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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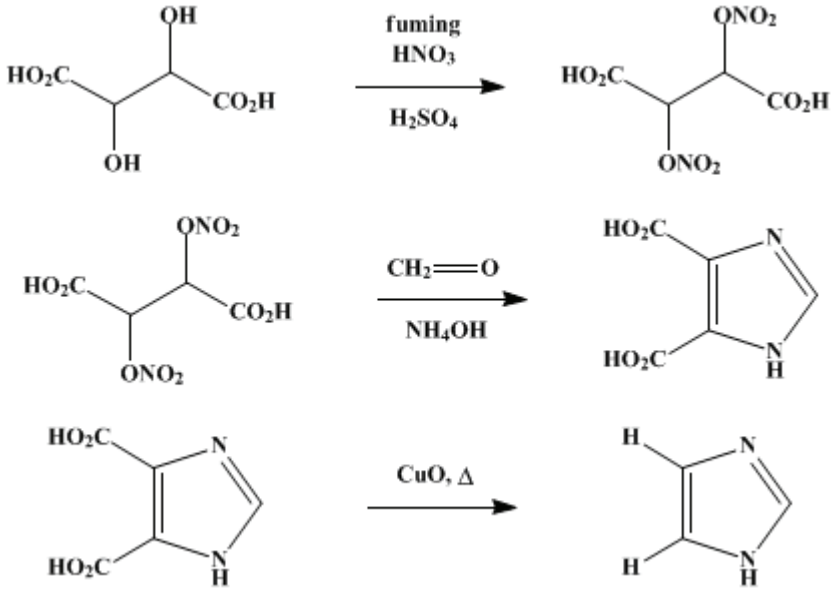

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1. Procedure

In a 2-l. three-necked round-bottomed flask fitted with a thermometer, mechanical stirrer, and 1-l. dropping funnel is placed 200 g. (1.33 moles) of powdered *d*-tartaric acid (Note 1). To this are added, successively, 432 ml. of nitric acid (sp. gr. 1.42) and 432 ml. of fuming nitric acid (sp. gr. 1.50). The mixture is stirred until the tartaric acid is all, or nearly all, in solution (5–10 minutes) (Note 2). Then 800 ml. of concentrated sulfuric acid (sp. gr. 1.84) is slowly added from the dropping funnel. As soon as the temperature of the reaction mixture reaches 38°, the flask is surrounded by a vessel of ice water, and the rate of addition of acid is regulated so that the temperature is maintained at 38–43° (Note 3). Near the end of the addition (about 15 minutes), tartaric acid dinitrate sometimes begins to crystallize. After all the sulfuric acid has been added the mixture is allowed to stand in a cool (20–25°) place for 3 hours.

The crystalline mass is broken up with a glass rod and collected on a glass filter cloth (Note 4) in an 18-cm. Büchner funnel. The resulting cake is pressed nearly dry by means of a large flat glass stopper or the bottom of a 125-ml. Erlenmeyer flask. After most of the mother liquor has been removed (Note 5), the solid is transferred in portions to a 4-l. beaker containing about 3 l. of *finely cracked ice* The ice is stirred to effect solution of each portion of the solid as it is added; a wooden stirring rod with a flat end is advisable. Not more than 10 minutes should be required.

The cold solution is poured *immediately* into a previously assembled apparatus, consisting of a 5-l. three-necked flask, immersed in a 20-in. tub of ice-salt mixture (Note 6), and provided with a stirrer, dropping funnel, and thermometer for reading low temperatures. The solution is neutralized by the addition of 600–700 ml. of concentrated ammonium hydroxide (sp. gr. 0.90) at such a rate that the temperature *never* exceeds −5°(Note 7); the tip of the dropping funnel should be placed directly over the vortex created by the stirrer. After 500 ml. of ammonium hydroxide has been added, the solution is tested with Congo red paper at intervals corresponding to the addition of 50 ml. of ammonium hydroxide; 3–4 hours is required for the neutralization. An additional 100 ml. of ammonium hydroxide is then added.

While the neutralization is in progress, a solution of hexamethylenetetramine (Note 8) is prepared by the cautious addition of 520 ml. of formalin (sp. gr. 1.08; approximately 7 moles) to 500 ml. of

ammonium hydroxide (sp. gr. 0.90; approximately 7.5 moles). The temperature must be maintained below 20° by external cooling with ice water. The solution is finally chilled to 0° and added dropwise to the cold ammoniacal solution of tartaric acid dinitrate; the temperature should not exceed 2°. The addition requires 30 minutes. Stirring is then discontinued, and the mixture is allowed to stand overnight. During this period the cooling bath and the reaction mixture come to room temperature.

The solution is now filtered, and 100 ml. of ethanol is added to the filtrate, which is then acidified (hood) to Congo red paper by the slow (30 minutes) addition of about 400 ml. of concentrated hydrochloric acid (sp. gr. 1.19). The acidified mixture is cooled in an icebox for 4–5 hours, and the imidazole-4,5-dicarboxylic acid is collected on an 18-cm. Büchner funnel. The solid is transferred to a 1-l. beaker, stirred with 400–500 ml. of water, and again filtered. It is washed on the funnel successively with three 150-ml. portions of water, two 75-ml. portions of methanol, and finally with 75 ml. of ether. After drying in the air, it weighs 90–100 g. (43–48%) and melts with decomposition at about 280°.

The imidazole-4,5-dicarboxylic acid is divided into two portions. Each portion is intimately mixed with about 0.5 g. of copper-chromium oxide catalyst [*Org. Syntheses* Coll. Vol. **2**, 142 (1943)] or powdered copper oxide (Note 9), and the resulting mixture is transferred to a 250-ml. Claisen flask having a modified side arm; the receiving flask is loosely placed over the side arm. The flask is heated gently with a free flame. After a small fore-run at 95–100°, the temperature rises sharply to 260° (Note 10), and the imidazole distils at 262–264°. The product is purified by dissolving it in 60–70 ml. of benzene, boiling the solution for a few minutes with 2–3 g. of decolorizing carbon (Note 11), filtering the mixture through a preheated Büchner funnel, and cooling the filtrate to 10° for 2 hours. The yield is 13–14.5 g. (68–76%) of a pure white product, m.p. 88–90° (Note 12).

2. Notes

1. The submitters used u.s.p. tartaric acid. The checkers used the Eastman Kodak Company acid, m.p. 169–171°.
2. It is possible to carry out the preparation without mechanical stirring, merely using a single-necked flask and shaking by hand. Temperature control is not so satisfactory under these conditions.
3. At lower temperatures tartaric acid dinitrate separates during the addition of the sulfuric acid. Under these conditions, it forms very fine crystals that are not easily filtered.
4. Vinyon fabric serves equally well. If a filter cloth is not available, a layer of glass wool is prepared on the funnel; the mixed wool and solid are then added to the cracked ice.
5. A fairly dry cake is obtained in about 45 minutes. Since the substance decomposes in the air, it is advisable not to leave it for a longer period.
6. Efficient cooling is extremely important; a small ice bath will not suffice.
7. The decomposition temperature is about 0°. A centrifugal-type stirrer is advisable.
8. No product was obtained when solid hexamethylenetetramine was substituted at this point.
9. Copper oxide gives a slightly lower yield.
10. If an ordinary 250-ml. distilling flask is used, the fraction boiling from 200° to 270° is collected as crude imidazole. The fore-run contains about 1 g. of imidazole, which can be recovered by boiling this fraction of the distillate with benzene, until the water is removed, and then evaporating to crystallization.
11. If a flask and fractionating column are used, the crude product is white; otherwise it is colored.
12. The benzene filtrate from the recrystallization contains about 0.5 g. of imidazole.

3. Discussion

Imidazole has been prepared from glyoxal and ammonia, with[1] or without[2] the addition of formaldehyde; from imidazolthione-2 and nitric acid;[3] and by decarboxylation of imidazole-4,5-dicarboxylic acid.[4,5,6] The procedure described is essentially that of Fargher and Pyman.[6]

References and Notes

1. Wallach, *Ber.*, **15**, 645 (1882).

2. Behrend and Schmitz, *Ann.*, **277**, 338 (1893).
3. Marckwald, *Ber.*, **25**, 2361 (1892).
4. Maquenne, *Ann. chim.*, (6) **24**, 525 (1891).
5. Dedichen, *Ber.*, **39**, 1835 (1906).
6. Fargher and Pyman, *J. Chem. Soc.*, **115**, 227 (1919).

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

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

glyoxal (107-22-2)

formaldehyde,
formalin (50-00-0)

nitric acid (7697-37-2)

decolorizing carbon (7782-42-5)

tartaric acid (87-69-4)

ammonium hydroxide (1336-21-6)

copper oxide (1317-38-0)

hexamethylenetetramine (100-97-0)

Copper-Chromium Oxide

Imidazole (288-32-4)

tartaric acid dinitrate

Imidazole-4,5-dicarboxylic acid (570-22-9)

imidazolthione-2

D-tartaric acid (147-71-7)