In situ Raman spectroscopy as a probe for the effect of power on microwave-promoted Suzuki coupling reactions†

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We report the use of *in situ* Raman spectroscopy as a probe for the effect of power on microwave-promoted Suzuki coupling reactions. We find that increased initial microwave power leads to greater acceleration of the reaction but that the product yield obtained is essentially independent of initial microwave power. The application of simultaneous cooling lengthens the reaction time but does not alter the relative rates of the Suzuki coupling and deboronation processes. Performing the reaction at an initial microwave power of 5 W leads to an improvement in product yield.

Introduction

Using microwave heating, it is possible to enhance the rate of many reactions and often improve product yields.[1,2] A problem with performing a reaction using microwave apparatus is that monitoring its progress generally requires stopping it, allowing the reaction mixture to cool and then using standard analysis techniques such as IR and NMR spectroscopy. As a result, optimization of reaction conditions such as time and temperature can often be a matter of trial and error. With conventional heating, where the reaction proceeds slower, 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. There have been some attempts to monitor reactions under microwave irradiation. Techniques include neutron and X-ray scattering,[3–6] and near IR spectroscopy.[7] Pivonka and Empfield have reported the use of Raman spectroscopy as a tool for monitoring organic transformations.[8] Building on this work, we reported an apparatus for the monitoring of organometallic reactions under microwave irradiation using *in situ* Raman spectroscopy.[9] We have also used our apparatus to study the Suzuki coupling reaction in aqueous media.[10] We probed the reaction of phenylboronic acid with three aryl bromides; namely 4-bromoacetophenone, 4-bromotoluene and 4-bromoanisole. We wanted to work with these three substrates because they cover the range of electron-rich, electron-neutral and electron-poor aryl bromides. It is essential that the reaction mixture is homogeneous in order to be able to record Raman spectra. Working on a 0.5 mmol scale, we found that for each reaction, the organic substrates could be dissolved in 3 mL of a 1: 2 water–ethanol mixture to give a homogeneous mixture. Although sodium carbonate is the best base for performing low catalyst loading Suzuki coupling reactions,[11,12] it is not totally soluble in the aqueous ethanol solvent. As a result, we drew on our recent finding that organic bases such as DBU can be used when performing the reaction in aqueous solvents with 0.4–1 mol% $Pd(OAc)_2$ as the catalyst.[13] We heated the reaction mixtures to 150 °C and held them at this temperature for 10 min, recording Raman spectra approximately every 7 s.

The Raman spectra of biaryls show a characteristic peak at approximately 1600 cm^{-1} that is not found in either aryl halide or boronic acid substrates. We chose this as the primary signal to follow during the course of the coupling reactions. While water is Raman-transparent, ethanol is not and any signals due to starting materials or the biaryl product would be masked. To overcome this problem we subtracted the time = 0 spectrum from subsequent spectra of the series so that features such as solvent and functional groups that are not impacted by the reaction do not appear in the profile. Using an initial microwave power of 50 W Raman monitoring showed that, regardless of the aryl bromide substrate used, the reaction was complete after approximately 135 s. The peak due to the biaryl that we were monitoring did not grow in relative intensity after this time. Product yields obtained with 4-bromoacetophenone, 4-bromotoluene and 4-bromoanisole were 87%, 97% and 55% respectively (Table 1, entries 1, 2 and 3). We suggested that the Suzuki coupling reaction is in competition with the deboronation of the phenylboronic acid. In the case of the 4-bromoacetophenone and 4-bromotoluene, the coupling reaction was faster than the deboronation whereas, with 4-bromoanisole, the two processes occurred at similar rates. By the time the reaction had run for 135 s, all the boronic acid had either reacted with the aryl bromide substrate or else had been deboronated (Table 1, entry 4). Using our Raman monitoring capability, we wanted to probe the reaction further and determine the effect of varying the initial microwave power used. We present the results of these investigations here.

Results and discussion

We performed the Suzuki reactions with the same substrates using the same reaction conditions (heat to 150 °C and hold for 10 min) but used an initial microwave power of 125 W instead of the 50 W used in our preliminary studies. We again recorded Raman spectra every 7 s during the course of the reaction. Selected spectra in the region 1540–1700 cm^{-1} for the reactions with the three aryl bromide substrates are shown in Fig. 1. They show that, in all three cases, the reaction is essentially complete after approximately 100 s

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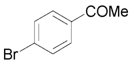
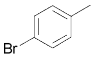
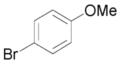
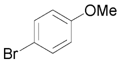
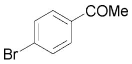
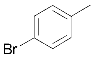
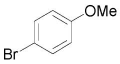
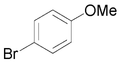
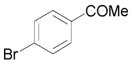
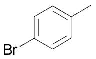
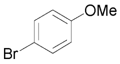
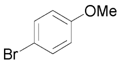
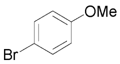
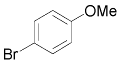
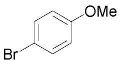
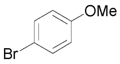
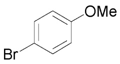
Table 1 Suzuki coupling reactions monitored by *in situ* Raman spectroscopy.[a]

Entry	Aryl halide	Initial mw power/W	Reaction time	Product yield (%)
1		50	10 min at 150 °C	87
2		50	10 min at 150 °C	97
3		50	10 min at 150 °C	55
4		50	Total rxn time of 135 s	55
5		125	10 min at 150 °C	89
6		125	10 min at 150 °C	94
7		125	10 min at 150 °C	56
8		125	Total rxn time of 100 s	54
9		200	10 min at 150 °C	87
10		200	10 min at 150 °C	95
11		200	10 min at 150 °C	53
12		200	Total rxn time of 70 s	56
13		80	Total rxn time of 120 s	55
14		170	Total rxn time of 80 s	53
15		50	10 min at 150 °C with simultaneous cooling on	54
16		125	10 min at 150 °C with simultaneous cooling on	53
17		50	20 min at 150 °C	72

[a] Reactions were run in a sealed tube using 0.5 mmol aryl halide, 0.5 mmol phenylboronic acid, 0.8 mol% Pd(OAc)$_2$, 2 mL ethanol and 1 mL water.

of microwave heating. The peak that we were monitoring due to the biaryl did not grow in relative intensity after this time. Product yields obtained with 4-bromoacetophenone, 4-bromotoluene and 4-bromoanisole were 89%, 94% and 56% respectively (Table 1, entries 5, 6 and 7). To confirm that the reactions had indeed gone to completion in this time, we re-ran the coupling of 4-bromoanisole and phenylboronic acid but stopped it after 100 s had elapsed. Analysis of the reaction mixture showed a 54% yield of biaryl and no remaining boronic acid (Table 1, entry 8). Of note is that the product yield in each case almost identical to that obtained when

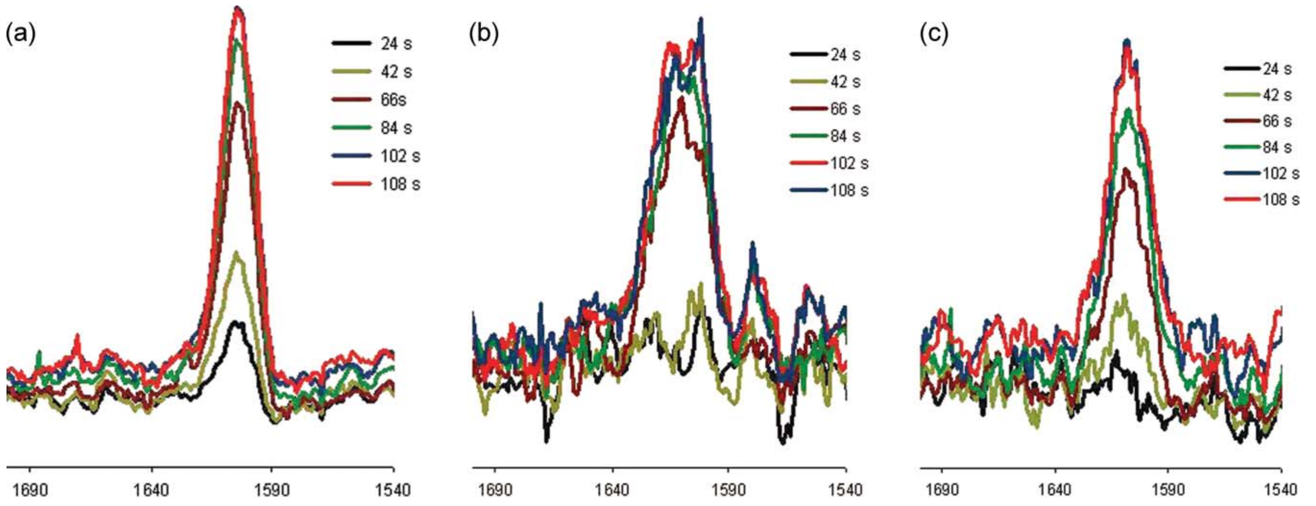


Fig. 1 *In situ* Raman monitoring of the reactions of (a) 4-bromoacetophenone, (b) 4-bromotoluene, and (c) 4-bromoanisole with phenylboronic acid using an initial microwave power of 125 W.

performing the reactions using an initial microwave power of 50 W but the reaction time is some 35 s shorter.

We next performed the couplings using an initial microwave power of 200 W, recording the Raman spectra every 7 s as before. Again all three reactions reached completion in the same time, in this case approximately 70 s of microwave heating. As an example, selected spectra for 4-bromoacetophenone are shown in Fig. 2. Product yields were again almost identical to those obtained when performing the reactions using an initial microwave power of 50 W or 125 W (Table 1, entries 9, 10 and 11). Re-running the coupling of 4-bromoanisole and phenylboronic acid but stopping it after 70 s had elapsed gave a 56% yield of biaryl and no remaining boronic acid (Table 1, entry 12), this confirming the assertion that the reactions are complete after this time.

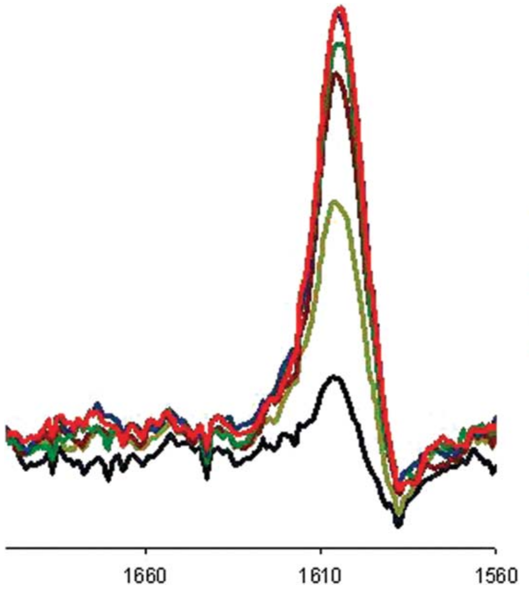


Fig. 2 *In situ* Raman monitoring of the reaction of 4-bromoacetophenone with phenylboronic acid using an initial microwave power of 200 W.

We looked at the temperature and time profiles for the reactions run at all three initial microwave powers. Our first observation was that, at a given initial microwave power, the profiles for the three substrates were almost identical. The profiles for an initial microwave power of 50 W are shown in Fig. 3. This shows that the reaction mixtures are all heated at the same rate. The comparison of the profiles for the couplings using 4-bromoanisole at 50, 125 and 200 W are shown in Fig. 4. Correlating these with the reaction times obtained from the Raman studies shows that, in all three cases, the reactions are complete within a few seconds of reaching the target temperature of 150 °C. Although we attribute our results to purely thermal effects, it is apparent that the initial microwave power does play an important role. Not surprisingly, the higher the initial microwave power used, the faster the reaction reaches completion. We attribute this to the well known phenomenon of localized superheating caused by the direct heating of the reaction mixture by microwave irradiation. Higher instantaneous localized heating would be expected at higher microwave powers, this being reflected in the shorter reaction time.

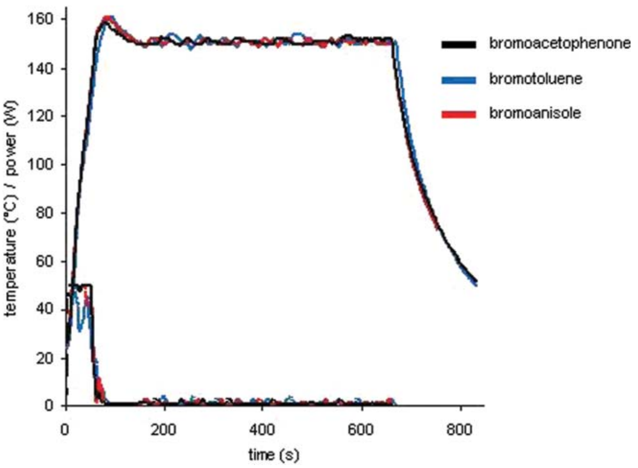


Fig. 3 Temperature and microwave power profiles for the reactions of aryl bromides with phenylboronic acids using an initial microwave power of 50 W.

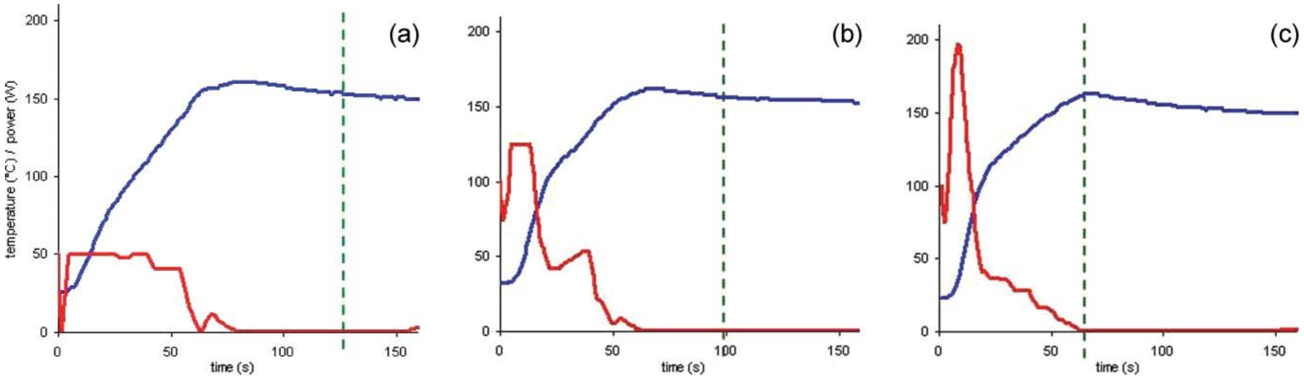


Fig. 4 Temperature and microwave power profiles for the reactions of 4-bromoanisole with phenylboronic acid using initial microwave powers of (a) 50 W, (b) 125 W and (c) 200 W.

Both the coupling and competitive deboronation are accelerated by an almost identical amount. This is clear from the observation that the product yields do not differ when the initial microwave power is increased from 50 W to 125 W to 200 W. A plot of reaction time *vs.* initial microwave power shows an almost linear relationship between the two (Fig. 5). To test whether it was possible to use this plot to predict the time for the reaction to reach completion at a particular initial microwave power, we undertook a further two coupling reactions. We performed the coupling of 4-bromoanisole and phenylboronic acid at 80 W and 170 W for 120 s and 80 s respectively, these being the predicted times at which the reaction would reach completion. In both cases we obtained an almost identical yield to that obtained at 50 W, 125 W and 200 W.

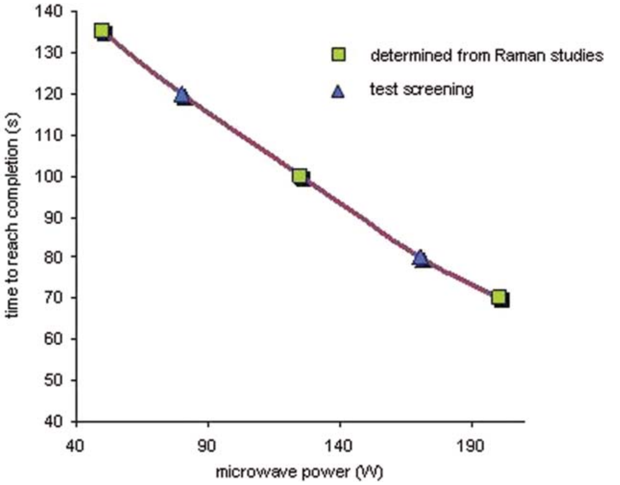


Fig. 5 Plot of reactions time *vs.* initial microwave power for the reactions of aryl bromides with phenylboronic acid.

We next wanted to determine whether the use of simultaneous cooling in conjunction with microwave heating would have a positive effect on the product yield in the coupling of 4-bromoanisole and phenylboronic acid. In principle, this technique allows for higher levels of microwave energy to be introduced into a reaction whilst maintaining the mixture at a particular bulk temperature by passing a stream of compressed air over the reaction vessel. Recent reports appearing in the literature have suggested that this can result in higher product yields and new pathways that were previously unattainable.[14,15]

There have been criticisms leveled at the technique, in particular focusing on whether the measurement of the reaction temperature is accurate. We have investigated the concept ourselves, looking specifically at the measurement of temperature when using simultaneous cooling and then assessing its use in different synthetic transformations.[16] We found that it is important to monitor the temperature of a reaction mixture accurately, and this involves the use of a fiber-optic temperature measurement set-up. Using external IR temperature measurement, the temperature recorded is lower than the bulk temperature of the reaction mixture because of the air passing over the reaction vessel. Having modified our Raman apparatus for use in conjunction with fiber-optic temperature measurement, we performed the Suzuki reaction between 4-bromoanisole and phenylboronic acid using the same reaction conditions as before but this time with the application of simultaneous cooling. We performed two reactions, one using an initial microwave power of 50 W and the other using an initial microwave power of 125 W. Analysis of the Raman spectra indicated that the time at which the reaction reached completion was longer than without the application of simultaneous cooling; 170 s for the case of 50 W and 145 s for the case of 125 W. This is not too surprising given that the reaction mixtures heat more slowly when they are being cooled externally. In both cases a product yield of approximately 50–55% was obtained, these being the same as in the respective reactions without the application of simultaneous cooling (Table 1, entries 15 and 16). This shows that the cooling does not have an effect on the relative rates of the Suzuki coupling and deboronation processes.

In another attempt to probe the reaction, we performed the coupling of 4-bromoanisole and phenylboronic acid using a significantly lower initial microwave power. We chose to run the reaction at 5 W. Our thought was that, at this low power with the reaction mixture being continually stirred, the effects of the microwave irradiation would be less marked than at 50–200 W. As a result, if localized superheating was responsible for the rapid deboronation of the boronic acid substrate as well as accelerating the desired Suzuki coupling, the effects would be less marked. Analysis of the Raman spectra recorded during the course of the experiment showed that the reaction reached completion after 17 min heating at 150 °C. A 72% yield of the desired biaryl product was obtained (Table 1, entry 17), this being significantly higher than that obtained at higher initial microwave power. As a final control experiment, we performed the coupling of 4-bromoanisole and phenylboronic acid using conventional heating and obtained an 80% yield of the desired product.

Conclusions

In summary, we have explored the effects of varying initial microwave power on the rate of and product yields obtained in the Suzuki coupling reaction of three aryl bromides with phenylboronic acid. We have achieved this using *in situ* Raman spectroscopy. We find that increased initial microwave power leads to greater acceleration of the reaction. An almost linear relationship between initial microwave power and time at which the reaction reaches completion was observed. When performing the coupling of 4-bromoanisole and phenylboronic acid at an initial microwave power of 50 W or higher we find that the product yield obtained is essentially independent of initial microwave power. We believe that the coupling is in competition with the deboronation of the boronic acid and that as the initial microwave power is increased both processes are accelerated by an almost identical amount. The deboronation of phenylboronic acid does not occur in the absence of the aryl bromide component. The application of simultaneous cooling lengthens the reaction time but does not alter the relative rates of the Suzuki coupling and deboronation processes. Performing the reaction at a low initial microwave power of 5 W leads to an improvement in product yield. We attribute all our results to purely thermal effects. We believe that localized superheating is responsible for the rapid deboronation of the boronic acid substrate as well as accelerating the desired Suzuki coupling, but at very low microwave power the effects are less marked. Work is now underway to expand the scope of the *in situ* monitoring technique to other important synthetic transformations.

Experimental

Reactions were conducted using a monomode microwave unit (CEM Discover®) interfaced with a Raman spectrometer (Enwave Optronics).

Typical experimental procedure

In a 10 mL glass tube was placed aryl bromide (0.5 mmol), phenylboronic acid (0.061 g, 0.5 mmol), DBU (0.075 mL, 0.5 mmol), palladium acetate (1 mg, 0.8 mol%), ethanol (2 mL), water (1 mL) and a magnetic stir bar. The vessel was placed into the microwave cavity and sealed with a pressure lock. The microwave source was then turned on and microwave irradiation of 50 W was used to ramp the temperature from r.t. to 150 °C, where it was held for 10 min by modulating the microwave power. Raman spectra were recorded approximately every 7 s throughout the reaction. Both the microwave and the Raman apparatii were started simultaneously. After allowing the reaction mixture to cool down to r.t., the vessel was opened and the contents poured into a separatory funnel. Water (25 mL) and diethyl ether (25 mL) were added and the organic material extracted and removed. After further extraction of the aqueous layer with diethyl ether, combining the organic washings and drying them over $MgSO_4$, the solvent was removed *in vacuo*, leaving the crude product.

4-Acetylbiphenyl. ^{1}H NMR ($CDCl_3$) δ 8.06 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 7.5 Hz, 2H), 7.50 (d, J = 7.5 Hz, 2H), 7.45 (d, J = 7.4 Hz, 1H), 2.66 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 197.8, 145.8, 139.9, 135.9, 129.0, 128.9, 128.2, 127.3, 127.2, 26.7.

4-Methylbiphenyl. ^{1}H NMR ($CDCl_3$) δ 7.64 (d, J = 7.1 Hz, 2H), 7.55 (d, J = 8.1 Hz, 2H), 7.48 (t, J = 7.5 Hz, 2H), 7.37 (t, J = 7.3 Hz, 1H), 7.30 (d, J = 7.9 Hz, 2H), 2.45 (s, 3H)); ^{13}C NMR ($CDCl_3$) δ 141.2, 138.4, 137.0, 129.5, 128.7, 127.0, 126.9, 126.1, 21.1.

4-Methoxybiphenyl. ^{1}H NMR ($CDCl_3$) δ 7.53–7.58 (m, 4H), 7.43 (t, J = 7.7 Hz, 2H), 7.32 (t, J = 7.4 Hz, 1H), 6.99 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.2, 140.9, 133.8, 128.7, 128.2, 126.8, 126.7, 114.2, 55.4.

Acknowledgements

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