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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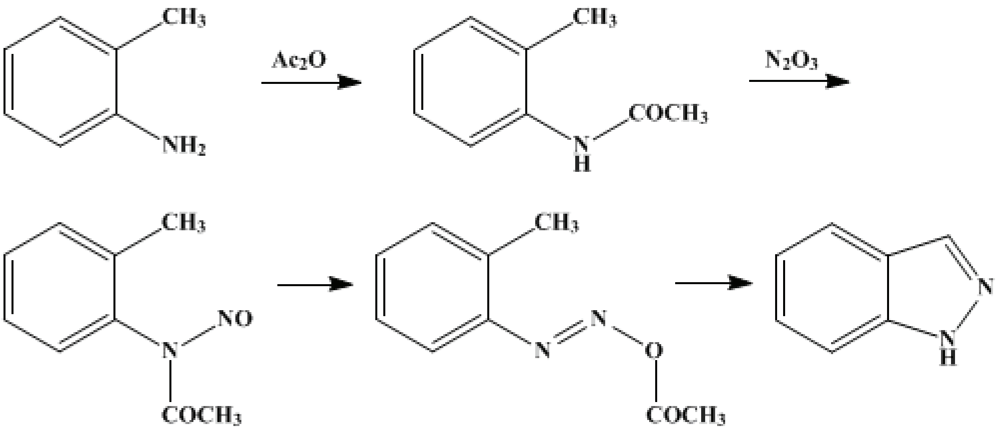
INDAZOLE

[Benzopyrazole]



Submitted by Rolf Huisgen and Klaus Bast[1].
Checked by W. E. Parham, Wayland E. Noland, and John W. Drenckpohl.

1. Procedure

Ninety grams (90.2 ml., 0.839 mole) of *o*-toluidine is slowly added to a mixture of 90 ml. of glacial acetic acid and 180 ml. (1.90 mole) of acetic anhydride contained in a 750-ml. two-necked flask equipped with a thermometer and a two-hole cork stopper for a gas inlet tube (Note 1). Acetylation occurs with evolution of heat. The mixture is cooled in an ice bath (Note 2) and nitrosated by rapid admission of a stream of nitrous gases (Note 3). The nitrous gases are obtained by the action of nitric acid (density 1.47) on sodium nitrite (Note 4). Technical grade, large-grain sodium nitrite (180 g.) is placed in a 1-l. suction flask to which a dropping funnel is fitted by means of a rubber stopper (Note 5). The acid (a total of about 250 ml. is used) is added dropwise from the dropping funnel. The rate of the gas evolution should be such that the temperature of the reaction mixture is kept between +1° and +4° (Note 6). The gas is passed through a wash bottle (with inlet and outlet positions reversed) containing some glass wool and positioned between the generating flask and the reaction flask. After about 6 hours the nitrosation is complete, and the solution exhibits a permanent black-green color due to excess N_2O_3 (Note 7).

The solution of N-nitroso-*o*-acetotoluidide is poured onto a mixture of 400 g. of ice and 200 ml. of ice water in a beaker, covered loosely with a watch glass, and allowed to stand in an ice bath for 2 hours. The oil which separates is transferred to a separatory funnel and extracted by shaking with several portions of benzene (total volume 500 ml.). The combined extract is washed with three 100-ml. portions of ice water and, after shaking with 30 ml. of methanol to remove remaining acetic anhydride, is allowed to stand, lightly covered, in an ice bath for 1 hour. Next, the mixture is washed with three 100-ml. portions of ice water, and the cold benzene solution is allowed to stand, loosely covered, over calcium chloride in the refrigerator overnight (Note 8). The brown solution is decanted from the drying agent into a 3-l. Erlenmeyer flask, and the calcium chloride is washed (by decantation) with 800 ml. of benzene. The combined benzene layer and washings are warmed to 35° in a large water bath and maintained at this temperature for 1 hour (internal temperature, (Note 9)(Note 10)), and then at 40–45° for 7 hours. These temperatures must be strictly adhered to; otherwise overheating can occur (Note 11).

After the completion of the decomposition, the solution is boiled for a short time by heating on a steam bath. The cooled solution is transferred to a separatory funnel and extracted with 200 ml. of 2*N* hydrochloric acid and then with three 50-ml. portions of 5*N* hydrochloric acid. The combined acid extracts are treated with excess ammonia, at which point the indazole precipitates. The mixture is kept in the refrigerator for 2 hours, and the solid is then collected on a Büchner funnel, washed with water, placed in a beaker covered with a piece of paper, and dried overnight at 100–105°. The yield of crude, light brown indazole, m.p. 144–147°, is 36–46 g. (36–47%) (Note 12). For purification, vacuum distillation in a Claisen flask, modified for distillation of solids, is suitable. This gives 33–43 g. of colorless indazole (b.p. 167–176°/40–50 mm.) with a melting point of 148° (Note 13).

2. Notes

1. The inlet tube should not be too narrow and should dip far enough into the reaction mixture to permit agitation of the reaction mixture by the gas stream.
2. Crystallization of *o*-acetotoluidide sometimes occurs at this stage and is allowed to go to completion. This is indicated by a decrease in the evolution of heat of crystallization. Addition of nitrous acid is not begun until the reaction mixture has reached 3°.
3. No harm is done by the separation of *o*-acetotoluidide, which sometimes occurs at this point.
4. The acid (density 1.47) is obtained by diluting 200 ml. of fuming nitric acid with 70 ml. of concentrated nitric acid.
The amount of N_2O_3 in the nitrous gases depends on the density of the nitric acid used. Density 1.40 corresponds to 13 vol. % N_2O_3 or its equivalent. Density 1.43 corresponds to 23 vol. % N_2O_3 or its equivalent. Density 1.45 corresponds to 41 vol. % N_2O_3 or its equivalent. Density 1.47 corresponds to 78 vol. % N_2O_3 or its equivalent.
5. The stopper is covered with a thin layer of paraffin. At the rubber tubing connections, the ends of the glass tubes should be in contact.
6. This is accomplished with an ice bath (without added salt).
7. Should the gas evolution become sluggish after 3–4 hours, the generator may be replaced by a new one containing one-half as much sodium nitrite.
8. It is necessary to begin the preparation early in the morning in order to bring it to this stage in one day.
9. If the water bath is heated by a hot plate controlled by a thermoregulator, it is only necessary to set the temperature at the thermoregulator.
10. At the beginning, the internal temperature is about 5–10° higher than the bath temperature because of the exothermic character of the indazole formation.
11. The use of a large bath simplifies dissipation of the heat of reaction.
12. The submitters regularly obtained yields as high as 55–61% of crude indazole and 52–58% of pure indazole.
13. This pressure range is used in order to give a boiling point sufficiently above the melting point of the indazole.

3. Discussion

The preceding method is that of Huisgen and Nakaten[2] and is based on the preparation of indazole (ca. 40% yield) from N-nitroso-*o*-benzotoluidide discovered by Jacobson and Huber.[3] Mechanistic studies[2] showed this reaction to be an intramolecular azo coupling with an initial acyl shift as the determining step. The yield of indazole from N-nitroso-*o*-benzotoluidide can be made almost quantitative.[2] Since the low solubility of *o*-benzotoluidide makes large quantities of acetic acid and acetic anhydride necessary, the method using the N-acetyl compound described here is more convenient.

With respect to time and cost, this method is superior to the five-step synthesis[4] from anthranilic acid. Older literature sources have been cited in an earlier volume of *Organic Syntheses.*[4] Indazole has also been prepared recently by the reaction of 2-hydroxymethylenecyclohexanone with hydrazine and dehydrogenation of the 5,6,7,8-tetrahydro derivative.[5]

References and Notes

1. Institut für Organische Chemie, Universität München, München 2, Germany.
2. R. Huisgen and H. Nakaten, *Ann.*, **586**, 84 (1954).

3. P. Jacobson and L. Huber, *Ber.*, **41**, 660 (1908).
4. E. F. M. Stephenson, *Org. Syntheses*, Coll. Vol. **3**, 475 (1955).
5. C. Ainsworth, *Org. Syntheses*, Coll. Vol. **4**, 536 (1963).

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

N_2O_3

N-nitroso-o-benzotoluidide

o-benzotoluidide

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

Benzene (71-43-2)

methanol (67-56-1)

acetic anhydride (108-24-7)

nitric acid (7697-37-2)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

Anthranilic Acid (118-92-3)

hydrazine (302-01-2)

Indazole,
Benzopyrazole (271-44-3)

2-Hydroxymethylenecyclohexanone (823-45-0)

o-toluidine (95-53-4)

o-acetotoluidide (120-66-1)

N-nitroso-o-acetotoluidide