Preparation and Structure Determination of Trimethylamine−Dibromocarboxyborane Esters

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We have developed a new method for the preparation of esters of trimethylamine−dibromocarboxyborane ($Me_3N{\cdot}BBr_2COOR$), from trimethylamine−carboxyborane, in a one-pot reaction. The reaction involves the treatment of trimethylamine−carboxyborane with 2.5 equiv of Br_2 in the appropriate alcohol for 4 h at 0 °C, for compounds **1**−**5** (R = Me, Et, *n*-Pr, CH_2CH_2Cl, CH_2CF_3), and 5 equiv of Br_2 for 8 h under the same conditions, for compounds **6**−**8** (R = *n*-Bu, *i*-Bu, *i*-Pe). Compounds **1**−**5** were obtained in high purity and in essentially quantitative yields (∼99%). Compounds **6**−**8** were purified from traces of monobromo product and the alcohol by column chromatography. Molecular structures for the compounds **2**, **6**, and **7** were determined by X-ray crystallography.

Introduction

Several methods have been described for the preparation of amine bromocarboxyborane esters.[1−6] Since a boron-attached bromine atom is considered to be a good-leaving group,[7] such compounds are considered as precursors for boron-substituted amine−carboxyboranes, amine·BY_2X, which are isoelectronic boron analogues of α-amino acids and their derivatives.[8] Amine−carboxyboranes and their derivatives have been shown to possess considerable biological activity.[8,9] Alcoholysis of *N*-ethylnitrilium salts [amine·$BH_2CNEt]^+BF_4^-$, derived from amine−carboxyboranes under acidic conditions for 48 h, leads to the corresponding esters in 10−34% yield.[1−3] Alternatively, alkaline treatment of the *N*-ethylnitrilium salts and hydrolysis of the intermediate $C_5H_5N{\cdot}BH_2C(OMe){=}NEt$ afforded a low yield of $C_5H_5N{\cdot}BH_2CO_2Me$.[10] In another procedure, amine−carboxyboranes were reacted with an alcohol in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) to give the corresponding ester in good yields (50−98%). The drawback of this method is the long reaction time (1−2 weeks), and also, the products were contaminated with dicyclohexylurea.[1,4−5] Spielvogel et al. synthesized several esters from methyl-, dimethyl-, and trimethylamine complexes of carboxyborane by treatment with alkyl chloroformates, in yields of 31−91%.[4] Esterification of amine−carboxyboranes with alcohols was effective in the presence of a catalytic amount of hydrogen bromide.[11] When HBr (2−3 mol %) was added to a suspension of the amine−carboxyboranes in methanol, ethanol, or 2-propanol, a rapid dissolution occurred and the ester was formed in nearly quantitative yield in a few minutes. The esterification of amine−bromocarboxyboranes with HBr/ROH was slower.[11] Györi et al.[6] synthesized amine−bromocarboxyborane esters from $Me_3N{\cdot}BH_2COOH$ using a two-step procedure. The yields were low (∼50%) and required long reaction times. They reported that bromination/esterification could be achieved simultaneously, but useful yields could be obtained only with monobromo compounds. Herein we report a one-pot preparation of trimethylamine−dibromocarboxyborane esters, $Me_3N{\cdot}BBr_2COOR$, from trimethylamine−carboxyborane, in essentially quantitative yield for those derivatives that were isolated directly (**1**−**5**; R = Me, Et, *n*-Pr, CH_2CH_2Cl, CH_2CF_3) and ∼50% isolated yield for those that required column chromatography (**6**−**8**; R = *n*-Bu, *i*-Bu, *i*-Pe). The structures of **2**, **6,** and **7** were determined by X-ray crystallography.

Results and Discussion

Preparation of Trimethylamine−Dibromo(alkoxycarbonyl)borane. Reaction of trimethylamine−carboxyborane ($Me_3N{\cdot}BH_2COOH$), with 2.5 equiv of Br_2 in methanol at 0 °C for 4 h produced trimethylamine−

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Table 1. Trimethylamine–Dibromocarboxyborane Esters $Me_3N{\cdot}BBr_2COOR$ (1–8), Prepared from $Me_3N{\cdot}BH_2COOH$

compd	R	$\delta(^{11}B)$ (ppm)	yield (%)[a]
1	Me	0.78	99
2[b]	Et	0.93	99
3	*n*-Pr	0.91	99
4	1-chloroethyl	0.80	98
5	trifluoroethyl	19.10	98
6[b]	*n*-Bu	−2.69	46
7[b]	*i*-Bu	−3.51	45
8	*i*-Pe	−2.27	43

[a] Isolated yield. [b] Crystal product.

dibromo(methoxycarbonyl)borane (**1**; $Me_3N{\cdot}BBr_2COOMe$) in high purity and excellent yield (Table 1, eq 1).

$$Me_3N{\cdot}BH_2COOH + 2Br_2 + MeOH \rightarrow Me_3NBBr_2COOMe + 2HBr + H_2O \quad (1)$$

Reducing the reaction time resulted in total conversion to the ester. However, a mixture of the unbrominated and the monobrominated esters was obtained. This observation indicates that esterification precedes the hydrogen/bromine exchange, as shown in the suggested reaction mechanism in Scheme 1. It was mentioned previously that HBr can be used as a catalyst for such esterification reactions.[11] HBr is produced in situ in our procedure and serves as a catalyst. It is known that the reaction of the $R_3P{\cdot}BH_3$ compounds with HBr produces the bromine-substituted derivative $R_3P{\cdot}BH_2Br$, with elimination of H_2.[12] This does not occur in our case, because no bubbling caused by evolution of H_2 gas was observed. HBr reacts with the trimethylamine–carboxyborane and forms the acyl bromide intermediate (Scheme 1, eq 2). In the presence of an alcohol the latter converted to the ester, $Me_3N{\cdot}BH_2COOR$ (Scheme 1, eq 3). The ester then reacts with bromine to give trimethylamine–dibromocarboxyborane ester (Scheme 1, eq 5).

Scheme 1. Suggested Mechanism for the Esterification/Bromination Reaction of Trimethylamine–Carboxyborane

Esterification:

$$Me_3NBH_2COOH + Br_2 + ROH \rightarrow Me_3NBH_2COBr + ROBr + H_2O \quad (2)$$

$$Me_3NBH_2COBr + ROH \rightleftharpoons Me_3NBH_2COOR + HBr \quad (3)$$

H/Br Exchange:

$$RO^-Br^+ + HBr \rightleftharpoons Br_2 + ROH \quad (4)$$

$$Me_3NBH_2COOR + 2Br_2 \rightarrow MeNBBr_2COOR + 2\,HBr \quad (5)$$

Preparation of New Dibromo Ester Derivatives of Trimethylamine–Carboxyborane. This method was successful for various types of alcohols, such as ethanol, propanol, *n*-butanol, isobutyl alcohol, trifluoroethanol, 2-chloroethanol, and isoamyl alcohol, and produced compounds **2**–**5** in very high yields (Table 1) and high purity. For compounds **6**–**8**, 5 equiv of bromine was necessary, and the reaction time was extended to 8 h, to reduce the amount of monobromo esters. To remove traces of trimethylamine–monobromocarboxyborane esters, column chromatographic purification was needed, which caused a reduction in the isolated yields of those compounds. All compounds were obtained as solids, and compounds **2**, **6**, and **7** were recrystallized from *n*-hexane.

Spectroscopic Analysis. All of the compounds were fully characterized by ^1H, ^{11}B, ^{19}F, and ^{13}C NMR, FT-IR, melting point, and elemental analysis. The ^1H and ^{13}C NMR spectra showed the expected downfield shift of the Me_3N peak due to replacement by an inductive bromine atom. The ^{11}B NMR chemical shifts for compounds **1**–**8** (Table 1) were also downfield in comparison to the value of the unbrominated ester $Me_3BH_2CO_2Me$ (δ −9.09),[1] and the multiplicity due to BH coupling disappeared. The IR vibrations are in the expected range: 2918–2980 cm^{-1}, C–H stretching vibrations; 1672–1681 cm^{-1}, C=O stretching vibrations; 1453–1460 cm^{-1}, C–H bending vibration; 1188–1205 cm^{-1}, C–O stretching vibrations; 603–608 cm^{-1}, B–Br stretching vibrations; 430–466 cm^{-1}, N–B stretching vibrations.

Crystallography. Crystals suitable for X-ray structure determination were obtained for compounds **2**, **6**, and **7**. Their molecular structures were determined by single-crystal X-ray diffraction. The results of the diffraction analysis, crystal data, and details of the structure determination are shown in Figure 1 and in the figures in the Supporting Information. The data are summarized in Table 2.

Molecular structures of the three compounds **2**, **6**, and **7** were determined at ca. 110 K with relatively high precision. They represent three independent and internally consistent determinations. The covalent parameters exhibit standard values characteristic to boron in tetrahedral sp^3 hybridization. Those of the N–BBr_2–C=O group are of particular significance in the present context and are summarized in Table 3. The conformation around the boron atom is nearly ideally tetrahedral, with Br–B–Br bond angles of 109° and slightly larger N–B–C bond angles of 112°. The observed data are comparable to those found in related compounds that contain a N–BBr_2–C fragment.[13,14]

The corresponding crystal structures reveal efficient intermolecular packing, which prevents any possible conformational disorder. These are stabilized by dispersion forces, including intermolecular van der Waals contacts between electron-rich and electron-deficient surfaces of neighboring species, as represented by the Br···H (3.0 Å) and O···H (2.6 Å) interactions. Worthy of note is the crystal packing of **6**, which shows further stabilization of the structure by roughly parallel alignment of the alkyl residues (Figure 2).

Conclusion

A series of trimethylamine–dibromcarboxyborane esters were prepared in excellent yields, using a one-

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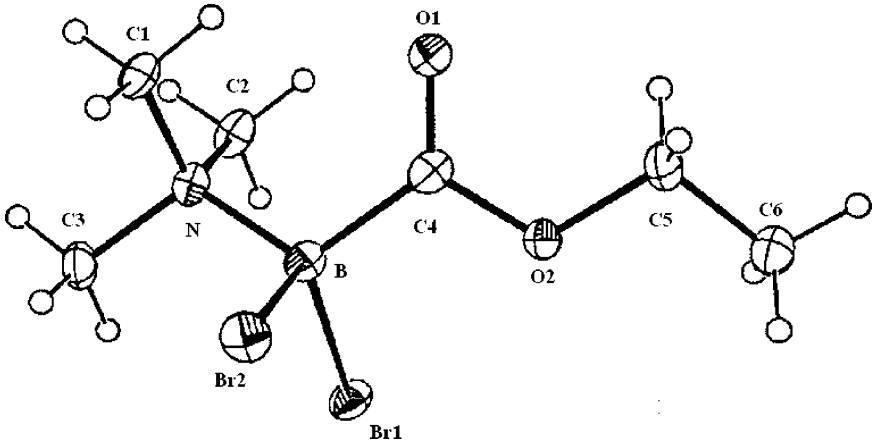

Figure 1. Molecular structure of compound **2**. Ellipsoids represent thermal displacement parameters at the 50% probability level. Selected bond distances (Å) and angles (deg): B−N = 1.605(4), B−C(4) = 1.626(5), B−Br(1) = 2.021(4), B−Br(2) = 2.034(4), O(1)−C(4) = 1.222(4), O(2)−C(4) = 1.355(4), O(2)−C(5) = 1.462(4); N−B−Br(1) = 109.1(2), N−B−Br(2) = 109.5(2), Br(1)−B-Br(2) = 109.18(17), C(4)−O(2)−C(5) = 116.6(3).

Table 2. Crystal Data and Structure Refinement Details for Compounds 2, 6, and 7

	2	**6**	**7**
formula	$C_6H_{14}BBr_2NO_2$	$C_8H_{18}BBr_2NO_2$	$C_8H_{18}BBr_2NO_2$
fw	302.81	330.86	330.86
habit	thin plates	plates	rods
color	colorless	colorless	colorless
temp, K	110(2)	110(2)	110(2)
radiation	Mo Kα	Mo Kα	Mo Kα
cryst size, mm	0.30 × 0.20 × 0.05	0.30 × 0.25 × 0.10	0.25 × 0.10 × 0.10
cryst syst	monoclinic	monoclinic	triclinic
space group	$P2_1/c$	$P2_1/c$	$P\bar{1}$
a, Å	13.8260(4)	16.3860(2)	6.8310(2)
b, Å	6.9220(3)	6.96400(10)	9.6340(3)
c, Å	11.6390(5)	11.7720(4)	10.7050(5)
α, deg	90.00	90.00	105.1380(12)
β, deg	107.3070(16)	110.5331(7)	98.8870(14)
γ, deg	90.00	90.00	98.772(3)
V, Å^3	1063.46(7)	1257.99(5)	658.00(3)
Z	4	4	2
D_{calcd}, g cm^{-3}	1.891	1.747	1.670
F(000)	592	656	328
μ, mm^{-1}	7.586	6.421	6.138
2*θ* range, deg	3.09−27.86	2.65−28.20	2.01−28.14
no. of unique rflns	2079	3014	2543
no. of restraints	0	0	0
hkl limits	−18 to +17, −9 to 0, 0−14	−21 to +20, −9 to 0, 0−15	0−8, −12 to +12, −13 to +13
no. of params	113	131	132
no. of rflns with $I > 2\sigma(I)$	2079	2630	3034
rinal *R* indices[a] ($I > 2\sigma(I)$)			
R1	0.0357	0.0490	0.0346
wR2	0.0805	0.0311	0.0781
$\|\Delta\rho\|$, e Å^{-3}	≤0.130	≤0.140	≤0.094
GOF	1.055	0.984	1.055

[a] R1 = $\sum||F_o| - |F_c||/\sum|F_o|$. wR2 = ×ed$\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]$×fd$^{1/2}$.

Table 3. Covalent Parameters of the N−BBr$_2$−C═O Groups in Compounds 2, 6, and 7

	2	**6**	**7**
B−N(sp^3)/Å	1.605	1.610	1.603
B−C(sp^2)/Å	1.626	1.633	1.624
B−Br/Å	2.021, 2034	2.023, 2.024	2.024, 2.031
Br−B−Br/deg	109.2	109.3	108.8
N−B−C/deg	112.0	112.2	112.2
N−B−Br/deg	109.1, 109.5	109.0, 109.6	109.3, 109.4
C−B−Br/deg	105.5, 111.1	106.7, 110.0	108.4, 108.8

pot bromination/esterification sequence, starting with trimethylamine−carboxyborane and bromine dissolved in the appropriate alcohol. Our method overcomes several disadvantages over previously published procedures. It involves short reaction times and is applicable to the preparation of diverse amine−dibromocarboxyborane esters. The molecular structures of **2**, **6**, and **7** were determined by single-crystal X-ray diffraction.

Experimental Section

General Comments. ^{1}H, ^{13}C, and ^{11}B NMR spectra were recorded in $CDCl_3$ and D_2O solution on a Varian Unity spectrometer (300, 75, 96 MHz) using Me_4Si as an internal standard. Infrared spectra were run for samples in KBr disks for solids on a Bruker Vector 22 FT-IR spectrophotometer. Elemental analyses were performed in house at the Hebrew University Microaanalysis laboratory. Melting points were measured on a Fisher Scientific melting point apparatus.

General Procedure. $Me_3N{\cdot}BH_2CN$ was prepared from $Me_3N{\cdot}HCl$ and $NaBH_3CN$ using the literature method.[15]

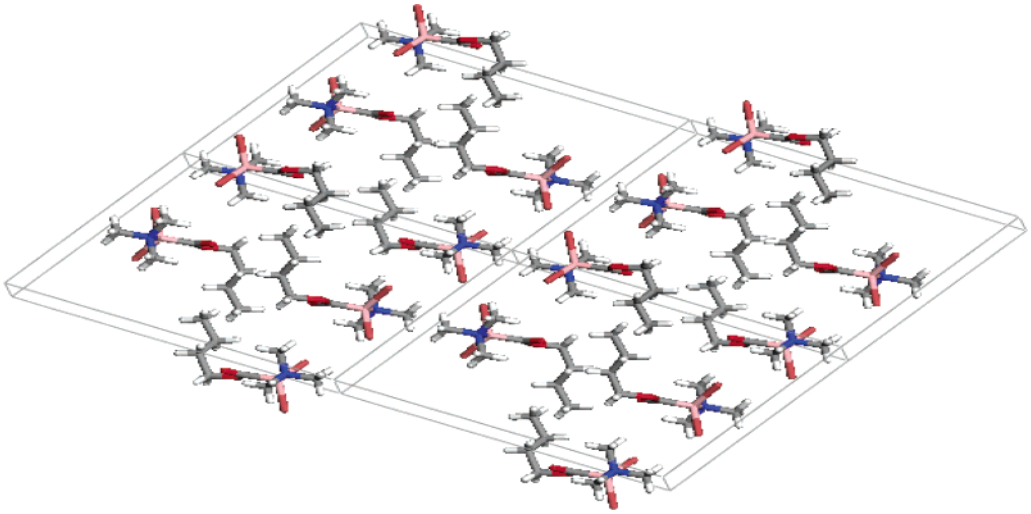

Figure 2. Crystal structure of compound **6**, viewed down the short *b* axis.

$Me_3N{\cdot}BH_2COOH$ was prepared using the literature method.[16] All reactions were carried out under nitrogen. Solvents were dried by the usual methods and distilled before use. All other chemicals were obtained from Sigma-Aldrich and used as received without any further purification.

Preparation of Compounds 1–5. $Me_3N{\cdot}BH_2COOH$ (0.06 g, 0.5 mmol) was dissolved in 2 mL of the appropriate alcohol cooled to 0 °C, and bromine (0.066 mL, 1.25 mmol) dissolved in 6 mL of the prospective alcohol was added dropwise. The reaction mixture was stirred at 0 °C for 4 h. The solvent was removed under high vacuum. Products **1**–**5** were obtained in high purity and yield.

Preparation of Compounds 6–8. The same procedure was used to prepare products **6**–**8**, which were obtained as a mixture with other byproducts and the nonvolatile alcohol. The products were purified by column chromatography on a silica gel 60 column, using gradient elution ranging from 10% ethyl acetate and 90% petroleum ether to 100% ethyl acetate.

X-ray Crystallographic Study. Colorless single crystals of compounds **2**, **6**, and **7** suitable for X-ray diffraction analysis were obtained from saturated hexane solutions at 25 °C. The crystal data and structure refinement parameters are summarized in Table 2. All diffraction measurements were carried out on a Nonius KappaCCD diffractometer at ca. 110 K, using graphite-monochromated Mo Kα (λ = 0.710 70 Å) radiation and 1° φ scans. The intensity data were integrated and scaled by DENZO-SMN and Scalepack programs.[17] The structures were solved by direct methods (SIR-92)[18] and refined by full-matrix least squares on F^2 (SHELXL-97).[19] All non-hydrogen atoms were refined anisotropically; the hydrogens were located in idealized positions and allowed to ride with thermal parameters 1.2 times those of their parent carbon.

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Supporting Information Available: Figures showing the molecular structures of compounds **6** and **7**, text giving ^1H, ^{11}B, ^{19}F, and ^{13}C NMR data, FT-IR data, melting pointss, and elemental analysis data for compounds **1**–**8**, and CIF files giving atomic positional and thermal displacement parameters, bond distances, bond angles, and torsion angles, together with details of data collection and structure solution and refinement for compounds **2**, **6**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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