



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.

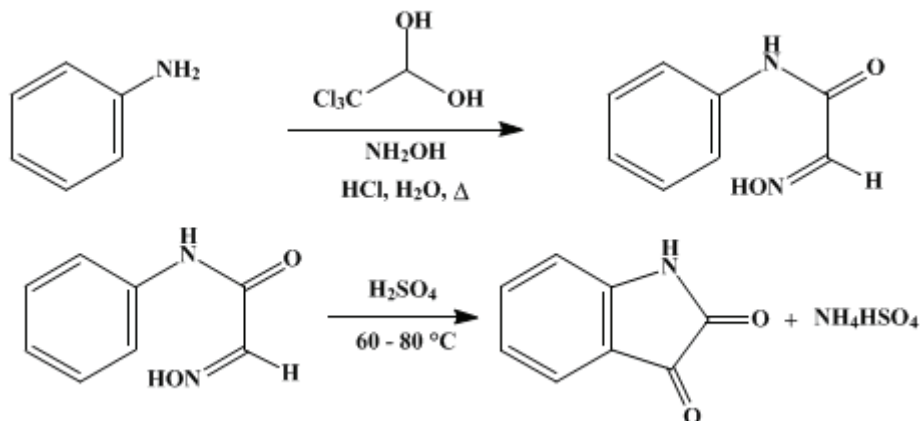
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior 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.

Organic Syntheses, Coll. Vol. 1, p.327 (1941); Vol. 5, p.71 (1925).

ISATIN



Submitted by C. S. Marvel and G. S. Hiers.

Checked by J. B. Conant

1. Procedure

(A) *Isonitrosoacetanilide*.—In a 5-l. round-bottomed flask are placed 90 g. (0.54 mole) of chloral hydrate and 1200 cc. of water. To this solution are then added, in order: 1300 g. of crystallized sodium sulfate (Note 1); a solution of 46.5 g. (0.5 mole) of aniline (Note 2) in 300 cc. of water to which 51.2 g. (43 cc., 0.52 mole) of concentrated hydrochloric acid (sp. gr. 1.19) has been added to dissolve the amine (Note 3); and, finally, a solution of 110 g. (1.58 moles) of hydroxylamine hydrochloride (Note 4) in 500 cc. of water. The flask is heated over a wire gauze by a Meker burner so that vigorous boiling begins in about forty to forty-five minutes. After one to two minutes (Note 5) of vigorous boiling the reaction is complete. During the heating period, some crystals of isonitrosoacetanilide separate. On cooling the solution in running water the remainder crystallizes, is filtered with suction, and air-dried. The yield is 65–75 g. (80–91 per cent of the theoretical amount) of a product melting at 175° .

(B) *Isatin*.—Six hundred grams (326 cc.) of concentrated sulfuric acid (sp. gr. 1.84) is warmed to 50° in a 1-l. round-bottomed flask fitted with an efficient mechanical stirrer, and, to this, 75 g. (0.46 mole) of dry (Note 6) isonitrosoacetanilide is added at such a rate as to keep the temperature between 60° and 70° but not higher (Note 7). External cooling should be applied at this stage so that the reaction can be carried out more rapidly. After the addition of the isonitroso compound is finished, the solution is heated to 80° and kept at this temperature for about ten minutes to complete the reaction. Then the reaction mixture is cooled to room temperature and poured upon ten to twelve times its volume of cracked ice. After standing for about one-half hour, the isatin is filtered with suction, washed several times with cold water to remove the sulfuric acid, and then dried in the air. The yield of crude isatin, which melts at $189-192^\circ$, is 47–52 g. (71–78 per cent of the theoretical amount). This product is pure enough for many purposes (Note 8).

For purification, 200 g. of the crude product is suspended in 1 l. of hot water and treated with a solution of 88 g. of sodium hydroxide in 200 cc. of water. The solution is stirred mechanically and the isatin passes into solution. Dilute hydrochloric acid is then added, with stirring, until a slight precipitate appears. This requires about 290–300 cc. of an acid made by diluting one volume of concentrated hydrochloric acid (sp. gr. 1.19) with two volumes of water (Note 9). The mixture is then filtered at once, the precipitate is rejected, and the filtrate is made acid to Congo red paper with hydrochloric acid. The solution is then cooled rapidly, and the isatin which separates is filtered with suction and dried in the air. The pure product thus obtained weighs 150–170 g. (Note 10) and (Note 11) and melts at $197-200^\circ$ (corr.).

Isatin may also be crystallized from three times its weight of glacial acetic acid. In this case it is

obtained in large brown-red crystals which melt at 196–197°.

2. Notes

1. Several runs were made in which the amounts of water and sodium sulfate were varied over a considerable range, and this concentration was found to give the best yield of product of good quality. The sodium sulfate seems to have more than a salting-out effect. If a saturated solution of sodium chloride is used no product is obtained.
2. Redistilled aniline boiling over a 2° range was used in these experiments. The ordinary "pure" grade gives slightly lower yields.
3. If the aniline is not in solution, a considerable quantity of tarry material is formed during the heating period. No tar is formed when the method described is used.
4. The hydroxylamine hydrochloride used was the crude material prepared as described on p. 318. Preliminary experiments showed that this reagent must be present in considerable excess. Equally good results were obtained by using a solution of crude hydroxylamine sulfate which also contained sodium sulfate and ammonium sulfate with a little excess sulfuric acid. The hydroxylamine content was determined in this solution by titration with potassium permanganate solution. When this crude solution is used, the addition of sodium sulfate is not always necessary.
5. Longer heating of the reaction mixture gives a lower yield of dark-colored product.
6. If too much moisture is left in the isonitrosoacetanilide it is not easy to control the reaction with sulfuric acid.
7. The reaction does not start below 45–50° but becomes too violent above 75–80°. If the temperature becomes too high, the entire run is lost by charring. Stirring is needed to prevent local overheating.
8. In some smaller preparations when the sulfuric acid solution was poured on ice a yellow compound precipitated, which was shown to be the oxime of isatin. It has also been isolated from the acid mother liquors from which the isatin has separated. The oxime probably owes its formation to the hydrolysis of some unaltered isonitrosoacetanilide (J. P. Wibaut,¹ private communication).
9. The correct amount of acid that must be added to precipitate the impurities but not the isatin will vary with different samples of crude isatin. If too much acid is added, some isatin comes down with the impurities. This may be saved and added to a subsequent run.
10. The yield of isatin is lower than for some of its derivatives. The explanation given in the literature is that some sulfonation occurs during the treatment with sulfuric acid, with corresponding loss of product.
11. This method can be applied successfully to other isatin derivatives. Thus, under the same conditions, 54 g. of *p*-toluidine gives 75–77 g. (83–86 per cent of the theoretical amount) of isonitrosoaceto-*p*-toluidine melting at 162°. Eighty grams of this isonitroso compound treated as described under isonitrosoacetanilide gives 65–68 g. (90–94 per cent of the theoretical amount) of crude 5-methyl isatin melting at 179–183°. This is purified as described under isatin by solution in sodium hydroxide and partial neutralization to throw out the impurities or by recrystallization from three parts of glacial acetic acid. The purified 5-methyl isatin melts at 187°.

3. Discussion

Isatin can be prepared by the oxidation of indigo;² and the condensation of aniline, chloral hydrate, and hydroxylamine salts, followed by the action of sulfuric acid.³ The latter method by Sandmeyer³ seemed most promising and has been studied in detail. The procedure described differs from it in the use of hydroxylamine hydrochloride itself instead of a crude solution of hydroxylamine sulfate, and in the use of sodium sulfate to salt out the isonitroso compound.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 635

References and Notes

1. Wibaut and Geerling, *Rec. trav. chim.* **50**, 41 (1931).

2. Erdmann, J. prakt. Chem. **24**, 11 (1841); Laurent, *ibid.* **25**, 434 (1842); Gericke, *ibid.* **95**, 177 (1865); Knop, *ibid.* **97**, 86 (1866); Knape, *ibid.* (2) **43**, 211 (1891); Hofmann, Ann. **53**, 10 (1845); Sommaruga, Ann. **190**, 369 (1878); Gericke, Jahresber. 580 (1865); Forrer, Ber. **17**, 976 (1884); Diez and Co., Ger. pat. 229,815 [Frdl. **10**, 353 (1910–12)]; Rabinovich and Dzirkal, Khim. Farm. Prom. 1933, 190 [C. A. **28**, 475 (1934)]; Henesy, J. Soc. Dyers Colourists, **53**, 345, 347 (1937).
 3. Sandmeyer, Helvetica Chim. Acta **2**, 237, 239 (1919); Geigy, Brit. pat. 128,122 [C. A. **13**, 2375 (1919)].
-

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

isonitroso compound

indigo

hydroxylamine salts

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

potassium permanganate (7722-64-7)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

Hydroxylamine hydrochloride (5470-11-1)

ammonium sulfate (7783-20-2)

hydroxylamine (7803-49-8)

Isatin (91-56-5)

chloral hydrate (302-17-0)

isonitrosoacetanilide (1769-41-1)

hydroxylamine sulfate (10046-00-1)

5-methyl isatin (608-05-9)

p-toluidine (106-49-0)

isonitrosoaceto-p-toluidine

Copyright © 1921-2005, Organic Syntheses, Inc. All Rights Reserved