Stability of Boronic Esters to Hydrolysis: A Comparative Study

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Boronic esters are key intermediates in the synthesis of biologically active compounds such as thrombin and proteasome inhibitors. However, they have low hydrolytic stability both during synthetic reactions and in biological media. We report the preparation of several boronic esters and a comparative study of their stability to hydrolysis vs. the corresponding pinanediol boronic esters, which are among the most hydrolytically stable. We discovered that the boronic esters derived from (1,1′-bicyclohexyl)-1,1′-diol are the most stable among those examined.

Boronic acids and esters play an important role in many fields of chemical research and technology. Examples of important reactions involving boronic acids are the multicomponent Petasis reaction or metal-catalysed Suzuki couplings.

Boronic esters are used as protecting groups and chiral auxiliary agents in highly stereoselective asymmetric synthesis. Particularly useful in organic synthesis is the asymmetric homologation via α-chloroboronic esters, which provides an extremely efficient method for constructing chiral centers.[1]

The reactivity of boronic acids with hydroxy groups has been exploited also by medicinal chemists for the synthesis of potent and selective peptide boronic inhibitors of thrombin[2] and proteasome.[3]

Our group has been involved in recent years in the search for novel proteasome inhibitors endowed with superior activity and reduced side effects.[3] Boronic esters were one of the key intermediates in the synthesis and a prodrug of the bioactive compound because of their stability at neutral pH and reduced stability in the acidic environment of tumor cells. Hence, their hydrolytic stability both during synthetic reactions and in a biological medium was one of the major problems we faced.

A detailed study on the stability of several boronic esters has already been published by Roy and Brown.[4] In this paper we present further investigations on this subject with the different aim to find new and more stable boronic esters.

For this purpose, an ^{1}H NMR comparative study has been performed to evaluate the hydrolytic stability of a number of isobutylboronic acids with respect to model compound **1** (pinanediol ester; Figure 1).[5]

The most promising diols were also reacted with 2-phenethylboronic acid in order to evaluate the hydrolytic stability of the resulting esters both by ^{1}H NMR and HPLC. In this case the model compound was derivative **2** (Figure 1).

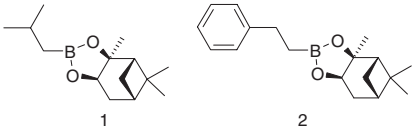


Figure 1. Chemical structures of model compounds **1** and **2**.

Further details of the different classes of compounds are reported in the following sections.

The empty p-orbital of boron is susceptible to interactions with electron donor atoms (dative bonds). Roy[4] showed that the trans-esterification rate of boronic esters with diols is increased by a nitrogen atom in the diol chain.

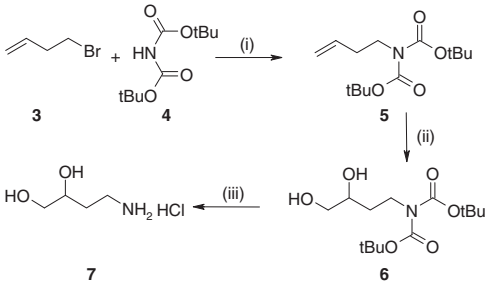
On the contrary, interaction with electron donors could stabilize boronic esters diols rendering them less prone to nucleophilic attacks. We tried to stabilize our cyclic boronic esters with extra oxygen or nitrogen atoms capable of coordinating the boron atom forming stable complexes. Examples of such complexes are known in the literature.[6]

The diols utilized for the synthesis of boronic esters are commercially available except **7** and **9**. (*RS*)-4-Aminobutane-1,2-diol[7] hydrochloride (**7**) (Scheme 1) was obtained by reaction of 4-bromobut-1-ene (**3**) with di-*tert*-butyl iminodicarboxylate (**4**) in the presence of potassium carbonate to give derivative **5**. The subsequent steps were the Upjohn dihydroxylation with osmium tetraoxide followed by Boc removal with hydrogen chloride.

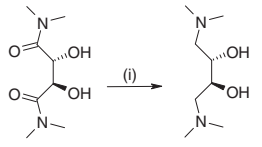
(2*S*,3*S*)-1,4-Bis(dimethylamino)butane-2,3-diol (**9**)[8] was obtained by reduction with lithium aluminum hydride of the corresponding amide **8** (Scheme 2). The general procedure for the synthesis of boronic esters consists of the reaction between isobutylboronic acid or 2-phenethylboronic acid, dissolved in diethyl ether, with a stoichiometric amount of the appropriate 1,2- or 1,3-diol (Scheme 3). Table 1 summarizes the results of the hydrolytic stability studies on the synthesized boronic esters compared to compound **1**. Unfortunately, none of the studied diols gave a boronic ester having the hydrolytic stability superior to that of **1**.

After 1 h under the ^{1}H NMR test conditions these esters were hydrolyzed to a significant extent or even completely.

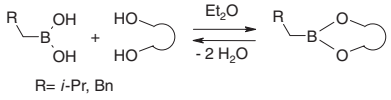
During hydrolysis, water molecules presumably attack the boron p-orbital from the less hindered face. Accordingly to Roy[4] observations, the increase of diol steric hindrance slows



Scheme 1. Reagents and conditions: (i) K_2CO_3, DMF, rt, 16 h; (ii) NMO, OsO_4, 2.5% w/v in *t*-BuOH, acetone/water 1/1; (iii) 4.0 M HCl aq, MeOH, rt, 12 h.

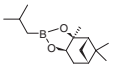
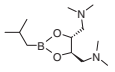
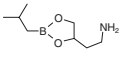
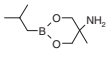
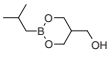


Scheme 2. Reagents and conditions: (i) $LiAlH_4$ 1.0 M in THF, 24 h, Et_2O, rt.



Scheme 3. General procedure for the synthesis of boronic esters **1**, **2**, and **10**–**17**.

Table 1. Hydrolysis of compounds **1** and **10**–**13**

Compd	Structure	Time/h	Hydrolysis/%[a]
1		1	0
		24	2
10		1	100
11		1	80
12		1	100
13		0.1	100

[a]From ^{1}H NMR integral data.

down boronic acid esterification. Our study demonstrates that the hydrolysis rate of the corresponding boronic ester is also reduced.

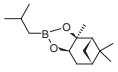
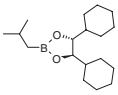
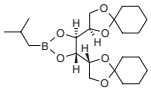
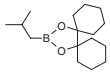
In order to extend hindrance to both faces of the complex, we synthetised esters of isobutylboronic acid with (1*R*,2*R*)-(−)-1,2-dicyclohexyl-1,2-ethandiol, 1,2:5,6-di-*O*-cyclohexylidene-D-mannitol, and (1,1′-bicyclohexyl)-1,1′-diol.[9] As shown by the data reported in Table 2, these esters have a stability comparable or superior to **1**.

In particular, the boronic ester of the (1,1′-bicyclohexyl)-1,1′-diol **16** was much more stable to hydrolysis than the corresponding pinanediol ester **1**. The derivative **16** was hydrolysed only to a barely detectable extent after 135 h in the ^{1}H NMR test conditions.

The most interesting diol, (1,1′-bicyclohexyl)-1,1′-diol, was also reacted with 2-phenethylboronic acid to study the hydrolysis of the resulting boronic ester compared to compound **2**, both by ^{1}H NMR and HPLC. The results are summarized in Table 3. Once again, compound **17** containing (1,1′-bicyclohexyl)-1,1′-diol showed a greatly enhanced stability toward hydrolysis versus the corresponding pinanediol ester **2**.

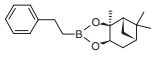
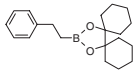
Among the favourable features of (1,1′-bicyclohexyl)-1,1′-diol are also a low molecular weight and an easy supply by pinacol synthesis.[10]

Table 2. Hydrolysis of compounds **1** and **14**–**16**

Compd	Structure	Time/h	Hydrolysis/%[a]
1		1	0
		24	2
14		1	0
		24	4
15		1	0
		24	4
16		1	0
		60	0
		135	0.2

[a]From ^{1}H NMR integral data.

Table 3. Hydrolysis of compounds **2** and **17**

Compd	Structure	Time/h	Hydrolysis/%[a]	
			NMR	HPLC
2		1	3.0	0
		21	4.9	0.4
17		1	0.1	0
		21	0.7	0

[a]From ^{1}H NMR integral data.

Our study of the stability of boronic esters to hydrolysis has shown that the most important factor affecting this reaction is the steric hindrance created around the boron atom by the diol moiety. We discovered that boronic esters of (1,1′-bicyclohexyl)-1,1′-diol as **16** and **17** are much more stable to hydrolysis with respect to pinanediol boronic esters **1** and **2**.

References and Notes

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