The application of stop-flow microwave technology to scaling-out S_NAr reactions using a soluble organic base†‡

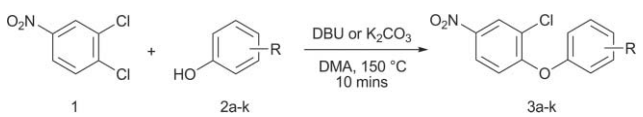
Jameel A. Marafie and Jonathan D. Moseley*

Received 22nd December 2009, Accepted 18th February 2010
First published as an Advance Article on the web 11th March 2010
DOI: 10.1039/b926537f

A model S_NAr reaction which gives a range of substituted diaryl ethers has been re-developed to function with the soluble organic base DBU in the place of insoluble potassium carbonate. Manufacture of these diaryl ethers has then been achieved by scaling-out in an automated stop-flow microwave reactor to give productivities of >0.5 kg per day. Analogous reaction partners have also been scaled up in this reactor to extend the scope of the study. Brief comparison in a scale-up batch microwave reactor is also made. Lastly, continuous 24 h processing is reported in this small microwave stop-flow reactor, which requires no manual intervention once started.

Introduction

Microwave synthesis has been widely adopted within the pharmaceutical industry at small scale, and is generally accepted in academia also.[1] Scale-up of microwave synthesis however, has proven more difficult to achieve and is still a challenging area.[2] We have reported on the scale-up of one simple thermal rearrangement in a variety of microwave reactors,[3] as well as more recently on a wider range of reactions in a subset of these reactors.[4] One such reaction which we have found particularly useful is a model S_NAr reaction (Scheme 1). This is typical of many heterogeneous pharmaceutical reactions in that it consists of two organic components combining in the presence of an inorganic base (K_2CO_3) suspended in a polar aprotic solvent.



Scheme 1 S_NAr reaction with substituted phenols. Key to compound structures in Table 1.

This proved to be an ideal probe reaction in the evaluation of large-scale microwave reactors[5] for several reasons. The reaction is very reliable under standard procedures; any failure in the reaction is, therefore, normally indicative of instrumentation issues. Reaction progress is dependent solely on the temperature since there is no catalyst or initiation period (we assumed and saw no evidence of a special microwave effect).[6] The reaction of 3,4-dichloronitrobenzene (DCNB, **1**) is almost completely selective at the 4-position, whilst leaving the 3-position open to further chemical elaboration. The phenol coupling partner **2** may be tuned across a range of electronic (4-MeO *vs.* 4-NO_2) and steric (H *vs.* 4-*t*Bu) features. Alternative nucleophiles may also be used *e.g.* thiophenols. Most of the product diaryl ethers **3** are crystalline and can be isolated by a simple aqueous drown-out with water. Furthermore, these simple structures are not as uninteresting as might be supposed, as several are claimed as potential agrochemicals/insecticides[7] and a surprising number are apparently novel. They are also representative of more complex diaryl ether structural motifs[8] which are found in many important biologically active molecules, including natural products, and potential and actual pharmaceuticals.[9] Lastly, and from a purely pragmatic point of view when working on larger scale, all of the starting materials were cheap and available on sufficient scale.

Whilst this reaction was useful in many respects for testing heterogeneous reactions in large scale microwave (and conventional) reactors, it could not be used in continuous flow or stop-flow microwave reactors, since these require a homogeneous reaction mixture. We have recently reported on a number of homogeneous reactions conducted in an automated stop-flow microwave reactor (the CEM Voyager),[10] and were keen to exemplify and further test the manufacturing capability of this reactor using this model reaction, since it has many other desirable features, as noted above. We therefore determined to replace insoluble K_2CO_3 with a soluble organic base to obtain a homogeneous reaction mixture which could be processed through continuous flow and stop-flow microwave reactors.

Details of the Voyager have been discussed at length in our previous report,[10] or as presented by others.[11] In brief, the Voyager has an 80 mL Pyrex glass vessel with ~50 mL operating volume, fed by three inlet lines and emptied by one exit line which may be collected as product or waste. Up to three reaction solutions/solvents may be pumped into the vessel, which is then sealed and heated by microwaves to the set temperature. At the end of the reaction, compressed air cooling rapidly cools the reaction mixture, which is then pumped out. All of the lines and the vessel may be flushed with fresh solvent if they require cleaning before the sequence is repeated again. This process of small batch microwave heating can be fully automated to run as many batches as required; it is essentially only limited by material availability. The Voyager is, thus, an interesting hybrid reactor, combining microwave heating

AstraZeneca, PR&D, Avlon Works, Severn Road, Hallen, Bristol, United Kingdom BS10 7ZE. E-mail: jonathan.moseley@astrazeneca.com; Fax: +44 117 938 5081; Tel: +44 117 938 5601

† This paper is part of an *Organic & Biomolecular Chemistry* web theme issue on enabling technologies for organic synthesis.

‡ Electronic supplementary information (ESI) available: HPLC spectra to support compound purity; photograph of the Voyager stop-flow microwave reactor. See DOI: 10.1039/b926537f

for rapid reaction, a small batch volume for rapid cooling, and continuous flow technology for automated sequencing.

Results and discussion

Development of homogeneous reaction conditions

The standard conditions used for the heterogeneous S_NAr reaction were to heat 1.2 equivalents of phenol **2** with 1.0 equivalents of DCNB (**1**) dissolved in *N*,*N*-dimethylacetamide (DMA) (12.5 wt%) slurried with 1.5 equivalents of K_2CO_3 (-352 mesh) at 140 °C for 10 min. On cooling and addition of an equal volume of water, the product diaryl ether **3** could be obtained by filtration in up to 100% yield and 99% purity as determined by HPLC and ^{1}H NMR.[4] The standard substrate used was 4-methoxyphenol (**2a**), since this was particularly cheap, and yielded the crystalline diaryl ether **3a** in excellent yield and quality. The standard conditions were modified slightly to 1.2 equivalents of organic base (and 1.1 equivalents of phenol **2a**), because the reactions were now homogeneous; a larger excess of K_2CO_3 had been used under heterogeneous conditions to compensate for the probable phase transfer effects involved with using an insoluble base. We identified 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) from earlier reports[12] as the most likely replacement for K_2CO_3, but decided to screen a range of common bases of varying pK_bs (*e.g.* pyridine, lutidine, 1,4-diazabicyclo[2.2.2]octane (DABCO) and triethylamine, amongst others) for the conversion of **1** and **2a** to give **3a**. Reactions were screened in 5 mL tubes on a small scale microwave reactor at 140 °C for 10 min each. DBU proved far superior to all the other bases tried, with only 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) giving near equivalent conversions.

A limited range of five substrates, varying from the already tested electron-rich **2a** (4-MeO) through to the electron-poor **2k** (4-NO_2) were then screened in small scale microwave tubes at a range of temperatures from 80 to 180 °C (10 min each). The results are shown in Fig. 1 (for **2a** and **2k** only) and confirm the expected trend, with **2a** having the highest conversions and **2k** the lowest, and the others being somewhat intermediate. From these results, it was extrapolated that conversions would be >90% for most substrates at ~160 °C, with the possible exception of those bearing very electron-poor substituents.

Control experiments were also performed at room temperature to determine the background rate of reaction under ambient conditions. The highest rate was for **2a**, which gave ~20% conversion to **3a** after 7 h and 40–50% after 24 h, whereas **2k** was effectively unreactive at RT up to 24 h. It was important to establish the background rate of reaction over the planned reaction times (3, 8 and 24 h) to determine if the two reagents **1** and **2** needed to be segregated. Although background reaction might appear desirable, and often is chemically, it can cause other issues. If premature precipitation of the product or other reaction by-products occurs in the feed vessels, this can result in blockages in the inlet lines.[10] It is also desirable that all batches are processed equally; if some reaction has already taken place before heating, the batch may effectively be over-heated, resulting in reduced quality from degradation products. Given that the background reaction rate at room temperature would be significant for some substrates, we decided to charge them from separate feed vessels for each batch.

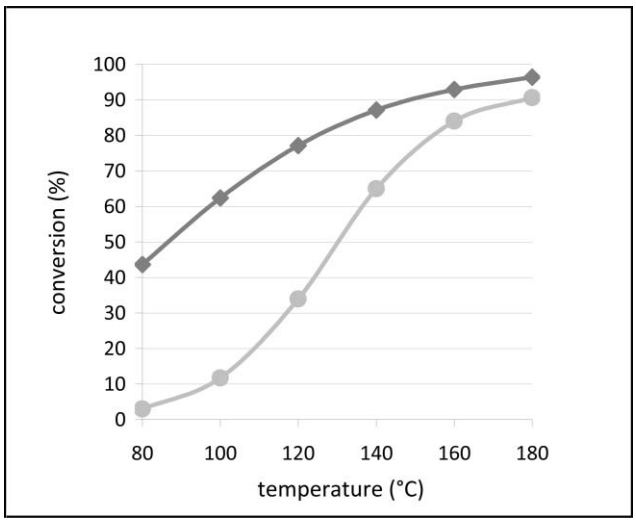


Fig. 1 Reaction conversion of **1** with **2a** (dark/diamonds) and **2k** (light/circles).

Development of isolation procedure

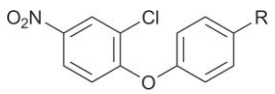
Portionwise addition of an equal volume of water to the K_2CO_3-mediated heterogeneous reaction mixtures had precipitated the desired diaryl ethers **3** in excellent yields and purities in most cases. When this was tried for several homogeneous reaction mixtures, the products tended to be highly coloured and crystallised with poor form or oiled out, despite the fact that they were known to be white or pale yellow-coloured solids under the heterogeneous reaction isolation conditions. A cursory analysis by ^{1}H NMR suggested that the samples were contaminated with residual DBU. In principle, this should be removed by washing with acid. We also rationalised that the high ionic strength of the heterogeneous reaction conditions (due to the presence of by-product KCl) probably aided good physical form and crystallisation of the product ethers **3**, and helped to ensure high yields. We therefore determined to replicate in the homogeneous reaction, as nearly as possible, the aqueous drown-out conditions from the heterogeneous reaction.

We used diaryl ether **3j** derived from **2j** (4-CN), because this appeared particularly crystalline and offered the best model for success. A stock solution of previously prepared **3j** was dissolved in the requisite volume of DMA along with 1.2 equivalents of DBU and 0.1 equivalents of phenol **2j** (the reaction excess), and separated into 50 mL portions, to which were added 50 mL portions of stock solutions of either 10 or 20 wt% aqueous KCl containing 3 equivalents of HCl. The recovered crystalline product was then slurry washed with 2 M HCl (to remove residual DBU) and then twice with water (to remove residual DMA and KCl). All combinations gave essentially quantitative recovery of **3j**, so the lower strength 10 wt% solution was preferred. Quality by HPLC and ^{1}H NMR was excellent, as was the form, and colour was typically pale yellow, much improved on the original process when using only water at neutral pH.

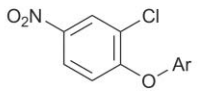
Initial stop-flow investigations

We were now ready to begin testing the scaling out capability of the Voyager for this S_NAr reaction. Where reference samples

had not already been isolated, 20 mL scale microwave reactions were performed and the product ethers **3** isolated by aqueous KCl drown-out to provide spectroscopic data and analytical markers peaks. Substitution patterns that did not give solid diaryl ethers of good form on aqueous drown-out (Scheme 2, **3l–q**) were passed over in favour of those that did. This was purely for the convenience of isolation in this study, since these products gave reactions of high conversion and analytical purity, and could have been isolated on larger scale using an extractive work-up.



3l (R = H)
3m (R = Me)
3n (R = Cl)



3o (Ar = 4-pyridyl)
3p (Ar = 1-naphthyl)
3q (Ar = 2-naphthyl)

Scheme 2 Additional substituted phenols investigated but not scaled up in the Voyager.

The initial scouting work was conducted on phenol **2a**. A stock solution of DCNB (**1**) at 25 wt% in DMA was prepared. A similar solution of phenol **2a** (1.1 eq.) was prepared in an equal volume of DMA with DBU added (1.2 eq.). We had established that phenol/DBU solutions were stable at RT for several days, whereas the DCNB/DBU solution started to degrade over this time. By co-charging the DBU with the phenol, one potential operation was removed from the protocol, which would help to keep the cycle time short. Appropriate volumes (~25 mL each) of the two reaction solutions were pumped into the reaction vessel through separate lines to give the correct stoichiometry. The vessel was sealed and heated by microwaves (300 W) to 150 °C for 10 min with stirring. At the end of the heating time, compressed air cooled the vessel and the reaction solution was pumped out at 90 °C to a receiver vessel. The next batch could then be charged automatically.

We have found that a proving trial of three to five batches is useful to adequately test a new method, for example by showing that lines do not gradually block between batches.[10] Air is used to blow the internal lines clear of starting materials and reaction products. Small line washes with fresh solvent can also be used to clean the lines. In this case, no line or vessel washes were required between batches. However, reaction conversions were incomplete at 150 °C for **2a**. This may be because the Voyager measures the internal temperature by fibre optic probe, whereas the scouting reactions had been conducted in a small scale microwave reactor using an IR pyrometer measuring the external temperature of the glass-walled vessels. Although good and consistent results can be obtained with these instruments using external IR pyrometers (irrespective of manufacturer), the vessel contents may be at a slightly higher temperature than that registered. Consequently, repeat three-batch trials were conducted up to 180 °C which showed complete reaction after 10 min with no loss in yield or purity (due to over-reaction).

Increasing the reaction temperature to 180 °C in the Voyager was entirely feasible, but had a number of drawbacks. A key parameter for scaling-out in a small vessel is the cycle time; increasing the reaction temperature to 180 °C would require both longer heating and cooling times. Furthermore, the extra 30 °C required the small 300 W microwave unit to work disproportionately hard to achieve 180 °C. This added too much time to a 10 min reaction, so we decided to reduce the cycle time by adjusting the stoichiometry.

The initial reaction stoichiometry had been chosen to match the efficiencies of very large scale production. Since all the materials were cheap, we decided an increase in stoichiometry could be used to increase the reaction rate without being economically deleterious. The phenol charge was raised to 1.2 equivalents and the DBU to 1.5 equivalents. The pump settings were adjusted to accommodate the slight changes in stoichiometry and volumes, and the three-batch proving trial showed complete reaction at 150 °C after 10 min. These conditions gave complete reaction for all substrates except **2k**, which required 10 min at 160 °C. The KCl drown-out solution worked just as well as before, giving identical yield and quality for all substrates.

Scaling-out stop-flow preparations

With the conditions now optimised (150 °C 10 min, 1.2 eq. phenol, 1.5 eq. DBU), all the diaryl ethers **3a–k** were prepared in automated sequences of 10 or 30 batches, as shown in Table 1. For each substrate, the pump on the Voyager was calibrated to dispense 23 mL of DCNB stock solution through line 1, and 27–31 mL of phenol/DBU stock solution through line 2. (The variation in volume was due to the differing molecular mass of the dissolved phenols required to maintain equivalent stoichiometries.) The single pump could be separately calibrated for both lines but had to be re-calibrated for each new phenol processed. This took only 5–10 min and once done, remained constant for all batches processed within that method. These charges achieved the finalised stoichiometric ratio of 1.2 eq. of phenol and 1.5 eq. of DBU, which were charged jointly. Each batch was heated with stirring to 150 °C for 10 min (160 °C for **3k**), before being cooled to 90 °C and removed from the vessel. The next batch in the sequence was then charged automatically.

The cycle time for each individual 50 mL batch took ~16 min to run and contained ~25 mmol. The 30 batch sequences took 8 h, during which time ~1.5 L of reaction solution was processed to give 800 mmol of diaryl ether product (typically ~200 g). Representative samples of product (typically 0.5 L of crude reaction solution) were isolated by aqueous drown-out in each case to confirm yield and quality, as shown in Table 1.

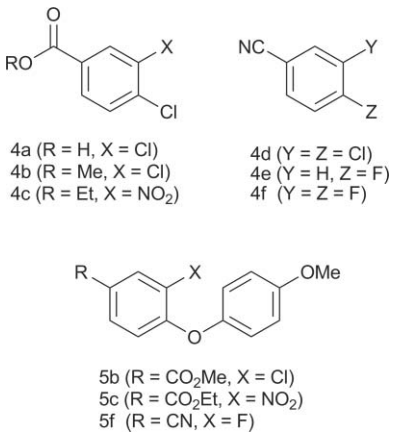
Alternative stop-flow preparations

Having established the principle of scaling out in the stop-flow microwave reactor, we then attempted to broaden the scope of the methodology with alternative substrates to **1**. Thus, compounds **4a–f** were tested under identical conditions in small scale microwave tubes using phenol **2a** as the standard nucleophile (Scheme 3). Unsurprisingly, methyl ester **4b** proved too deactivated to react at 150 °C, requiring instead 180 °C for 60 min to give **5b**, but at this temperature, adventitious hydrolysis of the ester group to **4a** started to occur (**4a** had also been found not to react).

Table 1 Summary of compounds prepared in the Voyager with batch numbers, yield and purity

Product	Coupling partner	Nucleophile	Nucleophile substituent	No. of batches	Yield (%)	Purity by LC (%)	mp/°C	Literature reference
3a	**1**	**2a**	4-MeO	30[a]	97	100	88–89	7e, 15
3b	**1**	**2b**	3-MeO	10	86	97	64–66	n/a
3c	**1**	**2c**	2-MeO	10	88	100	104–105	7e
3d	**1**	**2d**	4-tBu	10	85	95	91–93	7e, 16
3e	**1**	**2e**	4-Br	10	97	98	99–100	n/a
3f	**1**	**2f**	4-F	30	91	100	68–69	7e
3g	**1**	**2g**	4-Ph	10	99	95	98–104	n/a
3h	**1**	**2h**	4-CO_2Me	10	84	98	123–124	17
3i	**1**	**2i**	4-CHO	10	86	99	79–80	n/a
3j	**1**	**2j**	4-CN	30	96	99	109–110	7c
3k	**1**	**2k**	4-NO_2	10[b]	70	81	94–98	7a
5c	**4c**	**2a**	4-MeO	10	83	96	85–86	n/a
5f	**4f**	**2a**	4-MeO	10	83	98	59–60	18
7	**6c**	**2j**	4-CN	10[c]	45	96	90–92	n/a
9a	**1**	**8a**	4-MeO	10[d]	88	98	96–99	19

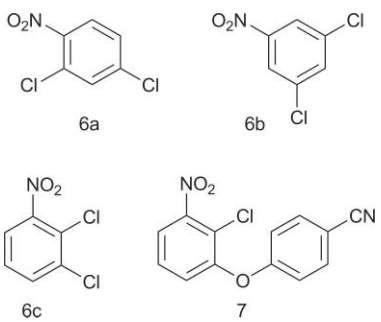
n/a: None available.[a] Also prepared on 90 batch scale. [b] Required 160 °C for 10 min. [c] Required 180 °C for 10 min. [d] Required 80 °C for 60 s.



Scheme 3 Alternative coupling partners to **1** investigated.

Ethyl ester **4c** with the additional nitro group performed very well, however, to give diaryl ether **5c** under the standard conditions. Of the nitriles, **4d** was too deactivated to react at 150 °C; **4e** did react but required 180 °C for 30 min for full conversion; but **4f** reacted cleanly under the standard conditions to give product **5f** in good yield and high purity (Table 1).

Alternative dichloro-substitution patterns to **1** retaining the activating nitro group were also investigated (Scheme 4). So the 2,4-DCNB equivalent **6a** gave complete conversion at 150 °C after 10 min to an unresolved mixture of three compounds, assumed to be the *ortho*-, *para*- and di-substituted products. The less activated *meta*-substituted **6b** required 180 °C for 10 min for full conversion to two products, assumed to be the mono- and di-substituted products. Lastly, the 2,3-DCNB equivalent **6c** was tested with **2j**, which also required 10 min at 180 °C for complete conversion to the single isomer **7** (Table 1). Despite the slower reaction, we persisted in this case to obtain an alternative substitution pattern, but the product proved difficult to isolate, and after an extensive extractive work-up (in place of the aqueous drown-out), only a 45% yield was obtained, albeit of good quality product (97%).

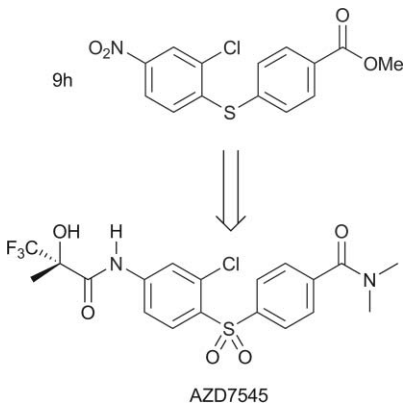


Scheme 4 Alternative substitution patterns to **1** investigated.

Alternative nucleophiles were also briefly investigated using **1** as the test-bed (Scheme 5). The thiophenol **8a** (sulfur analogue of **2a**) was found to require only 1 min at 80 °C for complete reaction, but with pumping the cycle time was 5.7 min per batch. Ten batches were prepared in less than 1 h from which the product diarylthioether **9a** was isolated in only moderate purity (82%) after the aqueous drown-out. Re-slurrying several times with methanol, however, gave good quality product (97%) in high yield (88%) (Table 1). Thiophenol **8k** was also investigated to prepare **9k** on small scale, but the reaction was found to be so fast it was not worth considering for microwave synthesis. Coincidentally, the sulfur analogue (**8h**) of **2h** would have been ideal for preparing **9h**, a proposed intermediate in the potential alternative synthesis of AZD7545, a former AstraZeneca development compound (Scheme 6).[13] Again, small scale microwave studies proved this was a viable transformation, but the work was not scaled up (solely due to the cost of **8h**).

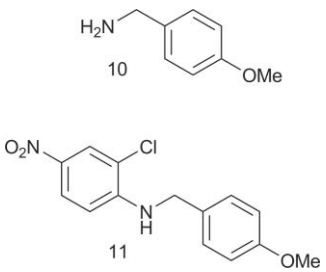
Scheme 5 S_NAr reaction with substituted thiophenols.

Several substituted anilines, including *p*-anisidine, were also investigated on small scale with **1**. Unsurprisingly, these failed to react under the standard conditions, presumably due to



Scheme 6 Potential synthesis of AZD7545.

poor nucleophilicity, but products were formed on heating to ~200 °C. Some of these reaction products appeared to be adducts with DBU (as determined by ^{1}H NMR analysis). Attempts to use triethylamine gave limited reaction at 200 °C and poor quality. The homologous benzylamine analogue **10** was investigated and did react to give **11**, but required 2 eq. of **10** (and 1.0 eq. of DBU) for the best results (83% conversion after 10 min at 165 °C). However, this was not taken into the stop-flow reactor.



Batch microwave scale-up preparations

As an adjunct to this study, the standard reaction set (Scheme 1) was also trialled in an alternative microwave batch reactor, the Anton Paar Synthos 3000.[14] This is a multimode microwave reactor which has sixteen 100 mL reaction tubes, each with an effective working volume of ~60 mL. Each tube is stirred magnetically and rotated slowly in the microwave cavity to ensure a uniform microwave field over the course of the reaction.

A stock solution of **1** and DBU (1.5 eq.) in DMA (12.5 wt% based on **1**) was made up and split between fourteen tubes (28 mmol of **1** each) to which were added 34 mmol (1.2 eq.) of phenols **2a–k** (3.8–6.0 g depending on molecular weight), including duplicate tubes of **2a**, **2j** and **2k**. The final two tubes were made up in a similar manner on 28 mmol scale using **4c** and **4f** with **2a**, respectively. The total volume in each tube was ~55–60 mL. A single run at 150 °C for 10 min converted all starting material combinations for all sixteen tubes to their respective products (**3a–k**, **5c** and **5f**) in ~40 min (allowing for heating and cooling). Conversions were marginally lower than in the Voyager, probably because of the initial over-heating of the reaction samples in the Voyager to ~160 °C, but there was no substantial preparative difference. Two of the duplicated samples were combined and isolated by aqueous drown-out to confirm yield and quality (**3a** 91% yield, 100% purity by HPLC; **3j** 93% yield, 98% purity by HPLC).

Overall, this shows that a modest scale-up (~30 mmol) can be achieved simultaneously for up to 16 related reaction products in less than 1 h, which should be of interest to medicinal chemists. Alternatively, a larger scale-up for one product (~0.5 mol) could be achieved in the same time if all tubes (total volume 1.0 L) were loaded with the same starting materials. However, this would not be as convenient as the automated stop-flow microwave reactor which can be left to run unattended.

Extended scale-out stop-flow preparation

As a final test of robustness of the stop-flow reactor, 90 batches of the standard reaction pair (**1** and **2a**) were processed in a continuous run over 24 h with no manual intervention. This included ~15 h of unattended operation overnight. A ten-batch portion (530 mL) of crude product reaction mixture was submitted to the optimised aqueous drown-out procedure which gave a 98% yield of product **3a** of >99% purity by HPLC. Overall, the total reaction volume processed was 4.7 L containing 2.3 moles of **1** which was accomplished in just under 25 h.

Conclusions

This paper reports on the manufacture of a range of potentially useful pharmaceutical and agrochemical diaryl ethers and related compounds through scaling-out in an automated stop-flow microwave reactor. The process is facile and requires no manual intervention once started, such that as much product can be prepared as required, given sufficient availability of starting materials and time. Of particular significance in this case, continuous 24 h processing has been achieved for the first time, which demonstrates that this relatively small-scale microwave stop-flow reactor is both robust and reliable. Furthermore, production rates of >0.5 kg per day can be achieved (for this reaction), which would meet the typical manufacturing requirements of early clinical pharmaceutical development. The production rates are facilitated by a combination of rapid microwave heating, fast cooling due to small vessel size, and automated charging through a stop-flow approach. Higher productivities could be achieved by the use of more reactors operating in parallel.

Experimental

General procedures

Reaction mixtures and products were analysed by reverse phase HPLC on an Agilent 1100 series instrument according to the following conditions: column, Varian Polaris Amide C18 3 μm, 50 × 3.0 mm i.d.; eluent A, 100% purified water, 0.03% v/v trifluoroacetic acid; eluent B, 100% acetonitrile, 0.03% v/v trifluoroacetic acid; flow rate 1.25 mL min^{-1}.; wavelength 230 nm; temperature 45 °C; injection volume 2 μL; at t = 0 min, 5% eluent B; at t = 6 min, 95% eluent B; at t = 7.5 min, 95% eluent B; post time 1.5 min. Typical retention times (RT) are noted in each case. Melting points were determined using a Griffin melting point apparatus (aluminium heating block) and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 400 spectrometer at 400 and 100.6 MHz respectively with chemical shifts given in ppm relative to TMS at $\delta = 0$. High resolution mass spectra were performed on a Micromass GCT mass spectrometer

with EI^+ source. Analytical TLC was carried out on commercially prepared plates coated with 0.25 mm of self-indicating Merck Kieselgel 60 F_{254} and visualised by UV light at 254 nm. Preparative scale silica gel flash chromatography (for purification of analytical samples only) was carried out by standard procedures using Merck Kieselgel 60 (230–400 mesh). Where not stated otherwise, assume standard practices have been applied.

Small scale microwave preparations

Small scale microwave reactions were performed in sealed, thick-walled glass tubes (5 or 20 mL) in a Biotage Initiator 300 W focused microwave reactor with external IR temperature probe and non-invasive pressure transducer. Stoichiometries and solvent volumes were as noted below in the general procedures for stop-flow preparations, and conducted on typically 2 mmol (5 mL tube) or 9 mmol (20 mL tube) scales. The heating time is not included in the quoted hold time for any given procedure; control studies show that the heating time has a negligible effect on overall conversion. Where products were isolated to provide reference markers and analytical data, the aqueous drown-out procedure described in the text was used if possible (for solids of good form), or alternatively an extractive procedure with ethyl acetate or MTBE followed by flash silica gel chromatography and/or recrystallisation from methanol was used instead.

Preparation of reaction solutions

The first reaction solution (SM1) consisted of the limiting reagent (**1**, **4c**, **4f** or **6c**) dissolved in DMA at 25 wt%. The second reaction solution (SM2) consisted of the nucleophile (**2a–k** or **8a**, 1.2 eq.) and DBU (1.5 eq.) dissolved in an equal volume of DMA (25 wt% based on SM1). The volume of these homogeneous reaction solutions was then measured and the volume of SM2 required to maintain the correct stoichiometry relative to SM1 calculated.

General procedure for stop-flow preparations (Voyager)

In a CEM Voyager 300 W microwave reactor, limiting reagent (SM1) was charged through the first input line (23 mL for **1**, ~28 mmol) followed by the nucleophile/DBU solution (SM2) through the second line (typically 27–31 mL depending on the mass of the nucleophile) into the 80 mL reaction vessel (50 mL working volume). The combined reaction mixture (~ 50 mL) was heated by microwaves to 150 °C (overshoots initially to ~160 °C) and held for 10 min with magnetic stirring. The reaction mixture was then cooled to 90 °C with compressed air and pumped out through the product line and collected. This cycle was then repeated automatically, with the number of cycles depending on the volume of the stock solutions used. To ensure that there were sufficient materials for the desired number of cycles and practice runs, stock solutions were made up to run a few more cycles than planned, therefore yields quoted are based on the number of moles that were processed by the Voyager and chosen for work up.

Aqueous drown-out isolation procedure

Hydrochloric acid (36 wt%, 127 mL) was added to a stock solution of potassium chloride (100 g, 10 wt%) dissolved in 1 L of water. An equal volume of this stock solution was added dropwise over 30 min with mechanical stirring to an equal volume of crude reaction product (generally performed on ~500 mL scale, representing a 10 batch run) during which time an exotherm of typically 12–16 K was observed initially. In most cases, a dense yellow precipitate formed about halfway through this addition. The reaction mixture was cooled back to 20 °C and the precipitate isolated by filtration. The product cake was slurry washed with 2 M hydrochloric acid (300 mL on 500 mL scale), followed by two slurry washes with water (500 mL each). Larger volumes do not affect yield and may be required to enhance quality in some cases. The product diarylethers (**3a–k**, **5c**, **5f**, **7**, **9a**) were dried to constant weight in a vacuum oven at 50 °C.

Stop-flow microwave preparations of diarylethers (3a–k, 5c, 5f, 7, and 9a)

The stop-flow preparation for **3a** is given in full; for other compounds, only differing parameters are given, in addition to physical and spectroscopic characterisation data. For all compounds, typically ~0.5 L of representative crude reaction solution (10 batches) was taken from which the desired products were isolated by aqueous drown-out with the procedure noted above. Physical and quality data and yields are taken from samples derived by aqueous drown-out directly from these large scale preparations, and were not further purified, except where noted.

2-Chloro-1-(4-methoxyphenoxy)-4-nitrobenzene (3a). DCNB (**1**) (160 g, 0.83 mole) was dissolved in DMA (640 mL, 25 wt%) and charged to a 1 L bottle. In a separate 1 L bottle, 4-methoxyphenol (**2a**) (124 g, 0.99 mole, 1.20 eq.) was dissolved in DMA (640 mL) and DBU (186 mL, 1.24 mole, 1.50 eq.) added and the contents stirred until homogeneous. One input line (SM1) was placed in the bottle containing **1** and the other input line (SM2) placed in the bottle containing **2a**/DBU. The materials were processed in a CEM Voyager microwave reactor in 30 continuous cycles to give 1560 mL of dark reaction mixture. Each batch consisted of 23 mL of **1** (~28 mmol) and 29 mL of **2a** (~33 mmol), took ~16.5 min to run and gave 52 mL of crude product mixture. In order to make the work-up more manageable (in the lab), the crude reaction mixture was split into three 520 mL portions, of which one was chosen at random to isolate representative product by the method noted above. The title compound was prepared as a pale yellow solid (69.2 g, 97% on 10 batch scale). HPLC (RT 4.87 min, 99.7%); mp 88-89 °C (lit.[15] 86-90 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (1H, d, $J = 2.8$ Hz), 8.02 (1H, dd, $J = 9.2$ Hz, $J = 2.8$ Hz), 7.06-7.02 (2H, m), 6.98-6.94 (2H, m), 6.79 (1H, d, $J = 5.2$ Hz), 3.84 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 160.00, 157.52, 147.63, 142.26, 126.53, 123.95, 123.69, 121.77, 115.65, 115.48, 55.78; HRMS (EI^+) (Found: M^+, 279.0281. $C_{13}H_{10}ClNO_4$ requires M, 279.0298).

2-Chloro-1-(3-methoxyphenoxy)-4-nitrobenzene (3b). Prepared on 0.31 mole scale of **1** (10 batches) with 3-methoxyphenol (**2b**) (45.9 g, 0.37 mole, 1.20 eq.), to yield the title compound as a beige solid (63.4 g, 86%). HPLC (RT 4.89 min, 96.6%); mp 64-66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (1H, d, $J = 2.5$ Hz), 8.05 (1H, dd, $J = 9.1$ Hz, $J = 2.7$ Hz), 7.33 (1H, t, $J = 8.0$ Hz), 6.92 (1H, d, $J = 8.7$ Hz, 6.83-6.80 (1H, m), 6.67-6.64 (2H, m), 3.82 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.44, 158.99, 155.65, 142.77, 130.89, 126.58, 124.76, 123.70, 117.12, 112.11, 111.43,

106.27, 55.62; HRMS (EI$^+$) (Found: M$^+$, 279.0284. $C_{13}H_{10}ClNO_4$ requires *M*, 279.0298).

2-Chloro-1-(2-methoxyphenoxy)-4-nitrobenzene (3c). Prepared on 0.31 mole scale of **1** (10 batches) with 2-methoxyphenol (**2c**) (45.9 g, 0.37 mole, 1.20 eq.), to yield the title compound as a pale yellow solid (63.5 g, 88%). HPLC (RT 4.79 min, 100%); mp 104-105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (1H, d, J = 2.8 Hz), 7.99 (1H, dd, J = 9.1 Hz, J = 2.7 Hz), 7.31-7.27 (1H, m), 7.15-7.00 (3H, m), 6.66 (1H, d, J = 9.2 Hz), 3.78 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.40, 151.36, 142.35, 142.22, 127.35, 126.38, 123.57, 123.31, 122.58, 121.60, 114.91, 113.32, 56.00; HRMS (EI$^+$) (Found: M$^+$, 279.0213. $C_{13}H_{10}ClNO_4$ requires *M*, 279.0298).

1-(4-*t*-Butylphenoxy)-2-chloro-4-nitrobenzene (3d). Prepared on 0.31 mole scale of **1** (10 batches) with 4-*tert*-butylphenol (**2d**) (56.3 g, 0.37 mole, 1.20 eq.), to yield the title compound as a pale beige solid (69.2 g, 85%). HPLC (RT 5.72 min, 95.2%); mp 91-93 °C (lit.[16] 104-107 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (1H, d, J = 2.5 Hz), 8.03 (1H, dd, J = 9.0 Hz, J = 2.6 Hz), 7.47-7.43 (2H, m), 7.03-7.00 (2H, m), 6.87 (1H, d, J = 9.2 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.51, 152.09, 148.94, 142.46, 127.34, 126.54, 124.44, 123.66, 119.83, 116.48, 34.66, 31.51; HRMS (EI$^+$) (Found: M$^+$, 305.0784. $C_{16}H_{16}ClNO_3$ requires *M*, 305.0819).

1-(4-Bromophenoxy)-2-chloro-4-nitrobenzene (3e). Prepared on 0.31 mole scale of **1** (10 batches) with 4-bromophenol (**2e**) (64.9 g, 0.37 mole, 1.20 eq.), to yield the title compound as a beige solid (81.1 g, 97%). HPLC (RT 5.19 min, 97.9%); mp 99-100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (1H, d, J = 2.8 Hz), 8.08 (1H, dd, J = 9.1 Hz, J = 2.7 Hz), 7.57-7.54 (2H, m), 6.99-6.96 (2H, m), 6.91 (1H, d, J = 9.3 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.46, 153.88, 143.17, 133.53, 126.75, 125.18, 123.75, 121.73, 118.54, 117.35; HRMS (EI$^+$) (Found: M$^+$, 326.9285. $C_{12}H_7BrClNO_3$ requires *M*, 326.9298).

2-Chloro-1-(4-fluorophenoxy)-4-nitrobenzene (3f). Prepared on 0.83 mole scale of **1** (30 batches) according with 4-fluorophenol (**2f**) (41.8 g, 0.99 mole, 1.20 eq.), to yield the title compound as a beige solid (62.2 g, 91%). HPLC (RT 4.84 min, 100%); mp 68-69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (1H, d, J = 2.6 Hz), 8.05 (1H, dd, J = 9.1 Hz, J = 2.7 Hz), 7.17-7.12 (2H, m), 7.10-7.05 (2H, m), 6.84 (1H, d, J = 9.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.41, 159.20 and 158.97 (1C, d, J = 23.0 Hz), 150.37 and 150.33 (1C, d, J = 3.0 Hz), 142.77, 126.68, 124.58, 123.73, 121.96 and 121.88 (1C, d, J = 8.4 Hz), 117.35 and 117.11 (1C, d, J = 23.8 Hz), 116.38; HRMS (EI$^+$) (Found: M$^+$, 267.0073. $C_{12}H_7ClFNO_3$ requires *M*, 267.0098).

2-Chloro-1-(4-phenylphenoxy)-4-nitrobenzene (3g). Prepared on 0.31 mole scale of **1** (10 batches) with 4-phenylphenol (**2g**) (65.1 g, 0.37 mole, 1.20 eq.), to yield the title compound as a pale beige solid (86.4 g, 99%). HPLC (RT 5.58 min, 94.7%); mp 98-104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (1H, d, J = 2.8 Hz), 8.08 (1H, dd, J = 9.1 Hz, J = 2.7 Hz), 7.67-7.57 (4H, m), 7.49-7.44 (2H, m), 7.41-7.37 (1H, m), 7.18-7.14 (2H, m), 6.97 (1H, d, J = 9.2 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.09, 154.07, 142.82, 140.00, 138.93, 129.14, 129.04, 127.70, 127.12, 126.67, 124.87, 123.76, 120.49, 117.0; HRMS (EI$^+$) (Found: M$^+$, 325.0511. $C_{18}H_{12}ClNO_3$ requires *M*, 325.0506).

1-(4-Carbomethoxyphenoxy)-2-chloro-4-nitrobenzene (3h). Prepared on 0.31 mole scale of **1** (10 batches) with methylparaben (**2h**) (57.1 g, 0.37 mole, 1.20 eq.), to yield the title compound as a bright orange solid (65.8 g, 84%). HPLC (RT 4.53 min, 98.3%); mp 123-124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (1H, d, J = 2.6 Hz), 8.13-8.10 (3H, m), 7.08 (2H, d, J = 8.7 Hz), 7.04 (1H, d, J = 9.2 Hz), 3.93 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.17, 158.87, 157.54, 143.79, 132.21, 127.05, 126.83, 126.16, 123.80, 119.10, 118.81, 52.36; HRMS (EI$^+$) (Found: M$^+$, 307.0273. $C_{14}H_{10}ClNO_5$ requires *M*, 307.0248).

2-Chloro-1-(4-formylphenoxy)-4-nitrobenzene (3i). Prepared on 0.31 mole scale of **1** (10 batches) with 4-hydroxybenzaldehyde (**2i**) (45.8 g, 0.37 mole, 1.20 eq.), to yield the title compound as a beige solid (61.6 g, 86%). HPLC (RT 4.46 min, 99.3%); mp 79-80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (1H, s), 8.43 (1H, d, J = 2.8 Hz), 8.16 (1H, dd, J = 9.2 Hz, J = 2.4 Hz), 7.97-7.94 (2H, m), 7.17-7.14 (2H, m), 7.12 (1H, d, J = 8.9 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 190.54, 160.22, 156.92, 144.22, 133.17, 132.27, 126.91, 126.70, 123.89, 120.05, 118.95; HRMS (EI$^+$) (Found: M$^+$, 277.0141. $C_{13}H_8ClNO_4$ requires *M*, 277.0142).

2-Chloro-1-(4-cyanophenoxy)-4-nitrobenzene (3j). Prepared on 0.83 mole scale of **1** (30 batches) with 4-cyanophenol (**2j**) (119 g, 0.99 mole, 1.20 eq.), to yield the title compound as a pale orange solid (67.0 g, 96%). HPLC (RT 4.53 min, 99.2%); mp 109-110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (1H, d, J = 2.6 Hz), 8.17 (1H, dd, J = 9.0 Hz, J = 2.8 Hz), 7.73-7.70 (2H, m), 7.14-7.08 (3H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.90, 156.45, 144.48, 134.69, 126.98, 126.93, 123.95, 120.38, 119.11, 118.19, 108.53; HRMS (EI$^+$) (Found: M$^+$, 274.0139. $C_{13}H_7ClN_2O_3$ requires *M*, 274.0145).

2-Chloro-1-(4-nitrophenoxy)-4-nitrobenzene (3k). Prepared on 0.31 mole scale of **1** (10 batches) with 4-nitrophenol (**2k**) (51.7 g, 0.37 mole, 1.20 eq.) *and heated to 160 °C for 10 min*, to yield the title compound as a brown solid (65.6 g, 70%). HPLC (RT 4.69 min, 80.7%); mp 94-98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (1H, d, J = 2.8 Hz), 8.32-8.28 (2H, m), 8.20 (1H, dd, J = 9.0 Hz, J = 2.8 Hz), 7.19 (1H, d, J = 9.0 Hz), 7.12-7.08 (2H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 160.51, 156.20, 144.78, 144.30, 127.24, 127.06, 126.37, 124.00, 120.90, 118.29; HRMS (EI$^+$) (Found: M$^+$, 293.9987. $C_{12}H_7ClN_2O_5$ requires *M*, 294.0043).

Ethyl 4-(4-methoxyphenoxy)-3-nitrobenzoate (5c). Prepared on 0.25 mole scale of **4c** (10 batches) with 4-methoxyphenol (**2a**) (38.1 g, 0.30 mole, 1.20 eq.), to yield the title compound as a pale beige solid (59.0 g, 83%). HPLC (RT 4.77 min, 96.3%); mp 85-86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (1H, d, J = 2.0 Hz), 8.08 (1H, dd, J = 8.8 Hz, J = 2.2 Hz), 7.08-7.04 (2H, m), 6.97-6.93 (2H, m), 6.90 (1H, d, J = 8.7 Hz), 4.40 (2H, q, J = 7.1 Hz), 3.84 (3H, s), 1.40 (3H, t, J = 7.1 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.36, 157.51, 155.57, 147.47, 139.87, 134.97, 127.37, 124.45, 121.77, 117.61, 115.44, 61.73, 55.77, 14.37; HRMS (EI$^+$) (Found: M$^+$, 317.0889. $C_{16}H_{15}NO_6$ requires *M*, 317.0899).

2-Fluoro-1-(4-methoxyphenoxy)-4-cyanobenzene (5f). Prepared on a 0.42 mole scale of **4f** (10 batches) with 4-methoxyphenol (**2a**) (63.6 g, 0.51 mole, 1.20 eq.), to yield the title compound as

a yellow solid (69.6 g, 83%). HPLC (RT 4.41 min, 98.4%); mp 59-60 °C (lit.[18] 68.3-70.5 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (1H, dd, J = 10.3 Hz, J = 1.8 Hz), 7.33 (1H, dt, J = 8.5 Hz, J = 1.8 Hz), 7.04-6.99 (2H, m), 6.95-6.91 (2H, m), 6.86 (1H, t, J = 8.2 Hz), 3.83 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 157.21, 153.62 and 151.11 (1C, d, J = 251.7 Hz), 150.98 and 150.88 (1C, d, J = 10.0 Hz), 147.84, 129.45 and 129.40 (1C, d, J = 4.6 Hz), 121.25, 120.68 and 120.48 (1C, d, J = 20.6 Hz), 118.32 and 118.30 (1C, d, J = 1.6 Hz), 117.82 and 117.80 (1C, d, J = 2.3 Hz), 115.35, 105.88 and 105.80 (1C, d, J = 8.4 Hz), 55.76; HRMS (EI$^+$) (Found: M$^+$, 243.0672. $C_{14}H_{10}FNO_2$ requires M, 243.0696).

6-Chloro-1-(4-cyanophenoxy)-2-nitrobenzene (7). Prepared on 0.31 mole scale of **6c** (10 batches) with 4-cyanophenol (**2j**) (45 g, 0.37 mole, 1.20 eq.), *and heated to 180 °C for 10 min*, to yield, after an extensive extractive work-up with MTBE and washing with NaOH solution, the title compound as a crimson solid (44.5 g, 45%). HPLC (RT 4.14 min, 96.2%); mp 90-92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (1H, dd, J = 8.0, 1.6 Hz), 7.87 (1H, dd, J = 8.4, 1.8 Hz), 7.64 (2H, d, J = 8.4 Hz), 7.43 (1H, t, J = 8.2 Hz), 6.93 (2H, d, J = 8.8 H z); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.99, 143.28, 135.63, 134.34, 130.97, 126.98, 124.38, 118.56, 16.26, 107.01; HRMS (EI$^+$) (Found: M$^+$, 274.0118. $C_{13}H_7ClN_2O_3$ requires M, 274.0145).

2-Chloro-1-[(4-methoxyphenyl)thio]-4-nitrobenzene (9a). Prepared on 0.31 mole scale of **1** (10 batches) with 4-methoxythiophenol (**8a**) (52.1 g, 0.37 mole, 1.20 eq.) *and heated to 80 °C for 1 min*, to yield the crude product (88.5 g of 82% purity by HPLC, 89% yield overall). Five slurry washes with methanol (100 mL each) yielded the title compound as light brown solid (74.2 g, 88%). HPLC (RT 5.35 min, 97.9%); mp 96-99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (1H, d, J = 2.4 Hz), 7.86 (1H, dd, J = 8.4, 2.4 Hz), 7.49 (2H, d, J = 8.8 Hz), 7.03 (2H, d, J = 6.8 Hz) 6.68 (1H, d, J = 9.2 Hz), 3.88 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.61, 149.62, 145.02, 137.71, 129.97, 125.86, 124.44, 121.91, 118.98, 116.09, 55.60; HRMS (EI$^+$) (Found: M$^+$, 295.0029. $C_{13}H_{10}ClNO_3S$ requires M, 295.0043).

General procedure for batch microwave preparations (Synthos 3000)

DCNB (**1**) (77.0 g, 0.40 mole) was dissolved in DMA (616 mL, 12.5 wt%) with DBU (91 mL, 0.60 mole, 1.50 eq.) and the contents well mixed to give a total volume of 750 mL. A 54 mL aliquot of this solution (28.6 mmol of **1**) was charged to each of fourteen Anton Paar HF-100 PTFE tubes. The requisite mass of each phenol **2a–k** was added to each tube to maintain a stoichiometry of 1.20 eq. (typically 3.8–6.0 g, 34.3 mmol) in one portion, with **2a**, **2j** and **2k** prepared in duplicate. In the final pair of tubes, **4c** and **4f** were charged at the same scale (28.6 mmol) in combination with **2a**. A magnetic stirrer bar was added to each PTFE tube which was sealed in a ceramic case inside a 16-position rotor and placed in the cavity of an Anton Paar Synthos 3000 microwave reactor. One tube (containing **1** and **2a**) was fitted with a gas-bulb thermometer; the temperature in the others was monitored by external IR probe. The reaction mixtures were heated with magnetic stirring to 150 °C over 10 min with 1400 W available power, held at 150 °C for 10 min, then cooled by fan air to ~50 °C over ~20 min. Two of the duplicated samples were combined (total volume ~110–115 mL each) and isolated by aqueous drown-out according to the procedure described above to confirm yield and quality (**3a** 14.4 g cream solid, 91% yield, 100% purity by HPLC; **3j** 14.4 g brown solid, 93% yield, 98% purity by HPLC).

Acknowledgements

We thank Sam Whitmarsh (AstraZeneca, Avlon) for HRMS data.

Notes and references

1 (*a*) *Microwaves in Organic Synthesis*, ed. A. Loupy, Wiley-VCH, Weinheim, 2nd edn, 2006; (*b*) C. O. Kappe and A. Stadler, *Microwaves in Organic and Medicinal Chemistry*, Wiley-VCH, Weinheim, 2005; (*c*) *Microwave Assisted Organic Synthesis*, ed. J. P. Tierney and P. Lidström, Blackwell, Oxford, 2005; (*d*) S. Caddick and R. Fitzmaurice, *Tetrahedron*, 2009, **65**, 3325–3355; (*e*) C. O. Kappe and D. Dallinger, *Mol. Diversity*, 2009, **13**, 71–193; (*f*) C. O. Kappe, *Chem. Soc. Rev.*, 2008, **37**, 1127–1139; (*g*) C. O. Kappe, *Angew. Chem., Int. Ed.*, 2004, **43**, 6250–6284; (*h*) B. L. Hayes, *Aldrichimica Acta*, 2004, **37**, 66–76; (*i*) M. Nüchter, B. Ondruschka, W. Bonrath and A. Gum, *Green Chem.*, 2004, **6**, 128–141.

2 (*a*) C. R. Strauss, *Org. Process Res. Dev.*, 2009, **13**, 915–923; (*b*) J. M. Kremsner, A. Stadler and C. O. Kappe, *Top. Curr. Chem.*, 2006, **266**, 233–278; (*c*) B. Ondruschka, W. Bonrath and D. Stuerga, in *Microwaves in Organic Synthesis*, ed. A. Loupy, Wiley-VCH, Weinheim, 2nd edn, 2006.

3 J. D. Moseley, P. Lenden, M. Lockwood, K. Ruda, J.-P. Sherlock, A. D. Thomson and J. P. Gilday, *Org. Process Res. Dev.*, 2008, **12**, 30–40.

4 J. D. Moseley and E. K. Woodman, *Energy Fuels*, 2009, **23**, 5438–5447.

5 For examples of the preparation of diaryl ethers by microwave-assisted S_NAr reaction on small scale, see: (*a*) Y.-J. Cherng, *Tetrahedron*, 2002, **58**, 4931–4935; (*b*) F. Li, Q. Wang, Z. Ding and F. Tao, *Org. Lett.*, 2003, **5**, 2169–2171; (*c*) G. L. Rebeiro and B. M. Khadilkar, *Synth. Commun.*, 2003, **33**, 1405–1410; (*d*) F. Li, Q. Meng, H. Chen, Z. Li, Q. Wang and F. Tao, *Synthesis*, 2005, 1305–1313; (*e*) H. Xu and Y. Chen, *Synth. Commun.*, 2007, **37**, 2411–2420.

6 (*a*) A. de la Hoz, A. Diaz-Ortez and A. Moreno, *Chem. Soc. Rev.*, 2005, **34**, 164–178; (*b*) L. Perreux and A. Loupy, in *Microwaves in Organic Synthesis*, ed. A. Loupy, Wiley-VCH, Weinheim, 2nd edn, 2006; (*c*) D. Obermayer, B. Gutmann and C. O. Kappe, *Angew. Chem., Int. Ed.*, 2009, **48**, 8321–8324.

7 (*a*) A. Creuzburg, H. J. Zschiegner, W. Kochmann, W. Kramer, R. Fritzsche, O. Sass and K. Naumann, *East Ger. Pat.*, DD 106542, 1974; (*b*) H. Debne and L. M. Seusse, *East Ger. Pat.*, DD 110651, 1974; (*c*) W. Sirrenberg, E. Klauke, J. Schramm, I. Hammann and W. Stendel, *Ger. Offen.*, DE 2638233, 1978; (*d*) J.-Z. Liu, L. Fan, M.-L. Ma, Y.-L. Zhang, Y.-L Wang, G.-F. Liu and S.-H. Chen, *Sichuan Daxue Xuebao Zian Kexueban*, 2002, **39**, 161–163; (*e*) Z.-X. Yang, H. Chen, Y.-Z. Bi, Y. Zou, T.-P. Hou and Y.-L. Wang, *Youji Huaxue*, 2008, **28**, 432–435.

8 For recent reviews on the preparation of diaryl ethers by various methods, including S_NAr reaction, see: (*a*) A. W. Thomas, *Science of Synthesis*, 2007, **31a**, 469–543; (*b*) R. Frlan and D. Kikelj, *Synthesis*, 2006, 2271–2285; (*c*) J. S. Sawyer, *Tetrahedron*, 2000, **56**, 5045–5065.

9 (*a*) O. N. Tolkachev, *Khimiya Prirodnykh Soedinenii*, 1981, 263–283; (*b*) J. S. Sawyer, *Drugs Future*, 1996, **21**, 610–614; (*c*) J. S. Sawyer, E. A. Schmittling, J. A. Palkowitz and W. J. Smith III, *J. Org. Chem.*, 1998, **63**, 6338–6343; (*d*) For the naturally-occuring, medically important compounds thyrozine and vancomycin, see: *The Merck Index*, ed. M. J. O'Neil, Merck and Co. Inc., Whitehouse Station NJ, 14th edn, 2006.

10 J. D. Moseley and E. K. Woodman, *Org. Process Res. Dev.*, 2008, **12**, 967–981.

11 (*a*) www.cem.com; (*b*) K. T. J. Loones, B. U. W. Maes, G. Rombouts, S. Hostyn and G. Diels, *Tetrahedron*, 2005, **61**, 10338–10348; (*c*) M. R. Pitts, P. McCormack and J. Whittall, *Tetrahedron*, 2006, **62**, 4705–4708.

12 (*a*) W.-C. Shieh, M. Lozanov, M. Loo, O. Repic and T. J. Blacklock, *Tetrahedron Lett.*, 2003, **44**, 4563–4565; (*b*) S. Chen, H. Huang, X. Liu, J. Shen, H. Jiang and H. Liu, *J. Comb. Chem.*, 2008, **10**, 358–360; (*c*) M. Iannelli, F. Bergamelli, C. M. Kormos, S. Paravisi and N. E. Leadbeater, *Org. Process Res. Dev.*, 2009, **13**, 634–637.

13 J. D. Moseley, D. Brown, C. R. Firkin, S. L. Jenkin, B. Patel and E. W. Snape, *Org. Process Res. Dev.*, 2008, **12**, 1044–1059.
14 (*a*) www.anton-paar.com; (*b*) A. Stadler, B. H. Yousefi, D. Dallinger, P. Walla, E. Van Der Eycken, N. Kaval and C. O. Kappe, *Org. Process Res. Dev.*, 2003, **7**, 707–716.
15 Ch. S. Frankovskii, E. S. El'kis and L. D. Borodkina, *Zhurnal Organicheskoi Khimii*, 1970, **6**, 2305–2309.
16 G. Neubauer, S. B. Cilianu, V. Tamas, C. I. Ionescu, G. Funieru, and A. Carstea, *Rom. Pat.*, RO 74124, 1981.
17 M. Seto and T. Ohashi, *PCT Int. Appl.*, WO 2007097470, 2007.
18 X.-M. Yan, B.-K. Ning and L.-P. Wang, *Yingyong Huagong*, 2007, **36**, 273–276.
19 Ch. S. Frankovskii and E. Z. Katsnel'son, *Zhurnal Organicheskoi Khimii*, 1968, **4**, 490–493.