Using *in situ* Raman monitoring as a tool for rapid optimisation and scale-up of microwave-promoted organic synthesis: esterification as an example

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Microwave-promoted esterification reactions have been monitored using *in situ* Raman spectroscopy. Having optimised a reaction on a 23 mmol scale, it was transferred to a larger reaction vessel and scaled up to 0.26 mol, again with Raman monitoring. With conditions in hand, an automated stop-flow apparatus was used to prepare 5.7 moles of product.

Introduction

Microwave heating is becoming a widely accepted tool for synthetic chemists. It is possible to improve product yields and enhance the rate of reactions as well as being a safe and convenient method for heating reaction mixtures to elevated temperatures.[1,2] A problem with performing a reaction using scientific microwave apparatus is that monitoring its progress is not easy. With conventional heating, where the reaction proceeds slowly, aliquots can be removed and analyzed over time, but with microwave heating the reaction may be complete within a matter of minutes or even seconds and accessing a sealed vessel during a reaction is not possible. As a result, optimization of reaction conditions such as time and temperature can often be a matter of trial and error. Techniques including neutron and X-ray scattering,[3–6] and near IR spectroscopy[7] have been interfaced with microwave apparatus for monitoring reactions as they progress. While having applications, particularly in materials chemistry, they are not trivial to set up. Pivonka and Empfield have reported the use of Raman spectroscopy as a tool for monitoring organic transformations.[8] They studied an imine formation reaction and a Knovenagel condensation. Building on this work, we recently reported a simple apparatus for the monitoring of reactions under microwave irradiation using *in situ* Raman spectroscopy. Our apparatus comprises a scientific monomode microwave apparatus and a commercially available Raman module. It is possible to follow ligand substitution reactions in organometallic complexes using this apparatus[9] as well as palladium-mediated Suzuki couplings in water–ethanol solvent mixtures.[10] To date, we have used standard 10 mL glass tubes as reaction vessels. The Raman tool allows us to optimise reaction conditions very easily and this motivated us to perform an exercise to see how quick it was to take a reaction, test conditions on a small scale, transfer it to a larger 80 mL reaction vessel, optimise reaction parameters and then prepare significant quantities of product using an automated stop-flow apparatus interfaced with the same 80 mL reaction vessel. We present our results here.

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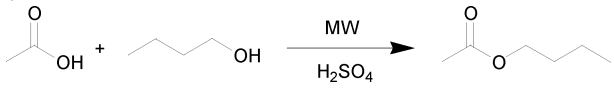
Results and discussion

For our study, we decided to focus on esterification reactions since these elementary, yet multifaceted, reactions find wide application in organic synthesis.[11] They are used on small and large scales in the chemical industry, in particular the fine chemicals and flavour and fragrance business.[12,13] Microwave heating has been used to facilitate acid-, base- and enzyme-catalysed esterification reactions.[14,15] We also wanted to study this reaction because it has been the subject of previous scale-up attempts using microwave heating.[16–19]

We started by studying the reaction of acetic acid with butanol using sulfuric acid as a catalyst in our monomode microwave apparatus equipped with the Raman monitoring interface. Initially, to drive the reaction to completion we used 13 mmol butanol, a 2.5-fold excess of acetic acid (32.5 mmol) and 30% sulfuric acid by volume based on acetic acid (19% based on entire volume). Using an initial microwave power of 150 W, we heated the reaction mixture to 130 °C and held it at this temperature until a total time of 10 min had elapsed. Working on a 13 mmol scale, quantitative conversion to butyl acetate was obtained (Table 1, entry 1). We recorded Raman spectra approximately every 6 s during the course of the reaction. The Raman spectrum of acetic acid shows a characteristic peak at approximately 800 cm^{-1} that is not found in either butanol or butyl acetate. Therefore, we chose this as the primary signal that we would follow during the course of the reactions. We subtracted the time = 0 spectrum from subsequent spectra of the series. As a result, features that are not impacted by the reaction do not appear in the profile. Selected spectra in the region 800–1000 cm^{-1} are shown in Fig. 1. From this, it can be seen that the reaction is essentially complete after approximately 18 s. The relative intensity of the peak due to the acetic acid that we were monitoring did not grow further after this time. To confirm that the esterification was indeed complete after this short period, we re-ran the reaction but stopped it after 18 s had elapsed. Analysis of the reaction mixture showed a quantitative conversion to butyl acetate (Table 1, entry 2). The temperature and power *vs.* time profiles are shown in Fig. 2. The reaction does not reach the target temperature of 130 °C in this short time, yet it is complete. With microwave irradiation, since the energy is interacting with the molecules at a very fast rate, the molecules do not have time to relax and the heat generated can be, for short times, much greater than the overall recorded temperature of the bulk reaction

Table 1 Microwave-promoted esterification



Entry	Reaction scale and conditions [a,b]	Conversion (%)
1[c]	10 mL vessel, 13 mmol scale, 2.5 : 1 ratio of acetic acid to butanol, 130 °C, 10 min	Quant.
2	10 mL vessel, 13 mmol scale, 2.5 : 1 ratio of acetic acid to butanol, heated for *18 s*	Quant.
3[c]	10 mL vessel, 13 mmol scale, *1 : 1 ratio* of acetic acid to butanol, 130 °C, 10 min	71
4	10 mL vessel, 13 mmol scale, *1 : 1 ratio* of acetic acid to butanol, heated for *42 s*	69
5[c]	*80 mL vessel*, *0.26 mol scale*, *1 : 1 ratio* of acetic acid to butanol, 150 °C, 10 min	73
6	80 mL vessel, *0.26 mol scale*, *1 : 1 ratio* of acetic acid to butanol, heated for *74 s*	73

[a] Reactions were run in a sealed tube. An initial microwave irradiation power of 150 W was used. [b] For clarity, changes in reaction conditions from entry 1 are noted in italic type. [c] The temperature was ramped from room temperature to 130 °C and held until a total reaction time of 10 min had elapsed. Sulfuric acid concentration was reduced to 1.6%.

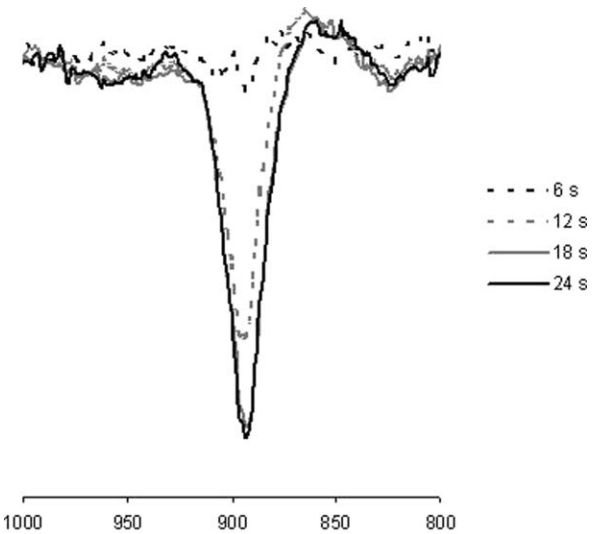


Fig. 1 *In situ* Raman monitoring of the reaction of acetic acid with butanol.

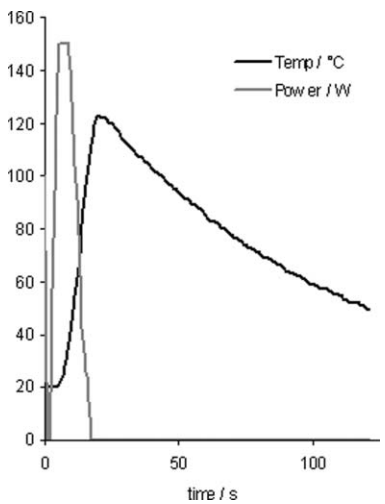


Fig. 2 Temperature and power *vs.* time profiles for the reaction of acetic acid with butanol.

mixture. There will be sites of instantaneous localised superheating where reactions will take place much faster than in the bulk. Therefore, a high bulk temperature is not necessarily required in order to facilitate the reaction. Similar observations were made on our study of the Suzuki reaction, the coupling being essentially complete by the time the reaction mixture reached the target temperature.[10]

We next performed the reaction using a 1 : 1 stoichiometric ratio of acetic acid to butanol and 1.6% sulfuric acid by volume based on acetic acid (0.64% based on entire volume), since these were conditions that we would want to use in any larger scale syntheses. On a 23 mmol scale, we heated the reaction mixture to 130 °C using an initial microwave power of 150 W and held it at this temperature until a total time of 10 min had elapsed. A 71% conversion of butyl acetate was obtained (Table 1, entry 3). Raman analysis showed that the reaction essentially reached completion after 42 s of microwave irradiation. Repeating the reaction for 42 s resulted in an almost identical yield, confirming this assertion (Table 1, entry 4).

In order to scale up the reaction, we moved from working in a 10 mL vessel to a larger 80 mL vessel. Increasing the maximum applied microwave power from 150 W to 300 W, and the maximum set temperature to 150 °C, we performed the reaction of acetic acid with butanol, again with Raman monitoring. This was the first time that attempts had been made to record Raman spectra of a reaction mixture in the larger 80 mL vessel, and we were pleased to find that it was possible to achieve this, with little modification. We were concerned that the thickness of the glass walls of the larger vessels (5 mm) would impede our ability to record Raman spectra of the contents. However, we found this not to be a problem. Working on a 0.26 mol scale, a 73% conversion to butyl acetate was obtained after heating the reaction mixture to 150 °C and holding it at this temperature until a total time of 10 min had elapsed (Table 1, entry 5). Raman analysis showed that the reaction essentially reached completion after 74 s of microwave irradiation, again being confirmed by running the reaction for this set time (Table 1, entry 6). Using the same reaction conditions, we performed the reactions of acetic acid with methanol, ethanol and propanol obtaining 81%, 72% and 73%, respectively. Returning to the reaction between acetic acid and butanol, we probed the effect of increasing the quantity of sulfuric acid used on the reaction rate. Using 5.12% H_2SO_4 by volume, it was possible to obtain a quantitative conversion to butyl acetate. Using 2.56% H_2SO_4 by volume, the reaction was complete within 48 s and a 71% conversion is obtained. Thus, it is possible to perform reaction

scouting quickly based around catalyst concentration as well as reaction time. If an expensive catalyst was being used, to have this additional ability may prove important.

To scale up the reaction further we used an automated stop-flow apparatus. This combines the advantages of a batch reactor with those of a continuous flow reactor.[20] It uses the same microwave system and the same 80 mL vessel that was used in the reaction optimisation studies and thus the chemistry is directly transferable without the need for changing any parameters. The reaction mixture is pumped into and out of the vessel by a peristaltic pump, these functions, as well as running the reaction, being controlled using a computer. This gives a high degree of automation to the process. The reaction mixture could be introduced into the microwave vessel from two separate feed lines. After the reaction is complete, the reaction vessel can be vented to remove an overpressure and then the contents of the reactor pumped into a collection vessel. Since only one reaction vessel is used, the time taken to cool the reaction mixture to room temperature at the end of the run is significantly shorter than those reported for the parallel batch reactors using multimode apparatus.[21–23] We set the apparatus to run 22 cycles of a 0.26 mol reaction using acetic acid and butanol as substrates (1 : 1 ratio) and sulfuric acid as catalyst (0.64% based on entire volume). Pumping of the reagents into the reaction vessel was easy, the acetic acid and sulfuric acid being introduced from one reservoir and butanol from another. The reaction was run for 74 s and, after the reaction mixture had cooled to 80 °C, the excess pressure in the reaction vessel was vented and the entire contents pumped into a cool collection vessel. Each cycle took approximately 6 min; 36 s to load the reaction vessel, 4.2 min for the reaction (74 s microwave irradiation and 3 min for cool-down to 80 °C) and 45 s to pump the product out. The overall conversion from the combination of all 22 product mixtures was 71%. Thus, in 2 h 12 min, 5.7 moles of product was obtained (816 mL).

Conclusions

In summary, this study illustrates that, using the Raman module as a tool, it is possible to optimise a reaction on a small scale, transfer it to a larger reaction vessel and scale it up. Since the reaction can be monitored continually using the Raman spectrometer, it is possible to use this for quality control during automated stop-flow scale-up. While the reaction studied here is fairly simple, the potential ease of optimisation and time savings possible using this protocol make it attractive for a wide range of other organic transformations. The whole procedure could be completed within one day, going from a test reaction in the morning to moles of product in the afternoon.

Experimental

General

All reagents were obtained from commercial suppliers and used without further purification. ^{1}H- and ^{13}C-NMR spectra were recorded at 293 K on a 400 MHz spectrometer.

Description and use of the microwave apparatus

Microwave reactions were conducted using a commercially available monomode microwave unit (CEM Discover). The machine consists of a continuously focused microwave power delivery system with operator selectable power output from 0–300 W. Reactions were performed either in 10 mL tubes (maximum working volume 7 mL) or in a thick-walled glass vessel (capacity 80 mL, maximum working volume 50 mL). Small tubes were sealed with a septum, and the pressure controlled by a load cell connected to the vessel. The temperature of the contents of the vessel was monitored using a calibrated infrared temperature control, mounted under the reaction vessel. Large vessels were sealed with a septum with ports for pressure and temperature measurement devices. The pressure was controlled by a load cell connected directly to the vessel. The pressure limit was set to 300 psi for all reactions, beyond which the apparatus shuts down. This upper limit was never reached in any of the runs but is set as a safety measure. The temperature of the contents of the vessel was monitored using a calibrated fiber-optic probe inserted into the reaction vessel by means of a sapphire immersion well. In all cases, the contents of the vessel were stirred, when required, by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stirrer bar in the vessel. Temperature, pressure and power profiles were monitored using commercially available software provided by the microwave manufacturer. For the automated stop-flow batch reactions, the basic running of the microwave steps remains the same as with the single experiments; the reactions being performed in the same thick-walled glass vessel, the pressure being controlled by a load cell connected directly to the vessel and the temperature monitored using a fiber-optic probe. One additional port allowed for introduction of the reagents into the reaction vessel *via* a PFA tube of 1.6 mm internal diameter (i.d.) and venting of the vessel at the end of the reaction. At the end of the reaction, the product was pumped out using the same PFA tube as that used for introduction of the reagents. Movement of material in and out of the vessel was by way of a peristaltic pump and an automated valve mechanism.

Raman apparatus and interface with the microwave unit

A commercially available Raman apparatus was used for the studies. It comprises an NIR, frequency-stabilised, narrow linewidth diode laser at 785 nm (laser power at sample ~200 mW), a permanently aligned two single fiber combination 100 μm excitation fiber, 200 μm collection fiber, high sensitivity linear CCD array, symmetrical crossed Czerny–Turner design spectrograph (resolution ~10 cm^{-1} at 785 nm, excitation spectral coverage of 300 cm^{-1} to 2400 cm^{-1}) and collection software. To interface the microwave unit and Raman spectrometer, a hole (0.8 cm i.d.) was drilled in the microwave cavity and an RF stub attached to the outer cavity wall (to prevent microwave leakage) and an extender (2.16 cm i.d.) attached to this, reaching through to the outer casing of the microwave unit. The fiber-optic probe was placed into the cavity and the laser focused through a quartz light tube.

General experimental procedure

Representative example of an esterification reaction using a 10 mL vessel for optimisation. In a 10 mL glass tube was placed acetic acid (1.32 mL, 23 mmol), 1-butanol (2.10 mL, 23 mmol) and sulfuric acid (0.02 mL). The vessel was sealed and placed into the microwave cavity. Initial microwave irradiation of 150 W was

used, the temperature being ramped from room temperature to the desired temperature of 130 °C. Once this was reached, the reaction mixture was held at this temperature until a total time of 10 min had elapsed. Raman spectra were recorded approximately every 6 s throughout the reaction. Both the microwave and the Raman apparatus were started simultaneously. After allowing the reaction mixture to cool to 50 °C, the vessel was opened, NMR spectra of the contents were recorded and product conversion determined.

Representative example of an esterification reaction using an 80 mL vessel for optimisation. In a 80 mL thick-walled glass tube was placed acetic acid (15 mL, 260 mmol), 1-butanol (25 mL, 260 mmol) and sulfuric acid (0.25 mL). The vessel was sealed and placed into the microwave cavity. Microwave irradiation to a maximum of 300 W was used, the temperature being ramped from room temperature to the desired temperature of 150 °C. Once this was reached, the reaction mixture was held at this temperature until a total time of 10 min had elapsed. Raman spectra were recorded approximately every 6 sec throughout the reaction. Both the microwave and the Raman apparatus were started simultaneously. After allowing the reaction mixture to cool to 50 °C, the vessel was opened, and NMR spectra of the contents were recorded and product conversion determined.

Reaction of acetic acid with butanol using the automated stop-flow apparatus. Two stock solutions were prepared, stock solution one containing acetic acid (450 mL) and sulfuric acid (7.5 mL), and stock solution two containing 1-butanol (600 mL). The apparatus was programmed to run a series of operations sequentially. Firstly, 15.25 mL of stock solution one was introduced into the reaction vessel followed by 25 mL of stock solution two. Next, in a heating step, microwave irradiation to a maximum of 300 W was used to heat the reaction mixture for 74 s; a maximum temperature of 150 °C was set as a safety measure. The temperature was ramped from room temperature to the desired temperature of 150 °C. Thirdly, in a cooling step, the reaction mixture was cooled to 80 °C using forced air passing around the glass reaction vessel and then any remaining overpressure was vented. Next, the whole contents of the vessel were pumped out into a collection container. This was the end of the procedure. The whole addition, heating, and removal process was then repeated a further 21 times to give a total of 22 cycles of 0.26 mol reactions. Each product mixture could be collected individually and the product conversion monitored or all pooled into one collection container. The product was characterised using the same procedure as in case of the 0.26 mol optimisation reactions.

Acknowledgements

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