Development and Application of a Continuous Microwave Reactor for Organic Synthesis

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Received November 16, 1993•

A laboratory-scale continuous microwave reactor (CMR) has been developed and used to conduct organic syntheses routinely, rapidly, and safely in a range of solvents, under pressures up to 1400 kPa and at temperatures up to 200 °C. Advantages and applications of the CMR are discussed, along with the rationale for the design. Reactions carried out with the CMR included nucleophilic substitution, addition, esterification, transesterification, acetalization, amidation, base- and acid-catalyzed hydrolysis, isomerization, decarboxylation, and elimination. Name reactions included the Michael addition, Hofmann degradation, Williamson ether synthesis, and the Mannich, Finkelstein, Baylis–Hillman, and Knoevenagel reactions.

Introduction

Given the extensive development of microwave applications for digestion of samples in analytical chemistry, it is perhaps surprizing that the technology was not introduced in organic synthesis until 1986.[1,2] The delay was possibly attributable to difficulties and hazards associated with monitoring and control of organic reactions in a microwave environment. The early publications on microwave-assisted organic synthesis reported the use of domestic microwave ovens and rudimentary vessels. This equipment did not allow adequate control and monitoring of temperature and pressure. As a result there were cases of reaction vessels deforming and explosions.[1,3] Since 1986, the field of microwave-assisted organic synthesis has grown exponentially despite the lack of specifically designed and commercially available hardware.[4–6]

Before substantial benefits of microwave technology can be realized in the organic chemistry laboratory, however, microwave units have to be engineered to operate reliably and safely on a routine basis in the presence of organic solvents. We became interested in microwave-assisted chemistry and in the design and fabrication of microwave equipment for organic chemical applications in mid-1988 and have since investigated aspects of this field.[7–9]

One of our developments is the continuous microwave reactor (CMR) which operates by passing a reaction mixture through a pressurized, microwave-transparent coil that is held in a microwave cavity.[10–12] The purpose of this paper is to discuss the rationale for the design of the CMR and to present reactions which demonstrate the technique for organic chemical applications.

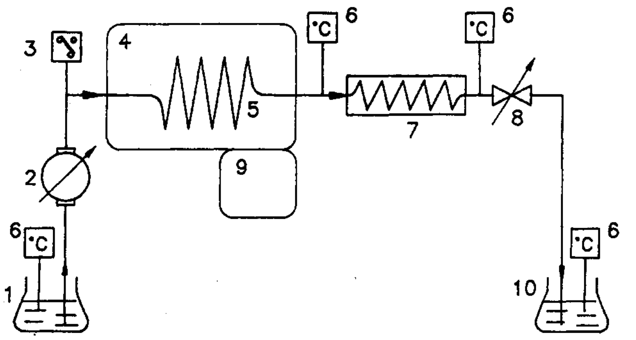

Figure 1. Schematic diagram of the CMR. 1, Reaction mixture; 2, pump; 3, pressure sensor; 4, microwave cavity; 5, reaction coil; 6, temperature sensor; 7, heat exchanger; 8, pressure control valve; 9, electronic key pad and display; 10, product mixture.

Discussion

Requirements for a CMR. To make continuous microwave reaction systems safe and useful for organic synthesis, the following main features were important: (a) the means to determine and control the temperature and pressure of reaction mixtures within the reaction vessel while the reaction was in progress; (b) if reactions became uncontrollably hot (*e.g.* as in thermal runaway situations) or if malfunctions (*e.g.* blockages or ruptures of the reaction coil) occurred during operation, it was essential that the system could be rapidly shut down; (c) the unit needed to provide, for the synthetic chemist, advantages that were not offered by existing laboratory equipment; and (d) the CMR required the potential for scaling-up and scaling-down in chemical processing applications.

Development of a CMR. Owing to the nature of the electromagnetic fields within a microwave cavity, it is difficult to obtain a uniform energy distribution and to control and monitor temperature. To overcome these problems, prototype CMRs were fitted with metering, monitoring, and control devices which were located outside the irradiation zone.

Each CMR (see Figure 1) consisted of a microwave cavity (microwave power 600–800 W) fitted with a coil fabricated

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• Abstract published in *Advance ACS Abstracts,* May 15, 1994.

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from a microwave-transparent, inert material.[13] The coil was attached to a metering pump and pressure gauge at the inlet end and a heat exchanger and pressure regulating valve at the effluent end. Solutions could be rapidly cooled under pressure immediately after they exited the irradiation zone. Thermosensors allowed monitoring of the temperature of the reaction mixture before it entered the microwave zone, after it exited, and after it had been cooled. Variables such as coil length, flow rates, and control of the applied microwave power conferred flexibility on the system. The in-line pressure regulating valve held the contents of the coil under adjustable and monitored pressures. The plumbing was designed to minimize contact between metal surfaces and reaction mixtures.

Feed-back microprocessor control was introduced, thereby allowing the operator to preset pump rates and temperatures for heating and cooling of reactions. In the case of heating, full microwave power would be applied until the preset temperature was attained, and then rapid switching of the magnetron such that the reaction temperature would remain within plus or minus 3 °C of the set point provided the control. Fail-safe parameters were included in the software so that the unit would shut down if the temperature exceeded the maximum allowable by at least 10 °C or in the event of blockages or ruptures in the reaction coil. Changes made to the programmed reaction conditions could be entered while the unit was operating and would take effect immediately.

Selection of Operating Parameters for the CMR. Data for boiling point versus pressure for a selection of commonly used solvents show that in many cases the boiling points increase significantly with pressures up to about 1400 kPa, and then these increases become less substantial with further pressure rises.[14] A maximum operating pressure of 1400 kPa would hence allow relatively high temperatures to be safely attained for a variety of solvents. Perfluoroalkoxy (PFA) Teflon[15] or quartz tubing were appropriate materials for the reaction coil because they are chemically inert, microwave transparent, and also allow physical observation of the reaction mixture in the microwave zone. Because of the tendency of PFA Teflon to flow at higher temperatures, however, an upper operating temperature limit of 200 °C was incorporated into the reactor software, with automatic shutdown if the temperature attained 210 °C. PFA Teflon tubing of 3 mm ($^1/_8$ in.) i.d. and 6 mm ($^1/_4$ in.) o.d. could be used satisfactorily at 200 °C and 1400 kPa. However, to allow for ruptures in the tubing during operation, a minimum pressure of 50 kPa was programmed into the software. It was found convenient to use tubing of *ca.* 3 m in length and flow rates of *ca.* 15 mL/min. These conditions allowed residence times of 1–2 min and processing rates of around 1 L/h. The volume of the system, excluding the reaction coil, was approximately 25 mL.

Reaction Time and Temperature. In CMR preparations the time taken to perform a reaction will depend upon the volume of material to be processed, the flow rate, the volume of coil used, and the number of passes required. We have taken the residence time of the reaction mixture in the microwave irradiation zone to be the reaction time. The temperature of the reaction mixture immediately upon exit from the microwave zone has been taken as the reaction temperature, even though there obviously would be thermal gradients in the material as it proceeds along the coil. The exit temperature may not necessarily be the maximum temperature attained by the reaction mixture, however, as this depends on a number of factors including the flux density at various points in the microwave cavity and the nature of the chemical reaction being conducted. If two polar reactants are undergoing condensation to give a less polar product for example, the exit temperature could well be lower than that elsewhere in the reaction coil. Since reaction times in the order of 1–2 min were used routinely, however, the reaction mixtures would not have had sufficient time to cool appreciably before exiting the microwave zone. In general, the exit temperature thus could be expected to approximate the maximum temperature in the reaction coil.

Examples. Table 1 presents data for 26 reactions which have been performed in the solvents and with the reactants listed. It shows that for several volatiles, it has been possible to carry out reactions in the CMR at temperatures up to 100 °C higher than the boiling point of the solvent at atmospheric pressure. These conditions have given accelerated reactions, with reaction times reduced by up to 3 orders of magnitude when compared with literature conditions. In two recent studies we have shown that for homogeneous reaction mixtures at least, the rate enhancements result from the elevated temperatures rather than from any specific "microwave effect".[7,9]

As indicated by Table 1, nucleophilic substitution, addition reactions, esterifications, transesterifications, acetalizations, base- and acid-catalyzed hydrolyses, isomerizations, oximations, decarboxylations, and eliminations have all been carried out by CMR. Name reactions include the Michael addition, Hofmann degradation, Williamson ether synthesis, Claisen rearrangement, and the Mannich, Finkelstein, Baylis–Hillman, Diels–Alder, and Knoevenagel reactions. Unoptimized reactions have been included among the examples to indicate the scope and potential of the CMR technique.

Entries 1–3 (Table 1) give typical parameters for and results from esterifications which employed sterically hindered reactants. The CMR preparation of *i*-PrOAc (entry 1) has been conducted several times and yields within the range of 85–98% have been obtained routinely when there has been an excess of HOAc in the reaction mixture. The reaction also has proceeded well with excess *i*-PrOH, at a reaction temperature in the range 140–4 °C, over 60 °C higher than the boiling point of *i*-PrOH at atmospheric pressure. Both the product yield of 81% and the reaction time of 1.7 min compare favorably with the methodology and results from literature methods.[16]

Esterification of 2,4,6-trimethylbenzoic acid (mesitylenecarboxylic acid) with a low boiling alcohol is difficult to achieve at reflux, but proceeds well under pressure in a microwave environment[7,8] (entries 2 and 3). A literature method for preparing esters of mesitylenecarboxylic acid involves addition of this acid to 100% sulfuric acid followed by the esterifying alcohol.[17] With the CMR, the methyl ester was prepared quantitatively after four passes of a

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[13] Modification of domestic microwave units for laboratory applications is not recommended for safety reasons.

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Table 1. Example Reactions and Conditions

entry no.	reaction	temp (°C)	mean press. (kPa)	time (min)	product	yield (%)	lit. ref
1	HOAc + *i*-PrOH/H^+	152–5	1200	1.3	*i*-PrOAc	98	16
2	2,4,6-trimethylbenzoic acid MeOH/H^+	148–59	1250	4[a] × 1.3	methyl 2,4,6-trimethylbenzoate	1[b]:83[c] 4:100	17
3	2,4,6-trimethylbenzoic acid + *i*-PrOH/H^+	155–64	1300	4 × 1.6	isopropyl 2,4,6-trimethylbenzoate	81	7, 8
4	glycerol in Me_2CO/H^+	132–5	1175	1.2	2,2-dimethyl-1,3-dioxolane-4-methanol	84	18
5	PhCOOMe + 5% aqueous NaOH	166–8	700	1.0	PhCOOH	100	3
6	PhCOOEt + MeOH/H^+	145–50	1050	4 × 1.4	PhCOOMe	1:46[c] 4:96[c]	
7	paraformaldehyde in 3% aqueous HCl	160–70	1100	1.2	aqueous HCHO	100	25
8	PhMe in aqueous $KMnO_4$/KOH	180	1050	1.3	PhCOOH	41[c,d]	1, 3
9	benzophenone + $NH_2OH{\cdot}HCl$ in pyridine/EtOH	164	500	1.5	benzophenone oxime	93	3
10	BnCl + NaOPh in MeOH	144–7	1000	1.5	BnOPh	67	19
11	*p*-chlorobenzaldehyde in EtOH/H^+	142–4	950	1.4	*p*-chlorobenzaldehyde diethyl acetal	59	26
12	methyl acrylate in aqueous HCHO/DABCO	158–64	950	1.5	methyl 2-(hydroxymethyl)acrylate	30	21
13	BuCl in NaI/Me_2CO	150	1000	1.5	BuI	36[c,e]	27
14	*s*-BuCl in NaI/Me_2CO	145	950	5 × 1.5	*s*-BuI	5[c,e]	16, 27
15	3-Hydroxy-2-methyl-4-pyrone in 25% aqueous $MeNH_2$	160–2	900	1.3	1,2-dimethyl-3-hydroxypyrid-4-one	65	24
16	indole in Me_2NH/aqueous HCHO	160–70	700	1.2	Gramine	97[e]	16
17	2-methylfuran in Me_2NH/aqueous HCHO	164–5	350	1.4	5-methylfurfuryldimethylamine	48	28
18	citronellal + NH_2OH in pyridine/EtOH	164	500	1.5	citronellaldoxime	82	3, 29
19	citronellaldoxime + Chloramine T in EtOH	128–33	800	1.5	3,3,6-trimethyl-3,3a,4,5,6,7-hexahydro-2,1-benzisoxazole	78	30
20	carvone + 1 M aqueous H_2SO_4 with emulsifier	165–75	740	4 × 1.5	carvacrol	1:32[c] 2:63[c] 3:73[c] 4:83[c]	22
21	furfural in diethyl malonate/pyridine	165	1200	1.6	2-furanacrylic acid	18 44[c]	31
22	PhCOMe in Me_2NH/HCHO	180–90	400	1.0	$PhCOCH_2CH_2NMe_2$	29	16
23	$[PhCOCH_2CH_2NMe_3]^+ I^-$ in water	90–5	100	1.6	$PhCOCH{=}CH_2$	96	16
24	2-formylphenoxyacetic acid in Ac_2O/HOAc with NaOAc	180	550	1.0	benzofuran	24[e]	32
25	$PhCH_2CH_2Br$ in NaOMe/MeOH	95	730	1.7	$PhCH{=}CH_2$ (75%) + $PhCH_2CH_2OMe$ (9%)	84[e]	33, 34
26	$PhCH_2CH_2Br$ in MeOH	138–45	1100	60 × 1.8	$PhCH_2CH_2OMe$	38[c]	34

[a] The integer refers to the number of passes of the reaction mixture through the microwave zone. [b] Pass number. [c] Conversion. [d] Highly exothermic reaction. See cautionary note in the text. [e] The reaction was interrupted periodically to clear blockages in the flow system.

reaction mixture which contained only 1.5% sulfuric acid by volume. The total reaction time for complete esterification was 5.2 min, but even after the first pass (reaction time 1.3 min), the conversion was 83%. Significantly, the temperature of the effluent stream was some 80–90 °C above the boiling point of MeOH at atmospheric pressure. When *i*-PrOH was condensed with mesitylenecarboxylic acid in the presence of catalytic quantities of sulfuric acid, isopropyl 2,4,6-trimethylbenzoate was obtained in 81% yield after only 6.4 min of total reaction time (four passes) at reaction temperatures in the range 155–64 °C (entry 3). To underscore the efficacy of the CMR technique, a comparable reaction proceeded in only 2.4% conversion after 28 h at reflux.[8]

The CMR preparation of the acetonide of glycerol proceeded cleanly, with a reaction time of 1.2 min and at a temperature over 70 °C higher than the boiling point of Me_2CO at atmospheric pressure (entry 4). As with the esterification reactions discussed above, no attempt was made to separate the water formed during the reaction. A conventional method of preparation takes 21–36 h and a yield of 87–90% of isopropylideneglycerol can be obtained.[18] Using the CMR method, the reaction was carried out 1000–1800 times faster than the literature procedure and in comparable yield.

The base-catalyzed hydrolysis of PhCOOMe was first carried out in a microwave environment by Gedye et al.[3] but without any monitoring of temperature or pressure. In that work, PhCOOH was obtained in 84% yield after treatment with 25% aqueous NaOH solution in a sealed vessel for 2.5 min. In the present study (entry 5), a reaction time of 1.0 min was selected, 5% aqueous NaOH was used, and the hydrolysis was quantitative. The oximation of Ph_2CO is another reaction which has been performed batchwise, under microwave irradiation, to give a 68% yield of benzophenone oxime after 2 min of heating.[3] That derivatization proceeded about 60 times faster than a corresponding conventional preparation.[3] The CMR preparation (entry 9) used the same proportions of reagents and solvents as employed[3] for the batch procedure. The reaction temperature was 164 °C and the purified oxime was obtained in 93% yield after a reaction time of 1.5 min. The Williamson synthesis of BnOPh was conducted at 144–7 °C in the CMR with 1.5 min reaction time, using MeOH as solvent (entry 10). The recrystallized product was obtained in 67% yield. This synthesis has been previously studied by microwave heating, including continuous processing in an unpressurized system which gave a conversion of 49% after a reaction time of 10 min.[19]

Entries 5, 9, and 10 indicate that reactions which have

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[19] Chen, S.-T.; Chiou, S.-H.; Wang, K.-T. *J. Chem. Soc., Chem. Commun.* **1990**, 807.

been carried out batchwise in a sealed vessel in a microwave zone can be readily modified for continuous processing under pressure in a CMR, provided that the reaction mixture can be pumped. In contrast with batchwise techniques,[1-3] there is no waiting time for the pressure and temperature to drop before accessing the reaction mixture. Analysis of samples from the reaction can be carried out while (or before) fresh material is processed.

The facility to readily remove the reaction mixture from a heating zone and then to rapidly cool it is highly advantageous for reactions that require heat but produce thermally labile products. Two such examples were the Hofmann degradation (entry 23) and the modified Baylis-Hillman reaction (entry 12). In the Hofmann degradation, phenyl vinyl ketone was produced by passage of a 5% aqueous slurry of *N*-(2-benzoylethyl)-*N*,*N*,*N*-trimethylammonium iodide through the microwave zone at 100 kPa pressure. The cooled aqueous effluent was immediately diluted into chilled Et_2O, thereby precluding polymerization of the monomer and allowing near quantitative yields. In conventional Hofmann degradation reactions[16] the ketone is steam distilled from the reaction mixture. The yields are lower, presumably because there are greater opportunities for polymerization of the product.

Kress et al.[20] have examined the application of methyl 2-(hydroxymethyl)acrylate for the preparation of new polymers. They prepared the methyl ester by a modified Baylis–Hillman reaction which was carried out at room temperature over several days.[21] These conditions are not conducive to the preparation of kilogram quantities of material. In contrast, CMR methodology has allowed us to carry out the syntheses of several alkyl 2-(hydroxymethyl)acrylates in a few minutes and to prepare the required quantities of material in yields which are comparable with those published. This work will be the subject of a future report.

With the CMR technique, the utilization of less aggressive reagents or the same reagent applied in lesser amounts but at high temperatures can substitute for the use of aggressive reagents at low temperatures. The CMR esterification of mesitylenecarboxylic acid (entries 2 and 3, discussed above) with catalytic amounts of sulfuric acid (rather than the quantities required in the traditional method) is an example. In addition, however, the CMR technique can facilitate chemoselectivity even though the temperature of reaction may be higher than reflux conditions. An illustration of this involves the preparation of methyl 2-phenylethyl ether from 2-(bromoethyl)benzene. The preparation of 2-phenylethyl ethers from 2-phenylethyl halides is difficult owing to the competing base-promoted elimination reaction which gives styrene. CMR treatment of 2-(bromoethyl)benzene with NaOMe in MeOH returned low yields of methyl 2-phenylethyl ether and high yields of styrene, at temperatures ranging from 20 to 95 °C (see entry 25). However, the desired ether was obtained by CMR at higher temperatures, but under nonbasic conditions, without giving styrene (entry 26). The reaction mixture consisting of 2-(bromoethyl)benzene in MeOH was recirculated through the system over several hours. Monitoring was carried out hourly, by GC-MS and NMR analysis of samples. After 7 h (approximately 60 passes), at temperatures of 138–145 °C, the solution contained nearly 40% of the desired product along with starting materials.

It also was considered that reactions which liberated gases could be problematic owing to the possibility of sudden pressure increases in the reaction coil, but reactions which were carried out to assess these potential risks proceeded without difficulty (entries 21 and 24).

Optimization of Reactions. Optimization of CMR reaction conditions can be conveniently achieved. If a large volume of starting material is prepared, the reaction conditions can be varied while sampling during a run. In preparations with reaction times of 1–2 min, a steady state has been typically obtained within *ca.* 7 min after commencement of the run. Conditions can then be changed, and the reaction mixture sampled after each steady state has been attained.

In other work we required carvacrol, which had been prepared in 40% yield by heating an acidified aqueous mixture of carvone on a steam bath for 4 h.[22] We have reported the kinetics of this isomerization when carried out batchwise in an organic solution under microwave conditions.[9] With the CMR, the best conditions found in water required the addition of an emulsifying agent to facilitate phase transfer. A temperature range of 165–75 °C afforded a conversion of 83% after 4 passes and a total reaction time of 6 min (entry 20).

Example 15 summarizes a CMR preparation of 1,2-dimethyl-3-hydroxypyrid-4-one, a potent iron chelator which has undergone extensive clinical trials over recent years.[23] The literature conditions[24] involved heating a solution of maltol and aqueous $MeNH_2$ for 6 h at reflux, and the product was isolated in 50% yield as colorless crystals after treatment with decolorizing charcoal. In our early attempts at the development of the CMR method, the product crystallized out in the cooling zone of the reactor. The optimized method required passage of hot effluent from the reactor directly into a flask containing chilled Me_2CO. The product crystallized from this solvent as pink rods which were filtered off and recrystallized from deionized water to give pure material. Reaction times of 1.0, 1.2, 1.3, 1.5, 1.8, and 2.3 min and molar ratios maltol:$MeNH_2$ of 1:1, 1:1.3, 1:2, 1:3, and 1:4 were explored. The most favorable conditions gave the product in 53% yield as a first crop, with further pure material (12%) recovered from the mother liquors.

Limitations of the CMR Technique. It is not likely that any single technology will be universally applicable in organic chemistry. The CMR technique described above would not be appropriate when solids or highly viscous liquids are to be heated, when the reaction requires low temperature conditions throughout, or when materials or reactions which are incompatible with microwave energy (*e.g.* metals or reactions involving predominantly nonpolar organics) are to be employed.

Solids. Most of the problems encountered with the technique have concerned blockages brought about by the presence of insoluble solids. Slurried material in the feed can be successfully processed, however, provided that the solid component is finely powdered (see entries 7 and 23, in which the feed material was slurried, but during the course of the reaction the solid was consumed). Solids

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[20] Kress, A. O.; Mathias, L. J.; Cei, G. *Macromolecules* **1989**, *22*, 537.

[21] Kusefoglu, S. H.; Kress, A. O.; Mathias, L. J. *Macromolecules* **1987**, *20*, 2326.

[22] Sattar, A.; Ahmad, R.; Khan, S. A. *Pak. J. Sci. Res.* **1980**, *23*, 177.

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[24] Kontoghiorges, G. J.; Sheppard, L. *Inorg. Chim. Acta* **1987**, *136*, L11.

formed in the reaction have presented more problems because the particle size can vary. In some cases (entries 13, 14, 15, 16, and 25) the reaction was interrupted periodically to clear blockages.

Safety. We have performed over 100 reactions by CMR and the only occasion on which we had an explosion involved an attempted amidation using 25% aqueous ammonia in a borosilicate glass reaction coil. The explosion was attributed to base attack on the glass, so this material has not been used subsequently for reaction tubing.

The potential for accidents exists mainly with exothermic reactions in which solids are formed and there is a risk of blockage or electrical discharge. An example was the permanganate oxidation of toluene (entry 8): it heated very rapidly, the oxidation was exothermic, and an insoluble solid, MnO_2, was formed. We conducted the reaction twice with the CMR, and both times solid accumulated in the reaction coil, near the exit point from the microwave cavity. Electrical discharge began to emanate from this, necessitating that the system be shut down immediately. It is notewothy that Gedye et al. reported that this reaction exploded during batchwise microwave heating,[1,3] and we therefore advise against the use of microwave-assisted chemistry for oxidations of this kind.

Advantages of the CMR. The CMR offers several advantages over conventionally heated equipment and these include the following: (a) Rapid response in comparison with conventional heating. Hence the times required for heating up and cooling down reaction mixtures are short, allowing operators more flexibility in the management of their work. (b) The irradiation chamber does not heat up substantially as the reaction mixture is heated directly and when the power is turned off heat input ceases immediately. This is an important safety consideration. (c) The continuous flow process allows unstable products to be quickly removed from the reaction zone and cooled (see entries 12 and 23). (d) There are minimal temperature gradients across the tube, so the temperature of the material on the wall of the reaction vessel is not significantly different from that in the body of the liquid. Pyrolysis on the inner wall of the tube is thus minimized. (e) Reactions which are known to require high temperatures and higher boiling solvents can be carried out under pressure at these temperatures, but in lower boiling solvents, thereby facilitating workup. (f) Low boiling reactants can be heated to high temperatures under the applied pressure and then cooled before exiting the pressurized zone. Losses of volatiles are thus minimized (see entries 7, 12, 16, 17, and 22). (g) Because of the flowthrough nature of the system, reactions can be sampled and analyzed while material is being processed. If necessary, reaction mixtures can be subjected to multiple passes through the CMR, or the conditions changed during a run (see entries 6, 20, and 26). (h) Reactions carried out on a laboratory scale should be more amenable to scale-up because of the continuous nature of the system (see entries 3, 7, 12, 15, and 23). (i) Moderate to high temperature reactions can be carried out in a vessel (tubing in the present case) which is fabricated from an inert material such as PFA Teflon, PTFE, or quartz. This would be beneficial where reactants or products are incompatible with metals or borosilicate glass.

Conclusion

A laboratory-scale CMR has been developed, which satisfies several criteria as a safe and useful laboratory tool in organic chemistry. The instrument has no counterpart at present: advantages and applications have been discussed, along with the rationale behind the design. The CMR should be readily amenable to scale-up in chemical processing, an aspect which is under active consideration.

The speed and versatility of the CMR for carrying out laboratory-scale reactions have been demonstrated by the examples quoted. Some reactions which have been difficult to conduct by conventional methodology, such as the esterification of 2,4,6-trimethylbenzoic acid, the Hofmann degradation, and the preparation of an alkyl 2-phenylethyl ether were easily achieved under CMR conditions.

Experimental Section

General. The CMRs used in this work comprised two prototype instruments which were fabricated in the CSIRO workshops and several commercially produced prototype units. The features of these machines are included in the Discussion section and in Figure 1. All of the CMR prototype units were fitted with PFA Teflon or PTFE (polytetrafluoroethylene) coils, 3 m long, 6 mm o.d., and 3 mm i.d., with a volume of 24 mL. Reaction conditions are summarized in Table 1.

^{1}H NMR spectra and GC-MS were carried out as previously described.[9] Melting points are uncorrected.

Spectral data for synthetic products agreed with those in the literature.

Example Preparations. Preparation of 2,2-Dimethyl-1,3-dioxolane-4-methanol (Entry 4, Table 1). A solution of glycerol (18.4 g, 0.2 mol) in Me_2CO (200 mL, 2.7 mol) containing TsOH (1.0 g) was passed through the CMR (20 mL/min; 132–5 °C; 1150–1200 kPa). The reaction mixture was collected in a flask containing $NaHCO_3$ (*ca.* 2 g) and equipped with a magnetic stirrer. After workup and distillation, the isopropylideneglycerol (21.5 g), boiling point 76 °C/6.5 mmHg, was obtained in 84% yield. When the reaction was carried out under milder conditions (20 mL/min; 100 °C; 450–500 kPa), a yield of 77% was obtained.

Depolymerization of Paraformaldehyde (Entry 7, Table 1). Paraformaldehyde (100 g) was mixed with water (300 mL) and 10 M HCl (5 mL). The mixture was stirred vigorously and pumped through the CMR (20 mL/min; 160–170 °C; 1000–1200 kPa), yielding a clear solution containing 25% HCHO as determined by wet chemical analysis.[25]

Acknowledgment. We are grateful to Dr. G. W. Simpson, Dr. B. Kasum, and Dr. R. B. Waring for helpful suggestions. Mr. I. Thomas, Mr. I. Marwick, and Mr. S. Wellink are thanked for their contributions regarding fabrication of prototype CMR units.

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