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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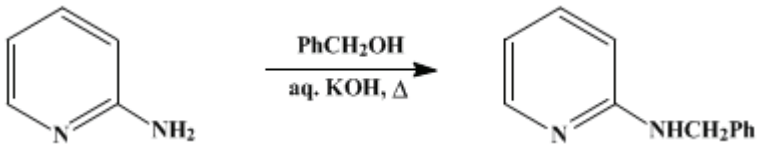
2-BENZYLAMINOPYRIDINE

[Pyridine, 2-benzylamino-]



Submitted by Yaïr Sprinzak[1]
Checked by Max Tishler and Matthew A. Kozlowski.

1. Procedure

A 500-ml. Claisen flask with a 35-mm. indented side arm (Note 1) is attached downward to a Liebig condenser for distillation. A thermometer, held by a cork stopper, is inserted through the neck of the flask and adjusted so that its bulb is close to the bottom. The flask is heated by means of an electric mantle or air bath. To the flask are charged 94 g. (1.0 mole) of 2-aminopyridine (Note 2), 150 g. (1.4 moles) of benzyl alcohol, and 9 g. of 85% potassium hydroxide. The mixture is heated to boiling and boiled vigorously enough to cause slow distillation of water accompanied by as little benzyl alcohol as possible (Note 3). The temperature of the boiling mixture rises gradually from 182° to 250° during a period of 30 minutes. The mixture is maintained at 250° for 3 minutes, then allowed to cool. The distillate amounts to 19–20 ml. of a water-rich layer and 2–4 ml. of a benzyl alcohol-rich layer.

The residual product is cooled to about 100° (Note 4) and poured into 250 ml. of water. The crystallized solid is crushed and collected on a 12-cm. Büchner funnel. Slight suction is applied at first, but, after most of the mother liquor has been removed, the crystals are pressed down with strong suction. The product is then washed thoroughly with water. After drying, the yield of colorless 2-benzylaminopyridine (Note 5) and (Note 6), m.p. 95–96°, amounts to 180–183 g. (98–99% of the theoretical amount). The product may be recrystallized from isopropyl alcohol with 90% recovery. For each gram of amine 3 ml. of solvent is employed. The melting point of recrystallized material is 96.0–96.7° (cor.), lit.[2] m.p. 97–98°.

2. Notes

1. A short Vigreux column or any other short column for distillation may be used.
2. 2-Aminopyridine was obtained from Matheson, Coleman and Bell, Inc., East Rutherford, New Jersey.
3. If the reaction mixture is heated too strongly or the vapors are inadequately fractionated, correspondingly greater amounts of benzyl alcohol will distill, with concomitant loss of yield. The distillate should be clear, not milky.
4. If the product has partially solidified, it should be melted for easy handling.
5. By essentially the same procedure N,N'-dibenzyl-*p*-phenylenediamine has been obtained in 92% yield. The heating period requires 1 hour, and the final temperature is 260°.
6. N-Benzylaniline has been obtained in 90–94% yield by an appropriate modification[3] of this method.

3. Discussion

For 2-benzylaminopyridine the methods of preparation of significance are condensation of 2-pyridinesulfonic acid and benzylamine,[4] condensation of the alkali metal salts of 2-aminopyridine with benzyl chloride[5] or benzyl alcohol,[6] reductive alkylation of 2-aminopyridine in the presence of benzaldehyde and formic acid,[2] oxidation of N-benzyl-N-pyridylaminoacetonitrile or N-benzyl-N-pyridylaminoacetaldoxime,[7] and the method described here modified by use of an inert solvent.[8]

References and Notes

1. The Weizmann Institute of Science, Rehovoth, Israel.
2. Kaye and Kogon, *Rec. trav. chim.*, **71**, 309 (1952).
3. Sprinzak, *J. Am. Chem Soc.*, **78**, 3207 (1956).
4. Mangini and Colonna, *Gazz. chim. ital.*, **73**, 313 (1943) [*C. A.*, **41**, 1224 (1947)].
5. Huttrer, Djerassi, Beears, Mayer, and Scholz, *J. Am. Chem. Soc.*, **68**, 1999 (1946).
6. Géczy, *Magyar Kém. Folyóirat*, **62**, 162 (1956) [*C. A.*, **52**, 10075 (1958)].
7. Bristow, Charlton, Peak, and Short, *J. Chem. Soc.*, **1954**, (616).
8. Hirao and Hagashi, *J. Pharm. Soc. Japan*, **74**, 853 (1954) [*C. A.*, **49**, 10308 (1955)].

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

formic acid (64-18-6)

benzaldehyde (100-52-7)

potassium hydroxide (1310-58-3)

isopropyl alcohol (67-63-0)

N-Benzylaniline (103-32-2)

benzyl chloride (100-44-7)

Benzyl alcohol (100-51-6)

2-aminopyridine (504-29-0)

benzylamine (100-46-9)

2-Benzylaminopyridine,
Pyridine, 2-benzylamino- (6935-27-9)

2-pyridinesulfonic acid

N-benzyl-N-pyridylaminoacetonitrile

N-benzyl-N-pyridylaminoacetaldoxime

N,N'-dibenzyl-p-phenylenediamine