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A Simple Continuous Flow Microwave Reactor

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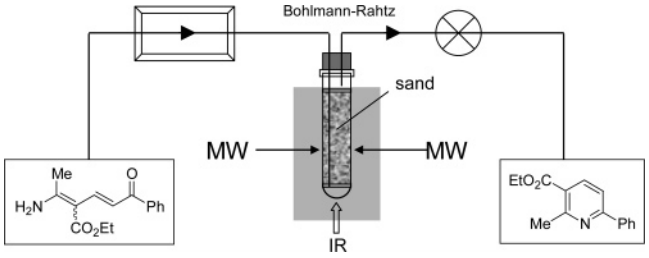

A new simple procedure for microwave-assisted organic synthesis under continuous flow processing has been developed for use in a monomodal microwave synthesizer with direct temperature control using the instrument's in-built IR sensor. This design makes optimum use of the standing wave cavity to improve the energy efficiency of microwave-assisted flow reactions.

Microwave-assisted organic synthesis (MAOS) has received increasing attention in recent years as a valuable alternative to the use of conductive heating for accelerating chemical reactions.[1] With no direct contact between the chemical reactants and the energy source, microwave-assisted chemistry is energy efficient, provides fast heating rates and enables rapid optimization of procedures. From the early experiments in domestic ovens[2] to the use of multimodal[3] or monomodal[4] instruments designed for organic synthesis, this technology has been implemented worldwide and continues to be developed.[5] However, although modern monomodal instruments dedicated for MAOS are very successful in small-scale operations, efforts to process this technology in continuous flow (CF) reactors are frustrated by the physical limitations of microwave heating, with a penetration depth of only a few centimeters and the limited dimensions of the standing wave cavity. Current technology has attempted to overcome these obstacles with conventional instruments by the use of CF reactors that pump the reagents through a small heated coil that winds in and out of the cavity,[6] with external temperature monitoring using a fiber optic sensor, although alternative methods, such as using a multimode batch[3,7] or CF reactor,[8] have also been described. We now wish to report our new method for carrying out MAOS under CF processing using a commercially available monomodal microwave synthesizer.

The principal design of our flow cell featured the need to make optimum use of the cavity and to be able to monitor the temperature of the flow cell directly using the instrument's in-built IR sensor. To this end, a standard pressure-rated glass tube (10 mL) fitted with a custom built steel head was filled with sand (~10 g) between two drilled frits (Figure 1) to minimize dispersion and effectively create a lattice of microchannels, charged with solvent (~5 mL volume), sealed using PTFE washers and connected to an HPLC flow system with a back-pressure regulator (Figure 2). The flow cell was inserted into the cavity of a self-tunable monomodal microwave synthesizer, irradiated, and stabilized at the required reaction temperature through moderation of microwave power before the introduction of reagents into the reactor. This system possessed a number of advantages over commercially available coils, including simple measurement of the flow cell temperature, no additional and expensive equipment required short of an HPLC pump, and the potential to carry out heterogeneous as well as homogeneous reactions simply by immobilizing a catalyst on the support in the glass tube.

The cell was first tested in two well-precedented microwave-assisted reactions operating under continuous flow (CF) processing, the hydrolysis of chloromethyl-

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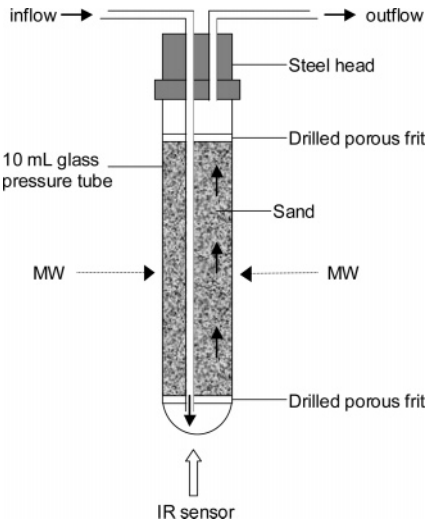


FIGURE 1. Flow cell schematic.

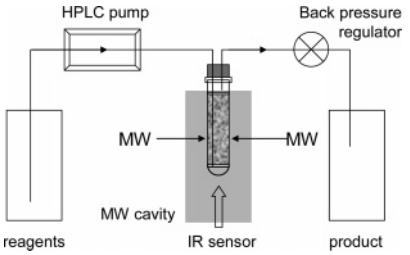
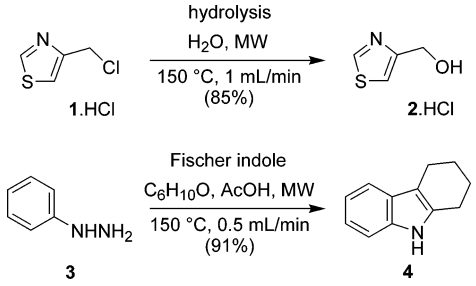


FIGURE 2. Schematic diagram of the CF reactor.

thiazole **1** to give hydrochloride **2**[9] and a Fischer indole synthesis[10] of **4** from hydrazine **3** and cyclohexanone in acetic acid, in both cases using sand as the packing agent. Under these conditions efficient conversions were achieved at 150 °C, processing 1 g in 15−30 min, to give alcohol **2** and indole **4** in 85% and 91% yield, respectively (Scheme 1).

Following the success of these flow reactions, efforts were made to develop a new microwave-assisted process

SCHEME 1. MW-Assisted CF Reactions



for the synthesis of pyridines based upon the Bohlmann−Rahtz (B-R)[11] reaction. The cyclodehydration of aminodienone **5** can be effected using conductive heating,[12] and with a Lewis[13] or Brønsted[14] acid catalyst, to give 2,3,6-trisubstituted pyridine **6** directly and with total regiocontrol, and this transformation has been applied in the synthesis of pyridine-containing thiopeptide antibiotics,[15] and their derivatives,[16] as well as pyrido[2,3-*d*]pyrimidines,[17] heterocyclic amino acids,[18] nonsteroidal antiinflammatory agents,[19] and combinatorial pyridine libraries.[20] Aminodienone **5** was prepared according to known procedures[12] and cyclodehydrated with CF processing under homogeneous conditions in toluene−acetic acid (5:1) over sand,[21] comparing the results to batch experiments carried out in a sealed tube and to the corresponding homogeneous CF process with a Teflon heating coil (Scheme 2). Under conditions that gave efficient conversion (>98%) to pyridine **6**, the processing rates of material using our glass tube reactor were considerably higher (Table 1). Additionally, CF reactions run at the same flow rate used less magnetron energy in a glass tube than in the heating coil (Table 1, Figures 3 and 4, and Supporting Information), demonstrating that a glass tube CF reactor

(9) For comparison, a solution of **1**·HCl (170 mg, 1.0 mmol) in H_2O (2 mL) was irradiated at 150 °C in a sealed glass tube (150 W) for 10 min and evaporated in vacuo to give **2**·HCl (151 mg, >98%). Comparable conductive heating procedures carried out at 150 °C in a sealed tube for 12 min, or at reflux for 30 min, gave thiazole **2**·HCl (90% or 85%, respectively, by HPLC). For related hydrolysis experiments using conductive heating, see: (a) Houssin, R.; Pommery, J.; Salauen, M.-C.; Deweer, S.; Goossens, J.-F.; Chavatte, P.; Henichart, J.-P. *J. Med. Chem.* **2002**, *45*, 533. (b) Hagen, S. E.; Domagala, J.; Gajda, C.; Lovdahl, M.; Tait, B. D.; Wise, E.; Holler, T.; Hupe, D.; Nouhan, C.; Urumov, A.; Zeikus, G.; Zeikus, E.; Lunney, E. A.; Pavlovsky, A.; Gracheck, S. J.; Saunders: J.; VanderRoest, S.; Brodfuehrer, *J. Med. Chem.* **2001**, *44*, 2319.

(10) For comparison, a solution of cyclohexanone (196 mg, 2 mmol) and **3** (220 mg, 2.2 mmol) in AcOH (4 mL) was irradiated at 150 °C in a sealed glass tube (150 W) for 10 min and then evaporated in vacuo. The residue was extracted with EtOAc, washed with H_2O, aqueous $NaHCO_3$ solution (2 N) and brine, dried ($MgSO_4$), and evaporated in vacuo to give **4** (212 mg, 62%), mp 113−115 °C. The comparable conductive heating procedure carried out at 150 °C in a sealed tube for 10 min gave **4** (94%), mp 115−117 °C, after purification by column chromatography on SiO_2 eluting with light petroleum−EtOAc (9:1). For related Fischer indole syntheses, see: (a) An, J.; Bagnell, L.; Cablewski, T.; Strauss, C. R.; Trainor, R. W. *J. Org. Chem.* **1997**, *62*, 2505. (b) Robinson, B. *Chem. Rev.* **1969**, *69*, 227. (c) Hughes, D. L. *Org. Prep. Proced. Int.* **1993**, *25*, 607. (d) Franco, L. H.; Palermo, J. A. *Chem. Pharm. Bull.* **2003**, *51*, 975. (e) Lipin'ska, T. *Chem. Heterocycl. Compd.* **2001**, *37*, 231. (f) Lipin'ska, T.; Guibe-Jampel, E.; Petit, A.; Loupy, A. *Synth. Commun.* **1999**, *29*, 1349.

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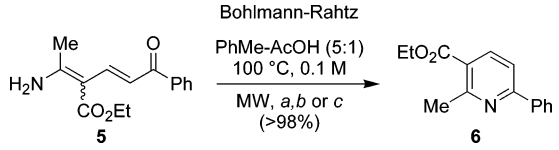
(21) The glass tube was filled with standard quartz sand, 40−100 mesh, suitable for use in chromatography. When aminodienone **5** was irradiated in toluene (without acetic acid) in the presence and absence of sand in a sealed tube, no appreciable difference was observed (13% versus 5% conversion, respectively), indicating that the sand has a negligible (if any) effect on the cyclodehydration.

SCHEME 2. Bohlmann–Rahtz Synthesis of 6[a]



[a] Reagents and conditions: (a) 150 W (initial power), sealed tube, 2 min; (b) 300 W (initial power), CF in Teflon heating coil, 1 mL/min; (c) 300 W (initial power) with simultaneous cooling,[22] CF in a glass tube charged with sand, 1 or 1.5 mL/min.

TABLE 1. Comparing MAOS of Pyridine 6 Using Sealed Tube or CF Processing

	sealed tube[a]	CF coil[b]	CF coil[b]	CF glass tube[c]	CF glass tube[c]
isolated yield, %	>98	>98	85[d]	>98	>98
residency time,[e] min	2	5[f]	3.3[f]	3	2
flow rate, mL min^{-1}		1	1.5	1	1.5
processing rate, mmol min^{-1}		0.1	0.15	0.1	0.15
total energy,[g] kJ		1411	762	850	735

[a] Batch experiment in a sealed glass tube. [b] CF processing in a Teflon heating coil. [c] CF processing in glass tube reactor charged with sand. [d] Based upon ^{1}H NMR analysis of crude reaction mixture. [e] Residency in the microwave cavity. [f] Residency in the heating coil. [g] Energy delivered by the magnetron in a flow reaction, obtained by integrating the power versus time profile.

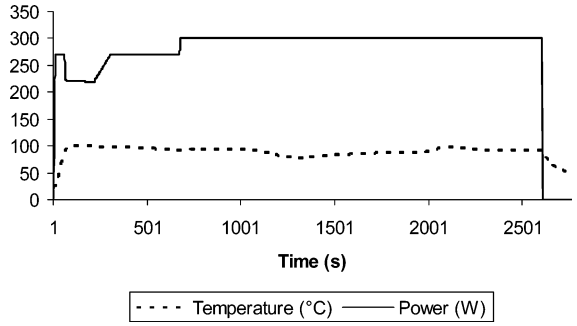


FIGURE 3. Reaction profile of the CF heating coil reactor at 1.5 mL min^{-1} flow rate.

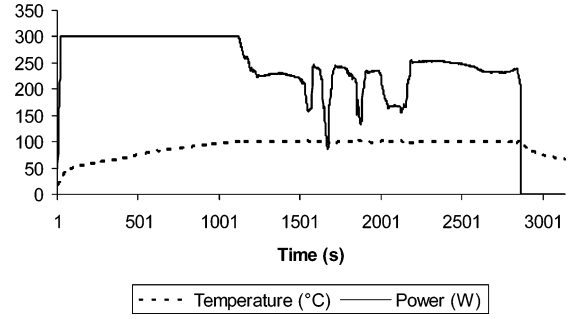


FIGURE 4. Reaction profile of the CF glass tube reactor at 1.5 mL min^{-1} flow rate.

offers (i) improved heating efficiency, (ii) the potential for operation on a large scale, (iii) successful transfer from batch to CF processing, and (iv) improved performance over commercial Teflon heating coils. A higher processing rate is possible with a glass tube reactor as a faster flow rate can be maintained without compromising the reaction temperature and yield. We have attributed this observation to be a direct consequence of the improved heating efficiency for reactions in the glass tube, as heating coils by design wind in and out of the optimum space.

In conclusion, a CF microwave reactor has been developed for use with a monomodal instrument for homogeneous reactions that enables the direct measurement of flow cell temperature using an IR sensor and possesses many advantages over existing CF technology. The use of this instrumentation in a heterogeneous process through use of an immobilized catalyst and the transfer of this processing technology to large-scale operations on a kilogram scale in an 80 mL cell are now underway and will be reported in due course.

Experimental Section

Microwave Reactions under CF Processing. The flow cell (see the Supporting Information for flow cell assembly) was primed with solvent at a given flow rate and stabilized at the reaction temperature. A flask was charged with the reaction mixture, which was then passed through the cavity at the given flow rate, washing with further batches of solvent.

4-Hydroxymethylthiazole (2) Hydrochloride. A solution of 4-chloromethylthiazole hydrochloride (2.0 g, 12 mmol) in H_2O (20 mL) was irradiated at 150 °C (150 W) in a pressure-rated glass tube (10 mL) filled with sand (~12 g) in a MW CF reactor at a flow rate of 1.0 mL min^{-1}. The cell was washed with H_2O (20 mL) at 150 °C and the combined solutions were evaporated in vacuo. Purification by recrystallization (Et_2O–EtOH) gave the title compound (1.5 g, 85%) as pale brown crystals, mp 112–114 °C (lit.[23] mp 115 °C) (found: $M^{\bullet+}$, 115.0093; C_4H_5NOS requires M 115.0092); ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.35 (1H, s), 8.20–7.70 (2H, br s), 7. 60 (1H, s), 4.65 (2H, s).

2,3,4,9-Tetrahydro-1*H*-carbazole (4). A solution of cyclohexanone (1.96 g, 20 mmol) and phenylhydrazine (2.20 g, 22 mmol) in glacial AcOH (40 mL) was irradiated at 150 °C (150 W) in a pressure-rated glass tube (10 mL) filled with sand (~12 g) in a MW CF reactor at a flow rate of 0.5 mL min^{-1}. The cell was washed with AcOH (15 mL) at 150 °C and the combined solutions were evaporated in vacuo. The residue was extracted with EtOAc, washed with H_2O and brine, dried ($MgSO_4$), and evaporated in vacuo. Purification by recrystallization (EtOAc–hexane) gave the title compound (3.1 g, 91%) as pale beige crystals, mp 114–116 °C (lit.[24] mp 115–116 °C) (found: $M^{\bullet+}$, 171.1057; $C_{12}H_{13}N$ requires M 171.1048); ^{1}H NMR (400 MHz, d_6-DMSO) δ 10.56 (1H, s), 7.30 (1H, d, J = 7 Hz), 7.20 (1H, d, J = 8 Hz), 6.96 (app t, 1H, J = 7 Hz), 6.89 (1H, app t, J = 8 Hz), 2.68 (2H, t, J = 5.7 Hz), 2.60 (2H, t, J = 6.0 Hz), 1.86–1.74 (4H).

Ethyl 2-Methyl-6-phenylpyridine-3-carboxylate (6): Batch Synthesis in a Sealed Tube. A solution of aminodienone **5**[11,12] (80 mg, 0.3 mmol) in PhMe–AcOH (5:1) (3 mL) was irradiated for 2 min at 100 °C (150 W) in a sealed pressure-rated glass tube. The reaction mixture was cooled by a flow of compressed air then partitioned between saturated aqueous $NaHCO_3$ and EtOAc, and the aqueous layer was further extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated in vacuo to give the title compound (75 mg, >98%) as a yellow oil. **CF Synthesis in a Heating Coil Reactor.** A solution of aminodienone **5** (1.3 g, 5.1 mmol) in PhMe–AcOH (5:1) (50 mL) was irradiated at 100 °C (300 W) in a Teflon heating coil in a MW CF reactor at a flow rate of 1 mL min^{-1} and quenched in a

(22) With simultaneous cooling, IR temperature measurement may not record the accurate bulk temperature of the reaction mixture; see: Leadbeater, N, E.; Pillsbury, S. J.; Shanahan, E.; Williams, V. A. *Tetrahedron* **2005**, *61*, 3565.

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solution of saturated aqueous $NaHCO_3$. The mixture was extracted three times with EtOAc and the organic extracts were combined, dried ($MgSO_4$), and evaporated in vacuo to give the title compound (1.2 g, >98%) as a yellow solid. **CF Synthesis in a Glass Tube Reactor.** A solution of aminodienone **5** (80 mg, 0.3 mmol) in PhMe−AcOH (5:1) (3 mL) was irradiated at 100 °C (300 W) in a pressure-rated glass tube (10 mL) filled with sand (∼12 g) in a MW CF reactor at a flow rate of 1.5 mL min^{-1}, while simultaneously cooling the tube in a flow of compressed air.[22] The mixture was quenched immediately in a solution of saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic extract was dried ($MgSO_4$) and evaporated in vacuo to give the title compound (75 mg, >98%) as a yellow solid, mp 44−45 °C (MeOH) (lit.[11] mp 44 °C) (found: C, 74.4; H, 6.5; N, 5.6l calcd for $C_{15}H_{15}NO_2$: C, 74.7; H, 6.3; N, 5.8) (found: MH^+, 242.1182; $C_{15}H_{15}NO_2$ requires *MH* 242.1182); IR (KBr) ν_{max} 2980, 2925, 2890, 1717, 1581, 1476, 1277, 1090, 1022 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (1H, d, J = 8.2 Hz), 8.00 (2H, m), 7.55 (1H, d, J = 8.2 Hz), 7.41 (3H), 4.33 (2H, q, J = 7.1 Hz), 2.85 (3H, s), 1.35 (3H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7 (C), 159.1 (C), 158.1 (C), 138.5 (CH), 137.6 (C), 128.7 (CH), 128.0 (CH), 126.5 (CH), 122.8 (C), 116.5 (CH), 60.3 (CH_2), 24.6 (Me), 13.5 (Me); MS (APcI) *m/z* (rel intensity) 241 (M^+, 91%), 240 (69), 212 (32), 196 (100), 195 (98), 168 (43), 167 (40).

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Supporting Information Available: General experimental procedures, diagrams and photographs of apparatus, instructions for assembly, and all power/temperature versus time flow reaction profiles for the synthesis of pyridine **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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