Multiple Microcapillary Reactor for Organic Synthesis

Christian H. Hornung,[†] Bart Hallmark,[†] Marcus Baumann,[‡] Ian R. Baxendale,[‡] Steven V. Ley,[‡] Patrick Hester,[§] Patrick Clayton,[§] and Malcolm R. Mackley*,[†]

Department of Chemical Engineering and Biotechnology, University of Cambridge, Pembroke St., Cambridge, CB2 3RA, U.K., Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, U.K., and Lamina Dielectrics Ltd., Daux Road, Billingshurst, RH14 9SJ, U.K.

This paper presents process characteristics and proof of concept reactions for a newly developed microreactor system, termed the Cambridge Disc Microreactor (CDM), using plastic microcapillary flow discs (MFDs). These flat reactor discs were constructed from a flexible, temperature resilient, solvent resistant fluoropolymer microcapillary film (MCF) comprising 10 parallel capillary channels with mean hydraulic diameters typically between 150 and 400 μm. The MFDs were heated inside the microreactor via conductive heat transfer from two heated surfaces, which were in contact with the flat outer surfaces of the disc. This allowed continuous flow processing of liquid phase reactions through the reactor at elevated temperatures and pressures at a precisely controlled residence time. The process characteristics of the reactor system were established experimentally by investigating the hydraulic response and the temperature profile or modeled analytically such that the residence time characteristics inside the device could be predicted. A series of organic chemical reactions, namely electrophilic fluorination and the formation of various mono- and bicyclic heteroaromatic compounds, were conducted in the system at temperatures between 110 and 120 C.

Introduction

The recent emergence of integrated reactor technology for laboratory scale continuous flow processing of liquid phase chemistry presents an interesting alternative to classical batch processing in a glass apparatus.[1−7] Using micro- and mesofluidic devices, these reactor systems give the opportunity to carry out continuous or semibatch reactions for small quantities of product in a fully confined and controlled environment.[8,9] Current microreactor technologies include chip-based reactors, individual or bundled capillaries, micromixer units, microfalling films, microbubble columns, liquid−liquid extractors, or lab-scale packed bed assemblies.[10−12] These reactors can be made from a variety of materials, including glass, metal, silica, polymers, and ceramics. A key benefit of capillary based flow reactors over classical batch processing is the ability to increase the reactor throughput by a simple numbering-up of the basic flow-components, as opposed to a classical scale-up approach, which often requires several design steps, ranging from normal laboratory scale through a pilot-plant stage to the final production scale. This approach can be viable for various synthetic applications with small production volumes such as pharmaceuticals or specialty chemicals. Currently, many of the laboratory scale flow chemistry systems are only capable of operating with a small number of reactor channels making numbering-up to small production scale impractical. These impracticalities stem from some of the reactor designs having a relatively large physical footprint in comparison to their reactor volume, from complex or inefficient thermal control and from their reliance on expensive reactor cartridges, requiring regular replacement and escalating production costs. Reactor systems circumventing these restrictions would be able to bridge the gap between laboratory and small-scale production, allowing for quick development of new reactions and shortening the lead-time between discovery and manufacture.

This paper describes a novel multichannel microreactor that can be used for a broad range of liquid phase reactions in organic synthesis. The reactor system shows good potential for process scale-up due to the presence of several microchannels per cartridge (10 at present) and the simplicity of arranging a number of these devices to function in parallel. The reactor cartridges are made from a thermoplastic film, which is manufactured by a continuous extrusion process.[13] The manufacturing costs for the cartridges are low, leading to the potential of using these microreactor devices as disposable units. Hence, issues relating to cleaning and sterilization of microfluidic components are eliminated, removing what is usually a time-consuming, costly, and complex procedure. In this paper, the design of the apparatus, its process characteristics, and the performance during three chemically different reactions are described.

Cambridge Disc Microreactor System

The Cambridge Disc Microreactor (CDM)[14] system uses disposable disc-shaped plastic cartridges containing multiple microchannels with diameters of typically 150−400 μm and with lengths of up to typically 30 m. These reactor cartridges, termed microcapillary flow discs (MFDs), can be readily heated up to temperatures of 150 C. They are fabricated from a flat polymer film in which bundles of parallel capillaries are embedded; this structure is termed a microcapillary film (MCF) and is manufactured by an extrusion process suitable for a series of different thermoplastic materials. In this extrusion process, a polymer melt is extruded over an array of gas injectors that are connected to air at ambient conditions, placed near the exit of a rectangular extrusion die.[13] The molten extrudate, containing an array of continuous, linear capillaries is quenched and solidified either by passing over a set of chilled rollers (e.g., in the case of polyethylene) or through a water bath (e.g., in the case of fuorinated polymers). For this work, MCFs with a mean capillary diameter of 200 μm were fabricated. The thickness of such a film is 0.5 mm, and its width is 4 mm. For these capillary

* To whom correspondence should be addressed. E-mail: mrm5@cam.ac.uk.
[†] Department of Chemical Engineering and Biotechnology, University of Cambridge.
[‡] Department of Chemistry, University of Cambridge.
[§] Lamina Dielectrics Ltd.

10.1021/ie901674h
Published on Web 04/09/2010

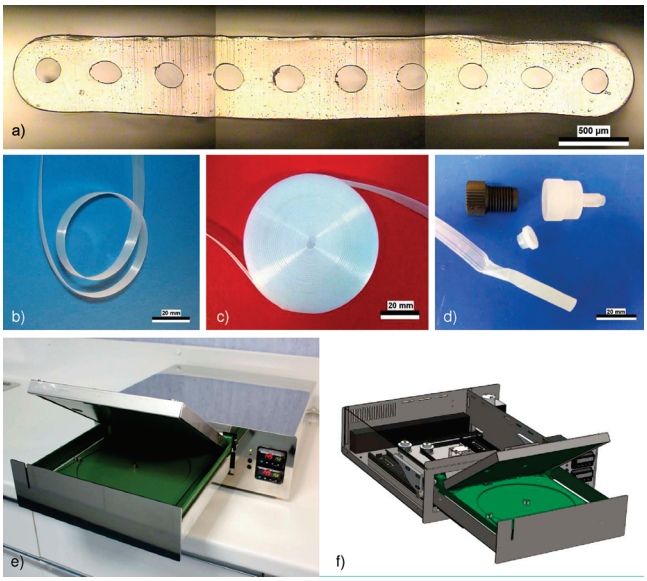


Figure 1. Photographic images of various reactor components: (a) microscope image of MCF cross section containing 10 capillaries, (b) side view of a single film, (c) double spiral MFD, (d) cylindrical MCF inlet unit with two plastic fittings and a plastic ferrule, (e) Cambridge Disc Microreactor,[14] (f) design drawing of the Cambridge Disc Microreactor showing the drawer mechanism.[14]

diameters, and the chosen process flow rates, the flow within each capillary is characterized as essentially laminar.[15] For use in the CDM, MCFs were made from fluorinated ethylene propylene (FEP), a highly temperature and solvent resistant thermoplastic, which has proved to be a very reliable polymer for chemical reactions up to temperatures of around 150 C.[14] FEP withstands repeated use of all commonly used solvents, including tetrahydrofuran, dimethyl sulfoxide, toluene, or chlorinated solvents such as dichloromethane, which soften or dissolve a wide range of other polymers, such as polystyrenes, poly(methyl methacrylate), polyurethanes, or epoxide derived polymers. Lengths of MCF were coiled in a double spiral fashion to form MFDs, which had a capillary length of 30 m and a combined reaction volume of 9 mL. These discs were suitable to carry out liquid phase organic synthesis with reaction times of between a few minutes and several hours. Figure 1 shows a microscope image of an MCF cross section, a side view of a typical MCF, an MCF connector, an MFD, and two images of the reactor. The double spiral configuration allows for both the inlet and the outlet of the reactor to be positioned on the outer edge of the MFD; the reaction mixture enters the disc tangentially at the circumference, progresses concentrically to the center, and subsequently from the center back to the circumference, where it exits the disc at the outlet. A more detailed description of the reactor, the MCF extrusion process, and the fabrication of MFDs can be found in previous publications.[13,16,17]

The connection between an MFD and standard microfluidic tubing or pumping devices was achieved using standard microfluidic fittings and a highly solvent resistant epoxy resin (Robnor Resins PX439XS). To fabricate the connector, short sections of commercially available FEP tubing with an outer diameter of 5/16 in. were sleeved over the ends of the MCF leads that entered and exited the MFD and then filled with epoxy. While curing, the connector was kept in a vertical orientation and the lower end of the FEP tube was blocked using BluTack to prevent epoxy from escaping. Following the curing stage, the end face of the connector was cut perpendicular to the capillaries, resulting in a flat, burr-free, face. The completed connector was then connected to standard Upchurch pipe-fittings (Upchurch Scientific P-684, U-660, and U-662).

The CDM is a reactor heater unit (see Figure 1e), which can perform continuous flow liquid phase reactions using a single MFD at controlled temperatures between ambient and 200 C. It should be noted that due to potential softening of the FEP at high temperatures, in combination with organic solvents, the use of MFDs made from FEP is restricted to temperatures of 150 C.[14] The MFD is placed on a retractable "drawer", in between two metal heater plates (see Figure 1f). When the drawer is retracted into the reactor housing, the upper lid is automatically closed bringing both heater plates in contact with the MFD. The heater plates contain two flat silicon heaters, each with a maximum power output of either 100 or 200 W. The temperature of each heater is sensed by a thermocouple and controlled by a PID control unit. A control panel on the front of the reactor unit operates both the automatic drawer mechanism and the PID controllers; this panel also displays the measured temperature of the heater plates. The flow through the MFD was provided using either one or several externally located HPLC pumps, in combination with microfluidic tubing, connectors, and backpressure regulators.

Process Characteristics. (a) Hydraulic Response. Because of the elliptical nature of capillaries inside MCFs, an equivalent diameter, d_{eq},[18] was introduced using eq 1 in order to calculate the pressure drop along a film.

$$d_{eq} = \left(\frac{32a^3b^3}{a^2 + b^2}\right)^{0.25} \tag{1}$$

Here, a and b are the major and minor semiaxes of the ellipse. The ellipse aspect ratio, a/b, of the capillaries used in this work was in the range between 1.0 and 1.4. The Hagen−Poiseuille equation for laminar flow, shown in eq 2,[19] was used to predict the pressure drop, Δp, along MCFs, based on the capillary length, l_c, the equivalent diameter, d_{eq}, the fluid viscosity, μ, and the volumetric flow rate, $\dot{V}$.

$$\Delta p = \frac{128 l_c \mu}{\pi d_{eq}^{\ 4}} \dot{V} \tag{2}$$

For multiple capillary films, the total volumetric flow through one film was split proportionally between the individual capillaries according to their size, with the larger capillaries receiving a higher flow rate fraction. The calculation of the flow rate fraction was based on the assumption that, under conditions of continuous flow, the pressure drop at a given distance from the inlet, l_x, in each capillary of an MCF was identical. Therefore, the flow rate fraction was proportional to d_{eq}.[4] For each capillary, the Reynolds number, Re, was calculated based on the mean or net flow velocity, v_m, through the capillary and its mean hydraulic diameter, d_c:

$$Re = \frac{v_m \rho d_c}{\mu} \tag{3}$$

Here, ρ is the fluid density. Note that d_c and d_{eq} can have different values, depending on the ellipticity of the capillary. The capillary net flow velocity, v_m, can be calculated using eq 4, where A_{cs} is the cross-sectional area of the capillary.

$$v_m = \frac{\dot{V}}{A_{cs}} \tag{4}$$

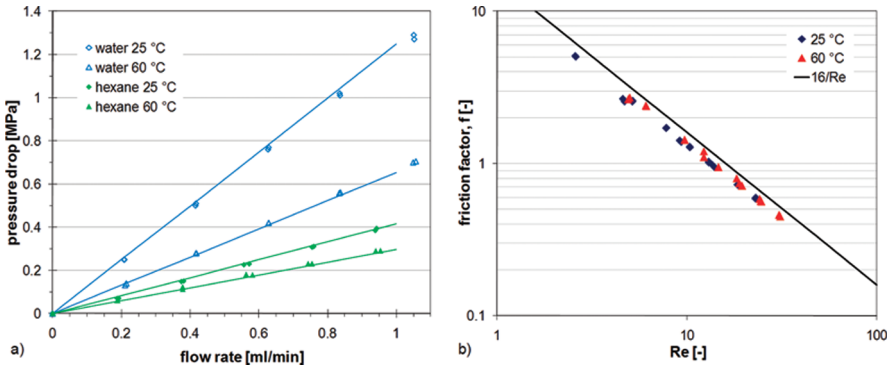


Figure 2. (a) Comparison of experimental pressure drop with analytical predictions for two different working liquids and two different temperatures, d_{eq} = 200 μm, capillary length = 33 m. (b) Fanning friction factor, f, in a 10-capillary film plotted against the mean Reynolds number, for two different temperatures; the line represents the theoretical law $f = 16/Re$.

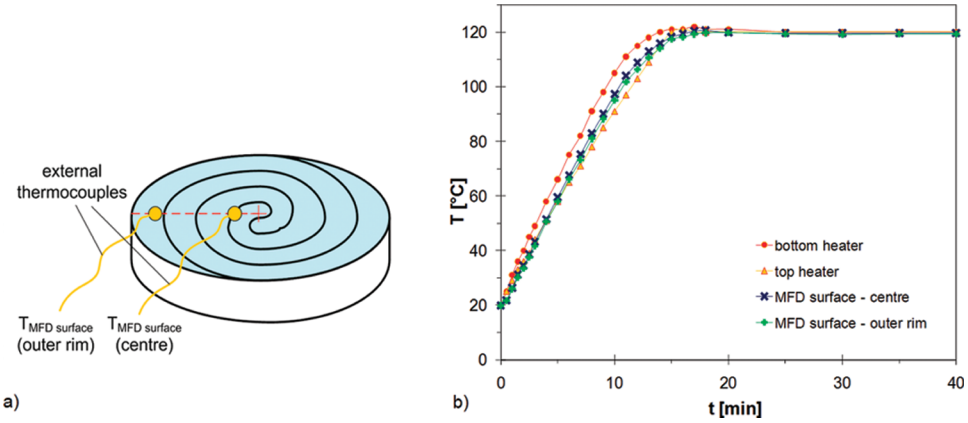


Figure 3. (a) Schematic drawing of an MFD showing the position of the two external thermocouples: one being attached to the top surface of the disc at its outer rim, the second being attached to the top surface close to the center of the disc. (b) Heating profile of an MFD inside the reactor, showing both the transient period (t = 0 to 18 min) and steady state (t > 18 min). The reactor operates with two 100 W heaters; target temperature 120 C; flow rate through disc 0.5 mL/min.

The Fanning friction factor, f, in a straight capillary is defined in eq 5.[19]

$$f = \frac{d_c}{2\rho v_m^2}\frac{\Delta p}{l} \tag{5}$$

A series of pressure drop experiments at different temperatures and with two different process fluids have been carried out in the CDM, using a simple experimental configuration consisting of a single HPLC pump, a pressure transducer, and the reactor. The liquid flow rate was adjusted between 0.2 and 1 mL/min using a Knauer-100 HPLC pump, and the pressure drop was monitored using a pressure transducer (Keller PA-21SR/35 bar/81520) with a digital read out. The capillary outlets were open to atmospheric pressure and fluid exiting the MFD was collected and weighed using a balance (Sartorius L2200) to gravimetrically calibrate the flow rate. To examine the effect of varying fluid viscosity, two liquids were used: deionized water and hexane, each at 25 and 60 C. Figure 2a compares the experimental results with predictions using eq 2.

The experimental data for water (hollow blue data points) and for hexane (filled green data points) show a good agreement with the linear theoretical predictions (lines), which were calculated for a mean equivalent capillary diameter of 200 μm. This value is very close to the measured mean hydraulic capillary diameter of the investigated MCF which lay between 192 and 205 μm. These values were determined from microscope images, showing that there is a slight variation in capillary diameter along their length. When this data is plotted as the Fanning friction factor, f, divided by the mean Reynolds number of the MCF, it shows a very good agreement with the theoretical model for laminar flow in a cylindrical pipe, which is plotted here as a black line representing $16/Re$ (see Figure 2b). The fact that microcapillaries are not perfectly cylindrical but have a slightly elliptical cross section is believed to be partially responsible for the small deviation of the experimental data from theory.[15]

(b) Temperature Profile. The temperature profile of an MFD inside the CDM (with 2 × 100 W heaters) during heating and at steady state was measured using four K-type thermocouples. In addition to the two inbuilt thermocouples of the reactor, which monitor the temperature of the top and bottom heater plate, two external thermocouples were attached to the top surface of the MFD using heat resistant Kapton tape. The later two thermocouples measured the surface temperature of the plastic disc at two positions: close to the center (center of reactor pathway) and close to the outer rim (close to the inlet and outlet of reactor pathway). Figure 3 shows schematically the position of the external thermocouples and the heating profile of a typical experiment, where the temperature set point of the reactor was set to 120 C.

The data was taken using acetonitrile (MeCN) as the process fluid at a constant flow rate of 0.5 mL/min. A 75 psi backpressure regulator was positioned in-line after the reactor, in order to prevent the liquid from boiling inside the capillaries. It was observed that the reactor reached the desired temperature after a heating period of roughly 18 min. After this initial transient period, the temperature of both hot plates equilibrated

Table 1. Comparison of Theoretical RTD Data Calculated for a 10 Capillary MFD (l_c = 30 m, d_c = 200 μm) with Experimental Data from a 19 Capillary MFD[20] (l_c = 10 m, d_c = 222 μm)[a]

	10 capillary MFD—model—30 m MCF, d_c = 200 μm		19 capillary MFD—experimental—10 m MCF, d_c = 222 μm	
	min flow rate	max flow rate	low flow rate	high flow rate
flow rate [mL/min]	0.1	1.5	0.5	2.0
Re [−]	1.14	17.1	2.52	10.1
D_{ax} [mm^2/s]	64	14315	579	4492
Pe **[−]**	**2714**	**181**	**190**	**98**

[a] Upper and lower flow rate boundaries are shown together with corresponding values for *Re*, D_{ax}, and *Pe*; for the given conditions, RTD in a 10 capillary MFD is expected to be plug-flow-like as $Pe > 100$.

to the set temperature of 120 °C. The temperatures measured on the disc's surface also followed the same trend and reached the same value as the plates in the steady state region after roughly 18 min. By fitting two heaters with double the power (2 × 200 W) to a newer version of the reactor, the heating period was substantially decreased. Repeating these experiments for several runs at set temperatures between 80 and 160 °C has shown that the measured temperature on the MFD surface under steady state conditions was never more than 1% below the set point value. Varying the flow rate through the disc between 0.5 and 1.5 mL/min did not result in lower MFD surface temperatures; consequently, it can be concluded, that the CDM heaters are capable of accurately controlling the reaction temperature inside MFDs. This allows for a quasi-isothermal operation of liquid phase reactions up to 200 °C for a complete range of practical flow rates.

(c) Residence Time Characterization. In any continuous flow process where chemical reactions occur, the residence time characteristics of the reactor can be of significant importance and reveal useful information. In general, a near plug flow response is most desirable, although in reality rarely achieved. Perfect plug flow characteristics imply that each fluid element passing through the reactor has the same residence time and therefore also reaction time, which means that the entire reaction mixture is processed under identical conditions, given a uniform temperature profile. A residence time distribution (RTD) that strongly deviates from plug flow, resulting in a spread of the reaction mixture slug as it is passed through the reactor, can lead to a reduced conversion rate or selectivity. Previous experimental studies of residence time characteristics in 19 capillary MCFs were carried out using fiber optic probes and step change concentration inputs.[20] This data was compared to analytical models assuming plug flow superimposed by axial dispersion. The MCFs showed residence time characteristics close to plug flow, which can be explained by the small dimensions of the capillaries in combination with the low flow velocities.

Laminar flow in tubular systems usually leads to considerable dispersion because of the parabolic velocity profile that develops across the tube; however, in slowly flowing systems with small channel diameters, molecular diffusion effects are dominant. The small diameters of many microreactors ensure that these effects, first described by Taylor in 1953,[21] result in a narrower distribution than expected from the parabolic velocity profile associated with laminar flow. Thus, the RTD in microreactors is often close to plug flow. With his theory, Taylor introduced an effective diffusion coefficient, D_{ax}, which characterizes the axial dispersion in the system. Soluble matter of a known concentration injected into a flow through a pipe with diameter, d_c, is dispersed relative to a plane, which moves with the velocity $v_m = 1/2 v_{max}$ exactly as though it were diffused by a mass transport process with the effective diffusion coefficient, D_{ax} (see eq 6).

$$D_{ax} = D + \frac{d_c^2 v_m^2}{192D} \tag{6}$$

Here, D is the diffusion coefficient, which for the herein presented model was assumed to be a concentration independent, material specific constant and was set to 1×10^{-10} m^2/s. This lies within the range of literature values for comparable systems, such as the work by Robinson.[22] The theoretical D_{ax} can be compared to experimental values, which were calculated from residence time curves taken with fiber optic probes in the 19 capillary MCFs described in earlier work.[20] How close the RTD in a reactor is to a plug flow profile, can be characterized by the axial dispersion number, sometimes also called Peclet number, *Pe*, which is defined as:

$$Pe = \frac{v_m l_c}{D_{ax}} \tag{7}$$

The higher the value of *Pe*, the closer the flow is to ideal plug flow. According to Levenspiel,[23] a system with $Pe > 100$ can be considered as plug-flow-like. In systems with $Pe < 100$, substantial axial dispersion occurs. Table 1 compares theoretical predictions based on Taylor's model, calculated for a 10 capillary MCF to previous experimental data from a 19 capillary MCF[20] for a range of practicable flow rates. The corresponding minimum and maximum *Re*, D_{ax}, and *Pe* were derived from the estimated process limits of a 10 capillary MCF (model data) and the investigated operation window of a 19 capillary MCF (experimental data). Upper flow rate limits are usually determined by the maximum pressure build-up inside the capillaries and lower limits by the minimum pump flow rate. Model and experimental data values have a similar magnitude and show the same trend. The predicted minimum *Pe* number of a 30 m long 10 capillary MCF of 181 leads to the conclusion that even at the maximum operating flow rate of 1.5 mL/min, the RTD inside such an MFD would be plug-flow-like. These theoretical predictions need to be verified by experimental investigations, which will be conducted in future work.

Organic Synthesis Reactions. Three different reactions at temperatures between 110 and 120 °C were chosen to validate the MFD technology. These include a fluorination reaction and the formation of various heterocyclic compounds. The reactions were performed on different scales; either as a small-scale run, where a short "slug" containing a few milligrams of material was processed, or a fully continuous run producing several grams over a given processing time. In the "slug injection" runs, the reagents were either premixed and therefore only one pump was used for the reaction or they were mixed continuously in a T-piece using two feed pumps. The fully continuous runs were

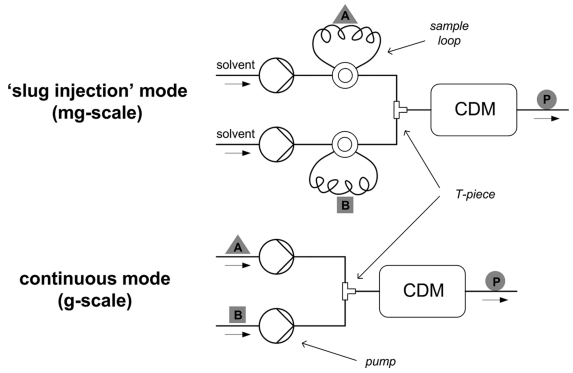
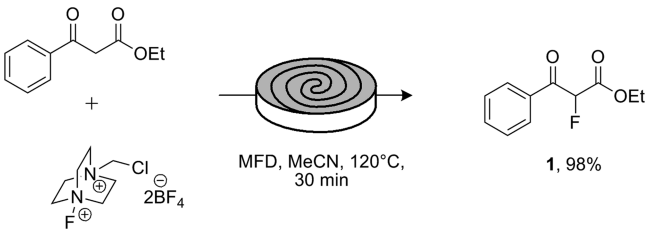


Figure 4. Schematic overview of two different operation modes used for chemical reactions inside a CDM: (top) slug injection mode, using two sample loops, for processing small amounts of liquid (typical volume per sample loop 1 to 5 mL); (bottom) continuous mode for fully continuous flow processing of larger volumes (typically >10 mL).

Scheme 1. Electrophilic Fluorination of Ethyl 3-Oxo-3-phenylpropanoate Using the Fluorinating Agent Selectfluor in a Cambridge Disc Microreactor, Using the Slug Injection Mode

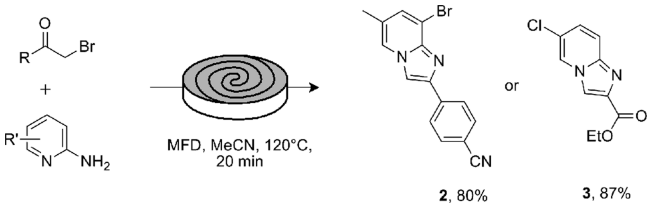


always performed using a two-pump configuration. The operating modes used for these two experiments are shown schematically in Figure 4. The objective in these reactions was to achieve both high conversion and purity of the product in a reliable fashion using a device capable of operating across a broad range of production scales.

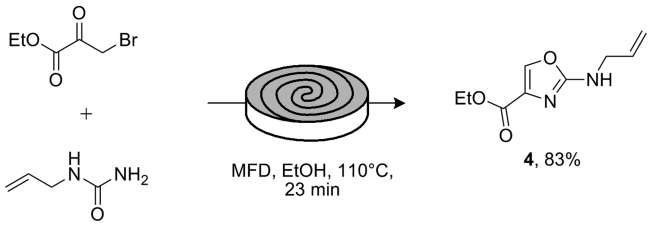
(a) Fluorination. As previously demonstrated, flow reactors are ideal instruments for the incorporation of fluorine[24−27] into organic substrates as the flow arrangement naturally allows for the convenient and safe handling of hazardous fluorinating reagents. In order to evaluate the CDM, an electrophilic fluorination reaction was performed using the commercially available reagent Selectfluor. In earlier work, it was found that this reagent is well-suited for α-fluorination of carbonyl compounds when the reaction is performed at temperatures around 120 C. Using the CDM in the slug injection mode, the desired monofluorinated product as shown in Scheme 1 was obtained in high yield and purity after scavenging the ionic Selectfluor reagent using a mixture of two commercially available resins: QP-SA (Quadrapure sulfonic acid) and QP-DMA (Quadrapure dimethyl amine base).[28]

(b) Formation of Bicyclic Heteroaromatic Compounds. The formation of heterocyclic scaffolds in a selective and highly efficient manner is a key component of today's pharmaceutical chemistry programs, as these compounds allow for the evaluation of structure activity relationships (SAR) for many new drug compounds.[29] Imidazo[1,2-*a*]pyridines and related substances are a well-described class of bicyclic compounds which can be found in many GABA receptor modulators such as zolpidem (Ambien), a drug used in the treatment of insomnia, as well as some brain disorders. Their synthesis can be accomplished by a Hantzsch-type condensation between a 2-aminopyridine and an α-haloketone and is usually performed at elevated temperature (see Scheme 2). The flow process to

Scheme 2. Synthesis of Bicyclic Heteroaromatic Compounds at Elevated Temperatures in a Cambridge Disc Microreactor, Using the Slug Injection Mode



Scheme 3. Synthesis of Amino Oxazoles at Elevated Temperatures in a Cambridge Disc Microreactor, Using the Continuous Mode



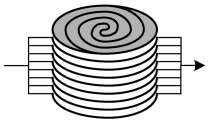
prepare these compounds involves mixing the two starting materials in a 1:1 ratio followed by the passage of this mixture as a slug through the CDM at 120 C. It was found that complete conversion could be achieved with a residence time of 20 min giving the desired compounds in high yield after treatment with a basic QP-DMA resin in order to remove the initially formed HBr salt from the product.

(c) Oxazole Formation. A second example of heterocycle formation using the CDM system, involved the synthesis of bifunctional oxazoles, which can be prepared conveniently from urea derivatives via a condensation with bromoethyl pyruvate.[30] Similar reactions have been reported in traditional batch mode; however, the need to reflux the reaction mixture for extended periods of time often leads to the formation of undesired byproduct. In comparison, we could obtain the desired amino oxazole product after 23 min reaction time at 110 C in continuous flow with an isolated yield of 83% after an aqueous workup. This interesting building block was reproducibly prepared using full continuous operation mode on scales of 15 mmol with a total flow rate of 0.4 mL/min (Scheme 3).

Summary and Conclusions

This paper reports the evaluation of a novel continuous flow microreactor system (the Cambridge Disc Microreactor or CDM) for liquid phase reactions up to 150 C. It was demonstrated that plastic Microcapillary Flow Discs which are manufactured from fluoropolymer Microcapillary Films can be used as reusable reactor cartridges. Each MFD had 10 parallel channels with capillary diameters of 200 μm and a length of 30 m. It is worth highlighting that these dimensions and number of capillaries is not the limit of the current system and both lower and higher volumetric throughputs could easily be achieved. Practical limits for the current CDM configuration are capillary diameters in the range of 400 μm at a length of several meters. Furthermore, it is possible to run several of these discs in parallel, which has already been shown in previous work.[17] MFDs can provide a low cost solution for micro- and mesoscale flow chemistry, which enables this technology to bridge the gap between laboratory scale and small production scale. The CDM system could provide a platform to carry out development of new synthesis routes in the laboratory and then progress these

Table 2. Comparison of Typical Reactor Specifications for Laboratory and Production Scale, Both Using Microcapillary Flow Discs

	Laboratory Scale	**Production Scale**
	optimisation of reaction conditions	*for production of g- to kg-quantities*
		
	1 x MFD (10 capillaries)	20 x MFD (20 capillaries each)
no. of capillaries	10	400
capillary diameter	200 to 400 μm	400 μm
capillary length	10 to 30 m	30 m
reactor volume	3 to 40 ml	1600 ml
throughput *(at 30 min reaction time)*	**0.1 to 1.3 ml/min**	**53.4 ml/min (3.2 l/h)**

processes to small production scale by simply increasing the number of reactor units. The optimization of the reaction conditions could be carried out using a single disc, while the production reactor could be operated using multiple discs, featuring hundreds or even thousands of microcapillaries run in parallel. This so-called numbering-up or scale-out does not require the redesign and optimization steps usually associated with the classical scale-up approach. We believe that MFD technology is very suitable for this concept due to its design and flexible manufacturing process. Table 2 presents theoretical scale-out calculations based on the herein presented work and practical limitations.

The proof of concept reactions described in this paper established the use of fluoropolymer MFDs for organic synthesis at elevated temperatures and demonstrated that MFD technology has certain strategic advantages over chip-based microreactor designs, such as longer reactor length leading to longer reaction times and low manufacturing costs. The low manufacturing cost of the device provides the option to use it as a disposable component, despite the fact that the MFDs exhibited sufficient robustness to enable extended and repeated usage. MFDs are able to operate at elevated pressure, provide excellent temperature control coupled with fast heat transfer and can offer a controlled residence/reaction time of between seconds and hours.

MFDs can sustain higher pressures than standard laboratory glassware reactors, which enables the generation of pressurized flows inside the microchannels yielding beneficial effects in terms of higher boiling points, greater solubility, and higher diffusion rates. Due to the use of fluorinated polymer, an excellent solvent and temperature resistance could be achieved, which makes MFDs suitable for almost all organic processes, at temperatures typically up to 150 C.

With the help of manufacturing technologies such as rapid prototyping, it will be possible to modify the CDM connectors such that the ten parallel channels can be individually addressed. In this mode the CDM will have a powerful potential for screening multiple reactions under identical processing conditions. This work is currently under investigation.

Experimental Section

Starting materials, reagents, and solvents were obtained from commercial suppliers and were used without further purification. ^{1}H NMR spectra were recorded on a Bruker Avance DPX-400 or Bruker DPX-600 spectrometer with residual chloroform as the internal reference (δ = 7.26 ppm).

Ethyl-2-fluoro-3-oxo-3-phenylpropanoate (1). Yield 98%. t_R = 4.27 min. m/z = 209.1 (M − H$^+$). ^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm 8.02 (2H, d, J = 8.4 Hz), 7.62 (1H, t, J = 8.4 Hz), 7.48 (2H, t, J = 8.4 Hz), 5.87 (1H, d, J = 48.6 Hz), 4.28 (2H, qd, J = 2.4, 7.2 Hz), 1.23 (3H, t, J = 7.2 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm 189.5 (C, d, J = 20 Hz), 164.9 (C, d, J = 24 Hz), 134.5 (CH), 133.4 (C, d, J = 2 Hz), 129.5 (2CH, d, J = 2 Hz), 128.8 (2CH), 89.9 (CHF, d, J = 197 Hz), 62.6 (CH_2), 13.9 (CH_3). ^{19}F-NMR (376 MHz, $CDCl_3$): δ/ppm −190.5 (s); IR (neat) ν = 2985.6 (w), 1758.5 (s), 1693.2 (s), 1597.7 (m), 1449.7 (m), 1372.27 (m), 1242.5 (s), 1202.0 (s), 1096.1 (s), 1015.0 (s), 976.4 (m), 943.0 (w), 925.3 (w), 882.8 (m), 854.1 (w), 771.4 (w), 746.6 (w), 688.1 (s) cm^{-1}. HRMS calculated for $C_{11}H_{12}O_3F$ 211.0770, found 211.0779.

4-(8-Bromo-6-methylimidazo[1,2-*a*]pyridine-2-yl)benzonitrile (2). Yield 80%. t_R = 4.09 min. m/z = 313.8 (M + H$^+$). ^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm 8.03 (2H, d, J = 8.4 Hz), 7.88 (1H, s), 7.86 (1H, s), 7.65 (2H, d, J = 8.4 Hz), 7.32 (1H, s), 2.30 (3H, s). ^{13}C NMR (150 MHz, $CDCl_3$): δ/ppm 143.8 (C), 142.9 (C), 137.8 (C), 132.7 (C), 132.4 (2CH), 130.9 (CH), 126.5 (2CH), 123.1 (C), 122.9 (CH), 119.1 (C), 111.0 (C), 110.9 (CH), 17.9 (CH_3). IR (neat) ν = 2222.8 (m), 1609.7 (m), 1519.9 (s), 1476.9 (s), 1414.1 (m), 1340.1 (s), 1294.5 (s), 1268.7 (m), 1208.9 (m), 1022.8 (s), 943.9 (s), 873.1 (m), 844.8 (s0, 832.3 (s), 739.6 (s), 706.2 (s), 666.8 (m) cm^{-1}. HRMS calculated for $C_{15}H_{11}N_3Br$ 312.0136, found 312.0147.

Ethyl-6-chloroimidazo[1,2-*b*]pyridazine-2-ylcarboxylate (3). Yield 87%. t_R = 3.51 min. m/z=225.8 (M + H$^+$). ^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm 8.41 (1H, s), 7.97 (1H, d, J = 9.6 Hz), 7.13 (1H, d, J = 9.6 Hz), 4.22 (2H, q, J = 7.2 Hz), 1.40 (3H, t, J = 7.2 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ/ppm 162.4 (C), 148.9 (C), 137.7 (C), 136.9 (C), 128.4 (CH), 121.3 (CH), 121.0 (CH), 61.6 (CH_2), 14.4 (CH_3). IR (neat) ν = 3079.8 (s), 3024.7 (s), 1731.6 (s0, 1531.9 (m), 1516.5 (m), 1456.5 (m), 1374.4 (m), 1298.8 (s), 1238.3 (m), 1186.0 (s), 1138.6 (s), 1118.7 (s), 1092.8 (s), 1022.6 (s), 939.6 (m), 838.0 (s), 796.1 (m), 749.6 (s), 730.2 (s), 712.1 (s) cm^{-1}. HRMS calculated for $C_9H_9N_3O_2Cl$ 226.0383, found 226.0394.

Ethyl-2-(allylamine)-oxazole-4-carboxylate (4). Yield 83%. $t_R = 3.64$ min. $m/z = 197.0$ ($M + H^+$). ^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm 7.72 (1H, s), 5.92 (1H, ddd, $J = 5.4$, 10.8, 16.8 Hz), 5.52 (1H, br s), 5.24 (1H, dd, $J = 1.2$, 16.8 Hz), 5.15 (1H, dd, $J = 1.2$, 10.2 Hz), 4.32 (2H, q, $J = 7.2$ Hz), 4.00 (2H, dd, $J = 6.0$ Hz), 1.33 (3H, t, $J = 7.2$ Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm 161.8 (C), 161.1 (C), 137.5 (CH), 134.2 (CH), 133.0 (C), 116.5 (CH_2), 60.8 (CH_2), 45.5 (CH_2), 14.3 (CH_3). IR (neat) $\nu = 3164.2$ (w), 2983.7 (w), 1722.4 (s), 1654.9 (s), 1421.3 (m), 1332.9 (m), 1244.3 (s), 1129.7 (s), 1093.4 (s), 1029.0 (m), 997.3 (m), 930.3 (s), 711.7 (s) cm^{-1}. HRMS calculated for $C_9H_{13}N_2O_3$ 197.0925, found 197.0926.

Acknowledgment

We gratefully acknowledge financial support from the Engineering and Physical Science Research Council (C.H.H.), the Royal Society (I.R.B.), the Cambridge European Trust and the Ralph Raphael Studentship award (M.B.), and the BP Endowment (S.V.L.).

Literature Cited

(1) Seeberger, P. H.; Blume, T. *New Avenues to Efficient Chemical Synthesis, Emerging Technologies*; Springer: Berlin, Germany, 2007.

(2) Hodge, P. Organic synthesis using polymer-supported reagents, catalysts and scavengers in simple laboratory flow systems. *Curr. Opin. Chem. Biol.* **2003**, *7*, 362.

(3) Kirschning, A.; Solodenko, W.; Mennecke, K. Combining Enabling Techniques in Organic Synthesis: Continuous Flow Processes with Heterogenized Catalysts. *Chem.—Eur. J.* **2006**, *12*, 5972.

(4) Ahmed-Omer, B.; Brandt, J. C.; Wirth, T. Advanced organic synthesis using microreactor technology. *Org. Biomol. Chem.* **2007**, *5*, 733.

(5) Mason, B. P.; Price, K. E.; Steinbacher, J. L.; Bogdan, A. R.; McQuade, D. T. Greener Approaches to Organic Synthesis Using Microreactor Technology. *Chem. Rev.* **2007**, *107*, 2300.

(6) Steven V. Ley, S. V.; Baxendale I. R. New Tools for Molecule Makers: Emerging Technologies. *Systems Chemistry*, Bozen, Italy,May 26−30, 2008.

(7) Sahoo, H. R.; Kralj, J. G.; Jensen, K. F. Multi-step Continuous Flow Microchemical Synthesis involving Multiple Reactions and Separations. *Angew. Chem. Int. Ed.* **2007**, *46*, 5704.

(8) DeWitt, S. H. Microreactors for chemical synthesis. *Curr. Opin. Chem. Biol.* **1999**, *3*, 350.

(9) deMello, A.; Wootton, R. But what is it good for? Applications of microreactor technology for the fine chemical industry. *Lab Chip* **2002**, *2*, 7N.

(10) Hessel, V.; Hardt, S.; Löwe, H. *Chemical Micro Process Engineering (1), Fundamentals, Modelling and Reactions*; Wiley-VCH: Weinheim, Germany, 2004.

(11) Jähnisch, K.; Hessel, V.; Löwe, H; Baerns, M. Chemistry in Microstructured Reactors. *Angew. Chem. Ind. Ed.* **2004**, *43*, 406.

(12) Kralj, J. G.; Sahoo, H. R.; Jensen, K. F. Integrated continuous microfluidic liquid-liquid extraction. *Lab Chip* **2007**, *7*, 256.

(13) Hallmark, B.; Mackley, M. R.; Gadala-Maria, F. Hollow microcapillary arrays in thin plastic film. *Adv. Eng. Mater.* **2005**, *7* (6), 545.

(14) http://www.laminadielectrics.com/

(15) Hornung, C. H.; Hallmark, B.; Hesketh, R. P.; Mackley, M. R. The fluid flow and heat transfer performance of thermoplastic microcapillary films. *J. Micromech. Microeng.* **2006**, *16*, 434.

(16) Hallmark, B.; Gadala-Maria, F.; Mackley, M. R. The melt processing of polymer microcapillary film (MCF). *J. Non-Newtownian Fluid Mech.* **2005**, *128*, 83.

(17) Hornung, C. H.; Mackley, M. R.; Baxendale, I. R.; Ley, S. V. A Microcapillary Flow Disc Reactor for Organic Synthesis. *Org. Process Res. Dev.* **2007**, *11*, 399.

(18) Lamb, H. *Hydrodynamics*, 6th edition; Dover: New York, 1945.

(19) Perry, R. H.; Green, D. W. *Perry's Chemical Engineer's Handbook*, 7th ed.; McGraw-Hill Co.: New York, 1997.

(20) Hornung, C. H.; Mackley, M. R. The measurement and characterisation of residence time distributions for laminar liquid flow in plastic microcapillary arrays. *Chem. Eng. Sci.* **2009**, *64*, 3889.

(21) Taylor, G. Dispersion of soluble matter in solvent flowing slowly through a tube. *Proc. R. Soc. A* **1953**, *219*, 186.

(22) Robinson, C. The Diffusion Coefficients of Dye Solutions and their Interpretation. *Proc. R. Soc. A* **1935**, *148*, 681.

(23) Levenspiel, O. *Chemical Reaction Engineering*, 3rd ed.; John Wiley & Sons: New York, 1999.

(24) Baumann, M.; Baxendale, I. R.; Martin, L. J.; Ley, S. V. Development of Fluorination Methods using Continuous-Flow Microreactors. *Tetrahedron* **2009**, *65*, 6611.

(25) Baumann, M.; Baxendale, I. R.; Ley, S. V. The Use of diethylaminosulfurtrifluoride (DAST) for Fluorination in a Continuous Flow Microreactor. *Synlett* **2008**, *14*, 2111.

(26) Gustafsson, T.; Gilmour, R.; Seeberger, P. H. Fluorination reactions in microreactors. *Chem. Commun.* **2008**, *3022*.

(27) Chambers, R. D.; Fox, M. A.; Sandford, G.; Trmcic, J.; Goeta, A. Elemental fluorine: Part 20. Direct fluorination of deactivated aromatic systems using microreactor techniques. *J. Fluorine Chem.* **2007**, *128*, 29.

(28) http://www.reaxa.com/.

(29) Baxendale, I. R; Hayward, J. J.; Ley, S. V.; Tranmer, G. K. Pharmaceutical Strategy and Innovation: An Academics Perspective. *ChemMedChem.* **2007**, *2*, 768.

(30) Baumann, M.; Baxendale, I. R.; Ley, S. V.; Smith, C. D.; Tranmer, G. K. Fully Automated Continuous Flow Synthesis of 4,5-Disubstituted Oxazoles. *Org. Lett.* **2006**, *8* (23), 5231.

Received for review October 28, 2009
Revised manuscript received February 10, 2010
Accepted March 4, 2010

IE901674H