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Real-Time Monitoring of Microwave-Promoted Suzuki Coupling Reactions Using in Situ Raman Spectroscopy

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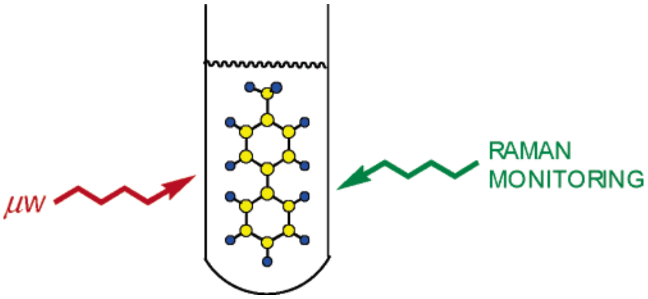
ABSTRACT



The progress of microwave-promoted Suzuki reactions has been monitored using an in situ Raman spectroscopy apparatus assembled from commercially available components. It was possible to see if any reaction occurred and, if so, when it reached completion. In addition, the monitoring technique has given us an insight into the reaction, confirming that, when run in aqueous media, the coupling is in competition with the rapid deboronation of the boronic acid.

Microwave irradiation is a valuable tool for synthetic chemistry. It is possible to enhance the rate of reactions and, in many cases, improve product yields.[1,2] We have used microwave heating extensively in the Suzuki reaction (palladium-catalyzed cross-coupling of aryl halides with boronic acids).[3,4] We find that it is possible to perform the reaction using low levels of ligandless palladium salts as the catalyst and water/ethanol mixtures as the solvent.[5,6] The reaction can be performed in either sealed or open vessels, the latter allowing for the reaction to be performed on up to a 3 mol scale.[7] Although sodium carbonate was found to be the best base for the low catalyst loading coupling reactions, organic

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(1) A number of books on microwave-promoted synthesis have been published recently: (a) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinhiem, 2005. (b) Lidström, P.; Tierney, J. P., Eds. *Microwave-Assisted Organic Synthesis*; Blackwell: Oxford, 2005. (c) Loupy, A., Ed. *Microwaves in Organic Synthesis*; Wiley-VCH: Weinheim, 2002. (d) Hayes, B. L. *Microwave Synthesis: Chemistry at the Speed of Light*; CEM Publishing: Matthews, NC, 2002.

(2) For recent reviews, see: (a) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250. (b) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717. (c) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlain, A. R. *J. Comb. Chem.* **2002**, *4*, 95. (c) Lidström, P.; Tierney, J. P.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225.

(3) For a review, see: Leadbeater, N. E. *Chem. Commun.* **2005**, 2881.

(4) For other reports of microwave-promoted Suzuki couplings in water, see: (a) Blettner, C. G.; Konig, W. A.; Stenzel, W.; Schotten, T. *J. Org. Chem.* **1999**, *64*, 3885. (b) Han, J. W.; Castro, J. C.; Burgess, K. *Tetrahedron Lett.* **2003**, *44*, 9359. (c) Appukkuttan, P.; Orts, A.; Chandran, R. P.; Goeman, J. L.; Van der Eycken, J.; Dehaen, W.; Van der Eycken, E. *Eur. J. Org. Chem.* **2004**, 3277. (d) Gong, Y.; He, W. *Org. Lett.* **2002**, *4*, 3803. (e) Namboodiri, V. V.; Varma, R. S. *Green Chem.* **2001**, *3*, 146. (f) Zhang, W.; Chen, C. H.-T.; Lu, Y.; Nagashima, T. *Org. Lett.* **2004**, *6*, 1473. (g) Solodenko, W.; Schön, U.; Messinger, J.; Glinschert, A.; Kirschning, A. *Synlett* **2004**, 1699.

(5) Arvela, R. K.; Leadbeater, N. E.; Sangi, M. S.; Williams, V. A.; Granados, P.; Singer, R. S. *J. Org. Chem.* **2005**, *70*, 161.

(6) (a) Arvela, R. K.; Leadbeater, N. E.; Mack, T. M.; Kormos, C. M. *Tetrahedron Lett.* **2006**, *47*, 217. (b) Arvela, R. K.; Leadbeater, N. E. *Org. Lett.* **2005**, *7*, 2101. (c) Arvela, R. K.; Leadbeater, N. E.; Collins, M. J. *Tetrahedron* **2005**, *61*, 9349.

10.1021/ol061803f CCC: $33.50

bases such as DBU can be used when performing the reaction with 0.4−1 mol % of $Pd(OAc)_2$.[8]

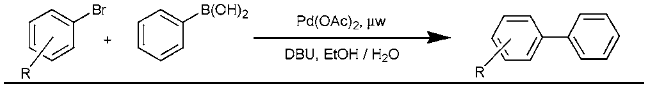
A significant problem with performing reactions using the microwave apparatus is that monitoring its progress generally requires stopping it, allowing the reaction mixture to cool, and then using standard analysis techniques such as IR and NMR spectroscopy. Therefore, optimization of reaction conditions such as time and temperature is often a matter of trial and error. With conventional heating, the reaction can be slow where aliquots are removed and analyzed over time; however, with microwave heating, the reaction may be complete within a matter of minutes and accessing a sealed vessel during a reaction is not possible.

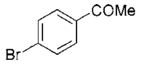
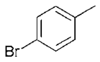
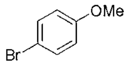
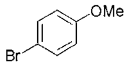
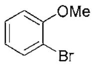
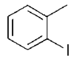
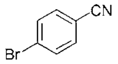
There have been some attempts to monitor reactions under microwave irradiation. Neutron and X-ray scattering have been used for studying the preparation of inorganic materials.[9−12] Near-IR spectroscopy has been used for the study of a C═O band shift during the reaction between 3-pentanone and triethylorthoformate to form 3,3-diethoxypentane and ethylformate.[13] Pivonka and Empfield have reported the use of Raman spectroscopy as a tool for monitoring organic transformations.[14] They studied an imine formation reaction and a Knovenagel condensation. Raman spectroscopy is a particularly useful technique for in situ spectroscopy because it relies on light scattering and hence no mechanical interaction with the sample. In addition, glass vessels typically give a low background signal in Raman scattering.

Building on the work of Pivonka and Empfield,[14] we have recently reported an apparatus for the monitoring of organometallic reactions under microwave irradiation using in situ Raman spectroscopy.[15] It comprises a scientific monomode microwave apparatus and a commercially available Raman module (excitation source 785 nm; spectral coverage 2400−300 cm^{-1}). Using this apparatus, we wanted to study the aqueous-phase Suzuki reaction to see if we could perform real-time in situ monitoring of the coupling. We report our initial results here.

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. Therefore, we chose this as the primary signal that we would follow during the course of the reactions. When using Raman spectroscopy as a monitoring tool, it is important that the reaction mixture is homogeneous. For this reason, when choosing reaction conditions for our study, we decided to draw on our previously published protocol using water/ethanol mixtures as the solvent and DBU as the base.[8] We wanted to probe the reaction of phenylboronic acid with three aryl bromides, namely, 4-bromoacetophenone, 4-bromotoluene, and 4-bromoanisole. 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.[16] This was based on using a 1:1 stoichiometric ratio of the aryl halide to boronic acid substrates. As the catalyst we decided to use palladium acetate (0.8 mol %). Product yields are shown in Table 1.

Table 1. Suzuki Coupling Reactions Monitored by in Situ Raman Spectroscopy[a]



entry	aryl halide	reaction time	product yield (%)
1		10 min	87
2		10 min	97
3		10 min	55
4		135 s	55
5		10 min	0
6		10 min	35
7		10 min	97

[a] Reactions were run in a sealed tube using 0.5 mmol of aryl halide, 0.5 mmol of phenylboronic acid, 0.8 mol % of $Pd(OAc)_2$, 2 mL of ethanol, and 1 mL of water. An initial microwave irradiation of 50 W was used, the temperature being ramped from room temperature to 150 °C where it was held for 10 min.

Although water is Raman transparent, ethanol is not. Therefore, any signals due to starting materials or the biaryl product would be masked by those due to ethanol. To overcome this problem, we subtracted the time = 0 spectrum from subsequent spectra of the series. As a result, features such as solvent and functional groups that are not impacted by the reaction do not appear in the profile. Starting with the coupling of bromoacetophenone with phenylboronic acid, we heated the reaction mixture to 150 °C and held it there for 10 min. An 87% yield of 4-acetylbiphenyl was obtained (Table 1, entry 1). During the course of the reaction, we recorded Raman spectra approximately every 7 s. Selected spectra in the region 1540−1700 are shown in Figure 1. From this, it can be seen that the reaction is essentially complete after approximately 135 s. The peak due to the biaryl that we were monitoring did not grow in relative intensity after this time.

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(8) Chanthavong, F.; Leadbeater, N. E. *Tetrahedron Lett.* **2005**, *47*, 1909.

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(15) Barnard, T. M.; Leadbeater, N. E. *Chem. Commun.* **2006**, 3615.

(16) This compares to a 1:1 ethanol/water mixture reported in ref 8.

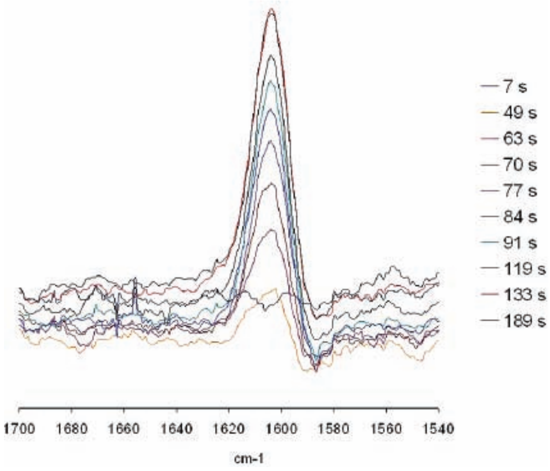

Figure 1. In situ Raman monitoring of the reaction of 4-bromoacetophenone and phenylboronic acid.

We performed identical experiments but used 4-bromotoluene and 4-bromoanisole as the aryl halide substrates. In the case of 4-bromotoluene, a 97% yield of 4-methylbiphenyl was obtained (Table 1, entry 2). Raman monitoring showed that the reaction was complete within 135 s of microwave irradiation as shown in Figure 2. With 4-bromoanisole, a 55% yield of 4-methoxybiphenyl was obtained (Table 1, entry 3). Again, the Raman monitoring showed that the reaction was complete within 135 s of microwave irradiation (Figure 3).

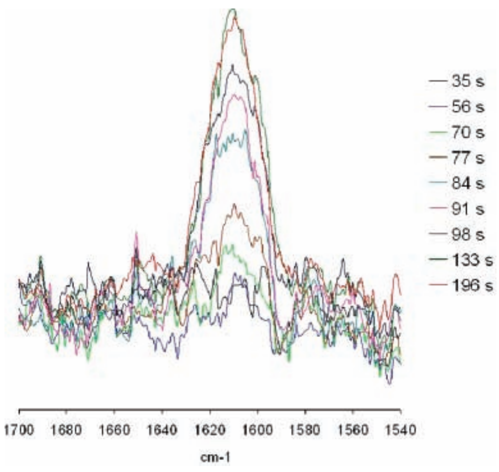

Figure 2. In situ Raman monitoring of the reaction of 4-bromotoluene and phenylboronic acid.

On the basis of these results, we believe that the Suzuki coupling reaction is in competition with the deboronation of the phenylboronic acid. In the case of 4-bromoacetophenone and 4-bromotoluene, the coupling reaction is faster than the deboronation, whereas with 4-bromoanisole, the two processes occur at similar rates. Thus, by the time the reaction had run for 135 s, all the boronic acid had either reacted with 4-bromoanisole or otherwise deboronated. Therefore, the yield of 55% was the maximum that could be achieved regardless of how long the reaction was run. To confirm this assertion, we reran the coupling of 4-bromoanisole and phenylboronic acid but stopped it after 135 s had elapsed. Analysis of the reaction mixture showed a 55% yield of biaryl and no remaining boronic acid (Table 1, entry 4).

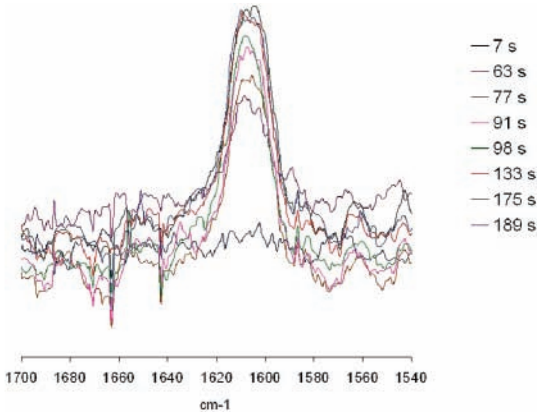

Figure 3. In situ Raman monitoring of the reaction of 4-bromoanisole and phenylboronic acid.

We next screened a range of other aryl halides in the Suzuki coupling protocol. In the case of 2-bromoanisole, no product was observed by Raman monitoring, and this was found to be the case on analysis of the reaction mixture. With 2-iodotoluene and 4-bromobenzonitrile, Raman monitoring showed that couplings took place and were again complete within 135 s. A 35% yield of 2-methylbiphenyl and a 97% yield of 4-cyanobiphenyl were obtained.

In summary, we have shown that the progress of a microwave-promoted Suzuki reaction can be monitored using in situ Raman spectroscopy. Although at this stage the product yield cannot be quantified using this technique, it is possible to see if any reaction occurs and, if so, when it reaches completion. In addition, the monitoring has given us an insight into the reaction, confirming an assertion we had made previously that, when working in aqueous media, the coupling is in competition with the deboronation of the boronic acid. This information is valuable when trying to optimize reaction conditions. Work is now underway to study the effect of varying the microwave power on the reaction and to expand the scope of the in situ monitoring technique to other important synthetic transformations.

Acknowledgment. The University of Connecticut Waring Fund is thanked for funding.

Supporting Information Available: Description of the apparatus, general experimental details, and general procedure for the Suzuki coupling reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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