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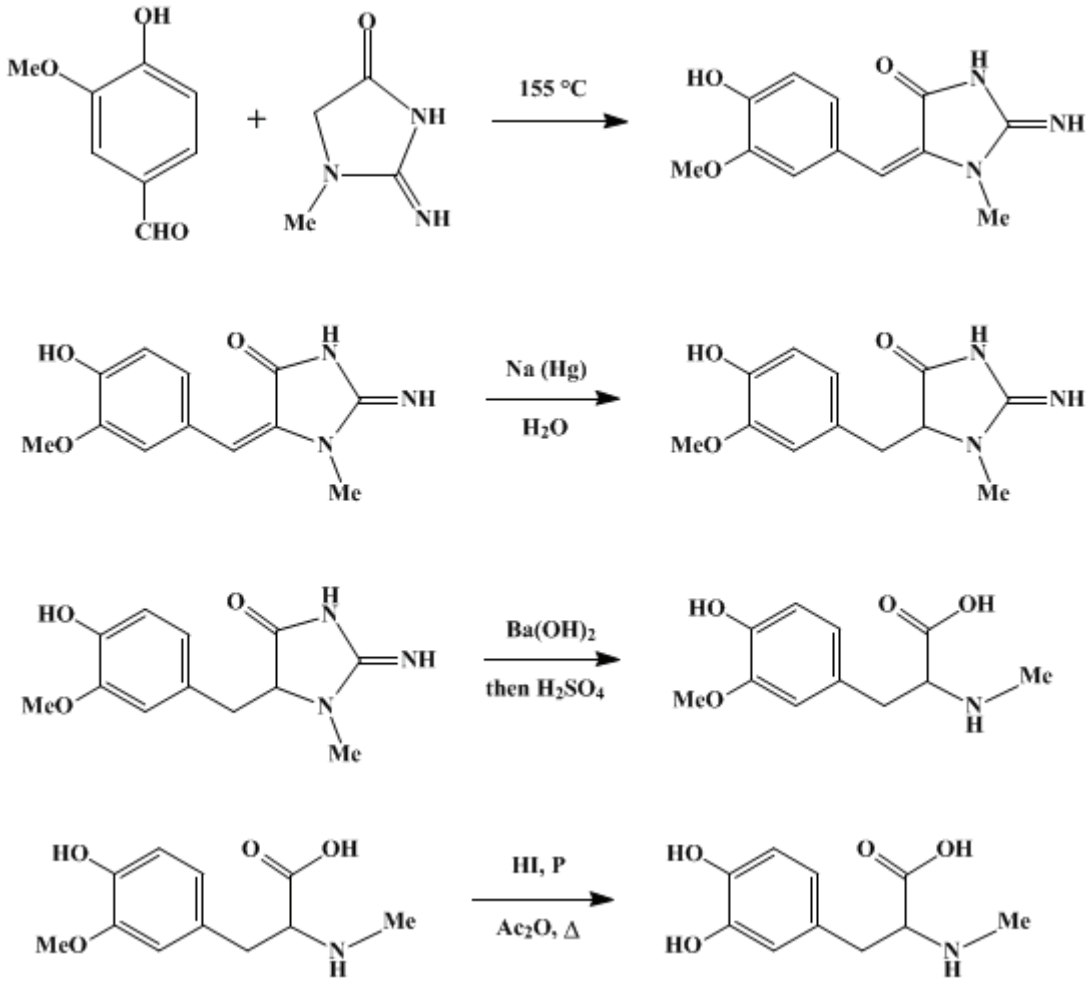
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.022.0089

Organic Syntheses, Coll. Vol. 3, p.586 (1955); Vol. 22, p.89 (1942).

N-METHYL-3,4-DIHYDROXYPHENYLALANINE

[Alanine, β-(3,4-dihydroxyphenyl)-N-methyl-]



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1. Procedure

A. 5-(3-*Methoxy*-4-*hydroxybenzal*)*creatinine* (I). In a large Pyrex test tube (51 mm. outside diameter and 200 mm. long) is placed an intimate mixture of 11.3 g. (0.1 mole) of creatinine [*Org. Syntheses* Coll. Vol. **1**, 172 (1941)] and 24 g. (0.16 mole) of vanillin. The tube is placed in an oil bath, which is then heated to 170°, and the mixture is melted while it is constantly agitated (Note 1). The temperature of the mixture reaches 155° in about 10 minutes; reaction then begins, and water is evolved. After 3–5 minutes longer, evolution of water ceases, and the mixture solidifies. The tube is heated for 3 minutes more, and then it is removed from the bath and allowed to cool.

When the temperature has fallen to 50–60°, 50 ml. of ethanol is added and the mixture is heated gently by occasional immersion in the warm oil bath. The solid partially disintegrates and forms a suspension. The suspension is filtered, and the solid remaining in the tube is warmed with a second 50-ml. portion of ethanol. This operation is repeated until all the orange-colored condensation product has been transferred to the filter. The material on the filter is then washed with three successive 30-ml. portions of water at 60°.

After drying, the crude product weighs 24 g. (95%), melts at 261–263°, and is suitable for use in the next step. A pure product, which melts at 273°, may be obtained by recrystallizing the crude material from acetic acid.

B. 5-(3-*Methoxy*-4-*hydroxybenzyl)creatinine* (II). To a suspension of 24 g. (0.1 mole) of the crude condensation product in 150 ml. of water, contained in a 500-ml. beaker, there is added, with continuous agitation, 180 g. of 3% sodium amalgam (Note 2). The amalgam is added in six portion, at intervals of 5 minutes. The solid dissolves, and the initial orange-red color of the solution slowly fades as the reduction proceeds. With good agitation, decolorization is complete in 45–60 minutes, if the starting material is pure. When the crude condensation product is used, the color of the solution fades to a faint, but permanent, yellow tint, which should mark the end point of the reduction.

The solution is decanted from the mercury and filtered from suspended impurities. The filtrate is stirred and is acidified with hydrochloric acid to *p*H 6.6, phenol red being used as the indicator (Note 3). After standing for 2 hours at 0°, the mixture is filtered and the solid is washed with a little cold water and dried. The product (free base) is microcrystalline, weighs 17.5–18 g. (72–74%), and usually melts at 167–169° (Note 4). After solidification from fusion, the substance melts at 226–228°. When recrystallized from water, the substance melts at 231–233°. The crude product may be used for the subsequent hydrolysis.

C. *N-Methyl*-(3-*methoxy*-4-*hydroxyphenyl)alanine* (III). In a 2-l. round-bottomed flask (Note 5), 18 g. (0.07 mole) of the crude reduction product is refluxed for 12 hours with a solution of 180 g. of crystalline barium hydroxide in 270 ml. of water. The hot solution is diluted with 1.2 l. of water, and the barium is precipitated by addition of 250–270 ml. of 6 *N* sulfuric acid (Note 6). The precipitated barium sulfate is separated by centrifuging and washed with two 100-ml. portions of water; the combined water; solutions are evaporated under reduced pressure at 50° to a volume of about 50 ml. The acid solution is made alkaline to litmus by addition of about 10 ml. of a 12% solution of ammonium hydroxide in water. After standing for 24 hours at 0°, the mixture is filtered, and the solid is washed with cold water and dried. The yield is 12 g. (74%) (Note 7). On rapid heating, the solid melts at 273–275°. When recrystallized from water, the substance melts at 276–278°. The crude product may be used for the next step.

D. *N-Methyl*-3,4-*dihydroxyphenylalanine* (IV). In a carbon dioxide atmosphere, 12 g. (0.05 mole) of the methoxy compound is boiled gently for 3 hours with 24 g. of red phosphorus and a mixture of 60 ml. of acetic anhydride and 60 ml. of hydriodic acid (sp. gr. 1.7). The phosphorus is then removed by filtration and washed with 25 ml. of 50% acetic acid. The filtrates are combined and, in a current of carbon dioxide, are evaporated to a syrup at 50° under 35 mm. pressure. A 60-ml. portion of warm water is then added, and the solution is evaporated as before. The residue is dissolved in 100 ml. of water, and dilute ammonia (10% by volume) is added until the solution does not change Congo red paper to blue (Note 8). The mixture is allowed to stand for 2 hours at 0°, and then the white crystalline precipitate is filtered. The precipitate is washed on the funnel with a little water containing sulfur dioxide, and is dried by washing with ethanol and ether. The product weighs 9.5 g. (82%). When slowly heated it becomes slightly brown at 230° and melts at 282–283°; when rapidly heated it becomes slightly brown at 255–260° and melts at 290–292°.

This material may be purified by boiling 1 g. of it with 50 ml. of water containing sulfur dioxide, filtering the solution, and keeping the filtrate at 0° for 24 hours. The purified product (0.74 g.), when slowly heated, becomes slightly brown at 245° and melts at 287°; when rapidly heated it becomes slightly brown at 260° and melts at 298–300°.

2. Notes

1. Sometimes the evolution of water is too rapid, and there is excessive foaming. The reaction may be moderated by removing the tube from the oil bath.
2. The amalgam may be made by adding 5-mm. cubes of sodium (5.4 g.) to 175 g. of mercury, warmed to 30–40°, and contained in a mortar or Erlenmeyer flask. The mortar is covered with an asbestos board having a small hole in the center. The cubes of sodium are fixed on the end of a pointed glass rod and are quickly pushed through this hole beneath the surface of the mercury. A more convenient method is

described in Fieser, *Experiments in Organic Chemistry*, 2nd Ed., 1941, D. C. Heath and Company, Boston, p. 419.
3. The solution becomes dark in color if allowed to stand overnight.
4. In some cases the melting point may be as low as 98°; but after melting and solidifying, the substance melts at 226–228°.
5. A large flask should be used, since the mixture foams during the hydrolysis.
6. An excess of acid must be added to make certain that all the amino acid is in solution.
7. The yield can be increased slightly by evaporation of the mother liquor.
8. If the solution is made too alkaline, colored impurities precipitate. Neutralization must be performed carefully since the end point to Congo red is reached just before the colored impurities precipitate.

3. Discussion

5-(3-Methoxy-4-hydroxybenzal)creatinine was first prepared by a similar method by Richardson, Welch, and Calvert.[1]

N-Methyl-3,4-dihydroxyphenylalanine has been prepared by methylation of α-acetamino-3,4-methylenedioxycinnamic acid, followed by reduction and hydrolysis of the product;[2] and by a method similar to that outlined above.[3]

N-Methylaminoaromatic acids have been prepared by a variety of methods: by the reaction between methylamine and an α-bromo acid;[4] by condensing methylhydantoin with aromatic aldehydes;[5] by condensation of creatinine[6] or benzoyl sarcosine with aromatic aldehydes;[7] by methylation of the toluenesulfonyl derivative of the amino acid;[8] and by substituting methylamine for ammonia in the Strecker synthesis.[9]

References and Notes

1. Richardson, Welch, and Calvert, *J. Am. Chem. Soc.*, **51**, 3074 (1929).
2. Heard, *Biochem. J.*, **27**, 54 (1933).
3. Guerrero and Deulofeu, *Ber.*, **70**, 947 (1937).
4. Friedmann and Gutmann, *Biochem. Z.*, **27**, 491 (1910).
5. Johnson and Nicolet, *Am. Chem. J.*, **47**, 459 (1912).
6. Nicolet and Campbell, *J. Am. Chem. Soc.*, **50**, 1155 (1928); Deulofeu and Mendivelzua, *Ber.*, **68**, 783 (1935).
7. Deulofeu, *Ber.*, **67**, 1542 (1934).
8. Fischer and Lipschitz, *Ber.*, **48**, 360 (1915).
9. Kanewskaja, *J. prakt. Chem.*, (2) **124**, 48 (1929).

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

N-Methylaminoaromatic acids

α-bromo acid

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

ether (60-29-7)

acetic anhydride (108-24-7)

phenol (108-95-2)

sulfur dioxide (7446-09-5)

PHOSPHORUS (7723-14-0)

mercury (7439-97-6)

carbon dioxide (124-38-9)

barium sulfate (7727-43-7)

sodium (13966-32-0)

hydriodic acid (10034-85-2)

Creatinine (60-27-5)

ammonium hydroxide (1336-21-6)

barium hydroxide (17194-00-2)

barium (7440-39-3)

methylamine (74-89-5)

vanillin (121-33-5)

N-Methyl-3,4-dihydroxyphenylalanine,
Alanine, β-(3,4-dihydroxyphenyl)-N-methyl- (53663-27-7)

α-acetamino-3,4-methylenedioxycinnamic acid

methylhydantoin (616-04-6)

benzoyl sarcosine (2568-34-5)

N-Methyl-(3-methoxy-4-hydroxyphenyl)alanine

5-(3-Methoxy-4-hydroxybenzal)creatinine (29974-40-1)

5-(3-Methoxy-4-hydroxybenzyl)creatinine