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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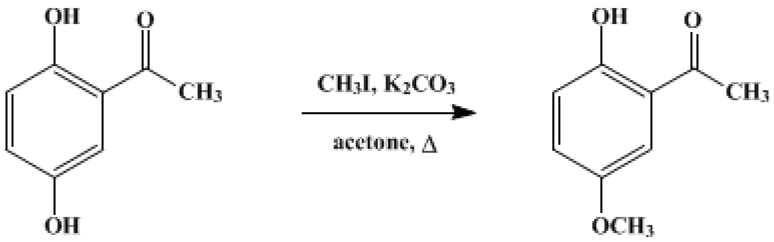
QUINACETOPHENONE MONOMETHYL ETHER

[Acetophenone, 2'-hydroxy-5'-methoxy-]



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1. Procedure

In a 1-l. round-bottomed flask fitted with a reflux condenser and a calcium chloride guard tube are placed 30.0 g. (0.197 mole) of quinacetophenone[2] (Note 1) and 300 ml. of acetone (Note 2). The mixture is warmed on a steam bath to dissolve the quinacetophenone. The resulting greenish solution is cooled to room temperature under tap water, and 28 g. (0.20 mole) of anhydrous potassium carbonate is added followed by 42 g. (0.295 mole) of methyl iodide. The mixture is allowed to reflux on a water bath at 60–70° for about 6 hours (Note 3).

As much of the acetone as possible is removed by distillation on the water bath (Note 4), and the residual dark-colored liquid is cooled and acidified with 2*N* sulfuric acid with cooling under the water tap. The resulting mixture is steam-distilled until no oily drops are seen collecting in the condenser. The distillate, which amounts to about 2.5 l., is allowed to stand overnight at room temperature, and the greenish crystals are separated by suction filtration, washed twice with cold water, and air-dried. The yield of quinacetophenone monomethyl ether, m.p. 48–50°, is 18–21 g. (55–64%) (Note 5).

The brown solution remaining in the distilling flask is filtered while hot; on being cooled it gives 6–7 g. of brownish needles of crude quinacetophenone.

2. Notes

1. The quinacetophenone[2] is dried in an oven at 100–110° for 2–3 hours.
2. The acetone is dried over anhydrous potassium carbonate and distilled.
3. The temperature of the water bath should not exceed 70°; otherwise serious bumping may occur.
4. The recovered acetone may be reused for another methylation.
5. The submitters state that the *dimethyl* ether of quinacetophenone is conveniently prepared by the following procedure: In a 1-l. round-bottomed flask fitted with a reflux condenser 60 g. (0.39 mole) of quinacetophenone[2] is dissolved in 300 ml. of ethanol by heating. The source of heat is then removed, and to the hot solution are alternately added in five installments with shaking a solution of sodium hydroxide (40 g. in 100 ml. of water) and dimethyl sulfate (120 g.). The heat evolved during the reaction makes the solution boil. After the addition is complete (about 20 minutes), the reaction mixture is made alkaline by the further addition of 10 g. of sodium hydroxide in 20 ml. of water and is allowed to reflux on the water bath for 3 hours. The dark mixture is distilled to remove most of the ethanol, and the residual liquid in the flask is steam-distilled. The distillate, which amounts to about 2.5 l., is cooled in an ice bath and saturated with sodium chloride, whereupon a thick oil settles to the bottom. Most of the aqueous layer is decanted, and the remaining oil is extracted with ether and dried over calcium chloride. The ether is removed by distillation, and the residue is fractionated at reduced pressure to give 50–52 g. (71–74% yield) of material boiling at 152–156°/15 mm., m.p. 20–22°.

3. Discussion

Quinacetophenone monomethyl ether has been prepared by the methylation of quinacetophenone with dimethyl sulfate and alkali,[3] by the partial demethylation of quinacetophenone dimethyl ether;[4] and by the acetylation of hydroquinone dimethyl ether with acetyl chloride in the presence of aluminum chloride.[5] It also has been obtained as a by-product in the preparation of quinacetophenone dimethyl ether.[6]

References and Notes

1. M. R. Science Institute, Gujarat College, Ahmedabad, India.
2. *Org. Syntheses Coll. Vol.* **3**, 280 (1955).
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4. Baker, Brown, and Scott, *J. Chem. Soc.*, **1939**, 1926.
5. Oliverio and Lugli, *Gazz. chim. ital.*, **78**, 16 (1948); Wiley, *J. Am. Chem. Soc.*, **73**, 4205 (1951).
6. Kauffmann and Beisswenger, *Ber.*, **38**, 792 (1905).

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

Quinacetophenone monomethyl ether

quinacetophenone

dimethyl ether of quinacetophenone

quinacetophenone dimethyl ether

ethanol (64-17-5)

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

ether (60-29-7)

sodium hydroxide (1310-73-2)

acetyl chloride (75-36-5)

sodium chloride (7647-14-5)

dimethyl sulfate (77-78-1)

acetone (67-64-1)

aluminum chloride (3495-54-3)

Methyl iodide (74-88-4)

hydroquinone dimethyl ether (150-78-7)

Acetophenone, 2'-hydroxy-5'-methoxy- (705-15-7)