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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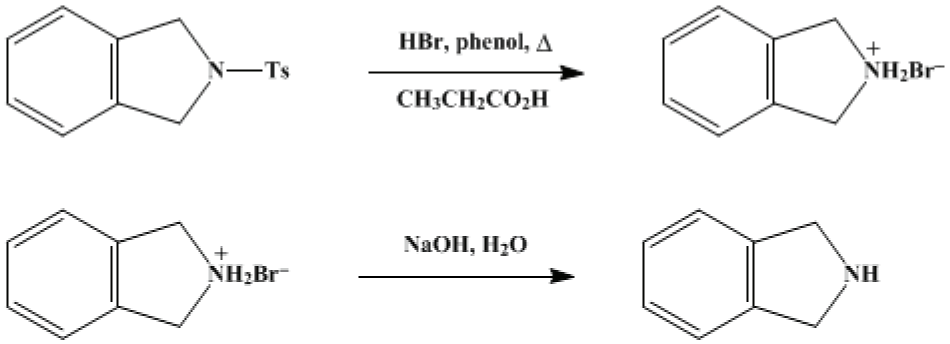
1,3-DIHYDROISOINDOLE

[Isoindoline]



Submitted by J. Bornstein, J. E. Shields, and A. P. Boisselle[1].
Checked by William G. Dauben and Harold B. Morris.

1. Procedure

In a 1-l. round-bottomed flask are placed 36.0 g. (0.132 mole) of 2-(*p*-tolylsulfonyl) dihydroisoindole,[2] 36.0 g. (0.38 mole) of phenol, 270 ml. of 48% hydrobromic acid (Note 1), and 45 ml. of propionic acid. A few boiling chips are added, and the flask is fitted with a reflux condenser in the top of which is placed a T-tube connected to a source of low-pressure nitrogen and to a mercury bubbler. The mixture is heated under reflux for 2 hours in an atmosphere of nitrogen. The deeply colored reaction mixture is cooled to room temperature, transferred to a 1-l. separatory funnel, and washed with two 200-ml. portions of ether (Note 2). The aqueous phase is then added dropwise over a 1-hour period to a vigorously stirred (Note 3) solution of 200 g. of sodium hydroxide in 600 ml. of water in a 2-l. Erlenmeyer flask immersed in an ice bath. The solution is transferred to a 3-l. separatory funnel and extracted with five 300-ml. portions of ether. The ethereal extracts are combined, dried over anhydrous potassium carbonate (Note 4), and filtered. The solvent is distilled, and the dark residual oil is transferred to a distillation flask and distilled through a low-holdup, semimicro column (Note 5). After removal of 1 or 2 drops of forerun, colorless 1,3-dihydroisoindole is collected at 96–97° (10 mm.) or 55–56° (2 mm.), n^{25}D 1.5686, d_4^{20} 1.081. The yield is 9.9–11.2 g. (63–71%) (Note 6).

2. Notes

1. The hydrobromic acid should be colorless. Reagent grade 47–49% hydrobromic acid, obtained from J. T. Baker Chemical Co., was used as supplied. A technical grade of the constant-boiling acid is suitable if purified by distillation from stannous chloride.
2. Detection of the water-ether interface may prove trouble-some; backlighting of the separatory funnel by an intense light source is recommended. The same volume of ether must be used for each washing, even when the preparation is carried out on a smaller scale, *e.g.*, one-half or one-third the scale described here.
3. Stirring is most conveniently accomplished with a magnetic stirrer.
4. Washing of the ethereal extract with water decreases the yield of product.
5. The submitters used a 7 × 300-mm. externally heated column packed with a helix of Chromel wire and fitted with a partial reflux head.[3]
6. Since the product slowly darkens on exposure to air, it should be stored under nitrogen in a refrigerator. The compound solidifies on cooling; m.p. 16.0–16.5°. Nuclear magnetic resonance spectrum (neat, tetramethylsilane internal standard): singlets at δ 7.00 (aromatic protons), 3.93 (CH_2), and 2.24 p.p.m. (NH).

3. Discussion

1,3-Dihydroisoindole has been prepared from phthalimide by electrolytic reduction[4] and by reduction with lithium aluminium hydride.[5] Other methods that have been used are reduction of 1-chlorophthalazine with zinc and hydrochloric acid[6] and hydrogenolysis of 2-benzyl-1,3-dihydroisoindole.[7] The present method is essentially that of Bornstein, Lashua, and Boisselle.[8]

4. Merits of the Preparation

This procedure illustrates a general method for the preparation of amines by reductive cleavage of sulfonamides by hydrobromic acid in the presence of phenol.[9] The present synthesis makes 1,3-dihydroisoindole readily accessible and is superior in certain respects to the other two practical methods of preparation. Thus the method here described is shorter and gives a higher overall yield than the three-step synthesis of Neumeyer,[7] and obviates the special apparatus and careful control required by the electrochemical process of Dunet, Rollet, and Willemart.[4]

References and Notes

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4. A. Dunet, J. Rollet, and A. Willemart, *Bull. Soc. Chim. France*, [5] **17**, 877 (1950).
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

phenol (108-95-2)

propionic acid (79-09-4)

HYDROBROMIC ACID (10035-10-6)

nitrogen (7727-37-9)

stannous chloride

zinc (7440-66-6)

Phthalimide (85-41-6)

lithium aluminium hydride (16853-85-3)

1,3-Dihydroisoindole,
Isoindoline (496-12-8)

1-chlorophthalazine

2-benzyl-1,3-dihydroisoindole (35180-14-4)

2-(p-Tolylsulfonyl)dihydroisoindole (32372-83-1)