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.

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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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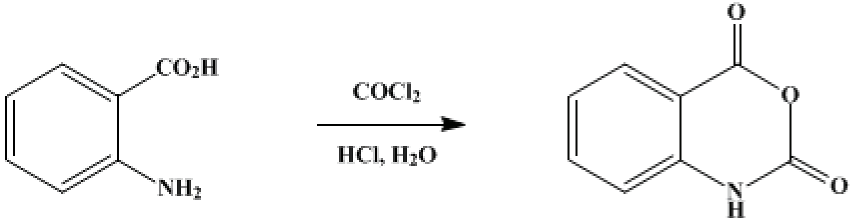
ISATOIC ANHYDRIDE



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1. Procedure

Phosgene is toxic. The apparatus should be set up in a good hood.

One hundred and thirty-seven grams (1 mole) of anthranilic acid is dissolved, with the aid of gentle warming, in a mixture of 1 l. of water and 126 ml. of concentrated hydrochloric acid (sp. gr. 1.19). The solution is filtered into a 2-l. three-necked flask fitted with a gas-tight, mechanically driven Hershberg stirrer. Through one of the side necks extends an inlet tube which ends in a coarse sintered-glass gas-dispersing tip extending well into the liquid into the liquid in the flask. The inlet tube is connected with a cylinder of phosgene through an empty safety flask. In the third neck of the flask is mounted an addition tube, through the vertical arm of which a thermometer (Note 1) is mounted so that the bulb is immersed in the reaction liquid. The outlet is attached to the lateral arm of the addition tube and is connected to an empty safety flask which in turn is connected to a Drechsel bottle charged with ammonium hydroxide.

With the stirrer in rapid motion (Note 2) phosgene is passed into the solution of anthranilic acid at such a rate that bubbles of gas escape slowly into the ammonia scrubber (about two bubbles per second). Isatoic anhydride appears as a precipitate soon after the stream of phosgene is started. The temperature rises but is prevented from exceeding 50° (Note 3) by regulation of the rate at which phosgene is introduced. The stream of phosgene is continued for 2–4 hours, or until the rate of absorption is clearly much decreased (Note 4). The flask is disconnected, and residual phosgene is blown out by passing a current of air through the mixture. The product is collected on a Büchner funnel and is washed with three 500-ml. portions of cold water. The first crop amounts to 54–56 g.

The mother liquor is returned to the reaction flask, the apparatus reassembled, and the passage of phosgene resumed (Note 5). When the rate of absorption has noticeably decreased (1–1.5 hours) the precipitated isatoic anhydride is collected on a filter and washed. The second crop amounts to 34–54 g. A third passage of phosgene at a considerably reduced rate will often yield a small additional crop (10–24 g.) of isatoic anhydride (Note 6).

The product is dried in air and then at 100°. The total yield is 118–123 g. (72–75%) of a white or nearly white product which decomposes at 237–240° cor.; this material is pure enough for most purposes. It may be recrystallized from 95% ethanol (about 30 ml. per gram) or from dioxane (about 10 ml. per gram). The former solvent permits the higher recovery (89–90%) and, except for the large volume required, is to be preferred. The mother liquor may be used for recrystallization of several successive lots of isatoic anhydride. The purified compound decomposes at 243° cor. (Note 7).

2. Notes

1. A thermometer with the graduation marks on the upper half of the stem is convenient.
2. The rate of absorption of phosgene is dependent upon the speed and efficiency of the stirring. This

also determines the amount of product obtained in each treatment with phosgene.
3. Operation below room temperature is without advantage. At 60° or above the yield of isatoic anhydride is decreased, or the process may yield precipitated material from which little or no isatoic anhydride can be obtained. Cooling of the mixture might become advisable during operation on a scale larger than specified.
4. It is advisable to precipitate the isatoic anhydride in several successive crops as directed, rather than to attempt to complete the reaction in one step, because the accumulation of precipitated isatoic anhydride slows the rate of absorption of phosgene to such an extent that prolonged passage of the gas at a decreasing and eventually very low rate would be necessary.
5. It is important to clean the glass gas-dispersing tip with hot dioxane before reassembling the apparatus.
6. A small (usually trifling) final crop of isatoic anhydride can be obtained by addition of 40 g. (1 mole) of sodium hydroxide to the liquid and by introducing phosgene slowly.
7. The method is capable of extension to other *o*-aminocarboxylic acids,[1] e.g., to 3-amino-2-naphthoic acid, 4,4'-diaminobiphenyl-3,3'-dicarboxylic acid, and 2-amino-*p*-toluic acid. With some acids other than anthranilic, difficulty may be encountered owing to the readiness with which their hydrochlorides are salted out of solution by hydrochloric acid.

3. Discussion

Isatoic anhydride has been prepared by prolonged refluxing of a mixture of anthranilic acid and ethyl chlorocarbonate,[2] a reaction usually accompanied by formation of considerable monoethyl or/and diethyl isatoate; or by action of phosgene upon anthranilic acid in a solution the acidity of which is moderated by occasional addition of sodium carbonate.[2] The method described is based upon a patented procedure[1] in which, under conditions not fully specified, phosgene is passed into a solution of anthranilic acid hydrochloride with no subsequent adjustment of the acidity.

References and Notes

1. Ger. pat. 500,916 [*Frdl.*, **17**, 500 (1930)]; Clark and Wagner, *J. Org. Chem.*, **9**, 60 (1944).
2. Erdmann, *Ber.*, **32**, 2159 (1899).

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

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

sodium hydroxide (1310-73-2)

sodium carbonate (497-19-8)

phosgene (75-44-5)

ammonium hydroxide (1336-21-6)

Anthranilic Acid (118-92-3)

ethyl chlorocarbonate (541-41-3)

dioxane (123-91-1)

3-Amino-2-naphthoic acid (5959-52-4)

Isatoic anhydride (118-48-9)

diethyl isatoate

anthranilic acid hydrochloride

2-amino-p-toluic acid

4,4'-diaminobiphenyl-3,3'-dicarboxylic acid

monoethyl isatoate