Boron Analogs of Valine, Leucine, and Isoleucine: Synthesis of Amine−Alkyl(*C*-alkoxycarbonyl)boranes and Amine−Alkyl(*N,N*-diethylcarbamoyl)boranes

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Received February 3, 1994[⊗]

Alkylation of amine−alkyl(*C*-alkoxy-*N*-ethylcyano)boranes with Et_3OBF_4 resulted in the isolation of amine−alkyl(*C*-alkoxy-*N,N*-diethylcyano)borane tetrafluoroborates, which, upon aqueous base hydrolysis, yielded both the amine−alkyl(*C*-alkoxycarbonyl)borane and the amine−alkyl(*N,N*-diethylcarbamoyl)borane in varyng ratios. Amine−alkyl(*C*-alkoxycarbonyl)boranes (amine = quinuclidine, pyridine; alkyl = *i*Bu, *i*Pr, *s*Bu; alkoxy R = Me, benzyl) representative of several amino acid analogues have been isolated and characterized. These are the first ester derivatives of a boron analog other than glycine.

Introduction

In 1937, Burg and Schlesinger discovered borane−carbonyl, formally the parent compound of all simple boron hydrides, substituted with a carbonyl-containing functional group.[1] A compound with the composition $H_3BCO{\cdot}2NH_3$ was also reported at this time.[1] Later work demonstrated that this compound had the structure, $NH_4[H_3BC(O)NH_2]$.[2] In 1967, Parry and Malone[3] discovered that, in addition to isolation of boranocarbonate ($K_2[H_3BC(O)O]$), it was possible to isolate the ester derivative ($K[H_3BC(O)OR]$) by reacting borane−carbonyl with a dry ice cooled solution of potassium alkoxide.

Many neutral amine−borane analogues of these anionic derivatives have been synthesized in recent years. Sodium cyanotrihydroborate was reacted with THF·HCl to produce the oligomer−$[BH_2CN]_x^-$. This oligomer was then reacted with a tertiary amine to produce, for example, $Me_3N{:}BH_2CN$. The cyano group was activated by the use of Et_3OBF_4 to form $[Me_3N{:}BH_2CNEt]BF_4$. Controlled hydrolysis of this salt in water or under mildly acidic conditions resulted in the isolation of $Me_3N{:}BH_2C(O)OH$, the amine−borane analogue of betaine.[4] The ester derivatives were prepared by either dissolution of the betaine derivative in alcohol with a stoichiometric amount of dicyclohexylcarbodiimide (DCC)[5] or reaction with a chloroformate in the presence of 4-(dimethylamino)pyridine (DMAP).[6] Alternatively, $[Me_3N{:}BH_2CNEt]BF_4$ was converted directly to $Me_3N{:}BH_2C(O)OEt$ by dissolving it in ethanol, to which a stoichiometric amount of concentrated hydrochloric acid had been added. Refluxing the mixture for 2 days afforded the ester in moderate yield.[7] Recently, a synthesis for esters of both NH-containing amine−carboxyboranes and $R_3N{\cdot}BH_2CO_2H$ has been reported. This involves reaction of the amine−carboxyborane with trialkylorthoformate and $Et_2O{\cdot}BF_3$ catalyst.[8] Many of these alkoxycabonylboranes have been shown to possess biological activity.[7,9]

Previously, we reported that amine−alkylcyanoborane and amine−alkyl(*N*-ethylcarbamoyl)borane analogs of certain other amino acids besides glycine could be isolated, as well as their imino ether derivatives.[10−13] Our attempts to directly convert any of these amino acid analogs of the form $R_3N{\cdot}R'BH{-}X$ (X = CN, C(O)NHEt, C(OR″)NEt) to the corresponding carboxylic acid by the published method[4] failed due to the increased hydridic character of the hydrogen atom bonded directly to boron, which made it more sensitive to acid attack. Others have observed similar problems with this chemistry.[14] Base hydrolyses cleaved neither the amides nor the imino ethers to yield amine−alkyl(carboxy)boranes.[12,13] Direct conversion of our imino ether derivatives in hot water to the ester failed, in contrast to the earlier observations of Mittakanti and Morse with $C_5H_5N{\cdot}BH_2C(OCH_3)NEt$ which did give the ester $C_5H_5{\cdot}BH_2C(O)OCH_3$.[15]

We have found the alkylation of amine−alkyl(*C*-alkoxy-*N*-ethylcyano)boranes with $Et_3O[BF_4]$ followed by aqueous base hydrolysis gave amine−alkyl(*C*-alkoxycarbonyl)borane and amine−alkyl(*N,N*-ethylcarbamoyl)borane in varying ratios, depending on the starting cyanoborane. This paper outlines the syntheses, characterization, and properties of some representative ester and *N,N*-diethyl amide derivatives (see Chart 1) of boron analogs of leucine, isoleucine, and valine.

Experimental Section

Techniques. Unless otherwise noted, all reactions were performed under an atmosphere of N_2 using methods described by Brown[16] and Shriver.[17] Nitrogen gas was dried by passage through a glass column

[⊗] Abstract published in *Advance ACS Abstracts,* August 15, 1994.

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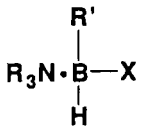
0020-1669/94/1333-4221$04.50/0

Chart 1



R_3N = quinuclidine {$N[CH_2CH_2]_3CH$} (number,letter)
R_3N = pyridine (number,letter')

(no number). R' = H 1. R' = *i*Bu
2. R' = *i*Pr 3. R' = *s*Bu

X=

a. -C≡N b. -C≡N-Et$^+$ c. -C(=O)-NHEt

d. -C(-OEt)=NHEt$^+$ e. -C(-OMe)=NEt

f. -C(-OEt)=NEt g. -C(-OCH$_2$Ph)=NEt

h. -C(-OMe)=NEt$_2^+$ i. -C(-OEt)=NEt$_2^+$

j. -C(-OCH$_2$PH)=NEt$_2^+$ k. -C(=O)-OMe

l. -C(=O)-OEt m. -C(=O)-OCH$_2$Ph

n. -C(=O)-NEt$_2$ o. -C(=O)-OH

containing 4-Å molecular sieves. All glassware was dried immediately before use under dynamic vacuum (0.01−0.2 mmHg). Where designated as "dry", reaction solvents were dried by distillation under N_2 from sodium and benzophenone (saturated and aromatic hydrocarbons and ethers) or P_2O_5 (CH_2Cl_2).[18] Diethyl ether was used as purchased from Mallinckrodt and stored under dry N_2. Acetonitrile was used as purchased and stored over molecular sieves. Chromatographic separations were conducted using HPLC grade solvents. Flash chromatography was performed according to the method of Still[19] using 230−400 mesh silica gel (Aldrich 60 Å or Merck grade 60).

Reagents. Triethyloxonium tetrafluoroborate was synthesized according to the Meerwein protocol.[20] Its potency was maintained for as long as 2 years by storage of the salt under Et_2O and N_2 and by washing it several times with fresh Et_2O just prior to use of the salt. Immediately after these washings, the final rinse was removed via cannula and the storage vessel was placed under dynamic vacuum until the Et_3OBF_4 crystals were dry. After the desired quantity of Et_3OBF_4 was transferred to the reaction vessel, dry Et_2O sufficient to completely immerse the remaining salt was transferred via cannula to the storage vessel. Imino ethers used in these reactions were prepared as previously reported.[13]

NMR Analysis. Proton NMR spectra were recorded in deuterated solvents on a Nicolet NT-360 (361.1 MHz) spectrometer locked to the solvent deuterium signal. Chemical shifts were established relative to the residual protons in the solvent and are reported in δ, parts per million (ppm) downfield from TMS: acetone-d_6, 2.08; chloroform-*d*, 7.25. Coupling constants (J) refer to H−H coupling unless otherwise noted. Due to quadrupolar effects and molecular asymmetry, B−*H* resonances were, if not indicated, obscured by other resonances or were of low intensity and very broad.

Boron-11 NMR spectra were recorded at 115.8 MHz on the Nicolet 360 spectrometer in the solvents indicated; the spectrometer was not usually locked to the deuterium signal as signal drift was a couple of orders of magnitude lower than the broadening of the ^{11}B signals. Chemical shifts are reported relative to $Et_2O{\cdot}BF_3$ as an external standard with positive shift values being downfield. Coupling constants indicate $^1H-^{11}B$ interactions unless otherwise noted.

Carbon-13 NMR spectra were obtained in deuterated solvents using the Nicolet (90.8 MHz) spectrometer. Chemical shifts are reported in ppm downfield of tetramethylsilane as established by comparison to the solvent chemical shifts: acetone-d_6, 2060, 29.8; chloroform-*d*, 77.0.

Other Characterization Techniques. Infrared spectra were recorded in cm^{-1} on a Perkin-Elmer 283 spectrometer as neat oils on NaCl plates or, if solid, ground with dry KBr and formed into pellets. Absorbances were referenced to polystyrene (1601.4 and 1583.1 cm^{-1}). More recent infrared spectra were obtained on a Nicolet 510P Fourier transform infrared spectrometer. Intensities are reported in accordance with the literature.[21] Melting points were obtained using a Meltemp device in sealed, evacuated capillaries and are uncorrected. Mass spectra were determined on a Kratos MS-80 using the technique indicated. Elemental analyses were performed by Galbraith Microanalytical Labs, Knoxville, TN.

Quinuclidine−Isobutyl(*C*-methoxy-*N*,*N*-diethylcyano)borane Tetrafluoroborate (1h). Recrystallized **1e** (0.545 g, 2.05 mmol) was dissolved in 1.5 mL of dry CH_2Cl_2. To a separated three-necked flask, Et_3OBF_4 (0.570 g, 3.00 mmol) was added under dual N_2 purge, followed by brief drying under dynamic vacuum for 15 min. This and the imino ether flask were fitted with rubber septa. The imino ether solution was quantitatively transferred to the Et_3OBF_4 flask, followed by three 0.5 mL rinses of the imino ether flask, for a total reaction volume of 3.0 mL of CH_2Cl_2. This was reacted for 24 h at room temprature and was worked up to afford crystalline **1h** (0.790 g). The infrared spectrum and ^{11}B NMR indicated that this material was 20% imino ether **1e** and 80% **1h**. Data for **1h**: ^{11}B NMR (CH_2Cl_2) δ −1.1 (s, BF_4^-), −6.25 (br d); ^1H NMR ($CDCl_3$) δ 4.32 and 4.23 (br s, br s, $-OCH_3$), 4.1−3.0 (multiplets, diastereotopic and rotamer $=N^+[CH_2CH_3]_2$), 3.10 (m, $N[CH_2]_3-$), 2.01 (septet, J = 3.1 Hz, $HC[CH_2]_3-$), 1.85 (td, J = 8.0, 2.8 Hz, $HC[CH_2]_3-$), 1.31, 1.23, and 1.18 (t, m, t, t, J = 7.1, 6.6, 7.1 Hz, rotamer and diastereotopic $=N[CH_2CH_3]_2$), 1.26 (m, $-CH_2CH-[CH_3]_2$), 0.85 and 0.34 (d, d, J = 5.1, 6.3 Hz, diastereotopic $-CH-[CH_3]_2$), 0.55 and 0.42 (m, m, diastereotopic $BHCH_2CH-$); FTIR (NaCl) ν_{max} 2948 s, 2880 s (C−H), 2664 w, 2458 m, 2318 vw (B−H), 1570 ms, ($C=NEt_2^+$), 1466 s, 1060 vs br cm^{-1}.

Quinuclidine−Isopropyl(*C*-methoxy-*N*,*N*-diethylcyano)borane Tetrafluoroborate (2h). Freshly-prepared **2e** (0.968 g, 3.84 mmol) was reacted with Et_3OBF_4 (0.677 g, 3.56 mmol) in CH_2Cl_2 for 3 days, and the mixture was worked up to afford impure semisolid iminium salt **2h** (60% **2h** by ^{11}B NMR). A nearly pure sample of **2h** was obtained from later fractions of the chromatography that yielded **2k** (*vide post*). Evaporation of the eluent acetone yielded a solid material which was recrystallized from CH_2Cl_2/hexane: ^{11}B NMR (CH_2Cl_2) δ −1.5 (s, BF_4^-), −2.16 (br d, J = 80 Hz); ^1H NMR ($CDCl_3$) δ 4.28 and 4.15 (s, s, major, minor rotamer $-OCH_3$), 3.91 and 3.73 (sextets, J_{gem} = *ca.* 14 Hz, $J_{H-C-C-H}$ = 7.0, 6.9 Hz, *anti* minor rotameter diastereotopic $=N^+CH_2CH_3$), 3.60, 3.50, 3.35, and 3.15 (sextets, J_{gem} = *ca.* 13.5 Hz, J = 6.8, 6.9, 6.8, 6.6 Hz, *anti* and *syn* major rotamer diastereotopic $=N^+[CH_2CH_3]_2$), 3.42, 3.11, and 3.02 (m, m, m, diastereotopic and rotamer $N[CH_2]_3-$ and *syn* minor rotamer $=N^+CH_2-CH_3$), 2.08 (septet, J = 3.2 Hz, $HC[CH_2]_3-$), 1.92 (m, minor rotamer $HC[CH_2]_3-$), 1.80 (m, major rotamer $HC[CH_2]_3-$), 1.28 and 1.15 (t, t, J = 7.1, 7.0 Hz, *anti* and *syn* minor rotamer $=N^+[Ch_2CH_3]_2$), 1.22 and 1.17 (t, t, J = 7.1, 7.1 Hz, *anti* and *syn* major rotamer $=N[CH_2CH_3]_2$), 0.98 and 0.57 (s, d, J = 0, 6.4 Hz, major rotamer $-CH[CH_3]_2$), 0.96 and 0.55 (s, d, J = 0, 5.1 Hz, minor rotamer $-CH-[CH_3]_2$), 0.88 (m, $BHCH[CH_3]_2$); ^{13}C NMR ($CDCl_3$) δ 195.8 (br, $BC(=N^+)O-$), 61.36 and 60.82 (minor, major rotamer $-OCH_3$), 56.54, 53.01, and 52.93 (minor, major rotamer $N[CH_2]_3-$), 49.09 and 45.44 (major rotamer *anti*, *syn* $=N^+[CH_2CH_3]_2$), 47.04 and 43.95 (minor rotamer *anti*, *syn* $=N^+[CH_2CH_3]_2$), 25.69 and 21.49 (major rotamer diastereotopic $-CH[CH_3]_2$), 25.05 and 21.95 (minor rotamer diastereotopic $-CH[CH_3]_2$), 24.23 and 23.66 (major, minor rotamer $HC-[CH_2]_3-$), 18.97 and 18.9 {shoulder} (major, minor rotamer HC-

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$[CH_2]_3-$), 15.3 (br, BH*C*H$[CH_3]_2$), 13.23 and 12.34 (major rotamer *anti, syn* $=N^+[CH_2CH_3]_2$), 12.50 and 12.28 {shoulder} (minor rotamer *anti, syn* $=N^+[CH_2CHI_3]_2$); IR (NaCl) ν_{max} 2940 s, 2870 ms, 2850 ms (C—H), 2430 m (B—H), 1561 s (C=NEt_2^+), 1465 s, 1450 ms, 1380 m sh, 1365 m, 1318 ms, 1280 s, 1205 m, 1157 m sh, 1050 vs br (BF_4^-), 974 m, 900 mw, 836 ms sh, 812 m sh, 767 mw sh, 722 w sh cm^{-1}.

Quinuclidine—Isobutyl(*C*-methoxycarbonyl)borane (1k). Compound **1h** (2.79 g) prepared as described above was stirred for 3 days at room temperature in a mixture of 20 mL of MeCN and 20 mL of 1 M aqueous NaOH. After evaporation of the solvents, the tannish oil was flash-chromatographed (s.g., $R_f = 0.73$, THF) to yield 0.387 g of **1k** (1.62 mmole, 22.4%). The ester was recrystallized from pentane at −15 °C to afford colorless analytically-pure crystals: mp 54.5−56.5 °C, ^{11}B NMR (CH_2Cl_2) δ −4.85 (d, J = 89.5 Hz); ^1H NMR ($CDCl_3$) δ 3.50 (s, $-OCH_3$), 3.26 and 2.98 (2nd order multiplets, diastereotopic $N[CH_2]_3-$), 1.98 (septet, J = 3.13 Hz, $HC[CH_2]_3-$), 1.72 (td, J = 7.83, 3.04, $HC[CH_2]_3-$), 1.47 (septet of t, J = 6.66, 2 Hz, $-CH_2CH[CH_3]_2$), 0.88 and 0.85 (d, d, J = 6.76, 6.77 Hz, diasteretopic $-CH[CH_3]_2$), 0.42 and 0.21 (2nd order septets, diastereotopic $BHCH_2$-CH−); ^{13}C NMR ($CDCl_3$) δ 196.0 (br, B*C*(=O)O−), 49.70 ($N[CH_2]_3-$), 47.59 ($-OCH_3$), 28.2 (br, $BHCH_2CH-$), 26.94 ($-CH[CH_3]_2$), 26.61 ($-CH_2CH[CH_3]_2$), 24.49 ($HC[CH_2]_3-$), 20.31 ($HC[CH_2]_3-$); IR (KBr) ν_{max} 2977 m, 2940 vs, 2871 s, 2802 m, 2390 ms, 2340 m, 1668 vs (C=O), 1464 s, 1419 mw, 1370 s sh, 1354, mw sh, 1323 mw, 1312 m, 1278 m, 1245 m, 1238 w, 1180 ms, 1125 ms, 1116 ms sh, 1092 ms, 1075 vs, 1039 s, 977 mw, 960 ms, 859 ms, 843 ms, 833 m, 811 m sh, 776 m, 719 w, 670 w, 352 mw cm^{-1}; HRMS (CI, NH_3) *m/e* 180.1930 ($M^+ - C(=O)OCH_3$, calcd for $C_{11}H_{23}N^{11}B$, *m/e* 180.1923). Anal. Found: C, 65.43; H, 10.92. Calcd for $C_{13}H_{26}NBO_2$: C, 65.29; H, 10.96.

Quinuclidine—Isobutyl(*N,N*-diethylcarbamoyl)borane (1n). From the reaction that produced **1k** above, flash-chromatography (s.g., R_f = 0.30, EtOAc) yielded also an oil, which solidified in a freezer (−15 °C) over 1 week to give crystal which remelted slowly upon reaching room temperature (20 °C) (0.154 g, 0.550 mmol, 30.0%). These were recrystallized from a small volume of pentane at −15 °C to yield an analytically-pure off-white solid: ^{11}B NMR (THF) δ −6.11 (br d, J = 62.1 Hz); ^1H NMR ($CDCl_3$) δ 3.69 and 3.27 (sextets, J_{gem} = *ca.* 14 Hz, $J_{H-C-C-H}$ = 7.05, 7.00 Hz, *anti*-diastereotopic $-NCH_2CH_3$), 3.51 and 3.09 (sextets, J_{gem} = *ca.* 13.9 Hz, $J_{H-C-C-H}$ = 6.92, 6.97 Hz, *syn* $-NCH_2CH_3$), 3.40 and 2.93 (complex 2nd order quintets, diastereotopic $N[CH_2]_3-$), 1.93 (septet, J = 3.13 Hz, $HC[CH_2]_3-$), 1.68 (td, J = 7.83, 3.09 Hz, $HC[CH_2]_3-$), 1.37 (br septet, J = 6.70 Hz, $-CH_2CH[CH_3]_2$), 1.07 (t, J = 7.02 Hz, *anti* $-NCH_2CH_3$), 1.02 (t, J = 7.08 Hz, *syn* $-NCH_2CH_3$), 0.86 and 0.84 (d, d, J = 6.56, 6.53 Hz, diastereotopic $-CH[CH_3]_2$), 0.46 and 0.25 (2nd order septets, diastereotopic $BHCH_2$-CH−); ^{13}C NMR ($CDCl_3$) δ 197.6 (br, B*C*(=O)N0−), 49.86 ($N[CH_2]_3-$), 41.45 (*anti* $-NCH_2CH_3$), 36.80 (*syn* $-NCH_2CH_3$), 29.65 (br, BCH_2CH-), 26.68 (coincident $-CH_2CH[CH_3]_2$, and one diastereotopic $-CH[CH_3]_2$), 25.94 (other diastereotopic $-CH[CH_3]_2$), 24.79 ($CH[CH_2]_3-$), 20.70 ($HC[CH_2]_3-$), 14.87 (*anti* $-NCH_2CH_3$), 13.42 (*syn* $-NCH_2CH_3$); IR (NaCl) ν_{max} 2965.ms, 2940 vs, 2870 s, 2801 m, 2387 ms, 2316 m, 2236 w, 1560 vs, 1474 s, 1405 s, 1376 ms, 1358 ms, 1341 m, 1315 m, 1262 s, 1223 m, 1209 ms, 1178 ms, 1128 s, 1118 ms, 1090 s br, 1066 m, 1035 s, 1020 mw, 980 ms, 939 mw, 900 w, 880 w, 834 s, 815 ms sh, 775 mw, 734 w, 660 m, 656 mw, 577 w, 561 vw cm^{-1}. Anal. Found: C, 68.86; H, 12.13. Calcd for $C_{16}H_{33}N_2BO$: C, 68.57; H, 11.87.

Quinuclidine—Isobutyl(*C*-(benzyloxy)carbonyl)borane (1m). Recrystallized **1g** (0.931 g, 2.72 mmol) was reacted with *ca.* five times excess Et_3OBF_4 in CH_2Cl_2 for 2 days, at which time, solid **1j** (1.167 g) was isolated [^{11}B NMR (CH_2Cl_2) −1.5 (s, BF_4^-), −6.6 (br d, boronium); IR (NaCl) 2430 ms, 1600 m, 1565 s cm^{-1}], contaminated with *ca.* 40% unreacted **1g**. The entire oil was dissolved in 5 mL of MeCN, and 5 mL of 1 M NaOH was added to it. This was stirred for 2 days. The mass was flash-chromatographed on silica gel in one portion to yield 0.311 g of **1m** (0.987 mmol, 36.3% based on starting **1g**) and 0.209 g of diethyl amide **1n** (0.747 mmol, 27.5%). The ester was recrystallized from CH_2Cl_2/hexane in a freezer (−15 °C) to yield analytically-pure white needles: mp 81−83 °C; ^{11}B NMR (CH_2Cl_2) δ −5.27 (d, J = 86.0 Hz); ^1H NMR ($CDCl_3$) δ 7.34 (d, J = 6.88 Hz, *o*-Ph *H*), 7.30 (t, J = 7.67 Hz, *m*-Ph *H*), 7.22 (t, J = 7.82 Hz, *p*-Ph *H*), 5.8 and 4.96 (d, d, J_{gem} = 12.81, 12.81 Hz, diastereotopic $-OCH_2Ph$), 3.26 and 2.99 (m, m, diastereotopic $N[CH_2]_3-$], 1.98 (septet, J = 3.14 Hz, $HC[CH_2]_3-$), 1.71 (td, J = 7.86, 3.02 Hz), 1.53 (septet of t, J = 6.58, 2.3 Hz, $CH_2CH[CH_3]_2$), 0.88 and 0.85 (d, d, J = 6.49, 6.53 Hz, diastereotopic $-CH[CH_3]_2$), 0.46 and 0.21 (2nd order septets, diastereotopic $BHCH_2CH[CH_3]_2$); ^{13}C NMR ($CDCl_3$) δ 195.4 (br, B*C*(=O)-O−), 138.43 ($-OCH_2C$[Ph]), 128.09 (*o*-Ph *C*), 127.6 (*m*-Ph *C*), 127.0 (*p*-Ph *C*), 62.0 ($-OCH_2Ph$), 49.8 ($N[CH_2]_3-$), 28.2 (br, BCH_2CH-), 27.1 ($-CH_2CH[CH_3]_2$), 26.8 and 24.5 (diastereotopic $-CH[CH_3]_2$), 24.6 {obscures high-field $-CH[CH_3]_2$ signal} $HC[CH_2]_3-$), 20.38 ($HC[CH_2]_3-$); FTIR (KBr) ν_{max} 3034 w, 3011 w (aryl C—H), 2965 m, 2948 s, 2890 m, 2876 ms, 2863 m, 2801 w (alkyl C—H), 2398 m, 2361 ms, 2336 ms, 2242 w (B—H), 1667 vs (C=O), 1630 w, 1611 w, 1496 mw, 1464 ms, 1401 m, 1377 w, 1360 m sh, 1318 m, 1285 w, 1262 m, 1211 m, 1183 ms, 1165 w, 1127 ms, 1119 m, 1090 s, 1073 s, 1049 ms, 1026 vs, 976 mw, 965 w, 912 w, 897 mw, 839 m, 833 m, 812 m, 805 m, 750 s sh, 700 ms sh, 667 mw sh, 627 vw, 579 w, 548 vw, 532 vw, 502 w, 473 w cm^{-1}. Anal. Found: C, 72.66; H, 9.79. Calcd for $C_{19}H_{30}NBO_2$: C, 72.39; H, 9.59.

Quinuclidine—Isopropyl(*C*-methoxycarbonyl)borane (2k). Compound **2h** (0.332 g) prepared as described above was stirred for 2 weeks at room temperature in a mixture of 3 mL of MeCN and 3 mL of 1 M aqueous NaOH. After evaporation of the solvents, the hydrolysis products were flash-chromatographed (s.g. R_f = 0.74, THF, 100 g) to yield 0.026 g of solid ester **2k**: ^{11}B NMR (CH_2Cl_2) δ −2.27 (d, J = 91.3 Hz); ^1H NMR ($CDCl_3$) δ 3.50 (s, $-OCH_3$), 3.30 and 3.04 (complex second-order quintets, diastereotopic $N[CH_2]_3-$), 1.98 (br septet, J = 3.72 Hz, $HC[CH_2]_3-$), 1.73 (td, J = 7.70, 2.82 Hz, $HC[CH_2]_3-$), 0.96 and 0.73 (br virtual triplet, br s, J = 2.94, 0 Hz, diastereotopic $-CH-[CH_3]_2$), 0.84 (br multiplet, J = 7.9 Hz, $BHCH[CH_3]_2$); ^{13}C NMR ($CDCl_3$) δ 195.7 (br, B*C*(=O)O−), 49.84 ($N[CH_2]_3-$), 47.34 ($-OCH_3$), 25.06 and 21.66 (diastereotopic $-CH[CH_3]_2$), 24.62 ($HC[CH_2]_3-$), 20.46 ($HC[CH_2]_3-$), 14.6 (br, $BHCH[CH_3]_2$); IR (KBr) ν_{max} 2936 vs, 2853 s, 2360 m, 2333 m, 1669 vs (C=O), 1537 w, 1462 ms, 1417 mw, 1379 mw, 1355 mw, 1338 w, 1312 mw, 1260 s, 1205 m, 1178 ms, 1124 ms, 1085 s, 1064 vs, 1035 s, 1005 m, 974 mw, 960 mw, 803 w, 843 ms, 829 m, 811 s sh, 801 s, 729 mw, 664 vw, 400 vw cm^{-1}; HRMS (+CI, CH_4) *m/e* 226.1966/225.1918 (M^+ + H, calcd for $C_{12}H_{25}{}^{11}BNO_2$ *m/e* 226.1978/M^+, calcd for $C_{12}H_{24}{}^{11}BNO_2$, *m/e* 225.1900).

Quinuclidine—Isopropyl(*N,N*-diethylcarbamoyl)borane (2n). From the reaction that produced **2k** above, further flash chromatography afforded **2n** (R_f = 0.64, THF; 0.26, EtOAc) as an oil (0.115 g) which crystallized at −15 °C and then remained solid at room temperature: ^{11}B NMR (CH_2CL_2) δ −2.95 (br d, J = 82.8 Hz); ^1H NMR ($CDCl_3$) δ 3.77 and 3.11 (sextets, J_{gem} = *ca.* 13.9 Hz, $J_{H-C-C-H}$ = 6.97, 6.92 Hz, diastereotopic *anti* NCH_2CH_3), 3.71 and 2.91 (sextets, J_{gem} = 13.9 Hz, $J_{H-C-C-H}$ = 6.98, 6.94 Hz, diastereotopic *syn* $-NCH_2CH_3$), 3.46 and 3.00 (complex second-order multiplets, diastereotopic $N[CH_2]_3-$), 1.93 (septet, J = 3.1 Hz, $HC[CH_2]_3-$), 1.69 (dt, J = 7.78 Hz, 3.04 Hz, $HC[CH_2]_3-$), 1.06 (t, J = 6.96 Hz, *anti* $-NCH_2CH_3$), 1.02 (t, J = 7.1 Hz, *syn* $-NCH_2CH_3$), 0.96 and 0.75 (br virtual triplet, br s, J = 3.6, 0 Hz, diastereotopic, $-CH[C_{H3}]_2$), 0.86 (br multiplet, $-BH-CH[CH_3]_2$); ^{13}C NMR ($CDCl_3$) δ 195.3 (br, B*C*(=O)N−), 49.56 ($N[CH_2]_3-$), 41.27 (*anti* $-NCH_2CH_3$), 36.32 (*syn* $-NCH_2CH_3$), 25.40 and 22.06 (diastereotopic $-CH[CH_3]_2$), 24.56 ($HC[CH_2]_3-$), 20.54 ($HC[CH_2]_3-$), 15.4 (br, $BHCH[CH_3]_2$), 14.42 (*anti* $-NCH_2CH_3$), 13.22 (*syn* $-NCH_2CH_3$); IR (NaCl) ν_{max} 2955 vs, 2890 s, 2875 s (C—H), 2368 ms, 2310 ms, 2255 m (B—H), 1555 vs (BC(=O)N−), 1463 s, 1405 s, 1378 ms, 1352 m, 1347 m, 1321 m, 1257 ms, 1228 mw, 1213 m, 1178 m, 1138 ms, 1100 vs, 1068 ms, 1036 s, 981 m sh, 941 w, 909 m sh, 842 ms, 834 s, 820 ms, 792 m, 712 mw, 662 mw, 587 m cm^{-1}; HRMS (+CI, NH_3) *m/e* 265.2469 (M^+ − H calcd for $C_{15}H_{30}BN_2O$, *m/e* 265.2451).

Pyridine—*sec*-Butyl(*C*-methoxycarbonyl)borane (3k′). A sample of **3e′** (1.564 g, 6.68 mmol) was reacted with *ca.* 3.0 g of Et_3OBF_4 (16 mmol) stirred in Et_2O for 2 days to form **3h′**. After evaporation of the solvent, the crude product was reacted with 20 mL of aqueous 1 N NaOH in 20 mL of acetonitrile for 2 weeks at room temperature. Boron-11 analysis of the product mixture indicated about a 1:1 ratio of **3k′** and **3n′**. After evaporation of the solvents, the crude mixture was flash-chromatographed [s.g., 200 g, R_f = 0.63 (THF)] to afford an oil (0.179 g, 0.864 mmol, 12.9% based on starting **3e′**) of **3k′**: ^{11}B

NMR (CH_2Cl_2) δ −2.41 (d, J = 89.5 Hz); ^{1}H NMR ($CDCl_3$) δ 8.72 and 8.71 (diastereomeric *o*-Pyr H), 8.02 (t, J = 7.55 Hz, *p*-Pyr H), 7.58 (t, J = 6.94 Hz, *m*-Pyr H), 3.55 and 3.54 (s, s, diastereomeric OCH_3), 1.33, 1.21, 1.05, 0.92 (complex multiplets, $-CHCH_2CH_3$), 0.71 (br multiplet, $-BHCH$), 0.58 (d, J = 6.86 Hz, $BHCHCH_3$); ^{13}C NMR ($CDCl_3$) δ 195.3 (br BC(+O)O−), 147.22 (*o*-Pyr C), 140.24 (*p*-Pyr C), 124.95 and 124.92 (diastereomeric, *o*-Pyr C), 48.02 and 47.98 (diastereomeric $-OCH_3$), 27.78 and 27.57 (diastereomeric $BHCHCH_2-$), 27.5 (br, BHCH), 17.05 and 16.90 (diastereomeric $BHCHCH_3$), 13.18 and 12.91 (diastereomeric, $-CHCH_2CH_3$); IR (NaCl) ν_{max} 3122 w, 3110 w, 3079 w, 3061 mw, 3047 vw, 2940 vs, 2860 s, 2830 m, 2372 ms (BH), 1668 vs (C=O), 1623 s sh, 1576 w, 1488 ms, 1461 s, 1455 s, 1422 m, 1370 m, 1347 mw, 1255 m, 1212 m, 1186 s, 1157 ms, 1090 vs, 1040 vs, 1001 m, 958 m, 712 m cm^{-1}; HRMS (+CI, NH_3) *m/e* 208.1505 (M^+ + H) calcd for $C_{11}H_{19}{}^{11}BNO_2$ *m/e* 208.1508.

Pyridine−Isopropyl(*N,N*-diethylcarbamoyl)borane (2n′). A sample of **2e′** (0.552 g, 2.51 mmol) was reacted with Et_3OBF_4 (0.956 g, 4.82 mmol) in 6 mL of CH_2Cl_2 for 24 h at room temperature. Evaporation of the solvent gave crystalline **2h′** [^{11}B NMR, CH_2Cl_2, δ −1.4 (BF_4^-), −2.0 (br d)]. These crystals were dissolved in 10 mL of MeCN and reacted with 5 mL of 1 M aqueous NaOH for 21 h at room temperature. The mixture was evaporated under vacuum and flash chromatographed (s.g., THF/EtOAc) to give 0.095 g of white solid. This was recrystallized from pentane at −15 °C to give pure **2n′**: mp 73−75 °C; ^{11}B NMR ($CDCl_3$) δ −2.03 (d, J = 63 Hz); ^{1}H NMR ($CDCl_3$) δ 8.92 (d, J = 6.8 Hz, *o*-Pyr H), 7.95 (t, J = 7.5 Hz, *p*-Pyr H), 7.51 (t, J = 6.8 Hz, *m*-Pyr H), 3.85 and 3.32 (sextets, J_{gem} = 14, $J_{H-C-C-H}$ = 7.04, 7.05 Hz, *anti* NCH_2CH_3), 3.70 and 2.98 (sextets, J_{gem} = 13.3 Hz, J_{HC-C-H} = 6.45, 6.57 Hz, *syn* NCH_2CH_3), 1.13 (t, J = 6.98 Hz, *anti* $-NCH_2CH_3$), 1.06 (t, J = 7.0 Hz, *syn* $-NCH_2CH_3$), *ca.* 0.8 (obscured m, $BHCH(Me)_2$), 0.79 and 0.61 (diastereotopic $-CH(CH_3)_2$; ^{13}C NMR ($CDCl_3$) δ 195.2 (br, BC(=O)=N−), 147.9 (*o*-Pyr C), 139.8 (*p*-Pyr C), 124.4 (*m*-Pyr C), 41.5 (*anti* $-NCH_2CH_3$), 37.0 (*syn* $-NCH_2CH_3$), 21.3 (br, $BCH(Me)_2$), 21.3 and 21.1 (diastereotopic $-CH(CH_3)_2$], 14.7 (*anti* $-NCH_2CH_3$), 13.4 (*syn* $-NCH_2CH_3$); IR (KBr) ν_{max} 3129 w, 3112 w, 3083 mw, 3007 mw (aryl C−H), 2971 s, 2946 s, 2932 s, 2919 s, 2886 ms, 2870 m, 2855 s sh, 2836 ms (alkyl C−H), 2390 m, 2373 m, 2317 w (B−H), 1622 m (ring distortion), 1551 vs (BC(=O)N−), 1483 m, 1464 s, 1453 vs, 1414 s, 1373 ms, 1360 m, 1345 mw, 1337 mw, 1310 m, 1265 s, 1256 s, 1223 m, 1202 m, 1167 m, 1152 w, 1119 s, 1094 vs, 1078 ms, 1065 s, 1055 m, 1034 mw, 1026 ms, 997 mw, 953 w, 939 mw, 912 vw, 901 w, 880 mw, 822 w, 777 s, 758 m, 741 mw, 963 s sh, 669 m, 650 vw, 619 w, 592 m, 505 w, 436 w cm^{-1}. Anal. Found: C, 66.96; H, 10.09. Calcd for $C_{13}H_{23}N_2BO$: C, 66.69; H, 9.90.

Results and Discussion

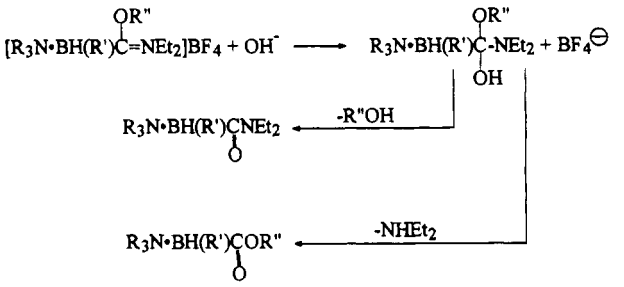
Borch reported that the reaction of a tertiary amide with Et_3OBF_4 afforded the *N,N*-dialkyl-*C*-ethoxy iminium salt.[22] These salts after exposure to moisture hydrolyzed to the ethyl ester rapidly. Alkylation of an amine−alkylborane imino ether with Et_3OBF_4 formed the corresponding iminium salt as illustrated in eq 1.

$$R_3N{\cdot}BH(R')\overset{OR''}{\underset{|}{C}}{=}NEt + Et_3OBF_4 \longrightarrow R_3N{\cdot}BH(R')\overset{OR''}{\underset{|}{C}}{=}NEt_2]BF_4 + Et_2O \qquad (1)$$

Hydrolysis of various amine−alkyl(*C*-alkoxy-*N,N*-diethylcyano)borane tetrafluoroborates was only partially complete at room temperature in 1−3 days. For two derivatives, **1h** and **2h**, this relative stability to moisture allowed partial characterization of the salts (i.e., NMR and IR; see Experimental Section). One derivative, **2h**, even survived column chromatography on silica gel. The products of this relatively slow hydrolysis were a mixture of amine−alkyl(*C*-alkoxycarbonyl)borane and amine−alkyl(*N,N*-diethylcarbamoyl)borane.

It was determined that the iminium salts would hydrolyze more quickly at room temperature in aqueous base. Thus, **1i** reacted with 1 M aqueous NaOH with MeCN as cosolvent in 28 h to give approximately 60% **1l**, 15% **1n**, 20% **1f**, and 5% starting iminium salt as determined by ^{11}B NMR. In general, the more sterically congested the iminium salt structure was, the longer the base hydrolysis took to go to completion. Of course, elevated temperatures could not be tolerated because amine−borane acid−base dissociation would occur, followed by irreversible decomposition of the borane to boronic acid.

Scheme 1. Proposed Route for Conversion of Amine−Alkyl(*C*-alkoxy-*N,N*-diethylcyano)borane Tetrafluoroborate by Aqueous Hydroxide to Amine−Alkyl(*C*-alkoxycarbonyl)borane and Amine−Alkyl(*N,N*-diethylcarbamoyl)borane



The ester and *N,N*-diethyl amide products were purified by flash chromatography and low-temperature (−15 °C) crystallization. A reaction sequence leading to these products is illustrated in Scheme 1. The hemiacetal intermediate in this scheme is a rather sterically-crowded structure. Under these congested circumstances, there does not appear to be a strong preference for elimination of either alcohol or diethylamine from this reactive intermediate to give diethyl amide or ester product, respectively. Thus, both products are formed in varying amounts in all cases studied to date.

Spectroscopic Considerations. Infrared. The carbonyl band in the infrared spectra of the ester derivatives is a strong absorbance in the range 1667−1669 cm^{-1}. This is very similar to the previously-reported carbonyl IR band of amine−borane esters such as $Me_3N{\cdot}BH_2CO_2Et$ (i.e., 1660 cm^{-1}).[6] For comparison, most nonconjugated organic esters display a carbonyl band in the range 1735−1750 cm^{-1}.[23]

The carbonyl band of the *N,N*-diethyl amide amine−boranes occurs in the range 1551−1560 cm^{-1}. The closely-related amine−alkyl(*N*-ethylcarbamoyl)boranes exhibit an amide I band at 1575−1590 cm^{-1}.[12] Typical organic secondary amides have a carbonyl stretch at 1640 cm^{-1}.[23]

NMR. Both the ^{13}C and ^{1}H NMR spectra of the *C*-methoxy-*N,N*-diethyl iminium salt, **2h**, show an interesting conformational rigidity. The *N*-ethyl groups are observed to be *syn* and *anti* relative to the *C*-methoxy group. Also, the protons of a given methylene group are diastereotopic. In addition, there is apparent restricted rotation (at room temperature) about the iminum carbon−boron bond, resulting in distinct ^{13}C and ^{1}H NMR signals for two rotamers of **2h**. Further variable-temperature NMR experiments would need to be done to confirm this interpretation.

The amine−alkyl(*N,N*-diethylcarbamoyl)boranes display conformational rigidity in the proton and ^{13}C NMR spectra due to some double bond character between the nitrogen and the carbonyl carbon. The ^{13}C NMR of *N,N*-diethylpropionamide exhibits similar *syn* and *anti* environments of the *N*-ethyl

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groups.[24] In the proton NMR spectrum of **2n'** four sextets at 3.85, 3.70, 3.32, and 2.98 ppm are due to the methylene protons of the *N*-ethyl groups. One of the chemical shift differences is caused by the protons on a given methylene group being diastereotopic, and the other shift difference is from conformational rigidity.

Attempted Conversion of Ester to Acid. Attempted saponification of ester **1l** by room temperature treatment with aqueous 10 M NaOH/MeCN for 3 weeks resulted in near-quantitative recovery of **1l**.

The conversion of a benzyl ester to the corresponding carboxylic acid by treatment with H_2 or cyclohexane in the presence of palladium on carbon is a well-known process.[25,26] Ester **1m** was reacted in ethanol for 1 day at room temperature with H_2 in the presence of palladium on carbon. The ^{11}B NMR spectrum revealed a doublet at −4.76 ppm (**1m** in ethanol, δ_B = −4.42) as well as a singlet due to alkyl boronic acid. The infrared spectrum of the isolated solid products contained a strong absorbance at 1640 cm^{-1} and a weaker intensity band at 1670 cm^{-1} due the carbonyl function of the remaining **1m**. This data suggests that some quinuclidine−isobutylcarboxylborane (**1o**) may have been formed. Carboxyboranes of the general formula $R_3N{\cdot}BH_2CO_2H$ have the carbonyl stretching band near 1640 cm^{-1}.[4,15] Since this synthetic route via the ester to the carboxyborane appears to be a low-yield process, no further study to obtain a fully-characterized carboxyborane by this method was attempted.

Acknowledgment. This work was supported in part by the Public Health Service.

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