



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.

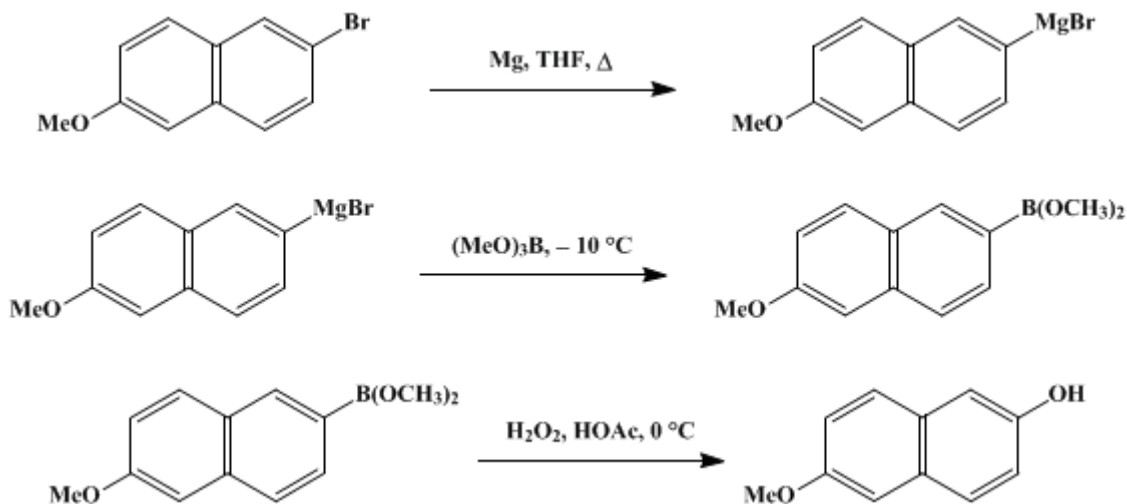
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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PHENOLS: 6-METHOXY-2-NAPHTHOL

[2-Naphthol, 6-methoxy-]



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1. Procedure

A 2-l. Three-necked flask equipped with a condenser and containing 27 g (1.1 mole) of **magnesium** is flame-dried and the atmosphere replaced with **nitrogen**. A 200-ml. portion of **tetrahydrofuran** (Note 1) is added along with several lumps, totaling about 95 g., of **6-bromo-2-methoxynaphthalene** (Note 2) and a small crystal of **iodine**. The mixture is heated to reflux until the boiling becomes spontaneous. An additional 600 ml. of **tetrahydrofuran** is added with more of the bromide to maintain a vigorous reflux, until 237.4 g. (1 mole) of **6-bromo-2-methoxy-naphthalene** has been added. After the spontaneous reflux has subsided, the dark solution is heated to reflux for 20 minutes.

A 5-l. three-necked flask fitted with a paddle stirrer, a Claisen adapter containing a thermometer well and nitrogen inlet, and a dropping funnel is flame-dried and placed under **nitrogen**. Into the flask are introduced 125 ml. (1.1 mole) of **trimethyl borate** (Note 3) and 600 ml. of **tetrahydrofuran**. This solution is cooled to -10° with an all-encompassing ice-salt bath or a dry ice-carbon tetrachloride bath. The dropping funnel is charged with the Grignard solution which is added over 30 minutes to the borate solution while stirring rapidly and maintaining the temperature between -10° and -5° . A white sludge separates from the solution during the addition. After stirring for an additional 15 minutes, 86 ml. (1.5 mole) of chilled **acetic acid** (Note 4) is added all at once. This is followed by the addition of a cold solution of 112 ml. (1.1 mole) of 30% **hydrogen peroxide** in 100 ml. of water, dropwise over 15 minutes, while maintaining the temperature below 0° (Note 5) and stirring vigorously.

The mixture is allowed to warm up over 20 minutes and is poured into a 2-l. separatory funnel. The purplish solution is washed with a saturated **ammonium sulfate** solution (about 1.5 l) containing **ferrous ammonium sulfate** until the rust-brown ferric color is no longer produced. The organic layer is dried over **magnesium sulfate** and concentrated, leaving a dark solid. Purification of the solid by high-vacuum short path distillation gives 127–142 g. (73–81%) of a pinkish or tan-colored product, b.p. $148\text{--}150^{\circ}$ (0.15 mm.), m.p. $145\text{--}147^{\circ}$. It may be further purified by sublimation, or recrystallization from **benzene-hexane**, m.p. $148\text{--}149^{\circ}$.

2. Notes

1. Reagent grade **tetrahydrofuran** (Mallinckrodt) has been used directly. The formation of the Grignard

reagent starts readily and no precipitates are formed. **Tetrahydrofuran** obtained from the Quaker Oats Company in 1-gal. cans has also been used; the reaction, however, is slower to start, a cloudy precipitate is formed, and the yield is slightly lower. *[Caution! See P. 976]*

2. This starting material is obtained conveniently from the bromination² and methylation of **2-naphthol**. The procedure is modified by not removing the tin salts.

After bromination of 144 g. (1 mole) of **2-naphthol**, the hot solution is poured into water and filtered. The dry precipitate is mixed with a solution of 200 ml. of concentrated **sulfuric acid** in 500 ml. of technical **methanol** and heated to vigorous reflux for 4 hours. An oily layer separates during the heating period. The hot mixture is poured into 3 l. of ice and water, and the solids are removed by filtration. The moist solid is triturated with 1 l. of hot 5% **sodium hydroxide**. After chilling the mixture to solidify the oil, it is filtered and the product is washed and dried. The **6-methoxy-2-bromonaphthalene** is purified by distillation, b.p. 114–118° (0.2 mm.). After distillation the product is most conveniently handled by remelting and pouring it into a mold to solidify. The overall yield is 173–208 g. (73–88%), m.p. 101.5–103°.

3. Commercial **trimethyl borate** contains an appreciable amount of **methanol**. It is removed by adding anhydrous **lithium chloride**³ to the bottle and allowing the mixture to stand with occasional shaking. The upper layer is decanted off and fractionated, b.p. 68–69°. The product must be protected from moisture.

4. Water added at this point hydrolyzes the arylboronic ester extremely rapidly to 2-methoxynaphthalene.

5. The reaction is exothermic. Except for a darkening of the product, no apparent harm results if occasionally the temperature rises to 10–15°.

3. Discussion

The classic caustic fusion of sulfonic acid salts has been used for preparing 2,6-dinaphthol⁴ and its derivatives. Other more recent procedures have employed the direct hydrolysis of aryl bromides⁵ and the oxidation of aryl Grignard reagents.⁶

The indirect oxidation of an aryl Grignard reagent through a boronic ester nearly doubles the yield of **phenol** obtained by direct oxidation and decreases the reaction time. **Tetrahydrofuran** is the preferred solvent. It facilitates the dissolution of the bromide, which is relatively insoluble in **diethyl ether**, solvates the Grignard reagent, and renders the oxidation reaction homogeneous.

The preparation of **6-methoxy-2-naphthol** is of particular interest as the starting point in many synthetic sequences. It is readily converted to **6-methoxy-2-tetralone** through a Birch reduction.⁷

References and Notes

1. Department of Chemistry, Southern Illinois University, Carbondale, Illinois.
2. C. F. Koelch, *Org. Syntheses, Coll. Vol. 3*, 132 (1955); H. E. French and K. Sears, *J. Am. Chem. Soc.*, **70**, 1279 (1948).
3. H. I. Schlesinger, H. C. Brown, D. L. Mayfield, and J. R. Gilbreath, *J. Am. Chem. Soc.*, **75**, 213 (1953).
4. R. Willstatter and J. Parnas, *Ber.*, **40**, 1406 (1907).
5. M. Gates and W. G. Webb, *J. Am. Chem. Soc.*, **80**, 1186 (1958).
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Appendix

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

sulfuric acid (7664-93-9)
acetic acid (64-19-7)
methanol (67-56-1)
diethyl ether (60-29-7)
sodium hydroxide (1310-73-2)
magnesium (7439-95-4)
phenol (108-95-2)
nitrogen (7727-37-9)
2-naphthol (135-19-3)
iodine (7553-56-2)
hydrogen peroxide (7722-84-1)
ammonium sulfate (7783-20-2)
magnesium sulfate (7487-88-9)
Tetrahydrofuran (109-99-9)
ferrous ammonium sulfate (10045-89-3)
benzene-hexane (1077-16-3)
Lithium chloride (7447-41-8)
6-Methoxy-2-naphthol,
2-Naphthol, 6-methoxy- (5111-66-0)
6-bromo-2-methoxynaphthalene,
6-bromo-2-methoxy-naphthalene,
6-methoxy-2-bromonaphthalene (5111-65-9)
trimethyl borate (121-43-7)
6-methoxy-2-tetralone (2472-22-2)