Organic Syntheses

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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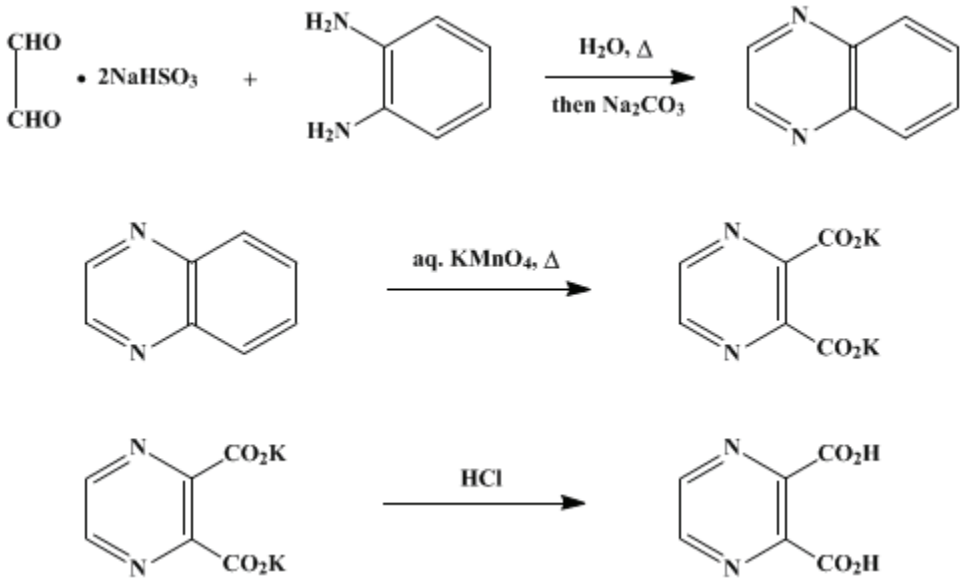
2,3-PYRAZINEDICARBOXYLIC ACID



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1. Procedure

A. *Quinoxaline.* One hundred thirty-five grams (1.25 moles) of *o*-phenylenediamine[2] is dissolved in 2 l. of water, and the solution is heated to 70°. With stirring, a solution of 344 g. (1.29 moles) of glyoxal-sodium bisulfite[3] (Note 1) in 1.5 l. of hot water (about 80°) is added to the *o*-phenylenediamine solution. The mixture is allowed to stand for 15 minutes and then is cooled to about room temperature and 500 g. of sodium carbonate monohydrate (Note 2) is added. The quinoxaline separates as an oil or as a crystalline solid if the mixture is sufficiently cool. The mixture is extracted with three 300-ml. portions of ether. The combined extracts are dried over anhydrous magnesium sulfate or sodium sulfate, filtered, and concentrated on the steam bath. The residual liquid, consisting of almost pure quinoxaline, is distilled under reduced pressure, and the fraction boiling at 108–112°/12 mm. (m.p. 29–30°) is collected. It weighs 138–147 g. (85–90%) (Note 3).

B. *2,3-Pyrazinedicarboxylic acid.* A 12-l. three-necked flask is provided with an efficient mechanical stirrer, a reflux condenser, and a 1-l. dropping funnel. In the flask are placed 4 l. of hot (about 90°) water and 145 g. (1.12 moles) of quinoxaline. With rapid stirring a saturated aqueous solution of 1050 g. (6.6 moles) of potassium permanganate (Note 4) is added through the dropping funnel in a thin stream. The rate of addition of the permanganate solution is adjusted so that the reaction mixture boils gently. The addition requires about 1.5 hours.

The reaction mixture is cooled somewhat (Note 5) and filtered through a large Büchner funnel. The manganese dioxide cake is removed from the funnel and stirred to a smooth paste with 1 l. of fresh water. The slurry is filtered, and the washing is repeated. The total filtrate, about 10 l., is evaporated under reduced pressure on the steam bath to a volume of approximately 3 l. (Note 6). The solution is swirled or stirred gently while 550 ml. (6.6 moles) of 36% hydrochloric acid is cautiously added (Note 7). Evaporation under reduced pressure is then continued until a moist cake of solid potassium chloride and 2,3-pyrazinedicarboxylic acid remains in the flask (Note 8).

The moist cake is scraped from the flask and allowed to dry in a 16-in. porcelain evaporating dish until the odor of hydrochloric acid is faint (about 24 hours, but this time can be reduced to about 8 hours if a gentle stream of air is directed onto the solid). The solid material is returned to the dried flask and

mixed thoroughly with about 200 ml. of water. Two liters of acetone is added, and the mixture is boiled under reflux for 15 minutes, then cooled to room temperature and filtered through a 6-in. Büchner funnel. The solid on the filter is returned to the flask, treated with 100 ml. of water, and extracted with 1 l. of boiling acetone as before (Note 9). The acetone filtrates are combined and distilled from a steam bath, finally under diminished pressure.

The solid in the flask is dissolved by refluxing with 2.5 l. of acetone. The mixture is cooled slightly, treated with 10 g. of decolorizing carbon, refluxed for an additional 5-minute period, and filtered hot. Evaporation of the pale yellow acetone filtrate leaves the acid as a light-tan crystalline solid. If the product still possesses an odor of hydrochloric acid it is dried in a vacuum desiccator over sodium hydroxide pellets for a few hours. Finally the product is dried in an oven at 100° for several hours (Note 10) and (Note 11). The yield of material melting at 165–167° (dec.) is 140–145 g. (75–77%) (Note 12).

If a purer product is desired the material may be recrystallized (with about 17% loss) from 150 ml. of water; the hot solution is decolorized with carbon. The melting point after drying at 110° for several hours is then 183–185° (dec.) (Note 11) and (Note 13).

2. Notes

1. In the absence of sodium bisulfite, aqueous glyoxal solutions react with *o*-phenylenediamine to give only about 30% yields of quinoxaline together with large quantities of resinous by-products. Therefore, if an aqueous glyoxal solution is to be used in this preparation it should be mixed with a water solution of two molar equivalents of sodium bisulfite before it is added to the *o*-phenylenediamine solution.
2. Potassium carbonate or sodium hydroxide may also be used.
3. 2-Methylquinoxaline may be prepared in 88–92% yields from *o*-phenylenediamine and pyruvic aldehyde-sodium bisulfite by this same procedure.
4. The volume of this solution can be held to the minimum, about 3–5 l., by dissolving the permanganate in hot water (90–100°).
5. The only reason for cooling is to make the flask easier to handle during the filtration.
6. A 5-l. round-bottomed flask fitted with a separatory funnel for continuous addition of the solution during the concentration is convenient.
7. There is a vigorous evolution of carbon dioxide, and unless the acid is added slowly the contents of the flask may foam over.
8. Excess hydrochloric acid is present, and the 2,3-pyrazinedicarboxylic acid tends to darken and decompose if it is heated too strongly or for too long a time.
9. The ease with which the dicarboxylic acid is removed from the potassium chloride depends upon the amount of water present. The potassium chloride should be set aside for an additional extraction if the yield of the crude product is low.
10. Drying at 100° converts any of the hydrated 2,3-pyrazinedicarboxylic acids to the anhydrous form.
11. The product darkens somewhat on heating.
12. 2-Methyl-5,6-pyrazinedicarboxylic acid may be prepared in 70–75% yields from 2-methylquinoxaline by this same procedure. The crude acid (m.p. 155–160°, dec) is somewhat unstable at elevated temperatures. It should not be heated above 100° for long periods of time. In order to obtain pure 2-methyl-5,6-pyrazinedicarboxylic acid (m.p. 175°, dec.) the crude product is best recrystallized from acetone.
13. The melting point is dependent on the rate of heating and the temperature of the bath at the time the sample is inserted. The figure given was obtained by insertion of the sample tube into a bath at 160°.

3. Discussion

Quinoxaline has been prepared by the reaction of glyoxal with *o*-phenylenediamine,[4] and 2-methylquinoxaline by the reaction of pyruvic aldehyde[5] or isonitrosoacetone[6] with *o*-phenylenediamine. 2,3-Pyrazinedicarboxylic acid has been prepared by the permanganate[7] or electrolytic[8] oxidation of quinoxaline. 2-Methyl-5,6-pyrazinecarboxylic acid has been obtained from 2-methylquinoxaline in the same way.[6,9] Also, the monopotassium salt of pyrazine-2,3-dicarboxylic acid has been prepared by the oxidation of quinoxaline with potassium permanganate.[10]

References and Notes

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

2-Methyl-5,6-pyrazinecarboxylic acid

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ether (60-29-7)

glyoxal (107-22-2)

sodium hydroxide (1310-73-2)

potassium permanganate (7722-64-7)

sodium sulfate (7757-82-6)

sodium bisulfite (7631-90-5)

carbon dioxide (124-38-9)

acetone (67-64-1)

decolorizing carbon,
carbon (7782-42-5)

manganese dioxide (1313-13-9)

potassium chloride (7447-40-7)

magnesium sulfate (7487-88-9)

o-Phenylenediamine (95-54-5)

sodium carbonate monohydrate (5968-11-6)

2,3-Pyrazinedicarboxylic acid (89-01-0)

glyoxal-sodium bisulfite

Quinoxaline (91-19-0)

2-Methylquinoxaline (7251-61-8)

pyruvic aldehyde-sodium bisulfite

2-Methyl-5,6-pyrazinedicarboxylic acid

pyruvic aldehyde (78-98-8)

isonitrosoacetone

monopotassium salt of pyrazine-2,3-dicarboxylic acid