Microwave Reactions Under Continuous Flow Conditions

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Abstract: Microwave chemistry has already impacted significantly on the everyday synthesis of organic molecules. The adoption and integration of this liberating technology has permitted a resurrection of many synthetic transformations that were previously considered too extreme in their conditions (temperatures, pressures, reaction times) to be synthetically useful. Furthermore, whole arrays of additional chemical transformations have been devised under microwave heating that allow access to more diverse chemical architectures *via* more expedient routes. Continuous flow processing of chemical intermediates taking advantage of the unique heating mechanism and characteristics of microwave irradiation will certainly be the next evolutionary step forward in this area. The synergistic combination afforded by the simultaneous application of these two core processing tools will enhance still further the synthetic capabilities of tomorrow's chemists. This short review aims to highlight the current developments and future potential offered by continuous flow microwave mediated synthesis.

Keywords: Microwave, flow, reactor, microreactor, mesoreactor, process intensification, scale up.

INTRODUCTION

The basic approach and methods used to construct molecules has remained relatively unchanged over the last few decades despite the many conceptual and technological advances made in synthetic chemistry. Traditionally, the necessity to carry out reactions on bulk scale has involved the adoption of batch processing techniques which chemists are rigorously trained to understand and manipulate. Consequently, the whole area of synthetic chemistry has been dominated by the requirement to conform to batch working practices. This can be seen in every experimental laboratory with the standardised range of round-bottom flasks, separating funnels, conical flasks and heating mantles, helpfully repeated in volumes from millilitres to litres. The situation is replicated when moving to pilot plants with their developmental rigs and on into the process labs with their large glass-jacketed batch reactors. In each case, the scale at which the chemistries are conducted increases but the general approach and equipment used is often simply a reflection of multiplying the volumes used. It is therefore not entirely surprising that the introduction of new technologically inspired synthesis tools is almost always designed to function in this same batch mode operation. An excellent example of this is the microwave reactor.

The introduction of microwave heating techniques has impacted significantly on the throughput of reactions and the range of chemistries available to the standard bench synthesis chemist. The development of the area of microwave-enhanced (assisted) chemical synthesis has been revolutionary as can be testified to by the exceptional level of published literature on improved reaction yields and purities as well as the development of new chemical reactions. As a synthesis tool microwave reactors have in recent years been readily adopted because of their ease of operation and enhanced processing capabilities. A number of popular commercial units are available based on the general idea of a sealed glass reaction vessel (or similarly microwave transparent material) which can be inserted into the microwave cavity for the heating sequence and then removed for additional chemical manipulation. These systems are now defined by high levels of control, reproducibility and safety in the reactions performed through the integration of effective temperature and pressure monitoring. Increasingly, additional functionality and information capture is being enabled by the incorporation of embedded IR cameras, photo-optics and spectral analysers enabling monitoring of the reacting solution using techniques such as Raman. The coupling to robotic platforms further enhances the devices usefulness especially for the preparation of compound libraries through automated sequential microwave-enhanced synthesis. In such guises modern commercially available microwave reactors have evolved to enable the processing of multigram quantities of material. However, significant technological problems are encountered in attempting to scale beyond these modest levels, especially when moving towards production scales [1].

The heating characteristics of a microwave irradiated reaction do not always follow a linear form as microwave power is increased. This is due to numerous factors, but principally owing to increased heat loss, changes in absorption, limited penetration depth of the radiation and additional reflection of the microwaves [2]. Therefore a steady state, reproducible situation can only be achieved for certain reactor volumes and power level ratios (microwave irradiation is a volumetrically limited heating process). The typical operating frequency of most commercial microwave reactors is 2.45 GHz which gives a restricted penetration depth of only a few centimetres into the reaction medium depending on the specific dielectric properties of the system. A simplified approximation of Maxwell's theory [3] as applied to microwave penetration is shown by Equation 1 which describes the relationship between the dielectric properties of the medium and the effective absorption of the microwave irradiation. This means that the power density will decrease exponentially

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from the surface to the inner region of the reactor and that if this dimension exceeds the penetration depth of the microwaves a non-homogeneous heating effect will be created [4]. Obviously, a model could be derived for the propagation of a standing wave into a reactor vessel however; the dynamically changing composition and polarity of all the reaction components also determine the penetration depth and the total absorption of the microwave energy. Therefore the specific ability to scale a reaction will always be dependent on the reaction and its conditions (solvents and reagents), all of which play a significant role in the reaction heating mechanism more so than in a classical reaction. In addition, differential absorption of microwaves as a consequence of reflection and refraction between local boundaries will also lead to differences in heating and the generation of localized thermal temperature zones, even 'hot spots', that cannot be duplicated by conventional heating techniques [5]. Such boundaries can be created by changes in composition as reactions progress, or even through temperature gradients which directly affect the dielectric properties of molecules. Indeed, temperature effects resulting from changes in molecular structure can have a significant effect on the absorption of microwaves as can be seen by the values for water (Table **1**).

$$D_p = \frac{\lambda_o}{2\pi(2\varepsilon')^{1/2}}[(1 + (\varepsilon''/\varepsilon')^2)^{1/2} - 1]^{-1/2}$$

Equation 1. Penetration depth of microwave irradiation [6].

Table 1. Permeation of Microwave Irradiation (2.45 GHz) into Materials at Given Temperatures [7]

Material	Temperature (°C)	Penetration Depth (mm)
Water	25	14
Water	95	57
Ice	-12	11000
Glass	25	350
Teflon	25	92000
Quartz	25	160000

Such intrinsic complications have tended to prevent the direct scaling of microwave reactors past a few litres, thus inhibiting their use for the production of larger quantities of material [8]. Alternatively some researchers and equipment manufacturers have explored the potential of continuous flow microwave processing. Such an approach offers many advantages in terms of processing agility, safety, reaction monitoring and optimisation [9]. Importantly this processing approach also avoids the limitations associated with the design of scaled microwave cavities, including the associated costs.

It was recognised early on in the development of microwave reactors that flow based applications offered tremendous advantages in terms of processing capabilities. Two of the early pioneers of microwave chemistry, Christopher Strauss and Shui-Tein Chen, were extolling the virtues of continuous microwave reactors (CMRs) as early as 1990 [10]. Considering the now accepted date for the first microwave publication in organic synthesis is acknowledged as 1986 this should have signalled a new direction in microwave technology [11]. However, most researchers continued to work using batch processes preferring the familiarity and similarity to conventional laboratory practices. It might be considered short sighted of these chemists to overlook the additional advantages presented by working in the flow mode; however, the area of microwave chemistry was also under pressure to prove itself. There was increasing debate and scrutiny regarding the merits of microwave reactions. Were there any additional advantages over conventional heating? Were there any special microwave effects? Could you induce changes in selectivity or access new chemistries that could not be attained under normal thermal conditions? Furthermore, this was all being evaluated in parallel to the introduction of dedicated focussed mono-modal microwave apparatus as superior replacements of the notoriously unstable domestic microwaves. This obviously raised numerous questions regarding the merits of microwaves and the economics in justifying the additional costs associated with the purchase of the new focussed microwave units. It also catalysed the rapid expansion of the chemical literature either demonstrating enhanced reaction profiles in terms of yield and purity or comparing reaction rates under microwave irradiation with standard oil baths heating. By the turn of the century an average of 500 papers a year were being published under the guise of microwave chemistry and the general acceptance of microwave reactors as standard synthesis tools was set [12]. Today it is difficult to find a synthesis lab that does not possess or have access to a dedicated microwave reactor; however, the area of continuous microwave processing or flow microwave synthesis seems to have been overlooked. It is the aim of this article to review this area and explain the merits of re-evaluating this technology within the context of modern synthesis and scale-up.

THE APPLICATION OF CONTINUOUS FLOW THROUGH MICROWAVE REACTORS: MODIFICATIONS OF DOMESTIC APPLIANCES

The key requirement of a continuous flow microwave reactor is the ability to continuously monitor and adjust the reaction parameters whilst in operation. This facilitates both easy reaction optimisation and with the introduction of automated safety controls ensures a reliable prolonged processing capability. To this end the original design of flow microwave reactors were simple in concept and fabrication, being based on coiled microwave-transparent Teflon or Quartz tubes located within a domestic microwave (600-800 W) oven (Fig. **1**) [10a,13]. A simple metering pump with an in-line pressure gauge was attached to the coil to supply a steady stream of the reaction mixture. The flow rate could be easily controlled by the pumping unit and the coil could be exchanged (equating to different lengths and channel diameters) to provide additional flexibility in terms of reaction residence times. The presence of a heat exchanger rapidly cooled the reacting mixture on exiting the irradiation chamber prior to collection for easy handling. All the components were constantly monitored and controlled with a microprocessor, permitting observation software to conduct a failsafe shut down in the event of any unanticipated change in conditions such as a leak, a sudden temperature rise or a blockage in the reactor.

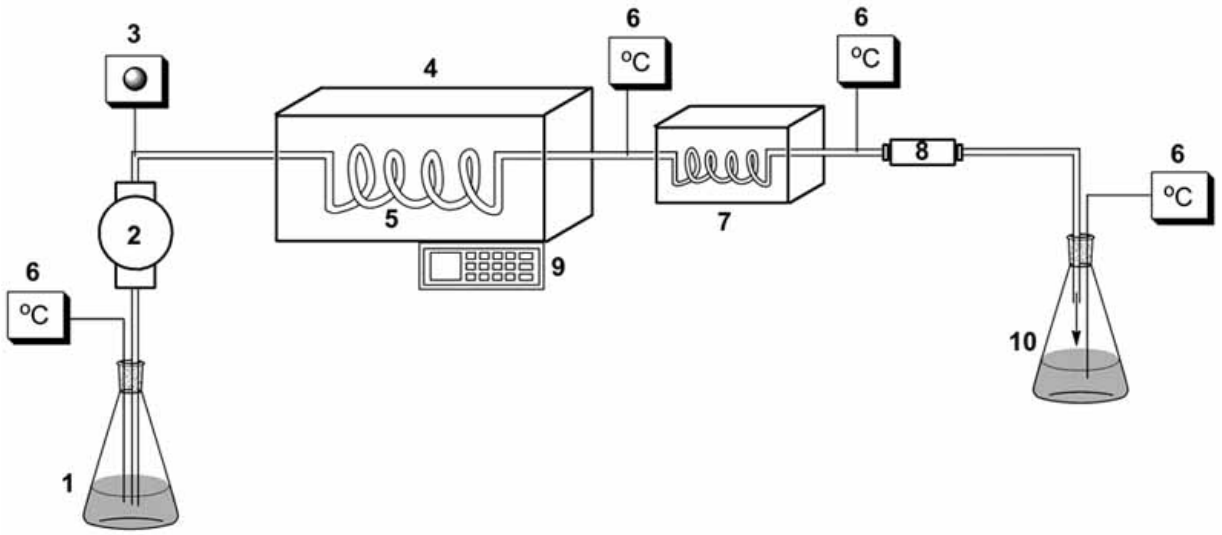


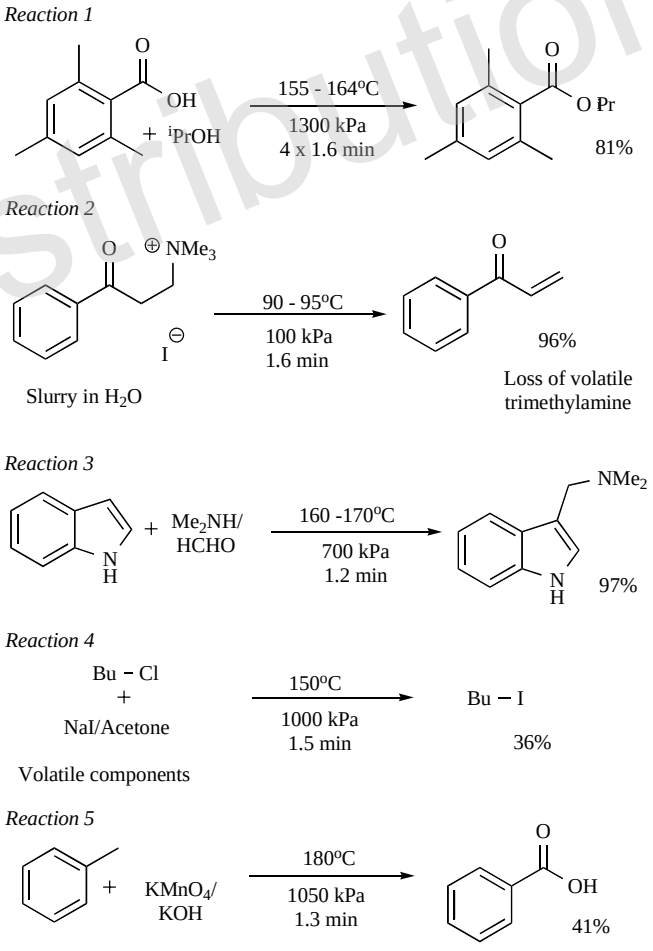
Fig. (1). Schematic illustration of the CMR. **1**. Reaction mixture; **2**. Pump; **3**. Pressure sensor; **4**. Microwave cavity; **5**. Reaction coil; **6**. Temperature sensor; **7**. Heat exchanger; **8**. Pressure control valve; **9**. Electronic key pad and display; **10**. Product mixture.

The operating conditions for the device enabled a complete range of parameters to be screened permitting reaction temperatures of up to 200ºC under pressures of 1400 kPa (14 bar; ~200 psi) and flow rates in the range of 15-20 mL/min to be used. At these flow rates a general residence time of 1-2 minutes was achieved allowing about 1 L an hour to be processed. As the reaction mixture was contained within the sealed environment of the reactor under elevated pressures, temperatures above the standard boiling point of the solvents/reagents (~100ºC) could be employed resulting in enhanced reaction rates. A wide range of different chemistries were successfully evaluated, including various substitution and elimination processes, a series of decarboxylation, esterfication and amidation reactions as well as an assortment of condensations. In total 26 different reactions were reported, a selection of which are shown in Scheme **1**.

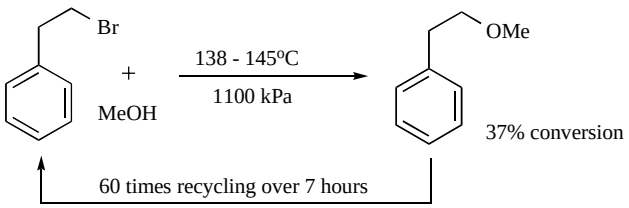
It was claimed by the authors that this type of reactor allowed the use of less aggressive reagents or a reduction in the quantity of reagents because of the elevated temperatures and pressures. This was certainly the case in comparing the yields and reaction times to the previous cited literature.

Although slurries of finely divided particles and precipitates were successfully processed (Scheme **1**; Reaction 2) the generation of solid mass within a continuous flow reactor can be problematic. Such an example was encountered with the highly exothermic oxidation of toluene to benzoic acid (Scheme **1**, Reaction 5) which generated insoluble MnO_2. Deposits of this oxide accumulated at the cooling zone of the reactor which eventually led to the system becoming blocked. However, once the reactor was stopped it could be rapidly cleaned by re-dissolution of the precipitate in hot solvent and the system restarted.

The relatively short reaction (retention) times provided by the reactor proved not to be a problem, even for combinations of reactants that require extended reaction times despite the elevated temperatures used. It was a relatively simple process to recycle material through the system, increasing the overall conversion to the product (Scheme **2**). Interestingly, the extended heating of this starting material over prolonged reaction times under classical conditions led to the accumulation of significant quantities of the styrene elimination product. The short but repeated reaction cycles used in these microwave reactions circumvented this problem.

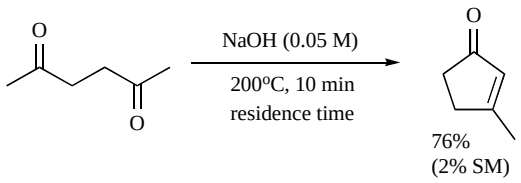


Scheme 1. Selected reactions performed in the CMR.



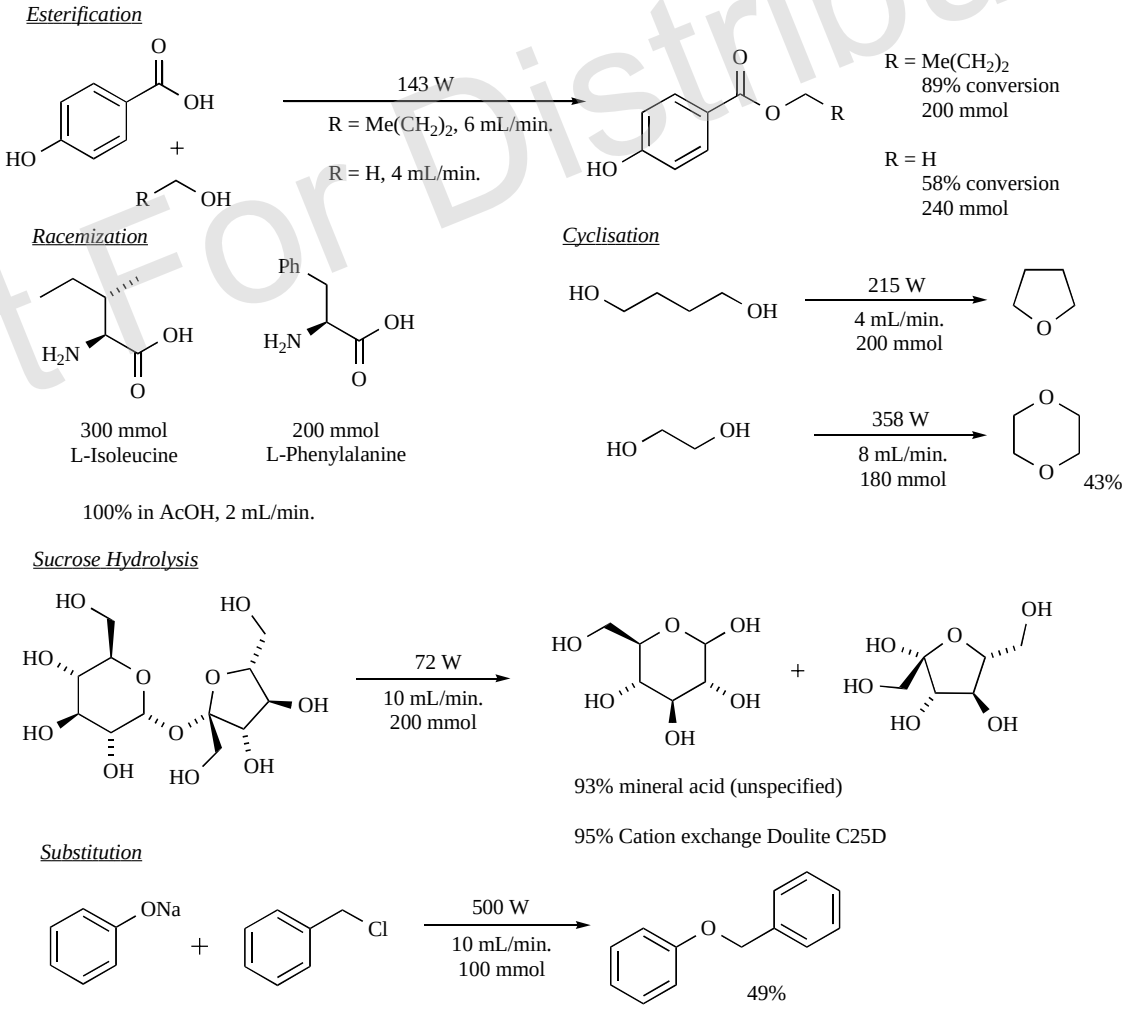
Scheme 2. Recycling of the reaction stream.

A large scale intramolecular aldol condensation to prepare hundred gram quantities of a cyclopentenone intermediate using the continuous microwave reactor (CMR, CSIRO [13a]) was also reported (Scheme **3**) [14]. Of additional interest was that the standard purification protocol for the product (distillation to remove small residual quantities of the starting material) was ineffective for large scale synthesis creating a new bottleneck. Alternatively a scavenging procedure for the starting *bis*-carbonyl moiety using a bisulfate functionalised ion exchange resin was employed. Indeed the final sequence used a bi-functional resin bed which also contained a sulfonic acid resin to remove the reaction base (NaOH). The enhanced processing capability provided by this solid phase purification approach demonstrates the superior throughput that can be achieved by an innovative combination of technologies.



Scheme 3. Preparation of 3-methylcyclopent-2-enone using a flow microwave.

An analogous, although slightly less sophisticated, continuous flow setup was reported for the preparation of a series of microwave reactions [10b]. In total five different types of organic reactions were studied at scales in excess of 20 g (Scheme **4**). As the irradiation source a domestic 650 W microwave oven was used to heat a 10 mL volume of Teflon capillary tubing which was continuously filled from a reservoir using a standard HPLC pump (Fig. **2**). For each transformation a direct comparison against a closed vessel reaction was given. The processing efficiency at various flow rates and power settings were explored. In the majority of cases the reactions performed equally well in flow as under batch operation. Unfortunately, no explanations regarding the concentration of reactants, or the manner of optimising the conditions were disclosed in this communication. However, a subsequent paper by the same authors [15] details



Scheme 4. General reaction classes performed in the microwave heated reactor.

their successive studies into the use of microwaves in biochemically-related reactions such as the formation and cleavage of peptide bonds and the hydrolysis of polysaccharide linkages. This work was carried out in custom-made Teflon-Pyrex hydrolysis tubes in batch, although the paper then goes on to report their previous summarised work (see above) in a little more detail. It is inferred from the progression of the work reported that although they had some success in using the flow reactor they found it more convenient to work in a batch mode especially for small scale biochemical reactions.

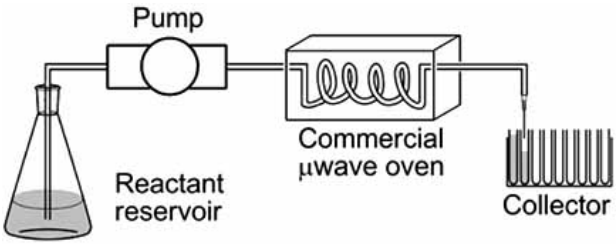


Fig. (2). Basic flow reactor design.

BASIC CHEMICAL PRODUCTION: FEEDSTOCK CHEMICALS

The easy introduction and control of applied energy by microwave-based processes has inspired an investigation into their use in the area of renewable chemicals. Microwave induced catalytic transformations have been reported as mimics for photosynthesis processes to construct small molecules as well as for the degradation of larger components into feed stock chemicals. This area has been inspired by the potential for selective microwave heating which can provide a significant economic advantage over traditional bulk heating methods. Although the energy provided by microwaves themselves is insufficient to enable direct bond breaking to take place, a heterogeneous catalyst within a microwave field can function as an efficient converter of incident microwave irradiation. This species can in turn provide the required activation energy for the process. Certain species (high Lossy materials), such as metal catalysts, can be utilised as surface catalyst sites as they are especially efficient in coupling and converting microwaves; they can thus localise the absorbance and reaction coordinates and hence focus the energy in an optimised fashion [16]. By regulation of the microwave power in pulsed cycles (power on/off sequences) it is possible to achieve an activation temperature at the catalyst surface and then allow desorption of the products and coordination of new reactants. All this can be achieved with minimal change in the bulk temperature of the flowing media due to the possibility of differential heating.

The reduction of carbon dioxide using water has been conducted over a supported nickel catalyst (Ni-1404, 3/8" pellets) in a flow microwave process (Fig. **3**) [17]. Specific tuning of the microwave power amplitude and pulse width was used to optimise the catalysts exposure to the microwave radiation. The reactants were introduced to the reactor as a gas stream (5-8 mL/min) of carbon dioxide which was passed through a water vapour saturator. Analysis of the exit stream and identification of the products was readily achieved using gas chromatography. It was found that several hydrocarbon adducts were formed including methane, ethane, methanol and acetone (the latter three components comprised 11.5% aggregate). Additional higher molecular weight alcohols (C3, 5.8%; C4, 28%) were also detected although methane (55.1%) was the singularly most abundant product. A comprehensive study of the temperature and microwave induction periods were reported as well as initial speculation on the mechanism and distribution of the products. From the supplied data the use of microwaves as a selective heating source indicated a lower power consumption and more consistent product distribution than in the corresponding thermal transformation.

Similarly, a gaseous processing procedure for the dry reforming of methane ($CH_4 + CO_2 \rightarrow 2CO + H_2$) by a γ-alumina-supported platinum catalyst at temperatures between 450-800°C has been reported, in which both microwave and conventional heating conditions were investigated [18]. The instrument comprised a tubular packed-bed reactor (i.d. 10×150 mm) located in a cylindrical microwave cavity. All the reaction parameters such as flow rates, temperature, power absorption and reflectance were logged in real time by automated control and acquisition programs. A general schematic is shown in Fig. **4**.

The product stream was rapidly chilled using an ice condenser to trap and remove any aqueous by-product (reverse water-gas shift reaction) before passing to a collection of needle valves and a quadrupole mass spectrometer which sampled the output periodically. Higher conversions were obtained under microwave heating at lower temperatures (450-650ºC) but the same thermal equilibrium was achieved at higher temperatures (≥700ºC). This discrepancy was accounted for by enhanced desorption of catalyst poisons (surface blocking components) under microwave irradiation enabled by the generation of temporary hot spots [19]. The research included a comprehensive evaluation of the other reaction parameters including catalyst loading, variance in the molar ratio of the CO_2:CH_4 and the evaluation of additional co-promoters (CeO_2, La_2O_3). As an exploratory investigation this work further highlights the advantageous nature of microwaves in the promotion of more efficient chemical processes.

THE PRODUCTION OF TOXIC MATERIALS

The hazards associated with transportation of toxic chemicals are often as significant as the original constraints on production. Indeed it might be argued that being able to generate such materials at the site of end use in the desired quantities is much preferred. Scientists at DuPont have developed a method for the continuous preparation of hydrogen cyanide, again utilising the differential heating provided by microwave heating mechanisms [1a,20]. The hydrogen cyanide is produced by reacting ammonia and a hydrocarbon gas in the presence of a platinum-group metal catalyst in the form of a woven gauze placed in the flow stream.

In an example preparation, a composite of Pt/Rh (9:1, ~5.5 g) in the form of a wire mesh was placed in the quartz tube reactor within the microwave cavity. Equimolar flows of methane gas and ammonia were injected into the device with a total processing volume of 50 mL/min (Fig. **5**). The selectivity of the reaction was 88.7% in terms of the hydrogen cyanide purity with the conversion of ammonia and methane being >90%. The device could be run for extended periods of time, generating significant quantities of material.

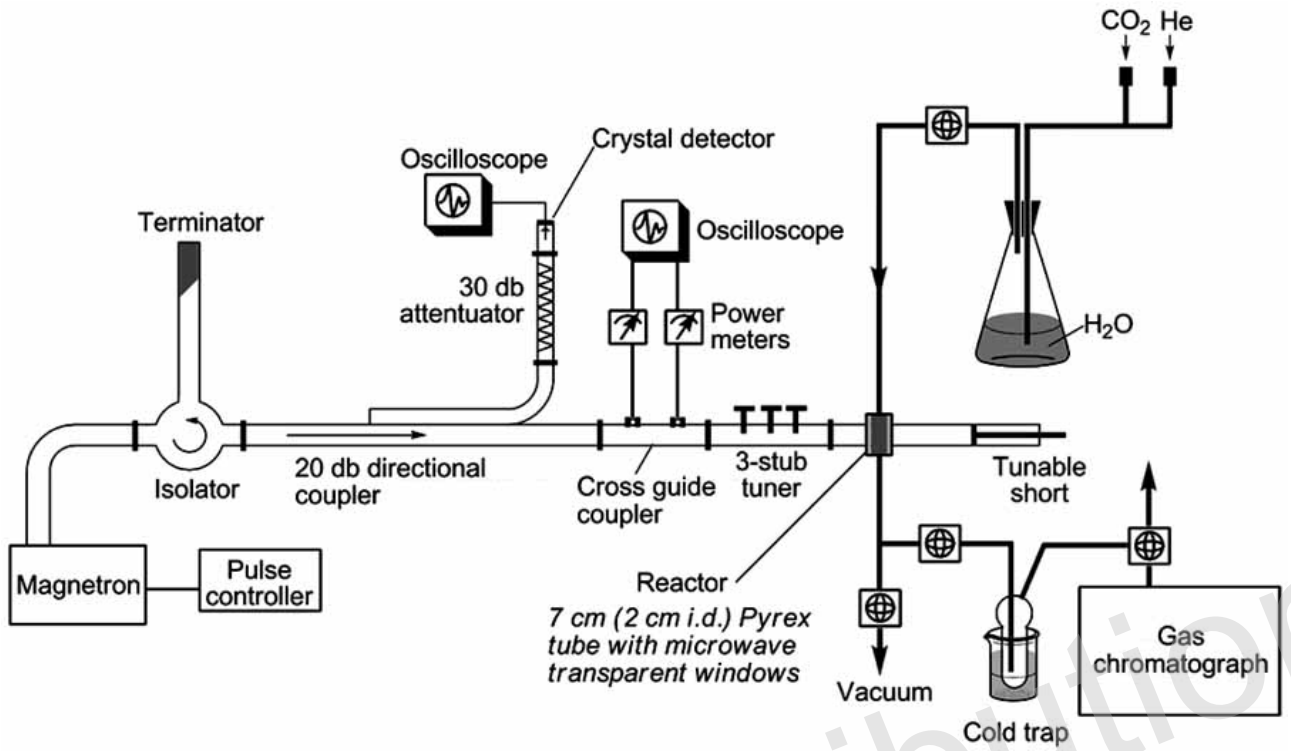


Fig. (3). Continuous flow reduction of carbon dioxide.

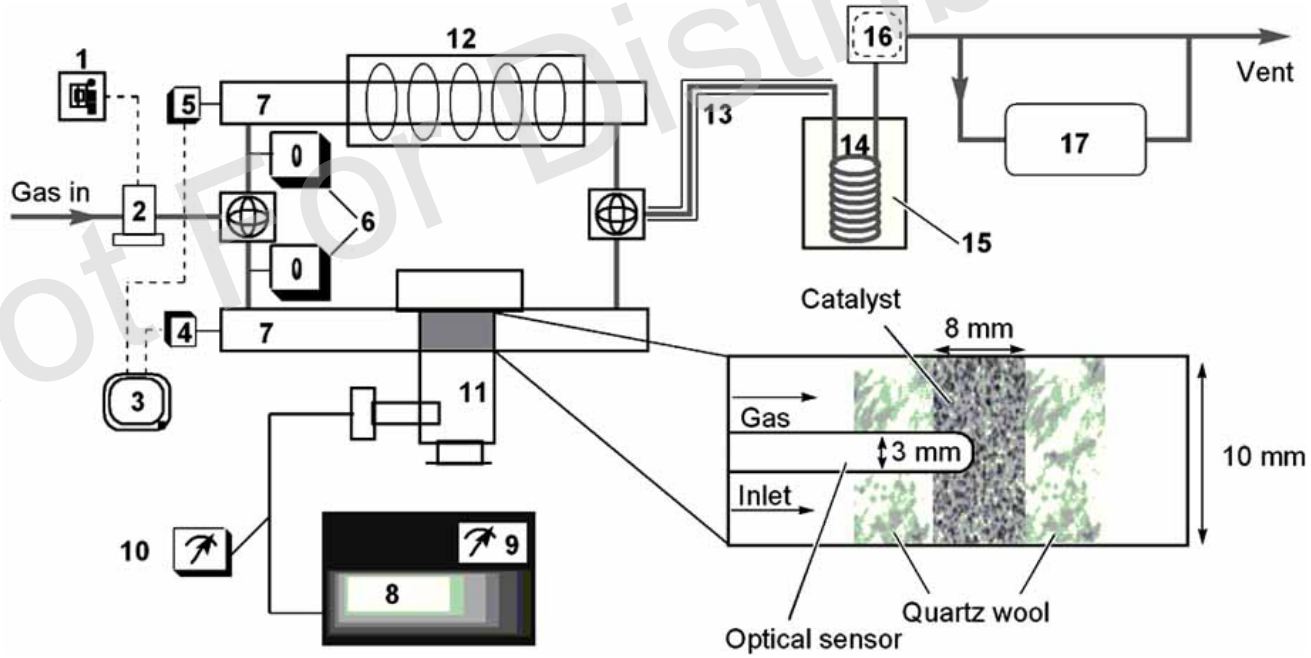


Fig. (4). General schematic of the microwave reactor for the dry reforming of methane. **1**. Mass control unit; **2**. Mass flow controller; **3**. Temperature display; **4**. Optical sensor; **5**. Thermal couple; **6**. Pressure gauges; **7**. Quartz reactors; **8**. Microwave generator; **9**. Forward power meter; **10**. Reflected power meter; **11**. Microwave cavity; **12**. Conventional furnace; **13**. Heating tapes; **14**. Cold trap; **15**. Ice-water Dewar; **16**. Filter; **17**. Quadrupole mass spectrometer.

$$CH_4 + NH_3 \xrightarrow[\text{Metal catalyst}]{\text{600 - 1200}^oC} HCN + 3H_2$$

Scheme 5. Continuous production of hydrogen cyanide gas stream.

MICROWAVE ASSISTED ESTERIFICATION REACTIONS IN CONTINUOUS PRODUCTION REACTORS

By far the most prevalent microwave reaction is ester formation from large, readily available acid and alcohol feed stocks. Simple and fatty ester product categories are valuable

and widely used materials found extensively in agrochemicals, pharmaceuticals, textiles, paints, detergents, cigarette filters and fuels, and are used as both solvents and lubricants. The production of many of these materials is on the multi-million ton scale meaning their efficient production at scale is of considerable economic importance. Such condensation reactions such as ester formation have been shown to be readily amenable to microwave reaction conditions.

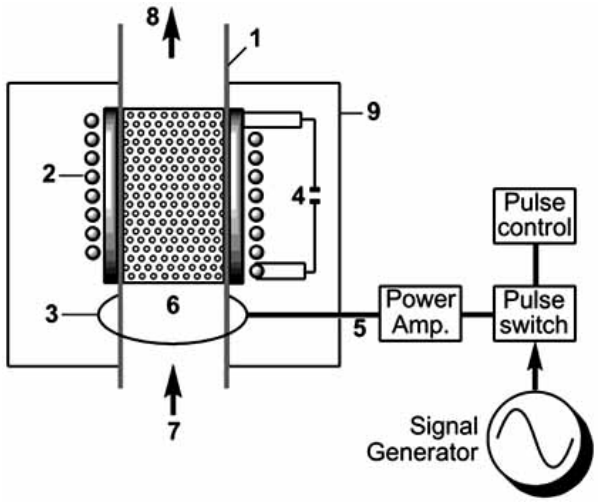


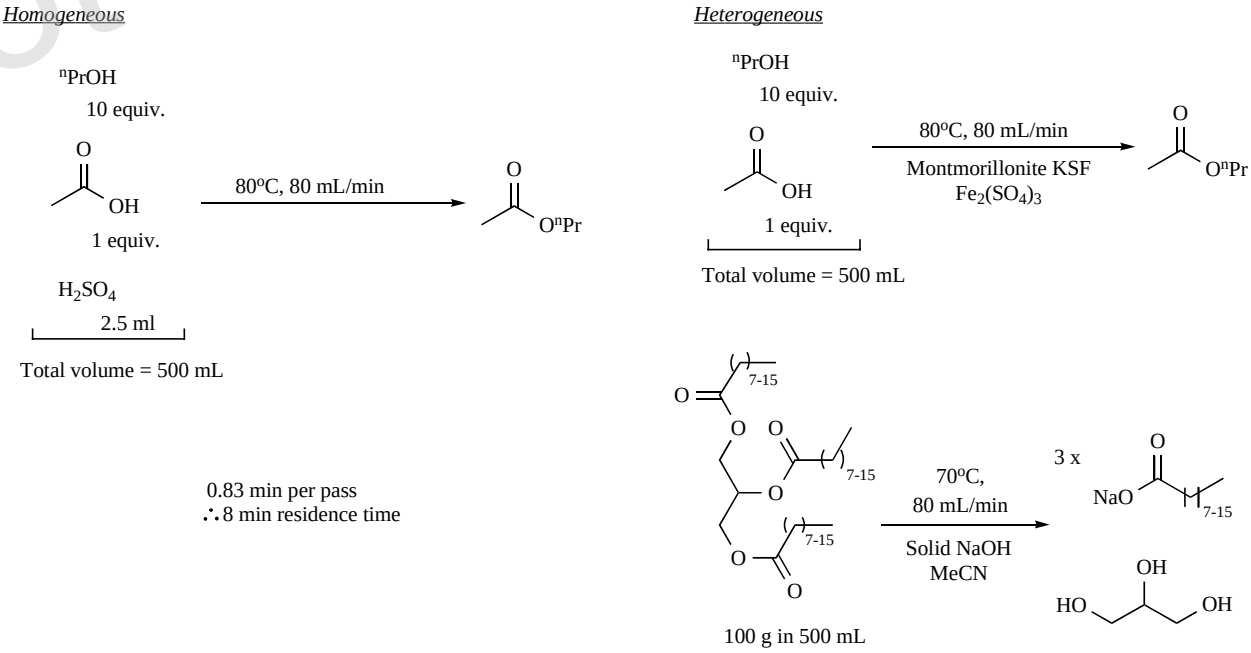
Fig. (5). Process reactor for the preparation of hydrogen cyanide. **1**. Quartz tube; **2**. Copper solenoid; **3**. Coupling coil; **4**. Capacitor; **5**. 50 Ohm cable; **6**. Catalyst; **7**. Inflow port; **8**. Product port; **9**. Aluminium enclosure.

The simple esterification of acetic acid with propanol was studied using both sulfuric acid and a particulate form of montmorillonite KSF/$Fe_2(SO_4)_3$ (4 mm spheres) as a heterogeneous acid catalyst (Scheme **6**) [21]. A comparison was run against the same reactions heated under classical thermal conditions. No discernable difference could be found using the mineral acid catalyst; however, the substitute reaction performed using the solid catalyst showed an improvement under microwave conditions. This was explained by the selective heating of the catalyst and the generation of localised 'hot spots' enhancing the conversion. The same general result was found when a quantitative assessment of the saponification of coconut or olive oil was performed. The triglycerides were hydrolysed with alkali metal hydroxides (added as a solid) in acetonitrile and the percentage of glycerol monitored. After 30 min there was a 20% increase in the formation of the soap product using the microwave heating conditions; again this was attributed to the microwave interaction with the solid sodium hydroxide resulting in differential heating.

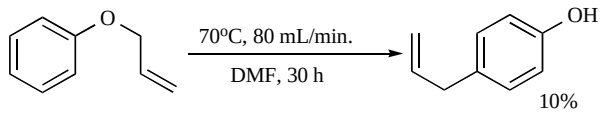
The authors also investigated the Claisen rearrangement of allyl phenyl ether, achieving a 10% conversion in approximately 32 h at 70ºC with an almost identical profile as derived from a standard thermally heated reaction (Scheme **7**) [21]. This also compared well with their previous attempts to synthesise this material under reflux conditions in DMF which after 80 h gave only a modest 23% yield.

The use of more classical solution phase chemistry has also been employed in the formation of simple esters. In order to better understand the heating characteristics and avoid any issues relating to differential heating Kabza *et al.* [22] used a low dielectric constant medium, namely hexane, as the reaction solvent. This enabled the extrapolation of reaction kinetics from the acid catalysed Fisher esterification of isopentyl alcohol and acetic acid in a recycling flow reactor (Fig. **6**).

Hexane was selected as the reaction solvent to avoid issues of solvent super-heating and maximise absorption of the microwave irradiation by the reacting species. The principle microwave absorber in the system was shown to be the localised heterogeneous bed of Amberlyst-15, a sulfonic acid-



Scheme 6. Condensation and hydrolysis reactions under continuous flow microwave heating.



Scheme 7. Claisen rearrangement conducted in flow.

cation exchange resin, contained in a radiolucent polyethylene tube within the microwave irradiation zone. The specific effects of residual water content in the catalyst was investigated which indicated a base level was required for effective acid catalysis. Direct sampling of the reaction stream over time plotted the conversion indicating the reaction had reached complete conversion after approximately 1 h of cycling. In conclusion the authors reported that no comparable differences between the microwave-mediated and classical thermal heating procedures were found for this particular reaction.

In a similar study Pipus *et al.* [23] used a tubular flow microwave reactor made from a Pyrex glass column (i.d. 1.07 × 42 cm) at elevated pressures (7 bar; 102 psi) and temperatures (140ºC) to evaluate sulfuric acid (2.1 wt.%) and Amberlyst-15 (1.8 mequiv./mL) as catalysts for the condensation of benzoic acid and ethanol (Fig. **7**). This kinetic study showed that the higher effective concentration of the catalyst in the tubular reactor provided by the heterogeneous ion exchange resin gave superior rates of conversion compared to analogous batch reactions. However, the conversions in the tubular reactor were similar at the same flow rates (1 L/h) and temperatures for both the sulfuric acid and Amberlyst-15 catalysed esterifications. Additional mathematical modelling was conducted to describe the heating profile in the tubular profile in the tubular reactor with the fixed bed catalyst. The results were used to predict the experimental conversions with excellent agreement.

A further example of this type of esterification was carried out in a laboratory scale continuous flow microwave reactor capable of recycling the fluidic stream [21]. The system is comprised of a quartz cylinder with an internal volume of 66 mL segmented by a perforated plate at the bottom which acts to retain a heterogeneous catalyst or any particulate material in the chamber (Fig. **8**). Liquid travels vertically up through the reactor delivered by a piston pump at flow rates of between 30 and 335 mL/min resulting in residence times of 12 s to 2 min. The constant injection of liquid creates a turbulent mixing region which is also capable of maintaining a heterogeneous fluidized bed. System controls in terms of temperature monitoring are located at the exit of the reactor, permitting precision tuning of the microwave power in order to maintain a constant thermal gradient. The unit can be operated in two distinct modes, either a closed or open-loop setting. In the closed loop configuration the liquid phase can be cycled to allow passage of the sample through the reactor multiple times. The open loop arrangement allows for a single passage of material in a continuous fashion for processing larger quantities of material.

A continuous flow reactor with an in-line UV detection system has been constructed to function as a FIA (Fluid Injection Analysis) device for derivatization of linear alcohols (i.e. C12-C16) [24]. Linear alcohols are important components of many surfactant mixtures and so it is desirable to have a fast and effective process for their identification and

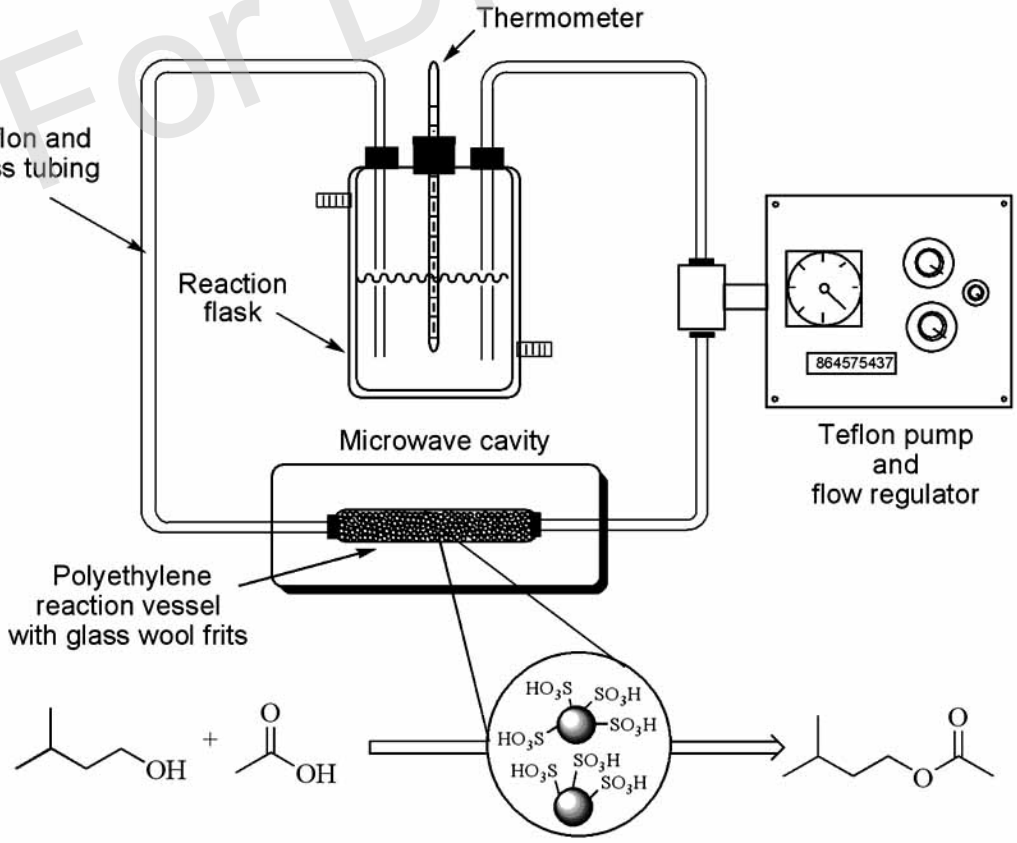


Fig. (6). Recycling flow reactor utilising an acid catalyst.

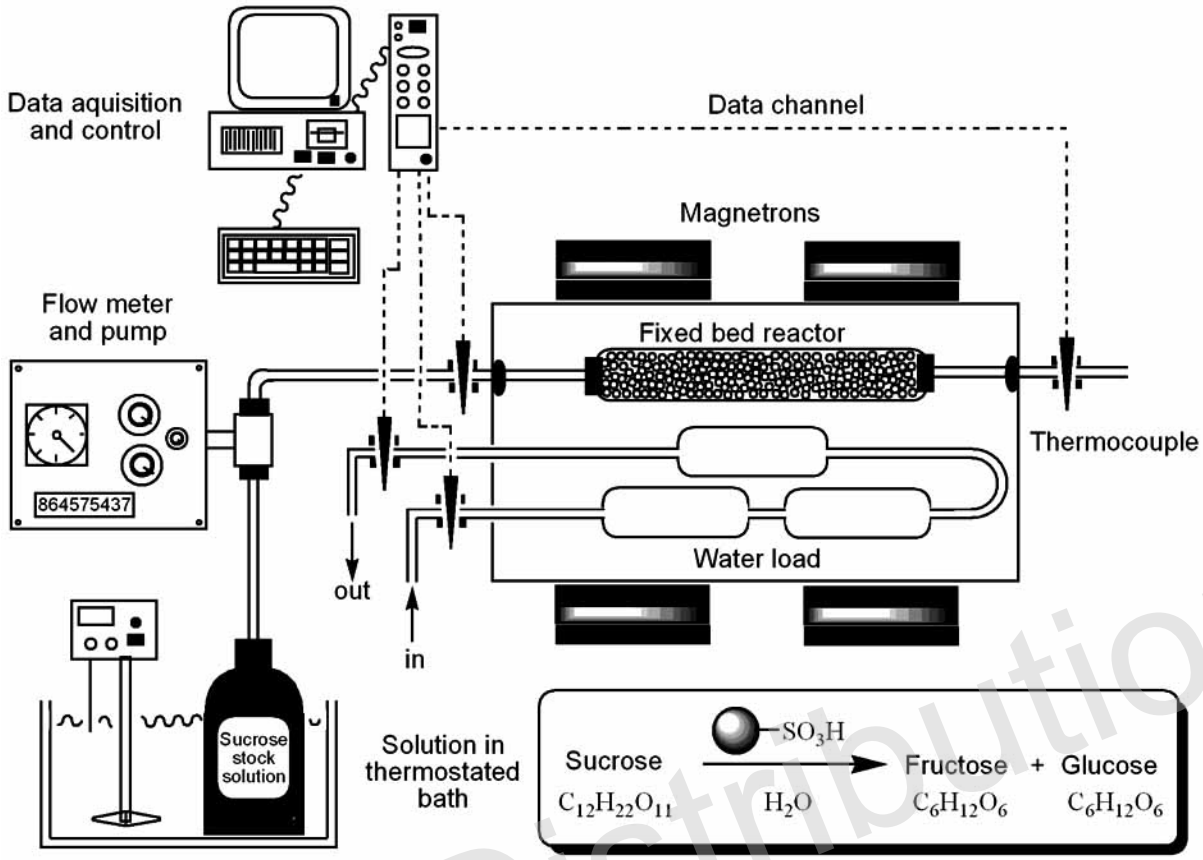


Fig. (7). Hydrolysis of sucrose in a continuous microwave reactor.

quantification. It has been shown that an integrated unit can reduce the analysis times required for quantification of such compounds in standard commercial polyethoxylated mixtures (Fig. **9**). To aid in spectroscopic detection a benzoyl chromophore was appended to the free alcohol by direct reaction with the corresponding acid chloride under microwave heating. Microwave heating proved a far superior induction method for this small volume (159 μL) micro reactor system. Rapid optimisation of the reaction conditions were enabled due to the instantaneous information feedback provided by the UV analysis of the reaction progress. The final calibrated device proved highly successful having a detection limit of 6 ng/L with <5% disparity and could process almost a sample per minute (56 samples per hour). Although not necessarily of major synthetic value to standard laboratory chemists the concepts from this paper do hold interest to other areas of analysis (fragrance and food industries, pharmaceutical impurity calibration), or even as a tool for small scale reaction design or optimisation.

Most of the esterification reactions described above have employed strong protic acids as catalysts for the transformation and have in the main been carried out on very simple substrates. An alternative procedure for the generation of methyl esters has been reported that utilises dimethyl carbonate as the methylating agent in the presence of DBU and can be applied to a variety of carboxylic acids [25]. The reactions were preformed in an ETHOS-CFR system commercially available from Milestone (Fig. **10**) [26].

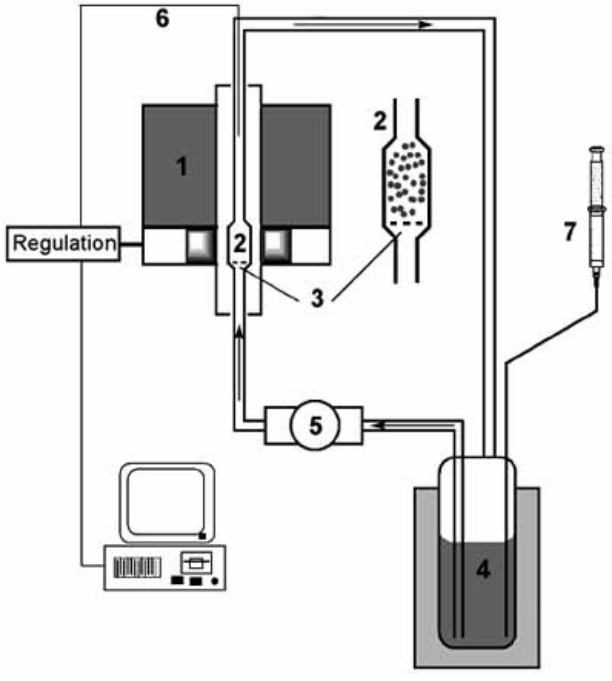


Fig. (8). Continuous flow recycling microwave reactor. **1**. Microwave oven; **2**. Microwave reactor; **3**. Perforated plate; **4**. Dewar vessel; **5**. Pump; **6**. Gas thermometer; **7**. Syringe.

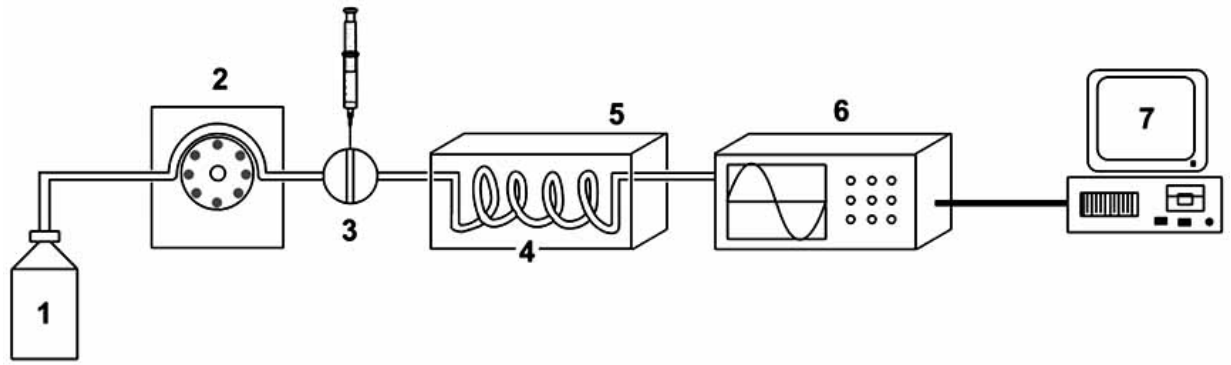
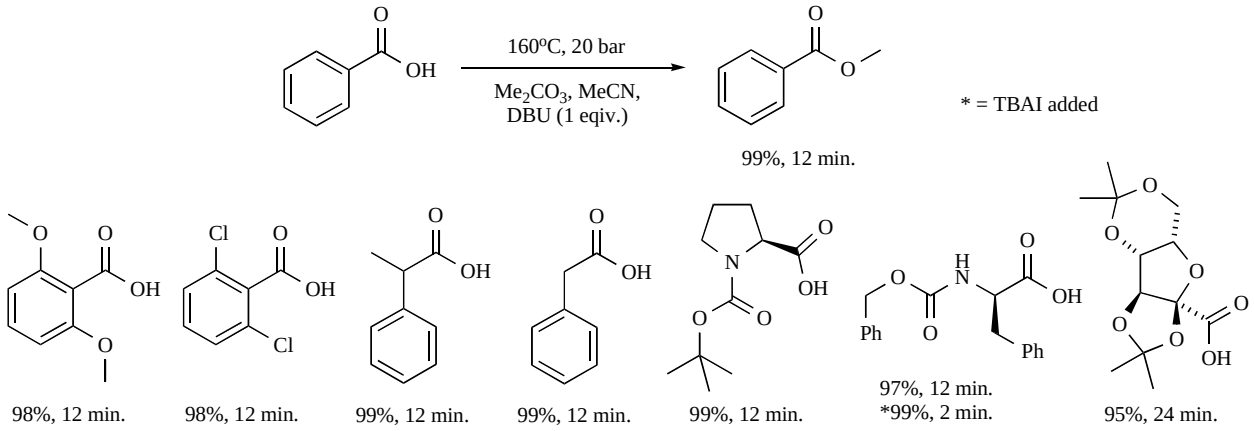


Fig. (9). Continuous microwave irradiation FIA-UV system. **1**. Solvent carrier (MeCN); **2**. Peristaltic pump; **3**. Injection valve; **4**. Coil reactor; **5**. Microwave oven; **6**. PDA-UV detector; **7**. Computer.

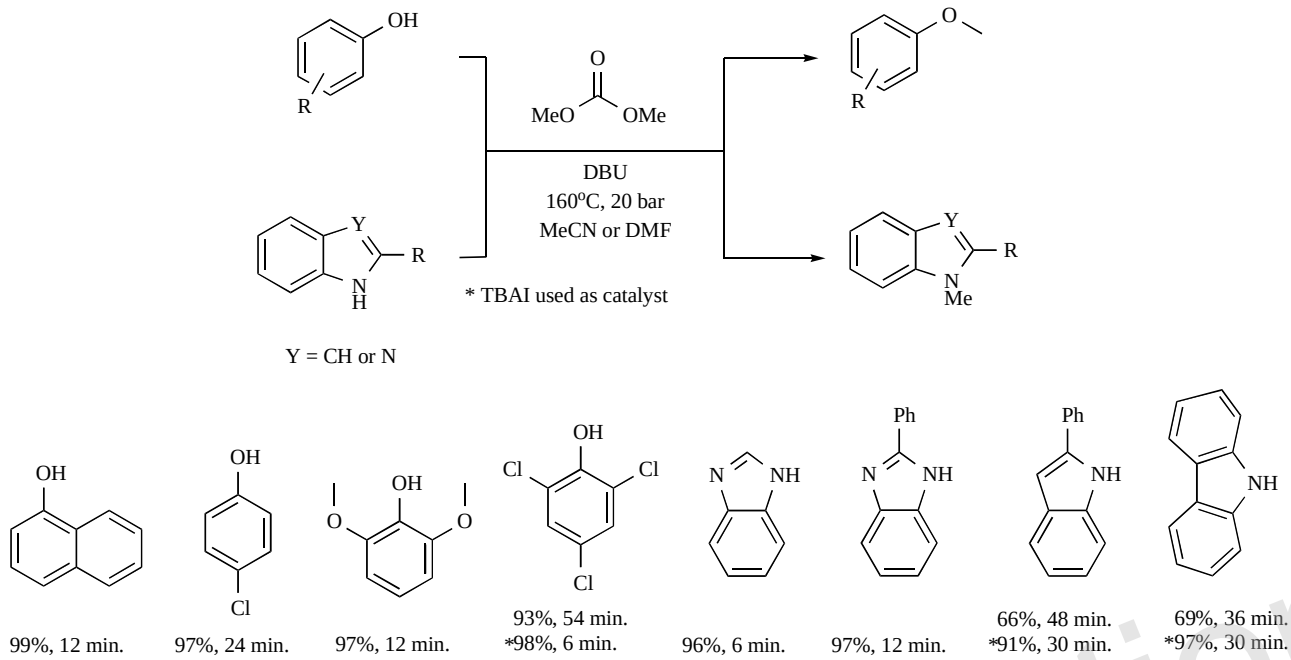
Fig. (10). ETHOS-CFR system.

A solution of the substrate and the volatile dimethyl carbonate in acetonitrile were flowed through the reactor and irradiated at 160ºC under 20 bar of pressure. A residence time of 6 min was used although the reaction mixture could be re-circulated to effect further transformation (Scheme **8**). Significantly shorter reaction times (40-80 times faster) were required at 160ºC compared to the 4-24 h with standard thermal heating at 90ºC. However, of more interest was the effect seen when a phase transfer catalyst tetrabutylammonium iodide (TBAI) was added to the reacting solution resulting in a larger step change giving a 480 times faster reaction. It should be noted that this result although highlighted in the paper is exaggerated by an additional rise in the reaction temperature to 190ºC which will account for some if not all of the rate enhancement. The use of this form of reaction doping did allow higher temperatures to be attained which were especially beneficial in preserving enantiomeric purity for example in the methylation of Cbz-protected phenylanaline. Under the extended reaction times required using conventional heating complete empimerisation occurred. Heating at 160ºC improved the situation yielding the product in 58% e.e., although the higher temperature adopted with TBAI gave the highest e.e. at 70%.

As an example of the ability to scale reactions using this system, a 10, 50 and 100 g synthesis of methyl benzoate was conducted each using a 20 min residence time. The reactions were shown to work equally well, reproducibly giving identical yields and purities.



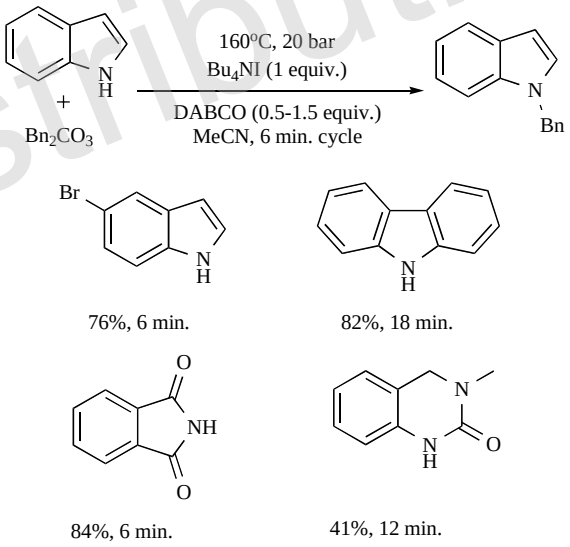
Scheme 8. Synthetic transformations conducted in a Milestone continuous flow reactor.



Scheme 9. Methylation of indoles and phenols under flow conditions.

As well as direct methylation of carboxylic acid moieties, indoles and phenols have also been alkylated using the same system in good to excellent yields (Scheme **9**) [27]. Again, TBAI was employed to further accelerate the reactions, thereby reducing reaction times and increasing throughput. Although the authors state that the contribution of the ionic salt is not fully understood it is well precedented that such materials can act as heat sinks for microwave energy creating localised hot spots. Such an effect would certainly account for the enhanced kinetics observed.

In an additional extension of this research a chemical variant was used for the benzyl protection of various indoles and *N*-heterocyclic compounds (Scheme **10**) [28]. The isolated yields reported were reasonably high (71-89%) and attained within only minutes (6 to 18) on 20 mmol scales. From these results it is apparent that this type of microwave reactor can be a valuable synthesis tool for many applications in the manufacture of laboratory scale intermediates and building blocks.



Scheme 10. Rapid benzylation of N-heterocyclic compounds.

SCALING OF CONTINUOUS MICROWAVE FLOW REACTIONS

The need to scale microwave based chemistry from the milligram through to kilogram quantities without significant redesign of the equipment is essential for rapid adoption of a process into the manufacturing plant. Reducing the development time or removing this aspect of the process completely can save significant time and money. Not only are resources saved in the redevelopment of the existing route but also in the legal requirements necessary in filing and documenting the manufacturing route such as GMP considerations and quality certificates.

Although the batch processing of small volumes in custom-built or commercially available microwave reactor systems is now straightforward as previously explained scaling a microwave cavity to increase production is not such a simple process. However, having the capability to continuously process at flow rates of several millilitres per min can soon generate several hundred grams of product in only a few hours. Couple this with the rapid heating profile that can be attained by microwave irradiation and the throughput of material can be significant even from a small reactor. Indeed the processing of small but constant quantities of material is ideally suited to microwave processing. A small volume of reaction mixture can be easily saturated with microwave irradiation giving rise to instantaneous heating with a steep thermal gradient. Rapidly attaining the required reaction temperature or even using elevated temperatures and pressures results in accelerated reactions which offer a significant advantage for continuous flow based applications. This is easily highlighted by considering the processing capacity of a reaction in terms of throughput when an increase in the

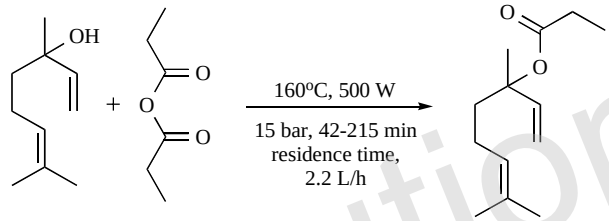
Table 2. Processing Times for Quantities of Material at a Given Flow Rate

Flow Rate	5 g	100 g	500 g	1 kg	Residence Time
1 mL/min	55 min	150 min	550 min	1050 min	50 min
2 mL/min	27.5 min	75 min	300 min	525 min	25 min
5 mL/min	11 min	30 min	110 min	210 min	10 min
10 mL/min	5.5 min	15 min	55 min	105 min	5 min
25 mL/min	2.25 min	6 min	22 min	42 min	2 min
50 mL/Min	1.1 min	3 min	11 min	21 min	1 min

Assumptions: Based on the weight of H_2O = 1 g/mL. 50 mL reactor volume.

reaction rate permits a reduction in the required residence time. In a hypothetical situation an increase of 10ºC should according to the Arrenhius equation result in an approximate doubling of the reaction rate; a halving of the reaction time (residence time) or a theoretical doubling of the reaction material that could be processed in the same period (Table **2**).

As can be easily seen from the values shown in Table **2** the ability to compact reaction times (residence times) can lead to high productivities. Consequently, a prototype pilot plant microwave reactor has been developed by Ondruschka and co-workers [29] and demonstrated in the esterification of linalool on a 25 kg scale. High flow rates of up to 36 mL/min (2.2 L/h) were possible (Fig. **11**, Scheme **11**). A range of differently dimensioned tubes (Quartz or ceramic) were tested at varying flow rates and pressures in an attempt to enhance the conversion. Ultimately it was shown that in order to achieve higher conversions the acid by-product needed to be distilled from the mixture to drive the equilibrium.



Scheme 11. Large scale formation of linalooyl propionate ester.

Laurydone (Scheme **12**), a component of the cosmetic industry often used in lipstick manufacture but also finding applications in transdermal drug delivery has been prepared at scale using a continuous microwave reactor. The commissioned reactor was developed as a joint collaboration be-

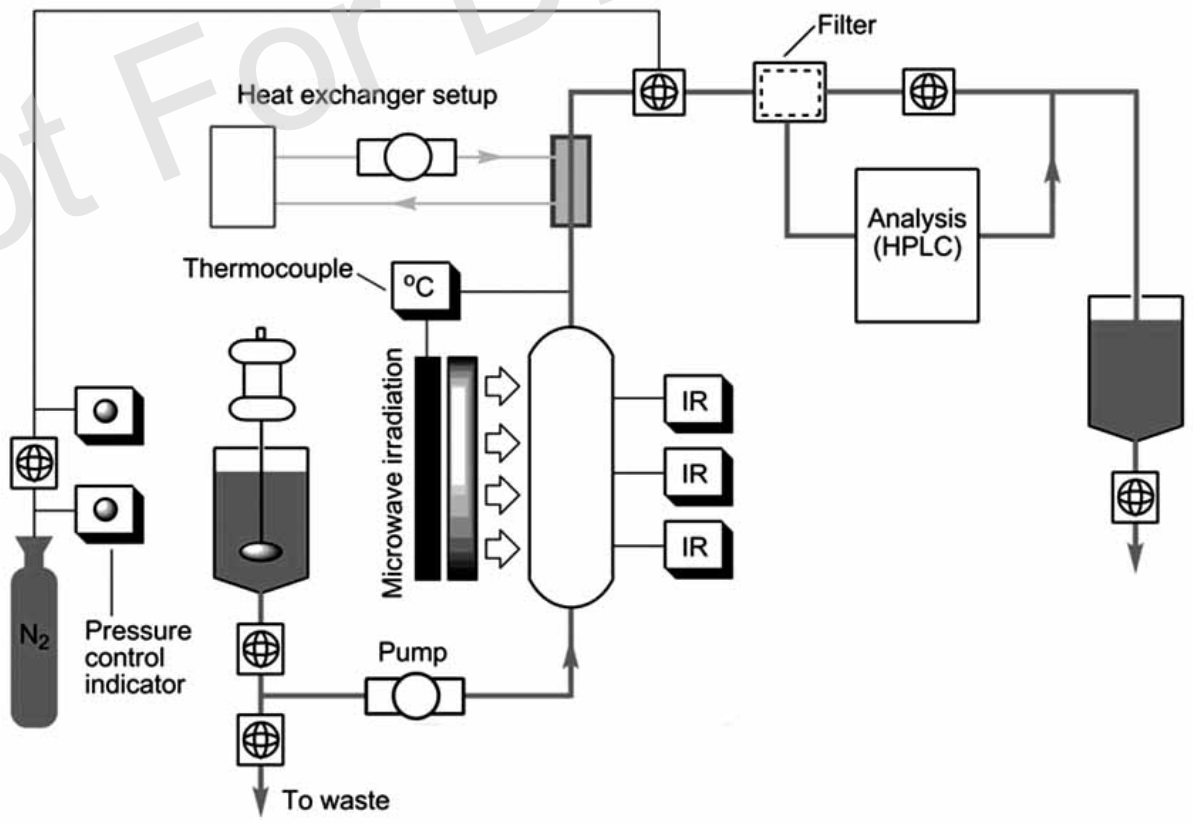
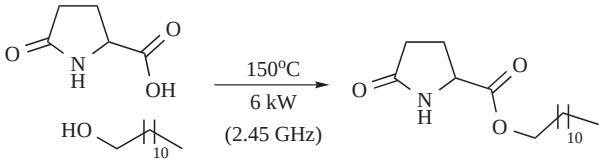


Fig. (11). Schematic of the flow microwave reactor developed for the esterification of linalool.

tween the microwave system manufacturer Sairem and the technology brokers Bioeurope and De Dietrich [30]. The recirculating reactor design fed by a 1 m^3 reservoir enabled the large scale preparation of Laurydone without the need for a solvent (normally toluene) or a catalyst (*p*-TSA). This was achieved because of the very efficient absorption of the microwave energy by the mixture permitting a relatively high but controlled temperature of 150°C to be rapidly reached. This additionally avoided safety concerns relating to the heating of the large volume content of the stirred tank.



Scheme 12. Flow scale-up of Laurydone.

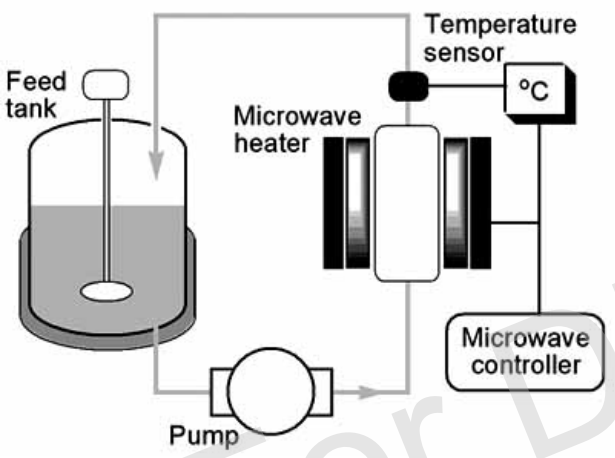
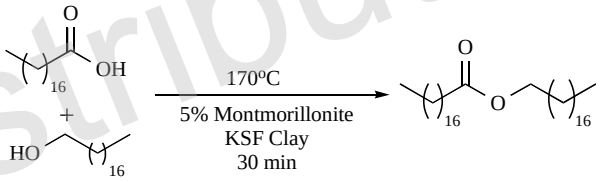


Fig. (12). Laurydone recirculating reactor.

Esveld *et al.* [31] have also constructed a small pilot plant scale continuous microwave reactor for the preparation of stearate esters under solvent free conditions (Scheme **13**). Microwave irradiation of dry media reactions allows effective heating of the reactants even in the absence of solvents and can lead to enhanced conversions and a higher throughput of material [32]. Although not truly a continuous 'flow' solution, the inclusion of this example highlights nicely the development and novel integration of microwave heating as an effective tool for scaling reactions. It also signifies an interesting transition in process design, transforming as it does a batch operation into a continuous procedure.

A powerful industrial microwave generator was used providing an output of 6kW (2.45 GHz) with such high field intensities that temperatures of up to 250ºC could be easily generated in short periods of time. The solid reaction mixture, comprising of a 1:1 blend of stearic acid, stearyl alcohol and 5 wt.% of the clay catalyst, was delivered to the reactor using open Pyrex oven dishes on a Teflon coated glass fibre web conveyor (1.5 m in length). Each dish had a surface area of 350 cm^2 and contained a depth of 13 mm of the reaction mixture equating to 493 g of material. The conveyor belt was set to travel at a constant 17 cm/min achieving an optimised reaction time and temperature of 30 min at 170ºC in the tunnel-like microwave cavity (dimensions 150×40×35 cm^3). Following the rapid microwave heating sequence a conventional hot-air tunnel was used to provide an isothermal holding phase. Such a device was employed to increase evaporation of water from the reaction bed producing an additional shift in the equilibrium by removal of the aqueous by-product.



Scheme 13. Esterification of stearic acid under microwave conditions.

The overall reaction time was dramatically reduced (a factor of between 20 to 30 times) compared to the same transformation conducted in a conventional thermal convention reactor. In addition the waxy esters product required only a simple filtration of the clay and no further purification in order to isolate the product in an overall yield of 95%. From a processing perspective this experimental plant can

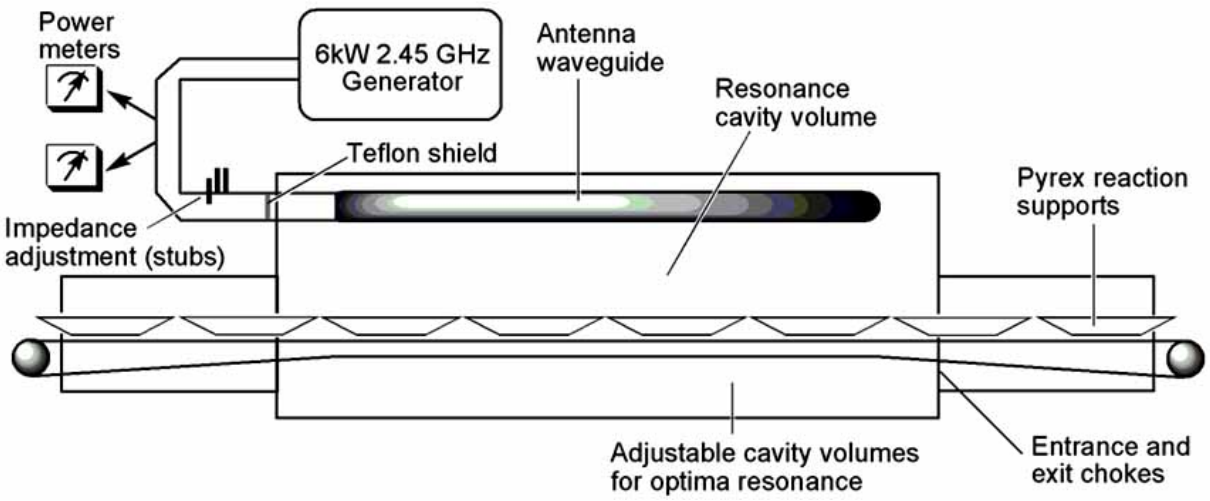


Fig. (13). Conveyor belt microwave continuous processing reactor.

process approximately 12 kg/h resulting in a total production of over 100 kg per day.

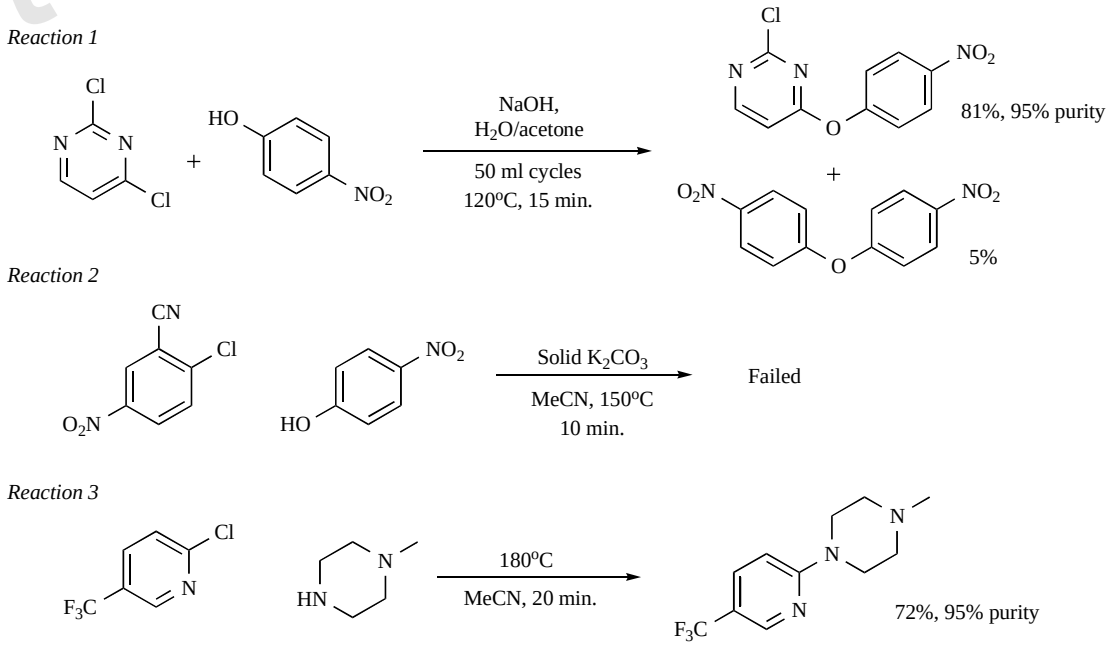
The use of such microwave conveyor belt reactors to treat large quantities of material has already found general acceptance for many industrial applications such as drying pharmaceuticals, fixing toners, processing foods and extracting hydrocarbon fuels from oil sand or shale. It would seem logical that additional examples of chemical processing applications will be soon forthcoming especially considering the increased throughput and greater utilisation of the microwave cavity offered.

The concept of scale-up under safe, reproducible and cost effective conditions is especially important for process research groups and consequently several industrial organisations have invested considerable effort into the evaluation of commercial microwave units [9e,33]. Scientists at Novartis have recently conducted a comparative study of a series of nucleophilic displacement reactions under microwave irradiation at scale [34]. Batch mono (Biotage Optimizer [35]) and multimodal reactors (Anton Paar Multiwave 3000 [36]), were run alongside the Voyager SF unit (CEM [37]) to ascertain direct processing times and efficiencies. The Voyager system functions in a semi-continuous fashion now known as stop-flow synthesis, which combines a batch heating sequence (80 mL glass reaction vessel) with the ability to pump the processed material out and to charge the vessel again for a subsequent run in a fully automated process. The pumping is conducted with a customised peristaltic pump capable of delivering slurries and suspensions of solid supported reagents [38]. The selected results for the continuous processing using the Voyager CF system are show in Scheme **14**.

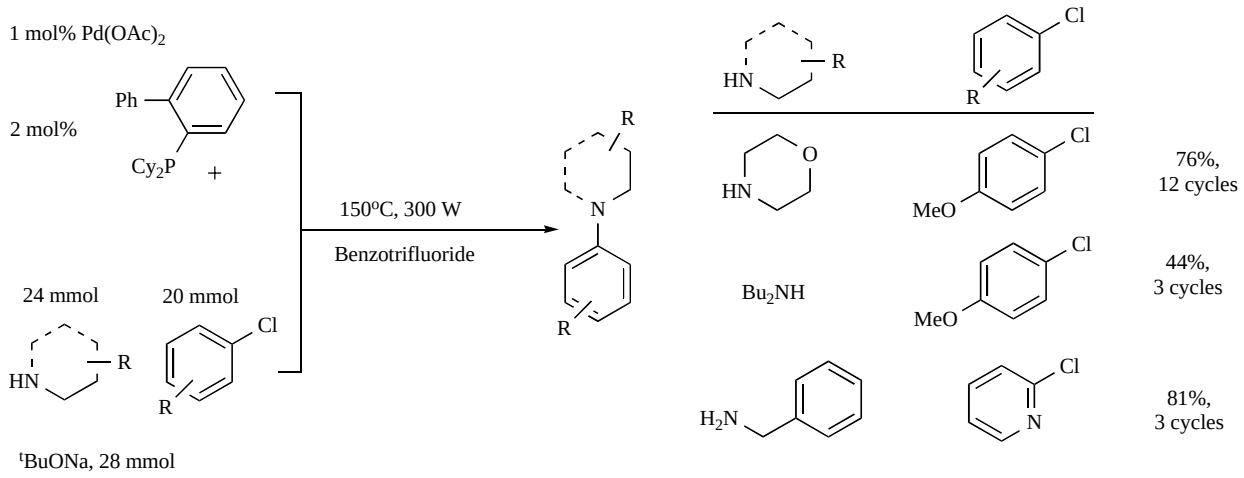
As an indication of the processing capacity the transformation of 400 mL of reaction mixture for the homogeneous reaction 1 (Scheme **14**) was accomplished in approximately 4 h involving eight separate cycles. This equates to around 30 min per batch (50 mL reaction volume). A cycle consists of a fill stage, reaching the hold temperature and maintaining 15 minutes of heating, a cooling period and the emptying of the reaction mixture from the vessel. Despite an in-built anti clogging device the authors report that this reaction (Reaction 1) and the subsequent reaction (Reaction 2) proved problematic due to blocking of the tube by the precipitating product in the first reaction and the loading of a solid base in the latter. However, it was reported that the final homogeneous reaction (Reaction 3) performed well in the Voyager device giving the highest yield and was most easily scaled to process 250 mL.

The use of a larger reaction vessel is not always conducive to direct scale up in microwave chemistry. This was noted in a series of palladium-catalysed amination reactions (Scheme **15**) [39]. The original conditions involving the use of toluene as the solvent gave 76% isolated yield after only 10 min (2 min ramp time to attain 150ºC). Unfortunately, when this was transferred to the Discover (CEM) batch 80 mL vessel (20×scale) the reaction failed to reach the specified temperature during the full 10 min cycle time (max temperature 128ºC; 38% yield). This volumetric heating problem was overcome by utilising benzotrifluoride (BTF) as a direct solvent replacement for the poor absorbing toluene. The solvent switch enabled reactions to be scaled using the larger batch reactor (Discover) and to further permitted repeated processing cycles using the Voyager stop-flow technique (Scheme **15**).

It has been our observation that this type of reactor (Voyager stop-flow reactor with 80 mL vessel) is not well suited to processing materials with very short reaction times (<10 min) that also require high temperatures (>135ºC). The bulk heating and cooling cycles often contribute disproportionately to the required processing time reducing the overall efficiency. However, for reactions that require longer heating times this tool offers a more convenient and proficient alternative to the standard sealed vial approach. This is well em-



Scheme 14. Comparative reactions attempted in the CEM Voyager SF.

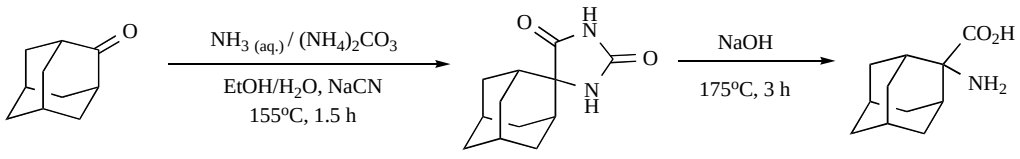


Scheme 15. Buchwald-Hartwig chemistry in the Voyager stop-flow system.

phasised by two synthetic transformations required for the formation of the recently withdrawn small lung cancer therapy Meclinertant (Sanofi-Aventis). The adamantane amino acid side chain is prepared *via* the Bucherer-Lieb synthesis (Scheme **16**) [40]. Elevated temperatures and pressures are required to effect condensation to the intermediate spirohydantoin as well as its subsequent hydrolysis to the desired amino acid. A comparative investigation was performed to profile the processing efficiency of the Voyager system (CEM; 80 mL reactor – 50 mL per run) against a vial based run (Biotage Emyrs 20 mL vials). A total of 2.4 L of reacting solution containing 0.6 M of the adamantan-2-one was split equally between the two systems. In the case of the vial based system this required a total of sixty 20 mL vessels which needed filling and capping then in post reaction operations decapping and solutions to be manually washed from the vessels (dilution with water to induce precipitation). These aspects were absent from the Voyager processing protocol including the need to dilute the reacted solution with water which could be automatically achieved as part of the reactor washing protocol. The individual cycle times and accumulated processing period are shown in Table **3** with both systems running uninterrupted and fully independent for the duration of the sequences. It can be easily seen from the total processing times that in this instance the Voyager stop-flow processing capability is far superior. The difference between the two methods will also widen with an increase in the throughput volume as the reaction is scaled or the individual reaction time increases. The same result can also be seen in the secondary hydrolysis step, where the increase in processing volume significantly reduces the practicality of using the smaller volume microwave vials.

THE APPLICATION OF FLOW SYNTHESIS TO MICROWAVE CHEMISTRY

Flow-based procedures for conducting chemical synthesis have been around for a number of decades [41,42]. Unfortunately, although the concepts of increased mixing efficiency, controlled scaling factors, enhanced safety ratings and continuous processing capabilities have all been well recognised these benefits have not been generically leveraged into conventional synthetic chemistry laboratories. Indeed, traditionally almost all chemical manipulations have been conducted as sequences of well-defined and sequentially optimised single-step transformations operated in batch mode. Therefore the majority of process innovations in terms of new tools and techniques that have helped define modern



Scheme 16. Bucherer-Lieb synthesis of 2-amino-adamantane-2-carboxylic acid.

Table 3. Processing Times for Bucherer-Lieb Synthesis

STEP 1	Heating Times	Reaction Time	Cooling Times	Wash and Prep Times	Total Cycle Time	Cycles Required	Total Processing Time
Voyager	14.5 min	90 min	20 min	11.5 min	130 min	24	54 hours
Vials	4 min	90 min	6 min	1 min	102 min	60	101 hours
STEP 2	-	-	-	-	-	-	-
Voyager	20 min*	180 min	24 min	12 min	236 min	10	39.3 hours
Vials	9 min*	180 min	7 min	2 min	198 min	25	82.5 hours

*Needed to be heated at reduced power to prevent overpressure.

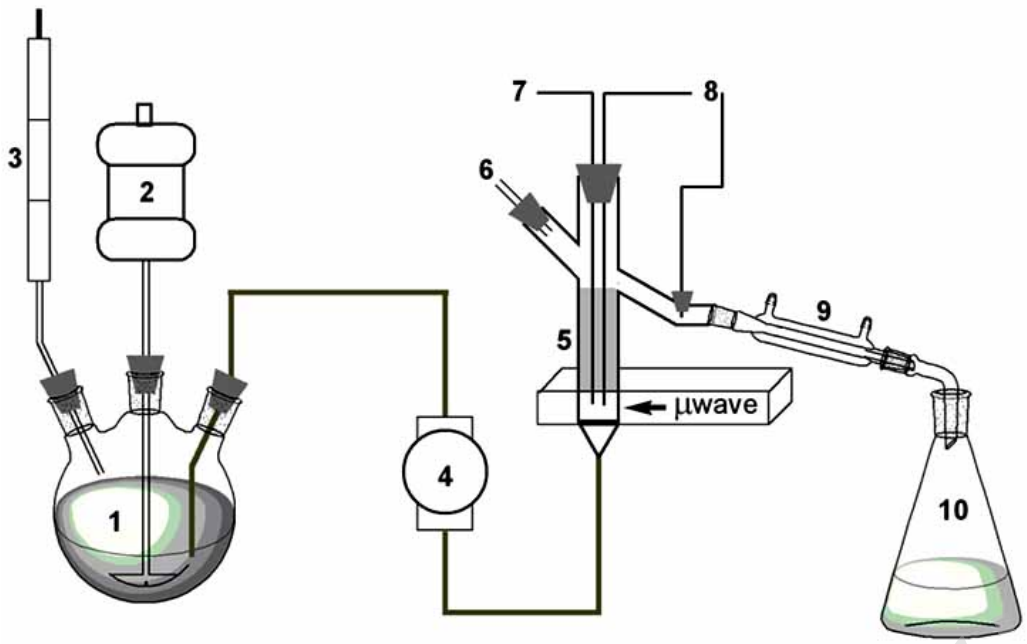


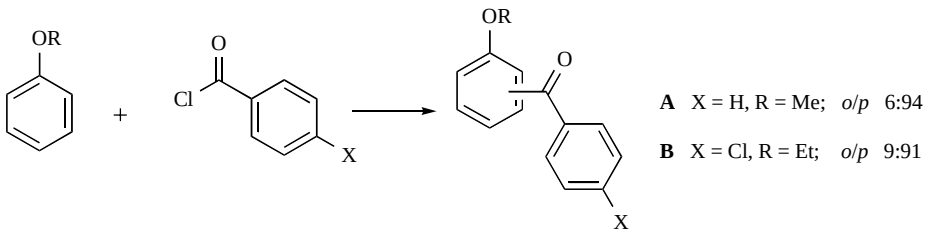
Fig. (14). Continuous-flow apparatus and reactor. **1**. Reaction mixture; **2**. Mechanical stirrer; **3**. Dehydrating agent ($CaCl_2$); **4**. Pump; **5**. Reactor (i. d. 3 cm, useful volume 33 mL, irradiated volume 11 mL); **6**. Gas exit; **7**. Nitrogen bubbler; **8**. Optical fibres; **9**. Condensor; **10**. Collector.

organic synthesis have been based on modifications to existing batch-processing protocols. The development of microwave-assisted organic synthesis as a batch procedure has gained acceptance as an established synthesis technology; the corresponding flow mode has taken much longer to gain recognition.

Lewis acid catalysed Friedel-Crafts acylation and sulfonylation reactions have been transferred to a continuous feed microwave reactor configuration (Fig. **14**) [43]. Unlike many of the examples seen so far this large scale preparative apparatus was run at ambient pressures. This was useful because the reaction generated large quantity of gaseous hydrogen chloride which could be continuously purged from the reaction stream by bubbling through a stream of nitrogen; this positive pressure was counterbalanced by a waste suction vent that siphoned off the eliminated acid. A large-volume stirred feed tank containing the premixed reactants and catalyst was used to fully mix the Lewis acid catalyst ($FeCl_3$) prior to introduction to the reactor. The resulting viscous solution was pumped into the base of the reactor passing into the irradiated region where it was rapidly heated. The microwave control unit permitted both the tuning of the energy input and the monitoring of the reflected microwaves, allowing an energy utilisation profile to be developed. The product was also analysed periodically by HPLC sampling to determine the extent of the reaction. In this way a comprehensive databank of reaction parameters was established allowing experimental design and further optimisation of the reaction to be conducted. Despite the enhanced processing capabilities described the bulk reaction mixture still required a standard manual aqueous work-up in order to isolate the product (Scheme **17**, Table **4**).

The higher boiling point of phenetole over anisole permitted the use of elevated temperatures resulting in a higher conversion to the desired product. In some ways this demonstrates a weakness in the atmospheric system especially for volatile substrates where an ideal reaction temperature may not be possible in terms of containment and venting of the built-up gases generated during the reaction.

A similar Friedel-Crafts process was also carried out for the sulfonylation of mesitylene (Scheme **18**). Again, good yields were obtained; however, the sensitivity of the reaction can be seen in that at a slightly lower temperature (125-127ºC) and on a larger scale (300 g) only an 86% isolated yield was obtained. It is of further interest to note that the sulfonylating agent used in this experiment is a solid but in the presence of the other reaction components becomes a homogeneous melt which is easily pumped into the reactor.

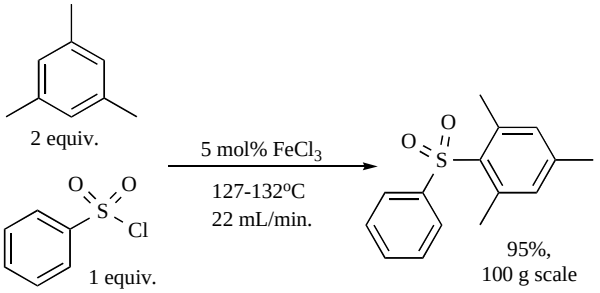


Scheme 17. Friedel-Crafts acylations in a modified domestic microwave oven continuous-flow reactor.

Table 4. Selected Results of the Continuous Microwave Friedel-Crafts Process

Reaction	ROPh	ArCOCl	$FeCl_3$	Flow Rate	Yield	Scale	Temp.
A	2 mol	0.5 mol	0.05 mol	48 mL/min.	72%	200g	120-140°C
A	2 mol	0.5 mol	0.05 mol	20 mL/min.	90%	155g	110-140°C
A	2 mol	1.0 mol	0.1 mol	22 mL/min.	85%	300g	140-145°C
B	2 mol	1.0 mol	0.1 mol	22 mL/min.	95%	230g	160-175°C

Obviously in situations such as this the pre-design of the experiment is very important to avoid problems associated with blocking of the reactor. Detailed knowledge on the physical properties of the starting materials, the reacting solution/melt and the final product all need to be taken into consideration. It is evident that more basic research is urgently needed in regard to the development of simple tools for the detection, evaluation and solution of this problem.



Scheme 18. Microwave assisted sulfonylation in flow.

In one of the first examples of the preparation of a drug substance in flow a single step multi-component Hantzsch ester synthesis of dihydropyridines was reported [44]. A circular glass arc reactor (65 mL internal volume) was fixed within a domestic microwave oven along the circumference of the turntable to attain the best heating. Additional Teflon tubing connectors (35 mL dead volume) were attached to the glass reactor through holes cut in the rear of the microwave leading to a delivery pump and stirred holding tank (Fig. **12**). The CMR had a maximum processing volume of 500 mL of reaction mixture but was only demonstrated on ~125 mL (0.15 mol scale) giving an isolation of 50 g of the desired product.

Initial operating conditions were optimised in batch (Scheme **19**, Route A) and employed ammonium hydroxide solution, which proved difficult to handle in the reactor due to volatility problems. A second route was therefore devised using the nitrogen pre-installed in the form of methyl 3-aminocrotonate (Scheme **19**, Route B). The reactions were not conducted in standard organic solvents but instead an aqueous hydrotrope solution was investigated for the solvation of the starting materials. Hydrotropes have received little attention in the literature but are considered advantageous because they are generally non-combustible, non-toxic, and relatively polar reaction solutions. Three different surfactant combinations were tested, 50% sodium *p*-toluene sulfonate (Na-PTSA), 40% sodium cumene sulfonate and

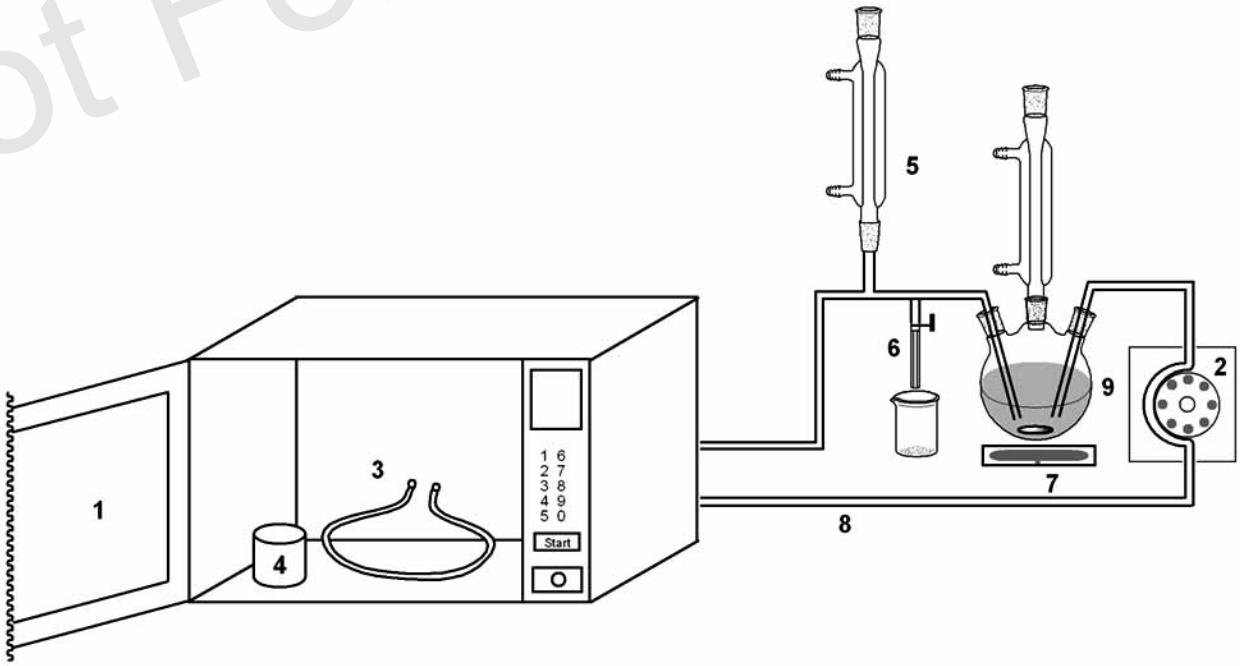
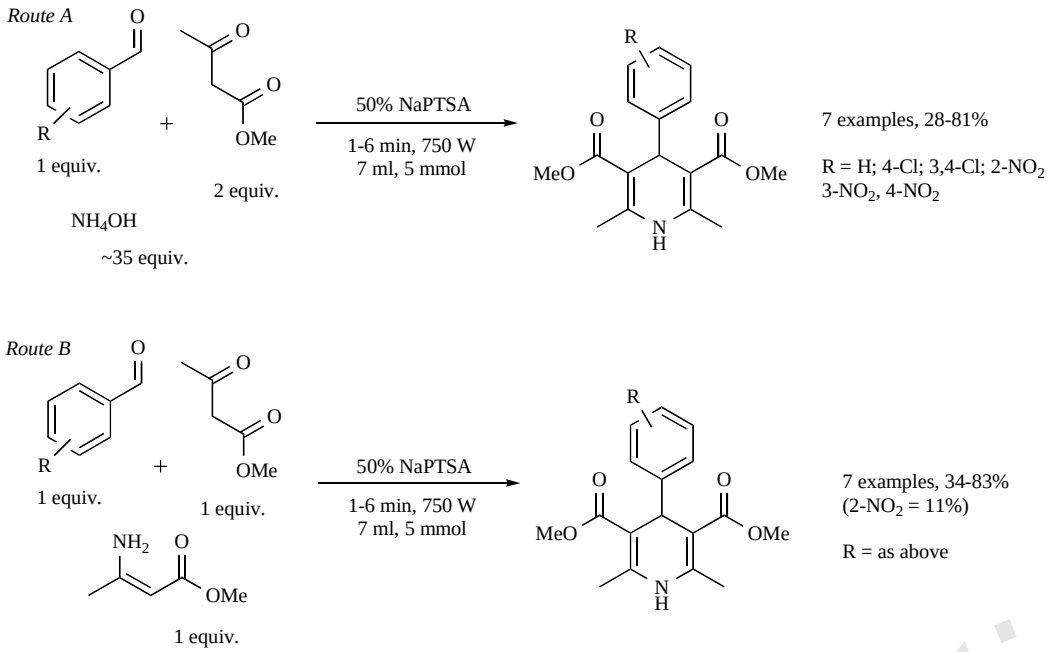


Fig. (15). Flow reactor based around a domestic microwave oven. **1**. IFB microwave oven (760 W, 2.45 GHz); **2**. Peristaltic pump; **3**. O-shaped glass coil; **4**. Alumina 110 g load; **5**. Double surface condenser; **6**. Sampling assembly; **7**. Magnetic stirrer; **8**. Teflon tubing; **9**. Round bottomed flask.



Scheme 19. (**A**) Batch optimisation of reaction conditions. (**B**) Continuous flow synthesis.

20% sodium *p*-xylene sulfonate in water although Na-PTSA generally gave higher yields of the desired products.

Once fully optimised the conditions were transferred to the flow reactor with reaction times being directly converted to residence times. In an example reaction for the synthesis of Nifedipine (3-NO_2; ester groups are ethyl; Table **5**), four repeated cycles of 6 min (flow rate of 100 mL/min) with 2 min between each sequence was used; the standing time was necessary to avoid excess heating. The product solidified on cooling and could be easily filtered (50.67 g product isolated, 94%), allowing the solvent to be recycled. A small selection of additional examples were also reported.

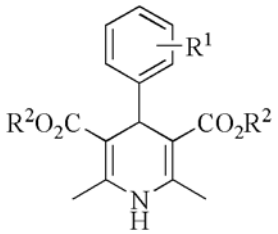
In exemplification of another microwave flow system, a series of demonstration reactions were conducted using a packed bed reactor. The device consisted of a Dressler vessel arrangement filled with an inert packing media of sand (Fig. **16**) [45]. The reaction mixture was pumped into the lower region of the container and permeates up through the static bed (which resides in the irradiated zone) before being removed at the head of the vessel. The system is maintained under constant positive pressure using a simple in-line back-pressure regulator situated at the exit of the reactor. The initial hydrolysis and Fischer indole test reactions performed well, being able to deliver gram quantities of material in around 15-30 mins (Scheme **20**).

Next the Bohlmann-Rahtz condensation to form a tri-substituted pyridine was also investigated. A series of reactions using the packed bed reactor, as well as a simple Teflon coil, were compared at different flow rates and residence times. The best conditions were found using the fixed bed flow reactor at a flow rate of 1.5 mL/min and a 2 min residence time. A throughput of 0.15 mmol/min or just over 2 g/h was possible. A larger scale device is under investigation based on an 80 mL cavity size.

The thermal rearrangement of a series of 2-amino-6*H*-1,3-thiazines into the corresponding dihydropyrimidine-2-thiones, a Dimroth heteroatom translation process, has been investigated under microwave irradiation [46]. Kappe and co-workers tested the transformation of a single substrate under dilute flow conditions, along with a Biginelli four-component coupling reaction (Scheme **21**). The same flow arrangement as originally used by Bagley *et al*. [45] was described, although modified in this commercial system to utilise small (1-3 mm) glass beads as a bulk packing medium instead of sand (Fig. **17**).

Wilson *et al.* adopted a more classical design of reactor attempting to maximise the residence times in their small monomodal cavity (Emrys Synthesizer – Biotage, *AKA* Smith Synthesizer – Personal Chemistry) by introducing a tightly packed spiral of glass turns [47]. The flow cell featur-

Table 5. Results of Large Scale Synthesis of Dihydropyridines



Reaction	R^1	R^2	Microwave (Min.)	Isolated Yield
1	3-NO_2	Et	24 (6 x 4 cycles)	94%
2	2-NO_2	Me	24 (6 x 3 cycles)	42%
3	3-NO_2	Me	18 (6 x 3 cycles)	98%
4	4-NO_2	Me	8 (6 + 2)	88%
5	2-Cl	Me	18 (6 x 3 cycles)	86%

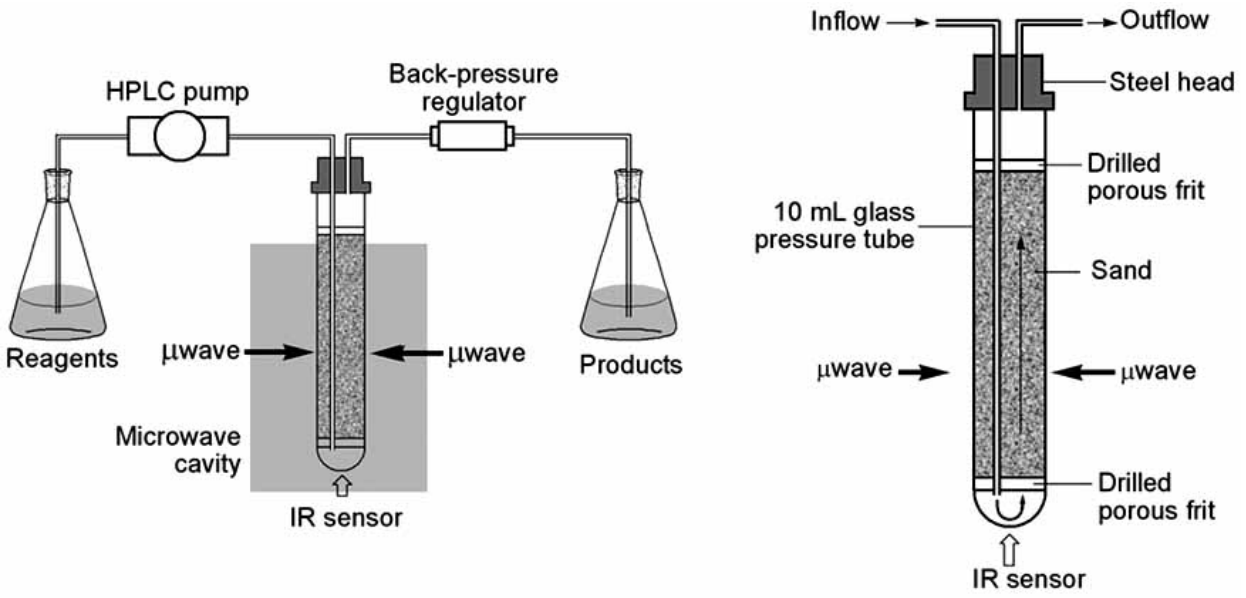
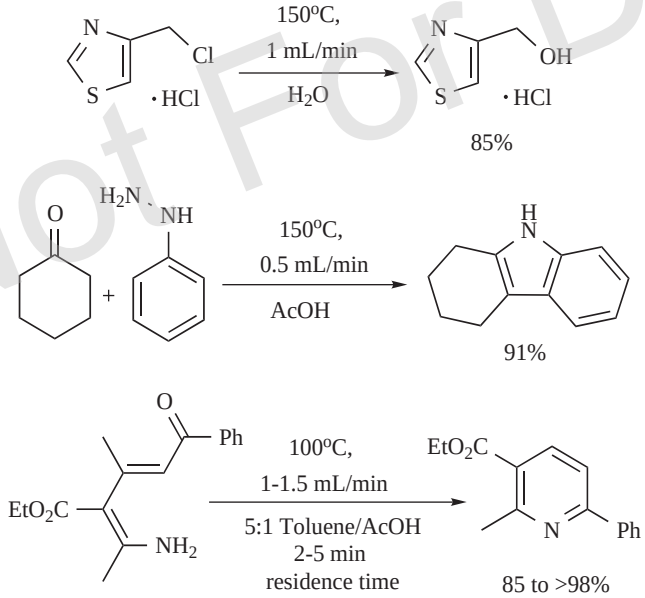


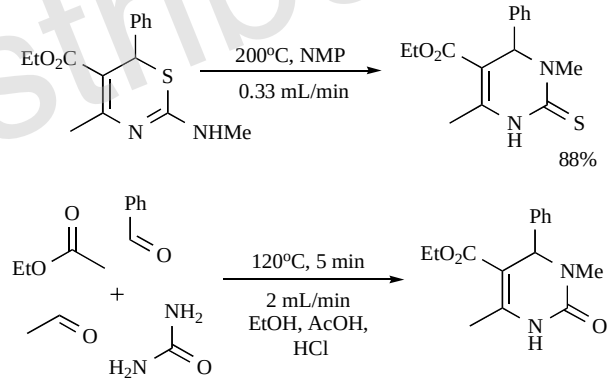
Fig. (16). Design of packed bed reactor and flow cell.

ing twenty two glass coils (i.d. 3 mm) creating an internal volume of 4 mL (estimated 2 mL within the microwave region) was additionally encased in a protective sheath and inserted into the microwave cavity. Temperature detection was achieved using the microwave unit's in-built IR facilities (Fig. **18**). Pressure was maintained in the tubular reactor using a standard 100 psi back pressure regulator which enabled temperatures above the atmospheric boiling points of the solvents to be reached.



Scheme 20. Examples of chemistry conducted under flow microwave conditions.

In a 5 h closed loop operation (24 min residence times) the reactor furnished respectively 54% and 81% (9.3 g) conversions in the nucleophilic aromatic substitution of two 2-fluoronitrobenzene compounds (Scheme **22**). However, a common failing of this type of small diameter tubular reactor was discovered in that the product crystallised out of solution whilst flowing out of the cell thereby blocking the channels. A manual intervention was therefore required to interrupt the run and unclog the reactor before resuming the run.



Scheme 21. Dimroth rearrangement and Biginelli reaction under flow conditions.

The small quantity of solution transported through the system compared to the large surface area of the capillary fittings and tubing result in very rapid heat transfer. The rapid cooling of the reaction mixture on leaving the irradiation zone encourages its crystallisation. For this reason it has often been found that alternative solvents with high solubilities are desirable or that the reaction needs to be performed under higher dilution than the equivalent batch reaction.

The acid catalysed esterification of mesitoic acid was also conducted to directly contrast the system against the earlier studies by Strauss and co-workers [10a,13]. Only a 50% conversion could be achieved even using an elevated temperature of 120°C (81% literature conversion at 80-90°C). Interestingly, in an oil bath at 80°C only a 14% conversion was found after 70 h, possibly indicating some disparity in the temperature measurements of the two microwave instruments.

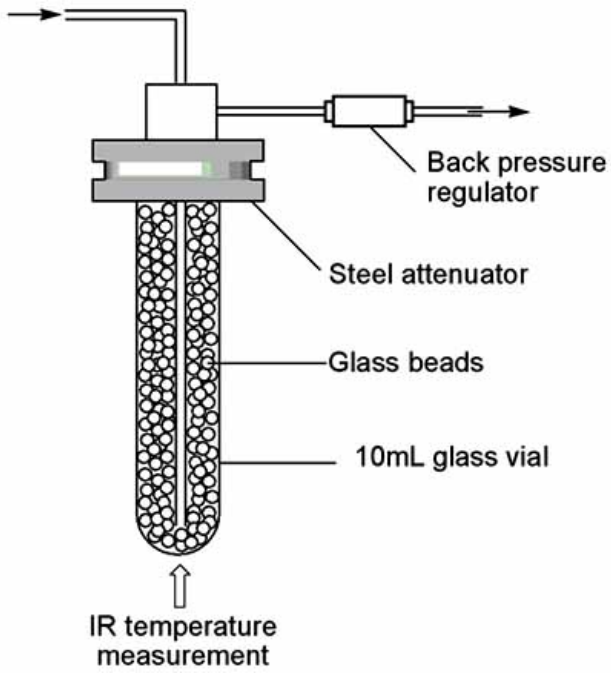


Fig. (17). Modified flow cell design.

Finally, the authors investigated a Suzuki cross-coupling reaction (Scheme **22**) over a 20 degree window. The reaction required only eight minutes residence time giving good overall conversions, the product being obtained by direct crystallisation from the reaction solution after passing through a silica plug to remove the palladium residues.

Direct temperature monitoring within a microwave flow reactor is not straightforward; normally a value is inferred from passive detectors such as an IR reflectance attained from the surface of an irradiated vessel or through a jacketed fibre optic probe inserted into the reactor. Additional observations can be gained by analysis of the inlet and outlet port temperatures with thermocouples. However, it should always be remembered that temperature variance can arise between these alternate modes of detection leading to inconsistent assessment of the reaction profile. All these methods depend on an isothermal gradient along the length of the reactor which is inevitably not a true reflection of the real systems in the flow domain. In a flow reactor, medium composition and temperature changes occur between the input point and outlet through dissipated heat transfer which will increase along the longitudinal axis. Additionally, radial temperature gradients and composition changes will exist due to laminar flow and resulting viscosity changes as a consequence of liberating heat to the reactor surface. Increasing the analysis points will give a better model but only when it is possible to monitor the entire length (and cross section) of any particular flow stream as a continuum in real time will valid kinetic data be representative.

Microwave reactors will invariably present a more challenging problem than other flow reactors because of the direct and selective heating of the different solution components and their complex interaction with the microwaves. Interference of an electromagnetic field by molecular permittivities generates a non uniform temperature distribution since permittivity has a non-linear dependence on temperature [48]. Although temperature is an easy parameter to monitor, perhaps, it is not entirely the most effective indicator, being an averaged bulk measurement. An analogy has been forwarded that using a global temperature measurement to describe a microwave heated reaction is like describing the world economic output with a single value. A figure can be produced and compared to previous years but this doesn't indicate how well each country is doing nor take account of any regions of immense flux. The same can be said about overall temperature measurements for microwave reactions which overlook microscopic thermal change ('hot spots') or the generation of possible pressure vesicles ('assumed cavitations'). However the counter argument may still hold that the average temperature still represents a practical parameter that defines the chemical requirement in terms of reproducibility. This still requires a very accurate calorimetric measurement which most current reactors designs have not fully addressed. More research in this field is sure to follow.

CATALYSED PROCESSES UNDER MICROWAVE IRRADIATION

It is no longer disputed that in heterogeneous solid-liquid reactions there exists the possibility of selective absorption of microwaves by one phase leading to elevated temperatures and accompanying enhanced reaction kinetics [49]. This differential heating mechanism is difficult to recreate under conventional conditions and so offers a unique advantage of microwave applications. Heterogeneous catalysis is

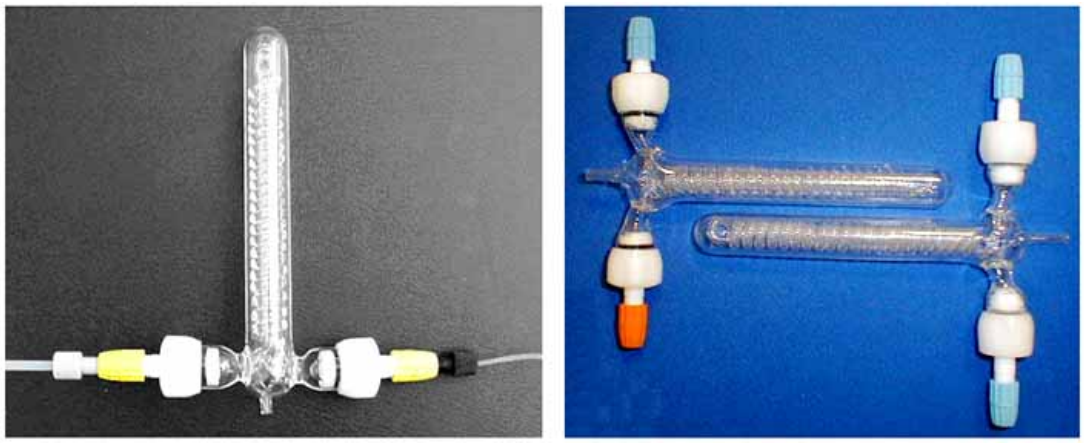
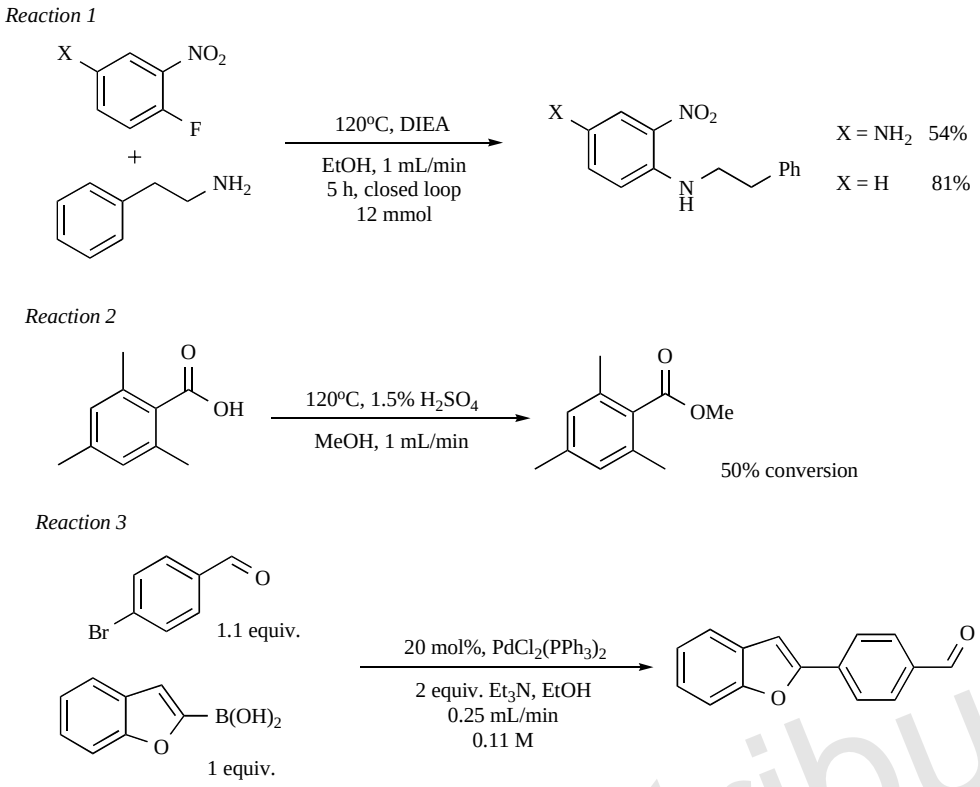


Fig. (18). Glass coiled flow cells.



Scheme 22. Examples of chemistry conducted in the glass flow cell insert.

one area that has benefited significantly from this type of focussed heating and has been further applied to flow based processes.

Hydrodechlorination of chloroaromatics over an aluminium oxide-supported palladium catalyst has been conducted as a continuous flow processes [50]. The reaction was conducted in a commercially available Voyager system (CEM; Fig. **19**) resulting in a higher conversion rate (up to 40% higher at 75ºC) and an increased lifetime of the catalyst under microwave heating conditions. The catalyst system slowly degraded with both microwave and conventional thermal treatment, albeit after 10 h the microwave system had lost only 6% of its steady state activity compared to the conventionally heated material at ~15%. This loss of catalytic activity in addition to the enhanced conversion rates results in a substantially better match between the catalyst and a microwave heating protocol.

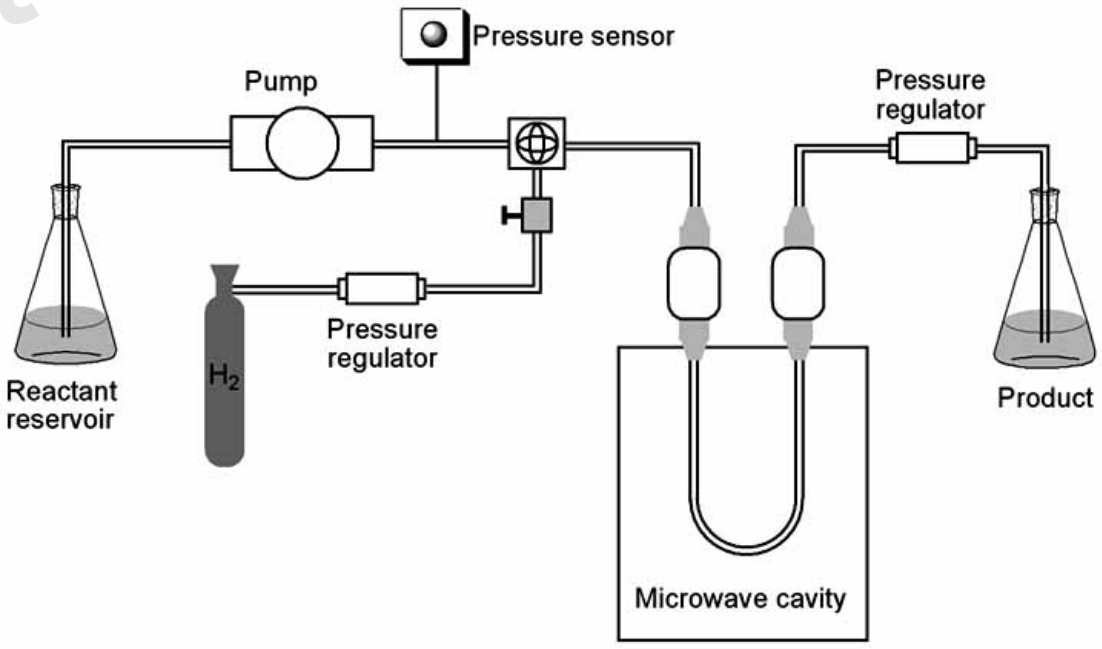


Fig. (19). Continuous Voyager (CEM) microwave reactor.

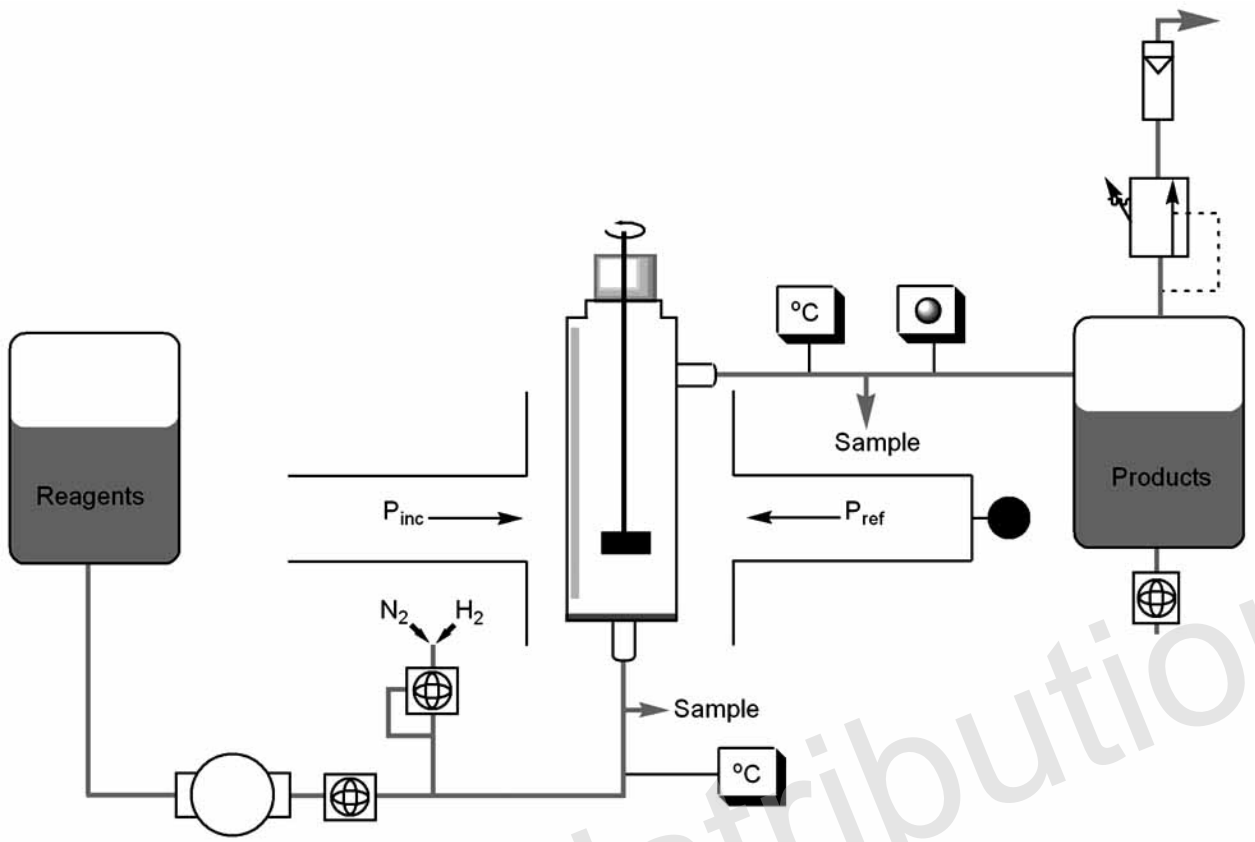
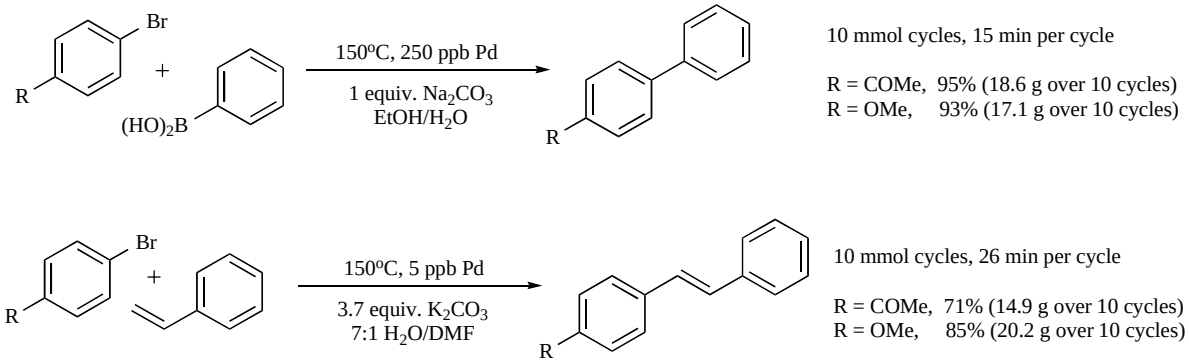


Fig. (20). Microwave reactor for the hydrogenation of nitrobenzene.

It was proposed that this increased reactivity was due to microwave-assisted desorbtion of poisonous chlorinated substances such as hydrochloric acid and chlorine from the catalyst, thereby extending its activity. Interestingly, the selective heating mechanism also led to an additional reduction in the power consumption for the process, approximately half of that needed for the conventional reaction. This was ascribed to the rapid heating of the chloroaromatics due to their high coupling ability with the microwave irradiation (chlorobenzene ε′ 2.6, ε″ 0.2 and δ 0.1) which is the reverse heating profile seen in the original thermal process.

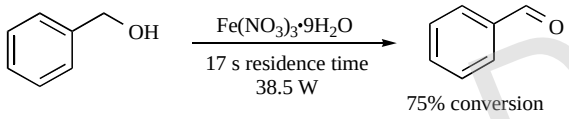
Similarly the hydrogenation of nitrobenzene has been studied with the aim of modelling the thermal characteristics of the reactions [48]. A sophisticated monomodal microwave unit capable of providing a maximum power of 1950 W was constructed and equipped with probes for analysing reflected and incident power levels. The flow reactor construct is shown above (Fig. **20**), comprising of a small volume (55 mL) reactor cavity containing a microwave transparent glass cylinder insert. The reactor is constantly fed by a variable pump from a stirred tank generating a high throughput (1.68 to 55 mL/min) of material. A perforated retention plate at the bottom of the reactor supports the heterogeneous palladium catalyst (fixed bed mode). The system was able to be run in two modes; with a fixed bed palladium on alumina catalyst and also a circulating fluidized bed of palladium on charcoal (maintained as a suspension when not being pumped by the stirred tank). The temperature was maintained between 50 and 75°C (100-200 W power) for each run and samples taken periodically to monitor the conversion. Complete conversion could be achieved at slow flow rates (1.68 to 4.98 mL/min). Further modifications to the experimental rig and reaction conditions are currently being investigated.



Scheme 23. Scale-up of Suzuki and Heck reactions.

The Voyager system (CEM) has also been used for the continuous batch scale-up of Suzuki and Heck coupling reactions employing a water/ethanol mixture as the reaction medium (stop-flow processing) [51]. The use of ultra low levels of palladium was investigated; as little as 5 ppb of the metal was found to be effective. The reactions could be directly scaled to a 10 mmol level in the Voyager system (Scheme **23**). Problematically the biaryl product solidified upon cooling below 90ºC preventing the reaction mixture from being directly removed from the vessel. The addition of 15 mL of ethyl acetate (DMF for heck reactions) to the reactor upon completion of the reaction solubilised the product allowing its removal.

The fabrication of a microwave heated continuous flow reactor for operation under isothermal conditions has been described. The standard oxidation of benzyl alcohol to the corresponding aldehyde was chosen to characterise the systems effectiveness [52]. A standard domestic microwave unit was used as the heating source. A custom made laminar flow reactor designed with a microwave transparent PTFE front plate and an aluminium heat transfer backing plate (cooled by constant water flow) was inserted into the microwave. The reactor had an exposure volume of 0.27 cm^3 allowing a residence time of 3-17 s at flow rates of 1-5 mL/min under microwave powers of 0-39 W. The introduction of the mixed reactants was easily achieved by pumping them through the narrow channel configuration using a standard HPLC pump.



Scheme 24 Oxidation of Benzyl alcohol.

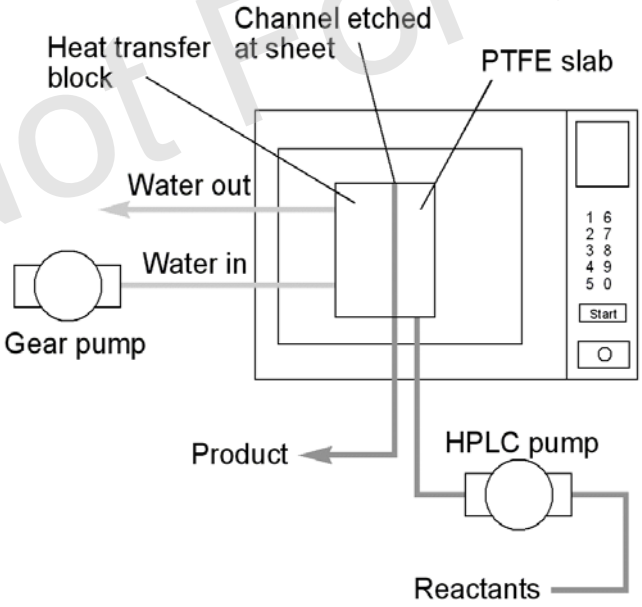
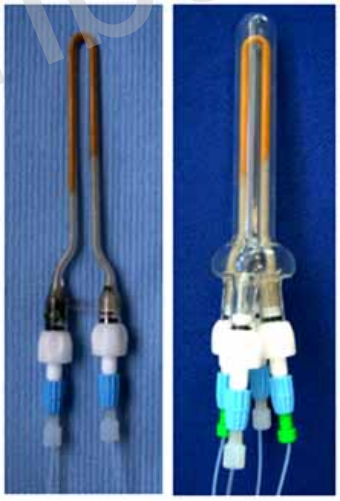


Fig. (21). Reactor setup for oxidation of benzyl alcohol using a continuous isothermal reactor under microwave irradiation.

The continuous passage of a solution through a fixed catalyst bed retained in a flow cell apparatus enables significant quantities of material to be processed. A microencapsulated polyurea palladium catalyst (Pd EnCat) has been applied to a range of cross-coupling reactions. The polyurea matrix is able to ligate and retain the palladium within the cavities of the microcapsule but permits the reactants to diffuse to the active catalyst and then products to exit back into solution. This transport mechanism results in very low levels of palladium leaching. Indeed, inductively coupled plasma (ICP) analysis of product mixtures has proven palladium levels to be less than 10 ppm, corresponding to less than 1% leaching of the original palladium content of the capsules. Additionally, should leaching become a problem, further passage through a Quadrapure TU® scavenging column leads to further enhanced product quality [53].

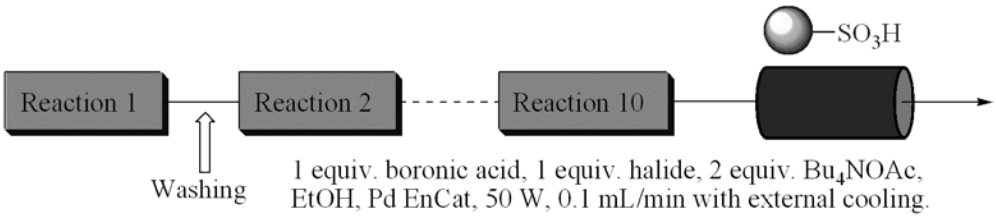
The reactor design used was based upon a simple continuous glass U-tube which was packed with the heterogeneous catalyst and inserted into the microwave cavity (Fig. **22**). Stock solutions of the boronic acid, aryl halide and $^nBu_4NOAc$ activator were prepared and constantly fed at a flow rate of 0.1 mL/min through the flow reactor (Fig. **22**). This configuration gave a total residence time of 225 s for the reactor assembly, although for only 65 s of this time was the solution present in the microwave cavity. As the reaction mixture exited the reactor chamber, it progressed through a column of Amberlyst-15 sulfonic acid resin to remove any residual base and boronic acid salts. The solution could then be collected and following evaporation the final product isolated without the need for further purification.

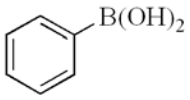
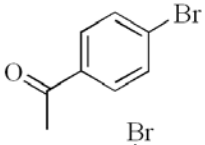
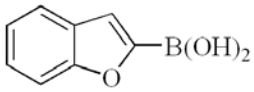
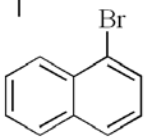
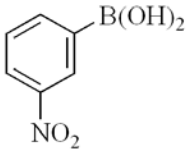
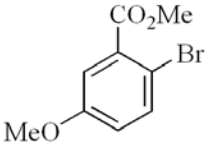
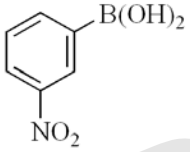
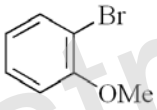
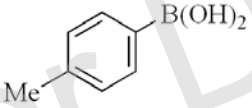
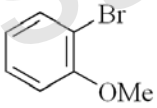
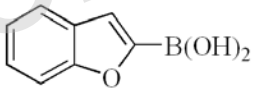
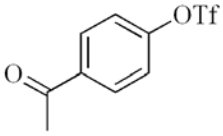
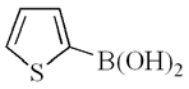
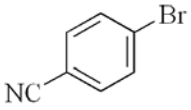
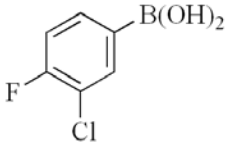
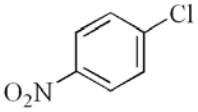
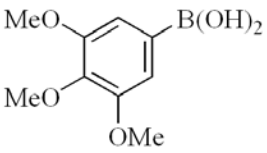
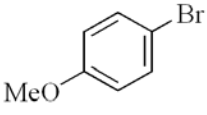
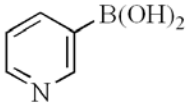
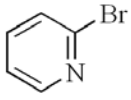
(**A**)



(**B**)

Fig. (22). (**A**) Microwave U-tube reactor inserts. (**B**) Microwave flow system.



Reaction No.	*Boronic acid*	*Halide*	*Yield (Purity)*
1			90%(>98%)
2			87%(>98%)
3			94%(>98%)
4			92%(92%)
5			88%(94%)
6			97%(91%)
7			76%(>98%)
8			89%(>98%)
9			94%(91%)
10			95%(82%)

Scheme 25. Sequential processing of Suzuki reactions in a continuous flow mode.

Interestingly, applying a cooling stream of compressed gas to the U-tube reactor while maintaining the microwave irradiation was found to further enhance the yield and purity of the products. Indeed, microwave heating has been shown to significantly improve the yields of reactions in which the reactants or products suffer from thermal decomposition because of the reduced reaction times and the more even application of energy.

The immobilisation of the catalyst in a pre-packed column format permits an easy automated recycling process to be established. A complete set of ten coupling reactions (Scheme **25**) were processed. Each substrate pairing was sequentially passed through the same reactor column without regeneration or replacement of the catalyst. The individual streams of substrates were separated using a blank solvent plug which also functioned to wash the catalyst bed before the next set of reactants arrived. Following this protocol, no cross-contamination of the products was detected. Clearly such a processing procedure is of intrinsic value to high-throughput automated synthesis of compound libraries.

In addition to the ability to prepare multiple products, it was also demonstrated that it was possible to scale up the reaction by using prolonged reaction times. In this way, multi-gram quantities of material could be readily isolated (Scheme **26**). The reactions were very efficient, progressing for several hours before the conversion dropped dramatically due to final deactivation of the catalyst. In this process, the yields of products isolated correspond to an ultimate catalyst loading of as little as 0.2 mol%, which is exceptionally low for this type of catalyst. The high catalytic turnover and short residence times required are certainly a consequence of the high effective catalyst-to-substrate ratios encountered within the reactor. The important principle that emerges from this study is the demonstration that a single reactor design can be utilised both for library generation and scaled synthesis.

DUAL APPLICATION OF MICROWAVE IRRADIATION AND ULTRASOUND

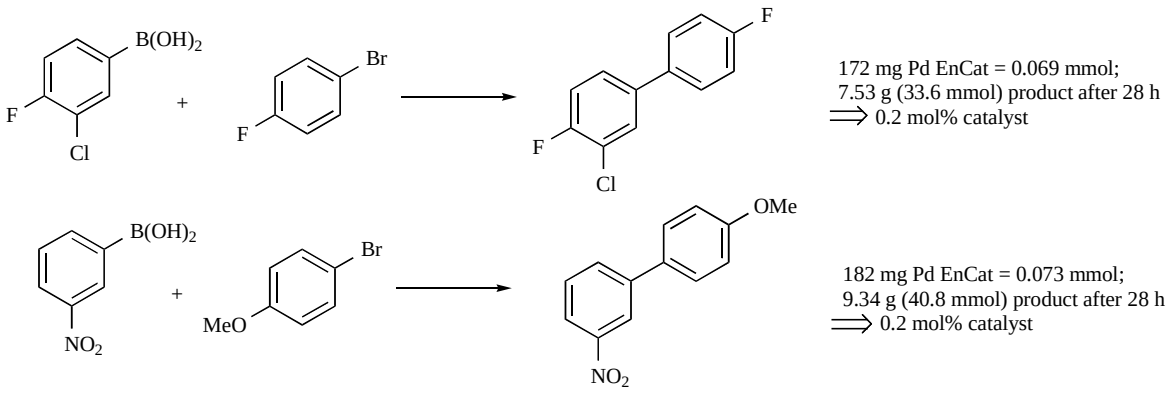
The simultaneous combination of microwave and ultrasound irradiation has been investigated to determine if these methods can provide any synergistic effects. There are as yet only a scattering of publications highlighting this area but some staggering accelerations in reaction kinetics have been documented [54]. A problem with this form of dual technology is the incompatibilities of materials needed for the design of equipment to generate each form of wave. However, this can be easily overcome by decoupling the two processes but maintaining contact through a flow channel. A flow system for the dual or separate sequencing of reactions has been constructed and tested for a selection of chemistries including Suzuki homo and cross couplings (Scheme **27**) [55,56]. The prototype reactor consisted of an air-cooled titanium horn (working at 20.5 kHz) which was inserted into a water jacketed ultra-sound reaction vessel and a Teflon microwave cell connected by two thermostatted tubes. A peristaltic pump was used to circulate the fluids with temperature detection being achieved using an IR thermometer and thermocouples.

CONTINUOUS FLOW MICROWAVE PROCESSING

The precise control of energy that can be transposed to the sample as well as the highly adjustable temperature profile enables more judicious heating in the face of constantly changing flow rates and reactant concentrations. In a recent study of non-metal-catalysed intramolecular cyclotrimerisation reactions Ley *et al.* [57] demonstrated the possibility of conducting such chemistry as a flow process at elevated temperatures (Scheme **28**) using a glass coil inserted into the microwave reaction cavity (Fig. **23**). The glass insert reactor was based on the design previously used by Wilson and co-workers [58].

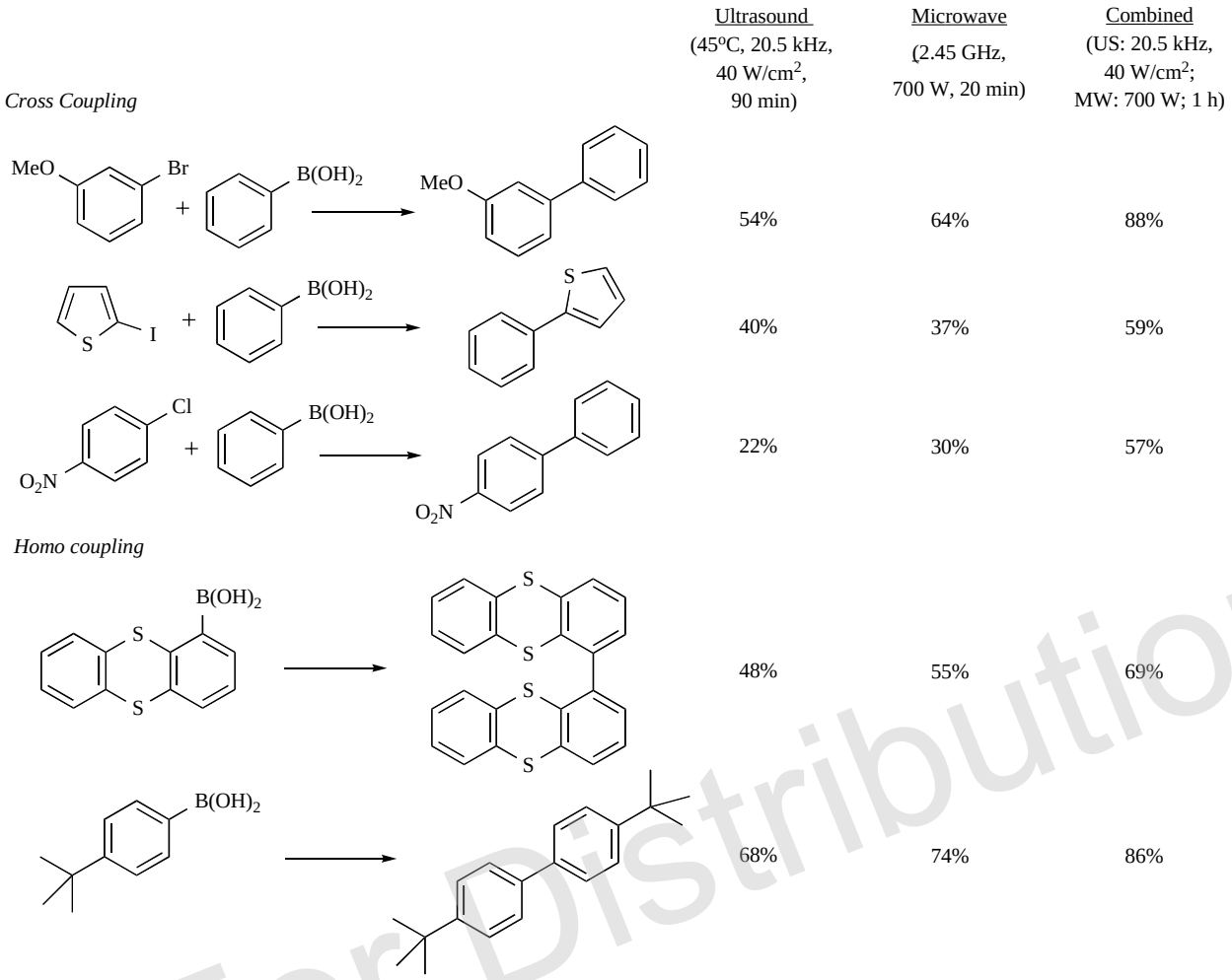
Gram quantities of material could thus be prepared by pumping a DMF solution of the precursor through a system heated to 200°C whilst maintaining reaction pressure by using a back pressure regulator. Interestingly, in the corresponding sealed batch process the decomposition of the DMF used as the solvent led to the generation of significant pressures. Using a continuous flow process avoided this problem by restricting the residence time of the DMF and constantly balancing the internal pressure, thereby reducing the issues of decomposition and associated pressure increase.

Microwave heating has been used to accelerate [3+2] cycloaddition reactions leading to the formation of triazoles from benzyl azide and a series of acetylenic coupling partners [59]. A single example of this reaction class was also run as a flow process (Scheme **29**). An early prototype of the



1 equiv. boronic acid, 1 equiv. bromide, 2 equiv. Bu_4NOAc, 0.1 M solution in EtOH, 0.2 mL/min, 50 W with compressed air cooling

Scheme 26. Scale-up of microwave flow Suzuki reactions.



Scheme 27. Suzuki reactions performed under tandem microwave and ultrasound.

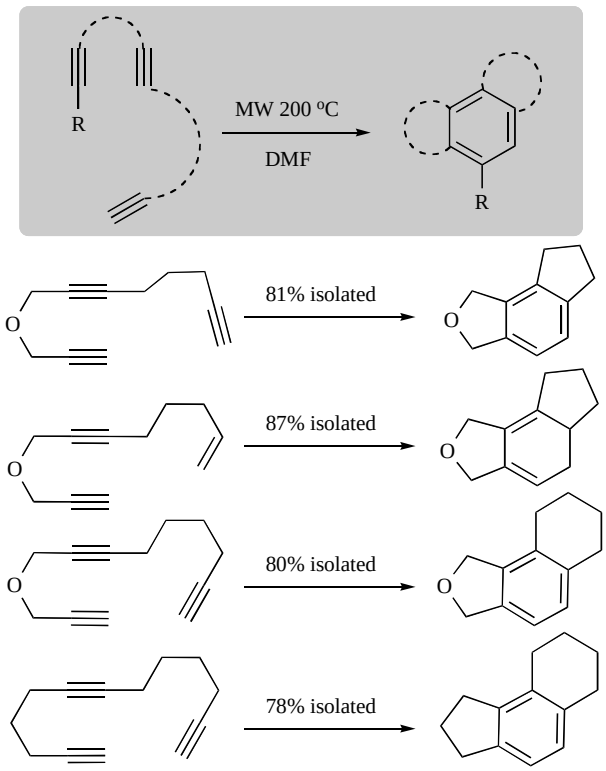
Voyager (CEM) unit containing a 10 mL capacity PTFE tube (i.d. 1 mm) in a Kevlar sheath was housed in the microwave reactor and a solution of the reactants passed through. Temperature was monitored by the use of a thermocouple probe and pressure by an in-line inducer. A reasonable conversion to the desired product was achieved, processing 6 mmol of material.

The rapid heating and cooling sequences that can be acheived using microwave reactors are extremely advantagous in transformations in which the reactants or products are thermally unstable. A modified Baylis-Hillman reaction between formalin and various acrylates catalysed by 1,4-diazabicyclo[2.2.2]octane (DABCO) has been demonstrated (Scheme **30**) [60]. The ability to quickly reduce the temperature following the short reaction sequence helps to minimise hydrolysis, dimerisation and polymerisation of the product.

The development of alternative methods to access functionalised benzonitriles avoiding the use of stoichiometric quantities of metal cyanides such as in the Rosenmund-von Braun or Sandmeyer reactions is of significant commercial interest. Pitts *et al.* demonstrated the feasibility of carrying out palladium-catalysed transfer cyanation reactions under microwave conditions in remarkably short times at significant scales [61]. Following an investigation into the effects of the cyanide source, catalyst and ligand system as well as any additives an optimised set of conditions were determined. Scale-up of the reaction was performed by direct transfer to a Voyager SF system (CEM) in a stop-flow process. Repeated batches of 50 mL could be processed (12 g of citalopram) permitting isolation of the product in 99% yield and purity >98.5% (Scheme **31**). Exemplification of this process was shown by the ability to produce 150 g of the product in under 2 h (11 cycles) using extremely low levels of catalyst (0.6 mol%). An additional range of substrates were also shown to undergo cyanation in equally efficient transformations.

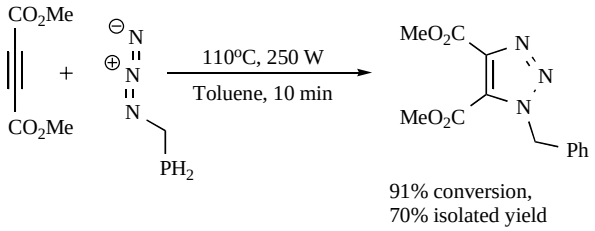
The preparation of diverse constructs using convergent multi-component reaction sequences has become a popular methodology for the generation of exploratory combinatorial libraries as potential biologically active leads [62]. These reactions have also been conducted in a flow mode utilizing microwave irradiation to enhance the rates of the reactions. A capillary reactor (1180 μm; Fig. **27**) continuously fed by up to three different syringe pump inputs provided good yields of the reaction products in seconds (Scheme **32**) [63]. In both examples the requirement for a high boiling point, good microwave-absorbing solvent was necessary because the system was irradiated under atmospheric pressure but required high temperatures to drive the reactions to comple-

tion within the short residence times provided by the capillary tubes.

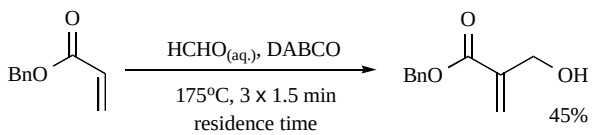


Scheme 28. Intramolecular cyclotrimerisation of acetylenic compounds.

Fig. (23). Flow microwave reactor comprising of a glass coil.



Scheme 29. Microwave assisted synthesis of triazoles.



Scheme 30. Alkyl 2-(hydroxymethyl) acrylate synthesis in a flow microwave reactor.

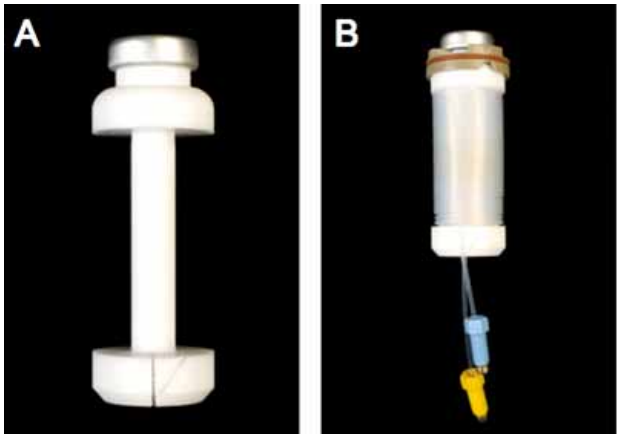


Fig. (24). (**A**) Teflon Core; (**B**) spiral coil cavity insert reactor.

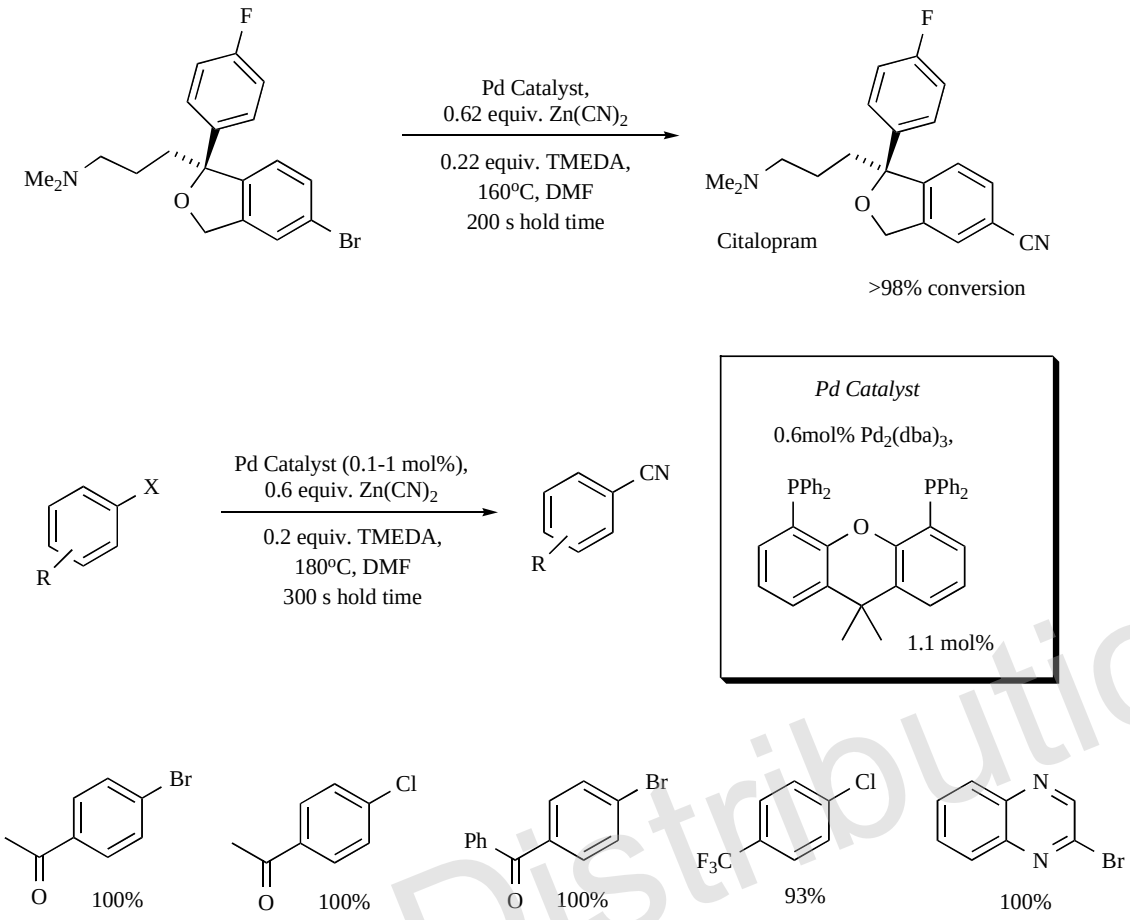
Microwaves have also proved useful for the preparation of various substituted pyrazole structures that have been prepared in flow using a modified tubing reactor inserted into the microwave cavity (Fig. **26**). Several meters (10–15 m) of microwave transparent tubing could be tightly spiralled around a Teflon column manufactured to fit into the microwave and mimic the action of a normal batch microwave vial. Connecting the input of the reactor to a reactant reservoir *via* a HPLC pump and the output to a twin column assembly containing a polymeric primary amine scavenger and activated carbon decolouriser completed the system. This simple flow setup was used for periods of 36 h at temperatures up to 150°C in order to prepare 120 g batches of bulk intermediates in high yields and excellent purities (Scheme **33**) [64].

MICROFLUIDIC APPLICATIONS TO MICROWAVE CONTINUOUS PROCESSING

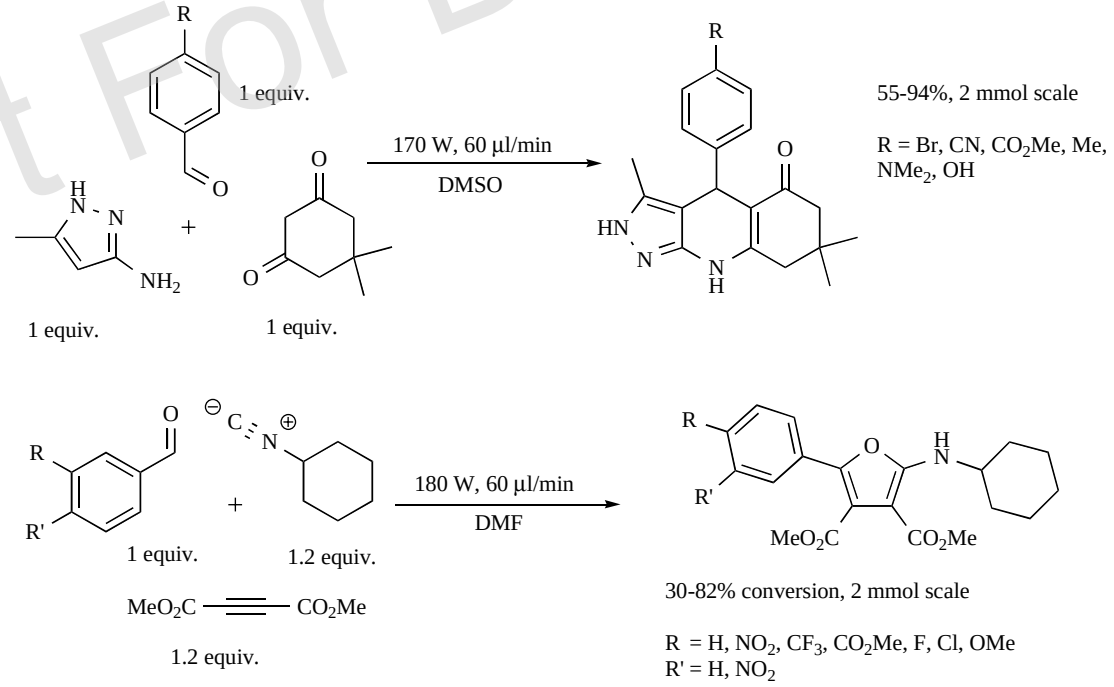
The combinations of microwave technology and microfluidic reactor vessels have shown great promise in the area of process intensification. A series of publications have demonstrated these benefits in terms of enhanced reaction processing and improved kinetics.

One of the original microfluidic reactors designed by Haswell was applied to Suzuki cross coupling reactions as a continuous flow procedure using milligram quantities of a recyclable heterogeneous palladium catalyst (immobilised on alumina) [65]. A thin gold film (10-15 nm) located under the reactor channel on the outer face of the glass reactor was used as a microwave heat transfer device for the delivery of specific heating. To achieve this the entire glass microreactor block (Fig. **25**) was placed in the cavity of a focussed microwave (Discover MW, CEM) and irradiated. The gold film rapidly coupled with the microwaves and enabled control of the heating profile by variation in the microwave power. Temperature readings were taken with an IR sensor located in the base of the microwave unit and was used to optimise the system. A premixed reactant stream was pumped into the reactor (channel dimensions: 1.5 mm wide, 50 or 80 μm deep and 15 mm long) and the products collected at the output into a cooled vial giving good conversions (Scheme **34**).

The immobilisation of metallic species on inorganic supports such as silica or alumina facilitate easy separation and

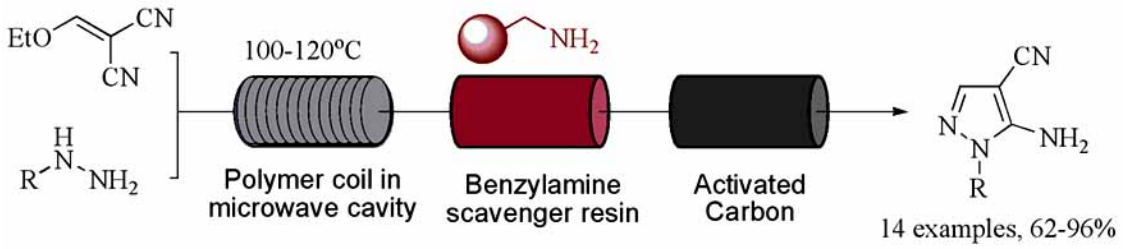


Scheme 31. A) Cyanation reaction of citalopram. B) Halide-exchange cyanation reactions substrates and conversions shown.



Scheme 32. Multi-component synthesis of small heterocyclic compounds under flow microwave conditions.

extended reuse by the constant flow of new material through the catalyst containing reactor. As in the previous example, a palladium on alumina system was utilised in a Suzuki C-C bond forming reaction using an alternative capillary glass U-tube (i.d. 800 µm; 138 mm) reactor mounted within the microwave cavity (Discover, CEM) [66]. The catalyst particles



Scheme 33. Continuous flow synthesis of pyrazoles under microwave irradiation.

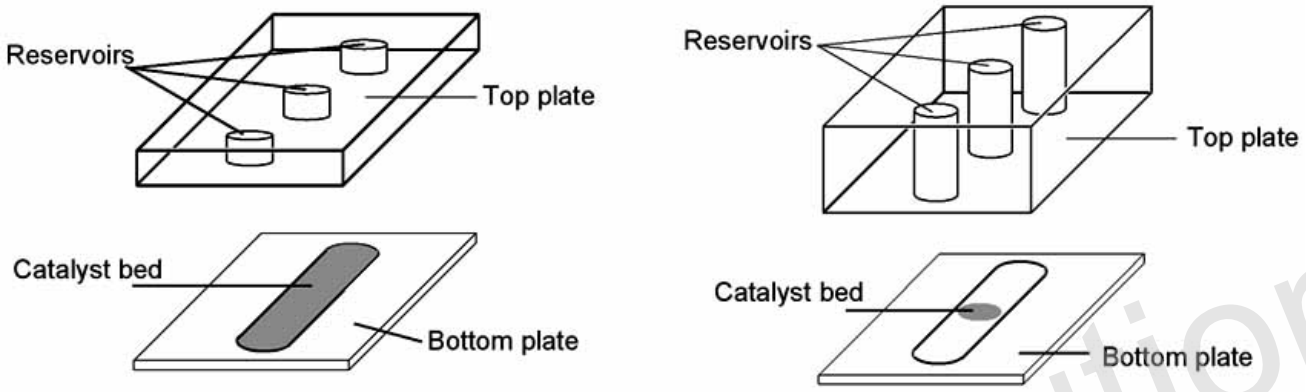


Fig. (25). Linear channel microreactor with catalyst bed.

were retained in the U-tube by the aid of two glass plunge rods inserted into the tube ends (Fig. **26**). The reactions were conducted on very small scales using a syringe pump to deliver the reactants which experienced catalyst contact times of less than 60 s at flow rates of 10 or 40 nL/min. Again, coating the tube with a thin layer of gold leaf aided heating and increased the yields whilst reducing the required microwave power input. It was also shown that the catalyst could be repeatedly used, albeit over a series of 4 runs. A modification using an electrical conductivity method for *in situ* temperature measurements was also studied [67]. The benzylation of 2-pyridone was carried out to demonstrate the real-time temperature monitoring capability (50 nL/min 48 s residence time). It was discovered that the outlet temperature was about 20ºC higher than the average (along the length of the capillary); however, the median was almost identical to that measured by the IR sensor on the outside of the capillary at the mid point.

In an analogous approach, a single and multi-addressable microcapillary reactor unit has been constructed to take advantage of this small scale reaction capability. The original reactor design used a stainless steel mixing chamber with three input ports to combine and deliver the reactants to a single capillary tube (i.d. 200-1150 μm) that is threaded through the microwave cavity (Biotage Smith Synthesiser) [68]. Additional tubing could be connected at the outlet in order to establish a link to a monitoring device or collection vessel (Fig. **27**).

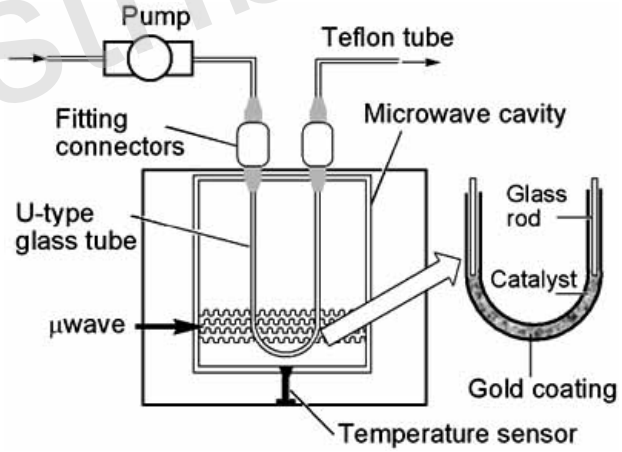
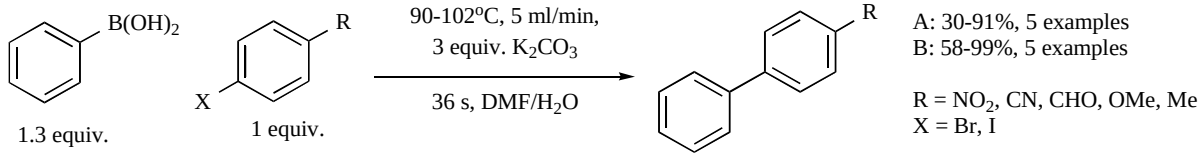


Fig. (26). Glass U-tube capillary reactor for Suzuki cross coupling reactions.

The much exploited Suzuki reaction was investigated using a variety of conditions and substrate pairings (Scheme **35**). By varying the capillary diameter and flow rates the residence time could be tuned to match the reaction kinetics.



Scheme 34. Suzuki cross coupling reactions performed in microwave heated microreactors A) chip reactor B) U-tube capillary reactor.

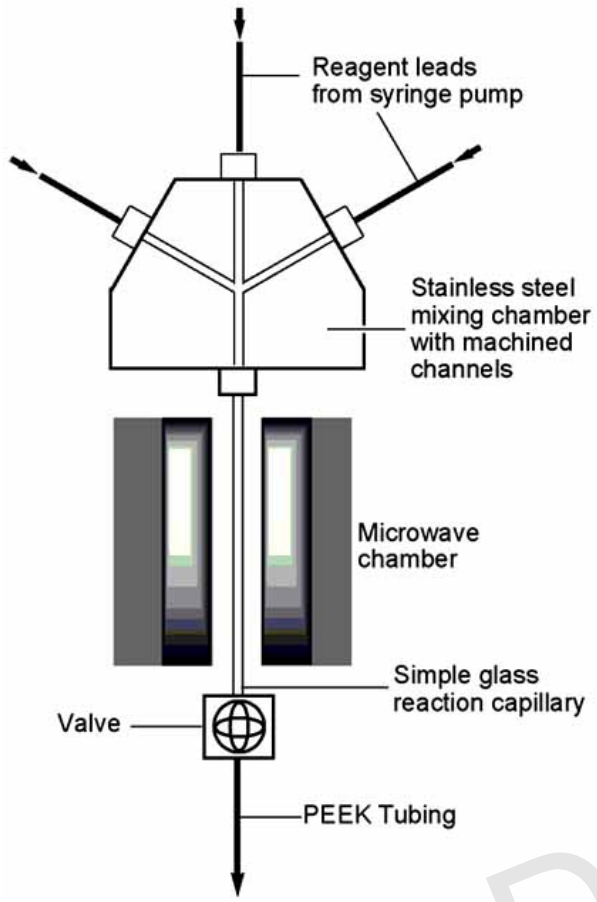
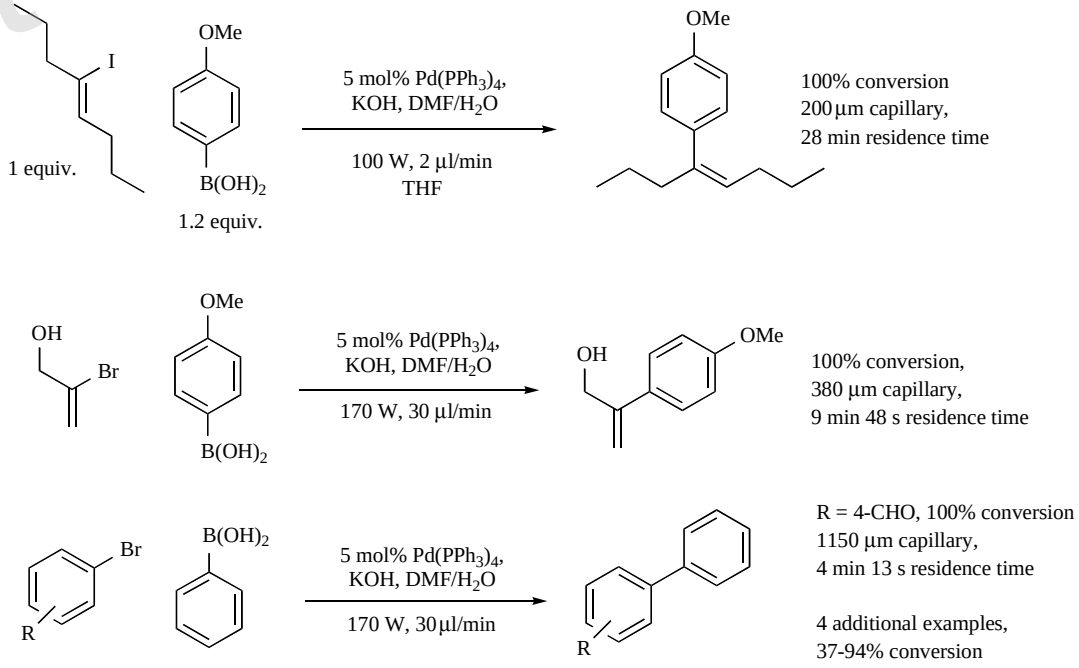


Fig. (27). Schematic display of the capillary flow reactor.

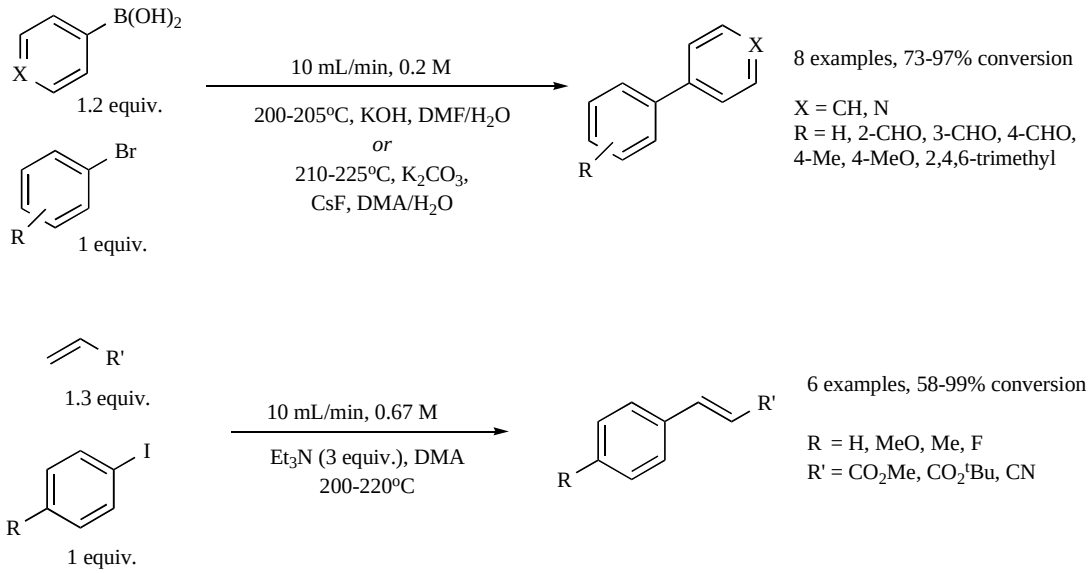
In an interesting aside it was shown that thin films of palladium deposited within the interior of the capillary tube were capable of catalysing the same coupling reactions. However, this was reported to also give rise to elevated reaction temperatures (estimated 188ºC compared to 60ºC) which led to the formation of by-products. In a subsequent publication [69] this concept was further developed by the thermally assisted aggregation and plating of a 6 μm layer of Pd(0) (derived from palladium acetate) onto the inner surface of 1050 μm glass capillaries. The resulting film was calculated to have a density of 3 g/cm^3. Its activity as a catalyst was again tested in the Suzuki-Miyaura coupling and extended to the Heck reaction (Scheme **36**). Good conversions for a number of substrates were achieved ratifying the approach.

The same capillary reactor system was also used in ring closing metathesis (RCM) reactions using 1 mol% of the Grubbs II catalyst (Reactions 1 and 2; Scheme **37**) and a series of nucleophilic aromatic substitutions (Reaction 3). Interestingly, a heterogeneous Wittig reaction was also processed in the capillary system without encountering problems of blocking (Reaction 4) [68].

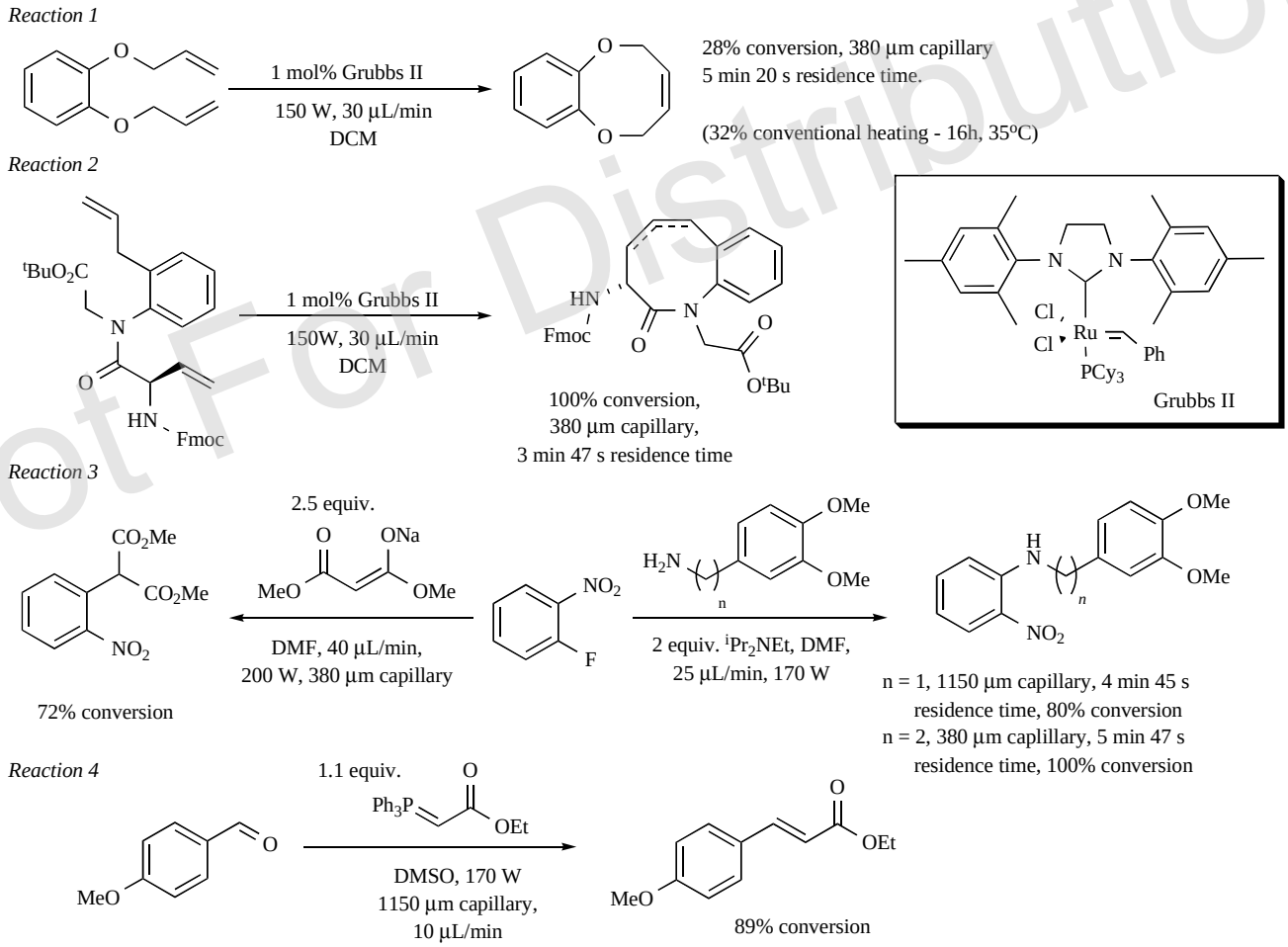
The concept of scale out or numbering up has been addressed using the capillary reactor device described above by the introduction of additional reaction channels [70]. A selection of parallel capillaries could be bundled together and heated in the same microwave cavity expanding the processing capacity of the reactor or allowing multiple reactions to be conducted simultaneously (Fig. **28**). Initially plugs of aryl halides and boronic acids in the presence of the palladium catalyst were combined and introduced sequentially into the reactor tube to generate a small showcase of biaryl compounds in good to excellent conversions (Scheme **38A**). A similar process was used to prepare a collection of aniline derivatives from simple nucleophilic aromatic substitution chemistries (Scheme **38B**). In both cases the reactants were brought together as two separate substrate streams in a static mixer before entering the preheated reactor tube. These results created the basis for the more advanced multi-channel parallel reactor design. For this the reactor was fitted with an 8 port valve with each connection paired with a neighbour, creating four merged but independent output channels into



Scheme 35. Selected results for the solution phase Suzuki reaction in flow.



Scheme 36. Suzuki and Heck reactions conducted using thin film palladium-coated capillaries.



Scheme 37. Ring closing metathesis reactions, nucleophilic aromatic substitutions and a heterogeneous Wittig reaction.

the capillary reactors. By splitting the flow streams from two amine inputs and two aromatic components a simple 2×2 array could be constructed as a single operation. A more complex shuffling and splitting of the input streams was conducted in a repeat of the earlier Suzuki chemistry that permitted a 2×4 array of the product to be created in two sequential runs (Fig. **29**).

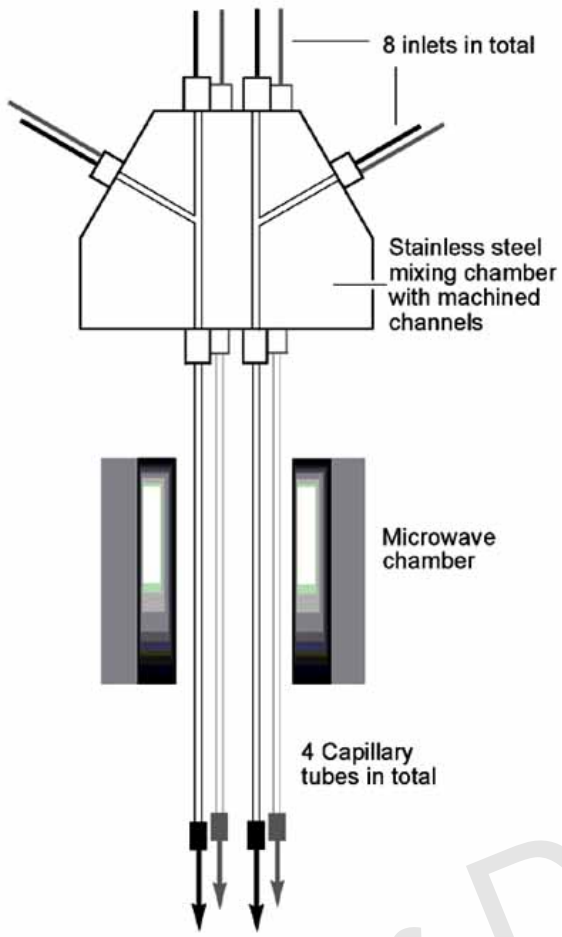
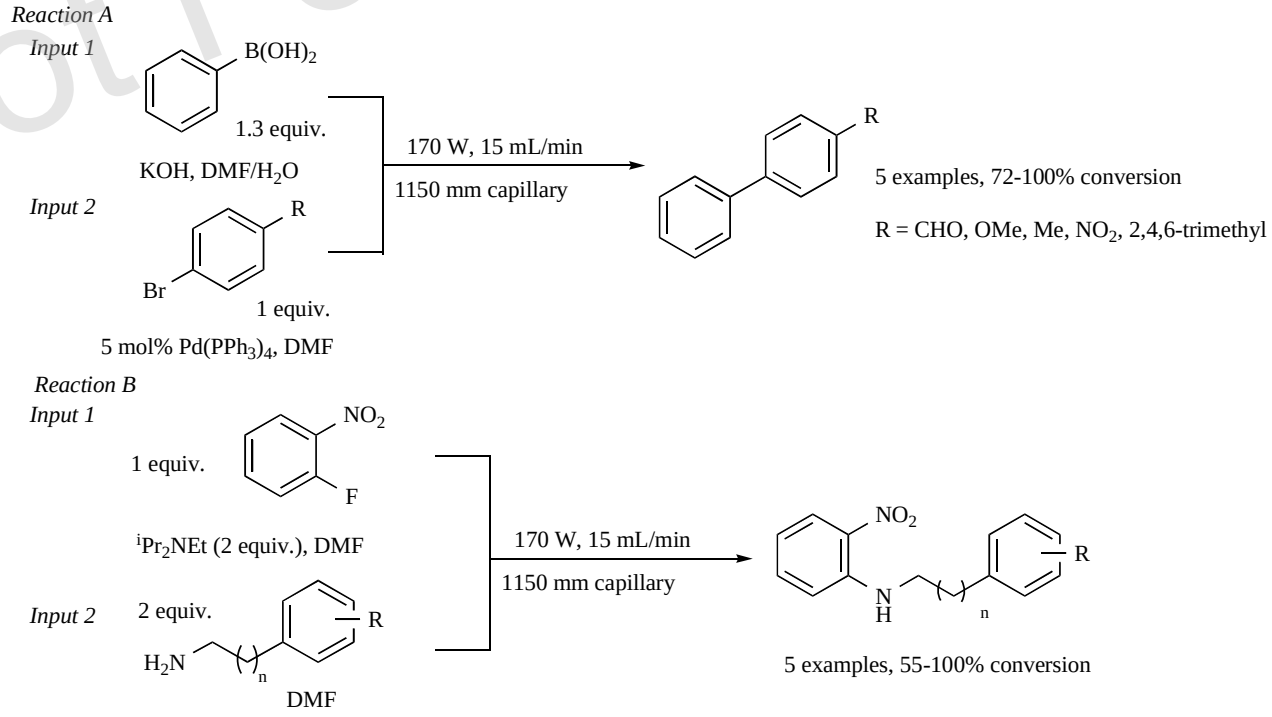


Fig. (28). Multi-capillary modification for numbering up of reaction streams.

APPLICATIONS IN INORGANIC CHEMISTRY

Continuous microwave processing in flow reactors has also found application in the area of rapid crystallisation. In a crystallisable solution containing a heat transfer agent (possibly the solvent) a metastable equilibrium exists which can be affected by simple chemical change such as hydrolysis or decomplexation. This has been demonstrated in the precipitation of calcite derived from calcium citrate and a carbonate/hydrogen carbonate solution [71]. A microwave digestion oven (Maxidigest MX 350, Prolabo) was modified to accommodate a 250 mL cylindrical vessel with a head fitting to allow solution input and a central rotor stirrer (700 rpm). A matching outlet is positioned at the bottom of the reactor for removal of the product at a constant rate to match the input flow. An overflow conjugate is installed as a third tube insert at the top of the reactor to balance the internal volume as a consequence of precipitation. It was noted that the rate of nucleation is two to three orders higher under microwave conditions, reducing the processing cycles required.

The reproducible formation of nanodispersed colloidal particulate silicates is becoming increasingly important in a number of areas because of their chemical and physical properties. As a result new synthesis methods are being evaluated to generate spherical beads with more defined modal sizes and shapes. Hydrothermal crystallisation is a popular approach and has been conducted under microwave heating, producing materials of high quality. The evaluation of the process in a commercial microwave flow reactor (MLS ETHOS continuous flow reactor) has also been conducted [72]. The optimised conditions involved hydrolysis of tetraethoxysilane (Scheme **39**). These preliminary results indicated an increase in crystallization compared to standard hydrothermal reactions.



Scheme 38. Parallel assembly of biaryl (**A**) and S_NAr derived compounds (**B**) in flow.

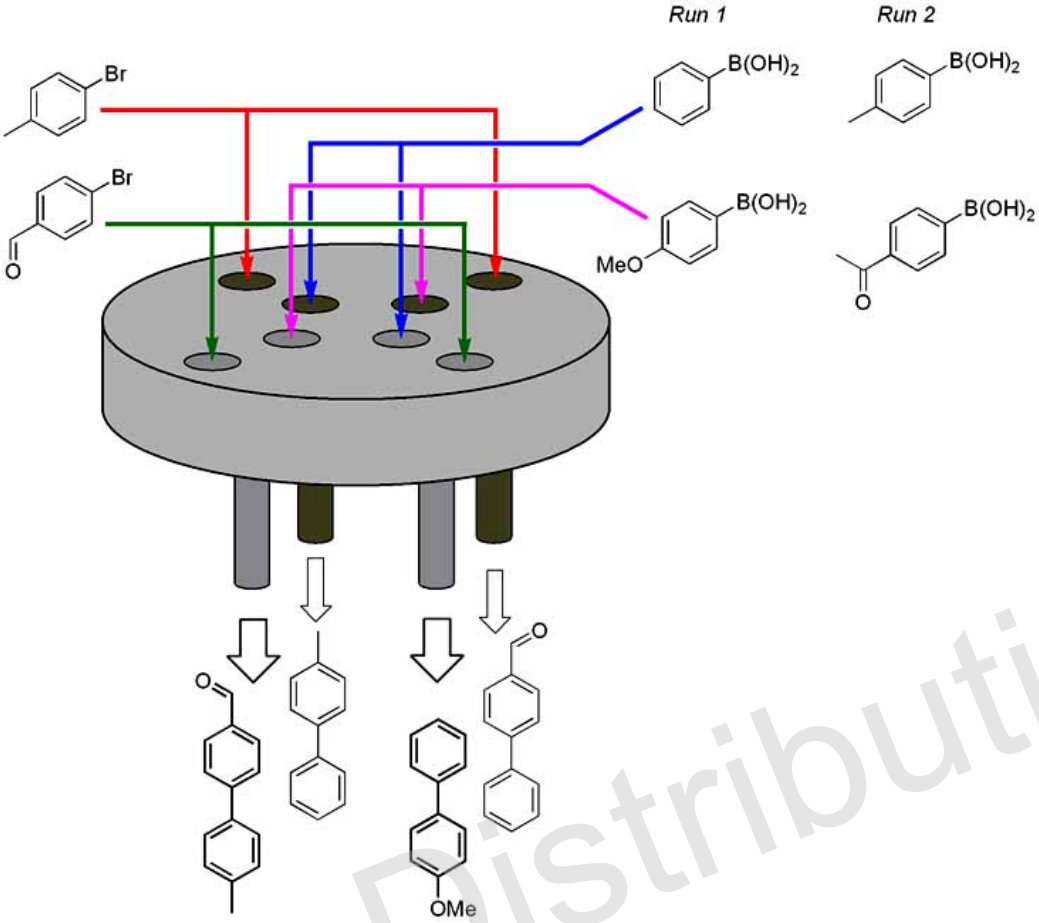


Fig. (29). Sequential parallel library preparation.

The same trend was found in the hydrothermal crystallisation of $AlPO_4$-5 [73]. An aqueous gel 390 mL ($Al_2O_3/P_2O_5/Pr_3N$ in H_2O) was pumped through the tubular reactor (120 mL) embedded in the microwave cavity of a Flow SYNTH unit (Milestone). The reaction temperature was maintained at between 180-190ºC. On average a yield of 100 mg of crystals could be obtained from a 2 g sample of the gel every 48 min.

CONCLUSION

While a growing number of applications of flow-based microwave synthesis are starting to appear in the literature, most have employed bespoke apparatus that is not yet generally available. Moreover, many of the applications are quite specific in nature requiring special engineering or design features to be incorporated. In addition, the majority of these examples have still not tackled the true issues and requirements of scaled manufacture in order to facilitate the continuous production of bulk commodity chemicals. The lack of generality and the fairly limited commercial availability of appropriate reactors or plants have consequently led to a relatively slow uptake of this mode of chemistry. In order for these systems to be more widely adopted the next generation of systems need to be versatile, operating over a wide range of chemistries and on a broad scale ranging from milligrams to kilos of material, thereby accommodating both library preparations as well as providing a platform for significant laboratory scale-up.

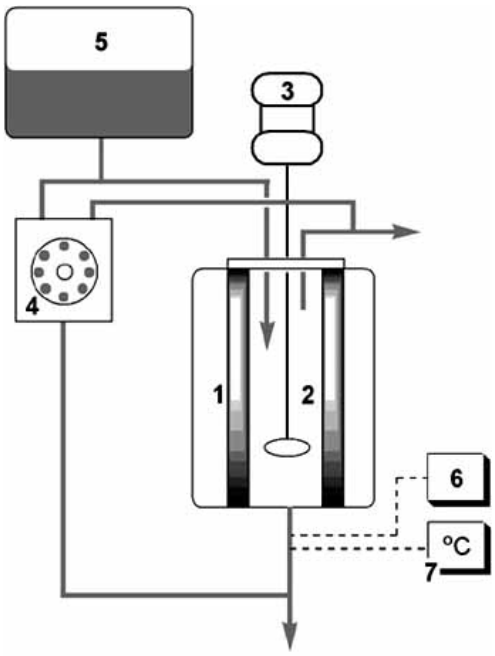


Fig. (30). Microwave oven modification for continuous flow processing. **1**. Microwave oven; **2**. PTFE reactor; **3**. Vertical shaker; **4**. Peristaltic pump; **5**. Feed tank; **6**. Conductimeter; **7**. Thermometer.

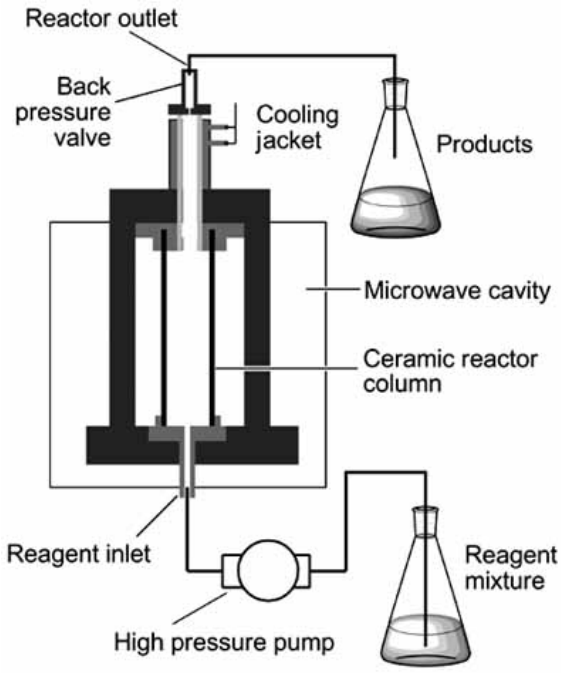
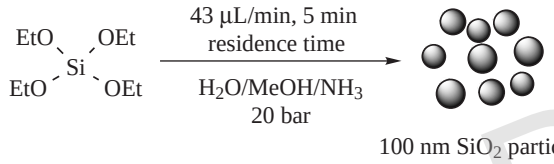


Fig. (31). Silica nanoparticle preparation in a continuous flow reactor.



Scheme 39. Formation of nanoparticulate silicas.

It is evident that the need for this type of synthesis equipment is becoming increasingly timely owing to the shift in focus towards more efficient flow chemistry methods, both at the micro and meso reactor levels. The ability to couple the rapid and controlled heating profiles provided by microwave irradiation with the fast optimisation and processing capacities of flow chemistry will certainly provide significant benefits. It can only be a matter of time before commercial flow microwave devices start to appear within research laboratories. For the bench chemist the new opportunities – as well as the released time and skilled manpower that such automated devices will provide – will certainly enhance the working enviroment and their productivity.

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REFERENCES

[1] a) Mehdizadeh, M. *Res. Chem. Intermed.*, **1994**, *20*, 79. b) Schwalbe, T.; Simons, K. *Chem. Today*, **2006**, *24*, 56.

[2] a) Baghursy, D.R.; Mingos, D.M.P. *Chem. Soc. Rev.*, **1991**, *20*, 1. b) Gabriel, C.; Gabriel, S.; Grant, E.H.; Halstead, B.S.; Mingos, D.M.P. *Chem. Soc. Rev.*, **1998**, *27*, 213. c) Kingston, H.M.; Haswell, S.J. *Microwave-Enhanced Chemistry. Fundementals, Sample Preparation and Applications*, ACS: Washington D.C., **1997**. d) Gedye, R.; Smith, F.; Westway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rusell, J. *Tetrahedron Lett.*, **1986**, *27*, 279. e) Larhed, M.; Olofsson, K. *Microwave Methods in Organic Synthesis*, Springer: Berlin **2006**. f) Loupy, A. *Microwaves in Organic Synthesis 2nd Ed*, Wiley-VCH: Weinheim **2006**.

[3] Maxwell, J.C. *A Treatise on Electricity and Magnetism*, Clarendon Press: Oxford, **1873**.

[4] a) Metaxas, A.C.; Meredith, R.J. *Industrial Microwave Heating*, Peregrinus, **1998**. b) Lidström, P.; Tieney, J.; Wathey, B.; Westman, J. *Tetrahedron*, **2001**, *57*, 9225. c) Mingos, D.M.P.; Baghurst, D.R. In *Microwave Enhanced Chemistry*; Kingston, H.M.; Haswell, S.J. Eds; ACS: Washington, DC **1997**, pp 3-54. d) Majetich, G.; Wheless, K. In *Microwave Enhanced Chemistry*; Kingston, H.M.; Haswell, S.J. Eds; ACS: Washington, DC **1997**, pp 455-506.

[5] Barringer, S.A.; Davis, E.A.; Gordon, J.; Ayappa, K.G.; Davis H.T. *AIChE J.l*, **1994**, *40*, 1433.

[6] Clark, D.E.; Sutton, W.H. *Annu. Rev. Mater. Sci.*, **1996**, *26*, 299.

[7] a) http://www.pueschner.com/basics/eindringtiefe_en.php. b) Bogdal D. *Microwave-assisted organic synthesis. One hundred reaction procedures*. Elsevier: Oxford, **2005**. c) Craig, D.Q.M. *Dielectric Aspects of Pharmacological Systems*, Talyor and Francis: London, **1995**.

[8] Meredith, R.J. *Power & Energy Engineers' Handbook of Industrial Microwave Heating*, Institution of Electrical Engineers: Stevenage, **1998**.

[9] a) Nüchter, M.; Ondruschka, B. *Mol. Divers.*, **2003**, *7*, 253. b) Howarth, P.; Lockwood, M. *Chem. Eng.*, **2004**, *756*, 29. c) Baxendale, I.R.; Pitts, M.R. *Chem. Today*, **2006**, *24*, 41. c) Estel, L.; Ledoux, A.; Salaün, P.; Abdelghani-Idrissi, M.A. 'Batch to continuous reactors using microwaves for organic synthesis' *Proceedings of the 33rd Microwave Power Symposium*, Chicago, IL July 11-15. **1998**, 63. d) Glasnov, T.N.; Kappe, C.O. *Macromolecular Rapid Communications*, **2007**, *28*, 395. e) Wolkenburg, S.E.; Shipe, W.D.; Lindsay, C.W.; Guare, P.J.; Pawluczyk J.M. *Curr. Opin. Drug Disc. Dev.*, **2005**, *8*, 701.

[10] a) Strauss, C.R. *Chem. Aust.*, **1990**, 186. b) Chen, S.-T.; Chiou, S.-H.; Wang K.-T. *J. Chem. Soc. Chem. Commun.*, **1990**, 807.

[11] a) Gedye, R; Smith, F.; Westway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. *Tetrahedron Lett.*, **1986**, *27*, 279. b) Giguere, R.J.; Bray, T.L.; Duncan, S.M.; Majetich, G. *Tetrahedron Lett.*, **1986**, *27*, 4945.

[12] Nüchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. *Green Chem.*, **2004**, *6*, 128.

[13] a) Cablewski, T.; Faux, A.F.; Strauss, C.R. *J. Org. Chem.*, **1994**, *59*, 3408. b) Roberts, B.A.; Strauss, C.R. *Acc. Chem. Res.*, **2005**, *38*, 653.

[14] Bagnell, T.; Bliese, M.; Cablewski, T.; Strauss, C.R.; Tsanaktsidis, J. *Aust. J. Chem.*, **1997**, *50*, 921.

[15] Chen, S.-T.; Chiou, S.-H.; Wang, K.-T. *J. Chin. Chem. Soc.*, **1991**, *38*, 85.

[16] a) McGill, S.L.; Walkiewicz, J.W. *J. Microwave Power Electromag. Energy*, **1987**, *22*, 175. b) Cameron, K.L.; Depew, M.C.; Wan, J.K.S. *Res. Chem. Intermed.*, **1991**, *16*, 221. c) Wan, J.K.S.; Tse, M.Y.; Husby, H.; Depew, M.C. *J. Microwave Power Electromag. Energy*, **1990**, *25*, 32.

[17] Wan, J.K.S.; Bamwenda, G.; Depew, M.C., *Res. Chem. Intermed.*, **1991**, *16*, 241.

[18] Zhang, X.; Lee, C.S.-M.; Mingos, D.M.P.; Hayward, D.O. *Cat. Lett.*, **2003**, *88*, 129.

[19] a) Zhang, X.L.; Hayward, D.O.; Mingos, D.M.P. *Chem. Commun.*, **1999**, 975. b) Zhang, X.L.; Hayward, D.O.; Lee, C.; Mingos, D.M.P. *Appl. Catal. B-Environ.*, **2001**, *33*, 137.

[20] a) Koch, T.A.; Krause, K.R.; Mehdizadeh, M. *Process Safety Prog.*, **1997**, *16*, 241. b) Wan, J.K.S.; Koch, T.A. *Res. Chem. Intermed.*, **1994**, *20*, 29. c) USPatent US/6287531. d) World Patent WO/1995/021126.

[21] a) Chemat, F.; Poux, M.; di Martino, J.-L.; Berlan, J. *Chem. Eng. Technol.*, **1996**, *19*, 420. b) Chemat, F.; Esveld, D.C.; Poux, M.; di Martino, J.-L. *J. Microwave Power and Electromagnetic Energy*, **1998**, *33*, 88.

[22] Kabza, K.G.; Chapados, B.R.; Gestwicki, J.E.; McGrath, J.L. *J. Org Chem.*, **2000**, *65*, 1210.

[23] Pipus, G.; Plazl, I.; Koloini, T. *Chem. Eng. J.*, **2000**, *76*, 239.

[24] Cáceres, A.; Jaimes, M.; Chávez, G.; Bravo, B.; Ysambertt, F.; Márquez, N. *Talanta*, **2005**, *68*, 359.

[25] Shieh, W.-C.; Dell, S.; Repič, O. *Tetrahedron Lett.*, **2002**, *43*, 5607.

[26] http://www.milestonesrl.com

[27] Shieh, W.-C.; Lozanov M.; Repič O. *Tetrahedron Lett.*, **2003**, *44*, 6943.

[28] Shieh, W.-C.; Dell, S.; Repič, O. *Org. Lett.*, **2001**, *3*, 4279.

[29] a) Ondruschka, B.; Nüchter, M. In *Advances in Microwave and Radio Frequency Processing*; Willert-Porada, M. Ed.; Springer: Berlin, **2006**; pp 390-397. b) Nüchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. *Green Chem.*, **2004**, *6*, 128. c) Bierbaum, R.; Nüchter, M.; Ondruschka, B. *Chem. Ing. Technol.*, **2004**, *76*, 961.

[30] French Patent 2833260

[31] a) Esveld, E.; Chemat, F.; van Haveren, J. *Chem. Eng. Technol.*, **2005**, *23*, 429. b) Esveld, E.; Chemat, F.; van haveren, J. *Chem. Eng. Technol.*, **2000**, *23*, 279.

[32] a) Bram, G.; Loupy, A. In *Preparative Chemistry using supported reagents*, Laszlo, P. Ed.; Academic Press: New York, **1987**; p 387-400. b) Hayes, B.L. *Microwave Synthesis; Chemistry at the speed of light*. CEM Publishing: Bloomington, IN; **2002**.

[33] a) Lehmann, F.; Pilotti, Å, Luthman, K. *Mol. Divers.*, **2003**, *7*, 145. b) Sarko, C.R. In *Microwave Assisted Organic Synthesis* Tierney, J.P.; Lidström, P., Eds; Blackwell Publishing: Oxford, **2005**, pp 222-236 and references therein. c) Borman S. *Chem. Eng. News*, **2001**, *79*, 49-58.

[34] Lehmann, H.; LaVecchia, L. *J. Assoc. Lab. Autom.*, **2005**, *10*, 412.

[35] www.biotage.com

[36] www.anton-parr.com

[37] www.cemsynthesis.com

[38] Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem Soc. Perkin Trans. 1*, **2000**, 3815 and references therein.

[39] Loones, K.T.J.; Maes, B.U.W.; Rombouts, G.; Hostyn, S.; Diels G. *Tetrahedron*, **2005**, *61*, 10338.

[40] I. R. Baxendale, unpublished results.

[41] Dye, J.L.; Lok, M.T.; Tehan, F.J.; Creaso, J.M.; Voorhees, K.J. *J. Org. Chem.*, **1973**, *38*, 1773.

[42] a) Jähnisch, K.; Hessel, V.; Löwe, H.; Baerns, M. *Angew. Chem. Int. Ed.*, **2004**, *43*, 406. b) Fletcher, P.D.I.; Haswell, S.J.; Pombo-Villar, E.; Warrington, B.H.; Watts, P.; Wong, S.Y.F.; Zhang, X. *Tetrahedron*, **2002**, *58*, 4735. c) Pennemann, H.; Watts, P.; Haswell, S.J.; Hessel, V.; Löwe, H. *Org. Process Res. Dev.*, **2004**, *8*, 422. d) Taghavi-Moghadam, S.; Kleemann, A.; Golbig, K.G. *Org. Process Res. Dev.*, **2001**, *5*, 652. e) Jas, G.; Kirschning, A. *Chem. Eur. J.*, **2003**, *9*, 5708. f) Smith, C.D.; Baxendale, I.R.; Tranmer, G.K.; Baumann, M.; Smith, S.C.; Lewthwaite R.A.; Ley, S.V. *Org. Biomol. Chem.*, **2007**, 1562. g) Ley S.V.; Baxendale, I.R. *Nat. Rev. Drug Discov.*, **2002**, *1*, 573. h) Hodge, P. *Ind. Eng. Chem. Res.*, **2005**, *44*, 8542. i) Ley, S.V.; Baxendale, I.R.; Myers, R.M. In *Comprehensive Medicinal Chemistry II*, Taylor, J.B.; Triggle, D.J. Eds; Elsevier: Oxford, **2006**, Vol. 3, pp 791-839. j) Hornung, C.H.; Mackley, M.R.; Baxendale, I.R.; Ley, S.V. *Org. Proc. Res. Dev.*, **2007**, 399. k) *Chemical Micro Process Engineering, Processing and Plants*, Hessel, V.; Löwe, H.; Müller, A.; Kolb, G., Eds; Wiley-VCH: Weinheim, **2005**. l) *Microreactors, New Technology for Modern Chemistry*, Ehrfield, W.; Hessel V.; Löwe, H., Eds; Wiley-VCH: Weinheim, **2000**. m) Baxendale, I.R.; Griffiths-Jones, C.M.; Ley S.V.; Tranmer, G.K. *Synlett*, **2006**, 427. n) Baxendale, I.R.; Deely, J.; Griffiths-Jones, C.M.; Ley, S.V.; Saaby, S.; Tranmer, G.K. *Chem. Commun.*, **2006**, 2566. o) Baxendale, I.R.; Ley, S.V.; Smith, C.D.; Tranmer, G.K. *Chem. Commun.*, **2006**, 4835. p) Baumann, M.; Baxendale, I.R.; Ley, S.V.; Smith, C.D.; Tranmer, G.K. *Org. Lett.*, **2006**, *8*, 5231. q) Luckarift, H.R.; Nadeau, L.J.; Spain, J.C. *Chem. Commun.*, **2005**, 383. r) Lee, C.K.Y.; Holmes, A.B.; Ley, S.V.; McConvey, I.F.; Al-Duri, B.; Leeke, G.A.; Santos, R.C.D.; Seville, J.P.K. *Chem. Commun.*, **2005**, 2175. s) Hafez, A.M.; Taggi, A.E.; Lectka, T. *Chem. Eur. J.*, **2002**, *8*, 4114. t) Hafez, A.M.; Taggi, A.E.; Wack, H.; Drury, W.J.; Lectka, T. *Org. Lett.*, **2000**, *2*, 3963. u) Doku, G.N.; Verboom, W.; Reinhoudt D.N.; van den Berg, A. *Tetrahedron*, **2005**, *61*, 2733.

[43] Marquié, J.; Salmoria, G.; Poux, M.; Laporterie, A.; Dubac, J.; Roques, N., *Ind. Eng. Chem. Res.*, **2001**, *40*, 4485.

[44] a) Khadilkar, B.M.; Madyar, V.R. *Org. Proc. Res. Dev.*, **2001**, *5*, 452. b) Khadilkar, B.M.; Madyar, V.R. *5th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-5)*, **2001**.

[45] Bagley, M.C.; Jenkins, R.L.; Lubinu, M.C.; Mason, C.; Wood, R. *J. Org. Chem.*, **2005**, *70*, 7003.

[46] Glasnov, T.N.; Vugts, D.J.; Koningstein, M.M.; Desai, B.; Fabian, W.M.F.; Orru, R.V.A.; Kappe, C.O. *QSAR Comb. Sci.*, **2006**, *25*, 509.

[47] Wilson, N.S.; Sarko, C.R.; Roth, G.P. *Org. Proc. Res. Dev.*, **2004**, *8*, 535.

[48] Bonnet, C.; Estel, L.; Ledoux, A.; Mazari, B.; Louis, A. *Chem. Eng. Proc.*, **2004**, *43*, 1435.

[49] a) De la Hoz, A.; Díaz-Ortiz, Á.; Moreno, A. *Chem. Soc. Rev.*, **2005**, *34*, 1640. b) Habermann, J.; Ponzi, S.; Ley, S.V. *Mini Reviews in Org. Chem.*, **2005**, *2*, 125.

[50] Pillai, U.R.; Sahle-Demessie, E.; Varma, R.S. *Green Chem.* **2004**, *6*, 295.

[51] Arvela, R.K.; Leadbeater, N.E.; Collins Jr., M.J. *Tetrahedron*, **2005**, 61, 9349.

[52] Jachuck, R.J.J.; Selvaraj, D.K.; Varma, R.S. *Green Chem.*, **2006**, *8*, 29.

[53] Baxendale, I.R.; Griffiths-Jones, C.M.; Ley, S.V.; Tranmer, G.K. *Chem. Eur. J.*, **2006**, *12*, 4407.

[54] a) Chemat, F.; Poux, M.; DiMartino, J.L.; Berlan, J. *J. Microwave Power Electromagn. Energy*, **1996**, 31, 19. b) Chemat, F.; Poux, M.; Galema, S.A. *J. Chem. Soc. Perkin Trans. 2*, **1997**, 2371. c) Strier, C.P.; Luche, J.L. In *Synthetic Organic Sonochemistry*, Luche, J.-L. Ed.; Plenum Press: New York, **1998;** pp. 53–57. d) Peng, Y.; Song, G. *Green Chem.*, **2001**, *3*, 302. e) Peng, Y.; Song, G. *Green Chem.* **2002**, *4*, 349. f) Peng, Y.; Song, G. *Green Chem.*, **2003**, *5*, 704. g) Peng, Y.; Dou, R.; Song, G.; Jiang, J. *Synlett*, **2005**, 2245.

[55] Cravotto, G.; Cintas, P. *Chem. Eur. J.*, **2007**, *13*, 1902.

[56] Cravotto, G.; Beggiato, M.; Penoni, A.; Palmisano, G.; Tollari, S.; Lévêque, J.-M.; Bonrath, W. *Tetrahedron Lett.*, **2005**, *46*, 2267.

[57] a) Saaby, S.; Baxendale, I. R.; Ley, S. V. *Org. Biomol. Chem.*, **2005**, *3*, 3365. b) Baxendale, I.R.; Ley, S.V. In *Ernst Schering Foundation Symposium Proceedings – Enabling Technologies*, Springer-Verlag: Berlin Heidelberg, **2007**.

[58] Wilson, N.S.; Sarko, C.R.; Roth, G.P. *Org. Proc. Res. Dev.*, **2004**, *8*, 535.

[59] Savin, K.A.; Robertson, M.; Gernert, D.; Green, S.; Hembre, E.J.; Bishop J. *Mol. Divers.*, **2003**, *7*, 171.

[60] Strauss, C.R.; Trainor, R.W. *Aust. J. Chem.*, **1995**, *48*, 1665.

[61] Pitts, M.R.; McCormack, P.; Whittall, J. *Tetrahedron*, **2006**, *62*, 4705.

[62] a) Weber, L. *Drug Discov. Today*, **2002**, *7*, 143. b) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**,*10*, 51. c) Tietze, L.F.; Modi, A. *Med. Res. Rev.*, **2000**, *20*, 304. d) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.*, **2000**, *6*, 3321.

[63] Bremner, W.S.; Organ, M.G. *J. Comb. Chem.*, **2007**, *9*, 14.

[64] Smith, C.J.; Iglesias-Sigüenza, J.; Baxendale, I.R.; Ley, S.V. *Org. Biomol. Chem.*, **2007**, in press. DOI**:** 10.1039/b709043a.

[65] He, P.; Haswell, S.J.; Fletcher, P.D.I. *LabChip*, **2004**, *4*, 38.

[66] He, P.; Haswell, S.J.; Fletcher, P.D.I. *Appl. Cat. A. Gen.*, **2004**, *274*, 111.

[67] He, P.; Haswell, S.J.; Fletcher, P.D.I. *Sensors and Actuators B*, **2005**, *105*, 516.

[68] Comer, E.; Organ, M.G. *J. Am. Chem. Soc.*, **2005**, *127*, 8160.

[69] Shore, G.; Morin, S.; Organ, M.G. *Angew. Chem. Int. Ed.*, **2006**, *45*, 2761.

[70] Comer, E.; Organ, M.G. *Chem. Eur. J.*, **2005**, *11*, 7223.

[71] Rodríguez-Clemente, R.; Gómez-Morles, J. *J. Crystal Growth*, **1996**, *169*, 339-346.

[72] Bonamartini, A.; Bondioli, F.; Ferrari, A.M.; Focher, B.; Leonelli, C. *Powder Technol.*, **2006**, *167*, 45.

[73] Braun, I.; Schulz-Ekloff, G.; Wöhrle, D.; Lautenschläger, W. *Micropor. Mesopor. Mater.*, **1998**, *23*, 79.

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