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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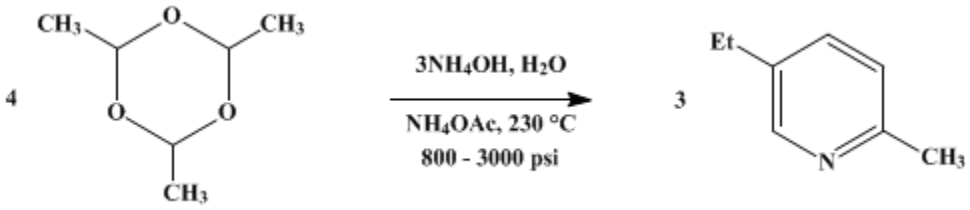
# 5-ETHYL-2-METHYLPYRIDINE

## [2-Picoline, 5-ethyl-]

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## 1. Procedure

Two hundred and sixty-seven grams (296 ml., 4.38 moles) of 28% aqueous ammonium hydroxide, 207.5 g. (209 ml., 1.57 moles) of paraldehyde, and 5.0 g. (0.065 mole) of ammonium acetate are heated to 230° with continuous agitation in a 2-l. steel reaction vessel (Note 1), and the temperature is maintained at 230° for 1 hour (Note 2). The autoclave is then allowed to cool, and the two layers of the reaction mixture are separated (Note 3). To the non-aqueous layer is added 60 ml. of chloroform, causing separation of water which is combined with the aqueous layer. The aqueous layer is extracted with three 50-ml. portions of chloroform, and the extracts are combined with the main portion of the chloroform solution. After removal of the chloroform by distillation at atmospheric pressure, fractional distillation under reduced pressure through a 30-cm. Fenske-type column[3] gives a fore-run of water, paraldehyde, and α-picoline, b.p. 40–60°/17 mm., followed by 72–76 g. (50–53%) of 5-ethyl-2-methylpyridine, b.p. 65–66°/17 mm.; $n_D^{20}$ 1.4971 (Note 4).

## 2. Notes

1. A steel reaction vessel of the type used for high-pressure catalytic hydrogenations is satisfactory. The pressure of the reaction mixture ranges from 800 to 3000 lb. A larger volume of reactants should not be used in a 2-l. reaction vessel.
2. The reaction is exothermic and in some reaction vessels may cause the temperature to rise above 230° for a short period. This has no apparent effect on the yield of product. The temperature measured is that of a thermocouple inserted in a well in the cover of the autoclave and corresponds to about 250° if the thermocouple is in the wall of the autoclave.
3. The mixture contains a small amount of solid material, apparently due to slight corrosion of the steel reaction vessel. If the solid causes the formation of an emulsion, it can be removed by filtration.
4. The yield may be increased to 60–70% by use of an 8:1 molar ratio of ammonium hydroxide to paraldehyde, but this is generally inconvenient because of the greatly increased volume of the reaction mixture.

## 3. Discussion

5-Ethyl-2-methylpyridine (also known as "aldehyde-collidine") has been prepared by heating aldehyde-ammonia;[4] aldehyde-ammonia and acetaldehyde[5,6,7] or paraldehyde;[7,8,9] aldol-ammonia and ammonia;[10] paraldehyde and ammonia;[11,12,13] acetamide,[14] or acetamide and phosphorus pentoxide[15] ethylene glycol and ammonium chloride;[16] ethylidene chloride[17,18] or bromide[19] and amonia; ethylidene chloride and acetamide, ethylamine, or *n*-amylamine;[16] crotonic acid and a calcium chloride-ammonia complex;[20] and by passage of acetylene[21] or acetaldehyde[22] and ammonia over alumina and other catalysts.

A study has been made of catalysts for the present reaction,[23] and a mechanism for the synthesis of pyridine and its derivatives by the Beyer-Chichibabin method has been published.[24]

## References and Notes


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

alumina

aldehyde-ammonia

aldol-ammonia

amonia

calcium chloride-ammonia complex

acetaldehyde (75-07-0)

acetylene (74-86-2)

Acetamide (60-35-5)

ammonia (7664-41-7)

ammonium acetate (631-61-8)

ammonium chloride (12125-02-9)

chloroform (67-66-3)

pyridine (110-86-1)

ethylene glycol (107-21-1)

ammonium hydroxide (1336-21-6)

crotonic acid (3724-65-0)

α-picoline (109-06-8)

ethylamine (75-04-7)

5-Ethyl-2-methylpyridine,
2-Picoline, 5-ethyl- (104-90-5)

ethylidene chloride (75-34-3)

phosphorus pentoxide (1314-56-3)

n-amylamine (110-58-7)

paraldehyde (123-53-7)