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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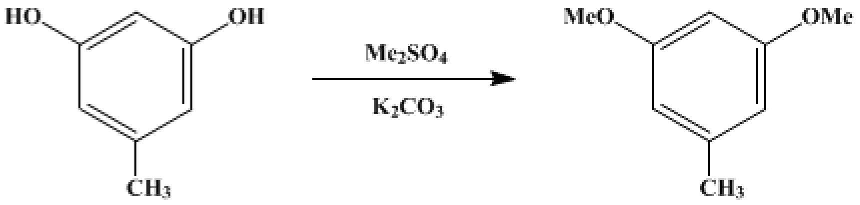
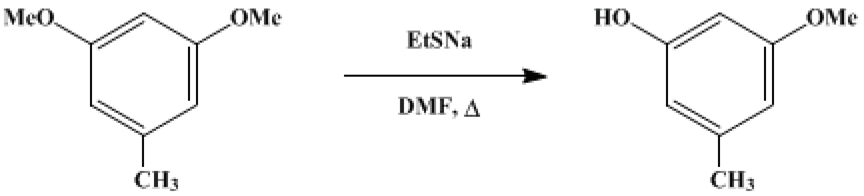
ORCINOL MONOMETHYL ETHER

[Phenol, 3-methoxy-5-methyl-]





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1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *Orcinol dimethyl ether.* A 1-l., three-necked flask fitted with a mechanical stirrer, a condenser, and a 100-ml. dropping funnel is charged with 124 g. (0.984 mole) of anhydrous potassium carbonate, 410 ml. of acetone (Note 1), and 42.6 g. (0.344 mole) of orcinol monohydrate (Note 2). The stirrer is started, and 94.5 g. (70.9 ml., 0.750 mole) of dimethyl sulfate is added from the dropping funnel to the pink mixture over a period of 2 minutes. The mixture warms appreciably and begins to reflux after an additional 5 minutes. When the spontaneous boiling has subsided (15–20 minutes after addition of the dimethyl sulfate), the stirred mixture is heated gently under reflux for 4 hours longer. The condenser is then arranged for distillation and 200 ml. of acetone is distilled. A 50-ml. portion of concentrated aqueous ammonia is added to the reaction mixture; stirring and heating are continued for 10 minutes. The mixture is diluted with water to a total volume of approximately 750 ml., the layers are separated, and the organic layer is combined with two 150-ml. ethereal extracts of the aqueous layer. The organic phase is washed with 50 ml. of water, twice with 50-ml. portions of 3 *N* sodium hydroxide solution (Note 3), once with 50 ml. of saturated aqueous sodium chloride, and dried over magnesium sulfate. After evaporation of the ether at atmospheric pressure, the residual liquid is distilled under reduced pressure, yielding 42.9–43.7 g. (94–96%) of orcinol dimethyl ether, b.p. 133–135° (40 mm.) (Note 4) and (Note 5).

Caution! Because hydrogen is evolved and large volumes of foul-smelling ethyl methyl sulfide are liberated, this step should be conducted in a well-ventilated hood.

B. *Orcinol monomethyl ether.* A 1-l., three-necked flask equipped with a magnetic stirrer, a condenser, a dropping funnel, and a nitrogen inlet is charged with 250 ml. of dry *N,N*-dimethylformamide (Note 6) and 22 g. (0.55 mole) of sodium hydride (60% oil dispersion). The suspension is stirred under an atmosphere of dry nitrogen and cooled with an ice bath while a solution of 31 g. (37 ml., 0.50 mole) of ethanethiol (Note 7) in 150 ml. of dry *N,N*-dimethylformamide (Note 6) is added slowly from the dropping funnel over a period of 20 minutes. The ice bath is removed and stirring is continued for an additional 10 minutes. A solution of 38.0 g. (36.5 ml., 0.250 mole) of orcinol dimethyl ether in 100 ml. of dry *N,N*-dimethylformamide (Note 6) is added in one lot, and the mixture is refluxed under an atmosphere of dry nitrogen for 3 hours (Note 8) and (Note 9). The mixture is cooled, poured into 1.8 l. of cold water, and extracted with two 250-ml. portions of petroleum ether (b.p. 50–70°), which are discarded. The aqueous layer is acidified with 330 ml. of ice-cold 4 *N* hydrochloric acid and extracted with three 250-ml. portions of ether. The combined ethereal extracts are washed with 100 ml. of saturated aqueous sodium chloride and dried over magnesium sulfate. After the ether is distilled at atmospheric pressure, the residual liquid is distilled under reduced pressure, yielding 28–30.5 g. (81–88%) of orcinol monomethyl ether, b.p. 89–90° (0.2 mm.) or 156–158° (25 mm.) (Note 10) and (Note 11)

2. Notes

1. Technical acetone containing about 1% water is quite satisfactory.
2. British Drug Houses Ltd. reagent grade orcinol monohydrate was used without further purification.
3. If the first washing is colorless, as is usually the case, the second washing is unnecessary. Washing with sodium hydroxide solution should be continued until the washings are colorless.
4. A similar run using 100 g. of orcinol monohydrate afforded 102 g. (95%) of orcinol dimethyl ether, b.p. 67.5–68.5° (0.2 mm.).
5. GC analysis of the product on two columns (silicone gum rubber SE-30 and OV-1) indicated the presence of traces of two other compounds with retention times longer than that of orcinol dimethyl ether. These impurities, which were most likely *C*-methylated materials,[2] totaled less than 0.5% of the product.
6. *N,N*-Dimethylformamide, b.p. 58° (25 mm.), was distilled from calcium hydride under a reduced pressure of nitrogen immediately before use.
7. British Drug Houses Ltd. reagent grade ethanethiol was distilled from calcium hydride before use (b.p. 36°).
8. The mixture may become gelatinous during this time, but stirring is not necessary.
9. A polythene tube leading from the top of the condenser to the back of the hood is advisable, preventing any diffusion of the by-product, ethyl methyl sulfide, into the laboratory. Alternatively, this by-product may be collected, if desired, by passing the vapors through a cold trap (dry ice in acetone).
10. This distillate, which is sufficiently pure for most reactions, solidifies after standing for 4–6 hours. A sample crystallizes from benzene-petroleum ether as off-white prisms, m.p. 61–62°, and is relatively free of sulfurous odor.
11. ^{1}H NMR (CCl_4): δ 2.19 (s, 3H, CH_3), 3.63 (s, 3H, OCH_3), 6.17 (m, 3H, C_6H_3), 6.38 (broad s, 1H, OH).

3. Discussion

Previous preparations of orcinol monomethyl ether have been effected by partial methylation of oricinol with methyl iodide and potassium hydroxide[3] or sodium ethoxide,[4] or with dimethyl sulfate and sodium hydroxide.[5] These procedures required tedious purification steps and the pure monomethyl ether was obtained in 37% yield at best.[5]

This procedure is characterized by the easy isolation of a high-purity product in excellent yield. The reaction illustrates a general method[6] for the conversion of aryl methyl ethers to the corresponding phenols, and has proved to be of special advantage with acid-sensitive substrates.[6,7]

A unique feature of this procedure is the selective monodemethylation of the dimethyl ether. The scope of this reaction is illustrated[6] in part by the preparation in high yield of 4-methoxyphenol, guaiacol, and phloroglucinol dimethyl ether from the respective fully *O*-methylated compounds. An exception is pyrogallol trimethyl ether which affords pyrogallol 1-monomethyl ether in high yield.[6]

References and Notes

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

petroleum ether

benzene-petroleum ether

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

dimethyl sulfate (77-78-1)

dimethyl ether (115-10-6)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

sodium ethoxide (141-52-6)

Guaiacol (90-05-1)

Methyl iodide (74-88-4)

magnesium sulfate (7487-88-9)

N,N-dimethylformamide (68-12-2)

sodium hydride (7646-69-7)

ethanethiol (75-08-1)

Pyrogallol 1-monomethyl ether (934-00-9)

calcium hydride (7789-78-8)

4-Methoxyphenol (150-76-5)

Orcinol monomethyl ether,
Phenol, 3-methoxy-5-methyl- (3209-13-0)

orcinol monohydrate (6153-39-5)

Orcinol dimethyl ether (4179-19-5)

ethyl methyl sulfide (624-89-5)

phloroglucinol dimethyl ether (500-99-2)

pyrogallol trimethyl ether (634-36-6)