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.

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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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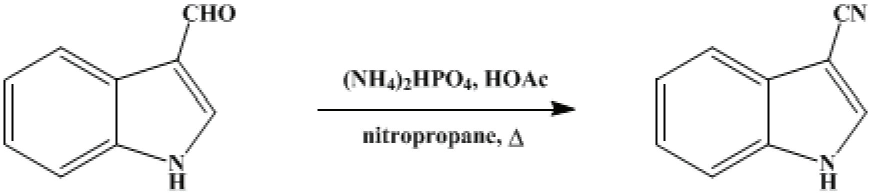
INDOLE-3-CARBONITRILE



Submitted by H. M. Blatter, H. Lukaszewski, and G. de Stevens[1].
Checked by Wayland E. Noland and Kent R. Rush.

1. Procedure

A mixture of 1.44 g. (0.0099 mole) of indole-3-carboxaldehyde,[2] 7.0 g. (0.053 mole) of diammonium hydrogen phosphate, 30 g. (30 ml., 0.34 mole) of 1-nitropropane, and 10 ml. of glacial acetic acid is refluxed for 12.5 hours. During the reflux period the pale-yellow mixture becomes dark red. The volatile reactants and solvent are removed under reduced pressure, and an excess of water is then added to the dark residue. After a short time, crude indole-3-carbonitrile precipitates rapidly. It is separated by filtration and dried under reduced pressure; weight 1.20–1.34 g. (85–95%). Crystallization from acetone-hexane, with decolorization by activated carbon, yields 0.68–0.89 g. (48–63%) of fairly pure indole-3-carbonitrile, m.p. 179.5–182.5° (Note 1).

2. Notes

1. The checkers obtained pure indole-3-carbonitrile, m.p. 182–184°, by subliming the product at a pressure of 1.5 mm. (bath temperature 165–170°) and recrystallizing the sublimate from a mixture of acetone and light petroleum ether. The recovery was 84%.

3. Discussion

Indole-3-carbonitrile has been prepared by the dehydration of indole-3-carboxaldehyde oxime,[3,4,5] indole-3-glyoxalic acid oxime,[4,6] or indole-3-carboxamide;[3] by the action of cyanogen chloride on indolylmagnesium iodide;[6] by the reaction of isoamyl formate with *o*-aminobenzyl cyanide in the presence of metallic sodium;[7,8] by mild basic hydrolysis of 1-acetylindole-3-carbonitrile;[7] and by the present method.[9]

4. Merits of the Preparation

This synthetic process is applicable to the preparation of other aromatic nitriles from aldehydes. The submitters have used it to prepare 5-bromoindole-3-carbonitrile, 7-azaindole-3-carbonitrile, *p*-chlorobenzonitrile, 3,4,5-trimethoxybenzonitrile, and *p*-N,N-dimethylaminobenzonitrile.[9] There are several advantages to its use. They include (*a*) readily available and inexpensive reagents, (*b*) a simple, time-saving procedure, and (*c*) fair to good yields of nitrile obtained by a *one-step* method.

References and Notes

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

petroleum ether

acetic acid (64-19-7)

acetone (67-64-1)

carbon (7782-42-5)

sodium (13966-32-0)

cyanogen chloride (506-77-4)

Indole-3-carboxaldehyde (487-89-8)

isoamyl formate (110-45-2)

Indole-3-carbonitrile (5457-28-3)

diammonium hydrogen phosphate (7783-28-0)

1-nitropropane (108-03-2)

acetone-hexane (821-55-6)

indole-3-carboxaldehyde oxime (2592-05-4)

indole-3-glyoxalic acid oxime

indole-3-carboxamide

indolylmagnesium iodide

1-acetylindole-3-carbonitrile

5-bromoindole-3-carbonitrile

7-azaindole-3-carbonitrile

3,4,5-trimethoxybenzonitrile (1885-35-4)

p-chlorobenzonitrile (623-03-0)

o-aminobenzyl cyanide (2973-50-4)

p-N,N-dimethylaminobenzonitrile (1197-19-9)