Use of a camera to monitor reaction stirring and reagent dissolution during a reaction; a MIDA boronate library generation case study.

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Introduction

Stirring of microwave reactions is important as it enables uniform heating of the reaction mixture. Indeed, it has been shown that, upon heating, the reaction temperature in microwaves can differ up to 30 °C between the middle and outside of the reaction vessel in the absence of an efficient stirring process.[1]

In this body of work we have only monitored reactions via an IR thermometer that measures the temperature of the external surface of the vial; this makes effective stirring key when reporting reproducible results. Use of the camera to monitor the reaction allows observations in real time of the effectiveness of stirring and gives a qualitative measure of heat distribution in the microwave vial, without the need for internal optical fiber temperature probes. Real time observation also enables the visual monitoring of the reaction progress such as color change, arcing….

As an example, we have revisited a series of reactions that we recently published and will discuss the synthesis of MIDA boronates from their boronic acid precursors.[2]

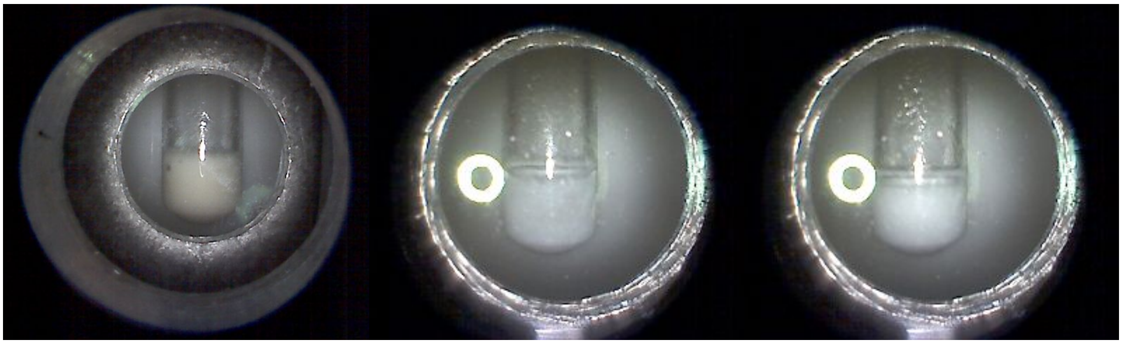
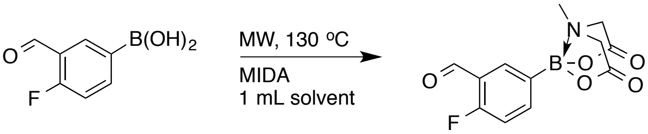


Image 1. From left to right, (a) neat MIDA (1 mmol) in MeCN (1 mL) heated at 130 °C for 4 min. (b) neat MIDA (1 mmol) in DMF (dry 1 mL) heated at 130 °C for 4 min. (c) neat MIDA (1 mmol) in PEG 300 (1 mL) heated at 130 °C for 4 min.

MIDA (N-methyliminodiacetic acid) solubility

When heating MIDA in acetonitrile (MeCN), dimethylformamide (DMF) or polyethylene glycol 300 (PEG) it never achieves complete dissolution (Image 1, note: the small rings are reflections from the LED lighting). On heating the reaction, shown in Scheme 1, to 130 °C it initially appeared cloudy. After maintaining heating for a further 3 minutes the reaction became clear. This shows that the reaction has gone to completion as the MIDA, which is insoluble in unreacted form, has been used up in forming the protected boronate product, which is soluble in hot MeCN (Image 2).



Scheme 1. Reaction in i) MeCN ii) DMF iii) PEG 300.

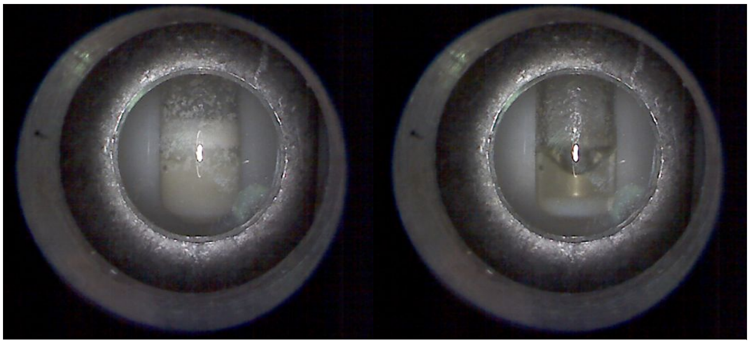


Image 2, (a) Initial reaction mixture; heated to 130 ºC in MeCN. (b) Mixture after a further 3 minutes of heating.

When the reaction was performed in DMF, its progress could be monitored by the disappearance of the cloudy suspension (Image 3). The reaction in PEG 300 did not follow this pattern as at no point did the reaction mixture fully dissolve (Image 4). This is potentially why there is a noticeable difference between the conversions in MeCN and DMF (95% and 97%) compared to that in PEG (69 %).

Stirring in the Microwave

The low solubility of MIDA in the reaction mixture can lead to sedimentation at the bottom of the microwave vial making it difficult to initiate stirring. When the reaction is performed in MeCN its low boiling point causes agitation of the MIDA sediment, which frees the magnetic

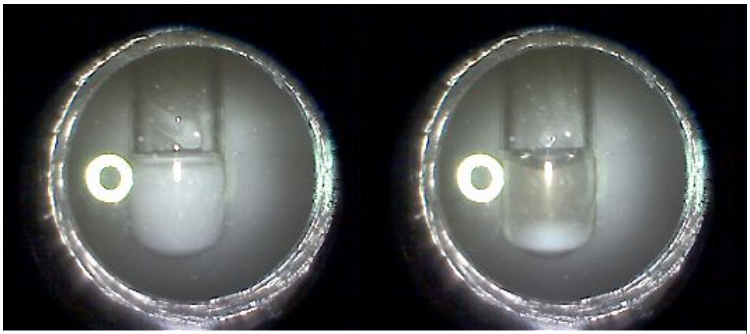


Image 3 (a) Initial reaction heated to 130 ºC in DMF. (b) Reaction after a further 1 minute of heating.

stirrer thus initiating stirring. When the reaction is performed in PEG 300, the viscosity in the reaction medium is higher than in MeCN, and it has been shown to limit the stirring rate in the microwave vial.[3,4] This, along with the sedimentation of the MIDA, causes difficulties in initiating stirring in the reaction vial. Due to the high boiling point of PEG 300, heating to 130 °C does not cause agitation and initiation of stirring, unlike with the more volatile MeCN. We found that using the hot keys to start and stop the stirring and the use of cross-shaped stirrer bars during the heating phase of the reaction helped dislodge the stirrer at the low speed setting, which could be monitored *in situ* via the camera. At elevated temperatures the stirrer could be turned up to a faster setting. A consequence of low speed stirring during the heating phase of PEG 300 was overheating. Upon increasing the stirrer speed, this causes the heat to rapidly transfer from the center to the outer surface of the vial, making the reaction temperature overheat by up to 40 °C in some cases. We found that reducing the maximum power from 200 W to 40 W increased the duration of the heating phase; this allowed for uniform heating at the low stirring rate and removed the problem of overshooting.

In Table 1, below, there are examples of different compounds that have been made via these methods. Note that these are scalable, and have been done in open vessel conditions when using DMF and PEG, as these solvents do not reach their boiling point.

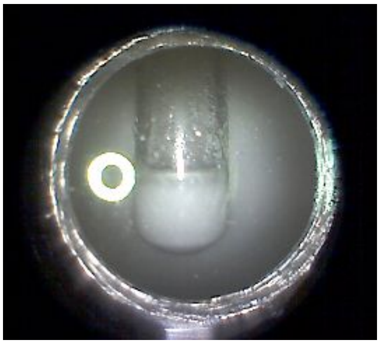


Image 4. Reaction mixture after 4 minutes of heating in PEG 300.

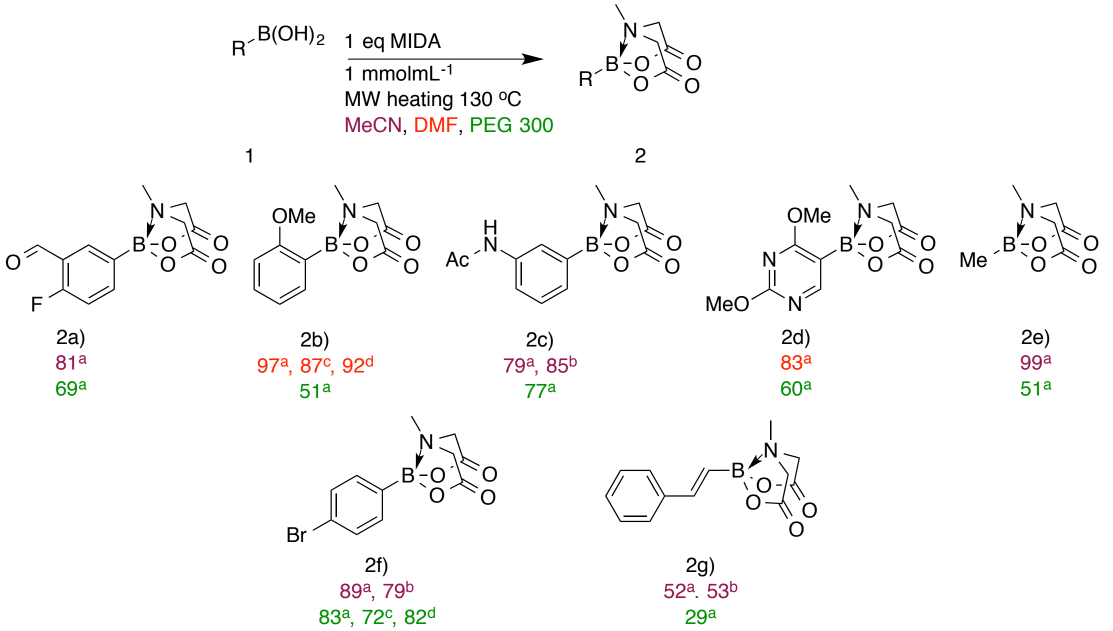


Table 1, Isolated yields (%) for MIDA boronates[2]
[a]1 mmol scale, [b]3.5 mmol scale, [c]5 mmol scale, [d]10 mmol scale

Conclusion

Thanks to qualitative observations, enabled by microwave camera reaction monitoring, we have been able to improve the synthesis of a library of MIDA boronates from their boronic acid precursors. This new method is quick with fast workup times compared with contemporary methods towards MIDA boronates, i.e. with a simple water addition and filtration required (Image 5). i.e. with a simple water addition and filtration required (Image 5).[5–8] This adds to a growing number of publications that demonstrate tangible advantages in monitoring and recording reactions via the use of a camera.[9,10]

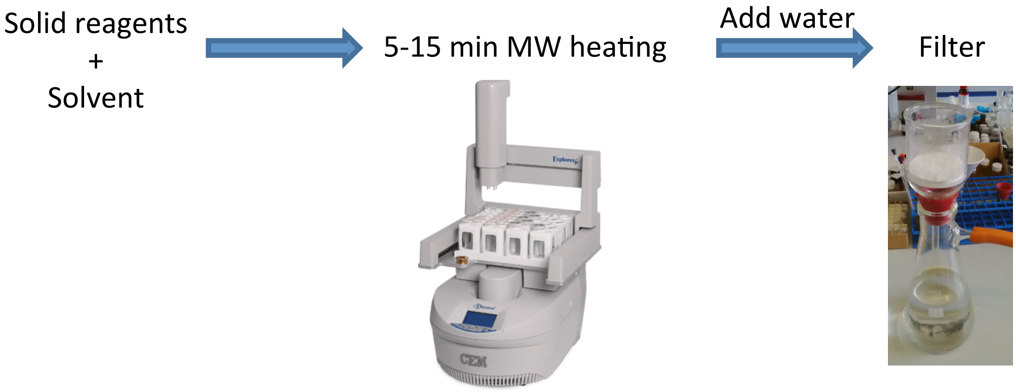


Image 5

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