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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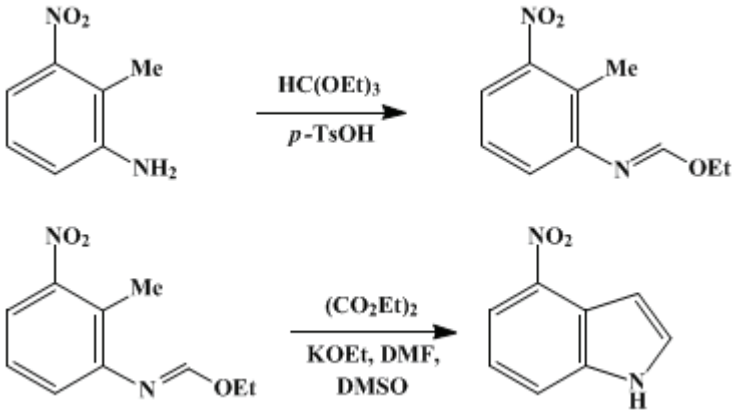
4-NITROINDOLE

[Indole, 4-nitro-]



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1. Procedure

A. *Ethyl N-(2-methyl-3-nitrophenyl)formimidate.* A 1-L, one-necked, round-bottomed flask, fitted with a Claisen condenser protected from moisture with a drying tube, is charged with 200 g (1.35 mol) of freshly distilled triethyl orthoformate, 1 g of *p*-toluenesulfonic acid and 152 g (1 mol) of 2-methyl-3-nitroaniline (Note 1) and (Note 2). The solution is heated to 120°C and all of the ethanol formed is continuously distilled off during ca. 1 hr. Fractional vacuum distillation of the residue gives at 156–158° C/6 mm, the imidate ester, 184 g (88%), as a light-yellow, solidifying oil, mp 57–58°C.

B. *4-Nitroindole.* To a solution of 22 g (0.15 mol) of diethyl oxalate in 50 mL of dry dimethylformamide in a 200-mL beaker is added, under cooling, 11 g (0.13 mol) of potassium ethoxide with vigorous stirring (Note 3) and (Note 4). The solution is immediately (within a few seconds) poured into a 250-mL flask containing a solution of 20.8 g (0.10 mol) of ethyl *N*-(2-methyl-3-nitrophenyl) formimidate in 75 mL of dry dimethyl sulfoxide (Note 5). The resulting deep-red solution is stirred for 1 hr at ca. 40°C (Note 6) and (Note 7). The solution is then transferred into a 1-L beaker and water is added under stirring at a rate that gives smooth precipitation of 4-nitroindole. The product is filtered off and dried, giving 16.3 g (ca. 100%) of a brownish-yellow solid, mp 195–201°C [sublimation (subl.)], which is sublimed at 170°C/0.5 mm giving 11.5 g (71%) of yellow crystals, mp 204–205°C (subl.) (Note 8).

2. Notes

1. 2-Methyl-3-nitroaniline and triethyl orthoformate were purchased from Fluka AG.
2. Trimethyl orthoformate is not suitable for this preparation because of side-product formation.
3. Diethyl oxalate was purchased from Merck and Company, Inc., and was used without further purification. Potassium ethoxide was purchased from Alfa Products, Johnson Mathey Co. or preferably was prepared from potassium metal and absolute ethanol.
4. The diethyl oxalate/potassium ethoxide complex can also be prepared by adding the oxalic ester to an ethanolic solution of potassium ethoxide and evaporating the solvent. However, this complex is less active and is difficult to store.
5. Dimethyl sulfoxide (DMSO) prevents precipitation of intermediate salts, which can also be achieved by using a larger volume of dimethylformamide (DMF) (ca. 200 mL). Attempts to prepare the diethyl oxalate/potassium ethoxide complex in DMSO have not been successful (i.e., it is not active).
6. At elevated temperatures (e.g., above 40°C) by-products are formed.

7. The reaction can be monitored by TLC (CH_2Cl_2). The spots were developed with an ethanolic solution of *p*-dimethylaminobenzaldehyde/HCl. The product gave a bright-red spot at R_f 0.5, and the imidate ester gave a yellow spot at R_f 0.6. Addition of small portions of diethyl oxalate/potassium ethoxide complex was continued if the starting material was not consumed after the initial reaction period.
8. Crude 4-nitroindole can also be purified by recrystallization from methanol, ethanol, or acetonitrile giving brownish-yellow crystals, mp 204–206°C.

3. Discussion

This procedure illustrates the synthesis of 4-nitroindoles; the present method can easily be extended to the 2-alkyl derivatives (using other *ortho* esters), 5-, 6- and/or 7-substituted derivatives and 1-alkyl derivatives (from the corresponding *N*-alkylanilides).[2,3] Other published preparations of 4-nitroindole (e.g., [4]) are of no practical value.

The mechanism of the formation of 4-nitroindole parallels the Reissert indole synthesis[5] and is discussed in [2] and [3].

References and Notes

1. Department of Organic Chemistry, Royal Institute of Technology, S-100 44 Stockholm, Sweden.
2. Bergman, J.; Sand, P.; Tilstam, U. *Tetrahedron Lett.* **1983**, *24*, 3665.
3. Bergman, J.; Sand, P. *Tetrahedron Lett.* **1990**, *46*, 6085.
4. Somei, M.; Inoue, S.; Tokutake, S.; Yamada, F.; Kaneko, C. *Chem. Pharm. Bull.* **1981**, *29*, 726.
5. Reissert, A. *Chem. Ber.* **1897**, *30*, 1030.

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

4-nitroindoles

ethanol (64-17-5)

HCl (7647-01-0)

methanol (67-56-1)

acetonitrile (75-05-8)

potassium (7440-09-7)

triethyl orthoformate (122-51-0)

potassium ethoxide (917-58-8)

dimethylformamide (68-12-2)

diethyl oxalate (95-92-1)

dimethyl sulfoxide (67-68-5)

p-Dimethylaminobenzaldehyde (100-10-7)

p-toluenesulfonic acid (104-15-4)

trimethyl orthoformate (149-73-5)

4-Nitroindole,
Indole, 4-nitro- (4769-97-5)

2-methyl-3-nitroaniline (603-83-8)

Ethyl N-(2-methyl-3-nitrophenyl)formimidate (115118-93-9)