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Synthesis of a novel boronated 1-aminocyclobutanecarboxylic acid as a potential boron neutron capture therapy agent†

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A boronated aminocyclobutanecarboxylic acid was synthesized for potential use in neutron capture therapy. The synthesis involves the preparation of hydroxymethylcyclobutanone ketal, which is then converted to an amino acid using Bucherer–Strecker methodology. The molecule is modeled after the unnatural amino acid, 1-aminocyclobutanecarboxylic acid, which has demonstrated high uptake in brain tumors. Copyright © 2003 John Wiley & Sons, Ltd.

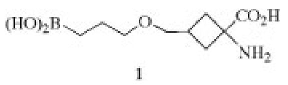
KEYWORDS: amino acids; boronic acids; neutron capture therapy; synthesis; cyclobutanecarboxylic acid; cyclobutanone

INTRODUCTION

Boron neutron capture therapy (BNCT) is a cancer treatment in which a compound containing ^{10}B is selectively delivered to a tumor tissue prior to its irradiation by neutrons. BNCT was proposed as a potential cancer therapy in 1936.[1,2] The clinical success of BNCT depends on two factors: delivery of a sufficient quantity of boron to the tumor and a neutron flux sufficient to achieve the prerequisite nuclear reaction while minimizing damage to healthy tissue. Because large cellular concentrations ($\sim$30 μg of ^{10}B per gram of tumor) are required for successful BNCT,[3,4] it is imperative that the boronated molecule be non-toxic. To date, a variety of molecules have been used to deliver boron to tumor cells. These include carbohydrates,[5–8] polyamines,[9,10] amino acids,[11–14] nucleosides,[15–19] antisense agents,[20–23] porphyrins,[24–28] antibodies[29] and liposomes.[30–34] In recent years, encouraging results have been obtained using 4-dihydroxyborylphenylalanine (BPA) as the tumor-specific boronated agent.[35–42] It is believed that amino acids are preferentially taken up by growing tumor cells and positron emission tomography (PET) investigations[43] carried out at The University of Tennessee on BNCT patients using ^{11}C labeled 1-aminocyclobutanecarboxylic acid (ACBC) demonstrated that this amino acid localizes in tumors more avidly than BPA. For this reason we have focused our efforts on the synthesis of boronated ACBCs. Carborane[44–47] and phenylboronic acid[48] substituted ACBC reagents have been prepared previously. We wish to report the synthesis of a novel alkylboronic acid ACBC derivative, **1** (Scheme 1).

RESULTS AND DISCUSSION

The key synthetic step in the preparation of **1** involves the synthesis of 3-(hydroxymethyl)cyclobutanone ethylene ketal (**6a**). Though there are several reported methods[49–51] for constructing **6a**, the most straightforward and efficient route involves the cyclocondensation of 1,3-dibromo-2,2-dimethoxypropane with diisopropyl malonate.[51] Unfortunately, this synthetic route produced low overall yields (14%) after four synthetic steps. We have developed a novel alternative approach to cyclobutanone ketals based on a [2 + 2] cycloaddition reaction of commercially available allyl benzyl ether with dichloroketene (Scheme 2). Cyclobutanone (**3**) was obtained by the [2 + 2] cycloaddition of **2** with dichloroketene,



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Scheme 1.

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†Dedicated to Professor Thomas P. Fehlner on the occasion of his 65th birthday, in recognition of his outstanding contributions to organometallic and inorganic chemistry.

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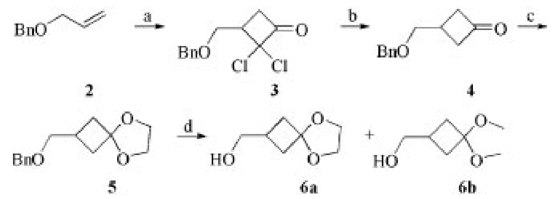
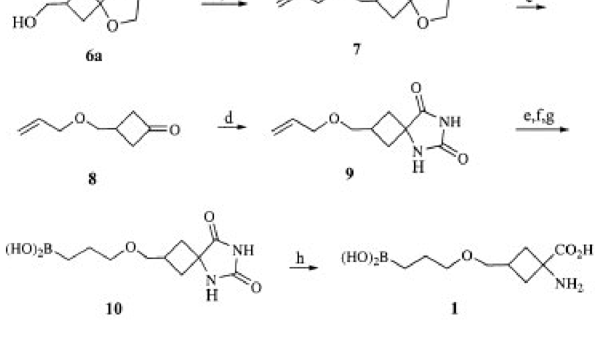


Scheme 2. Regents and reaction conditions: (a) Cl_3CCOCl, $POCl_3$, Zn–Cu, Et_2O; (b) Zn, HOAc; (c) ethylene glycol, PTSA, benzene; (d) Pd/C, methanol, H_2 (1 atm), rt.

which was generated *in situ* from trichloroacetyl chloride in the presence of a zinc–copper couple and phosphorus oxychloride.[52–54] The reductive dechlorination of **3** with zinc and acetic acid produced cyclobutanone (**4**) in 56% isolated yield (two steps). Cyclobutanone (**4**) was then protected as the ethylene ketal (**5**) by reaction with ethylene glycol using standard procedures.[55]

Though the removal of benzyl groups by hydrogenation is a classic organic reaction, the removal of the benzyl group in ketal **5** produced mixtures of **6a** and **6b** when carried out in methanol. The NMR spectrum of **6b** was identical to that reported in the literature.[51] The ratio of **6a** to **6b** was variable. Using ethyl acetate as solvent (in place of methanol) eliminated the formation of dimethyl ketal (**6b**). Ketal **6a** was unstable on silica gel, so the crude reaction product was used to prepare **7** (Scheme 3).

Treatment of crude **6a** with sodium hydride and allyl bromide in dry tetrahydrofuran (THF) generated **7** in moderate yield. The ethylene ketal group was removed by the action of dilute hydrochloric acid in ethyl ether at room temperature to generate ketone **8**. In comparison with the cleavage of ethylene ketals of cyclohexanone or cyclopentanone in refluxing ethanol,[56,57] formation of ketone **8** under such mild reaction conditions is somewhat notable. Ketone **8** was then converted to the corresponding hydantoin **9** by allowing it to react with potassium cyanide and ammonium carbonate in an Ace® pressure tube at 60 °C for 8 h (86% yield).[58,59] Hydantoin (**9**) was obtained as a 3 : 1 ratio of stereoisomers with the *cis*-isomer predominating. The observed selectivity can be attributed to the steric interaction of the 3-allyloxymethyl substituent during the formation of the hydantoin, i.e. during the addition of cyanide to the imine.[60] The hydroboration of **9** was realized by treatment with 3.0 equivalents of diisopinocampheylborane (Ipc_2BH) in THF at room temperature.[61] The hydrolysis of **10** in the presence of 2 M sodium hydroxide gave the desired ACBC derivative **1** in good yield.



Scheme 3. Regents and reaction conditions: (a) NaH, THF, 0 °C to rt. (b) Allyl bromide, THF, 0 °C to rt. (c) HCl (2 M), Et_2O, rt. (d) $(NH_4)_2CO_3$, KCN, EtOH/H_2O, 60 °C (e) $(Ipc)_2BH$, THF, 0 °C to rt. (f) CH_3CHO, THF, 0 °C to rt. (g) HCl (2 M), rt. (h) NaOH (2 M), 150 °C.

CONCLUSION

We report the synthesis of a novel ACBC containing an alkylboronic acid substituent. The evaluation of **1** as a potential BNCT agent is currently under way.

EXPERIMENTAL

General methods

All reagents were used as received. Diethyl ether and THF were distilled from sodium benzophenone ketyl. Column chromatography was performed using silica gel (60 Å230–400 mesh, ICN Biomedicals GmbH, Eschwege, Germany). Analytical thin-layer chromatography was performed using 260 μm silica (Analtech Inc., Newark, DE) and was visualized by a phosphomolybdic acid, palladium chloride and silver nitrate solution.

^1H NMR and ^{13}C NMR spectra were recorded at 250.13 MH$_3$ and 62.89 Mz respectively. In cases where more than one isomer was formed, we have reported the spectrum of the major isomer. Chemical shifts for ^1H and ^{13}C NMR spectra were referenced to tetramethylsilane and measured with respect to the residual protons in the deuterated solvents. Microanalyses were performed by Atlantic Microlab, Inc., Norcross, GA. High-resolution (HR) fast atom bombardment (FAB) mass spectrometry (MS) (M + 1) was performed on a ZABEQ instrument in a glycerol matrix.

Synthesis of 3-(benzyloxymethyl)-2,2-dichloro cyclobutanone (3)

A 250 ml three-necked, round-bottomed flask, equipped with an addition funnel and reflux condenser, was charged with allyl benzyl ether (30 mmol, 4.4 g), freshly prepared zinc–copper couple (100 mmol, 6.5 g) and anhydrous diethyl ether (50 ml). A solution of trichloroacetyl chloride (60 mmol, 6.7 mL) and phosphorus oxychloride (60 mmol, 5.6 ml) in diethyl ether (100 ml) was placed in the addition funnel and the solution added dropwise over a period of 30 min. After the addition was complete, the reaction mixture was refluxed at 55 °C (oil bath) for 2 days under an argon atmosphere, cooled

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to room temperature, and filtered through a pad of Celite. Additional diethyl ether was used to wash the Celite. The solvent from the combined filtrate was removed *in vacuo* and the residue dissolved in petroleum ether (3 × 100 ml). The clear yellow solution was decanted into a separatory funnel, washed with water (2 × 50 ml), brine (50 ml), dried over anhydrous magnesium sulfate, and concentrated on a rotary evaporator to obtain **3** as a light yellow liquid. Compound **3** was unstable on silica gel and used directly for the next step.

Synthesis of 3-(benzyloxymethyl)cyclobutanone (4)

Crude **3** was dissolved in glacial acetic acid (25 ml) and zinc dust (10 g, excess) was added in portions. The reaction mixture was stirred at room temperature for 30 min and then heated at 120 °C (oil bath) for 12 h. Thin-layer chromatography indicated disappearance of the starting material. The mixture was cooled to room temperature, neutralized with saturated sodium bicarbonate at 0 °C and passed through a pad of Celite. Ethyl acetate was used to wash the Celite. The filtrate was then extracted with ethyl acetate (3 × 50 ml). The combined organic layer was washed with water (2 × 20 ml) and then brine (20 ml), dried over anhydrous magnesium sulfate, and concentrated to obtain a light yellow thick liquid. The crude product was purified by column chromatography (hexane/EtOAc: 15/1). 3-(Benzyloxymethyl)cyclobutanone (**4**) was obtained as a colorless liquid (3.2 g, 56% yield based on allyl benzyl ether). ^{1}H NMR ($CDCl_3$): δ 7.22–7.42 (m, 5H), 4.55 (s, 2H), 3.58 (d, $J = 6.68$ Hz, 2H), 3.05–3.17 (m, 2H), 2.78–2.94 (m, 2H), 2.62–2.71 (m, 1H). ^{13}C NMR: δ 207.2, 138.0, 128.3, 127.6, 127.5, 73.1, 72.8, 50.0, 23.6. MS: 190 (M^+), 92, 91, 65.

Synthesis of 3-benzyloxymethylcyclobutanone ethylene ketal (5)

A 250 ml three-necked, round-bottomed flask equipped with a Dean–Stark apparatus and a reflux condenser was charged with ketone **4** (20 mmol, 3.8 g), ethylene glycol (21 mmol, 1.3 g), *p*-toluenesulfonic acid (300 mg) and benzene (150 ml). The reaction mixture was refluxed at 120 °C (oil bath) for 14 h and monitored by thin-layer chromatography. After 14 h, the flask was cooled to room temperature and saturated sodium bicarbonate was added to neutralize the reaction mixture. The mixture was transferred to a separatory funnel, washed with water (15 ml) and then brine (15 ml), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to yield a colorless oil. The product was purified by column chromatography (hexane/EtOAc: 20/1) to yield 4.4 g (97% yield) of a colorless liquid. ^{1}H NMR ($CDCl_3$): δ 7.23–7.34 (m, 5h), 4.52 (s, 2h), 3.87 (s, 4H), 3.49 (d, $J = 6.37$ Hz, 2H), 2.40–2.44 (m, 3H), 2.08–2.11 (m, 2H). ^{13} C NMR: δ 138.5, 128.3, 127.6, 127.5, 106.7, 74.2, 72.9, 63.9, 63.6, 38.5, 24.5. MS: 234 (M^+) , 91, 86. Anal. Found: C, 71.49; H, 7.62. Calc. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74%.

Synthesis of 3-hydroxymethylcyclobutanone ethylene ketal (6a)

To a 50 ml round-bottomed flask fitted with a septum, 3-benzyloxymethyl cyclobutanone ethylene ketal **5** (10.0 mmol, 2.34 g), Pd/C (234 mg, 10%) and ethyl acetate (30 ml) were added. The air in the flask was removed using a water aspirator and hydrogen gas was introduced using a hydrogen-filled balloon fitted with a needle. After stirring for 12 h at room temperature, the reaction mixture was filtered and the residual Pd/C was washed with ether. Removal of the solvent under reduced pressure yielded 1.42 g of the colorless crude product **6a**. ^{1}H NMR ($CDCl_3$): δ 3.86 (s, 4H), 3.60–3.63 (m, 2H), 2.90 (s, 1H), 1.85–2.45 (m, 5H). ^{13}C NMR: δ 106.6, 66.5, 63.9, 63.7, 37.6, 26.6. MS: 144 (M^+) . When methanol was used as solvent, **6b** was detected. The NMR spectrum of **6b** was identical to that reported in the literature.[51] ^{1}H NMR ($CDCl_3$): δ 3.61–3.64 (m, 2H), 3.16 (s, 3H), 3.13 (s, 3H), 2.90 (s, 1H), 1.85–2.45 (m, 5H). ^{13}C NMR: δ 100.7, 66.6, 48.4, 48.2, 34.0, 26.6.

Synthesis of 3-allyloxymethylcyclobutanone ethylene ketal (7)

Crude **6a** was placed in a 50 ml round-bottomed flask along with dry THF (15 ml) at 0 °C. Sodium hydride (270 mg, 11 mmol) was added in four portions. The reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 30 minutes, the reaction mixture was cooled to 0 °C and allyl bromide (11 mmol, 1.3 g) in THF (5 ml) was added via syringe. The mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed under reduced pressure, the residue hydrolyzed with water and extracted into diethyl ether (3 × 20 ml). The combined ethereal layer was dried over anhydrous magnesium sulfate, concentrated under reduced pressure, and the residue purified by column chromatography (hexane/EtOAc: 20/1) to afford ketal **7** as a colorless liquid (1.18 g, 64% yield based on **5**). ^{1}H NMR ($CDCl_3$): δ 5.83–5.97 (m, 1H), 5.15–5.30 (m, 2H), 4.12 (d, $J = 7.16$ Hz, 2H), 3.96 (s, 4H), 3.52 (d, $J = 6.41$ Hz, 2H), 2.27–2.47 (m, 3H), 2.04–2.12 (m, 2H). ^{13}C NMR: δ 134.7, 116.8, 106.7, 74.2, 71.9, 63.7, 63.6, 38.4, 24.4. MS: 183 ($M^+ - 1$), 113, 86. Anal. Found: C, 65.03; H, 9.01. Calc. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75%.

Synthesis of 3-allyloxymethylcyclobutanone (8)

A 100 ml round-bottomed flask was charged with ketal **7** (20 mmol, 3.67 g) in ethyl ether (50 ml) along with hydrochloric acid (1.5 ml, 2.0 M). The contents of the flask were stirred overnight at room temperature; thin-layer chromatography indicated complete disappearance of the starting ketal. The ethereal layer was separated and dried over anhydrous magnesium sulfate, concentrated under reduced pressure, and purified using a silica gel chromatography (hexane/EtOAc: 10/1) to obtain **8** as a colorless liquid (2.7 g, 96% yield). ^{1}H NMR ($CDCl_3$): δ 5.84–5.99 (m, 1H), 5.18–5.33 (m, 2H), 4.02 (d, $J = 5.54$ Hz, 2H), 3.52 (d, $J = 6.43$ Hz, 2H),

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3.08–3.20 (m, 2H), 2.83–2.93 (m, 2H), 2.66–2.71 (m, 1H). ^{13}C NMR: δ 207.4, 134.5, 117.1, 72.8, 72.0, 49.9, 24.5. MS: 139 ($M^+ - 1$), 80, 55. HRMS Calc. for $C_8H_{12}O_2$: 140.0837. Found: 140.0834.

Synthesis of hydantoin of 3-allyloxymethylcyclo butanone (9)

A 25 ml Ace pressure tube was charged with **8** (5.0 mmol, 0.70 g), aqueous ethanol (50%, 12 ml), potassium cyanide (10 mmol, 650 mg), and ammonium carbonate (25 mmol, 2.4 g). The reaction vessel was sealed and heated at 60 °C (oil bath) for 8 h. A faint yellow precipitate formed. The mixture was cooled to room temperature, carefully opened in a fume hood, and concentrated under reduced pressure. The solid obtained was purified by column chromatography (hexane/EtOAc: 1/3) to afford **9** as a white solid (0.9 g, yield: 86%). ^{1}H NMR ($CDCl_3$): δ 8.90 (s, 1H), 6.23, (s, 1H), 5.86–5.99 (m, 1H), 5.16–5.33 (m, 2H), 4.03 (d, $J = 5.94$ Hz, 2H), 3.45 (d, $J = 4.25$ Hz, 2H), 2.61–2.76 (m, 2H), 2.42–2.46 (m, 1H), 2.18–2.26 (m, 2H). ^{13}C NMR: δ 177.6, 156.2, 134.6, 117.6, 72.1, 59.6, 34.8, 27.3. Anal. Found: C, 57.01; H, 6.63; N, 13.16. Calc. for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33%.

Synthesis of boronohydantoin 10

$(Ipc)_2BH$ was prepared according to literature procedures:[61] 100 ml round-bottomed flask was fitted with a septum cap, a magnetic stirring bar and connected to a nitrogen bubbler. The flask was flushed with nitrogen and held at a positive static pressure of nitrogen. Boron–THF (50 ml of 1.0 M solution in THF, 50 mmol) was added to the flask, which was cooled to 0 °C, α-pinene (18.4 ml, 115 mmol) was added slowly and the mixture stirred at 0 °C for 1 h. The reaction was maintained at 0 °C for 3 days to generate the required crystalline product, which was used immediately. Compound **9** (0.63 g, 3.0 mmol) was placed in a 150 ml round-bottomed flask and dissolved in THF (15 ml) at 0 °C. $(Ipc)_2BH$ (9.0 mmol) was added dropwise via a syringe. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. Freshly distilled acetaldehyde (10 mmol) was added. The reaction mixture was stirred for 8 h and then hydrolyzed with hydrochloric acid (5 ml of 2 M solution). The solvent was removed under reduced pressure and the residue purified by column chromatography (methanol) to afford **10** as a white solid (0.65 g, 85%). ^{1}H NMR (DMSO–d_6): δ 8.17 (s, 1H), 7.39 (s, 1H), 3.28–3.35 (m, 4H), 2.34–2.51 (m, 3H), 1.9–2.01 (m, 2H), 1.51–1.57 (m, 2H), 0.59 (t, $J = 7.75$ Hz, 2H). ^{13}C NMR: δ 178.8, 156.0, 73.6, 72.6, 57.9, 35.2, 34.7, 26.2, 24.3. HR-FAB-MS ($M + H + gly - 2H_2O$; obtained in a glycerol matrix). Calc. for $C_{13}H_{22}BN_2O_6$: 313.1573. Found: 313.1577.

Synthesis of 1

Hydantoin **10** (384 mg, 1.5 mmol) was placed in a 25 ml Ace pressure tube along with aqueous sodium hydroxide (4 ml, 2 M). The tube was sealed and heated to 150 °C (oil bath) for 40 min. It was then cooled to room temperature, carefully opened (hood), charcoal added, and the mixture filtered through a pad of Celite. The Celite pad was washed with water. The filtrate was neutralized by adding aqueous hydrochloric acid (1 M). After removing the water *in vacuo*, a white solid remained which was extracted with dry methanol (3 × 20 ml) to remove the NaCl. The crude product was purified via a short column chromatography (methanol) to afford **1** as a white solid (280 mg, yield: 85%). ^{1}H NMR (D_2O): δ 3.35–3.55 (m, 4H), 2.14–2.45 (m, 3H), 1.95–2.05 (m, 2H), 1.49–1.53 (m, 2H), 0.61 (t, $J = 7.69$ Hz, 2H). ^{13}C NMR: δ 182.3, 76.2, 73.4, 66.2, 35.0, 34.1, 25.6, 24.0. HR-FAB-MS ($M + H + gly - 2H_2O$; obtained in a glycerol matrix). Calc. for $C_{12}H_{23}BNO_6$: 288.1621. Found: 288.1616.

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