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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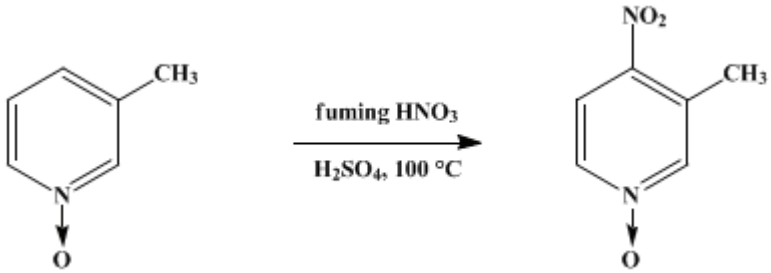
3-METHYL-4-NITROPYRIDINE-1-OXIDE

[3-Picoline, 4-nitro-, 1-oxide]



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1. Procedure

One hundred and eighty grams (1.65 moles) of liquefied 3-methylpyridine-1-oxide (Note 1) is added to 630 ml. of cold (0–5°) sulfuric acid (sp. gr. 1.84) contained in a 3-l. round-bottomed flask immersed in an ice-salt bath. The resulting mixture is cooled to about 10°, and 495 ml. of fuming yellow nitric acid (sp. gr. 1.50) is added in 50-ml. portions with shaking. An efficient spiral condenser (52 × 4 cm.) is attached to the flask, and the latter is placed in an oil bath. The temperature is slowly raised to 95–100° during 25–30 minutes, at which time gas evolution begins. After about 5 minutes the rate of gas evolution increases, and the oil bath is removed. A spontaneous and vigorous reaction commences which must be controlled by the application of an ice-water bath (Note 2). After the vigorous reaction has subsided to a moderate rate (about 5 minutes) the ice-water bath is removed, and the reaction is allowed to proceed for an additional 5–10 minutes. The oil bath is then replaced, and heating is continued at 100–105° for 2 hours.

The reaction mixture is cooled to 10° and poured onto 2 kg. of crushed ice carbonate in a 4-l. beaker. Addition of 1.36 kg. of sodium carbonate monohydrate (*Hood!*) (Note 3) in small portions with stirring causes the separation of the yellow crystalline product along with sodium sulfate. The mixture is then allowed to stand for 3 hours to expel nitrogen oxides. The yellow solid is collected by suction filtration, thoroughly washed with water, and rendered as dry as possible on the filter. The filtrates (about 4 l.) are transferred to a separatory funnel.

The collected solid is extracted twice with 400–500 ml. portions of boiling chloroform, the combined extracts are used to extract the aqueous filtrates contained in the separatory funnel, and the extraction is repeated with several fresh 500-ml. portions of chloroform. The combined chloroform extracts are then given preliminary drying over anhydrous sodium sulfate and evaporated to dryness by distillation under reduced pressure. The residue is transferred to a 2-l. Erlenmeyer flask and dissolved in 1.5 l. of boiling acetone. The acetone solution is concentrated on a steam bath to 800–900 ml. (crystallization begins when the volume is about 1 l.) and then cooled at 5° for 6–8 hours. The product is filtered by suction, the filtrates are removed and saved, and the collected solid is washed with ether and dried. The yield is 162–173 g. (64–68%), m.p. 137–138°. The acetone filtrates mentioned above are boiled down to 150 ml. and chilled in an ice bath, and the crude product so obtained (m.p. 131–135°) is recrystallized from acetone to give an additional 13.5–16.5 g., m.p. 136–138°. The total yield is 178–187 g. (70–73%).

2. Notes

1. Freshly distilled 3-methylpyridine-1-oxide (b.p. 101–103°/0.7–0.8 mm.) will remain in a supercooled liquid state for several hours before solidifying. The highly hygroscopic solid may be melted on a steam bath in a tightly closed, previously weighed flask, and the melt poured slowly into the sulfuric acid. A

large amount of heat is liberated in the mixing.

3-Methylpyridine-1-oxide (3-picoline-1-oxide) may be prepared by a method similar to that employed for pyridine-1-oxide (p.828). To a mixture of 600–610 ml. of glacial acetic acid and 200 g. (2.15 moles) of freshly distilled 3-methylpyridine (b.p. 141–143°) contained in a 2-l round-bottomed flask is added, with shaking, 318 ml. (2.76 moles) of cold (5°) 30% hydrogen peroxide. The mixture is heated in an oil bath for 24 hours, with the internal temperature adjusted to 70 ± 5° The excess acetic acid and water are removed under reduced pressure (30 mm.), and, after 500 ml. of distillate has been collected, the residue is diluted with 200 ml. of water and concentrated again, with the collection of 200 ml. of distillate. The residual mixture is cooled to 0–5° in an ice-salt bath, and 500 ml. of cold (0–5°) 40% acqueous sodium hydroxide solution is added slowly with shaking. The strongly alkaline solution is extracted with 2 l. of chloroform, and the extracts are given preliminary drying over anhydrous sodium carbonate. The extracts are filtered and concentrated by distillation under reduced pressure. The product is distilled under vacuum, b.p. 84–85°/0.3 mm., and the yield of 3-methylpyridine-1-oxide is 175–180 g. (73–77%).

2. Vigorous refluxing with evolution of nitrogen oxides occurs. Serious flooding of the condenser may result if no cooling is applied.

3. During the addition of sodium carbonate, large volumes of nitrogen oxides are evolved. In experiments where smaller quantities of sodium carbonate were used, lower yields (ca. 62%) were obtained.

3. Discussion

3-Methylpyridine-1-oxide has been prepared by the oxidation of 3-methylpyridine with hydrogen peroxide in glacial acetic acid,[3,4] with 40% peracetic acid and sodium acetate,[5] and with perbenzoic acid in benzene.[6]

3-Methyl-4-nitropyridine-1-oxide has been prepared by the nitration of 3-methylpyridine-1-oxide hydrochloride with a mixture of concentrated sulfuric acid and potassium nitrate,[5] and by the nitration of 3-Methylpyridine-1-oxide with a mixture of concentrated sulfuric acid and fuming nitric acid.[7] The preparation of this compound has been mentioned briefly by Talikowa.[8]

References and Notes

1. Princeton University, Princeton, New Jersey.
2. University of illinois, Urbana, Illinois.
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7. Itai and Ogura, *J. Pharm. Soc. Japan*, **75**, 292 (1955) [*C. A.*, **50**, 1808 (1956)].
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

nitric acid (7697-37-2)

sodium carbonate (497-19-8)

carbonate (3812-32-6)

sodium sulfate (7757-82-6)

acetone (67-64-1)

hydrogen peroxide (7722-84-1)

potassium nitrate (7757-79-1)

peracetic acid (79-21-0)

3-METHYL-4-NITROPYRIDINE-1-OXIDE,
3-Picoline, 4-nitro-, 1-oxide (1074-98-2)

3-methylpyridine-1-oxide,
3-picoline-1-oxide (1003-73-2)

pyridine-1-oxide (694-59-7)

3-methylpyridine (108-99-6)

3-methylpyridine-1-oxide hydrochloride

sodium carbonate monohydrate (5968-11-6)

Perbenzoic acid (93-59-4)