Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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.

DOI:10.15227/orgsyn.029.0054

Organic Syntheses, Coll. Vol. 3, p.475 (1955); Vol. 29, p.54 (1949).

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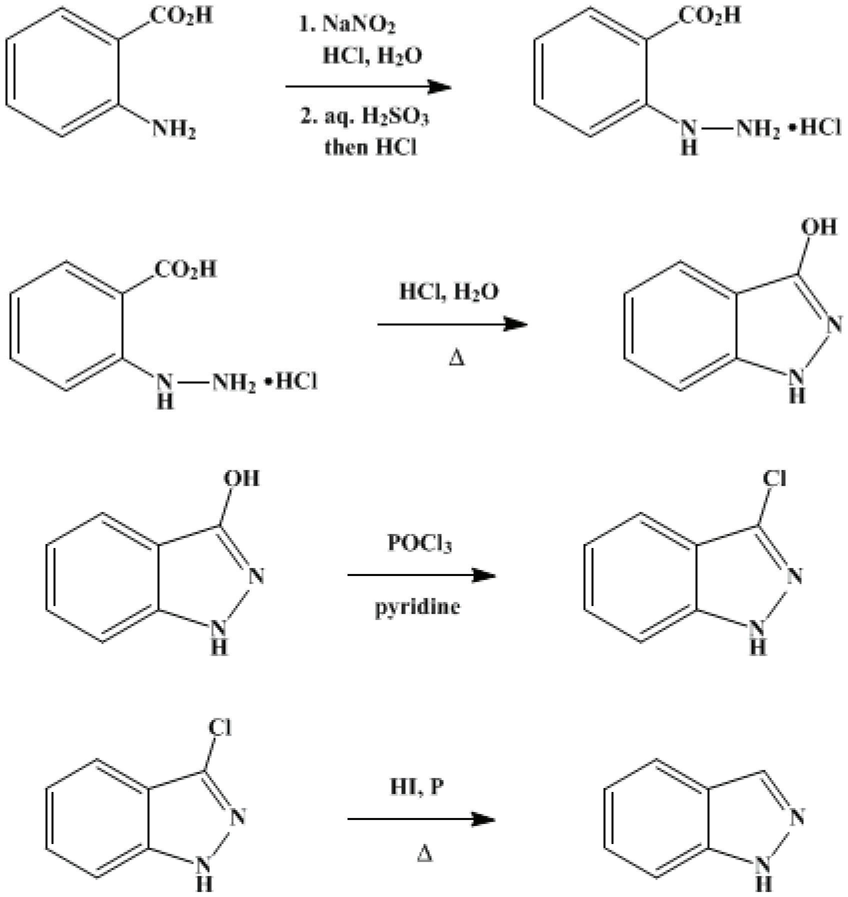

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1. Procedure

A. *o-Hydrazinobenzoic acid hydrochloride*. In a 2-l. beaker, provided with a stirrer and a low-temperature thermometer, and cooled in an ice-salt bath, are placed 42 g. (0.31 mole) of anthranilic acid and 300 ml. of water. The stirrer is started, and 340 ml. of concentrated hydrochloric acid (sp. gr. 1.18) is added in one portion; the anthranilic acid dissolves, and its hydrochloride begins to separate almost immediately. After the mixture has been cooled to 0°, a solution of 21.6 g. (0.31 mole) of technical sodium nitrite in 210 ml. of water is added from a dropping funnel, the tip of which extends below the surface of the suspension, at such a rate that the temperature never rises above 3°. The addition requires about 30 minutes; stirring is continued for 15 minutes longer, and at the end of this period a positive test with starch-iodide paper should be obtained (Note 1). The clear brown solution is then diluted with 150 ml. of ice water.

In a 12-l. flask, equipped with a low-temperature thermometer and surrounded by an ice-salt bath, a solution of sulfurous acid is prepared by saturating 2.4 l. of water at 0–5° with sulfur dioxide from a cylinder. A brisk stream of the gas is continued (Note 2) while the cold diazonium salt solution is added in about 150-ml. portions over a 30-minute period and the temperature is maintained at 5–10°; the reaction mixture assumes a dark orange color (Note 3). The cooling bath is removed, but sulfur dioxide is passed into the mixture for an additional 30 minutes. After the mixture has been allowed to stand for 12 hours at room temperature, 3 l. of concentrated hydrochloric acid (sp. gr. 1.18) is added; the *o*-hydrazinobenzoic acid hydrochloride separates at once. The mixture is chilled to 0–5° and filtered through a precooled Büchner funnel; the product is washed with two 50-ml. portions of ice-cold dilute (1:1) hydrochloric acid. The yield is 50–51 g. (86–88%); the salt melts at 194–195° with decomposition (Note 4) and is suitable for the next step without further purification (Note 5).

B. *Indazolone*. In a 2-l. round-bottomed flask to which a reflux condenser is attached are placed 47.1 g. (0.25 mole) of *o*-hydrazinobenzoic acid hydrochloride, 1.25 l. of water, and 12.5 ml. of concentrated hydrochloric acid (sp. gr. 1.18). The mixture is refluxed for 30 minutes. The resulting pale yellow solution is transferred in two portions to a 23-cm. evaporating dish and concentrated on the steam bath to about one-fourth its original volume. The indazolone separates at an early stage of the evaporation but redissolves as the concentration of acid increases. Sodium carbonate is added to the warm solution in small portions until the acid is neutralized (Note 6), and the suspension is allowed to stand for 2 hours. The nearly colorless indazolone is removed by filtration, washed with two 25-ml. portions of cold water, and air-dried. The yield of product, m.p. 246–249°, is 30–33 g. (90–98%) (Note 7).

C. 3-*Chloroindazole*. In a 200-ml. flask connected by a glass joint to an air condenser protected by a drying tube are placed 26.8 g. (0.2 mole) of dry indazolone and 15.8 g. (16 ml., 0.2 mole) of dry pyridine (Note 8); 46.1 g. (27.6 ml., 0.3 mole) of phosphorus oxychloride is then added, with shaking, over a 10-minute period. Heat is evolved, and acid fumes are generated. The mixture is heated with occasional shaking in an oil bath, which is maintained at 128–130° for 1 hour and at 130–140° for 4 hours. The clear brown solution is then cooled to 70° and poured, with hand stirring, upon 500 g. of cracked ice. This mixture is allowed to stand for 24 hours. The pale buff solid is removed, washed on the filter, first with 100 ml. of 0.5 *N* hydrochloric acid and then with 40 ml. of cold water, and air-dried (Note 9). The 3-chloroindazole is crystallized from 3 l. of 20% ethanol. The yield is 21–22.5 g. (68–74%) of material melting at 148–148.5° (Note 10).

D. *Indazole*. In a 300-ml. flask are placed 15.3 g. (0.1 mole) of 3-chloroindazole, 18.6 g. (0.15 mole) of red phosphorus, and 100 ml. of constant-boiling hydriodic acid (sp. gr. 1.7) (Note 11). The mixture is refluxed for 24 hours (Note 12), cooled, and filtered through a sintered-glass funnel (Note 13) to remove the phosphorus; the flask and the solid are washed with two 20-ml. portions of water. The clear filtrate is transferred to a 300-ml. Claisen flask and concentrated to about 40 ml. by heating in a water bath at a reduced pressure. The residue is washed into a 250-ml. beaker with 70–80 ml. of hot water, and the clear solution is cooled in an ice bath and made strongly alkaline with concentrated ammonium hydroxide (about 80 ml. is required). The next day, the indazole is collected and dried; the white solid melts at 143–145° (Note 14).

The product is added to 75 ml. of benzene, and the suspension is boiled until the frothing has ceased, the benzene lost being replaced (Note 15); the resulting suspension is filtered to remove the insoluble material. The clear filtrate is heated to boiling, diluted with 25 ml. of petroleum ether (b.p. 70–90°), and allowed to cool slowly. The yield of white product, m.p. 145–146.5°, is 9.7–10.2 g. (82–86%). The over-all yield from anthranilic acid is 43–55%.

2. Notes

1. If the starch-iodide test is negative at this point a little solid sodium nitrite may be added.
2. This operation should be carried out in a hood or out-of-doors.
3. Small amounts of a red crystalline solid were obtained at this point by the checkers in several runs. This substance can be converted to *o*-hydrazinobenzoic acid by the addition of 5 ml. of concentrated hydrochloric acid to a suspension of 1 g. of the solid in 25 ml. of dilute (1:1) hydrochloric acid. The red solid changes to the white *o*-hydrazinobenzoic acid hydrochloride without apparent solution.
4. The melting point varies with the rate of heating. The values given were obtained with a bath preheated to 180°.
5. The free acid may be obtained by treatment of a solution of the hydrochloride with a concentrated aqueous solution of sodium acetate. The powdered hydrochloride (18.9 g., 0.1 mole) is dissolved in 567 ml. of water, and sodium acetate solution (8.2 g. [0.1 mole] of anhydrous sodium acetate in 30 ml. of water) is added. *o*-Hydrazinobenzoic acid separates at once; the mixture is chilled, and the light-tan acid is removed by filtration, washed with two 25-ml. portions of water, and air-dried. The yield is 13.1 g. (86%); m.p. 248–250°. If a purer acid is required, the crude material may be recrystallized from ethanol

(50 ml. per g.); the pale tan product then melts at 250–251.5°.
6. About 20 g. of sodium carbonate is required.
7. The indazolone may be purified further by recrystallization from methanol (24 ml. per g.), with filtration of the hot solution through a layer of Norit. It separates as white needles, m.p. 250–252°; the recovery is about 50%. An additional 10% of material (m.p. 246–248°) may be obtained by dilution of the filtrate with 2 volumes of water.
The submitter reports that the described method of purification gives a better product than is obtained by solution in dilute sodium hydroxide and reprecipitation with acid.
8. The submitter reports that dimethylaniline can be used but that it is less desirable because a small amount of a green by-product is formed.
9. The crude chloroindazole, m.p. 143–145°, is difficult to dry. Small quantities may be crystallized satisfactorily from water (250 ml. per g.). The submitter reports that a good product can be obtained by steam distillation but that even with superheated steam the distillation is very slow.
10. In a run 2.5 times this size, the checkers dissolved the crude product in 190 ml. of ethanol and diluted the hot filtrate with 260 ml. of water; the chloroindazole was obtained in 80% yield.
11. It is essential to use acid of this concentration.
12. This reaction time ensures complete conversion of the chloroindazole.
13. As an alternative procedure, the mixture may be diluted with 70 ml. of water and filtered through S & S No. 596 filter paper.
14. The crude indazole is so difficult to dry that the weight at this stage is not significant.
15. This operation is carried out in an open flask in the hood and at a point remote from flames; the indazole is dried by the steam distillation of the water with the benzene.

3. Discussion

The preparations of *o*-hydrazinobenzoic acid hydrochloride and indazolone are essentially those given by Pfannstiel and Janecke.[1] The procedure for the conversion of indazolone to indazole is a modification of that of Fischer and Seuffert.[2] A procedure involving the decarboxylation of indazole-3-carboxylic acid is described by Schad.[3]

Indazole has been obtained in a variety of ways which are of no preparative value. The elimination of the amino group from aminoindazoles, first utilized by Witt,[4] by the action of ethanol or sodium stannite on the diazonium compounds appears to be the only other useful procedure.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 536
- Org. Syn. Coll. Vol. 5, 650

References and Notes

1. Pfannstiel and Janecke, *Ber.*, **75**, 1104 (1942).
2. Fischer and Seuffert, *Ber.*, **34**, 796 (1901).
3. Schad, *Ber.*, **26**, 217 (1893).
4. Witt, Nölting, and Grandmougin, *Ber.*, **23**, 3642 (1890).

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

red phosphorus

petroleum ether

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

sodium carbonate (497-19-8)

sulfur dioxide (7446-09-5)

PHOSPHORUS (7723-14-0)

sodium nitrite (7632-00-0)

Phosphorus Oxychloride (21295-50-1)

pyridine (110-86-1)

hydriodic acid (10034-85-2)

ammonium hydroxide (1336-21-6)

dimethylaniline (121-69-7)

Anthranilic Acid (118-92-3)

sodium stannite

sulfurous acid (7782-99-2)

Indazole (271-44-3)

Indazolone (5686-93-1)

3-Chloroindazole,
chloroindazole (29110-74-5)

indazole-3-carboxylic acid (4498-67-3)

o-Hydrazinobenzoic acid hydrochloride (52356-01-1)

o-hydrazinobenzoic acid (5326-27-2)