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.

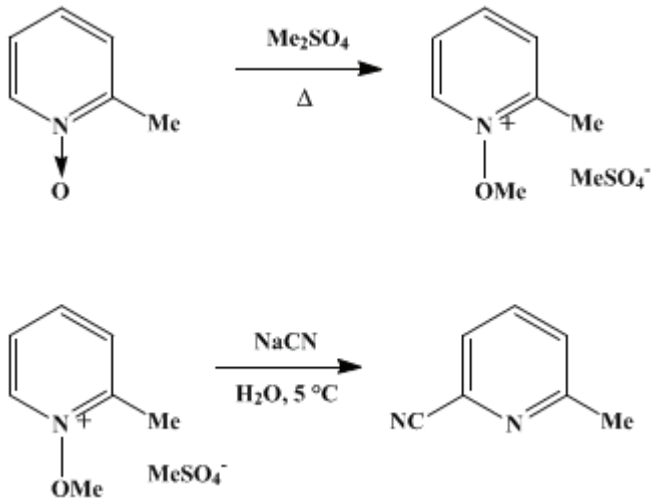
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.042.0030

Organic Syntheses, Coll. Vol. 5, p.269 (1973); Vol. 42, p.30 (1962).

2-CYANO-6-METHYLPYRIDINE

[6-Methylpicolinonitrile]



Submitted by Wayne E. Feely, George Evanega, and Ellington M. Beavers[1].
Checked by William E. Parham, Stuart W. Fenton, and William W. Henderson.

1. Procedure

Caution! All the operations should be carried out in a well-ventilated hood because of the toxic natures of dimethyl sulfate, hydrogen cyanide, and cyanide solutions.

A. *1-Methoxy-2-methylpyridinium methyl sulfate*. In a 1-l. three-necked flask equipped with a Hirshberg stirrer, a thermometer which extends deep into the flask, and a 250-ml. pressure-equalizing, dropping funnel fitted with a calcium chloride drying tube is placed 109 g. (1.0 mole) of dry powdered 2-picoline-1-oxide (Note 1). The stirrer is started at a slow rate, and 126 g. (1.0 mole) of dimethyl sulfate (Note 2) is added dropwise at a rate such that the temperature of the reaction mixture slowly rises to between 80° and 90° and remains in this range throughout the addition (Note 3). When the addition is about two-thirds complete, gentle heating with a steam bath is necessary to maintain this temperature. After complete addition (about 1 hour), the mixture is heated for an additional 2 hours on a steam bath at 90–100°. The molten salt is then poured into a large evaporating dish and placed in a vacuum desiccator under partial vacuum to cool. The salt is obtained as a white crystalline mass in essentially quantitative yield (235 g.) (Note 4) and (Note 5).

B. *2-Cyano-6-methylpyridine*. In a 2-l., three-necked, round-bottomed flask equipped with a Hershberg stirrer, a 500-ml. pressure-equalizing, dropping funnel without a stopper, and a thermometer-gas inlet adapter (Note 6) fitted with a thermometer which reaches deep into the flask is placed a solution of 147 g. (3.0 mole) of sodium cyanide dissolved in 400 ml. of water. The stirrer is started and the apparatus is flushed with prepurified nitrogen for 1 hour (Note 7). The solution in the flask is then cooled to 0° with an ice bath, and a solution of 235 g. (1.0 mole) of 1-methoxy-2-methylpyridinium methyl sulfate dissolved in 300 ml. of water is added dropwise over a period of 2 hours. The dropping funnel and the thermometer-adapter are then quickly removed and replaced by stoppers, and the flask is allowed to stand in a refrigerator overnight (12–16 hours). The flask, containing needles of the crude nitrile (Note 8), is removed from the refrigerator and the contents stirred at room temperature for 6 hours. After addition of 200 ml. of chloroform, the contents of the flask are transferred to a large separatory funnel and the layers separated. Extraction of the aqueous phase is repeated twice with 100-ml. portions of chloroform, and the combined extracts are dried over anhydrous magnesium sulfate.

After removal of the drying agent by filtration, the filtrate is concentrated on a steam bath to remove chloroform, and the residual crude cyanopicoline (90–110 g.) is transferred, while hot, to a distilling flask. Distillation under reduced pressure (30 mm.) (Note 9) gives three fractions: Fraction I, b.p. 99–106°, weighs 15–20 g.; Fraction II, b.p. 106–124°, weighs 5–10 g.; and Fraction III, b.p. 125–131°, weighs 60–70 g. (Note 10). Fraction III is dissolved in 1 l. of hot 10% ethyl alcohol, treated with 0.5 g. of activated carbon, filtered, and the filtrate is allowed to cool slowly to room temperature. The 2-cyano-6-methylpyridine separates as white prismatic needles, m.p. 71–73°, and weighs 48–54 g. (40–46% based on 2-picoline-1-oxide) (Note 11) and (Note 12).

2. Notes

1. The preparation of 2-picoline-1-oxide is described by Boekelheide and Linn.[2] The oxide is hygroscopic, and best results are obtained if it is redistilled just before use. The submitters used 2-picoline-1-oxide, obtained from the Reilly Tar and Chemical Company, Indianapolis, Indiana, which was freshly redistilled and boiled at 118–120°/10 mm.
2. Eastman Kodak Company practical grade was used. Dimethyl sulfate is toxic and must be handled with caution. Provision should be made for containing the contents should breakage occur. Ammonia is a specific antidote for dimethyl sufate and should be at hand to destroy any accidentally spilled.
3. The submitters have observed that, when 1-methoxypyridinium methyl sulfate salts are heated above about 140–150°, violent explosions usually result.
4. The salt is very hygroscopic. Aqueous solutions of the salt slowly hydrolyze upon standing to di(1-methoxy-2-methylpyridinium) sulfate but may be used in the subsequent step without adverse effects.
5. The salt may be recrystallized from anhydrous acetone, giving colorless prisms, m.p. 67–70°.[3]
6. A thermometer adapted with a gas-addition tube may be purchased from Ace Glass Inc., Vineland, New Jersey (Cat. No. 5266).
7. The presence of small amounts of air during the formation of the nitrile rapidly darkens the reaction mixture.
8. The crude 2-cyano-6-methylpyridine which has separated (40–50 g.) may be recrystallized from dilute ethyl alcohol to yield 35–45 g. of pure product.
9. The distillation is conveniently performed in a Claisen flask with a fractionating side arm. The checkers used a heat lamp to prevent solidification of product in the condenser.
10. Fraction **I**, b.p. 99–106°/30 mm., is mostly 4-cyano-2-methylpyridine and is best purified by redistillation.[4] Fraction **II**, b.p. 106–125°/30 mm., contains a mixture of the two nitriles and may be further purified by redistillation.
11. Physical constants reported for 2-cyano-6-methylpyridine are b.p. 135–136°/38 mm.,[5] m.p. 69–71°,[5] m.p. 72–74°.[6,7]
12. This general method has been used to prepare 2- and 4-cyanopyridine from pyridine-1-oxide in 32% and 49% yields, respectively; 2-cyano-4,6-dimethylpyridine (73%) from 4,6-dimethylpyridine-1-oxide; 2-cyanoquinoline (93%) from quinoline-1-oxide; and 1-cyanoisoquinoline (95%) from isoquinoline-2-oxide.[3]

3. Discussion

The present method is essentially that given by Feely and Beavers.[3] 2-Cyano-6-methylpyridine also has been prepared by the fusion of sodium 6-methylpyridine-2-sulfonate with potassium cyanide.[5] In addition, this nitrile has been prepared from 2-chloro-6-methylpyridine[6] (no yield stated) and from a catalytic reaction of 2,6-lutidine with air and ammonia in low yield.[6,7]

4. Merits of Preparation

This preparation describes a convenient and general method for preparing cyano derivatives of pyridine, quinoline, and isoquinoline from the corresponding, and readily available, amine oxides.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 303
- Org. Syn. Coll. Vol. 5, 370

References and Notes

1. Research Laboratories, Rohm and Haas Co., Philadelphia, Pennsylvania.
2. V. Boekelheide and W. J. Linn, *J. Am. Chem. Soc.*, **76**, 1286 (1954).
3. W. E. Feely and E. M. Beavers, *J. Am. Chem. Soc.*, **81**, 4004 (1959).
4. E. Ochiai and I. Suzuki, *Pharm. Bull. (Tokyo)*, **2**, 247 (1954).
5. I. Suziki, *Pharm. Bull. (Tokyo)*, **5**, 13 (1957).
6. G. Mayurnik, A. F. Moschetto, H. S. Block, and J. V. Scudi, *Ind. Eng. Chem.*, **44**, 1630 (1952).
7. Pyridium Corp., Brit. pat. 671,763 [C.A. **47**, 1746 (1953)].

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

2- and 4-cyanopyridine

ethyl alcohol (64-17-5)

ammonia (7664-41-7)

chloroform (67-66-3)

sodium cyanide (143-33-9)

hydrogen cyanide (74-90-8)

nitrogen (7727-37-9)

cyanide (57-12-5)

potassium cyanide (151-50-8)

dimethyl sulfate (77-78-1)

acetone (67-64-1)

carbon (7782-42-5)

pyridine (110-86-1)

Quinoline (91-22-5)

2,6-Lutidine (108-48-5)

magnesium sulfate (7487-88-9)

isoquinoline (119-65-3)

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

2-Cyano-6-methylpyridine,
6-Methylpicolinonitrile (1620-75-3)

2-picoline-1-oxide (931-19-1)

1-Methoxy-2-methylpyridinium methyl sulfate (55369-05-6)

cyanopicoline

1-methoxypyridinium methyl sulfate

di(1-methoxy-2-methylpyridinium) sulfate

4-cyano-2-methylpyridine (2214-53-1)

2-cyano-4,6-dimethylpyridine

4,6-dimethylpyridine-1-oxide

2-cyanoquinoline (1436-43-7)

quinoline-1-oxide (1613-37-2)

1-cyanoisoquinoline (1198-30-7)

isoquinoline-2-oxide (1532-72-5)

sodium 6-methylpyridine-2-sulfonate

2-chloro-6-methylpyridine (18368-63-3)