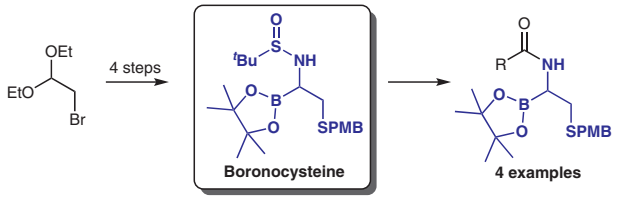
Synlett S. M. Gibson et al. Letter

Synthesis of Boronocysteine

Samantha M. Gibson
Derek Macmillan
Tom D. Sheppard*

Department of Chemistry, University College London,
20 Gordon St, London, WC1H 0AJ, UK
tom.sheppard@ucl.ac.uk



Received: 22.08.2017
Accepted after revision: 16.09.2017
Published online: 20.10.2017
DOI: 10.1055/s-0036-1591491; Art ID: st-2017-d0637-l

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,

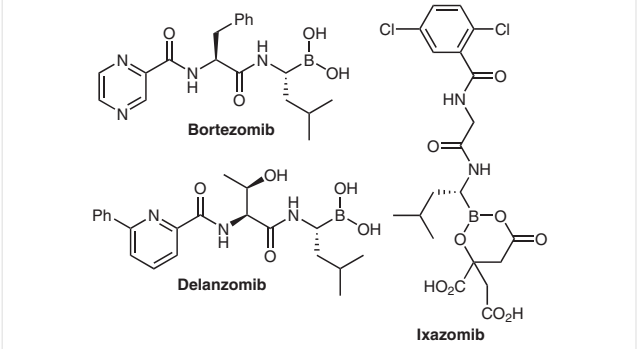
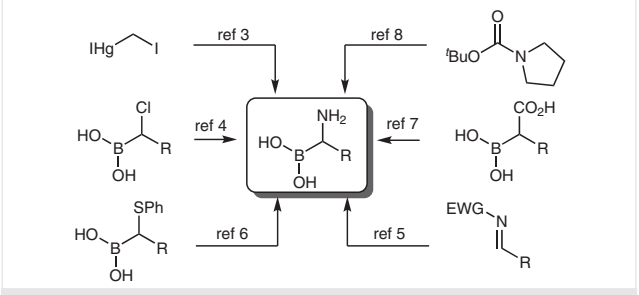


Figure 1 Medicinally useful α-aminoboronic acid derivatives

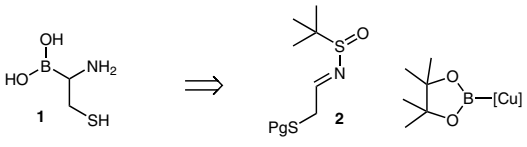


Scheme 1 Synthetic approaches to α-aminoboronic acid derivatives

Downloaded by: UNSW Library. Copyrighted material.

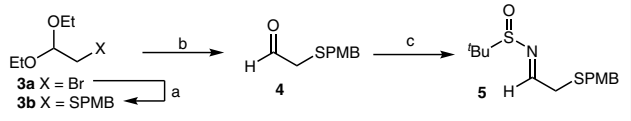
we report a concise synthesis of protected boronocysteine, and its use in the synthesis of *N*-acyl derivatives including dipeptide analogues.

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

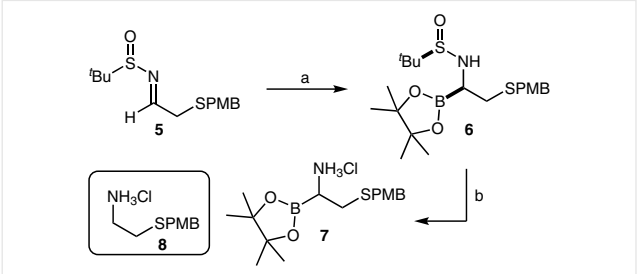
Bromoacetaldehyde dimethyl acetal **3a** was converted into the corresponding sulfide **3b** by reaction with *p*-methoxybenzyl thiol (PMBSH) and sodium hydroxide (Scheme 3).[13] After deprotection of the acetal, the aldehyde **4**[14] was then converted into sulfinimine **5** through condensation with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

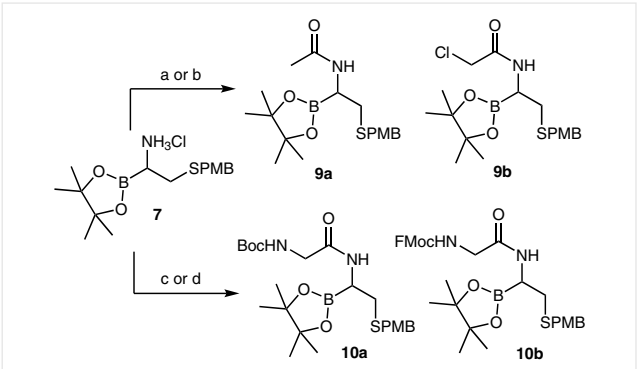
With the required sulfinimide in hand, the Cu-catalysed borylation reaction was investigated. Pleasingly, by using CuCl in the presence of KO^{t}Bu and *rac*-BINAP as a ligand,[5a] the desired boronate **6** was obtained in 60% isolated yield as a single diastereoisomer (Scheme 4). As reported previously, 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.

Funding Information

This work was supported by an Engineering and Physical Sciences Research Council Studentship.

Acknowledgment

We would like to thank the Department of Chemistry, University College London for providing a studentship to support this work.

Downloaded by: UNSW Library. Copyrighted material.

Supporting Information

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

References and Notes

(1) (a) Yang, W.; Gao, X.; Wang, B. *Med. Res. Rev.* **2003**, *23*, 346. (b) Dembitsky, V. M.; Al Aziz Quntar, A.; Srebnik, M. *Mini-Rev. Med. Chem.* **2004**, *4*, 1001. (c) Dembitsky, V. M.; Srebnik, M. *Tetrahedron* **2003**, *59*, 579. (d) Matteson, D. S. *Med. Res. Rev.* **2008**, *28*, 233. (e) Andrés, P.; Ballano, G.; Calaza, M. I.; Cativela, C. *Chem. Soc. Rev.* **2016**, *45*, 2291.

(2) Matteson, D. S.; Sadhu, K. M. *Organometallics* **1984**, *3*, 614.

(3) Matteson, D. S.; Cheng, T.-C. *J. Organomet. Chem.* **1966**, *6*, 100.

(4) (a) Tsai, D. J. S.; Jesthi, P. K.; Matteson, D. S. *Organometallics* **1983**, *2*, 1543. (b) Matteson, D. S. *J. Organomet. Chem.* **1999**, *581*, 51.

(5) (a) Beenen, M. A.; An, C.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 6910. (b) Buesking, W.; Bacauanu, V.; Cai, I.; Ellman, J. A. *J. Org. Chem.* **2014**, *79*, 3671. (c) Solé, C.; Gulyás, H.; Fernández, E. *Chem. Commun.* **2012**, *48*, 3769.

(6) Jagannathan, S.; Forsyth, T. P.; Kettner, C. A. *J. Org. Chem.* **2001**, *66*, 6375.

(7) He, Z.; Zajdlik, A.; St Denis, J. D.; Assem, N.; Yudin, A. K. *J. Am. Chem. Soc.* **2012**, *134*, 9926.

(8) Batsanov, A. S.; Grosjean, C.; Schütz, T.; Whiting, A. *J. Org. Chem.* **2007**, *72*, 6276.

(9) For other approaches, see: (a) Zheng, B.; Deloux, L.; Pereira, S.; Skrzypczak-Jankun, E.; Cheesman, B. V.; Sabat, M.; Morris, S. *Appl. Organomet. Chem.* **1996**, *10*, 267. (b) Touchet, S.; Carreaux, F.; Molander, G. A.; Carboni, B.; Bouillon, A. *Adv. Synth. Catal.* **2011**, *353*, 3391. (c) Kawamorita, S.; Miyazaki, T.; Iwai, T.; Ohimiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2012**, *134*, 12924. (d) Hu, N.; Zhao, G.; Zhang, Y.; Liu, X.; Li, G.; Tang, W. *J. Am. Chem. Soc.* **2015**, *137*, 6746. (e) Li, C.; Wang, J.; Barton, L. M.; Yu, S.; Tian, M.; Peters, D. S.; Kumar, M.; Yu, A. W.; Johnson, K. A.; Chatterjee, A. K.; Yan, M.; Baran, P. S. *Science* **2017**, *357*, in press; DOI: 10.1126/science.aam7355.

(10) (a) Kettner, C.; Mersinger, L.; Knabb, R. *J. Biol. Chem.* **1990**, *265*, 18289. (b) Lebarbier, C.; Carreaux, F.; Carboni, B.; Boucher, J. L. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2573. (c) Watanabe, T.; Momose, I.; Abe, M.; Abe, H.; Sawa, R.; Umezawa, Y.; Ikeda, D.; Takahashi, Y.; Akamatsu, Y. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2343. (d) Lebarbier, C.; Carreaux, F.; Carboni, B. *Synthesis* **1996**, 1371. (e) Matteson, D. S.; Michnick, T. J.; Willett, R. D.; Patterson, C. D. *Organometallics* **1989**, *8*, 726.

(11) (a) Cowper, B.; Shariff, L.; Chen, W.; Gibson, S. M.; Di, W.-L.; Macmillan, D. *Org. Biomol. Chem.* **2015**, *13*, 7469. (b) Macmillan, D. *Synlett* **2017**, *28*, 1517.

(12) Matteson, D. S. *J. Organomet. Chem.* **1999**, *581*, 51.

(13) Lantos, I.; Razgaitis, C.; Sutton, B. M. *J. Heterocycl. Chem.* **1982**, *19*, 1375.

(14) Yoneda, K.; Ota, A.; Kawashima, Y. *Chem. Pharm. Bull.* **1993**, *41*, 876.

(15) Ghosh, S.; Tochtrop, G. P. *Tetrahedron Lett.* **2009**, *50*, 1723.

(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)

Downloaded by: UNSW Library. Copyrighted material.

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}.

Downloaded by: UNSW Library. Copyrighted material.