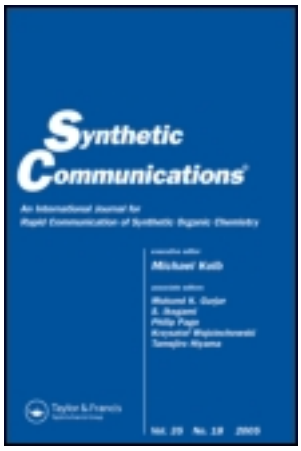

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# The Use of Ultrasound in the Synthesis of 2-Carboxy Substituted Diphenylethers Using Water as Solvent

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## ABSTRACT

An improved synthesis of 2-carboxy substituted diphenylethers using water as solvent can be achieved by ultrasound irradiation. A number of diphenylethers was prepared in good yields in a very short reaction time.

*Key Words:* Ultrasound; 2-Carboxy diphenylethers; Water as solvent

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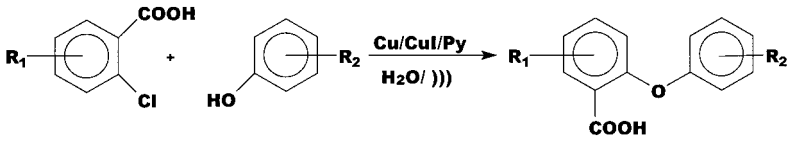
Numerous studies have been reported on the Ullmann reaction, in which an aryl halide and a phenolate react to give the diaryl ethers. This reaction is promoted by copper compound and a base, and requires high temperature and a large excess of copper, particularly when less reactive aryl halide is employed.[1]

Ultrasound can be used in chemistry to increase reaction rates and yields of products. The synthesis of diaryl ethers was found to be improved by the use of ultrasound.[2] The yields of the products were significantly higher than the literature yields without sonication and the reaction also proceeds faster and at lower temperatures.

The usual procedure for the synthesis of diphenylethers using the Ullmann-Goldberg condensation is to reflux a mixture of the *o*-halogenobenzoic acid with a phenol in a solvent, often amyl alcohol, in the presence of copper as catalyst and a base such as potassium carbonate to remove the hydrogen halide liberated in the reaction.[3]

In the present work, we decided to examine the effect of ultrasound on the Ullmann-Goldberg reaction in the synthesis of 2-carboxydiphenylethers from *o*-chlorobenzoic acid and phenol derivatives using water as solvent.




## RESULTS AND DISCUSSION

In a previous paper,[4] phenols were shown to react in 2 h with *o*-chlorobenzoic acid in presence of copper and pyridine as catalysts to obtain 2-carboxy substituted diphenylethers by Ullmann-Goldberg reaction using water as solvent.

As a continuation of our previous studies about the Ullmann-Goldberg reaction using water as solvent, we described recently the 2-carboxydiphenylether acid synthesis optimization.[5] The optimum concentration conditions determinated for each reactant were: *o*-chlorobenzoic acid:phenol:potassium carbonate:pyridine as 1:2.5:1.5:0.75 and the reaction time 2.4 h. Several other 2-carboxydiphenylether acid derivatives were prepared with these conditions. In all cases the yield obtained was equal or superior to those reported in the literature where a high boiling point alcohol (130–170°C) is employed as solvent.

*Table 1.* Effect of the time reaction on the yield.

| Reaction time (min.) | Yield (%) | Standard deviation (%) |
|---|---|---|
| 30 | 84 | 1.5 |
| 25 | 83 | 1.0 |
| 20 | 84 | 1.7 |
| 15 | 55 | 1.0 |

In order to reduce the reaction time and improve the yields we examined the effect of ultrasound on the Ullmann-Goldberg condensation using the reaction of *o*-chlorobenzoic acid with phenol in presence of copper, cuprous iodide and pyridine as catalysts in water as solvent as a model, employing the optimized quantities of each reactant.

To establish the minimum time necessary for the reaction, we scanned various reaction times from 15–30 min (Table 1). It is noteworthy that with reaction times of more than 20 min ultrasonic irradiation the yield of the acid remains constant. Under these conditions the use of 2.5 moles of phenol and 0.75 mole of pyridine per mole of *o*-chlorobenzoic acid are critical to obtain a good yield.

All experiments performed in this work were repeated five times. The yields reported represent an average of the obtained values for each reaction.

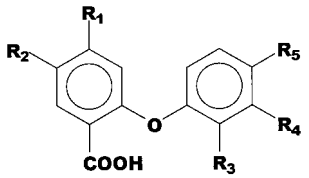
Table 2 shows the results of the 2-carboxyphenylether acid derivatives synthesized from *o*-chlorobenzoic acid and several phenol derivatives in presence of water as solvent. The corresponding yields obtained using refluxing water (2.4 h) and using ultrasonic irradiation (20 min) are reported.

## EXPERIMENTAL

### Standard Procedure

A mixture of *o*-chlorobenzoic acid (0.04 mol), phenol (0.1 mol), anhydrous potassium carbonate (0.06 mol), copper powder, (0.1 g), cuprous iodide (0.1 g), pyridine (0.03 mol) and water (25 mL) was irradiated for 20 min with a sonic horn at 20 kHz. The reaction mixture was cooled and acidified with diluted HCl (1:1). The solid was filtered off, washed with water and dissolved in aqueous sodium hydroxide solution (10%). The basic solution was acidified by addition of AcOH:$H_2O$ (1:3). The 2-carboxydiphenylether is crystallized from EtOH/$H_2O$ (1:1) ($^1$H NMR and $^{13}$C-NMR data in tables 3 and 4 respectively).

***Table 2.*** Results of the synthesis of 2-carboxydiphenylether acid derivatives, experimental microanalysis and molecular ion in mass spectra.




| No. | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | Yield (%) (2.4 h. reflux) | Yield (%) (ultras. 20 min.) | M.p. (uncorr.) (°C) | M.p. lit. (°C) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | H | H | H | H | H | 61 | 84 | 110–12 | 113[6,7,8] |
| 2 | Cl | H | H | H | H | 58 | 82 | 114–16 | 115[9] |
| 3 | H | H | Cl | H | H | 60 | 80 | 114–15 | 114[7,8] |
| 4 | Cl | H | Cl | H | H | 58 | 82 | 164–65 | 163[8] |
| 5 | H | H | Cl | H | Cl | 61 | 83 | 166–67 | 166.5[7,8] |
| 6 | Cl | H | Cl | H | Cl | 59 | 81 | 169–70 | 169[7,8] |
| 7 | H | H | $CH_3$ | H | H | 62 | 83 | 133–34 | 133.5[7,8] |
| 8 | H | H | H | $CH_3$ | H | 63 | 76 | 94–96 | 95[10] |
| 9 | H | H | H | H | $CH_3$ | 70 | 83 | 117–19 | 118[6] |
| 10 | H | $OCH_3$ | H | H | H | 58 | 85 | 156 | 156[11] |

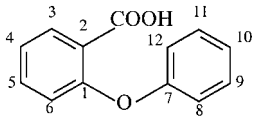
| | | Calculated (%) | | Experimental (%) | | |
|---|---|---|---|---|---|---|
| No. | Formula | C | H | C | H | *m/z* |
| 1 | $C_{13}H_{10}O_3$ | 72.89 | 4.67 | 72.76 | 4.83 | 214 |
| 2 | $C_{13}H_9O_3Cl$ | 62.77 | 3.62 | 62.91 | 3.85 | 248 |
| 3 | $C_{13}H_9O_3Cl$ | 62.77 | 3.62 | 62.87 | 3.77 | 248 |
| 4 | $C_{13}H_8O_3Cl_2$ | 55.12 | 2.82 | 54.70 | 2.91 | 282 |
| 5 | $C_{13}H_8O_3Cl_2$ | 55.12 | 2.82 | 55.42 | 3.26 | 282 |
| 6 | $C_{13}H_7O_3Cl_3$ | 49.13 | 2.20 | 48.49 | 2.32 | 316 |
| 7 | $C_{14}H_{12}O_3$ | 73.68 | 5.26 | 73.46 | 5.60 | 228 |
| 8 | $C_{14}H_{12}O_3$ | 73.68 | 5.26 | 73.41 | 5.73 | 228 |
| 9 | $C_{14}H_{12}O_3$ | 73.68 | 5.26 | 73.86 | 5.40 | 228 |
| 10 | $C_{14}H_{12}O_4$ | 68.85 | 4.92 | 68.75 | 4.31 | 244 |

ultras. ultrasound; M.p. melting point; uncorr. uncorrected; lit. literature.

## CONCLUSIONS

The use of ultrasound irradiation improved the synthesis of 2-carboxy substituted diphenylethers using water as solvent. A number

***Table 3.*** $^{1}$H NMR Data of 2-carboxydiphenylether acid derivatives.




| No. | H3 | H4 | H5 | H6 | H8 | H9 | H10 | H11 | H12 | H($CH_3$) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 7.85 | 7.25 | 7.59 | 7.40 | 7.10 | 7.71 | 6.99 | 7.71 | 7.10 | — |
| 2 | 7.81 | 6.96 | — | 7.49 | 7.20 | 7.75 | 7.12 | 7.75 | 7.20 | — |
| 3 | 7.98 | 7.41 | 7.53 | 7.65 | — | 7.90 | 7.19 | 7.86 | 6.92 | — |
| 4 | 7.87 | 7.02 | — | 7.63 | — | 7.80 | 7.17 | 7.71 | 6.85 | — |
| 5 | 7.89 | 7.23 | 7.58 | 7.39 | — | 7.79 | — | 7.70 | 6.59 | — |
| 6 | 7.81 | 7.05 | — | 7.27 | — | 7.76 | — | 7.56 | 6.52 | — |
| 7 | 7.91 | 7.40 | 7.57 | 7.37 | — | 7.68 | 7.11 | 7.68 | 7.26 | 2.23 |
| 8 | 7.99 | 7.41 | 7.62 | 7.38 | 7.01 | — | 6.89 | 7.67 | 6.99 | 2.32 |
| 9 | 7.93 | 7.47 | 7.64 | 7.58 | 7.12 | 7.62 | — | 7.62 | 7.12 | 2.27 |
| 10 | 7.59 | — | 7.26 | 7.62 | 7.11 | 7.75 | 7.08 | 7.75 | 7.11 | 3.77 |

***Table 4.*** $^{13}$C-NMR Data of 2-carboxydiphenylether acid derivatives.

| No. | C1 | C2 | C3 | C4 | C5 | C6 |
|---|---|---|---|---|---|---|
| 1 | 157.3 | 120.7 | 133.2 | 123.5 | 134.6 | 118.9 |
| 2 | 156.5 | 118.9 | 132.9 | 123.8 | 137.3 | 118.1 |
| 3 | 156.8 | 120.3 | 133.3 | 123.6 | 134.6 | 117.8 |
| 4 | 155.6 | 119.8 | 133.3 | 123.7 | 137.6 | 119.0 |
| 5 | 153.9 | 120.5 | 131.8 | 124.2 | 133.8 | 119.4 |
| 6 | 156.1 | 119.7 | 133.5 | 124.2 | 138.7 | 119.5 |
| 7 | 157.7 | 120.4 | 133.4 | 122.8 | 134.7 | 119.8 |
| 8 | 157.6 | 120.3 | 133.1 | 125.5 | 134.6 | 118.7 |
| 9 | 156.4 | 120.1 | 131.3 | 120.1 | 136.7 | 112.5 |
| 10 | 149.6 | 120.6 | 118.2 | 153.8 | 122.8 | 121.1 |

| No. | C7 | C8 | C9 | C10 | C11 | C12 | C($CH_3$) |
|---|---|---|---|---|---|---|---|
| 1 | 155.8 | 119.6 | 130.1 | 124.6 | 130.1 | 119.6 | — |
| 2 | 156.0 | 120.2 | 130.0 | 123.8 | 130.0 | 120.2 | — |
| 3 | 151.4 | 121.3 | 128.2 | 125.7 | 131.0 | 125.7 | — |
| 4 | 151.6 | 122.1 | 128.8 | 124.0 | 130.7 | 125.3 | — |
| 5 | 152.3 | 123.9 | 128.4 | 127.2 | 129.8 | 124.7 | — |
| 6 | 151.1 | 120.6 | 128.2 | 129.3 | 130.2 | 125.8 | — |
| 7 | 152.8 | 120.5 | 127.6 | 125.6 | 130.3 | 131.9 | 18.0 |
| 8 | 155.5 | 117.3 | 129.8 | 123.4 | 130.4 | 118.7 | 18.7 |
| 9 | 154.1 | 120.4 | 129.9 | 131.8 | 129.9 | 120.4 | 20.3 |
| 10 | 155.4 | 120.1 | 130.1 | 123.2 | 130.1 | 120.1 | 55.7 |

of 2-carboxydiphenylether derivatives was prepared in good yields in a very short reaction time.

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