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Reproducibility and Scalability of Microwave-Assisted Reactions

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1. Introduction

High-speed microwave synthesis has attracted a considerable amount of attention in the last two decades.

Since 2000 the number of publications related to MAOS has increased dramatically. One of the reasons for the increased interest in the use of microwave heating was the introduction, at the dawn of the 21st Century, of dedicated monomode and multimode instruments with appropriate temperature and pressure controls, a development that allows reproducibility of results. However, when the microwave methodology was introduced twenty years ago, most reactions were performed in domestic ovens without appropriate temperature control.

In recent years, a number of reports have disclosed the reproducibility of results between monomode and multimode microwave instruments for solution chemistry, the application in parallel and combinatorial chemistry, and some comparisons between homogeneous and heterogeneous systems and reactions performed in closed or open vessels. In the same way, it has been shown that solvent-free reactions can be updated and applied in microwave reactors and the influence of the polarity on the reproducibility of these processes has been highlighted. Furthermore, computational calculations can assist in explaining and/or predicting whether a reaction will be reproducible or not.

Possible approaches to scale-up microwave-assisted reactions include continuous-flow reactors, small-scale batch stop-flow protocols or large-scale single-batch reactors. However, the scalability of microwave-induced processes represents an important obstacle due to numerous factors, but principally owing to increased heat loss, changes in absorption, limited penetration depth of the radiation into the reaction medium (only a few centimetres at 2.45 GHz) and the additional reflection of the microwaves. Such intrinsic complications have prevented the use of microwave reactors for volumes larger than a few litres, thus inhibiting the use of this approach for the production of larger quantities of material.

Alternatively, some researchers and microwave manufacturers have explored the potential of continuous flow microwave systems. Such an approach offers many advantages in terms

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of processing versatility, safety, reaction monitoring and optimization. Importantly, this processing method also avoids the limitations associated with the design of scaled microwave cavities, including the associated costs.
In this chapter we intend to highlight the most important reports studying and solving problems concerning the reproducibility and scalability of microwave-assisted processes, from the early reactions performed in unmodified domestic ovens to the recent syntheses utilizing dedicated apparatus or suitable flow instrumentation.

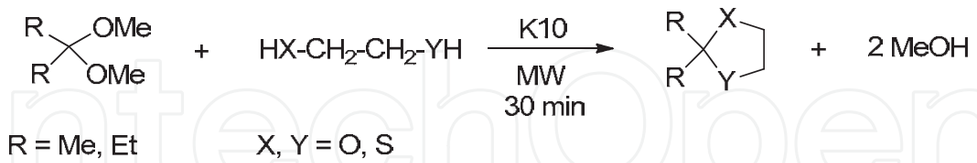
2. Reproducibility under microwaves

The microwave applicator is the component of a processing system in which energy is applied to the product to be heated. In a domestic oven the radiation power is generally controlled by on-off cycles of the magnetron. Large switching periods are undesirable in chemistry because of the absence of irradiation between switching steps. In this situation some areas may receive large amounts of energy whereas others may receive very little energy. Typically it is not possible to monitor the reaction temperature in a reliable way. Heating organic solvents in open vessels can lead to violent explosion induced by electric arcs inside the cavity or sparking as a result of switching of the magnetron. On the other hand, working with sealed vessels without monitoring of the pressure can also lead to serious accidents. For these reasons, the use of such equipment in chemistry cannot be recommended. In contrast, dedicated microwave reactors for synthesis feature built-in magnetic stirrers, direct temperature measurement of the reaction mixture with the aid of fibre-optic probes or IR sensors, and software that allows on-line temperature/pressure control by regulation of the microwave power (Kappe & Stadler, 2005).
Multimode instruments allow the use of bigger reaction vessels or an increase in reaction throughput by the use of multivessel rotors for parallel synthesis or scale-up. A general disadvantage associated with multimode instruments is the poor level of performance in small-scale experiments (<3 mL). While the generated microwave power is high (1000–1400 W), the power density of the field is generally rather low.
Monomode instruments generate a single, highly homogeneous energy field of high power density. These systems couple efficiently with small samples and the maximum power output is in most cases limited to 300 W (Ondruschka et al., 2006).
The question of reproducibility and scale-up will always involve the question of reaction conditions. In addition, the reaction medium (phase) plays a much more important role for this kind of power input compared with classical reactions. Besides the molecular mass, the polarity of the reaction mixture is a critical factor for the absorption of microwave power.

2.1 Reproducibility in scaled-up microwave-assisted reactions

One of the limitations of microwave scale-up technology is the restricted penetration depth of microwave irradiation into absorbing materials. This means that solvent or reagents in the centre of large reaction vessel are heated by convection and not by direct 'in core' microwave dielectric heating. For this reason, many researchers have studied the scale-up and reproducibility in batch of the reactions performed on a small scale.
In 1998 Hamelin studied the large-scale synthesis of dioxolanes, dithiolanes and oxathiolanes from 2,2-dimethoxypropane and 3,3-dimethoxypentane in the absence of solvent. These reactions had previously been performed in a Prolabo Synthewave 402 apparatus on a 10 mmol scale and were reproduced in a Synthewave 1000 reactor on a 2 mol

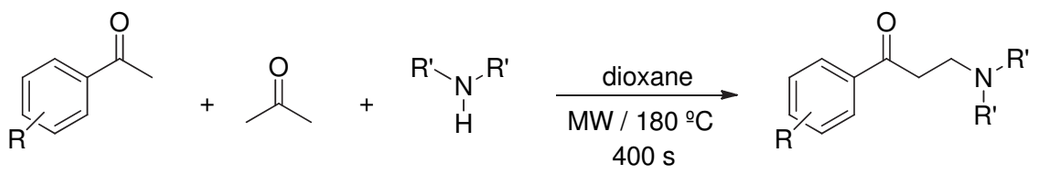
scale (Perio et al., 1998) (Scheme 1). The authors found that the 2-mol scale was easier than the 10-mmol scale owing the possibility of continuous distillation of methanol under irradiation in the Synthewave 1000 with a packed column, a set-up that is not possible in the smaller Synthewave 402.



Scheme 1. Synthesis and scale-up of dioxolanes, dithiolanes and oxathiolanes

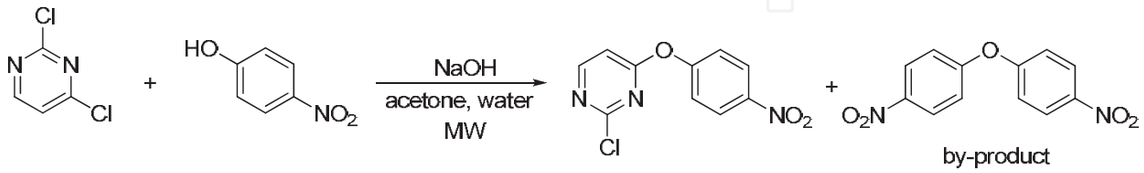
Similar results were reported by Loupy for the reproducibility and scale-up of several reactions (potassium acetate alkylation, regioselective phenacylation of 1,2,4-triazole, deethylation of 2-ethoxyanisole, and typical examples in carbohydrate chemistry) to several hundred grams in a larger batch reactor (Synthewave 1000), with yields equivalent to those obtained under similar conditions (temperature, reaction time) in laboratory-scale experiments (Synthewave 402) (Cléophax et al., 2000).

Luthman studied the appropriate reaction conditions in terms of choice of solvent, reaction temperature and reaction time to allow the fast and reproducible production of Mannich bases from small (2 mmol) to large (40 mmol) scale reactions in moderate to high yields (18–60%) and high purity (F. Lehmann et al., 2003) (Scheme 2).



Scheme 2. Microwave-assisted Mannich reactions using substituted acetophenones

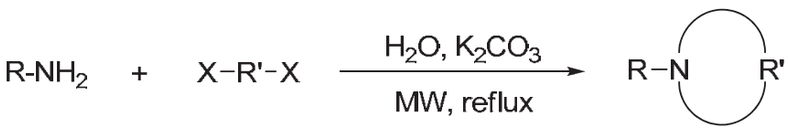
Two different microwave systems designed for large-scale operation, such as the Anton Paar 3000 multimode batch reactor (8 × 100 mL PTFE vessels in a ceramic vessel jacket, filling volume of 60–70 mL for each vessel) and the CEM Voyager SF stop-flow reactor (80 mL glass vessel, filling volume 50 mL), were evaluated by Lehmann (H. Lehmann & LaVecchia, 2005) for special use in a kilolab. As a model reaction, the aromatic substitution of aryl halides with nucleophiles like phenolates or amines was chosen (Scheme 3).



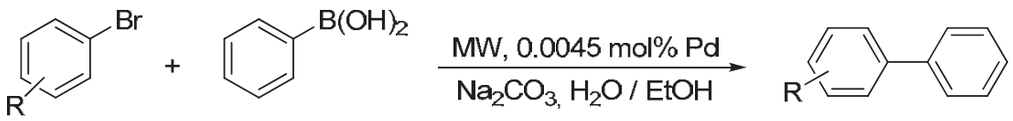
Scheme 3. Aromatic substitution of 2,4-dichloropyrimidine with *p*-nitrophenol

These reactions were previously performed in a small-scale Emrys Optimizer microwave reactor (20 mL glass vials). The study was focused on temperature/pressure limits, handling of suspensions, ability for rapid heating and cooling, robustness, and overall processing time.

A green approach to *N*-heterocyclization reactions ranging in scale from 20 mmol (CEM Discover) to 1 mol (CEM MARS) performed under microwave irradiation in open vessels was investigated by Barnard (Barnard et al., 2006) (Scheme 4). On using water as the solvent and in the absence of transition metal catalysts, *N*-heterocycles were formed in a fraction of the time needed on using classical heating. These reactions had previously been performed on a small scale by Varma in sealed vessels (Ju & Varma, 2006). Analogously, representative Suzuki couplings in water using low catalyst concentrations in conjunction with microwave heating have been transferred from sealed-vessel to open-vessel reaction conditions, and scale-up to the mole scale using the dedicated multimode apparatus CEM MARS (Arvela et al., 2005; Leadbeater et al., 2006) (Scheme 5). In both processes, single-mode and multimode cavities were used for open-vessel synthesis without changing the reaction times and these produced similar yields.



Scheme 4. *N*-Heterocyclization reactions in water



Scheme 5. Open-vessel microwave-promoted Suzuki reactions in water

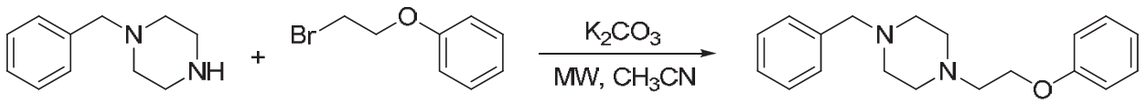
2.2 Reproducibility in parallel microwave-assisted reactions

In general, two approaches have been used for microwave-assisted parallel and combinatorial chemistry: On the one hand, series' of compounds can be prepared sequentially in an automated single-mode instrument, which allow for control of temperature and pressure in each reaction independently. On the other hand, compounds can be prepared in parallel arrays using a multimode instrument. The use of a single-mode instrument offers the advantage of full control of each reaction. However, in this case, all reactions must be processed sequentially and this could lead to a bottleneck in productivity, especially for large series' of compounds. Multimode instruments offer the possibility of performing multiple reactions in one irradiation experiment, but reactions are usually performed without appropriate control of the temperature, which in turn limits the reproducibility of the experiments – especially when unmodified domestic ovens are used. In an effort to overcome these problems, several dedicated microwave reactors have been developed since 2003.

Nüchter demonstrated that a multiPREP reactor system (36 pressure reactors or 15 reflux reactors), combiCHEM (plates with 24, 48 and 96 reactions vessels sealed with Teflon-laminated silicon mats), and an HPR system (6–10 small autoclaves for pressurized reactions at up to 50 bar and 250 °C) allow parallel reactions to be carried out with up to 96 reactor chambers in a microwave field with total reproducibility in yield and/or selectivity (Nüchter & Ondruschka, 2003a). The authors studied different processes such as nucleophilic substitutions, condensation reactions, oxidations, and multi-centre reactions.

Also in 2003, Kappe scaled different organic reactions from the 1 mmol to 100 mmol scale using a prototype multimode microwave reactor from Anton Paar that allowed parallel processing in either quartz or PTFE-TFM vessels with maximum operating limits of 300 °C and 80 bar of pressure (eight-vessel rotor employing either 100 mL PTFE-TFM or 80 mL quartz vessels) (Stadler et al., 2003). The transformations included multicomponent chemistries, transition metal-catalyzed carbon-carbon cross-coupling protocols, solid-phase organic synthesis, and Diels–Alder cycloaddition reactions using gaseous reagents in prepressurized reaction vessels.

Alcázar investigated the possibility of scaling up the synthesis of several compounds simultaneously in one irradiation experiment (Alcázar et al., 2004). This parallel approach would allow reduced reaction times in comparison with the sequential irradiation of single samples in single-mode instruments. The authors studied an *N*-alkylation reaction and used optimized reaction conditions to probe the total reproducibility of five parallel reactions performed in a multimode system (3 mmol scale) and the same reaction carried out in a single-mode reactor on one-tenth of the scale (0.3 mmol) (Scheme 6, Figure 1).



Scheme 6. *N*-Alkylation of *N*-benzylpiperazine

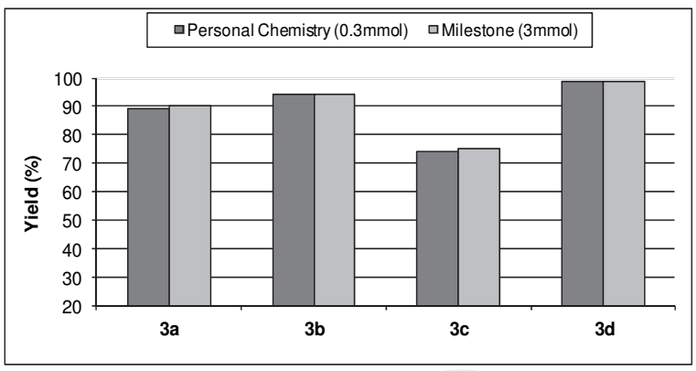
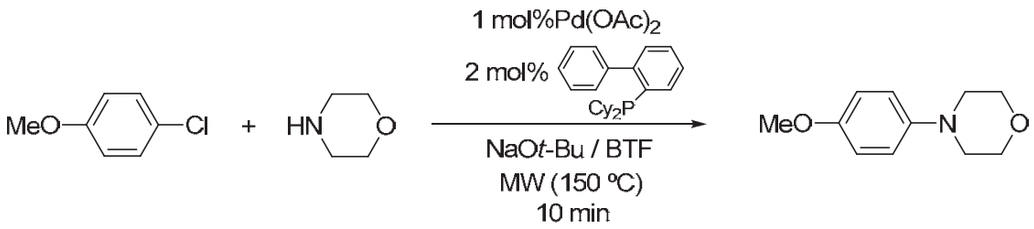


Fig. 1. Yield comparison between systems for *N*-alkylations of *N*-benzylpiperazine

On the basis of these results, a multimode combiCHEM reactor was used to assess the heating homogeneity of a multiwell plate with 24 equal reactions (Alcázar, 2005). Interestingly, reaction yields were slightly higher in the multimode instrument than in a single-mode set-up, and the author concluded that the former system offered enough reproducibility to develop further parallel chemistry. Once the performance of the multiwell plate had been evaluated, a set of 24 different compounds was prepared in parallel using the fully optimized conditions by combining four amines with six alkylating agents. In order to make an appropriate correlation across instruments, the same reactions were performed in a single-mode reactor. The results showed that good reproducibility was achieved between the two instruments: on average, the difference in yield was only 2.3%. However, to complete the whole sequence of reactions the single-mode instrument required 2.5 h, whereas the multimode instrument required only 40 min to achieve comparable results. This system combined the advantages of the parallel approach and microwave heating.

As mentioned above, for the scale-up from gram to kilogram scales two different approaches have been used historically – batch and continuous-flow. The major limitation of the continuous microwave reactor is that these systems are unsuitable for heterogeneous mixtures and viscous liquids. For these reasons, Maes performed a comparative study between a stop-flow system (CEM Voyager system based on the Discover single-mode platform equipped with an 80 mL glass vessel, a peristaltic pump and two valves) and two multi-mode platforms that allow parallel processing of several vessels per batch: Milestone MicroSYNTH equipped with a rotor with 10 vessel positions (vessel volume 100 mL) and CEM MARS equipped with a fourteen rotor positions (80 mL) (Loones et al., 2005). The reaction model used was the Buchwald–Hartwig amination (Scheme 7). They found that rapid Pd-catalyzed amination of aryl chlorides under microwave irradiation can be easily scaled-up on both single-mode and multi-mode platforms with similar yields if BTF (trifluoromethylbenzene) is used as the solvent. However, the stop-flow Voyager system was preferred since it is a completely automated unit that allows the continuous production of reaction product without the need to manually load and unload reaction vessels. Moreover, the Voyager system allows pumping of heterogeneous mixtures, which is problematic in continuous-flow units.



Scheme 7. Scale-up of the Pd-catalyzed amination of 4-chloroanisole with morpholine

2.3 Reproducibility across instruments

Reworking some of the reactions described in the literature that were originally performed in household microwave devices showed that it is absolutely necessary to analyze any result obtained in these specific devices. Due to the incomplete description of many reactions reported in microwave chemistry, reproducibility is difficult to assess in most cases. Only in rare cases are identical microwave devices available. Additionally, devices of the same series can have different field homogeneity. Only in a few cases are all reaction conditions known precisely and reproducibly. Even the use of different amounts of starting materials can produce different results, a factor that can usually be neglected for conventionally heated reactions. Moreover, the applied settings of the microwave devices are often insufficiently reported or the importance of these parameters is completely ignored (Nüchter et al., 2003b). In 1994 Login reported that commercial domestic ovens have limitations that can result in non reproducible fixation results in pathology and he developed a calibration protocol to identify the best locations for fixation within household microwave ovens (Login & Dvorak, 1994).

Microwave-assisted extraction (MAE) is a process in which microwave energy is used to heat solvents in contact with a sample in order to partition analytes from the sample matrix into the solvent. In most cases, recoveries of analytes and reproducibility are improved compared to conventional techniques. The basic principles and main studies, including reproducibility, on the use of microwave energy for extraction have been reviewed (Eskilsson & Björklund, 2000).

Mastragostino reported the microwave-assisted synthesis of $Ag_2V_4O_{11}$ starting from V_2O_5 and Ag_2CO_3 (Arbizzani et al., 2007). Although acceptable reproducibility may be attained in the exploratory phase by using low-cost domestic ovens modified to read the temperature of the reaction mixture (the irradiation was manually stopped when the temperature of the sample reached a set value), properly controlled synthesis conditions can be achieved only with scientific microwave systems with control of irradiation power and reaction temperature (such as the CEM Discover single-mode reactor).

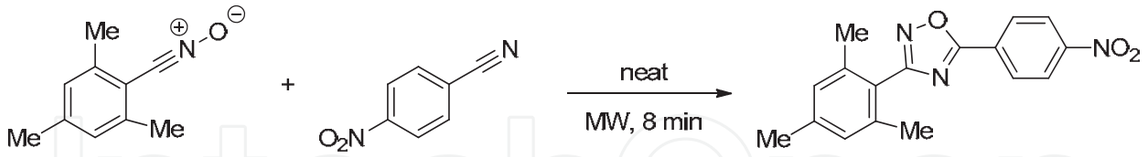
The influence of microwave energy on the rate of cleavage of –C–S– and –S–S– bonds by azide ions has been investigated using a domestic oven. It was found that microwaves do not accelerate the cleavage of the –C–S– bond whereas –S–S– bond cleavage is faster. However, the reproducibility of this reaction is very poor and the microwave technique is not recommended for quantitative determination (Kurzawa & Stachowiak, 2001).

When the microwave methodology was introduced twenty-five years ago, most reactions were performed in domestic ovens without appropriate temperature and pressure controls. As a consequence, there is a plethora of interesting organic transformations that have been reported to take place in domestic ovens. However, reactions performed in this kind of instrument, i.e. without appropriate temperature and pressure controls, are generally considered as not reproducible, thus limiting the application of such reactions.

The polarity of the solvent is the most important parameter to consider when microwave reactions are performed in solution. Polar solvents absorb the microwave radiation directly and the polarity of the substrate is relatively unimportant. In the case of non-polar solvents, however, the radiation is absorbed by the substrates, but the differences in absorption of the substrates are moderated by the solvent, especially in dilute solution. In both cases, the reaction temperature is limited by the solvent boiling point and microwave-assisted reactions in solution are easily controlled. In neat reactions, radiation is again absorbed by the substrates but there is no solvent to stabilize the temperature. In this situation, the nature of the substituents and the polarity of the substrates influence the absorption of microwave energy and, hence, the yield. Moreover, in the absence of solvent the temperature is not limited by the boiling point of the solvent. A process involving highly polar reagents, intermediates or transition states can hardly be controlled under microwave irradiation. Hence, it does not follow that a solvent-free reaction previously performed in a domestic oven will be controllable and reproducible in dedicated microwave reactors in a similar way to reactions in solution, as the field density is very different from one instrument to another (Nüchter et al., 2004).

In 2007 Díaz-Ortiz & Alcázar showed for the first time that solvent-free reactions performed in domestic ovens could be reproduced, scaled and parallelized in controlled microwave monomode and multimode reactors (Díaz-Ortiz et al., 2007). The 1,3-dipolar cycloaddition of nitrile *N*-oxides with nitriles (Scheme 8) was selected as a model reaction, and this was previously performed by the same authors using a domestic oven (Díaz-Ortiz et al., 1996). The study was structured in four steps. The first step involved the translation of the 1,3-dipolar cycloaddition reaction conditions from the domestic oven to the single-mode CEM Discover microwave reactor by increasing the temperature gradually in successive experiments to prove that a linear dependence between the yield and temperature is observed for this solvent-free reaction (Figure 2). The second step was to study the reproducibility of the reaction under non-optimized conditions because under such conditions reactions are more sensitive to temperature differences. In this case, four identical reactions were performed in parallel in the MicroSYNTH multimode reactor at 100 ^{o}C on a

scale five times larger than the one used in the monomode instrument. It can be concluded that there is good reproducibility between the two systems (Figure 2).



Scheme 8. 1,3-Dipolar cycloaddition of nitrile with nitrile *N*-oxide

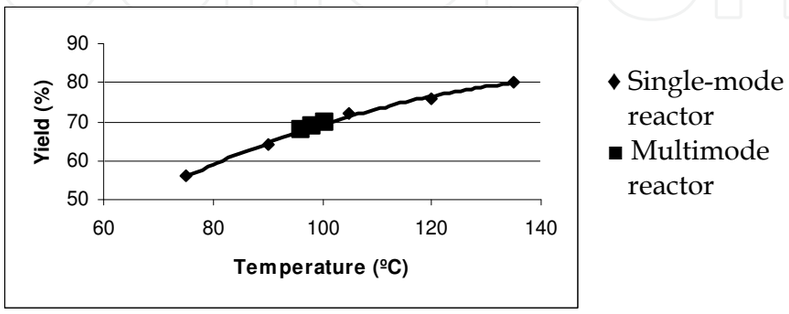


Fig. 2. Plot of yield versus temperature for 1,3-dipolar cycloaddition reactions

The third step in the study concerned the scalability of the reaction. For this purpose, eight different nitriles were reacted with a nitrile *N*-oxide using optimized reaction conditions. Reactions were performed in both single-mode and multimode microwave ovens. On average, the difference in yield between the two instruments was 2.2%. The fourth step was to study the preparation of 24 different compounds in a multiwell plate under microwave irradiation to provide an effective combination of productivity and speed. To overcome the problem of different absorption levels in each reaction, due to the different polarity induced by the substituents, the authors took advantage of a Weflon well plate (Nüchter, 2003a). Finally, the results obtained for the 8 substrates used in all experiments (single-mode, multi-mode, Weflon plate and isolated yield) were compared and good reproducibility was found for each compound under each set of conditions: the average yield difference was 3.75% (Figure 3). Similar conclusions were reported by Leadbeater in a study into the rapid optimization of reaction conditions (Leadbeater & Schmink, 2007).

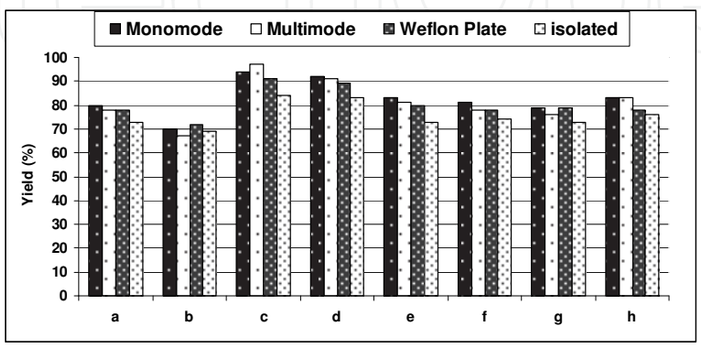
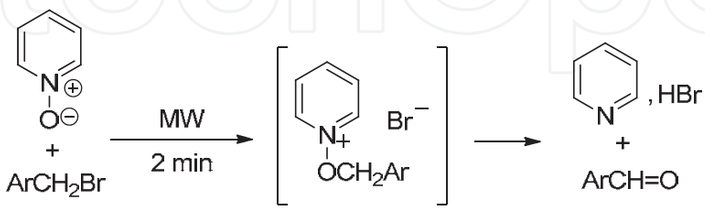


Fig. 3. Comparative results for eight nitriles in different applications and isolated yields obtained

In order to extend the preliminary results to see whether any solvent-free reaction previously performed in a domestic oven can be reproduced in dedicated apparatus, the same authors studied four new reactions that cover a wide range of chemical transformations (Díaz-Ortiz et al., 2011). It was found that *N*-alkylation of (1*H*)-benzotriazoles, condensation of anilines with urea (or thiourea) and Beckmann rearrangement of ketoximes are reproducible in both single-mode and multimode microwave instruments using temperature-controlled conditions. However, all attempts to reproduce and control the oxidation of benzylic bromides with pyridine *N*-oxide in single-mode or multimode reactors failed (Scheme 9).



Scheme 9. Oxidation of benzylic bromides

With the aim of explaining why the oxidations of benzylic bromides are not reproducible processes under microwave irradiation, a computational study on this reaction and the aforementioned 1,3-dipolar cycloaddition – which is easily reproduced - was performed (Table 1). The results show that reactions involving a moderate or medium increase in polarity in the pathway from reactants to products (Table 1, Entry 1) are relatively easy temperature-controlled processes under microwaves. In contrast, large increases in polarity during the reaction path (Table 1, Entries 2 and 3) give rise to extreme absorptions of microwave energy and make these processes more difficult to control and reproduce.

Entry	Process	Dipole Moments (Debyes)	
		Reactants	Intermediate
1	1,3-Dipolar cycloaddition solution (acetonitrile)	5.51	11.27
2	Oxidation of benzylic bromides S_N2 solution (bromobenzene)	5.05	25.02
3	Oxidation of benzylic bromides S_N1 solution (bromobenzene)	5.55	52.04

Table 1. Dipole moments (Debyes) of selected stationary points

A combined (multimode and single-mode) microwave device (MLS ETHOS 1200 Combi) was used by Ondruschka to perform a comparative study of both single-mode and multimode microwave irradiation methods (Nüchter et al., 2003b). The authors studied a lipase-catalyzed transesterification process, and Biginelli and Hantzsch reactions. The results were similar for both single-mode and multimode microwave devices in all reactions. Differences in the yields of the pure products were due to different workup procedures and small systematic errors. The authors completed their work with a useful study of the heating behaviour of polar systems in the multimode microwave field: energy input in pure substances, and mixtures of polar and non-polar substances.

3. Large-scale production under microwaves

Most examples of microwave-assisted chemistry published to date have been performed on a scale of less than 1 g, with a typical reaction volume of 1–5 mL. The main applications have been to accelerate and optimize well-known and established synthetic procedures. In microwave-assisted synthesis there is a need to develop techniques that can ultimately provide products on a multikilogram scale before this approach can become a fully accepted industrial technology. Thus, the further development of large reactors is required, at least on the pilot plant scale to enable multikilogram production of lead compounds. It was not until the mid-1990s that the issue of scale-up was first investigated (Raner et al., 1995; Cablewski et al., 1994; Roberts & Strauss, 2005). Since that time, a significant number of prototypical and commercial microwave scale-up reactors have been reported, for both batch and continuous operation, and most of these were described by chemical engineering groups.

The scale-up of microwave chemistry clearly has several benefits to offer over conventional heating. However, there are some problems that make the scale-up of microwave chemistry difficult to achieve. The big challenge for process scale-up involving microwave technology is to establish a reliable and safe process setup where issues like physical properties (i.e., penetration depth), temperature control, and reactor design have to be carefully considered. On using batch reactors, the user is confronted with problems in heating large volumes due to the limited penetration depth of microwave irradiation (Nüchter et al., 2004).

The scale-up of microwave-mediated transformations can be defined in different ranges, leading to the use of different concepts and varying instrumentation. Depending on the user, the term "scale-up" will have different meanings. In the case of method development, scale-up starts with processing a 50 mL reaction mixture, corresponding to a 10- to 100-fold scale-up of reactions performed in standard single-mode microwave vials with a processing volume of 0.5–5.0 mL. A possibility for further scale-up would be the use of the "numbering up" approach, i.e. running the same reaction several times in sequence. This approach is aided by existing robotic equipment, which allows unattended vessel transfer in and out of the microwave cavity. Alternatively, such reactions can also be performed by parallel synthesis in corresponding multivessel rotor systems on switching to multimode instruments. From an industrial viewpoint, scale-up means process development and the highest possible throughput, a situation that virtually excludes the use of batch reactors. In fact, it is the productivity and not the size of the vessel that is important, which clearly indicates that flow systems, regardless of whether applied in stop-flow (SF) or continuous flow (CF) mode, have distinct benefits over batch process reactors.

The approaches can be categorized as: scale-up in parallel, scale-up in sequence, and scale-up by continuous flow (Figure 4). Hybrid approaches have also been devised.

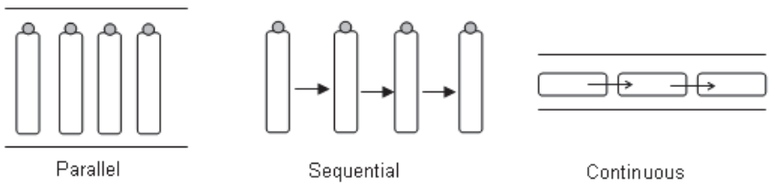


Fig. 4. Strategies for microwave scale-up

3.1 Scale-up in batch

The advantages of microwave heating in chemistry results in the need for scale-up possibilities. Moreover, the direct homogenous heating of reaction mixtures under microwave irradiation is believed to facilitate direct scaling without heat and mass transport issues (Kappe & Stadler, 2005). In fact, direct scaling of microwave-assisted synthesis in batch mode, without the need for process optimization, has already been demonstrated in organic synthesis on using open or closed reaction vessels (Leadbeater, 2010).

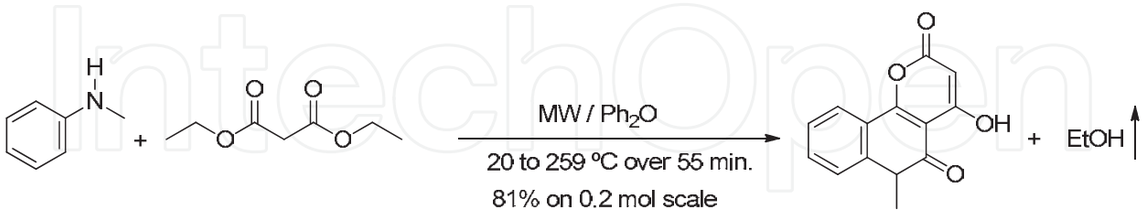
3.1.1 Scale-up in a single large open vessel

When considering batch scale-up, one approach is to use a single, larger, reaction vessel. This avoids the problem of tedious charging and discharging of multiple reaction vessels. However, penetration depth and/or power density could become issues as the vessel size increases.

If the reaction can be carried out in the absence of solvents, or superheated solvents are not required, or if the process can be performed successfully below the boiling point of the solvent, the large reaction can be run in an open-vessel model. At present there are several commercially available microwave ovens to carry out this scale-up mode, including CEM MARS, MILESTONE Micro-SYNTH and MINILABOTRON SAIREN.

This methodology has some disadvantages. For example, the penetration depth or power density may be an issue and of course reactions that need elevated temperatures and pressures cannot be carried out. However, considerable scale-up can be – and has been – achieved in such reactors.

Open-vessel conditions prove advantageous for driving equilibrium reactions to completion when the product or by-product is a more volatile component than the starting materials. A Milestone MicroSYNTH reactor has been used to perform a fractional distillation in the synthesis of a tricyclic heterocycle (Razzaq & Kappe, 2007). *N*-Methylaniline was reacted with two moles of diethyl malonate in a cyclocondensation reaction with elimination of four moles of ethanol to give the product pyranoquinoline on a 0.2 molar scale. On this scale, the distillation took only 82 min as compared to 3-5 h conventionally. When the reaction was performed in a sealed-vessel microwave system only <5% product formation was achieved (Scheme 10).

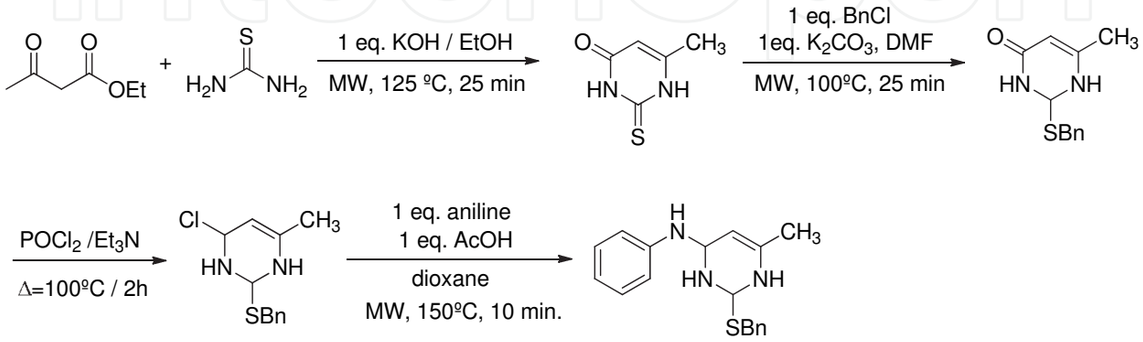


Scheme 10. Reaction between *N*-methylaniline and diethyl malonate

The Hantzsch 1,4-dihydropyridine synthesis (Bowman et al., 2008a) was also scaled up successfully to the 0.5–1 mol level in the MARS unit and this involved heating up to 1 L of reaction mixture. One batch provided 250 g of dihydropyridine product in less than 1 h.

Leadbeater et al. evaluated a new batch reactor, designed by AccelBeam Synthesis, that allows reactions to be performed on scales from 2–12 L (Schmink et al., 2010). A number of reactions have been investigated, including palladium-mediated transformations, condensation reactions, nucleophilic aromatic substitution reactions, and alkylations. One

important aspect of this work was that a linear scaling approach was taken and changes were not made to the protocol on moving from the small, developmental scale to larger scales. In some cases reactions were scaled over 18,000-fold on moving from small (0.1–1 mmol) to large (1–18 mol) runs. It is noteworthy that in order to simulate a situation where multiple sequential microwave steps were employed to reach a desired target compound, these authors developed a sequence of reactions as a medicinal chemist might do at the 10 mmol scale in order to synthesize a drug-like molecule (Scheme 11). Overall, the sequence employed three microwave steps and afforded 473 g of the target molecule in 38% yield, almost identical to the 39% obtained in the small scale process.



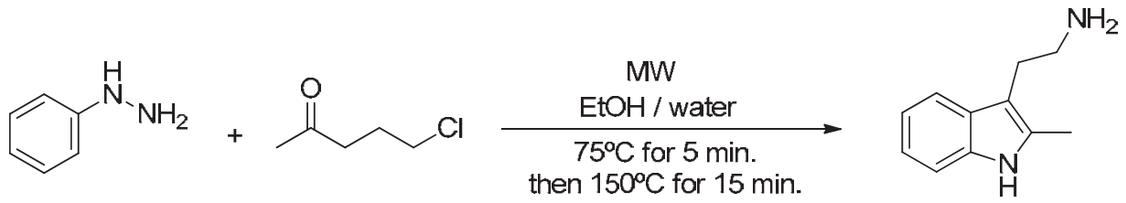
Scheme 11. Preparation of 2-(benzylthio)-6-methyl-4-(phenylamino)pyrimidine

Horikoshi et al. employed a batch reactor to synthesize silver nanoparticles in aqueous media by reduction of a diaminosilver(I) complex with carboxymethylcellulose (Horikoshi et al., 2010). The microwave process yielded smaller silver particles with a narrower distribution than the conventional heating process.

3.1.2 Scale-up in a single large sealed vessel

Another approach to perform the scale-up involves the use of a single large sealed vessel. In this case, it is possible to carry out reactions in heterogeneous conditions, in the presence of solvents, and at pressure. Despite this versatility, the limiting factor is the vapour pressure generated by a superheated solvent due to safety concerns. While moderately high pressures (~20 bar) are easily contained in small scale microwave reactors, the use of large vessel sizes requires more safety features and greater engineering expertise in the system design. This results in more complex reactors that are less easy to use and more expensive. In this sense, to contain the pressures likely to be generated, strong materials must be used to construct the reaction vessels, but they must also be microwave transparent. This rules out the use of metals on this scale and leaves thick-walled (quartz) glass, ceramics, and polytetrafluoroethene (PTFE or Teflon), or combinations thereof. However, these materials are all thermal insulators. In either case, cooling is further compromised by the necessarily thick-walled vessels such that, for larger microwave reactors, the cooling time is often notably longer than the combined heat-up and reaction periods. This situation increases the cycle time per batch and reduces the overall output, thus lessening the benefit of rapid microwave heating. Some of these problems have been solved in certain systems. For example, flash evaporation using the mechanical pressure of superheated solvent in the vessel can discharge the reaction mixture while it is still hot into a collection vessel, thus allowing the cooling to occur off-line from the reactor.

Commercially available microwave reactors in which sealed-vessel scale-up can be performed are the BIOTAGE ADVANCER 350, Batch SYNTH, Ultraclave, MILESTONE ETHOS 1600, Anton Paar monowave 300, and Anton Paar Masterwave BTR.
Scale-up in a single sealed vessel represents perhaps the least utilized scale-up option. This may be because the reactors are large and expensive and that more expertise is required for their use.
One particular example of pharmaceutical interest was the Grandberg synthesis of 2-methyltryptamine (Scheme 12) (Bowman et al., 2008b). A conventional approach to this reaction had already been scaled up to 20 kg at Novartis (Slade et al., 2007). However, the Advancer reactor was used to give results on a 0.2 mol scale that are comparable to those achieved by the Novartis group.



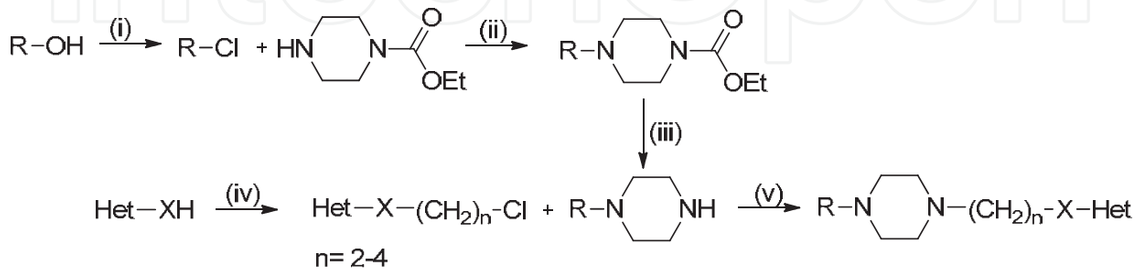
Scheme 12. Grandberg synthesis of 2-methyltryptamine

Schubert reported ring-opening polymerizations in batch mode of 2-ethyl-2-oxazoline on scales up to 100 g without the need for process optimization (Paulus et al., 2006). Nevertheless, it should be noted that this pressurized process cannot be scaled indefinitely in batch mode for safety reasons.
Deetlefs reported the use of a CEM MARS system for the synthesis of a wide range of ionic liquids based on nitrogen-containing heterocycles (Deetlefs & Seddon, 2003). The process can be performed on a range of reaction scales (50 mmol to 2 mol) in either sealed or open vessels.

3.2 Scale-up in parallel synthesis

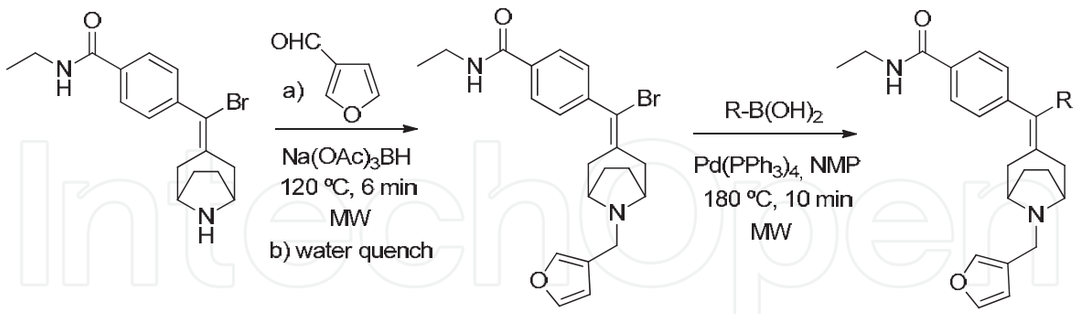
Laboratory-scale batch microwave reactors generally offer a maximum batch size of 1 L reaction volume and in most cases this is divided into several smaller reaction vessels (multivessel rotor systems). This approach does not exactly match the "one vessel" philosophy, but the parallel setup allows for the processing of several batches of either the same reaction mixture or of closely related mixtures. In fact, this combination of batch synthesis and parallel processing can furnish either compound libraries on the gram scale or a larger amount of one single compound in a short time. Although the Milestone UltraCLAVE system provides a 3.5 L single vessel cavity, it has proven to be more effective to heat smaller volumes in parallel rather than one big batch, given that identical microwave output power is applied (Loones et al., 2005; Cléophax et al., 2000).
The demands made on industry, especially the pharmaceutical industry, are changing at an unprecedented pace, making speed critical in modern chemistry. For this reason, high-speed microwave synthesis and combinatorial chemistry have attracted a considerable amount of attention in recent years. These approaches offer significant advantages to the synthetic chemist: reduced reaction times and improved yields as a result of microwave heating and increased productivity due to the implementation of combinatorial chemistry. However, the evolution of microwave instrumentation is delivering new systems that allow reactions to be

carried out in specialized multiwell plates under temperature and pressure controlled conditions (Nüchter & Ondruschka, 2003; Alcázar, 2005; Kremsner et al., 2007).
Caliendo et al. disclosed the synthesis of series of piperazine derivatives as 5-HT1A agonists using microwave irradiation in all the reactions (Caliendo et al., 2001; Caliendo et al., 2002) (Scheme 13). They compared the results obtained with microwave heating with those obtained using traditional heating. In all cases, compounds were obtained in higher overall yields and reaction times were reduced from hours to minutes on using microwave irradiation. Reactions were performed in a multimode instrument using parallel racks that allow the preparation of sets of compounds in a single irradiation experiment.



Scheme 13. Synthesis of *N*-substituted piperazine derivatives. (i) $SOCl_2$, toluene, 55 °C, 20 min, MW; (ii) K_2CO_3, NaI, DMF, reflux, 1 h, MW; (iii) KOH, water, methanol, reflux, 1 h, MW; (iv) $Br(CH_2)_nCl$, K_2CO_3, DMF, MW; (v) K_2CO_3, DMF, 70 min, MW

Researchers at Johnson & Johnson Pharmaceuticals have described tropanylidene derivatives as combined mu/delta opioid receptor agonists (Costas et al., 2004). The preparation of these analogues was achieved by developing a parallel solution phase strategy under microwave irradiation, which allows multiple sequential reactions to occur in a single reaction vessel (Scheme 14).



Scheme 14. Preparation of tropanylidene derivatives

This approach allowed the synthesis of 192 compounds in a quicker and more efficient manner than using the corresponding solid phase approach. Additionally, the parallel solution phase approach allowed rapid scale-up of selected compounds for further *in vivo* studies.
Caliendo et al. described an efficient, facile, and practical parallel combinatorial synthesis of substituted-benzoxazines under microwave irradiation (Caliendo et al., 2004). The procedure involved the use of a specially designed microwave oven for organic synthesis that was suitable for the parallel synthesis of solution libraries. As a demonstration, a library

of 19 substituted *N*,*N*-dimethyl- and *N*-methyl-benzoxazineamide derivatives, structurally related to the potassium channel opener cromakalim, was generated by both conventional and microwave procedures, with a reduction in the library generation time for the microwave approach from 7 h to 30–36 min (Figure 5).

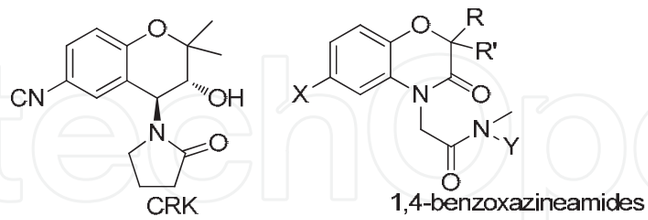
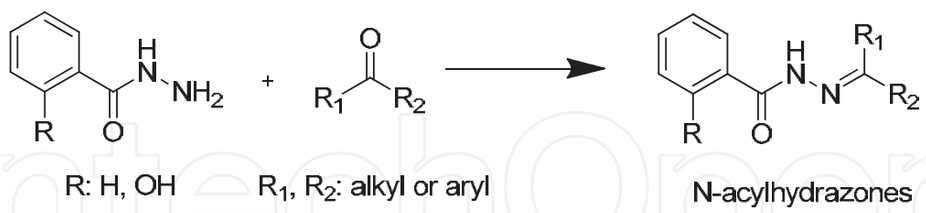


Fig. 5. Structure of cromakalin (CRK) and 1,4-benzoxazineamides

To facilitate the preparation of β-peptide libraries in parallel, Murray and Gellman adapted the reaction conditions for the solid-phase synthesis of 14-helical β-peptides for use in a multimode microwave reactor (Murray & Gellam, 2006). The low temperature and pressure requirements of microwave-assisted β-peptide synthesis were found to be compatible with multiwall filter plates composed of polypropylene. Microwave heating of the 96-well plate was sufficiently homogeneous to allow the rapid preparation of a β-peptide library in acceptable purity.

An environmentally friendly method based on microwave radiation has been developed for the synthesis of a library of *N*-acylhydrazones (Andrade & Barros, 2010). With this protocol, the use of solvents and catalysts can be avoided, and the products are obtained in short reaction times and in very good yields. A variety of *N*-acylhydrazones were synthesized under microwave irradiation within 2.5–10 min, starting from benzo, salicyloyl, and isonicotinic hydrazides. The results are reproducible on a 500 mg to 5 g scale and this approach could be applied to a large number of ketones and aldehydes. The reported method could be a useful synthetic path to obtain *N*-acylhydrazones on an industrial scale (Scheme 15).



Scheme 15. *N*-acylhydrazones synthesized under microwave irradiation

The combination of parallel synthesis and microwave chemistry has clearly improved the efficiency in the preparation of derivatives. The synthesis of compound libraries in single-mode instruments fully integrated into automatic platforms in a sequential way is well established. Additionally, integration of reaction performance in multiwell plates under microwave irradiation with automatic platforms for sample preparation and work up is expected to further optimize library synthesis.

3.3 Scale-up in continuous flow systems

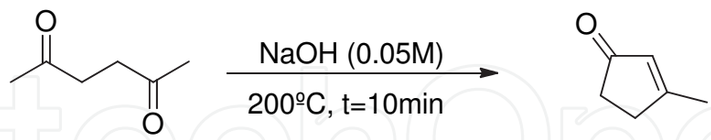
Although dedicated modern microwave instruments for MAOS are very successful in small-scale operations, microwave scale-up in batch mode beyond a reaction volume of approx. 1

L is not feasible (Glasnov & Kappe, 2007). The penetration depth of only a few centimetres and the limited dimensions of the standing wave cavity are the main reasons for the development of continuous or stop-flow microwave reactors. In these systems the reaction mixture is passed through a relatively small microwave-heated flow cell, which avoids the aforementioned drawbacks.

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 extolled the virtues of continuous microwave reactors as early as the 1990s (Chen et al., 1990; Cablewski et al., 1994). However, such pioneering developments received little recognition or further development due to a combination of inferior technology, poor quality manufacture and the fact that the adoption of continuous flow protocols was in direct contradiction to the emerging, at that time, Combinatorial Chemistry (small scale multiparallel batch processes).

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 easy reaction optimization, introduction of automated safety controls and ensures a reliable and prolonged processing capability. Additionally, the combination of such processing techniques with the enabling technology of immobilized reagents, scavengers and catalysts to effect multi-step synthetic transformations has allowed the generation of novel pharmaceutical architectures and more complex natural products.

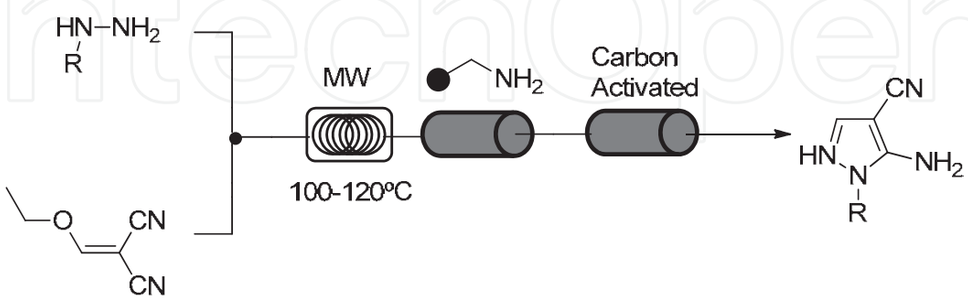
One of the first successful examples of scale-up was developed by Strauss (Cablewski et al., 1994). These authors prepared hundred gram quantities of a cyclopentenone intermediate using the continuous microwave reactor that they developed themselves (Scheme 16). The standard purification protocol for the product (distillation to remove small residual quantities of the starting material) was ineffective for large scale syntheses and, as a result, a scavenging procedure using a bisulfate-functionalized ion exchange resin to remove the reaction base (NaOH) was employed. 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 16. Preparation of 3-methylcyclopent-2-enone using a flow microwave reactor

Recently published examples of continuous flow organic microwave synthesis involve, for example, the synthesis of 5-amino-4-cyanopyrazoles (Smith et al., 2007). The design consists of fluorinated polymer tubing wound around a Teflon core that is fitted with a dummy pressure cap. This flow device has the basic shape of a 20 mL vial suitable for the Biotage EXP single-mode instrument. The input tube is connected to an HPLC pump and a 7 bar back-pressure regulator is placed at the exit. Both connections are physically located at the bottom of the microwave unit. In addition, with this system, purification can be facilitated by passing the exiting flow stream through columns packed with polymer-supported reagents or scavengers. The synthesis of various 5-amino-4-cyanopyrazoles by reaction of a set of hydrazines with ethoxymethylene malononitrile in methanol was performed at temperatures between 100–120 ºC with a residence time of 0.8–4 min (Scheme 17).

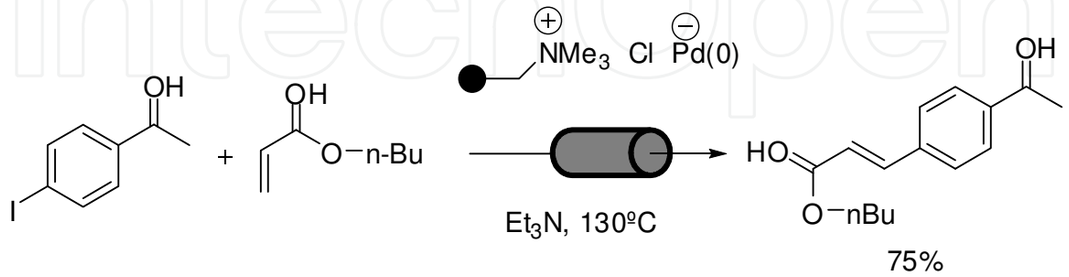
Subsequent passage of the reaction mixture through a column with supported benzylamine to scavenge any unreacted malononitrile, followed by a column packed with activated carbon to remove coloured impurities, furnished the desired product in high purities, good to excellent yields and in quantities up to 250 g. A benefit of this flow device is its versatility, since different tubing lengths can be wrapped in the system to provide reactors with different internal volumes. The application of multiple bundle tubings allows different reactions to be performed in parallel in one single reactor.



Scheme 17. Flow microwave synthesis of 5-amino-4-cyanopyrazoles

Microwave heating seems to be particularly competitive with transition metal-catalyzed processes, not only bringing long reaction times down to minutes but also minimizing the levels of undesired side products and preventing collapse of the catalytic system (Nikbin et al., 2007).

The combination of reactor design with immobilization techniques is very important for the flow process as it facilitates maximal interaction between reagents and catalysts without causing clogging problems. Moreover, the immobilized catalysts could be used over several cycles without a significant drop in activity. Kappe described a Heck cross-coupling reaction using a continuous-flow reactor based on a megaporous glass carrier material with suitable polymer functionalization introduced into the pore volume of this support (Kunz et al., 2005). For this purpose, a basic ion-exchange resin-loaded monolith was used in order to create the close neighbourhood of ionic sites and Pd(0) sites (Scheme 18). Pure products were collected without the need for extensive purification steps. The combination of composite-based flow-through reactors with microwave irradiation may lead to new and effective methods to scale up organic reactions.



Scheme 18. Heck transformation applying a continuous-flow reactor

Recently, Organ has prepared highly porous Pd films composed of nanometer-sized particles (Comer & Organ, 2005). These Pd films served as an excellent catalyst for Heck reactions under continuous flow microwave conditions. The authors showed that 10 mg of product can be

obtained from this reactor system within 1 min. Gram quantities of the products were obtained by flowing reaction mixtures through a single capillary for about 90 min.
Another interesting study was described by Wilson (Wilson et al., 2004), who developed a continuous microwave reactor that eliminates the potential reaction parameter re-optimization (time and temperature) typically required when methods are transferred from small-volume, single-mode systems to larger (but limited)-volume multimode systems (Figure 6). The representative chemistries explored include S_NAr, esterification, and the Suzuki cross-coupling reaction, all of which were successfully and safely scaled up to multigram quantities using a home-made continuous flow microwave cell (Scheme 19).

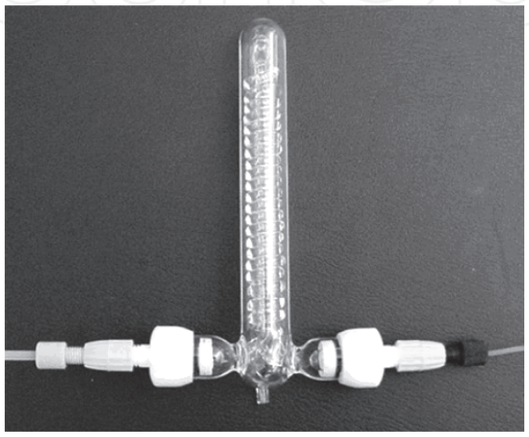
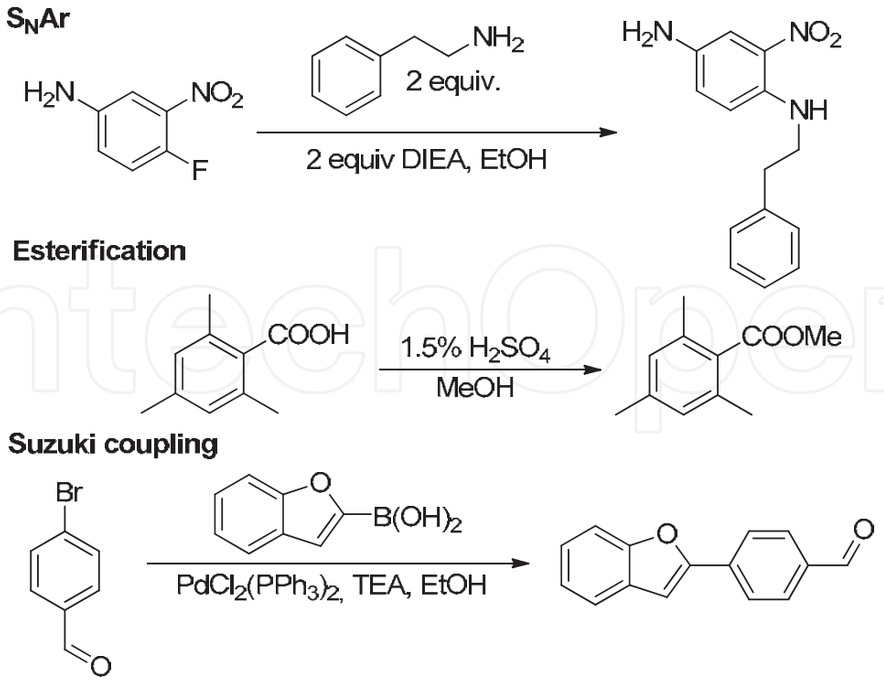
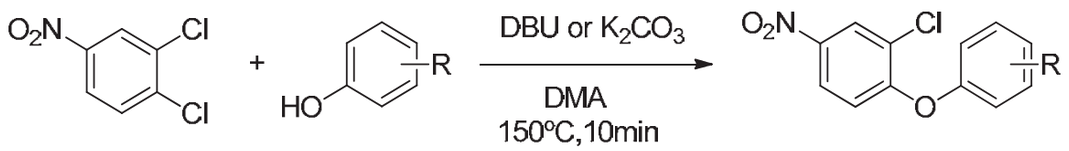


Fig. 6. Glass coiled flow cell

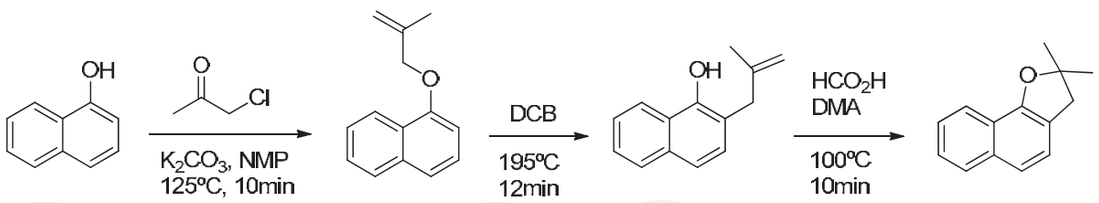


Scheme 19. S_NAr, esterification, and a Suzuki cross-coupling reaction in a microwave-flow reactor

When reactions need to be performed on several hundred gram or kilogram scales, typical for pilot or manufacturing plants, microwave synthesis is not easily scalable (Singh et al., 2008). As a result, the development of stop-flow or continuous flow microwave reactors, capable of working with slurries, are key for the successful translation of the reaction conditions. In this way Moseley (Marafield & Moseley, 2010) used S_NAr reactions to evaluate the stop-flow approach, where reagents were loaded into the microwave vial, the reaction proceeded and finally the vial was emptied in an automatic process without manual intervention. This approach gave production rates of >0.5 Kg per day, which would meet the manufacturing requirements of early clinical pharmaceutical development.
The same transformation shown in Scheme 20 was used in a recent article to validate the Milestone FlowSYNTH, a commercially available continuous flow microwave reactor designed for working at manufacturing scale (Bergamelli et al., 2010). This instrument gave productivities up to 0.65 mol/h (~170 g/h). Even higher productivities were achieved for the ortho Claisen rearrangement, in which nearly 30 kg of material per day could be produced in one unit. The rearrangement was included in a three-step microwave synthesis of naphthofuran, which was successfully scaled up, although the first reaction, naphthol *O*-alkylation, was performed in a 2L batch reactor as pumps became blocked by the heavy slurry (Scheme 21).



Scheme 20. S_NAr evaluated in a stop-flow reactor

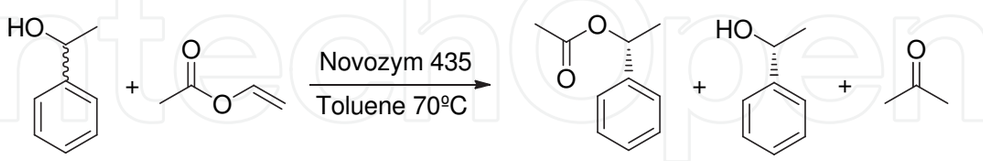


Scheme 21. Synthesis of naphthofuran

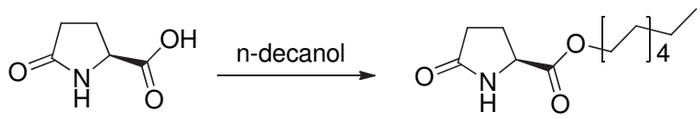
In order to improve the performance of the system, Dressen modified five key points to reduce the potential blockage by solids (Dressen et al., 2010). The modified system was assessed in the enantiomerically selective esterification of (*R*,*S*)-1-phenylethanol with vinyl acetate using Novozym 435 and the esterification of (*S*)-pyroglutamic acid with *n*-decanol (Scheme 22). Despite these improvements, plugging problems still occurred as a result of solid reactant /product deposition. Despite these issues the authors concluded that scaling up heterogeneous reactions by microwave irradiation is still feasible as the results obtained are comparable to those from the batch procedure.
To sum up this section, the scale up of processes using microwave irradiation in continuous flow systems has proved to be a valuable tool when homogeneous reactions are involved. In the case of heterogeneous reactions, solid reagents in cartridges have proven efficacy on the multigram scale. In the case of kilogram scale heterogeneous reactions, improvements in the handling of heavy slurries have been achieved, even though further development of this

technology is still needed to overcome clogging and plugging problems. Other factors that must be taken into account, as introduced by different authors (Bergamelli et al., 2010; Dressen et al., 2010), concern the concept of energy efficiency. Energy cost is a key factor when deciding between different technologies.

Enantiomerically selective esterification of (R,S)-1-phenylethanol.



Esterification of (S)-pyroglutamic acid with n-decanol.



Scheme 22. Esterification reactions of (*R*,*S*)-1-phenylethanol and (*S*)-pyroglutamic acid

4. Conclusions

The application Microwave Assisted Organic Synthesis on the laboratory scale has been very successful – especially since the introduction of dedicated microwave instruments. However, the expansion of this technique as the first choice to perform a chemical synthesis has been hindered by the following limitations:

- The use of various instruments from different companies and with different characteristics (power density, volume, waveguides etc.).
- The indistinct use of monomode and multimode instruments with and without control of the incident power, respectively.
- The general use, until 2000, of domestic kitchen-type microwave instruments, the results of which are considered to be non-reproducible.
- The low penetration depth of microwave irradiation, which hinders the scale up of reactions assisted by microwaves.

In this first part of the review we have described the efforts made to solve the problems of reproducibility. Reproducibility between microwave instruments can be achieved through accurate control of the reaction conditions, especially when the temperature of the reaction is the parameter to be controlled. This reproducibility can be extended from kitchen-type microwave instruments to monomode and multimode reactors and even when the reaction is scaled-up. Reproducibility can be attained regardless of the polarity of the solvent and also in solvent-free conditions, where the polarities of the substrates have a dramatic influence on the absorption of microwave irradiation. The only exceptions are the reactions in which the polarity increases dramatically along the reaction coordinate.

In the second part of the review, the strategies for scaling-up microwave reactions have been covered. One approach involves the use of large microwave cavities (volumes up to 12 L) in batch and, in some cases, with specially designed multimode microwave instruments.

A second approach concerns parallel reactions in multimode systems and probably the most promising is the use of continuous flow systems that combine the advantages of microwave irradiation, volumetric heating with a high heating rate, and flow reactors, especially the efficient heat transfer and the possible application of the same reaction conditions from laboratory scale to pilot plant.

5. Acknowledgments

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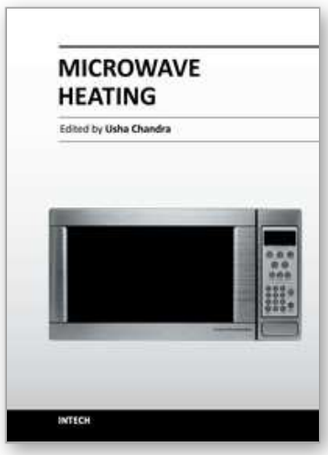

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