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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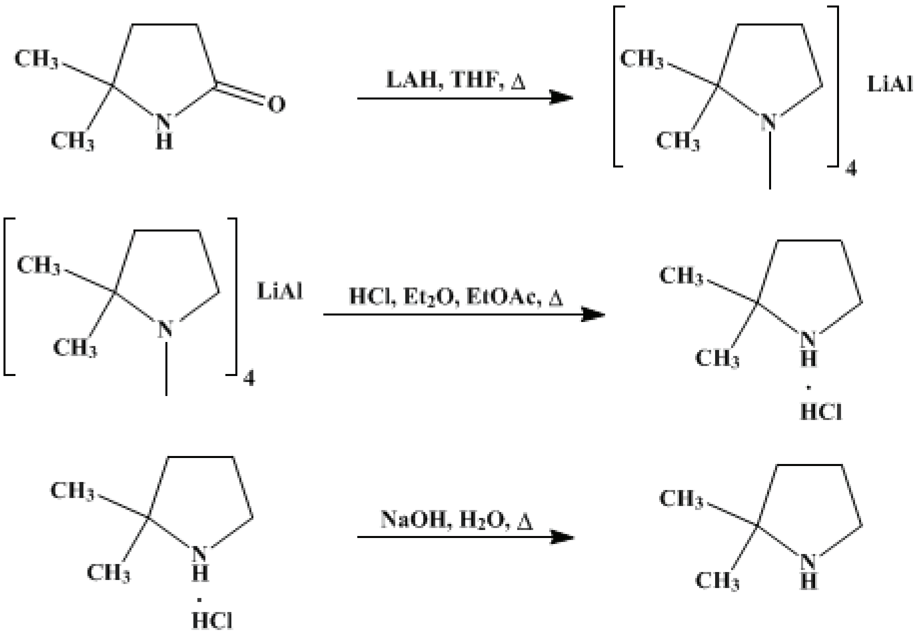
2,2-DIMETHYLPYRROLIDINE

[Pyrrolidine, 2,2-dimethyl-]



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1. Procedure

A 3-l. three-necked round-bottomed flask is placed on a steam bath and fitted with a mercury-sealed Hershberg stirrer, a dropping funnel, and an efficient reflux condenser topped with a tube containing soda lime and calcium chloride. In this flask are placed 38 g. (1 mole) of pulverized lithium aluminum hydride (Note 1) and 400 ml. of dry tetrahydrofuran (Note 2). The mixture is heated under reflux with stirring for 15 minutes or until most of the lithium aluminum hydride has dissolved. A solution of 90.5 g. (0.8 mole) of 5,5-dimethyl-2-pyrrolidone (p.357) in 200 ml. of dry tetrahydrofuran (Note 2) is added slowly at such a rate that the solvent refluxes gently without external heating. When the addition is complete and the initial reaction subsides, the mixture is stirred and heated at gentle reflux for 8 hours.

The condenser is then set for downward distillation, and, while the mixture is stirred, about 450 ml. of solvent is distilled (Note 3) and (Note 4). The condenser is reset in the reflux position, and 300 ml. of ether (commercial anhydrous) is added slowly from the dropping funnel with vigorous stirring. This is followed by 50 ml. of ethyl acetate added very slowly with vigorous stirring and finally by 500 ml. of 6*N* hydrochloric acid added in the same manner.

The condenser is again set downward, and the dropping funnel is replaced by a tube reaching nearly to the bottom of the flask. Steam is passed in, and the distillation is continued for several minutes after the boiling point reaches 100° (Note 5). The distillate is discarded. The mixture in the flask is cooled, and to it is added carefully 350 ml. of 12*N* sodium hydroxide with stirring (Note 6). The alkaline mixture is then steam-distilled until the distillate is no longer basic (Note 7).

The 2,2-dimethylpyrrolidine may be recovered from the aqueous distillate in two ways: (*a*) the distillate can be extracted continuously with ether;[2] or (*b*) the distillate can be acidified with hydrochloric acid and concentrated to dryness under reduced pressure to give crude 2,2-dimethylpyrrolidine hydrochloride. The base is then liberated by adding an excess of saturated aqueous sodium hydroxide solution. The oily layer is separated. The aqueous layer and salt are extracted several times with ether, which is combined with the amine. In either case the ether solution is dried thoroughly over anhydrous potassium carbonate (Note 8).

The drying agent is removed by filtration, and the ether is stripped through a short helices-packed column. The residue is fractionally distilled at 103–105°/745 mm.; n_D^{20} 1.4330; n_D^{25} 1.4304; d_4^{25} 0.8211. The yield is 53–62 g. (67–79%).

2. Notes

1. The hydride can be pulverized rapidly and safely by breaking the large pieces with a spatula, followed by careful crushing with a mortar and pestle. Caution must be observed because the solid may inflame on prolonged grinding or abrasion. The hydride dust is caustic and irritating.
2. Tetrahydrofuran from E.I. du Pont de Nemours and Company can be dried conveniently by adding to it lithium aluminum hydride in small portions until no further reaction (evolution of hydrogen) ensues. After the mixture has been stirred for a few minutes, most of the tetrahydrofuran is distilled from it with stirring (to prevent bumping) (Note 3), and collected in a receiver protected from moisture by a calcium chloride tube.
3. Care must be taken in distilling solutions of lithium aluminum hydride. Explosions have been reported[3] toward the end of distillations of such solutions, especially if they contained carbon dioxide. It is therefore recommended that these distillations be carried out behind a shield and that not more than *three-fourths* of the solvent be removed.
4. If this tetrahydrofuran is collected in a receiver protected from moisture it may be used in subsequent runs.
5. This steam distillation removes ether, tetrahydrofuran, and other volatile neutral products. If too much water accumulates in the flask, it may be heated in an electric heating mantle after most of the ether has been removed.
6. At this point the mixture should be a very strongly basic, mobile, milky slurry.
7. From time to time an aliquot of the distillate being collected can be titrated with standard acid to determine whether significant amounts of amine are distilling.
8. Sufficient drying agent should be used so that no aqueous liquid phase appears.

3. Discussion

2,2-Dimethylpyrrolidine has been prepared by the hydrogenation of 5-amino-2,2-dimethylpyrroline-N-oxide or 5-imino-2,2-dimethylpyrrolidine in the presence of Raney nickel[4] or by reduction with sodium and alcohol.[4] The present procedure has been published.[5]

References and Notes

1. The Upjohn Company, Kalamazoo, Michigan.
2. *Org. Syntheses Coll. Vol.* **1**, 277 (1941).
3. Barbaras, Barbaras, Finholt, and Schlesinger, *J. Am. Chem. Soc.*, **70**, 877 (1948).
4. Buckley and Elliott, *J. Chem. Soc.*, **1947**, 1508.
5. Moffett and White, *J. Org. Chem.*, **17**, 407 (1952).

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

soda lime

amine

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

carbon dioxide (124-38-9)

Raney nickel (7440-02-0)

sodium (13966-32-0)

hydride

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

2,2-Dimethylpyrrolidine,
Pyrrolidine, 2,2-dimethyl- (35018-15-6)

5,5-Dimethyl-2-pyrrolidone (5165-28-6)

2,2-dimethylpyrrolidine hydrochloride

5-amino-2,2-dimethylpyrroline-N-oxide

5-imino-2,2-dimethylpyrrolidine