



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.

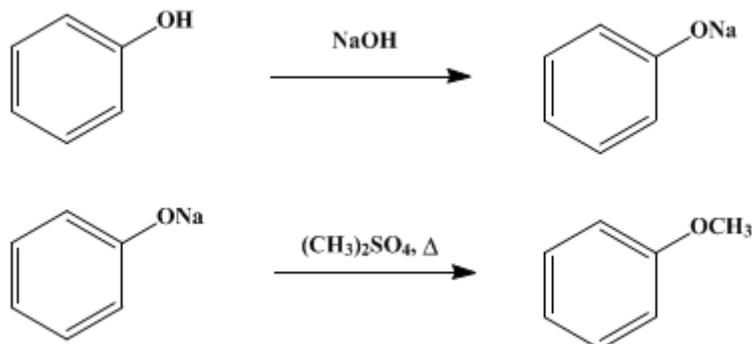
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior 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.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

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.

Organic Syntheses, Coll. Vol. 1, p.58 (1941); Vol. 9, p.12 (1929).

ANISOLE



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1. Procedure

In a 5-l., three-necked, round-bottomed flask fitted with an efficient stirrer, separatory funnel, and reflux condenser is placed a mixture of 235 g. (2.5 moles) of phenol and 100 g. (2.5 moles) of sodium hydroxide (Note 1) in 1 l. of water. The mixture is cooled, with stirring, in an ice-salt bath to below 10°. There is then added through the separatory funnel, with stirring, 315 g. (235 cc., 2.5 moles) of dimethyl sulfate (Note 2). This addition requires about one hour, and the cooling bath is not removed until the addition is complete. The mixture is then heated on a water bath for one-half hour. At the end of this time there is added through the separatory funnel a mixture of 235 g. (2.5 moles) of phenol and 100 g. (2.5 moles) of sodium hydroxide in 1 l. of water. This addition requires about fifteen minutes. The mixture is then refluxed vigorously over a free flame for fifteen hours (Note 3).

The mixture is cooled and the anisole layer is separated. The aqueous portion is extracted with about 200 cc. of benzene (Note 4). The combined anisole-benzene portion is washed once with water, dried over calcium chloride and distilled from a modified Claisen flask (p. 130). The portion boiling at 100–153° is refractionated. The main fraction distils at 153–154°/748 mm. The yield is 388–405 g. (72–75 per cent of the theoretical amount) (Note 5) and (Note 6).

2. Notes

1. The sodium hydroxide was a high quality technical grade.
2. Dimethyl sulfate is toxic, but with due care to avoid spattering of the liquid and inhaling of the vapor the operation may be carried out without the use of a hood. Ammonia is a specific antidote for dimethyl sulfate and should be kept at hand to destroy any of the ester accidentally spilled. A good technical grade of dimethyl sulfate was used.
3. When the period of refluxing is shorter, the yield is materially decreased. The first methyl group reacts easily but the second only with considerable difficulty. A longer period of refluxing does not give much larger yields. As the sodium sulfate concentration increases, the dimethyl sulfate hydrolyzes less readily. It is recommended that the addition of dimethyl sulfate is best effected at the lowest temperature where reaction takes place readily. With phenol this is 25–35°. For the second methyl group, the mixture is not refluxed but the anisole is boiled out, during which time the reaction completes itself (W. W. Hartman, private communication).
4. A separate fractional distillation of this benzene extract yields 9–18 g. of anisole. The major part of the anisole contained in the aqueous layer may be recovered by steam distillation instead of a benzene extraction. Neither method of recovery is wholly satisfactory.
5. When only one-half the amount of phenol is used, the yield is 85–92 per cent but with fairly inexpensive phenol it is more profitable to operate in such a manner that both methyl groups of the

dimethyl sulfate are used.

6. Other methyl ethers may be prepared by a similar procedure. Methyl β -naphthyl ether is obtained in a 65–73 per cent yield by adding the dimethyl sulfate over a period of thirty minutes to equivalent quantities of β -naphthol and sodium hydroxide kept cool by an ice-water bath, then heating for one hour at 75–78°, and, finally, crystallizing from benzene to obtain the pure methyl ether which melts at 71°.

3. Discussion

Anisole can be prepared from phenol or its salts by the use of the following methylating agents: methyl chloride;¹ sodium methyl sulfate;² methyl alcohol in the presence of thorium oxide;³ methyl alcohol and β -naphthalenesulfonic acid⁴ or potassium hydrogen sulfate⁵ or boron fluoride;⁶ dimethyl sulfate;⁷ and methyl ether and boron fluoride.⁸

References and Notes

1. Vincent, Bull. soc. chim. (2) **40**, 106 (1883).
2. Nollau and Daniels, J. Am. Chem. Soc. **36**, 1890 (1914).
3. Sabatier and Maihle, Compt. rend. **151**, 359 (1910).
4. Krafft and Roos, Ger. pat. 76,574 [Frdl. **4**, 17 (1894–97)]; Rodionow, Bull. soc. chim. (4) **45**, 118 (1929); Terlinck, Ing. chim. **8**, 233 (1924) [C. A. **21**, 1978 (1927)].
5. Aktien-Gesellschaft für Anilin-Fabrikation, Ger. pat. 23,775 [Frdl. **1**, 43 (1877–87)].
6. Sowa, Hennion, and Nieuwland, J. Am. Chem. Soc. **57**, 709 (1935).
7. Lewis, Shaffer, Trieschmann, and Cogan, Ind. Eng. Chem. **22**, 34 (1930); Wolford, ibid. **22**, 397 (1930); Hodgson and Nixon, J. Chem. Soc. 2166 (1930).
8. Kolka and Vogt, J. Am. Chem. Soc. **61**, 1463 (1939).

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

anisole-benzene

calcium chloride (10043-52-4)

ammonia (7664-41-7)

Benzene (71-43-2)

methyl alcohol (67-56-1)

sodium hydroxide (1310-73-2)

phenol (108-95-2)

sodium sulfate (7757-82-6)

β -naphthol (135-19-3)

Anisole (100-66-3)

dimethyl sulfate (77-78-1)

Methyl β -naphthyl ether (93-04-9)

methyl ether (115-10-6)

methyl chloride (74-87-3)

sodium methyl sulfate (512-42-5)

thorium oxide

β -naphthalenesulfonic acid (120-18-3)

potassium hydrogen sulfate (7646-93-7)

boron fluoride (7637-07-2)