Syntheses of the First Amine-dicarboxyboranes and Their Bis(methylester) and Bis(*N*-ethylamide) Derivatives

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Amine-bis(*N*-ethylcarbamoyl)boranes [A·BH(CONHEt)$_2$, **3**; A = trimethylamine (Me_3N, **a**), quinuclidine (Q, **b**), pyridine (py, **f**), 4-picoline (pic, **g**)] have been prepared after deprotonation of [amine-bis(*C*-hydroxy-*N*-ethylimidate)hydroboron(2+)] cations (**2**), which were formed by the hydrolysis of [amine-bis(ethylnitrilium)-hydroboron(2+)]tetrafluoroborates (**1**). Numerous representatives of **3** [A = diethylamine (Et_2NH, **c**), piperidine (pip, **d**), pyrrolidine (pyrr, **e**), 4-aminopyridine (4-NH_2-py, **h**), 4-(dimethylamino)pyridine (DMAP, **i**), imidazole (Him, **j**), 1-methylimidazole (Mim, **k**)] have been prepared by base exchange reactions from **3a**. **3a**−**e** are extremely stable in aqueous media, either acidic or alkaline, probably because of the considerable steric hindrance of possible reaction centers. However, they were transformed into amine-dicarboxyboranes [A·BH(COOH)$_2$, **4a**−**e**] in acidic medium under vigorous conditions (100−130 °C). This transformation was accompanied by significant decomposition, probably owing to the protonation on the N atom, resulting in the rupture of the B−N bond. As an exception, **4b**, where N atom in a rigid bicycle is not prone to attacks, could be isolated in very good yield. On the other hand, amine-bis(*N*-ethylcarbamoyl)boranes containing amines with sp^2-hybridized N atoms (**3f**−**k**) undergo complete decomposition under similar conditions probably because of the increased hydridic character of the hydrogen adjacent to boron. Base exchange reactions starting from **4b** resulted in the ammonium salts of **4c**−**e**, **h**, **i** of composition [A·BH(COOH)(COO$^-$)][AH$^+$], which in turn could be transformed into the diacids **4**, except **4h**, by protonation. As salt formation indicates, the **4** compounds are stronger acids as univalent acids than the corresponding A·BH$_2$(COOH) complexes. **4a**−**e**, **i** were readily esterified into amine-bis(methoxycarbonyl)-boranes (**5a**−**e**, **i**) in methanol, employing a catalytic amount of HBr. **5a**−**e**, **i** are stable in alkaline medium but are readily hydrolyzed in acidic medium. Hydrolysis of [amine-bis(*C*-methoxy-*N*-ethylimidate)hydroboron(2+)] cations did not give the corresponding bisesters **5** in alkaline, neutral, or acidic medium.

Introduction

Amine carboxyboranes (A·BH$_2$COOH) can be regarded as isoelectronic analogues of protonated α-amino acids,[1] or more properly, aliphatic carboxylic acids.[2] This resemblance inspired extensive biological screening of these molecules, and the promising early results led to the syntheses of a large number of ester,[3−6] amide,[4,7] peptide,[8,9] hydroxamic acid,[10] and transition metal complex[11−13] derivatives of amine carboxyboranes (A·BH$_2$COX; X = OR, NR′R″, NHOH) containing a broad range of amines. The recent advances in the chemistry of these substances, among other amine boranes, have been reviewed recently.[14] Today many of these molecules are known to possess remarkable antitumor,[15,16] antiosteoporotic,[17] antiinflammatory,[18] and hypolipidemic[8] activities, and their mode of action is under study.[19]

Of course, the syntheses of derivatives substituted on the boron (A·BH(X)COOH) have been attempted as well, but these efforts in other laboratories yielded only a limited number of new molecules so far.[20] Experiments to prepare boron analogues of amino acids other than glycine were unsuccessful mainly because electron-donating groups on the boron destabilized the B−N bond.[21] Since attaching electron-withdrawing groups to

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the boron atom should yield stable amine borane complexes, we focused our efforts on the preparation of amine carboxyboranes substituted on the boron. As a result, several new types of compounds (A·BH(X)COOH; X = Br,[2,22] amines,[23,24] COOH,[25] CN[26]) have been synthesized in our laboratory.

Here we report the syntheses of a number of amine dicarboxyboranes, isoelectronic analogues of substituted malonic acids, and their bis-*N*-ethylamide and bis-methylester derivatives. From a knowledge of the biological activities of the parent compounds, these molecules should be considered as promising candidates for biological activity studies. Limitations of the synthetic methods starting from various precursors are discussed also.

Experimental Section

Methods and Materials. All reactions, except those involving water or noted otherwise, were performed under an oxygen- and water-free N_2 atmosphere using the general Schlenk techniques in flamed or oven-dried glassware with absolute solvents freshly distilled prior to use. Extractions of the solid materials were carried out according to the standard Schlenk periodic extraction technique.[27]

Acetonitrile was distilled from P_2O_5 after drying with CaH_2. Dichloromethane was distilled from CaH_2, then refluxed with $NaBH_4$/diglyme and fractionally distilled. Chloroform was distilled from P_2O_5 after shaking with concentrated H_2SO_4 and drying with $CaCl_2$. Ether was distilled from Na-benzophenone. Methanol was distilled from $Mg(OCH_3)_2$. Pentane was fractionally distilled. Water denotes twice distilled water.

Methanolic HBr solution was prepared by dropwise addition of concentrated aqueous HBr solution to P_2O_5 under vigorous stirring and by dissolving the liberated HBr gas, after drying by Granusic A (J. T. Baker), in methanol. Molecular sieves (4 Å pore size, Aldrich) were activated by keeping them under dynamic vacuum for 3 h at 220 °C and storing them under dry N_2.

Quinuclidine was recrystallized from ether. 4-Aminopyridine was extracted with ether. Diethylamine, pyrrolidine, pyridine, imidazole, 1-methylimidazole, and picoline were distilled from KOH. Piperidine was distilled from CaH_2.

DMAP (Janssen), 48% aq HBr solution (Fluka), lithium metal (BDH, in liquid paraffin), and $Na[BPh_4]$ (Reanal) were used as received.

$[Et_3O][BF_4]$,[28] $Me_3N{\cdot}BH(CN)_2$,[29] pic·$BH(CN)_2$,[29] $[Q{\cdot}BH(CNEt)_2][BF_4]_2$.[29] $[py{\cdot}BH(CNEt)_2][BF_4]_2$,[29] and $\{Q{\cdot}BH[C(OMe)=NHEt]_2\}[BF_4]_2$ [29] were prepared according to known procedures.

NMR spectra were recorded on a Bruker AM 360 instrument in 5 mm o.d. tubes at room temperature. ^1H (360.1 MHz) spectra were referenced to internal DSS in D_2O and internal TMS in $CDCl_3$, acetone-d_6, and DMSO-d_6. During measurements in H_2O, a capillary tube filled with D_2O solution of DSS was used for locking and referencing. Protons adjacent to boron generally gave distinguishable but broad signals, and their chemical shifts are omitted. ^{13}C (90.5 MHz) spectra were referenced to solvent signals ($CDCl_3$, 77.0 ppm; acetone-d_6, 29.9 ppm; DMSO-d_6, 39.5 ppm), and DSS in D_2O was used as an external reference. Ambiguities in assigning ^1H and ^{13}C signals were cleared with homonuclear decoupling and chemical shift correlation ($^1H-^1H$ and $^{13}C-^1H$) experiments. Carbons directly attached to boron could not be observed probably because of the broadening effect of quadrupolar boron nuclei, which is why CO chemical shifts are not given. ^{11}B (115.5 MHz) spectra were referenced to $Et_2O{\cdot}BF_3$ in a capillary inserted into the tube. In cases when multiplicities could only be revealed by mathematical resolution enhancement, multiplets are marked "broad" and coupling constants are not given.

IR spectra were recorded on a Perkin-Elmer Paragon PC 1000 FT-IR spectrometer.

The boron content of the samples was determined with acid−base titration in the presence of mannitol after fusion with sodium hydroxide and potassium hydroxide. Analyses of the BF_4 salt were performed in the presence of a large excess of $CaCl_2$. Elementary analyses were performed at the Department of Organic and Pharmaceutical Chemistry, Faculty of Medicine, University of Pécs using an EA-1110 analyzer (CE Instruments).

Syntheses. $Me_3N{\cdot}BH(CONHEt)_2$ (3a). $Me_3N{\cdot}BH(CN)_2$ (1.050 g, 8.539 mmol) was added to the CH_2Cl_2 solution of $[Et_3O][BF_4]$ (3.570 g, 18.79 mmol, in 6 mL), and after 20 h of reflux the volatile components were evaporated. The residue was dissolved in water (1.5 mL), and the pH of the solution was adjusted to ~11 by NaOH solution (1.9 mL, 9.5 M). The insoluble parts were filtered off, the filtrate was extracted with CH_2Cl_2 (1.0 mL), and the organic phase was discarded. The aqueous phase was then extracted with CH_2Cl_2 by continuous extraction. The CH_2Cl_2 phase was dried over $MgSO_4$ and evaporated to obtain the white solid product. Yield: 1.379 g (75%). Anal. Found (calcd) for $C_9H_{22}BN_3O_2$: C, 50.60 (50.26); H, 10.28 (10.17); B, 5.07 (5.03); N, 19.48 (19.54). ^1H NMR ($CDCl_3$, δ): 1.11 (t, $J = 7.3$ Hz, 6H, Et-CH_3), 2.83 (s, 9H, NCH_3), 3.28 (m, 4H, Et-CH_2), 6.36 (br s, 2H, NH). ^{11}B NMR ($CDCl_3$, δ): −5.6 (d, $J = 86$ Hz). ^{13}C $\{^1H\}$ NMR ($CDCl_3$, δ): 15.11 (Et-CH_3), 32.50 (Et-CH_2), 51.64 (NCH_3). IR (KBr, cm^{-1}): ν(N−H), 3374, 3343; ν(B−H), 2374; amide I−II, 1603, 1576, 1527, 1496.

Q·BH(CONHEt)$_2$ (3b). $[Q{\cdot}BH(CNEt)_2][BF_4]_2$ (2.435 g, 5.99 mmol) was dissolved in aqueous NaOH (15 mL, 1.0 M), and the solution (pH ≈ 11) was extracted with CH_2Cl_2 by continuous extraction. The CH_2Cl_2 phase was dried over $MgSO_4$ and evaporated to obtain the white solid product. Yield: 1.453 g (91%). Anal. Found (calcd) for $C_{13}H_{26}BN_3O_2$: C, 58.03 (58.44); H, 9.68 (9.81); B, 4.02 (4.05); N, 15.60 (15.73). ^1H NMR ($CDCl_3$, δ): 1.10 (t, $J = 7.3$ Hz, 6H, Et-CH_3), 1.75 (m, 6H, CCH_2), 2.00 (h, $J = 3.3$ Hz, 1H, CH), 3.26 (m, 4H, Et-CH_2), 3.35 (m, 6H, NCH_2), 6.43 (br s, 2H, NH). ^{11}B NMR ($CDCl_3$, δ): −6.4 (d, $J =$ 70 Hz). ^{13}C $\{^1H\}$ NMR ($CDCl_3$, δ): 15.11 (Et-CH_3), 20.07 (CH), 24.52 (CCH_2), 32.41 (Et-CH_2), 50.64 (NCH_2). IR (KBr, cm^{-1}): ν(N−H), 3340; ν(B−H), 2369; amide I−II, 1605, 1572, 1530, 1508.

$Et_2NH{\cdot}BH(CONHEt)_2$ (3c). Et_2NH (10 mL) was added to **3a** (0.91 g, 4.23 mmol), and the mixture was boiled at a slow boil under a reflux condenser for 1.5 h. The atmosphere was continuously purged by employment of a slow N_2 stream. The mixture was then concentrated to 3 mL, stirred with ether (25 mL) for 20 min, and filtered. The solid product was washed with ether (3 × 5 mL) and dried in an N_2 stream. Yield: 0.92 g (95%). Anal. Found (calcd) for $C_{10}H_{24}BN_3O_2$: C, 52.28 (52.42); H, 10.74 (10.56); B, 4.70 (4.72); N, 18.20 (18.34). ^1H NMR ($CDCl_3$, δ): 1.11 (t, $J = 7.3$ Hz, 6H, amide-Et-CH_3), 1.22 (t, $J = 7.3$ Hz, 6H, amine-Et-CH_3), 2.99 (m, 4H, amine-Et-CH_2), 3.29 (m, 4H, amide-Et-CH_2), 5.31 (br s, 1H, amine-NH), 6.13 (br s, 2H, amide-NH). ^{11}B NMR ($CDCl_3$, δ): −9.8 (d, $J = 77$ Hz). ^{13}C $\{^1H\}$ NMR ($CDCl_3$, δ): 11.37 (amine-Et-CH_3), 15.11 (amide-Et-CH_3), 32.66 (amide-Et-CH_2), 44.34 (amine-Et-CH_2). IR (KBr, cm^{-1}): ν(N−H), 3347, 3288; ν(B−H), 2413; amide I−II, 1604, 1572, 1524.

pip·BH(CONHEt)$_2$ (3d). 3a (0.200 g, 0.93 mmol) was dissolved in piperidine (5 mL), and the solution was kept at 80 °C for 5 h. The volatile components were then evaporated in vacuo, the residue was suspended in ether (10 mL), and the suspension was filtered. The raw product was extracted with ether (15 mL) to a point when only a small amount of jelly substance remained on the filter. The product was filtered off the extract, washed with ether (2 × 3 mL), and dried in an N_2 stream. Yield: 0.119 g (89%). Anal. Found (calcd) for $C_{11}H_{24}BN_3O_2$: C, 55.06 (54.69); H, 10.20 (10.03); B, 4.51 (4.48); N, 17.30 (17.43). ^1H NMR ($CDCl_3$, δ): 1.10 (t, $J = 7.3$ Hz, 6H, Et-CH_3), 1.39 (m, 1H, 4-CH_2 ax), 1.60−1.85 (m, 5H, 3,5-CH_2 + 4-CH_2 eq), 2.67 (m, 2H, 2,6-CH_2 ax), 3.21−3.33 (m, 6H, Et-CH_2 + 2,6 CH_2 eq), 5.39 (br, 1H, pip-NH), 6.18 (br, 2H, EtNH). ^{11}B NMR ($CDCl_3$, δ): −8.4 (br d). ^{13}C $\{^1H\}$ NMR ($CDCl_3$, δ): 15.18 (Et-CH_3), 22.89 (4-CH_2),

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24.97 (3,5-CH_2), 32.68 (Et-CH_2), 50.01 (2,6-CH_2). IR (KBr, cm^{-1}): ν(N−H), 3334, 3233; ν(B−H), 2402; amide I−II, 1604, 1511.

pyrr·BH(CONHEt)$_2$ (3e). Pyrrolidine (0.47 mL, 0.402 g, 5.65 mmol) was added to the acetonitrile solution of **3a** (0.606 g, 2.817 mmol, in 15 mL). The mixture was refluxed for 3 h, while the atmosphere was continuously purged by employment of a slow N_2 stream. The solution was left to stand at room temperature for 2 h, and the precipitated crystals were then filtered off and washed with ether (2 × 5 mL). The filtrate was evaporated to dryness, the solid residue was dissolved in boiling acetone, and the solution was allowed to cool to room temperature while a part of the product precipitated. The volume of the mixture was doubled with ether, and the product was filtered off the slurry after 2 h, washed with ether (2 × 5 mL), and dried in an N_2 stream. Yield: 0.545 g (85%). Anal. Found (calcd) for $C_{10}H_{22}BN_3O_2$: C, 53.03 (52.89); H, 9.87 (9.76); B, 4.72 (4.76); N, 18.23 (18.50). ^{1}H NMR ($CDCl_3$, δ): 1.09 (t, J = 7.2 Hz, 6H, Et-CH_3), 1.89 (m, 4H, 3,4-CH_2), 2.76 (m, 2H, 2,5-CH_2), 3.25 (m, 4H, Et-CH_2), 3.39 (m, 2H, 2,5-CH_2), 6.44 (br s, 2H, amide-NH), 7.00 (br s, 1H, amine-NH). ^{11}B NMR ($CDCl_3$, δ): −8.8 (br). ^{13}C {^{1}H} NMR ($CDCl_3$, δ): 15.07 (Et-CH_3), 24.18 (3,4-CH_2), 32.57 (Et-CH_2), 50.47 (2,5-CH_2). IR (KBr, cm^{-1}): ν(N−H), 3341, 3300; ν(B−H), 2419; amide I−II, 1576, 1510.

py·BH(CONHEt)$_2$ (3f). [py·BH(CNEt)$_2$][BF_4]$_2$ (0.845 g, 2.26 mmol) was dissolved in aqueous NaOH (4.70 mL, 1.0 M), the solution (pH ≈ 11) was extracted with CH_2Cl_2 (4.0 mL), and the organic phase was discarded. The aqueous phase was then extracted with CH_2Cl_2 by continuous extraction. The CH_2Cl_2 phase was dried over $MgSO_4$ and evaporated to obtain the white solid product. Yield: 0.397 g (75%). Anal. Found (calcd) for $C_{11}H_{18}BN_3O_2$: C, 56.14 (56.20); H, 7.57 (7.72); B, 4.57 (4.60); N, 17.77 (17.87). ^{1}H NMR ($CDCl_3$, δ): 1.11 (t, J = 7.2 Hz, 6H, Et-CH_3), 3.29 (m, 4H, Et-CH_2), 6.40 (br s, 2H, NH), 7.64 (m, 2H, 3,5-CH), 8.07 (m, 1H, 4-CH), 8.80 (m, 2H, 2,6-CH). ^{11}B NMR ($CDCl_3$, δ): −7.5 (br d). ^{13}C {^{1}H} NMR ($CDCl_3$, δ): 15.08 (Et-CH_3), 32.76 (Et-CH_2), 125.36 (3,5-CH), 140.92 (4-CH), 147.77 (2,6-CH). IR (KBr, cm^{-1}): ν(N−H), 3405, 3323, 3289; ν(B−H), 2408; amide II, 1582, 1526.

pic·BH(CONHEt)$_2$ (3g). pic·$BH(CN)_2$ (0.674 g, 4.29 mmol) was added to a CH_2Cl_2 solution of [Et_3O][BF_4] (1.79 g, 9.42 mmol, in 4.4 mL), and the mixture was refluxed for 25 h. The volatile components were then evaporated, and the residue was dissolved in aqueous NaOH (14.40 mL, 1.0 M). The solution (pH ≈ 11) was extracted with CH_2Cl_2 (10 mL), and the organic phase was discarded. The aqueous phase was then extracted with CH_2Cl_2 by continuous extraction. The CH_2Cl_2 phase was dried over $MgSO_4$ and evaporated to obtain the white solid product. Yield: 0.722 g (68%). Anal. Found (calcd) for $C_{12}H_{20}BN_3O_2$: C, 57.18 (57.86); H, 8.03 (8.09); B, 4.36 (4.34); N, 16.61 (16.87). ^{1}H NMR ($CDCl_3$, δ): 1.11 (t, J = 7.3 Hz, 6H, Et-CH_3), 2.52 (s, 3H, Pic-CH_3), 3.29 (m, 4H, Et-CH_2), 6.49 (br s, 2H, NH), 7.41 (m, 2H, 3,5-CH), 8.61 (m, 2H, 2,6-CH). ^{11}B NMR ($CDCl_3$, δ): −7.7 (br d). ^{13}C {^{1}H} NMR ($CDCl_3$, δ): 15.08 (Et-CH_3), 21.47 (Pic-CH_3), 32.76 (Et-CH_2), 126.11 (3,5-CH), 147.04 (2,6-CH), 153.86 (*ipso*-C). IR (KBr, cm^{-1}): ν(N−H), 3350, 3296; ν(B−H), 2393; amide I−II, 1636, 1605, 1576, 1504.

4-NH_2-py·BH(CONHEt)$_2$ (3h). 4-NH_2-py (0.448 g, 4.76 mmol) was added to an acetonitrile solution of **3a (**0.512 g, 2.38 mmol, in 15 mL). The mixture was refluxed for 2.5 h, while the atmosphere was continuously purged by employment of a slow N_2 stream. The mixture was left to stand at room temperature for 1 h, and the precipitated product was then filtered off. The product was washed with acetonitrile (3 × 3 mL) and dried in an N_2 stream. The raw product was extracted with acetone (20 mL) to a point when only a small amount of noncrystalline substance remained on the filter. The extract was concentrated to one-third its volume by evaporation, and ether (10 mL) was added. The product was filtered off the mixture after 1 h, washed with ether (2 × 5 mL), and dried in an N_2 stream. Yield: 0.496 g (83%). Anal. Found (calcd) for $C_{11}H_{19}BN_4O_2$: C, 52.54 (52.83); H, 7.53 (7.66); B, 4.35 (4.32); N, 22.28 (22.40). ^{1}H NMR (DMSO-d_6, δ): 0.95 (t, J = 7.3 Hz, 6H, Et-CH_3), 3.03 (m, 4H, Et-CH_2), 6.60 (m, 2H, 3,5-CH), 7.23 (s, 2H, NH_2), 7.27 (br t, 2H, amide-NH), 7.85 (m, 2H, 2,6-CH). ^{11}B NMR (DMSO-d_6, δ): −7.3 (br). ^{13}C {^{1}H} NMR (DMSO-d_6, δ): 15.36 (Et-CH_3), 31.64 (Et-CH_2), 108.09 (3,5-CH), 147.22 (2,6-CH), 157.15 (*ipso*-C). IR (KBr, cm^{-1}): ν(N−H), 3332, 3292; ν(B−H), 2375; amide I−II, 1661, 1640, 1586, 1522.

DMAP·BH(CONHEt)$_2$ (3i). DMAP (3.35 g, 27.42 mmol) was added to the acetonitrile solution of **3b** (0.732 g, 2.74 mmol, in 20 mL), and the mixture was refluxed for 3 h. The volatile parts were then evaporated, the residue was suspended in ether (25 mL), and the insoluble product was filtered off and extracted with the filtrate to a point when only a small amount of slowly sedimenting material remained on the filter. The product was filtered off the extract, washed with ether (4 × 5 mL), and dried in an N_2 stream. Yield: 0.616 g (81%). Anal. Found (calcd) for $C_{13}H_{23}BN_4O_2$: C, 56.61 (56.13); H, 8.20 (8.33); B, 3.87 (3.89); N, 19.88 (20.14). ^{1}H NMR ($CDCl_3$, δ): 1.10 (t, J = 7.3 Hz, 6H, Et-CH_3), 3.13 (s, 6H, NCH_3), 3.28 (m, 4H, Et-CH_2), 6.43 (br s, 2H, NH), 6.58 (m, 2H, 3,5-CH), 8.14 (m, 2H, 2,6-CH). ^{11}B NMR ($CDCl_3$, δ): −7.6 (br). ^{13}C {^{1}H} NMR ($CDCl_3$, δ): 15.38 (Et-CH_3), 32.71 (Et-CH_2), 39.72 (N−CH_3), 106.72 (3,5-CH), 146.98 (2,6-CH), 155.79 (*ipso*-C). IR (KBr, cm^{-1}): ν(N−H), 3317; ν(B−H), 2403; amide I−II, 1637, 1602, 1557, 1514.

Him·BH(CONHEt)$_2$ (3j). Imidazole (0.33 g, 4.85 mmol) was added to an acetonitrile solution of **3a** (0.510 g, 2.37 mmol, in 15 mL). The mixture was refluxed for 3 h, while the atmosphere was continuously purged by employment of a slow N_2 stream. Acetonitrile (10 mL) was added to the mixture thick with the microcrystalline precipitate, and the precipitate was filtered off after cooling to room temperature. The product was washed with acetonitrile (2 × 2 mL) and then with ether (2 × 5 mL) and dried in an N_2 stream. Yield: 0.443 g (83%). Anal. Found (calcd) for $C_9H_{17}BN_4O_2$: C, 48.44 (48.24); H, 7.68 (7.65); B, 4.86 (4.83); N, 24.64 (25.00). ^{1}H NMR (DMSO-d_6, δ): 0.95 (t, J = 7.2 Hz, 6H, Et-CH_3), 3.04 (m, 4H, Et-CH_2), 7.08 (m, 1H, 4-CH), 7.30 (br, 2H, amide-NH), 7.33 (m, 1H, 5-CH), 8.45 (m, 1H, 2-CH) 12.03 (br s imidazole-NH). ^{11}B NMR (DMSO-d_6, δ): −11.4 (br). ^{13}C {^{1}H} NMR (DMSO-d_6, δ): 15.28 (Et-CH_3), 31.71 (Et-CH_2), 117.25 (4-CH), 125.06 (5-CH), 137.08 (2-CH). IR (KBr, cm^{-1}): ν(N−H), 3337, 3240; ν(B−H), 2360; amide I−II, 1584, 1529, 1557, 1496.

Mim·BH(CONHEt)$_2$ (3k). 1-Me-imidazole (0.344 mL, 0.354 g, 4.31 mmol) was added to an acetonitrile solution of **3a** (0.464 g, 2.157 mmol, in 10 mL). The mixture was refluxed for 14 h, while the atmosphere was continuously purged with a slow N_2 stream. The solution was evaporated in vacuo, and ether (15 mL) was added to the oily residue. After crystallization of the oil the product was filtered off, washed with ether (4 × 3 mL), and dried in an N_2 stream. Yield: 0.456 g (89%). Anal. Found (calcd) for $C_{10}H_{19}BN_4O_2$: C, 50.62 (50.45); H, 8.15 (8.04); B, 4.60 (4.54); N, 23.55 (23.53). ^{1}H NMR (DMSO-d_6, δ): 0.95 (t, J = 7.2 Hz, 6H, Et-CH_3), 3.03 (m, 4H, Et-CH_2), 3.78 (s, 3H, Mim-CH_3), 7.07 (m, 1H, 4-CH), 7.24 (m, 2H, NH), 7.36 (m, 1H, 5-CH), 8.48 (m, 1H, 2-CH). ^{11}B NMR (DMSO-d_6, δ): −11.4 (br). ^{13}C {^{1}H} NMR (DMSO-d_6, δ): 15.36 (Et-CH_3), 31.65 (Et-CH_2), 34.49 (Mim-CH_3), 121.18 (4-CH), 125.69 (5-CH), 138.75 (2-CH). IR (KBr, cm^{-1}): ν(N−H), 3317, 3270; ν(B−H), 2365; amide I−II, 1603, 1568, 1547, 1515.

Me_3N·BH(COOH)$_2$ (4a). An HCl solution (28.0 mL, 0.326 M, 9.128 mmol HCl) of 80−85 °C was added to the aqueous solution of **3a** (0.517 g, 2.403 mmol, in 2.8 mL) in a flask connected to a mercury manometer and equipped with a Teflon stopcock to prevent overpressure. The pressure was quickly increased to ca. 1.3 bar, and the reaction vessel was placed in a large oil bath of 130−132 °C with vigorous stirring of the reaction mixture. Eight minutes after the beginning of the boiling, during which the pressure in the flask was kept at 1.6−1.7 bar, the solution was cooled to 100 °C and kept at this temperature for 20 min. It was then cooled to 50 °C, NaOH solution (10.3 mL 1.00 M) was added, and then the solution was evaporated to 5−6 mL in a 60 °C bath. Water (5−6 mL) was added to the residue, and this solution was evaporated in vacuo to half its volume. This procedure was repeated until the condensed distillate, after acidification, did not give precipitate with Na[BPh_4]. The pH of the solution was adjusted between 2.5 and 2.6 using 1 and 0.1 M HCl (ca. 1.65−1.70 mL 1 M HCl), and it was evaporated in vacuo to 1−2 mL in a 60 °C bath. The remaining solution was evaporated to dryness without heating, and the residue was kept under vacuum (<0.5 mbar) for 0.5 h. The residue was redissolved in methanol (5 mL), this solution was evaporated to dryness, and this procedure was repeated. The residue

was suspended in ether (10 mL), and the suspension was filtered. The filtered solid was washed with ether (2 × 3 mL), and the filtrate was evaporated to dryness. The residue was redissolved in water (2 mL), and the solution was acidified with HCl (0.5 mL 0.1 M), concentrated to ca. 0.5 mL by employment of a fast N_2 stream in a 60 °C bath, and then evaporated to dryness without heating. Yield: 0.0863 g (22%). Anal. Found (calcd) for $C_5H_{12}BNO_4$: C, 37.42 (37.31); H, 7.63 (7.51); B, 6.80 (6.72); N, 8.63 (8.70). ^{1}H NMR (DMSO-d_6, δ): 2.79 (s, NCH_3). ^{11}B NMR (DMSO-d_6, δ): −7.8 (br). ^{13}C {^{1}H} NMR (DMSO-d_6, δ): 50.08 (NCH_3). IR (KBr, cm^{-1}): ν_{assoc}(O−H), 2736, 2629; ν(B−H), 2429; ν(C═O), 1664, 1637.

Q·BH(COOH)$_2$ (4b). 3b (0.893 g, 3.34 mmol) was dissolved in aqueous HCl (13 mL, 1.0 M) in a flask connected to a mercury manometer and equipped with a Teflon stopcock to prevent overpressure. The solution was heated in an oil bath (124−128 °C) for 11 min, when the first crystals appeared in the mixture. The pressure in the flask was kept at ca. 1.5 bar over this period. After the appearance of the crystals, the mixture was placed in an ice−water bath for 0.5 h and the precipitate was filtered off. Acetone (15 mL) was added through a reflux condenser to the suspension of the raw product in water (10 mL) in a 75−80 °C water bath. Addition of acetone was continued in 1 mL portions until there was complete dissolution of the crystalline material (ca. 20 mL altogether). The small amount of noncrystalline insoluble residue was filtered off and washed with a water−acetone (1:2) mixture. Acetone was removed from the filtrate by bubbling N_2 through the solution. The residual mixture was placed in an ice−water bath for 0.5 h. The precipitated crystals were filtered, washed with 0 °C water (2 × 1.5 mL), and dried by air suction. Yield: 0.510 g (72%). Anal. Found (calcd) for $C_9H_{16}BNO_4$: C, 51.20 (50.74); H, 7.64 (7.57); B, 5.06 (5.08); N, 6.55 (6.58). ^{1}H NMR (DMSO-d_6, δ): 1.72 (m, 6H, CCH_2), 1.93 (h, J = 3.3 Hz, 1H, CH), 3.27 (m, 6H, NCH_2), 10.64 (s, 2H, COOH). ^{11}B NMR (DMSO-d_6, δ): −9.9 (br). ^{13}C {^{1}H} NMR (DMSO-d_6, δ): 19.50 (CH), 23.65 (CCH_2), 49.50 (NCH_2). IR (KBr, cm^{-1}): ν_{assoc}(O−H), 2728, 2650; ν(B−H), 2446; ν(C═O), 1655, 1636.

Et$_2$NH·BH(COOH)$_2$ (4c). An HCl solution at 80−85 °C (25.0 mL, 0.345 M, 8.625 mmol HCl) was added to an aqueous solution of **3c** (0.520 g, 2.269 mmol, in 4 mL), and the mixture was quickly heated to boiling, kept under boiling conditions under a reflux condenser for 18 min, and quickly cooled to 50 °C. The pH was adjusted to 9.5−10 using 1 M NaOH, and the solution was concentrated in vacuo to 7−8 mL in a 60 °C bath. The solution was diluted with water to double its volume, the pH was adjusted to 9.5−10, and half the solvent was evaporated as indicated above. This procedure was repeated until the pH did not decrease during distillation and the condensed distillate, after acidification, did not give a precipitate with Na[BPh_4]. The pH was adjusted between 2.5 and 2.6 using 1 and 0.1 M HCl (ca. 1.8−1.9 mL, 1 M HCl), and it was evaporated in vacuo to 1−2 mL in a 60 °C bath. The remaining solution was evaporated to dryness without heating, and the residue was kept under vacuum (<0.5 mbar) for 0.5 h. The residue was redissolved in methanol (5 mL), and the solution was evaporated to dryness. This procedure was repeated once. The residue was suspended in ether (5 mL), and the suspension was filtered. The filtered solid was washed with ether (2 × 3 mL), and the filtrate was evaporated to dryness. The residual oil was redissolved in water (2 mL). The solution was acidified with HCl (0.5 mL 0.1 M) and concentrated to ca. 0.5 mL by employment of a fast N_2 stream in a 60 °C bath, then evaporated to dryness without heating. Yield: 0.1554 g (39%). Anal. Found (calcd) for $C_6H_{14}BNO_4$: C, 41.39 (41.18); H, 8.10 (8.06); B, 6.02 (6.18); N, 7.87 (8.00). ^{1}H NMR (DMSO-d_6, δ): 1.12 (t, J = 7.3 Hz, 6H, Et-CH_3), 2.91 (m, 4H, Et-CH_2), 6.01 (br s, 1H, NH). ^{11}B NMR (DMSO-d_6, δ): −13.4 (br). ^{13}C {^{1}H} NMR (DMSO-d_6, δ): 11.13 (Et-CH_3), 45.42 (Et-CH_2). IR (KBr, cm^{-1}): ν(NH), 3141; ν_{assoc}(O−H), 2851; ν(B−H), 2391; ν(C═O), 1673, 1623.

pip·BH(COOH)$_2$ (4d). Method A. An HCl solution at 80 °C (20.00 mL, 0.362 M, 7.24 mmol HCl) was added to an aqueous solution of **3d** (0.4596 g, 1.906 mmol, in 4.3 mL), and the mixture was quickly heated to boiling, kept at this temperature for 32 min under a reflux condenser, then quickly cooled to room temperature. The solution was extracted with CH_2Cl_2 in a continuous extraction for 4 h. The extract, containing some product already precipitated, was evaporated to dryness, the residue was suspended in ether (5 mL), the suspension was filtered, and the product was washed with ether (2 × 2 mL) and dried in an N_2 stream. Yield: 0.0987 g (28%). Anal. Found (calcd) for $C_7H_{14}BNO_4$: C, 45.63 (44.96); H, 7.56 (7.55); B, 5.84 (5.78); N, 7.39 (7.49).

pip·BH(COOH)$_2$ (4d). Method B. 4b (0.3204 g, 1.504 mmol) was dissolved in piperidine (4.0 mL). The solution solidified in 5 min. It was then warmed to 70 °C and kept at that temperature until it solidified again (25−30 min). The volatile parts were removed in vacuo, the residue was suspended in ether (5 mL), and the suspension was filtered. The filtered solid was redissolved in water (20 mL), and under stirring, aqueous Na[BPh_4] solution (3.20 mL, 0.5 M, 1.60 mmol Na[BPh_4]) was added in small portions. The precipitate was filtered off after 2 h of slow stirring and washed with water (4 × 2 mL), the filtrate was concentrated to 5−6 mL in vacuo, and [BPh_4]$^-$ ions were precipitated as a potassium salt by employment of 0.1 M KCl in small portions. After filtering off K[BPh_4], the pH of the filtrate was adjusted between 2.6 and 2.7 using 1 M and later 0.1 M HCl (1.4−1.5 mL of 1 M HCl) and it was evaporated to dryness in a 40 °C bath. The residue was suspended in 40 °C acetonitrile (15 mL), the suspension was filtered and washed with 40 °C acetonitrile (3 × 3 mL), and the filtrate was evaporated to dryness in vacuo. The residue was suspended in ether (10 mL), the suspension was filtered, and the product was washed with ether (2 × 5 mL) and dried in an N_2 stream. Yield: 0.2384 g (85%). Anal. Found (calcd) for $C_7H_{14}BNO_4$: C, 45.79 (44.96); H, 7.65 (7.55); B, 5.75 (5.78); N, 7.47 (7.49). ^{1}H NMR (DMSO-d_6, δ): 1.20−1.38 (m, 1H, 4-CH_2 ax), 1.50−1.77 (m, 5H, 3,5-CH_2 + 4-CH_2 eq), 2.75−2.93 (m, 2H, 2,6-CH_2 ax), 2.96−3.14 (m, 2H, 2,6-CH_2 eq), 6.26 (br, 1H, NH), 11.06 (s, 2H, COOH). ^{1}H NMR (acetone-d_6, δ): 1.50 (m, 2H, 4-CH_2), 1.84 (m, 4H, 3,5-CH_2), 3.20 (m, 4H, 2,6-CH_2), 5.29 (br, 1H, NH), 10.6 (br s, 2H, COOH). ^{11}B NMR (DMSO-d_6, δ): −11.6 (br). ^{13}C {^{1}H} NMR (DMSO-d_6, δ): 22.43 (4-CH_2), 23.51 (3,5-CH_2), 48.60 (2,6-CH_2). IR (KBr, cm^{-1}): ν(N−H), 3198, ν_{assoc}(O−H), 2864, 2634; ν(B−H), 2381; ν(C═O), 1653, 1637.

pyrr·BH(COOH)$_2$ (4e). Pyrrolidine (2.0 mL) was added to **4b** (0.363 g, 1.704 mmol), and the stirred suspension was kept at 70 °C for 2 h while the solid starting material dissolved and crystals precipitated. The reaction mixture was evaporated to dryness, the solid residue was suspended in ether (20 mL), and the suspension was filtered. The insoluble material was extracted five times with the extract and dried in an N_2 stream. This material, the pyrrolidinium salt of **4e**, was redissolved in water (25 mL), and Na[BPh_4] solution (3.66 mL 0.5 M, 1.83 mmol Na[BPh_4]) was added at 40 °C. The mixture was left to cool to room temperature, and then it was kept in a refrigerator overnight. The precipitated solid was filtered off and washed with 0 °C water (3 × 2 mL), and the filtrate was concentrated in vacuo to 6−7 mL in a 40 °C bath. [BPh_4]$^-$ ions were precipitated by adding 0.1 M KCl solution in small portions, K[BPh_4] was filtered off, and the pH of the filtrate was adjusted between 2.6 and 2.65 using 1 M and later 0.1 M HCl solution (1.6−1.7 mL of 1 M HCl). The mixture was evaporated to dryness in vacuo in a 40 °C bath. The residue was suspended in acetonitrile (20 mL) at 40 °C, the suspension was filtered, the insoluble parts were washed with acetonitrile (3 × 3 mL) at 40 °C, and the filtrate was evaporated to dryness in vacuo. The residue was suspended in ether (10 mL), the suspension was filtered, and the material filtered off was extracted with the filtrate 15 times and dried in an N_2 stream. Yield: 0.2558 g (87%). Anal. Found (calcd) for $C_6H_{12}BNO_4$: C, 40.99 (41.66); H, 7.08 (6.99); B, 6.38 (6.25); N, 7.98 (8.10). ^{1}H NMR (DMSO-d_6, δ): 1.67−1.91 (m, 4H, 3,4-CH_2), 2.68−2.81 (m, 2H, 2,5-CH_2), 3.16−3.25 (m, 2H, 2,5-CH_2), 6.90 (br, 1H, NH), 10.89 (s, 2H, COOH). ^{11}B NMR (DMSO-d_6, δ): −11.9 (br). ^{13}C {^{1}H} NMR (DMSO-d_6, δ): 24.05 (3,4-CH_2), 49.95 (2,5-CH_2). IR (KBr, cm^{-1}): ν(N−H), 3244, 3209; ν_{assoc}(O−H), 2854, 2724; ν(B−H), 2427; ν(C═O), 1662, 1637.

4-NH$_2$-py·BH(COOH)(COONa) (Na Salt of 4h). 4-NH_2-py (1,37 g, 14.56 mmol) was added to an acetonitrile solution of **4b** (0.3100 g, 1.455 mmol, in 6 mL), and the mixture was refluxed for 3 h. The mixture was allowed to cool to room temperature under stirring, and the resulting suspension was evaporated to dryness in vacuo. The residue was kept under diminished pressure (<2 mbar) for 0.5 h and then suspended in ether (18−20 mL). The suspension was filtered, and the solid on the filter was extracted with the filtrate 20−25 times until it

proved to be free from 4-NH_2-py by evaporating small portions of the extract. The material was dried in an N_2 stream. This material was redissolved in water (20 mL), and $Na[BPh_4]$ solution (2.60 mL 0.5 M, 1.30 mmol) was added. Addition of $Na[BPh_4]$ solution was continued in 25 μL portions until a small, filtered sample of the solution did not give a precipitate with $Na[BPh_4]$. After 0.5 h the precipitate was filtered off and washed with water (3 × 2 mL), and the filtrate was concentrated in vacuo to a viscous oil in a 40 °C bath. Acetonitrile (5 mL) was added to the residue, and this solution was evaporated under vigorous stirring. This procedure was repeated twice. The solid residue was kept under vacuum for 0.5 h and suspended in acetonitrile (8 mL), the suspension was filtered, and the solid residue was washed with acetonitrile (2 × 3 mL) and dried in an N_2 stream. Yield: 0.2994 g (94%). Anal. Found (calcd) for $C_7H_8BN_2NaO_4$: C, 39.16 (38.58); H, 3.64 (3.70); B, 4.92 (4.96); N, 12.78 (12.85). ^{1}H NMR (DMSO-d_6, δ): 6.61 (d, J = 6.8 Hz, 2H, 3,5-CH), 7.29 (br s, 2H, NH), 7.78 (d, J = 6.8 Hz, 2H, 2,6-CH). ^{11}B NMR (DMSO-d_6, δ): −10.6 (br). ^{13}C {^{1}H} NMR (DMSO-d_6, δ): 108.15 (3,5-CH), 146.94 (2,6-CH), 156.92 (*ipso*-C). IR (KBr, cm^{-1}): ν(N−H), 3472, 3356; ν(B−H), 2385; ν(C═O), 1648.

DMAP·BH(COOH)$_2$ (4i). DMAP (0.598 g, 4.89 mmol) was added to the acetonitrile solution of **4b** (0.103 g, 0.483 mmol, in 2 mL), and the solution was kept at 75−80 °C for 2 h. The mixture was evaporated to dryness, the residue was suspended in ether, and the suspension was filtered. The solid on the filter was thoroughly suspended in aqueous HCl (0.6 mL, 1 M), filtered, and washed with water until the filtrate remained neutral (3 × 0.5 mL). The product was dried in an N_2 stream. Yield: 0.086 g (84%). Anal. Found (calcd) for $C_9H_{13}BN_2O_4$: C, 48.15 (48.25); H, 5.77 (5.85); B, 4.83 (4.83); N, 12.29 (12.51). ^{1}H NMR (DMSO-d_6, δ): 3.12 (s, 6H, NCH_3), 6.83 (d, 2H, 3,5-CH), 7.92 (d, 2H, 2,6-CH), 11.0 (br, 2H, COOH). ^{11}B NMR (DMSO-d_6, δ): −9.6 (br). ^{13}C {^{1}H} NMR (DMSO-d_6, δ): 39.19 (N−CH_3), 106.58 (3,5-CH), 146.48 (2,6-CH), 155.39 (*ipso*-C). IR (KBr, cm^{-1}): ν_{assoc}(O−H), 2719, 2586; ν(B−H), 2402; ν(C═O), 1644 (br).

Me$_3$N·BH(COOMe)$_2$ (5a). Methanolic HBr solution (103 μL, 0.276 M) was added to a solution of **4a** (0.0762 g, 0.473 mmol) in superdry methanol (4 mL). After 30 min of stirring at room temperature, molecular sieves (0.195 g) were added to the solution. After 3 h the molecular sieves were filtered off and the filtrate was evaporated in vacuo. The residue was dissolved in $CHCl_3$ (2 mL), the insoluble parts were filtered off, and the filtrate was evaporated to dryness by employment of an N_2 stream. Yield: 0.0829 g (93%). Anal. Found (calcd) for $C_7H_{16}BNO_4$: C, 45.33 (44.48); H, 8.44 (8.53); B, 5.79 (5.72); N, 7.33 (7.41). ^{1}H NMR ($CDCl_3$, δ): 2.89 (s, 9H, NCH_3), 3.59 (s, 6H, OCH_3). ^{11}B NMR ($CDCl_3$, δ): −7.9 (d, J = 105 Hz). ^{13}C {^{1}H} NMR ($CDCl_3$, δ): 48.77 (NCH_3), 51.09 (OCH_3). IR (KBr, cm^{-1}): ν(B−H), 2420; ν(C═O), 1680, 1664.

Q·BH(COOMe)$_2$ (5b). The procedure described for **5a** was applied to **4a** (0.1985 g, 0.932 mmol) in superdry methanol (7.5 mL) using methanolic HBr (205 μL, 0.276 M), molecular sieves (0.362 g), and $CHCl_3$ (5 mL). Yield: 0.2150 g (96%). Anal. Found (calcd) for $C_{11}H_{20}BNO_4$: C, 55.86 (54.80); H, 8.40 (8.36); B, 4.44 (4.48); N, 5.71 (5.81). ^{1}H NMR ($CDCl_3$, δ): 1.80 (m, 6H, CCH_2), 2.05 (h, J = 3.3 Hz, 1H, CH), 3.43 (m, 6H, NCH_2), 3.57 (s, 6H, OCH_3). ^{11}B NMR ($CDCl_3$, δ): −9.8 (d). ^{13}C {^{1}H} NMR ($CDCl_3$, δ): 20.01 (CH), 24.38 (*C*CH_2), 48.72 (OCH_3), 50.18 (NCH_2). IR (KBr, cm^{-1}): ν(B−H), 2419; ν(C═O), 1680.

Et$_2$NH·BH(COOMe)$_2$ (5c). The procedure described for **5a** was applied to **4c** (0.0579 g, 0.331 mmol) in superdry methanol (3 mL) using methanolic HBr (72 μL, 0.276 M) and molecular sieves (0.140 g). The raw product was redissolved in ether (4 mL), the opalescent solution was filtered, and the filtrate was evaporated in an N_2 stream to obtain an oil, which later crystallized. The solid was suspended in pentane (5 mL), and the product was filtered off, washed with pentane (2 × 1 mL), and dried in an N_2 stream. Yield: 0.0542 g (81%). Anal. Found (calcd) for $C_8H_{18}BNO_4$: C, 47.48 (47.32); H, 8.91 (8.94); B, 5.32 (5.32); N, 6.67 (6.90). ^{1}H NMR ($CDCl_3$, δ): 1.28 (t, J = 7.3 Hz, 6H, Et-CH_3), 3.09 (m, 4H, Et-CH_2), 3.62 (s, 6H, OCH_3), 4.08 (br s, 1H, NH). ^{11}B NMR ($CDCl_3$, δ): −11.8 (d, J = 86 Hz). ^{13}C {^{1}H} NMR ($CDCl_3$, δ): 12.19 (Et-CH_3), 45.82 (Et-CH_2), 49.15 (OCH_3). IR (KBr, cm^{-1}): ν(N−H), 3148; ν(B−H), 2416; ν(C═O), 1684, 1646.

pip·BH(COOMe)$_2$ (5d). The procedure described for **5a** was applied to **4d** (0.078 g, 0.417 mmol) in superdry methanol (3.2 mL) using methanolic HBr (95 μL, 0.276 M) and molecular sieves (0.126 g). Yield: 0.0857 g (96%). Anal. Found (calcd) for $C_9H_{18}BNO_4$: C, 51.00 (50.27); H, 8.28 (8.44); B, 4.96 (5.03); N, 6.47 (6.51). ^{1}H NMR ($CDCl_3$, δ): 1.40−1.55 (m, 1H, 4-CH_2 ax), 1.55−1.75 (m, 2H, 3,5-CH_2 ax), 1.86 (m, 3H, 3,5-CH_2 eq + 4-CH_2 eq), 2.93 (m, 2H, 2,6-CH_2 ax), 3.35 (m, 2H 2,6-CH_2 eq), 3.61 (s, 6H, OCH_3), 6.26 (s, 1H, NH). ^{11}B NMR ($CDCl_3$, δ): −11.6 (d). ^{13}C {^{1}H} NMR ($CDCl_3$, δ): 22.8 (4-CH_2), 25.5 (3,5-CH_2), 49.24 (OCH_3), 50.22 (2,6-CH_2). IR (KBr, cm^{-1}): ν(N−H), 3176; ν(B−H), 2434; ν(C═O), 1676, 1658.

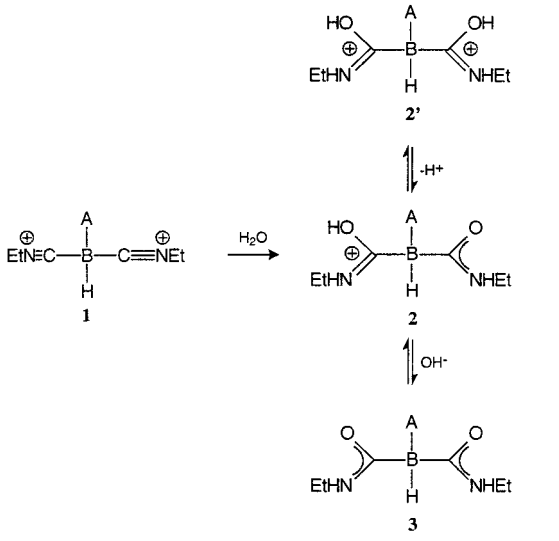
pyrr·BH(COOMe)$_2$ (5e). The procedure described for **5a** was applied to **4e** (0.0952 g, 0.550 mmol) in superdry methanol (4.5 mL) using methanolic HBr (120 μL, 0.276 M) and molecular sieves (0.153 g). Yield: 0.0994 g (90%). Anal. Found (calcd) for $C_8H_{16}BNO_4$: C, 47.99 (47.80); H, 7.86 (8.02); B, 5.36 (5.38); N, 6.89 (6.97). ^{1}H NMR ($CDCl_3$, δ): 1.82−2.07 (m, 4H, 3,4-CH_2), 2.87 (m, 2H, 2,5-CH_2), 3.51 (m, 2H, 2,5-CH_2), 3.60 (s, 6H, OCH_3), 5.45 (s, 1H, NH). ^{11}B NMR ($CDCl_3$, δ): −10.9 (d, J = 86 Hz). ^{13}C {^{1}H} NMR ($CDCl_3$, δ): 24.25 (3,4-CH_2), 49.03 (OCH_3), 50.94 (2,5-CH_2). IR (KBr, cm^{-1}): ν(N−H), 3178; ν(B−H), 2425; ν(C═O), 1674, 1653.

DMAP·BH(COOMe)$_2$ (5i). The procedure described for **5a** was applied to **4i** (0.0845 g, 0.377 mmol) in superdry methanol (3 mL) using methanolic HBr (82 μL, 0.276 M) and molecular sieves (0.068 g). Yield: 0.0914 g (96%). Anal. Found (calcd) for $C_{11}H_{17}BN_2O_4$: C, 52.68 (52.41); H, 6.87 (6.80); B, 4.34 (4.29); N, 11.08 (11.11). ^{1}H NMR ($CDCl_3$, δ): 3.15 (s, 6H, NCH_3), 3.59 (s, 6H, OCH_3), 6.61 (m, 2H, 3,5-CH), 8.12 (m, 2H, 2,6-CH). ^{11}B NMR ($CDCl_3$, δ): −9.1 (d, J = 77 Hz). ^{13}C {^{1}H} NMR ($CDCl_3$, δ): 39.42 (NCH_3), 48.77 (OCH_3), 106.12 (3,5-CH), 147.00 (2,6-CH), 155.62 (*ipso*-C). IR (KBr, cm^{-1}): ν(B−H), 2444; ν(C═O), 1680, 1664.

Li[BH(OMe)(CONHEt)$_2$]. Decrusted lithium metal (0.250 g, 36.03 mmol) was added to methanol (7 mL) at 0 °C under argon. After 0.5 h the cooling bath was replaced by a heater and the mixture was refluxed for 1 h. The suspension was concentrated to one-third its volume using an N_2 stream, and ether (5 mL) was added. The suspension was filtered, and the solid was washed with ether (3 × 4 mL) and dried to reach a constant weight using an N_2 stream. (Yield: 1.08 g of LiOMe, 79%). The LiOMe (0.180 g, 4.74 mmol) was added to the methanolic solution of **3a** (0.505 g, 2.348 mmol, in 4 mL), and the mixture was refluxed for 12 h and evaporated in vacuo. Ether (4 mL) was added to the solid residue, the suspension was vigorously stirred for 5 min, and the volatile components were evaporated in vacuo. The suspension−evaporation cycle was repeated twice. The residue was suspended in ether (25 mL), filtered off, and extracted with the filtrate 60−70 times. The precipitate was filtered off from the extract and dried in an N_2 stream. Yield: 0.353 g (78%). Anal. Found (calcd) for $C_7H_{16}BLiN_2O_3$: C, 43.43 (43.35); H, 8.48 (8.32); B, 5.60 (5.57); N, 14.31 (14.44). ^{1}H NMR (D_2O, δ): 1.06 (t, J = 7.3 Hz, 6H, Et-CH_3), 3.14 (q, J = 7.3 Hz, 4H, Et-CH_2), 3.15 (s, 3H, OCH_3). ^{11}B NMR (D_2O, δ): −4.7 (d, J = 96 Hz). ^{13}C {^{1}H} NMR (D_2O, δ): 16.83 (Et-CH_3), 35.37 (Et-CH_2), 56.77 (OCH_3). IR (KBr, cm^{-1}): ν(N−H), 3398; ν(B−H), 2306; amide I−II, 1560, 1518.

[Q·BH(CONHEt)−C(OMe)═NHEt][BF$_4$]. {Q·BH[C(OMe)═NHEt]$_2$}[BF_4]$_2$ (0.093 g, 0.198 mmol) was dissolved in HCl (1.5 mL, 1 M), and the solution was kept at the boiling point for 3 min. After cooling to room temperature, the solution was extracted with CH_2Cl_2 (4 × 1.5 mL) and the organic phase was dried over $MgSO_4$ and evaporated. The product was a pale-yellow oil. Yield: 0.045 g (62%). Anal. Found (calcd) for $C_{14}H_{29}B_2F_4N_3O_2$: C, 45.61 (45.57); H, 7.90 (7.92); B, 5.74 (5.86); N, 11.21 (11.39). ^{1}H NMR ($CDCl_3$, δ): 1.16 (t, J = 7.3 Hz, 3H, amide Et-CH_3), 1.30 (t, J = 7.4 Hz, 3H, imidate Et-CH_3), 1.87 (m, 6H, Q-CCH_2), 2.06 (h, J = 3.2 Hz, 1H, CH), 3.0−3.5 (m, 6H, Q-NCH_2), 3.28 (m, 2H, amide Et-CH_2), 3.53 (m, 2H, imidate Et-CH_2), 4.37 (s, 3H, OCH_3), 7.05 (br, 1H, amide NH), 11.19 (br, 1H, imidate NH). ^{11}B NMR ($CDCl_3$, δ): −1.2 (s, [BF_4]$^-$), −12.4 (br d, complex). ^{13}C {^{1}H} NMR ($CDCl_3$, δ): 15.07 (amide Et-CH_3), 20.06 (imidate Et-CH_3), 20.14 (CH), 24.48 (Q-*C*CH_2), 32.35 (amide Et-CH_2), 48.34 (OCH_3), 49.90 (imidate Et-CH_2), 50.58 (Q-NCH_2). IR (KBr, cm^{-1}): ν(N−H), 3398, 3237; ν(B−H), 2460; amide and imidate, 1637, 1576, 1535, 1487, 1465.

Scheme 1



A = Me_3N (**a**), Q (**b**), py (**f**), 4-pic (**g**)

Results and Discussion

Amine-bis(*N*-ethylcarbamoyl)boranes. As reported earlier, 2 molar equiv of water add readily to [amine-bis(*N*-ethylnitrilium)hydroboron(2+)] cations (**1**). Very low pK_{a1} values of the formal addition products (**2′**) allow their preparation from water in singly deprotonated form (**2**) only.[29] On further deprotonation with NaOH, these complex cations can be transformed into neutral amine-bis(*N*-ethylcarbamoyl)boranes (**3**), which can be prepared in good yields and in pure form after extraction from alkaline aqueous solution into dichloromethane (Scheme 1).

After synthesis of the Me_3N complex, additional amine-bis(*N*-ethylcarbamoyl)boranes can be prepared via amine exchange reactions, taking advantage of the volatility of Me_3N:

$$\underset{\mathbf{3a}}{Me_3N{\cdot}BH(CONHEt)_2} + A \xrightarrow[\text{or neat}]{MeCN} A{\cdot}BH(CONHEt)_2 + Me_3N \quad (1)$$
$$\mathbf{3c-e, h-k}$$

A = Et_2NH (**c**), pip (**d**), pyrr (**e**), 4-NH_2-py (**h**), DMPA (**i**), Him (**j**), Mim (**k**)

This method can be applied to the preparation of amine-bis(*N*-ethylcarbamoyl)boranes not available starting from amine-dicyanoboranes via **1** and **2**.[29]

Amine-bis(*N*-ethylcarbamoyl)boranes are fairly stable in alkaline solution even at elevated temperatures. For instance, Q·$BH(CONHEt)_2$ could be quantitatively recovered after treatment with 1 M NaOH for 20 min at 120 °C and 1.5 atm, and slow decomposition took place only in 50% NaOH close to its boiling point. The aqueous solution of **2** ⇌ **3**, where the nitrogen atom in the amine is sp^3-hybridized, can be stored at room temperature for weeks in either 1 M DCl or neutral solutions without any change in their NMR spectra. This behavior is contrary to that of [amine-(*C*-hydroxy-*N*-ethylimidate)dihydroboron(1+)] cations, which, formed upon the hydrolysis of [amine-(*N*-ethylnitrilium)dihydroboron(1+)]tetrafluoroborates in acidic medium, transformed into amine-carboxyboranes.[4,30-32]

Table 1. ^1H NMR Monitoring Data Characterizing the Formation from **3** and Decomposition of A·$BH(COOH)_2$ in 0.3 M HCl (**3**/HCl = 1:3.8) at 100 °C

	maximum yield amount[a]/ reaction time (min)		rate of decomposition[b]	
amine	D_2O/H_2O (5:2)	H_2O	D_2O/H_2O (5:2)	H_2O
Me_3N	22/90	15/80	<0.05	<0.05
Q	85/40	85/40	<0.02	<0.02
Et_2NH	51/17	54/10	1.0	4.3
piperidine	51/38	34/30	0.63	0.92
pyrrolidine	46/27	35/18	0.90	1.4

[a] Expressed in percentage of **3**. [b] Expressed in percentage of the maximum yield/minute.

The infrared spectra of **3** show characteristic bands in the 3230−3400 cm^{-1} (ν(NH)), 2370−2410 cm^{-1} (ν(BH)), and 1500−1640 cm^{-1} (amide I−II) regions. ^1H and ^{13}C NMR spectra represent the nuclei of the complexing amines and −NHEt groups because protons and carbons adjacent to boron atoms give very broad signals due to the quadrupole moment of boron. These spectra show considerable downfield shift of the signals relative to those in the free bases because of the complexation. The effect is more expressed for the nuclei close to nitrogen. Unambiguous assignment of the ^1H NMR spectrum of the piperidine complex (**3d**) necessitated $^{13}C-^1H$ and $^1H-^1H$ correlation experiments because the complexation stiffens the otherwise flexible piperidine ring into the chair conformation with the borane moiety in equatorial position, similar to pip·$BH(CN)_2$.[29] ^{11}B NMR spectra of **3** show well-resolved doublets except those recorded in DMSO-d_6. Chemical shifts generally range between −7.3 and −9.8 ppm.

Amine-dicarboxyboranes. Tertiary and secondary amine complexes of bis(*N*-ethylcarbamoyl)boranes (**3a−e**) were hydrolyzed into amine-dicarboxyboranes (**4a−e**) in acidic aqueous media at high temperature,

$$\underset{\mathbf{3a-e}}{A{\cdot}BH(CONHEt)_2} \xrightarrow[100-130\ ^\circ C]{0.3-1\ M\ HCl} \underset{\mathbf{4a-e}}{A{\cdot}BH(COOH)_2} + 2EtNH_3Cl \quad (2)$$

and the products could be isolated in moderate yields except **4b** (78%). The reactions took place via the "semihydrolyzed" amine-carboxy-(*N*-ethylcarbamoyl)boranes (or their protonated derivatives) whose maximum concentration appeared to be 17 (**a**), 11 (**b**), 16 (**c**), 21 (**d**), and 15 (**e**) mol %. On the other hand, boric acid and AH^+ cations appeared in the reaction mixtures because of decomposition processes involving the rupture of the B−N bond. The amounts of these species (except H_3BO_3) were followed by ^1H NMR monitoring of the reactions in D_2O-H_2O mixtures and in water, and the results are summarized in Table 1. The temperature (100 °C) and the concentrations (0.079 M **3** and 0.3 M HCl) were set on the basis of yield optimization experiments.

The data presented in Table 1 clearly show that the reason for low or moderate yields (except **4b**) is the rupture of the B−N bond in the starting materials and intermediates rather than in the products. In other words, the B−N bond in amine-dicarboxyboranes is more stable toward protons than that in amine-bis(*N*-ethylcarbamoyl)boranes or amine-carboxy-(*N*-ethylcarbamoyl)boranes. Qualitative evaluation of the differences between observations in a D_2O-H_2O mixture and water

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shows that both amide hydrolysis and B−N bond rupture are faster in water. The isotope effect is most striking for the decomposition of secondary amine complexes of $BH(COOH)_2$, particularly $Et_2NH{\cdot}BH(COOH)_2$.

Hydrolyses of **3a**−**c** were studied at 130 °C and 1.5 bar also. Under these conditions yields of **4b** and **4c** remained essentially unaffected, whereas the yield of **4a** was 32% after 10 min, double that observed at 100 °C. Hydrolysis of **3a** at 80 °C resulted in 85% conversion in 2.5 h; however, the formation of **4a** was only 5%. Yields slightly increase when the concentration of HCl solutions decrease and vice versa. **4b** is an exception; its yield did not show a detectable decrease even in 1 M HCl at 130 °C.

The decomposition of amine-bis(*N*-ethylcarbamoyl)boranes and amine-carboxy-(*N*-ethylcarbamoyl)boranes is probably due to a complexation competition between the proton and the disubstituted borane on the amine, where the rupture of the B−N bond is irreversible. The exceptional behavior of **3b** is probably a consequence of the rigid bicyclic geometry of quinuclidine, which does not favor the formation of a transition state with the five-coordinate nitrogen center necessary for the decomposition. This assumption is supported by our earlier observations in the study of decomposition of pyrrolyl-cyanoborates [AH]-$[BH(NC_4H_4)_2CN]$, showing that the quinuclidinium salt, contrary to 11 other amines, did not undergo decomposition yielding $A{\cdot}BH(NC_4H_4)_2CN$ and pyrrole. It was explained by steric factors rendering the formation of a transition state with five-coordinate nitrogen sterically hindered.[33]

After all, it is clear that hydrolyses of amine-bis(*N*-ethylcarbamoyl)boranes require much more vigorous conditions than hydrolyses of the corresponding amine-*N*-ethylcarbamoylboranes, which take place even at room temperature or can be accomplished in few minutes at 60−80 °C.[4,30−32] The huge difference occurs probably because of the markedly different steric hindrance of the acyl carbons rather than because of electronic factors.[34] If electronic factors prevailed, the order of the hydrolysis rates should be reversed because the electron density over the acyl carbon is probably less in bisamides than in monoamides.

In contrast to the previously mentioned amine-bis(*N*-ethylcarbamoyl)boranes, **3f**−**k**, each containing an sp^2-hybridized nitrogen atom, underwent complete decomposition in acidic hydrolyses. Signals implying the presence of **4f**−**k**, or $A{\cdot}BH(CONHEt)(COOH)$ complexes, did not appear in the spectra during ^1H NMR monitoring of the reactions. $DMAP{\cdot}BH(COOH)_2$ (**4i**) and the acid salt $4\text{-}H_2N\text{-}py{\cdot}BH(COOH)(COONa)$, prepared by another route (see below), also quickly decomposed in acidic aqueous solutions. The reason for the unexpectedly low stability of these complexes toward acidic medium may be the "too strong" electron-donating property of pyridine bases through B−N bond, which results in an increased hydridic character of the hydrogen adjacent to boron; consequently, the B−H group is more susceptible toward an attack by the proton as an oxidating agent. This assumption is supported by the findings of Funke and Mayr, who studied the kinetics and mechanism of the reactions between amine-boranes and carbenium ions. They concluded that BH_3 complexes of substituted pyridines, despite the lower basicities of the amines toward the proton, are stronger hydride donors than trialkylamine complexes. Furthermore, they found that the reactivities of pyridine-boranes increased with the electron-donating ability of the substituents in pyridine and found $DMAP{\cdot}BH_3$ to be by far the strongest hydride donor of all studied complexes.[35]

4d, **4e**, and **4i** were synthesized in base exchange reactions from **4b**, obtained in good yield from acidic hydrolysis of **3b**, under conditions similar to those applied in analogous syntheses of amine-carboxyboranes: large excess of the amine, without solvent or with a small amount of acetonitrile as cosolvent.[36] These reactions resulted in the formation of the acid salts of composition $[AH^+][A{\cdot}BH(COOH)(COO^-)]$. This experience, which was not reported for any amine-carboxyboranes, may be explained by the fact that amine-dicarboxyboranes, at least at their first base, are stronger acids than amine-carboxyboranes, presumably owing to the electron-withdrawing effect of the carboxyl group. In agreement with these observations, the −COOH resonances in ^1H NMR (in DMSO-d_6 solution) can be found at lower fields for amine-dicarboxyboranes than those of amine-carboxyboranes. **4i**, because of its poor solubility in water, could be prepared by acidifying the aqueous solution of its acid salt. The solutions of the other two acid salts were transformed into sodium salts by treating with equimolar $Na[BPh_4]$ and filtering off $[AH][BPh_4]$, and the dicarboxylic acids were obtained by acidifying the solution using equimolar HCl, evaporation, and separation from NaCl by filtering from acetonitrile. Preparation of **4h** failed because this material, formed upon acidification of the aqueous solution of the acid salt $4\text{-}H_2N\text{-}py{\cdot}BH(COOH)(COONa)$ that was in turn obtained by the above method, showed considerable decomposition in acidic aqueous solution, even at room temperature.

The infrared spectra of **4** gave characteristic bands in the 2363−2446 cm^{-1} (ν(BH)), 1636−1664 (ν(CO)), and 2566−2736 cm^{-1} (ν_{assoc}(OH)) regions. Because of their poor solubility in other solvents, NMR spectra of **4** were recorded in DMSO-d_6. The ^1H NMR spectra show −COOH resonance between 10.6 and 11.3 ppm. ^{11}B NMR spectra of **4** show a broad band between −9.9 and −13.4 ppm, except the Me_3N complex (−7.8 ppm).

Amine-bis(methoxycarbonyl)boranes. Amine-dicarboxyboranes (**4**) exhibit relatively poor solubility in organic solvents. To facilitate further transformations, which may require reactions in organic solvents, the preparation of their esters, or in other words, the protection of the carboxylic group, was attempted. Similar to amine-carboxyboranes, all amine-dicarboxyboranes (**4a**−**e**, **i**) underwent esterification in methanol in the presence of a catalytic amount (3 mol % relative to carboxyl groups) of HBr, and the corresponding amine-bis(methoxycarbonyl)boranes (**5**) were obtained in practically quantitative yields:

$$\underset{\mathbf{4a-e,\ i}}{A{\cdot}BH(COOH)_2} \xrightarrow{\text{6 mol \% HBr/MeOH}} \underset{\mathbf{5a-e,\ i}}{A{\cdot}BH(COOMe)_2} \quad (3)$$

The reactions took somewhat longer times in comparison with those of amine-carboxyboranes (5−10 min in contrast to virtually instantaneous esterification), and the esters proved to be fairly sensitive to water. Failing to add the molecular sieves before evaporation resulted in contamination of the product with considerable amounts of the half ester $A{\cdot}BH(COOMe)(COOH)$.

Amine-bis(methoxycarbonyl)boranes **5a**−**e** are all readily crystallizing solids and very soluble in organic solvents.

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Amine-bis(methoxycarbonyl)boranes **5a**−**e** underwent ester hydrolysis readily in acidic aqueous solutions (pH = 1−2) at 50 °C, employing constant N_2 bubbling through the reaction mixtures, and the corresponding amine-dicarboxyboranes were obtained after evaporation of the solvent and treatment with ether. **5i** is very poorly soluble in water, so the hydrolysis was attempted in a 1:2 acetonitrile/water mixture at 40−50 °C at pH ≈ 1, which resulted in the decomposition of the complex, probably for the same reason as described for the failure of the hydrolysis of **3i** to **4i.** Our experiments aimed at the alkaline ester hydrolysis of amine-bis(methoxycarbonyl)boranes remained unsuccessful. ^{1}H NMR monitoring of the reactions showed that esters remained unchanged at pH > 8 at 50 °C for a couple of hours. Similar experience can be found in the literature for the attempted alkaline hydrolysis of Q·BH(Bu^i)-COOEt.[21]

The difficulties of alkaline ester hydrolysis and the ease of acidic ester hydrolysis of A·BH(X)COOMe (X = H,[6] COOMe, CN[26]) type compounds can be explained by one common reason: the strong electron-releasing effect of the ≡N−B≡ unit toward the methoxycarbonyl group on the boron hinders the alkaline hydrolysis by forming relatively large electron density over the acyl carbon and rendering the attack of OH^- more difficult. The same effect advances acidic hydrolysis by promoting the protonation of the methoxycarbonyl group.

Attempts for Alternative Syntheses of Amine-bis(methoxycarbonyl)boranes. As we have seen earlier, the known pathways for the syntheses of amine-dicarboxyboranes are limited in either scope or yield. On the basis of the fact that **5a**−**e** readily hydrolyze into **4a**−**e**, alternative synthetic pathways were examined for preparation of amine-dicarboxyboranes via amine-bis(methoxycarbonyl)boranes as well.

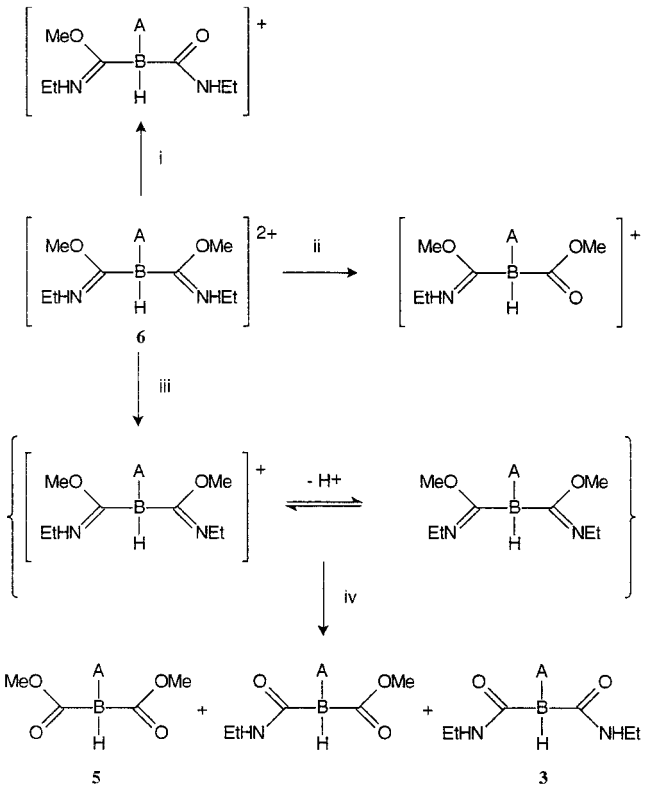
The amide → ester transformation (**3a** → **5a**) was attempted by nucleophilic substitution in HBr/MeOH and with LiOMe in MeOH. Unlike the carboxamide group attached to boron in multipolar framework compounds,[20] **3a** did not give **5a** in acidic methanol, but slow decomposition took place instead. In the reaction between **3a** and LiOMe the substitution took place on the boron instead of the acyl carbon, resulting in the formation of $[(MeO)BH(CONHEt)_2]^-$ anion, which could be isolated as a lithium salt in good yield.

The synthesis of **5** was attempted by acidic hydrolysis of the known [amine-bis(*C*-methoxy-*N*-ethylimidate)hydroboron(2+)] cations (**6**):[29]

$$\underset{\mathbf{6}}{[A\cdot BH\{C(OMe)NHEt\}_2][BF_4]} \xrightarrow[?]{H^+/H_2O} \underset{\mathbf{5}}{A\cdot BH(COOMe)_2} \rightarrow \underset{\mathbf{4}}{A\cdot BH(COOH)_2} \quad (4)$$

These experiments were based on literature data stating that hydrolyses of *C*-alkoxy-*N*-alkylimidates in acidic media typically result in the formation of carboxylic acid esters[37] and some amine-alkoxycarbonylboranes are known to be synthesized from [amine-(*N*-ethylnitrilium)dihydroboron(1+)] cations via amine-(*C*-alkoxy-*N*-ethylimidate)dihydroboron(1+)] species.[4,38] Therefore, the hydrolyses of **6a,b,f**, which were readily obtained by nucleophilic addition of methanol to **1a,b,f**,[29] were systematically studied (basically by ^{1}H NMR monitoring) at various pH values. Our findings, different from those expected, can be summarized in Scheme 2. The first step of the acidic hydrolysis (1 M HCl) seemed to be the appearance of methanol for each studied complex at room temperature, as well as at boiling point, and simultaneous formation of the $\{Q\cdot BH(CONHEt)[C(OMe)=NHEt]\}^+$ cation (step i of Scheme 2). The tetrafluoroborate salt of this cation could be obtained in good yield from the reaction mixture by CH_2Cl_2 extraction. This reaction was accompanied by the decomposition of the complexes via the rupture of the B−N bond, particularly for **6f**. In neutral medium, the B−N bond in **6f** proved to be stable even at temperatures close to the boiling point. The hydrolytic reactions yielded multicomponent mixtures containing species mostly extractable into CH_2Cl_2. The major component (70 mol %) of the products of the hydrolysis could be identified as the $\{py\cdot BH(COOMe)[C(OMe)=NHEt]\}^+$ cation (step ii of Scheme 2), but attempts to isolate the ion remained unsuccessful. In 1 M NaOH hydrolytic reactions of **6a,b,f** resulted in the mixtures of **3** (25−40 mol %), **5** (20−25 mol %), and A·BH(CONHEt)(COOMe) (40−50 mol %). The hydrolysis of **6f** yielded two more unidentified components also. It is noteworthy that *C*-methoxy-*N*-ethylimidate base (−C(OMe)=NEt) groups did not seem to be present in the CH_2Cl_2 extracts because every *N*-CH_2 proton shared relatively strong (7−11 Hz) scalar couplings with NH-s in the amide region of ^{1}H NMR spectra. Although it seems obvious that $-[C(OMe)=NHEt]^+$ groups undergo deprotonation in alkaline aqueous solutions (step iii of Scheme 2), the aforementioned observation may make one conclude that −C(OMe)=NEt groups on the boron are not stable in these compounds. One possible explanation is their fast nucleophilic substitution by OH^-, resulting in the formation of *N*-ethylamide or methylester groups (step iv of Scheme 2). This assumption is supported by the proportions of the three possible products,

Scheme 2



Conditions: (i) pH = 1, A = Me_3N, Q; (ii) pH = 7, A = py; (iii) pH = 13, A = Me_3N, Q, py; (iv) pH = 13, A = Me_3N, Q.

(37) Neilson, D. G. In *The Chemistry of Amidines and Imidates*; Patai, S., Ed.; Wiley: London, 1975; p 422.
(38) Mittakanti, M.; Charandabi, M. R. M. D.; Morse, K. W. *Inorg. Chem.* **1990**, *29*, 3218.

showing overwhelmingly amide groups. The proclivity of −C(OMe)═NEt groups for nucleophilic substitution is probably caused by the presence of an electron-withdrawing substituent (here, $-[C(OMe)=NHEt]^+$) on the boron because several amine-borane complexes are known in the literature with the composition A·BH(X)−C(OR)═NEt (X = H, alkyl) and those with an alkyl group on the boron were observed to withstand hydrolysis in even relatively harsh conditions.[21]

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