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.

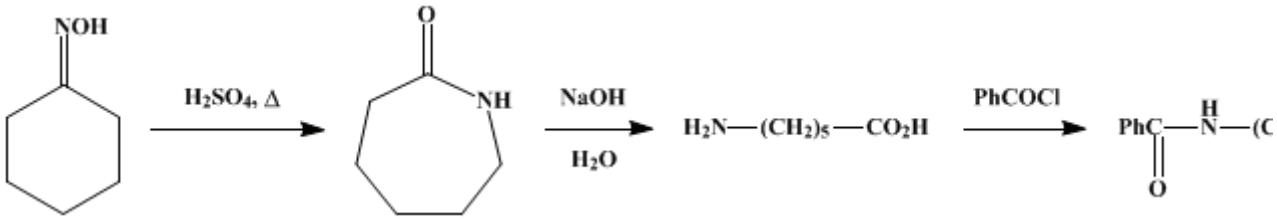
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.019.0020

Organic Syntheses, Coll. Vol. 2, p.76 (1943); Vol. 19, p.20 (1939).

ε-BENZOYLAMINOCAPROIC ACID

[Caproic acid, ε-benzamido-]



Submitted by J. C. Eck and C. S. Marvel.
Checked by C. R. Noller and William Munich.

1. Procedure

(*A*) *Cyclohexanone Oxime.*—In a 5-l. flask, fitted with an efficient mechanical stirrer and an 8-mm. glass inlet tube reaching to within 5 cm. of the bottom of the flask, are placed 1.5 kg. of cracked ice and a solution of 182 g. (2.5 moles) of technical sodium nitrite (95 per cent) in 500 cc. of water (Note 1). The flask is placed in an ice-salt mixture, and a cold (−8°) solution of sodium bisulfite, prepared by saturating with sulfur dioxide a solution of 143 g. (1.35 moles) of anhydrous sodium carbonate in 600 cc. of water, is added. While the temperature is kept below 0°, a moderate stream of sulfur dioxide is passed into the mixture until it is acid to Congo red and then just enough longer to remove the dark color which appears shortly before the solution becomes acid.

To this solution are added 196 g. (2 moles) of technical cyclohexanone and 500 cc. of 85 per cent ethyl alcohol; the cooling bath is replaced by a steam bath, the stirrer started, and the mixture heated to 75°. The flask is then packed in mineral wool or other insulating material and allowed to cool slowly, with effective stirring, for forty-eight hours. The solution at room temperature is exactly neutralized to litmus with a 50 per cent solution of sodium hydroxide, with cooling and stirring. About 330 g. of sodium hydroxide solution is required.

The oily layer is separated and the aqueous solution extracted with two 200-cc. portions of ether. The oil and ether extracts are combined, the ether is removed, and the residue distilled from a 500-cc. modified Claisen flask having a 25-cm. fractionating side arm. The fraction boiling at 95–100° at 5 mm. weighs 170–190 g. and melts at 78–80°. This product is transferred to a large mortar, allowed to cool, and ground with 120 cc. of petroleum ether (b.p. 35–60°). After filtering with suction, and allowing the solvent to evaporate from the crystals, there is obtained 133–147 g. of cyclohexanone oxime (59–65 per cent of the calculated amount) melting at 86–88° (Note 2).

(*B*) ε-*Benzoylaminocaproic Acid.*—The rearrangement of 100 g. (0.88 mole) of pure cyclohexanone oxime (Note 3) is carried out in the following way. In a 1-l. beaker are placed a 10-g. portion of the oxime and 20 cc. of 85 per cent sulfuric acid (sp. gr. 1.783) (Note 4). The beaker is heated with a low flame and the contents are mixed with a rotary motion until bubbles first appear. The beaker is then removed from the flame immediately, and the violent reaction, which lasts a few seconds, is allowed to subside. The acid solution of ε-caprolactam is transferred to a 5-l. round-bottomed flask, and another 10-g. portion of the oxime is placed in the beaker and rearranged with sulfuric acid as before. The combined acid solution from the ten operations is diluted with 2.5 l. of water and boiled gently for one and one-half hours with 5 g. of decolorizing carbon. The solution is filtered and exactly neutralized to litmus with 50 per cent sodium hydroxide solution. About 510 g. of sodium hydroxide solution is usually required. The neutral solution is boiled for one-half hour with 5 g. of decolorizing carbon and filtered.

The filtrate is placed in a 5-l. flask fitted with a mechanical stirrer, cooled in an ice bath to 10°, and a solution of 55 g. (1.37 moles) of sodium hydroxide in 55 cc. of water added. The temperature being

kept at 10°, 94 g. (0.67 mole) of benzoyl chloride is added dropwise from a separatory funnel over a period of thirty-five to forty minutes, with rapid stirring. The mixture is stirred for an hour longer, filtered, and placed in a 4-l. beaker. The cold filtrate is slowly acidified to Congo red by adding 10 per cent hydrochloric acid, with hand stirring (about 450 cc. of acid is required). The solid (Note 5) is filtered with suction, washed with water, and spread out to dry. When dry, the product is washed with two 100-cc. portions of petroleum ether (35–60°) to remove the admixed benzoic acid. The adhering petroleum ether is allowed to evaporate from the crystals, and the final drying is carried out in a vacuum desiccator over sulfuric acid. The yield of purified product, m.p. 77–80°, is 135–150 g. (65–72 per cent of the calculated amount, based on cyclohexanone oxime).

2. Notes

1. The sodium nitrite may be added directly to 2 kg. of ice, but, if this is done, the nitrite and ice should be mixed thoroughly outside the flask to prevent caking of the ice.
2. Cyclohexanone oxime can be prepared with better yields from the ketone, hydroxylamine hydrochloride (Org. Syn. Coll. Vol. I, **1941**, 318), and sodium carbonate according to the procedure given on p. 314. The preparation using hydroxylamine hydrochloride, however, is more expensive than that given above.
3. The rearrangement of the oxime is carried out in 10-g. portions and in a large open beaker because of the violence of the reaction. It is essential to use oxime of good quality or a product of inferior grade results.
4. Acid of this concentration may be prepared by mixing five volumes of concentrated sulfuric acid with one volume of water.
5. If the acid separates as an oil, it should be allowed to stand with occasional stirring until it solidifies.

3. Discussion

ε-Benzoylaminocaproic acid has been prepared by treatment of benzoylpiperidine with phosphorus pentachloride to form ε-benzoylaminoamyl chloride, conversion to the nitrile, and hydroylsis to the acid,[1] and by the procedure described above.[2]

Directions for the rearrangement of cyclohexanone oxime and isolation of ε-caprolactam and ε-aminocaproic acid are to be found on pp. 371 and 28.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 74
- Org. Syn. Coll. Vol. 2, 371
- Org. Syn. Coll. Vol. 6, 90
- Org. Syn. Coll. Vol. 8, 568

References and Notes

1. Braun, Ber. **42**, 839 (1909).
2. Eck and Marvel, J. Biol. Chem. **106**, 387 (1934).

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

petroleum ether

Congo red

ε-benzoylaminoamyl chloride

ethyl alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

phosphorus pentachloride (10026-13-8)

Cyclohexanone (108-94-1)

sodium carbonate (497-19-8)

sulfur dioxide (7446-09-5)

sodium nitrite (7632-00-0)

Benzoic acid (65-85-0)

sodium bisulfite (7631-90-5)

decolorizing carbon (7782-42-5)

benzoyl chloride (98-88-4)

Benzoylpiperidine (776-75-0)

Hydroxylamine hydrochloride (5470-11-1)

ε-AMINOCAPROIC ACID (60-32-2)

ε-caprolactam (105-60-2)

Cyclohexanone oxime (100-64-1)

ε-Benzoylaminocaproic acid,
Caproic acid, ε-benzamido- (956-09-2)