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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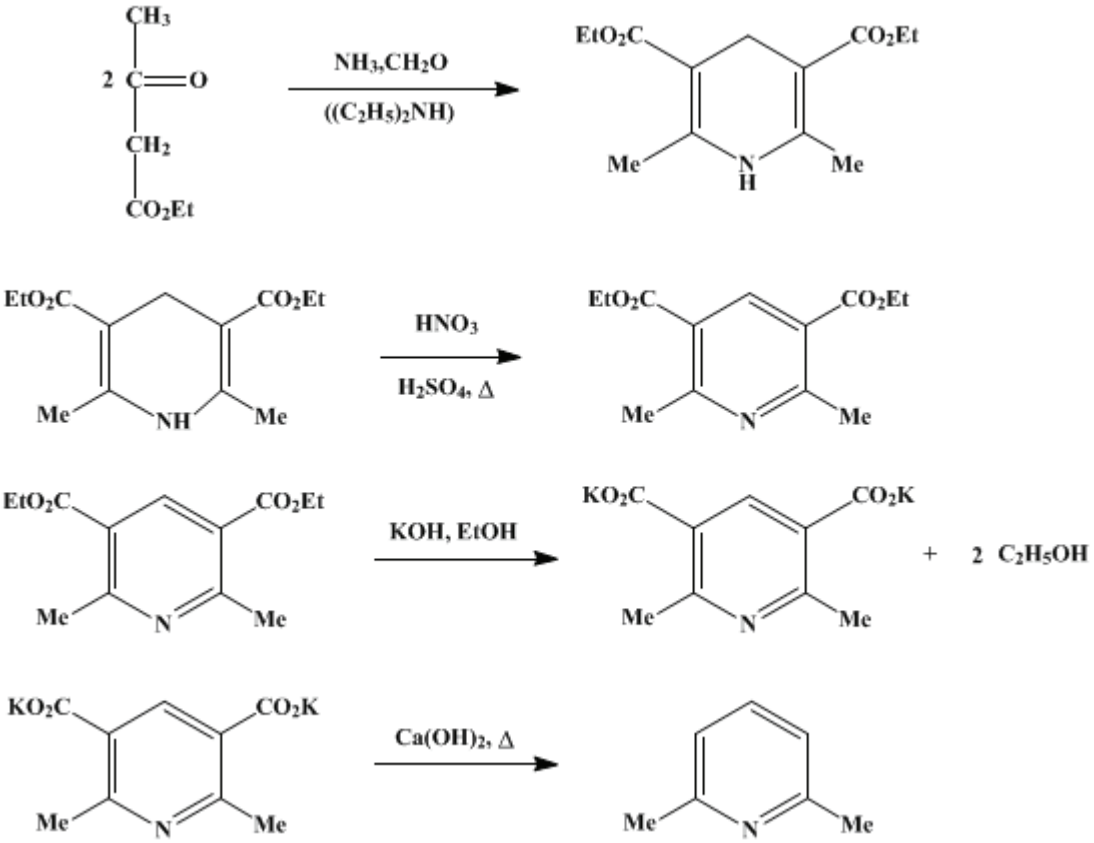
2,6-DIMETHYLPYRIDINE

[2,6-Lutidine]



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1. Procedure

To 500 g. (3.85 moles) of freshly distilled ethyl acetoacetate in a 1-l. flask, set in ice and well cooled, are added 152 g. (2 moles) of 40 per cent aqueous formaldehyde solution and 20–25 drops of diethylamine. The flask and contents are kept cold for six hours and are then allowed to stand at room temperature for forty to forty-five hours. At the end of this time two layers are present, a lower oily layer and an upper aqueous layer. The layers are separated, and the aqueous layer is extracted with 50 cc. of ether. The ether solution is added to the oily layer, and the resulting solution is dried over 30 g. of calcium chloride. The ether is then removed by distillation on a steam bath. The residue, amounting to approximately 500 g., is diluted with an equal volume of alcohol and is thoroughly cooled in an ice bath. Ammonia is then passed into the mixture until the solution is saturated. This requires from four to eight hours, and during this time the flask is kept packed in ice. The ammoniacal alcoholic solution is allowed to stand at room temperature for forty to forty-five hours. Most of the alcohol is now evaporated; the residue is cooled, and the solid 1,4-dihydro-3,5-dicarbethoxy-2,6-dimethylpyridine is removed from the remaining alcohol on a suction filter. The dried ester melts at 175–180° and weighs 410–435 g. (84–89 per cent of the theoretical amount).

To 200 g. (0.79 mole) of the ester in a 5-l. flask is added a mixture of 270 g. of water, 72 g. of concentrated nitric acid (sp. gr. 1.42), and 78 g. of concentrated sulfuric acid. The flask is then very cautiously heated, and the contents are kept in a swirling motion by a slow shaking of the flask by hand. The oxidation is accompanied by considerable foaming if the heating is too rapid, part of the reaction

mixture may be lost by excessive frothing. After the foaming has subsided, the reaction mixture is again warmed cautiously until the liquid assumes a deep red color. The entire oxidation is carried out in ten to fifteen minutes. After the liquid has ceased boiling, it is treated with 500 cc. of water and 500 g. of finely chopped ice. The resulting solution is made strongly alkaline by the gradual addition of ammonium hydroxide (sp. gr. 0.90). The precipitated 3,5-dicarbethoxy-2,6-dimethylpyridine is filtered with suction, dried on a porous plate, and then distilled (Note 1). The yield of product boiling at 170–172°/8 mm. is 115–130 g. (58–65 per cent of the theoretical amount based on the dihydro ester).

A solution of 130 g. (0.52 mole) of this ester in 400 cc. of ethyl alcohol is placed in a two-necked 2-l. flask, carrying a dropping funnel and a reflux condenser, and is heated to boiling. Then one-third of a solution (Note 2) of 78.5 g. (1.4 moles) of potassium hydroxide in 400 cc. of alcohol is added from the dropping funnel, and the alcoholic solution is boiled until it becomes clear. Then a second third of the alkali solution is added, and the reaction mixture is again boiled until any precipitate disappears. Finally, the last third of the alcoholic potassium hydroxide solution is added. The addition of the alkali requires about twenty minutes. The reaction mixture is then boiled for forty minutes longer.

The contents of the flask while still hot are poured into a 30-cm. evaporating dish and the alcohol is evaporated on a steam bath. The dry salt is pulverized and thoroughly mixed with 390 g. of calcium oxide, placed in a 2-l. copper retort (Note 3), and heated with the full flame of a Meker burner. The distillate is placed in a distilling flask and heated on a steam bath; all material distilling under 90° is removed and discarded. The residue is then allowed to stand over solid potassium hydroxide for twelve hours and is finally fractionated. The dimethylpyridine distils at 142–144°/743 mm. The yield is 35–36 g. (63–65 per cent of the theoretical amount based on the 3,5-dicarbethoxy-2,6-dimethylpyridine, or 30–36 per cent based on the original ethyl acetoacetate).

2. Notes

1. Before the pressure is reduced, the 3,5-dicarbethoxy-2,6-dimethylpyridine should be melted by immersing the distilling flask in boiling water. If this is not done, considerable foaming takes place during the distillation.
2. If the entire amount of alcoholic potassium hydroxide solution is added at this point, there is precipitated a colorless solid, which does not dissolve even on prolonged heating.
3. A metal retort is very desirable for this decomposition since glass flasks soften at the temperature necessary for the reaction.

3. Discussion

2,6-Dimethylpyridine has been isolated from the basic fraction of coal tar[1] and also from the bone oil fraction distilling at 139–142°.[2] It has been prepared from ethyl acetopyruvate and ethyl β-aminocrotonate.[3] A procedure for the oxidation of the dihydroester and the saponification and decarboxylation of the product, similar to the procedure given above, has been published.[4]

References and Notes

1. Lunge and Rosenberg, Ber. **20**, 129 (1887); Heap, Jones, and Speakman, J. Am. Chem. Soc. **43**, 1936 (1921); Komatsu and Mohri, J. Chem. Soc. Japan **52**, 722 (1931) [C. A. **26**, 4936 (1932)].
2. Ladenberg and Roth, Ber. **18**, 51 (1885).
3. Mumm and Hüneke, ibid. **50**, 1568 (1917).
4. Oparina, Karasina, and Smirnov, J. Applied Chem. (U.S.S.R.) **11**, 965 (1938) [C. A. **33**, 1732 (1939)].

Appendix
Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

ethyl alcohol,
alcohol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

ether (60-29-7)

formaldehyde (50-00-0)

nitric acid (7697-37-2)

potassium hydroxide (1310-58-3)

ammonium hydroxide (1336-21-6)

calcium oxide

Ethyl acetoacetate (141-97-9)

Ethyl acetopyruvate (615-79-2)

diethylamine (109-89-7)

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

1,4-Dihydro-3,5-dicarbethoxy-2,6-dimethylpyridine (1149-23-1)

3,5-Dicarbethoxy-2,6-dimethylpyridine (1149-24-2)

dimethylpyridine (583-61-9)

ethyl β-aminocrotonate (626-34-6)