Organic Process Research & Development **2008,** *12,* 1007–1011

Continuous Flow Microwave-Assisted Reaction Optimization and Scale-Up Using Fluorous Spacer Technology

Otman Benali,* Martyn Deal,† Elizabeth Farrant,‡ David Tapolczay,§ and Rob Wheeler

GlaxoSmithKline Pharmaceuticals, Technology Development, New Frontiers Science Park (North), Third Avenue, Harlow, Essex CM19 5AW, U.K.

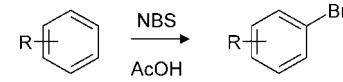
Abstract:

Microwave-assisted organic synthesis in a laboratory-scale monomodal microwave reactor is investigated for continuous flow applications using fluorous spacer technology. The benchtop continuous flow microwave described allows sequential processing of multiple plugs using small amounts of reagents for reaction optimization, scale-up and array synthesis. The system features online monitoring of temperature, pressure and microwave power. Several different reactions have been scaled up, including a Suzuki−Miyaura cross-coupling reaction and nucleophilic substitutions. In all cases it was possible to optimize the reaction conditions on a small scale (∼300 μL processing volume), and achieve similar conversions on an intermediate scale (∼30 mL), offering the potential for further scale-up without modifying the optimized conditions (direct scalability) producing similar isolated yields in the C−C bond formation reaction.

Introduction

In recent years the use of emerging technologies such as microwave heating[1] and microreactors for organic synthesis[2] has attracted considerable interest, particularly within the pharmaceutical and fine chemical communities where the benefits associated with rate enhancement, higher yields and greater product selectivity have been reported. One problem with existing microwave technology is that it is currently limited in scale by the size of the reactor available, which is in turn limited by safety considerations and the penetration depth being the limiting factor on scale-up. The combination therefore of microwave irradiation with a capillary-based flow reactor in which chemical synthesis can be performed offers the possibility of realizing many of the individual advantages associated with these two techniques in one integrated system[1a,b,3] and provides a route to a scalable system not limited by the size of the reactor. One of the problems associated with attempting to scale up reactions under continuous flow microwave conditions is that optimized batch conditions are not always transferable to flow, necessitating a further reaction reoptimization step. The use of small discrete plugs is not possible due to the dilution that occurs when reaction plugs disperse into the reaction solvent used to separate different reaction mixtures. Large amounts of material are thus needed to achieve the steady-state concentrations required to find the optimized conditions for a particular reaction. This shortcoming can be overcome by exploiting the use of the immiscible, low microwave absorber fluorinated spacer[4] to form discrete plugs under microwave irradiation.

Scheme 1. **Bromination reaction**



1 **2**

In this present study, a fluorinated solvent was used as an inert immiscible spacer, to separate between different reaction plugs, for reaction optimization, array synthesis and scale-up under continuous flow microwave-assisted organic synthesis conditions.

Experimental Section

Materials. All reagents and solvents, obtained from commercial sources, were of analytical grade and were used without further purification. NMR spectra were recorded on a Bruker Avance Ultrashield 400 using tetramethylsilane (TMS) as an internal standard. LC/MS analyses were carried out on an Agilent Series 1100 HPLC coupled to a Waters Micromass ZQ mass spectrometer.

* Author for correspondence. 29 Station Rd., Shepreth, Cambridgeshire SG8 6GB, U.K. Telephone: +44(0) 7952394118. E-mail: otman.benali@uniqsis.com.

† Radleys.

‡ Pfizer Limited.

§ Sigma Aldrich.

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10.1021/op700225u CCC: $40.75
Published on Web 08/22/2008

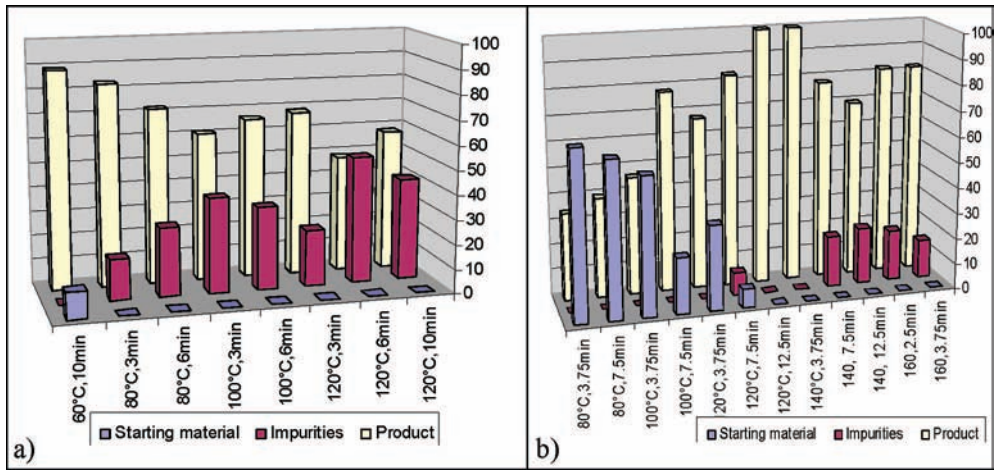


Figure 1. **Optimization of the bromination reaction in (a) batch and (b) flow under microwave irradiation.**

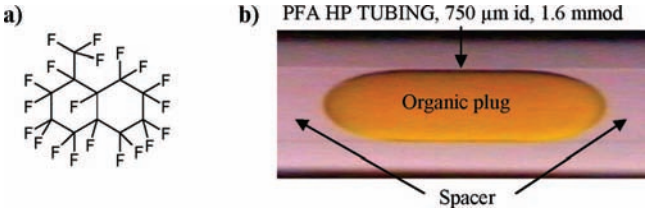


Figure 2. **(a) Perfluromethyldecalin (PFMD). (b) Acrylic acid derivative/DMF contained within spacer.**

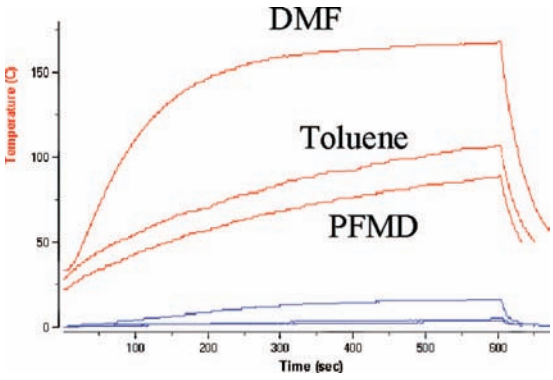
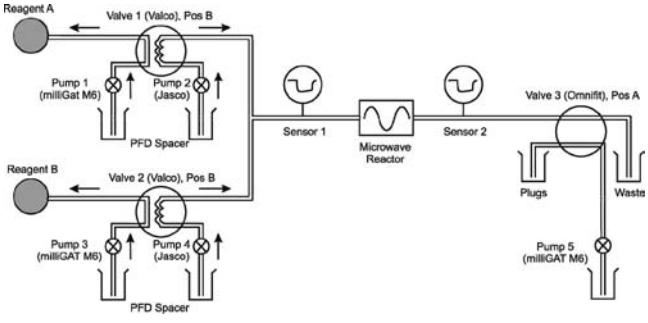


Figure 3. **Batch comparison between microwave absorption of DMF and PFMD. One milliliter of solvent microwaved at 50 W for 10 min. Temperature was measured using the microwave built-infrared sensor.**

Scheme 2. **Schematic diagram of the flow system coupled to a microwave instrument**



Results and Discussion

In the course of a drug discovery programme, a large amount of intermediate **2** (Scheme 1) was required. The bromination reaction[5] was rapidly optimized by performing a series of reactions in the CEM-Explorer[6] (Figure 1a). The optimal batch conditions were then transferred to the commercial flow microwave. The Voyager-CF consists of a four-channel LC pump connected to a helically coiled high-purity perfluoro-alkoxy alkane (HP PFA) tube of 750 μm inner diameter (i.d.) and 1.6 mm outer diameter (o.d.) (~3 mL volume), mounted on a PTFE[7] frame within the cavity of the microwave which is capable of delivering 0−300 W microwave power at 2.45 GHz. When the optimized conditions (60 °C for 10 min) were used in the flow microwave, only 34% of the desired product was obtained (Scheme 2).

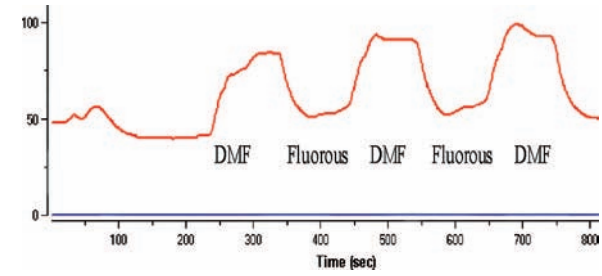


Figure 4. **500 μL DMF sandwiched between 500 μL PFMD (flow rate 200 μL/min).**

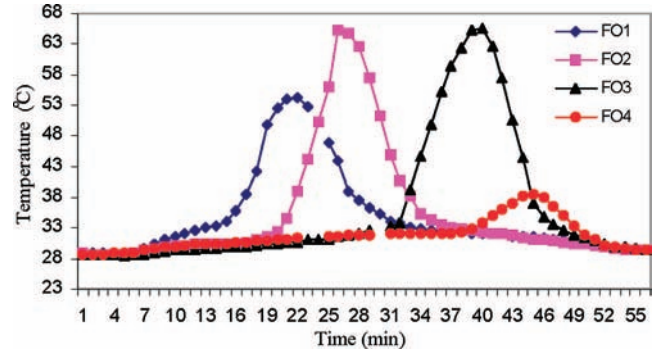


Figure 5. **Stable temperature achieved with monitoring at four points along the reactor; 5-mL reaction plug of DMF, 500 μL PFMD at 0.5 mL/min, power 50 W.**

(5) Srinivasan, S. P.; Gnanapragasam, N. S. *J. Ind. Chem. Soc.* **1983**, *60*, 953.
(6) CEM-Explorer and Voyager-CF are commercially available from CEM Corporation.
(7) Registered trade name of Dupont.

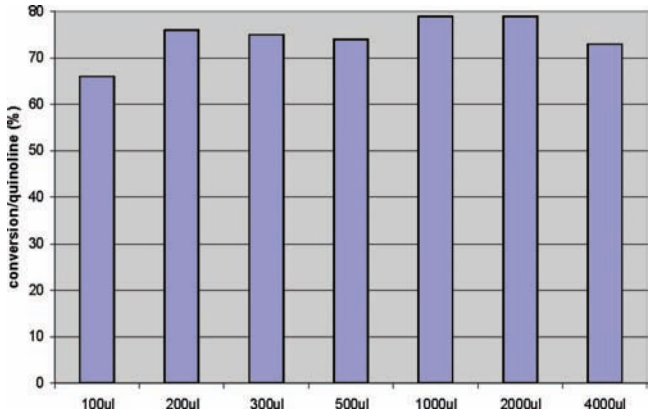


Figure 6. **Comparison of different plug sizes. Power 60 W, flow rate 260 μL/min (~5 min residence time), 100 psi back pressure using an Upchurch back pressure regulator (BPR).**

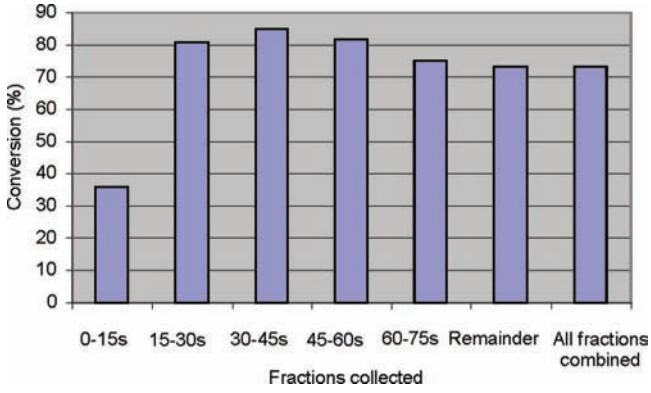


Figure 7. **Plug analysis. Power 60 W, flow rate 260 μL/min (~5 min residence time), 100 psi back pressure.**

The reaction therefore required reoptimization under flow conditions. The Voyager-CF reactor was filled with reaction solvent, and the temperature was allowed to stabilize with neat solvent. The system was then filled with reactants and pumped for 10 min at the required flow rate in order to reach steady-state conditions. The product was then collected for 2−4 min for analysis. Optimized conditions in this case were 300 W, 120 °C, 0.65 mL/min. The system was then run continuously for approximately 1 h to process 37 mL. Isolated yield of the bromination product was 1.4 g (89% yield, 91% purity).

Although the reaction was successfully optimized, the requirement to achieve steady-state conditions is time-consuming and wasteful of starting materials and outweighs many of the synthetic advantages of microwave-mediated synthesis.

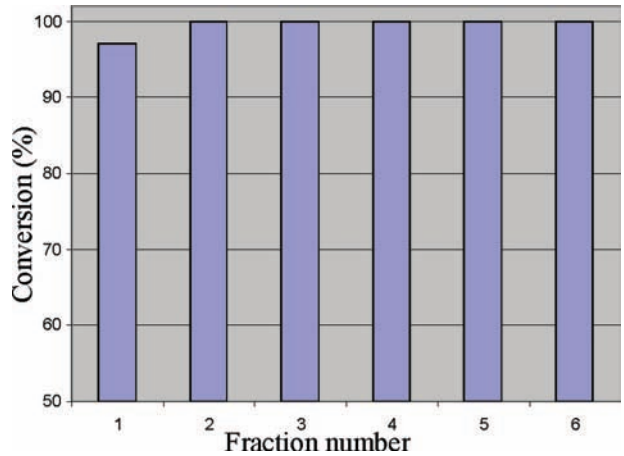


Figure 8. **LC/MS analysis of the 30 mL plug every 5 min.**

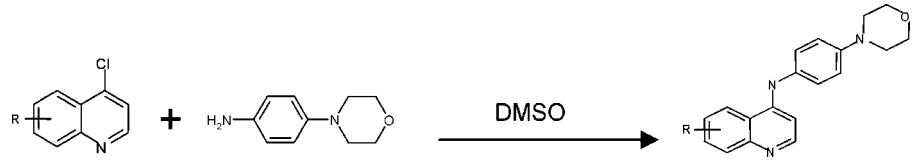
Table 1. **Results of bromide array testing (reaction with the phenylboronic acid derivative)**

sample	bromide	flow/batch	% conversion
1	phenyl bromide	flow	100
1	phenyl bromide	batch	100
2	4-bromobenzaldehyde	flow	91
2	4-bromobenzaldehyde	batch	100
3	4-bromoanisole	flow	96
3	4-bromoanisole	batch	100
4	2-bromometaxylene	flow	100
4	2-bromometaxylene	batch	49
5	4-bromonitrobenzene	flow	86
5	4-bromonitrobenzene	batch	100

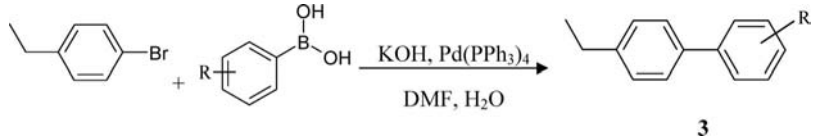
To improve reaction optimization protocols the system was reconfigured to allow for the use of an inert and immiscible spacer solvent, perfluoromethyldecalin (PFMD) (Figure 2a). This modification enabled the use of small reaction volumes and avoids plug dilution due to dispersion. In addition, due to the good wetting properties of the fluorous carrier solvent and the fluorinated polymer walls, the reaction plug is entirely surrounded by the spacer, thus eliminating contamination of the system by reactants and the need for system washing to avoid carryover from reaction to reaction. Figure 2b shows 3-(3-nitro-4-tetrahydro-1*H*-pyrrol-1-ylphenyl) acrylic acid, dissolved in DMF, surrounded by PFMD.

The behavior of the PFMD under microwave irradiation was investigated. Under batch conditions, PFMD was compared to DMF (a high absorber) and toluene (a low absorber). Each

Scheme 3. **Nucleophilic substitution reaction**



Scheme 4. **C−C coupling**



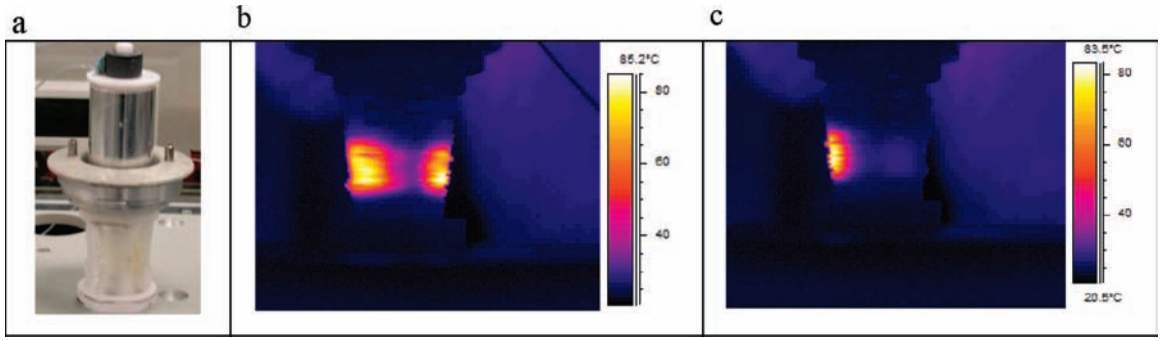


Figure 9. **In the CEM microwave, under stopped flow conditions, 800 μL DMF plug contained between PFMD spacer in a PFA HP 20 ft, 750 μm i.d. 1.6 mm o.d. tubing. Power 10 W for 1 min. Pictures (b) and (c) are thermal images of different sides of the reactor (a).**

solvent was irradiated for 10 min and the temperature monitored. As shown in Figure 3, PFMD is a low absorber of microwave energy.

To investigate the behavior of the spacer in the flowing system, a fiber-optic contact probe (CEM) was located at the midpoint of the reactor on the surface of the tubing; 500 μL plugs of DMF were flowed through the system separated by fluorous spacer. The probe temperature trace clearly showed increased heating of DMF relative to PFMD (Figure 4).

To track the plug as it proceeds through the reactor a four-fiber-optic sensor allowing multiposition monitoring was used. The probes were located near the inlet of the reactor (*FO1*), in the middle (*FO2* and *FO3*) and at the outlet (*FO4*). The probes recorded an increase in temperature as the organic plug passes by each sensor reaching a stable temperature (*FO2* and *FO3*), and the last sensor showed a quick decrease returning to room temperature without the need for active cooling of the reaction mixture when exiting the reactor (Figure 5).

The system was then tested using the displacement of an aromatic chloride by a secondary amine (Scheme 3). The HP PFA tubing described earlier (1.6 mm o.d.), was substituted with a custom-made HP PFA 750 μm i.d., 3.2 mm o.d. in order to increase the temperature and pressure rating of the reactor.

First, the scalability of the reaction was tested. Plugs of different sizes were irradiated and analyzed for conversion to the desired product. The results showed similar conversions for plug volumes between 200 μL and 4000 μL (Figure 6). This indicates that conditions identified from optimization reactions carried out on plugs of 200 μL can successfully be applied to plug volumes of 4000 μL, reducing the amount of material needed for an optimization sequence.

To compare homogeneity within a plug, the composition of a 4000 μL plug was analyzed every 15 s and compared to the remainder of the plug. Analysis of the fractions showed similar conversions after the first 100 μL (Figure 7). The lower conversion observed for the first 100 μL fraction could be explained by a slight delay in reaching the set temperature caused by heat dissipation into the coil and the environment within the cavity.[8]

A Suzuki−Miyaura cross-coupling reaction[9] (Scheme 4) was used as an example for reaction optimization, scale-up and array synthesis.

Reaction conditions were optimized using design of experiments methodology (DoE)[10] on a series of 500 μL plugs, and these conditions were applied to 200, 300, 500, 1000 and 2000 μL plugs. Conversions were similar for plugs with a volume of 300 μL and greater but were lower for a 200 μL plug.

As before, the 2000 μL plug was analyzed by fractions showing uniform conversions except the first 100 μL fraction as shown for the 4-chloroquinoline displacement. Liquid−liquid extraction and purification through a small plug of silica gel of the 2 mL plug yielded the pure product (60% yield).

A comparison with conventional heating in a flowing system, using the developed in-house heating block was carried out. The reactor, heating block in this case, consisted of an aluminium cylinder sitting on an IKA hotplate stirrer surrounded with 6.7 mL of HP PFA fluoropolymer tubing 750 μm i.d. and 1.6 o.d. Optimization studies revealed that 100 °C for 15 min reaction time gave complete conversion. The yield obtained was 40% under these conditions.

In order to scale up further the previously optimized conditions were used under continuous flow. A two-channel syringe pump (developed in collaboration with Syrris Ltd.[11]) was used to continuously pump the solutions. An automated BPR (commercially available from Tescom Corp.[12]) was used to maintain the system at 250 psi, connected to a pressure sensor (commercially available from Entran[13]), located at the inlet of the reactor.

The reactor ran continuously for 35, min processing a total volume of 30 mL of reaction mixture. The mixture was analyzed every 5 min by LC/MS which revealed similar conversion to product throughout the course of the reaction (Figure 8) although again the results showed less conversion for the first 5 min. The output is 0.5 g/h (2.6 mmol/h), and the overall yield was 58% which is consistent both with the result obtained during the optimization experiment (60%) and with results obtained when performing the reaction in a batch microwave reactor (55%).

We prepared a demonstration array of compounds using the fluorous spacer technology/MW-irradiation with the optimized conditions obtained above to afford the biaryl library in excellent conversion. Flow and batch results were similar (Table 1).

In conclusion, we have described a strategy and methodology for the optimization and scale-up of microwave-mediated reactions by using scalable flow reactors. Some issues remain, however. The fluoropolymer tubing is not robust and can fail, particularly when used in continuous flow mode without the PFMD carrier solvent, as in some cases when palladium black

sticks to its surface and causes the tube to overheat and break. We are looking to alternatives including fused silica capillary tubing.

In addition, infrared pictures (infrared camera Thermacam SC 3000) of the reactor coil indicate inhomogeneous heating of the reactor coil.

The reactor shown in the picture (Figure 9a) was irradiated with microwaves for the specified time then placed in front of the camera to record videos. Hot spots were observed in stopped flow conditions (Figure 9b and c). Work is underway to develop a new cavity which allows more homogeneous application of microwave energy.

Conclusions

In summary, we have described the first example of reaction optimization using the fluorous spacer technology under microwave conditions which marks a new direction for microwave reaction scale-up. This strategy minimizes the amount of solvent and material wasted during the screening of reaction parameters and allows direct scale-up of the optimized reaction conditions and the ability to make small arrays.

Acknowledgment

This work was supported by GlaxoSmithKline. We thank Roger Hutton for his valuable help to use the IR camera for thermal imaging.

Received for review October 7, 2007.

OP700225U

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