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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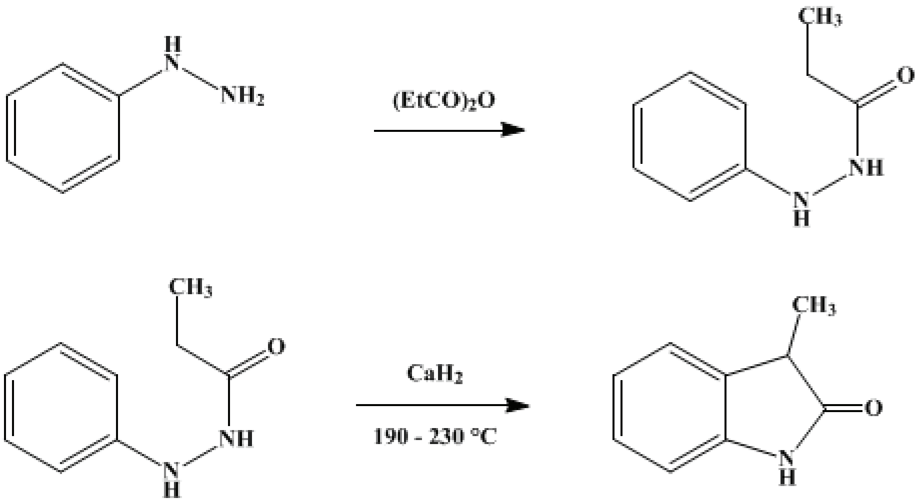
3-METHYLOXINDOLE

[Oxindole, 3-methyl-]



Submitted by Abraham S. Endler and Ernest I. Becker[1].
Checked by James Cason and Warren N. Baxter.

1. Procedure

A. *β-Propionylphenylhydrazine*. To 130 g. (1.0 mole) of propionic anhydride(Note 1), contained in a 500-ml. wide-mouthed Erlenmeyer flask which is cooled in an ice bath, there is added slowly with swirling 108 g. (1.0 mole) of phenylhydrazine(Note 1) at such a rate that the maximum temperature does not exceed 60°. After addition is complete, the flask is corked (not so tightly as to give a vacuum which may collapse the flask) and allowed to stand 72 hours at room temperature. At the end of this period, the resultant solid cake is broken up and slurried with 100 ml. of toluene. The suspension is cooled to 5° in an ice bath; then the product is collected by suction filtration and washed with 200 ml. of a mixture of equal parts of cyclohexane and toluene, precooled to 5°. The yield of vacuum-dried, almost white crystals, m.p. 158–159°, is 140–145 g. (85–88%).

B. *3-Methyloxindole*. A mixture of 33 g. (0.20 mole)(Note 2) of β-propionylphenylhydrazine and 14 g. (0.33 mole) of freshly ground commercial calcium hydride (Note 3) is placed in a 500-ml. round-bottomed flask, which is equipped with a 15-cm. air condenser of 2.5 cm. in diameter. The flask is immersed to two-thirds its depth in an oil bath, in a forced-draft hood, and the bath is heated, cautiously as 190° is approached. In the range 190–215°, a very vigorous exothermic reaction sets in (sometimes after a brief delay), and considerable gas and vapor is expelled through the air condenser. The vigorous reaction abates in 5 minutes or less, and the oil bath is raised to about 230°. After heating at this temperature has been continued for 30 minutes, the flask is removed from the bath and cooled to room temperature.

A mixture of 50 ml. of methanol and 20 ml. of water is cautiously added to the cooled reaction mixture, and this is followed by slow addition of concentrated hydrochloric acid (Note 4) until the pH is brought to 1–2 (Hydrion test paper). When effervescence has stopped, 50 ml. of water is added, and the contents of the flask are boiled gently for 1 hour. Additional concentrated hydrochloric acid is added as needed to maintain the specified pH (Note 5). At this point, all solid material should have been decomposed. The mixture is transferred to a 600-ml. beaker, using 10 ml. of methanol to wash out the flask, sufficient sodium hydroxide is added (Note 6) to bring the pH to about 3 (Hydrion test paper or more accurately with methyl orange indicator), and water is added to bring the volume to about 300 ml. The mixture is stirred in an ice bath until the oily layer solidifies, and the crude crystalline material is collected by suction filtration at about 15° and washed with 100 ml. of water. After vacuum drying at

70°, the yield of crude product is 16–19 g., but this material should be purified before further use.

The crude product is distilled in a short-path distillation apparatus composed of a 125-ml. Claisen flask connected by a ground-glass joint to a receiver which is a 300-ml. round-bottomed flask with side tubulature for evacuation. A 50-g. portion(Note 7) of crude 3-methyloxindole is placed in the distillation flask, which is completely immersed in an oil bath. The product is collected at approximately 132° /1.5 mm. The solid distillate is dissolved in 75 ml. of hot methanol, then 25 ml. of hot water is added. After crystallization has been continued for 24 hours at about 20°, there is obtained 35–37 g. (41–44% from β-propionylphenylhydrazine) of light-yellow crystals, m.p. 122.5–123.5° (softening at 121.5°) (Note 8). Five grams of less pure material is recoverable from the mother liquor and may be distilled with a succeeding batch.

2. Notes

1. Phenylhydrazine and propionic anhydride from Fisher Scientific Company were used without purification by the submitters. The checkers distilled the propionic anhydride before use, since old samples contained considerable propionic acid.
2. The ring closure is so highly exothermic that runs no larger than that described as recommended. Several lots may be combined for distillation, as suggested in the description.
3. The checkers used 40-mesh calcium hydride, from Metal Hydrides, Inc. The submitters report that there may also be used freshly ignited lime (22 g., 0.39 mole), but with a reduction of 10–20% in the yield.
4. The amount of concentrated hydrochloric acid is usually 40 ml. or more, depending on the quality of the calcium hydride.
5. This procedure is for the purpose of hydrolyzing unchanged starting material.
6. The final pH is brought to about 3 in order to minimize the solubility of 3-methyloxindole in strong acid without precipitating the phenylhydrazine which is present at this point.
7. The checkers obtained the same yields when the product of a single ring closure was distilled and crystallized.
8. After two crystallizations from butanol and two from toluene, the product may be obtained in about 25% recovery as white crystals of m.p. 123.8–124.6°.

3. Discussion

3-Methyloxindole has been prepared by the reduction of α-(2-nitrophenyl)propionic acid,[2] by heating β-propionylhydrazine with lime[3] or with sodium alkoxides,[4] by the reduction of the benzoyl derivative of oxindole-3-aldehyde[5] or 3-(methylaminometehylene)-oxindole,[6] and by the oxidation of skatole with potassium persulfate.[7]

References and Notes

1. Polytechnic Institute of Brooklyn, Brooklyn, New York.
2. Trinius, *Ann.*, **227**, 274 (1885).
3. Brunner, *Monatsh.*, **18**, 533 (1897).
4. C.F. Boehringer and Söhne (Waldhof b. Mannheim), Ger. pat. 218,727, Kl.12 p., Jan. 10, 1910 [Frdl., **9**, 968 (1908–1910)].
5. L. Horner, *Ann.*, **548**, 134 (1941).
6. Wenkert, Udelhofen, and Bhattacharyya, *J. Am. Chem. Soc.*, **81**, 3763 (1959).
7. Dalgliesh and Kelly, *J. Chem. Soc.*, **1958**, 3726.

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

β-Propionylphenylhydrazine

β-propionylhydrazine

3-(methylaminometehylene)-oxindole

hydrochloric acid (7647-01-0)

methanol (67-56-1)

sodium hydroxide (1310-73-2)

propionic acid (79-09-4)

Phenylhydrazine (100-63-0)

cyclohexane (110-82-7)

butanol (71-36-3)

toluene (108-88-3)

potassium persulfate (7727-21-1)

propionic anhydride (123-62-6)

calcium hydride (7789-78-8)

3-Methyloxindole,
Oxindole, 3-methyl- (1504-06-9)

oxindole-3-aldehyde

skatole (83-34-1)

methyl orange (547-58-0)

α-(2-nitrophenyl)propionic acid