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.

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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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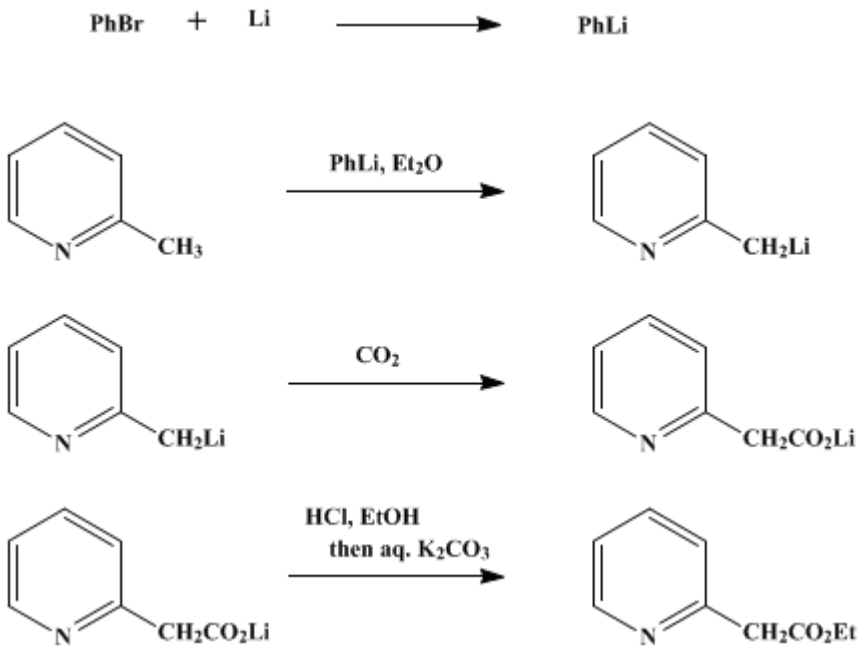
ETHYL 2-PYRIDYLACETATE

[2-Pyridineacetic acid, ethyl ester]



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1. Procedure

A 2-l. round-bottomed three-necked flask is fitted with a reflux condenser, a dropping funnel, and an efficient mechanical stirrer. A calcium chloride tube is attached to the condenser to protect the apparatus from moisture. To the flask are added 800 ml. of absolute ether and 13.9 g. (2 gram atoms) of lithium chips or shavings (Note 1). The stirrer is started, and 105 ml. (157 g., 1 mole) of dry bromobenzene is placed in the dropping funnel. About 5–15 ml. of the bromobenzene is added to initiate the reaction; when the ether begins to reflux, the balance is added at such a rate that the solvent refluxes continuously (1 hour) (Note 2). The mixture is then stirred and refluxed until most of the lithium disappears (45–90 min.). While stirring is continued, 97 ml. (93.1 g., 1 mole) of α-picoline is added dropwise in about 5–10 minutes. The dark red-brown solution of picolyllithium is stirred for an additional 30 minutes and is then poured slowly and with shaking onto 500–750 g. of crushed Dry Ice contained in a 3-l. round-bottomed flask (Note 3). The mixture is stirred well until the dark color of the picolyllithium is discharged, and the excess of Dry Ice is allowed to evaporate. The ether is removed by distillation under reduced pressure at room temperature. The lumpy residue of lithium salts is broken up, and to it is added 750 ml. of commercial absolute ethanol. The solution is saturated with dry hydrogen chloride while cooling in an ice bath. The esterification mixture is allowed to stand overnight, after which the solvent is removed as completely as possible by distillation under reduced pressure on a steam bath. The syrupy residue is dissolved in 750 ml. of chloroform, and a paste prepared from 225 g. of potassium carbonate and 135 ml. of water is slowly added to the solution with mechanical stirring. After the paste has been added, the solution is stirred vigorously and is kept just below the boiling point for 1 hour. The chloroform solution is decanted from the inorganic salts, and the chloroform is removed by distillation. The residue is fractionated under reduced pressure from a modified Claisen flask with a fractionating side arm. About 40 g. of α-picoline is recovered in the fore-run, and the ethyl 2-pyridylacetate is obtained as a light yellow liquid, b.p. 135–137° /28 mm., 142–144° /40 mm., 109–112° /6 mm.; n_D^{25} 1.4979. The yield is 58–66 g. (35–40% based on lithium) (Note 4) and (Note 5).

2. Notes

1. The most convenient method of preparing the lithium chips is as follows. Pieces of lithium several grams each in size and slightly moist with paraffin oil are pounded with a hammer into thin sheets on a dry surface. The sheets are quickly cut into small chips by means of a pair of scissors and are added immediately to the absolute ether.
2. The use of a nitrogen atmosphere is not essential if the solution is kept protected from oxygen by an atmosphere of ether vapor. For this purpose the solution is kept at the reflux point throughout.
3. Rapid filtration of the picolyllithium solution onto the Dry Ice through a thin layer of glass wool is useful in removing unreacted lithium at this point.
4. Runs twice the size of the one described give comparable yields.
5. Methyl 2-pyridylacetate, b.p. 122–125° /21 mm., can be obtained in similar yield by use of methanol in the esterification.

3. Discussion

2-Pyridylacetic esters have been obtained by the alcoholysis of 2-pyridylacetanilide, in turn prepared by Beckmann rearrangement of the oxime of 2-phenacylpyridine,[1] and by the carbethoxylation of α-picoline in the presence of potassium amide.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 611

References and Notes

1. Oparina and Smirnov, *Khim. Farm. Prom.*, **1934**, No. 4, 15 [*C. A.*, **29**, 1820 (1935)]; *J. Gen. Chem.* U.S.S.R., **5**, 1699 (1935) [*C. A.*, **30**, 2567 (1936)].
2. Weiss and Hauser, *J. Am. Chem. Soc.*, **71**, 2023 (1949).

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

oxime of 2-phenacylpyridine

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrogen chloride (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

chloroform (67-66-3)

oxygen (7782-44-7)

nitrogen (7727-37-9)

bromobenzene (108-86-1)

lithium (7439-93-2)

potassium amide

Ethyl 2-pyridylacetate,
2-Pyridineacetic acid, ethyl ester (2739-98-2)

picolyllithium

Methyl 2-pyridylacetate (1658-42-0)

2-pyridylacetanilide

α-picoline (109-06-8)