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.

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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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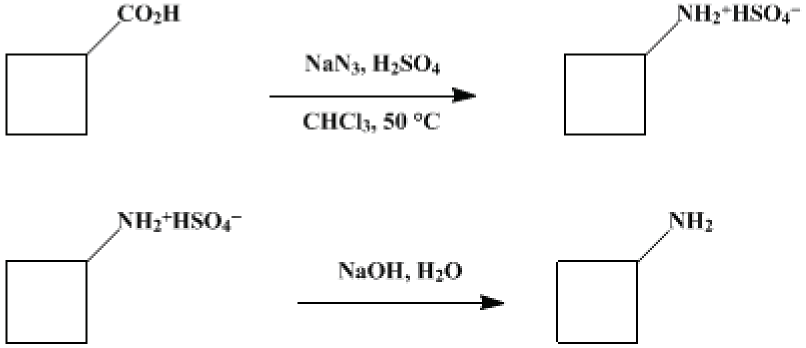
Organic Syntheses, Coll. Vol. 5, p.273 (1973); Vol. 47, p.28 (1967).

CYCLOBUTYLAMINE



Submitted by Newton W. Werner and Joseph Casanova, Jr.[1].
Checked by Donald Barth and Kenneth B. Wiberg.

1. Procedure

Caution! The reaction should be carried out in a good hood because hydrazoic acid is very toxic. Care should also be taken in handling sodium azide.

In a 1-l. three-necked, round-bottomed flask equipped with a mechanical stirrer, reflux condenser, and powder funnel are placed 180 ml. of reagent grade chloroform, 16.0 g. (0.16 mole) of cyclobutanecarboxylic acid (Note 1), and 48 ml. of concentrated sulfuric acid. The flask is heated in an oil bath to 45–50°, and 20.0 g. (0.31 mole) of sodium azide (Note 2) is added over a period of 1.5 hours (Note 3). After the addition of sodium azide is complete, the reaction mixture is heated at 50° for 1.5 hours. The flask is cooled in an ice bath, and approximately 200 g. of crushed ice is added slowly. A solution of 100 g. of sodium hydroxide in 200 ml. of water is prepared, cooled to room temperature, and then added slowly to the reaction mixture until the pH of the mixture is approximately 12–13. The mixture is poured into a 2-l. three-necked, round-bottomed flask, the flask is set up for steam distillation, and about 2 l. of distillate is collected in a cooled receiver containing 90 ml. of 3*N* hydrochloric acid (Note 4). The water and chloroform are removed by distillation under reduced pressure (Note 5), and the amine hydrochloride is transferred to a 50 ml. round-bottomed flask with a few milliliters of water. A straight condenser is connected to the flask, and the flask is cooled in an ice bath. A slush is prepared by grinding potassium hydroxide pellets in a mortar and then adding a minimum volume of water. The slush is added in portions through the top of the condenser. After the mixture has become sufficiently basic, the amine appears as a separate phase. More potassium hydroxide pellets are added to dry the amine phase. The condenser is replaced by a heated, vacuum-jacketed Vigreux column equipped with a soda-lime tube, and the fraction having a boiling point of 79–83° is collected. The distillate is dried over potassium hydroxide pellets for 2 days. The liquid is decanted into a distilling flask containing a few potassium hydroxide pellets and distilled through the apparatus described above to give 7–9 g. (60–80%) of cyclobutylamine, b.p. 80.5–81.5°, n^{25}D 1.4356 (Note 6), (Note 7).

2. Notes

1. Cyclobutanecarboxylic acid was purchased from the Aldrich Chemical Co., Milwaukee, Wisconsin. A synthesis of the acid is described in *Org. Syntheses*, Coll. Vol. **3**, 213 (1955).
2. Eastman practical grade was used.
3. The sodium azide is added at such a rate that a gentle reflux of vapors in the powder funnel is maintained. After somewhat more than the theoretical amount of azide has been added, the rate of addition may be much more rapid.
4. The distillation should be carried out carefully at first until all the chloroform has distilled. A

distilling adapter dipping just below the surface of the acid solution should be used in order to minimize loss of cyclobutylamine. Care must be taken that the basic solution in the distillation flask which still contains sodium azide does not come in contact with the hydrochloric acid solution in the receiver.
5. A water aspirator is sufficient.
6. Contact of the amine with the atmosphere should be avoided since the amine reacts with carbon dioxide.
7. The purity of the product was checked by vapor phase chromatography on a polyethylene glycol on Teflon column at 72°, 15 p.s.i., and a flow rate of 102 ml. of helium per minute. The sample appeared to be homogeneous, but, since the amine tails badly on the column, it is not possible to detect the presence of a small amount of water (less than 3%).
An n.m.r. spectrum of cyclobutylamine in carbon tetrachloride showed no resonance signals at less than 1 p.p.m. from tetramethylsilane. This suggests that no cyclopropylcarbinylamine was formed by rearrangement during the reaction.

3. Discussion

The preparation of cyclobutylamine from cyclobutanecarboxylic acid and hydrazoic acid has been reported previously.[2,3] Cyclobutylamine has also been prepared by the Hofmann-type rearrangement of cyclobutanecarboxamide.[4,5,6,7] More recently it has been prepared in 82–87% overall yield from cyclobutanecarboxamide by oxidative rearrangement with lead tetraacetate or iodosobenzene diacetate.[8]

4. Merits of the Preparation

This procedure permits the synthesis of cyclobutylamine from cyclobutanecarboxylic acid in one step and in high yield. The procedures involving the Hofmann rearrangement[4,5,6,7] require the preparation of the amide from the acid and afford lower yields of the amine.

The interest in the synthesis of compounds containing the cyclobutyl ring system is due to the observation that reactions which are thought to proceed through cationic intermediates give rise to rearrangement products. For example, deamination of cyclobutylamine in aqueous solution gives cyclopropylcarbinol and allylcarbinol as well as cyclobutanol.[9] Recent investigations have been concerned with the exact nature of these cationic intermediates.[10,11]

References and Notes

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

hydrazoic acid

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

carbon tetrachloride (56-23-5)

amine hydrochloride

carbon dioxide (124-38-9)

potassium hydroxide (1310-58-3)

sodium azide (26628-22-8)

Cyclobutanecarboxylic acid (3721-95-7)

helium (7440-59-7)

tetramethylsilane (75-76-3)

Cyclobutylamine (2516-34-9)

cyclopropylcarbinylamine (2516-47-4)

Cyclobutanecarboxamide (1503-98-6)

Iodosobenzene diacetate (3240-34-4)

cyclobutyl (4548-06-5)

cyclopropylcarbinol (2516-33-8)

allylcarbinol (627-27-0)

Cyclobutanol (2919-23-5)

lead tetraacetate (546-67-8)