-l. flask fitted with a reflux condenser. The mixture is heated to about 80°, and 202 g. (1 mole) of isopropylmalonic ester (Note 1) is added through the condenser over a period of about one hour. The mixture should be shaken well to prevent the formation of two layers. The saponification proceeds rapidly, forming a clear solution. The solution is transferred to a 20-cm. evaporating dish, the flask is rinsed with 50 cc. of water, and the solution and washings are evaporated practically to dryness on a steam bath (Note 2).

The residue is dissolved in 200 cc. of water, transferred to a 1-l. flask, and cooled to 0° in an ice-salt bath. A mixture of 400 cc. of concentrated hydrochloric acid (sp. gr. 1.19) and 200 g. of cracked ice is added slowly until the mixture is acid to Congo red. The temperature of the mixture must not rise above 10° (Note 3). Potassium chloride separates. The mixture is extracted with two 200-cc. portions and four 100-cc. portions of alcohol-free ether (Note 4) to remove the isopropylmalonic acid. The ether solution (Note 5) is placed in a flask fitted with a reflux condenser, and 160 g. (1 mole) of bromine is added gradually over a period of about two hours at such a rate that the ether boils gently (Note 6). When the bromination is complete, the ether solution is washed with 100 cc. of water to remove the hydrobromic acid, dried over 25 g. of calcium chloride, and freed from ether by distillation on the steam bath. The crude isopropylbromomalonic acid is heated in the distilling flask in an oil bath at 125–130° until no more carbon dioxide is evolved. It is then distilled under reduced pressure; the fraction distilling at 140–160°/40 mm. is collected separately and redistilled (Note 7). The yield of product boiling at 148–153°/40 mm. (125–130°/15 mm.) is 100–120 g. (55–66 per cent of the theoretical amount) (Note 8).

2. Notes

1. The isopropylmalonic ester was prepared by the method used for *n*-butylmalonic ester (Org. Syn. Coll. Vol. I, **1941**, 250). The yield of product boiling at 132–135°/44 mm. was 70–75 per cent of the theoretical amount.
2. Unless the saponification is complete, the final product will contain ethyl α-bromoisovalerate, which will appear in the low-boiling fraction. If all the alcohol is not removed, some esterification will occur on acidification.
3. A rise in temperature favors the loss of carbon dioxide with the formation of isovaleric acid, which will escape bromination.
4. The ether used for extraction is first extracted with one-tenth its volume of saturated calcium chloride solution to remove the alcohol, which would otherwise cause partial esterification of the acid.
5. No special drying is necessary before the bromination, but the ether and aqueous layers should be separated carefully.
6. Usually the bromination starts easily. Sometimes, however, the mixture has to be heated after the first few drops of bromine are added. The mixture may have to be heated to complete the bromination.
7. The product on the first distillation does not have a constant boiling point, as some carbon dioxide is liberated from undecomposed isopropylbromomalonic acid. This cannot be avoided by preliminary heating, even at temperatures much higher than those used.
8. This is a general method for preparing α-bromo acids. By using exactly analogous directions α-bromo-*n*-caproic acid may be obtained in 65–70 per cent yields from *n*-butylmalonic ester; α-bromoisocaproic acid in 65–70 per cent yields from isobutylmalonic ester; and α-bromo-β-methylvaleric acid in 75–80 per cent yields from *sec*.-butylmalonic ester.

3. Discussion

α-Bromoisovaleric acid has been prepared from bromine and isovaleric acid alone,[1] or in the presence of phosphorus,[2] or phosphorus trichloride;[3] and by the action of heat on isopropylbromomalonic acid.[4]

References and Notes

1. Ley and Popoff, Ann. **174**, 63 (1874).
2. Schleicher, ibid. **267**, 115 (1892).
3. Org. Syn. **20**, 106.
4. Koenigs and Mylo, Ber. **41**, 4437 (1908).

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

Congo red

isopropylmalonic ester

isobutylmalonic ester

n-butylmalonic ester

sec.-butylmalonic ester

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

ether (60-29-7)

α-Bromoisovaleric acid,
Isovaleric acid, α-bromo- (565-74-2)

HYDROBROMIC ACID (10035-10-6)

bromine (7726-95-6)

PHOSPHORUS (7723-14-0)

α-bromo-n-caproic acid (616-05-7)

carbon dioxide (124-38-9)

potassium hydroxide (1310-58-3)

phosphorus trichloride (7719-12-2)

potassium chloride (7447-40-7)

isopropylmalonic acid (601-79-6)

isopropylbromomalonic acid

ethyl α-bromoisovalerate (609-12-1)

isovaleric acid (503-74-2)

α-Bromoisocaproic acid (49628-52-6)

α-Bromo-β-methylvaleric acid (42880-22-8)