Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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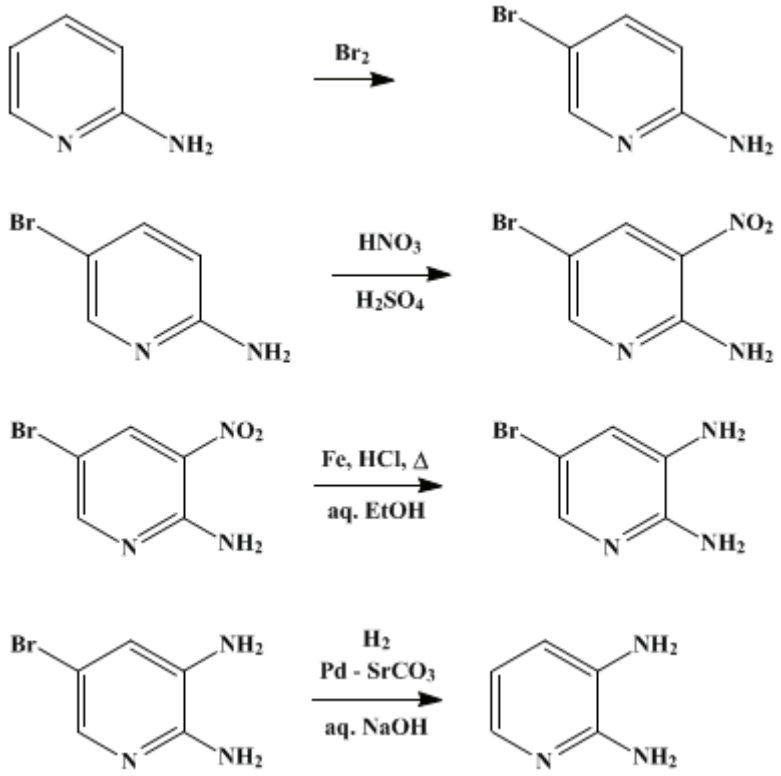
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.044.0034

Organic Syntheses, Coll. Vol. 5, p.346 (1973); Vol. 44, p.34 (1964).

2,3-DIAMINOPYRIDINE

[Pyridine, 2,3-diamino-]



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1. Procedure

Caution! The bromination and nitration steps should be carried out in a well-ventilated hood.

A. *2-Amino-5-bromopyridine.* In a 2-l. three-necked flask equipped with stirrer, dropping funnel, and condenser is placed a solution of 282 g. (3.0 moles) of 2-aminopyridine (Note 1) in 500 ml. of acetic acid. The solution is cooled to below 20° by immersion in an ice bath, and 480 g. (154 ml., 3.0 moles) of bromine dissolved in 300 ml. of acetic acid is added dropwise with vigorous stirring over a period of 1 hour. Initially the temperature is maintained below 20°, but after about half the bromine solution has been added it is allowed to rise to 50° to delay as long as possible the separation of the hydrobromide of 2-amino-5-bromopyridine. At 50° the hydrobromide usually begins to crystallize when about three-quarters of the bromine has been added. When addition of bromine is completed, the mixture is stirred for 1 hour and is then diluted with 750 ml. of water to dissolve the hydrobromide. The contents of the flask are transferred to a 5-l. beaker and are neutralized, with stirring and cooling, by the addition of 1.2 l. of 40% sodium hydroxide solution.

The precipitated 2-amino-5-bromopyridine, contaminated with some 2-amino-3,5-dibromopyridine, is collected by filtration and, after washing with water until the washings are free of ionic bromide, is dried at 110° (Note 2). The 2-amino-3,5-dibromopyridine is removed from the product by washing with three 500-ml. portions (Note 3) of hot petroleum ether (b.p. 60–80°). The yield of 2-amino-5-bromopyridine, m.p. 132–135°, sufficiently pure for use in the next stage, is 320–347 g. (62–67%) (Note 4) and (Note 5).

B. *2-Amino-5-bromo-3-nitropyridine.* A 1-l. three-necked flask immersed in an ice bath and equipped with stirrer, dropping funnel, condenser, and thermometer is charged with 500 ml. of sulfuric acid (sp. gr. 1.84), and 86.5 g. (0.5 mole) of 2-amino-5-bromopyridine is added at such a rate that the temperature does not exceed 5°. Twenty-six milliliters (39 g., 0.57 mole) of 95% nitric acid is added dropwise with stirring at 0°, and the mixture is stirred at 0° for 1 hour, at room temperature for 1 hour, and at 50–60° for 1 hour. The contents of the flask are cooled and poured onto 5 l. of ice and neutralized with 1350 ml. of 40% sodium hydroxide solution. The yellow precipitate of 2-amino-5-bromo-3-nitropyridine is collected by filtration and washed with water until the washings are free of sulfate, slightly acidulated water being used at the end to prevent colloidal break-through. The product is dried at room temperature to constant weight. The yield of 2-amino-5-bromo-3-nitropyridine, m.p. 204–208°, sufficiently pure for the next stage, is 85–93 g. (78–85%) (Note 6) and (Note 7).

C. *2,3-Diamino-5-bromopyridine* (Note 8). A 100-ml. flask fitted with a reflux condenser is charged with 10.9 g. (0.05 mole) of 2-amino-5-bromo-3-nitropyridine, 30 g. of reduced iron, 40 ml. of 95% ethanol, 10 ml. of water, and 0.5 ml. of concentrated hydrochloric acid (Note 9) and (Note 10). The mixture is heated on a steam bath (Note 11) for 1 hour, and at the end of this period the iron is removed by filtration and is washed three times with 10-ml. portions of hot 95% ethanol. The filtrate and washings are evaporated to dryness, and the dark residue is recrystallized from 50 ml. of water, 1 g. of activated carbon being used and the mixture being filtered while hot. The charcoal is washed with hot ethanol to avoid losses. 2,3-Diamino-5-bromopyridine crystallizes as colorless needles, m.p. 163°. The yield is 6.5–7.1 g. (69–76%).

D. *2,3-Diaminopyridine* (Note 12). In an apparatus for catalytic hydrogenation (Note 13) 56.4 g. (0.3 mole) of 2,3-diamino-5-bromopyridine suspended in 300 ml. of 4% sodium hydroxide solution is shaken with hydrogen in the presence of 1.0 g. of 5% palladized strontium carbonate (Note 14). When absorption of hydrogen is completed, the catalyst is removed by filtration, and, after saturation with potassium carbonate (about 330 g. is required), the resulting slushy mixture is extracted continuously with ether until all the precipitate completely disappears (usually about 18 hours, but this depends on the efficiency of the extraction apparatus). The ether is removed by distillation, and the residue of crude 2,3-diaminopyridine is recrystallized from benzene (about 600 ml. is required) using 3 g. of activated charcoal and filtering rapidly through a preheated Büchner funnel. The yield of 2,3-diaminopyridine, obtained as colorless needles, m.p. 115–116°, pK_a 6.84, is 25.5–28.0 g. (78–86%) (Note 15).

2. Notes

1. The checkers used a pure grade of 2-aminopyridine (m.p. 58–60°) obtained from Matheson, Coleman and Bell.
2. The checkers dried their product at room temperature to constant weight in order to avoid loss of product due to its high volatility at 110°. It was found that 95% of an aliquot had sublimed during drying for 24 hours at 110° and atmospheric pressure. The residue analyzed high in bromine, indicating that the monobromo derivative is more volatile than the dibromo derivative.
3. The checkers washed their crude product by first refluxing its suspension in 600 ml. of petroleum ether (b.p. 60–71°) for about 20 minutes. The product, obtained by filtration, was slurry-washed on the funnel with two 600-ml. portions of boiling petroleum ether followed by air-drying to constant weight.
4. The checkers' yield, for reasons outlined in (Note 2), were appreciably higher. In two runs using one-half the quantities of reactants they obtained 211 g. and 224 g. (81–86%), of product, m.p. 132–133.5° and 133.5–135°, respectively; water content (K.F.) in both products was 0.2%.
5. If required, the 2-amino-5-bromopyridine may be recrystallized from benzene as colorless prisms, m.p. 137°.
6. The checkers' yield was 85.3 g. (78.2%), m.p. 202–204°.
7. Pure 2-amino-5-bromo-3-nitropyridine, yellow needles, m.p. 210°, may be obtained by recrystallizing the product from ethyl methyl ketone.
8. The method is essentially that of Petrow and Saper.[3]
9. Attempts to reduce larger quantities of the amino-nitro compound by this method usually give lower yields. For larger quantities several reductions may be carried out simultaneously, and the filtrates may be combined for isolation of the diamine.
10. The checkers reduced a double batch and obtained 12.8 g. (68%), m.p. 159.5–160°. In this run,

heating time was doubled and charcoal was extracted repeatedly (by recycling mother liquors) to assure complete extraction.
11. The checkers employed a mechanical stirrer.
12. This is essentially the procedure of Leese and Rydon.[4]
13. The apparatus described in *Org. Syntheses*, Coll. Vol. **1**, 61 (1941), or a commercial equivalent of it, is suitable.
14. The palladized strontium carbonate is prepared as follows. Suspend 33 g. of strontium carbonate in 350 ml. of water at 70°. Add 2 g. of palladium chloride dissolved in 10 ml. of concentrated hydrochloric acid, and stir the mixture at 70° for 15 minutes. Filter the mixture, wash the product thoroughly with hot water, and dry the product at 110°.
15. The checkers' yields were 74.8%–84.7% of analytically pure material giving a negative Beilstein test.

3. Discussion

2,3-Diaminopyridine has been prepared by reduction of 2-amino-3-nitropyridine with iron and aqueous acidified ethanol,[3] tin and hydrochloric acid,[5] or stannous chloride and hydrochloric acid,[5] by catalytic reduction of 3-amino-2-nitropyridine,[6] by reduction of 3-amino-2-nitropyridine,[7] 2-amino-5-chloro-3-nitropyridine,[8] or 2-amino-5-bromo-3-nitropyridine[4] with sodium hydroxide solution and an aluminum nickel alloy, and by catalytic reduction of 2-amino-5-bromo-3-nitropyridine.[4] Amination of 3-aminopyridine with sodamide[9] and of 3-amino-2-chloropyridine with concentrated aqueous ammonia[10] have also been employed.

4. Merits of the Preparation

By this method of preparation 2,3-diaminopyridine is obtained in 26–43% yield from the readily available 2-aminopyridine. The intermediates 2-amino-5-bromopyridine and 2-amino-5-bromo-3-nitropyridine are prepared in higher yields than previously recorded.

Methods of preparation of 2,3-diaminopyridine which involve the reduction of 2-amino-3-nitropyridine are laborious. The material is obtained in yields of less than 10% by nitration of 2-aminopyridine, and its separation from 2-amino-5-nitropyridine, which is the major product of the nitration, is tedious and inconvenient. Reduction of amino-nitro or amino-halo-nitro compounds with sodium hydroxide solution and an aluminum nickel alloy gives variable yields of an inferior product, and the method can be used only for preparing comparatively small quantities of 2,3-diaminopyridine. Catalytic reduction of 3-amino-2-nitropyridine gives a good yield of 2,3-diaminopyridine, but preparation of the amino-nitro compound is a difficult and time-consuming process. The method of Schickh, Binz, and Schulz,[10] which involves chlorination of 3-aminopyridine to 3-amino-2-chloropyridine and amination of the latter by heating for 20 hours at 130° with concentrated aqueous ammonia, suffers from the disadvantage that 3-aminopyridine is less readily available than is 2-aminopyridine. Furthermore the yields obtained in the amination stage are somewhat erratic, and the yields obtained by the submitters never approached the 57% reported.

References and Notes

1. Science and Food Technology Department, Salford Technical College, Salford 5, England.
2. Department of Chemistry, Color Chemistry and Dyeing, Huddersfield College of Technology, Huddersfield, England.
3. V. Petrow and J. Saper, *J. Chem. Soc.*, 1390 (1948).
4. C. L. Leese and H. N. Rydon, *J. Chem. Soc.*, 4039 (1954).
5. T. Takahashi and S. Yajima, *J. Pharm. Soc. Japan*, **64**, (7a) 30 (1944).
6. J. W. Clark-Lewis and M. J. Thompson, *J. Chem. Soc.*, **442** (1957).
7. H. M. Curry and J. P. Mason, *J. Am. Chem. Soc.*, **73**, 5046 (1951).
8. J. B. Ziegler, *J. Am. Chem. Soc.*, **71**, 1891 (1949).
9. A. Konopnicki and E. Plazek, *Ber.*, **60**, 2045 (1927).
10. O. V. Schickh, A. Binz, and A. Schulz, *Ber.*, **69**, 2593 (1936).

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

petroleum ether

palladized strontium carbonate

ethanol (64-17-5)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

Benzene (71-43-2)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

iron (7439-89-6)

nitric acid (7697-37-2)

bromide (24959-67-9)

bromine (7726-95-6)

tin (7440-31-5)

stannous chloride

carbon (7782-42-5)

2-aminopyridine (504-29-0)

palladium chloride (7647-10-1)

ethyl methyl ketone (78-93-3)

sodamide (7782-92-5)

3-Aminopyridine (462-08-8)

strontium carbonate (1633-05-2)

3-amino-2-chloropyridine (6298-19-7)

2,3-Diaminopyridine,
Pyridine, 2,3-diamino- (452-58-4)

2-Amino-5-bromopyridine (1072-97-5)

2-amino-3,5-dibromopyridine (35486-42-1)

2-Amino-5-bromo-3-nitropyridine (6945-68-2)

2,3-Diamino-5-bromopyridine (38875-53-5)

2-amino-3-nitropyridine (4214-75-9)

3-amino-2-nitropyridine (13269-19-7)

2-amino-5-chloro-3-nitropyridine

2-amino-5-nitropyridine (4214-76-0)