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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 2165–2169

Unusual behaviour of pyridinylboronic acids in the Petasis boronic Mannich reaction

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Received 1 December 2005; revised 19 January 2006; accepted 23 January 2006
Available online 13 February 2006

Abstract—The implementation of the Petasis boronic Mannich reaction in pyridine series allowed us to obtain original compounds whose structure was investigated and determined a stable complex (1:1) of dioxaborolanone and amine.

Combinatorial organic synthesis has been developed over the last decade into an important tool for the generation of libraries of pharmacologically attractive molecules. Compared to traditional synthesis approaches, which involve the separate synthesis of each individual compound, combinatorial strategies produce large numbers of compounds based on a common core structure with a minimum time and effort.

The majority of libraries that have been synthesized to date make use of a linear strategy, consisting of functional group manipulations in a sequential fashion starting with a support-bound functionality. An alternative strategy for the preparation of chemical libraries involves the use of multi-component condensation reactions (MCC), in which three or more reactants are brought together in a single event to produce a final product containing features of all reactants. Compared to the linear strategy, this method therefore allows savings in time and effort since the product is formed in a single step.

Reaction of vinyl boronic acids with the adducts of secondary amines and paraformaldehyde giving tertiary allylamines have been described by Petasis et al.[1] This MCC reaction is a simple and practical method to produce several functionalized and geometrically pure allylamines (Scheme 1).

Then, this reaction was widened in a solution-phase protocol[2–4] for the synthesis of α-aminoacids in one step by a three-component boronic Mannich reaction (BMR) based on simply mixing an aryl or alkenyl boronic acid, an amine and an aldehyde at room temperature.

The reaction was performed with structurally different aldehydes, including alkyl, aryl and heterocyclic aldehydes, under the same reaction conditions and with primary and secondary amines. The Petasis reaction has also been developed in a solid-phase approach by Klopfenstein et al.[5] and Schlienger et al.[6] Several examples of chiral induction using chiral aldehydes and chiral boronic acids have been considered to lead to optically pure aminoacids.[7–10] Recently, the use of boronic esters in the Petasis reaction has been published.[11,12] Finally, optimization of the Petasis reaction under microwave conditions has been described by McLean et al.[13] and Follman et al.[14]

Several examples of this reaction with *m*- and *p*-substituted aryl boronic acids as well as 3-thienyl, 2-thienyl, 2-furyl, 2-benzo[*b*]furyl and 2-benzo[*b*]thienyl boronic acids have been described (Scheme 2).

Nevertheless, to our knowledge, no example using boronic acid bearing strong electron-withdrawing groups has

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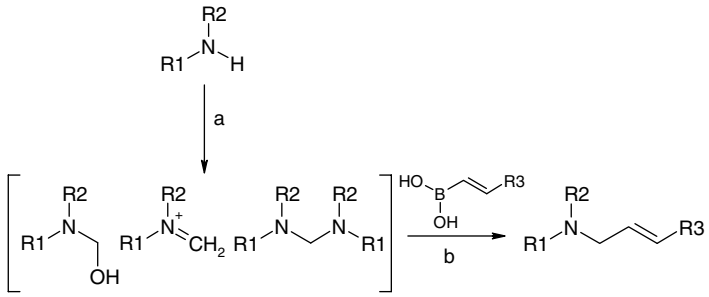
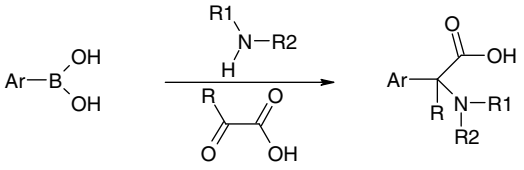
doi:10.1016/j.tetlet.2006.01.115



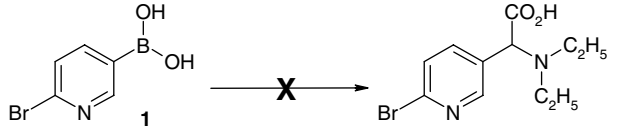
Scheme 1. Reagents: (a) $(CH_2O)_n$ dioxanne or toluene, 90 °C, 10 min; (b) 90 °C, 30 min or 25 °C, 3 h.



Scheme 2.

been described. Interestingly, no study has been reported with electron-poor aromatic boronic acids, and particularly with pyridinylboronic acids.

Therefore, we applied this reaction to novel halogenopyridinylboronic acids recently synthesized and isolated in our laboratory. These compounds are prepared taking into account a regioselective halogen–metal exchange or a regioselective *ortho*-lithiation.[15–18]



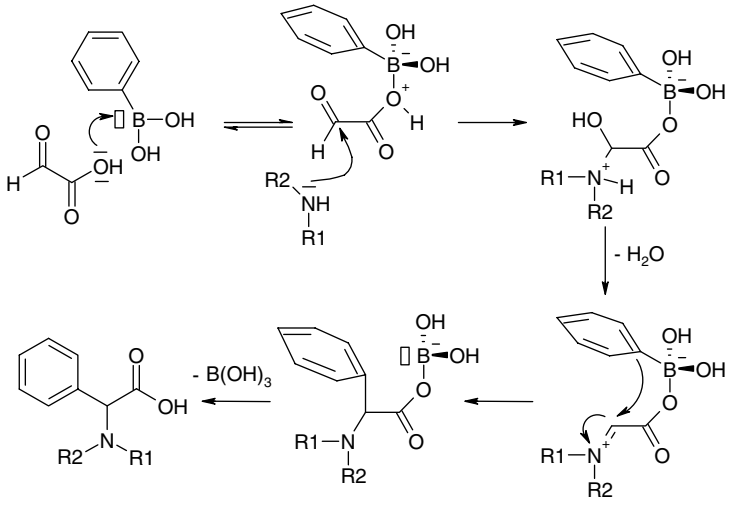
Scheme 3. Reagents: $CHOCOOH{\cdot}H_2O$, 1 equiv, $HN(C_2H_5)_2$, 1 equiv, CH_2Cl_2, 25 °C, 24 h.

Firstly, we chose to apply the Petasis conditions to the 6-bromopyridin-3-yl-boronic acid **1** with glyoxylic acid and diethylamine in dichloromethane at room temperature. After 24 h, a precipitate was formed and isolated as expected but the first analytical data were not in accordance with a pyridylglycine structure (Scheme 3).

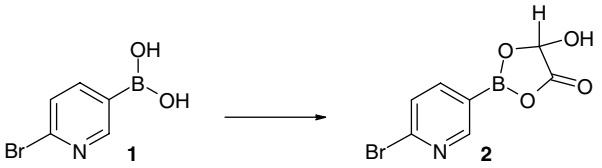
Secondly, we tried to modify the conditions of the reaction using varying solvents and temperature conditions, unfortunately all these attempts remained unsuccessful.

Then, we took into account the results of Schlienger who has found that the order of introduction of the three reactants is very important to improve the yield of the Petasis reaction. The first step of this reaction must be an interaction between the boronic acid and the glyoxylic acid, which forms a tetra-coordinated intermediate playing an essential role in the mechanism of the BMR. The second step of the reaction was an attack of the aldehyde by the amine as illustrated in Scheme 4.

So, we chose to break up the reaction into two steps in order to better understand the mechanism and we applied the Schlienger's conditions to the boronic acid **1** with glyoxylic acid in ethylacetate at room temperature. After 24 h, a white precipitate was isolated in good yield (80%) and characterized by NMR (^1H, ^{13}C,



Scheme 4.



Scheme 5. Reagents: $CHOCOOH{\cdot}H_2O$, 1 equiv, AcOEt, 25 °C, 24 h.

HMBC ^{1}H–^{13}C) as 2-(6-bromopyridin-3-yl)-5-hydroxy[1,3,2]-dioxaborolan-4-one **2** (Scheme 5).[19]

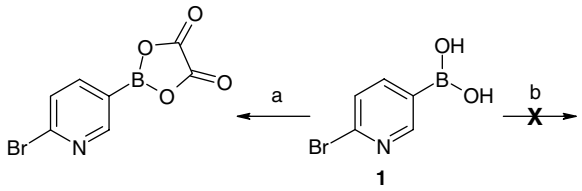
The exact determination of this structure was also based on studies published by Springsteen[20] who described the strong interaction of boronic acids with diols to form boronic esters. Therefore, a suggestion for a mechanism of the formation of the dioxaborolanone involving pyridinium glyoxylate as the aldehyde component is shown in Scheme 6.

The hypothesis that the first step is the reaction of the carboxylate moiety and not the diol one is reinforced by the fact that no reaction occurs with ethylglyoxylate. Furthermore, if the boronic acid is mixed with oxalic acid, the dioxaborolanedione is formed (Scheme 7). Unlike, no complex is observed with acetic acid.

In the same way, we obtained several mixed esters **3**–**9** with corresponding pyridinylboronic acids in good yields (Table 1).

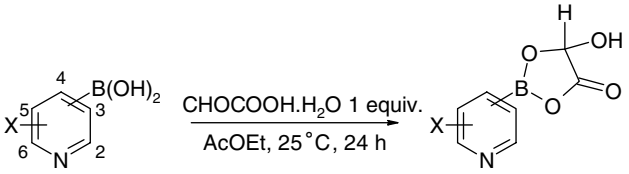
The position of the boronic acid, the position (compounds **2**, **6** and **8**) and the nature of the halogen (compounds **2**, **3** and **4** on the one hand, compounds **7**, **8**, **9** on the other hand) exert no effect on the dioxaborolanone formation even if the position of the halogen has a greater effect on the pyridine nitrogen basicity.

To date, we did not find any description of such dioxaborolanones in aromatic and heteroaromatic series. Indeed, when glyoxylic acid was involved without amine, but with phenylboronic acid, no complex formation was observed and the reaction gave only a gummy mixture of starting materials. Finally, we have not found



Scheme 7. Reagents: (a) $(COOH)_2$, 1 equiv, AcOEt, 25 °C, 24 h. (b) CH_3COOH 1 equiv, AcOEt, 25 °C, 24 h.

Table 1.

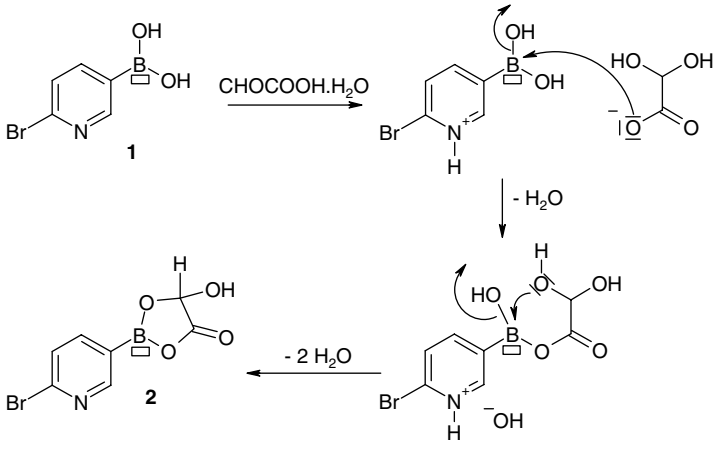


$B(OH)_2$ position	X	Compounds	Yields (%)
3	6-Br	**2**	80
3	6-Cl	**3**	74
3	6-F	**4**	57
2	6-Br	**5**	75
3	5-Br	**6**	62
3	2-Cl	**7**	89
3	2-Br	**8**	78
3	2-F	**9**	36

any relevant study concerning this type of reaction in aromatic and heteroaromatic series.

Then, diethylamine was used to react with the 2-(6-bromopyridin-3-yl)-5-hydroxy[1,3,2]dioxaborolan-4-one **2**. Preliminary results using ^{11}B NMR indicate that the boron was conserved and substitution degree was determinate to be consistent with a tetracoordinated boronate (δ 11.42 ppm, CD_3OD, $B(OMe)_3$, 128 MHz).

Complementary one- and two-dimensional NMR spectra (1D 1H and 13C, 2D 1H–1H NOESY, 1H–13C HMQC and HMBC) suggested that the reaction of the

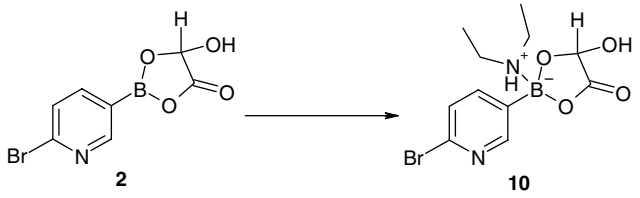


Scheme 6.

dioxaborolanone **2** with diethylamine in dichloromethane at room temperature afforded the (1:1) complex of 2-(6-bromopyridin-3-yl)-5-hydroxy[1,3,2]dioxaborolan-4-one and diethylamine **10** in good yields (78%) but did not lead to expected pyridylglycines (Scheme 8).[21]

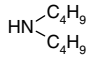
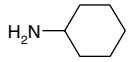
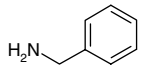
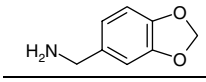
All of dioxaborolanones were used to form complexes with primary and secondary amines with an emphasis parallelization, and 180 complexes were obtained in high purity (>95%).[22] To summarize, Table 2 shows a few examples of complexes synthesized in the same way.

After having suggested the complex structure and with the aim of confirming it, we focused on complexes of boronic esters and amines in the literature. Studies concerning these complexes are disparate and far from our model. However, Finch et al.[23] have described boronates and amines complexes. A general method was given, and the (1:1) complex of 2-phenyl-1,3,2-dioxaborolane with benzyl-amine was synthesized from 1 equiv of boronate and 1 equiv of benzylamine at room temperature. In our case, the reaction of 2-[3-(6-bromo)-pyridine]-4,4,5,5-tetramethyl-1,3-dioxaborolane with diethylamine at room temperature gave the (1:1) complex of 2-[3-(6-bromo)-pyridine]-4,4,5,5-tetramethyl-1,3-dioxaborolane with diethylamine. The conditions we used to implement the Petasis reaction are near to the conditions described to form complexes and we have to take into account the strong affinity of the dioxaborolanones for amines. Moreover, the high stability of our complexes has to be noticed since only strongly acidic conditions can lead to boronic acids whereas boronate complexes rapidly dissociate in aqueous conditions.



Scheme 8. Reagents: $HN(C_2H_5)_2$, 1 equiv, CH_2Cl_2, 25 °C, 24 h.

Table 2. Yields of products resulting from the reaction of dioxaborolanones (**2**, **3**, **4**, **7**, **8** and **9**) and several amines

	2	**3**	**4**	**7**	**8**	**9**
H_2N–$(CH_2)_6$–CH_3	53	58	51	52	63	54
	66	90	68	65	92	72
	88	96	84	80	86	79
	40	60	55	58	56	59
	73	96	85	71	79	84
	95	90	87	91	90	88

In conclusion, the Petasis reaction with pyridinylboronic acids do not lead to expected pyridylglycines. Nevertheless, novel stable complexes have been synthesized and characterized. The synthetic applications of dioxaborolanones have to be developed in order to study their reactivity. Besides, the complexes could have many pharmacological potential applications as, for example, carriers of bioactive amino-compound.

Acknowledgements

The authors thank Dr. Nathalie Schlienger and Dr. Markus Follman for fruitful exchanges in this study. Financial support from Laboratoires Servier, Conseil Régional de Basse-Normandie and FEDER (Fonds Européens de Développement Economique Régional) is gratefully acknowledged.

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19. Typical procedure: To a stirred solution of boronic acid (0.5 g) in 10 mL of ethylacetate was added glyoxylic acid monohydrate (1 equiv). The reaction was then continued at room temperature during 24 h and the white precipitate was isolated by filtration as dioxaborolanones.
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21. Typical procedure: To a stirred solution of dioxaborolanone (0.5 g) in 10 mL of dichloromethane was added amine (1 equiv). The reaction was then continued at room temperature during 24 h and the white precipitate was isolated by filtration as complexes.
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