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A Commercial Continuous Flow Microwave Reactor Evaluated for Scale-Up

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Abstract:

Six pharmaceutically relevant reactions covering a range of physical parameters have been investigated in a commercially available microwave flow reactor. The reaction conditions were scaled-up from tube or large batch scale microwave conditions, largely without change. Energy consumption measurements were also taken. In summary, this microwave flow reactor provided potentially successful manufacture for five out of six reactions investigated where homogeneous reactions solutions could be obtained. Production rates of between 0.5 and 3.0 mol/h (1−6 L/h) have been achieved with minimal redevelopment of the chemistry.

Introduction

Microwave-assisted organic synthesis (MAOS)[1,2] is now widely established in pharmaceutical discovery departments for the initial synthesis of potential new drugs.[1b] However, scaling up MAOS has continued to present a significant challenge[3] whilst still being a desirable capability within pharmaceutical synthesis.[4] A major factor is the limited penetration depth of microwaves, which is only a few centimeters in most solvents.[2c,5] Consequently, many have concluded that, for effective scale-up, a continuous flow system will be required.[6] This note builds on an earlier initial evaluation[7] of such a commercially available continuous flow microwave reactor, the Milestone FlowSYNTH (Figure 1).[8] This is a 1600 W multimode microwave reactor based on the Milestone MicroSYNTH platform with a magnetron which is able to deliver power in 1 W increments. The reaction chamber consists of a PTFE tube of 200 mL capacity protected by a quartz-fibre reinforced PEEK sheath and is vertically mounted in the microwave cavity. A steel frame provides the required mechanical strength. The reaction mixture is pumped by a high-pressure membrane pump from the base upwards through the column to the top where a chiller unit then rapidly cools it. An Archimedean screw provides plug-flow characteristics within the column. This is fitted with three Weflon baffles which also aid heating. The reaction mixture then exits through a back pressure regulator which regulates the pressure of the system/solvent, although in principle this is

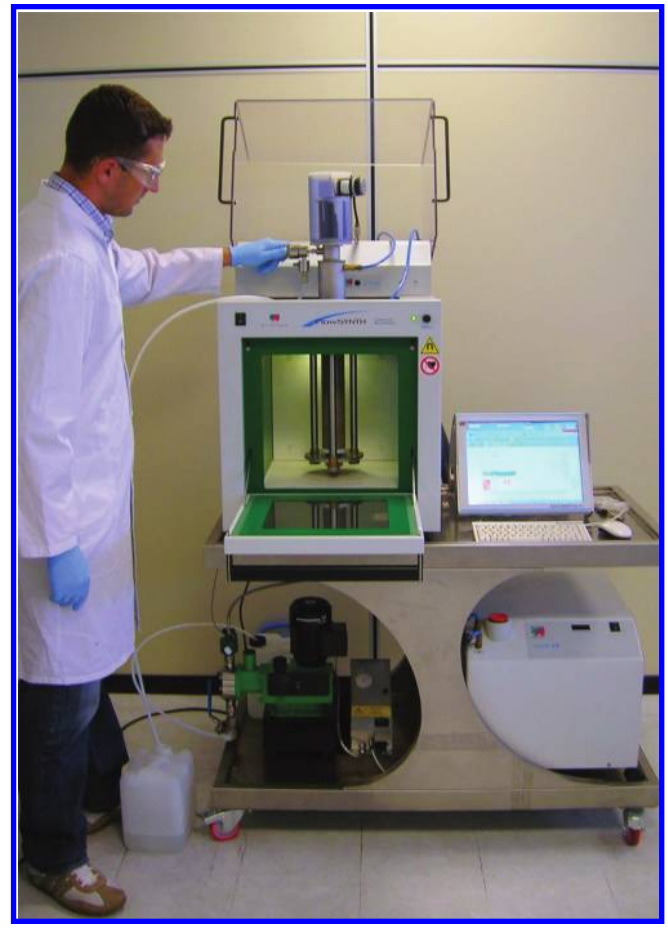

Figure 1. **The Milestone FlowSYNTH. Photo courtesy of Milestone (Italy).**

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(1) (a) *Microwaves in Organic Synthesis* (2nd ed.); Loupy, A., Ed.; Wiley-VCH: Weinheim, 2006 (*2 volumes*). (b) Kappe, O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, 2005. (c) *Microwave Assisted Organic Synthesis*, Tierney, J. P.; Lidström, P., Eds.; Blackwell: Oxford, 2005; (d) Hayes, B. L. *Microwave Synthesis: Chemistry at the Speed of Light*; CEM: Matthews, 2002.

(2) (a) Caddick, S.; Fitzmaurice, R. *Tetrahedron* **2009**, *65*, 3325–3355. (b) Kappe, C. O.; Dallinger, D. *Mol. Diversity* **2009**, *13*, 71–193. (c) Kappe, C. O. *Chem. Soc. Rev.* **2008**, *37*, 1127–1139. (d) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284. (e) Hayes, B. L. *Aldrichimica Acta* **2004**, *37*, 66–76. (f) Nüchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. *Green Chem.* **2004**, *6*, 128–141.

(3) (a) Strauss, C. R. *Org. Process Res. Dev.* **2009**, *13*, 915–923. (b) Kremsner, J. M.; Stadler, A.; Kappe, C. O. *Top. Curr. Chem.* **2006**, *266*, 233–278. (c) Ondruschka, B.; Bonrath, W.; Stuerga, D. in *Microwaves in Organic Synthesis*, ed. Loupy, A. Wiley-VCH, Weinheim, 2nd edn., 2006. (d) Roberts, B. A.; Strauss, C. R. *Acc. Chem. Res.* **2005**, *38*, 653–661.

(4) (a) Moseley, J. D.; Lenden, P.; Lockwood, M.; Ruda, K.; Sherlock, J.-P.; Thomson, A. D.; Gilday, J. P. *Org. Process Res. Dev.* **2008**, *12*, 30–40. (b) Bowman, M. D.; Holcomb, J. L.; Kormos, C. M.; Leadbeater, N. E.; Williams, V. A. *Org. Process Res. Dev.* **2008**, *12*, 41–57.

(5) Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, *27*, 213–223.

(6) For a recent brief discussion comparing batch and continuous flow microwave synthesis, see: Moseley, J. D. *Chimica Oggi/Chemistry Today* **2009**, *27* (2), 6–10.

(7) Moseley, J. D.; Lawton, S, J. *Chimica Oggi/Chemistry Today* **2007**, *25* (2), 16–19.

(8) www.milestonsrl.com.

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not needed when operating below the solvent boiling point. The entire system is monitored and controlled by computer interface, wherein data can also be collected (Figure 1).

The FlowSYNTH can operate at temperatures up to 230 °C and pressures up to 30 bar (435 psi).[8] The pump can operate at flow rates between 10 and 200 mL/min i.e. up to one column volume per minute or ~12 L/h. This means the FlowSYNTH can process significant quantities of materials per day. Assuming 24 h operation, ~300 L could be processed per day, which for a typical 10 wt %/volume pharmaceutical process would represent nearly 30 kg of material processed. In principle, the FlowSYNTH can process slurries when operating below the solvent boiling point. However, in practice, the back pressure regulator is required when operating near or above the solvent boiling point, and when other volatile reaction components are present. In these cases, slurries cannot be processed because the back pressure regulator contains a frit which is easily blocked by solids (or by solids forming during the reaction).

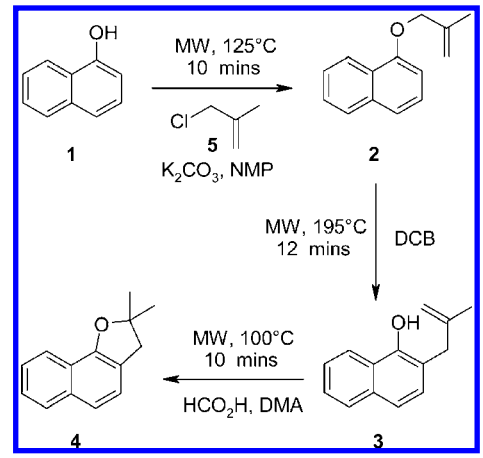
In our initial evaluation,[7] we studied the unimolecular homogeneous Newman−Kwart rearrangement (NKR).[9] This established the baseline performance for this reactor and also provided a comparison to other larger-scale microwave reactors.[4a] We have now expanded the scope of this work by investigating more challenging reactions. For this purpose, we chose the following reactions: an ortho Claisen rearrangement, an acid-catalysed benzofuran formation, an alkylation reaction, a Heck reaction, and a nucleophilic aromatic substitution (S_NAr) reaction (making six in total with the NKR). These reactions covered a range of physical parameters, particularly the important aspects of second-order and heterogeneous reactions, and all were related to previous AstraZeneca projects to ensure they were of relevance to potential pharmaceutical manufacture. They had also been studied at AstraZeneca in an unrelated stop-flow microwave reactor,[10] which provided a useful comparison. Each reaction is discussed separately below. In addition, some energy consumption data is also presented.

Results and Discussion

Ortho Claisen Rearrangement. We started with the simple, high-temperature, unimolecular ortho Claisen rearrangement[11] of **2** to **3** (Scheme 1) using the conditions previously employed.[10] Thus, the reaction mixture was diluted 2:1 wt/volume with 1,2-dichlorobenzene (DCB) even though this was probably not needed for mobility in the FlowSYNTH. The reaction settings required 195 °C for 12 min for 95% conversion, which equated to a flow rate of 16.7 mL/min. After tuning, the actual pump settings of 40% with a 20% stroke rate were found to give a flow rate of 15.0 mL/min, which equated to a residence time of 13.3 min, slightly longer than required, but well within the scope of the previously tested conditions.[10] The exit temperature on the chiller unit was set to 80 °C to mimic the previous study.

The entire system was flushed with fresh DCB for 30 min whilst the chamber was heated to 195 °C. The reaction mixture

Scheme 1



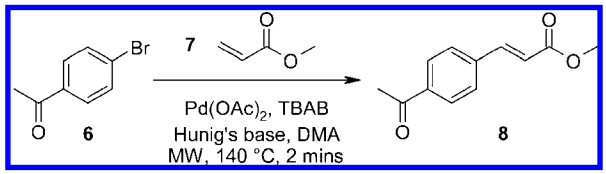
was then introduced, but samples were not taken until one column volume had passed (200 mL, 13.3 min), due to slight dilution from some unavoidable back-mixing in the reaction chamber despite assumed plug flow characteristics. Analysis at 10-min intervals over 40 min showed stable and complete reaction conversion of *O*-allyl ether **2** to *C*-allyl ether product **3**, with no degradation to 1-naphthol (**1**), which can occur under over-harsh conditions. Complete conversion was a benefit of the slightly longer reaction time, although a few minor impurities were also detected, presumably from over-reaction, but the overall quality was very similar to that from the previous result.[10] The flow rate was very stable, with no blockages occurring during the >1 h run, and the production rate was 3.0 mol/h at these dilutions.

Naphthofuran Formation. The bulk of the reaction mixture from the previous reaction (crude **3**) was used directly in the formation of naphthofuran (**4**) (Scheme 1), which had required only 10 min at 100 °C in a large-scale microwave *batch* reactor.[12] Two volumes of formic acid (based on input **2**) were added to the crude reaction mixture containing **3**. Unfortunately, this resulted in the formation of two phases, almost certainly due to the presence of the DCB, since formic acid and neat **3** had been a single phase in all previous preparations. Although dual feed of two liquid phases is in principle possible in the FlowSYNTH, separation of the phases in the vertical column was likely to occur. Separation of these phases was thought to have been the cause of the unsuccessful direct conversion of **2** into **4** in the stop-flow reactor preparation.[10] An alternative solution to the problem was found in this case by adding one volume of *N*,*N*-dimethylacetamide (DMA) (relative to **2**) to the reaction mixture of crude **3**, which then formed a single phase with DCB and formic acid (**Caution:** heat of mixing noted on 1 L scale).

A residence time of 10 min required a flow rate of 20 mL/min. After priming of the system with a formic acid/DMA solution and heating to 100 °C, one column volume was allowed to pass before samples were taken at 10-min intervals over a 40-min period. Once again, stable and complete conversion of starting material **3** to product **4** was observed. An impurity of up to 16% was detected, but it should be noted that the reaction mixture had not been purified at the previous stage, and this

(9) Lloyd-Jones, G. C.; Moseley, J. D.; J. S. Renny, J. S. *Synthesis* **2008**, 661–689.
(10) Moseley, J. D.; Woodman, E. K. *Org. Process Res. Dev.* **2008**, *12*, 967–981.
(11) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939–3002.
(12) Marafie, J. A.; Moseley, J. D. Unpublished results.

Scheme 2



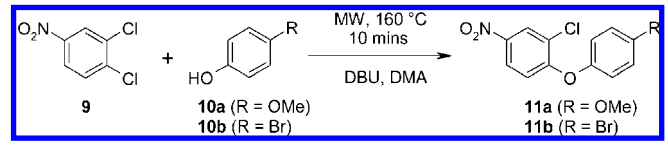
impurity may have been an artifact of storage during transport before analysis could take place. Significantly, no acid-catalysed breakdown back to **1** was detected because the previous reaction had left no unconverted *O*-allyl ether (**2**). Overall, product quality was similar to that prepared previously, but with some different impurities. Significantly, the FlowSYNTH had performed well again and without error to provide a production rate of 1.3 mol/h for a slightly more dilute process performed at a moderate temperature.

Alkylation Reaction. The preparation of **2** for the foregoing studies had been achieved by the alkylation of 1-naphthol (**1**) with isobutenyl chloride (**5**) (Scheme 1) at 125 °C over 10 min on a 2-L scale in a large-scale microwave batch reactor.[12] The reaction mixture was heavily loaded with K_2CO_3 to give an ~16 wt %/volume slurry of the insoluble inorganic base in NMP. However, the reaction temperature of 125 °C was well below the bp of NMP (202 °C), and the volatile isobutenyl chloride (bp 77 °C) was expected to react sufficiently quickly that the system could be run without the back pressure regulator in operation; this would permit a slurry to be pumped into the reactor. However, although the well-stirred reaction mixture appeared to be drawn up by the pump initially, the reaction could not be attempted because the pump became blocked before the mixture could pass through the microwave chamber. This was due to the inability of the pump to handle such a heavy slurry, rather than the microwave reactor itself, which remains untested for such reactions in our hands.

Heck Reaction. A model Heck reaction between 4-bromoacetophenone (**6**) and methyl acrylate (**7**) to give Heck adduct **8** was investigated next (Scheme 2). This had been studied previously where conditions were typically 140 °C for 1 min which gave >95% conversion.[10] However, a considerable overshoot in temperature to ~150 °C had been unavoidable in that case; thus, to compensate, the planned parameters for this study were 140 °C for 2 min (Heck #1). The reaction used a loading of only 0.1 mol % $Pd(OAc)_2$ solubilised in DMA which gave a completely homogeneous reaction mixture, although the byproduct HBr salt of the Hunig's base was crystalline. The methyl acrylate provided a volatile component (bp 80 °C) which was expected to react before it developed pressure in the microwave chamber.

A solution of the homogeneous reaction solution was made up as for the other reaction trials, and the FlowSYNTH was primed with fresh DMA and heated to 140 °C. The residence time of just 2 min required a flow rate of 100 mL/min, which consumed the stock solution of 2.5 L (1 mol) in less than 30 min. Unfortunately however, the conversion during stable flow was only 55%. This was not entirely surprising as this reaction was known from our earlier studies to be capricious; it behaves as if the reaction vessel needs to be conditioned before good conversions can be achieved.[10] In this case, the reactor consumed all the available starting materials before high

Scheme 3



conversions could be achieved. In this respect, the FlowSYNTH suffers from its high potential, in that it can process very large volumes at high flow rates, but this requires large quantities of sample for initial trials.

The incompletely converted reaction mixture was then recirculated through the reactor at a flow rate of 20 mL/min to give a residence time of 10 min (Heck #2). The conversion now increased to ~75%, still somewhat disappointing, but conversion may have been limited by loss of volatile methyl acrylate between the reaction cycles since only a slight excess had been used. Microwave tube tests, which are normally reliable for this reaction, performed on this reaction mixture some days later also gave 75% conversion, indicating the reaction mixture may have been compromised. Even so, the standard workup procedure by aqueous drown-out with dilute HCl gave an isolated yield of 60% and excellent quality from this mixture.

High back pressure had been noted during these runs, and when the reaction chamber was opened, some residues of Pd-black were found inside, along with large white crystals of the HBr salt of Hunig's base which had crystallised on cooling. Pd-black residues in this reaction are often indicative that the reaction has not "initiated" properly; a Pd mirror often forms when it is performing well, although it must be conceded this would probably interfere with prolonged performance. Assuming that correct initiation of the reaction could be achieved to give >90% conversion during a longer run, a flow rate of 100 mL/min would give a production rate of 2.4 mol/h, or at 20 mL/min, 0.47 mol/h.

Nucleophilic Aromatic Substitution Reaction (S_NAr). Another two-component reaction using K_2CO_3 that has been studied at AstraZeneca is the S_NAr reaction of 3,4-dichloronitrobenzene (**9**) with substituted phenols (**10**) to give the substituted diaryl ethers (**11**) (Scheme 3). This requires typically 150 °C for 10 min in a microwave batch reactor with a K_2CO_3 loading of ~10 wt %/volume as a slurry in DMA.[12] Our earlier experience with the alkylation reaction indicated this was not going to be successful using K_2CO_3. We therefore decided to change over to a soluble organic base (1,8-diazabicyclo[5.4.0]undec-7-ene, DBU) which Milestone had used successfully in a recent alkoxycarbonylation reaction.[13]

A homogeneous solution of all three components could be prepared and this was trialled in the FlowSYNTH with a flow rate of 20 mL/min to achieve a 10-min residence time. This gave slightly incomplete reaction for the model system (R = OMe, **10a**/**11a**), so the temperature was increased to 160 °C. With this minor adjustment, the reaction was performed for ~50 min at 160 °C with a 10-min residence time. Multiple samples taken during this time showed consistent reaction conversion of >98%. Several 50 mL aliquots of reaction mixture were then

(13) Iannelli, M.; Bergamelli, F.; Kormos, C. M.; Paravisi, S.; Leadbeater, N. E. *Org. Process Res. Dev.* **2009**, *13*, 634–637.

Table 1. **Summary of reaction data with energy usage**

reaction	temp (°C)	residence time (mins)	flow rate (mL/min)	flow rate (L/h)	concentration (L/kg)	productivity (mol/h)	energy usage (kW·h/mol)
naphthofuran	100	10.0	20	1.2	3.5	1.3	0.56
Heck #1[a]	140	2.0	100	6.0	10	2.4	0.38
Heck #2[b]	140	10.0	20	1.2	10	0.47	1.49
S_NAr	160	10.0	20	1.2	8	0.65	0.31
Claisen	195	13.3	15	0.9	0.5	3.0	0.25
NKR[c]	200	10.0	20	1.2	10	0.53	nd[d]
NKR[c]	200	10.0	20	1.2	4	1.3	nd[d]

[a] 140 °C for 2.0 min. [b] 140 °C for 10 min. [c] Data from text of ref 4a. [d] nd = not determined.

worked up by aqueous drown-out into a dilute KCl/HCl solution (HCl to remove excess DBU) which gave high yields (95%) of product **11a** with >97% purity with only ~1.5% **9** remaining, and no residual phenol **10a** or DBU. The reaction conditions were repeated for the bromo analogue (R = Br, **10b/11b**) which gave similar results at the same temperature and flow rate, and isolated product quality of 95% with 1.5% of **10b** remaining but <1% of **9**. These reaction conditions have also been applied to a wider range of substituents in both stop-flow and batch microwave reactors.[14] Overall, the FlowSYNTH achieved a production rate of 0.65 mol/h for this S_NAr reaction, in which DBU was successfully substituted for K_2CO_3 to make the microwave-heated continuous flow process viable.

Summary and Energy Consumption Data. A summary of key parameters for all reactions, including the NKR[4a] but omitting the unsuccessful alkylation reaction, is collected in Table 1. Temperature and residence time are given for ease of comparison to standard batch conditions. The flow rates are given in mL/min (the reactor setting) but also in the more meaningful L/h. From this it can be seen that a flow rate of ~1 L/h is common across a range of temperatures (100−200 °C) and concentrations (10 L/kg down to no dilution) for a typical 10-min reaction time. For fast reactions (e.g., the Heck reaction at 140 °C for 2 min), much higher flow rates are achievable. The productivity is also given, expressed here in mol/h of input material, which has the advantage of ignoring molecular mass differences, the yield and the efficiency of the isolation procedure (although in practical cases these would have to be considered). Expressed in this way, an easy comparison is possible between the reactions. Unsurprisingly, productivity is highest for the most concentrated reactions (Claisen, naphthofuran, NKR) and the fast reaction (Heck #1) at 1−3 mol/h, but is lower at ~0.5 mol/h for the other three examples at more typical reaction concentrations of 8−10 L/kg.

We also noted the energy consumption for five sets of conditions using a commercial watt meter. The energy was measured for a fixed period of stable flow when the reaction was at the desired temperature, and the figures extrapolated to 1 h to give a figure in kJ/h. The priming period was excluded from this time. The energy measured included only the microwave reactor and the agitator drive, but not the pump, chiller unit, or computer; although these are required for effective use, they were on separate leads so could not be measured concurrently. Therefore the figures would be somewhat larger if the ancillary units were included, so these results can only be used in a relative sense, but they provide some indication of energy consumption for these reactions.

Most reactions were monitored for 30−40 min of stable flow. The energy usage proved to be remarkably linear for all five reactions when presented in graphical form, such that even for the first Heck reaction, where only a 10-min period could to be used, we are confident that the energy consumption was representative. This should in any case be expected if the reactor is heating a consistent reaction mixture flowing through at a steady rate. Using the productivity figures (mol/h), we determined the energy usage expressed in kW·h/mol (Table 1). This shows a roughly inverse trend for most reactions i.e. the highest productivities tend to have the lowest energy use per mol. This can be explained because these reactions are either very concentrated (Claisen, naphthofuran) or fast (Heck #1). The S_NAr reaction proved to be quite efficient in energy terms per mol, despite being more dilute, but this is probably due to the high polarity of the solvent (DMA) and the reaction components coupling well with microwaves to give efficient heating. The more concentrated naphthofuran synthesis, using lower-polarity materials and solvents, was relatively less efficient per mol, indicating that the microwave had to work harder even to achieve a lower level of heating at the same flow rate. The first Heck reaction, again using high polarity DMA and reaction components, was efficient for a 2-min residence time, but on increasing the residence time to 10 min (Heck #2, one-fifth of the flow rate) the efficiency per mol increased 4-fold, roughly in line with expectation. Overall, this tends to indicate that the energy usage is most dependent on the flow rate and ease of heating a given reaction mixture (polar vs nonpolar); the temperature required is less of a factor.

Conclusions

In summary, the FlowSYNTH provided potentially successful manufacture for five out of six reactions investigated where homogeneous reactions solutions could be achieved. Although the FlowSYNTH can process slurries when operating below the solvent boiling point, this proved not to be possible in the one case attempted here. However, production rates of between 0.5 and 3.0 mol/h (1−6 L/h) have been achieved with minimal redevelopment of the chemistry from tube scale, as noted in Table 1. Assuming 24 h of operation, this would represent up to 72 mol/day, or 144 L/day. For a typical 10 wt %/vol pharmaceutical process running at the maximum flow rate of 12 L/h, this would result in nearly 30 kg of material processed per day in one unit. This represents a substantial manufacturing

(14) Marafie, J. A.; Moseley, J. D. *Org. Biomol. Chem.* **2010**, *8*, 2219–2227.
(15) Moseley, J. D.; Woodman, E. K. *Energy Fuels* **2009**, *23*, 5438–5447.

capability equivalent to pilot-plant scale, with the additional advantages of continuous processing over batch processing. This should be of interest to process chemists operating at this scale. In addition, the energy usage measurements have also been taken and compared.

Experimental Section

Full experimental details, including general methods, HPLC conditions, and physical and spectroscopic details for all compounds prepared, have been given previously in this journal for the Claisen, Heck, and naphthofuran formation reactions,[10] and for the NKR.[4a] Details for the homogeneous S_NAr reaction[14] are given below. Conversions reported are based on HPLC data in most cases, and for all isolated samples, which provides further confirmation of reaction success. TLC data were only used for the initial Claisen reaction where the product **3** was used directly in the next step without purification.

General Procedure for Use of the FlowSYNTH. The FlowSYNTH is primed with neat reaction solvent and the flow rate calibrated to ensure the required residence time is achieved. The flow rate is adjusted from the pump settings operating on both pump speed and stroke volume to achieve the desired flow rate. As a general consideration, it is opportune to set low stroke volumes and high pump speed for relatively high-viscosity reaction mixtures while high stroke volumes and low pump speeds better suit low-viscosity systems. The back pressure regulator is set at a pressure to largely counterbalance the vapour pressure generated by the reaction mixture at the temperature of operation. The agitator is typically set to 20−25% of its maximum speed. Higher speeds may be required for temperatures above 180 °C and high flow rates to ensure a more efficient heat exchange during the cooling step. The product cooler is set typically to 30 °C, but this may be much higher if required (e.g., 80−90 °C to avoid product crystallising in the outlet line). Once the reaction solvent is flowing through at the desired temperature and flow rate, the inlet tube can be transferred to the reaction mixture to begin processing. Typically, 700−800 mL is a sensible minimum volume for useful trials although 400−500 mL can be used as the absolute minimum. Larger volumes present no issues. The first column volume from any given run should be ignored since some inevitable back-mixing of the priming solvent due to imperfect plug-flow will have occurred; stable reaction conversion should be expected from the second column volume onwards. Energy usage (kW·h) was measured using a Gossen-Metrawatt SECUTEST SIII instrument, and only the microwave heating and agitator functions of the FlowSYNTH were measured.

S_NAr Reaction; Preparation of 2-Chloro-1-(4-methoxyphenoxy)-4-nitrobenzene (11a). DCNB (**9**) (125 g, 0.65 mol), 4-methoxyphenol (**10a**) (97 g, 0.78 mol, 1.2 equiv) and DBU (149 mL, 0.97 mol, 1.5 equiv) were dissolved in DMA (1000 mL) to give an orange-coloured homogeneous solution. This solution was processed through the FlowSYNTH at a stable temperature of 160 °C at 20 mL/min (10-min residence time). Aliquots of reaction solution (typically 50 mL) were worked up by adding an equal volume of KCl/HCl stock solution (made up from hydrochloric acid (36 wt %, 127 mL) and potassium chloride (100 g) dissolved in 1 L of water), added dropwise with stirring at 0 °C. A dense, brown precipitate was formed which was isolated by vacuum filtration, washed with hydrochloric acid and then water, and dried to yield the title compound as a light-brown solid (7.1 g, 94% on 50-mL scale). HPLC (RT 4.87 min, 98.7%); ^{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).

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