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Hydroboration of Alkene-Containing Hydantoins

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Abstract:

A direct hydroboration of alkene-containing hydantoins using diisopinocampheylborane has been developed that can be used to prepare boronated amino acids. The method is successful because boronic acids are stable to the conditions employed for hydrolyzing hydantoins.

In recent years, functionalized amino acids containing sulfur,[1] selenium,[1g,2] phosphorus,[1b,3] fluorine,[4] and boron[5] have become increasingly important. As potential pharmaceuticals, boronated amino acids have been used as arginase[6] and dihydroorotase[7] inhibitors, as boron neutron capture therapy (BNCT) agents,[8] and as anti-HIV agents.[9] The oxidation of boronated amino acids also affords a route to amino acids bearing hydroxyl or carboxyl groups.[10] However, current preparations of boronated amino acids are somewhat limited due to the incompatibility of the boronic acid moiety with the reagents used in many synthetic methods. Although the Miyaura cross-coupling reaction between pinacol diboronate and aromatic halides simplified the preparation of arylboronic acids containing functional groups, including amino acids,[11] this reaction is not suitable for preparing alkylboronic acids.

Positron emission tomographic (PET) investigations of BNCT patients using carbon-11 labeled 1-aminocyclobutanecarboxylic acid (ACBC) demonstrated that this amino acid localizes in tumors more avidly than dihydroxyborylphenylalanine (BPA),[12,13] the pharmaceutical of choice for BNCT. For these reasons, we have focused our efforts on the synthesis of boronated cyclic amino acids.[14] Among the existing routes to cyclic amino acids, the Bücherer−Strecker reaction,[15] in which ketones are first converted to hydantoins by treatment with ammonia and hydrogen cyanide, has proven to be most effective. Another advantage of the Bücherer−Strecker reaction is that the precursor ketone group can be masked as an unreactive ketal during preliminary functionalization of the molecules. During our investigation, we found that the hydantoin group (the precursor of the amino acid) will tolerate hydroboration reactions. This discovery provides a novel route to boronated amino acids, since boronic acids are stable to the conditions employed during hydantoin hydrolysis.[14c,16]

Results and Discussion

Diisopinocampheylborane (Ipc_2BH) was chosen as the hydroboration reagent because the steric bulk of this reagent maximizes the regioselectivity of the hydroboration reaction and minimizes undesired reductive side reactions. In addition, the isopinocampheyl groups are readily removed by simple reductive reactions with aldehydes to provide boronic ester derivatives.[17] Ipc_2BH can also be prepared in a chiral form and thus can be used to induce chirality. In our study, Ipc_2-

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(1) (a) Burgess, K.; Ho, K.-K. *J. Org. Chem.* **1992**, *57*, 5931. (b) Gaoni, Y.; Chapman, A. G.; Parvez, N.; Pook, P. C.-K.; Jane, D. E.; Watkins, J. C. *J. Med. Chem.* **1994**, *37*, 4288. (c) Rozema, D. B.; Phillips, S. T.; Poulter, C. D. *Org. Lett.* **1999**, *1*, 815. (d) Zhu, Y.; van der Donk, W. A. *Org. Lett.* **2001**, *3*, 1189. (e) West, C. W.; Estiarte, M. A.; Rich, D. H. *Org. Lett.* **2001**, *3*, 1205. (f) Liu, S.; Dockendorff, C.; Taylor, S. D. *Org. Lett.* **2001**, *3*, 1571. (g) Jacob, C.; Giles, G. I.; Giles, Niroshini M.; Sies, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4742.

(2) (a) Gieselman, M. D.; Xie, L.; van der Donk, W. A. *Org. Lett.* **2001**, *3*, 1331. (b) Braga, A. L.; Ludtke, D. S.; Paixao, M. W.; Alberto, E. E.; Stefani, H. A.; Juliano, L. *Eur. J. Org. Chem.* **2005**, *20*, 4260.

(3) (a) Allan, R. D.; Hanrahan, J. R.; Hambley, T. W.; Johnston, G. A. R.; Mewett, K. N.; Mitrovic, A. D. *J. Med. Chem.* **1990**, *33*, 2905. (b) Volk, F.-J.; Wagner, M.; Frahm, A. W. *Tetrahedron: Asymmetry.* **2003**, *14*, 497.

(4) (a) Shoup, T. M.; Goodman, M. M. *J. Labelled Compd. Radiopharm.* **1999**, *42*, 215. (b) Martarello, L.; McConathy, J.; Camp, V. M.; Malveaux, E. J.; Simpson, N. E.; Simpson, C. P.; Olson, J. J.; Bowers, G. D.; Goodman, M. M. *J. Med. Chem.* **2002**, *45*, 2250. (c) Kirihara, M.; Kawasaki, M.; Takuwa, T.; Kakuda, H.; Wakikawa, T.; Takeuchi, Y.; Kirk, K. L. *Tetrahedron: Asymmetry* **2003**, *14*, 1753.

(5) (a) Kabalka, G. W.; Yao, M.-L. *Anticancer Agents Med. Chem.* **2006**, *6*, 111. (b) Yang, W.-Q.; Gao, X.-M.; Wang, B.-H. *Med. Res. Rev.* **2003**, *23*, 346. (c) Kinder, D. H.; Ames, M. M. *J. Org. Chem.* **1987**, *52*, 2452.

(6) (a) Kim, M. N.; Cox, J. D.; Baggio, R. F.; Emig, F. A.; Misry, S. K.; Harper, S. L.; Speicher, D. W.; Morris, S. M.; Ash, D. E.; Traish, A.; Christianson, D. W. *Biochemistry* **2001**, *40*, 2678. (b) Collet, S.; Carreaux, F.; Boucher, J.-L.; Pethe, S.; Lepoivre, M.; Danion-Bougot, R.; Danion, D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 177. (c) Baggio, R.; Elbaum, D.; Kanyo, Z. F.; Carroll, P. J.; Cavalli, R. C.; Ash, D. E.; Christianson, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 8107.

(7) Kinder, D. H.; Frank, S. K.; Ames, M. M. *J. Med. Chem.* **1990**, *33*, 819.

(8) (a) Hawthorne, M. F.; Maderna, A. *Chem. Rev.* **1999**, *99*, 3421. (b) Barth, R. F.; Coderre, J. F.; Vicente, M. G. H.; Blue, T. E. *Clin. Cancer Res.* **2005**, *11*, 3987.

(9) Chen, X.; Bastow, K.; Goz, B.; Kucera, L.; Morris-Natschke, S. L.; Ishaq, K. S. *Antiviral Chem. Chemother.* **1996**, *7*, 108.

(10) (a) Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *J. Org. Chem.* **1989**, *54*, 5930. (b) Racherla, U. S.; Khanna, V. V.; Brown, H. C. *Tetrahedron Lett.* **1992**, *33*, 1037.

(11) (a) Nakamura, H.; Fujiwara, M.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 7529. (b) Nakamura, H.; Fujiwara, M.; Yamamoto, Y. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 231. (c) Malan, C.; Morin, C. *J. Org. Chem.* **1998**, *63*, 8019.

(12) Aoyagi, M.; Agranoff, G. W.; Washburn, L. C.; Smith, O. R. *J. Neurochem.* **1988**, 50, 1220.

(13) Hubner, K. F.; Thie, J. A.; Smith, G. T.; Kabalka, G. W.; Keller, I. B.; Cliefoth, A. B.; Campbell, S. K.; Buonocore, E. *Clin. Positron Imaging* **1998**, *1*, 165.

(14) (a) Srivastava, R. R.; Singhaus, R. R.; Kabalka, G. W. *J. Org. Chem.* **1997**, *62*, 4476. (b) Srivastava, R. R.; Kabalka, G. W. *J. Org. Chem.* **1997**, *62*, 8730. (c) Srivastava, R. R.; Singhaus, R. R. Kabalka, G. W. *J. Org. Chem.* **1999**, *64*, 8495. (d) Das, B. C.; Kabalka, G. W.; Srivastava, R. R.; Bao, W.; Das, S.; Li, G. *J. Organomet. Chem.* **2000**, *614−615*, 255. (e) Das, B. C.; Das, S.; Li, G.; Bao, W.; Kabalka, G. W. *Synlett* **2001**, 1419. (f) Kabalka, G. W.; Yao, M.-L. *Appl. Organomet. Chem.* **2003**, *17*, 398. (g) Kabalka, G. W.; Yao, M.-L. *Synthesis* **2003**, 2890. (h) Kabalka, G. W.; Yao, M.-L. *J. Org. Chem.* **2004**, *69*, 8280. (i) Kabalka, G. W.; Yao, M.-L.; Naravane, A. *Tetrahedron Lett.* **2005**, *46*, 4915.

(15) Yet, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 875.

(16) Kabalka, G. W.; Das, B. C.; Das, S. *Tetrahedron Lett.* **2001**, *42*, 7145.

(17) Brown, H. C.; Gupta, A. K. *J. Organomet. Chem.* **1988**, *341*, 73.

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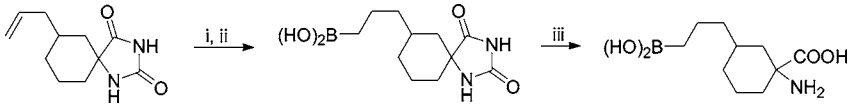
Scheme 1. **New route to boronated amino acid**[a]



[a] Reagents and conditions: (i) Ipc_2BH, THF, 0 °C; (ii) CH_3CHO, THF, rt; (iii) HCl (12 N), 150 °C.

BH was prepared according to the literature procedure,[18] and hydroborations were performed in THF at 0 °C (Scheme 1). The resultant air-sensitive triorganoborane products were allowed to react in situ with an excess of acetaldehyde. The hydantoin carbonyl group was not affected by the hydroboration reagent, but the reaction did require 3 equiv of Ipc_2-BH (hydrogen gas was released during hydroboration).[19] The hydroboration reaction proceeded smoothly, and the boronated hydantoins were isolated in good yields. Hydrolysis of the boronated hydantoins afforded the boronated amino acids in high yields.[14c,16]

The reaction was used to successfully hydroborate a variety of alkene-containing hydantoins. The results are summarized in Table 1.

Although the hydroboration of vinylglycine and allylglycine has been reported,[20] the application of the new methodology to the hydroboration of alkene-containing hydantoins was remarkable. Unlike other amino acid templates, ketone precursors to hydantoins can be masked as ketals during early stages of the syntheses. Although we only report the hydroboration of alkene derivatives, there is good reason to believe that alkyne hydroborations are achievable utilizing diisopinocampheylborane.

Conclusion

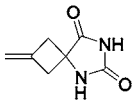
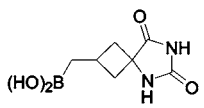
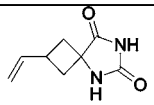
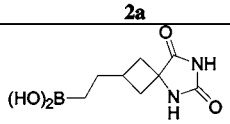
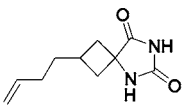
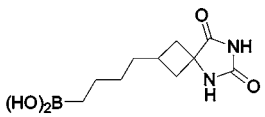
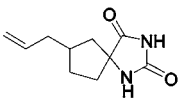
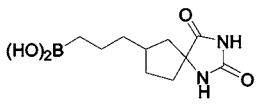
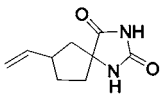
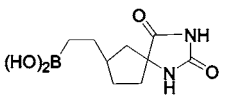
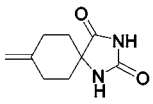
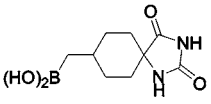
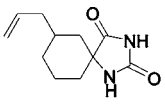
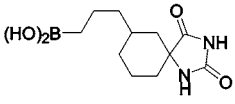
The hydroboration of alkene-containing hydantoins using diisopinocampheylborane provides a convenient route to the corresponding boronated hydantoins. Since boronic acids are stable to conditions used for hydrolyzing hydantoins, the method offers a new route to boronated amino acids.

Experimental Section

General Remarks. All reagents were used as received. Column chromatography was performed using silica gel (60 Å, 230−400 mesh, ICN Biomedicals GmbH, Eschwege, Germany). Analytical thin-layer chromatography was performed using 250 μm silica (Analtech, Inc., Newark, DE). ^{1}H NMR and ^{13}C NMR spectra were recorded at 250.13 and 62.89 MHz, respectively. Chemical shifts for ^{1}H NMR and ^{13}C NMR spectra were referenced to TMS and measured with respect to the residual protons in the deuterated solvents.

Representative Procedure for the Preparation of 2-Boronomethyl-5,7-diazaspiro[3,4]octane-6,8-dione 2a. 2-Methylene-5,7-diazaspiro[3,4]octane-6,8-dione **1a** (380 mg, 2.5 mmol) was placed in a 150-mL round-bottomed flask and dissolved in THF (10 mL) at 0 °C. $(Ipc)_2BH$ (7.5 mmol) in THF (10 mL) was added dropwise via a syringe. The mixture was allowed to warm to room temperature and stirred for 16 h. Freshly distilled acetaldehyde (12 mmol) was added, and the mixture stirred for an additional 12 h. Volatiles were removed under reduced pressure, and the mixture hydrolyzed with aqueous hydrochloric acid (5 mL, 2 M). The mixture was extracted with ethyl acetate (3 × 30 mL), and the combined organic phase dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (methanol) to afford **2a** as a white solid (302 mg, yield: 61%). ^{1}H NMR (DMSO-d_6) δ 8.49 (s, 1H), 7.44 (s, 1H), 1.74−2.48 (m, 5H), 0.72−

Table 1. **Hydroboration of alkene-containing hydantoins**

Entry	Reactant	Product	Yield (%)
1	 **1a**	 **2a**	61
2	 **1b**	 **2b**	73
3	 **1c**	 **2c**	85
4	 **1d**	 **2d**	87
5	 **1e**	 **2e**	77
6	 **1f**	 **2f**	86
7	 **1g**	 **2g**	69

(18) Petter, A.; Smith, K.; Brown, H. C. *Borane Reagents*; Academic Press: New York, 1988; p 427.

(19) According to the literature, the hydroboration of N-olefin-substituted ureas and carbamates is not affected by the NH group, but hydrogen gas is released during the hydroboration due to reaction of the NH group with Ipc_2BH to produce a borate intermediate which is hydrolized upon workup to regenerate the NH moiety. See ref: Butler, D. N.; Soloway, A. H. *J. Am. Chem. Soc.* **1966**, *88*, 484.

(20) Denniel, V.; Bauchat, P.; Danion, D.; Danion-bougot, R. *Tetrahedron Lett.* **1996**, *37*, 5111.

0.88 (m, 2H). ^{13}C NMR δ 177.5, 156.3, 59.5, 34.2, 25.7. HRMS-FAB (M + H + gly − $2H_2O$; obtained in a glycerol matrix) calcd for $C_{10}H_{16}BN_2O_5$ 255.1154, found 255.1148.

Synthesis of Boronohydantoin (2b). The synthesis was carried out as described for compound **2a**. Compound **1b** (0.50 g, 3.0 mmol) and Ipc_2BH (9.0 mmol) were used. After stirring at room temperature overnight, acetaldehyde (14.0 mmol) was added. The product was purified by silica gel column chromatography (MeOH) to afford compound **2b** as a white solid (0.46 g, 73%). ^{1}H NMR (DMSO-d_6): δ = 10.00 (s, 1 H), 7.43 (s, 1 H), 1.89−2.51 (m, 7 H), 0.47−0.63 (m, 2 H). ^{13}C NMR (62.89 MHz, DMSO-d_6): δ = 178.9, 155.9, 57.5, 38.0, 36.7, 26.6. HRMS-FAB: *m*/*z* calcd for $C_{11}H_{18}BN_2O_5$ (M + H + gly − $2H_2O$; obtained in a glycerol matrix) 269.1310, found 269.1322.

Synthesis of Boronohydantoin (2c). The synthesis was carried out as described for compound **2a**. Compound **1c** (0.63 g, 3.0 mmol) and Ipc_2BH (9.0 mmol) were used. After stirring at room temperature overnight, acetaldehyde (15.0 mmol) was added. The product was purified by silica gel column chromatography (MeOH) to afford compound **2c** as a white solid (0.65 g, 85%). ^{1}H NMR (DMSO-d_6): δ = 8.52 (s, 1 H), 7.42 (s, 1 H), 2.47−2.58 (m, 2 H), 2.17−2.31 (m, 3 H), 1.04−1.48 (m, 6 H), 0.62 (t, J = 7.75 Hz, 2 H). ^{13}C NMR (62.89 MHz, DMSO-d_6): δ = 178.8, 155.9, 57.6, 38.3, 36.5, 29.5, 26.3, 24.1. HRMS-FAB: *m*/*z* calcd for $C_{13}H_{22}BN_2O_5$ (M + H + gly − $2H_2O$; obtained in a glycerol matrix) 297.1624, found 297.1618.

Synthesis of Boronohydantoin (2d). The synthesis was carried out as described for compound **2a**. Compound **1d** (0.58 g, 3.0 mmol) and Ipc_2BH (9.0 mmol) were used. After stirring at room temperature overnight, acetaldehyde (18.0 mmol) was added. The product was purified by silica gel column chromatography (MeOH−EtOAc, 1:10) to afford compound **2d** as a white solid (0.63 g, 87%). ^{1}H NMR (250 MHz, DMSO-d_6): δ 9.94 (s, 1H), 8.18 (s, 1H), 1.99−1.12 (m, 11H), 0.47−0.59 (m, 2H). ^{13}C NMR (63.9 MHz, DMSO-d_6): δ 179.7, 158.2, 67.7, 43.7, 40.4, 38.5, 38.0, 36.9, 31.2, 23.1. HRMS-FAB: *m*/*z* calcd for $C_{13}H_{22}BN_2O_5$ (M + H + gly − $2H_2O$; obtained in a glycerol matrix) 297.1624, found 297.1621.

Synthesis of Boronohydantoin (2e). The synthesis was carried out as described for compound **2a**. Compound **1e** (0.50 g, 2.2 mmol) and Ipc_2BH (6.7 mmol) were used. After stirring at room temperature overnight, acetaldehyde (13.6 mmol) was added. The product was purified by silica gel column chromatography (MeOH−EtOAc, 1:10) to afford **2e** as a white solid (0.52 g, 77%). ^{1}H NMR (250 MHz, DMSO-d_6): δ 10.54 (s, 1H), 8.18 (s, 1H), 1.15−2.04 (m, 9H), 0.52−0.57 (m, 2H). ^{13}C NMR (63.9 MHz, DMSO-d_6): δ 179.8, 158.2, 67.7, 43.7, 31.4, 29.9, 20.8. HRMS-FAB: *m*/*z* calcd for $C_{12}H_{20}BN_2O_5$ (M + H + gly − $2H_2O$; obtained in a glycerol matrix) 283.1468, Found 283.1462.

Synthesis of Boronohydantoin (2f). The synthesis was carried out as described for compound **2a**. Compound **1f** (0.56 g, 3.1 mmol) and Ipc_2BH (9.6 mmol) were used. After stirring at room temperature overnight, acetaldehyde (19.17 mmol) was added. The product was purified by silica gel column chromatography (MeOH−EtOAc, 1:10) to afford compound **2f** as a white solid (0.60 g, 86%). ^{1}H NMR (250 MHz, DMSO-d_6): δ 10.34 (s, 1H), 8.40 (s, 1H), 0.92−1.95 (m, 9H), 0.78−0.86 (m, 2H). ^{13}C NMR (63.9 MHz, DMSO-d_6): δ 178.7, 156.4, 60.9, 37.4, 32.3, 24.2, 23.8. HRMS-FAB: *m*/*z* calcd for $C_{12}H_{20}BN_2O_5$ (M + H + gly − $2H_2O$; obtained in a glycerol matrix) 283.1468, found 283.1471.

Synthesis of Boronohydantoin (2g). The synthesis was carried out as described for compound **2a**. Compound **1g** (0.53 g, 2.6 mmol) and Ipc_2BH (7.7 mmol) were used. After stirring at room temperature overnight, acetaldehyde (15.3 mmol) was added. The product was purified by silica gel column chromatography (MeOH−EtOAc, 1:10) to afford compound **2g** as a white solid (0.45 g, 69%). ^{1}H NMR (250 MHz, DMSO-d_6): δ 10.50 (s, 1H), 8.37 (s, 1H), 0.79−1.68 (m, 15H). ^{13}C NMR (63.9 MHz, DMSO-d_6): δ 178.5, 156.3, 62.8, 41.2, 33.1, 31.7, 31.4, 21.2, 20.8. HRMS-FAB: *m*/*z* calcd for $C_{14}H_{24}BN_2O_5$ (M + H + gly − $2H_2O$; obtained in a glycerol matrix) 311.1781, found, 311.1782.

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