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.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

*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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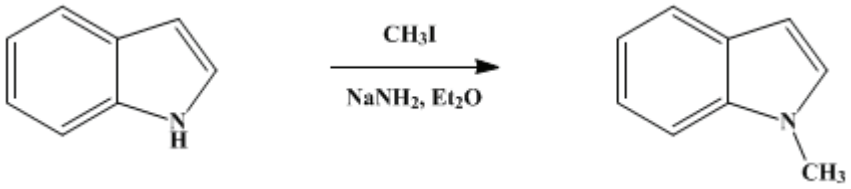
*Organic Syntheses, Coll. Vol. 5, p.769 (1973); Vol. 40, p.68 (1960).*

# 1-METHYLINDOLE

## [Indole, 1-methyl-]




Submitted by K. T. Potts and J. E. Saxton[1].
Checked by W. E. Parham, Wayland E. Noland, and Bryce A. Cunningham.

## 1. Procedure

*Caution! Ammonia gas is an extreme irritant and can cause serious burns to the eyes, etc. It is necessary to carry out the entire reaction under a well-ventilated hood.*

In a 1-l. three-necked flask fitted with a motor stirrer (Note 1), gas inlet tube, dropping funnel, and a wide-bore soda-lime tube are placed 400–500 ml. of liquid ammonia and 0.1 g. of ferric nitrate nonahydrate (Note 2).

In small portions, just sufficient to maintain the blue color, 5.0 g. (0.22 gram atom) of clean, metallic sodium is added with vigorous stirring. After dissolution is complete (Note 3), a solution of 23.4 g. (0.20 mole) of indole (Note 4) in 50 ml. of anhydrous ether is added slowly and then, after an additional 10 minutes, a solution of 31.2 g. (0.22 mole) of methyl iodide in an equal volume of anhydrous ether is added dropwise. Stirring is continued for a further 15 minutes. The ammonia is allowed to evaporate (Note 5), 100 ml. of water is added, followed by 100 ml. of ether. The ether layer is separated, the aqueous phase extracted with an additional 20 ml. of ether, and the combined ether extracts washed with three 15 ml.-portions of water (Note 6) and dried over anhydrous sodium sulfate. The solvent is removed at atmospheric pressure, and the crude oil ($n^{18.5°}_{D}$ 1.6078) is purified by distillation under reduced pressure. 1-Methylindole is obtained as a colorless oil, b.p. 133°/26 mm., $n^{18.5°}_{D}$ 1.6082. In several runs the yield is 22.3–24.9 g. (85–95%).

## 2. Notes

1. Any sealed mechanical stirrer may be used. Those of the Hershberg[2] type were found particularly efficient during the formation of the sodium amide.
2. It was found most advantageous to run in the liquid ammonia from the commercial cylinder, laid on the floor with the foot raised slightly, and connected to the gas inlet tube with rubber tubing approximately 1 cm. in diameter. The large excess of liquid ammonia used obviates the need of a dry iceacetone cooling bath and permits a reasonably rapid formation of sodium amide.
3. This occurs when the blue color has disappeared. The formation of the light gray sodium amide is usually complete within 20 minutes and may be observed by washing a portion of the outside of the flask with a little alcohol.
4. A commercial grade of indole is satisfactory.
5. The checkers removed the ammonia by distillation (water aspirator).
6. The checkers extracted with two 50-ml. portions of ether and three 50-ml. portions of water.

## 3. Discussion

1-Methylindole has been prepared from the *as*-methylphenylhydrazone of pyruvic acid,[3] by the action of sodium amide or sodium hydride on indole followed by methyl iodide at elevated

temperatures,[4,5] by treatment of indole with methyl *p*-toluenesulfonate and anhydrous sodium carbonate in boiling xylene,[6] and by the action of methyl sulfate on indole previously treated with sodium amide in liquid ammonia.[7] The present method is essentially that of Potts and Saxton.[8]

1-Methylindole has also been prepared by lithium aluminum hydride reduction of 1-methylindoxyl.[9] Compounds giving rise to NH absorption in the infrared (indole, skatole) can be completely removed[10] by refluxing the crude 1-methylindole over sodium for 2 days and then distilling the unreacted 1-methylindole from the sodio derivatives and tarry decomposition products.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 104
- Org. Syn. Coll. Vol. 6, 106

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## References and Notes


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

as-methylphenylhydrazone of pyruvic acid

1-methylindoxyl

ammonia (7664-41-7)

ether (60-29-7)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

sodium (13966-32-0)

xylene (106-42-3)

Methyl iodide (74-88-4)

methyl sulfate (75-93-4)

sodium amide (7782-92-5)

lithium aluminum hydride (16853-85-3)

sodium hydride (7646-69-7)

Indole (120-72-9)

1-Methylindole,
Indole, 1-methyl- (603-76-9)

skatole (83-34-1)

ferric nitrate nonahydrate (7782-61-8)

Methyl p-toluenesulfonate (80-48-8)