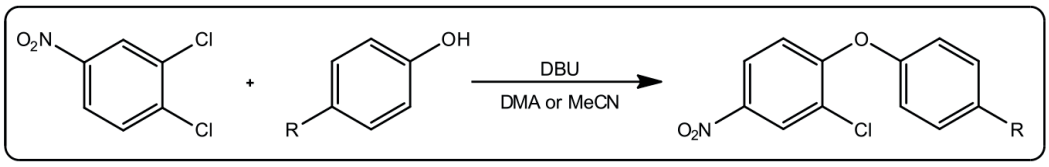
CHEMTRIX
Scalable Flow Chemistry

Application Note 13

Dr Charlotte Wiles

Chemtrix BV

Application Note 13: Translation of Microwave Methodology to Continuous Flow for the Synthesis of Diaryl Ethers via an S_NAr Reaction



Diaryl ethers **1** are a synthetically interesting sub-unit, with examples found in a series of medicinally significant natural products such as (-)-K-13,[1] riccardin C[2] **1** and combretastatins,[3] along with synthetic herbicides such as RH6201[4] (Figure 1). Installation of the diaryl ether can however be synthetically challenging, as illustrated by the wide number of techniques developed which include; Ullmann ether synthesis,[5] Pummerer-type rearrangements,[6] Buchwald-Hartwig couplings,[7] phenolic additions to amines,[8] potassium fluoride/alumina mediated couplings[9] and the used of solid-supports.[10]

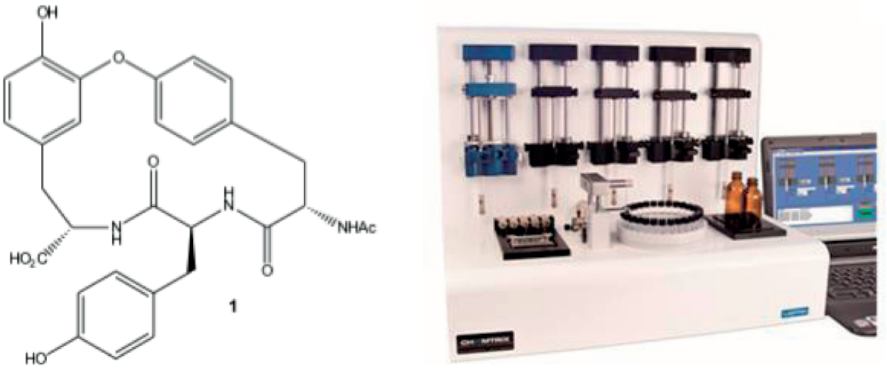


Figure 1. (a). Illustration of a synthetically interesting diaryl ether natural product, (b). Labtrix® S1 the automated micro reactor development equipment used in this investigation.

Recently Moseley and co-workers[11,12] demonstrated the largely overlooked nucleophilic substitution reaction of aromatic halides to phenols, reporting that under microwave irradiation reaction times of the order of ten's of minutes could be obtained for the synthesis of diaryl ethers. Like microwave reactors, continuous flow systems can be readily heated and pressurised in order to access 'extreme' reaction conditions, whilst having the added advantage that microwave transparent solvents and reagents can be employed over a wide temperature range. To demonstrate any additional advantages that continuous flow reactors may have compared to microwave reactors, the nucleophilic substitution reaction between 3,4-dichloronitrobenzene **2** and 4-methoxyphenol **3** was investigated under previously reported literature conditions (Scheme 1).

Scheme 1. Schematic illustrating the model reaction used to compare microwave and micro reactors.

CHEMTRIX
Scalable Flow Chemistry

Experimental Conditions: Reactions were performed using a Labtrix® S1 system (Figure 1b), fitted with a glass micro reactor (Reactor volume = 10 µl (3223)) and 3 x 1.0 ml gas-tight syringes (SGE) containing a static mixer (Figure 2). A 25 bar ULDV-BPR (Upchurch Scientific) was fitted to the system and used for all experiments in order to maintain reactants in the liquid phase. Prior to performing a micro reaction, the micro reactor was filled with the reaction solvent at a total flow rate of 25 µl min^{-1} for 5 min, after which time the syringes were replaced with those containing the reactant solutions and the reactor primed, again at a total flow rate of 25 µl min^{-1}, for 5 min (25 °C). For condition screening the reaction products were collected in aliquots of 25 µl and analysed using GC-FID (Injector temperature = 200 ºC, carrier gas flow rate = 1.6 ml min^{-1}, oven temperature = 50 ºC for 0.1 min then ramped to 300 ºC at 60 ºC min^{-1} and held for 1.0 min). Full characterisation of the materials prepared was performed using NMR spectroscopy and mass spectrometry.

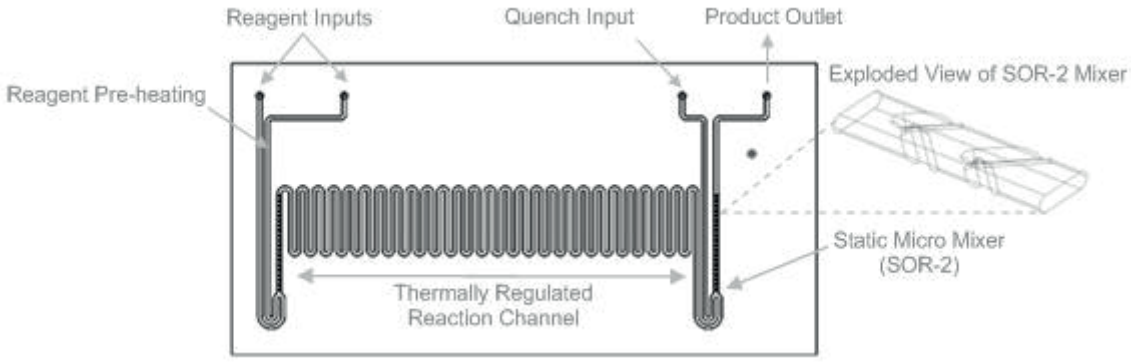


Figure 2. Schematic illustrating the main features of the glass micro reactors employed herein.

Reaction Optimisation: To screen the reaction under flow conditions, two stock solutions (5 ml) were prepared, the first comprised of 3,4-dichloronitrobenzene **2** and 4-methoxyphenol **3** (1.3 M and 1.56 M respectively) in DMA or MeCN and the second contained the base under investigation (1.95 M) in DMA or MeCN. Prior to analysis, the reaction products were diluted via the introduction of additional reaction solvent (or acetone) through the quench inlet (Figure 3). Employing reaction times ranging from 30 s to 10 min, the effect of reactor temperature was investigated over the range 25 to 195 ºC. In all cases, equilibration times of three times the reactor volume were employed and samples collected in triplicate to ensure system stability and reproducibility (% RSD < 0.5).

Structural Characterisation: Where full characterisation of the diaryl ethers was required, 500 µl samples were collected employing the optimal reaction conditions identified from the reaction screening and the reaction solvent evaporated prior to dissolution of the organic residue in DCM (25 ml). The organic layer was then washed with saturated ammonium chloride (3 x 25 ml) to remove the organic base **4** and the organic layer dried over $MgSO_4$ prior to concentrating *in vacuo* to afford the target diaryl ether.

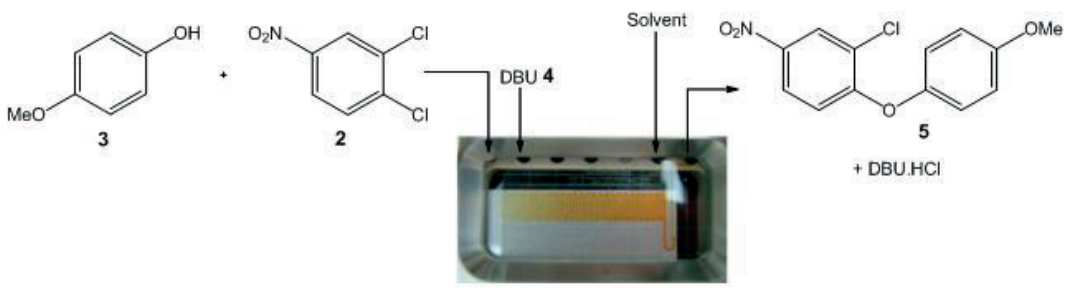


Figure 3. Schematic illustrating the reaction set-up employed for the continuous flow synthesis of diaryl ethers; with the orange coloration indicating ether formation.

Results and Discussion: Employing the reaction set-up illustrated in Figure 3, the effect of reaction temperature was initially investigated under flow conditions at a fixed reaction time of 10 min. As Figure 4 illustrates, this enabled a direct comparison with the work of Moseley and co-workers[11] to be performed, highlighting the transferability of existing microwave methodology to flow.

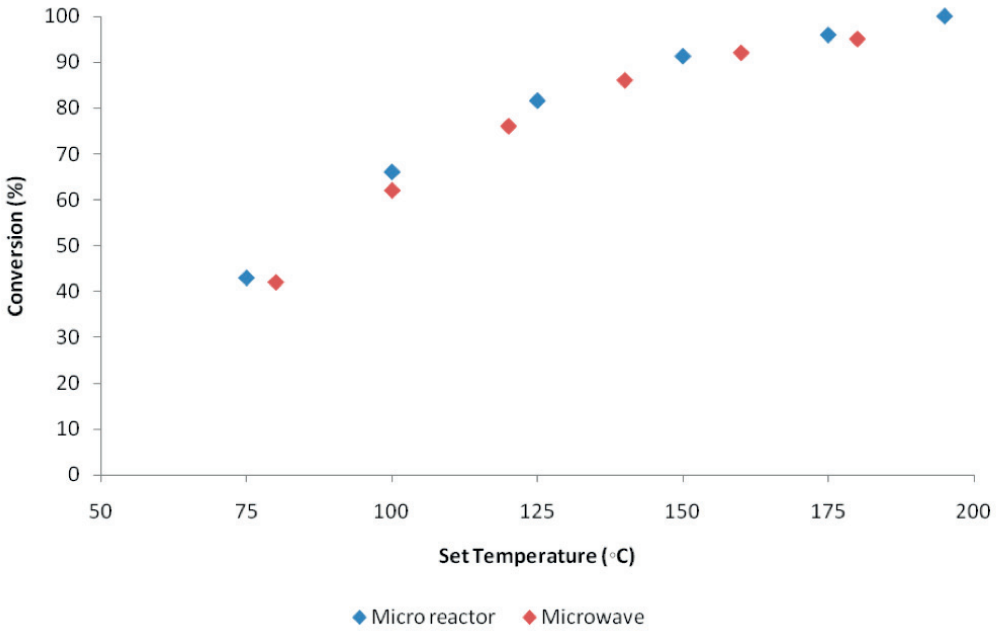


Figure 4. Graph comparing the effect of reactor temperature on the synthesis of 2-chloro-1-(4-methoxyphenoxy)-4-nitrobenzene **5** in a microwave and micro reactor.

Under flow conditions, it was possible to obtain the target diary ether **5** in quantitative conversion however the use of DMA as a reaction solvent and a 1.2 eq. excess of phenol **3** made product isolation at the mg-scale challenging. Having demonstrated that it was possible to obtain analogous results in flow and microwave reactors, the effect of reaction solvent and substrate stoichiometry was subsequently investigated. Reducing the phenol **3** to 1 eq. and maintaining a 1.3 M substrate concentration, the temperature screen (25 to 195 ºC) was repeated using MeCN as the reaction solvent; with comparable results obtained at a reaction time of 10 min. Maintaining the reactor at 195 ºC, the reaction time was reduced to see if a more efficient method could be developed whilst retaining high diaryl ether **5** purity. Using this approach, the reaction time was successfully reduced to 60 s without affecting the degree of 3,4-dichloronitrobenzene **2** conversion.

Under the optimal conditions of 1.5 eq. DBU **4**, 195 ºC and 60 s reaction time, the reactor was operated continuously for 50 min and 500 µl of material collected prior to concentrating *in vacuo* and extracting with DCM. Using this approach, it was possible to isolate 2-chloro-1-(4-methoxyphenoxy)-4-nitrobenzene **5** in 99.7 % yield (90.4 mg) (Table 1).

Effect of Phenol Substituent: To demonstrate the generality of the technique developed, the effect of the *para*-substituent was investigated. In all cases, 1 eq. of the phenol derivative was employed and the conversion at sub-optimal conditions appraised. As Figure 5 illustrates, the *para*-substituent was found to affect the conversion to the respective diaryl ether with 4-methoxyphenol **3** being the most reactive and 4-cyanophenol the least; an observation which is in accordance with that of Moseley *et al*..[11] Table 1 illustrates the isolated yields obtained for five *para*-substituted phenols and the optimal conditions employed for the diaryl ether synthesis.

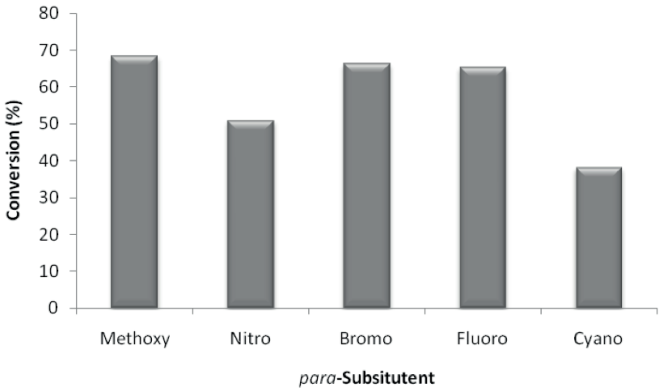
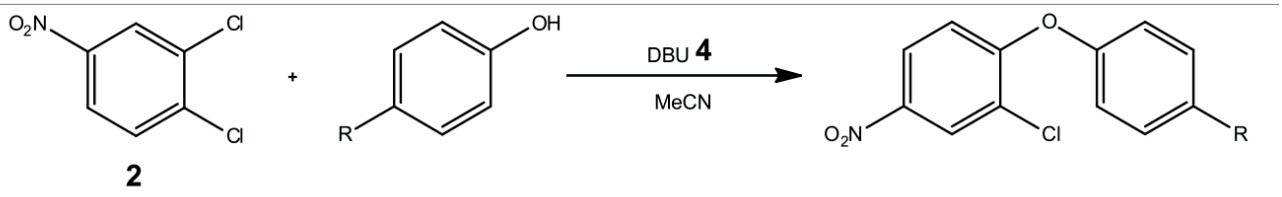


Figure 5. Illustration of the effect of *para*-substitution of the phenol derivative on the formation of diaryl ethers with a 30 s reaction time and a reactor temperature of 195 ºC.



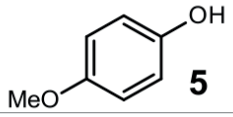
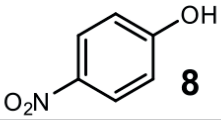
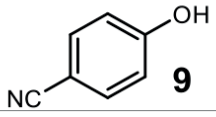
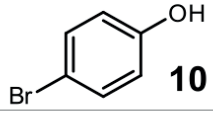
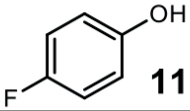
Phenol	Residence Time (min)	Conversion (%)	Yield (%)
	1	quant.	99.69
	5	quant.	99.84
	10	quant.	99.72
	1	quant.	99.86
	2	quant.	99.79

Table 1. Summary of the optimal reaction times employed for the synthesis of diaryl ethers under continuous flow at 195 ºC.

Summary: Whilst microwaves have found widespread application at a research level, their implementation at a large scale is less established, largely due to the challenges associated with efficient irradiation of large reaction vessels. With a significant proportion of the cost savings obtained associated with the reduced reaction times accessed due to the use of pressurised vessels,[13] these benefits can also be obtained through the use of flow reactors, with the added advantage been that the techniques developed at a research level can be scaled should larger volumes of the material be required.[14]

In this instance, the use of a micro reaction platform proved advantageous as it enabled detailed process optimisation to be performed on mg-quantities of substrate. Consequently, the microwave process was improved upon, allowing the use of a low boiling solvent, stoichiometric substrates and shorter reaction times. In the case of 2-chloro-1-(4-cyanophenoxy)-4-nitrobenzene, this led to an increase in yield from 42 % in the microwave reactor to 99.7 % in the micro reactor.

CHEMTRIX
Scalable Flow Chemistry

References:

1. D. L. Boger and D. Yohannes, *J. Org. Chem.*, 1989, 54, 2498-2502.
2. A. Gottsegen, B. Vermes, M. Kajtarperedy, E. Bibatsikarasai and M. Nogradi, *Tetrahedron Lett.*, 1988, 29, 5039-5040.
3. A. Cirla and J. Mann, *Nat. Prod. Rep.*, 2003, 20, 558-564.
4. W. O. Johnson, G. E. Kollman, C. Swithenbank and R. Y. Yih, *J. Agric. Food Chem.*, 1978, 26, 285-287.
5. Mark. D. M. T. Chan, K. L. Monaco, R. P. Wang and M. P. Winteres, *Tetrahedron Lett.*, 1998, 39, 2933-2936.
6. M. E. Jung, D. Jachiet, S. Khan and C. Kim, *Tetrahedron Lett.*, 1995, 36, 361-364.
7. C. H. Burgos, T. E. Barder, X. Huang and S. L. Buchwald, *Angew. Chem. Int. Ed*. 2006, 45, 4321-4326.
8. J. J. Kulagowski and C. W. Rees, *Synthesis*, 1980, 215.
9. J. Scott Sawyer, E. A. Schmittling, J. A. Palkowitz and W. J. Smith III, *J. Org. Chem.*, 1998, 63, 6338-6343.
10. N. Jung and S. Bräse, *J. Combi. Chem.*, 2009, 11, 47-71.
11. J. A. Marafie and J. D. Moseley, *Org. Biomol. Chem.*, 2010, 8, 2219-2227.
12. J. D. Moseley and E. K. Woodman, *Energy Fuels*, 2009, 23, 5438-5447.
13. J. D. Moesley and C. O. Kappe, *Green Chem.*, 2011, DOI: 10.1039/c0gc00823k.
14. C. Wiles and P. Watts, in 'Micro reactors in organic chemistry', 2011, CRC-Press.