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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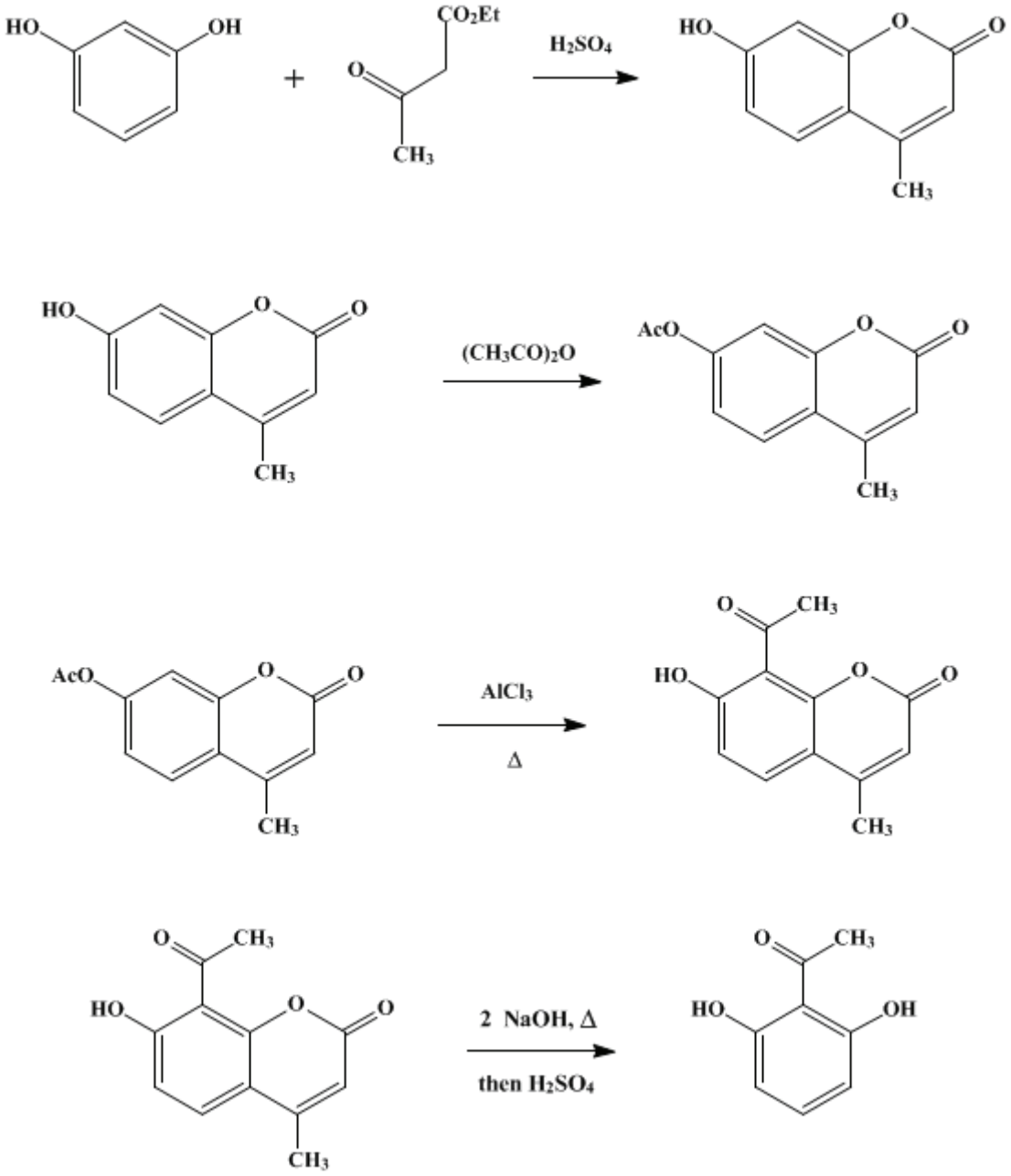
2,6-DIHYDROXYACETOPHENONE

[Acetophenone, 2,6-dihydroxy-]



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1. Procedure

A. *4-Methyl-7-hydroxycoumarin* (I). In a 5-l. three-necked round-bottomed flask, fitted with a mechanical stirrer, a thermometer reaching to the bottom, and a dropping funnel, is placed 2 l. of concentrated sulfuric acid (sp. gr. 1.84). The flask is surrounded by an ice bath, and when the temperature falls below 10° a solution of 220 g. (2 moles) of resorcinol in 260 g. (2 moles) of freshly

distilled ethyl acetoacetate is added dropwise. The mixture is stirred, and the temperature is kept below 10° by means of ice and salt. After all the solution has been added (about 2 hours) the reaction mixture is set aside for 12–24 hours without further cooling. The reaction mixture is now poured with vigorous stirring into a mixture of 4 kg. of ice and 6 l. of water. The precipitate is collected on a filter and washed with three 50-ml. portions of cold water. The crude product is then dissolved in 3 l. of 5% aqueous sodium hydroxide solution, the solution is filtered, and the substituted coumarin is reprecipitated from the filtrate by the slow addition of dilute (1:10) sulfuric acid until the solution is acid to litmus. About 1.1 l. of dilute sulfuric acid is required. During the neutralization, the reaction mixture must be well stirred. The product is collected on a Büchner funnel, washed with four 50-ml. portions of cold water, and dried. The yield of 4-methyl-7-hydroxycoumarin is 290–320 g. (82–90%). It is sufficiently pure for use in the next step but may be purified by recrystallization from 95% ethanol using about 15 ml. of ethanol for 5 g. of product. The recrystallized material forms stout almost colorless needles melting at 185°.

B. 4-*Methyl*-7-*acetoxycoumarin* (II). A mixture of 286 g. (1.6 moles) of crude, dry 4-methyl-7-hydroxycoumarin and 572 g. (5.6 moles) of acetic anhydride is placed in a 2-l. round-bottomed flask fitted to a reflux condenser by a ground-glass joint. The mixture is refluxed for 1.5 hours, cooled to about 50°, and poured with vigorous stirring into a mixture of 4 kg. of cracked ice and 4 l. of water. The precipitate is collected on a Büchner funnel, washed with five 50-ml. portions of cold water, and spread on absorbent paper to dry. The drying is completed by placing the product in a steam oven for 10 hours. The yield of crude 4-methyl-7-acetoxycoumarin is 320–340 g. (90–96%). It may be purified by recrystallization from 95% ethanol (5 g. of compound to 20 ml. of solvent) and forms fibrous needles melting at 150–151°. The crude oven-dried product is finely powdered and used in the next step.

C. 4-*Methyl*-7-*hydroxy*-8-*acetylcoumarin* (III). In a clean, dry, 5-l. round-bottomed flask are placed 200 g. (0.92 mole) of dry, powdered 4-methyl-7-acetoxycoumarin and 453 g. (3.4 moles) of technical anhydrous aluminum chloride. The flask is stoppered and shaken vigorously for 3–5 minutes in order to mix the ingredients thoroughly. The stopper is removed and the flask attached to a reflux condenser fitted with a gas-absorption tube. The flask is placed in an oil bath the temperature of which is raised quickly to 125° and then slowly over a period of 2 hours to 170°. At the end of this time the flask is removed from the oil bath, allowed to cool, and immersed in an ice bath. About 1 kg. of cracked ice is added, and then 2.4 l. of dilute (1:7) hydrochloric acid is added over a period of about 2 hours. The mixture is then heated on a steam bath for 30 minutes with vigorous stirring in order to effect complete decomposition. The mixture is filtered and the precipitate washed with four 50-ml. portions of cold water and sucked dry. This crude product is recrystallized by dissolving it in 4 l. of hot 95% ethanol, filtering the hot solution through a warm funnel, and chilling the filtrate. The crystals are collected on a funnel and air-dried. The product melts at 162–163°, and the yield is 145–155 g. (72.5–77.0%) (Note 1).

D. 2,6-*Dihydroxyacetophenone* (IV). A 5-l. three-necked round-bottomed flask is fitted with a reflux condenser, a dropping funnel, and a glass tube, extending to the bottom of the flask, connected to a cylinder of nitrogen (Note 2). In the flask are placed 148 g. (0.68 mole) of 4-methyl-7-hydroxy-8-acetylcoumarin and 500 ml. of distilled water. A rapid stream of nitrogen is bubbled through the water suspension until all the air in the apparatus is displaced, and then a slow stream of the gas is kept passing through the solution (Note 3). A solution of 129 g. (3.23 moles) of sodium hydroxide in 580 ml. of water is added through the dropping funnel, and the mixture is heated on a steam bath for 5 hours. The solution is then cooled and acidified by the addition of about 1 l. of dilute (1:3) hydrochloric acid. The stream of nitrogen gas is continued throughout the period of heating and while the solution is cooling. It may be stopped after the solution is acid. The crude 2,6-dihydroxyacetophenone which separates on acidification is collected on a filter, washed three times with 50-ml. portions of cold water, and air-dried. A yield of 90–95 g. (87–92% based on the 4-methyl-7-hydroxy-8-acetylcoumarin) of light-yellow solid is obtained.

The purification is accomplished by dissolving the crude product in 1 l. of 95% ethanol, adding 20 g. of Norit, and heating the mixture on a steam cone for 15 minutes with occasional shaking. After this time, 800 ml. of warm water is added, and the solution is heated 5 more minutes and filtered through a hot funnel. The greenish filtrate is chilled in an ice-salt bath, and the first crop (about 65 g.) of lemon-yellow needles of 2,6-dihydroxyacetophenone is removed by filtration. The filtrate is then concentrated

under reduced pressure to a volume of 800 ml., again chilled, and the second crop of product (about 15 g.) collected on a filter. The total yield of purified 2,6-dihydroxyacetophenone, melting at 154–155°, is 75–85 g. (a recovery of 83–89%) (Note 4).

2. Notes

1. The mother liquor from this crystallization contains the isomeric acetyl derivative, 4-methyl-6-acetyl-7-hydroxycoumarin.
2. Hydrogen or illuminating gas may be used in place of nitrogen, provided that proper precautions are taken to conduct the gas from the condenser to a flue.
3. It is important to prevent oxygen from coming in contact with the alkaline solution of the 2,6-dihydroxyacetophenone since it causes the formation of oxidation products which materially lower the yield and cause difficulty in purification. The inert atmosphere must be maintained until after the mixture is acidified.
4. The first two steps in this preparation have been carried out using four times the quantities stated with no reduction in the yields. The third step, involving the Fries rearrangement, usually gives lower yields when larger amounts are used. The amounts of materials in the fourth step may be doubled.

3. Discussion

2,6-Dihydroxyacetophenone has been prepared by the action of methylmagnesium iodide on 2,6-dimethoxybenzonitrile[1] followed by cleavage of the ether linkages with aluminum chloride. The present method is based on the procedures described by Limaye[2] and by Baker.[3]

References and Notes

1. Mauthner, *J. prakt. Chem.*, **139**, 290 (1934).
2. Limaye, *Ber.*, **67**, 12 (1934).
3. Baker, *J. Chem. Soc.*, **1934**, 1953.

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

2,6-DIHYDROXYACETOPHENONE

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic anhydride (108-24-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

oxygen (7782-44-7)

nitrogen (7727-37-9)

Acetophenone (98-86-2)

Norit (7782-42-5)

aluminum chloride (3495-54-3)

methylmagnesium iodide (917-64-6)

Ethyl acetoacetate (141-97-9)

resorcinol (108-46-3)

coumarin

4-Methyl-7-hydroxycoumarin (90-33-5)

4-Methyl-7-acetoxycoumarin (2747-05-9)

4-Methyl-7-hydroxy-8-acetylcoumarin (2555-29-5)

4-methyl-6-acetyl-7-hydroxycoumarin

2,6-Dimethoxybenzonitrile (16932-49-3)