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LETTERS

Synthesis of diaryl ethers through the copper-catalyzed arylation of phenols with aryl halides using microwave heating

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Abstract—The copper-catalyzed arylation of phenols with a variety of aryl halides using microwave heating is described. © 2003 Elsevier Science Ltd. All rights reserved.

Diaryl ethers are valuable intermediates in organic synthesis[1] and are found in a variety of naturally occurring and biologically important compounds.[2] As the traditional protocols for the Ullmann diaryl ether synthesis usually require harsh reaction conditions and stoichiometric amounts of copper,[3] a number of methodologies have been recently developed. Chan[4] and Evans[5] independently described the diaryl ether synthesis through the copper(II)-promoted arylation of phenols with arylboronic acids, and a catalytic version of this cross-coupling was also reported.[6] Buchwald and co-workers demonstrated that the arylation of phenols can be accomplished using the copper(I)- ($(CuOTf)_2$·benzene)[7] or palladium-catalyzed[8] coupling reactions with aryl halides. Even with these recent improvements, there is still a need for general methods for the preparation of diaryl ethers. In a recent medicinal chemistry program, we found that microwave heating can be used to facilitate the arylation of phenols. Microwave irradiation has become increasingly popular in recent years to improve the yield and shorten reaction times in a variety of reactions.[9–11] However, to our knowledge, the microwave-mediated methodology on the arylation of phenols with aryl halides has not yet been reported. This report describes the microwave-assisted synthesis of diaryl ethers using copper(I) iodide as the copper source, thus obviating the need of air-sensitive copper(I) triflate.[7]

Treatment of 1-iodo-4-*tert*-butylbenzene with 2 equiv. phenol in the presence of copper(I) iodide (10 mol%) and cesium carbonate (2 equiv.) in *N*-methylpyrrolidinone (NMP) at 195°C for 2 h under microwave irradiation provided 4-phenoxy-*tert*-butylbenzene in 90% yield after purification of the crude product using silica gel flash chromatography (Table 1, entry 1). As a control experiment, the same reaction mixture was heated at 195°C for 2 h in a sealed tube using an oil bath, and the product was obtained in 74% yield. This observation demonstrates the advantage of microwave radiation over conventional heating techniques. As shown in Table 1, our microwave conditions worked well for a variety of aryl iodides (entries 2–9). The yield of this reaction appears to be dependent on the steric hindrance of phenols (entries 8 and 9). For example, the coupling of *o*-cresol with iodobenzene (entry 8) gave a lower yield than that of *m*- or *p*-cresol (entries 7 and 6). The 45% yield obtained for the coupling of the sterically hindered 2,6-dimethylphenol with 5-iodo-*m*-xylene (entry 9) is also noteworthy compared with the 20–30% reported by Buchwald and co-workers[7] for the same coupling using $(CuOTf)_2$·benzene (2.5 mol%) and cesium carbonate (2 equiv.) in toluene at 110°C. To test the scope of our methodology, phenol was treated with several bromides (entries 10–14) under the above conditions, and the yields were comparable to those obtained with the corresponding iodides. It should be pointed out that the yield of the reaction was not greatly influenced by the presence of electron-donating or electron-withdrawing groups on the aryl halides. However, this type of arylation reaction does not seem to work well on aryl chlorides. For example, a substantial amount of starting materials were recovered after a mixture of phenol and chlorobenzene in the presence of copper(I) iodide (10 mol%) and cesium carbonate (2 equiv.) in NMP was heated at 195°C under microwave irradiation for 14 h.

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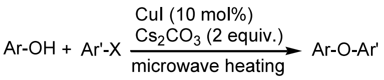
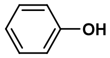
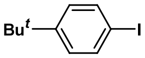
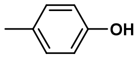
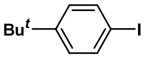
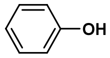
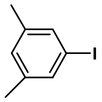
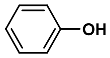
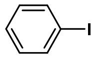
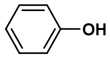
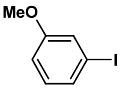
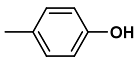
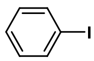
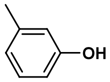
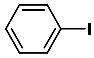
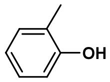
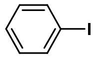
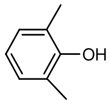
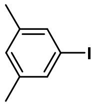
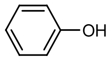
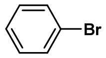
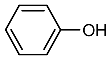
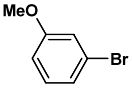
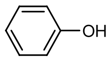
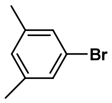
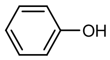
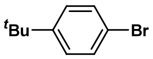
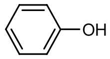
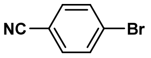
Table 1. Arylation of phenols with aryl halides



$$\text{Ar-OH} + \text{Ar'-X} \xrightarrow[\text{microwave heating}]{\text{CuI (10 mol\%)},\ Cs_2CO_3\ \text{(2 equiv.)}} \text{Ar-O-Ar'}$$

Entry	Ar-OH	Ar'-X	Time	Yield[a]
1			2 h	90%
2			3 h	80%
3			2 h	74%
4			1 h	76%
5			2 h	71%
6			2 h	78%
7			2 h	71%
8			2 h	65%
9			2 h	45%
10			2 h	74%
11			2 h	80%
12			2 h	82%
13			2 h	89%
14			2 h	64%

[a] isolated yield.

In summary, we have developed an operationally simple and efficient method for the copper-catalyzed coupling of a variety of aryl bromides and iodides with phenols using microwave heating.[12]

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12. *Representative procedure*: To a solution of 1-iodo-4-*tert*-butylbenzene (130 mg, 0.5 mmol) and phenol (94 mg, 1 mmol) in NMP (0.67 mL) in a microwave vial were added cesium carbonate (325 mg, 1 mmol), and copper (I) iodide (9.5 mg, 0.05 mmol). The vial was sealed and heated in a Smith Creator® at 195°C for 2 h. The temperature of the contents of the vessel was monitored using a calibrated infrared temperature control mounted under the reaction vessel. The cooled reaction mixture was passed through a 2 g silica gel cartridge eluting with hexanes to give 4-phenoxy-*tert*-butylbenzene (102 mg, 90%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29–7.35 (4H, m), 7.07 (1H, m), 7.00 (2H, m), 6.93 (2H, m), and 1.31 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.6, 154.7, 146.1, 129.6, 126.5, 122.9, 118.6, 118.5, 34.3, and 31.5. The spectroscopic data is in full agreement with that described in the literature.[7]