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Microwave assisted Petasis boronic-Mannich reactions

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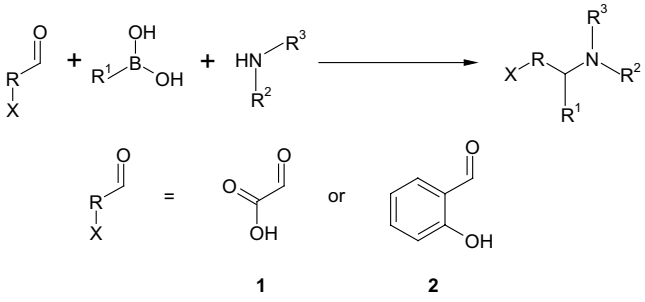
Abstract—We have used a design of experiments (DOE) approach to optimise rapidly a set of microwave assisted conditions for the Petasis reaction. The optimal conditions involved the microwave heating of the reaction components in dichloromethane (1 M concentration) at 120 °C for 10 min in a focussed microwave (CEM Explorer). These conditions were successfully applied to a range of Petasis reactions employing either glyoxylic acid or salicylaldehyde as the carbonyl component along with a number of aryl/heteroaryl boronic acids and amine components.

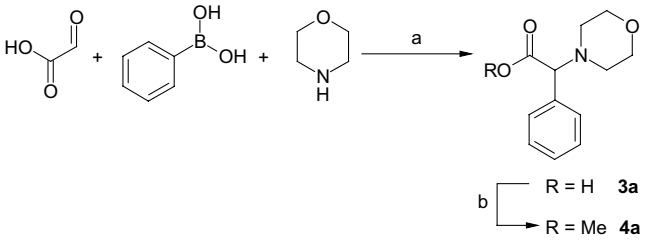
1. Introduction

The Petasis or boronic-Mannich reaction involves the reaction between an aldehyde, an amine and a boronic acid (Scheme 1). The reaction is most frequently carried out with an aldehyde possessing a coordinating group, which can form a boronate complex and thus facilitate the carbon–carbon bond forming step. The two aldehydes most commonly used are glyoxylic acid **1** and salicylaldehyde **2** although other hydroxy aldehydes have also been utilised.[1–8] In general the reaction works well for alkenyl boronic acids and electron neutral or electron rich aryl and heteroaryl boronic acids. The range of amines is also varied with secondary amines performing best and hindered primary amines performing well in some cases. Anilines and hydrazines have also been applied to the Petasis reaction to good effect.[9]



Scheme 1. The Petasis or boronic-Mannich reaction.

In general the reaction conditions employed for the Petasis reaction involve stirring at room temperature for periods of 24 h or more. The solvents employed vary depending on the application and include dichloromethane (DCM), toluene, ethanol and acetonitrile. In some cases refluxing conditions have been employed but these cases usually involve a second transformation in addition to the initial Petasis step.[10,11] In our current work to develop rapid and efficient methods for the synthesis of compound libraries we have sought to speed up multicomponent reactions using focussed microwave sources.[12] In this communication we describe our results achieved when applying this approach to the Petasis reaction of glyoxylic acid and salicylaldehyde, respectively.



Scheme 2. The Petasis reaction of glyoxylic acid, phenyl boronic acid and morpholine and subsequent esterification: (a) microwave irradiation; (b) TMS–diazomethane, THF, rt, 3 h.

Keywords: Petasis; Boronic acid; Mannich; Microwaves; Design of experiments.

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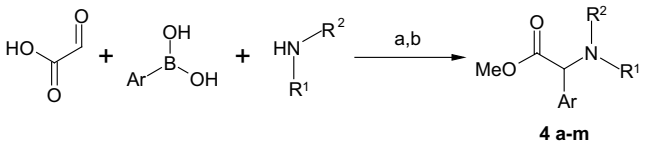
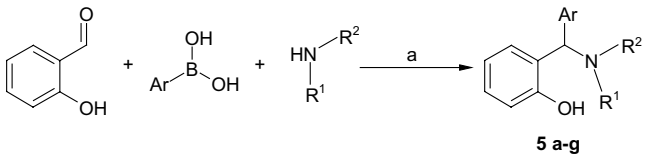


Scheme 3. The Petasis reaction of glyoxylic acid under optimised conditions: (a) microwave irradiation, 120 °C, 10 min, DCM; (b) TMS–diazomethane, THF, rt, 3 h.



Scheme 4. The Petasis reaction of salicylaldehyde under optimised conditions: (a) microwave irradiation, 120 °C, 10 min, DCM.

2. Results and discussion

Initial efforts focussed on the optimisation of the reaction between phenyl boronic acid, glyoxylic acid and morpholine to give the amino acid derivative **3a** (Scheme 2). We used LC–MS to determine the extent of conversion by comparing the integration of the product peak with residual boronic acid in the UV trace. Isolation of product **3a** proved problematic[13] so we opted to transform the crude product to the corresponding methyl ester **4a** in order to simplify the purification process.

Optimisation of the reaction was carried out using a design of experiments (DOE)[14] approach screening reaction temperature (50–100 °C), time (10–30 min), concentration (0.1–0.5 M) and solvent (MeOH or DCM) using a CEM Explorer focussed microwave.[15] The screen determined that DCM was the best solvent, time was of little importance and the temperature and concentration should be high. Two further reactions were carried out in DCM at 1 M concentration, the first at 120 °C for 10 min and the second for 30 min.[16] The conversions were determined to be 63% and 72%, respectively, by LC–MS analysis. The crude products were then esterified and isolated to give the desired product **4a** in 40% and 60% yields, respectively. Although the conversion of the 30 min reaction was marginally higher we chose to adopt the shorter time of 10 min for further studies to increase the throughput of the process.[17]

The optimised reaction conditions were then applied to a range of aryl boronic acids and amines to assess the versatility of the microwave assisted reaction (Scheme 3 and Table 1).

In general the reaction gave moderate to good conversion across a range of boronic acids with the electron poor 4-fluorophenyl boronic acid giving the lowest result as expected (**4d**, 53%). The isolated yields of the ester derivatives were moderate and generally followed the trends of the conversions with the exception of the benzofuran derivative (**4g**, 10%), which was isolated in low yield due to decomposition during chromatography. Of the range of amines employed the secondary amines generally performed best with the exception of diethyl-

Table 1. Scope of the microwave assisted Petasis reaction with glyoxylic acid

Compound	Boronic acid	Amine	Conversion (%)[a]	Yield (%)[b]
4a	Phenyl	Morpholine	63	40
4b	3-MeO-phenyl	Morpholine	78	42
4c	4-Br-phenyl	Morpholine	60	35
4d	4-F-phenyl	Morpholine	53	34
4e	4-*t*-Bu-phenyl	Morpholine	78	31
4f	2-Thiophenyl	Morpholine	100	62
4g	2-Benzofuranyl	Morpholine	66	10
4h	1-Naphthyl	Morpholine	91	65
4i	Phenyl	Aminodiphenylmethane	50	17
4k	Phenyl	Diethylamine	54	18
4l	Phenyl	Dibenzylamine	82	83
4m	Phenyl	*p*-Anisidine	52	27

[a] Conversion to acid assessed by LC–MS.
[b] Isolated yield of ester after column chromatography.

Table 2. Scope of the microwave assisted Petasis reaction with salicylaldehyde

Compound	Boronic acid	Amine	Conversion (%)	Yield (%)
5a	Phenyl	Morpholine	77	76
5b	Phenyl	Aminodiphenylmethane	—	Imine
5c	Phenyl	*p*-Anisidine	—	Imine
5d	Phenyl	Dibenzylamine	nd	50
5e	3-MeO-phenyl	Morpholine	75	62
5f	4-F-phenyl	Morpholine	57	75
5g	2-Benzofuranyl	Morpholine	92	23

amine, which gave only a moderate conversion and the product being isolated in low yield (**4k**, 18%). The hindered primary amine and the aniline derivative gave only moderate conversions as expected.

The microwave assisted protocol was then applied to reactions involving salicylaldehyde (Scheme 4 and Table 2). In this case the product from the Petasis reaction could be isolated directly by column chromatography.[18]

The reaction proceeded well across the range of boronic acids employed. Again the yield of the benzofuran derivative **5g** was low due to poor stability. In contrast to the reaction with glyoxylic acid the range of amines applicable to this reaction was largely reduced with only secondary amines giving the desired products. In the case of the primary amine and the aniline only the intermediate imine could be detected. This observation is consistent with results published by Petasis[4] who only achieved a low yield of product when employing a primary amine in a reaction with a more electron rich boronic acid in a protic solvent. Attempts to catalyse our reaction by addition of acetic acid to the reaction mixture were unsuccessful.

3. Conclusion

We have developed a rapid, microwave assisted protocol for carrying out Petasis reactions of glyoxylic acid or salicylaldehyde, which give comparable results to existing literature methods but only require a 10 min reaction time as opposed to many hours. The method is applicable to a wide range of aryl boronic acids but generally only gives good results when secondary amines are employed. Use of a DOE approach allowed us to rapidly screen reaction conditions against a number of variables and efficiently determine the optimum conditions for the microwave assisted reaction.

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13. Ref. 2 above describes the use of ion exchange chromatography but this was not practical in our hands.
14. We used the MODDE 6.0 programme from Umetrics. See www.umetrics.com.
15. The Explorer microwave is a focussed microwave with a robotic arm. See www.cem.com.
16. The maximum temperature of 120 °C can be achieved in DCM solvent at 300 W power.
17. Typical procedure: Glyoxylic acid (0.5 mmol) was dissolved in DCM (0.5 mL) in a 10 mL microwave tube and the boronic acid (0.5 mmol) was added with stirring. The amine (0.5 mmol) was then added at room temperature and the tube sealed with a pressure cap. The tube was irradiated in a CEM Explorer microwave for 10 min at 120 °C (300 W). After cooling to room temperature the solvent was blown off under a stream of nitrogen gas. The crude residue was dissolved in THF (2 mL) and TMS–diazomethane (1.0 mmol) added dropwise with stirring. After 3 h at room temperature the solvent was evaporated and the product purified by flash column chromatography on silica gel eluting with an appropriate ethyl acetate/hexane mixture. Analytical data for compound **4h**: yield 65%; ^{1}H NMR (400 MHz, $CDCl_3$) 8.52 (1H, d, *J* 8.6), 7.89–7.80 (2H, m), 7.68 (1H, dd, *J* 7.1, 1.0), 7.60–7.42 (3H, m), 4.77 (1H, s), 3.75–3.68 (4H, m), 3.65 (3H, s), 2.63–2.47 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) 183.18 (C=O), 134.39 (C), 132.36 (C), 131.71 (C), 129.52 (CH), 129.04 (CH), 127.8 (CH), 126.79 (CH), 126.26 (CH), 125.71 (CH), 124.56 (CH), 71.37 (CH), 67.43 (CH_3), 52.38 (CH_2), 51.99 (CH_2); MS (ES^+) 286 $(M+H)^+$.
18. Typical procedure: Salicylaldehyde (0.5 mmol) was dissolved in DCM (0.5 mL) in a 10 mL microwave tube. The boronic acid (0.5 mmol) was added with stirring followed by the amine (0.5 mmol). The vessel was sealed with a pressure cap and irradiated in a CEM Explorer microwave for 10 min at 120 °C (300 W). After cooling to room temperature the solvent was evaporated and the crude product purified by column chromatography on silica gel eluting with an appropriate ethyl acetate/hexane mixture. Analytical data for compound **5e**: yield 62%; ^{1}H NMR (400 MHz, $CDCl_3$) 11.67 (1H, s), 7.22 (1H, t, *J* 7.9), 7.15–7.09 (1H, m), 7.06–6.97 (2H, m), 6.95 (1H, dd, *J* 7.6, 1.6), 6.85 (1H, dd, *J* 8.1, 1.2), 6.79 (1H, ddd, *J* 8.2, 2.6, 0.9), 6.73 (1H, dt, *J* 7.5, 1.1), 4.36 (1H, s), 3.77 (3H, s), 3.77–3.74 (4H, m), 2.76–2.40 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) 159.9 (C), 156.06 (CH), 140.93 (CH), 129.97 (C), 129.38 (CH), 128.71 (CH), 124.69 (C), 119.61 (CH), 117.04 (CH), 113.09 (C), 76.84 (CH), 66.92 ($2\times CH_2$), 55.18 (CH_3); MS (ES^+) 300 $(M+H)^+$.