



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](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.

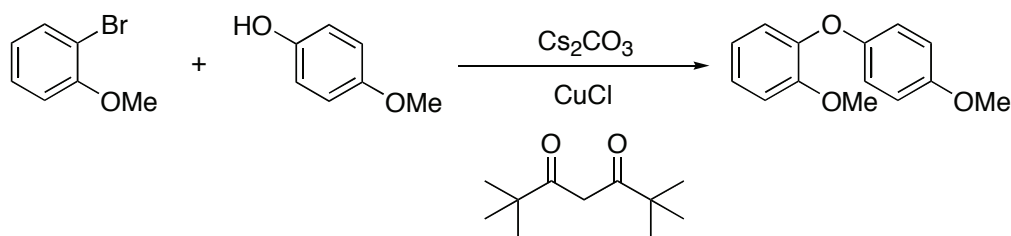
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior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

*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

Copyright © 2005 Organic Syntheses, Inc. All Rights Reserved

**PREPARATION OF 1-METHOXY-2-(4-METHOXYPHENOXY)BENZENE**  
**(Benzene, 1-methoxy-2-(4-methoxyphenoxy)-)**



Submitted by Elizabeth Buck and Zhiguo J. Song.<sup>1</sup>

Checked by Scott E. Denmark and John D. Baird.

### 1. Procedure

To a 500-mL, three-necked, round-bottomed flask equipped with reflux condenser, nitrogen inlet, thermocouple and mechanical stirrer is added 14.0 g (113 mmol, 2.0 equiv) of 4-methoxyphenol (Note 1) and 95 mL of 1-methyl-2-pyrrolidinone (NMP) (Note 2). To this solution is then added 36.8 g (113 mmol, 2.0 equiv) of cesium carbonate (Note 3). The resulting slurry is degassed by evacuation and filling with nitrogen three times. Then 10.5 g (56.1 mmol) of 2-bromoanisole (Note 4) and 1.0 g (5.4 mmol, 0.096 equiv) of 2,2,6,6-tetramethylheptane-3,5-dione (Note 5) are added followed by 2.8 g (28 mmol, 0.5 equiv) of copper (I) chloride (Note 6). The reaction mixture is degassed by evacuation and filling with nitrogen three times and then is heated to 120 °C under nitrogen. The reaction is monitored by HPLC analysis (Note 8) and is stopped after 25 h when >98 % conversion (by peak area) is obtained. The reaction mixture is cooled to room temperature and is diluted with 125 mL of methyl *t*-butyl ether (MTBE). The slurry is filtered and filter cake is washed with 125 mL of MTBE. The combined filtrates are washed subsequently with 175 mL of aqueous 2N HCl solution, 175 mL of 0.6N aqueous HCl solution, 150 mL of 2M aqueous NaOH solution, and 150 mL of 10% aqueous NaCl solution. The resulting organic layer is dried over MgSO<sub>4</sub> and is concentrated by rotary evaporation under vacuum at ≤ 30 °C to remove all solvents. The crude, brown solid is triturated by magnetic stirring in 55 mL of hexanes (Note 9), then is aged for 4 h and filtered to give 9.9-10.1 g (78% average

yield) of an off-white solid (mp 77 – 78 °C) of 99% purity as determined by HPLC analysis (Note 10).

## 2. Notes

1. 4-Methoxyphenol was purchased from Aldrich Chemical Co. and was used as received. Use of less than two equivalents resulted in a longer reaction time.

2. Anhydrous 1-methyl-2-pyrrolidinone (NMP) was purchased from Aldrich Chemical Co. and was used as received. NMP that was dried over 4Å molecular sieves with water content  $\leq 100$   $\mu\text{g/mL}$  (Karl Fisher titration) gave slightly faster reactions.

3. Cesium carbonate was purchased from Alfa Aesar and was used as received. It is hygroscopic and should be weighed with minimum exposure to the air. Use of less than two equivalents resulted in slower reactions.

4. 2-Bromoanisole was purchased from Aldrich Chemical Co. and was used as received.

5. 2,2,6,6-Tetramethylheptane-3,5-dione was purchased from Aldrich Chemical Co. and was used as received.

6. Copper (I) chloride was purchased from Acros and was used as received.

7. MTBE (methyl t-butyl ether) was purchased from EM Science and was used as received.

8. The HPLC instrument used was a HP1100. HPLC conditions: Perkin Elmer 3X3 CR C18; MeCN/0.1% H<sub>3</sub>PO<sub>4</sub>; 2 mL/min; gradient: time 0 min 25/75, 1 min 25/75, 9 min 95/5, 10 min 95/5; UV detector 210 nm. Retention times: 4-methoxyphenol 0.6 min, 2-bromoanisole 3.4 min, product 4.3 min.

9. Hexanes was purchased from Fisher Scientific Co. and used directly as received.

10. Purity is reported as HPLC area percent (A%). Assay yields are reported using isolated material as standard. Analytical Data: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$ : 7.09-7.05 (m, 1 H), 7.00-6.98 (m, 1 H), 6.97-6.93 (m, 2 H), 6.90-6.84 (m, 4 H), 3.88 (s, 3 H), 3.79 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$ : 155.3, 150.8, 150.7, 146.6, 123.7, 120.9, 119.3, 119.0, 114.6, 112.5, 55.9, 55.6. Anal. Calcd. for C<sub>14</sub>H<sub>14</sub>O<sub>3</sub>: C, 73.03; H, 6.13. Found: C, 73.27; H, 6.05. MS (EI) *m/z* 230 (M<sup>+</sup>, 100).

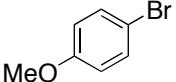
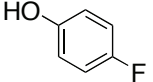
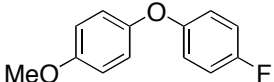
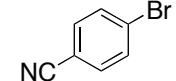
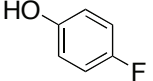
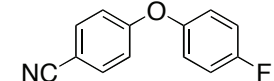
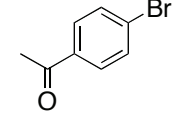
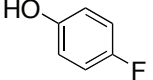
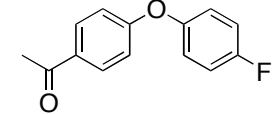
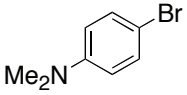
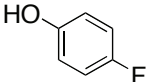
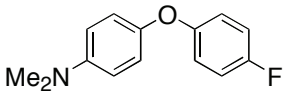
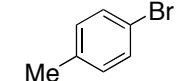
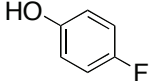
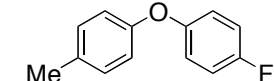
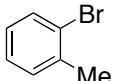
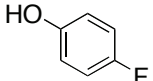
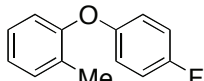
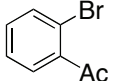
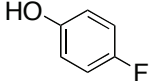
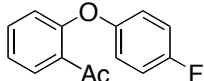
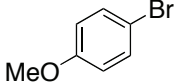
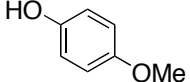
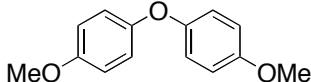
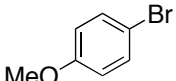
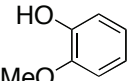
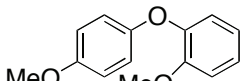
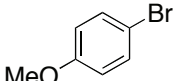
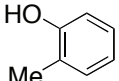
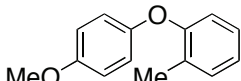
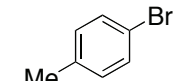
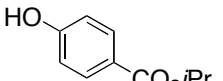
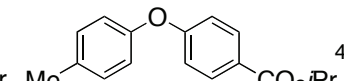
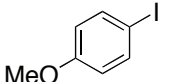
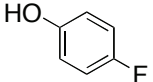
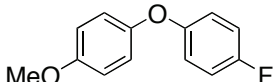
## Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

### 3. Discussion

The Ullmann ether formation has traditionally been carried out under rather harsh conditions, usually at high temperatures in pyridine as the solvent.<sup>1-3</sup> The yields are typically low to moderate and reactions between electron-rich aryl halides and electron-deficient phenols typically do not work well. Other milder conditions, employing more expensive reagents or catalysts such as palladium or copper (II) triflate, are also available.<sup>5,6</sup> The major advantages of the process reported here are low cost of the copper additive and the simplicity of operation. Relative to other less expensive ligands for copper such as pyridine-based ligands or phosphine-based ligands,<sup>5a,b</sup> 2,2,6,6-tetramethylheptane-3,5-dione (TMHD) accelerates the Ullmann coupling reaction more effectively, allowing some of the electronically unfavorable substrates to undergo ether formation readily, as listed in Table 1. Nevertheless, these reactions exhibit the general trend that electron-donating groups on the phenol and electron-withdrawing groups on the halide make the reaction more favorable. Some tolerance of electron-withdrawing groups on the phenols was observed. The major side reaction in these Ullmann ether formations is the reduction of the aryl halides to the arene (Aryl-Br to Aryl-H). The reaction of an aryl iodide is faster and higher yielding than the corresponding bromide, as indicated by a comparison of entries 12 and 1.

**Table 1. 2,2,6,6-Tetramethylheptane-3,5-dione Catalyzed Ullmann Ether Formation**

Ar-X	ArOH	ether product	reaction time (h)	assay yield (%)	isolated yield (%)
			10	70	55
			1.5	90	82
			4	83	60
			15	79	59
			7.5	86	63
			15	97	85
			24	67	61
			10	85	77
			10	80	66
			10	92	79
			47	56	51
			6	77	68

1. Department of Process Research, Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065.
2. This procedure was first reported by: Buck, E.; Song, Z. J.; Tschaen, D.; Dormer, P. G.; Volante, R. P.; Reider, P. J. *Org. Lett.* **2002**, *4*, 1623.
3. For reviews: (a) Sawyer, J. S. *Tetrahedron* **2000**, *56*, 5045. (b) Theil, F. *Angew Chem., Int. Ed.* **1999**, *38*, 2345. (c) Lindley, J. *Tetrahedron* **1984**, *40*, 1433.
4. Some earlier reports: (a) Williams, A. L.; Kinney, R. E.; Bridger, R. F. *J. Org. Chem.* **1967**, *32*, 2501. (b) Bacon, R. G. R.; Rennison, S. C. *J. Chem. Soc.(C)* **1969**, 312. (c) Bacon, R. G. R.; Stewart, O. J. *J. Chem. Soc.* **1965**, 4953.
5. For palladium mediated ether synthesis: (a) Torraca, K. E.; Huang, X.; Parrish, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 10770. (b) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369. (c) Mann, G.; Hartwig, J. F. *Tetrahedron Lett.* **1997**, *38*, 8005. (d) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224. (e) Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. *J. Am. Chem. Soc.* **2000**, *122*, 10718.
6. For some recent reports of copper mediated ether formations: (a) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315. (b) Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043. (c) Marcoux, J.-F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539. (d) Kalinin, A. V.; Bower, J. F.; Riebel, P.; Snieckus, V. *J. Org. Chem.* **1999**, *64*, 2986. (e) Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937. (f) Palomo, C.; Oiarbide, M.; Lopez, R.; Gomez-Bengoa, E. *Chem. Commun.* **1998**, 2091. (g) Smith, K.; Jones, D. *J. Chem. Soc. Perkin Trans. I* **1992**, 407. (g) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973.

## Appendix

### Chemical Abstracts Nomenclature

4-Methoxyphenol: Phenol, 4-methoxy-; (150-76-5)

1-Methyl-2-pyrrolidinone (NMP): 2-Pyrrolidinone, 1-methyl-; (872-50-4)

Cesium carbonate: Carbonic acid, dicesium salt; (534-17-8)

2-Bromoanisole: Benzene, 1-bromo-2-methoxy-; (578-57-4)

2,2,6,6-Tetramethylheptane-3,5-dione: 3,5-Heptanedione, 2,2,6,6-tetramethyl-: (1118-71-4)

Copper (I) chloride: Copper chloride: (7758-89-6)

Methyl *t*-butyl ether (MTBE): Propane, 2-methoxy-2-methyl-: (1634-04-4)