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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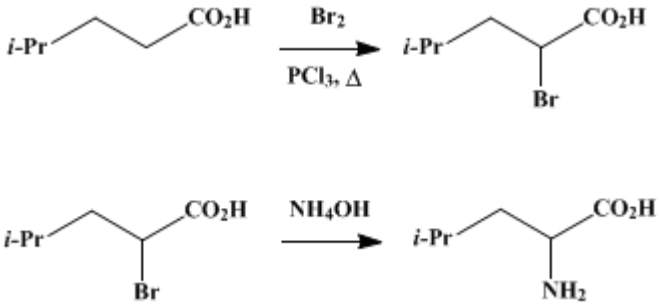
dl-LEUCINE

[Isocaproic acid, α-amino]



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1. Procedure

A. *α-Bromoisocaproic acid.* Five hundred grams (4.3 moles) of commercial isocaproic acid is mixed with 250 ml. of benzene in a 2-l. round-bottomed flask, and the water and benzene are removed by distillation through a short column until the temperature of the vapors reaches 100°. The temperature rises rapidly as soon as the last of the benzene is removed. The residual acid is cooled to room temperature, 743 g. (4.65 moles, 243 ml.) of dry bromine (Note 1) is added, and the flask is fitted with a long condenser and placed in an oil bath. The top of the condenser is connected to an empty 500-ml. Erlenmeyer flask which acts as a safety flask, and this in turn leads to a gas-absorption trap (Note 2). Ten milliliters of phosphorus trichloride is added to the mixture through the top of the condenser, and the flask is heated to 80–85°. The bromination proceeds smoothly at this temperature and is allowed to continue for 8–15 hours until the dark red color of bromine disappears from the condenser. When it has, the temperature is raised to 100–105° and kept there 2 hours. The contents of the flask are transferred to a 1-l. modified Claisen flask or a flask attached to a Widmer column and distilled. The fraction boiling at 125–131°/12 mm. is collected. The yield amounts to 530–550 g. (63–66%). The low-boiling fraction is mainly isocaproic acid (Note 3).

B. *dl-Leucine*. To 1.5 l. of technical ammonium hydroxide (sp. gr. 0.90) in a 3-l. round-bottomed flask is added 300 g. (1.56 moles) of α-bromoisocaproic acid. A rubber stopper is wired in, and the flask is allowed to stand for a week at room temperature. The crude leucine from four such flasks is collected on a filter and washed with 400 ml. of ethanol. This crop amounts to about 300 g. The ammonia is removed from the filtrate by heating the solution in a 12-l. flask on a steam cone overnight. The solution is concentrated under reduced pressure until vigorous bumping occurs (about 2.5 l.). The mixture is then cooled to about 15° and filtered. The precipitate is washed with 250 ml. of cold water and 250 ml. of 95% ethanol. The total yield of crude leucine in the two fractions is 440–460 g.

The amino acid is recrystallized by dissolving all the crude material in 12.5 l. of water heated to 95° on a steam cone. The hot solution is treated with 20 g. of Norit for 30 minutes and filtered hot. An equal volume of 95% ethanol is added immediately, and the flask is placed in the ice chest overnight. The crystalline material is collected on a filter and washed with 200 ml. of 95% ethanol. The yield of pure leucine in this fraction is 290–300 g. An additional crop is obtained by evaporating the mother liquors under reduced pressure until considerable solid separates (liquid volume about 1 l.), adding an equal volume of ethanol, and cooling. This crop is washed with 100 ml. of cold water and then with 200 ml. of ethanol; it amounts to 60–65 g. The total yield of pure leucine is 350–365 g. (43–45%). It decomposes at 290–292° (uncor.) in a sealed capillary (Note 4).

2. Notes

1. The bromine is dried by shaking with 500 ml. of C.P. concentrated sulfuric acid.
2. The hydrogen bromide may be collected in water and distilled to give constant-boiling hydrobromic acid. See *Org. Syntheses* Coll. Vol. **1**, 26 (1941).
3. The low-boiling fractions (105–115 g.) may be combined with the next portion of acid to be brominated, or several such fractions may be collected and brominated together. If this last is done only two-thirds as much bromine is used as in the original run.
4. The amino nitrogen content of leucine prepared in this way checks with the theoretical value.

3. Discussion

dl-Leucine has been prepared by the hydrolysis of isobutylhydantoin with barium hydroxide;[2] by reduction and hydrolysis of α-oximinoisocaproate; [3] by racemization of *l*-leucine;[4] by the action of ammonia and hydrogen cyanide on isovaleraldehyde followed by hydrolysis;[5] by the action of heat on isobutylmalonylazidic acid followed by hydrolysis; [6] by the action of ammonia on α-bromoisocaproic acid;[7] by the condensation of isobutyl halides and sodio aminomalonic ester[8] or sodio benzoylaminomalonic ester[9] followed by hydrolysis; by the condensation of isobutyraldehyde and hippuric acid followed by reduction and hydrolysis,[10] by reduction of α-ketoisocaproic acid phenylhydrazone;[11] by the action of sodium hypobromite on ethyl isobutylmalonamate;[12] by the action of hexamethylene tetramine on α-chloro and α-bromoisocaproic acids;[13] and by hydrogenation and subsequent hydrolysis of methallyl acetamidomalonic ester.[14] The method described above is essentially that of Fischer[7] and is the cheapest and best procedure for the synthesis of large amounts of this amino acid.

References and Notes

1. These directions are the results of the efforts of many men who have worked on the preparation of leucine at the University of Illinois.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

Benzene (71-43-2)

hydrogen cyanide (74-90-8)

HYDROBROMIC ACID,
hydrogen bromide (10035-10-6)

bromine (7726-95-6)

Norit (7782-42-5)

phosphorus trichloride (7719-12-2)

ammonium hydroxide (1336-21-6)

barium hydroxide (17194-00-2)

Hippuric acid (495-69-2)

hexamethylene tetramine (100-97-0)

sodium hypobromite

α-Bromoisocaproic acid (49628-52-6)

isobutyraldehyde (78-84-2)

Isocaproic acid, α-amino,
DL-Leucine (328-39-2)

leucine,
l-leucine (61-90-5)

isocaproic acid (646-07-1)

isobutylhydantoin

α-oximinoisocaproate

isovaleraldehyde (590-86-3)

isobutylmalonylazidic acid

α-ketoisocaproic acid phenylhydrazone

ethyl isobutylmalonamate