



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.

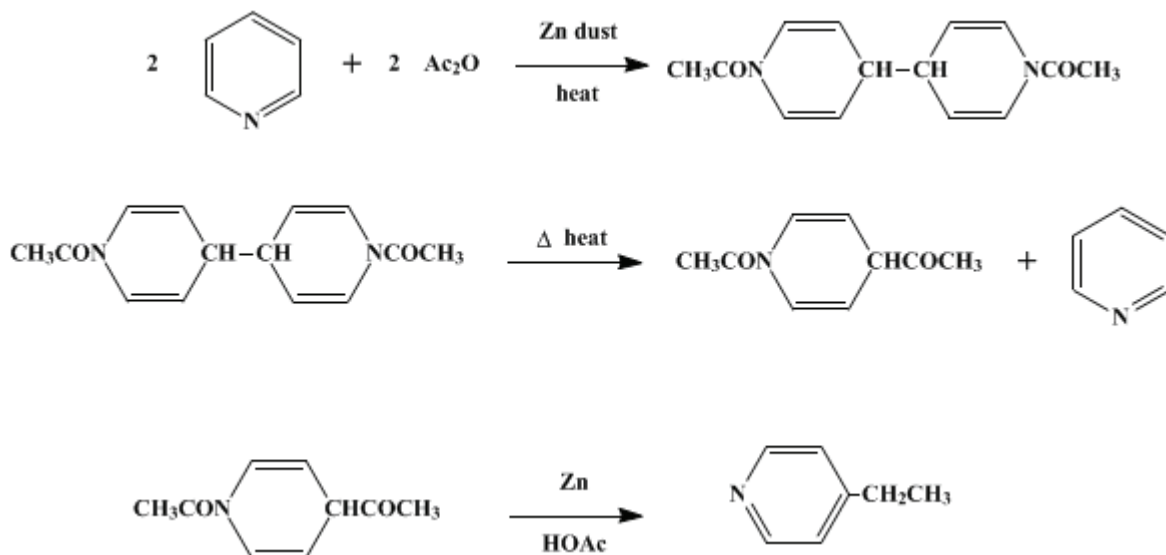
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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4-ETHYLPYRIDINE

[Pyridine, 4-ethyl-]



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1. Procedure

In a 3-l. three-necked round-bottomed flask fitted with a Hershberg stirrer and a thermometer are placed 1500 ml. of **acetic anhydride** and 300 g. (306 ml., 3.80 moles) of dry **pyridine** (Note 1). Three hundred grams (4.6 gram atoms) of **zinc dust** (Note 2), in amounts of 5–10 g., is added with stirring over a period of 3 hours. Heat is evolved almost immediately, and a cooling bath of water may be necessary. The reaction mixture becomes green after about 20 minutes. The temperature of the contents of the flask should be maintained between 25° and 30°. After the addition of the first 300-g. portion of **zinc**, 300 ml. of **acetic acid** is added to the reaction mixture and a reflux condenser is attached to the flask. Then 120 g. (1.83 gram atoms) of **zinc dust** is added in small portions. Heat is evolved during the addition, and the reaction may become rather violent. The mixture is refluxed with stirring for 30 minutes. A third portion of 180 g. (2.75 gram atoms) of **zinc dust** is added all at once, and refluxing is continued for an additional half hour. The solution is now orange-brown.

The flask is allowed to cool, and the contents are transferred to a 5-l. round-bottomed flask. The mixture is cautiously neutralized with 2 l. of a 40% aqueous solution of **sodium hydroxide**. The mixture is steam-distilled until 3 l. of distillate is collected, after which the residue is discarded. The distillate, which separates into two layers, is saturated with 1.5–1.8 kg. of solid **potassium carbonate** (Note 3). The organic layer is removed by decantation; the remaining water layer is divided into two portions, and each is extracted once with 150 ml. of **chloroform**. The **chloroform** extracts are combined with the organic layer.

The mixture is distilled using an efficient fractionating column (Note 4). There is a large fore-run of **chloroform**, **pyridine**, and water (Note 5), after which the temperature rises and 145–167 g. of material, b.p. 145–165°/760 mm., is collected. This is refractionated, and 135–155 g. (33–38%) of **4-ethylpyridine**, b.p. 163–165°/760 mm., n_D^{20} 1.5010, is obtained (Note 6).

2. Notes

1. The **pyridine** is dried over **calcium oxide** and redistilled.

2. The [zinc](#) is activated before use by stirring 830 g. of [zinc](#) dust in 300 ml. of 10% [hydrochloric acid](#) for 2 minutes, filtering, and washing the [zinc](#) with 600 ml. of water, then with 200 ml. of [acetone](#).
3. An equal weight of [sodium chloride](#) may be used instead of [potassium carbonate](#).
4. A Fenske-type column 30 cm. in length and 18 mm. in diameter packed with glass helices gave satisfactory separations.
5. It does not appear feasible to recover the [pyridine](#) from the mixture of [chloroform](#), water, and [pyridine](#).
6. This procedure has been employed by Arens and Wibaut² to prepare other 4-alkyl derivatives of pyridine. The yields tend to decrease as the molecular weight of the anhydride increases. The boiling points are as given below: [4-propylpyridine](#) 189°, [4-n-butylpyridine](#) 207–209°, [4-isobutylpyridine](#) 197–199°, [4-isoamylpyridine](#) 222–223°, and [4-n-octylpyridine](#) 265–268°.

3. Discussion

[4-Ethylpyridine](#) has been prepared by heating [N-ethylpyridinium iodide](#) in a sealed tube at 300°;³ by heating [pyridine](#) with [ethyl iodide](#);⁴ from [4-ethylpyridinecarboxylic acid](#) through distillation from lime;⁵ and in small amounts by distilling [brucine](#) with [potassium hydroxide](#).⁶ [Pyridine](#) when heated with [ferric chloride](#) in an autoclave gives a mixture of alkylated pyridines from which [4-ethylpyridine](#) can be isolated.⁷ A general method for 4-alkylpyridines involves heating 5-(γ -pyridyl)-5-alkylbarbituric acids with alkali followed by an acid cleavage to remove the [carbon dioxide](#).⁸ [4-Ethylpyridine](#) has been isolated from California petroleum.⁹ The most useful method involves the treatment of [pyridine](#) with [acetic anhydride](#) and [zinc](#).^{10,11}

References and Notes

1. Work done under contract with the Office of Rubber Reserve, Reconstruction Finance Corporation.
2. Arens and Wibaut, *Rec. trav. chim.*, **61**, 59 (1942).
3. Ladenburg, *Ber.*, **16**, 2059 (1883); **18**, 2961 (1885); *Ann.*, **247**, 1 (1888).
4. Ladenburg, *Ber.*, **32**, 42 (1899).
5. Gabriel and Colman, *Ber.*, **35**, 1358 (1902).
6. Oechsner de Coninck, *Ann. chim.*, (5) **27**, 507 (1882).
7. Morgan and Burstall, *J. Chem. Soc.*, **1932**, 20.
8. Gebauer (Chemische Fabrik von Heyden, A.-G.), Ger. pat. 638,596 [*C. A.*, **31**, 3067 (1937)].
9. Hackmann, Wibaut, and Gitsels, *Rec. trav. chim.*, **62**, 229 (1943).
10. Dohn and Horsters (Chemische Fabrik auf Actien vorm. E. Schering), Ger. pat. 390,333 [*Chem. Zentr.*, **1924**, II, 891].
11. Wibaut and Arens, *Rec. trav. chim.*, **60**, 119 (1941).

Appendix

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

[potassium carbonate](#) (584-08-7)

[hydrochloric acid](#) (7647-01-0)

[acetic acid](#) (64-19-7)

[acetic anhydride](#) (108-24-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium chloride (7647-14-5)

carbon dioxide (124-38-9)

acetone (67-64-1)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

zinc (7440-66-6)

ferric chloride (7705-08-0)

calcium oxide

brucine

Ethyl iodide (75-03-6)

Pyridine, 4-ethyl-,
4-ethylpyridine (536-75-4)

4-propylpyridine (1122-81-2)

4-isobutylpyridine (4810-79-1)

4-isoamylpyridine

N-ethylpyridinium iodide

4-ethylpyridinecarboxylic acid (4021-13-0)

4-n-butylpyridine (5335-75-1)

4-n-octylpyridine