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.

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.

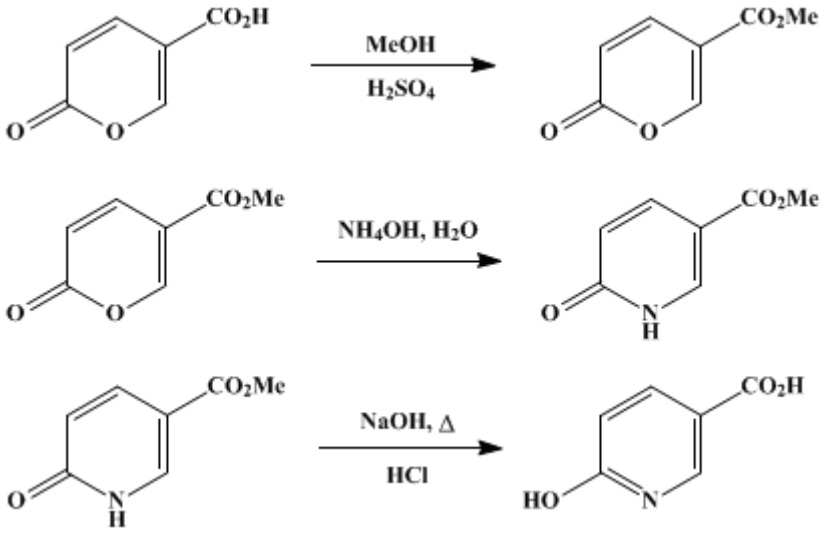
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.036.0044

Organic Syntheses, Coll. Vol. 4, p.532 (1963); Vol. 36, p.44 (1956).

6-HYDROXYNICOTINIC ACID

[Nicotinic acid, 6-hydroxy-]



Submitted by J. H. Boyer and W. Schoen[1].
Checked by T. L. Cairns and W. J. Linn.

1. Procedure

A. *Methyl coumalate.* In a 500-ml. round-bottomed flask provided with a thermometer is placed 139 ml. of concentrated sulfuric acid. To the acid is added, with swirling, 50 g. (0.36 mole) of pulverized coumalic acid (p. 201) in small portions. The reaction is slightly exothermic, and the mixture is maintained between 20° and 30° by occasional immersion of the flask into an ice bath. Methanol (70 ml.) is then added in small portions with frequent swirling, and the temperature is held between 25° and 35°. The mixture is heated on a steam bath for 1 hour, cooled to about 40°, and poured slowly with stirring into 800 ml. of water in a 2-l. beaker while the temperature is maintained below 40° by an ice bath (Note 1). Anhydrous sodium carbonate is added in small portions with stirring until the mixture is slightly alkaline (Note 2). The precipitated ester is freed of inorganic salts by slurrying four times with 100-ml. portions of cold water, filtered, and air-dried overnight. The yield of methyl coumalate, m.p. 68–70°, is 17.5–24.5 g. (32–45%). This crude product is used for the preparation of 6-hydroxynicotinic acid.

B. *6-Hydroxynicotinic acid.* In a 500-ml. beaker provided with a thermometer, magnetic stirring, and external cooling is placed 117 ml. of 14% ammonium hydroxide. With stirring, 45 g. (0.29 mole) of methyl coumalate is added over a period of 10 minutes, during which time the solution is kept below 20°. Stirring is continued for an additional 45 minutes at about 20° (Note 3).

A solution of 600 ml. of approximately 17% aqueous sodium hydroxide is placed in a 2-l. beaker and heated almost to the boiling point. At the end of the 45-minute period, the ammoniacal solution is added to the hot sodium hydroxide solution, and the mixture is heated rapidly to the boiling point. After it has boiled vigorously for 5 minutes, the stirred solution is cooled in an ice bath to room temperature. With the temperature held below 30°, concentrated hydrochloric acid is added with stirring until the solution is strongly acid (Note 4). The heavy, yellow, microcrystalline solid which separates after stirring and cooling for about an hour is collected on a Büchner funnel, washed twice with water, and dried at 80°. The yield of bright yellow 6-hydroxynicotinic acid, m.p. 299–300° (dec., uncor.), is 29–37 g. (72–91%) (Note 5).

2. Notes

1. A turbid, brown solution containing a small amount of fine precipitate is obtained.
2. A small amount of curdy, brown precipitate is obtained at first. About 220 g. of anhydrous sodium carbonate is required.
3. Most of the ester dissolves; a turbid, red solution is formed.
4. About 250 ml. of acid is required.
5. The product is sufficiently pure for further synthetic work; a purer product may be obtained by recrystallization from 50% aqueous acetic acid.

3. Discussion

The procedure for preparing methyl coumalate is based on a method described by von Pechmann.[2] Methyl coumalate has also been prepared by direct esterification of the reaction mixture from malic acid and fuming sulfuric acid[3] and from coumalyl chloride and methanol.[4]

The procedure for preparing 6-hydroxynicotinic acid is also based on a method described by von Pechmann.[5] 6-Hydroxynicotinic acid has also been prepared by decarboxylation of 6-hydroxy-2,3-pyridinedicarboxylic acid;[6,7] by heating 6-hydrazinonicotinic acid or its hydrazide with hydrochloric acid;[8] by the action of carbon dioxide on the sodium salt of α-pyridone at 180–200° and 20 atm.;[9] by heating the nitrile of 6-chloronicotinic acid with alcoholic sodium hydroxide or hydrochloric acid;[10] from 6-aminonicotinic acid;[11,12] by the prolonged action of concentrated ammonium hydroxide on methyl coumalate;[3] and by carbonating 2-hydroxypyridine in the presence of potassium carbonate.[13]

References and Notes

1. Tulane University, New Orleans, Louisiana.
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12. Räth and Prange, *Ann.*, **467**, 9 (1928).
13. Baine, Adamson, Barton, Fitch, Swayampati, and Jeskey, *J. Org. Chem.*, **19**, 510 (1954).

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

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methanol (67-56-1)

sodium hydroxide (1310-73-2)

sodium carbonate (497-19-8)

carbon dioxide (124-38-9)

ammonium hydroxide (1336-21-6)

malic acid (617-48-1)

Coumalic acid (500-05-0)

6-Hydroxynicotinic acid,
Nicotinic acid, 6-hydroxy- (5006-66-6)

Methyl coumalate (6018-41-3)

coumalyl chloride

6-hydrazinonicotinic acid

6-chloronicotinic acid (5326-23-8)

6-aminonicotinic acid (3167-49-5)

2-hydroxypyridine (142-08-5)

6-hydroxy-2,3-pyridinedicarboxylic acid

sodium salt of α-pyridone