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.

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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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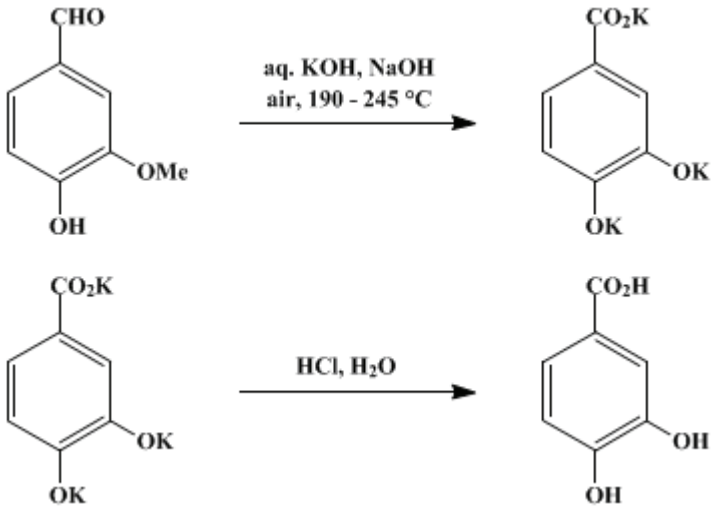
PROTOCATECHUIC ACID

[Benzoic acid, 3,4-dihydroxy-]



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1. Procedure

In a stainless-steel beaker of approximately 3-l. volume (180 mm. by 150 mm.) (Note 1), equipped with an efficient mechanical stainless-steel stirrer and heated by an electric hot plate, are placed 84 g. (2 moles) of 97% sodium hydroxide pellets, 332 g. (5 moles) of 85% potassium hydroxide pellets (Note 2), and 50 ml. of water. The mixture is stirred and heated. When the temperature of the fluid mixture reaches 160°, 152 g. (1 mole) of vanillin is added in portions over a period of 2.5–3 minutes at a rate sufficient to maintain the reaction (Note 3). The temperature at this point is 190–195°. Stirring is continued, and heat is applied until the temperature reaches 240–245° (Note 4). The temperature is maintained at 240–245° for 5 minutes. The hot plate is removed, and the mixture is allowed to cool with stirring. When the mixture has cooled to about 150–160°, 1 l. of water is added, and the mixture is stirred until all the fusion mixture is dissolved. The solution is transferred to a 4-l. beaker, another 500 ml. of water is added, and sulfur dioxide gas is introduced for 2 minutes (Note 5); the mixture is then completely acidified with 1.5 l. of 6 *N* hydrochloric acid. The acidified mixture is cooled in an ice bath (5°) for 2 hours, and the crystalline precipitate is filtered, washed on the filter with two 100-ml. portions of ice water, and air dried. The tan crystals of protocatechuic acid melting at 196–198° weigh 90–100 g. Extraction of the filtrate and washings with two 1-l. portions of ether yields an additional 45–55 g. of protocatechuic acid melting at 190°. The total yield of crude protocatechuic acid amounts to 135–153 g. (89–99%) (Note 6).

2. Notes

1. In the checkers' opinion a 2-l. beaker is sufficiently large, and the contents are easier to stir. Iron or nickel pots have also been used.
2. The exact proportion of sodium hydroxide to potassium hydroxide is not too critical as long as the total amount of alkali is more than 7 moles. Mixtures containing from 10% to 60% sodium hydroxide become fluid between 120° and 130°. Increased percentages of sodium hydroxide in the mixture result in darker protocatechuic acid, but yields are not affected until 70% sodium hydroxide is reached.
3. This reaction is the oxidation of vanillin to vanillic acid with the liberation of hydrogen.
4. The demethylation of vanillic acid to protocatechuic acid takes place to a slight degree between 210° and 235° but goes to completion only at temperatures above 240–245°.

5. The sulfur dioxide treatment prevents the formation of a very dark-colored product when the reaction mixture is acidified with a strong acid.
6. The first crop of acid is light tan and is suitable for most purposes. It can be improved slightly by recrystallizing from hot water, with 3 ml. per g. and 1 g. of Norit for every 10 g. of acid; the recovery is 75%, the remainder being retained by the charcoal. This recrystallized acid is a cream color and melts at 199–200°. If the Norit is omitted, the recovery is 90%, m.p. 198–199°, and color unchanged.
The second crop is of decidedly inferior quality. It is easily purified as follows: Fifteen grams of crude product is dissolved in 100 ml. of 10% sodium hydroxide solution at room temperature, 2 g. of Norit is added, and the mixture is stirred for 10 minutes and filtered. Sulfur dioxide is then passed in for 2 minutes, after which 60 ml. of 6 *N* hydrochloric acid is added. After chilling and standing, 10 g. (67%) of purified protocatechuic acid, m.p. 196–198°, is recovered.

3. Discussion

The only practical method for the preparation of protocatechuic acid is by the alkaline fusion of vanillin.[1,2,3]

References and Notes

1. Pearl, *J. Am. Chem. Soc.*, **68**, 2180 (1946).
2. Tiemann and Haarman, *Ber.*, **7**, 617 (1874).
3. U. S. pat. 2,547,920 [*C. A.*, **45**, 8042 (1951)].

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

hydrochloric acid (7647-01-0)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sulfur dioxide (7446-09-5)

Norit (7782-42-5)

potassium hydroxide (1310-58-3)

vanillin (121-33-5)

protocatechuic acid,
Benzoic acid, 3,4-dihydroxy- (99-50-3)

Vanillic acid (121-34-6)