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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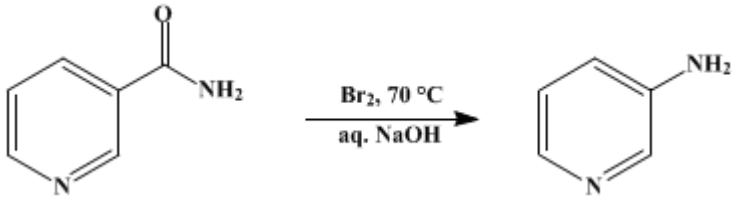
3-AMINOPYRIDINE

[Pyridine, 3-amino-]



Submitted by C. F. H. Allen and Calvin N. Wolf[1].
Checked by Cliff S. Hamilton and Marjorie Debrunner.

1. Procedure

In a 2-l. beaker equipped with a mechanical stirrer and immersed in an ice-salt bath is placed a solution of 75 g. (1.87 moles) of sodium hydroxide in 800 ml. of water. To the solution is added, with stirring, 95.8 g. (30.7 ml., 0.6 mole) of bromine. When the temperature of the solution reaches 0°, 60 g. (0.49 mole) of nicotinamide (Note 1) is added all at once with vigorous stirring. After being stirred for 15 minutes, the solution is clear. The ice-salt bath is replaced by a bath containing water at 75°, and the solution is stirred and heated at 70–75° for 45 minutes.

The solution is cooled to room temperature, saturated with sodium chloride (about 170 g. is required), and extracted with ether in a continuous extractor (Note 2). The extraction time is 15–20 hours. The ether extract is adjusted to a volume of 1 l., dried over 4–5 g. of sodium hydroxide pellets, and filtered, and the ether is removed by distillation from a steam bath. The residue crystallizes on cooling. The yield of dark red crystals melting at 61–63° is 39–41 g. (85–89%).

The crude product is dissolved in a mixture of 320 ml. of benzene and 80 ml. of ligroin (b.p. 60–90°) and heated on a steam bath with 5 g. of Norit and 2 g. of sodium hydrosulfite for 20 minutes. The hot solution is filtered by gravity, allowed to cool slowly to room temperature, and then chilled overnight in a refrigerator. The product is isolated by gravity filtration (Note 3), washed on the filter with 25 ml. of ligroin, and dried in a vacuum desiccator. The yield of white crystals melting at 63–64° amounts to 28–30 g. (61–65%). By concentrating the combined filtrate and washings to a volume of 150 ml., an additional 2–3g. of pale yellow crystals melting at 62–64° can be obtained. The total yield of 3-aminopyridine is 30–33 g. (65–71%).

2. Notes

1. The nicotinamide should be finely powdered to facilitate rapid solution.
2. The continuous extractor described by Pearl[2] was used. If the material is extracted in a separatory funnel, four 800-ml. portions and ten 500-ml. portions of ether are required to give the above yield.
3. Since 3-aminopyridine is somewhat hygroscopic, it tends to liquefy if collected on a suction filter.

3. Discussion

3-Aminopyridine has been prepared by heating nicotinamide in an alkaline potassium hypobromite solution at 70°;[3,4] by hydrolysis of β-pyridylurethane with oleum;[5] by heating 3-aminopyridine-2-carboxylic acid at 250°;[6] by reduction of 3-nitropyridine with zinc and hydrochloric acid;[7] by heating 3-bromopyridine with ammonia and copper sulfate in a sealed tube,[8,9] and by the hydrolysis of benzyl 3-pyridylcarbamate, prepared from nicotinic acid hydrazide through the corresponding azide.[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 27

References and Notes

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2. Pearl, *Ind. Eng. Chem., Anal. Ed.*, **16**, 62 (1944).
3. Camps, *Arch. Pharm.*, **240**, 354 (1902).
4. Philips, *Ann.*, **288**, 263 (1895).
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

ligroin

β-pyridylurethane

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

bromine (7726-95-6)

copper sulfate (7758-98-7)

sodium hydrosulfite (7775-14-6)

Norit (7782-42-5)

zinc (7440-66-6)

potassium hypobromite

3-Aminopyridine,

Pyridine, 3-amino- (462-08-8)

nicotinamide (98-92-0)

3-aminopyridine-2-carboxylic acid

3-nitropyridine (2530-26-9)

3-bromopyridine (626-55-1)

benzyl 3-pyridylcarbamate

nicotinic acid hydrazide (553-53-7)