



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.

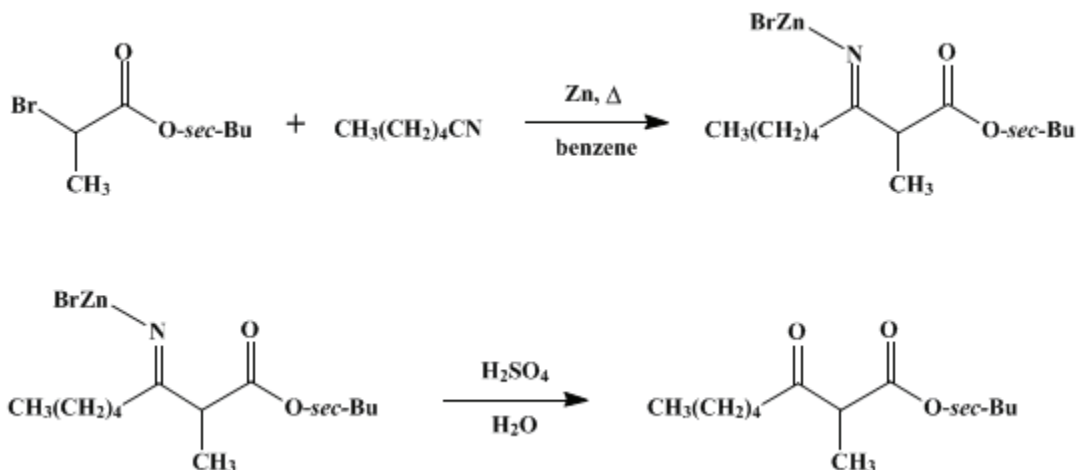
The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries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

Organic Syntheses, Coll. Vol. 4, p.120 (1963); Vol. 35, p.15 (1955).

***sec*-BUTYL α -*n*-CAPROYLPROPIONATE**

[Octanoic acid, 2-methyl-3-oxo-, *sec*-butyl ester]



Submitted by Kenneth L. Rinehart, Jr.¹

Checked by John C. Sheehan and J. Iannicelli.

1. Procedure

A 2-l. three-necked round-bottomed flask is fitted with a condenser arranged for distillation, a 200-ml. dropping funnel, and a mercury-sealed mechanical stirrer. Connections are most conveniently made with ground-glass joints, and the flask is heated on a steam cone. Cupric bromide (0.4 g.), 39.2 g. (0.60 g. atom) of freshly sand-papered zinc foil cut into narrow strips, and 1.2 l. of benzene previously dried over sodium are added to the flask. To dry the apparatus and contents, 300 ml. of benzene is slowly distilled from the flask with stirring. Heating is interrupted, and the condenser is quickly arranged for reflux and fitted with a calcium chloride drying tube. To the flask are added rapidly with stirring 38.9 g. (0.40 mole) of *n*-capronitrile (Note 1) and 125.4 g. (0.60 mole) of *sec*-butyl α -bromopropionate (Note 2). Refluxing is resumed, and after a 3–5 minute induction period blackening of the zinc surface and clouding of the solution are noted as the first signs of reaction. Heating is maintained a total of 45 minutes, after which the solution is cooled for 15 minutes in an ice bath (Note 3).

To the cooled solution is added with vigorous stirring 400 ml. of ice-cold 12*N* sulfuric acid. The ice bath is removed, and stirring is continued at room temperature for a total of 2 hours (Note 4). The reaction mixture is poured into a 2-l. separatory funnel; after separation, the aqueous lower layer is drained into a 2-l. separatory funnel containing 800 ml. of water which has been used to wash the reaction flask. The aqueous layer is extracted twice with 200-ml. portions of benzene which have also been employed to rinse the reaction flask. The original organic layer and the combined benzene extracts are kept separate and are washed successively with 400-ml. portions of water, saturated sodium bicarbonate solution, and again with water. The two organic portions are combined and allowed to stand over anhydrous sodium sulfate until clear. The solvent is removed at atmospheric pressure by flash distillation through a fractionating column (Note 5). For this operation, a side-arm distilling flask equipped with a dropping funnel is heated by an oil bath whose temperature is maintained at 140–150°. After all the solvent has been added, the dropping funnel is replaced by a capillary, and the last of the solvent is removed at reduced pressure furnished by a water pump. Finally, an oil pump is attached and the product is fractionated at about 5 mm. pressure (Note 6). After a small fore-run, *sec*-butyl α -*n*-caproylpropionate is obtained as a clear liquid; b.p. 112–114°/4.5 mm. (134–136°/12 mm.), n_D^{25} 1.4293 (Note 7) and (Note 8). The yield is 46.0–52.9 g. (50–58% based on *n*-capronitrile) (Note 9).

2. Notes

1. Commercial *n*-capronitrile (Eastman Kodak white label grade) is distilled through a fractionating column before use; b.p. 161–163°, n_D^{25} 1.4052.
2. α -Bromoesters are severe lachrymators, and it is necessary to conduct reactions involving them in a well-ventilated hood. *sec*-Butyl α -bromopropionate is prepared from commercially available ethyl α -bromopropionate (Sapon Laboratories, Inc., 543 Union Street, Brooklyn 15, New York) by transesterification with *sec*-butyl alcohol using sulfuric acid catalyst. The product boils at 97–98°/39 mm. and has n_D^{25} 1.4420. Darkening of the α -bromoester is prevented by storage over a few drops of mercury.
3. Unreacted zinc usually remains at this point, and the solution is yellow to brown. Most of the color is discharged on subsequent addition of the acid.
4. With 3-methylnonanoicnitrile it is necessary to continue the stirring in sulfuric acid for an additional period; a total of 19 hours is sufficient.
5. A 50 cm. by 8 mm. simple Podbielniak column² with partial-reflux head is adequate for this and subsequent distillations.
6. Fractionation at higher pressures and temperatures leads to some thermal decomposition of the product.
7. An analytical sample of a redistilled center cut had n_D^{25} 1.4302.
8. β -Ketoesters with alkyl substituents in the α -position give a blue-violet color with ferric chloride.³ Copper chelates of the α -alkyl- β -ketoesters could not be isolated. The corresponding 5-pyrazolones, although often difficultly crystallizable, appear to be the most suitable derivatives. The 5-pyrazolone from *sec*-butyl α -*n*-caproylpropionate is prepared according to von Auwers and Dersch⁴ and has a melting point of 80.4–82.9°.
9. This method is suitable for the preparation of mono- and di- α -substituted β -ketoesters. Bromoacetates fail in this reaction. Yields with ethyl α -bromopropionate are considerably lower (30–36% with capronitrile); however, ethyl esters are useful for higher-molecular-weight compounds whose *sec*-alkyl esters are cracked by distillation. With 3-pentyl α -bromopropionate, the yields are slightly higher (53–60% with capronitrile). Both aromatic and aliphatic nitriles are suitable; benzonitrile gives yields comparable to those obtained with capronitrile. Alkyl substitution in the α - and β -positions (cf. (Note 4)) of aliphatic nitriles lowers the yield to 29% and 38%, respectively; γ -substitution has no effect. Recently it has been shown that a significant improvement in the yields of ketoesters is obtained by the use of a mixture of benzene and ether as a solvent.⁵

3. Discussion

The procedure is essentially that of Horeau and Jacques⁶ as modified by Cason, Rinehart, and Thornton.⁷ The reaction described is that discovered by Blaise⁸ and is more extensively discussed in the second-named paper. Ethyl α -*n*-caproylpropionate has been prepared by the alkylation of ethyl *n*-caproylacetate with methyl iodide in the presence of sodium ethoxide.⁹ This method would not be expected to yield a pure product owing to contamination with starting ketoester and disubstituted ketoester.

References and Notes

1. University of California, Berkeley, California.
 2. Podbielniak, *Ind. Eng. Chem., Anal. Ed.*, **3**, 177 (1931); **5**, 119 (1933).
 3. Henecka, *Ber.*, **81**, 188 (1948).
 4. von Auwers and Dersch, *Ann.*, **462**, 115 (1928).
 5. Cason and Fessenden, *J. Org. Chem.*, **22**, 1326 (1957).
 6. Horeau and Jacques, *Bull. soc. chim. France*, **1947**, 58.
 7. Cason, Rinehart, and Thornton, *J. Org. Chem.*, **18**, 1594 (1953).
 8. Blaise, *Compt. rend.*, **132**, 478, 978 (1901); Blaise and Courtot, *Bull. soc. chim. France*, [3] **35**, 599 (1906).
 9. Locquin, *Bull. soc. chim. France*, [3] **31**, 596 (1904).
-

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

sulfuric acid (7664-93-9)

Benzene (71-43-2)

ether (60-29-7)

benzotrile (100-47-0)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

mercury (7439-97-6)

zinc (7440-66-6)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

ferric chloride (7705-08-0)

Methyl iodide (74-88-4)

ethyl α -bromopropionate (535-11-5)

cupric bromide (7789-45-9)

capronitrile,
n-capronitrile (628-73-9)

Octanoic acid, 2-methyl-3-oxo-, sec-butyl ester,
sec-BUTYL α -n-CAPROYLPROPIONATE (53663-40-4)

3-methylnonanoicnitrile

5-pyrazolone

3-pentyl α -bromopropionate

sec-butyl alcohol (78-92-2)

sec-butyl α -bromopropionate (22710-17-4)

Ethyl α -n-caproylpropionate

ethyl n-caproylacetate

