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.

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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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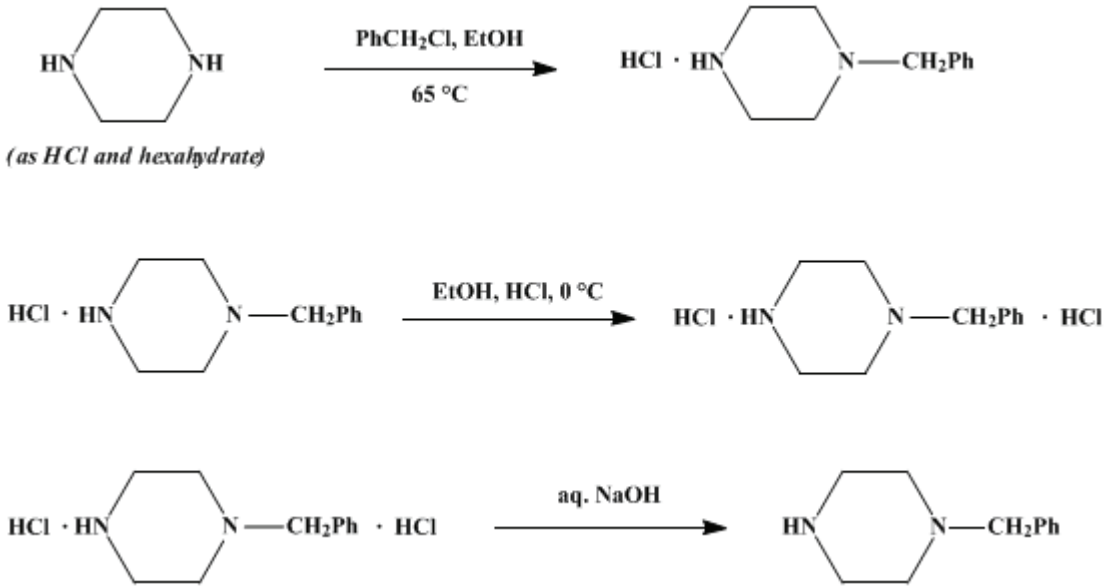
1-BENZYLPIPERAZINE

[Piperazine, 1-benzyl-]



Submitted by J. Cymerman Craig and R. J. Young[1].
Checked by James Cason and Taysir Jaouni.

1. Procedure

A solution of 24.3 g. (0.125 mole) of piperazine hexahydrate in 50 ml. of absolute ethanol, contained in a 250-ml. Erlenmeyer flask, is warmed in a bath at 65° as there is dissolved in the solution, by swirling, 22.1 g. (0.125 mole) of piperazine dihydrochloride monohydrate (Note 1). As warming in the bath at 65° is continued, there is added during 5 minutes, with vigorous swirling or stirring, 15.8 g. (14.3 ml., 0.125 mole) of recently distilled benzyl chloride. The separation of white needles commences almost immediately. After the solution has been stirred for an additional 25 minutes at 65°, it is cooled, and the unstirred solution is kept in an ice bath for about 30 minutes. The crystals of piperazine dihydrochloride monohydrate are collected by suction filtration, washed with three 10-ml. portions of ice-cold absolute ethanol, and then dried. Recovery of the dihydrochloride is 21.5–22.0 g. (97–99%) (Note 2).

The combined filtrate and washings from the piperazine dihydrochloride are cooled in an ice bath and treated with 25 ml. of absolute ethanol saturated at 0° with dry hydrogen chloride (Note 3). After the solution has been well mixed, it is cooled for 10–15 minutes in an ice bath. The precipitated white plates of 1-benzylpiperazine dihydrochloride are collected by suction filtration, washed with dry benzene, and dried. The product, which melts at about 280° with decomposition, after sintering at about 254° (Note 4), amounts to 29.0–29.5 g. (93–95%). A solution of this salt in 50 ml. of water is made alkaline (pH > 12) with about 60 ml. of 5*N* sodium hydroxide, then extracted twelve times with 20-ml. portions (Note 5) of chloroform. The combined extracts are dried over anhydrous sodium sulfate, and the pale-brown oil (Note 6) remaining after removal of solvent is distilled at reduced pressure in a Claisen flask. The yield of pure 1-benzylpiperazine, b.p. 122–124°/2.5 mm., n_D^{25} 1.5440–1.5450, is 14.3–16.5 g. (65–75%).

2. Notes

1. Piperazine dihydrochloride monohydrate, which is recovered almost quantitatively in this procedure, may be purchased from K and K Laboratories, Jamaica 33, New York, or from L. Light and Co., Ltd.,

Poyle, Colnbrook, Bucks, England. It may be readily prepared in essentially quantitative yield from the free base by the following procedure.
A brisk stream of hydrogen chloride gas is passed for 5–8 minutes into a solution of 24.3 g. (0.125 mole) of piperazine hexahydrate in 50 ml. of absolute ethanol contained in a 250-ml. Erlenmeyer flask. A wide gas-inlet tube (about 10 mm.) is used to avoid clogging, and the flask is cooled in an ice bath to keep the temperature at about 25°. After the gas stream has been discontinued, the contents of the flask are cooled to about 0°, and the crystalline product is collected by suction filtration and washed with two 25-ml. portions of ice-cold absolute ethanol. The yield is about 22 g. (0.125 mole).
2. If the filtrate from this isolation is evaporated to dryness at reduced pressure, crude 1-benzyl-4-piperazinium chloride is left as a residue. For removal of any piperazine dihydrochloride, the chloride may be crystallized after rapidly filtering a hot solution in about 50 ml. of absolute ethanol. Concentration of the filtrate, followed by cooling, gives 12.4 g. (84%) of 1-benzyl-4-piperazinium chloride as prismatic plates, m.p. 167–168°. This salt may be converted to the dihydrochloride by treatment with ethanolic hydrogen chloride.
3. When absolute ethanol is saturated with hydrogen chloride at 0°, the resultant solution is about 10.5*N* in hydrogen chloride.
4. The melting point has been reported as 253° by Baltzly and co-workers.[2]
5. The checkers found continuous extraction with chloroform to be convenient.
6. The free base rapidly absorbs carbon dioxide on exposure to air and should therefore be protected during both manipulation and storage. The undistilled oil may be converted in good yield to 1-benzoyl-4-benzylpiperazine hydrochloride, m.p. 245–245.5°, by treatment with benzoyl chloride in benzene solution.

3. Discussion

1-Benzylpiperazine has been prepared[2,3] by the reaction of piperazine and benzyl chloride, followed by fractionation of piperazine, and the mono- and dibenzyl derivatives. It has also been obtained[4] by alkaline hydrolysis of 1-benzyl-4-carbethoxypiperazine. The present method, which is a modification of that first reported by Cymerman Craig, Rogers, and Tate,[5] is simple and yields an easily purified product.

4. Merits of Preparation

The benzyl group, easily removed by hydrogenolysis, is an ideal blocking group for the preparation of 1-monosubstituted, and of 1,4-unsymmetrically disubstituted, piperazines.

Published methods for preparation of 1-benzylpiperazine involve either fractionation of mixtures of piperazine and its 1-benzyl- and 1,4-dibenzyl derivatives or the use of 1-carbethoxypiperazine as an intermediate. The procedure here described is simple; it yields, in 30 minutes, pure 1-benzylpiperazine dihydrochloride, stable to storage, from readily available starting materials, and free of any disubstituted compound.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 904

References and Notes

1. Department of Chemistry, University of Sydney, Sydney, Australia.
2. R. Baltzly, J. S. Buck, E. Lorz, and W. Schon, *J. Am. Chem. Soc.*, **66**, 263 (1944).
3. R. E. Lutz and N. H. Shearer, *J. Org. Chem.*, **12**, 771 (1947).
4. B. W. Horrom, M. Freifelder, and G. R. Stone, *J. Am. Chem. Soc.*, **77**, 753 (1955).
5. J. Cymerman Craig, W. P. Rogers, and M. E. Tate, *Australian J. Chem.*, **9**, 397 (1956).

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

ethanol (64-17-5)

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

carbon dioxide (124-38-9)

benzoyl chloride (98-88-4)

benzyl chloride (100-44-7)

1-Benzylpiperazine,
Piperazine, 1-benzyl- (2759-28-6)

piperazine hexahydrate (142-63-2)

piperazine dihydrochloride monohydrate

piperazine dihydrochloride (142-64-3)

1-benzylpiperazine dihydrochloride

1-benzyl-4-piperazinium chloride

1-benzoyl-4-benzylpiperazine hydrochloride

piperazine (110-85-0)

1-benzyl-4-carbethoxypiperazine

1-carbethoxypiperazine (120-43-4)