

General Synthesis Method of Diaryl- and Diaryl Thio-Ethers via S_NAr Using Microwave-assisted Synthesis

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Introduction

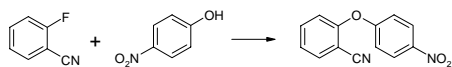
The synthesis of diaryl ethers and diaryl thioethers via an ordinary S_NAr-type reaction, involving a phenol or thiophenol and an aryl halide along with a base in a solvent, is a very attractive method due to its simplicity. Unfortunately, the generality of this method is restricted by the inherent properties of the starting materials (*e.g.* requiring nucleophilic phenols, deactivated aryl halides and strong bases) and the harsh conditions required (high temperature and prolonged reaction times).

In 1998, Sawyer *et al*¹ published a method using 37 % potassium fluoride on alumina (1-5 g per g nucleophile), and 18-Crown-6 (10 mole%) in acetonitrile (reflux) or DMSO (140 °C). The reaction times were 1-336 hours and the yields 13-99 %, depending on the substitution pattern of the corresponding nucleophile and electrophile.

We decided to see if we could further generalize and simplify the method by using potassium carbonate as a base,² acetonitrile as solvent, and in particular, if we could shorten the reaction times, by applying microwave heating.

Results and discussion

The reaction (*Scheme 1*) with the longest reaction time (336 h = 2 weeks) and lowest yield (13%) presented in the publication was chosen as model reaction to be optimised with reference to time and temperature on Emrys™ Optimizer.



Scheme 1.

The optimization experiments revealed complete conversion in 1 hour at 210 °C, when reacting 1.0 mmol 2-fluorobenzonitrile with 1.0 mmol 4-nitrophenol using 1.2 mmol potassium carbonate as base, in acetonitrile. The mixture was purified by chromatography on Horizon™ HPFC™ System using a prepacked silica column cartridge. The yield was 47% of the desired product (along with the by-products 4,4'-dinitrophenyl ether (21%) and 2,2'-dicyanophenyl ether (14%).

This specific reaction was uniformly scaled up 50 times and run on Advancer (*Figure 1*). The same temperature and time parameters were used and the outcome from this reaction after purification was 48 % product along with 24% and 18% of the corresponding by-products.

In order to examine the general applicability of this method, we ran several reactions with different aryl halides, phenols and thiophenols and compared the isolated yields with those published (*Table*). All reactions with phenols or thiophenols that required up to 72 hours conventional heating were successfully finished within 0.5 hour with 2 exceptions which required 1 hour (*Table*). The remaining reactions were performed for 1 hour.

Reference:

- Sawyer, J.S.; Schmittling, E.A.; Palkowitz, J.A. and Smith, W.J. III. *J. Org. Chem.* **1998**, *63*, 6338
- Li, F.; Wang, Q.; Ding, Z. and Tao, F. *Org. Lett.* **2003**, *5*, 2169



Figure 1. Advancer

General Experimental Procedure

A 10 mL reaction vial loaded with a mixture of 1.00 mmol phenol (or thiophenol), 1.00 mmol aryl halide, 1.20 mmol potassium carbonate and 3.00 mL acetonitrile was capped and heated to 210 °C in Emrys™ Optimizer for the time stated in the table. After cooling, the vial was decapped and the solids were filtered off and washed with 5 mL acetonitrile. The solution was concentrated and the residue was purified by chromatography on Horizon™ HPFC™ System using a prepacked silica column cartridge. The products were analysed by HPLC-MS and characterized by ¹H- and ¹³C-NMR and the purities were found to be >95 %.

Conclusion

In this poster, a general method for the synthesis of diaryl- and diarylthio ethers is described. This method dramatically shortens the reaction times from days and weeks to only 0.5 or 1 hour for S_NAr reactions, by heating the reaction mixtures with microwaves.

Using microwave heating, even unfavourable nucleophiles as 4-nitrophenol can react to completion. Furthermore, the use of potassium carbonate as base and acetonitrile as solvent simplifies the reaction procedure. Two reactions were scaled up five times in Emrys™ Optimizer EXP, and one reaction, was scaled up from 1 mmol on Emrys™ Optimizer EXP to 50 mmol Advancer. All three scaled up reactions, gave comparable results with those run in 1 mmol scale.

Two of the reactions (*Table*) were scaled up 5 times on Emrys Optimizer EXP in 20 mL vials. Both experiments were in good agreement with those run in the original 5 mL vials.

Reaction	Convent. ¹		MW	
	h	%	h	%
	48	98	0.5	99 98 ²
	72	91	0.5	95
	72	99	0.5	96
	72	99	0.5	96
	40	68	0.5	97
	218	80	1	95 90 ²
	192	72	1	68
	336	13	1	47 48 ³
	16	70 ⁴	1	81
	48	66 ⁴	1	86
	2.5	82	0.5	81
	12	91 ⁴	0.5	90
	24	85 ⁴	0.5	77

¹ 37 % (w/w) KF·Al₂O₃ (1-5 g/g substrate), 18-crown-6 (10 % by mole), CH₃CN, reflux
² Run on Emrys™ Optimizer EXP
³ Run on Advancer
⁴ 37 % (w/w) KF·Al₂O₃ (2 g/g substrate), 18-crown-6 (10 % by mole), DMSO, 140 °C

Table

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