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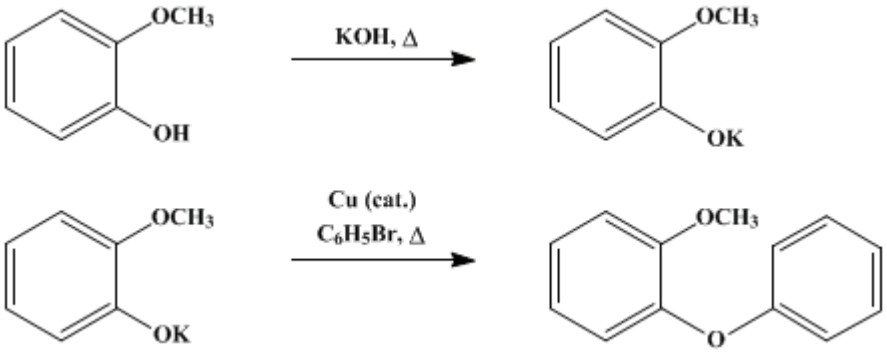
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.026.0050

Organic Syntheses, Coll. Vol. 3, p.566 (1955); Vol. 26, p.50 (1946).

2-METHOXYDIPHENYL ETHER

[Benzene, 1-methoxy-2-phenoxy-]



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1. Procedure

Powdered potassium hydroxide (29.4 g., 0.43 mole) is placed in a 500-ml. round-bottomed flask. Guaiacol (75 g., 0.60 mole) is added, and the mixture is allowed to react exothermically. After the reaction is complete, the mixture is stirred with a glass rod and then heated under reduced pressure for 3 hours at 150° in an oil bath (Note 1).

To the dry salt is added 0.3 g. of copper powder (Note 2), 81 g. (0.51 mole) of bromobenzene, and a few drops of guaiacol (Note 3). The mixture is stirred thoroughly with a glass rod; the flask is fitted with an air condenser and heated in a metal bath (Note 4). A reaction becomes evident at a bath temperature of 160–180°, liquefaction occurs, and the color of the mixture changes to red or purple. The temperature is gradually raised to 200° and maintained at 200° for 2 hours.

After cooling, the products are extracted from the reaction mixture with successive portions of water and ether. Extraction is facilitated by breaking up the solid material with a glass rod. The total amounts. of solvents required are approximately 750 ml. of water and 150 ml. of ether. The combined ether and water solutions are transferred to a 3-l. round-bottomed flask and steam-distilled with superheated steam maintained at 180–200°. After removal of the ether, 300 ml. of distillate is collected. This distillate contains the unreacted starting materials. Continued distillation gives 64–69 g. (62–67%) of crude solid 2-methoxydiphenyl ether in 14 l. of distillate. The product is filtered with suction and dried. Crystallization from a mixture of 600 ml. of low-boiling petroleum ether (b.p. 30–60°) and 435 ml. of higher-boiling petroleum ether (b.p. 60–70°) yields 54–61 g. of 2-methoxydiphenyl ether melting at 77–78°. Other 2-methoxydiphenyl ethers have been prepared by this procedure (Note 5).

2. Notes

1. The salt of guaiacol is heated under reduced pressure, in order to remove water, which is a negative catalyst in the Ullmann reaction.[1]
2. The copper catalyst may be prepared by the method of Brewster and Groening.[2]
3. An excess of guaiacol is essential. Weston and Adkins[1] have found that the phenol, copper, and air form the active catalyst in the Ullmann reaction.
4. The checkers used an electrically heated oil bath.
5. Yields of 54% of 2-methoxy-4'-methyldiphenyl ether from *p*-bromotoluene and guaiacol, and 60% of 2-methoxy-5-methyldiphenyl ether from 3-bromo-4-methoxytoluene and phenol, have been obtained by the same method in the laboratory of the submitters.

3. Discussion

The procedure above is a modification of the method of Ullmann and Stein[3] for the same compound. Sartoretto and Sowa[4] used the same general method. The need for a catalyst can be avoided by heating a mixture of guaiacol potassium, guaiacol, and chlorobenzene at 200° under pressure.[5] Ullmann and Stein[6] have prepared the compound by using phenol, *o*-bromoanisole, copper powder, and potassium hydroxide. 2-Hydroxydiphenyl ether can be converted to the methoxy derivative by treating it with methanol, methyl iodide, and potassium hydroxide.[7]

References and Notes

1. Weston and Adkins, *J. Am. Chem. Soc.*, **50**, 859 (1928).
2. Brewster and Groening, *Org. Syntheses*, **14**, 66 (1934); Coll. Vol. **2**, 446 (1943).
3. Ullmann and Stein, *Ber.*, **38**, 2212 (1905); **39**, 623 (1906).
4. Sartoretto and Sowa, *J. Am. Chem. Soc.*, **59**, 603 (1937).
5. Fritzsche and Co., Ger. pat. 269,543 (1914) (*Chem. Zentr.*, **1914**, I, 591).
6. Ullmann and Stein, *Ber.*, **39**, 623 (1906).
7. Norris, MacIntire, and Corse, *Am. Chem. J.*, **29**, 127 (1903).

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

petroleum ether

methanol (67-56-1)

ether (60-29-7)

phenol (108-95-2)

copper,
copper powder (7440-50-8)

chlorobenzene (108-90-7)

potassium hydroxide (1310-58-3)

bromobenzene (108-86-1)

Guaiacol (90-05-1)

Methyl iodide (74-88-4)

2-Methoxydiphenyl ether,
Benzene, 1-methoxy-2-phenoxy- (1695-04-1)

2-methoxy-5-methyldiphenyl ether

3-bromo-4-methoxytoluene (22002-45-5)

guaiacol potassium

2-Hydroxydiphenyl ether

p-Bromotoluene (106-38-7)

o-bromoanisole (578-57-4)

2-methoxy-4'-methyldiphenyl ether