Boron Analogues of α-Amino Acids: Synthesis and Characterization of Some Amine-methoxycarbonylboranes and Trimethylamine-(alkylcarbamoyl)boranes

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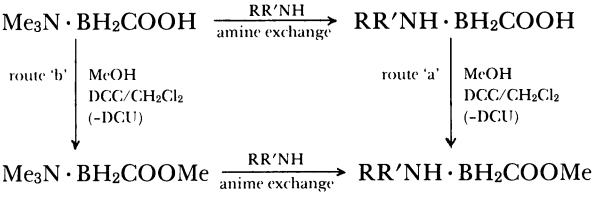
Syntheses of a number of amine-methoxycarbonylboranes $R_{2-n}H_nN \cdot BH_2COOCH_3$ and trimethylamine-(alkylcarbamoyl)boranes, $Me_3N \cdot BH_2CONRR'$ are reported. Both types of compounds have been prepared by condensing appropriate amine-carboxyboranes with methanol and an amine, respectively, in presence of dicyclohexylcarbodiimide, and have bean characterized by elemental analysis, IR and NMR (^1H and ^{11}B) spectra.

Amine-carboxyboranes and their derivatives have attracted considerable attention because of their various biological activities.[1-5] This has encouraged us to synthesize a number of such compounds,[6] and now we report here the syntheses of a number of esters and amides.

Results and Discussion

(i) Amine-methoxycarbonylboranes. Only four amine-methoxycarbonylboranes[7] have so far been reported by amine-exchange from $Me_3N \cdot BH_2COOMe$. These have been shown to possess significant hypolipidemic activity in rodents.[5] Therefore, methyl esters of the amine-carboxyboranes[6] reported earlier have been synthesized by either of the two general methods shown in Scheme 1. (DCC=dicyclohexylcarbodiimide, DCU=dicyclohexylurea).



No.	R	R′	No.	R	R′
1	H	n-C_3H_7	**5**	C_2H_5	C_2H_5
2	H	n-C_4H_9	**6**	i-C_3H_7	i-C_3H_7
3	H	s-C_4H_9	**7**	n-C_4H_9	n-C_4H_9
4	H	i-C_3H_7	**8**	i-C_4H_9	i-C_4H_9

Scheme 1.

Five alkylamine-methoxycarbonylboranes derived from secondary and primary amines (**4—8**) have been synthesized by route 'a' while the rest three (**1—3**) by route 'b' from $Me_3N \cdot BH_2COOMe$. The latter method was found to be the better one, as it gives purer products free from DCU.

In the IR the ν(N-H) absorptions occur at 3240—3060 cm^{-1} and the ν(B-H) modes occur at 2400—2295 cm^{-1}, while ν(C=O) modes occur as strong bands at 1665—1652 cm^{-1} which are in good agreement with those reported earlier.[7] In the ^1H NMR, ester methyl group resonances occur at 3.58—3.8 ppm, and the alkyl protons of the amines in their usual positions and patterns. The $\delta(^{11}B)$ values of −7.8 to −18.8 ppm suggest tetracoordinated nature of boron bonded to an electronegative substituent, having electronegativity similar to that of a cyano[8] or carboxy substituent.[6]

(ii) Trimethylamine-(alkylcarbamoyl)boranes. Three knowrn *N*-ethylcarbamoyl derivatives have been prepared by the amine exchange[9] from $Me_3N \cdot BH_2CONHEt$.[1] The reported method therefore cannot give any other *N*-alkylcarbamoyl derivatives. Consequently, a new general method was developed by which five amides have been prepared by the direct reaction between an amine and a representative amine-carboxyborane in presence of the peptide condensing agent, DCC (Eq. 1).

$$Me_3N \cdot BH_2COOH + RR'NH \xrightarrow[CH_2Cl_2,\ r.t.]{DCC} Me_3N \cdot BH_2CONRR' + DCU \quad (1)$$

No.	R	R′
9	H	i-C_3H_7
10	H	n-C_4H_9
11	H	s-C_4H_9
12	i-C_3H_7	i-C_3H_7
13	n-C_4H_9	n-C_4H_9

In this reaction large excess of DCC is required to shift the reaction towards product side, but the net excess DCC can be removed by hydrolysis to DCU. All compounds excepting the (diisopropylcarbamoyl)borane adduct which is a solid, are pale yellow liquids. For the amides derived from primary amines (**9—11**) the ν(N-H) modes are found as strong bands at 3240—3040 cm^{-1}, while the ν(B-H) modes occur at 2410—2320 cm^{-1}. For the CONH function of (isopropylcarbamoyl)-, (butylcarbamoyl)-, and (*s*-butylcarbamoyl)boranes the amide I bands appear at 1645 cm^{-1}, 1620 cm^{-1}, and 1635 cm^{-1}, respectively while the amide II modes appear at 1590 cm^{-1}, 1600 cm^{-1}, and 1620 cm^{-1}, respectively. For the other two amides (**12** and **13**) the ν(C=O) modes occur at 1670 cm^{-1} and 1620 cm^{-1}, respectively. The ^1H NMR spectra of the five

(alkylcarbamoyl)boranes show the presence of the aliphatic amide groups with the pattern expected for such groups. For (isopropylcarbamoyl)borane adduct a doublet at 1.15 ppm, and for the (diisopropylcarbamoyl)borane adduct double doublets at 1.1 and 1.44 ppm were found for CH_3 group of the isopropyl unit, in consonance with the corresponding amine-carboxyboranes.[6b] The CH protons could not be detected in most cases. For the rest three, typical butyl absorptions have been obtained. The $\delta(^{11}B)$ values of −5.6 to −11.7 are in consonance with those reported earlier for the acids[6] and amides[9] and are indicative of the presence of tetracoordinated boron with electronegative substituents.

Trimethylamine-(ethylcarbamoyl)borane has been shown to possess significant antitumour,[1] antiinflammatory, and antiarthritic[2] and antihyperlipidemic[3] activities in biological models. Biological studies on 10 random compounds which include phosphine-boranes and their derivatives,[11] aromatic amine-cyanoboranes[8] and the amide $Me_3N \cdot BH_2CON(i\text{-}C_3H_7)_2$ (**12**) have been carried out.[12] Antitumour, antiinflammatory, and antihyperlipidemic activity studies, in addition to other cytotoxicity, have been carried out on CF_1 male mice. Preliminary biological screens[12] in CF_1 male mice have demonstrated an inhibition of 86% of tumour growth for **12** in Ehrich Ascites screen and 66% control in antiinflammatory activity, both at a dosage of 8 mg kg^{-1} day^{-1}. After 16 days of administration at the same dosage level, serum cholesterol and triglyceride controls were 61±5% and 55±3%, respectively, compared to 87±5% and 75±5%, respectively, for clofibrate (at 150 mg kg^{-1} day^{-1}). Detailed studies on **12** and others are in progress and will be published soon.

Experimental

All chemicals and reagents were of reagent grade quality. The amines and solvents were purified and dried by standard methods. Dicyclohexylcarbodiimide (DCC) (Riedel) was used without further purification. $Me_3N \cdot BH_2COOH$[2] and other amine-carboxyboranes[6] were prepared by published methods. Infrared spectra were recorded on a Perkin-Elmer 883 spectrophotometer, as thin films or as KBr pellets. ^1H NMR spectra were recorded in $CDCl_3$ on a JEOL JNM-FX-100 spectrometer (TMS, internal standard) and ^{11}B NMR spectra in $CDCl_3$ on a JEOL FX-90Q or a Bruker AM-500 FT-NMR spectrometer ($BF_3 \cdot OEt_2$, external standard). Boron was estimated volumetrically[10] and nitrogen by Kjeldhal method.

(i) Preparation of Amine-methoxycarbonylboranes, $RR'NH \cdot BH_2COOMe$. Compounds **1—3** were prepared by procedure (a), while **4—8** by procedure (b), described below.

Procedure (a): A mixture of $Me_3N \cdot BH_2COOMe$ (1.0 g, 7.6 mmol) and excess of respective amine (ca. 10 ml) was refluxed for 6 h in a round bottomed flask (100 ml), using a $CaCl_2$ drying tube. On cooling, excess of amine was removed in vacuum leaving behind a thick yellow liquid, which was triturated with dry ether several times. It was filtered to remove insolubles and solvent was removed similarly leaving a light yellow-colored liquid as product, which was dried in vacuum. Yield 50—70 %.

Procedure (b): To a solution of $RR'NH \cdot BH_2COOH$ (10 mmol) in dichloromethane (25 ml) in a round bottomed flask (100 ml) equipped as in (a) and with a magnetic stirring bar, anhydrous methanol (10 ml) and dicyclohexylcarbodiimide (DCC) (3.09 g, 15 mmol, 50% excess) were added and allowed to stir for two weeks at room temperature. Gradually the solution became cloudy due to the formation of insoluble dicyclohexylurea (DCU). On completion of the reaction, water (25 ml) was added to the solution and stirred. Then the organic part was extracted with dichloromethane (3×25 ml portions) and the combined extract was dried over anhydrous $MgSO_4$ and finally removed on a rotary evaporator, leaving behind the product. The contaminated DCU was removed by dissolving the product in dichloromethane (25 ml) and filtering the undissolved particles and removing the solvent in vacuum. The process may be repeated, if required, to remove DCU completely. Yield 50—70%.

(ii) Preparation of Trimethylamine-(alkylcarbamoyl)-boranes, $Me_3N \cdot BH_2CONRR'$. $Me_3N \cdot BH_2COOH$[2] (1.17 g, 10 mmol) was dissolved in dichloromethane (25 ml) in a round bottomed flask (100 ml) having a similar setup as in (i) (b). To this solution the appropriate amine (10 mmol) and DCC (15 mmol, 50% excess) were added. The solution was allowed to stir for seven days at room temperature when it gradually turned cloudy due to precipitation of DCU. The rest of the procedure was the same as that for the methyl esters [vide i(b)]. Yield 60—70%.

(n-C_3H_7)$NH_2 \cdot BH_2CO_2Me$ (1). 0.6 g (60%); ν(NH) 3235 s, 3145 s; ν(BH) 2380 s, 2300 sh; ν(CO) 1652 s; $\delta(^1H)$=0.98 (t, CH_3), 1.70 (q, CH_2), 2.75 (q, NCH_2), 3.58 (s, OCH_3); $\delta(^{11}B)$=−14.4. Found: B, 8.33; N, 10.48%. Calcd for $C_5H_{14}NBO_2$: B, 8.25; N, 10.69%.

(n-C_4H_9)$NH_2 \cdot BH_2CO_2Me$ (2). 0.78 g (70%); ν(NH) 3240 s, 3158 s; ν(BH) 2395 s, 2295 sh; ν(CO) 1660 s; $\delta(^1H)$=0.97 (t, CH_3), 1.40 (q, CH_2), 1.70 (q, CH_2), 2.8 (q, NCH_2), 3.58 (s, OCH_3); $\delta(^{11}B)$=−18.8. Found: B, 7.19; N, 9.94%. Calcd for $C_6H_{16}NBO_2$: B, 7.45; N, 9.66%.

(s-C_4H_9)$NH_2 \cdot BH_2CO_2Me$ (3). 0.55 g (50%); ν(NH) 3220 s, 3130 s; ν(BH) 2400 s, 2300 s; ν(CO) 1658 s; $\delta(^1H)$=0.99 (t, CH_3), 1.23 (d, CH_3CH), 2.88 (m, NCH_2), 3.60 (m, OCH_3); $\delta(^{11}B)$=−18.5. Found: B, 7.29; N, 9.96%. Calcd for $C_6H_{16}NBO_2$: B, 7.45; N, 9.66%.

(i-C_3H_7)$NH_2 \cdot BH_2CO_2Me$ (4). 0.39 g (70%); m.p. 76 °C; ν(NH) 3240 s, 3160 s; ν(BH) 2390 s, 2300 s; ν(CO) 1660 s; $\delta(^1H)$=1.3 (d, CH_3), 3.30 (m, NCH), 3.80 (s, OCH_3); $\delta(^{11}B)$=−14.2. Found: B, 7.98; N, 11.1%. Calcd for $C_5H_{14}NBO_2$: B, 8.25; N, 10.69%.

(C_2H_5)$_2NH \cdot BH_2CO_2Me$ (5). 0.43 g (70%); ν(NH) 3160 s; ν(BH) 2395 s, 2360 sh; ν(CO) 1660 s; $\delta(^1H)$=1.28 (t, CH_3), 2.96 (q, NCH_2), 3.65 (s, OCH_3); $\delta(^{11}B)$=−14.0. Found: B, 7.73; N, 9.42%, Calcd for $C_6H_{16}NBO_2$: B, 7.45; N, 9.66%.

(i-C_3H_7)$_2NH \cdot BH_2CO_2Me$ (6). 0.53 g (60%); ν(NH) 3060 s; ν(BH) 2400 s, 2360 sh; ν(CO) 1665 s; $\delta(^1H)$=1.20, 1.32 (double doublets, CH_3), 3.24 (m, NCH), 3.58 (d, OCH_3); $\delta(^{11}B)$=−7.8. Found: B, 5.95; N, 8.43%. Calcd for $C_8H_{20}NBO_2$: B, 6.25; N, 8.09%.

(n-C_4H_9)$_2NH \cdot BH_2CO_2Me$ (7). 0.6 g (55%); ν(NH) 3060 m; ν(BH) 2400 s, 2380 sh; ν(CO) 1658 s; $\delta(^1H)$=0.96 (t, CH_3), 1.32 (m, CH_2), 1.64 (m, CH_2), 2.8 (m, NCH_2), 3.68 (s, OCH_3);

$\delta(^{11}B)=-11.7$. Found: B, 4.94; N, 7.35%. Calcd for $C_{10}H_{24}NBO_2$: B, 5.37; N, 6.96%.

$(i\text{-}C_4H_9)_2NH \cdot BH_2CO_2Me$ (8). 0.43 g (50%); ν(NH) 3160 s; ν(BH) 2400 s, 2360 sh; ν(CO) 1660 s; $\delta(^1H)=0.96$ (d, CH_3), 2.16 (m, $CHCH_2$), 3.68 (s, OCH_3); $\delta(^{11}B)=-14.3$. Found: B, 4.98; N, 7.32%. Calcd for $C_{10}H_{24}NBO_2$: B, 5.37; N, 6.96%.

$(CH_3)_3N \cdot BH_2CONH(i\text{-}C_3H_7)$ (9). 0.75 g (60%); ν(NH) 3040 s; ν(BH) 2410 s, 2370 sh; ν(CO) 1645 (amide I), 1590 (amide II); $\delta(^1H)=1.15$ (d, $CHCH_3$), 2.7 (s, NCH_3); $\delta(^{11}B)=-11.7$. Found: B, 6.51; N, 17.89%. Calcd for $C_7H_{19}N_2BO$: B, 6.84; N, 17.72%.

$(CH_3)_3N \cdot BH_2CONH(n\text{-}C_4H_9)$ (10). 0.77 g (60%); ν(NH) 3080 s; ν(BH) 2400 s, 2360 sh; ν(CO) 1620 s (amide I), 1600 m (amide II); $\delta(^1H)=0.88$ (t, CH_3), 1.3 (br, $(CH_2)_2$), 1.8 (br, NCH_2), 2.7 (s, NCH_3); $\delta(^{11}B)=-6.6$. Found: B, 5.92; N, 16.56%. Calcd for $C_8H_{21}N_2BO$: B, 6.28; N, 16.28%.

$(CH_3)_3N \cdot BH_2CONH(s\text{-}C_4H_9)$ (11). 0.92 g (62%); ν(NH); 3240 s; ν(BH) 2420 s, 2360 s; ν(CO) 1635 s (amide I), 1620 s (amide II); $\delta(^1H)=0.92$, 1.12 (double doublets, CH_3), 1.4 (m, CH_2), 2.79 (s, NCH_3); $\delta(^{11}B)=-11.7$. Found: B, 6.19; N, 16.22%. Calcd for $C_8H_{21}N_2BO$: B, 6.28; N, 16.28%.

$(CH_3)_3N \cdot BH_2CON(i\text{-}C_3H_7)_2$ (12). 0.89 g (65%); mp 112—114 °C; ν(BH) 2360 s, 2320 sh; ν(CO) 1580 s; $\delta(^1H)=1.1$, 1.44 (double doublets, CH_3), 3.24 (m, NCH), 2.7 (s, NCH_3); $\delta(^{11}B)=-5.6$. Found: B, 5.18; N, 14.46%. Calcd for $C_{10}H_{25}N_2BO$: B, 5.40; N, 14.0%.

$(CH_3)_3N \cdot BH_2CON(n\text{-}C_4H_9)_2$ (13). 1.2 g (70%); ν(BH) 2410 s, 2360 s; ν(CO) 1620 s; $\delta(^1H)=0.9$ (t, CH_3), 1.1—1.8 (br, $(CH_2)_3$), 2.61 (s, NCH_3); $\delta(^{11}B)=-7.3$. Found: B, 4.51; N, 12.27%. Calcd for $C_{12}H_{29}N_2BO$: B, 4.74; N, 12.28%.

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