

# A Superior Synthesis of Diaryl Ethers by the Use of Ultrasound in the Ullmann Reaction

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The use of ultrasound in the reactions of phenols with bromoarenes, in the presence of potassium carbonate and copper(I) iodide but without added solvent, gives better yields of diaryl ethers (typically 70–90%) at lower temperature (140 °C) than is customary for traditional Ullmann reactions; the role of ultrasound is primarily to break up the particles of the inorganic solids.

Despite the importance of many substituted examples in the agrochemical and pharmaceutical industries, methods for the synthesis of diaryl ethers are poor. The most general approach involves the reaction of an alkali metal phenolate with a halogenobenzene in the presence of a catalyst of copper or a copper salt, as developed by Ullmann and co-workers at the turn of the century.<sup>1</sup> However, the reaction requires high temperatures (typically 180–220 °C)<sup>2</sup> and long reaction times (up to 20 h if a solvent is used)<sup>3</sup> and often produces only moderate yields (40–60%) for substituted examples unless there are electron-withdrawing groups on the halogenobenzene moiety.<sup>4</sup> It was therefore of interest to see if the method could be improved.

Many reactions have been shown to benefit from irradiation with ultrasound.<sup>5</sup> Indeed, the Ullmann synthesis of biaryls (copper catalysed coupling of aryl halides) benefits from sonication,<sup>6</sup> though there is no record of the use of sonication in the diaryl ether synthesis. We therefore decided to investigate the effect of ultrasound, different catalysts and the presence of solids on the Ullmann diaryl ether synthesis.

We now report that sonication of mixtures of a phenol and a halogenobenzene, in the absence of solvent and presence of copper(I) iodide as catalyst and potassium carbonate as base, produces good yields of diaryl ethers at relatively low temperatures.

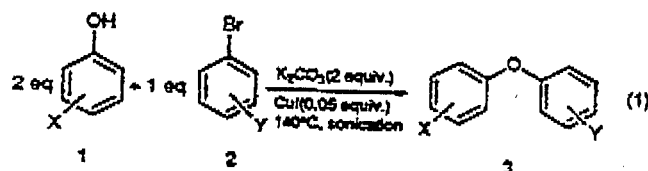
Initial studies concentrated on the reaction between phenol and bromobenzene. The reaction was found to require the presence of both a base and a catalyst in order to proceed at a reasonable rate at 180 °C. Copper(I) halides were better catalysts than copper metal or copper oxides, as previously reported by Weingarten.<sup>7</sup> The reaction was most conveniently carried out without added solvent,<sup>8</sup> and with potassium carbonate as base,<sup>9</sup> conditions which have separately been used before in Ullmann reactions. The maximum yield of diphenyl ether was obtained after *ca.* 6 h at 180 °C when an excess of potassium carbonate and 0.25 mol equiv. of copper(I) chloride were used. Reaction times were shorter with copper(I) iodide as catalyst, but added solids (Celite, Bentonite) gave no beneficial effects.

The effect of ultrasound was then investigated. In order to provide a more critical test of the process, the amount of catalyst was reduced to 0.05 mol equiv., the amount of potassium carbonate to 1 mol equiv. per mol equiv. of phenol, and the temperature to 140 °C. Under these conditions the reaction was essentially complete in 2 h, especially if an excess of phenol was used. The conditions were, therefore, applied to the reactions of a range of substituted phenols **1** with substituted bromobenzene **2** [eqn. (1)]. The yields of the product diaryl ethers **3** obtained are reported in Table 1 along with those from reactions carried out under traditional, more forcing conditions. As can be seen

Table 1 Yields of diaryl ethers formed according to equation (1)

X	Y	Time (h)	Yield <b>3</b> (%) <sup>a</sup>	Lit. yield (%)	Lit. ref.
H	2-MeO	2	75	62	11
H	4-MeO	2	85	70	11
H	2-Me	3	72	58	11
H	3-Me	2	97	42	12
H	4-Me	3	95	67	11
2-Me	H	4	50	54	15
3-Me	H	4	89	63	15
4-Me	H	4	78	55	15
2-MeO	H	3	62	60	8
2-MeO	3-Me	4	73	63	13
2-MeO	2-Me	3	70		
2-MeO	4-MeO	3	57	55	11
H	1-Naphthyl	2	74	50	14
3,5-Me <sub>2</sub>	H	4	88		

<sup>a</sup> Determined by GC using an internal standard: the phenol (20 mmol), bromoarene (10 mmol), potassium carbonate (20 mmol) and copper(I) iodide (0.5 mmol) were all mixed and stirred at 140 °C whilst sonication (100 W tapered probe) was maintained for the time indicated.



from Table 1, the yields of products **3** are generally significantly higher than for comparable reactions carried out under traditional conditions. The reactions also proceed more quickly and at significantly lower temperatures. The general procedure is, therefore, recommended for the Ullmann synthesis of diaryl ethers.

Ultrasound clearly has a significant influence on the reaction. In order to determine whether the effect was exerted on the reaction directly or exerted merely on the particles of potassium carbonate and/or copper(I) iodide, a series of experiments was conducted in which sonication was carried out in an initial lower temperature step and heating at 140 °C with stirring was then carried out, without sonication. When all materials were present during the sonication step the eventual yield was only a little lower than when continuous sonication was used, even though the yield of ether was minimal at the point when sonication was stopped. This indicates that the effect of sonication was primarily to break up the particles of the base and/or catalyst. When either of these components was absent during the sonication step, but present during heating at 140 °C,

the yield was higher than without sonication but lower than when both components were present. This suggests that the effect is exerted on both the base and the catalyst. These findings suggest that it should be possible to prepare a suitable base/catalyst component outside of the reaction vessel if this would be more practical for industrial scale reactions.

**Representative Procedure.**—To a 50-ml round bottomed flask were added 3-bromotoluene (1.727 g, 10.1 mmol), phenol (1.89 g, 20.1 mmol), potassium carbonate (2.76 g, 20.0 mmol) and copper(I) iodide (0.10 g, 0.50 mmol). A tapered ultrasonic probe (100 W) was placed into the mixture so that the tip reached just below the surface. (It is important to ensure that the probe does not touch the glass of the vessel.) A silicone oil bath preset to 140 °C was placed around the flask to such a depth as to immerse the contents and the ultrasonic probe was switched on at maximum power for 2 h. At the end of this period the heating bath was removed and the irradiation stopped. The contents of the flask were dissolved in dichloromethane (15 ml) and washed with aqueous KOH (2 mol dm<sup>-3</sup>; 20 cm<sup>3</sup>) and then with water (2 × 20 cm<sup>3</sup>), dried (MgSO<sub>4</sub>), filtered and evaporated to leave phenyl *m*-tolyl ether (1.80 g, 97%), which was essentially pure (GC and NMR).

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