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Communications to the Editor

Development and Applications of a Practical Continuous Flow Microwave Cell

Noel S. Wilson,* Christopher R. Sarko, and Gregory P. Roth

Boehringer Ingelheim Pharmaceuticals, Inc., Department of Medicinal Chemistry, P.O. Box 368, 900 Ridgebury Road, Ridgefield, Connecticut 06877-0368, U.S.A.

Abstract:

A series of synthetic transformations were successfully and safely scaled up to multigram quantities using focused microwave irradiation with a continuous flow reaction cell that was developed in-house and which can be easily adapted to commercially available instrumentation. The representative reactions that were investigated included aromatic nucleophilic substitution (S_NAr), esterification, and the Suzuki cross-coupling reaction. In general, the product yields were equivalent to or greater than those run under conventional thermal heating conditions.

Introduction

Over the last several years, microwave-assisted organic synthesis has gained significant recognition among organic chemists as revealed by the numerous recent reviews.[1] This popularity is primarily due to significant advancements in single-mode microwave technology that is directed towards streamlining organic synthesis. Interestingly, given the significant surge in microwave-based chemistries being employed and the availability of safe and reliable instruments, it is surprising that very little has been done to investigate and address downstream issues such as preparative or large-scale synthesis using microwaves.

Typically, two methods are available for the scale-up of microwave chemical processes; batch reactors[2] and continuous flow systems. The earliest reported system, by Strauss and co-workers,[3] demonstrated that the concept of accelerating organic reactions in a continuous flow manner with microwave energy was indeed feasible. Although these systems have proven to be synthetically useful in scaling up chemical processes, they depend on the chemist transferring optimized chemistry from smaller single-mode systems to either larger batch-type systems or multimode microwaves.[4] Unfortunately, this transfer from single- to multimode may not be linear and may result in the chemist re-optimizing the reaction prior to scale-up.

Our interest in developing a continuous microwave reactor (CMR) originates from our need to eliminate the potential reaction parameter re-optimization (time and temperature) typically required for scale-up as methods are transferred from small-volume, single-mode systems to larger (but limited)-volume multimode systems. Therefore, we focused our attention on developing a CMR which used commercially available single-mode systems, such as the Discover[5] and Emrys Synthesizer.[6] This would allow us to directly transfer optimized chemistry from small to large scale without changing from single- to multimode. The CMR operates by passing a reaction mixture though a microwave transparent coil that is held in the cavity of the focused microwave chamber. In this report we describe the design of the CMR and present applications demonstrating the synthetic usefulness of the tool.

Requirements for the CMR. Unlike the earlier CMRs that employed multimode systems, we focused our attention on using a commercially available single-mode microwave, the Emrys Synthesizer. We felt this would provide us with the added advantage of focused microwave heating which would produce an even heating distribution and greater heating control. A disadvantage of developing a CMR centered on the single-mode microwave is that the microwave chamber is considerably smaller than multimode systems. Therefore, for a CMR to be designed for a single-mode reactor, the cell must utilize the cavity space to it fullest potential. To address this issue we developed a CMR consisting of a series of glass coils (Figure 1).

Description of the CMR. The flow cell consists of 22 3-mm (1/8 in.) i.d. borosilicate glass coils encased in a 100 mm × 10 mm protective borosilicate glass sheath. The coiled glass reactor was found to be an efficient method to maximize the time the reaction mixture was exposed to microwave irradiation, and the total flow cell volume was 4 mL. The glass reactor, shown in Figure 1, was fitted with Omni glass threaded connectors, two fixed-length PTFE end fittings with porous 25 μm PTFE frits, and silicone O-rings

* To whom correspondence should be addressed. E-mail: nwilson@rdg.boehringer-ingelheim.com.

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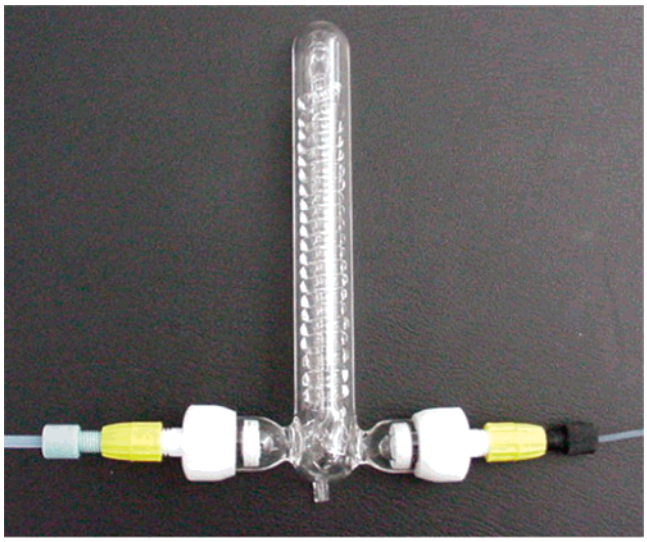

Figure 1. **Glass coiled flow cell.**

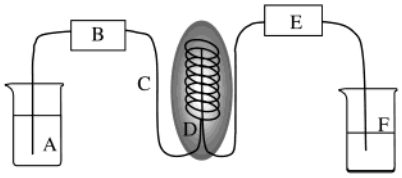

Figure 2. **Schematic diagram of the CMR in an open-loop mode. (A) Reaction mixture, (B) HPLC pump, (C) microwave cavity, (D) flow cell, (E) back-pressure regulator, (F) product reservoir.**

cut from an Omnifit 10-mm i.d. glass chromatography column. These fittings were connected with 3-mm (1/8 in.) i.d. TFE Teflon tubing rated for pressures up to 500 psi and an operating temperature of 200 °C. The inlet tube was connected to a Rainin HPXL pump, and the outlet was connected to a 100 psi back-pressure regulator (Figure 2). The system has the flexibility of running either in an open- or closed-loop mode. The flow cell was inserted into the cavity of the single-mode microwave from the bottom of the instrument.[7] In this configuration the flow cell temperature was monitored and controlled through the microwave's internal IR sensor (located in the cavity) and instrument software.[8]

Examples. *Nucleophilic Aromatic Substitution.* A common reaction used in the synthesis of medicinally relevant pharmacophores is the S_NAr reaction.[9] Typically the S_NAr product is a common intermediate used in library design, and therefore large-scale synthesis of the intermediate is required. Although the microwave-assisted methodologies have been investigated,[10] to our knowledge no CMR systems have been utilized for the preparation of S_NAr products.

(7) The Emrys Synthesizer was raised to gain access to the bottom of the instrument and flow cell inserted into the microwave cavity from underneath the instrument.

(8) Caution: bypassing software may result in safety issues.

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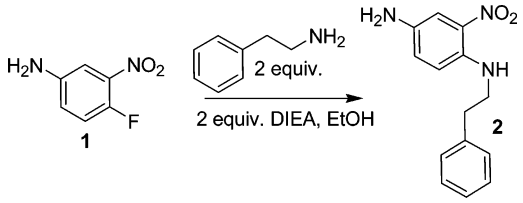
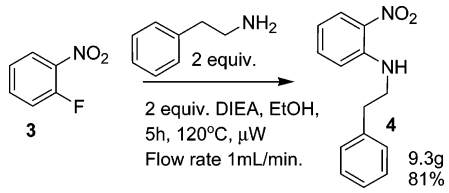
Table 1. **Nucleophilic aromatic substitution of 4-fluoro-3-nitroaniline with phenethylamine**



entry[a]	heating method	temp (°C)	flow rate (mL/min)	time (h)	% conversion[b]
1	NA	rt	NA	5	0
2	oil bath	100	NA	18	20
3	CMR	120	1	5	54

[a] 50 mL, 0.24 M solution. [b] Determined by LC−MS.

Scheme 1. **Nucleophilic aromatic substitution of 2-fluoro-3-nitrobenzene**

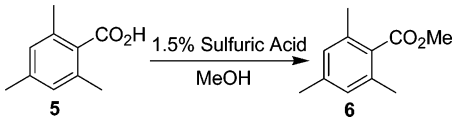


Our studies involved the nucleophilic aromatic substitution of 4-fluoro-3-nitroaniline with phenethylamine (Table 1). The reaction did not proceed at room temperature and was sluggish at reflux temperatures (entries 1 and 2). Only 20% conversion was observed even after prolonged heating. In comparison, our closed-loop CMR system provided 54% conversion after 5 h (entry 3). The total irradiation time per mL of reaction mixture was 24 min, and the 5 h processing time reflects the time required to react 12 mmol of material overall. The methodology was further expanded to the large-scale synthesis of compound **4** (Scheme 1). Although an 81% yield of product **4** was obtained, a common limitation of CMRs was observed. As the reaction progressed, the S_NAr product crystallized from the solution as a fine orange powder. The result was that the particles eventually clogged the lines and frits. It was necessary to terminate the reaction before complete consumption of the starting material.

Esterification. To directly compare the effectiveness of our CMR system we attempted the esterification of 2,4,6-trimethylbenzoic acid with methanol (MeOH) as described by Strauss and co-workers.[3] The published example reports the esterification of 2,4,6-trimethylbenzoic acid, with methanol, in 83% conversion, using only 1.5% sulfuric acid (by volume) after 1 min. They reported that the temperature of the system was 80−90 °C above the boiling point of MeOH, and this was a safety concern to us.

We first investigated the chemistry using small scale and the Emrys Synthesizer to evaluate potential safety issues associated with superheating MeOH above its boiling point. Since the pressure of MeOH at 150 °C was in excess of 250 psi, we choose to reduce the temperature to 120 °C, resulting in a pressure of 61 psi. When our CMR was used at 120 °C for 2 min in an open-loop system, 50% of the 2,4,6-trimethylbenzoic acid was converted to the methyl ester

Table 2. **Esterification of 2,4,6-trimethylbenzoic acid**

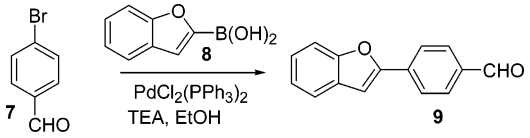


5 6

entry[a]	heating method	temp (°C)	flow rate (mL/min)	time	% conversion[b]
1	NA	rt	NA	1 h	0
2	oil bath	80	NA	70 h	14
3	CMR	120	1	2 min	50

[a] 100 mL, 0.15 M solution. [b] Determined by LC−MS.

Table 3. **Suzuki coupling results**



entry	heating method	temp (°C)	flow rate (mL/min)	time	% conversion
1	sealed microwave tube	140	NA	6 min	86[a]
2[c]	NA	rt	NA	6 h	11[b]
3[c]	CMR	120	0.25	8 min	73[b]
4[c]	CMR	130	0.25	8 min	82[b]
5[c]	CMR	140	0.25	8 min	84[a]

[a] Isolated yield. [b] Determined by ^{1}H NMR, 250 MHz. [c] 50 mL, 0.11 M solution.

(Table 2). In comparison, with prolonged heating only a low conversion (14%) was obtained using traditional heating techniques.

Suzuki Reaction. The Suzuki reaction has become one of the most important carbon−carbon bond formation reactions in organic synthesis. During the past few years several microwave conditions have been developed;[11] however, typically these methods require an aqueous workup. Recently, Öhlberg and Westman obtained compound **9** without an aqueous workup and in excellent yield when ethanol (EtOH) was used for the solvent and triethylamine (TEA) for the base.[12] The coupled product **9** was obtained in excellent yield upon treatment of 1.1 equiv of aryl halide with 1 equiv of the boronic acid in the presence of 20 mol % $PdCl_2(PPh_3)_2$ and 2 equiv of TEA while heating at 140 °C for 6 min (Table 3, entry 1). However, at the time of their report the only methods for scale-up of a microwave Suzuki reaction obtained in a single mode was via batch production or re-optimization using conventional heating techniques or a multimode microwave.

To validate the safety issues associated with transferring the optimized chemistry to our CMR we decided to lower temperature for our initial run (Table 3, entry 3). Although some palladium did not dissolve and precipitated out as a mirror on the surface of the flow cell, no clogging of the lines and no temperature effects were observed. Upon raising the temperature, results comparable to those reported by Öhlberg and Westman were obtained (entries 1, 4, and 5). To verify that the reaction did not proceed prior to treatment with microwave irradiation an equivalent reaction stirring at room temperature was performed (entry 2). Only an 11% yield of the Suzuki product was obtained after 6 h. The workup of the reaction is very straightforward and does not require an aqueous wash. The mixture is simply filtered through a plug of silica gel to remove the Pd catalyst and the product then crystallizes directly from the filtrate.

Conclusions

A variety of chemical processes were successfully and safely scaled up to multigram quantities using our continuous flow microwave cell. The CMR can be easily fabricated and proved to be a cost-effective alternative to purchasing commercially available microwave scale-up systems since it is adaptable for a variety of single-mode microwaves. The representative chemistries explored included S_NAr, esterification, and the Suzuki cross-coupling reaction. In all cases product yields were equivalent to or greater than conventional heating methods and scaled up to multigram quantities with clogging of the lines and over-pressurization as the only limitations observed. Nonetheless, our CMR does have the advantage that it does not require a re-optimization step when transferring chemistries from small to large scale.

Experimental Section

All ^{1}H NMR were recorded on either a Bruker Biospin AC250 (250 MHz) or a Bruker Biospin DPX-400 (400 MHz) instrument in $CDCl_3$. The ^{1}H NMR spectra were referenced to the ^{1}H resonance of residual chloroform (δ 7.26). Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t =triplet, q = quartet, m = multiplet, br = broad signal), coupling constant (Hz), and integration. All LC−MS data were analyzed by an HPLC/UV/MS system utilizing a Gilson 215, Agilent HP 1100 LC, a Sedex 55 ELSD (evaporative light-scattering detector), and a Micromass Platform II mass spectrometer. The ionization mode utilized was positive electrospray ionization. The HPLC column employed was Zorbax SB-C8 (4.6 mm × 30 mm).

A Typical Procedure for the Nucleophilic Aromatic Substitution of 2-Fluoro-3-nitrobenzene. A 250-mL Erlenmeyer flask was charged with 1-fluoro-2-nitrobenzene (5 mL, 47.4 mmol), ethanol (67 mL), phenethylamine (2 equiv, 11.9 mL, 94.8 mmol), and DIEA (2 equiv, 16.5 mL, 94.8 mmol). The CMR was primed with ethanol, and the single-mode microwave was programmed to heat the sample to 120 °C for 5 h. The intake line to the HPLC pump was placed in the reaction mixture, along with the outtake line from the flow cell, creating a closed-loop system. The HPLC was set to pump at 1 mL/min, and the microwave was turned on. The solution changed from yellow to dark red after 1 h, and an orange precipitate developed. After 5 h the solution was cooled, and the precipitate was collected, providing the

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product in 81% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16 (dd, 1H, J = 8.61 Hz, J = 1.56 Hz), 8.10 (brs, 1H), 7.43 (ddd, 1H, J = 8.61 Hz, J = 7.04 Hz, J = 1.76), 7.37 (m, 2H), 7.29 (m, 3H), 6.86 (dd, 1H, J = 8.8 Hz, J = 1.17 Hz), 6.64 (ddd, 1H, J = 8.22 Hz, J = 6.65 Hz, J = 1.18 Hz) 3.59 (dt, 2H, J = 7.24 Hz, J = 5.28 Hz) 3.05 (t, 2H, J = 7.24 Hz).

A Typical Procedure for the Esterification of 2,4,6-Trimethylbenzoic Acid. A 250-mL Erlenmeyer flask was charged with 1.5% H_2SO_4 (by volume) in MeOH (total volume 100 mL) and the acid (2.5 g, 15 mmol). The CMR was primed with methanol, and the single mode microwave was programmed to heat the sample to 120 °C for 5 h. The intake line to the HPLC pump was placed in the reaction mixture, and the outtake line from the flow cell was placed into a second 100-mL Erlenmeyer flask, creating an open-loop system. The HPLC was set to pump at 1 mL/min, and the microwave was turned on (2-min resonance time). After 5 h the solution was cooled, and concentrated under reduced pressure. The crude material was diluted with ethyl acetate, washed with water (2×), and brine (1×), dried over $MgSO_4$, and concentrated to provide the product in 50% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.85 (s, 2H), 3.90 (s, 3H), 2.29 (s, 9H).

A Typical Procedure for the Suzuki Coupling of 4-Bromobenzaldehyde. A 100-mL Erlenmeyer flask was charged with $PdCl_2(PPh_3)_2$ (0.20 mol %, 80 mg, 1.14 mmol) and 48.4 mL of ethanol. To the stirring suspension was added 2-benzofuranboronic acid (1 equiv, 5.7 mmol, 0.93 g), 4-bromobenzaldehyde (1.1 equiv, 6.3 mmol, 1.16 g), and TEA (2 equiv, 11.4 mmol, 1.6 mL). The CMR was primed with ethanol, and the single-mode microwave was programmed to heat the sample to 140 °C for 5 h. The intake line to the HPLC pump was placed in the reaction mixture, and the outtake line from the flow cell was placed into a second 100-mL Erlenmeyer flask, creating an open-loop system. The HPLC was set to pump at 0.25 mL/min, and the microwave was turned on. The collected sample was filtered through a plug of silica to remove the Pd catalyst, and the product was crystallized from the filtrate in 84% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.04 (s, 1H), 7.93 (dd, 4H, J = 8.41 Hz, J = 8.22 Hz), 7.74 (d, 1H, J = 7.83 Hz), 7.56 (d, 1H, J = 8.42 Hz), 7.35 (dt, 1H, J = 8.41 Hz, J = 1.37 Hz), 7.27 (t, 1H, J = 7.63 Hz), 7.22 (s, 1H)

Acknowledgment

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Supporting Information Available

Outlined procedure for the continuous flow cell setup and operation. This material is available free of charge via the Internet at http://pubs.acs.org.

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