



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.

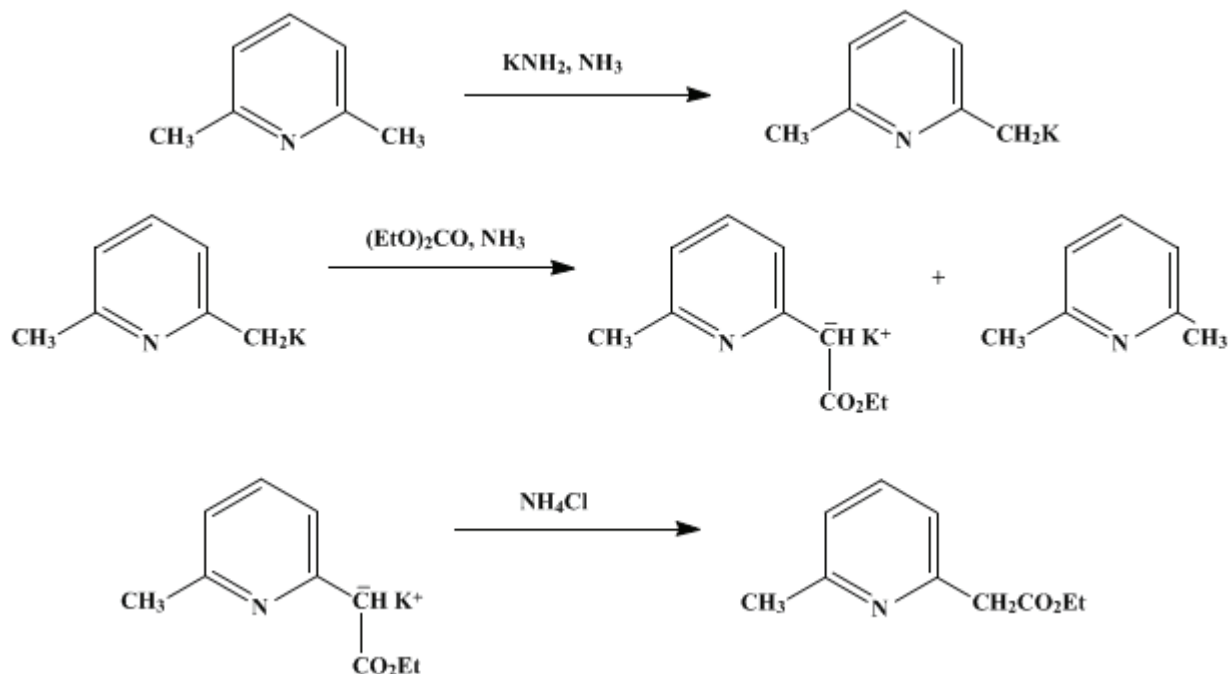
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 6, p.611 (1988); Vol. 52, p.75 (1972).

METALATION OF 2-METHYLPYRIDINE DERIVATIVES: ETHYL 6-METHYLPYRIDINE-2-ACETATE

[Pyridineacetic acid, 6-methyl-, ethyl ester]



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1. Procedure

Caution! This preparation should be carried out in a good hood to avoid exposure to ammonia.

A 1-l., three-necked flask is fitted with an acetone-dry ice condenser, a glass stirrer, and a glass stopper (Note 1). Potassium amide is prepared in 400 ml. of liquid ammonia with 8.0 g. (0.20 g.-atom) of potassium metal (Note 2). The glass stopper is replaced with an addition funnel containing 32.1 g. (0.300 mole) (Note 3) of 2,6-lutidine dissolved in *ca.* 20 ml. of anhydrous diethyl ether. The lutidine solution is added to the amide solution, and the funnel is rinsed with a little ether, which is also added. The resulting orange potassiolutidine solution is stirred for 30 minutes, then cooled in an acetone-dry-ice bath (Note 3). As rapidly as possible, 11.8 g. (0.100 mole) of freshly distilled diethyl carbonate is added, the cooling bath is removed, and the solution changes to a green color. After 5 minutes the reaction mixture is neutralized by the addition of 10.7 g. (0.200 mole) of ammonium chloride. The green color is discharged; the final mixture is gray. The condenser is removed, and the ammonia is allowed to evaporate (Note 4). The residue is stirred with 500 ml. of ether, filtered, and extracted with an additional 100 ml. of ether. The combined ethereal extracts are concentrated with a rotary evaporator, and the residual oil is distilled using a modified Claisen flask. 2,6-Lutidine (22 g., 69%) is collected at 46–56° (10 mm.), and 10.7–13.4 g. (59–75%) of the ester is collected at 87° (0.7 mm.) as a bright yellow liquid, n_D^{25} 1.4995, d_4^{20} 1.0608 (Note 5).

2. Notes

1. A Teflon stirrer should not be used since Teflon is attacked by alkali metals, metal amides, and

carbanions.

2. The preparation of **potassium amide** is described in *Org. Synth.*, **Coll. Vol. 5**, 187 (1973). *Caution! Potassium may form an explosive red or orange peroxide coating. Potassium is a silver-gray metal with a blue-violet cast, and any potassium showing an orange or red color, or with an appreciable oxide coating, should be considered extremely hazardous.*²

3. The use of an extra mole of **2,6-lutidine** and rapid addition of **diethyl carbonate** both decrease formation of **urethane**. The use of a dry-ice bath to cool the reaction mixture permits rapid addition of **diethyl carbonate** without excessive foaming. If **urethane** is formed from **diethyl carbonate** and **ammonia**, the yield of product is decreased and the distillation is difficult.

4. A steam bath or hot air gun may be used with care to speed up evaporation of the **ammonia**.

5. The ester has been reported³ to boil at 132° (18 mm.). It was reported as a colorless oil, giving a hydrochloride melting at 112–115°. **Ethyl pyridine-2-acetate** was reported in *Org. Synth.*, **Coll. Vol. 3**, 413 (1955) as a light-yellow liquid, b.p. 135–137° (28 mm.). The ¹H NMR spectrum of the present product is in accord with the structure assigned, and the hydrochloride melts at 115°.

3. Discussion

Ethyl pyridine-2-acetate⁴ and **ethyl 6-methylpyridine-2-acetate** have previously been prepared by carboxylation of the lithio derivatives of α -picoline and **2,6-lutidine**, respectively. Use of **diethyl carbonate** to acylate the organometallic derivative avoids the intermediacy of the (unstable) carboxylic acid, and the yield is better. In the present procedure **potassium amide** is used as the metalating agent; the submitters report that the same esters may be formed by metalation with **sodium amide** (43% yield) or ***n*-butyllithium** (39% yield). The latter conditions also yield an appreciable amount of the acid (which decarboxylates).

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References and Notes

1. Department of Chemistry, University of Akron, Akron, Ohio 44325.
2. J. F. Short, *Chem. Ind. (London)*, 2132 (1964) and references therein; D. P. Mellor, *Chem. Ind. (London)*, 723 (1965); M. S. Bil, *Chem. Ind. (London)*, 812 (1965).
3. V. Boekelheide and W. G. Gall, *J. Org. Chem.*, **19**, 499 (1954).
4. R. B. Woodward and E. C. Kornfeld, *Org. Synth.*, **Coll. Vol. 3**, 413 (1955).
5. L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, Wiley, New York, 1967, p. 907.

Appendix

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

ammonia (7664-41-7)

ether,
diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

potassium (7440-09-7)

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

lutidine (583-61-9)

urethane (51-79-6)

sodium amide (7782-92-5)

n-butyllithium (109-72-8)

diethyl carbonate (105-58-8)

potassium amide

Ethyl pyridine-2-acetate (2739-98-2)

Ethyl 6-methylpyridine-2-acetate,
Pyridineacetic acid, 6-methyl-, ethyl ester (5552-83-0)

potassiolutidine