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Two Reducible Protecting Groups for Boronic Acids

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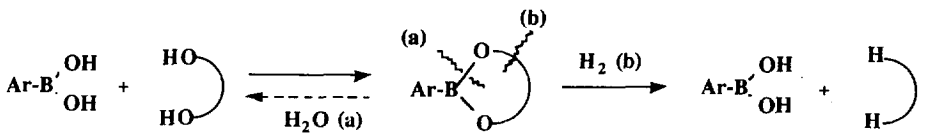
Abstract: *New boronic acid protecting groups, which undergo deprotection under mild conditions, are presented.* Copyright © 1996 Elsevier Science Ltd

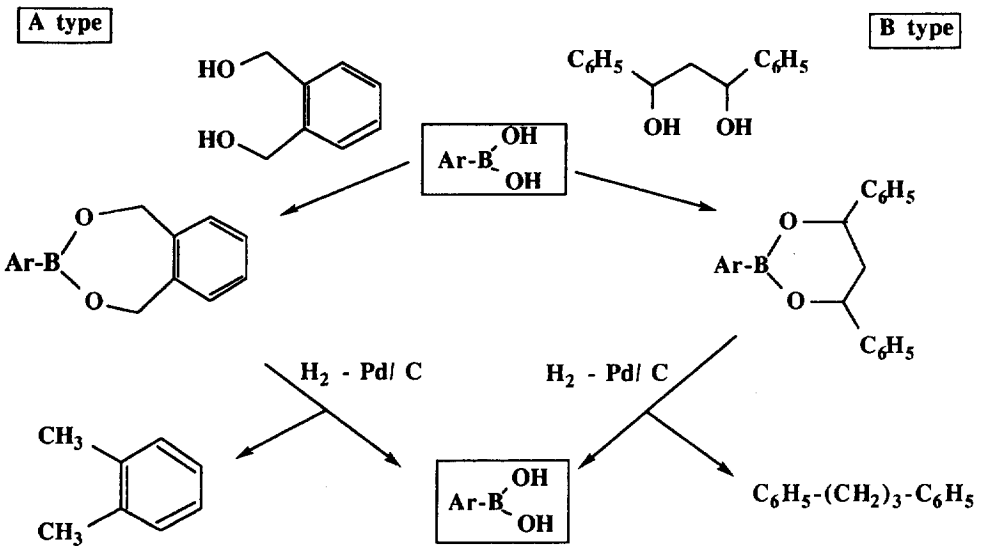
Boron analogues of biomolecules [1] are of current interest as transition state inhibitors and as vectors for use in boroneutrotherapy;[2] recognition processes based on interactions with boronic acids are also receiving increasing attention [3] as is the transport by boron substrates of water-insoluble compounds across membranes, a concept coined "boradeption".[4] When protection of the boronic acid is needed during preparation of an analogue, a diester (boronate) is used; however regeneration/isolation of the free boronic acid is not always trouble-free in that the diol, which in most cases is water soluble, must be eliminated due to an equilibrium (see equation); in addition, some esters are too stable to hydrolysis. Thus biological evaluation of boronic acids derivatives has quite often been performed on the corresponding boronates, which have been considered "pro-substrates".[5] While other deprotection methods exist (*e.g.* transesterification processes, [5-9] use of sodium periodate[7] or boron trichloride [10]) there is definitely the need for additional effective procedures. We now disclose two readily introduced boronic acid protecting groups which undergo efficient deprotection under particularly mild conditions.

In contrast to solvolytic processes in which B-O bonds are cleaved (path a), reductive cleavage of the adjacent O-C bonds (path b) would lead to the boronic acid and an hydroxyl-free by-product. Involving no equilibrium now, this would allow a straightforward separation of the free boronic acid from the lipophilic species formed after reduction. Hence reducible protecting groups, particularly benzylic type esters were considered.



Given the known stability of cyclic boronates, [11,12] several cyclic benzylic boronates were evaluated and it was shown through model experiments carried out with benzeneboronic acid (Ar = C_6H_5) that esters of type A and B were satisfactory. Such esters are quantitatively formed by esterification with the readily available 1,2-benzenedimethanol [13] and 1,3-diphenylpropane-1,3-diol [14], respectively, in the presence of a dehydrating agent.

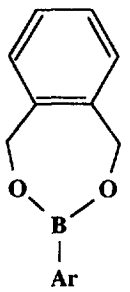
Regeneration of the boronic acid could be efficiently performed by catalytic hydrogenolysis. In the case of A , filtration of the reaction mixture followed by evaporation of the volatiles affords directly benzeneboronic acid as the sole compound, whereas in the case of B, the separation of the non-volatile 1,3-diphenylpropane can be easily performed by extractive work-up.



The choice of the particular ester, A or B, for transient protection, depends on the following considerations: both boronates A and B can be chromatographed, but A-type esters are nonetheless quite susceptible to hydrolysis; with A however, the nmr resonances of the protecting group are simple, and furthermore after hydrogenation simple evaporation of the volatiles affords directly the boronic acid with no further purification needed. For B-type esters, both diastereomers of the diol are equally effective, but due to the presence of diastereotopic protons in the *meso* isomer, which complicates the ^{1}H-nmr spectra,[14] use of the more readily available d,l compound [14,15] is preferred. Stability studies performed on the corresponding ester have shown good aqueous stability and only slow loss in 2M trifluoroacetic acid/CH_2Cl_2 (90 % recovery after 1 day);[16] in contrast, it is not stable to aqueous base (1M NaOH), thus giving an alternative deprotection method since 1,3-diphenylpropane-1,3-diol can be extracted into organic solvents.

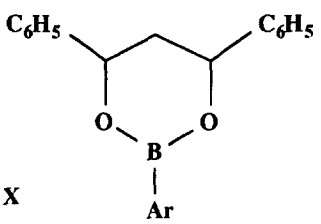
As shown in the accompanying table, this procedure has been satisfactorily applied to various phenylboronic acids. To underscore its synthetic utility, it has been used for purification of the reaction mixture obtained after reaction of ferrocene and boron tribromide: thus, reaction of the crude with an excess of 1,2-benzenedimethanol gave the corresponding ferroceneboronic A-type ester, which was sufficiently stable for chromatographic purification; this was followed by hydrogenolysis to give pure ferroceneboronic acid.[17] On the other hand, during an enantiospecific synthesis of 4-borono-*L*-phenylalanine, [18] the B-type protecting group was used, which permitted effective purification of the coupling product.[19] It is anticipated that other applications are possible, several of which are currently being explored in our laboratory.

A-type



Ar = -C_6H_4-X

B-type



A-type	B-type
X = H (98-100°C; 98%)[20]	X = -H (139°C; 100 %)[e,20]
X = *p*-OH (155°C; 75%)[21]	X = *p*-OH (oil; 97%)[21]
X = *p*-OTHP (137-9°C; 86%)[a,22]	X = *p*-COOH (248-50°C; 93%)[25]
X = *p*-CHO (175-6°C; 97%)[b,23]	X = *p*-CHO (oil; 96%)[b,e,23]
X = *p*-Br (177-8°C; 96%)[c,24]	X = *p*-Br (108-9°C; 97 %)[c,e,24]
	X = *p*-CH_3 (100-1°C; 98%)[e,26]
	X = *o*-CH_3 (oil; 96%)[d,e,f,27]

Table : Esters prepared (m.p., deprotection yield, literature reference to the free boronic acid).
a) it is necessary to pre-wash the glassware with base to avoid deprotection of the THP group.
b) gives p-tolylboronic acid (ref. 25) upon deprotection. c) gives phenylboronic acid (ref. 20).
d) formation of the ester is much slower (2 days), presumably due to steric hindrance.
e) for catalytic hydrogenation, THF is added due to insolubility of the ester in methanol.
f) in this case, chromatography is necessary to isolate the product.

General experimental procedure :

- Formation of the boronates : A solution of equimolar amounts of the boronic acid and the diol in THF is stirred for 15 minutes, then dried (Na_2SO_4), filtered, and evaporated to give the desired boronate in quantitative yield. Characteristic nmr resonances for A-type esters : CH_2 : 5.1-5.2 ppm; CH_2 : 66 ppm; ^{11}B : 27.5 ppm (broad). Characteristic resonances for B-type esters : CH_2 : 2.3 ppm, OCH : 5.3 ppm; OCH : 70 ppm; ^{11}B : 28.5-29.5 ppm (broad).

- Reductive cleavage of the boronates : A 0.2-0.3 M solution of the boronate in methanol is hydrogenated overnight (the presence of 3-5 % acetic acid decreases the reaction time to a few hours), in the presence of 10 % Pd/C (20 % w/w), then filtered through Celite. The Celite was washed with dichloromethane, methanol, and then water, and the combined filtrates concentrated under reduced pressure to afford the boronic acid. In case of B-type esters, it is necessary to remove the 1,3-diphenylpropane through extraction of the residue 3 x with dichloromethane under sonication.

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