# Concise synthesis of ω-borono-α-amino acids

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**A short protocol for the practical scale synthesis of several ω-borono-α-amino acids is described *via* the alkylation of benzophenone glycinimines with various electrophiles.**

Boronic acids $-B(OH)_2$ often function as inhibitors for various enzymes due to their unique electronic and physicochemical properties.[1] The $pK_a$ values and stereo-electronics of boronic acids are similar to those of carboxylic acids. Aminoboronic acids mimic natural amino acids and act as bioisosteres in many biochemical reactions. The mechanism of action is believed to be the nucleophilic attack of an enzyme on to the electron deficient $sp^2$ boron of boronic acid, resulting in the $sp^3$ hybridized boron "ate" complex.[1,2] While the carboxylic acid–enzyme tetrahedral complex is unstable, the corresponding boronic acid–enzyme "ate" complex is highly stable resulting in the inhibition of the enzyme (Fig. 1).

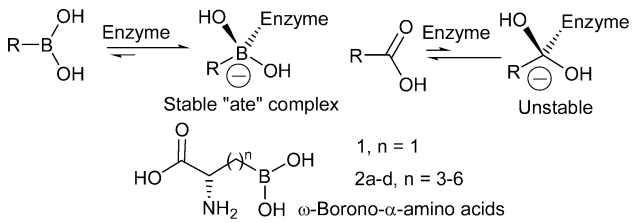


**Fig. 1** Binding of boronic acids with enzymes.

It is well established that ω-borono-α-amino acids (**1**, **2a–d**, Fig. 1) act as potent inhibitors of several enzymes such as serine protease, arginase, dihydroorotase and dipeptidyl peptidase.[3] There have been numerous reports in the literature about the utility of aminoboronic acids as pharmaceutical agents *e.g.* Velcade® **3**, Talabostat **5**, *etc.* (Fig. 2).[4]

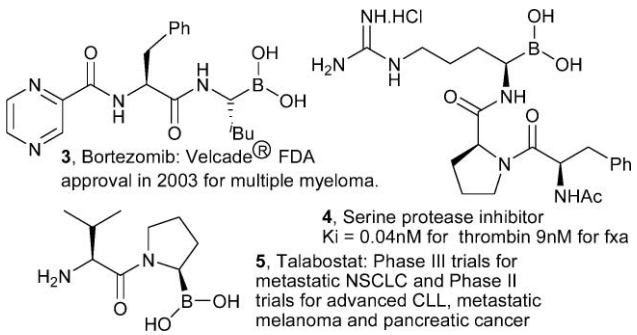


**Fig. 2** Aminoboronic acids as pharmaceutical agents.

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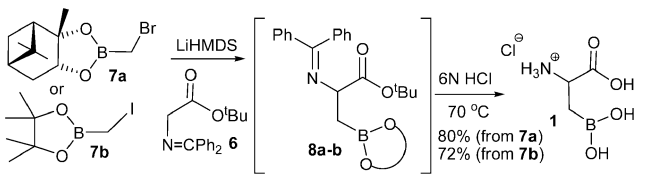
Owing to the general importance of aminoboronic acids in various areas of medicinal chemistry, and also their being the precursors in our ongoing project involving the synthesis of boronic acid based folate antagonists, we required multigram quantities of ω-borono-α-amino acids. However, the current procedures available for preparing aminoboronic acids are somewhat limited for large scale applications.[5] Hence highly tunable, inexpensive, and practical procedures for the synthesis of aminoboronic acids are highly desirable. We envisaged that the alkylation of glycinimine Schiff base **6**, with halomethyl boronate electrophiles **7a–b** should provide protected aminoboronates that upon acidic hydrolysis could readily afford β-boronoaspartic acid **1**.[6] In addition, we also envisioned that the glycine esters alkylated at the α-position with terminal alkenyl groups upon hydroboration and subsequent hydrolysis should provide the remaining ω-borono-α-amino acids **2a–d**. Our results on the synthesis of ω-borono-α-amino acids are described below.

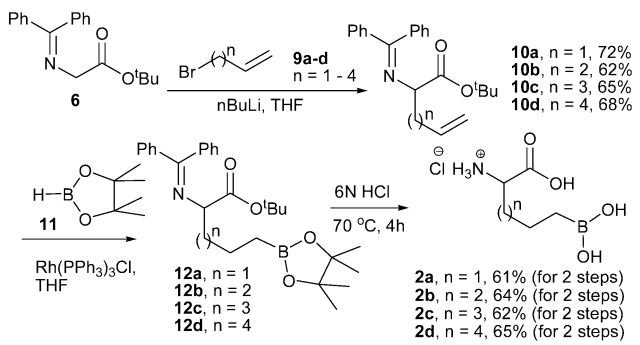
We initiated the synthesis of β-boronoaspartic acid **1** with the preparation of halomethylboronates **7a–b**. Bromomethyl pinanediolboronate **7a** was prepared by the reaction of dibromomethane with triisopropylborate in the presence of $^n$BuLi and TMSBr, followed by transesterification with pinanediol.[7a] α-Iodomethylpinacol boronate **7b** was synthesized by the reaction of *B*-isopropoxypinacolboronate with lithiated $CH_2I_2$.[7b] The alkylation of benzophenone glycinimine **6** with both **7a** and **7b** provided the unstable intermediates **8a–b**. Heating **8a–b** with 6 N HCl at 70 °C led to the simultaneous hydrolysis of the $^t$butyl ester to carboxylic acid, benzophenone imine to the amine, and the pinacol/pinanediolboronate to the boronic acid. Washing with $CH_2Cl_2$ to remove the organic by-products such as benzophenone, and pinanediol/pinacol, followed by concentration of the aqueous layer and trituration with acetone provided the β-boronoaspartic acid **1** as a white hygroscopic powder. The reaction with the more stable pinanediolboronate **7a** provided higher yield (80%) as compared with the relatively unstable pinacolboronate **7b** (72%) (Scheme 1).




**Scheme 1** Synthesis of β-borono-α-aspartic acids.

After accomplishing the synthesis of β-boronoaspartic acid **1**, we embarked upon the synthesis of the other ω-borono-α-amino acids **2a–d**. We chose commercially available and inexpensive ω-halo-1-alkenes **9a–d** as the electrophiles for the alkylation of

glycinimine. The requisite α-substituted glycine esters **10a–d** were obtained *via* the alkylation of Schiff base **6** with various ω-bromo-1-alkenes (**9a–d**) in very good yields. Pinacolborane **11** was chosen as the hydroborating agent because of its relative inertness towards several functional groups for achieving chemoselective hydroboration. Moreover, the corresponding pinacolboronates obtained *via* hydroboration are also air-stable and can be readily chromatographed over silica gel without decomposition or hydrolysis. Hydroboration of alkenes with pinacolborane proceeds very slowly even at elevated temperatures. However, the rate of hydroboration can be tremendously increased by the addition of transition metal catalysts.[8] Accordingly, hydroboration of these terminal olefins **10a–d** with pinacolborane **11** was performed in the presence of Wilkinson's catalyst. To our delight, hydroboration proceeded with utmost ease and the corresponding pinacolboronates **12a–d** were obtained in high regioselectivity favoring the terminal position of the olefin. Hydrolysis of the resulting boronates by heating with 6 N HCl, followed by trituration with acetone provided the ω-borono-α-amino acids **2a–d** as white hygroscopic solids (Scheme 2). As compared with the previous synthesis of these ω-borono-α-amino acids, the current protocol is operationally simple and readily assembles the boronic acids in 3 steps in an overall yield of 40–45% starting from the glycinimine Schiff base. We were able to demonstrate the robustness of the protocol *via* the synthesis of multigram quantities of β-borono aspartic acid **1** as well as γ-boronoarginine **2a**.




**Scheme 2** Synthesis of ω-borono-α-amino acids.

In conclusion, we have developed a preparative scale procedure for the synthesis of β-boronoaspartic acid *via* the alkylation of benzophenone glycinimine Schiff base with halomethyl boronates. We have also developed a simple and practical procedure for the synthesis of various other ω-borono-α-amino acids *via* the alkylation of benzophenone glycinimine with bromoalkenes, followed by catalytic hydroboration with pinacolborane and hydrolysis. As the chemical tolerance of pinacolborane towards several functional groups is well precedented, the present methodology provides an opportunity for the synthesis of several boronated analogs of amino acids. Given the simple experimental techniques, inexpensive starting materials, and the importance of aminoboronic acids, we believe that the present methodology would be highly amenable for large scale synthesis and would attract the attention of organic and medicinal chemists.

## Experimental

### Synthesis of β-boronoaspartic acid 1

To a stirred solution of benzophenone glycinimine **6** (5.90 g, 20 mmol) in THF, was added LiHMDS (22 mL, 22 mmol, 1 M solution) at −78 °C followed by α-bromomethylpinanediolboronate **7a** (6.56 g, 24.0 mmol) dissolved in 10.0 mL THF and stirred for 5 h. The reaction mixture was worked up with ether and water. The combined organic layers were dried ($MgSO_4$), concentrated, and the complete hydrolysis of the crude mixture was achieved by heating at 70 °C for 4 h in the presence of 6 N HCl (40 mL). The organic by-products were removed by washing the aqueous layer repeatedly with $CH_2Cl_2$ (3 × 40 mL). The aqueous layer was concentrated in vacuum at 40 °C to afford a white powder. Trituration with acetone and $CH_2Cl_2$ provided 2.72 g of pure β-boronoaspartic acid **1** in 80% overall yield. $^1$H-NMR (500 MHz, $D_2O$): $\delta$ 4.17 (1H, dd, *J* 7.0 and 9.7), 1.37 (1H, dd, *J* 7.0 and 14.9), 1.20 (1H, dd, *J* 10.0 and 15.0); $^{13}$C-NMR (125 MHz, $D_2O$): $\delta$ 175.2, 52.5, 18.7 (br); ESI-MS: 191 [$(M - H + Na)^+$, 100%]$^+$.

### Synthesis of ω-borono-α-amino acids

Pinacolborane **11** (0.86 mL, 6 mmol) was added to a solution of Wilkinson's catalyst (277 mg, 0.3 mmol, 5 mol%) in 10 mL dry THF and stirred for 30 minutes. Alkene **10c** (1.6 g, 4 mmol) was added slowly and stirred overnight. The reaction mixture was worked up with ether and water. The organic layer was concentrated *in vacuo* and the residue was heated at 70 °C for 4 h in the presence of 6 N HCl (20 mL) so as to affect complete hydrolysis. Work up with $CH_2Cl_2$ to remove organic by-products and concentration of the aqueous layer *in vacuo* at 40 °C yielded a white powder. Trituration with acetone provided 0.56 g (62% combined yield for two steps) of the aminoboronic acid **2c**. $^1$H-NMR (500 MHz, $D_2O$): $\delta$ 3.82 (1H, t, *J* 6.2), 1.70–1.90 (2H, m), 1.05–1.45 (6H, m), 0.77 (2H, t, *J* 7.9); $^{13}$C-NMR (125 MHz, $D_2O$): $\delta$ 172.4, 53.6, 31.4, 30.1, 28.1, 24.0, 17.0; ESI-MS: 244 [$(M + H + H_2O)^+$, 100%], 226 $(M + H)^+$.

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