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A Microcapillary System for Simultaneous, Parallel Microwave-Assisted Synthesis

Eamon Comer and Michael G. Organ*[a]

Abstract: A continuous flow, microwave-assisted, parallel-capillary microreactor has been developed. Libraries of drug candidates were prepared on the milligram scale with this reactor by injecting plugs of reagents from separate syringes into common reaction capillaries, thereby producing discrete compounds in excellent yield and purity. Microwave irradiation provides the necessary energy that existing room-temperature microreactor technology lacks for higher activation barrier transformations, producing the required amounts of desired compounds in minutes or less.

Keywords: combinatorial chemistry · cross-coupling · microreactors · microwaves · parallel synthesis

Introduction

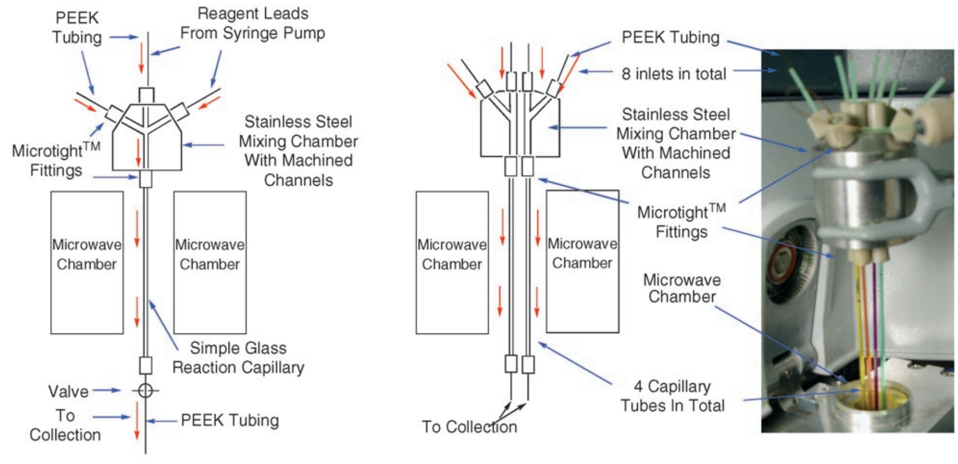
High-throughput synthetic strategies used in the discovery of new drug candidates, materials, and catalysts have relied on two prevailing methods, namely mix and split, and parallel synthesis.[1,2] These so-called "high-speed synthesis" approaches actually have slower chemical transformations because they are often heterogeneous. To address this, various techniques have been applied including microwave-assisted organic synthesis (MAOS),[3–6] which provide faster, cleaner and higher yielding reactions.[6–12] However, the one-at-a-time nature of preparing reactions in single, specialized (and expensive) microwave vials does much to offset the benefits of faster chemical conversion. One way to overcome these handling issues is to perform reactions in a flow format. Additionally, there is merit in miniaturizing the combinatorial process,[13,14] which has been achieved by microflow systems called microreactors.[15–17] However, the fabrication of chip-type microreactors requires specialized, expensive facilities, and the laminar flow associated with microchannel devices can lead to poor reactivity.[17] Further, existing microfluidic technology does not address fully the issue of heating in these reaction systems, which limits application. The goals of high-throughput synthesis might be better served through miniaturization in a flow format incorporating the reaction-rate-promoting benefits and higher yields of MAOS.[18,19]

[a] E. Comer, Prof. M. G. Organ
The Department of Chemistry, York University
4700 Keele Street, Toronto, Ontario, M3J 1P3 (Canada)
Fax: (+1) 416-735-5936
E-mail: organ@yorku.ca

Results and Discussion

Most flow-through, microscale combinatorial reaction systems have used a sequential-flow approach to the preparation of libraries, whereby compounds were produced, one after another, through the same reactor channel.[13,14] Significantly, virtually all libraries prepared by this approach[20] have been synthesized at room temperature by using glass microchips that carry the associated limitations discussed above.[21] With the aim of greatly improving this process we designed and prepared a single capillary reactor (Figure 1A).[22] The assembly consists of a stainless steel mixing chamber with three inlets that merge to a single outlet that can be connected to capillary tubes of various internal diameters (200–1150 μm) and, ultimately, to collection vessels. We prepared a demonstration array of compounds using a consecutive-flow/MW-irradiation strategy based on the Suzuki–Miyaura cross-coupling reaction[23] (Table 1). A constant stream of phenyl boronic acid (**1**) and base (syringe A) was fed into the reaction chamber (Figure 1A), while plugs of aryl halides **2**–**6** and catalyst (syringes B1–B5) were introduced sequentially through a second lead into the reaction capillary to afford the biaryl library, separated by time, in very good to excellent conversion.

This methodology was then applied to the nucleophilic substitution of aromatic fluorides (S_NAr) with primary amines that produced the anilines shown in Table 2. It is



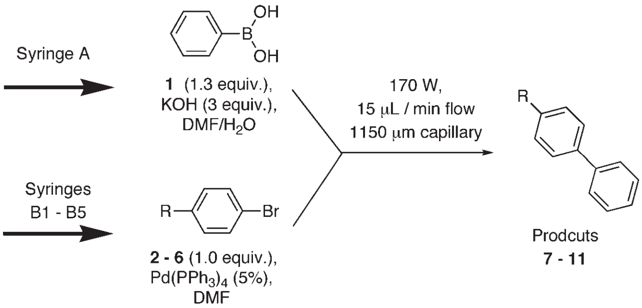
A B C

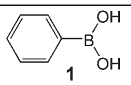
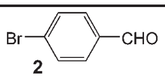
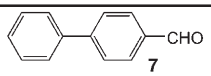
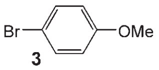
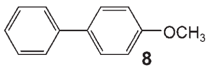
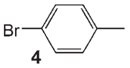
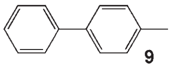
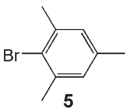
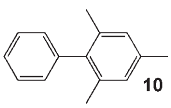
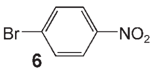
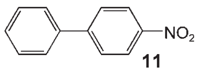
Figure 1. Continuous flow, capillary MW microreactors. A) Schematic of the single capillary reactor system. B) Schematic of the parallel, capillary multireactor system. C) Photograph of the parallel, capillary multireactor system.

worth noting that despite the small channel size, no laminar flow[17] of the two reacting streams was observed and no blockage of the reactor occurred where products crystallized, which was shown to be problematic in other, even larger diameter flow systems.[24]

Having established the concept of a MW-assisted continuous/sequential-flow library synthesis and prepared two small libraries, we felt we were in a unique position to significantly advance microscale, flow parallel synthesis using our capillary reactor approach.[25] The multireactor assembly (shown in Figures 1B and C) was designed specifically for library preparation and consists of a stainless steel holder with four pairs of two inlet ports (8 ports in total), in which the channels of each pair merged to afford four outlet ports. Capillary tubes were connected to each of these outlets to form a multireactor system and all reactions could be heated simultaneously while they flowed through each capillary. We elected

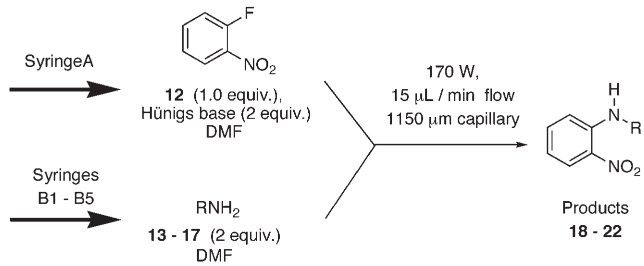
Table 1. A cross-coupling library prepared by sequential injection of stock solutions by continuous flow capillary microwave irradiation.

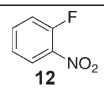
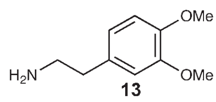
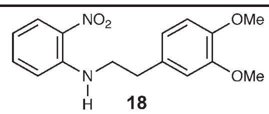
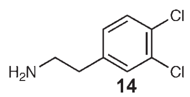
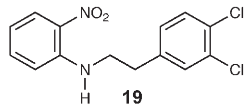
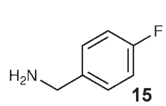
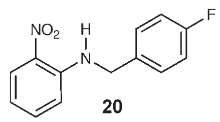
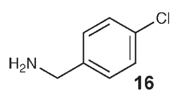
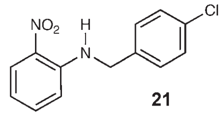
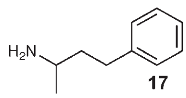
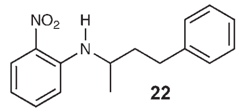


Stream A	 1	Product	Conversion [%][a]
stream B1	 2	 7	97
stream B2	 3	 8	76
stream B3	 4	 9	90
stream B4	 5	 10	72
stream B5	 6	 11	100

[a] Percent conversion was determined by ^{1}H NMR spectroscopy and is relative to residual starting halide **2–6**.

Table 2. A S_NAr library prepared by sequential injection of stock solutions by flow capillary microwave irradiation.



Stream A	 12	Product	Conversion [%][a]
stream B1	 13	 18	100
stream B2	 14	 19	56
stream B3	 15	 20	100
stream B4	 16	 21	67
stream B4	 17	 22	55

[a] Percent conversion was determined by ^{1}H NMR spectroscopy and is relative to residual starting fluoride **12**.

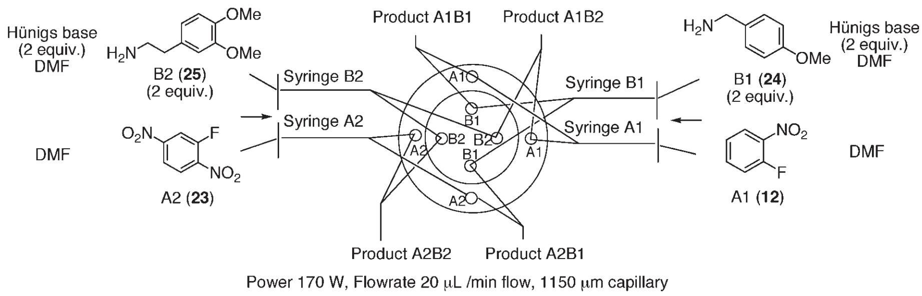
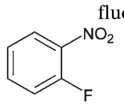
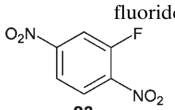
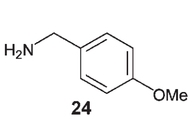
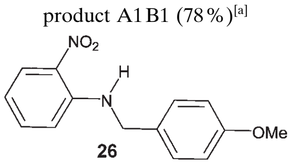
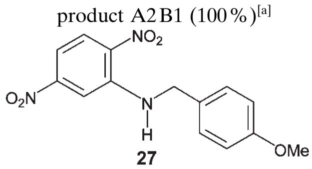
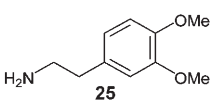
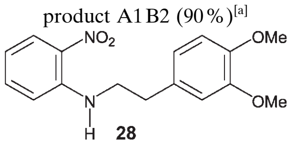
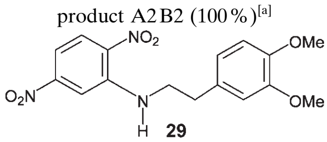


Figure 2. Top view of multireactor system schematic for a 2×2 parallel library.

Table 3. Preparing libraries of compounds simultaneously by parallel capillary irradiation using the multi-inlet reactor (shown in Figure 2).

	fluoride A1	fluoride A2
	 12	 23
amine B1  24	product A1B1 (78%)[a]  26	product A2B1 (100%)[a]  27
amine B2  25	product A1B2 (90%)[a]  28	product A2B2 (100%)[a]  29

[a] Percent conversion was determined by ^{1}H NMR spectroscopy and is relative to residual starting fluoride.

to use the S_NAr reaction for the parallel synthesis in which fluorides **12** and **23** (syringes A1 and A2) and amines **24** and **25** (syringes B1 and B2) were the two reagent pairs (see Figure 2 and Table 3). Thus, for example, a stream of amine **25** from syringe B2 was split into two and fed equally into different inlets whereby one stream could combine with fluoride **12** (from syringe A1), while the other mixed with **23** (from syringe A2). By using this technique four streams containing all possible combinations were collected separately and the conversion ranged from very good to excellent.

A perceived drawback of flow parallel synthesis is the necessity to have as many syringe pumps as starting reagents and as many reaction channels as products.[13] Additionally, it is a common belief that once a parallel reaction system has been built, the number of components in the library are fixed.[13] These concerns could be eliminated, or at least minimized, through the new concept of continuous-flow, sequential, parallel synthesis using the multireactor assembly shown in Figures 1B, 1C, and 3 (for results see Table 4). Aryl bromides **6** and **2** were continuously fed into inlet ports A1 and A2 using syringes A1 and A2, respectively. The boronic acids from syringes B1 and B2 were each split into two streams and pumped into their respective inlets as denoted in Figure 3. There they mixed with either bromide stream A1 or A2 and were subjected to microwave irradiation to afford all possible products. Streams B1 and B2 were then simply switched to B3 and B4 giving rise to a sequential, parallel synthesis. By using this technique the number of products was doubled relative to the example in Table 3. The total number of products obtainable by this methodology is only limited by the number of reagents employed, and, once again, the products are separated by time.

This strategy demonstrates that the number of products obtainable in this parallel synthesis strategy is no longer limited to the number of reaction vessels as is the case with conventional parallel synthesis. To prepare the library shown in Table 4 by using a conventional microreactor approach would require a single channel reactor to perform eight continuously flowing separate reactions, one after another, in the same channel; this series of reactions would require minimally four times the amount of time to complete. This aside, our system represents the first MW- (or indeed thermally)-assisted parallel synthesis in a continuous flow format and, as such, marks a potentially new direction for high-throughput synthesis.

In summary, we have developed a new capillary-based approach to parallel synthesis, whereby the reagents flow in sequence into a multicapillary reactor device and the transformations are accelerated by microwave irradiation to provide collections of compounds in a very rapid, clean, and efficient manner.

Experimental Section

Preparation of cross-coupling library prepared by sequential injection of stock solutions using a flow capillary reactor with microwave irradiation (Table 1): Stock solutions containing aryl halides **2** (stream B1), **3** (stream B2), **4** (stream B3), **5** (stream B4) and **6** (stream B5) (0.3 mmol, 1 equiv) and $Pd(PPh_3)_4$ (17 mg, 0.015 mmol, 5 mol%) in DMF (1 mL) were prepared and loaded into Hamilton gas-tight syringes B1 to B5, respectively. A stock solution containing phenylboronic acid (**1**; stream A) (48 mg, 0.39 mmol, 1.3 equiv), and 2 M KOH (0.45 mL, 3.0 equiv, 0.9 mmol) in DMF (1 mL) was prepared and loaded into Hamilton gas-tight syringe A. The continuous flow microwave system was primed with DMF and syringes A and B1 were connected to the reactor system as shown in Figure 1A, with the aid of Microtight™ fittings. The syringes

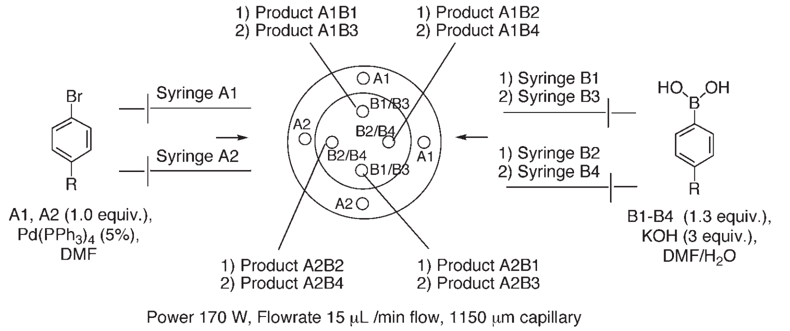
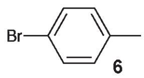
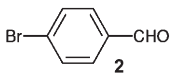
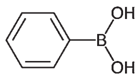
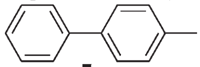
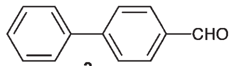
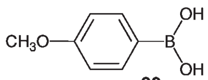
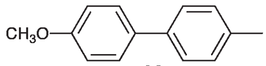
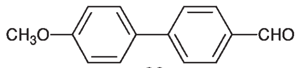
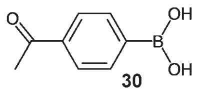
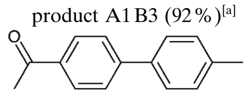
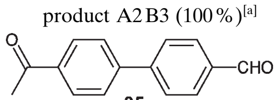
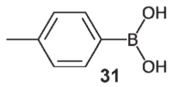
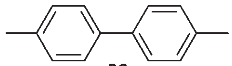
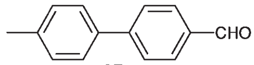


Figure 3. Top view of multireactor system schematic for a 2×4 parallel, sequential synthesis.

Table 4. Preparing libraries of compounds by sequential, parallel capillary irradiation using the multi-inlet reactor (shown in Figure 3).

	bromide A1	bromide A2
	 **6**	 **2**
boronic acid B1  **1**	product A1 B1 (67 %)[a]  **7**	product A2 B1 (100 %)[a]  **3**
boronic acid B2  **29**	product A1 B2 (91 %)[a]  **32**	product A2 B2 (100 %)[a]  **33**
boronic acid B3  **30**	product A1 B3 (92 %)[a]  **34**	product A2 B3 (100 %)[a]  **35**
boronic acid B4  **31**	product A1 B4 (91 %)[a]  **36**	product A2 B4 (100 %)[a]  **37**

[a] Percent conversion was determined by ^{1}H NMR spectroscopy and is relative to residual starting fluoride.

were placed in a Harvard 22 syringe pump that was set to deliver 15 μL min^{-1}, and the single mode microwave (Biotage Smith Creator Synthesizer™) was programmed to heat constantly at 170 W. The syringe pump and MW were turned on and the effluent from the reactor was fed into collection tubes and analyzed directly by ^{1}H NMR spectroscopy immediately after the reaction. When 0.15 mL of B1 had been fed into the reactor, the syringe was switched to one containing just DMF that was ran for 30 s to clean the lines. The syringe was then switched to B2 and the process repeated until all stock solutions B1 to B5 had passed through the reactor. All products are known and the ^{1}H NMR spectra obtained for compounds **7**, **8**, and **9**;[26] **10**;[27] and **11**[28] were consistent with the literature data for these compounds. All compounds in this study were isolated by silica gel chromatography for the purpose of spectroscopic identification.

Preparation of an array of compounds by nucleophilic aromatic substitution *via* two-stream infusion into the microreactor of the MACOS system (Table 2): Stock solutions containing the aryl amines **13** (stream B1), **14** (stream B2), **15** (stream B3), **16** (stream B4) and **17** (stream B5), (1.5 mmol, 2 equiv) were prepared and loaded into Hamilton gas-tight syringes B1 to B5, respectively. A stock solution containing 2-fluoronitrobenzene (**12**; stream A; 104 mg, 0.74 mmol, 1 equiv) and diisopropylamine (0.26 mL, 0.74 mmol) in DMF (0.74 mL) was prepared and loaded into Hamilton gas-tight syringe A. The continuous flow microwave system was primed with DMF and syringes A and B1 were connected to the reactor system as shown in Figure 1A, with the aid of Microtight™ fittings. The syringes were placed in a Harvard 22 syringe pump that was set to deliver 15 μL min^{-1} and the single mode microwave (Biotage Smith Creator Synthesizer™) was programmed to heat constantly at 170 W. The syringe pump and MW were turned on and the output from the reactor was fed into collection tubes and was analyzed directly by ^{1}H NMR spectroscopy immediately after reaction. When 0.15 mL **of B1** had been fed into the reactor, the syringe was switched to one containing just DMF that was ran for 30 s to clean the lines. The syringe was then switched to B2 and the process repeated until all stock solutions had passed through the reactor. Products **18**,[29] **20**,[30] and **21**[31] are known and the ^{1}H NMR spectra obtained were consistent with literature data. Compounds **19** and **22** gave ^{1}H NMR data consistent with samples prepared previously in our laboratories. All compounds in this study were isolated by silica gel chromatography for the purpose of spectroscopic identification.

Preparation of libraries of compounds by simultaneous parallel capillary irradiation using the multi-inlet reactor (Table 3): Two separate stock solutions containing the aryl amines **24** (amine B1), and **25** (amine B2) (1.2 mmol, 2 equiv) in DMF (1.21 mL) were prepared and loaded into Hamilton gas-tight syringes B1 and B2, respectively. Similarly, two separate stock solutions containing fluoronitrobenzene **12** (fluoride A1) and **23** (fluoride A2) (0.6 mmol, 1 equiv), each containing diisopropylamine (0.21 mL, 1.2 mmol) in DMF (1 mL), were prepared and loaded into Hamilton gas-tight syringes A1 and A2, respectively. The continuous flow, multi-inlet microwave system was primed with DMF and syringes A1, A2, B1, and B2 were connected to the reactor system as shown in Figures 1B and 1C and Table 3 with the aid of Microtight™ fittings. The syringes were placed in a Harvard 22 syringe pump that was set to deliver 20 μL min^{-1} and the single mode microwave (Biotage Smith Creator Synthesizer™) was programmed to heat constantly at 170 W. The syringe pump and MW were turned on and the output from the reactor was fed into collection tubes and was analyzed directly by ^{1}H NMR spectroscopy immediately after reaction. Product **26** is known and the ^{1}H NMR spectrum obtained was consistent with the literature.[31] Compounds **27, 28**, and **29** gave ^{1}H NMR data consistent with samples prepared previously in our laboratories. All compounds in this study were isolated by silica gel chromatography for the purpose of spectroscopic identification.

Preparation of libraries of compounds by sequential, parallel, capillary irradiation using the multi-inlet reactor (Table 4): Two separate stock solutions containing aryl halides **6** (bromide A1) and **2** (bromide A2) (6 mmol, 1 equiv) and each containing Pd(PPh$_3$)$_4$ (34 mg, 0.003 mmol, 5 mol %) in DMF (2.9 mL) were prepared and loaded into Hamilton gas-tight syringes A1 and A2, respectively. Similarly, four separate stock solutions containing boronic acids **1** (boronic acid B1), **29** (boronic acid B2),

30 (boronic acid B3) and **31** (boronic acid B4) (7.8 mmol, 1.3 equiv), each containing 2 M KOH (0.9 mL, 3.0 equiv, 1.8 mmol) in DMF (2 mL), were prepared and loaded into Hamilton gas-tight syringes B1 to B4, respectively. The continuous flow multi-inlet microwave system was primed with DMF and syringes A1, A2, B1 and B2 were connected to the reactor system as shown in Figures 1B, 1C, and 3 and Table 4 with the aid of Microtight™ fittings. The syringes were placed in a Harvard 22 syringe pump that was set to deliver 20 μL min^{-1} and the single mode microwave (Biotage Smith Creator Synthesizer™) was programmed to heat constantly at 170 W. The syringe pump and MW were turned on and the output from the reactor was fed into collection tubes and was analyzed directly by ^{1}H NMR spectroscopy immediately after reaction. When 0.15 mL of the four streams had been fed into the reactor, the syringe was switched to one containing just DMF that was ran for 30 s to clean the lines. The syringes were then switched to B3 and B4 and the process repeated until all stock solutions had passed through the reactor. Products **7**,[26] **3**,[26] **32**,[32] **33**,[33] **34**,[34] **35**,[35] **36**,[36] and **37**[36] are known and the ^{1}H NMR spectra obtained were consistent with the literature. All compounds in this study were isolated by silica gel chromatography for the purpose of spectroscopic identification

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