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Watching microwave-promoted chemistry: reaction monitoring using a digital camera interfaced with a scientific microwave apparatus

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Abstract—By interfacing a digital camera with a scientific microwave unit it is possible to monitor macroscopic effects as reactions proceed, including color and viscosity changes, evolution of gases, metal-mediated couplings, and arcing.

The use of scientific microwave apparatus for preparative organic chemistry is becoming increasingly common.[1] Microwave heating offers advantages such as short reaction times and good yields of desired products. There are two main categories of scientific microwave apparatus. Monomode microwave units have been used with great success for small-scale reactions using sealed glass tubes up to a working volume of approximately 50 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. When performing chemistry using a microwave unit, in particular a monomode apparatus, it is not generally possible to monitor a reaction as it proceeds. Some approaches have been developed, including the use of Raman spectroscopy as a tool for in situ monitoring of reactions.[2] We have used this to probe both organic and organometallic reactions and found that the ones we have investigated reach completion in a matter of seconds.[3] While Raman spectroscopy is a useful tool, something that preparative chemists do conventionally is watch their reactions as they proceed. Macroscopic phenomena such as changes in color, viscosity, or the dissolution or deposition of solids can be indicative of product formation or, in some cases, decomposition. Thus, when using microwave heating, to be able to see a reaction as it runs would not only be useful, but would add an extra degree of safety. When using domestic microwave ovens, it can be possible to watch reactions using the naked eye. However, it is not possible to monitor key parameters such as temperature, pressure, and microwave power. Also, it is inherently unsafe to perform chemistry in a domestic microwave oven since they are not designed for preparative chemistry and are not built to withstand a vessel failure. However, using scientific microwave apparatus it is possible to monitor very closely a range of parameters and they are safe to use for chemistry. However, the design of a scientific monomode microwave is such that the cavity is sealed and you cannot see your reaction mixture. Here we show how, by interfacing a digital camera with a monomode microwave apparatus, it is possible to watch reactions as they take place and we highlight the benefits this brings.

To perform our experiments, a commercially available monomode microwave apparatus was interfaced with a digital camera.[4,5] The microwave unit contained an access port in the side of the cavity, through which a 1.3 megapixel camera could be interfaced. The face of the lens was positioned outside the cavity wall. To be able to watch reactions as they proceed it was clearly necessary to illuminate the microwave cavity. This was achieved by placing white light LEDs in the bottom of the microwave cavity these providing enough light to illuminate a vessel. The end of the camera lens was protected with a plastic cover in case of a vessel failure in the microwave cavity. The camera was connected to a

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PC and controlled using computer software. Reactions were performed in sealed 10 mL glass tubes and were recorded digitally. The videos are cited in the text here and either the full experiment or else excerpts can be found in Supplementary data.

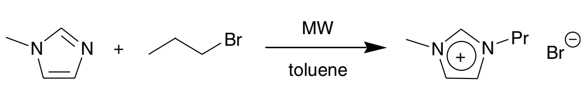
As a starting point, we studied the effects of microwave heating on a reaction vessel containing water. Compared to using a hotplate to heat a reaction mixture, microwave irradiation leads to heating on a molecular level. Since the microwave energy is interacting with the molecules at a very fast rate, the molecules do not have time to relax and the heat generated can, for short times, be much greater than the overall recorded temperature of the bulk reaction mixture.[6] In essence, there will be instantaneous localized superheating. We wanted to see if this localized superheating could be physically seen. To do this, we placed 2 mL water in a 10 mL glass tube, put a septum on the vessel and placed it into the microwave cavity. We then programmed the apparatus to heat the water to a target temperature of 150 °C. Looking at the video of the experiment [video 1], localized heating is clearly apparent upon microwave irradiation. We found that this became more significant once the bulk temperature of the water was above 130 °C. To be able to see the superheating more clearly, we performed an analogous experiment using 6 M sodium hydroxide into which we had placed a small quantity of fluorescein [video 2]. Again superheating is apparent upon microwave irradiation. It is important to note that both of these experiments were performed in the absence of stirring. With stirring, more homogeneous heating is observed.

Polar solvents absorb microwaves effectively while nonpolar solvents do not. To see the effect of this on the superheating we performed an experiment using two immiscible solvents, dichloromethane and aqueous sodium hydroxide (containing fluorescein for clarity). Since the density of dichloromethane is greater than that of water, the organic solvent sits below the aqueous. Heating this using microwave irradiation, localized superheating is clearly seen, but only in the more polar, aqueous layer [video 3]. Repeating the experiment but using toluene in place of dichloromethane puts the organic layer above the aqueous layer and again localized heating is seen to originate solely from the more polar, aqueous layer [video 4].

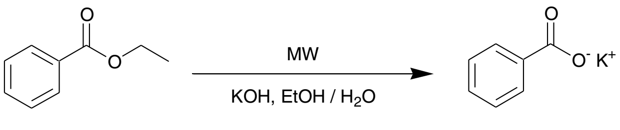
We moved from our foundation experiments to monitoring reactions. We first looked at the preparation of an ionic liquid (Scheme 1).[7] Conventional synthesis of ionic liquids has several disadvantages. First, long reflux times are often needed to obtain reasonable yields. Also, the purification of the ionic liquid is often problematic and large quantities of organic solvents are required to extract impurities. This is especially true with halide based ionic liquids where the excess of halide is difficult to remove completely. This has prompted the use of microwave-mediated approaches for the preparation of ionic liquids and several reports have appeared in the literature.[8] For our study, we prepared a solution of *N*-methylimidazole and 1-bromopropane in toluene. Heating this to a target temperature of 160 °C, using an initial microwave power of 300 W, and monitoring the reaction using the camera, the formation of 1-propyl-3-methylimidazolium bromide ([BMIM]Br) was evident. The initially clear solution first becomes cloudy and then, after about 45–50 s, the yellow ionic liquid starts to separate out of solution. The reaction, performed on a 10 mmol scale, is complete after 90 s microwave heating [video 5].

Our next reaction for study was the hydrolysis of ethyl benzoate in aqueous ethanol containing potassium hydroxide.[9] In this case we wanted to follow the reaction colorimetrically. Using a 1:1 stoichiometric ratio of ethyl benzoate to potassium hydroxide and by adding phenolphthalein to the solution, we proposed that it would be possible to watch for disappearance of the purple coloration, indicating point when all the KOH was consumed by the benzoic acid formed in the hydrolysis reaction (Scheme 2). Heating the reaction mixture to a target temperature of 120 °C, using an initial microwave power of 200 W, and monitoring the reaction using the camera, we find that the hydrolysis is complete within 35–40 s of irradiation [video 6].

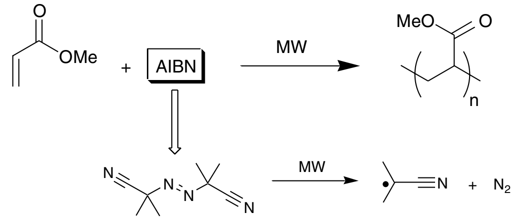
The use of microwave irradiation in polymer chemistry is an emerging field of research, which is attracting attention not only because reactions can be greatly accelerated but because polymers with novel properties can be prepared.[10] We wanted to study a polymerization reaction using our reaction monitoring apparatus. We chose the free-radical polymerization of methyl acrylate for our study.[11] Using azobisisobutyronitrile (AIBN) as an initiator we expected to be able to see the decomposition of this to give 2-cyanoprop-2-yl radicals and nitrogen gas and then the rapid polymerization of the alkene to give polymethylacrylate. Performing the reaction solvent-free, heating to a target temperature of 80 °C, using an initial microwave power of 150 W, and monitoring the reaction using the camera, we find that the AIBN initiates the polymerization after about 45 s of irradiation, this corresponds to a bulk temperature of 75 °C and then the process being complete within 80 s [video 7]. Performing the reaction using water as a solvent the decomposition of AIBN is again clearly seen as is the onset of polymerization, this time after approximately 25 s of microwave irradiation. The polymerization reaction is complete after a total time of 45–50 s had elapsed [video 8] (Scheme 3).



Scheme 1.



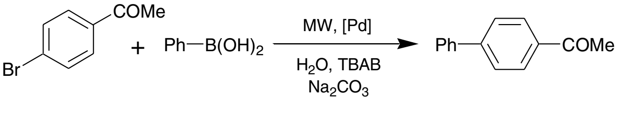
Scheme 2.



Scheme 3.

Transition metal-catalyzed reactions can be performed very efficiently using microwave heating and palladium-mediated reactions have attracted particular attention.[12] For this reason, and because it is a more challenging reaction to probe, we included a Suzuki coupling in our study.[13] We have shown previously that Suzuki reactions can be performed using water as the solvent, ppm levels of a ligandless palladium salt as the catalyst, sodium carbonate as base, and tetrabutylammonium bromide as a phase-transfer agent.[14] The mixture is heated to 150 °C and the reaction is complete within the period of 1–3 min, depending on the substrate used. Using these conditions, we performed the coupling of 4′-bromoacetophenone and phenylboronic acid with the in situ camera monitoring (Scheme 4). First we ran the reaction without stirring [video 9]. When the reaction mixture is placed into the microwave cavity it is cloudy. Within 20 s of microwave heating, a layer forms on the top of the water and it appears that the reaction is taking place there. Upon cooling at the end of the reaction, the product crystallizes out on top of the water layer. A 95% yield of 4-acetylbiphenyl was obtained. When the reaction is run with stirring, again a second phase forms upon heating and, at the end of the reaction the product crystallizes out on top of the water layer [video 10]. The product yield was comparable regardless of whether the reaction mixture was or was not stirred.

One safety issue when using metal catalysts in conjunction with microwave heating is that deposition of metal on the surface of a glass tube can lead to arcing and superheating. This in turn can result in localized melting of the glass and a pinhole fracture of the tube. If the contents of the vessel are under pressure, a small fracture can lead to a catastrophic destruction of the tube. While metal deposition is not a major issue when using low levels of metal catalysts, as the concentration increases so does the potential for an issue. To illustrate this, we heated a solution of palladium acetate in toluene using a microwave power of 150 W and monitored the effects using the camera [video 11]. To accentuate any effects, the mixture was not stirred. The formation of metallic palladium is observed after 3.5 min together with some observable superheating. After 4 min, deposition of palladium metal on the surface of the glass above the solvent meniscus is observed and then this is followed by significant arcing. At this point the input of microwave power was stopped manually. In this case the vessel did not fail since the pressure inside the tube was not excessive. The camera allows reactions in which arcing is a possibility to be closely monitored and stopped before vessel failure.



Scheme 4.

In summary, we show here that, by interfacing a digital camera with a scientific microwave unit, it is possible to monitor macroscopic effects as reactions proceed. These include color and viscosity changes, evolution of gases, metal-mediated couplings and arcing. The application of the apparatus to these and other reactions and the ability to see a reaction as it runs is something that will aid chemists in performing their microwave-promoted chemistry.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.097.

References and notes

1. (a) A number of books have been published recently. See: *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.
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3. (a) Leadbeater, N. E.; Smith, R. J.; Barnard, T. M. *Org. Biomol. Chem.* **2007**, 822; (b) Leadbeater, N. E.; Smith, R. J. *Org. Lett.* **2006**, *8*, 4589; (c) Barnard, T. M.; Leadbeater, N. E. *Chem. Commun.* **2006**, 3615.
4. King, E. E. U.S. Patent: US 2007/0062934 A1.
5. Microwave reactions were conducted using a commercially available monomode microwave unit (CEM Discover S-class). A 1.3 megapixel camera was interfaced with the microwave unit by means of an access port in the side of the microwave cavity. The face of the lens was positioned outside the cavity wall and protected with a plastic cover. Three white light LEDs were placed at the bottom of the microwave cavity to illuminate the reaction vessel. The use of external lighting meant that it was also necessary to have a means for preventing the illumination source from saturating the infrared temperature detector. The camera was connected to a PC via an USB 2.0 interface and controlled using computer software. Using this, it was possible to record temperature, pressure, and microwave power profiles at the same time as the video images.

6. For a review on the concepts see: Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, *27*, 213.
7. In a 10 mL glass tube were placed *N*-methylimidazole (0.25 mL, 3.14 mmol), 1-bromopropane (0.60 mL, 6.61 mmol), and toluene (1.0 mL). The tube was sealed with a septum and placed into the microwave cavity. Using an initial microwave power of 300 W, the reaction mixture was heated to a target temperature of 160 °C and held there until a total time of 5 min had elapsed. Upon cooling to room temperature, the ionic liquid product was isolated by decanting, washed with ethyl acetate (2 × 5 mL) and its identity confirmed by comparison of NMR data with that in the literature.
8. See, for example: (a) Varma, R. S.; Namboodiri, V. V. *Chem. Commun.* **2001**, 643; (b) Khadilkar, B. M.; Rebeiro, G. L. *Org. Process. Res. Dev.* **2002**, *6*, 826; (c) Deetlefts, M.; Seddon, K. R. *Green Chem.* **2003**, *5*, 181.
9. In a 10 mL glass tube containing a magnetic stir bar were placed ethyl benzoate (0.25 mL, 1.74 mmol), KOH (0.5 mL of a 3 N solution in water, 1.5 mmol), ethanol (0.5 mL), and phenolphthalein solution (0.1 mL). The tube was sealed with a septum and placed into the microwave cavity. Using an initial microwave power of 200 W, the reaction mixture was heated to a target temperature of 120 °C and held there until the color of the solution changed from purple to colorless (35–40 s).
10. For a recent review see: Hoogenboom, R.; Schubert, U. S. *Macromol. Chem. Rapid Commun.* **2007**, *28*, 368.
11. In a 10 mL glass tube containing a magnetic stir bar were placed methyl acrylate (2.0 mL, 22.2 mmol) and AIBN (6.0 mg, 36.5 μmol). The tube was sealed with a septum and placed into the microwave cavity. Using an initial microwave power of 150 W, the reaction mixture was heated to a target temperature of 80 °C and held there until a total time of 90 s had elapsed. Evolution of nitrogen gas occurred when the bulk temperature of the reaction mixture reached 72 °C, this being followed by a significant increase in viscosity as polymerization occurred. The reaction was repeated using identical reaction conditions but with the addition of water (1 mL) to the tube prior to sealing.
12. For a recent review see: Olofsson, K.; Nilsson, P.; Larhed, M. In *Microwaves in Organic Chemistry*; Loupy, A., Ed.; Wiley-VCH, 2006, Chapter 15, p 685.
13. In a 10 mL glass tube were placed 4′-bromoacetophenone (199 mg, 1.0 mmol), phenylboronic acid (122 mg, 1.0 mmol), Na_2CO_3 (392 mg, 3.7 mmol), tetrabutylammonium bromide (322 mg, 1.0 mmol), palladium stock solution (0.5 mL of a 20 ppm solution in water), and water (1.5 mL) to give a total volume of water of 2 mL and a total palladium concentration of 5 ppm. The vessel was sealed with a septum and placed into the microwave cavity. Using an initial microwave power of 150 W, the reaction mixture was heated to a target temperature of 150 °C and held there until a total reaction time of 5 min had elapsed. The reaction was repeated using identical reaction conditions but with the addition of a magnetic stir bar to the tube prior to sealing. After allowing the mixture to cool to room temperature, the reaction vessel was opened and the contents poured into a separating funnel. Water (30 mL) and ethyl acetate (30 mL) were added and the organic material extracted and removed. After further extraction of the aqueous layer with ethyl acetate, combining the organic washings and drying them over $MgSO_4$, the ethyl acetate was removed in vacuo leaving the crude product, which was isolated and characterized by comparison of NMR data with that in the literature.
14. Arvela, R. K.; Leadbeater, N. E.; Sangi, M. S.; Williams, V. A.; Granados, P.; Singer, R. S. *J. Org. Chem.* **2005**, *70*, 161.