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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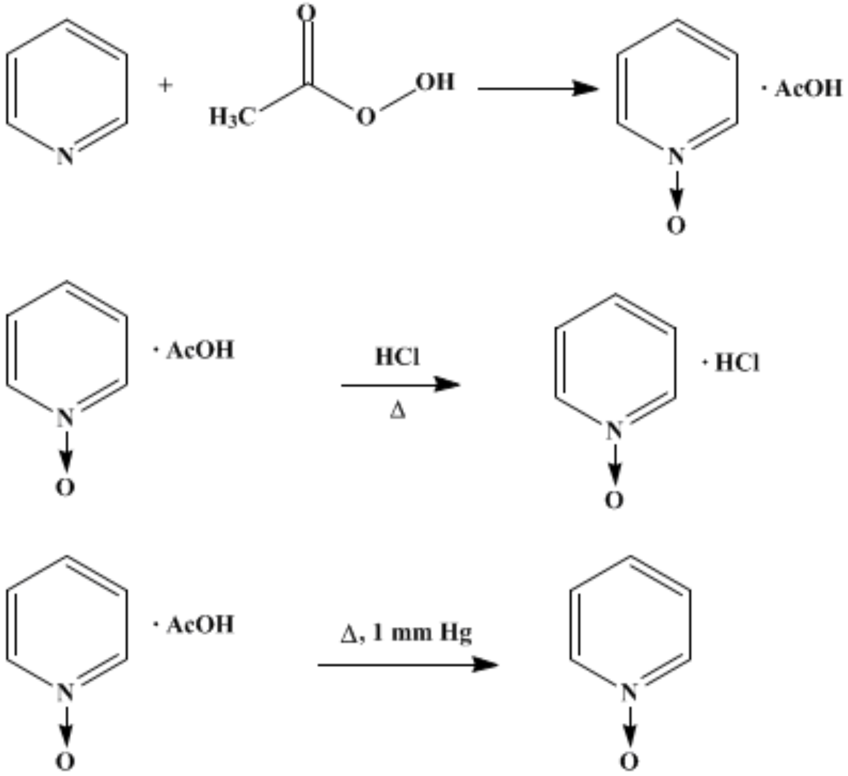
PYRIDINE-N-OXIDE

[Pyridine-1-oxide]



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1. Procedure

Caution! Reactions and subsequent operations involving peracids and peroxy compounds should be run behind a safety shield. Peroxy compounds should be added to the organic material, never the reverse. For relatively fast reactions, the rate of addition of the peroxy compound should be slow enough so that it reacts rapidly and no significant unreacted excess is allowed to build up. The reaction mixture should be stirred efficiently while the peroxy compound is being added, and cooling should generally be provided since many reactions of peroxy compounds are exothermic. New or unfamiliar reactions, particularly those run at elevated temperatures, should be run first on a small scale. Reaction products should never be recovered from the final reaction mixture by distillation until all residual active oxygen compounds (including unreacted peroxy compounds) have been destroyed. Decomposition of active oxygen compounds may be accomplished by the procedure described in Korach, M.; Nielsen, D. R.; Rideout, W. H. Org. Synth. 1962, 42, 50 (Org. Synth. 1973, Coll. Vol. 5, 414). [Note added January 2011].

In a 1-l. three-necked flask equipped with a stirrer (Note 1), a thermometer, and a dropping funnel is placed 110 g. (1.39 moles) of pyridine. The pyridine is stirred, and 250 ml. (285 g., 1.50 moles) of 40% peracetic acid (Note 2) is added at such a rate that the temperature reaches 85° and is maintained there. After the addition, which requires 50–60 minutes, the mixture is stirred until the temperature drops to 40°.

A. *Pyridine-N-oxide hydrochloride.* The acetate is converted to the hydrochloride by bubbling a slight excess over the theoretical amount (51 g.) of gaseous hydrogen chloride into the reaction mixture by way of a 7-mm. gas inlet tube which replaces the dropping funnel in the reaction flask. The acetic acid and excess peracetic acid are removed by warming on the steam bath under vacuum (Note 3). The residual pyridine-N-oxide hydrochloride is purified by heating under reflux for 30 minutes with 300 ml. of isopropyl alcohol, cooling to room temperature, and filtering. The colorless crystals are washed with 50 ml. of isopropyl alcohol followed by 50 ml. of ether. The yield is 139–152 g. (76–83%) (Note 4), m.p. 179.5–181°.

B. *Pyridine-N-oxide.* The acetic acid solution is evaporated on the steam bath under the pressure of a water aspirator, and the residue (180–190 g.) is distilled at a pressure of 1 mm. or less in an apparatus suitable for collecting a solid distillate (Note 5). The vacuum pump must be protected with a Dry Ice trap capable of holding about 60 ml. of acetic acid, which distils as the pyridine-N-oxide acetate dissociates at low pressure. Heat is provided by an oil bath, the temperature of which is not allowed to rise above 130° (Note 6). The product is collected at 100–105°/1mm. (95–98°/0.5 mm.). The yield is 103–110 g. (78–83%) of colorless solid, m.p. 65–66° (sealed capillary). The base is deliquescent and must be stoppered immediately.

2. Notes

1. A convenient seal for stirring under vacuum (see (Note 3)) is made by running an 8-mm. glass rod, with propeller or paddle stirrer at the end, through the outside member of an 18/9 spherical joint which is inserted into a suitable rubber stopper. The inner member of the 18/9 spherical joint is then slipped over the stirrer and held in place with a piece of rubber tubing. This rotating seal may then be lubricated with a drop of oil. Alternatively, one may use a Trubore stirring system.
2. Becco peracetic acid (40%) was used. The composition and properties of this commercial preparation are described fully in *Bulletin* 4 of the Buffalo Electro-Chemical Company, Buffalo, New York. The manufacturer's recommendations for storing and handling should be followed. Experiments using proportionate amounts of 10% or 20% peracetic acid in acetic acid were equally successful. The strength of the peracetic acid, as well as the progress of the reaction, can be determined iodimetrically.[2]
3. The vacuum evaporation proceeds much more smoothly and rapidly if the mixture is stirred mechanically during the process.
4. The submitters report that the same procedure is successful with four times the amounts given here. With the increased amounts, a water bath is used for cooling during the initial addition, which then requires about 45 minutes.
5. *Caution! Before distillation, absence of peroxide should be established by test with potassium iodide.* The apparatus for distillation of solids in vacuum described in *Organic Syntheses*[3] is satisfactory, as is a combination of standard taper flasks, short column, and adaptors.
6. It is imperative that the pressure be maintained at 1 mm. or lower. Decomposition is usually extensive at higher pressures; however, the removal of the acetic acid may be initiated at 5–10 mm. pressure. The oil-bath temperature must not exceed 130° if decomposition is to be avoided. A fore-run of 15–20 g., b.p. 90–98°/0.5 mm., can be saved and redistilled in combination with similar cuts from successive runs. About 9–10 g. (7%) of additional crystalline pyridine-N-oxide is obtained per run in this manner.

3. Discussion

Pyridine-N-oxide has been prepared by oxidation of pyridine with perbenzoic acid,[4] with monoperphthalic acid,[5] with peracetic acid (hydrogen peroxide and acetic acid),[6,7] and with hydrogen peroxide and other carboxylic acids.[7].

References and Notes

1. Stanford University, Stanford, California.
2. Smit, *Rec. trav. chim.*, **49**, 691 (1930).
3. *Org. Syntheses Coll. Vol.* **3**, 133 (1955).

4. Meisenheimer, *Ber.*, **59**, 1848 (1926).
5. Bobranski, Kochanska, and Kowalewska, *Ber.*, **71**, 2385 (1938).
6. Ochiai, Ishikawa, and Zai-Ren, *J. Pharm. Soc. Japan*, **64**, 73 (1944) [*C. A.*, **45**, 8526*h* (1951)]; Hertog and Combé, *Rec, trav., chim.*, **70**, 581 (1951).
7. Ochiai, Katada, and Hayashi, *J. Pharm. Soc. Japan*, **67**, 33 (1947) [*C. A.*, **45**, 9541*i* (1951)]; Ochiai, *J. Org. Chem.*, **18**, 534 (1953).

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

Monoperphthalic acid

hydrogen chloride (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

potassium iodide (7681-11-0)

pyridine (110-86-1)

isopropyl alcohol (67-63-0)

hydrogen peroxide (7722-84-1)

peracetic acid (79-21-0)

pyridine-1-oxide,
PYRIDINE-N-OXIDE (694-59-7)

pyridine-N-oxide hydrochloride

pyridine-N-oxide acetate

Perbenzoic acid (93-59-4)