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# Microwave flow chemistry: the next evolutionary step in synthetic chemistry?

**ABSTRACT**

*Microwave assisted chemistry is an increasingly important tool in the medicinal chemist's quest to speed up drug development. With the development of commercial focussed-microwave reactors, reactions can be carried out safely and reproducibly at a useful laboratory scale. Attention is now turning to the scale-up of these processes with chemists increasingly investigating continuous flow applications. This review intends to highlight the significant benefits in terms of efficiency and control that flow-based microwave applications offer modern organic synthesis.*

## INTRODUCTION

The top pharmaceutical companies have moved away from the synthesis of large combinatorial libraries instead concentrating on smaller and more focussed subsets. This change in focus has significantly impacted on their synthesic procedures placing new emphasis on compound preparation times. In addition synthetic chemists are being challenged to deliver improvements in terms of yield, purity and diversity of their compound collections. Consequently new reliable synthesis methodologies and flexible purification strategies are required to assist in furthering these quality and productivity gains. Microwave assisted chemistry has provided such an opportunity and has thus become a principal synthesis aid in the medicinal chemist's toolbox (1, 2). Considerable precedent exists in the range of reactions that can now be routinely, safely and reproducibly carried out at a useful laboratory scale. Indeed, a significant proportion of medicinal lead candidates are currently prepared via a route that involves at least one microwave mediated step. The ready acceptance and rapid integration of microwave heating protocols into standard laboratory syntheses can be ascribed to the high degree of confidence in the commercial focussed microwave reactors. Modern microwave equipment has evolved to the point where multigram quantities of material can be prepared, but reactor size is strictly limited by the necessary design of the microwave cavities used for homogenous microwave fields. An inherent problem therefore arises in attempting to move beyond these laboratory scales. One particularly attractive approach from a manufacturing point of view is to move away from a batchwise processing strategy. Microwave chemistry is ideal for adoption into a continuous flow process, since the reaction times (and therefore residency times in a reactor) are short. Such methods therefore open up the possibility of carrying out reaction sequences in an automated flow system, with additional in line clean-up and purification. As with microreactor technology, such systems can be easily "scaled-out" by duplication to approach the processing requirements for manufacture without the need for further optimisation (3). This review will cover the work to date in this area, highlighting the benefits in reaction purity and control in such an approach.

## DISCUSSION

To avoid blockages in a simple microwave flow system (Figure 1) it is important that reagents and products are soluble under the reaction conditions employed. Slurries of finely divided particles have been successfully processed in stop-flow microwave reactors (4), but the generation of solid mass within a continuous flow reactor can prove troublesome. Pressure regulators are easily blocked by precipitation of deactivated catalyst aggregates, such as palladium black, and even by high-purity products crystallising out of solution (5).
A growing number of reactions have been tested in simple microwave flow systems since pioneering work was carried out in the mid 1990's (6, 7). This early apparatus was based on Teflon coils in a domestic-type microwave cavity. Valves at either end of the coil allowed reactions to be carried out under a controlled pressure, and a heat exchanger rapidly cooled the mixture on exiting the cavity. Microprocessor control was employed with feedbacks from thermocouples at the start and end of

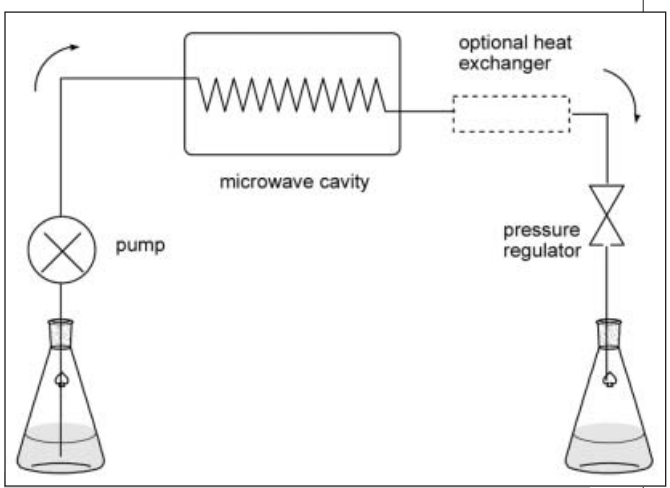



Figure 1. A simple set-up for a continuous-flow microwave system

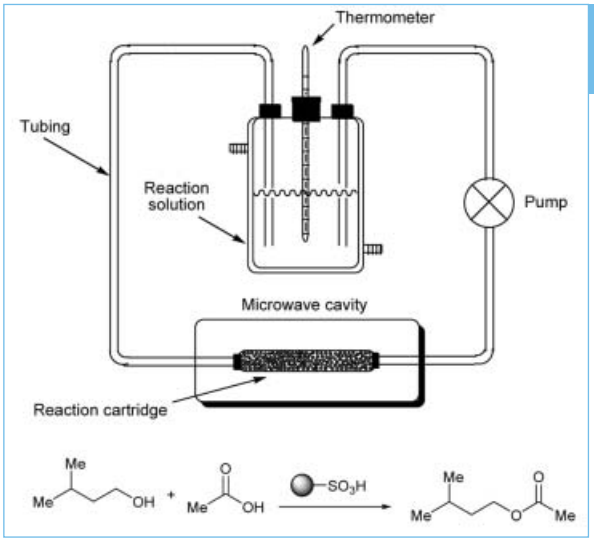



Figure 2. Continuous flow microwave mediated ester formation

the coil. Over twenty different reactions were investigated, most with short (<2 min) reaction times. However the non-homogenous field in such a set-up required relatively fast flow rates (and thus short reaction times) to avoid temperature gradients, and perhaps limited its use. A complex arrangement using a 'single-mode' microwave (i.e. a single standing wave focussed on the reaction tube) has been used to carry out Friedel-Crafts acylation chemistry (8). The reaction mixture was pumped through a manually tuned microwave applicator. The system was designed only for use at atmospheric pressure.
Similarly, the simple Fischer-type esterification of isopentyl alcohol with acetic acid using a heterogeneous polymer-supported sulfonic acid resin has been described. The sulfonic acid resin was used as a strong protic acid catalyst under microwave heating conditions to search for evidence of athermal microwave effects, derived from the preferential heating of the immobilised catalytic sites. A continuous-flow reactor (Figure 2) was used to enable continuous monitoring of the reaction, while various experimental parameters were altered and kinetic data acquired. In this way it was shown than no additional athermal effects were in action and that the rate enhancements determined could be attributed to the effective reactant to catalyst concentration within the microwave reactor being higher than in the corresponding stirred tank reactor.
The hydrolysis of sucrose to form fructose and glucose, catalysed by strongly acidic ion exchange resins under microwave irradiation as flow type processes, has also been studied (11). The principle work by Wang and co-workers used a modified domestic microwave oven containing a Teflon coil as a readily adaptable continuous flow reactor. The coil situated within the microwave cavity (ca. 10 ml in volume) was packed with the immobilised catalyst and a solution of sucrose was slowly pumped through the system. The reaction required only a 10 minute residence time at 72 W in order to achieve a 95 percent conversion. Of significant interest is the observation that the use of the acidic resin gave better results than analogous experiments using a mineral acid. Subsequently, Plazl reinvestigated this reaction under both conventional and microwave heating with a view to analysing the response of the reaction to changes in the heating mechanism (12-14). Initial reactions were conducted in a stirred tank reactor, which was housed in the chamber of a domestic microwave oven. Later a more sophisticated fixed bed reactor was constructed. In this set up the immobilised catalyst was located in a Pyrex glass tube sited in the microwave cavity (Figure 3). Automated on-line monitoring of the various fluid inputs and outputs allowed a detailed analysis and the development of a mathematical model to predict the heating requirements and thermal profile of the reactor. In this way, it was possible for the researchers to optimise the power settings, flow rates and temperature requirements, in order to produce a given conversion of the sucrose or successfully predict a given level of transformation from a set of experimental parameters.
Recent developments have been based around the widely adopted commercial systems, with cells designed to fit inside the cavities of these single-mode reactors (e.g. Figure 4). The cells are connected with standard HPLC fittings and tubing to pumping equipment and other devices. The first of these was designed to fit the Emrys Synthesiser (Biotage) unit and was used to perform different reactions all showing superior yields and reaction times to conventional heating (Scheme 1) (15). A simple amination reaction was performed in a closed loop system, whereas a Suzuki cross-coupling reaction carried out in the flow reactor was shown to give yields comparable to the microwave batch method on a single pass. Another commercial system, the Ethos-CFR (Milestone) was used to scale the esterfication of carboxylic acids up to 100 g within a continuous flow reactor (16). Simple methyl esters were efficiently formed using dimethyl carbonate and catalytic DBU in acetonitrile at 160 °C and pressures of 20 bar in reaction times (residency times) of only 12 min. The products thus derived were generally isolated in greater than 98 percent yield and prepared in the order 20-80 times faster than the corresponding thermal process, albeit at elevated temperatures. In addition, chiral acids showed lower levels of epimerisation. Simple capillary tubes (200 – 1150 μm diameters) have

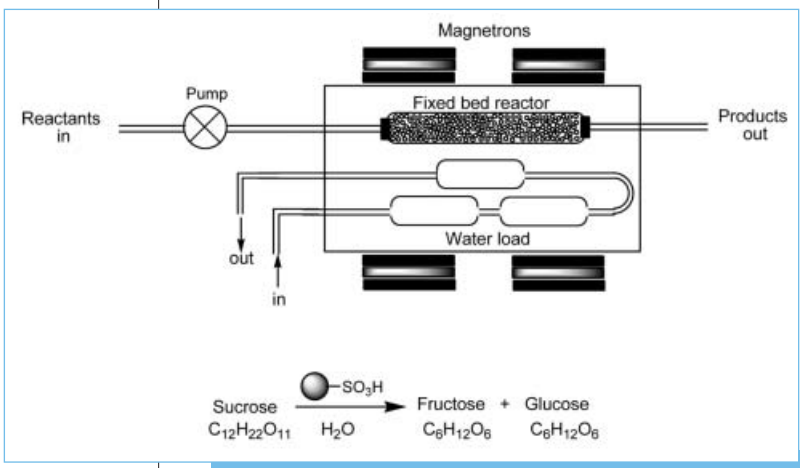



Figure 3. Experimental design flow reactor for hydrolysis of sucrose

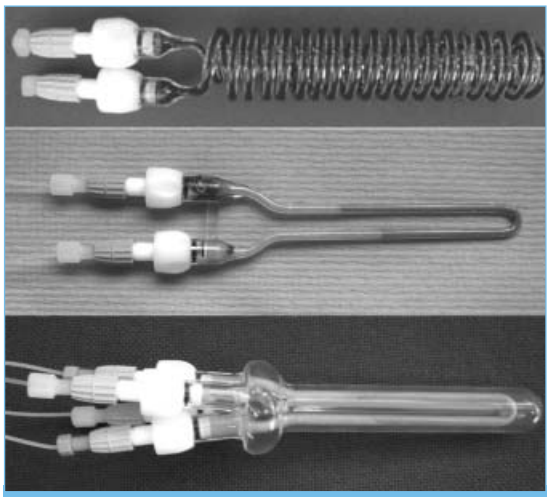
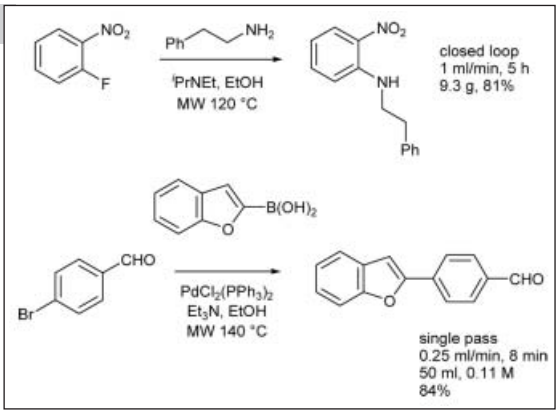
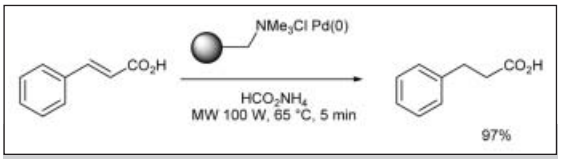


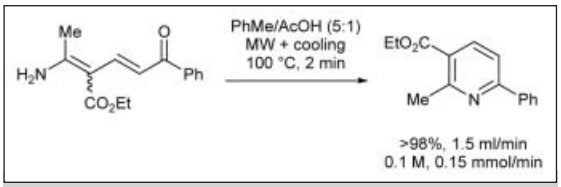
Figure 4. Cavity insert glass reactors for continuous flow microwave heating

Scheme 1

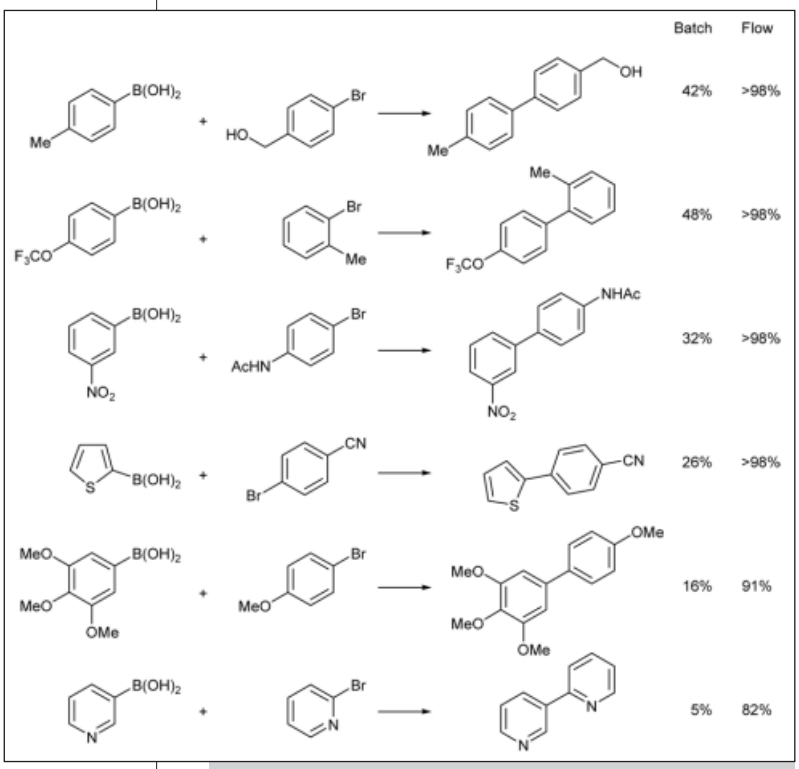



Scheme 2




Scheme 3




Scheme 4

also been employed to operate within the Emrys microwave chamber (17). Reactions analogous to those tested by Wilson et al. were successfully carried out, albeit on a limited scale. Interestingly, palladium residues from homogenous palladium acetate reactions plated out on the walls of the capillaries. Such coated tubes could promote Suzuki coupling reactions; however, concomitant reduction of functionality was observed. Use of the more solution soluble and ligand stabilised palladium tetrakistriphenylphosphine was necessary to avoid this deposition. It should be noted that Haswell and co-workers have employed indirect microwave heating on a microscale (18, 19).

Reactions were passed through a gold coated capillary that was heated, with a high degree of control, by application of microwaves. Such applications involving the precise thermal control of fluidic streams via simple and immediate power changes as supplied by microwave irradiation offers major benefits for the field of microfluidics. Indeed, as diagnostic capabilities advance the real time monitoring and instantaneous adjustment of flow stream conditions will provide the essential information for rapid reaction screening and optimisation.

Kirschning developed a composite polymer/glass material with palladium(0) immobilised on the surface of the support (20). This catalyst is prepared by exchange of chloride ions on the support (packed in a tube) with sodium tetrachloropalladate and subsequent washing with borohydride solution to form palladium(0) nanoparticles. This system was utilised to conduct transfer hydrogenation of unsaturated hydrocarbons, nitro and benzyl reductions and Suzuki cross couplings. The system has recently been adapted to a flow-through microwave reduction of cinnamic acid (Scheme 2) (21).

The Discover (CEM) reactor has been equipped with a 10 ml vessel adapted to allow material to flow through the channels of a packed bed (22). The Bohlmann-Rahtz pyridine synthesis (condensation) was exemplified in the apparatus, using sand as the packing agent (Scheme 3). The packed tube was demonstrated to operate more efficiently than a simple coiled tube for the same reaction and showed good potential for further scaling of microwave procedures. A chemically reactive packing agent, such as an immobilised reagent or catalyst, could potentially be utilised in this apparatus. Such an arrangement has been demonstrated by Ley and co-workers to achieve Suzuki couplings in a continuous flow manner (23). The equipment consisted of a simple U-tube (Figure 5) packed with microencapsulated palladium acetate (PdEnCat) that was inserted into the microwave cavity. Remarkably the yield and purity of reactions were found to be consistently improved on the equivalent microwave batch reactions. The continuous flow system even allowed production of material that had shown little conversion in batch conditions. Some selected examples are shown in Scheme 4.

The microencapsulated palladium catalyst is particularly suited to a flow reactor as it is not a source of soluble palladium species. Homogeneous palladium(0) species readily agglomerate to form palladium black and precipitate out of solution blocking filters and valves in flow systems or depositing on vessel walls in batch reactors. The unique feature of the polyurea encapsulation approach with EnCat, is the ability of the microcapsules to retain the palladium by virtue of the ligating functionality of the polymer, with reaction occurring within the polymer bead. Very low metal contamination of product and waste stream has been

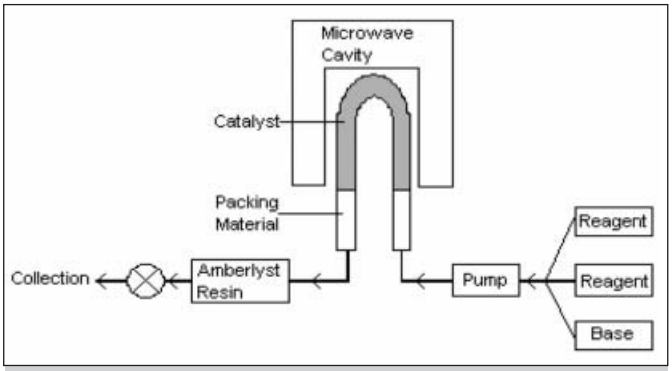
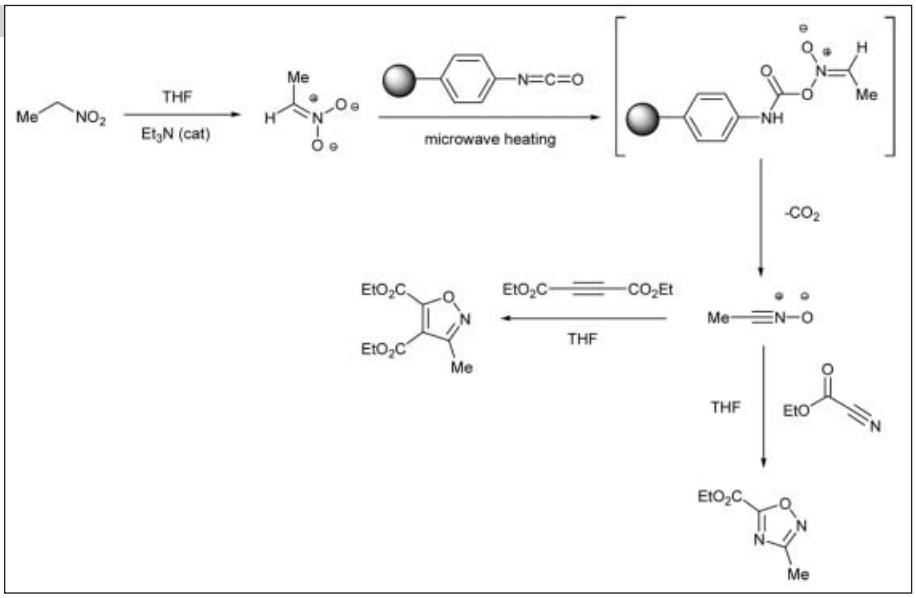



Figure 5. Pictorial representation of the flow reactor setup

Scheme 5




demonstrated with this technology under conventional conditions (24, 25). The benefits of selective heating of a catalyst bed over the bulk reaction mixture with microwave irradiation was elegantly demonstrated by Chemat and Esveld (26). They investigated several reactions promoted by a heterogeneous catalyst. The catalyst bed was situated in an external loop on a stirred tank reactor and the bulk material recycled across it. They used three arrangements for application of heat; 1) microwaves applied directly to the catalyst, 2) microwaves applied directly to the bulk and 3) the catalyst heated conventionally. They found no difference in the latter two in terms of reaction rate or yield but a significant increase in both for the microwave heated catalyst. They calculated the improved rate was due to a 7 K difference in the catalyst temperature over the bulk.

The EnCat work was an extension of the application of continuous flow microwave chemistry to the production of complex libraries by Ley. For the thermal non-metal catalysed intramolecular [2+2+2] cyclotrimerisation of alkynes, a glass coil was used to provide a longer residency time than the simple U-tube (27). Working in a dynamic continuous process also offers advantages when preparing reactive species; many potentially synthetically useful reactions are avoided because of the instability and resulting decomposition of the valuable intermediates. One such example is the generation of nitrile oxides which can be prepared thermally from the readily available nitroalkane and an isocyanate component. Unfortunately, the thus formed nitrile oxides undergo facile dimerisation accelerated by the thermal conditions especially at higher concentrations, and the resultant contamination of the amine by-product (from the isocyanate) can be problematic. Rapid flash microwave heating has been shown to facilitate a cleaner transformation through shorter heating cycles but still doesn't provide a complete solution (28). A superior approach yielding substantially cleaner products that can be easily telescoped into an additional reaction stream can be achieved working in a microwave flow reactor. Flowing a solution of the nitroalkane through an immobilised bed of isocyanate eliminates the amine contaminant and using a short residence time reduces the dimerisation adducts. Subsequent combination of this solution of the reactive intermediate with a secondary stream of the dipolarophile results in excellent conversion to the corresponding heterocyclic system (Scheme 5). Work is underway in several academic and industrial groups around the world to extend the processes covered in this review to larger flow cells and therefore higher flow rates and throughput. Indeed, it may well be possible to produce kilogram quantities in days using existing commercial reactors.

## CONCLUSION

In conclusion, flow microwave chemistry presents the classically trained chemist with an entirely new *modus operandi* that augments and enhances the conventional tools of batch processing. It replaces traditional glassware with columns and reactors that can in addition be easily packed with immobilised reagents, catalysts or scavengers thereby permitting effective removal of unwanted contaminants in a continuous dynamic fashion. Such processing methods allow for the immediate collection of a pure product upon exit from the system in an expedited cost-conscious manner. Microwave irradiation as a heating mechanism for flow based applications has already demonstrated significant benefits in terms of efficiency and control. These benefits are achieved due to the improved reactions rates and more efficient heating mechanisms associated with microwaves. So undoubtedly it will continue to evolve to become an important component of modern organic synthesis.

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