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Use of a scientific microwave apparatus for rapid optimization of reaction conditions in a monomode function and then substrate screening in a multimode function

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Abstract—Recently, a new apparatus has become available, which aims to bring together in one unit the advantages of a monomode and a multimode microwave device. We have assessed the applicability of the apparatus toward rapid optimization of reaction conditions in a monomode function and then substrate screening in a multimode function. We have also probed the effects of differences in microwave absorptivity of reaction mixtures on the product conversions in screening multiple substrates simultaneously in a multimode microwave apparatus. We find that when the microwave absorptivity of a reaction mixture is dictated by the solvent, there is little effect on the heating profile of varying the substrate in a screening run. However, this is not the case when reactions involving non-microwave absorbant solvents are used. In this case the characteristics of the substrate can affect significantly the outcome of the reaction.

1. Introduction

By using microwave heating it is often possible to enhance the rate of reactions and improve product yields.[1,2] Much of the early microwave-promoted synthesis was performed using domestic (household) microwave apparatus. As well as being inherently unsafe due to the fact that a domestic microwave apparatus is not designed for synthetic chemistry, it can be hard to measure temperature accurately and there can be issues with reproducibility. With the advent of scientific microwave apparatus many of these problems have been overcome. There are two main classes of scientific microwave apparatus used by synthetic chemists. Monomode microwave units have been used with great success for small-scale reactions using sealed glass tubes up to a working volume of approximately 20 mL or open round-bottom flasks to a volume of up to 125 mL. Multimode apparatus has been used for scaling up reactions as well as performing chemistry in multiple vessels. The biggest difference between the two types of apparatus is the size of the microwave cavity. In monomode units, the cavity is small since it is designed for the length of only one wave (mode). By placing the sample in the middle of the cavity it can be irradiated constantly with microwave energy. Using a monomode apparatus, it is possible to heat samples of as little as 0.2 mL very effectively. Multimode cavities are larger and as the microwaves come into the cavity they will move around and bounce off the walls. They generate pockets of high energy and low energy as the moving waves either reinforce or cancel out each other. This means that the microwave field in the microwave cavity is not uniform. The microwave field can be homogenized either by ensuring that the dimensions of the cavity avoid whole-number multiples of the microwave full or half wavelength. Also, some means must be employed to physically disrupt any standing waves that may form as a consequence of items placed in the cavity. This is best performed with a mechanical mode stirrer, typically a periodically moving metal vane that continuously changes the instantaneous field pattern inside the cavity.

While it is possible to translate chemistry developed in monomode apparatus to a multimode microwave with the objective of either scaling up a synthesis or else performing multiple reactions in a carousel,[2c,3] the chemist must be in possession of two separate units. Recently, a new apparatus has become available, which claims to bring together in one unit the advantages of a monomode and a multimode microwave device. In this report we present three different chemistries performed in this new unit. We discuss the feasibility for rapid optimization of conditions in a single reaction vessel before either running multiple reactions or else performing the chemistry on a larger scale in the same unit. As well as showing the applicability of the apparatus we also discuss in general terms some important considerations that need to be taken into account when preparing small libraries of compounds in a multimode microwave cavity.

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2. Results and discussion

2.1. Description of the apparatus

The MultiSynth apparatus is a single-magnetron system with a variable output power of up to 800 W, controlled via a microprocessor (Fig. 1). The microwave cavity measures 26.5×24.5×20.0 cm. Direct temperature monitoring and control is possible via a fiber-optic probe inserted into one reaction vessel. Contact-less temperature monitoring and control is possible for all vessels using an infrared sensor located in the cavity wall. Reaction vessels are mechanically shaken during the course of the reaction to ensure agitation of reaction mixtures. A range of reaction vessels can be used with the apparatus. For small-scale reactions (0.25–5 mL), the reagents are placed into a glass tube, this in turn being placed into a protective Teflon sleeve and sealed with a screw-top fitted with a ceramic thermowell. The Teflon sleeve is spring loaded at the bottom such that when the top is screwed down, the spring is compressed, holding the vessel in tight contact with the top. In the monomode function, the vessel in its protective sleeve is placed in a holder (Fig. 2). The internal temperature can be measured by placing a fiber-optic probe into the thermowell. While there is no direct pressure measurement, the spring mechanism in the Teflon vessel covers ensures a pre-calibrated pressure point of 20 bar is not exceeded. In the case of overpressure the system automatically releases the pressure and the vials are resealed. Reaction parameters (temperature, microwave power, and desired time) are programmed into a controller unit and the progress of the experiment can be monitored as it runs. If necessary, parameters can be modified during the course of the reaction. When processing samples in parallel, the software utilizes the fiber-optic sensor in the control vessel and the continuous stream of data from the contact-less infrared temperature sensor to display individual temperature profiles for the complete collection of vessels. This provides detailed information on reaction conditions for each processed sample. To move from single to parallel processing in the multimode function, up to 12 vessels in their protective sleeves can be placed into a 12-place holder (Fig. 3). One of the vessels acts as the control and onto this is secured the screw-top fitted with a ceramic thermowell for internal temperature measurement. For larger scale parallel reactions, up to six PEEK vessels of working volume 10–35 mL can be used, again it being possible to measure the internal temperature of only one vessel. At the end of a reaction, vessels can be cooled by passing compressed air over them in the cavity.

Figure 1. The MultiSynth apparatus used in this study.

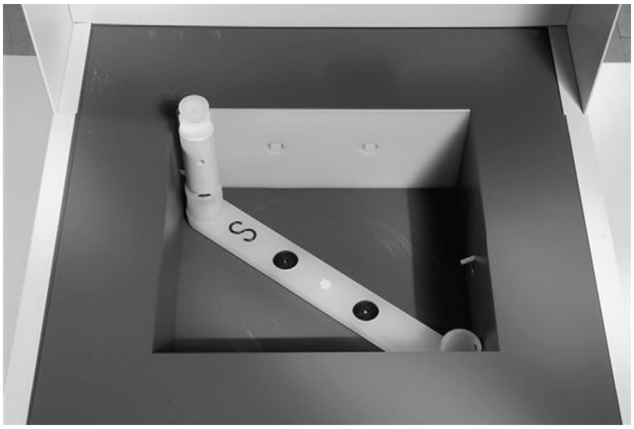
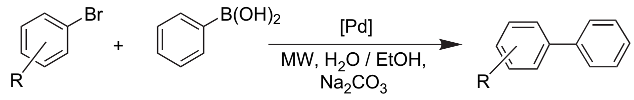


Figure 2. The MultiSynth apparatus in the monomode function.

Figure 3. The MultiSynth apparatus in the multimode function.

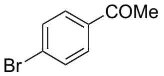
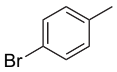
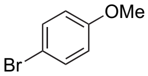
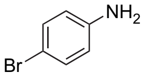
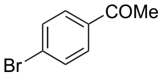
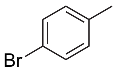
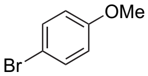
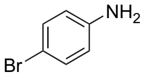
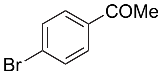
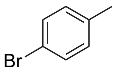
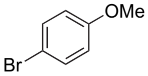
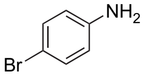
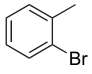
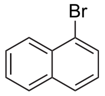
2.2. Suzuki coupling reactions

The Suzuki reaction (palladium-catalyzed cross coupling of aryl halides with boronic acids) is used extensively for the selective construction of carbon–carbon bonds, in particular for the formation of biaryls.[4] As the biaryl motif is found in a range of pharmaceuticals, herbicides, and natural products, as well as in conducting polymers and liquid crystalline materials, development of improved conditions for the Suzuki reaction has received much recent attention. In our group we have focused considerable effort on development of protocols for performing the reaction in water as a solvent in conjunction with microwave heating.[5–8] Since we are very familiar with the Suzuki coupling on a variety of scales we decided to use it as a baseline for our assessment of the MultiSynth unit. Results are shown in Table 1.



Our previous experience using monomode apparatus had shown that the reaction can be performed using low loadings of ligandless palladium sources. Working in a 1: 1 water/ethanol mix as solvent, heating the reaction mixture to 150 °C, and holding at this temperature for 5 min proved sufficient for the coupling of a range of aryl bromide substrates. Using the MultiSynth in the monomode format we first performed the Suzuki coupling of 4-bromoacetophenone with phenylboronic acid. Working on a 1 mmol scale and using 0.1 mol % Pd as catalyst, we heated the reaction mixture to 150 °C over the period of 2 min and held it at this temperature for 5 min. A 99% conversion to the desired product was obtained (Table 1, entry 1). We screened three other aryl bromide substrates using the same reaction conditions and again obtained good conversions to the desired biaryl products (Table 1, entries 2–4). The heating profile for the coupling of 4-bromoacetophenone and phenylboronic acid is shown in Figure 4. It can be seen that the IR and internal (fiber optic) temperature profiles closely track each other during the course of the reaction.

Table 1. Microwave-promoted Suzuki coupling reactions between aryl bromides and phenylboronic acid[a]

Entry	Aryl halide	Conditions	Product yield/%
1		A	99
2		A	99
3		A	98
4		A	96
5		B	99
6		B	98
7		B	98
8		B	97
9		C	99
10		C	98
11		C	97
12		C	97
13		C	85
14		C	97

Conditions A: 1 mmol scale, 0.1 mol % $Pd(OAc)_2$, monomode function, 2 min ramp to 150 °C, and 5 min hold at this temperature.
Conditions B: 3×1 mmol, 0.1 mol % $Pd(OAc)_2$, multimode function in 12-position rotor, 3 min ramp to 150 °C, and 5 min hold at this temperature.
Conditions C: 10 mmol, 0.05 mol % $Pd(OAc)_2$, multimode function in 6-position rotor, 5 min ramp to 150 °C, and 5 min hold at this temperature.
[a] Reactions were run in a sealed tube using a 1:1 stoichiometric ratio of aryl halide to phenylboronic acid and a 1:1 volume ratio of water/ethanol as solvent.

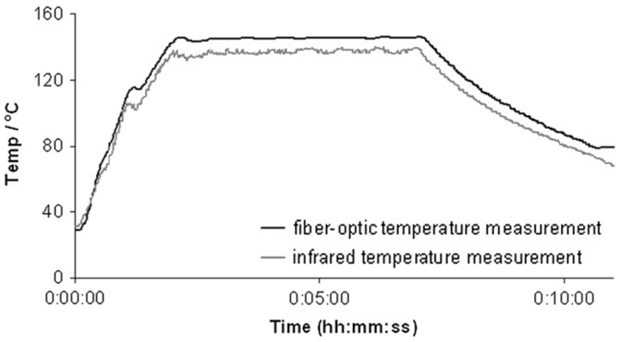


Figure 4. Heating profile for the coupling of 4-bromoacetophenone and phenylboronic acid.

We next moved to the multimode function and, using the 12-position rotor, ran all four of our aryl bromide substrates in triplicate (i.e., three tubes for each of the four substrates). We used identical reaction conditions with the exception of the time taken to reach the target temperature, which was extended from 2 to 3 min. The product conversions obtained correlated very well to those obtained for the substrates using the monomode function showing that, in this case, translation to the multimode function was possible with no deleterious effect (Table 1, entries 5–8). The composite heating profiles for the reactions are shown in Figure 5. When looking at the temperature plots of the 12 reaction vessels measured using the IR sensor in the apparatus the first observations are that there is significant noise and that they all read a significantly lower value than the internal fiber-optic

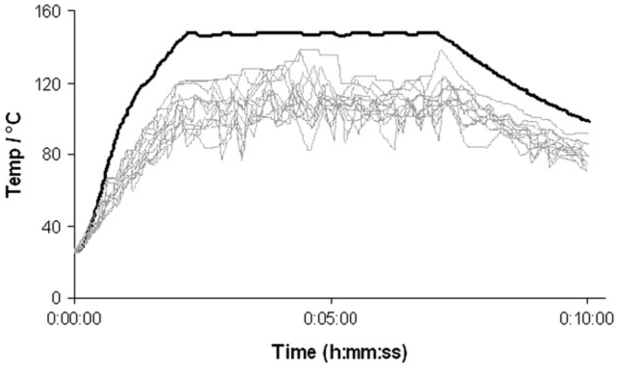


Figure 5. Composite heating profiles for the Suzuki coupling reactions run in the 12-position rotor.

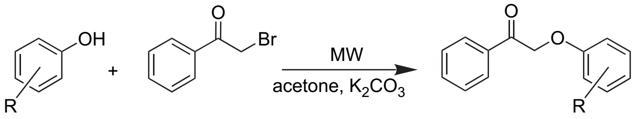
device placed in one of the vessels. Both of these factors can be attributed to the means by which the IR probe measures the temperature. In essence it takes a shot of every vessel each time it rotates around the cavity in the carousel. If the point at which the shot is taken varies even slightly then some significant noise would be expected. In addition, while rotating, the carousel is also being agitated in a lateral motion in order to ensure efficient mixing of the vessel contents. This adds to the issue of measuring the temperature of all 12 vessels accurately. However, we know from the product conversions obtained from each vessel that the contents were at the necessary bulk temperature to ensure effective coupling.

Another point for consideration is that in these reactions, the solvent mixture used (water/ethanol) is significantly microwave absorbent. Since the quantities of substrates used are small in comparison to the volume of solvent, variation in their microwave absorptivity would not be expected to impact the heating profile considerably. This is seen when looking at the temperature plots of the 12 reaction vessels measured using the IR sensor in the apparatus, all of them being relatively closely bunched to one another.

We wanted to scale up the reaction and so performed the chemistry using the multimode function but in larger vessels. Using the six-position rotor, we screened six aryl bromide substrates working on the 10 mmol scale in 100 mL capacity vessels, allowing us to make gram quantities of biaryls. We knew from previous scale-up experience that it was possible to reduce the catalyst loading when moving up in scale in sealed vessels. Thus, we used a palladium loading of 0.05 mol %, heated the mixtures to 150 °C over the period of 5 min and then holding them at this temperature for 5 min. Product conversions again correlated very well to those obtained for the substrates using the monomode function (Table 1, entries 9–14).

2.3. Williamson ether synthesis

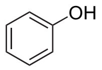
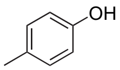
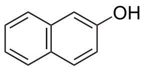
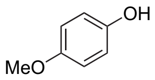
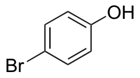
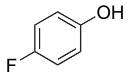
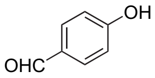
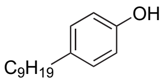
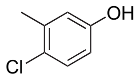
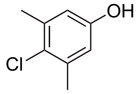
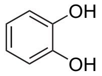
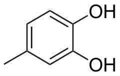
We next wanted to probe a reaction in which one of the components was heterogeneous and also where the effects of microwave absorptivity of substrates can begin to be probed. We chose the Williamson ether synthesis as our first test case. This reaction is typically carried out in refluxing acetone for 2–4 h using potassium carbonate as a base.[9] We wanted to study this reaction using microwave heating.[10] Since acetone is not particularly microwave absorbent, functionality on the substrates could have a significant effect on the heating profile of the reaction mixture. Also, since potassium carbonate is only sparingly soluble in acetone, efficient agitation of the reaction mixture would be important. We decided to focus our attention on the reaction of phenacyl bromide (α-bromoacetophenone) with a range of phenols with different electronic properties.



We first optimized the reaction on the 2 mmol scale using phenol as substrate and found that optimal conditions were 1 M phenacyl bromide in acetone, 1.3 equiv phenol, 2 equiv potassium carbonate as base, heating to 130 °C and holding at this temperature for 20 min. This led to a quantitative conversion to the desired product. Decreasing the reaction temperature or quantity of base had a significantly deleterious effect on the product conversion. Reducing the reaction time from 20 to 10 min led to a slight reduction in product conversion.

With optimized conditions in hand, we screened twelve phenols in the reaction using the 12-position rotor. The phenols screened and product conversions obtained are shown in Table 2. The fiber-optic probe for internal temperature measurement was placed into the vessel containing phenol and thus it was this vessel that was used to control the microwave power input. The temperature of all 12 vessels was monitored using the external IR sensor. The heating profiles for all the reaction vessels are shown in Figure 6. There is a clear variation in the temperature measured across the 12 vessels. Some vessels reach a significantly higher temperature than

Table 2. Microwave-promoted Williamson ether synthesis between phenacyl bromide and a range of phenols[a]

Entry	Phenol	Conversion/%	
		No additive	0.25 mmol TBAB
1		88	92
2		97	91
3		96	63
4		97	91
5		99	92
6		98	82
7		dec	dec
8		52	16
9		99	69
10		79	31
11		Mixture	Mixture
12		Mixture	Mixture

[a] Reactions were run in a sealed tube using 2 mmol phenyacylbromide, 1.3 equiv phenolic substrate, and 2 equiv K_2CO_3. The temperature was ramped to 130 °C over the period of 2 min and held there for 20 min.

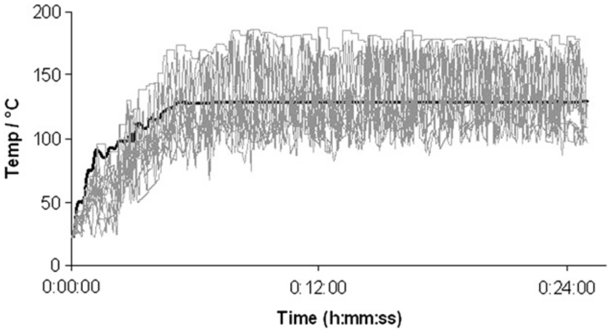


Figure 6. Composite heating profiles for the etherification reactions run in the 12-position rotor.

the 130 °C set and some fall considerably short of the target temperature, even taking into account the 20–30 °C difference expected between the fiber optic and IR temperature profiles. This shows that the microwave absorptivity of the phenolic substrate has a significant effect on the heating characteristics of the contents of a particular reaction vessel.

In the combinatorial chemistry field, an approach used by chemists to ensure even heating of multiple vessels in a microwave field has been to use a solid heating element such as silicon carbide or Weflon, a proprietary mixture of carbon and fluoropolymer, which are both excellent absorbers of microwaves.[11,12] To overcome the temperature differential from vessel to vessel we see in our etherification reactions, we decided to re-run them but this time with the addition of 0.25 mmol tetrabutylammonium bromide (TBAB) to each. The TBAB, because it is charged, will interact very strongly with the microwave irradiation and we predicted this would outweigh any effects from variations in the absorption characteristics of the phenolic substrates. A similar approach of adding ionic compounds to nonpolar reaction mixtures has been used previously to ensure efficient heating when using microwave irradiation.[13] In our case, although the reaction mixtures were heated effectively without an additive, we wanted to moderate the heating so as to maintain a similar bulk temperature in each of our 12 vessels. The heating profiles obtained in the presence of the TBAB additive are shown in Figure 7.

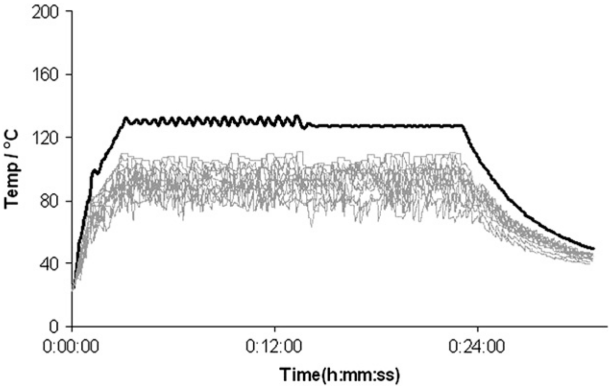
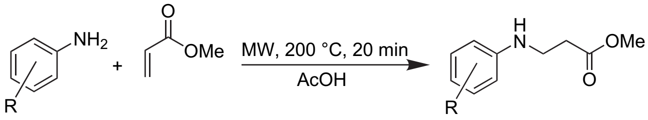


Figure 7. Composite heating profiles for the etherification reactions run in the 12-position rotor with the addition of TBAB.

We find that the profiles for the 12 vessels are now more similar to one another and all are 25–35 °C below the internal temperature measured in the reference vessel using the fiber-optic probe. Conversions to the desired products are in some cases similar to those in the absence of the additive but a deleterious effect of using the additive is observed with several substrates. These differences could be attributed back to the original heating profiles where, in fact, some reaction mixtures were heated to greater than or less than the target temperature. This may have had a positive effect on the product yield in that our optimal conditions determined for phenol may not be the optimal conditions for every substrate screened.

2.4. Michael addition of anilines to alkenes

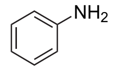
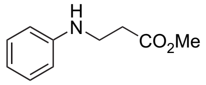
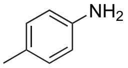
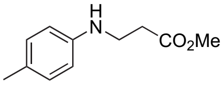
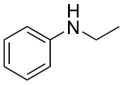
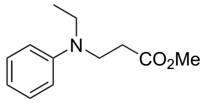
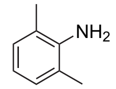
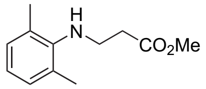
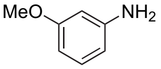
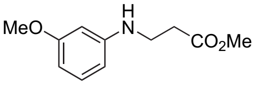
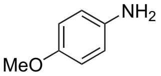
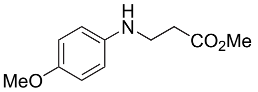
We have recently reported the rapid, simple, microwave-promoted synthesis of *N*-aryl functionalized β-amino esters using a Michael addition protocol.[14] Reactions are performed neat at 200 °C for 20 min and are catalyzed by acetic acid. We wanted to use this as part of our current study since, being a solvent-free protocol, any effects due to differences in microwave absorptivity between reagents, or indeed products, would be exacerbated. In addition, this chemistry is highly temperature dependent. Insufficient heating leads to very poor yields and too much heating leads to side-product formation and decomposition.



Our previous experiments were performed using a dedicated monomode microwave apparatus. To determine whether moving from that to the MultiSynth apparatus required reoptimization of reaction conditions, we initially focused attention on the acid-catalyzed addition of aniline to methyl acrylate. Working on a 15 mmol scale, heating a 1:1 mixture of the substrates with 10 mol % acetic acid at 200 °C for 20 min resulted in a 80% yield of the desired product, this correlating well with that obtained using the monomode apparatus in our previous studies. Using the 12-place carousel we performed the reaction between aniline and methyl acrylate in 10 separate reaction vessels to probe the vessel-to-vessel reproducibility of the apparatus in the multimode format. We obtained an average conversion of 82% with a standard deviation of 3% conversion. With our conditions in hand we next turned our attention to screening six aniline substrates in the reaction with methyl acrylate using the 12-place carousel using the multimode configuration. Each substrate was run in duplicate on the rotor with us choosing aniline, *p*-toluidine, *N*-ethylaniline, 2,6-dimethylaniline, *m*-anisidine, and *p*-anisidine. The results are shown in Table 3.

It is immediately apparent that the yields obtained using the multimode configuration differ from those of our previous report using a monomode microwave apparatus. With the

Table 3. Microwave-promoted Michael addition of anilines to α,β-unsaturated alkenes[a]

Entry	Aniline	Product	Conversion (MultiSynth)/%	Conversion (monomode)/%[b]
1			77	81
2			87	79
3			26	43
4			12	29
5			dec	79
6			dec	70

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[a] Reactions were run in a sealed tube using 15 mmol aniline, 15 mmol methyl acrylate, and 1.5 mmol acetic acid. The temperature was ramped to 200 °C over the period of 10 min and held there for 20 min.

[b] Results from previous report. Reactions performed individually in a dedicated monomode apparatus [Ref. 14].

exception of *p*-toluidine (Table 3, entry 2) the product yields are lower than those from the monomode experiments. The heating profiles for all the reaction vessels in the run using the multimode apparatus are shown in Figure 8. As in the case of the etherification reaction, there is a clear variation in the temperature measured across the 12 vessels. Indeed in this case the effect is even greater. Some vessels reach in excess of 250 °C and some fall considerably short of the target temperature of 200 °C, even taking into account the 20–30 °C difference expected between the fiber optic and IR temperature profiles. At first glance this suggests that the microwave absorptivity of the aniline substrate has a significant effect on the heating characteristics of the contents of the vessel. The fact that we see lower yields in most cases when running the reactions in the multimode apparatus corroborates this. The data suggest that either the reaction mixtures did not reach temperature (*N*-ethylaniline, 2,6-dimethylaniline; Table 3 entries 3 and 4) or else were overheated (*m*-anisidine, *p*-anisidine; Table 3 entries 5 and 6).

In our previous investigation using the monomode apparatus, because the reactions were run individually, the heating profiles were much more similar, the target temperature being reached and not exceeded in each case. To probe in more detail the variation in heating across the anilines studied we turned to a monomode apparatus (CEM Discover). We ran the reaction between aniline and methyl acrylate using an initial microwave power of 100 W. The reaction mixture took almost 5 min to reach the target temperature of 200 °C (Fig. 9). After holding at this temperature for 20 min, we cooled the reaction mixture down to room temperature. We then exposed the same reaction mixture to the same reaction conditions (i.e., microwave heating of 100 W to

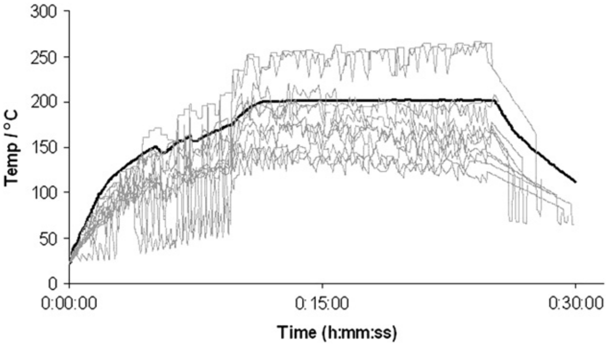


Figure 8. Composite heating profiles for the Michael addition reactions run in the 12-position rotor.

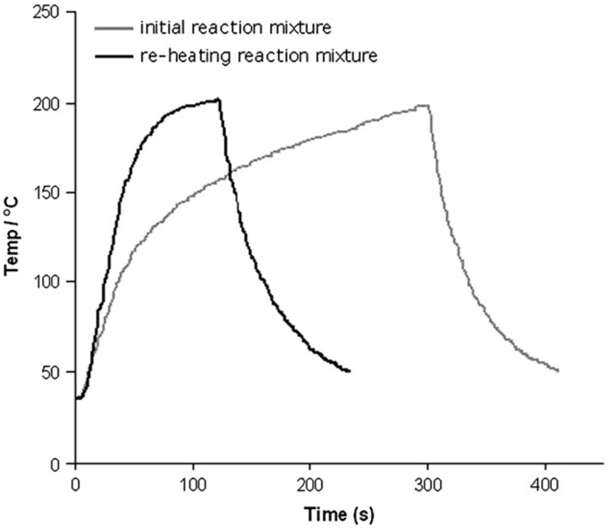
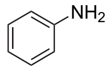
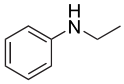
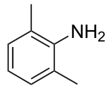
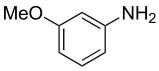


Figure 9. Heating profile for the reaction between aniline and methyl acrylate using an initial microwave power of 100 W.

Table 4. Probing effects in the microwave-promoted Michael addition of anilines to α,β-unsaturated alkenes[a]

Entry	Aniline	Conversion (%) in trial 1[b]	Conversion (%) in trial 2[c]	Conversion (%) in trial 3[d]	Conversion (monomode)[e]/%
1		77	66	50	81
2		26	22	12	43
3		12	10	7	29
4		dec	60	41	79
Average microwave power delivered by magnetron		516	339	264	—

[a] Reactions were run in a sealed tube using 15 mmol aniline, 15 mmol methyl acrylate, and 1.5 mmol acetic acid. The temperature was ramped to 200 °C over the period of 10 min and held there for 20 min.

[b] Control vessel containing aniline.

[c] Control vessel containing 2,6-dimethylaniline.

[d] Control vessel containing *m*-anisidine.

[e] Results from previous report. Reactions performed individually in a dedicated monomode apparatus [Ref. 14].

200 °C) and found that the target temperature was reached in less than 2 min (Fig. 9). This suggests that the product is significantly more microwave absorbent than the starting mixture of aniline and methyl acrylate. Therefore, in the multimode run, it could well be that the rate of heating is dictated not only by the microwave absorptivity of the starting aniline but also by the product. As a consequence, even if the aniline used was not microwave absorbent but was highly reactive, rapid heating could still be possible, this coming about from the high microwave absorptivity of the product being formed.

Our results show that when performing a screening experiment using a range of substrates in a multimode microwave apparatus, a key parameter for consideration is into which vessel the fiber-optic probe should be placed, i.e., which vessel should be the control. To determine the effects of this we ran a version of our aniline screen three times having as the control a vessel containing either aniline (trial 1), 2,6-dimethylaniline (trial 2) or *m*-anisidine (trial 3). We determined not only the product conversion obtained in each trial but also the average microwave power delivered by the magnetron. Our results are shown in Table 4. When aniline is used as the control vessel, an average microwave power of 516 W is delivered by the magnetron during the course of the run to reach and maintain the target temperature of 200 °C. This decreases to 339 W in the case of 2,6-dimethylaniline as the control and to 264 W in the case of *m*-anisidine. Thus there is clearly a significant difference depending on which vessel is used as the control. As the microwave power delivered decreases so does the product conversion in the case of aniline, *N*-ethylaniline, and 2,6-dimethylaniline (Table 4, entries 1–3). This can be attributed to the fact that as the microwave power decreases so the temperature attained in these vessels decreases also. As already discussed, insufficient heating leads to poorer yields. The case of *m*-anisidine is particularly interesting (Table 4, entry 4). When the control vessel contains aniline, decomposition is observed in the vessels containing *m*-anisidine, presumably because the reaction is rapid and the product generated absorbs microwave radiation very rapidly leading to overheating. When the control vessel is 2,6-dimethylaniline a good yield of product is obtained with *m*-anisidine, the lower microwave power allowing for efficient heating but not overheating. When the control vessels contain *m*-anisidine itself, a 41% conversion is obtained.

In an attempt to unify the heating profiles of the different anilines and negate effects from variation of the control vessel, we took a similar approach as in the etherification reactions. The reactions were run using 0.25 mmol tetrabutylammonium acetate (TBAOAc) as an additive. This has the desired effects and the yields obtained are more closely parallel to those obtained in the monomode apparatus. The heating profiles are shown in Figure 10 and the product conversions in Table 5. Each aniline substrate was run in duplicate to probe the vessel to vessel uniformity in terms of product conversion obtained and the results obtained show consistency.

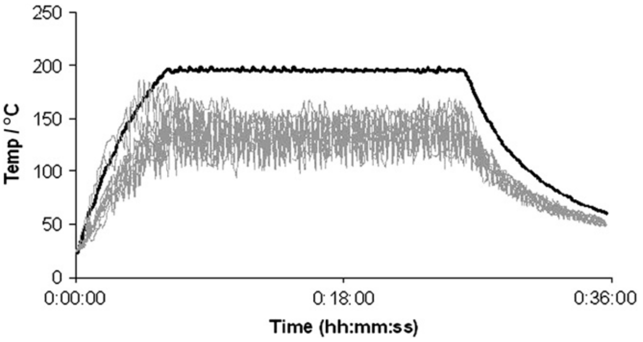
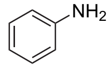
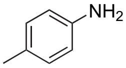
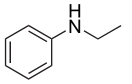
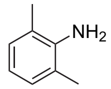
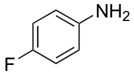
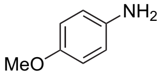


Figure 10. Composite heating profiles for the Michael addition reactions run in the 12-position rotor with the addition of TBAOAc.

Table 5. Microwave-promoted Michael addition of anilines to α,β-unsaturated alkenes using 0.25 mmol TBAOAc as an additive[a]

Entry	Aniline	Conversion (MultiSynth)[b]/%	Conversion (monomode)/%
1		82/83	81[c]
2		77/75	79[c]
3		28/27	43[c]
4		18/16	29[c]
5		66/67	64
6		69/71	70[c]

[a] Reactions were run in a sealed tube using 15 mmol aniline, 15 mmol methyl acrylate and 1.5 mmol acetic acid. The temperature was ramped to 200 °C over the period of 6 min and held there for 20 min.

[b] Reactions performed in duplicate.

[c] Results from previous report. Reactions performed individually in a dedicated monomode apparatus [Ref. 14].

3. Summary

The objective of this study was twofold. Firstly, we wanted to assess the applicability of the MultiSynth apparatus towards rapid optimization of reaction conditions in a monomode function and then substrate screening in a multimode function. Secondly, we wanted to probe the effects of differences in microwave absorptivity of reaction mixtures on the product conversions in screening multiple substrates simultaneously in a multimode microwave apparatus. We find that the apparatus is a useful tool for performing reactions in a single vessel and then moving to multiple vessels. Unsurprisingly, the efficiency of heating reaction mixtures is dependent on the microwave absorptivity of the reagents and solvent used. We do however find that this effect is more marked when using the MultiSynth than with other monomode apparatus. Discussion of this will form the basis of a later article. Our results show that when the microwave absorptivity of a reaction mixture is dictated by the solvent, there is little effect on the heating profile of varying the substrate in a screening run. However, this is not the case when reactions involving non-microwave absorbant solvents are used. In this case the characteristics of the substrate can affect significantly the outcome of the reaction. This effect is further marked when a reaction is performed solvent-free. Another parameter for consideration when performing a screening experiment using a range of substrates in a multimode microwave apparatus is into which vessel the fiber-optic probe should be placed and thus is used as the control. We find that effects of uneven heating of substrates and variation of the control vessel can be mollified by adding a small quantity of a highly microwave absorbent material to each reaction vessel in a screening set.

4. Experimental

4.1. General experimental

Reactions were performed using a Milestone MultiSynth microwave apparatus or, in the case of the two monomode heating experiments discussed in the Michael addition case study, a CEM Discover unit. The former is discussed in detail in Section 2 and for information on the latter the reader is directed to previous reports in the literature. All reagents were obtained from commercial suppliers and used without further purification. The palladium stock solution used in the Suzuki coupling experiments was elemental Pd in 20% HCl; Concentration 1000 mg/mL; J.T. Baker cat. no. 5772-04. ^{1}H and ^{13}C NMR spectra were recorded at 293 K on a 400 MHz Bruker Avance spectrometer.

4.2. Suzuki coupling of 4-bromoacetophenone and phenylboronic acid using the monomode function

In a 10-mL glass tube were placed 4-bromoacetophenone (1.0 mmol, 199.0 mg), phenylboronic acid (1.1 mmol, 134 mg), Na_2CO_3 (3.7 mmol, 390 mg), 1000 μg/mL palladium solution in HCl (0.2500 mL, 0.0024 mmol Pd), ethanol (1 mL), and deionized water (1 mL). The glass tube was placed in a Teflon outer jacket and secured with a Teflon top containing a ceramic thermo well. A fiber-optic probe was placed into the thermal well and the reaction vessel placed into the holder in the microwave cavity. The microwave apparatus was set to 'monomode irradiation' function and the sample was irradiated with the maximum power needed to reach 150 °C in 2 min at which point the temperature was held constant for an additional 5 min. The reaction vessel was agitated in an elliptical motion while undergoing microwave irradiation, the agitation being set to 50% of maximum. After allowing the mixture to cool to room temperature, the reaction vessel was opened and the contents poured over 15 mL deionized water. The organic material was extracted using ethyl acetate (3×20 mL), the organic washings combined and dried over $MgSO_4$, the ethyl acetate removed under vacuum leaving the crude product, which was characterized by comparison of NMR data with that in the literature. ^{1}H NMR ($CDCl_3$): δ 7.90 (d, 2H, J=7.3 Hz), 7.50 (t, 1H, J=7.4 Hz), 7.40 (t, 2H, J=7.3 Hz), 7.20 (t, 2H, J=7.6 Hz), 7.90 (t, 3H, J=7.8 Hz), 5.18 (s, 2H).

4.3. Suzuki couplings of aryl bromides and phenylboronic acid using the multimode function on the 1 mmol scale

In a 10-mL glass tube were placed 4-bromoacetophenone (1.0 mmol, 199.0 mg), phenylboronic acid (1.1 mmol, 134 mg), Na_2SO_4 (3.7 mmol, 390 mg), 1000 μg/mL palladium solution in HCl (0.2500 mL, 0.0024 mmol Pd), ethanol (1 mL), and deionized water (1 mL). The glass tube was placed in a Teflon outer jacket and secured with a Teflon top containing a ceramic thermowell. Eleven other vessels with variously substituted aryl bromide substrates were similarly prepared, these being secured with a Teflon top but with no thermal well. All the vessels were loaded onto a 12-place rotor within the microwave cavity. The fiber-optic probe was placed into the reaction vessel containing the thermal well. The vessels were irradiated using the 'multimode irradiation' function with the maximum power needed to reach 150 °C in 2 min at which point the temperature was held constant for an additional 5 min. Additionally, while under irradiation, the samples were set to oscillate 360° in a clockwise–counterclockwise fashion while being agitated in a horizontal motion, the agitation being set to 50% of maximum. After allowing the reaction mixtures to cool to room temperature, they were opened and the products isolated and characterized in an identical manner to the case of the single reaction experiment.

4.4. Suzuki couplings of aryl bromides and phenylboronic acid using the multimode function on the 10 mmol scale

In a 75-mL capacity Teflon tube were placed 4-bromoacetophenone (10.0 mmol, 1.990 g), phenylboronic acid (10.0 mmol, 1.2330 g), Na_2CO_3 (12.0 mmol, 1.272 g), 1000 μg/mL palladium solution in HCl (1.2500 mL, 0.012 mmol Pd), 10.0 mL ethanol, and 8.75 mL deionized water. The 80-mL tube was placed into an outer protective jacket secured with a screw-top containing a ceramic thermowell. Eleven other vessels with variously substituted aryl bromide substrates were similarly prepared, these being secured with a Teflon top but with no thermal well. All the vessels were loaded onto a 6-place rotor within the microwave cavity. The fiber-optic probe was placed into the reaction mixture containing the 4-bromoacetophenone. The vessels were irradiated using the 'multimode irradiation' function with the maximum power needed to reach 150 °C in 5 min at which point the temperature was held constant for an additional 5 min. Additionally, while under irradiation, the samples were set to oscillate 360° in a clockwise–counterclockwise fashion while being agitated in a horizontal motion, the agitation being set to 50% of maximum. After allowing the reaction mixtures to cool to room temperature, they were opened and the products isolated and characterized in an identical manner to the case of the single reaction experiment.

4.5. Etherification of phenol with phenacyl bromide using the monomode function

In a 10-mL glass tube were placed α-bromoacetophenone (2.0 mmol, 199.0 mg), K_2CO_3 (4.0 mmol, 550.0 mg), phenol (2.6 mmol, 245.0 mg), and acetone (2 mL). The glass tube was placed in a Teflon outer jacket and secured with a Teflon top containing a ceramic thermowell. A fiber-optic probe was placed into the thermal well and the reaction vessel placed into the holder in the microwave cavity. The microwave apparatus was set to 'monomode irradiation' function and the sample was irradiated with the maximum power needed to reach 130 °C in 5 min at which point the temperature was held constant for an additional 20 min. The reaction vessel was agitated in an elliptical motion while undergoing microwave irradiation, the agitation being set to 50% of maximum. After allowing the mixture to cool to room temperature, the reaction vessel was opened and the contents poured over 15 mL deionized water. The organic material was extracted using diethyl ether (3×20 mL), the organic washings combined, washed twice with 2.0 M NaOH solution (2×10 mL), washed with brine, and then dried over $MgSO_4$. The ether was removed under vacuum leaving the crude product, which was characterized by comparison of NMR data with that in the literature. ^{1}H NMR ($CDCl_3$): δ 7.90 (d, 2H, J=7.3 Hz), 7.50 (t, 1H, J=7.4 Hz), 7.40 (t, 2H, J=7.3 Hz), 7.20 (t, 2H, J=7.6 Hz), 6.90 (t, 3H, J=7.8 Hz), 5.18 (s, 2H).

4.6. Etherification of phenols with phenacyl bromide using the multimode function

In a 10-mL glass tube were placed α-bromoacetophenone (2.0 mmol, 199.0 mg), K_2CO_3 (4.0 mmol, 550.0 mg), phenol (2.6 mmol, 245.0 mg), and acetone (2 mL). The glass tube was placed in a Teflon outer jacket and secured with a Teflon top containing a ceramic thermowell. Eleven other vessels with variously substituted phenol substrates were similarly prepared, these being secured with a Teflon top but with no thermal well. All the vessels were loaded onto a 12-place rotor within the microwave cavity. The fiber-optic probe was placed into the reaction containing the thermal well. The vessels were irradiated using the 'multimode irradiation' function with the maximum power needed to reach 130 °C in 5 min at which point the temperature was held constant for an additional 20 min. Additionally, while under irradiation, the samples were set to oscillate 360° in a clockwise–counterclockwise fashion while being agitated in a horizontal motion, the agitation being set to 50% of maximum. After allowing the reaction mixtures to cool to room temperature, they were opened and the products isolated and characterized in an identical manner to the case of the single reaction experiment.

4.7. Etherification of phenols with phenacyl bromide using the multimode function and with the addition of TBAB

A 125 mM stock solution of tetrabutylammonium bromide (TBAB) (3.75 mmol, 1.210 g in 30 mL acetone) was prepared. The reaction vessels were loaded and heated in an identical manner to the case of the analogous experiments above, substituting this stock solution (2 mL) for the pure acetone (equating to 0.25 mmol TBAB per vessel).

4.8. Reaction of aniline with methyl acrylate using the monomode function

In a 10-mL glass tube were placed aniline (15.0 mmol, 1.395 g, 1.360 mL), methyl acrylate (15.0 mmol, 1.290 g, 1.350 mL), and acetic acid (1.5 mmol, 0.090 g, 0.086 mL). The glass tube was placed in a Teflon outer jacket and secured with a Teflon top containing a ceramic thermowell. A fiber-optic probe was placed into the thermal well and the reaction vessel placed into the holder in the microwave cavity. The microwave apparatus was set to 'monomode irradiation' function and the sample was irradiated with the maximum power needed to reach 200 °C in 10 min at which point the temperature was held constant for an additional 20 min. The reaction vessel was agitated in an elliptical motion while undergoing microwave irradiation, the agitation being set to 50% of maximum. After allowing the mixture to cool to room temperature, the crude product was characterized by comparison of NMR data with that in the literature. ^{1}H NMR ($CDCl_3$): δ 7.18 (t, 2H, J=7.5 Hz), 6.70

(t, 1H, J=7.3 Hz), 6.62 (d, 2H, J=7.7 Hz), 4.00 (br, 1H), 3.70 (s, 3H), 3.46 (t, 2H, J=6.4 Hz), 2.63 (t, 2H, J=6.4 Hz).

4.9. Reaction of anilines with methyl acrylate using the multimode function

The glass tube was placed in a Teflon outer jacket and secured with a Teflon top containing a ceramic thermowell. Eleven other vessels with variously substituted aniline substrates (a total of two vessels each of six anilines) were similarly prepared, these being secured with a Teflon top but with no thermal well. All the vessels were loaded onto a 12-place rotor within the microwave cavity. The fiber-optic probe was placed into the reaction containing the thermal well. The vessels were irradiated using the 'multimode irradiation' function with the maximum power needed to reach 200 °C in 10 min at which point the temperature was held constant for an additional 20 min. Additionally, while under irradiation, the samples were set to oscillate 360° in a clockwise–counterclockwise fashion while being agitated in a horizontal motion, the agitation being set to 50% of maximum. After allowing the reaction mixtures to cool to room temperature, the crude products were characterized by comparison of NMR data with that in the literature.

4.10. Reaction of anilines with methyl acrylate using the multimode function and with the addition of TBAOAc

The reaction vessels were loaded and heated in an identical manner to the case of the analogous experiments above but with the addition of tetrabutylammonium acetate (0.25 mmol, 76.0 mg) to each vessel. Additionally, the vessels were irradiated using the 'multimode irradiation' function with the maximum power needed to reach 200 °C in 6 min rather than10 min. The hold time was the same (20 min).

Acknowledgements

Milestone is thanked for the provision of a MultiSynth microwave apparatus. Funding from the University of Connecticut is acknowledged.

References and notes

1. A number of books on microwave-promoted synthesis have been published recently: (a) *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2006; (b) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinhiem, 2005; (c) *Microwave-Assisted Organic Synthesis*; Lidström, P., Tierney, J. P., Eds.; Blackwell: Oxford, 2005.
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3. For an example of translation from monomode to multimode, see: (a) Perio, B.; Dozias, M.-J.; Hamelin, J. *Org. Process Res. Dev.* **1998**, *2*, 428; (b) Cleophax, J.; Liagre, M.; Loupy, A.; Petit, A. *Org. Process Res. Dev.* **2000**, *4*, 498.
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