

Boron Analogues of Amino Acids. 4.¹ Synthesis of Glycine and N-Methylated Glycine Ester Analogues

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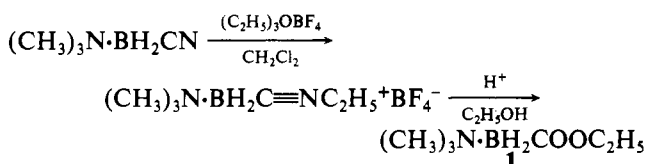
Selected representatives of a series of esters derived from boron analogues of amino acids and having the general formulation amine·BH₂COOR (amine = (CH₃)₃N, (CH₃)₂NH, CH₃NH₂, NH₃; R = CH₃, CH₂CH₃, CH₂CH₂Cl) were prepared in good to excellent yields by condensing the corresponding acids and alcohols with dicyclohexylcarbodiimide (DCC) at room temperature in CH₂Cl₂. (CH₃)₂NH·BH₂COOCH₃ and H₃N·BH₂COOCH₃ were prepared in 67% and 49% yields, respectively, by amine-exchange reactions of (CH₃)₃N·BH₂COOCH₃ with (CH₃)₂NH and NH₃. (CH₃)₃N·BH₂COOSi(CH₃)₃ was obtained by reacting (CH₃)₃N·BH₂COOLi and (CH₃)₃SiCl.

Introduction

Isoelectronic and isosteric boron analogues of the amino acids glycine and betaine (H₃N·BH₂COOH² and (CH₃)₃N·BH₂COOH,³ respectively) and their derivatives and precursors have been shown to possess interesting biological activities, in particular, significant antitumor, antiarthritic, and hypolipidemic activities in rodents.⁴⁻⁶ For example, (CH₃)₃N·BH₂COOH afforded 82% inhibition of tumor growth in the Ehrlich Ascites screen⁴ and lowered serum cholesterol levels by 49% at low dosages.⁶ An ester, trimethylamine-carbethoxyborane, (CH₃)₃N·BH₂COOC₂H₅ (**1**), produced 74% inhibition of the induced arthritic state⁵ and lowered serum cholesterol levels⁶ by 36% in animal model studies. In view of their potential biological activities, we have therefore prepared selected representative members of a series of alkyl esters having the general formulation amine·BH₂COOR (amine = (CH₃)₃N, (CH₃)₂NH, CH₃NH₂, NH₃; R = CH₃, CH₂CH₃, CH₂CH₂Cl, Si(CH₃)₃) for structure-activity relationship studies. These compounds may also prove to be useful in boron neutron capture therapy for the treatment of cancer.⁷

Results and Discussion

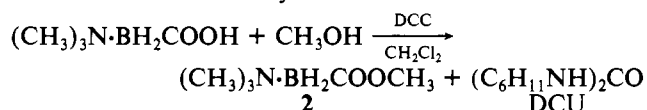
Trimethylamine-carbethoxyborane, (CH₃)₃N·BH₂COOC₂H₅ (**1**), was prepared as described previously⁵ by refluxing a solution of (CH₃)₃N·BH₂CN⁸ in CH₂Cl₂ with 2 equiv of (C₂H₅)₃OBF₄⁹ under dry N₂ for 24 h. The resulting N-



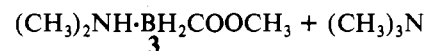
ethylnitrilium salt (not isolated) was alcoholized at reflux temperature for 48 h with 95% ethanol and concentrated HCl. After neutralization, workup resulted in a yellow liquid, which was either crystallized or sublimed to give a 34% yield of the ethyl ester. This ester (**1**) was also made by an alternative method in 45% yield by dehydrating a solution of (CH₃)₃N·BH₂COOH³ and absolute ethanol with dicyclohexylcarbodiimide (DCC) at room temperature for 6 days. The relatively high volatility and solubility in water of this sweet-smelling ester probably contributed to its low yield by either of these procedures.

Trimethylamine-carbomethoxyborane, (CH₃)₃N·BH₂COOCH₃ (**2**), was prepared in 82% yield by condensing (CH₃)₃N·BH₂COOH and CH₃OH with DCC at room temperature for 1 week; extension of the reaction period to 2 weeks

led to an increase in the yield of **2** to 98%.

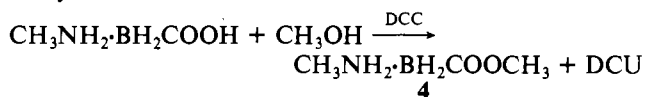


Dimethylamine-carbomethoxyborane, (CH₃)₂NH·BH₂COOCH₃ (**3**), was prepared in 67% yield by an amine-exchange reaction of (CH₃)₃N·BH₂COOCH₃ (**2**) with an 8-fold excess (CH₃)₂NH →

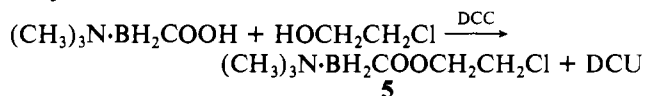


(by weight) of (CH₃)₂NH in a glass pressure reaction vessel for 2 weeks at room temperature. Ca. 8% unreacted **2** in the product mixture was readily removed by washing with H₂O and vacuum pumping. The ester linkages in the starting material and product were not cleaved by the excess amine. The amine-exchange process is the preferred route as the alternative preparation of **3** by condensation of (CH₃)₂NH·BH₂COOH and CH₃OH with DCC at room temperature for 4 days gave only a very low yield (8%).

Methylamine-carbomethoxyborane, CH₃NH₂·BH₂COOCH₃ (**4**), was prepared in 21% yield of condensing CH₃NH₂·BH₂COOH and CH₃OH with DCC at room temperature for 6 days.



Trimethylamine-(carbo-2-chloroethoxy)borane, (CH₃)₃N·BH₂COOCH₂CH₂Cl (**5**), was prepared in 61% yield in a manner similar to the preparation of **4** by condensing (CH₃)₃N·BH₂COOH and HOCH₂CH₂Cl with DCC at room temperature for 1 week.



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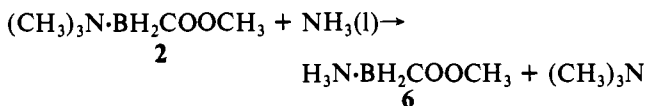
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Table I. Physical and Spectral Data for Esters of Boron Analogues of Amino Acids

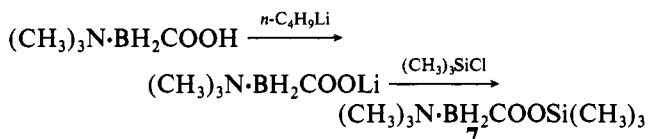
compd	ester	bp/mp, °C	yield, %	¹¹ B chem shifts, ppm ^a	J _{B-H} , Hz
1	(CH ₃) ₃ N·BH ₂ COOC ₂ H ₅	45–47	34–41	–9.17 (t)	98
2	(CH ₃) ₃ N·BH ₂ COOCH ₃	90–92	82–98	–9.09 (t)	99
3	(CH ₃) ₂ NH·BH ₂ COOCH ₃	52–53	67	–12.57 (t)	95
4	CH ₃ NH ₂ ·BH ₂ COOCH ₃	56–57	21	–16.22 (t)	98
5	(CH ₃) ₂ N·BH ₂ COOCH ₂ CH ₂ Cl	...	61	–8.75 (t)	97
6	H ₃ N·BH ₂ COOCH ₃	92–93	49	–20.45 (t)	94
7	(CH ₃) ₃ N·BH ₂ COOSi(CH ₃) ₃	60 (0.2 torr)	58		

^a (C₂H₅)₂O·BF₃ was used as an external standard; all chemical shifts reported here were (negative) upfield from the standard.

Ammonia-carboxymethoxyborane, H₃N·BH₂COOCH₃ (**6**), was prepared in 49% yield by an amine-exchange reaction¹⁰ involving (CH₃)₃N·BH₂COOCH₃ (**2**) and excess liquid NH₃ at room temperature for 2 weeks.



Trimethylamine-(carbotrimethylsiloxy)borane, (CH₃)₃N·BH₂COOSi(CH₃)₃ (**7**), was prepared by a different procedure involving lithiation of (CH₃)₃N·BH₂COOH with *n*-C₄H₉Li under dry N₂ in ether and subsequent reaction of the lithium salt (not isolated) with (CH₃)₃SiCl at ambient temperature for ca. 16 h. Workup and vacuum distillation afforded 58% of the silyl ester **7** as a clear, moisture-sensitive liquid that solidified on standing.



All of the new compounds were characterized by elemental analysis and IR, ¹H NMR and ¹¹B NMR spectroscopy. Physical and spectral data of the esters are given in Table I. IR spectra exhibited characteristic B—H and C=O absorptions; ¹H and ¹¹B NMR spectral data were consistent with the structures shown for the compounds.

Studies on the biological activities of these esters are in progress and will be reported elsewhere.

Experimental Section

General Data. IR spectra were recorded on a Perkin-Elmer 297 spectrometer. Solid samples were prepared as KBr disks, as Nujol mulls between NaCl disks, or as solutions in suitable solvents; oils were recorded neat. Proton and boron NMR spectra were obtained on Varian EM 360A and JEOL FX 90Q spectrometers, respectively. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, or Schwarzkopf Microanalytical Laboratory, Inc., Woodside, NY. The following compounds were purchased and used without further purification: (CH₃)₃N·HCl (Aldrich), ClCH₂CH₂OH (Aldrich), NaBH₃CN (Aldrich), (CH₃)₂NH (Eastman), CH₃NH₂ (Union Carbide), *N,N'*-dicyclohexylcarbodiimide (Chemalog), *n*-C₄H₉Li (Alfa). (CH₃)₃N·BH₂CN was prepared⁸ from (CH₃)₃N·HCl and NaBH₃CN. (CH₃)₃N·BH₂COOH was prepared³ from (C-H₃)₃N·BH₂CN and (C₂H₅)₂O·BF₃⁹ followed by hydrolysis. (C-H₃)₂NH·BH₂COOH and CH₃NH₂·BH₂COOH were prepared⁷ from (CH₃)₃N·BH₂COOH by amine-exchange reactions with (CH₃)₂NH and CH₃NH₂, respectively, in 250 mL glass pressure reaction vessels that were purchased along with their safety shields from Lab-Crest Scientific Co., Warminster, PA. (CH₃)₃SiCl (Aldrich) was distilled prior to use. (C₂H₅)₂O·BF₃ was either purchased (Aldrich) or prepared by a known method.⁹

Preparation of (CH₃)₃N·BH₂COOC₂H₅ (1**).** **Method a.** A solution of (CH₃)₃N·BH₂COOH (15.00 g, 0.128 mol) and DCC (29.12 g, 0.141

mol, 10% excess) in absolute ethyl alcohol (100 mL) was stirred at ambient temperature for 6 days. The solution became cloudy, and the insoluble *N,N'*-dicyclohexylurea (DCU) that formed was filtered off. Water (100 mL) was added to the filtrate, and the resulting solution was extracted with CH₂Cl₂ (4 × 100 mL). The CH₂Cl₂ extracts were treated with charcoal, dried over MgSO₄, and filtered. The filtrate was concentrated in a rotary evaporator, and the resulting oily material was vacuum sublimed at 50 °C. Finally, the product was crystallized from CH₂Cl₂/pentane (2:1) to give sweet-smelling crystalline **1** (7.5 g, 40.4%); the physical and chemical properties of the compound perfectly matched those reported for method b.

Method b.⁵ A solution of the *N*-ethylnitrilium salt, (CH₃)₃N·BH₂C≡NC₂H₅⁺BF₄⁻, was prepared by refluxing a mixture of (C-H₃)₃N·BH₂CN (19.56 g, 0.2 mol) and 1 N (C₂H₅)₃OBf₄ in CH₂Cl₂ (400 mL, 0.4 mol, 100% excess) for 24 h. Following the addition of 95% C₂H₅OH (200 mL) and concentrated HCl (8 mL), the mixture was refluxed for 48 h, then cooled, and neutralized with a saturated NaHCO₃ solution, and the excess C₂H₅OH was removed under reduced pressure. The product was extracted from the aqueous solution with CH₂Cl₂. Drying the organic portion over MgSO₄ followed by solvent removal produced a yellow liquid. Purification by crystallization from diethyl ether or by sublimation afforded the sweet-smelling volatile ester **1** as a white crystalline solid (9.9 g, 34%): mp 45–47 °C; IR (CDCl₃) 2380 (ν_{BH}), 1660 (ν_{CO}) cm⁻¹; ¹H NMR (CDCl₃) δ 1.22 (t, CH₃), 2.76 (s, (CH₃)₃N), 4.07 (q, CH₂); ¹¹B NMR (CDCl₃, (C₂H₅)₂O·BF₃) δ –9.17 (t, J_{B-H} = 98 Hz). Anal. Calcd for C₆H₁₆BNO₂: C, 49.70; H, 11.12; B, 7.46; N, 9.77. Found: C, 49.96; H, 11.04; B, 7.56; N, 9.56.

Preparation of (CH₃)₃N·BH₂COOCH₃ (2**).** A solution of (C-H₃)₃N·BH₂COOH (9.36 g, 0.08 mol) and DCC (25 g, 0.12 mol, 50% excess) in anhydrous CH₃OH (150 mL) was stirred at ambient temperature for 1 week. The initially clear solution turned cloudy, and DCU was precipitated gradually. Following the addition of H₂O, the mixture was extracted repeatedly with CH₂Cl₂ (5 × 100 mL). The organic portion was dried over MgSO₄, and the solvent was removed by rotary evaporation to give white needles of ester **2** along with some DCU as impurity. The crude product was dissolved in CH₂Cl₂, the insoluble DCU filtered off, and the solvent removed. Recrystallization of the ester from diethyl ether/pentane gave white needles (8.58 g, 82%): mp 90–92 °C; IR (CDCl₃) 2950 (ν_{CH}), 2385 (ν_{BH}), 1660 (ν_{CO}) cm⁻¹; ¹H NMR (CDCl₃) δ 2.72 (s, (CH₃)₃N), 3.48 (s, OCH₃); ¹¹B NMR (CDCl₃, (C₂H₅)₂O·BF₃) δ –9.09 (J_{B-H} = 99 Hz). Anal. Calcd for C₅H₁₄BNO₂: C, 45.85; H, 10.77; N, 10.69. Found: C, 45.95; H, 10.99; N, 10.56.

A similar reaction was carried out with (CH₃)₃N·BH₂COOH (11.2 g, 0.109 mol) and DCC (27 g, 0.131 mol, 20% excess) in CH₃OH (250 mL) for 2 weeks at ambient temperature. After similar workup, the crude product was purified by vacuum sublimation at 100 °C to give **2** (14 g, 98%).

Preparation of (CH₃)₂NH·BH₂COOCH₃ (3**).** Anhydrous (C-H₃)₂NH (50 g, 1.1 mol) was cooled to 0 °C and poured into a glass pressure reaction vessel containing (CH₃)₃N·BH₂COOCH₃ (**2**) (6 g, 0.046 mol) maintained at 0 °C. The vessel was assembled and stored at ambient temperature for 2 weeks with occasional shaking each day. The reaction vessel was then cooled to 0 °C and opened slowly. Pentane (ca. 80 mL) and CH₂Cl₂ (50 mL) were added to the solution, and the excess volatile amines were allowed to evaporate off. The remaining amines and solvent were removed by rotary evaporation. The thick liquid thus obtained solidified on standing and contained ca. 8% of unreacted ester **2** (by ¹H NMR). The mixture was dissolved in CH₂Cl₂, treated with MgSO₄ and activated charcoal, and then filtered over Celite. Removal of the solvent gave 5.4 g of a brown oily material, which was taken up in CH₂Cl₂, washed with water (2

(10) The ammonia-exchange reaction was carried out in a stainless steel pressure vessel obtained from Pope Scientific, Inc., Menomonee Falls, WI.

× 60 mL), and dried over MgSO₄. After removal of the solvent, pure solid ester (3.6 g, 67.1%) was obtained. An analytical sample was prepared by recrystallization from diethyl ether at -78 °C: mp 52–53 °C; IR (CDCl₃) 2940 (ν_{CH}), 2380 (ν_{BH}), 1660 (ν_{CO}) cm⁻¹; ¹H NMR (CDCl₃) δ 2.5 (d, (CH₃)₂N), 3.5 (s, OCH₃); ¹¹B NMR (CDCl₃, (C₂H₅)₂O·BF₃) δ -12.57 (t, J_{B-H} = 95 Hz). Anal. Calcd for C₄H₁₂BNO₂: C, 41.08; H, 10.34; N, 11.98. Found: C, 41.25; H, 10.32; N, 11.88.

Preparation of CH₃NH₂·BH₂COOCH₃ (4). A solution of CH₃NH₂·BH₂COOH⁷ (1.68 g, 0.019 mol) and DCC (4.29 g, 0.021 mol, 10% excess) in anhydrous CH₃OH (100 mL) was stirred at ambient temperature for 6 days. The initially clear solution subsequently became cloudy, and to the resulting suspension was added H₂O (ca. 100 mL). The entire mixture was then filtered and washed with CH₂Cl₂ (3 × 50 mL). The residue resulting from evaporation of the CH₃OH/H₂O portion under reduced pressure was taken up in diethyl ether and placed in a freezer. Crude ester **4** precipitated and was recrystallized from CH₂Cl₂/pentane (3:1) in a freezer. Finally, the crystalline ester was washed with a small portion of cold water to yield 0.41 g (21%) of **4**: mp 56–57 °C; IR (Nujol) 2400 (ν_{BH}), 1650 (ν_{CO}) cm⁻¹; ¹H NMR (CDCl₃) δ 2.55 (t, (CH₃)₃N), 3.57 (s, OCH₃), 4.35 (broad s, NH₂); ¹¹B NMR (CDCl₃, (C₂H₅)₂O·BF₃) δ -16.22 (t, J_{B-H} = 98 Hz). Anal. Calcd for C₃H₁₀BNO₂: C, 35.01; H, 9.79; B, 10.50; N, 13.61. Found: C, 35.22; H, 9.67; B, 10.27; N, 13.62.

Preparation of (CH₃)₃N·BH₂COOCH₂CH₂Cl (5). A solution of (CH₃)₃N·BH₂COOH (5.85 g, 0.5 mol), HOCH₂CH₂Cl (4.03 g, 0.5 mol), and DCC (10.32 g, 0.5 mol) in CH₂Cl₂ (200 mL) was stirred at ambient temperature for 1 week. The resulting insoluble DCU was filtered out, and additional CH₂Cl₂ (50 mL) was added to the filtrate, which was then washed with water (3 × 50 mL). The organic portion was dried over MgSO₄, and the solvent was removed by rotary evaporation. The oily product was then vacuum pumped, and some DCU was filtered out. This process was repeated several times until all DCU was removed and semisolid ester **6** (6 g, 61%) was obtained: IR (CDCl₃) 3100 (ν_{CH}), 2400 (ν_{BH}), 1660 (ν_{CO}) cm⁻¹; ¹H NMR (CDCl₃) δ 2.73 (s, (CH₃)₃N), 3.7 (t, CH₂Cl), 4.7 (t, OCH₂); ¹¹B NMR (CDCl₃, (C₂H₅)₂O·BF₃) δ -8.75 (t, J_{B-H} = 97 Hz).

Preparation of H₃N·BH₂COOCH₃ (6). Anhydrous NH₃ condensed into a stainless-steel pressure reaction vessel containing (CH₃)₃N·B-

H₂COOCH₃ (**2**) (3.69 g, 0.0282 mol) maintained at -78 °C. The vessel was assembled and stored at ambient temperature for 1 week, following which it was vented of excess NH₃ under N₂. The yellow residue obtained was first washed with CH₂Cl₂ (3 × 50 mL) and then dissolved in CH₃OH (50 mL). The resulting solution was treated with activated charcoal and filtered over Celite, and CH₃OH was removed under reduced pressure to yield solid **6** (1.24 g, 49% pure by ¹H and ¹¹B NMR). An analytical sample was obtained by recrystallization from methanol/diethyl ether/petroleum ether at -30 °C: mp 92–93 °C; IR (KBr disk) 2370 (ν_{BH}), 1660 (ν_{CO}) cm⁻¹; ¹H NMR (D₂O) δ 3.57 (s, OCH₃); ¹¹B NMR (D₂O, (C₂H₅)₂O·BF₃) δ -20.47 (t, J_{B-H} = 94 Hz). Anal. Calcd for C₂H₈BNO₂: C, 27.02; H, 9.07; N, 15.76. Found: C, 27.04; H, 9.05; N, 15.66.

Preparation of (CH₃)₃N·BH₂COOSi(CH₃)₃ (7). To a 250-mL three-necked flask equipped with a condenser, dropping funnel, magnetic stirrer, nitrogen inlet, and oil bubbler were added (C-H₃)₃N·BH₂COOH (5.85 g, 0.050 mol) and diethyl ether (150 mL). The slurry was cooled to 0 °C, and 2.45 M *n*-C₄H₉Li in hexane (20.4 mL, 0.050 mol) was added slowly under N₂. The resulting mixture was stirred at room temperature for 1 h. Freshly distilled (CH₃)₃SiCl (6.4 mL, 0.050 mol) was then added slowly to the mixture, which was stirred at room temperature overnight and filtered under N₂, and the solvent was removed under reduced pressure. Finally, the crude silyl ester was vacuum distilled to give a clear moisture-sensitive liquid that solidified on standing (5.5 g, 58%): bp 60 °C (0.2 torr); IR (neat) 2875 (ν_{CH}), 2380 (ν_{BH}), 1640 (ν_{CO}) cm⁻¹; ¹H NMR (CDCl₃) δ 0.22 (s, (CH₃)₃Si), 2.68 (s, (CH₃)₃N). Anal. Calcd for C₇H₂₀BNO₂Si: C, 44.45; H, 10.66; B, 5.72; N, 7.41. Found: C, 44.71; H, 10.59; B, 5.81; N, 7.41.

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Registry No. **1**, 75519-14-1; **2**, 91993-52-1; **3**, 91993-53-2; **4**, 91993-54-3; **5**, 91993-55-4; **6**, 92009-78-4; **7**, 91993-56-5; DCC, 538-75-0; DCU, 2387-23-7; (CH₃)₃N·BH₂COOH, 89277-72-5; CH₃NH₂·BH₂COOH, 91993-57-6; (CH₃)₃N·BH₂C≡NC₂H₅⁺BF₄⁻, 60788-38-7; (CH₃)₃N·BH₂CN, 30353-61-8; (C₂H₅)₃OBF₄, 368-39-8; C₂H₅OH, 64-17-5; CH₃OH, 67-56-1; HOCH₂CH₂Cl, 107-07-3; (CH₃)₃SiCl, 75-77-4.