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Synthesis of Boronocysteine

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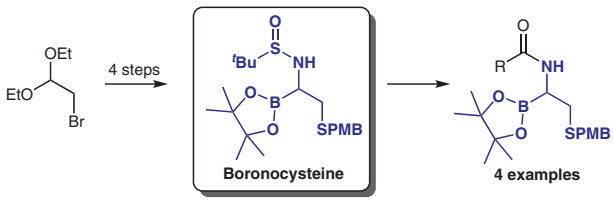

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Abstract Herein we report the first synthesis of protected boronocysteine. The target compound was prepared via copper-catalysed diastereoselective nucleophilic borylation of a sulfinimine. After deprotection to give the amine as the hydrochloride salt, four boronocysteine amide derivatives were prepared through reaction with a variety of different active acylating agents.

Key words amino acids, boron, copper, imines, peptides

α-Aminoboronic acids have attracted considerable attention as analogues of amino acids with potential applications in medicinal chemistry.[1] Bortezomib (Velcade®), a peptide analogue incorporating an α-aminoboronic acid used in cancer treatment, became the first drug on the market containing a boron atom (Figure 1). Subsequently, other α-aminoboronic acid derivatives have reached the market including ixazomib and delanzomib. The synthesis of α-aminoboronic acids has proved to be especially challenging, however, as free α-aminoboronate compounds readily undergo rearrangement to *N*-boryl compounds leading to protodeboronation.[2]

Nevertheless, Matteson was able to carry out the first synthesis of an α-aminoboronic acid derivative in 1966 starting from iodomethylmercuric iodide (Scheme 1).[3] He was subsequently able to access a wider range of α-aminoboronic acids via rearrangement reactions of boronate esters using dichloromethyllithium.[4] Alternative approaches to α-aminoboronic acid derivatives have included copper-catalysed nucleophilic borylation of imines,[5] alkylation of α-sulfenyl boronates followed by nucleophilic displacement of the sulfur,[6] Curtius rearrangement of α-borylcarboxylic acids,[7] and lithiation/borylation of protected amine derivatives.[8] Notably, whilst a wide range of α-aminoboronic acid derivatives have been reported,[4–9] there are relatively few examples containing heteroatomic functional groups on the side chain.[10] For an ongoing project involving the study of peptides containing C-terminal cysteine derivatives,[11] we required access to the boron analogue of cysteine. Interestingly, no previous synthesis of this compound (or a protected derivative) has been reported in the literature. Herein,

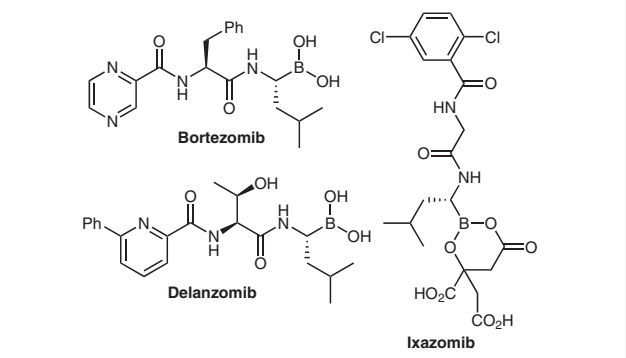
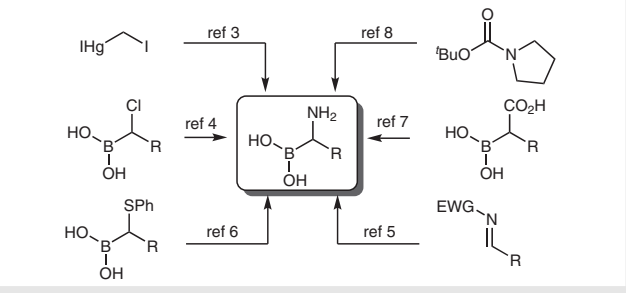


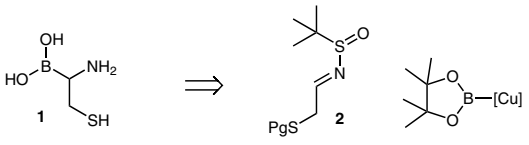
Figure 1 Medicinally useful α-aminoboronic acid derivatives



Scheme 1 Synthetic approaches to α-aminoboronic acid derivatives

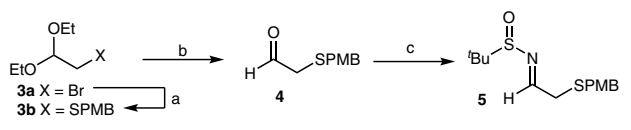
we report a concise synthesis of protected boronocysteine, and its use in the synthesis of *N*-acyl derivatives including dipeptide analogues.

Matteson has previously noted that rearrangement of a thioether-functionalised alkylboronate using dichloromethyllithium was unsuccessful, probably due to loss of a sulfur-stabilised carbanion from the 'ate' complex.[12] We therefore envisaged that boronocysteine **1** could readily be constructed by Cu-catalysed borylation of a suitably protected sulfinimine **2** (Scheme 2).[5] The required imine **2** should be readily available from commercially available bromoacetaldehyde diethyl acetal.



Scheme 2 Proposed synthetic strategy for preparing boronocysteine

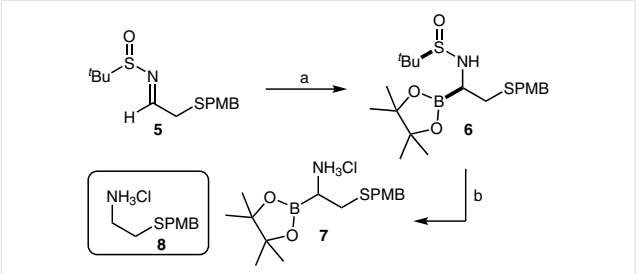
Bromoacetaldehyde dimethyl acetal **3a** was converted into the corresponding sulfide **3b** by reaction with *p*-methoxybenzyl thiol (PMBSH) and sodium hydroxide (Scheme 3).[13] After deprotection of the acetal, the aldehyde **4**[14] was then converted into sulfinimine **5** through condensation with the sulfinimide.



Scheme 3 Synthesis of imine **5**. *Reagents and conditions*: a. NaOH, PMBSH, EtOH, 52%; b. HCl, acetone, 99%. c. ^{t}BuSONH$_2$, CuSO$_4$, CH$_2$Cl$_2$, 80%.[16]

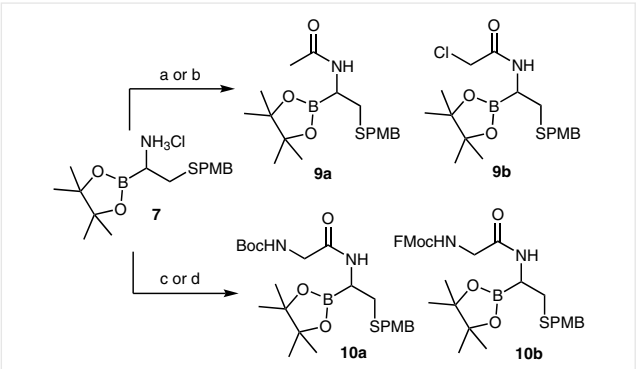
With the required sulfinimide in hand, the Cu-catalysed borylation reaction was investigated. Pleasingly, by using CuCl in the presence of KO^{t}Bu and *rac*-BINAP as a ligand,[5a] the desired boronate **6** was obtained in 60% isolated yield as a single diastereoisomer (Scheme 4). As reported previously, the sulfinimide could be removed using HCl to give the corresponding α-aminoboronate as the hydrochloride salt **7**.[5a] This compound required careful handling as it readily underwent protodeboronation to give the corresponding 2-aminoethylthio ether **8**.[15] For example, deboronated compound **8** was obtained when **6** was exposed to HCl for 24 h instead of the 3 h reaction time required to produce **7**.

We were, however, able to prepare boronocysteine amides derived from **7** through reaction with appropriate acylating reagents (Scheme 5). Thus, reaction of **7** with acid chlorides provided the acetamide **9a** and chloroacetamide



Scheme 4 Copper-catalysed borylation of imine **5** and sulfinamide deprotection. *Reagents and conditions*: a. CuCl, (±)-BINAP, KO^{t}Bu, B$_2$pin$_2$, THF, 60%;[17] b. HCl, dioxane, MeOH, 82%.[18]

9b. Dipeptide analogues **10** were obtained through reaction with either an *in situ* generated mixed anhydride **10a**, or a pre-formed acyl fluoride **10b**. These reactions demonstrate that boronocysteine can readily be converted into amide derivatives through reaction with a range of different active acylating agents.



Scheme 5 Synthesis of boronocysteine amides. *Reagents and conditions*: a. MeCOCl, pyridine, MeCN, 22% (**9a**); b. ClCH$_2$COCl, *N*-methylmorpholine, CH$_2$Cl$_2$, 85% (**9b**); c. Boc-Gly-OH, *N*-methylmorpholine, ^{i}BuOCOCl, CH$_2$Cl$_2$, then **7**, 89% (**10a**);[19] d. FMoc-Gly-F, ^{i}Pr$_2$NEt, CH$_2$Cl$_2$, 60% (**10b**).

In summary, we have described the first synthesis of protected boronocysteine, and demonstrated its application in the formation of amide derivatives.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591491.

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(16) **(*E*)-*N*-{2-[(4-Methoxybenzyl)thio]ethylidene}-2-methylpropane-2-sulfinamide (5)** Copper(II) sulfate (1.27 g, 7.94 mmol) and aldehyde **4** (779 mg, 3.97 mmol, 1.1 equiv) were added to a solution of (±)-*tert*-butyl sulfinamide (438 mg, 3.61 mmol) in anhydrous CH_2Cl_2 (7.2 mL). The reaction was stirred at r.t. for 18 h, before filtering through Celite. The solvents were removed *in vacuo* and the residue obtained was purified by column chromatography to give an orange oil (865 mg, 2.89 mmol, 80%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.98 (1 H, t, *J* = 5.6 Hz, NCH), 7.23 (2 H, d, *J* = 6.5 Hz, ArH), 6.85 (2 H, d, *J* = 6.5 Hz, ArH), 3.79 (3 H, s, OCH_3), 3.66 (2 H, s, $ArCH_2$), 3.35 (1 H, dd, *J* = 14.3, 6.0 Hz, 1 × SCH_2CH), 3.31 (1 H, dd, *J* = 14.3, 5.3, 1 × SCH_2CH), 1.22 (9 H, s, ^{t}Bu). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.2, 158.9, 130.3, 129.2, 114.1, 57.0, 55.4, 35.02, 34.3, 22.5. LRMS (CI): m/z (%) = 420 (100), 300 (37) [M + H$^+$], 240 (30), 195 (32) [M – SO^{t}Bu]$^+$), 121 (88) [PMB$^+$]. HRMS: *m/z* calcd for $C_{14}H_{22}NO_2S_2$: 300.10865; found: 300.10877. IR (film): ν_{max} = 2958 (C–H), 1609 (C=C), 1510 (C=N), 1458 (C=C), 1083 (S=O) cm^{-1}.

(17) **N-{2-[(4-Methoxybenzyl)thio]-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl}-2-methylpropane-2-sulfinamide (6)** Using flame-dried glassware under an argon atmosphere, CuCl (38.4 mg, 0.388 mmol), (±)-BINAP (111.1 mg, 0.1784 mmol), and B_2pin_2(1.331 g, 5.242 mmol) were dissolved in anhydrous THF (4 mL). KO^{t}Bu (1 M in THF, 1.4 mL, 1.4 mmol) was added whilst stirring at r.t. After 10 min, the reaction was cooled to –20 °C, and aldehyde **5** (1.0338 g, 3.4522 mmol) was added followed by MeOH (300 µL, 7.41 mmol) and the reaction stirred overnight. The solvent was removed *in vacuo* and the resultant oil purified by flash column chromatography using EtOAc in CH_2Cl_2 (20 → 35%) to give **6** as an orange oil (878 mg, 2.056 mmol, 60%); R_f = 0.08 (EtOAc/CH_2Cl_2 = 1:4). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.24 (2 H, d, *J* = 8.6 Hz, ArH), 6.82 (2 H, d, *J* = 8.6 Hz, ArH), 3.78 (3 H, s, OCH_3), 3.71 (1 H, d, *J* = 5.6 Hz, NH), 3.69 (s, 2 H, $ArCH_2S$), 3.22 (1 H, m, CHB), 2.77 (1 H, dd, *J* = 13.4, 6.3 Hz, 1 × SCH_2CH), 2.72 (1 H, dd, *J* = 13.4, 7.9 Hz, 1 × SCH_2CH), 1.25 (s, 6 H, 2 × pinacol-CH_3), 1.23 (s, 9 H, ^{t}Bu), 1.20 (s, 6 H, 2 × pinacol-CH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 158.7, 130.1, 130.0, 114.0, 84.3, 56.2, 55.3, 41.3 (br), 35.2, 34.6, 25.0 (2 C), 22.6. LRMS (CI): *m/z* (%) = 428 (41), [M + H]$^+$, 371 (18) [M$^+$ – ^{t}Bu)], 322 (38) [M$^+$ – SO^{t}Bu), 121 (100) [PMB$^+$]. IR: ν_{max} = 2977 (C–H), 2930 (C–H), 1609 (Ar), 1511 (Ar), 1544 (Ar), 1369 (B–O), 1246, 1140 (B–C), 1033 (S=O). HRMS: *m/z* calcd for $C_{20}H_{34}BNO_4S_2$: 428.2095; found: 428.2095.

(18) **2-[(4-Methoxybenzyl)thio]-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethanamine hydrochloride (7)** A solution of HCl in dioxane (4 M, 585 µL, 2.34 mmol) was added to **6** (99.7 mg, 0.233 mmol) dissolved in anhydrous MeOH (3 mL) to give a pale yellow solution. The reaction was stirred for 3 h. The solvent was removed *in vacuo* to give an orange residue (75.3 mg). The residue was washed with Et_2O, sonicated, and centrifuged to give **7** as a light brown solid (68 mg, 0.190 mmol, 82%). ^{1}H NMR (400 MHz, MeOD-d_4): δ = 7.29 (2 H, d, *J* = 8.7 Hz, ArH), 6.89 (2 H, d, *J* = 8.7 Hz, ArH) 3.80 (3 H, s, OCH_3), 3.79 (2 H, s, $ArCH_2$), 3.01 (1 H, dd, *J* = 8.7, 4.7 Hz, CHB), 2.85 (1 H, dd, *J* = 14.3,4.8 Hz, 1 × CH_2CH), 2.73 (1 H, dd, *J* = 14.3, 8.8 Hz, 1 × CH_2CH), 1.33 (12 H, s, 4 × CH_3). ^{13}C NMR (100 MHz, MeOD-d_4): δ = 159.1, 129.9, 129.5, 113.7, 85.5, 74.4, 54.5, 35.1, 30.4, 23.8, 23.7. LRMS (CI): *m/z* (%) = 323 (100) [M + H]$^+$, 198 (18) [M – Bpin]$^+$. HRMS: *m/z* calcd for $C_{16}H_{27}BNO_3S$: 323.1836; found: 323.18359. IR (solid): ν_{max} = 2975 (C–H), 2958 (C–H), 2831 (C–H), 1607, 1583, 1411 cm^{-1}.

(19) ***tert*-Butyl [2-({2-[(4-Methoxybenzyl)thio]-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl}amino)-2-oxoethyl]carbamate (10a)** Using flame-dried glassware under an argon atmosphere, Boc-Gly-OH (87.5 mg, 0.50 mmol) was dissolved in anhydrous CH_2Cl_2 (1.5 mL) and cooled to –20 °C. To this was added NMM (66 µL, 0.60 mmol) followed by IBCF (58 µL, 0.45 mmol), and the mixture stirred for 5 h at –20 °C. HCl salt **7** (23.4 mg, 65.1 µmol)

was added, followed by NMM (7 µL, 65 µmol), and the reaction stirred overnight. The reaction mixture was concentrated *in vacuo* and the resultant oil purified by flash column chromatography using deactivated silica (35% water w/w) eluting with MeOH in EtOAc (0 → 10%) to give **10a** as a pale yellow oil (28 mg, 58.0 µmol, 89%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.51 (1 H, br s, CHN*H*), 7.21 (2 H, d, *J* = 8.7 Hz, ArH), 6.82 (2 H, d, *J* = 8.7 Hz, ArH), 5.29 (1 H, br s, CH_2NH), 3.93 (2 H, d, *J* = 5.7, $NHCH_2$), 3.78 (3 H, s, OCH_3), 3.65 (2 H, s, $ArCH_2$), 2.81 (1 H, br d, *J* = 11.5 Hz, CHB), 2.75 (1 H, dd, *J* = 14.1, 3.2 Hz, 1 × SCH_2CH), 2.46 (1 H, dd, *J* = 14.1, 11.5 Hz, 1 × SCH_2CH), 1.44 (9 H, s, Bu), 1.18 (6 H, s, 2 × pinacol-CH_3), 1.16 (6 H, s, 2 × pinacol-CH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 174.9, 158.7, 130.3, 130.1, 114.1, 81.6, 55.4, 54.0, 41.4, 35.2, 33.6, 29.8, 28.4, 25.0, 24.9, 14.3. LRMS (CI): *m/z* (%) = 481 (100) [M + H]$^+$. HRMS: *m/z* calcd for $C_{23}H_{37}BN_2O_6S$: 480.2574; found: 480.2575. IR (film): ν_{max} = 2970 (C–H), 2926 (C–H), 1697 (br, C=O), 1609 (C=O), 1511, 1456 cm^{-1}.